

Investigating Adverse Drug Events and Adverse Drug Withdrawal Effects Associated with Heart Failure Pharmacotherapy in Older People with Frailty

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A thesis submitted in fulfilment of requirements for the degree of

Doctorate of Philosophy

2025

“Ever tried. Ever failed. No matter. Try again. Fail again. Fail better.”

-Samuel Beckett, *Worstward Ho!*

DECLARATION

This is to certify that to the best of my knowledge, the content of this thesis is my own work.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

This thesis has not been previously submitted, in part or whole, to any university or institution for the award of any qualifications.

31st January 2025

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AUTHOR CONTRIBUTIONS

This thesis comprised two review papers (Chapter 2, Section 2.3 and Chapter 3, Section 3.3) published in peer-reviewed journals.

I, Mai Duong, was responsible for the work compiled in this thesis, accomplished under the supervision of Professor Sarah Hilmer, Associate Professor Danijela Gnjidic and Professor Andrew McLachlan. My contributions to all the publications and work presented in this thesis involved the following authorship attribution statements in accordance with the contributor Roles Taxonomy (CRediT) for each content chapter in this thesis.

Chapter 2: The candidate's role were conceptualisation, methodology, software, data collection and curation, validation, formal analysis, investigation, resources, writing- original draft, writing-review and editing, visualisation, project administration, funding acquisition.

Chapter 3: The candidate's role were conceptualisation, methodology, software, data collection and curation, validation, formal analysis, investigation, resources, writing- original draft, writing-review and editing, visualisation, project administration, funding acquisition.

Chapter 4: The candidate's role were conceptualisation, methodology, software, validation, formal analysis, investigation, resources, data curation, writing- original draft, writing-review and editing, visualisation, project administration, funding acquisition.

Chapter 5: The candidate's role were conceptualisation, methodology, data collection and curation, validation, formal analysis, investigation, resources, data curation, writing- original draft, writing-review and editing, visualisation, project administration, funding acquisition.

DEDICATION

I dedicate this to:

Nick, my wonderful partner and phenomenal co-author in life, thank you for always grounding me with love, acceptance, joy and laughter. I appreciate your steady and gentle support, courage, and sacrifice. Thank you for believing in me, being there when I needed you most and holding my hand all the way to the finish line.

My family, thank you mom and dad for all your love, care and encouragement to pursue my dreams, strive for excellence and keep learning. Your courage, tenacity, kindness and commitment to community service are my inspiration. Thank you to my siblings, Michelle, Michael and Alan, for always having my back. Elliott, you are the greatest joy at the end of the rainbow. Ben and Arlene, your care, wisdom and friendship have been among my most cherished blessings. Snowball, I am so lucky to have a bestie who is always there to support me and my crazy ideas.

Thank you to all my friends and adopted families around the world for all the love and support and always checking in. Thank goodness for Wolf and the kittens.

In loving memory of the strong women who raised me, Ba Ngoai, Bay, Diana, and Mrs Hoeffler. Thank you for teaching me kindness, compassion, social service, determination, hard work and the importance of practice, practice and more practice.

ACKNOWLEDGEMENTS

I am deeply grateful to my extraordinary supervisors, Sarah, Danijela, and Andrew, for believing in me and persevering with me to achieve this dream. You are individually outstanding humans and together make the best team! Thank you for your wisdom, unwavering support and compassion, generosity with your time, fantastic mentorship and genuine friendship.

It has been a privilege to work with a fabulous and professional team of collaborators. I am grateful to Parag Goyal, Stephanie Mathieson, Alexandra Bennett, Marissa Sakiris, Mitchell Redston, Lisa Kouladjian O'Donnell, Kevin Winardi, Rebecca Kozor, Ritu Trivedi, David Le Couteur, and Fiona Blyth for their contributions to this research.

I acknowledge the graphical designs of Mr Ryan Snow, and technical support from the University of Sydney Dr Yulia Ulyannikova in library services and Mr Jim Matthews and Mr Omar Arnaiz at the Informatics Hub. I acknowledge Elite Editing for thesis editing services.

I acknowledge gratitude for my mentors and sponsors, Melissa Baysari, Bridgin Munro, Ben Basger, Jane Hanrahan, Barbara Mintzes, and Gemma Figtree.

Thanks to my colleagues at the Kolling Institute and Laboratory of Pharmacology and Ageing, University of Sydney School of Pharmacy, ACvA, HROz and Digital Health Network. Special thanks to my tennis and PhD buddies Maureen Bartels, Gizem Gemikonakli, Bonnie Liu, Ritu Trivedi and Karan Rao for sharing this journey.

FUNDING

This doctoral work was funded by the National Health and Medical Research Council (NHMRC) postgraduate scholarship 2020 APP1191018, awarded from 2021 to 2024, and by Heart Research Australia (HROz) post-graduate scholarship, awarded from 2023 to 2024.

The University of Sydney postgraduate research support scheme (PRSS), the Australasian Pharmaceutical Science Association (APSA) student travel grant, and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) student travel grant provided additional support.

THESIS ABSTRACT

Background

Frailty is common among older people with heart failure (HF). Optimising HF pharmacotherapy can improve clinical outcomes, but efficacy and safety are uncertain for older people with frailty.

Aim

To explore the prevalence and management of adverse drug events (ADEs) and adverse drug withdrawal effects (ADWEs) associated with optimising and deprescribing HF pharmacotherapy for older people with frailty.

Methods

Participants: Older adults with HF diagnosis on HF pharmacotherapy and doctors, nurses and pharmacists. Design: Systematic reviews and meta-analysis (**Study 1, 2**); a multi-hospital cross-sectional study (**Study 3**); and a qualitative study in primary care and hospital (**Study 4**).

Results

Study 1: Of 2,416 studies, three observational studies of people ≥ 65 years with objective frailty reported ADEs. Frail people on renin-angiotensin system inhibitors (RASIs) had a 2-fold risk of mortality, and digoxin probably caused falls, tiredness and nausea. **Study 2:** Of 5,461 studies, six randomised controlled trials and 27 observational studies reported deprescribing of HF pharmacotherapy in HF patients ≥ 50 years. Four studies reported outcomes for people ≥ 75 years. No studies reported outcomes by frailty status. Worsening HF was the most common ADWE. **Study 3:** Of 439 (22%) inpatients ≥ 75 years with unspecified HF, 305 (69.5%) had frailty risk. Diuretic use was common with RASI (n=67, 16%) or beta-blockers (n=62, 15%). Increasing frailty risk showed a higher prevalence of ADEs (31-84%), falls (12-46%), and delirium (8- 49%).

Study 4: Interviews and focus groups with consumers (n=4) and healthcare professionals (n=28) identified three main themes: individual factors, medications and access to healthcare. A conceptual model describes the interplay between frailty, ADEs, and ADWEs of HF pharmacotherapy on quality of life in older people, which needs further development.

Conclusion

Future research of HF pharmacotherapy in older people may report objective frailty and HF phenotypes.

LIST OF PUBLICATIONS

Duong MH, Gnjjidic D, McLachlan AJ, Winardi K, Bennett AA, Blyth F, Le Couteur D, Hilmer SN. Prevalence of Heart Failure Pharmacotherapy Utilisation, Frailty and Adverse Drug Events Among Hospitalised Adults Over 75 years: A Multicentre Cross-Sectional Study (TO HOME). *Internal Medicine Journal* 2024;1-11. doi: 10.1111/imj.16612.

Duong MH, Gnjjidic D, McLachlan AJ, Redston MR, Goyal P, Mathieson S, Hilmer SN. Discontinuation and Down-titration of Heart Failure Pharmacotherapy in Older People: A Systematic Review and Meta-analysis. *British Journal of Clinical Pharmacology* 2024: 23-37. doi:10.1111/bcp.16223.

Duong MH, Gnjjidic D, McLachlan AJ, Sakiris MA, Goyal P, Hilmer SN. The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review. *Drugs and Aging* 2022;39, 631–643. [doi: 10.1007/s40266-022-00957-8](https://doi.org/10.1007/s40266-022-00957-8)

Currently under review

Duong MH, Gnjjidic D, McLachlan AJ, Kouladjian O'Donnell L, Truvedi R, Kozor R, Hilmer S. Adverse drug events associated with heart failure pharmacotherapy in older people living with frailty: a qualitative study. *Canadian Journal of Cardiology Open* (2025) [*under review*]

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Masnoon N, Lo S, Baysari M, Bennett A, McLachlan AJ, Blyth F, **Duong M**, Hilmer N. Consumer and multidisciplinary clinician experiences after implementation of the Drug Burden Index intervention bundle to facilitate deprescribing in older inpatients: A mixed method study. *Journal of Evaluation and Clinical Practice* 2025;31(1):e14220. doi: 10.1111/jep.14220.

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Duong MH, Gnjdic D, McLachlan AJ, Kouladjian O'Donnell L, Trivedi R, Kozar R, Hilmer SN. Consumer and clinician perspectives of adverse drug events and adverse drug withdrawal effects of heart failure medications in frail older people. *Pharmacy Education*; 2023. 23(6): 187-187. doi: 10.46542/pe.2023.236.158191

LIST OF PRIZES AND AWARDS

Prizes

Outstanding Oral Presentation in Pharmacy Practice for the abstract entitled, “Consumer and clinician perspectives on adverse drug events and adverse drug withdrawal effects of heart failure medications in frail older people”. This was presented to the 81st International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences 2023 hosted in Brisbane, Australia in September 2023.

Runner-up Best Lighting 3-minute Oral presentation for the abstract entitled, “Adverse drug events and adverse drug withdrawal effects of heart failure pharmacotherapy in frail older people”. This was presented at the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) Cardiovascular Special Interest group Student and Early Career Researcher Cardiovascular Symposium in October 2023.

Awards

Paulette Isabel Jones Career Award. Awarded by the University of Sydney for early PhD submission in August 2024.

The University of Sydney Postgraduate Research Support Scheme (PRSS) to subsidise research activities from 2022 to 2024.

Australasian Pharmaceutical Science Association (APSA) student travel award 2023 to partially subsidise airfare to the annual conference in Brisbane.

Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) student travel award 2022 to subsidise airfare to the annual conference in Perth.

LIST OF PRESENTATIONS

Conferences and Presentations

Accepted Abstracts for Oral Presentations

Duong MH, Gnjjidic D, McLachlan A, Kouladjian O Donnell L, Trivedi R, Kozar R, Hilmer S. Adverse drug events and adverse drug withdrawal effects of heart failure pharmacotherapy in frail older people. Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) Student and Early Career Researcher Cardiovascular Special Interest Group Symposium. Virtual, 2023.

Duong MH, Gnjjidic D, McLachlan A, Kouladjian O Donnell L, Trivedi R, Kozar R, Hilmer S. Consumer and clinician perspectives of adverse drug events and adverse drug withdrawal effects of heart failure medications in frail older people. Pharmacy Education; 2023. 23(6): 187-187. doi: <https://doi.org/10.46542/pe.2023.236.158191>. Presented at the International Pharmaceutical Federation (FIP) 81st World Congress. Health and medicines information section and Australasian Pharmaceutical Science Association (APSA). Brisbane, 2023.

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S. Deprescribing in Heart Failure. St. George Hospital, Cardiology Department, research and training seminar, Sydney – Review and meta-analysis. Resident medical officer presentation. Presented by Redston M on behalf of research team. Sydney, 2023.

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S. Evaluating deprescribing of heart failure medications during optimisation: a systematic review and meta- analysis. Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT). Perth, 2022.

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S. A systematic review and meta-analysis evaluating the effects of deprescribing during optimisation of heart failure medications in older adults. Australian Deprescribing Network annual meeting. Perth, 2022.

Duong MH, Gnjjidic D, McLachlan A, Sakiris M, Goyal P, Hilmer S. A systematic review of adverse drug reactions or adverse drug events of heart failure treatment in frail older adults Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) annual conference. Virtual, 2021.

Accepted Abstracts for Poster Presentations

Duong MH, Gnjjidic D, McLachlan A, Winardi K, Bennett A, Hilmer S. Prevalence of heart failure-pharmacotherapy, adverse events and frailty in inpatients ≥ 75 years Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) and Australasian Pharmaceutical Science Association (APSA) joint annual conference. Melbourne, 2024.

Duong MH, Gnjjidic D, McLachlan A, Kouladjian O, Donnell L, Trivedi R, Kozor R, Hilmer S. Adverse effects of heart failure pharmacotherapy in frail older people. Toronto-Ottawa Heart Summit. Toronto, Canada, 2023.

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S. Down-titrate and discontinue heart failure medications in older people. Toronto-Ottawa Heart Summit. Toronto, Canada, 2023.

Duong MH, Gnjdjic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S.

Evaluating deprescribing of heart failure medications during optimisation: a systematic review and meta- analysis. Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) annual conference. Perth, 2022.

Duong MH, Gnjdjic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S.

Deprescribing Heart Failure Medications in Older People: A Systematic Review and Meta-analysis. International Conference on Deprescribing (ICOD). Copenhagen, Denmark (virtual), 2022.

Duong MH, Gnjdjic D, McLachlan A, Sakiris M, Goyal P, Hilmer S. A systematic review of

adverse drug reactions or adverse drug events of heart failure treatment in frail older adults.

Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) annual conference. Virtual, 2021.

Invited Speaker

Duong MH. Exploring Adverse Drug Events and Adverse Drug Withdrawal Effects from

Heart Failure Pharmacotherapy in Older People Living with Frailty Final thesis seminar.

Ageing and Pharmacology Laboratory. Kolling Medical Research Institute. Sydney, 2024

Duong MH, Gnjdjic D, McLachlan A, Winardi K, Bennett A, Blyth F, Le Couteur D, Hilmer

S. The Prevalence of Heart Failure Pharmacotherapy, Frailty and Adverse Drug Events in

Hospitalised Adults over 75 years: A Multi-Centre Cross-Sectional Study of TO HOME. Aged Care Department, Royal North Shore Hospital. Sydney, 2024.

Duong MH. Journal club presentation. Ageing and Pharmacology Laboratory. Kolling Medical Research Institute. Sydney, 2024

Duong MH. Journal club presentation. Australian Deprescribing Network Webinar and Journal Club series. Virtual, 2023.

Duong MH. Developing a taxonomy of adverse drug events and adverse drug withdrawal effects of heart failure medications in frail older people. Westmead Applied Research Centre, Cardiology. Sydney, 2023

Duong MH. Developing a taxonomy of adverse drug events and adverse drug withdrawal effects of heart failure medications in frail older people. Ageing and Pharmacology Laboratory. Kolling Medical Research Institute. Sydney, 2023

Duong MH. Heart Research Australia (HROz) Dinner. Ormeggio Restaurant. Sydney, 2023.

Duong MH. Developing taxonomies of adverse drug reactions and adverse drug withdrawal events to support deprescribing in frail older people with heart failure. Ageing and Pharmacology Laboratory. Kolling Medical Research Institute. Sydney, 2022

Media and Activities

NSLHD newsletter November 2023 – “Awards Highlight the Impact of Drugs on Frail Older People with Heart Failure”. Available at the NSLHD e-newsletter, page 6

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Duong MH. “Poster of ADRs and ADEs from HF medications in frail older adults: a systematic review.(2021)”. ASCEPT 2021 poster presentation (virtual). Available at <https://www.youtube.com/watch?v=4Y5aKC99XSE> (last accessed on August 28, 2024)

LIST OF ABBREVIATIONS, ACRONYMS AND DEFINITIONS

95% CI	95% Confidence Interval
ACC	American College of Cardiology
ACEI	Angiotensin Converting Enzyme Inhibitor
ADE	Adverse Drug Event
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
ADHF	Acute Decompensated Heart Failure
ADWE	Adverse Drug Withdrawal Event/Effect
AF	Atrial Fibrillation
AHA	American Heart Association
aHR	adjusted Hazard Ratio
aOR	adjusted Odds Ratio
ARB	Angiotensin Receptor Blocker/Antagonist
ARNI	Angiotensin Receptor Neprilysin Inhibitors
ASCEND-HF	Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial
ATHENA -HF	Efficacy and Safety of Spironolactone in Acute Heart Failure Trial
ATLAS	Assessment of Treatment with Lisinopril and Survival Trial
AUD	Australian dollar
BB	Beta-blocker
BEAUTIFUL	Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction trial

BETAWIN-AHF	BETA-blocker Withdrawal during Acute decompensation Heart Failure study
b.i.d.	bis in die (twice daily)
BP	Blood Pressure
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CCI	Charlson Comorbidity Index
CFS	Clinical Frailty Scale
CHADS-VASc	Congestive heart failure, Hypertension, Age (> 65 = 1 point, > 75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points).
CHARM	Effects of candesartan in patients with chronic heart failure trial
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
C _{max}	C _{max} highest concentration of a drug in the blood
COMET	Carvedilol Or Metoprolol European Trial
COPD	Chronic Obstructive Pulmonary Disorder
CR/XL	Controlled Release/Extended Release
CRT	Cardiac Resynchronisation Therapy
CSA	Cross-Sectional Area of the myofiber
CV	CardioVascular
CVD	CardioVascular Disease
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial
DIG	Digoxin
DOAC	Direct Oral AntiCoagulant

DOSE	Diuretic Strategies in Patients with Acute Decompensated Heart Failure Trial
ECG	EchoCardioGram
E/e' ratio	Tissue doppler E/e' is a parameter for assessing diastolic heart failure
EF	Ejection Fraction
ECT	ElectroConvulsive Therapy
EMPHASIS-HF	Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms Trial
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction Trial
EPHESUS	Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
ESC	European Society of Cardiology
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan
Feasibility	the proportion of people who discontinued or down-titrated the dose of their HF-pharmacotherapy and subsequently did not re-start or switch pharmacotherapy
FI	Frailty Index
Frailty	a reversible syndrome involving multisystem deficiencies
Fried	Fried Frailty Phenotype Score
GALATIC-HF	Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure
GDMT	Guideline-Directed Medical Therapy
GFR	Glomerular Filtration Rate
GP	General Practitioner

GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GWTG-HF	Get with The Guidelines registry
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction (LVEF>50%)
HFrEF	Heart Failure with Reduced Ejection Fraction (LVEF<40%)
HFmEF	Heart Failure with Mildly-Reduced Ejection Fraction (LVEF 40-50%)
HCP	HealthCare Professional
HFRS	Hospital Frailty Risk Score
HR	Hazard Ratio
HTN	HyperTension
Hy-C	HYdralazine versus angiotensin-converting enzyme inhibition with Captopril Trial
Hyperpolypharmacy	Use of ≥ 10 regular medications
ICD	Implantable Cardioverter Defibrillator
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
I _f channel	Site for selective inhibition of heart rate that has a mixed sodium and potassium inward current identified in the sinoatrial node of the heart
IQR	InterQuartile Range
K ⁺	Potassium
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVI	Left Atrial Volume Index
LOS	Length Of Stay
LV	Left Ventricular
LVAD	Left Ventricular Assist Devices
LVEF	Left Ventricular Ejection Fraction

MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
MI	Myocardial Infarction
MLHFQ	Minnesota Living with Heart failure Questionnaire
MRA	Mineralocorticoid receptor antagonist
MU	Motor Unit
BNP	Brain Natriuretic Peptide
NA	Not Available
Na ⁺	Sodium
NSAID	Non-Steroidal Anti-Inflammatory Drug
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA class	New York Heart Association class (I-IV)
o.d.	omne in die (once daily)
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
OR	Odds Ratio
PARADIGM-HF	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PICOS	population, intervention, comparator, outcome, study design
PINNACLE	Practice Innovation and Clinical Excellence registry
PIONEER-HF	Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode
Polypharmacy	Use of ≥ 5 regular medications
PRESS	Peer Review of Electronic Search Strategies checklist

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses checklist
PROSPERO	International database of prospectively registered systematic reviews
OTC	Over-the-Counter medication
q.i.d.	quar in die (four times a day)
QoL	Quality Of Life
RAA	Renin-Angiotensin Aldosterone
RADIANCE	Randomized Assessment of the effect of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme Study
RALES	Randomized Aldactone Evaluation Study
RASI	Renin-Angiotensin System Inhibitors
RCT	Randomised Controlled Trial
RR	Risk Ratio
SBP	Systolic Blood Pressure (mmHg)
SCREAM	Stockholm CREATinine Measurements (SCREAM) health care-utilization cohort
SD	Standard Deviation
SENIORS	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure
SGLT2-i	Sodium-glucose cotransporter 2 inhibitors
SHIFT	Systolic Heart failure treatment with the If inhibitor Ivabradine Trial
SkM	Skeletal Muscle Cell
SMX/TMP	Sulfamethoxazole and trimethoprim
SOLVD	Studies of Left Ventricular Dysfunction
SR	Sinus Rhythm

TGF- β	Transforming Growth Factor-Beta. A mechanism that causes fibrosis and hypertrophy of the myocardium.
t.i.d.	ter in die (three times a day)
TOPCAT	Treatment Of Preserved Cardiac function heart failure with an Aldosterone AnTagonist
TRED-HF	withdrawal of pharmacological Treatment for Heart Failure in patients with REcovered Dilated cardiomyopathy
TO HOME	Towards Optimizing Hospitalized Older adults' MEdications
US	United States of America
USD	United States Dollar
WHO	The World Health Organization
Val-HeFT	The Valsartan Heart Failure Trial
VICTORIA	Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction
YLD	Years Lost to Disability

NOTES

Terms used interchangeably throughout thesis:

- Heart failure and HF
- ADWE, Adverse drug withdrawal effects and adverse drug withdrawal events
- Adverse outcomes and adverse events
- Geriatric outcomes and geriatric syndromes

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LIST OF CHAPTERS

This thesis consists of six chapters. The description and contributing publications are summarised for each chapter in Figure A. Chapters 2 through 5 address the aims of the thesis.

Figure A: Summary of thesis chapters and contributing papers

Chapter 1 **Introduction**

Chapter 2 **Describe adverse drug events associated with optimisation of heart failure pharmacotherapy among older people with frailty**

Contributing Paper:

Duong MH, Gnjjidic D, McLachlan AJ, Sakiris MA, Goyal P, Hilmer SN. The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review. *Drugs and Aging*; 2022. 39: 631–643.0
doi: [10.1007/s40266-022-00957-8](https://doi.org/10.1007/s40266-022-00957-8)

Chapter 3 **Describe adverse drug withdrawal effects associated with deprescribing heart failure pharmacotherapy among older people**

Contributing Paper:

Duong MH, Gnjjidic D, McLachlan AJ, Redston MR, Goyal P, Mathieson S, Hilmer SN. Discontinuation and Down-titration of Heart Failure Pharmacotherapy in Older People: A Systematic Review and Meta-analysis. *British Journal of Clinical Pharmacology*; 2024:1-15 doi: [10.1002/BCP.16223](https://doi.org/10.1002/BCP.16223)

Chapter 4 **Evaluate heart failure pharmacotherapy utilisation and adverse geriatric outcomes among hospitalised patients over age 75 years with heart failure and frailty risk**

Contributing Paper:

Duong MH, Gnjjidic D, McLachlan AJ, Winardi K, Bennett AA, Blyth F, Le Couteur D, Hilmer SN. Prevalence of Heart Failure Pharmacotherapy Utilisation, Frailty and Adverse Drug Events Among Hospitalised Adults Over 75 years: A Multicentre Cross-Sectional Study. *Internal Medicine Journal*; 2024:1-11. doi: [10.1111/imj.16612](https://doi.org/10.1111/imj.16612)

Chapter 5 **Explore approaches to managing adverse drug events and adverse drug withdrawal effects associated with heart failure pharmacotherapy among older people with frailty**

Contributing Paper:

Duong MH, Gnjjidic D, McLachlan AJ, Kouladjian O'Donnell L, Trivedi R, Kozor R, Hilmer S. Adverse drug events associated with heart failure pharmacotherapy in older people living with frailty: a qualitative study. *Canadian Journal of Cardiology Open*; 2025. (Under review).

Chapter 6 **Discussion and Conclusion**



INTRODUCTION

1.1 Overview

The risk of heart failure (HF) increases as the population ages, placing a heavy burden on the healthcare system and resources. There is an unmet need to understand the impact of ageing on the cardiovascular diseases that are most prevalent in older people, such as HF, particularly because our understanding of HF aetiology and treatments is still emerging.

Frailty is a reversible syndrome that is highly prevalent in older populations with HF, and can affect prognosis and tolerance to the optimisation of vital treatments. People with frailty have diminished capacity to reach homeostasis after experiencing adverse events during the optimisation of HF medications, putting them at high risk of lower medication adherence, treatment failure and poorer outcomes.

This introductory chapter describes the epidemiology, aetiology, pathophysiology, diagnosis and treatment of HF in older people with frailty. Adverse events are more common in older people. Optimising HF medication management must be individualised for older people, particularly those at risk of frailty. This chapter describes the physiological, pharmacological and clinical rationales for this approach to individualised HF treatment and the considerations needed when managing adverse drug events in older frail patients compared with younger and robust patients.

In situations where older HF patients cannot tolerate medications, the potential adverse drug withdrawal effects and outcomes of deprescribing these critical medications should also be carefully considered and individualised to manage HF in these complex patients. The background describing the gaps in the literature provides the rationale for this research.

1.2 Heart failure in older adults with frailty risk

1.2.1 Epidemiology

Heart failure (HF), also referred to as congestive heart failure (CHF), is a global epidemic affecting over 64 million people worldwide (8.5 per 1,000 inhabitants).^{1,2} The prevalence of HF is on the rise as the population ages, and the optimisation of new and emerging treatments improves patient survival and outcomes.³ Similar to most developed countries, the prevalence of HF in Australia is estimated at 1%–2% of the adult population, rising to 10% in people aged over 75 years,⁴ with an incidence of 30,000 (2.1 per 1,000 population) new cases of HF diagnosed each year.^{4,5} Frailty is prevalent in 12% of the general older population,⁶ and this group are at risk of suffering from multiple comorbidities, cognitive impairment, falls and fractures, resulting in increased hospitalisation and mortality. Frailty is common among people with HF. The prevalence of frailty in patients with advanced HF was found to be 50%⁷ and higher (75%) among older adults aged ≥ 75 years living in the community.⁸

Throughout the world, adults aged over 60 years have a 20-fold higher odds (odds ratio [OR] 21.9, 95% confidence interval [CI] 21.8–22.0, $P < 0.001$) of developing HF compared with adults under 60 years.² The prevalence of HF is significantly higher in women (OR 1.19 95% CI 1.18–1.20; $P < 0.001$),² including a higher prevalence of HF with preserved ejection fraction (HFpEF).⁹ Differences in race and ethnicity have shown that there is an increased risk of HF in Black Americans compared with Caucasian Americans.⁴ In Australia, HF with reduced ejection fraction (HFrEF) is prevalent in 6.3% (95% CI 5.0%–7.7%) of hospitalised patients aged >60 years¹⁰ and higher in the community, with approximately 16.1% prevalence in general practitioner (GP) clinics in rural towns compared with 12.4% in metropolitan GP clinics.¹¹

HF is associated with high mortality and morbidity. Approximately 50% of patients diagnosed with HF die within five years of diagnosis, and many require frequent and prolonged hospitalisation.^{12,13} HF is the cause of 10% of hospitalisations, with primary diagnosis as the cause for 1%–4% of all hospital admissions.¹³ Half of patients hospitalised for HF are aged over 75 years.¹⁴ A systematic review of hospitalisations in Australia reported that 30-day and 1-year readmissions ranged between 20% and 56%, and the median length of stay ranged between 5 and 8 days.¹⁵ Although HF was been found to be more prevalent in women, all-cause mortality was higher in American men compared with women, and the risk of cardiovascular death was higher in Black Americans compared with Caucasian Americans.⁴ In older people, frailty is a better predictor of mortality and hospitalisation risk than comorbidities. Among people aged over 80 years, mortality risk was found to be higher in people with poor function/disability (hazard ratio [HR] 2.36, 95% CI 0.63–8.83), or disability and multimorbidity (HR 3.91, 95% CI 1.53–10.00) compared with those with neither disability nor multimorbidity.^{16,17} Increased frailty risk has demonstrated dose-dependent trends for predicting the risk of hospitalisation over time.^{17,18}

HF imposes high direct costs on healthcare systems and indirect costs on society through early death, morbidity, loss of productivity and unpaid care costs, with the global economic burden estimated at USD 108 billion per annum in 2012.¹⁹ The high global prevalence of HF accounts for an estimated 9.91 million years lost to disability (YLDs) and USD 346.17 billion in expenditure.² The burden of HF on healthcare spending and resources accounts for approximately 1%–3% of overall annual healthcare spending, with the highest healthcare costs incurred from frequent hospitalisation and prolonged hospital stays.^{5,13} In Australia, this accounts for an estimated AUD 867 million for community management and AUD 2.68 billion for additional in-patient costs per annum.²⁰ In the United States of America

(US), where one in four persons will develop HF within their lifetime,⁴ the estimated median total medical costs of treating HF were found to be USD 24,383 per patient per year, and HF-specific hospitalisations accounted for a median of USD 15,879 per patient.²¹ Healthcare costs also include frequent physician visits, laboratory tests, medical imaging, medication costs, allied health support and the management of comorbidities.

1.2.2 Aetiology of heart failure

The causes of HF vary across geographical regions. In Western countries such as the US and Europe, the most common causes of HF are hypertension, coronary artery disease (CAD), ischemic heart disease, myocardial infarction (MI) and valvular heart disease.^{2,22,23} People with obesity and diabetes are particularly at high risk. Other causes of HF include rheumatic heart disease, chronic obstructive pulmonary disease, cardiotoxic medications and cardiomyopathies.^{14,22,23} Prescription medications such as those listed in Table 1.1 can cause or exacerbate HF.²²

Table 1.1: Prescription medications that may cause or exacerbate heart failure.

Drug or therapeutic class
COX, non-selective inhibitors (NSAIDs)
COX, selective inhibitors (COX-2 inhibitors)
Thiazolidinediones
Saxagliptin
Alogliptin
Flecainide
Sotalol
Dronedarone
Alpha-1 blockers
Doxazosin
Diltiazem
Verapamil
Nifedipine

Footnote: Adapted from Heidenrich et al. (2022).²²

1.2.3 Pathophysiology

1.2.3.1 Pathophysiology of heart failure

Heart failure is a complex syndrome associated with signs of structural or functional impairment relating to ventricular filling or ejection of blood, limiting the heart's ability to fill and pump sufficient amounts of blood throughout the body.²² HF causes elevated intracardiac pressure and heart rate, and/or insufficient cardiac output at rest or during exercise.²³ This dysfunction leads to increased sympathetic activity, lowered blood pressure, reduced renal perfusion and renal damage, and oedema.^{24,25} This can cause elevated natriuretic peptide levels, which promotes vasoconstriction and diuresis, and/or B-type natriuretic peptide (BNP), and inhibits sympathoadrenergic and renin–angiotensin–aldosterone activation.^{24,25} Over time, functional abnormalities and inadequate blood flow throughout the body lead to structural changes in the myocardium, and exacerbate new and existing dysfunction in vital organs. Functional changes in HF present as classic symptoms such as breathlessness, ankle swelling and fatigue, which may limit exercise tolerance, and/or signs of elevated jugular venous pressure, pulmonary crackles and peripheral oedema.^{22,23,26}

Acute and chronic renal impairment commonly occur in patients with HF owing to lowered glomerular filtration rate and renal blood flow, and the development of renal fibrosis over time, through mechanisms associated with haemodynamic, neurohormonal and cardiovascular disease.²⁵ Abnormal liver functions (e.g. elevated alkaline phosphatase, bilirubin, alanine transaminase, low albumin) in HF patients can indicate cholestasis, impaired hepatocyte function and reduced metabolic synthesis capacity.²⁷ Chronic hepatic congestion can lead to the prolongation of prothrombin time, hypoalbuminaemia, hepatic fibrosis and cirrhosis. In the gastrointestinal tract, thickening of the small and large intestine

walls can lead to reduced gastric emptying, hypoperfusion and absorption owing to the increased permeability of bacterial growth, thus reducing drug absorption.

1.2.3.2 Pathophysiology of ageing and heart failure

The process of ageing has an impact on all organ system functions, including the heart, kidney, muscle, bone, brain, liver and gastrointestinal tract.²⁸ The molecular changes that occur in ageing ultimately affect longevity and functional decline, and have been summarised as the ‘hallmarks of ageing’ by Lopez-Otin et al. (2013)²⁹ and Lopez-Otin et al. (2023).³⁰ These hallmarks are the primary causes of cellular damage (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy) and the antagonistic response to damage (deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence), and the end results are responsible for the functional decline associated with ageing and longevity (stem cell exhaustion, altered intercellular communication, chronic inflammation, dysbiosis).^{29,30} These hallmarks are interconnected and can influence the body’s ability to adequately maintain homeostasis and respond to stress.

In cardiovascular ageing, these mechanisms explain the changes that occur at cellular and clinical levels, as described in detail by Paneni et al. (2017).³¹ Similar ageing mechanisms that contribute to chronic oxidative stress and inflammation can lead to cardiovascular disease.^{31,32} For example, endothelial and vascular dysfunction can be caused by genomic instability and epigenetic changes that alter oxidative and inflammatory gene expression, telomere shortening caused by cardiovascular risk factors or disease, endothelial senescence and mitochondrial oxidative stress.³¹

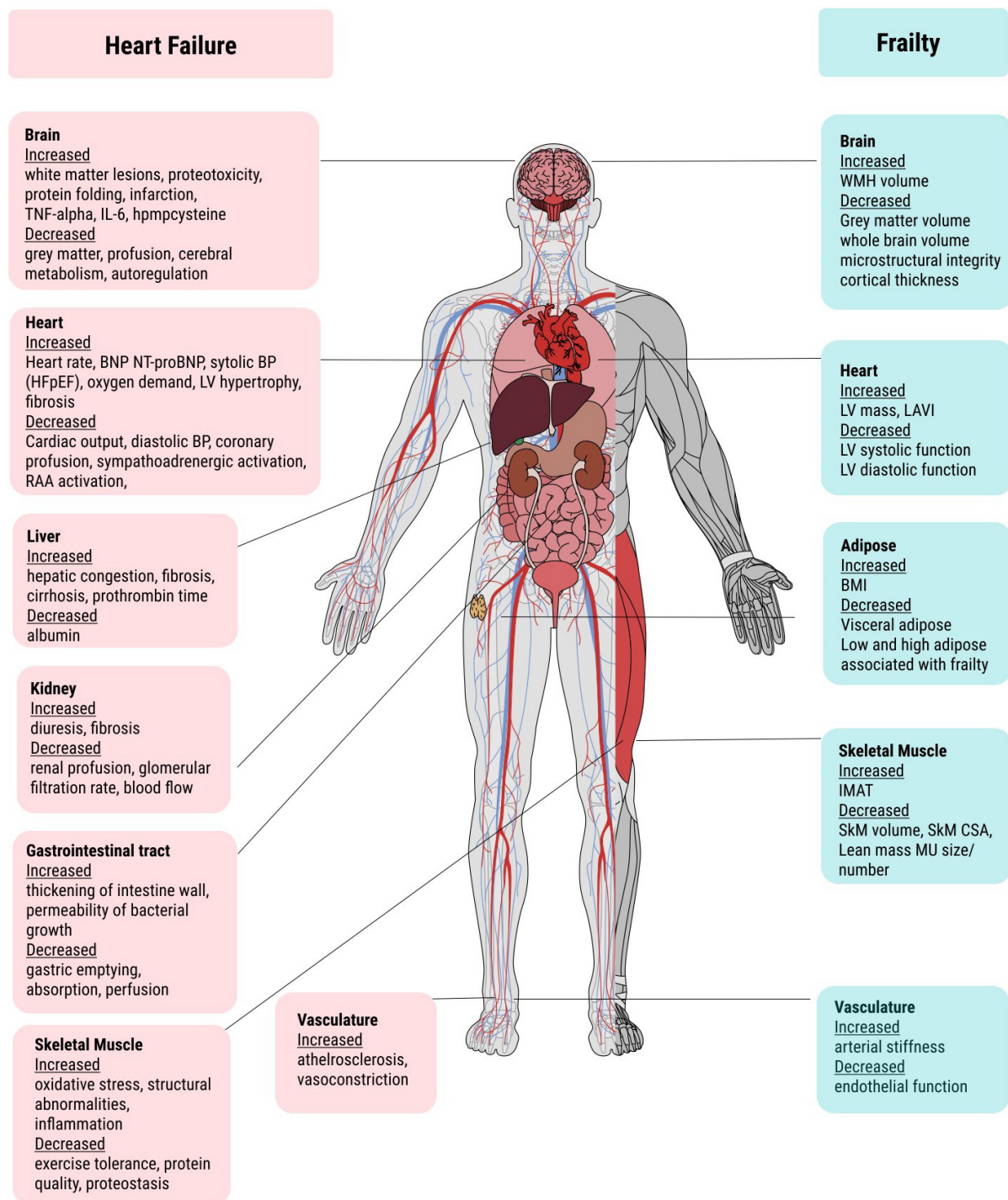
In HFpEF, ageing increases aortic stiffening via decreased elastin from the overexpression of inflammatory cells and increased collagen accumulation in the aortic wall.³¹ Age-related increases in vasoconstriction and impaired endothelial-dependent vasoconstriction contribute to increased systolic blood pressure and afterload while decreasing diastolic blood pressure and coronary perfusion, ultimately limiting oxygen supply. In HFrEF, increased demand for oxygen supply from chronic systolic pressure can lead to left ventricular hypertrophy. The mechanisms that cause fibrosis and hypertrophy of the myocardium involve mediators (i.e. transforming growth factor-beta [TGF- β], angiotensin II and mineralocorticoid aldosterone).³¹ This can be exacerbated by age-related coronary atherosclerosis, changes in large artery function, and hypertension promote remodelling of the myocardium and myocardial vasculature.

1.2.3.3 Pathophysiology of frailty

The pathophysiological changes associated with frailty increase with age and involve multi-organ systems, including sarcopenia (the loss of muscle mass)³³ and HF.³⁴ Figure 1.1 illustrates the overlapping concurrent physiological changes that can occur during frailty, ageing and HF, involving organs such as the brain, heart, skeletal muscle and vasculature. Dysfunction leading to increased oxidative stress and inflammatory mechanisms overlap in the ageing process and cardiovascular diseases such as HF.

The concept of ageing is complex and involves consideration of chronological (number of years lived) and biological (physiological changes in cells and tissue) age. The definition of older age (generally considered aged ≥ 65 years) may vary amongst individuals, including people in low to high income countries, due to a range of diverse physiological and socioeconomic characteristics (e.g. gender, ethnicity, health behaviours, education).^{35,36}

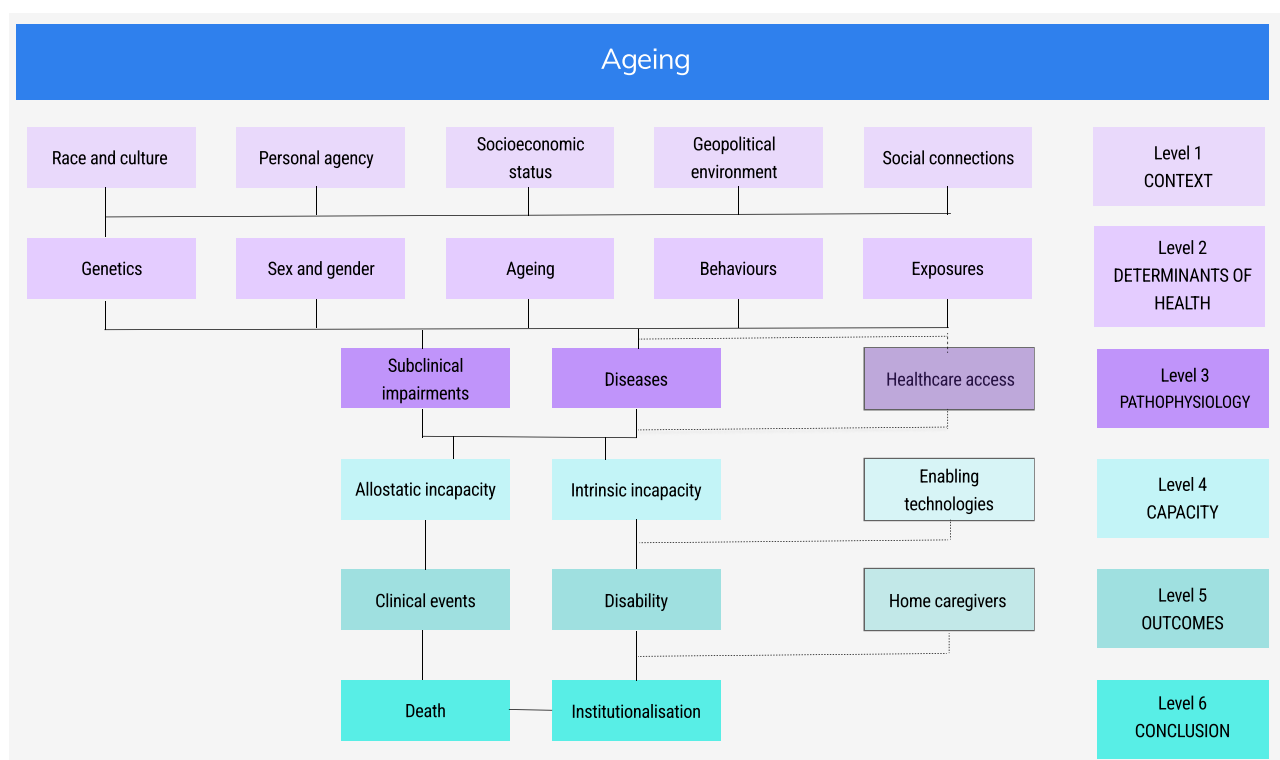
Figure 1.1: Common physiological multi-organ system characteristics of heart failure and frailty.



Footnote: Adapted from Taylor et al. (2023).³⁴

Frailty is prevalent in 4% of people aged 50 years and over compared to 17% of people aged over 65 years.³⁶ Approximately 15%-35% of European people aged over 75 years require some form of assistance with activities of daily living.³⁶ The interplay between ageing, frailty and incident cardiovascular disease is described by Afilalo (2024)³⁵ in Figure 1.2. The healthy ageing process demonstrates how multi-system domain function related to frailty and cardiovascular disease processes can reflect a person's age more completely the number of years lived and considers people with diverse backgrounds and health care access or needs.^{35,36}

Figure 1.2: The process of ageing and health in frailty and cardiovascular disease.



Footnote: Adapted from Afilalo (2024).³⁵

1.2.4 Definitions of heart failure

A universal definition of ‘heart failure’²⁶ was proposed to provide a contemporary and comprehensive description for HF diagnosis, involving the clinical assessment of symptoms and signs supported by objective evidence. Bozkurt et al. (2021)²⁶ defined HF as:

‘a clinical syndrome with current or prior symptoms and or signs (as shown in Table 1.2) caused by a structural and/or functional cardiac abnormality, as determined by an ejection fraction (EF) <50%, abnormal cardiac chamber enlargement, E/e’ ratio of >15, moderate/severe ventricular hypertrophy or moderate/severe valvular obstructive or regurgitant lesion. This is to be corroborated by at least one of the following:

- i) elevated natriuretic peptide levels for BNP, pg/mL: ambulatory ≥ 35 , hospitalised/decompensated ≥ 100 or for NT-proBNP, pg/mL: ambulatory ≥ 125 , hospitalised/decompensated ≥ 300 ; or
- ii) objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities, such as imaging (e.g., by chest radiograph or elevated filling pressures by echocardiography) or hemodynamic measurement (e.g., right heart catheterisation, pulmonary artery catheter) at rest or with provocation (e.g., exercise).’

Table 1.2 Signs and symptoms of heart failure.

Symptoms of HF	Signs of HF
Typical	More specific
Breathlessness Orthopnea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Increased time to recover after exercise Inability to exercise Fatigue, tiredness Swelling of ankles Swelling of part of the body other than ankles Bendopnea*	Elevated jugular venous pressure Hepatojugular reflux Third/fourth heart sound (gallop rhythm) Cardiomegaly Laterally displaced apical impulse Hepatojugular reflux Cheyne–Stokes respiration in advanced HF
Less typical	Less specific
Nocturnal cough Wheezing Feeling bloated Postprandial satiety Loss of appetite Decline in cognitive function, confusion (especially in older people) Depression Dizziness Syncope	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Pleural effusion Tachycardia Irregular pulse Tachypnoea Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

Footnote: *Shortness of breath when leaning forward corresponds with advanced heart failure. Adapted from Bozkurt et al. (2021)²⁶ and McDonagh et al. (2021).²³

1.2.4.1 Classification of heart failure

A diagnosis of HF is determined according to the left ventricular ejection fraction (LVEF). There are four classifications of HF phenotypes based on structural and functional alterations of the heart as the underlying cause for the clinical presentation of HF.^{22,26,36}

Table 1.3: Classification of heart failure by left ventricular ejection fraction.

Classification of heart failure (HF)	Left Ventricular Ejection Fraction (LVEF)	Criteria and cause
HF with reduced ejection fraction (HFrEF)	LVEF <40%, also known as systolic HF (systolic dysfunction)	- Caused by impaired contractability of the heart enlargement and remodelling of the myocardium.
HF with mildly reduced ejection fraction (HFmrEF)	LVEF 41%–49%	- Requires evaluation of ejection fraction over time for patients who are usually in a dynamic ejection fraction trajectory, including worsening HF or improvement from HFrEF. - Distinction from HFpEF can be challenging and should be confirmed with additional objective measures of cardiac dysfunction to determine diagnostic specificity.
HF with preserved ejection fraction (HFpEF)	LVEF >50%, also known as diastolic HF (diastolic dysfunction)	- Is caused by increased stiffening of the left ventricle and impairs left ventricular relaxation during diastole (after blood is pumped out of the heart) - This physiological dysfunction leads to impaired ventricular filling and/or increased pressure, which increases the risk of atrial fibrillation (AFib) and pulmonary hypertension.
HF with improved ejection fraction (HFimpEF)	baseline LVEF <40%, and >10-point increase from baseline LVEF, and second measurement of LVEF >40%	- Improvements in LVEF may be attributed to interventions (e.g. valve replacement, pharmacotherapy, physical rehabilitation).

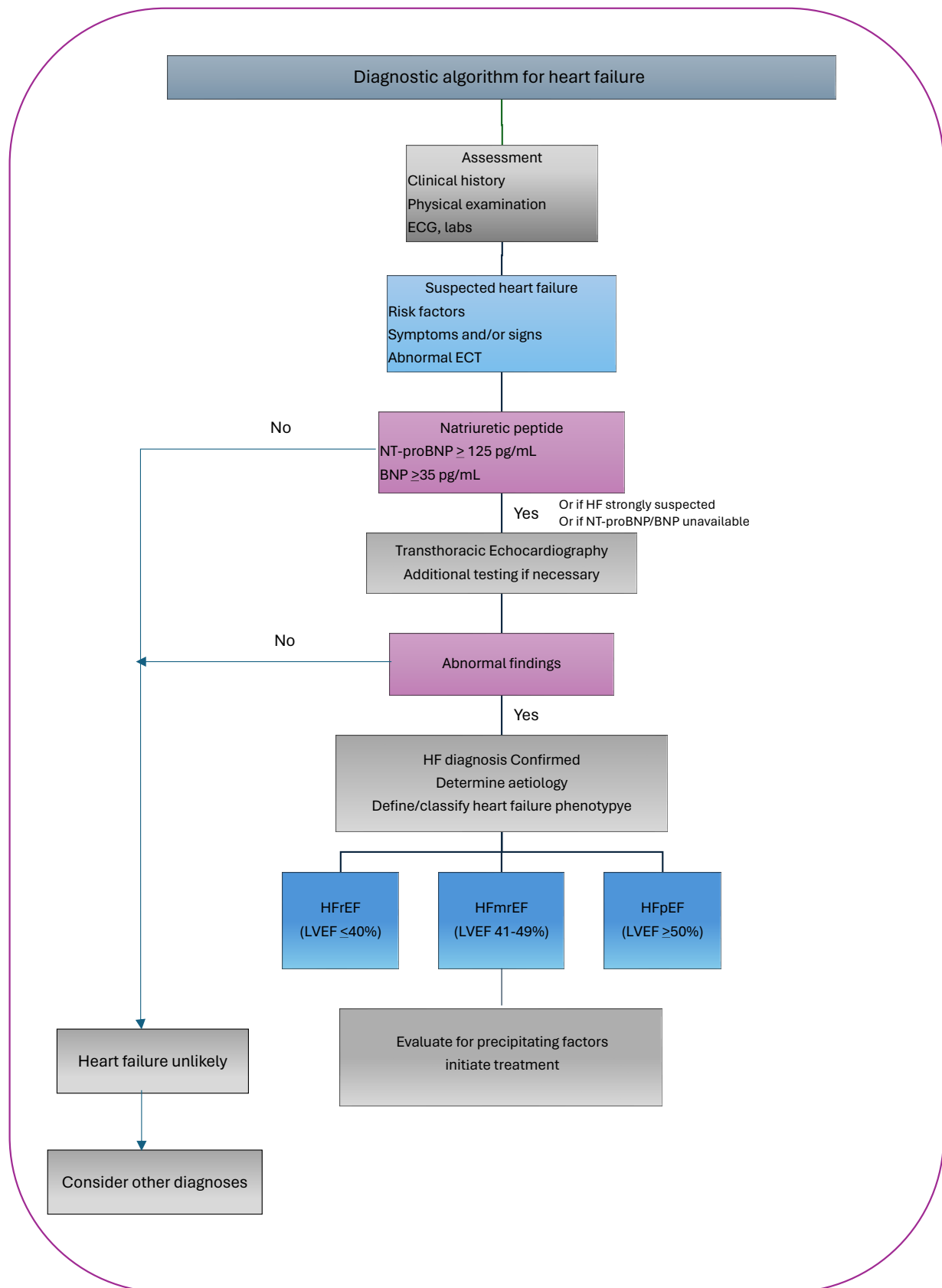
Footnote: Adapted from Bozkurt et al. (2021)²⁶ and McDonagh et al. (2021).²³

1.2.4.2 Diagnosis of heart failure

Diagnosing HF requires a clinical assessment from a physical examination and a clinical history to identify the symptoms and signs of HF that require confirmation with abnormal findings from objective measures such as natriuretic peptides, echocardiography and laboratory results. Figure 1.3 summarises diagnosis algorithms in patients with suspected HF that combine clinical assessment and objective evidence of cardiac dysfunction to confirm HF classification to evaluate precipitating or causative factors, and initiate pharmacological and non-pharmacological treatments.

In younger people, a decrease in function occurring in one system generally manifests as classic disease symptoms when individuals have enough functional reserve to maintain homeostasis. However, as people advance in age, a decline in multi-organ systems occurs simultaneously and presents as atypical manifestations of the disease (e.g. confusion, delirium, falls and the less specific signs shown in Table 1.2), and may be accompanied by a decline in global function and eventually disability.²³ Older people will likely experience functional problems before cardiovascular disease,³⁵ and may present with less specific symptoms such as confusion, delirium or other less specific signs.²³

Figure 1.3: Diagnostic algorithm for heart failure.



Footnote: Adapted from Heidenrich et al. (2022)²² and McDonagh et al. (2021).²³ **Abbreviations:** ECG Electrocardiogram, ECT Electroconvulsive Therapy, NT-proBNP Natriuretic Peptide Test prohormone Brain (B-Type) Natriuretic Peptide, BNP Brain Natriuretic Peptide, HF Heart Failure, HF_rEF Heart Failure with Reduced Ejection Fraction, HF_mrEF Heart Failure with Mildly-reduced Ejection Fraction, HF_pEF Heart Failure with Preserved Ejection Fraction, LVEF Left Ventricular Ejection Fraction.

1.2.4.3 Severity of heart failure

Categorisation of the severity of HF has been described by the New York Heart Association (NYHA) in its functional classification system. Table 1.4 summarises the terminology adapted as stages of HF by the American College of Cardiology (ACC) and the American Heart Association (AHA),²² and outlines the effect on symptoms and physical activity as described by the European Society of Cardiology (ESC).²³

Table 1.4: Stages of heart failure and New York Heart Association functional classification based on severity of symptoms and physical activity.

Stage	HF	NYHA class	Symptoms and physical activity
Stage A	At risk of HF	Class I	People who are at risk for HF but without symptoms or signs of HF, and without structural or functional heart disease or abnormal biomarkers. Risk factors for people in this stage include hypertension, cardiovascular disease, diabetes, obesity, exposure to cardiotoxic agents, genetic variants for cardiomyopathy and family history of cardiomyopathy. No functional limitations. Ordinary physical activity does not cause undue breathlessness, fatigue or palpitations.
Stage B	Pre-HF	Class II	People without current or previous symptoms/signs of HF but with evidence of either structural heart disease, increased filling pressures in the heart or other risk factors, and increased natriuretic peptide levels/persistent elevated cardiac troponin in the absence of competing diagnoses. Slight limitation of physical function. Comfortable at rest, but ordinary physical activity results in undue breathless, fatigue or palpitations.
Stage C	Symptomatic HF	Class III	People with current or previous symptoms/signs of HF. Marked limitation of physical function. Comfortable at rest, but less ordinary activity results in breathless, fatigue or palpitations.
Stage D	Advanced HF	Class IV	People with marked HF symptoms that interfere with daily life functions and repeated hospitalisations, despite attempts to optimise guideline-directed medical therapy (GDMT). Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Footnote: Adapted from Heidenrich et al. (2022)²² and McDonagh et al. (2021).²³

Abbreviations: HF heart failure; NYHA New York Heart Association

1.2.4.4 Clinical presentation of heart failure

In community and acute care clinical settings, patients can present with well-controlled and stable chronic HF, or new onset or acute HF. The clinical presentation of acute HF warrants urgent treatment and immediate hospitalisation for patients presenting to hospital with acute decompensated HF (ADHF), acute pulmonary oedema, isolated right ventricular failure or cardiogenic shock.²³

1.2.4.5 Advanced heart failure

Stage D advanced HF is characterised by patients experiencing severe persistent symptoms, despite optimised therapy, often resulting in recurrent hospitalisation. Traditional evidence-based treatments may no longer be effective, such as in cases of resistance to loop diuretics. Early referral to advanced care services are recommended for patients who progress from stable chronic HF to advanced HF to optimise patient outcomes. Advanced care HF services include heart transplantation, left ventricular assist devices, mechanical circulatory devices, intravenous diuretics or inotropes, and palliative care planning.^{22,23} Treatments focus on improving quality of life (QoL) for patients, and for some cases, may also improve outcomes.^{22,23} Advanced care planning is directed by patient goals of care to manage QoL, HF symptoms and comorbidities through shared decision-making. This may also include considerations for end-of-life care. Thus, the selection of interventions should consider the individualised goals of care for advanced HF.

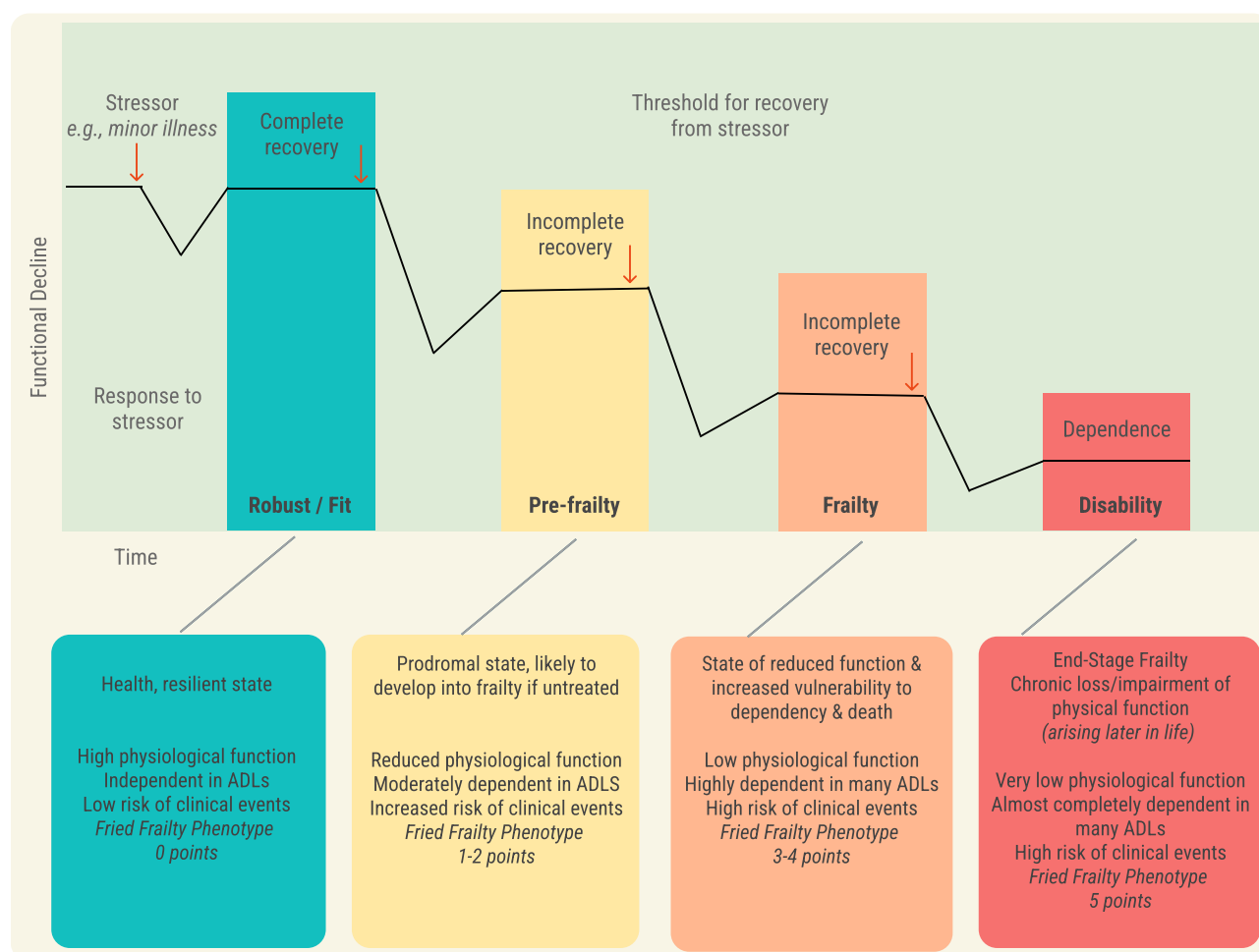
1.2.5 Definition of frailty

Over a lifetime, cumulative molecular and cellular damage can lead to a loss of physiological reserves in multiple organ systems (e.g. cardiovascular, respiratory, nervous, renal systems), which increases the risk of disease, mortality and disability. These physiological changes can also be amplified in frailty and affect pharmacokinetics in older people^{37,38} (Table 1.8). Frailty is a multifactorial syndrome defined as ‘a state of increased vulnerability to poor resolution of homeostasis following a stress, increasing the risk of adverse outcomes including falls, delirium and disability’ (Clegg et al., 2013 p. 752).³⁹ Frailty risk depends on cumulative deficits in physical, psychological, social, cognitive, nutritional and pharmacological characteristics.^{40,41}

1.2.5.1 Classification of frailty

Depending on the instrument of measurement, the spectrum of frailty ranges include non-frail and frail; robust, pre-frail and frail; robust, moderate frailty and severe frailty/disability; and low, intermediate and high frailty risk. Figure 1.4 illustrates the key stages of frailty as well as the cascading functional decline and loss of resilience to recover from injury or insult.³⁴

Figure 1.4: Key stages of frailty development and functional decline.



Abbreviations: ADL = activities of daily living. **Footnote:** Adapted from Taylor et al. (2023),³⁴ Dent et al. (2019)⁴² and Kim & Rockwood (2024).⁴³ The line demonstrates a decreased threshold for recovery after stressors in older adults from robust independence to dependent disability.

1.2.5.2 Measuring Frailty

Frailty is often identified incorrectly when subjectively measured. Subjective measures of frailty may lead to misleading assessments of patients and an underestimation of frailty in patients with HF. In patients with HF referred for advanced therapies, frailty was correctly identified 1.7%–17.6% of the time by cardiologists with subjective assessments compared with 62.8% of the time ($P < 0.001$) with objective measures.⁴⁴ Compared with objective measures, the subjective assessment of frailty by cardiologists was usually correct

($n = 16/19$, 84%) at identifying individuals as frail, but significantly underestimated frailty ($n = 64/162$, 40%) when designating individuals as not frail.⁴⁴

Frailty can be routinely measured to detect short-term risk of functional deterioration, and can potentially be reversed. There are various tools used to objectively measure frailty,⁴⁵ including categorical measures such as phenotype scores,⁴⁶ the Clinical Frailty Scale (CFS)^{47,48} and the Hospital Frailty Risk Score (HFRS);⁴⁹ or continuous measures using the frailty index (FI).^{50,51} These tools have been applied in various clinical settings and all have advantages and disadvantages. A systematic review reported that no gold standard frailty score exists to measure frailty in advanced HF, but the Rockwood FI and the Fried phenotype score were the most used.^{7,52} The preference for objective measures was adjusted based on the research context.

1.2.5.3 Multimorbidity

The dysfunction of functional mechanisms during the ageing process puts older people at high risk of cardiovascular disease and multimorbidity, affecting multi-organ systems. The presence of comorbidities often requires patients to receive concurrent treatment for conditions such as ischemia and other cardiovascular diseases, cancer, diabetes, chronic obstructive pulmonary disorder, anaemia and renal failure. The cumulative risk of comorbidities can be calculated using tools such as the Charlson Comorbidity Index (CCI) to predict the survival rate in patients with multiple comorbidities.⁵³ This is calculated using a weighted score for select comorbidities. CCI scores are generally categorised as mild (1–2), moderate (3–4) or severe (≥ 5) to indicate the level of mortality risk in people with comorbidities. A study of HF patients aged ≥ 65 years reported a mean CCI score of >2 , demonstrating a high risk of mortality,⁵⁴ but the CCI was not a strong predictor of long-term

mortality.⁵⁵ Patients aged over 65 years with a CCI score of >2 had higher risk of readmission.⁵⁵

1.2.5.4 Polypharmacy

The management of multimorbidity and cardiovascular disease with pharmacological treatments increases polypharmacy (use of ≥ 5 regular medications) and hyperpolypharmacy (use of ≥ 10 regular medications). Polypharmacy increases the risk of drug–drug interactions, drug–disease interactions and adverse drug reactions (ADRs). Multiple comorbidities and polypharmacy compound the risk of ADRs caused by drug interactions. Non-adherence is a strong predictor of hospitalisation and mortality, and can lead to treatment failure and risk of adverse outcomes. A Canadian survey showed early discontinuation of medications in 30% of participants, and 25% never filled their prescriptions.^{56,57} Approximately 50% of older people are non-adherent to ≥ 1 medication and, overall, adherent to 70%–80% of all medications.⁵⁸ Adherence to complex medication regimens becomes increasingly challenging for older people, particularly for individuals with cognitive and/or functional impairment, and limited access to healthcare services they can afford.

1.2.5.5 Deprescribing

One approach to reducing polypharmacy is deprescribing, which is the withdrawal of inappropriate medications supervised by a health professional.⁵⁹ This can help in managing adverse drug events and improving outcomes.⁶⁰ Older HF patients often have multiple physiological dysfunctions, altered pharmacokinetics and cognitive impairment. Reducing medication regimen complexity and drug interactions can support the maintenance of independence and wellbeing. This process includes down-titration and the discontinuation of cardiovascular and non-cardiovascular medications that increase adverse geriatric outcomes (also known as geriatric syndromes) such as fall risk, delirium, incontinence and frailty.⁶²

One systematic review reported that older people in good physical health were willing to deprescribe their antihypertensive medications, most commonly a diuretic, if the doctor said it was possible (OR 0.12; 95% CI 0.04–0.34).⁶¹ Low quality evidence from a systematic review on the effects of deprescribing diuretics identified recurrence of HF and peripheral oedema as common reasons for restarting diuretics; but these studies did not determine whether patients received optimised HF pharmacotherapy.⁶²

1.3 Treatment of heart failure in older adults with frailty risk

1.3.1 Treatment for heart failure

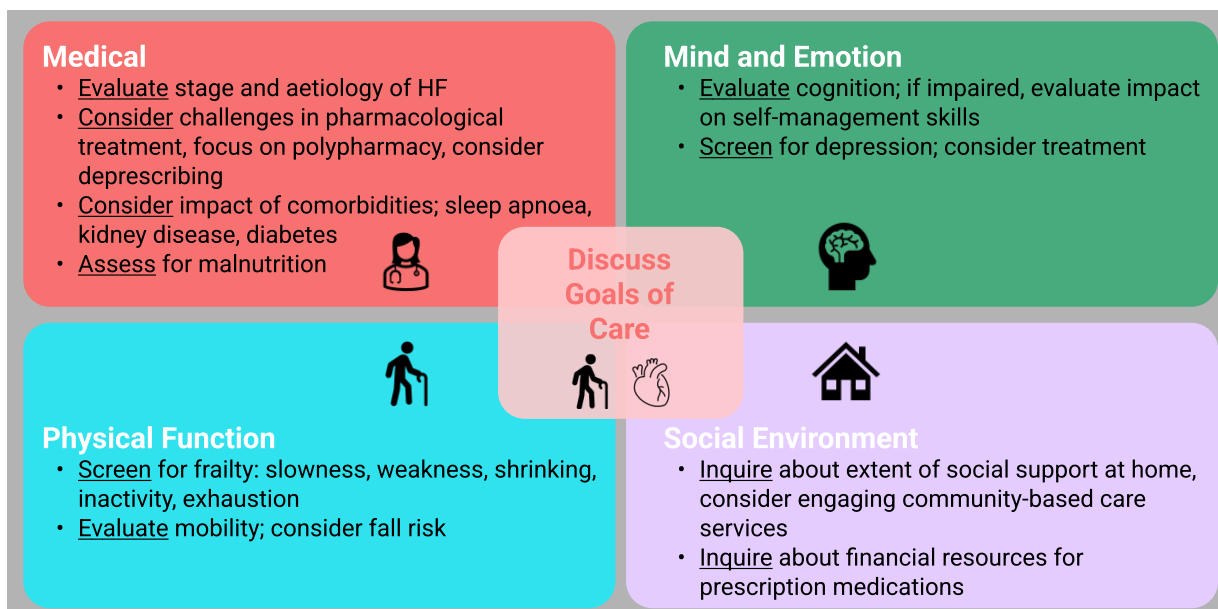
Pharmacological and non-pharmacological treatments are recommended for the management of HF for various HF phenotypes. The majority of evidence available from clinical trials supports pharmacological treatment for patients with HFrEF.^{22,23} In contrast, there is less data to support pharmacotherapy for patients with HFpEF, as well as the more recently defined HF with mildly reduced ejection fraction (HFmrEF) and HF with improved ejection fraction (HFimpEF). As our understanding of HF aetiology and treatments evolves, it is expected that more data will better inform treatment selection for all types of HF phenotypes.

A domain management approach to HF treatment is recommended in robust and frail geriatric patients, warranting continual discussions about changing goals of care.^{63,64}

Interventions should take into consideration medical, functional, psychosocial and environmental factors, as summarised by Gorodeski et al. (2018)⁶² in Figure 1.5. Patient goals of care often prioritise QoL. Some common tools to measure QoL specific to HF include the accessible Kansas City Cardiomyopathy Questionnaire⁶⁴ and the comprehensive Minnesota Living with Heart Failure Questionnaire.⁶⁵ Opportunities to reverse frailty may

support the optimisation and tolerance of HF pharmacotherapy and improve patients' sense of wellbeing.

Figure 1.5: Domain management of heart failure in older patients.



Footnote: Adapted from Gorodeski et al. (2018).⁶²

1.3.1.1 Pharmacological treatments for patients with heart failure with reduced ejection fraction

The use of pharmacological treatments is critical for managing HFrEF. The aim of pharmacotherapy is to prolong survival, prevent hospitalisations caused by worsening HF symptoms, and improve QoL and functional capacity.^{22,23} The management of HF involves the use of first-line (supported with strong evidence) or second-line (alternative treatments supported with weaker evidence) pharmacotherapies with disease-modifying effects at recommended target doses, as summarised in Table 1.5. In addition, the acute and severe onset of HF symptoms requiring hospitalisation requires specific pharmacological interventions to treat congestion. Information regarding quality of evidence, age summary and industry funding is also reported for the key clinical trials guiding HF treatments described in Table 1.6. Table 1.6 shows that clinical trials (mostly industry funded) do not routinely report objective frailty risk and widely underrepresent people aged over 75 years, with exception of the SENIORS trial.⁷⁵

Table 1.5: Pharmacological treatments for heart failure with reduced ejection fraction and acute symptoms.

Drug class	Pharmacotherapy	Starting dose	Target dose	Evidence from clinical trials
Renin–angiotensin system inhibitors (RASIs)				
Angiotensin receptor neprilysin inhibitors (ARNIs)	Sacubitril/valsartan	49/51 mg b.i.d.	97/103 mg b.i.d.	PARADIGM-HF ⁶⁶ PIONEER-HF ⁶⁷
Angiotensin-converting enzyme inhibitor (ACEI)	Captopril Enalapril Lisinopril Ramipril Trandolapril	6.25 mg t.i.d. 25 mg b.i.d. 2.5–5 mg daily 2.5 mg b.i.d. 0.5 mg daily	50 mg t.i.d. 10–20 mg b.i.d. 20–35 mg daily 5 mg b.i.d. 4 mg daily	SOLVD ⁶⁸ ATLAS ⁶⁹
Angiotensin receptor antagonist/blocker (ARB)	Candesartan Losartan Valsartan	4–8 mg daily 25–50 mg daily 420–0 mg b.i.d.	32 mg daily 150 mg daily 160 mg b.i.d.	HEAAL ⁷⁰ CHARM ⁷¹ Val-HeFT ⁷²
Beta-blocker	Bisoprolol Carvedilol CR Metoprolol (CR/XL) Nebivolol	1.25 mg daily 10 mg daily 12.5–25 mg daily 1.25 mg daily	10 mg daily 80 mg daily 200 mg daily 10 mg daily	MERIT-HF ⁷³ COMET ⁷⁴ SENIORS ⁷⁵
Mineralocorticoid receptor antagonists (MRAs)	Spironolactone Eplerenone	12.5–25 mg daily 25 mg daily	50 mg daily 50 mg daily	RALE/S ⁷⁶ EMPHASIS-HF ⁷⁷ EPHESUS ⁷⁸ ATHENA-HF ⁷⁹
Sodium–glucose co-transporter-2 inhibitors (SGLT2-i)	Dapagliflozin Empagliflozin	10 mg daily 10 mg daily	10 mg daily 10 mg daily	DAPA-HF ⁸⁰ EMPEROR-Reduced ^{81,82}
Soluble guanylate cyclase stimulators	Vericiguat	2.5 mg daily	10 mg daily	VICTORIA ⁸³
Digitalis glycosides	Digoxin	0.0625–0.125 mg daily	0.25 mg daily Individualised to achieve serum digoxin concentration 0.5–0.9 ng/mL	Digitalis Investigation Group ⁸⁴ (DIG) trial ⁸⁵
For management of congestion in chronic HF				
Loop diuretics	Furosemide Bumetanide Torsemide	20–40 mg o.d.–b.i.d. 0.5 mg o.d.–b.i.d. 10–20 mg daily	600 mg daily 10 mg daily 200 mg daily	DOSE ⁸⁶ EVEREST ⁸⁷
Thiazide diuretics	Chlorthiazide Chlorthalidone Hydrochlorothiazide Indapamide Metolazone	250–500 mg o.d.–b.i.d. 12.5–25 mg daily 25 mg o.d.–b.i.d. 2.5 mg daily 2.5 daily	1000 mg 100 mg 200 mg 5 mg 20 mg	

Drug class	Pharmacotherapy	Starting dose	Target dose	Evidence from clinical trials
Inotropes				
Cardiac myosin activators	Omecamtiv mecarbil	25 mg b.i.d.	25–50 mg b.i.d.	GALACTIC-HF ⁸⁸
Vasodilators	Hydralazine Isosorbide dinitrate	25–50 mg t.i.d.–q.i.d. 20–30 mg t.i.d.–q.i.d.	300 mg daily 120 mg daily	Hy-C trial ⁸⁹ A-HeFT ⁹⁰
I _f channel inhibitor	Ivabradine	5 mg b.i.d.	7.5 mg b.i.d.	BEAUTIFUL ⁹¹ SHIFT ⁹²

Abbreviations: o.d. = omne in die (once daily); b.i.d. = bis in die (twice daily); t.i.d. = ter in die (three times a day); q.i.d. = quar in die (four times a day); I_f = the funny channel is a site for selective inhibition of heart rate that has a mixed sodium and potassium inward current identified in the sinoatrial node of the heart.

Footnote: Adapted from McDonagh et al. (2021),²³ Heidenrich et al. (2022)²² and Butzner et al. (2022).⁹³

Table 1.6: Age of participants included in heart failure clinical trials.

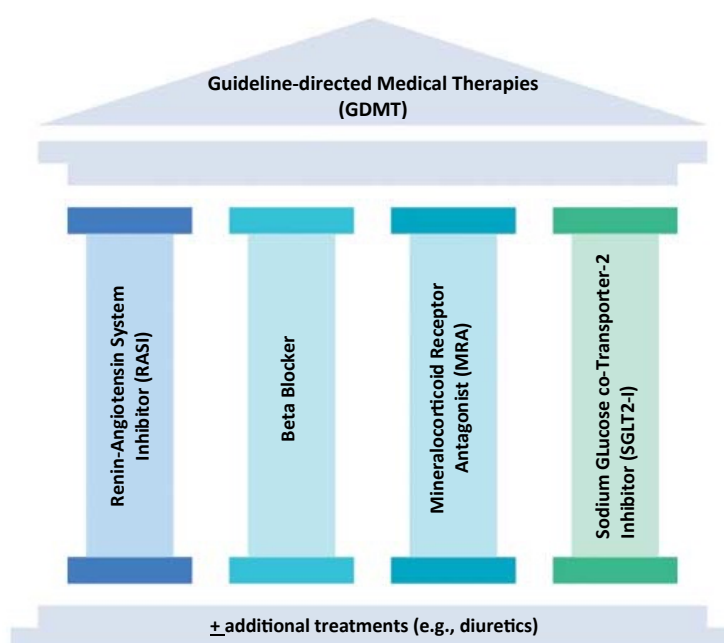
Clinical trial name	Quality rating (1–5)	Number (n) and age (years) of population (mean (SD) or *median (IQR))		Industry funding
		Intervention group	Control group	
Renin–angiotensin system inhibitors (RASIs)				
PARADIGM-HF ⁶⁶	1	Sacubitril/valsartan <i>n</i> = 4187; 63.8 (11.5)	Enalapril <i>n</i> = 4212; 63.8 (11.3)	Yes
PIONEER-HF	1	Sacubitril/valsartan <i>n</i> = 440; *61 (51–71)	Enalapril <i>n</i> = 441; *63 (54–72)	Yes
SOLVD	1	Enalapril <i>n</i> = 1285; 60.7 (NA)	Placebo <i>n</i> = 1284; 61(NA)	Yes
ATLAS ⁶⁹	1	high-dose lisinopril <i>n</i> = 1568; 63.6 (10.5)	low-dose lisinopril <i>n</i> = 1596; 63.6 (10.3)	Yes
Val-HeFT ⁷²	1	Valsartan <i>n</i> = 2511; 62.4 (11.1)	Placebo <i>n</i> = 2499; 63.0 (11.0)	Yes
Beta-blockers				
SENIORS ⁷⁵	1	Nebivolol <i>n</i> = 1067; 76.1 (4.8)	Placebo <i>n</i> = 1061; 76.1 (4.6)	Yes
MERIT-HF ⁷³	1	Metoprolol CR/XL <i>n</i> = 1990; 63.9 (NA)	Placebo <i>n</i> = 2001; 63.7 (NA)	Not reported
Mineralocorticoid receptor antagonists (MRA)				
RALES ^{76,77}	1	Spironolactone <i>n</i> =822; 65 (12)	Placebo <i>n</i> = 841; 65 (12)	Yes
ATHENA-HF ⁷⁹	1	High-dose spironolactone <i>n</i> =182; *65 (57–76)	Usual care alone <i>n</i> = 178; *65 (54–74)	No
Sodium–glucose co-transporter-2 inhibitors (SGLT2-i)				
EMPEROR-Reduced ^{82,94}	1	Empagliflozin <i>n</i> = 1863; 67.2 (10.8)	Placebo <i>n</i> = 1867; 66.5 (11.2)	Yes
DAPA-HF ⁸⁰	1	Dapagliflozin <i>n</i> = 2373; 66.2 (11.0)	Placebo <i>n</i> = 2371; 66.5 (11)	Yes
(post-hoc analysis with frailty index) ⁹⁵	3	FI < 0.21 not frail <i>n</i> = 2392, 50%, 63.6 (11.6) FI = 0.21–0.310 more frail <i>n</i> = 1606, 34%; 68.8 (9.4) FI > 0.311 most frail <i>n</i> = 744, 16%; 69.8 (9.0)		
Soluble guanylate cyclase stimulators				
VICTORIA ⁸³	1	Vericiguat <i>n</i> = 2526; 67.5 (12.2)	Placebo <i>n</i> = 2524; 67.2 (12.2)	Yes
Omecamtiv mecarbil				
GALACTIC-HF ⁸⁸	1	SBP ≤100 mmHg: <i>n</i> = 1473; 63.4 (11.9)	SBP >100 mmHg: <i>n</i> = 6759; 64.8 (11.2)	Yes
Diuretics				
DOSE ⁸⁶	1	Furosemide IV bolus every 12 hours <i>n</i> = 156, 66.2 (13.2) Continuous infusion <i>n</i> = 152, 65.8 (14.1)	Furosemide oral Low dose <i>n</i> = 151, 65.9 (13.3) High dose <i>n</i> = 157, 66.2 (13.9)	No

Abbreviations: NA = not available; SD = standard deviation; IV = intravenous; SBP = systolic blood pressure. **Footnote:** Quality rating was adapted from the Oxford Centre for Evidence-based Medicine for ratings of individual studies.

1.3.1.2 Optimisation of guideline-directed medical therapies

Guideline-directed medical therapies (GDMTs), also known as the four pillars of HF pharmacotherapy, are among the gold standard first-line pharmacological treatments for the management of chronic and acute HFrEF, and are recommended by international cardiac societies (Figure 1.6). International guidelines support the optimisation of GDMT in HFrEF with a high certainty of evidence and benefits for mortality and hospitalisation, including number needed to treat 1-year all-cause mortality ranging from 18–77, and 3-year all-cause mortality 6–26.^{22,23}

Figure 1.6: The four pillars of guideline-directed medical therapies for management of heart failure with reduced ejection fraction.



The initiation of pharmacotherapy for HFrEF is well described in the 2022 consensus statement on the management of HF in Figure 1.7. These pharmacotherapies are supported with strong evidence from clinical trials, shown to reduce mortality, improve HF symptoms and reduce hospitalisations when prescribed at target doses⁹⁶ (Table 1.5).

Figure 1.7: Recommendations for the initiation of heart failure pharmacotherapy.

ARNI/ACEI*, beta-blocker [#] , MRA and SGLT2-i [§] recommended in ALL patients with HFrEF ARNI* is preferred to ACEI			
Diuretics to manage congestion	Multidisciplinary heart failure service and exercise training	Congested	Euvolaemic
		ARNI/ACEI* and SGLT2-i [§]	ARNI/ACEI* and beta-blocker [#]
		Add MRA	Add MRA and SGLT2-i [§]
		Add beta-blocker [#] once euvolaemic	
		Up-titrate heart failure therapy to maximum tolerated dose (generally favour up-titrating beta-blocker [#] initially unless congested or heart rate <50 bpm)	
		If LVEF<35% after 3 months: ICD and/or CRT (if QRS>130ms)	If SR>70 bpm + LVEF<35%: add ivabradine
		Additional Treatment Options for Persistent HFrEF: Consider nitrates + hydralazine if ARNI/ACEI/ARB contraindicated or not tolerated Consider nitrates +/- hydralazine and/or digoxin if refractory symptoms Consider vericiguat if recent hospitalisation and high risk of readmission Consider omecamtiv mercapril if persistent LVEF <35% Consider intravenous ferric carboxymaltose if ferritin <100 or if ferritin 100-299 and transferrin saturation <20%	

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronisation therapy; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT2-i = sodium–glucose co-transporter-2 inhibitor; SR = sinus rhythm. **Footnote:** *ARNI preferred. ACEI can be considered an alternate if problematic hypotension and consider switching to ARNI later # recommend using beta-blocker with outcome trial proven for HFrEF efficacy (e.g. carvedilol, bisoprolol or metoprolol succinate or nebivolol) § Recommend using STL2-I with outcome trial proven for HFrEF efficacy (e.g. dapagliflozin, empagliflozin). Overall, recommend to commence all patients on the four destination therapies of ARNI/ACE inhibitor*, beta-blocker#, MRA and SGLT2-i§ as soon as clinically possible, given their early morbidity and mortality benefit. **Footnote:** Adapted from the Cardiac Society of Australian and New Zealand 2022 consensus statement on the management of HF with reduced ejection fraction. Adapted from Sindone et al. (2022).³⁶

Optimising HF-GDMT in older people with frailty can be more challenging owing to concomitant physiological changes from multiple comorbidities and organ dysfunction that reduces homeostasis and resilience to adverse events.²⁷ Non-adherence and lower doses of GDMT have been reported for older people with HF who are at increased risk of adverse drug events (ADEs), but who may have a reduced threshold for tolerating adverse effects.⁹⁶ Despite the existence of evidence to optimise multiple HF pharmacotherapies to target doses

in clinical trials, observational cohort studies have reported adults aged over 80 years using lower doses and fewer GDMT compared with those aged <60 years.^{97,98}

1.3.1.3 Pharmacological treatments for patients with heart failure with preserved ejection fraction

HFpEF is more prevalent in older populations and can present as symptomatic or asymptomatic HF. The management of HFpEF is complex because of contributing factors such as comorbidities, which include hypertension, diabetes, obesity, CAD, chronic kidney disease (CKD), cardiac amyloidosis and atrial fibrillation (AF). In patients with asymptomatic HFpEF, management prioritises treating the underlying comorbidities.²²

It is recommended that HFpEF patients with HF symptoms are treated with diuretics on an as-needed basis to balance the need to treat congestion with potential adverse effects.²² Recently, moderate evidence has supported the use of sodium–glucose co-transporter-2 inhibitor (SGLT2-i) to reduce hospitalisation and mortality.⁹⁹ Clinical trials have shown that GDMT has no-to-low benefit for mortality and leads to slight reductions in HF hospitalisations; however, guidelines recommend considering GDMT for patients with an LVEF closer to 50%, who may be more likely to benefit by improving HF symptoms and outcomes.^{22,100,101} The evidence suggests that there is no benefit to the routine use of nitrates and vasodilators to improve QoL in HFpEF.¹⁰² Limitations to the evidence guiding the treatment of HFpEF can be attributed to inconsistent definitions of HFpEF (LVEF >40%, 45% or 50%) and varying evidence of structural heart disease such natriuretic peptides.¹⁰³ There is very limited evidence to support treatment with GDMT in people over 75 years, and there are no clinical trials reporting outcomes according to objective frailty measures.^{22,23}

1.3.1.4 Pharmacological treatments for patients with heart failure with mildly-reduced ejection fraction or heart failure with improved ejection fraction

Among patients with HFmrEF, SGLT2-i has shown moderate benefit.^{99,104} The use of GDMT in HFrEF is recommended for consideration to reduce cardiovascular mortality and HF hospitalisations.²² Similarly, it is recommended that patients with HFimpEF continue and optimise GDMT to prevent relapses of HF and left ventricular dysfunction. HFrEF reverse remodelling and structural abnormalities do not fully normalise in HFimpEF. Even though HF symptoms may resolve, left ventricular dysfunction and biomarker abnormalities (e.g. natriuretic peptide) may persist and reoccur if GDMT is discontinued.

1.3.2 Treatments for frailty

Frailty is potentially reversible (partial or full recovery from injury or insult),³⁴ unlike most diseases caused by cellular dysfunction, which are non-reversible. Physical exercise programs can increase physical functional status along the frailty spectrum and, in some cases, a return to robust status and improved QoL.^{105,106} Therefore, assessing frailty in older patients at all functional stages is critical in the early detection of frailty to employ prevention and interventions that lower the risks associated with frailty, improve functional status and avoid disability. Owing to the wide variability among older populations, the consideration of functional status rather than age should guide decisions around individualising treatment in older people. A recent network meta-analysis, which identified 19 components in complex interventions, showed moderate certainty that individualised multidomain assessment and management with medication reviews probably improves the odds of older people living independently at home up to 1 year (OR 1.12, 95% CI 0.93–1.59), but was unable to estimate the effects of frailty because of a lack of comparison groups and wide confidence intervals.¹⁰⁷

HF interventions in people with frailty often focus on physical function owing to increased inflammation, sarcopenia and reduced global function.^{63,108} Multidomain rehabilitation, diet, nutritional and cognitive support are among some of the interventions that can support improved outcomes.⁶³ In addition, social isolation, malnutrition, cognition and polypharmacy should also be considered composite measures that contribute to individuals' social determinants of health.⁵⁶

1.4 Outcomes

1.4.1 Outcomes associated with pharmacotherapy in heart failure with reduced ejection fraction

The optimisation of multiple GDMTs to target doses compared with single therapy in patients with HFrEF has demonstrated significant improvements in outcomes. International guidelines support the optimisation of GDMT in HFrEF with strong certainty of evidence and benefits for mortality and hospitalisation.^{22,23} Table 1.7, which summarises the outcome benefits of combination GDMT in HFrEF from a systematic review and network meta-analysis by Tromp et al. (2022)⁹⁷ demonstrates a significant decrease in cardiovascular mortality and HF hospitalisation risk. Pharmacological treatment also improves other outcomes such as QoL and worsening HF leading to hospitalisation.

New and emerging pharmacotherapies have provided additional benefits to managing HF, with and between drug classes. For example, angiotensin receptor neprilysin inhibitors (ARNIs), if tolerated, are preferred to angiotensin-converting enzyme inhibitors (ACEIs) because of the benefits to increased outcomes and improved QoL scores demonstrated by the PARADIGM-HF trial.¹⁰⁹ Recently, epidemiology studies have reported reversals in the decline in HF mortality in the US, despite advances in pharmacological treatment, indicating the need for further investigation.^{3,110}

Table 1.7: The risk of cardiovascular mortality or heart failure hospitalisation in combination guideline-directed medical therapies compared with angiotensin-converting enzyme inhibitor monotherapy.

Treatment	HR (95% CI)	Risk of CV mortality or HF hospitalisation
CV mortality or HF hospitalisation		
ARNI + BB + MRA + SGLT2-i	0.36 (0.29–0.46)	64% reduced risk
ARNI + BB + MRA	0.47 (0.38–0.58)	53% reduced risk
ACEI + BB + MRA	0.58 (0.47–0.71)	42% reduced risk
ACEI + BB	0.84 (0.73–0.96)	18% reduced risk
ARB + BB	0.65 (0.55–0.77)	35% reduced risk
ARNI + BB	0.68 (0.58–0.79)	32% reduced risk
BB	0.75 (0.65–0.87)	25% reduced risk
All-cause mortality		
ARNI + BB + MRA + SGLT2-i	0.39 (0.31–0.49)	61% reduced risk
ARNI + BB + MRA	0.44 (0.37–0.54)	56% reduced risk
ACEI + BB + MRA	0.52 (0.44–0.61)	48% reduced risk
ACEI + BB	0.69 (0.61–0.77)	31% reduced risk
ARB + BB	0.74 (0.66–0.82)	26% reduced risk
ARNI + BB	0.58 (0.50–0.68)	32% reduced risk
BB	0.78 (0.72–0.84)	22% reduced risk
CV mortality		
ARNI + BB + MRA + SGLT2-i	0.33 (0.26–0.43)	67% reduced risk
ARNI + BB + MRA	0.38 (0.31–0.47)	62% reduced risk
ACEI + BB + MRA	0.47 (0.39–0.57)	53% reduced risk
ACEI + BB	0.84 (0.73–0.96)	18% reduced risk
ARB + BB	0.64 (0.56–0.73)	36% reduced risk
ARNI + BB	0.68 (0.59–0.78)	32% reduced risk
BB	0.77 (0.70–0.85)	23% reduced risk

Abbreviations: ARNI = angiotensin receptor neprilysin inhibitors; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist/blocker; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2-i = sodium–glucose co-transporter-2 inhibitor; HR = hazard ratio; CI = confidence interval; CV = cardiovascular; HF = heart failure. **Footnote:** Adapted from Tromp et al. (2022).⁹⁶

1.4.2 Outcomes in older patients associated with heart failure with preserved ejection fraction and frailty

A systematic review of 25 randomised controlled trials (RCTs) reported beta-blocker use in HFpEF decreased all-cause mortality compared with the placebo (relative risk [RR] 0.78, 95% CI 0.65–0.94, $P = 0.008$).¹¹¹ However, there was no statistical difference in all-cause mortality and CV hospitalisation between nebivolol and the placebo in older patients (mean age 76 ± 5 years) with HFpEF (HR 0.81, 95% CI 0.63–1.04).¹¹² Further, there was no

statistical difference in CV mortality demonstrated for ACEIs, angiotensin receptor antagonist/blockers (ARBs), mineralocorticoid receptor antagonists (MRAs) or other therapeutic classes compared with the placebo.¹¹¹ ACEI use in a small sample of patients ≥ 70 years (mean age 76 ± 5 years) with HFpEF was shown to have no statistical significance in all-cause mortality (HR 0.692: 95% CI 0.474–1.010; $P = 0.055$) or reduced HF hospitalisation (HR 0.628: 95% CI 0.408–0.966; $P = 0.033$) for perindopril compared with the placebo groups.¹¹³ However, functional class ($P < 0.030$) and 6-minute walk distance ($P = 0.011$) improved in the participants on perindopril. In HFpEF, GDMT was not shown to reduce HF hospitalisation compared with the placebo.¹¹¹

Recently, SGLT2-i has demonstrated CV mortality and HF hospitalisation benefits. The EMPEROR-Preserved trial of HFpEF patients demonstrated a 21% reduction in hospitalisation with empagliflozin compared with the placebo groups (HR 0.79; 95% CI, 0.69–0.90, $P < 0.001$).⁹⁹ The benefit for HF hospitalisations was similar for patients taking SGLT2-i with LVEF $> 40\%$, including for HFpEF, HFmrEF and HFimpEF.¹¹⁴

1.4.3 Treatment outcomes in older people with heart failure and frailty

Multiple comorbidities along with cognitive impairment, falls and fractures resulting in increased hospitalisation and mortality have a significant impact on individuals' independence and QoL. Loss of function, functional reserve and limited capacity to maintain homeostasis lead to a high risk of adverse outcomes. As older people become frail, they may lose independence, which can lead to loneliness and isolation. This contributes to social frailty, the loss of social roles, networks and activities that may occur prior to physical and psychological frailty, and increases the risk of adverse events, including hospitalisation.¹¹⁵⁻¹¹⁷

Frailty risk in people with HF is associated with longer hospital stays, mortality and higher healthcare costs.¹¹⁸ Frailty in chronic HF is associated with a 1.5-fold increased risk of death (HR 1.54; 95% CI, 1.34–1.75; $P < 0.001$) and hospitalisation (HR 1.56; 95% CI, 1.36–1.78; $P < 0.001$).¹¹⁹ Older HF patients with frailty are also at higher risk of geriatric outcomes. Community-dwelling women aged over 70 years with frailty were found to have a higher risk of falls or fracture-related hospitalisation, and all-cause mortality compared with those who were robust.¹²⁰ The severity of physical frailty was considered an independent predictor of the underuse of HF-GDMT, including ACEI/ARBs (OR 1.23 95% CI 1.05–1.43) and beta blockers (OR 1.32, 95% CI 1.06–1.64), using the physical frailty category.¹²¹ In hospitalised older patients (n=188, 61%), social frailty was independently associated with a two-fold higher composite event rate (mortality and readmission) after adjusting for prognostic markers (adjusted hazard ratio [aHR] 2.01, 95% CI 1.07 to 3.77, $p=0.04$).¹¹⁶

In addition to preventing hospitalisation and death, geriatric outcomes (geriatric syndromes) such as falls, fractures and cognitive impairment are also important to consider within the context of optimising cardiovascular function in older people to align care plans with patient priorities and health goals.^{122,123} Older patients with HF are often concomitantly treated for several other conditions, warranting the need to balance interventions with patients goals of care and changing priorities. Multidisciplinary management of these conditions can cause tension in cases where treatment recommendations are conflicting across specialties. Although treatment outcomes from clinical trials emphasise mortality and preventing hospitalisation, patients also want to maintain their QoL and activities of daily living to live independently.

1.4.4 Pharmacokinetics and pharmacodynamics

1.4.4.1 Impact of heart failure on pharmacokinetics

HF can have an impact on the pharmacokinetics of CV and non-CV medications.

Pathophysiological changes occurring in HF as a result of systemic lowered arterial perfusion, venous congestion and neurohormonal activation can negatively affect key organ functions, particularly the kidney, liver and gastrointestinal tract¹²² (Table 1.8).

Pathophysiological changes can also influence the pharmacokinetics of CV and non-CV medications.¹²² Pharmacokinetics in HF patients compared with controls demonstrate significant changes for CV medications. Digitalis glycosides, some diuretics, ACEIs and antiarrhythmics (summarised in Table 1.8) can affect the absorption, distribution, biotransformation and excretion of drugs. In addition, as the population ages, HF is increasingly prevalent in older people, who undergo physiological changes that further exacerbate the effects of HF.

1.4.4.2 Pharmacokinetics of cardiovascular medications in the ageing population

Metabolising most medications involves enzymatic changes (biotransformed) in the liver via cytochrome P450 (CYP450) isoforms. The inhibition of enzymes can reduce biotransformation, which may lead to increased drug plasma concentrations and ADRs, requiring decreased doses or reduced active metabolites of prodrugs (e.g. ACEI, clopidogrel), which may become less effective.⁵⁸ Inducing drug metabolism can decrease the plasma concentration of drugs and their active metabolites, and increase the efficacy and ADRs of active metabolites.

Older people have a reduced first-pass effect that increases the oral bioavailability and plasma concentration of some medications (e.g. metoprolol, nitrates, dabigatran).⁵⁸ In

addition, hepatic blood flow is further decreased by HF and medications, and hypoalbuminemia plasma protein binding is a determinant of hepatic drug clearance. Table 1.8 characterises the physiological changes in older people that alter plasma drug concentrations, requiring dose adjustments and increasing the risk of ADRs. In older people, hypoalbuminemia can reduce plasma protein binding, resulting in higher plasma drug levels and reduced hepatic drug clearance.¹²³ In addition, lower doses may be needed in women compared with men owing to physiological sex differences in drug metabolism.⁹ Thus, monitoring liver function is critical in older patients, particularly when prescribing highly metabolised drugs, although concentrations of standard serum enzymes measured as ‘liver function tests’ is not well correlated with reduction in drug clearance (Table 1.8). This puts older people at risk of drug-drug interactions of highly metabolised cardiovascular medications (Table 1.9).

Table 1.8: Physiological changes that may affect pharmacokinetics and pharmacodynamics in older adults.

	Absorption	Distribution	Biotransformation	Excretion
Body composition	–	↓extracellular & total body water (5%–10%) ↓muscle mass (sarcopenia) ↑total body fat (<i>men:</i> 18%–35%; <i>women:</i> 30%–45%) ↓plasma albumin ↑α1-acid glycoprotein	–	–
Heart	–	↓cardiac output ↓tissue perfusion	–	↑comorbidities (i.e. HTN, HF, haemorrhage, cardiogenic shock)
Kidney	–	–	–	↓renal blood flow (30%–35%) ↓glomerular filtration rate (GFR) ↑filtration rate ↓tubular secretion ↓reabsorption ↓renal excretion ↑C _{max} and half-life of renally excreted drugs ↑comorbidities that ↓renal blood flow
Gastro-intestinal tract	↓gastric acid production and emptying ↓gastric blood flow ↓gastric motility ↓drug absorption ↑oral bioavailability	–	–	–
Liver	↓first-pass metabolism	↑free drug levels of highly protein-bound drugs ↑volume of distribution and half-life of lipophilic drugs ↓volume of distribution and half-life of hydrophilic drugs	↓liver size (20%–30%) ↓hepatic blood flow (20%–50%) ↓CYP450-mediated phase I reactions ↓ability to recovery from injury malnutrition hypoalbuminemia more common to see alcohol, malnutrition and hepatic disease (cirrhosis, carcinoma) ↓bioavailability of predrugs (i.e. ACEIs) ↑C _{max} and half-life of highly metabolised drugs	–

Abbreviations: HTN = hypertension; HF = heart failure; ACEI = angiotensin-converting enzyme inhibitor; C_{max} = highest concentration of a drug in the blood. **Footnote:** Adapted from Kaski et al. (2020)¹²⁴ and Bernes-Salazar et al. (2015).⁵⁸

Table 1.9: Drug–drug interactions and highly metabolised cardiovascular medications in older adults.

Drug class	Highly metabolised cardiovascular drugs	Interacting drugs	Effects
ACEI	Enalapril, perindopril, quinapril, ramipril, trandolapril	K ⁺ supplements, K ⁺ sparing diuretics, SMX/TMP	↑K ⁺
Antianginals	Ranolazine	–	–
Antiarrhythmics	Amiodarone, diltiazem, dofetilide, dronedarone, flecainide, lidocaine, propafenone, quinidine, verapamil, vernaklant	–	–
Antiaggregants	Cilostazol, P2Y ₁₂ receptor blockers	–	–
Anticoagulants	Acenocumarol, argatroban, DOACs, warfarin	Amiodarone, ciprofloxacin, NSAIDs, SMX/TMP	↑ bleeding
Antihypertensives	Methyldopa, alpha adrenergic blockers	Loop diuretics	↑ urinary incontinence
ARBS	Candesartan, losartan, irbesartan, telmisartan	K ⁺ supplements, K ⁺ sparing diuretics, SMX/TMP	↑ K ⁺
Beta-blockers	Bisoprolol, carvedilol, metoprolol, propranolol, timolol	–	–
Calcium channel blockers	–	Clarithromycin, erythromycin	↑ hypotension
Diuretics	Indapamide, loop diuretics, eplerenone, spironolactone	Lithium	↑ lithium toxicity
Glucose-lowering drugs	Pioglitazone, SGLT2-i, sulfonylureas	–	–
Lipid-lowering drugs	Ezetimibe, fibrates, statins	–	–
Morphine	–	–	–
Digoxin	–	Amiodarone, macrolides, verapamil	↑ digoxin toxicity

Abbreviations: DOACs = direct oral anticoagulants; NSAIDs = non-steroidal anti-inflammatory drugs; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; SMX = sulfamethoxazole; TMP = trimethoprim. **Footnote:** Adapted from Kaski et al. (2020)¹²³ and Bernes-Salazar et al. (2015).⁵⁸

1.4.5 Adverse drug events

1.4.5.1 Adverse drug events associated with heart failure pharmacotherapy

Managing HF is complex and dynamic. The use of HF pharmacotherapy requires continuous vigilance to adequately control HF symptoms while monitoring tolerance to adverse effects, often exacerbated by interactions with comorbidities and concurrent medications. There is clear benefit to treating HF with pharmacotherapy, but patients commonly experience at least one ADE from these pharmacological treatments.^{93,125} This becomes increasingly complex to manage in older individuals with multiple comorbidities, polypharmacy, cognitive impairment and changing goals of care.

1.4.5.2 Definitions

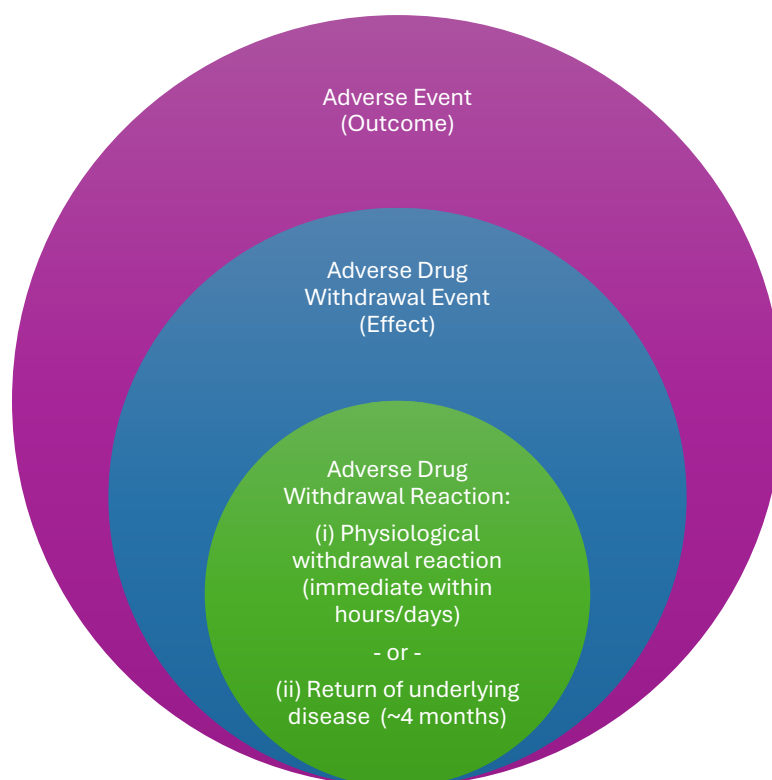
The relationships among the different definitions used to describe adverse events are summarised in Figure 1.8. An adverse outcome is an adverse event experienced by an individual. ADEs are any adverse outcome occurring in people taking a medication. ADEs include ADRs, which refer to any response to a drug that is noxious and unintended, and involves a causal relationship between medication and adverse reaction,¹²⁶ occurring during the initiation, continuation or withdrawal of medications. The causality of ADRs can be measured with assessments tools such as the Naranjo score,¹²⁷ to measure the probability of ADRs, and the Hallas scale, to measure whether it was possibly preventable.¹²⁸ A cross-sectional study of inpatients aged ≥ 65 years reported ADR-related admissions accounted for approximately 10% of hospitalisation (10%, 95% CI 9.1%–11.0%).¹²⁹ One systematic review reported that approximately one-quarter of older hospitalised patients experienced an ADR during admission, of which 90% were predictable and preventable.¹³⁰ Among the predictors of ADRs during hospitalisation were polypharmacy and disease-related risks such as HF.¹³⁰

Figure 1.8: The relationships among adverse events, adverse drug events, adverse drug reactions and adverse drug withdrawal effects caused by optimisation or withdrawal of a medication.

A. Occur in individuals taking a medication.



B. Occur in individuals withdrawing a medication.



Footnote: The terms 'Adverse Drug Withdrawal Events' and 'Adverse Drug Withdrawal Effects' are used interchangeably and describe the same purpose.

Diuretics, beta-blockers and renin–angiotensin system inhibitors (RASIs) are among the most common therapeutic classes involved in ADRs.¹²⁹ The most common characteristics of ADEs resulting from HF pharmacotherapy are described in Table 1.10. A systematic review by Butzner et al. (2022)⁶⁶ reported that bradycardia, dizziness, hypotension, hyperkalaemia, cough and renal impairment were the most common ADEs across HF-GDMTs in patients with HFrEF.

Most ADEs occur within the first weeks of initiating pharmacotherapy. Strategies to improve tolerance and/or mitigate the impact of ADEs can guide clinicians to up-titrate to target doses and inform patients about how to manage adverse effects or when to seek advice from a health professional. In a cross-sectional study of primary care and outpatient clinics, 91% of patients with HF perceived ADEs as a chronic problem.¹²⁵ Almost half (46%) of these patients perceived the ADEs as serious, and 40% reported that the ADE(s) had major consequences for their daily activities and QoL.¹²⁵ Consequently, a cohort study of previously hospitalised HF patients with a mean age of 70 years¹³¹ reported that medication changes were 38% (RR 1.83, 95% CI 1.35–2.49) more likely if patients were perceived to have experienced an ADE. Physiological and pharmacological changes can account for some differences in patient experiences.

Table 1.10: Common adverse drug events among heart failure pharmacotherapy.

Drug class	Adverse effects
ACEI	Hypotension (dizziness) Worsening renal function Hyperkalaemia (τ creatinine) Chronic cough Angioedema
ARB	Hypotension (dizziness) Worsening renal function Hyperkalaemia (τ creatinine)
ARNI	Hypotension (dizziness) Angioedema
Beta-blocker	Hypotension (dizziness) Bradycardia Fatigue Bronchospasm Impotence Worsening heart failure Masking hypoglycaemia (e.g. tachycardia, tremor) Sleep disturbance/nightmares
MRA	Hyperkalaemia Worsening renal function Hypotension (dizziness) Gynaecomastia (spironolactone)
Diuretic	Renal dysfunction Hypokalaemia May precipitate gout Urge/frequency incontinence
Ivabradine	Visual disturbances (phosphenes, areas of enhanced brightness) Headache Bradycardia Atrial fibrillation Angina, ventricular extrasystoles
Digoxin	Bradycardia Digoxin toxicity
SGLT2-i	Ketoacidosis Genitourinary infections Volume depletion Worsening renal function
Soluble guanylate cyclase stimulators (vericiguat)	Hypotension (dizziness), syncope Anaemia Headache, dyspepsia, nausea, vomiting
Cardiac myosin activators ¹³² (omecamtiv mecarbil)	Hypotension (dizziness) Worsening renal function
Vasodilators (hydralazine, isosorbide dinitrate)	Hypotension (dizziness) Headache, nausea, flushing Palpitations, tachycardia, angina, oedema Lupus-like symptoms

Abbreviations: ARNI = angiotensin receptor neprilysin inhibitors; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist/blocker; MRA = mineralocorticoid receptor antagonist; SGLT2-i = sodium–glucose co-transporter-2 inhibitor. **Footnote:** Adapted from Hopper & Easton (2017)¹³³ and the *Australian Medicines Handbook* (2024).¹³⁴

1.4.6 Adverse drug withdrawal effects

Adverse drug withdrawal effects (ADWEs), also known as adverse drug withdrawal events, are defined as symptoms or signs related to the discontinuation of a drug that can be characterised as physiological withdrawal reactions or the return of the underlying disease.¹³⁵⁻¹³⁷ Although physiological ADWEs are more likely to occur immediately, the return of the underlying disease can occur up to four months after discontinuation.¹³⁶ The discontinuation of some CV medications such as beta-blockers and alpha blockers have been found to demonstrate physiological ADWEs (Table 1.11).^{137,138} Similar assessment tools to those used to identify the causality¹²⁷ and preventability¹²⁸ of ADRs also apply to ADWEs.

Conversely, ACEIs/ARBs are among the CV agents/classes without physiological withdrawal reactions in frail older people, according to the STOPP-Frail criteria.¹³⁷ A systematic review of adults aged over 18 years with HFrEF reported that deprescribing increased the risk of worsening HF, hospitalisation and mortality.¹³⁷ Although some evidence of physiological withdrawal reactions has been established, the summary in Table 1.11 shows that there is limited evidence to determine whether deprescribing may result in physiological withdrawal symptoms and the worsening of HF symptoms.

Deprescribing trials of HF pharmacotherapy have been conducted in younger robust cohorts.¹³⁸ For example, the TRED-HF trial¹³⁹ reported the concurrent withdrawal of multiple GDMTs with HFrEF or HFimpEF over six months, resulting in the relapse of LVEF and natriuretic peptide levels, the recurrence of HF symptoms and worsening QoL. Physiological withdrawal reactions to beta-blockers, nitrates and digoxin have been reported but have not been determined for other HF pharmacotherapies, and the effects are uncertain in older people with frailty.

Table 1.11: Physiological withdrawal reactions from cardiovascular medications.

CV drug class	Physiological adverse withdrawal symptom
Beta-blockers	Angina, myocardial infarction, anxiety, tachycardia, hypertension
Nitrates	Myocardial ischemia
Alpha adrenergic receptor antagonists (for hypertension)	Hypertension, palpitations, headache, agitation
Calcium channel blockers	Arrhythmia, angina
Digoxin (for HF)	Worsening HF
Aspirin	Acute coronary thrombosis,
Heparin (for unstable angina)	Unstable angina
HMG-CoA reductase inhibitors (Statins)	Myocardial infarction, HF, ventricular tachycardia
ACEIs	Unlikely physiological withdrawal reactions
ARBs	Unlikely physiological withdrawal reactions
ARNI	Cannot be determined with existing evidence
MRA	
SGLT2-i	
Loop diuretics	
Inotropes	
Cardiac myosin inhibitor (omecamtiv mercabil)	
Soluble guanylate cyclase activator (vericiguat)	

Abbreviations: ARNI = angiotensin receptor neprilysin inhibitors; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist/blocker; MRA = mineralocorticoid receptor antagonist; SGLT2-i = sodium–glucose co-transporter-2 inhibitor; HF = heart failure. **Footnote:** Adapted from Hanlon et al. (2021)¹³⁷, Hanlon et al. (2022)¹³⁶ and Reidenberg et al. (2011)¹³⁵

1.5 Gaps in the literature

International guidelines, supported by strong evidence, recommend the optimisation of HF-specific pharmacotherapy to reduce mortality and hospitalisation in HFrEF. However, these recommendations are informed by clinical trials that persistently and widely exclude older people, particularly those with frailty.¹⁴⁰⁻¹⁴² The outcomes reported in these guidelines do not include the impact on geriatric outcomes or provide strategies to manage the potential physiological challenges, pharmacokinetic changes and adverse events in frail older people. Further investigation is needed to determine appropriate treatments and outcomes in older

people with HFpEF, HFmrEF and HFimpEF. Recently, contradicting results have been reported in epidemiological studies of CV disease,^{3,111} showing a reversal of trends and increased incidence of HF and mortality. In a retrospective study involving Taiwan's national health insurance research database of older HF patients over 65, less than one-third of deaths were reportedly due to CV disease,¹⁴³ thus raising concerns about whether the benefits and risks of optimisation support approaches to treating other organ dysfunctions.

ADEs from HF pharmacotherapy are common and older people are at higher risk of ADRs than younger people.^{129,144} Optimising HF pharmacotherapy in older people with frailty can be challenging due to variable tolerability, non-adherence and lack of evidence whether deprescribing is safe and feasible. Improved reporting of ADEs and ADWEs¹⁴⁵ in people of advanced age at risk of frailty is needed to provide clinical guidance to ensure that older people have the opportunity to derive maximum benefit from their pharmacotherapy and have treatment tailored to their needs. Although care can be taken to start at very low doses and go slowly, titrating according to individual tolerance, the prevalence of suboptimal doses of HF pharmacotherapy in older people with frailty warrants further investigation. Clinical practical tips have been provided to health professionals to improve tolerance during initiation and optimisation of HF-GDMT in older people, but these are not supported with high-quality clinical trials and require vigilant monitoring.¹⁴⁶

1.6 Hypothesis

The hypothesis of this thesis is that there is limited evidence to determine the prevalence of ADEs, ADRs and ADWEs in older people with HF according to frailty status. Older people with HF and frailty must navigate frequent access to private and/or public services across multiple health professionals, specialists, and health centres. This leads to fragmented communication across multiple providers.

1.7 Objectives

This thesis aimed to investigate the prevalence and management of ADEs and ADWEs associated with HF pharmacotherapy during optimisation and deprescribing for older people with frailty.

This thesis aimed to:

1. identify the gaps in the literature by describing the prevalence, causality and severity of ADRs or ADEs from HF medications among frail compared with non-frail older adults and investigate whether interventions to discontinue or down-titrate HF pharmacotherapy are feasible and associated with risks in older people
2. evaluate HF pharmacotherapy utilisation and the prevalence of polypharmacy, ADEs, falls, delirium and renal impairment in hospitalised adults ≥ 75 years according to frailty status
3. explore consumer and healthcare professional (HCP) perspectives on the ADEs and ADWEs related to HF pharmacotherapy to inform the key domains of a conceptual model for prescribing and deprescribing for older people with frailty
4. synthesise the findings from these studies to develop a novel taxonomy of ADEs and ADWEs from HF pharmacotherapy to support tailoring to older people with frailty.

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CHAPTER 2

2.1 Overview

Frailty is highly prevalent in older heart failure populations and a major risk factor for adverse drug reactions (ADRs) and adverse drug events (ADEs). The expanding available treatments and the optimisation of guideline-directed medical therapy to improve clinical outcomes in heart failure patients is a high priority among clinicians internationally. Understanding the balance between the benefits and potential harms of these foundational therapies is increasingly critical.

Chapter 2 highlights the lack of evidence describing prevalence, causality and severity of ADRs or ADEs from heart failure medications among frail compared to non-frail older adults. Three studies with low and very low graded level of evidence met inclusion criteria for this systematic review. Frail older people were significantly underrepresented in clinical trials related to heart failure. This knowledge gap may inadvertently put older heart failure patients with frailty at harm in clinical practice because we have limited understanding of how they are impacted by these medications. Improving our understanding of the safety and potential medication-related harms of foundational therapies can support optimal prescription of and adherence with medications critical in improving clinical outcomes in vulnerable patients.

2.2 Authorship Attribution Statement

Chapter 2 of this thesis is published as:

Duong MH, Gnjdic D, McLachlan AJ, Sakiris MA, Goyal P, Hilmer SN. The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review. *Drugs and Aging*; 2022. 39: 631–643.

doi: [10.1007/s40266-022-00957-8](https://doi.org/10.1007/s40266-022-00957-8)

The coauthors of the paper, “Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review”, confirm that Mai H Duong has made the following contributions:

I, Mai Duong, co-designed the study with co-authors, provided resources and software, collected, curated, validated and extracted the data, conducted analysis, visualisation and interpretation of the findings, wrote the original draft of the manuscript and revised and edited the manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Sarah N Hilmer

January 31, 2025

2.3 Manuscript: The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review.



The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review

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Accepted: 2 June 2022 / Published online: 28 June 2022
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Abstract

Introduction Frailty is highly prevalent in heart failure populations and a major risk factor for adverse drug reactions (ADRs) and adverse drug events (ADEs). This review aimed to describe the prevalence, causality and severity of ADRs or ADEs from heart failure medications among frail compared with non-frail older adults.

Methods A systematic search of CENTRAL, MEDLINE, Embase, Ageline, CINAHL, International Pharmaceutical Abstracts, PsychInfo, Scopus, registries and citations prior to 18 May 2021 was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist. Risk of bias and quality of evidence were assessed. Eligible studies included randomised controlled trials (RCTs) and observational studies of people diagnosed with heart failure, aged ≥ 65 years, with frailty defined by an objective measurement, and reported ADRs/ADEs from/with heart failure medications.

Results Two reviewers screened 2419 articles; interrater reliability kappa = 0.88. Three observational studies ($n = 2596$), a secondary analysis of two RCTs ($n = 2098$) and two cohort studies ($n = 498$) were included in a narrative synthesis. Frail patients in randomised trials of sacubitril/valsartan, aliskiren, or enalapril had twice the risk of mortality (hazard ratio [HR] 2.09, 1.62–2.71) and hospitalisations (HR 1.82, 1.37–2.41) compared with robust patients, which may reflect responsiveness to medications and/or factors unrelated to medication use. Hospitalisations from falls, tiredness and nausea were probably attributable to digoxin and possibly preventable according to the Naranjo and Hallas scales, respectively.

Conclusion The potential harms from heart failure medications in frail older people are poorly studied and understood. Clinical trials and pharmacovigilance studies should include frailty as a covariate to inform medication optimisation for this vulnerable and growing population.

Registration Prospero registration number: CRD 42021253762.

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Graphical Abstract

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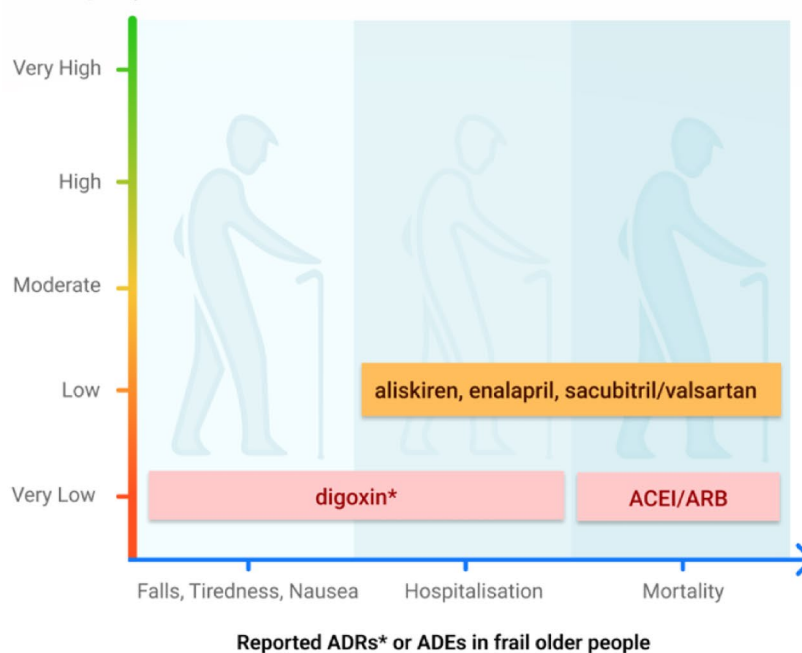
The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review

Mai H. Duong, Danijela Gnjidic, Andrew J. McLachlan, Marissa A. Sakiris, Parag Goyal, Sarah N. Hilmer

Key Findings

- The scarcity of knowledge and uncertainty of reported potential harms from heart failure medications in frail older people, suggests this vulnerable population is very underrepresented in studies.
- In three studies, there were very low to low levels of evidence in frail older people to support a 2-fold risk of hospitalisation and mortality with renin-angiotensin system inhibitors and that falls, nausea and tiredness from digoxin led to possibly avoidable hospital readmissions.
- There is a need for high quality research in older heart failure patients to include measures of frailty and frail participants, to inform patient-tailored treatment plans.

GRADE quality of evidence



* The causes and avoidability of ADRs were defined with the Naranjo and Hallas scales. All other studies were limited to reporting ADEs

ACEI/ARB angiotensin converting enzyme inhibitors or angiotensin receptor blockers, ADEs adverse drug events, ADRs adverse drug reactions.



This graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online. © The authors, CC-BY-NC [2022].

Key Points

The scarcity of knowledge and uncertainty of reported potential harms from heart failure medications in frail older people, suggests this vulnerable population is very underrepresented in studies.

In three studies, there were very low to low levels of evidence in frail older people to support a twofold risk of hospitalisation and mortality with renin-angiotensin system inhibitors, and that falls, nausea and tiredness from digoxin led to possibly avoidable hospital readmissions.

There is a need for high-quality research in older heart failure patients to include measures of frailty and frail participants, to inform patient-tailored treatment plans.

1 Introduction

Heart failure affects approximately 65 million people worldwide and 50–75% die within 5 years of diagnosis [1–3]. Heart failure is the most common cause of hospitalisation in older people, accounting for 10% of hospitalisations among adults aged ≥ 75 years, and adults aged ≥ 75 years account for 50% of heart failure-related hospitalisations [4–6].

A critical aspect of providing care to older adults with heart failure is medication management, particularly optimising use of disease modifying and symptomatic treatments and minimising adverse drug reactions (ADRs). ADRs refer to “any response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function” [7]. Adverse drug events (ADEs) broadly refer to any adverse outcome occurring in people taking a medication, whereas ADRs involve a causal relationship between medication and adverse reaction. Frailty, a syndrome associated with multisystem deficiencies or disabilities that lower individuals’ resilience to stressors and risk decompensation at lower thresholds, is present in up to 74% of older adults with heart failure [8]. Frailty is associated with increased risk of adverse outcomes and exacerbates the risk of ADRs in older heart failure patients [9, 10].

Yet the risk of ADRs among older people with heart failure and frailty are not well-established and are poorly represented in clinical trials of pharmacological interventions [11]. Understanding ADRs and ADEs in this population could ultimately help inform interventions to improve

outcomes in this vulnerable population, since over half the hospital admissions due to ADRs are believed to be preventable [12]. Therefore, this review aimed to describe the prevalence, causality and severity of ADRs or ADEs from heart failure medications among frail compared with non-frail older adults.

2 Methods

A systematic review was conducted according to the protocol (Prospero registration number: CRD 42021253762) [13], and amended with additional authorship and data validation implemented at the data analysis stage. The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist [14]. A search of eight databases, including CENTRAL, MEDLINE, Embase, Ageline, CINAHL, International Pharmaceutical Abstracts, PsychInfo, and Scopus, was performed for human studies prior to 18 May 2021 disseminated in English. Published and unpublished studies were searched in Prospero and ClinicalTrials.gov, as well as citations in relevant studies. The search terms applied were frail older adults, heart failure-specific medications, and ADRs or ADEs. Validated filters for ADRs and ADEs were adapted from Golder et al. [15] (Electronic Supplementary Material [ESM] Table S1). The search was validated using the Peer Review of Electronic Search Strategies (PRESS) checklist [16] (ESM Table S2).

Eligible studies included randomised controlled trials (RCTs), meta-analyses, or observational study designs, across all health care settings. Qualitative studies, self-reports, case reports, case series, expert opinion, reviews and trials of pharmacotherapy with cardiovascular agents for indications other than heart failure were excluded. In cases where outcomes were reported in parallel studies that were ineligible, authors were contacted to request missing data of subgroup analysis. We included studies of individuals or analysis of subgroups for participants who were diagnosed with heart failure, treated with heart failure-specific medications, aged ≥ 65 years and described as frail using an objective criteria or frailty measurement. The term ‘frail’ was defined using systematically defined criteria specified by the authors (e.g., Frailty Phenotype [17], Frailty Index (FI) score [18], Clinical Frailty Score [19]). Guideline-directed heart failure-specific medications (ESM Table S3) were administered alone or in combination and in fixed or titrated (up/down) regimens. We included studies that measured ADRs or ADEs with definitions and/or causality assessment criteria secondary to a specific medication or pharmacological class, or specific ADRs or ADEs. Categories of severity ranged from

mild or moderate clinical symptoms to severe outcomes of serious clinical risk or leading to death. Studies that only reported prevalence of heart failure medication use without reporting ADR or ADE outcomes were excluded.

The eligibility criteria were pilot tested on a 5% random sample of studies by the entire research team. Two review authors (MD and MS) independently performed screening and risk of bias, and disagreements were resolved by consultation with a third reviewer (DG/AM/PG/SH). Search results were screened with Covidence software (Melbourne, VIC, Australia) and duplicates were removed using the automated duplicate removal function, or manually identified. Data from the included studies were entered into a standard data form for participant and study characteristics, quality or risk of bias, outcomes and adverse events. Studies were grouped by study design and frailty status. One reviewer (MD) collected data into spreadsheets and a second reviewer (MS) validated 30% of the data for accuracy of reporting. Results were reviewed by the entire research team. A narrative synthesis of the key findings was summarised in tables and/or described, and forest plots were generated using R studio software. Study design and frailty groups were presented separately.

Risk of bias was assessed using the ROBINS-I Cochrane Collaboration risk of bias assessment tool for non-randomised studies of interventions (ESM Fig. S1) [20]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (ESM Table S4) [21, 22] was used to summarise the overall quality of evidence for outcomes assessed by two reviewers (MD and MS). Analysis of prevalence, causality and severity of ADRs and ADEs was stratified according to the assessment model or GRADE score.

3 Results

The search identified 2419 studies; 923 studies were identified as eligible and 3 met the inclusion criteria selected for analysis (Fig. 1). The kappa statistic was 0.88 for inter-rater reliability of screening. Three observational studies ($n = 2596$), including a secondary analysis of two RCTs ($n = 2098$) and two prospective observational cohort studies ($n = 498$), were identified and are summarised in Table 1. All studies reported severe ADEs of mortality and/or hospitalisation and one study reported mild to moderate ADRs

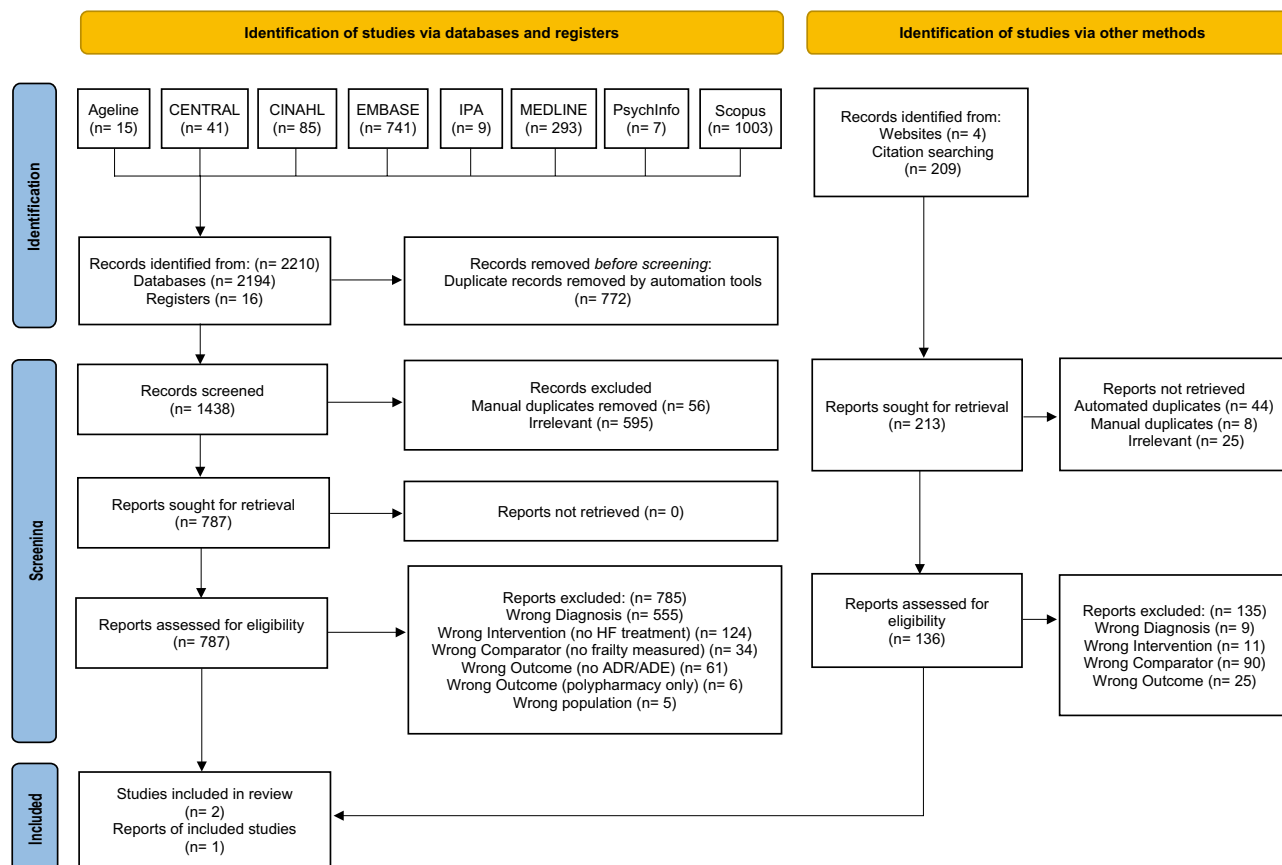


Fig. 1 Search strategy results. HF heart failure, ADR adverse drug reaction, ADE adverse drug event

Table 1 Summary of study characteristics in frail older people

Study	Country	Setting (setting, age, study time-frame: follow-up, inclusion, exclusion)	Study population [sample size; mean age, years (SD); no. of females (%)]	HF classification	Frailty definition	Frailty prevalence	Medication (intervention, comparator)	Primary outcomes (severe ADEs)	Definition of adverse outcomes (ADR/ADE)	Secondary outcomes: mild to moderate ADRs/ADEs (prevalence, causality)	Key findings	Level of evidence (GRADE)	Comments
Randomised controlled trials													
Dewan et al. (2020) [25]	North/Latin America, Western/Central Europe, Asia-Pacific	Multicentre hospital/clinic, 2009–2014; median PAR-ADIGM-HF 26.6 months, ATMOSPHERE 36.7 months)	2098 67.1 (10.3) 882 (24.4%)	HF+EF	Frail FI > 0.210 Subgroups: FI < 0.210 FI 0.211–0.310 FI > 0.311	77.4% 37.9% (FI 9.22–0.310) 39.5% (FI > 0.311)	Sacubitril/valsartan (ARNI), enalapril (ACEI), aliskiren, combined aliskiren and enalapril	Mortality, hospitalisation	ADE	NA for > 75 years of age	Frail with FI > 0.311 had twice the risk of mortality and hospitalisation compared with non-frail ($p < 0.001$)	Low	Retrospective analysis of two similar clinical trials ($n = 13,265$). No differences in outcomes among any subgroups analysed except for race Frailty data for the >75 years of age subgroup ($n = 2098/2544$, 15.8%)
Observational prospective cohort studies													

Table 1 (continued)

Study	Country	Setting (setting, age, study time-frame; follow-up, inclusion, exclusion)	Study population [sample size; mean age, years (SD); no. of females (%)]	HF classification	Frailty definition	Frailty prevalence	Medication (intervention, comparator)	Primary outcomes (severe ADEs)	Definition of adverse outcomes (ADR/ADE)	Secondary outcomes: mild to moderate ADRs/ADEs (prevalence, causality)	Key findings	Level of evidence (GRADE)	Comments
Ekerstad et al. (2017) [23]	Sweden	Single-centre, hospital (TREEE), 2013–2015: 3 months Include: > 75 years of age, frail Exclude: Patients receiving acute care at an organ-specific medical unit (e.g., acute MI, stroke)	48 85.7 (5.1) 221 (57%)	Both HF+EF/ HFpEF	Frail >2 FRESH: tiredness from short walk, general fatigue, frequent/ anticipa- tion of falls, depend- ence in shopping and more than three ER visits in the past 12 months	100%	Digoxin	Rehospitalisation within 30 days	ADR NS >4 or clinical judge- ment Hallas criteria avoid- able hospi- talisa- tion	Two ADRs due to digoxin Probable cause of ADR by digoxin NS: falling (NS = 5), nausea, tiredness (NS = 6) Hallas scale: possibly avoidable	HF was the most frequent indication of ADRs causing rehospitali- sation Falls, nausea and tired- ness from digoxin leading to hospitalisa- tion were preventable ADRs	Very low	96/390 patients were readmitted early, 48/96 with HF

Table 1 (continued)

Study	Country	Setting (setting, age, study time-frame; follow-up, inclusion, exclusion)	Study population [sample size; mean age, years (SD); no. of females (%)]	HF classification	Frailty definition	Frailty prevalence	Medication (intervention, comparator)	Primary outcomes (severe ADEs)	Definition of adverse outcomes (ADR/ADE)	Secondary outcomes: mild to moderate ADRs/ADEs (prevalence, causality)	Key findings	Level of evidence (GRADE)	Comments
Vidán et al. (2016) [28]	Spain	Single-centre, hospital (FRail-HF), 2009–2011: up to 1 year Include: > 70 years of age, frail/non-frail Exclude: Severe dependence preadmission (inability to independently perform three or more basic ADLs), moderate to severe dementia (MMS ≤ 15), transferred from nursing home	450 80 (6.1) 206 (49%)	Both HFpEF/ HFpEF	Frail > 3 FP: slowness, weakness, weight loss, exhaustion physical activity	76%	ACEI/ARB	Mortality (overall survival time from initial admission to death)	ADE	NA	Frailty on ACEI/ARB had no effect on survival ($p = 0.14$) Frail had a twofold risk of 1-year mortality (HR 2.13, 1.07–4.23)	Very low	66.5% frail taking an ACEI/ARB

ACEI angiotensin-converting enzyme inhibitor, ADEs adverse drug events (no validated method used to screen for ADRs/ADEs), ADLs activities of daily living, ADRs adverse drug reactions, ARB angiotensin receptor blocker, ARNI angiotensin receptor neprilysin inhibitors (i.e. sacubitril/valsartan), eGFR estimated glomerular filtration rate, ER emergency room, FI Frailty Index, FP Frailty Phenotype, FRESH Frail Elderly Support Research group screening instrument, GRADE Grading of Recommendations Assessment, Development and Evaluation, HF heart failure, HFpEF heart failure with preserved ejection fraction, HFpEF heart failure with reduced ejection fraction, HR hazard ratio, MI myocardial infarction, MMS mini-mental score, NA not available, NS Naranjo score, SBP systolic blood pressure, SD standard deviation

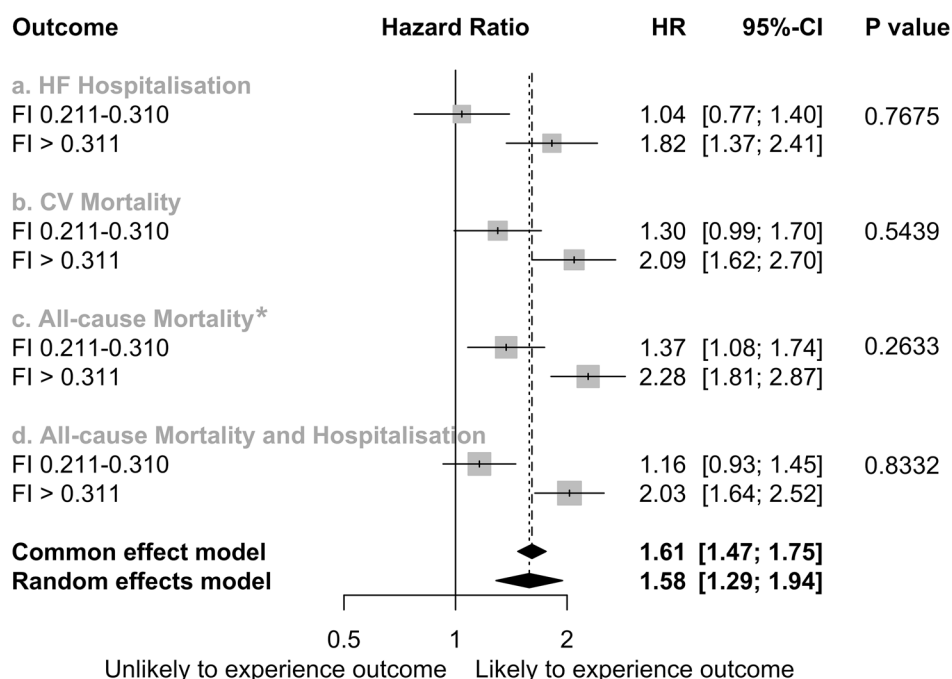
leading to preventable hospitalisation [23]. The adapted FI [24] and modified frailty phenotype criteria [17] were used to define frailty in these studies.

A secondary analysis of two RCTs [25] compared outcomes by frailty group among participants with heart failure with reduced ejection fraction (HFrEF) from the PARADIGM-HF [26] (sacubitril/valsartan vs. enalapril) and ATMOSPHERE [27] (aliskiren with/without enalapril vs. enalapril) trials, which had identical inclusion and exclusion criteria and similar study protocols (ESM Table S5). For both trials, frailty was defined from an adapted FI [24], involving cumulative deficits in a 42-item FI. Participants with an FI ≤ 0.210 were considered non-frail/robust and patients with an FI > 0.210 were considered frail, and were further divided into groups by increments of 0.100 (0.211–0.310 or ≥ 0.311). Increased frailty score was associated with increased risk of adverse outcomes in a subgroup analysis of participants aged ≥ 75 years from both trials [25], but the prevalence of mortality and/or hospitalisation was not reported in this subgroup. Figure 2 shows an exposure–response trend between increasing frailty and risk of mortality and hospitalisations for participants taking sacubitril/valsartan, enalapril or aliskiren. Frail participants with an FI > 0.311 had an approximately twofold increase in mortality and hospitalisation compared with non-frail participants with an FI < 0.210 . Frail participants with an FI > 0.311 had a higher risk of cardiovascular mortality (sub-distribution hazard ratio [sHR] 2.09, 1.62–2.71), all-cause mortality (hazard ratio [HR] 2.28, 1.81–2.87), heart failure hospitalisation (sHR 1.82, 1.37–2.41) and primary

composite (sHR 2.03, 1.64–2.52) than those with an FI < 0.210 . However, only all-cause mortality was statistically significantly higher in patients with FI scores between 0.211 and 0.310 than in those with an FI < 0.210 (HR 1.37, 1.08–1.74). There was no significant difference ($p = 0.77$, 0.54, 0.26, 0.83) in treatment effect of sacubitril/valsartan compared with enalapril between the frailty groups across all age groups, non-specific to ages ≥ 75 years, among the reported outcomes in Fig. 2. These outcomes (all-cause mortality and hospitalisation) were scored as having a low level of evidence and low risk of bias (ESM Fig. S1 and Table S4).

FRAIL-HF [28] was a prospective cohort study that evaluated the impact of frailty in non-dependent people aged ≥ 70 years hospitalised for HF. A twofold risk of mortality and heart failure readmission, as well as increased disability in frail compared with non-frail older inpatients, was reported [25]. The modified frailty phenotype definition [17] was applied to identify frail participants. The reported use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in frail compared with non-frail participants was 66.5% and 82.7%, respectively ($p = 0.002$). Frailty was associated with an increased risk of 1-year mortality (HR 2.13, 1.07–4.23), with no interaction between frailty and the effect of ACEIs/ARBs on survival ($p = 0.14$). During the 1-year follow-up period, deaths were reported in 25.0% ($n = 79$) of frail participants and 11.0% ($n = 11$) of non-frail participants ($p < 0.001$). The risk of mortality with frailty in heart failure patients was scored as

Fig. 2 Severe adverse drug events by Frailty Index Score for sacubitril/valsartan, or enalapril [25]. The p -value interaction for each outcome is provided for treatment effect on overall frailty. *HR* hazard ratio, *CI* confidence interval, *HF* heart failure, *CV* cardiovascular



having a very low level of evidence and moderate risk of bias (ESM Fig. S1 and Table S4).

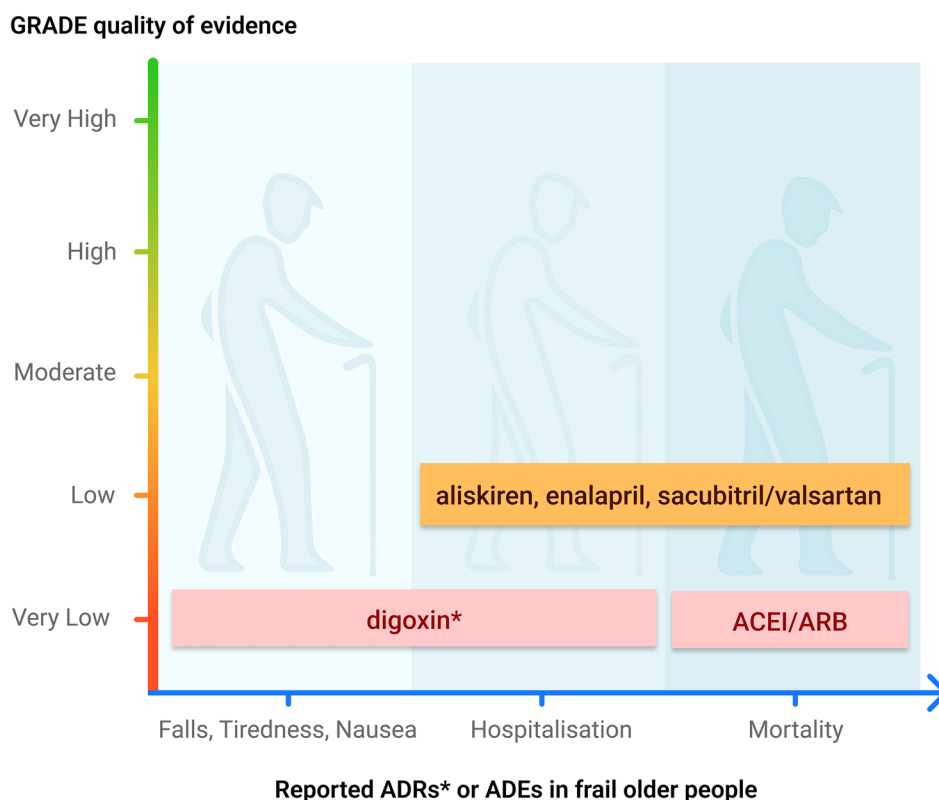
The TREEE study [23] was a prospective cohort study examining the impact of medications on hospital readmission within 30 days in frail patients, defined using the modified frailty phenotype criteria [17], aged ≥ 75 years. ADRs were identified using the Naranjo score and the avoidability of readmissions was determined using the Hallas criteria and clinical judgement [29, 30]. The TREEE study reported 13 ADRs that were causes of readmissions. Of the 96 patients readmitted, heart failure was the most common diagnosis ($n = 48$, 50%), chronic heart failure was reported as an independent predictor for early hospitalisation ($p = 0.024$), and no deaths were reported. In the heart failure subgroup, two ADRs were classified as probably caused by digoxin use indicated for heart failure. The reasons for ADRs leading to hospitalisation were falls (Naranjo score = 5) and tiredness and nausea (Naranjo score = 6). Hospitalisation due to these ADRs were reported as possibly avoidable according to the Hallas criteria, with at least one or more alternative approaches or prevention available in theory. Readmissions attributed to adverse effects of dyspnoea ($n = 8$), tiredness ($n = 2$) and worsened general condition ($n = 1$) from under-use of ACEIs, ARBs or β -blockers were more frequently

reported than ADRs from digoxin use ($n = 2$). Only the TREEE study reported the likelihood and preventability of ADRs from heart failure-specific medications in this review; however, the quality of evidence for falls, nausea, tiredness and hospitalisation was very low and with serious risk of bias. Due to the paucity of data, we could not report the prevalence for many common ADRs for other drug classes, reflected in the grading of evidence (ESM Fig. S1 and Table S4). Figure 3 summarises the prevalence of ADRs and ADEs with heart failure medications in frail compared with non-frail older people according to the GRADE quality of evidence.

4 Discussion

The scarcity of knowledge in the literature highlights the poor representation of older frail populations in standard clinical trial and observational study protocols. ADRs and ADEs were not frequently reported for well-defined frail older populations with heart failure, and when investigated, very few outcomes were included. Regardless of the definition of frailty applied, increased risk was reported in frail compared with robust older people. While some increased

Fig. 3 The graded quality of evidence in frail compared with non-frail older people summarising the risk of ADRs or ADEs from heart failure medications. *The causes and avoidability of ADRs were defined using the Naranjo and Hallas scales. All other studies were limited to reporting of ADEs. ADRs adverse drug reactions, ADEs adverse drug events, GRADE Grading of Recommendations Assessment, Development and Evaluation



ACEI/ARB: Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blocker*

risk of adverse outcomes from heart failure treatments were observed in frail compared with non-frail older people, these results were difficult to interpret and were uncertain.

The lack of high-quality studies in the literature reflects the widespread exclusion of vulnerable populations from heart failure clinical trials [31, 32]. Standard trial protocols often report findings for subgroups by age, sex, ethnicity, geography, and various cardiac-related factors. However, frailty and advancing age remain underrepresented in clinical and observational study designs despite evidence they are independent risk factors in heart failure. Most clinical trials related to heart failure were in those aged < 65 years, even though most real-world patients were older, had increased risk of multimorbidity and polypharmacy, and 50% of heart failure-related hospitalisations occur in those ≥ 75 years of age [6, 32]. The participation prevalence ratio (PPR), used to indicate underrepresentation ($\text{PPR} < 0.8$) or overrepresentation ($\text{PPR} > 1.2$) of older people compared with their 'real world' disease population, was significantly lower for people ≥ 65 years (PPR 0.48–0.62) and ≥ 75 years (PPR 0.20–0.33) of age in cardiovascular drug trials for heart failure [31]. This was further exacerbated by similar trends excluding frail participants from clinical trials and reported in limited observational studies [33, 34]. Additionally, clinical trials designed with run-in phases exclude patients who were non-adherent or unable to tolerate the intervention drug. However, this step may inadvertently exclude people at higher risk of adverse effects and may potentially lead to ADE estimations that do not reflect general populations and/or report biased underestimates of potential medication-related harms. In the PARADIGM-HF trial, approximately 20% of participants did not complete the run-in phase and were at higher risk of lower blood pressure (odds ratio [OR] 1.11, 1.07–1.14), lower glomerular filtration rate (OR 1.49, 1.35–1.65) or more severe heart failure with increased NT-ProBNP (1.20, 1.14–1.26) [35].

The overall prevalence of ADRs and ADEs were additionally challenging to generalise due to the varying definitions of frailty across studies [36]. The reporting of prevalence can vary in the same study population depending on the wide range of frailty measurements used. In the study by Purser et al. [37], the prevalence of frailty was reported as 63% with the FI score and 27% with the phenotype criteria. Regardless of the frailty definition used, frail compared with non-frail participants had a similar direction and increased magnitude of risk associated with adverse outcomes. Frailty is an independent risk factor of heart failure and has been associated with an approximately 1.5-fold increase in death and hospitalisation [9]. Although there was a study of frail heart failure with preserved ejection fraction (HFpEF) patients aged ≥ 50 years, taking spironolactone in the TOPCAT trial, this was not included because the study population

was aged < 65 years [38]. However, the TOPCAT trial also demonstrated a similar exposure–response trend between increasing FI score and increased risk of mortality and hospitalisations. Those with higher FI scores ($\text{FI} > 0.5$) had an approximately twofold increase in cardiovascular mortality (HR 1.89, 1.24–2.89) and a fourfold increase in heart failure hospitalisations (HR 4.12, 3.00–5.65) compared with non-frail patients, with no significant difference in treatment effect on the outcomes between the frailty groups. Therefore, the findings in this review parallel the trends reported in younger frail populations, other heart failure types and drug classes [9, 38].

Although clear CONSORT guidance [39] for the appropriate reporting of harms for clinical trials exist, ADRs and ADEs were poorly represented in the literature, limiting the generalisability of the prevalence, severity and causality of ADRs and ADEs for the reported heart failure medications. This challenge is not unique to heart failure. Zorzela et al. [40] found similar limitations existed in general reporting of harms data in primary studies across all diseases. The challenges observed in non-specific disease studies were paralleled in studies of frail older heart failure populations. Older people are at increased risk of adverse events due to complex comorbidities, frailty, polypharmacy, and advanced stages of heart failure. Conversely, confounding can make it difficult to differentiate whether ADEs were due to the medication or pathology of disease progression [41, 42]. This review builds on work by Sztramko et al. [43], which found risk factors for ADEs with heart failure medications included advanced age, poor left ventricular function and increased New York Heart Association class. Although frailty was not evaluated, it supported that ADEs were poorly represented in the literature and reinforced the need to improve the characterisation and understanding of the magnitude and frequency of adverse events in this vulnerable population.

There was inconsistency between the increased risk of mortality and hospitalisation in frail compared with non-frail older patients and the general efficacy of heart failure medications to reduce mortality and hospitalisation. These factors confound our understanding of the pharmacological efficacy in older frail patients with advancing heart failure. Without factoring in frailty risk, Catananti et al. [10] found older hospitalised heart failure patients were at increased risk of developing ADRs (unadjusted OR 1.78, 1.52–2.09; adjusted OR 1.29, 1.06–1.56) compared with those without heart failure, commonly caused by diuretics, digoxin, and ACEIs. Overall, the ADRs were considered severe (52, 4.9%), moderate (508, 47.8%) and mild (499, 47%). Despite vulnerability to frequent heart failure medication adjustments and polypharmacy-related adverse effects, the reporting in frail older people of mild to moderate ADRs and ADEs (e.g., clinical symptoms, quality of

life, activities of daily living) from common heart failure medications was rare (ESM Table S5). However, there were no statistically significant differences in treatment efficacy between frailty groups reported in this review [25]. Findings highlight the uncertainty of how the potential benefits of guideline-directed medical therapy (GDMT) can be weighed against potential medication-related harms due to lack of high-quality evidence in frail older people, necessitating cautious interpretation, individualised treatment plans and close monitoring.

Strategies to rehabilitate and reverse frailty status can offer valuable opportunities to improve prognosis and customise medication management to mitigate the increased risk of adverse outcomes in frail older people with heart failure. Age and frailty are important characteristics to predict mortality and rehospitalisation [44]. Due to potential multisystem deficiencies, frailty and associated disabilities may predispose patients to decompensate at lower thresholds and increase health care utilisation, requiring more outpatient and hospital visits [8]. Identifying this risk can support frailty-based management in older heart failure patients to improve prognosis and patient tolerance, optimise medication management, or support safe withdrawal of medications [45]. With the growing complexities attributed to aging, older age and frailty are independent risk factors that should be factored into emerging research and patient-tailored interventions, particularly since frailty is a potentially reversible syndrome [46]. These patients would benefit from a referral to a heart failure specialty team to review the management of their heart failure and potential ADRs and ADEs of GDMT [47]. Adequate reporting of ADRs and ADEs is critical to delivering clear communication that supports clinicians' and patients' shared decision making to improve medication adherence and identify triggers that merit safe withdrawal of these medications. The communication and confidence between prescribers and patients can be strengthened during initiation and adjustments of medications through understanding how the balance of treatment benefits with potential medication-related harms can impact clinical outcomes [48, 49]. This complementary knowledge combines individual patient values with tailored interventions to optimise quality of life and/or accommodate palliative care [50].

There were several limitations in this study. The very low to low grades of evidence and the absence of evidence for many common potential ADRs in frail older cohorts and drug classes significantly contributed to uncertainty in the reported outcomes. For example, we were careful to draw conclusions from a single study that reported ADRs from digoxin use in two participants [23]. Furthermore, cautious interpretation was applied in studies that extrapolated characteristics from clinical trials originally designed to evaluate efficacy of aliskiren or sacubitril/valsartan compared with enalapril, but not randomised to compare efficacy and

potential harms between frailty groups. The review included data from the ATMOSPHERE [27] trial, which compared enalapril with aliskiren, even though aliskiren has limited use in practice. A meta-analysis was not performed on the few and variable outcomes, nor were subanalyses conducted by drug classes, frailty status, heart failure types, or predictors of advancing heart failure due to limited data. Therefore, we must be careful not to overestimate the impact of the findings that showed increased mortality and hospitalisation in frail older patients from these heart failure medications unless more evidence is available to adequately inform decision making on the potential harms of heart failure medications in frail older people. Both clinical trials and observational studies are necessary to fill this knowledge gap.

5 Conclusions

The complexities associated with advancing age, frailty, polypharmacy, comorbidities and complications from heart failure emphasise the importance of incorporating frailty into decision making and patient-tailored interventions. While pharmacotherapy utilisation data were collected, there remains opportunity for further evaluation and reporting on the impact of drug use patterns in frail older heart failure patients on specific and global health outcomes. Improved understanding of the prevalence, severity, causes and predictors of potential harms of these critical medications in frail older people can facilitate communication and trust between clinicians and patients and/or their careers. This may inform shared decision making on prescribing and deprescribing medications to not only optimise management of these patients but also improve the quality of decision making. We may unknowingly harm patients with frailty simply because data are limited on how they are impacted by these medications. Emerging heart failure-related clinical trials and observational study protocols should include frailty subgroups of older participants to improve reporting of efficacy and potential harms. Improvement in our understanding of the safety and potential medication-related harms of foundational therapies can support optimal prescription of and adherence with medications critical in improving clinical outcomes in vulnerable patients.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40266-022-00957-8>.

Acknowledgements The authors acknowledge the collaboration of Prof. Geoffrey Tofler for his clinical specialist advice, librarian Dr Yulia Ulyannikova for technical assistance and PRESS validation, Mr Ryan Snow for graphic design support, and the technical assistance

of Mr Jim Matthews of the Sydney Informatics Hub, a Core Research Facility of the University of Sydney.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions.

Declarations

Funding MD is supported by a grant funded by the Commonwealth of Australia for the National Health and Medical Research Council (NHMRC) Postgraduate Scholarship Grant APP1191018 awarded in 2020.

Conflicts of interest Mai H. Duong, Danijela Gnjidic, Andrew J. McLachlan, Marissa A. Sakiris, Parag Goyal, and Sarah N. Hilmer declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions MD, DG, AM and SH contributed to the study conception and design. MD performed project administration and data collection. MD and MS screened all studies and assessed the risk of bias and quality of evidence. SH and PG provided clinical expertise. The manuscript was written by MD. All authors contributed to validation of eligible studies, data analysis, and visualisation, commented on previous versions of the manuscript and approved the final draft.

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2.4 Supplementary Material

Refer to Appendix A: Chapter 2 Supplementary Materials

2.5 Research Presentations

Preliminary results were presented in oral and poster presentations as:

Duong M,H Gnjidic D, McLachlan A, Sakiris M, Goyal P, Hilmer S. A systematic review of adverse drug reactions or adverse drug events of heart failure treatment in frail older adults Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) annual conference 2021. (virtual).

Available online

Duong MH. “Poster of ADRs and ADEs from HF medications in frail older adults: a systematic review.(2021)”. ASCEPT poster presentation 2021 (virtual). Available at <https://www.youtube.com/watch?v=4Y5aKC99XSE> (last accessed on August 28, 2024)”



CHAPTER 3

3.1 Overview

Optimisation of multiple guideline-directed medical therapies (GDMT) to reduce mortality and hospitalisations in heart failure (HF) patients is a high priority among clinicians managing cardiovascular disease globally. However, in some scenarios, it may be reasonable to consider down-titration or discontinuation of GDMT agents, particularly in older adults who have an increased prevalence of multimorbidity, polypharmacy and frailty, and an increased risk of adverse drug reactions.

Chapter 3 provides a comprehensive overview from a systematic review and meta-analysis (including 33 studies) on the feasibility and safety of down-titration or discontinuation of HF-pharmacotherapy, providing data on mortality, hospitalisation, HF symptoms and adverse drug withdrawal effects. Only one observational study reported frailty status of participants who discontinued beta-blockers; but no studies reported outcomes by frailty status. Four studies, mostly of diuretics, reported outcomes in participants aged ≥ 75 years. Moderate level of evidence showed it was feasible to down-titrate renin-angiotensin system inhibitors (RASIs) in patients with chronic kidney disease and discontinue beta-blockers in patients with preserved ejection fraction, with no difference in 1-year mortality. High level of evidence showed risk of readmission and worsening heart failure need ongoing monitoring after discontinuation of diuretics or digoxin in patients with heart failure with reduced ejection fraction. Clinical decisions for individualised patient-care plans need to be informed by further clinical trials and longitudinal studies, particularly with inclusion of participants aged ≥ 75 years and outcomes reported according to objective measures of frailty.

3.2 Authorship Attribution Statement

Chapter 3 of this thesis is published as Appendix C S3:

Duong MH, Gnjdic D, McLachlan AJ, Redston MR, Goyal P, Mathieson S, Hilmer SN.

Discontinuation and Down-titration of Heart Failure Pharmacotherapy in Older People:

A Systematic Review and Meta-analysis. *British Journal of Clinical Pharmacology*;

2024;23-37. doi: [10.1002/BCP.16223](https://doi.org/10.1002/BCP.16223)

The coauthors of the paper, “Discontinuation and Down-titration of Heart Failure Pharmacotherapy in Older People: A Systematic Review and Meta-analysis”, confirm that Mai H Duong has made the following contributions:

I, Mai Duong, co-designed the study with co-authors, provided resources and software, collected, curated, validated and extracted the data, conducted analysis, visualisation and interpretation of the findings, wrote the original draft of the manuscript and revised and edited the manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Sarah N Hilmer

January 31, 2025

3.3 Manuscript: The Effect of Down-titration and Discontinuation of Heart Failure Pharmacotherapy in Older People: A Systematic Review and Meta-analysis

Authors:

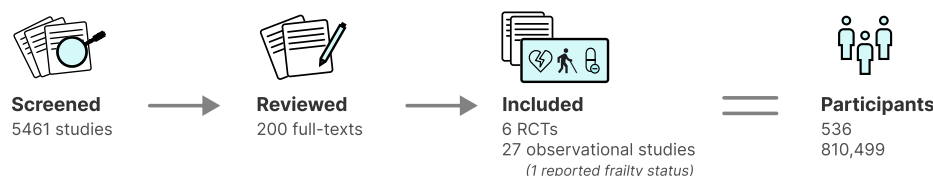
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Graphical abstract

Systematic Search



Summary of RCTs

Pharmacotherapy	Feasibility of intervention		Adverse drug withdrawal effects (ADWE)	GRADE level of evidence for ADWE
ACEI/ARB <i>in patients with HF & CKD</i>	feasible* RR 1.76 (1.14-2.73)	→	not reported Mortality RR 0.64 (0.34-1.64)	Moderate
Beta blocker <i>in patients with HFpEF</i>	feasible RR 1.00 (0.68-1.47)	→	not reported Atrial fibrillation with rapid ventricular rate RR 3.00 (0.13-70.36)	Low
Diuretic (furosemide) <i>in patients with HFrEF</i>	feasible RR 1.32 (0.72-2.43)	→	re-initiation 25% likely Worsening HF RR 3.45 (0.68-17.46)	High
Digitalis glycoside (digoxin) <i>in patients with HFrEF</i>	feasible RR 1.09 (0.89-1.35)	→	not reported Mortality RR 0.30 (0.03-2.87) Hospitalisation RR 5.48 (1.26-23.80) Worsening HF RR 5.26 (1.89-14.58)	High

Abbreviations: HF Heart Failure; ACEI/ARB Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker (ACEI/ARB), RR Risk ratio; RCT Randomised Controlled Trials; GRADE Grading of Recommendations, Assessment, Development and Evaluations; CKD Chronic Kidney Disease; HFpEF Heart Failure with preserved Ejection Fraction; HFrEF Heart Failure with Reduced Ejection Fraction

Low Moderate High GRADE level of evidence

3.3.1 Abstract

Aim: To investigate if interventions to discontinue or down-titrate heart failure (HF)-pharmacotherapy are feasible and associated with risks in older people.

Methods: A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines. Electronic databases were searched from inception to March 8th 2023. Randomised controlled trials (RCTs) and observational studies included people with HF, aged ≥ 50 years and who discontinued or down-titrated HF-pharmacotherapy. Outcomes were feasibility (whether discontinuation or down-titration of HF-pharmacotherapy was sustained at follow-up) and associated risks (mortality, hospitalisation, adverse drug withdrawal effects [ADWE]). Random-effects meta-analysis was performed when heterogeneity was not substantial (Higgins $I^2 < 70\%$). Sub-analysis by frailty status was conducted.

Results: Six RCTs (536 participants) and 27 observational studies (810,499 participants) across six therapeutic classes were included, for 3-260 weeks follow-up. RCTs were conducted in patients presenting with stable chronic HF. Down-titrating a renin-angiotensin system inhibitor (RASi) in patients with chronic kidney disease was 76% likely than continuation (Risk Ratio [RR] 1.76, 95%CI 1.14-2.73), with no difference in mortality (RR 0.64, 95%CI 0.30-1.64). Discontinuation of beta-blockers were feasible compared to continuation in preserved ejection fraction (RR 1.00, 95%CI 0.68-1.47). Participants were 25% likely to re-initiate discontinued diuretics (RR 0.75, 95%CI 0.66-0.86). Digoxin discontinuation was associated with 5.5-fold risk of hospitalisation compared to continuation. Worsening HF was the commonest ADWE. One observational study measured frailty but did not report outcomes by frailty status.

Conclusions: The appropriateness and associated risks of down-titrating or discontinuing HF-pharmacotherapy in people aged ≥ 75 years is uncertain. Evaluation of outcomes by frailty status necessitates investigation.

3.3.2 Introduction

Medication management in older adults with heart failure (HF) is complex due to disease heterogeneity, multi-morbidities, deficits across multiple health domains, changes in life expectancy and patient priorities.¹ Pharmacological management for stable chronic HF and acute decompensated HF (ADHF) are recommended by international cardiology organisations as Guideline-Directed Medical Therapies (GDMT), with strong evidence to reduce hospitalisation and improve survival in HF-patients.^{2,3} Current guideline recommendations are based on the limited evidence on clinical presentation and drug use in older people and can also lead to increased medication burden. Polypharmacy, a risk factor for adverse drug events (ADEs), is highly prevalent in people living with HF with 95% of patients taking ≥ 5 medications at hospital discharge and nearly half taking ≥ 10 medications.⁴ Frailty, prevalent in up to 75% of community-dwelling HF-patients,⁵ can reduce the ability to tolerate adverse effects.^{6,7} Up to 91% of HF-patients perceived their ADE as a chronic problem.⁸ Persistent intolerance to HF-pharmacotherapy can impact quality of life (QoL) associated with 38% likelihood of dose changes or discontinuation.⁹ Older adults report lower adherence and higher medication discontinuation rates.^{10,11}

Deprescribing, defined as the supervised withdrawal of a medication¹² with monitoring for adverse drug withdrawal effects (ADWEs), may be useful when harms outweigh benefits of treatment. With increasing recognition of the potential value of deprescribing in select settings involving patients with HF,^{13,14} it is important to understand the evidence regarding feasibility and risks of deprescribing interventions. Such evidence is critical to guide shared decision-making for older adults regarding their medication, a key priority in HF management.¹⁵ This review examined whether HF-pharmacotherapy in older

adults can be down-titrated or discontinued; and evaluate the effects on mortality, hospitalisation, HF symptoms and ADWEs, according to frailty status.

3.3.3 Methods

This systematic review was registered in PROSPERO (CRD42021285380)¹⁶ and conducted according to the PRISMA 2020 checklist.¹⁷ We searched electronic databases (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Ageline, CINAHL, PsychInfo, International Pharmaceutical Abstracts) from inception to March 8th 2023 for studies of older adults, who reduced or discontinued HF-pharmacotherapy and reported withdrawal effects. The intervention was compared to continuation of optimised maintenance doses as per usual care or placebo (Table S3.1). The complete search strategy (Table S3.2) included studies in English and was validated with the Peer Review of Electronic Search Strategies (PRESS) checklist.¹⁸ Manual searches of PROSPERO, clinicaltrials.gov, connectedpapers.com and references of screened manuscripts were performed.

Study selection

Search results were screened with Covidence software ([Melbourne, Australia](#)). Duplicates were removed using automation and manual identification. Two reviewers (MHD and MRR) independently screened titles, abstracts and full texts. Disagreements were resolved by consensus with a third reviewer (DG, AJM or SNH). Eligible studies included randomised controlled trials (RCTs), meta-analyses, or observational studies. Interventions included discontinuation or dose down-titration of a HF-GDMT (Table S3.1).^{2,3} Participants were aged ≥ 50 years or this age group was separately reported in subgroup-analysis, were diagnosed with HF and from any clinical setting. Older adults were defined with age cut-off ≥ 50 years to avoid unintended exclusion of minority high-risk groups with lower life

expectancy or participants from developing countries, based on WHO recommendations for research in older people.¹⁹ Subgroup-analysis of individuals ≥ 75 years was conducted. Self-reports, case reports/series, expert opinion, reviews, qualitative and non-human studies were excluded.

Outcomes

Outcomes were reported for medicines grouped by therapeutic class (e.g., beta-blockers) and prioritised by study design. Feasibility refers to whether the reduction in dose or cessation occurred and/or was sustained. In RCTs, interventions were ‘feasible’ if there were no statistical differences between study arms or favoured the intervention compared to control arm, with respect to (i) discontinuation or dose-reduction of HF-pharmacotherapy; and/or (ii) sustained discontinuation or dose-reduction at follow-up (risk ratio (RR) and 95% confidence intervals (95%CI) were >1). In observational studies consisting of ≥ 1 comparator groups, ‘feasibility’ of interventions was measured as the proportion of participants in whom HF-pharmacotherapy was (i) dose-reduced or discontinued and (ii) discontinuation was sustained, compared to the proportion of participants in the comparator group who continued HF-pharmacotherapy in usual care. Secondary outcomes were the number of serious adverse events (mortality, hospitalisation) and ADWEs (e.g., worsening-HF symptoms as defined by the study authors, new cardiovascular (CV) events).

Data collection and synthesis

Study and participant characteristics and outcomes were manually recorded into a piloted data form in Microsoft Excel 2014 by MHD (details in PROSPERO ([CRD42021285380](https://doi.org/10.1186/CRD42021285380)) protocol.¹⁶ A second reviewer (MRR) validated accuracy of data extracted from 50% of studies.²⁰ Study authors were contacted to confirm eligibility or obtain

missing data. Searched studies were summarised in a PRISMA 2020 flow diagram.¹⁷

Mortality, hospitalisation and ADWEs were extracted as number-of-incidences per participant. ADWEs report the proportion (%) of events in the intervention groups. Follow-up time-points were categorised as short (≤ 30 days), intermediate (5-24 weeks) and long (> 24 weeks), using the last time-point if multiple were provided.

Statistical analyses

Analysis was conducted separately for RCTs and observational studies by therapeutic class. Meta-analysis of pooled measures of treatment effect from point-estimates (e.g., RR, hazard ratio (HR), and 95%CI) were calculated using meta v7.0 in R/RStudio v4.2.2 (Boston, USA). Meta-analyses were conducted on outcomes using the random-effects model, Higgins I^2 , and Hartung-Knapp and maximum-likelihood method to calculate 95%CI and p-values. Outcome measures were pooled by therapeutic class if the level of heterogeneity was not considerable ($I^2 < 70\%$).²¹ Where substantial heterogeneity was present, narrative synthesis described study design, participant characteristics, feasibility and outcomes. Subgroup-analyses were planned according to frailty, as defined by study authors. Meta-regression was performed for study level factors: therapeutic class, HF-classification,²² HF presentation (stable chronic/acute) and aged ≥ 75 years.

Assessment of risk of bias and the certainty of the evidence

Two reviewers (MHD and MRR) independently assessed risk of bias using the Cochrane assessment tools, RoB2 for RCTs and ROBINS-I for observational studies.^{23,24} Sensitivity analysis on outcomes were conducted removing high risk of bias studies. The quality level of evidence was assessed using the Grading of Recommendations, Assessment,

Development and Evaluations (GRADE) approach (Table S3.6).²⁵ GRADEpro GDT software (Hamilton, Canada) generated the effect and certainty of evidence for each outcome.

3.3.4 Results

Thirty-three studies (participants(n) = 797,690), consisting of six-RCTs (n = 532) and 27 observational studies (n = 797,158), were included (Figure S3.1). Most studies were conducted in Europe (17 studies) and North America (12 studies), three in low-to-middle income countries, and both Europe and North America (1 study). One observational study reported frailty status. Studies of discontinuation (32 studies) and/or down-titration (five studies) of HF-pharmacotherapy had short (seven studies), intermediate (seven studies) and long (19 studies) follow-up time-points (Table 3.1).

Participant characteristics

Studies evaluated patients with HF with reduced ejection fraction (HFrEF) (12 studies, n = 407,492), HF with preserved ejection fraction (HFpEF) (five studies, n = 516), or unspecified (undifferentiated single or combination) HF-classifications (16 studies, n = 389,682), which include combinations with HF with mildly-reduced ejection fraction (HFmrEF) (two studies, n = 118). Patients with stable chronic HF (23 studies, n = 764,455) were mainly living in or discharged to community settings; while those with ADHF were all in hospital settings (10 observational studies, n = 33,235). In RCTs and observational studies, the mean age (years) was 61-78 and 64-84 (median 67-87), respectively. Four observational studies (n = 12,944) mostly of diuretics, reported outcomes in participants ≥ 75 years (Table S3.4).

Risk of bias and certainty of evidence

Risk of bias was assessed as low in three-studies (9%), moderate in seven-studies (21%), high in 14-studies (42%) and serious in nine-studies (28%) (Figure S3.7).²⁶⁻³² Ten studies were industry funded (30%) (Table S3.3). GRADE quality of evidence was deemed higher for mortality, hospitalisation and worsening-HF outcomes; and lower for ADWEs (Table S3.6c).

Outcomes

Feasibility results are summarised for RCTs in Figure 3.1 and for observational studies in Figure S3.2 and Figure S3.3. There were too few RCTs to pool mortality and hospitalisation. Risk of hospitalisation for people with HFrEF in observational studies are summarised in Figure 3.2. ADWEs are summarised in Table 3.2.

(i) Angiotensin-converting enzyme inhibitor(ACEI)/Angiotensin receptor antagonist(ARB)

RCTs. A single-centre unblinded RCT³³ ($n = 47$) examined down-titrating the dose of enalapril or losartan by 50% compared to maintaining the optimised dose per usual care. The study included hospitalised patients ≥ 50 years with unspecified chronic HF, New York Heart Association class I-III, chronic kidney disease (CKD) (creatinine clearance $< 60 \text{ ml/min/1.63 m}^2$) and anaemia. It was feasible to down-titrate the ACEI/ARB. Participants in the intervention group ($n = 30$) were 76% more likely to down-titrate their ACEI/ARB than to continue their optimised dose (RR 1.76, 95%CI 1.14 to 2.73, 1 trial). There was no statistical difference in 1-year mortality (RR 0.64, 95%CI 0.30 to 1.64, 1 trial, moderate-quality evidence). No participants were hospitalised nor reported worsening-HF. No eligible RCT of angiotensin receptor-neprilysin inhibitor (ARNI) was identified.

Six **observational studies**^{10,34-38} ($n = 19,704$) of ACEI/ARB discontinuation in registry HFpEF patients with ADHF showed no statistical difference in 1-year readmission compared to continuation (HR 1.10, 95%CI 0.97 to 1.24, two studies, $n = 19,704$, $I^2 = 0\%$, high-quality evidence, Figure 3.2).^{35,37} One-year mortality risk was 65% higher in those that discontinued ACEI/ARBs compared to continued (RR 1.65 95%CI 1.39 to 1.96, two-studies, $I^2 = 65\%$, moderate-quality evidence study, Figure S3.4b).^{35,37} ADWEs in one registry³⁶ ($n = 374,580$) of ambulatory-cardiology care were orthopnoea (16.8%, rate ratio 2.8) and dyspnoea (19.1%, rate ratio 3.4) after discontinuation or down-titration of ACEI/ARBs ($n = 241,230$) or beta-blockers ($n = 262,206$).

(ii) Beta-blockers

RCTs. A multi-centre unblinded crossover trial³⁹ ($n = 52$) of community-dwelling patients with stable chronic HFpEF and chronotropic incompetence, examined discontinuing beta-blockers compared to maintaining the optimised dose per usual care. It was feasible to taper, then discontinue a beta-blocker for 15-days, with no statistical differences between the proportion in discontinuation and continuation groups (RR 1.00, 95%CI 0.68 to 1.47, one trial). After completion of the crossover trial, 88% ($n = 46$) remained on a lower dose or discontinued their beta-blocker due to improved functional capacity during discontinuation. There was no difference in hospitalisation during the intervention period. One participant in each intervention arm experienced atrial fibrillation (AF) with rapid ventricular rate (successfully cardioverted) after discontinuation and withdrew from the study (RR 3.00, 95%CI 0.13 to 70.36, one-trial, low-quality evidence). After six-months, three participants with unspecified CV-events were hospitalised; none died.

Ten **observational studies**^{10,26,38,40-45} ($n = 363,784$) reported similar findings in people with HFpEF⁴⁴ but increased risk in HFrEF. Discontinuation of beta-blockers in hospitalised HFrEF patients with ADHF showed 2-fold risk of mortality (RR 2.06, 95%CI 1.31-3.24, five-studies, $n = 178,849$, $I^2 = 69\%$, very low-quality evidence, Figure S3.4b)^{26,40,42,43,45} and 7% increased risk of 1-year readmission compared to continuation (HR 1.07, 95%CI 1.02 to 1.13, 2-studies, $n = 357,782$, $I^2 = 3\%$, moderate-quality evidence, Figure 3.2)^{41,45} and no statistical difference in risk of 8-52-week hospitalisation (RR 1.00, 95% CI 0.84 to 1.19, four-studies, $n = 362,136$, $I^2 = 69\%$, very low-quality evidence, Figure S3.6b).^{26,41,42,45} ADWEs included ventricular arrhythmia ($n = 8$, 5%), AF ($n=44$, 3%), acute coronary artery syndrome ($n = 12$, 8%) and syncope ($n = 3$, 2%); but no significant change in activities of daily living (ADLs).

Frailty was reported in one-observational study⁴⁵ ($n = 357,030$), defined as frailty index >0.25 . In hospitalised HFrEF American Medicare patients ≥ 65 years, 23% ($n = 83,353$) were frail. Overall, 21% ($n = 73,869$) of participants discontinued a beta-blocker. Outcomes were not reported by frailty status.

(iii) Diuretics

RCTs. Two unblinded RCTs ($n = 234$), one single²⁹ and one multi-centered,³¹ examined discontinuation of furosemide among community-dwelling patients ≥ 65 years with stable chronic unspecified HF-classification and HFpEF. The proportion of participants that discontinued versus continued diuretics could not be pooled ($I^2 = 78\%$). Participants that discontinued a diuretic were 25% likely to re-initiate furosemide within 26-weeks (RR 0.75, 95%CI 0.66 to 0.86, two-trials, $I^2 = 0\%$). No deaths or hospitalisations occurred. There was no statistical difference in worsening-HF symptoms between study arms (RR 3.45, 95%CI 0.68 to 17.46, two-trials, $I^2 = 48\%$, moderate-quality evidence).

Eight **observational studies**^{30,36,38,46-50} ($n = 237,328$) reported similar feasibility and risk of worsening-HF. In two before-and-after studies ($n=37$), 25% (HFrEF)⁴⁶ and 55% (HFpEF)⁴⁸ of participants discontinued and did not re-initiate their diuretic after 3-26-weeks. No hospitalisation or death occurred (Table S3.5). ADWEs included worsening-HF symptoms of oedema ($n = 344$, 30%), hypertension ($n = 267$, 8%), myocardial infarction ($n = 33$, 3%), stroke ($n = 33$, 3%), and peripheral oedema ($n = 267$, 7%). One study³⁶ ($n = 224,748$) reported orthopnoea (8.8%, rate ratio 2.3) and dyspnoea (10.6%, rate ratio 3.0) after reducing or discontinuing a diuretic.

(iv) *Digitalis glycosides (digoxin)*

RCTs. A blinded multi-centre RCT²⁷ ($n = 178$) examined 12-week discontinuation of digoxin compared to continuation in stable chronic HFrEF (LVEF<35%) patients with reduced exercise capacity for >3 months on optimised doses of ACEI. There were no statistical differences in the proportion of participants in both study arms (RR 1.09, 95%CI 0.89 to 1.35, one-trial), nor all-cause mortality (RR 0.30, 95%CI 0.03 to 2.87, one trial, high-quality evidence). Participants that discontinued digoxin had 5.5-fold risk of hospitalisation (RR 5.48, 95%CI 1.26 to 23.80, one trial, high-quality evidence) and 5.3-fold risk of worsening-HF (RR 5.26, 95%CI 1.89 to 14.58, one trial, high-quality evidence).

A single-centre double-blind crossover trial⁵¹ ($n = 21$) of outpatients with stable chronic unspecified HF were randomised to take digoxin and placebo for two consecutive 12-week periods. Fourteen (67%) participants remained off digoxin and seven (33%) failed to complete both treatment periods due to worsening-HF (placebo $n = 4$; digoxin $n = 1$), supraventricular tachycardia (placebo $n = 1$) and digoxin toxicity (digoxin $n = 1$). One (5%)

participant died from oedema and MI. Three (14%) participants withdrew early from worsening-HF during the first treatment phase while taking digoxin ($n = 1$) and placebo ($n = 2$).

Four **observational studies**^{28,52-54} ($n = 1,451$) reported similar feasibility, hospitalisation and worsening-HF. In aged care residents with HFpEF and hospital patients with HFrEF,^{28,53} it was feasible to discontinue digoxin, with no statistical difference compared to continued use (RR 1.12, 95%CI 0.77 to 1.64, two-studies, $n = 1,419$, $I^2 = 50\%$). HFrEF patients²⁸ showed no statistical difference in 4-year mortality (HR 1.09, 95%CI 0.96 to 1.23, one study, $n = 1,396$, high-quality evidence, Figure S3.6a) and 16% increased hospitalisation between those who discontinued and continued digoxin (HR 1.16, 95%CI 1.03 to 1.30, one study, $n = 1,396$, moderate-quality evidence, Figure S3.6b). ADWEs included worsening-HF symptom of oedema ($n = 231$, 22%), sinus tachycardia ($n = 219$, 2%), MI ($n = 199$, 1%), AF ($n = 199$, 2%), unstable angina ($n = 178$, 1%) and upper respiratory tract infection ($n = 32$, 16%); but no significant changes in ADLs.

(v) Mineralocorticoid receptor antagonists (MRA)

No eligible RCT was identified.

Five **observational studies**^{10,32,38,55,56} ($n = 30,385$) on discontinuing spironolactone or eplerenone in community-dwelling HFpEF and HFrEF patients could not pool feasibility ($I^2 = 99\%$) and mortality ($I^2 = 98\%$). ADWE included 6% increased risk of major CV-events (e.g., CV-death, MI, stroke, HF) (HR 1.06, 95% CI 1.01 to 1.12, one study, $n = 3,955$, moderate-quality evidence).⁵⁵

(vi) Sodium-glucose cotransporter-2 inhibitors (SGLT2-i)

No eligible RCT was identified.

Two **observational studies**^{38,57} ($n = 5,525$) on discontinuing SGLT2-i were scarce. In a single-centre study⁵⁷ ($n = 86$) of patients across HF-classifications and presentations, participants were 46% more likely to continue than discontinue SGLT2-i (RR 0.54, 95%CI 0.39 to 0.74), with no statistical difference for re-initiation within 1-year of discontinuation (RR 1.10, 95%CI 0.98 to 1.24). There was no statistical difference in 1-year mortality (HR 0.71, 95% CI 0.16-3.16, one study, low-quality evidence, Figure S3.4a) and hospitalisation between study arms (RR 1.73, 95%CI 0.94 to 3.19, one study, low-quality evidence, Figure S3.5).⁵⁷ ADWE of increasing diuretic dose was 17% more likely in discontinued SGLT2-i compared to continuation (HR 1.17, 95%CI 1.01 to 1.32, one study, low-quality evidence).⁵⁷

3.3.5 Discussion

In situations where optimisation of GDMT is not tolerated, these findings provide a roadmap of the current knowledge on deprescribing HF-pharmacotherapy in adults ≥ 50 years. Outcomes are unknown in frail adults ≥ 75 years, precluding recommendations for this sub-population. During stable chronic HF, evidence from limited RCTs demonstrate down-titration of ACEI/ARBs in patients with CKD and discontinuation of beta-blockers in HFpEF was feasible and not associated with increased risk of 1-year mortality and hospitalisation. Decisions to discontinue diuretics or digoxin may want to consider potential risks of worsening-HF and hospitalisation.

Similar to efficacy-trials, the population in this review are mostly younger, more robust and overrepresent HFrEF compared to real-world treatment populations with multiple comorbidities, polypharmacy, cognitive impairment and variable access to healthcare

services⁵⁸. In single-agent HF-trials, up to 85% of participants experience ≥ 1 adverse event, but discontinuation rates did not differ from placebo.⁵⁹ Inclusion of frail adults ≥ 75 years, with objective frailty measures in HF-trials would help inform the appropriateness to continue or discontinue current and emerging therapies.^{6,60-64} RCTs and larger scale studies are needed to evaluate discontinuation of contemporary HF-pharmacotherapies.³

The shift in focus on providing symptomatic relief in HF, improving QoL and daily function, can take priority over longevity in frail older adults who may not tolerate or achieve target doses recommended from clinical trials.^{65,66} Only half of adults ≥ 80 years reached target doses^{10,11} and as low as 1.68% reached median beta-blocker target doses.⁶⁷ ACEI/ARB adherence is 10% lower (69%) and discontinuation is 10% higher (51%) in adults ≥ 80 years compared to those < 65 years.¹⁰ Reasons to deprescribe can include uncertain benefit, new contraindications, non-tolerable ADEs, nonadherence, interactions with acute/chronic disease, drug-interactions, geriatric outcomes or GDMT-optimisation (e.g., diuretic tapering).⁶⁸ Some patients may prioritise decreasing medication burden over benefits of HF-pharmacotherapy.

Limited RCTs demonstrate a potential role for down-titrating ACEI/ARBs³³ and discontinuing beta-blockers³⁹ in select situations. Data suggests that down-titrating ACEI/ARBs in the setting of CKD may improve serum creatinine levels, without much short-term harm. However, existing data cannot address whether reducing doses of ACEI/ARB in people with CKD will ultimately preclude the long-term benefits of high-dose ACEI/ARB. While beta-blockers are not indicated in patients with HFpEF,^{2,3} data on effects of deprescribing beta-blockers after chronic therapy is needed.⁶⁹ Caution must be exercised when deprescribing diuretics and digoxin in frail stable chronic HF-patients ≥ 75 years to

weigh ADEs (e.g., falls, hospitalisation, fatigue) with potential ADWEs (e.g., hospitalisation, CV-events, worsening-HF) that require ongoing monitoring.^{6,70}

Discontinuation of beta- blockers in HFrEF patients with ADHF is not recommended due to increased risk of mortality and readmission.

Strengths and Limitations

This novel review evaluates ADWEs and frailty status during deprescribing of HF- pharmacotherapy in older adults, which should be considered with the benefits and adverse effect(s) rationalising discontinuation.^{6,59,71} Compared to previous works focussed on deprescribing of anti-hypertensives medications in older people in 2020⁷² or of HF medications in people with stable chronic HFrEF in 2012,⁷³ this review evaluated studies of all HF phenotypes; and also sub-analyses by age ≥ 75 years and frailty. This comprehensive review included studies over a range of years and includes medication classes that may no longer be prioritised in contemporary guidelines (e.g. digoxin). The degree of inclusion of frail people and the impact on clinical outcomes is unknown. The mean study age does not reflect advanced age ≥ 80 years, warranting attention in prospective research. There was limited reporting of QoL and ADLs; and no data on falls and confusion.

Low generalisability and substantial heterogeneity reflect the complexity of individualising HF-pharmacotherapy. Interpretation is particularly limited for drug classes with low number of clinical trials and observational studies such as SGLT2-i, MRAs and ARNIs. This is an area of increasing research focus, and there may be benefit of repeating this review in the near future, when additional trials currently registered are completed and published, especially for contemporary and emerging HF treatments. (e.g., SGLT2-i,

ARNIs, soluble guanylate cyclase stimulators, inotropes). Moreover, existing research does not distinguish whether outcomes were caused by changes in HF-pharmacotherapy or disease progression. HF phenotypes were reported alongside results to mitigate bias of interpretation in this review, particularly for studies with combination HF phenotypes (e.g., HF_rEF, HF_mrEF, HF_pEF) where outcomes were not reported separately by authors. Non-adherence, planned deprescribing, tapering regimens or palliative care plans could not be differentiated in observational studies.⁷⁴ Interpretation of data was limited by reporting/selection bias and confounding of exposure time-points/outcomes, education and socioeconomic or health status; and did not discern baseline function between groups.⁷⁵

3.3.3 Conclusion

Interventions must be considered within the holistic context of patient needs and priorities; given the benefit of the HF-pharmacotherapy and risks of underuse will vary between and within patients over time. Few RCTs suggest stable chronic HF-patients ≥ 50 years may down-titrate ACEI/ARBs in CKD or discontinue beta-blockers in HF_pEF. Effects of deprescribing HF-pharmacotherapy remain uncertain in frail adults ≥ 75 years due to the limited number of studies with high level of evidence. RCTs and longitudinal studies of current and novel HF-pharmacotherapies that include objective measures of frailty at baseline are needed to evaluate deprescribing outcomes that are important to older adults, especially among those with frailty.

3.3.7 Author contribution statement

Mai H Duong: conceptualisation, methodology, software, validation, formal analysis, investigation, resources, data curation, original manuscript preparation & editing, visualisation, project administration, funding acquisition. **Danijela Gnjidic:** supervision, conceptualisation, methodology, validation, manuscript review & editing. **Andrew J McLachlan:** supervision, conceptualisation, methodology, validation, manuscript review & editing. **Mitchell R Redston:** validation, formal analysis, investigation, manuscript review & editing. **Parag Goyal:** methodology, manuscript review & editing. **Stephanie Mathieson:** methodology, visualisation, manuscript review & editing. **Sarah N Hilmer:** supervision, conceptualisation, methodology, validation, manuscript review & editing.

3.3.8 Acknowledgements

We acknowledge the collaboration of Mr Ryan Snow for graphic design support, librarian Dr Yulia Ulyannikova for technical assistance and PRESS validation, and the technical assistance of Mr Jim Matthews of the Sydney Informatics Hub, a Core Research Facility of the University of Sydney.

3.3.9 Funding

This work was supported by the Commonwealth of Australia National Health and Medical Research Council (NHMRC) Postgraduate Scholarship 2020 (grant APP1191018 to MHD); Heart Research Australia (HROz) Postgraduate Scholarship 2023/2024 to MHD; American Heart Association (grant 20CDA35310455 to PG); National Institute on Aging (grant K76AG064428 to PG), and Junior Investigator Intensive Program of the US

Deprescribing Research Network, funded by the National Institute on Aging (R24AG064025) to PG.

3.3.10 Disclosure of interest

None declared. MHD, DG, SNH, SM, are members of the Australian Deprescribing Network (ADeN) and PG is a member of the United States Deprescribing Network (USDeN).

3.3.11 Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Table 3. 1: Study characteristics

Study Name	Country, Setting, Prospective (P)	HF classification, presentation	Deprescribing Intervention	Sample size (n, %) Intervention Continue	Age (years) Mean (SD) or *Median (IQR)	Female (n, %)	Follow up (weeks)	Main Outcomes	Quality Rating
Randomised Controlled Trials (RCTs)									
Guideline-Directed Medical Therapies (GDMT) for heart failure									
Angiotensin-converting enzyme inhibitor or Angiotensin receptor blocker (ACEI/ARB)									
Pita-Fernandez 2014 ³²	Spain, single centre, hospital, P	unspecified, stable chronic	Reduce	30, 64% 17, 36%	78 (8) 74 (6)	30, 64%	52	mortality, clinical/lab outcomes	1
Beta-blocker									
Palau 2021 ³⁸ (PRESERVE-HR)	Spain, multi centre, hospital outpatient clinic, P	HFpEF (LVEF>50%), stable chronic	discontinue (tapered)	26, 50% 26, 50%	*77(72-80) *73 (68-77)	31, 60%	4.3 25	exercise HR, peak VO ₂ , VO ₂ %, MMSE, MoCA, MLHFQ, mortality, CV admissions	1
Diuretics									
VanKraaij 2000 ³⁰	Netherlands, multi centre, hospital, community, P	HFmrEF/HFpEF, stable chronic	discontinue	21, 66% 11, 34%	75 (4)	17, 53%	12	HF score, HF symptoms, 6MWT, BP, weight, FEV1	1
Walma 1997 ²⁸	Netherlands, single centre, community, P	unspecified, stable chronic	discontinue	102, 50.5% 100, 49.5%	76 (1) (>65)	151, 75%	26	HF symptoms, BP, HR, SOB, oedema, symptoms	1
Other treatments for heart failure:									
Digitalis glycoside (digoxin)									
Packer 1993 ²⁶ (RADIANCE)	USA, Canada, multi centre/setting, P	HFpEF, stable chronic	discontinue	3, 52.2% 85, 47.8%	59(1)	42, 24%	12	mortality, hospitalisation, frequency/reasons, worsening HF, symptoms, ADEs, exercise, NYHA, QoL	1
Taggart 1983 ³⁰	Ireland, single centre, aged care, P	unspecified, stable chronic	discontinue	19, 90.5% 21, 100%	66 (8)	8, 38.1%	12	MI, HF, digitalis toxicity, tachycardia, NYHA class	1

Abbreviations: HF = heart failure; LVEF = left ventricular ejection fraction; HFpEF = heart failure with preserved ejection fraction (LVEF>50%), HFmrEF = heart failure with mildly reduced ejection fraction (LVEF 41%-49%); HFimpEF = heart failure with improved ejection fraction (improved to LVEF>40%); ADHF= acute decompensated heart failure; NYHA=New York Heart Association; ADEs=adverse drug events; CV=cardiovascular; MI=myocardial infarction; QoL=quality of life; BP=blood pressure; 6MW=6-minute walk test; ECG = echocardiogram; LVEDD; HR heart rate; SOB= shortness of breath; Scr=Serum creatinine; PEP/LVET=pre-ejection period/left ventricular ejection time; BNP=B-type natriuretic peptide ; NT-proBNP=N-terminal pro-B-type natriuretic peptide; eGFR=estimated glomerular filtration rate, ADRD=Alzheimer's disease or a related dementia; AHD=atherosclerotic heart disease; CRT=cardiac resynchronisation therapy; MLHFQ=Minnesota living with heart failure questionnaire; MoCA=Montreal cognitive assessment; VO₂=Oxygen consumption attainable during physical exertion; MMSE=Mini-Mental State Examination. Note: Quality Rating was adapted from Oxford Centre for Evidence-based Medicine for ratings of individual studies.

Table 3.1: Study characteristics (*continued....2*)

Study Name	Country, Setting, Prospective (P)	HF classification, presentation	Intervention	Sample size (n, %)		Age (years) Mean (SD) or *Median (IQR)	Female (n, %)	Follow up (weeks)	Main Outcomes	Quality Rating
Observational studies										
GDMT for heart failure										
Angiotensin-converting enzyme inhibitor or Angiotensin receptor blocker (ACEI/ARB)										
Gilstrap 2017 ³⁴ (GWTG-HF)	USA, single centre, hospital	HFrEF, ADHF	discontinue	308, 2% 9572, 60%	16,052	78 (8)	6718, 42%	52	mortality, readmission, composite (30d, 90d, 1yr)	3
Mathew 2021 ³⁶	USA, multi centre, hospital	HFrEF, ADHF	discontinue	717 1715	3652	72 (11) 71 (10)	59, 1.6%	52	Mortality, readmission, worsening renal function	4
Nicholls 1982 ³³	New Zealand, single centre, hospital, P	Unspecified, stable chronic	discontinue	5, 100%	5	54-73	1, 20%	4	NYHA, haemodynamics, hormones, clinical effects	3
Beta-blocker										
Brouse 2006 ³⁹	USA, single centre, hospital	HFrEF/HFpEF, ADHF	discontinue, reduce	21, 28% 19, 25% 26, 34%	76	*67 (57, 83) *67 (59, 82) *67(58, 82)	1, 5%	52	mortality, arrhythmias, LOS, HF readmission, worsening HF indicators	3
Fonarow 2008 ²⁵ (OPTIMIZE-HF)	USA, multi centre, hospital	HFrEF, ADHF	discontinue	79, 3% 1350, 57%	2364	69 (13)	977, 41%	12	60-90-day mortality, readmission	3
Gilstrap 2023 ⁴⁴	USA, multi centre, hospital	HFrEF, stable chronic	discontinue	73869, 21% 110914, 31%	357030	(all ≥65) 79.2	182,085, 51%	52	90-day,1 year mortality and readmission, frailty status	3
Metra 2007 ⁴⁰ (COMET)	Europe, multi centre, hospital	HFrEF, ADHF	discontinue, reduce	61, 8% 162, 22% 529, 70%	752	64 (11)	180, 24%	232	all-cause mortality, readmission, predictors	3
Miro 2016 ⁴¹ (BETAWIN-AHF)	Spain, multi centre, hospital	HFrEF/HFpEF, ADHF	discontinue	1460, 73% 530, 27%	1990	78 (10)	1103, 55%	8	mortality, rehospitalisation	3
Nambiar 2020 ⁴³	USA, single centre, rehab/ cardiac clinic, P	HFpEF, stable chronic	discontinue, switch	22, 100% 11, 50%	22	77 (8)	16, 73%	52	NT-proBNP	3
Orso 2009 ⁴²	Italy, multi centre, hospital	unspecified, ADHF	discontinue	141, 9% 362, 23%	1572	72 (11)	577, 37%	12	all-cause mortality, clinical events, LOS	3

Table 3.1: Study characteristics (*continued....3*)

Study Name	Country, Setting, Prospective (P)	HF classification, presentation	Intervention	Sample size (n,%)		Age (years) Mean (SD) or *Median (IQR)	Female (n, %)	Follow up (weeks)	Main Outcomes	Quality Rating
				Intervention	Total					
Mineralocorticoid receptor antagonist (MRA)										
Ferreira 2020 ³¹ (TOPCAT)	USA, Canada, Brazil, Argentina, multi centre/setting	HFpEF (LVEF>45%), stable chronic	discontinue, placebo	225, 25%	386	<75 114/1020 (23)	187, 48%	52	mortality, hospitalisation, hypokalaemia, renal function, BP, QoL	3
			discontinued subgroup	161, 18%		>75 111/747 (28)				
Jonsson-Holmdahl 2022 ⁵⁵	Sweden, single centre, hospital	HFrEF (LVEF<40%), ADHF	discontinue	297, 52% 275, 48%	572	77 (12) 72 (11)	178, 31%	260	Mortality, frequency of discontinuation and reasons	3
Trevisan 2021 ⁵⁴ (SCREAM)	Sweden, multi centre/setting	unspecified, stable chronic	discontinue	1519, 30% 2436, 48%	3955	*79 (71,85)	1740, 44%	24	mortality, CV event, fracture, hyperkalaemia	3
Sodium-glucose cotransporter-2 inhibitor (SGLT2-i)										
Nakagaito 2021 ⁵⁶	Japan, single centre, hospital, P	HFrEF/HFmr EF/ HFpEF, ADHF	discontinue	30, 35% 56, 56%	86	72 (12)	31, 36%	52	mortality, HF hospitalisation, BNP, eGFR, ADEs	2
Diuretics										
Braunschweig 2002 ⁴⁵	Sweden, multi centre/setting, P	HFrEF, stable chronic	discontinue	4, 100%	4	65 (8)	-	3	6MWT, QoL, Doppler ECG	3
DeVore 2015 ²⁹ (ASCEND-HF)	Americas, Europe, Asia Pacific, multi centre, hospital	HFrEF/HFpEF, ADHF	discontinue, reduce	213, 4% 583, 10% 1912, 31%	6119	*69 (57, 78) *68 (57, 77) *67 (56, 77)	2089, 34%	4	mortality, 30-day readmission, dyspnoea, dose change post discharge	3
			discontinue, reduce	296, 46% 126, 19% 137, 21%	648	71 (11) 73 (10) 73 (11)	214, 33%	36	mortality, HF readmission, BP, SCr, NYHA, LVEF, LVEDD, successful withdrawal	3
Martens 2017 ⁴⁶	Belgium, single centre, hospital	HFrEF/HFimp EF, stable chronic (post CRT)	discontinue, reduce	296, 46% 126, 19% 137, 21%	648	71 (11) 73 (10) 73 (11)	214, 33%	36	mortality, HF readmission, BP, SCr, NYHA, LVEF, LVEDD, successful withdrawal	3
Straand 1993 ⁴⁷	Norway, multi centre, community, P	HFpEF, stable chronic	discontinue	18, 55% 15, 45%	33	(all ≥75) *82 (75, 95)	25, 76%	26	severe ADE, causality of restart / discontinue, severity	3
vanKraaij 1997 ⁴⁸	Netherlands, multi centre, hospital	unspecified, stable chronic	discontinue	74, 28% 186, 72%	260	(all ≥75) *82 (75, 102)	-	52	diuretic free after 1-year	3
vanKraaij 1998 ⁴⁹	Netherlands, multi centre, aged care	unspecified, stable chronic	discontinue	23, 30% 54, 70%	77	(all ≥75) 84 (6)	62, 80%	52	mortality, hospitalisation	3

Table 3.1: Study characteristics (*continued...4*)

Study Name	Country, Setting, Prospective (P)	HF classification, presentation	Intervention	Sample size (n,%) Intervention Continue	Total (n,%)	Age (years) Mean (SD) or *Median (IQR)	Female (n, %)	Follow up (weeks)	Main Outcomes	Quality Rating
Other treatments for heart failure:										
Digoxin glycoside (digoxin)										
Dall 1970 ⁵¹	Scotland, multi centre/setting, P	unspecified, stable chronic	discontinue	12, 15% HF subgroup	12	*74 (58, 99)	62, 78%	12	HF, respiratory infection, anaemia, AHD	3
Forman 1991 ⁵²	USA, multi centre, aged care, P	HFrEF, stable chronic	discontinue	14, 60.9% 9, 39.1%	23	*87 (65, 101)	33, 70%	9	ejection fraction, sinus rhythm	3
Malik 2019 ²⁷ (OPTIMIZE-HF)	USA, multi centre, hospital	HFrEF (LVEF<45%), stable chronic	discontinue	698, 50% 698, 50%	1396	76 (11)	566, 40.5%	208	mortality, hospitalisation	3
Sommers 1981 ⁵³	South Africa, single centre, community, P	HFrEF(LVEF <45%), stable chronic	discontinue	20, 100%	20	*73 (52, 84)	14,70%	5	HF, tachycardia, ECG, chest infection, PEP/LVET ratios	3
Combination treatments										
Allen 2018 ³⁵ (PINNACLE)	USA, multi centre, hospital	HFrEF/HFpEF stable chronic	discontinue /reduce ACEI/ARB beta-blocker diuretic	241,230, 64% 262,206, 70% 224,748, 60%	374580	(≥65 subgroup) 77 (8)	175 303, 47%	52	NYHA class, dyspnoea, orthopnoea, signs	4
Garred 2022 ¹⁰	Denmark, multi centre, hospital or HF clinic	HFrEF, stable chronic	discontinue ACEI/ARB beta-blocker MRA	-	20033 13746 6287	(65-79 subgroup) *73 (69-76) (≥80 subgroup) *84 (82-87)	9862, 33%	260	mortality, hospitalisation, average daily target dose, adherence, discontinuation	3
Sammour 2022 ³⁷	USA, multi centre, cardiology clinics	HFrEF, stable chronic	discontinue ACEI/ARB beta-blocker MRA, SGLT2-I diuretic	-	5439	68 (14)	1849, 34%	52	HF-pharmacotherapy initiation or discontinuation	4

Abbreviations: HF = heart failure; LVEF = left ventricular ejection fraction; HF+EF = heart failure with reduced ejection fraction (LVEF<40%), HFpEF = heart failure with preserved ejection fraction (LVEF>50%), HFmrEF = heart failure with mildly reduced ejection fraction (LVEF 41%-49%); HFimpEF = heart failure with improved ejection fraction (improved to LVEF>40%); ADHF= acute decompensated heart failure; NYHA=New York Heart Association; ADEs=adverse drug events; CV=cardiovascular; MI=myocardial infarction; QoL=quality of life; BP=blood pressure; 6MW=6-minute walk test; ECG = echocardiogram; LVEDD; HR heart rate; SOB= shortness of breath; Scr=Serum creatinine; PEP/LVET=pre-ejection period/left ventricular ejection time; BNP=B-type natriuretic peptide ; NT-proBNP=N-terminal pro-B-type natriuretic peptide; eGFR=estimated glomerular filtration rate, ADRD=Alzheimer's disease or a related dementia, AHD=atherosclerotic heart disease; CRT=cardiac resynchronisation therapy; MLHFQ=Minnesota living with heart failure questionnaire; MoCA=Montreal cognitive assessment; VO₂=Oxygen consumption attainable during physical exertion; MMSE=Mini-Mental State Examination. Note: Quality Rating was adapted from Oxford Centre for Evidence-based Medicine for ratings of individual studies.

Table 3.2: Summary of adverse drug withdrawal effects from discontinuing or down-titrating heart failure -pharmacotherapy in older people
Adverse drug withdrawal effects **No. of studies** **Study design** **No. events/sample, proportion (%)** **Control** **Total sample** **Point estimate and 95%CI; or score and p-value** **GRADE quality of evidence**

Guideline-directed medical therapies (GDMT) for heart failure							
Angiotensin-converting enzyme inhibitor or Angiotensin receptor blocker (ACEI/ARB)							
Worsening HF	1	NR	1/5	20%	-	5	Very low
Beta-blocker							
Worsening HF	1	NR	48/61	79%	475/529	590	High
Ventricular arrhythmia	2	NR	8/162	5%	27/388	1648	Very low
	1*	NR	2/19	11%	2/26	76	Very low
Atrial fibrillation with rapid ventricular rate	3	R & NR	45/1674	3%	109/1648	1674	Very low to low
	1*	NR	1/19	5%	1/76	76	Very low
acute coronary syndrome	1	NR	12/141	9%	42/362	1572	Moderate
Other:	2	NR	ADLs 78.7(25.5)	ADLs 79.6(23.3)	-	1572	Low to moderate
Barthel Index for ADLs, syncope, cognition (MMSE, MOCA), MQoLHF			syncope 3/141, 2% baseline MMSE 28(2) baseline MoCA 22(4) baseline MQoLHF 25(13-35)	syncope 16/362, 4% baseline MMSE 27(3) baseline MoCA 20(5) baseline MQoLHF 27(11-40)	- MMSE 28, p=0.929 MOCA 23, p=0.420 physical 22, RR -1.8(-4 - 0.4), emotional 27 RR-2.4 (-4.7 - -0.01)		
Sodium-glucose cotransporter-2 inhibitor (SGLT2-i)							
Escalating diuretic	1	NR	-	-	-	86	Low
Diuretic							
Worsening HF/Oedema	2	R	27/123	22%	5/111	234	Moderate
	2	NR	26/56	47%	0/87	110	Very low
Hypertension	2	R	10/123	8%	5/111	234	Low
	1	NR	3/33	9%	0/33	33	Very low
Myocardial infarction	1	NR	1/33	3%	0/33	33	Very low
Stroke	1	NR	1/33	3%	0/33	33	Very low
Other							
Oedema (peripheral)	2	R	8/123	7%	1/111	234	Low
	1	NR	3/33	9%	0/33	33	Very low
Dyspnoea (shortness of breath)	1	R	6/102	6%	0/100	202	Moderate
Other: anxiety, malignancy, MQoLHF	1	NR	3/33	3-6%	0/33	33	Very low
							MQoLHF: baseline 12, stop 9

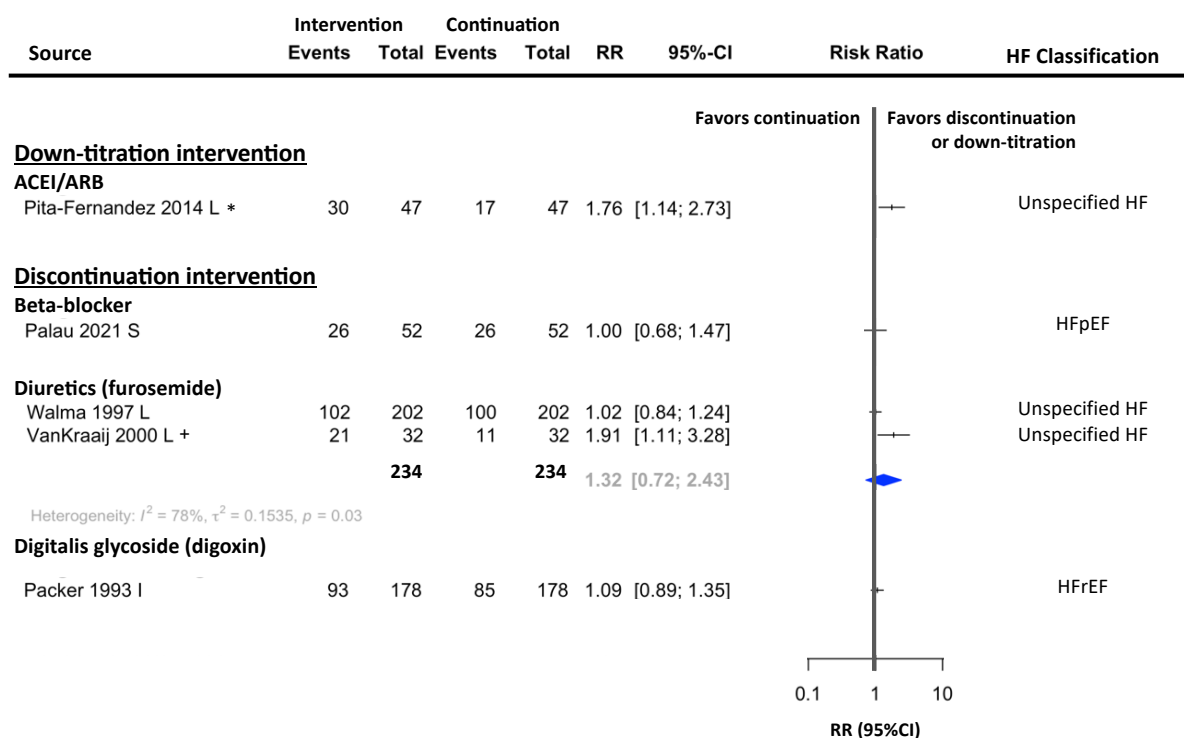
Abbreviations: HF=heart failure; RCT=Randomised controlled trial; NonRCT=observational study; ADE=adverse drug events; ADW= adverse drug withdrawal events; CI=confidence interval; "Other"= Includes sum of all "other ADWs"/sum of N or T (not duplicated denominator); * Reduced dose; MQoLHF=Minnesota quality of life in heart failure scale; URTI=upper respiratory tract infection; UTI=urinary tract infection; MI=myocardial infarction; CV=cardiovascular; ADL=activities of daily living; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment

Table 3.2: Summary of adverse drug withdrawal effects from discontinuing or down-titrating heart failure-pharmacotherapy in older people (continued....2)									
Adverse drug withdrawal effects	No. of studies	Study design (RCT [R], Non-RCT (NR))	No. events/sample, proportion (%)	Control	Total sample	Point estimate and 95%CI; or score and p-value	GRADE quality of evidence		
Mineralocorticoid receptor antagonist (MRA)									
Major CV event (composite CV death, MI, stroke and HF)	1	NR	-	-	3995	HR 1.06 (1.01-1.12)	Moderate		
Other									
2-year risk of fracture	1	NR	-	-	3995	HR 1.17 (0.97-1.36)	High		
Moderate to severe hyperkalaemia	1	NR	-	-	3995	HR 0.73 (0.66-0.8)	Moderate		
Additional treatments for heart failure									
Digoxin									
Worsening HF	1	R	23/93	25%	4/85	5%	178	RR 5.26 (1.89-14.58)	High
	3	NR	9/53	17%	-	-	53	-	Very low
Sinus Tachycardia	3	NR	3/131	2%	-	-	219	-	Very low
Myocardial infarction	1	R	1/111	1%	2/106	2%	217	-	Very low
Atrial fibrillation	2	R	2/111	2%	0/106	0%	217	-	Very low
unstable angina	1	R	1/93	1%	0/85	0%	178	-	Low
Other									
URTI (including bronchitis)	3	NR	6/131	5%	-	-	131	-	Very low
Escalating diuretic	1	R	11/93	12%	4/85	5%	178	-	Moderate
Dyspnoea	1	R	22/93	24%	12/85	14%	178	-	Moderate
Fatigue		R	22/93	24%	13/85	15%	178	-	Moderate
MHFQoL improved	1	R	19/93	20%	34/85	40%	178		Moderate
MFHQoL deteriorated			28/93	30%	30/85	35%			
Patient feeling better/unchanged			61/93	66%	30/85	35%			
Patient feeling worse			70/93	75%	13/85	15%			
Other:	3	R & NR	3/103	1-5%	0/105	0%	208	-	Very low to low
hyponatremia, thyrotoxicosis, renal carcinoma									
Abbreviations: HF=heart failure; RCT=Randomised controlled trial; NonRCT=observational study; ADE=adverse drug events; ADW= adverse drug withdrawal events; CI=confidence interval; “Other”= Includes sum of all “other ADWEs” /sum of N or T (not duplicated denominator); * Reduced dose; MQoLHF=Minnesota quality of life in heart failure scale; URTI=upper respiratory tract infection; UTI=urinary tract infection; MI=myocardial infarction; CV=cardiovascular; ADL=activities of daily living; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment									

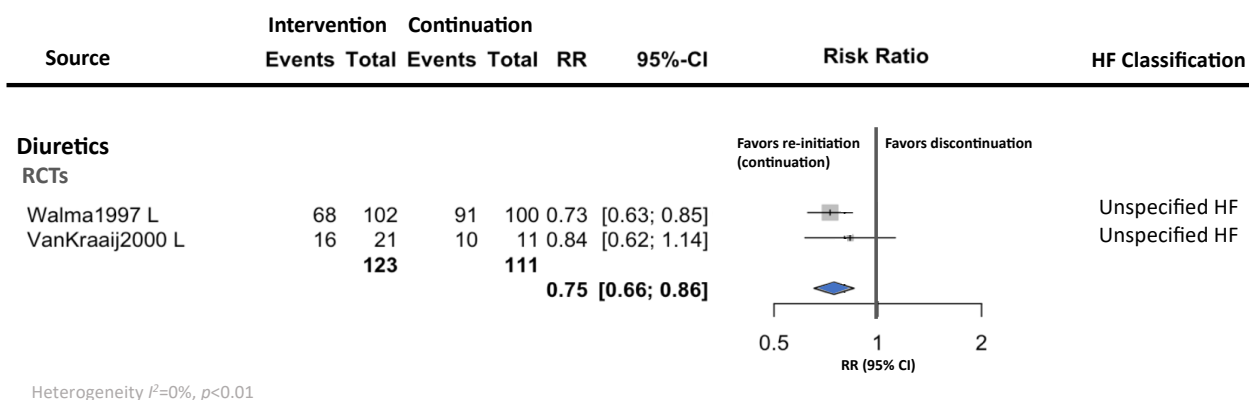
Abbreviations: HF=heart failure; RCT=Randomised controlled trial; NonRCT=observational study; ADE=adverse drug events; ADW= adverse drug withdrawal events; CI=confidence interval; "Other"= Includes sum of all "other ADWEs"/sum of N or T (not duplicated denominator). * Reduced dose; MOoLHF=Minnesota quality of life in heart failure scale; URTI=upper respiratory tract infection; UTI=urinary tract infection; MI=myocardial infarction; CV=cardiovascular; ADL=activities of daily living; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment

Figure 3.1: Feasibility of intervention during stable heart failure presentation in randomised controlled trials

A) Feasibility of down-titration or discontinuation of intervention compared to continuation.

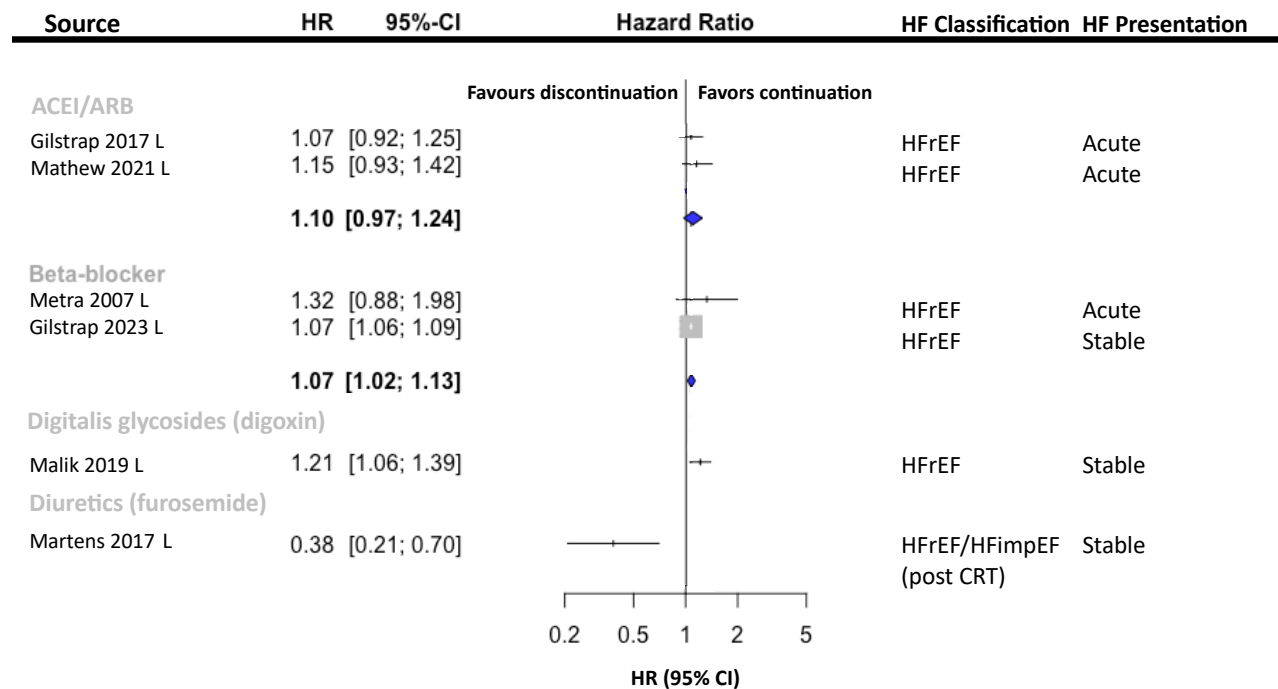


B) Feasibility of sustained discontinuation of interventions at follow-up.



Footnote: Feasibility refers to whether the reduction in dose or cessation occurred and/or was sustained. Figure 1(i) shows the proportion of participants in whom HF-pharmacotherapy was down-titrated or discontinued compared to continued at optimised dose. Figure 1(ii) shows the proportion of participants who sustained discontinued HF-pharmacotherapy at follow-up compared to re-initiation at optimised dose. Re-initiation was not reported for ACEI/ARB, beta blockers and digoxin. Abbreviations: ACEI/ARB = Angiotensin-converting enzyme or Angiotensin receptor blocker; S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (>24 weeks); HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; RR= risk ratio; 95%CI; * down-titrated in hospital setting; + discontinued in hospital or outpatient settings;

Figure 3.2: Hospitalisation in heart failure with reduced ejection fraction patients discontinuing heart failure-pharmacotherapy in observational studies



Heterogeneity: Overall $I^2=74\%$, $p < 0.01$; ACEI/ARB $I^2=0\%$, $p < 0.01$; Beta-blocker $I^2=3\%$, $p < 0.01$.

Footnote: This demonstrates the risk of hospitalisation in HFrEF patients that discontinued HF-pharmacotherapy compared to continued use as per usual care during acute decompensation and stable chronic presentation of HF in observational studies. Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (> 24 weeks); HFrEF=Heart failure with reduced ejection fraction; RASI renin-angiotensin system inhibitor; Post-CRT=after cardiac resynchronization therapy; HR=Hazard ratio; 95%-CI 95% confidence interval.

3.3.12 References

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3.4 Supplementary Material

Refer to Appendix B: Chapter 3 Supplementary Materials

3.5 Research Presentations

Preliminary results were presented in oral and poster presentations as:

Oral Presentations

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S.

Evaluating deprescribing of heart failure medications during optimisation: a systematic review and meta-analysis. Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT). Perth, 2022.

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S. A systematic review and meta-analysis evaluating the effects of deprescribing during optimisation of heart failure medications in older adults. Australian Deprescribing Network annual meeting. Perth, 2022.

Conference Poster Presentations

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S. Down-titrate and discontinue heart failure medications in older people. Toronto-Ottawa Heart Summit. Toronto, Canada, 2023.

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S.

Evaluating deprescribing of heart failure medications during optimisation: a systematic review and meta-analysis. Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) annual conference. Perth, 2022.

Duong MH, Gnjjidic D, McLachlan A, Redston M, Goyal P, Mathieson S, Hilmer S. Deprescribing Heart Failure Medications in Older People: A Systematic Review and Meta-analysis. International Conference on Deprescribing. Copenhagen, Denmark (virtual), 2022.

Media Activities

Duong MH. “Deprescribing heart failure medications in older people: a systematic review & meta-analysis”. Rapid Fire presentation at Australian Deprescribing Network meeting 2022. Available at <https://www.youtube.com/watch?v=uY0cHk3KF4A&t=25s> (last accessed on August 28, 2024)

Duong MH. “Deprescribing HF medications in older people”. Poster presentation at International Conference on Deprescribing 2022. Available at <https://www.youtube.com/watch?v=PGKUQyrceIQ> (last accessed on August 28, 2024)



CHAPTER 4

4.1 Overview

Evidence to optimise HF-pharmacotherapy in people with advanced age, multimorbidity and frailty is uncertain. Although adverse drug events (ADEs) with these medications are common, findings from Chapter 2 demonstrated that studies of older people with heart failure did not report data on geriatric outcomes with objective frailty measures.

Chapter 4 fills this gap by providing new data on the prevalence of geriatric outcomes in people living with heart failure and frailty. The retrospective cross-sectional multi-site study provides a snapshot of HF-pharmacotherapy utilisation and prevalence of polypharmacy, ADEs, falls, delirium, renal impairment and hospitalisation in older inpatients admitted to geriatric medicine, general medicine or rehabilitation services, according to frailty status. Findings suggest most older inpatients with undifferentiated HF are prescribed loop diuretics, either as monotherapy or in combination with beta-blockers or renin-angiotensin system inhibitors (RASi). HF patients with high frailty risk often continued beta-blockers but discontinued RASi at discharge. Renal impairment was common across all frailty groups. Increasing frailty risk status among older inpatients with HF was associated with longer hospital stays and increased prevalence of ADEs, falls and delirium. Assessment of appropriate HF-pharmacotherapy optimisation was limited by poor documentation of heart failure phenotypes in hospital electronic medical records. Given the association of adverse outcomes with frailty risk, future investigation is needed to understand the association between HF-pharmacotherapy utilisation in older people with frailty and adverse geriatric outcomes, including outcomes of improved frailty status.

4.2 Authorship Attribution Statement

Chapter 4 of this thesis is published as (Appendix C S4):

Duong MH, Gnjidic D, McLachlan AJ, Winardi K, Bennett AA, Blyth F, Le Couteur D, Hilmer SN. Prevalence of Heart Failure Pharmacotherapy Utilisation, Frailty and Adverse Drug Events Among Hospitalised Adults Over 75 years: A Multicentre Cross-Sectional Study (TO HOME). *Internal Medicine Journal*; 2024:1-11. doi: 10.1111/imj.16612.

The coauthors of the paper, “Prevalence of Heart Failure Pharmacotherapy Utilisation, Frailty and Adverse Drug Events Among Hospitalised Adults Over 75 years: A Multicentre Cross-Sectional Study”, confirm that Mai H Duong has made the following contributions:

I, Mai Duong, co-designed the study with co-authors, provided resources and software, validated and curated the data, conducted investigation, analysis, performed visualisation and interpretation of the findings, wrote the original draft of the manuscript and revised and edited the manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Sarah N Hilmer

January 31, 2025

4.3 Manuscript: Prevalence of Heart Failure Pharmacotherapy Utilisation, Frailty and Adverse Drug Events Among Hospitalised Adults Over 75 years: A Multicentre Cross-Sectional Study.

Authors

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4.3.1 Abstract

Background: Optimal heart failure (HF)-pharmacotherapy (Guideline-Directed Medical Therapy [GDMT] and diuretics) in older people with frailty is uncertain due to limited evidence.

Aims: To evaluate utilisation of HF-pharmacotherapy and prevalence of polypharmacy, adverse drug events (ADEs), falls, delirium, renal impairment and duration of hospitalisation in older inpatients, according to frailty status.

Methods: A descriptive retrospective cross-sectional study of the TO HOME cohort of 2000 consecutive inpatients ≥ 75 years diagnosed with HF admitted for ≥ 48 hours to rehabilitation services, geriatric or general medicine from 1/7/2016 to 30/6/2017 across six hospitals in Sydney, Australia. Data was collected from electronic medical records. ICD-10-AM codes were used to identify HF diagnosis, ADEs and frailty using hospital frailty risk score. Outcomes included utilisation of HF-pharmacotherapy; polypharmacy; ADEs, falls, delirium, renal impairment; and duration of hospitalisation.

Results: In the TO HOME cohort, 439 (22.0%) patients had undifferentiated HF. Of the 412 (94%) patients who took ≥ 1 HF pharmacotherapy, 284 (64.7%) had intermediate or high risk of frailty. There were 357 (81.3%) patients on loop diuretics. Patients with high frailty risk continued beta blockers ($n = 26$, 70%) and discontinued renin-angiotensin system inhibitors (RASIs) ($n = 21$, 57%). Most patients were prescribed polypharmacy ($n = 426$, 97.0%). Renal impairment ranged between 67%-76% across frailty groups. Increasing frailty risk (low, intermediate, high) was associated with increasing prevalence of ADEs (31%, 56%, 84%), falls (12%, 25%, 46%), and delirium (8%, 27%, 49%) and longer hospitalisation.

Conclusions: Diuretics were common in older inpatients with HF and frailty during hospitalisation, and documentation of HF phenotype is poor. The association of adverse outcomes in older HF patients with HF-pharmacotherapy according to frailty status needs investigation.

4.3.2 Introduction

Heart failure (HF) is a complex syndrome increasingly prevalent in the ageing population and associated with high risk of hospitalisation and death.¹ Half of HF hospitalisations involve people aged ≥ 75 years.² Frailty, a reversible syndrome involving multisystem deficiencies, affects up to 75% of people living with HF in the community.³ Utilisation and optimisation of heart failure Guideline-Directed Medical Therapies (GDMTs) (i.e. Renin-Angiotensin System Inhibitors [RASIs], HF-specific beta blockers, Mineralocorticoid Receptor Antagonists [MRA], and more recently Sodium-GLucose co-Transporter-2 Inhibitors [SGLT2-i]) have demonstrated reduced mortality and hospitalisation.⁴ Older people report lower tolerance and higher discontinuation rates of HF-GDMT.^{5,6}

Polypharmacy is highly prevalent in patients with HF, especially as their age increases. Ninety-five percent take ≥ 5 medications and 50% take ≥ 10 medications, increasing the risk of adverse drug reactions (ADRs).⁷ Up to 91% of HF patients report experiencing chronic adverse drug events (ADEs).⁸ Previous studies of hospitalised older adults reported HF in approximately 13% of inpatients,⁹ 40% were affected by frailty and 8.6%-18.4% reported ADRs in hospital.¹⁰⁻¹³ The prevalence of ADRs in people aged under 65 years compared to those over 65 years differed by 30-60%.¹⁴ Hospitalisation of older patients with HF are often admitted under the care of multidisciplinary teams, which may or may not include cardiology specialists.

The management of HF and optimisation of medications in frail older people can be complex due to disease progression, changes in cognition, multimorbidity, life expectancy and changing patient priorities. Frail older people are persistently and widely excluded from HF clinical trials, which measure cardiovascular outcomes rather than geriatric outcomes; thus evidence on efficacy and safety in this population is limited.^{15,16} Research evaluating geriatric outcomes is needed to fill this knowledge gap to support shared decision-making.

This study aims to evaluate the utilisation of HF-GDMT and diuretics in hospitalised patients ≥ 75 years with heart failure, according to frailty status. Secondary objectives are to determine the duration of hospitalisation and evaluate the prevalence of polypharmacy and geriatric relevant adverse events in patients with heart failure on HF-GDMT or diuretics at hospital discharge by frailty status.

4.3.3 Methods

Data source

This retrospective cross-sectional descriptive study included 2000 consecutive patients aged ≥ 75 years admitted for ≥ 48 hours to geriatric, general and rehabilitation medicine between 1 July 2016 to 30 June 2017 across six hospitals in Sydney, Australia. Data was collected from patient electronic medical records in routine care and verified by a research clinician on medications, clinical characteristics and outcomes (e.g., changes in medication utilisation, ADEs, falls, delirium and renal impairment) during admission. Information was collected from the Emergency department assessment, progress notes, medication charts, medication management plans and discharge summary relevant to the hospital stay. Data was obtained from the Towards Optimizing Hospitalized Older adults' Medications (TO HOME) dataset, designed to look at overall medication management in adults aged >75 years during routine care in general medical, geriatric and rehabilitation services, previously published methods and characteristics.¹⁷ Although data was collected from retrospective patients from 2017, this dataset was the most up-to-date information available for analysis. Patients with HF who present with geriatric syndromes or non-cardiac reasons for admission (e.g. infection, falls), with or without active cardiac diagnosis, are likely to be admitted to general medical and geriatric hospital services for HF or non-HF admissions. This study did not capture data for patients admitted under cardiology service, more likely to be admitted for initial diagnosis of HF, acute treatment of severe HF requiring critical care or HF without other active diagnoses.

Study Subjects

Patients were identified using coding of diagnoses during hospital admission with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes. ICD-10-AM coding for HF diagnosis and related cardiomyopathy¹⁸ included undifferentiated HF (U82.2, I50, I50.0, I50.1, I50.9,

I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-42.9, I43, P29.0, E10.53, E11.53, E13.53, E14.53), heart failure with reduced ejection fraction (HFrEF) (I50.2x, I50.4x) and heart failure with preserved ejection fraction (HFpEF) (I50.3). Demographic characteristics were determined for patients with HF diagnosis compared to those with no HF diagnosis. The Charlson comorbidity index (CCI) score was calculated using ICD-10-AM codes and manually validated in 300 individuals in the total TO HOME cohort ($n = 2000$).¹⁷

Frailty Measurement

Frailty risk status of each patient was calculated with ICD-10-AM codes according to the Hospital Frailty Risk Score (HFRS), a numerical score determined by relevant ICD-10-AM codes during admission as previously reported.¹⁹ The HFRS calculates the risk of frailty into three categories: low (<5 points), intermediate (5-15 points) or high (>15 points). All outcomes were reported by frailty status (HFRS categories) to mitigate reporting bias. This study evaluated prevalence of medication utilisation and highly prevalent outcomes among geriatric populations with cardiovascular disease, particularly polypharmacy, duration of hospitalisation, ADEs, falls, delirium and renal impairment, according to frailty risk status.²⁰

HF-Pharmacotherapy Utilisation

Anatomical Therapeutic Chemical Classification (ATC) codes for HF-GDMT⁴ include Renin-Angiotensin System Inhibitors (C09), beta blockers (C07), Mineralocorticoid Receptor Agonists (C03D, C03DA) and loop diuretics (C03, C03CA, C03CA01). The codes for sodium-glucose co-transporter-2 inhibitors (A10BK) were not included in this analysis since they were not recommended in HF-guidelines at the time of data collection. RASIs mostly referred to Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Antagonists (ARBs) as sacubitril/valsartan was not approved in Australia during the entire data collection period. Diuretics include loop diuretics (i.e., furosemide, bumetanide, etacrynic acid) and exclude thiazide diuretics.

The primary outcome measure was HF-pharmacotherapy utilisation by individual therapeutic class and combination (i.e., taking at least one GDMT or diuretic). This categorical data is reported as the frequency and proportion of initiation, continuation, up-titration, down-titration, discontinuation, and re-initiation of each class of HF-pharmacotherapy at discharge. Utilisation information was ascertained from the type of change made to admission medications collected from documentation of best possible medication history and medication reconciliation on admission, where available.¹⁷ The types of medication changes during admission were documented as dose reduction (down-titration) or dose increase (up-titration). Medications listed in the discharge summary that were taken prior to admission (with/without dose modifications) were documented as continued (continuation) and medications omitted in the discharge summary but taken prior to admission were documented as ceased (discontinued).

Analysis did not discern whether individual doses for each HF-pharmacotherapy met criteria for recommended optimised doses in clinical trials. Polypharmacy (the use of ≥ 5 regular medications) and hyperpolypharmacy (the use of ≥ 10 regular medications) at admission and discharge were reported for all HF-patients. The frequency of two, three and four HF-pharmacotherapy combinations per patient and prevalence of overall pairwise-combinations was reported.

Clinical Outcomes

Secondary outcomes were measured as the frequency and proportion of clinical outcomes, reported as ADEs, falls, delirium and renal impairment for patients taking ≥ 1 HF-pharmacotherapy at discharge. Adverse drug events (ADEs), defined as any adverse outcome occurring in people taking a medication²¹, were identified with ICD-10-AM codes using Du et al.²² published criteria, specifically, the external cause codes (Y40-59)²³ and the codes

assigned a causality rating of A, B, C and D. ICD-10-AM codes documented at admission during the hospital stay were coded by local health district medical record coders, which include primary reasons for admission. Additional validation on a subset of 600 (30%) patients from the TO HOME cohort demonstrated that a clinical research pharmacist identified ADEs in 68 (90.6%) of the 75 patients identified with ICD-10-AM codes.²⁴ Falls and delirium were extracted from the free text in the electronic medical records. Renal Impairment (acute or chronic) was defined as glomerular filtration rate (GFR) $<60\text{mL/min/1.73m}^2$ measured at admission.²⁵ Missing data ($n = 1$) for renal impairment identified in one HF-patient with intermediate frailty was coded as no renal impairment. Duration of hospitalisation (Length Of Stay [LOS]) was measured as the number of days (mean, standard deviation) between patient initial admission and discharge.

Statistical analysis

A descriptive analysis was performed on the TO HOME cohort, stratified by frailty risk status. Sample size was determined by the TO HOME cohort. A retrospective power analysis was conducted. A clinically significant difference in prevalence of ADRs was considered as 10% in patients aged ≥ 65 years in a recent systematic review.^{26,27} Therefore, the study had 0.87 power to detect a 10-18% difference in ADRs from HF-pharmacotherapy when comparing people with low, intermediate and high risk of frailty.^{11,28}

Descriptive statistics were applied to calculate frequency and proportions of all outcomes. The mean (standard deviation) was reported for continuous variables and count (%) was reported for categorical variables, binary groups and frailty risk and graphed. Sociodemographic and hospital admission data in patients with and without HF were compared using the Pearson Chi-Squared Test for categorical variables and the Mann-Whitney U test for continuous variables. Differences between patients with HF and no HF

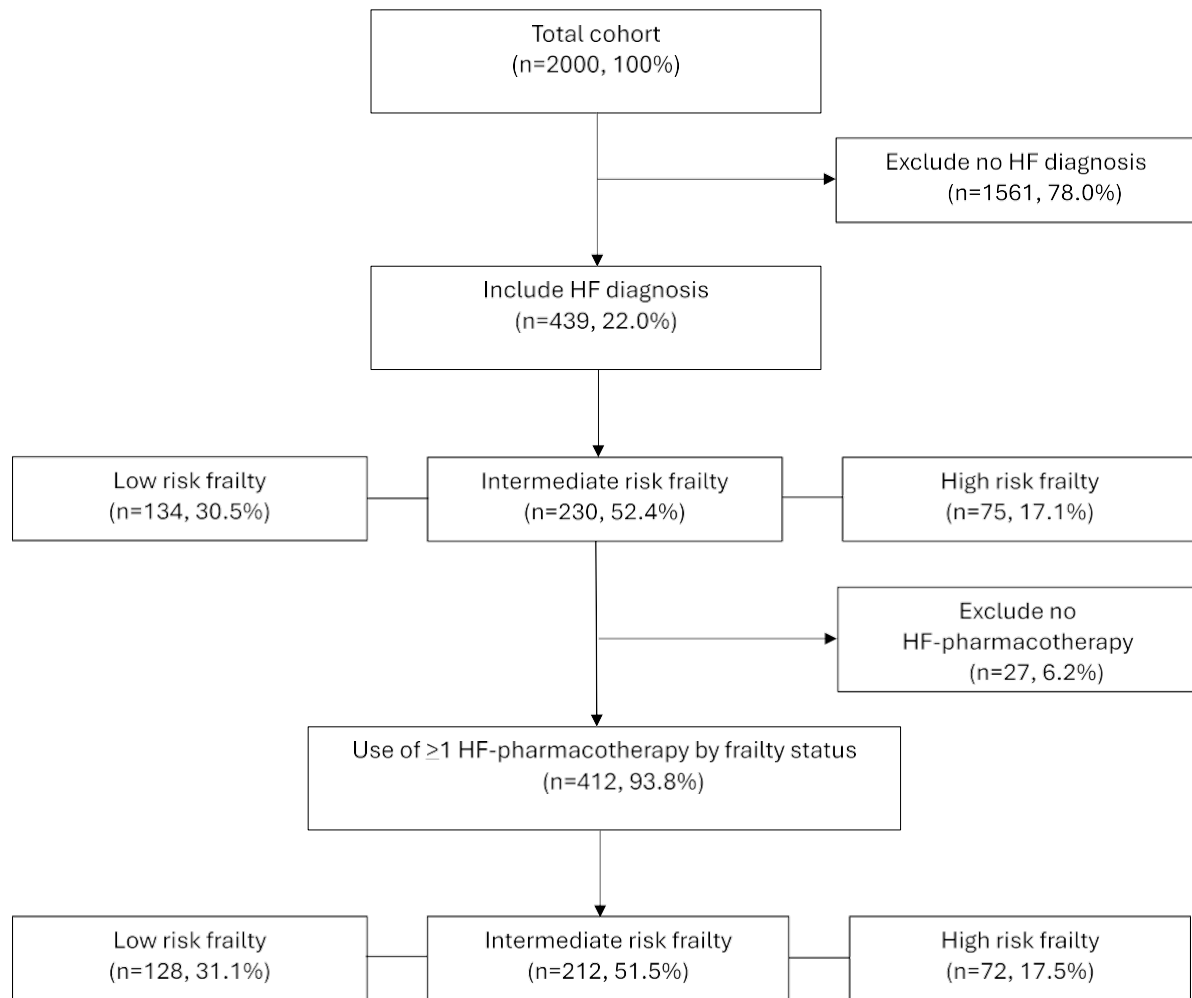
diagnosis were deemed statistically significant if p-value <0.05. Subgroup analysis reported outcomes by frailty risk. Patterns between frailty groups were not compared statistically. Instead, weighted utilisation for individual therapeutic classes were grouped by frailty status using radar plots,^{29,30} and heatmaps of HF-pharmacotherapy pairwise- combinations per person with annotations of frequency and proportions of ADEs, were visualised.³¹ Data analysis and visualisation were performed in R/Rstudio version v4.2.2 software using ggplot2 (v3.5.0), ggradar (v0.2) and ComplexHeatmap (v2.14.0) along with Microsoft Excel 2014.

4.3.4 Results

Demographics

Undifferentiated heart failure was identified in 439 (22%) patients; no coding reported HF_rEF or HF_pEF (Figure 4.1). Table 4.1 describes patient characteristics in those with HF compared to no HF diagnosis. The proportion of frailty risk was similar among patients with diagnosis of HF ($n = 305$, 69.5%) and no HF ($n = 1,107$, 70.9%). In patients with HF, there was low ($n = 134$, 30.5%), intermediate ($n = 230$, 52.4%) and high ($n = 75$, 17.1%) frailty risk. The mean age was 87 (5.6) years, 59.0% ($n = 259$) were female, 15.3% ($n = 90$) had dementia, 7.1% ($n = 42$) had mild cognitive impairment, 134 (30.5%) with high comorbidity (Charlson comorbidity index ≥ 3),³² and 67.2% ($n = 295$) considered English as their preferred language. The primary reason for admission was cardiac or circulatory system-related in 28.5% ($n = 125$) of HF-patients, including 22.1% ($n = 97$) for HF. The most common non-cardiovascular reasons for admission were respiratory ($n = 91$, 20.7%) and musculoskeletal or connective tissue ($n = 65$, 14.8%) conditions (Table S4.6). Prior to admission, 68.8% ($n = 302$) lived at home and 50.1% ($n = 220$) were discharged home.

Figure 4.1 Flow chart of study population



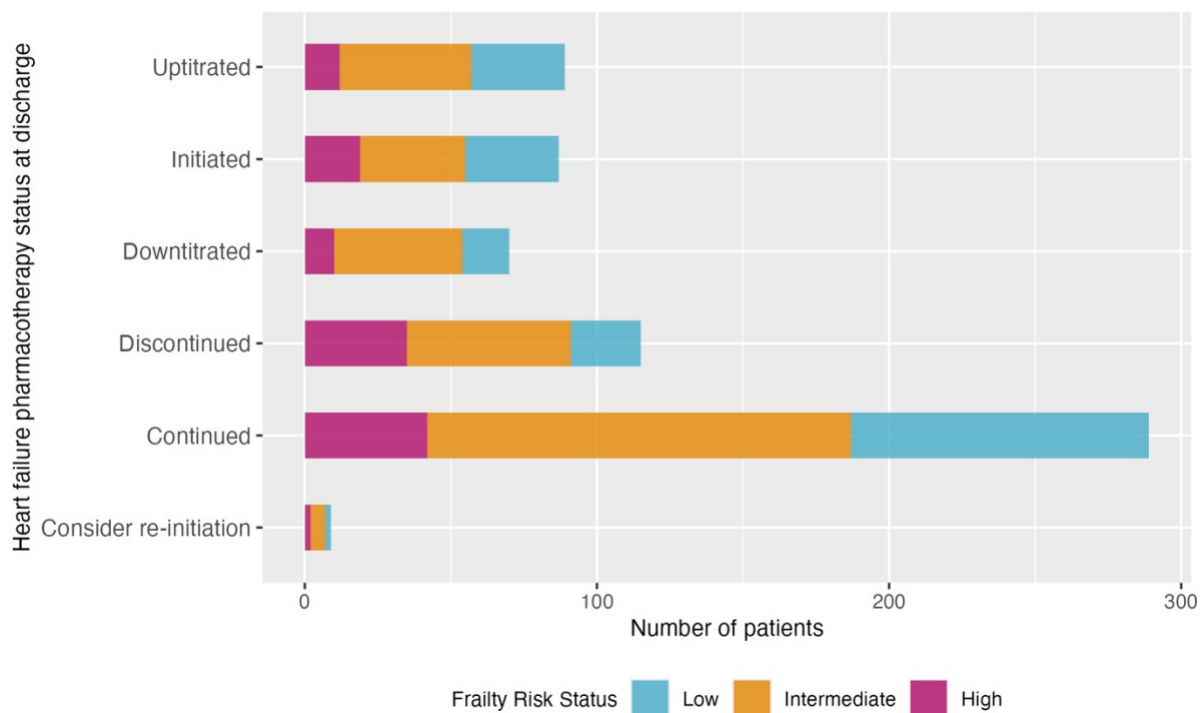
Footnote: HF = heart failure.

Table 4.1. Patient Characteristics

Characteristics (n, %)	Total		Heart Failure		No Heart Failure	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Sample size	2000	100%	439	22%	1561	78%
Age (years), mean (SD)	86 (5.8)	-	87 (5.6)	-	86 (5.8)	-
75-79	307	15.4%	44	10%	263	17%
80-89	1116	55.8%	245	56%	871	56%
>90	577	28.9%	150	34%	427	27%
Sex (Female)	1181	59.1%	259	59.0%	922	59.1%
Preferred language spoken at home						
English	1381	69%	295	67.2%	1092	70.0%
Language other than English	613	31%	144	32.8%	469	30.0%
Frailty status (Hospital Frailty Risk Score [HFRS])						
Low (HFRS<5)	588	29.4%	134	30.5%	454	29.1%
Intermediate (HFRS 5-15)	1087	54.4%	230	52.4%	857	54.9%
High (HFRS >15)	325	16.3%	75	17.1%	250	16.0%
Number of comorbidities (Charlson Comorbidity Index)						
Low: Score 0-2	1665	83.2%	305	69.4%	1360	87.1%
High: Score 3+	335	16.8%	134	30.5%	201	12.9%
Cognition						
Dementia documented*	517	26%	90	15.3%	427	27.4%
Mild cognitive impairment	197	10%	42	7.1%	155	9.9%
Primary reason for admission						
Cardiac and circulatory system*	220	11%	125	28.5%	95	6.1%
Heart Failure	97	4.9%	97	22.1%	-	-
Low risk (HFRS<5)	48	2.4%	48	11%	-	-
Intermediate risk (HFRS 5-15)	43	2.2%	43	10%	-	-
High risk (HFRS >15)	6	<1%	6	1.4%	-	-
Length of hospital stay (days) mean (SD)	13.4 (15.6)	-	13.5 (12.7)	-	13.4 (16.3)	-
History of a previous ADR [#] prior to admission	831	41.6%	207	47.2%	624	40.0%
Living status prior to admission						
Home	1458	73%	302	68.8%	1156	74.1%
Residential aged care facility	421	25%	108	24.6%	313	20.1%
Other	121	22%	29	6.6%	92	5.9%
Discharge destination						
Home	1050	53%	220	50.1%	830	53.2%
Residential aged care facility	506	25%	123	28.0%	383	24.5%
Assisted living	78	4%	20	4.6%	58	3.7%
Hospice/palliative care	1	<1%	0	0.0%	1	0.1%
Other	365	18	76	17.3%	289	18.5%

Footnote: [#]participant had documented adverse drug reactions. *Difference between HF and no HF was statistically significant (p<0.05).

Figure 4.2. The frequency of heart failure pharmacotherapy initiated, up-titrated, down-titrated continued, discontinued, and considered for re-initiation by general practitioner at discharge amongst hospitalised patients over 75 years with heart failure, stratified by their risk of frailty.



HF-Pharmacotherapy Utilisation

The use of at least one HF-pharmacotherapy was reported in 412 (94%) patients with a documented diagnosis of heart failure. At discharge, HF-pharmacotherapy was frequently continued ($n = 289$, 65.8%). HF-pharmacotherapy withheld or discontinued during hospital admission was commonly not recommended for re-initiation at discharge, with $< 1\%$ were recommended for re-initiation if deemed appropriate by their family physician (Figure 4.2, Table S4.1). During hospitalisation, patients with HF were frequently prescribed loop diuretics ($n = 357$, 81.3%, predominantly furosemide [$n = 355$, 80.9%]), half were prescribed RASI ($n = 218$, 49.7%) and/or beta blockers ($n = 216$, 49.2%) (Table S2). MRAs were less frequently prescribed ($n = 100$, 22.8%). Continuation of beta blockers ($n = 160$, 36.4%) and diuretics ($n = 142$, 32.3%) were most prevalent across frailty subgroups (Figure 4.3). Discontinuation was most prevalent for RASIs ($n = 75$, 17.1%). Loop diuretics were most

frequently adjusted during hospitalisation, as doses were initiated ($n = 68$, 15.5%), up-titrated ($n = 74$, 16.9%) and down-titrated ($n = 41$, 9.3%). High frailty risk patients frequently continued beta blockers ($n = 26$, 70.3%), discontinued RASIs ($n = 21$, 56.8%), and MRAs were similarly continued ($n = 5$, 38.5%) and discontinued ($n = 5$, 38.5%). There were 88 (20.0%) patients with no HF-GDMT and 27 (6.6%) without GDMT or diuretic (Table S4.2).

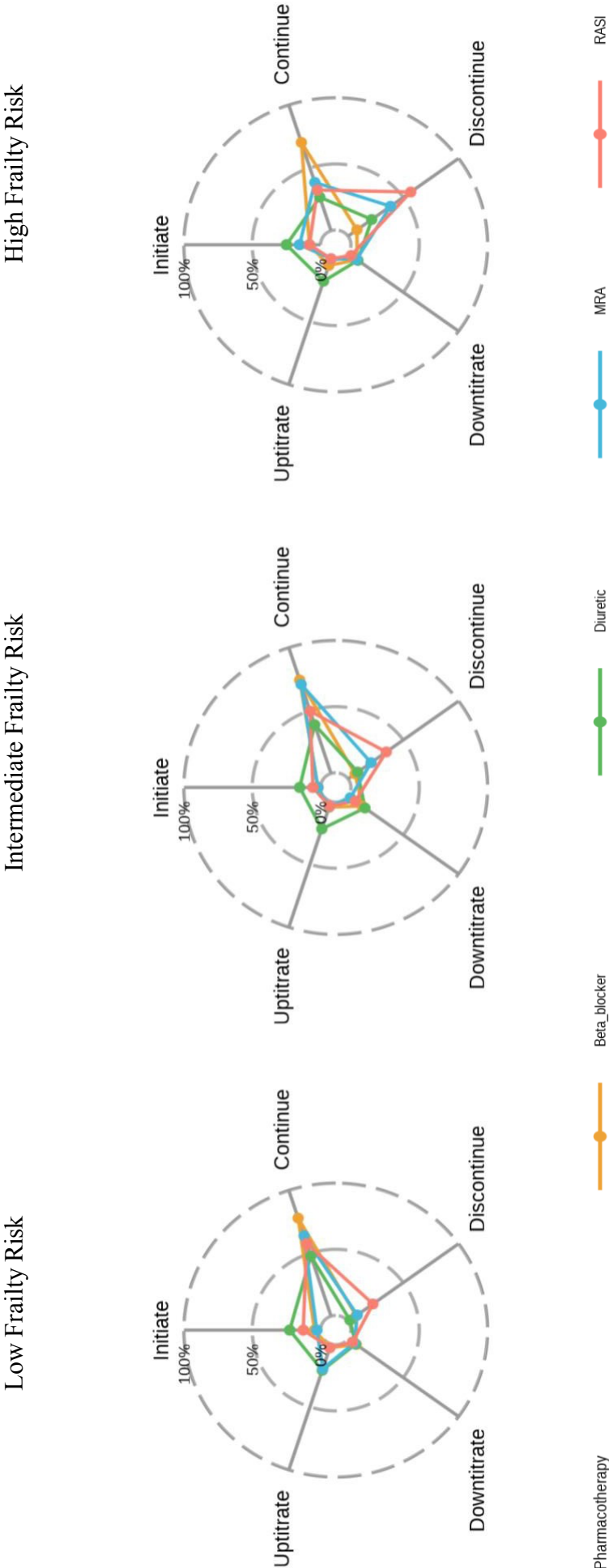
Polypharmacy

Polypharmacy ($n = 411$, 93.6%,) and hyperpolypharmacy ($n = 219$, 50.0%,) at admission, increased at discharge ($n = 426$, 97.0% and $n = 281$, 64.0%, respectively) (Table S4.2). The proportion of HF-patients with hyperpolypharmacy was 10% higher in those with high compared to low frailty risk (high 56.0%, intermediate 50.4%, low 45.5%). Eighty-eight (20.0%) patients with HF had no HF-GDMT; of whom 27 (6.2%) were on neither HF-GDMT nor diuretic (Table S4.2). Monotherapy diuretic use was reported in 61 (13.9%) patients. Multi-drug combinations with diuretics were frequent. Use of two ($n = 170$, 41.3%) or three ($n = 118$, 28.6%) HF-pharmacotherapies were most frequent, but use of four ($n = 25$, 6.1%) was uncommon (Table S4.2, Figure 4.4). The proportion of pairwise-combinations, most frequently diuretic-beta blocker ($n = 184$, 44.7%), diuretic-RASI ($n = 183$, 44.4%) and beta blocker-RASI ($n = 112$, 27.2%) combinations, did not vary across frailty risk groups (Figure 4.3, Table S4.3).

Clinical Outcomes and Adverse Drug Events

Hospital LOS increased with increasing frailty among HF patients with low (7.8[6.9] days), intermediate (14.7[12.9] days) and high (20.3[15.3] days) frailty risk; and up to 2.6-fold longer in high compared to low frailty risk groups.

Figure 4.3. The proportion of heart failure pharmacotherapy utilisation in hospitalised patients over 75 years with heart failure, by frailty status.

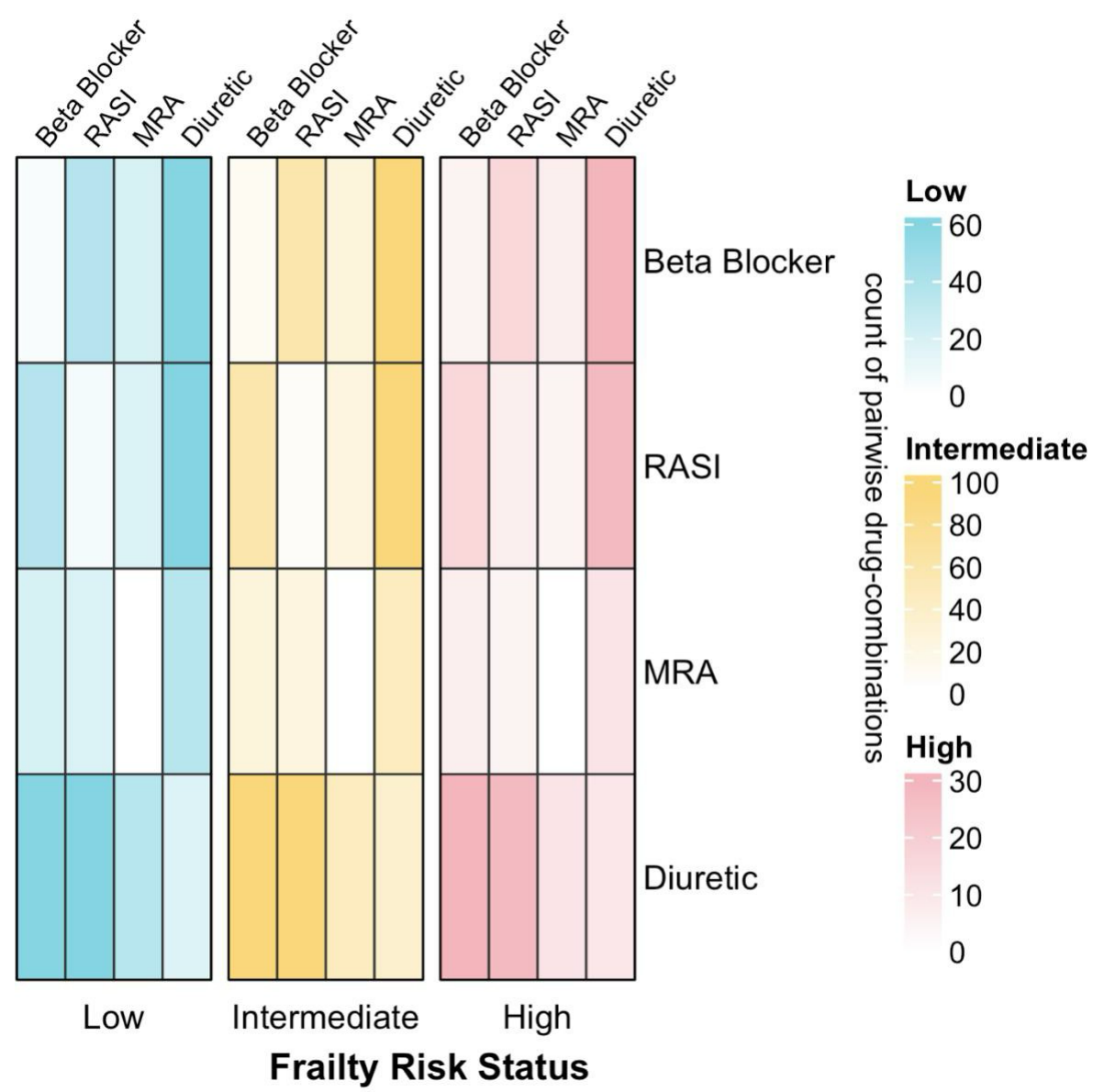


Legend: Total number (*n*) of patients with medication change by frailty risk

	Low frailty risk	Intermediate frailty risk	High frailty risk
Up-titrate	32	45	12
Initiate	34	37	19
Continue	102	145	42
Discontinue	24	56	35
Down-titrate	16	44	10

Footnote: RASI = Renin-angiotensin system inhibitor; MRA = mineralocorticoid receptor antagonist

Figure 4.4. Heatmap demonstrating the frequency and proportion of heart failure-pharmacotherapy pairwise-combinations in hospitalised patients aged over 75 years, by frailty risk status.

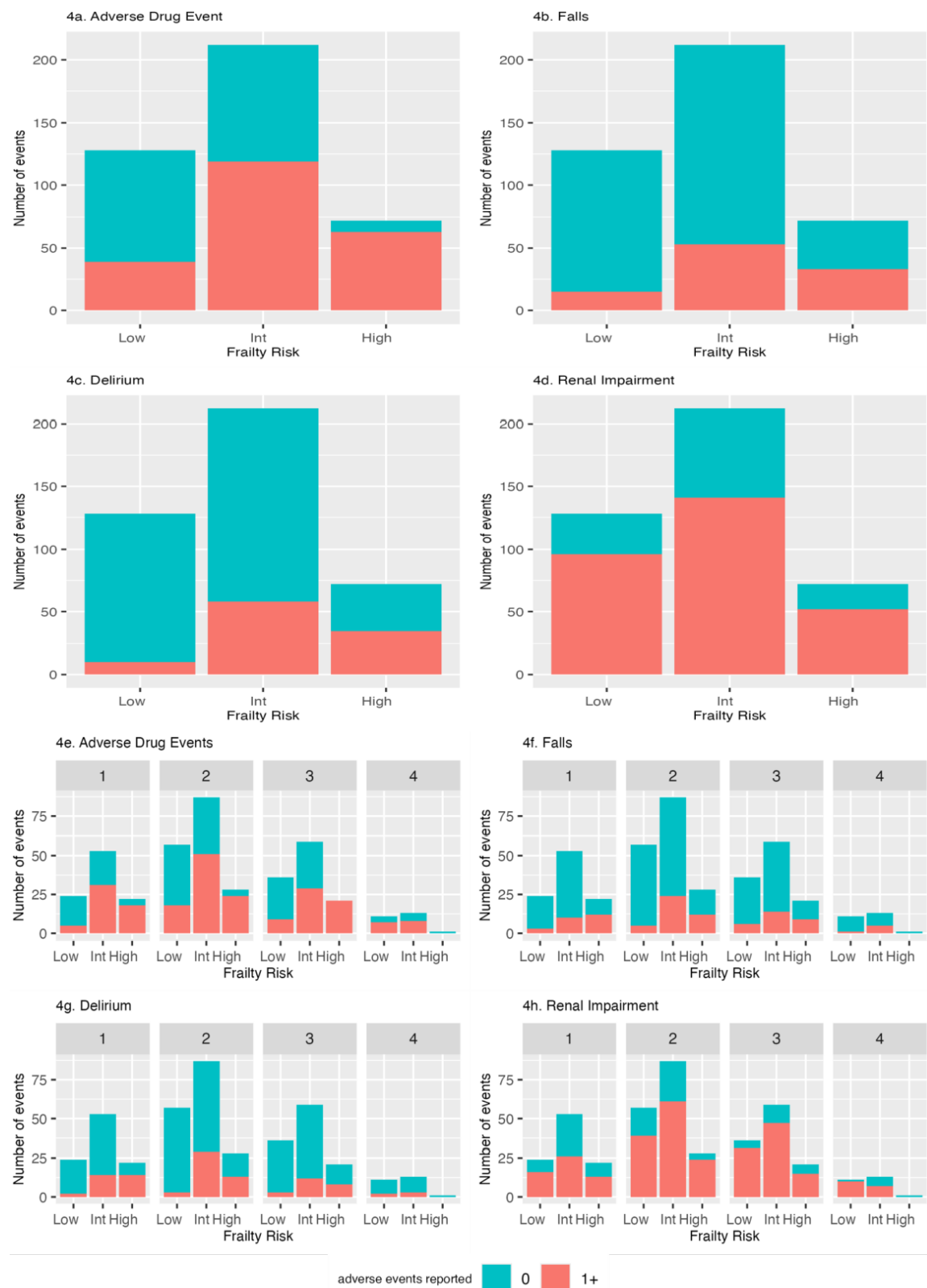


Abbreviations: RASI = Renin-angiotensin system inhibitor; MRA = mineralocorticoid receptor antagonist

ADEs were high, occurring in approximately half of patients with HF ($n = 227$, 51.7%). ADEs were identified in patients with low ($n = 40$, 29.9%), intermediate ($n = 124$, 53.9%) and high frailty risk ($n = 63$, 84.0%) (Figure 4.5, Table S4.5, Figure S4.2). Similar prevalence of falls ($n = 106$, 24.1%) and delirium ($n = 110$, 25.1%) were reported in patients with HF; of whom 25 (6.1%) patients experienced both falls and delirium, but mostly occurred in those with high frailty risk ($n = 17$, 68.0%). Falls were identified in patients with low ($n = 15$, 11.2%), intermediate ($n = 57$, 24.8%) and high ($n = 34$, 45.3%) frailty risk. Delirium was identified in patients with low ($n = 10$, 7.5%), intermediate ($n = 63$, 27.4%) and high ($n = 37$, 49.3%) frailty risk. Renal impairment ($n = 305$, 69.5%) in patients with HF was similar across frailty risk groups, ranging between 66% and 74%, and was often prevalent in patients using ≥ 2 HF- pharmacotherapies (Figure 4.4).

In frequent pairwise-combinations, the proportions of ADEs in people with high frailty risk for diuretic-beta blocker ($n = 29/30$, 97%; $n = 18/60$, 30%), diuretic-RASI ($n = 24/28$, 86%; $n = 23/61$, 38%) and beta blocker- RASI ($n = 14/16$, 88%; $n = 13/37$, 35%) were higher than combinations in low frailty risk (Figure 4.3, Table S4.4).

Figure 4.5. Frequency of adverse drug events and adverse clinical outcomes in hospitalised patients over 75 years on at least one heart failure-pharmacotherapy (4.5a. to 4.5d.); and on monotherapy or two, three or four combination heart failure-pharmacotherapies (4.5e. to 4.5h.), according to frailty status.



Footnote: All outcomes had p-value>0.05 between frailty risk groups.

Abbreviation: Int = Intermediate frailty risk.

4.3.5 Discussion

This descriptive study demonstrated that among hospitalised patients over 75 years with HF, most were at risk of frailty; diuretics were frequently continued, up-titrated or initiated during hospitalisation; beta-blockers were mostly continued at discharge; and few were prescribed MRAs. Older patients with HF at high risk of frailty frequently discontinued RASIs compared to those with low frailty risk. Polypharmacy, hyperpolypharmacy and combination use of diuretic-beta-blocker and diuretic-RASI were frequent; ADEs were highly prevalent among those with high frailty risk. Despite the evidence showing benefits of improved mortality and hospitalisation outcomes with use of multiple HF-GDMTs, patients on ≥ 3 HF-pharmacotherapies (mainly diuretics, beta-blocker and RASI) with increasing frailty risk had longer hospitalisation and increasing proportions of ADEs, falls and delirium. Renal impairment was common across all frailty subgroups.

This study provides new insights on the prevalence of ADEs, falls, delirium, and renal impairment in a geriatric hospital population with HF and frailty risk. The adverse clinical outcomes reported in this study can significantly impact the quality of life in people of advanced age with frailty, who may no longer prioritise longevity, and have more difficulty tolerating HF-pharmacotherapy or recovering from ADEs. A systematic review of ADEs associated with HF-pharmacotherapy in older people with HF and frailty reported a 2-fold increased risk of mortality and hospitalisation in frail compared to robust people on RASIs,¹⁵ but overall there was no data for adverse geriatric outcomes. These findings support consideration of global function and patient preference during medication management of HF in people with advanced age and frailty who may prefer to optimise quality of life and avoid

hospitalisation. In addition, these patients may benefit from uptake of strategies to reverse frailty status.

The ADEs and adverse clinical outcomes reported in this study are important to consider within the context of potential benefits of HF-pharmacotherapy. Findings showed increased number of pharmacotherapies increased the prevalence of ADEs, falls and delirium with increasing frailty risk. A recent study³³ conducted in Taiwan ($n = 38,843$) reported similar frailty distribution and showed 27.3% of HF patients died of cardiovascular diseases. Compared to robust patients with HF, severely frail patients had increased risk of all-cause mortality (adjusted hazard ratio [aHR] 1.16, 95% confidence interval [CI] 1.11-1.21) and all-cause re-admissions (sub-distributional hazard ratio [sHR] 1.21, 95% CI 1.16-1.25).³³ Use of any triple HF-pharmacotherapy or more combinations compared to monotherapy was shown to decrease risk of 2-year all-cause readmissions (adjusted odds ratio [aOR] 0.49, 95% CI 0.44-0.54) across all frailty groups.³³ In addition, older patients hospitalised with ADRs often have more comorbidities (mean 6.1) compared to those without ADRs (mean 5.2).¹¹ In the global REPORT-HF study ($n = 18,553$), patients presenting with acute HF and higher number (≥ 5) of comorbidities ($n = 4449$, 24%) were more likely to use potentially HF-worsening medications and were less likely to receive HF-GDMT (i.e., RASI, MRA) at discharge.³⁴ Thus, the benefit and risks of these medications should be personalised for each individual when supporting optimisation in people with HF, multimorbidity and high frailty risk.

Barriers to evidence-based management of changes during hospitalisation included poor documentation of HF-phenotype and rationale for deprescribing. Appropriate medication optimisation could not be evaluated in the absence of accurate HF diagnosis. The frequency of deprescribing (~40%) was similar among patients with acute and chronic stable HF but did not distinguish whether deprescribing was intended to be permanent or if

medications were temporarily ceased to manage acute issues. Specific reasons for deprescribing were not captured in this dataset; however, potential reasons include management of hypotension, acute kidney injury, syncope, falls, drug interactions, infections, changes in cognition etc. Among community aged care residents with dementia, deprescribing of anti-hypertensives (without HF diagnosis) was associated with 16% reduced odds of cognitive decline (OR 0.84, 95%CI 0.72-0.98) compared with continued use in usual care³⁵. A systematic review found low quality evidence failed deprescribing of diuretics was most often due to recurrence of HF and peripheral oedema.³⁶ Future investigation is needed to explore safety and rationale for deprescribing HF-pharmacotherapy or potentially high-risk medications³⁷ in this population.

Strengths and limitations

This descriptive study provides novel data on adverse geriatric outcomes in older hospitalised adults with HF and frailty risk that can be applied to optimisation and management of adverse events by multidisciplinary teams. In a cohort of older people, adverse outcomes were particularly high in patients with high frailty risk, supporting the need to consider not just age, but global function in shared decision-making.

Data was not available to determine causal relationships between medication and adverse reactions and there was no confirmation whether adverse outcomes were caused by HF-pharmacotherapy or related to other potentially inappropriate medications treating comorbidities. The prevalence of ADEs was broadly considered and a sub-analysis specifying the causality of ADEs was not performed since the data was not available but should be considered in future studies.²⁴ Retrospective ICD-10-AM diagnosis codes could contribute to both frailty risk and the associated outcomes, specifically for delirium and falls.

The association of underutilisation or optimised HF-pharmacotherapy utilisation with adverse outcomes, mortality and readmission were not investigated. The 20% (n = 88) of patients without GDMT may represent potential under treatment and opportunities for medication review.³⁸ Although data was collected from retrospective patients from 2017, this dataset was the most up-to-date information available for analysis and may not reflect current prescribing practices but provides rich quality data. The frequency of ADEs in pairwise-combinations were counted per patient; thus, careful interpretation is needed to avoid over-representation of ADEs occurring for multiple combinations per patient. Evaluation of SGLT2-i and emerging therapies (e.g., vericiguat, omecamtiv mercabil) and sub-analysis of potential confounders (e.g., age, sex, renal function, ethnicity) were not performed due to small sample size. Cardiovascular biomarkers and HF phenotypes were not included at the time of data collection, and small sample size in an urban Australian population limited generalisability of results. Future prospective cohort studies and clinical trials of HF-pharmacotherapy utilisation and optimisation in older people should build on our findings by considering the inclusion of these variables and analyses.

4.3.6 Conclusion

This study demonstrated that older adults with HF and frailty risk were frequently prescribed diuretics, diuretic-GDMT combinations and continued beta-blockers during hospitalisation. HF phenotype was not documented and it is unknown whether it guided therapeutic choices. Reasons for lack of documentation in this older population should be explored. A higher proportion of people with high frailty risk discontinued RASIs. Polypharmacy and renal impairment were prevalent across all frailty groups. Duration of

hospitalisation and reported prevalence of ADEs, falls and delirium increased with increased frailty risk. These findings can be considered when managing cardiovascular outcomes in complex older patients with limited global function. Research reporting adverse outcomes of mortality, hospitalisation, cardiovascular biomarkers, geriatric outcomes and frailty is needed to inform shared decision-making and advanced care planning.

4.3.7 Funding And Acknowledgements

Mai Duong is funded by the Commonwealth of Australia National Health and Medical Research Council (NHMRC) Postgraduate Scholarship Grant APP1191018 awarded in 2020, HROz Scholarship awarded in 2023-24 and the University of Sydney Postgraduate Research Support Scheme 2022-24. We acknowledge the collaboration of AProf Patrick Kelly and Prof Rosalie Viney for contributions to the conceptualisation and management of the TO HOME database, statistical advice from AProf Ana Capuano, and technical assistance from Mr Omar Arnaiz of the Sydney Informatics Hub, a Core Research Facility of the University of Sydney.

4.3.8 Disclosures

None.

4.3.9 References

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4.4 Supplementary Material

Refer to Appendix C: Chapter 4 Supplementary Materials

4.5 Supplementary Material

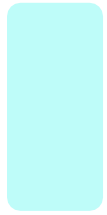
Preliminary results were presented as:

Invited Speaker Presentation

Duong MH, Gnjjidic D, McLachlan A, Winardi K, Bennett A, Blyth F, Le Couteur D, HilmerS. The Prevalence of Heart Failure Pharmacotherapy, Frailty and Adverse Drug Events in Hospitalised Adults over 75 years: A Multi-Centre Cross-Sectional Study of TO HOME. Aged Care Department, Royal North Shore Hospital. Sydney, 2024.

Conference Poster Presentation

Duong MH, Gnjjidic D, McLachlan A, Winardi K, Bennett A, Hilmer S. Prevalence of heart failure-pharmacotherapy, adverse events and frailty in inpatients ≥ 75 years
Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) and Australasian Pharmaceutical Science Association (APSA) joint annual conference. Melbourne, 2024.



CHAPTER 5

5.1 Overview

Gaps in the literature discussed throughout this thesis highlights the importance of considering patient-centred outcomes across multiple health domains and multi-disciplinary teams in the management of heart failure in older adults with frailty.

In Chapter 5, qualitative findings were used to synthesise a novel conceptual model that highlights the complex interplay between adverse drug events (ADEs), adverse drug withdrawal effects (ADWEs), progression of heart failure symptoms, and quality of life in older adults with frailty. Perspectives from 32 consumers and healthcare professional on the identification and management of ADEs and ADWEs of heart failure pharmacotherapy in people older adults with frailty were explored. Key findings suggest optimisation of heart failure pharmacotherapy in older adults with frailty is influenced by factors related to the individual, medications and access to healthcare services. Consumers and healthcare professional showed they shared goals for improving patient quality of life, but their approaches to achieving this may differ due to dynamic and complex influences. Most participants perceived the benefits of heart failure pharmacotherapy and ADWEs of worsening heart failure symptoms outweighed the risks of ADEs and were hesitant to deprescribe. Improved multi-disciplinary coordination is needed. The proposed patient-centred conceptual model needs to be further developed in future research.

5.2 Authorship attribution statement

Chapter 5 of this thesis is a manuscript under review submitted as:

Duong MH, Gnjidic D, McLachlan AJ, Kouladjian O'Donnell L, Trivedi R, Kozor R, Hilmer S. Adverse drug events associated with heart failure pharmacotherapy in older people living with frailty: a qualitative study. *CJC Open*. 2024; (*Under review, Dec 12, 2024*).

The coauthors of the paper, “Adverse drug events associated with heart failure pharmacotherapy in older people living with frailty: a qualitative study”, confirm that Mai H Duong has made the following contributions:

I, Mai Duong, co-designed the study with co-authors, provided resources and software, collected, validated and curated the data, conducted investigation, analysis, performed visualisation and interpretation of the findings, wrote the original draft of the manuscript and revised and edited the manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Sarah N Hilmer

January 31, 2025

5.3 Manuscript: Adverse Drug Events Associated With Heart Failure Pharmacotherapy In Older People Living With Frailty: A Qualitative Study.

Authors

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5.3.1 Abstract

Background: Adverse drug events (ADEs) from Heart Failure (HF) pharmacotherapy are common in older people with frailty but evidence to optimise HF-pharmacotherapy is uncertain. This study explores consumer and healthcare professional (HCP) perspectives on ADEs and adverse drug withdrawal effects (ADWEs) related to HF-pharmacotherapy to inform key domains of a conceptual model.

Methods: A purposive and snowball sample were contacted directly or recruited by distribution of advertisements to professional and community networks in Australia/New Zealand to participate in qualitative semi-structured interviews and focus groups. Frailty was explained as a measure of cumulative deficits and consumers (caregivers or individuals ≥ 65 years with HF and frailty) and HCPs caring for older patients with HF and frailty were invited according to their self-perception or evaluation of frailty. General inductive analysis identified themes. Consensus of responses informed the conceptual model.

Results: Thirty-two participants were recruited (consumers ($n = 4$), cardiologists/other physicians ($n = 9$), nurses ($n = 8$), and pharmacists ($n = 11$)). Three main themes and eight subthemes related to individual factors, medications and access to healthcare services were identified. Consumers stated they want support to maintain their quality of life but have complex issues. Most HPC participants perceived the benefits of HF-pharmacotherapy outweigh the risks of ADEs and are hesitant to deprescribe. Participants wanted improved coordination of multi-disciplinary teams and patient access to healthcare services.

Conclusion: Perspectives unique to medication management in older people with HF and frailty characterise how individualising the interplay of ADEs and ADWEs contribute to individuals' well-being and may be developed for future research and practice.

5.3.2 Introduction

The prevalence of heart failure (HF) is increasing in the aging population, particularly in people aged over 75 years.¹ HF is associated with high mortality (50% die within 5 years of diagnosis) and hospitalisation.² Optimisation of guideline-directed medical therapies (GDMT) has improved mortality and hospitalisation outcomes, particularly for HF with reduced ejection fraction (HFrEF).³ However, treatment for HF with preserved ejection fraction (HFpEF), more prevalent amongst older people, focuses on providing symptomatic relief and managing comorbidities.³ Despite potential benefits of GDMT, patients frequently experience adverse drug events (ADEs) which impact their quality of life (QoL) and increase the likelihood of medication changes.⁴ Compared to those aged under 65 years, people over 80 years report lower adherence and higher rates of discontinuation.⁵

Frailty, a reversible syndrome involving multi-system deficiencies, is a measure of cumulative deficits in individuals' physical, pharmacological, cognitive, nutritional, and psychosocial status. Frailty is prevalent in up to 75% of older HF patients living in the community⁶ and associated with increased risk of adverse outcomes and 2-fold risk of mortality.⁷ As the threshold to recover from injury or insult decreases, patients become more focused on improving QoL and report they value maintaining their health, well-being and happiness.^{8,9} Reduced tolerance to ADEs from treatments guided by medication regimens trialled in younger robust populations that prioritise prolongation of life, create challenges to optimising HF-pharmacotherapies. This approach may not always be suitable in individuals with advanced age, who may value optimising QoL over longevity.¹⁰

Deprescribing, the supervised withdrawal of a medication, may be considered in situations where adverse effects cannot be tolerated and harm outweighs the risk of continuing medications. However, a paucity of evidence is available to provide guidance on how to guide complex HF medication management in older people with frailty that supports person-centred outcomes. Managing polypharmacy in this population requires a multi-disciplinary team to optimise therapy in line with patients' functional status and goals.¹¹ This study aims to explore the perspectives of consumers and healthcare professionals (HCPs) on ADEs and adverse drug withdrawal effects (ADWEs) of HF-pharmacotherapy in frail older people. The secondary aims use these perspectives to inform key domains and structure of a conceptual model for prescribing and deprescribing HF-pharmacotherapy in older people with frailty.

5.3.3 Methods

Recruitment

Ethics approval for this qualitative study was obtained from the Human Research Ethics Committee, the University of Sydney (2022/811). A purposive and snowball sample was recruited from 01/02/2023 to 15/06/2023 from primary, long-term and hospital care settings in Australia and New Zealand. Participants were approached directly by the researcher (MHD) or recruited through electronically distributed advertisements to professional and community networks and invited to contact the research team. Frailty was explained to participants as a measure of cumulative deficits (i.e., Fried phenotype, frailty index) and were invited according to their self-perception or evaluation of frailty. Participants were recruited until thematic saturation was achieved.¹²

Participants

Consumer participants included people ≥ 65 years with lived experience of HF and frailty or their caregivers and consumer advocates who perceived that the person they cared for was frail. HCPs caring for patients with HF who they identified as frail in their routine care were interviewed, this included specialist physicians (i.e., cardiologists, geriatricians, hospital general physicians, advanced trainees), nurses and pharmacists. Written informed consent was obtained from all participants.

Data collection

Semi-structured interview questions were developed with the existing frameworks for cardiovascular disease management, adverse drug reaction (ADR) classifications, frailty, medication review, and the deprescribing process¹³⁻¹⁵ to provide a comprehensive overview

of relevant factors to investigate. These frameworks of outcomes and adverse effects were used to develop questions pertaining to HF-pharmacotherapy ADEs, particularly regarding identification, severity, cause, and management. The interview guide [Supplementary S5.2] was piloted with a research pharmacist (LKO) and a hospital staff member aged ≥ 70 years for content validity. A research pharmacist (MHD) with extensive qualitative methodology experience conducted interviews and focus groups in-person or via telephone/videoconferencing with consumers and HCPs. The flexibility to participate in interviews or focus groups was adapted to the privacy, functional capacity or workflow needs of participants. Interviews and focus groups were audio-recorded, transcribed verbatim, verified for accuracy (MHD), and de-identified.

Data analysis

A general inductive approach¹⁶ guided coding of the transcripts to explore issues related to management of ADEs and ADWEs in frail older people to determine main themes and subthemes in Microsoft Excel®2023. Three reviewers (MHD, RT, LKO) independently reviewed de-identified transcripts and coded the data. The investigator team, which included multidisciplinary HCPs (e.g., geriatricians, cardiologists, pharmacists, pharmacologists) and researchers with expertise in qualitative research, met periodically during data collection and analysis to discuss themes. Disagreements of themes were discussed until consensus was reached. Data from sub-themes were used to synthesise the conceptual model. Consumer and HCP reported clinical outcomes, ADEs and ADWEs were identified and compared for overlapping terms to synthesise a conceptual model. Face-validity of themes and the conceptual model was agreed among the multi-disciplinary investigatory team. Data was reported according to the Consolidated Criteria for Reporting Qualitative Research checklist [Supplementary Table S5.1].¹⁷

5.3.4 Results

Thirty-two participants, including four consumers (individuals with lived experience ($n = 2$), caregivers ($n = 2$)) and 28 HCPs (specialist physicians ($n = 9$), nurses ($n = 8$), pharmacists ($n = 11$), participated in semi-structured interviews ($n = 22$) and focus groups ($n = 4$) lasting mean 53 ± 13.5 minutes, across a range of health settings and specialties (Table 5.1). Interested participants were deemed ineligible if they were people with lived experience ($n = 4$) who described their function as robust and did not identify as frail, or HCPs (pharmacists $n = 3$, cardiologists $n = 2$, nurses $n = 2$) that expressed interest in the study but did not submit consent forms after the researcher followed-up.

The three main themes identified and supported with supporting quotes were (1) individual factors, (2) medications and (3) access to healthcare. Eight subthemes describe management and characteristics of ADEs and ADWEs in this population. General and therapeutic class-specific ADEs and ADWEs are described in Supplementary Tables S1-S2. Consensus on the identification of outcomes, ADEs, and ADWEs reported showed all participants shared similar goals for patients. However, the approach to achieving these outcomes and which aspects of the individual to support, differed between specialties. Findings support that optimising patient outcomes and HF-pharmacotherapy in frail older people necessitates holistic and individualised approaches to care.

Table 5.1: Participant characteristics (*n* = 32).

Consumers (<i>n</i> = 4)		
Sample, <i>n</i> (%)	Person with lived experience Caregivers	2 (50%) 2 (50%)
Gender, <i>n</i> (%)	Female	3 (75%)
Age (years) (mean, SD)	Person with lived experience Caregivers	80, 5.5 62, 0
Average minutes for interviews (mean, SD)		52, 11.4
Healthcare professionals (HCP) (<i>n</i> = 28)		
Sample, <i>n</i> (%)	Physician	9 (32%)
	Cardiologist	5 (18%)
	Other:	4 (14%)
	Geriatrician	3 (11%)
	Clinical Pharmacologist	1 (4%)
	Nurses	8 (29%)
	Practitioner	4 (14%)
	Registered	4 (14%)
	Pharmacists	11 (39%)
Gender, <i>n</i> (%)	Female	27 (82%)
Age (years)* (mean, SD)		45, 13.5
Setting, <i>n</i> (%)	Hospital	14 (50%)
	Outpatient Service/Rehab/Clinic	3 (11%)
	Residential Aged Care	1 (4%)
	Primary Care/Community	3 (11%)
	Combination	
	Hospital/Community	4 (14%)
	Hospital/Cardiology clinic	2 (7%)
	Cardiology Clinic/Community	1 (4%)
Number of years in practice role, <i>n</i> (%)	1-10 years	7 (25%)
	11-20 years	9 (32%)
	> 20 years	12 (43%)
Average minutes (mean, SD) for		54, 24.1
Interviews		52.1, 12.5
Focus groups		54.9, 8.8

Abbreviation: HCP = healthcare professional; SD = standard deviation; Rehab = rehabilitation;

Footnote: *4 HCP participants did not disclose age.

Theme 1: Individual factors

Complex patient factors: All consumers and HCPs described older people living with frailty and HF have multiple complex issues to consider; including their HF phenotype, changes in cognition and function, and interaction with treatment of other comorbidities, which can influence the extent of benefit from HF-pharmacotherapy and/or tolerate adverse effects.

“In older patients, I see a lot of high potassium, renal function is off and [their] blood pressure has dropped.” -Pharmacist-9

“It's that extra effort one has to put into chores. It's quite hard. It's a range of [anxiety] about things and may come from the stroke and having low vision. I go to do something and feel like I can't. In all fairness, I can't blame the medication for that.” -Consumer-55

Although defining frailty status can determine an individual's potential reserve or threshold to adjust to functional or cognitive changes, objective measures of frailty are not routinely assessed. HCPs described various approaches to considering frailty in management of patients with HF.

“You have to adapt your approach to frailty. I don't know how good I am, or my field, is, at engaging frailty. The way I gauge frailty might be very different to someone else. I tend to overcall frailty based on mobility, which is not the same thing.” -Cardiologist-29

Supporting patients' autonomy: Older individuals who identified as frail described that they want the dignity, confidence, and choice to live independently at home and perform daily activities they enjoy and maintain social engagements.

“[Diuretics] caused frequency. The thought that [dad] could humiliate himself by not making it to a bathroom in time is degrading. It's challenging to an older person's dignity, and the knock-on effects are they tend to withdraw from social activities. They

don't want to risk making fools of themselves [or] be too far from a bathroom.” - Consumer- 53

Individuals’ goals and expectations can vary, and participants suggest the support of caregivers and advocates can support shared decision-making to optimise the individuals’ QoL and perform the activities that are valuable to them. They also acknowledged the balance between optimisation and QoL should be flexible and tailored for individuals with limited function and frailty.

“The goal is to improve connections so I can be confident enough to do the things I used to thoroughly enjoy doing. I am very lucky I've got people that care. I'm in quite a privileged safe environment. I'm not alone. I've got family and good support.” - Consumer-55

Theme 2: Medications

Medication management: There was variation in how participants prioritise their medications and health outcomes. Consumers explained maintaining their QoL was most important.

“Quality of life is at the top. Rebuilding a joie de vivre [joy of living].”-Consumer-55

HCPs described using evidence-based GDMT to prolong life, reduce hospitalisation and improve functions needed to perform activities of daily living. HCPs describe optimising GDMT entails dynamic and frequent changes; including re-challenging or up-titrating medications once ADEs resolve. HCPs acknowledge very old and frail patients seldom reach target doses from clinical trials. Therefore, they recommend initiating GDMT at lower doses and up-titrating very slowly in smaller increments and wider intervals. This allows individuals more time to adjust to a single-agent, one change at a time and with close monitoring.

“Single-agent might be more appropriate and up-titrating that one, rather than the combinations of medications that can increase adverse effects.” -Pharmacist-18

However, the under-use of GDMT in frail older people was commonly described by HCPs.

This can be attributed to limited tolerability of side effects and shifting focus on symptomatic relief to maintain QoL, if possible.

“The titrating and the people coming in and out of their life. It's the [use of] diuretics, the pill burden, and the burden of getting to and from medical appointments in the frail that potentially have equal consequences as the tablets.” -Nurse-10

Participants describe optimisation of GDMT and the potential benefits and harms in very old frail people is not supported by the evidence, particularly for people with HFpEF.

“HFpEFs pretty straightforward as to what the evidence is. HFpEF is still evolving. I find it so much more difficult to treat.” -Nurse-11

Due to the absence of frailty measures in clinical trial data, HCPs expressed uncertainty of how to tailor medications, with shifting health priorities from longevity to maintaining QoL. Particularly in those with cognitive impairment or dementia, who have difficulty adhering to medication regimens, consumers expressed high anxiety from using multiple-medications, potential drug-interactions, adverse effects or frequent medication/dose changes. This response varied depending on patients' attitudes and beliefs around medications. Although polypharmacy and the associated challenges was highly prevalent among this patient population, HCPs preferred optimising GDMT to target clinical outcomes and viewed polypharmacy as an issue separate from managing HF symptoms.

“The issue of polypharmacy, pills interacting and having too many pills, is a separate issue. It's a matter of which ones required, and which are not. Patients don't like taking medications; I wouldn't, no one does. Polypharmacy is a real issue. Cardiologists get a label they struggle to stop things, pro-intervention, pro-treatment, pro-lengthening life, potentially at a cost.” -Cardiologist-29

Identification and management of ADEs: HCPs explained how they expect adverse effects and consider preventing or mitigating them during selection, initiation, and up-titration of GDMT. HCPs described that they closely monitor common adverse effects (e.g.,

postural hypotension, dizziness, worsening renal function, electrolyte imbalance), but did not probe patients for all potential side effects.

“You could have frequency and incontinence with diuretics. Dehydration with rise in creatinine, people feeling weak, dizzy and often their blood pressure goes down. Electrolyte abnormalities, like low potassium or sodium, often is symptomatic. They may be drowsy, low or reduced level of consciousness, hypotensive, and very dry. Delirium is not just dioxin toxicity. You can have delirium as a consequence of any of these side effects, low sodium, dehydration, AKI (acute kidney injury).” -Physician-19

Participants described that this was underscored by difficulty sometimes distinguishing whether symptoms were caused by underlying comorbidities or medications.

“If you don't have the skills to recognise fluid overload, you'll miss the decompensation and treat the symptoms as being medication-related and not decompensation. Worsening creatinine and they don't assess the volume status. Non-HF doctors will go, ‘the creatinine is rising, they're dehydrated. Quick stop things’. That can be worsening congestion.” -Cardiologist-12

“When withdrawing therapies because of QoL, is it the medication causing this deterioration or something deeper? Some patients are so cachexic, frail and malnourished with albumin above 15. Is ketoacidosis progression of their dementia due to effectively no oral intake or is this HF-related?” -Cardiologist-28

HCPs explained they ranked the severity of ADEs mostly based on the patients' symptomatic response and how the ADE impacted the patient's function or increased risk of severe outcomes (e.g., hyperkalemia, hospitalisation due to falls).

“Rise in creatinine is so ubiquitous in cardiac failure, in that you always ignore them unless they're very impressive. Blood pressure... We're big advocates of, ‘if it's not symptomatic hypotension, it's not hypotension’. It's life-limiting symptoms that matter. If it's tolerable, not life-limiting or not hospitalisation-inducing, then it doesn't really matter that much, you kind of ignore it or try and push through.” -Cardiologist-12

HCPs described adjusting treatment if patients raised specific concerns about symptoms, which depend on the patients' preference to engage. But most consumers reported little knowledge of what adverse effects to expect and likely noticed only those that impacted their QoL or ability to engage in normal daily activities.

“When you have so many medications, you don't know the effects of one medication against the other. Whether it could be a mixture of that medication that's causing a problem.” -Consumer-50

“It depends on the person. A lot of patients volunteer everything and a lot volunteer nothing until you probe them. Then other people grin and bear, don't really notice the side effects, but if you ask, on next follow-up they would tell me. I always ask about postural hypotension, dizziness, palpitations, chest pain tightness, breathlessness, exercise intolerance in every patient”. -Cardiologist-25

All participants acknowledged the importance of HF-medications and the challenges involved in weighing the benefits of preventing decompensation and worsening HF against the potential adverse effects and impact on their QoL. These medications were associated with adverse effects that individuals accepted and often self-managed to maintain their benefits or switch to alternative medications. These adjustments are not always manageable, and some participants express concern about the burden of tolerating adverse effects on the QoL of very frail old individuals with shorter life-expectancy.

“The problem is the number of medications and potential interactions. One of our big issues is patients falling down with hypotensive drugs. With furosemide, needing to get to the bathroom quickly [is a] falls concern.” -Nurse-13

ADWE considerations: Most HCPs noted ADWEs of GDMT were rarely observed. But when they occurred, were severe and urgent (e.g., angina, decompensation), requiring immediate re-initiation of the ceased medication. Deprescribing was seen as very dynamic, particularly during acute illness.

“Discontinued can be different than stopped for a while. Doesn't mean they can't ever have it again. It just means we need to start again, but not all of them. If they need some antibiotic that's going through the kidneys, then you are going to give that priority and stop diuretics. We can stop [SGLT2-i] and start them again. It's flexible.” - Nurse-6

The most common ADWE described by HCPs was worsening of HF symptoms requiring hospitalisation. Due to the lack of evidence-based guidance and loss of potential treatment

benefit, HCPs expressed hesitancy to deprescribe HF-medications. HCPs viewed the loss of treatment benefit on mortality, hospitalisation and HF symptom control to be particularly harmful in patients with HFrEF. In patients with stable asymptomatic HF, HCPs have reported harm from deprescribing.

“We leave the HF meds in because we think it might be contributing to them feeling better. We’re trying to make things better and taking those drugs away may make them feel worse. It’s to try and improve their QoL, reduce hospitalisations, reduce death.” Pharmacist-4

“I fully support deprescribing, particularly in older patients. But if you’re committed to HF, I don’t support deprescribing. Those patients have got to be on it. There’s literature around stopping medications at the end-of-life.” -Pharmacologist-24

All HCPs considered maintaining GDMT in HFrEF patients necessary if safe to do so and preferred deprescribing non-HF medications to reduce the patients’ drug burden. However, some HCPs viewed deprescribing in HFpEF as appropriate due lack of clinical trials demonstrating clear benefit.

“If they’ve HFpEF, it’s easy. There’s no evidence for it. Although it’s interesting, the evidence from [SGLT2-i trials].” -Physician-23

HCPs provided some examples where deprescribing was considered if the benefit of deprescribing outweighed the risk such as obvious drug-related harm (e.g., risk of cardiac arrest from hyperkalaemia).

“It’s more than patients reporting how they feel. You have to anticipate harm to that patient, because they’re not going to feel hyperkalaemia until they have an arrest. There’s clear harm it’s going to cause that patient because we’ve initiated or up titrated their ACE-inhibitor. Hyperkalaemia is a likely cause of hospitalisation we want to try and minimise. Sudden hypotension related to a change, if a big change rather than a small change, degrees of change.” -Nurse-14

Permanent deprescribing was also considered when withholding medications improved patient stability after repeated episodes of adverse events or the treatment was no longer effective (e.g., diuretic resistance, urosepsis). Most commonly, deprescribing of HF-

medications was viewed as a response to progressive deterioration, end-of-life, or improved healthy lifestyle habits (e.g., diet, exercise) that reduce the need for symptom control.

“If you have to constantly cease and then restart, because they can't tolerate, I don't think that's a good idea. Especially with Entresto, when you start that's where hypotension affects [them] and then before you know [it] you have to stop again.” - Cardiologist-27

Facilitators and barriers to patient education and information about benefits

and harms: Communication with older people with frailty and their caregivers can be challenging when discussing the balance between taking medications and maintaining an acceptable QoL.

“Getting a new or upping a medication I always talk to the GP, ‘how's this going to affect everything else that I take?’ Because that's important. They throw in the tablets and say, ‘oh, this will be good for bloating’, or something like that. But I always ask, ‘how does it affect everything else?’” - Consumer-55

“These patients have very limited capacity to take on information. When you first see them, they're mentally dull, can't follow conversations, so slow. I write everything down because I assume they're going to remember nothing and give them to take it home.” -Physician-24

Study participants suggested facilitating communication during shared decision-making with consumers can involve repeating the benefits and harms of medications, referencing patients' function, and adjusting treatment approaches to support their QoL.

“We use functionality because the word frailty can have a negative connotation if you are telling them they're frail. I focus on safety because you don't want anything to happen at the expense of increasing a drug that they have a fall into a hip and then they've pneumonia and in hospital.” -Nurse-26

Conversely, consumers expressed frustration from the lack of knowledge, confidence and availability of HCPs to help them manage their ADEs and ADWEs.

“I've changed doctors because some of them I just got, “no, I don't know”. I really struggle with them because of their ideas and then they've got no idea on medication. I don't know why, but I get more brains out of my pharmacist. He's very good.” - Consumer-50

HCPs describe having limited time and opportunity with patients; thus, discern the most relevant information to communicate effectively.

“Not that GPs don't care, [but] that it's not their focus. They have 5-15 minutes with a patient. They don't do pre-reading. They don't have the capacity. Whatever they've got in front of them, they do... [The cardiology team] see patients the most and do that. The whole goal of many of the clinics is to titrate patients up to the maximally titrated doses.” -Nurse-6

Theme 3: Access to Healthcare Services

Multidisciplinary approach: Participants describe frail older people receive care across multiple health settings, requiring coordination and communication across multiple specialties to manage adverse effects. While all HCPs agree the overall patient status is always taken into consideration during shared decision-making, they also express conflicting approaches between different specialties in managing outcomes for single-organ diseases compared to global patient function.

“The battle is, not always but sometimes, each of the individual organ systems are actually in opposition. That's the challenge for us as a multidisciplinary team, is we're all trying to optimise the organ system that we are specialists in to the best of our ability. But it comes at a cost to other organ systems when you have a frail patient.” - Cardiologist-28

“The final common denominator for the geriatrician is overall function. Whereas for the cardiologist, it's cardiac function.” -Physician-19

This tension can create challenges during sharing of information or overall responsibility of the patient's care.

“At the end of the day, if you are a clinician looking after this patient, like a geriatrician, you should make the call, don't even bother consulting cardiology. Some teams will do too much and some too little. It's better if there's some middle ground that the team can get to [and] doctor-dependent. Especially if they're quite frail and advanced in age, probably cardiology is not going to be the best team to manage them.” -Cardiologist-27

Consumers and HCPs expressed frustration in the provision of ongoing care and follow up of older frail HF patients, particularly when sharing information.

“Whether it's HFrEF or HFpEF is very difficult to find in medical notes and discharge summaries to see the results of an echo, which are not often enclosed. Sometimes the cardiologist is the only one who knows whether it's HFrEF or HFpEF.” -Pharmacist-2

Oftentimes specialists optimising GDMT are not often the same ones managing adverse effects caused by the GDMT and/or co-morbidities in individuals living at home. Thus, all HCPs expressed improved coordinated multidisciplinary expertise is needed to navigate complex frail older people and provide advice on how to adjust dosing during GDMT optimisation for specific ADEs between health settings and HCPs.

“I've gotten very frail patients to target doses over a long time. They get hospitalised for something else and non-cardiac teams stop all their pills. I build them back up again from scratch.” -Cardiologist-12

Patient access to care: In order for frail older people to adhere to the strategies described by HCPs, they require frequent monitoring and access to support by caregivers and health services. Health services extending into the community where individuals could receive support at home to manage and coordinate their care were particularly valuable.

“True adverse effects, the serious ones, don't come to a clinic. You get the reason why something started was stopped taken out of context, it's tricky. There's a role for HF specific clinics and nurse practitioner education clinics where someone is dedicated and patients are followed a lot more.” - Cardiologist-29

However, the physical and cognitive demands on very frail older individuals to coordinate access healthcare services (e.g., mobilising to the GP's office, pathology laboratory, pharmacy, physiotherapy, specialist clinic, hospital) to achieve optimal benefit from their HF-treatments or manage adverse effects may not always be feasible, practical or affordable; further exacerbating health inequities.

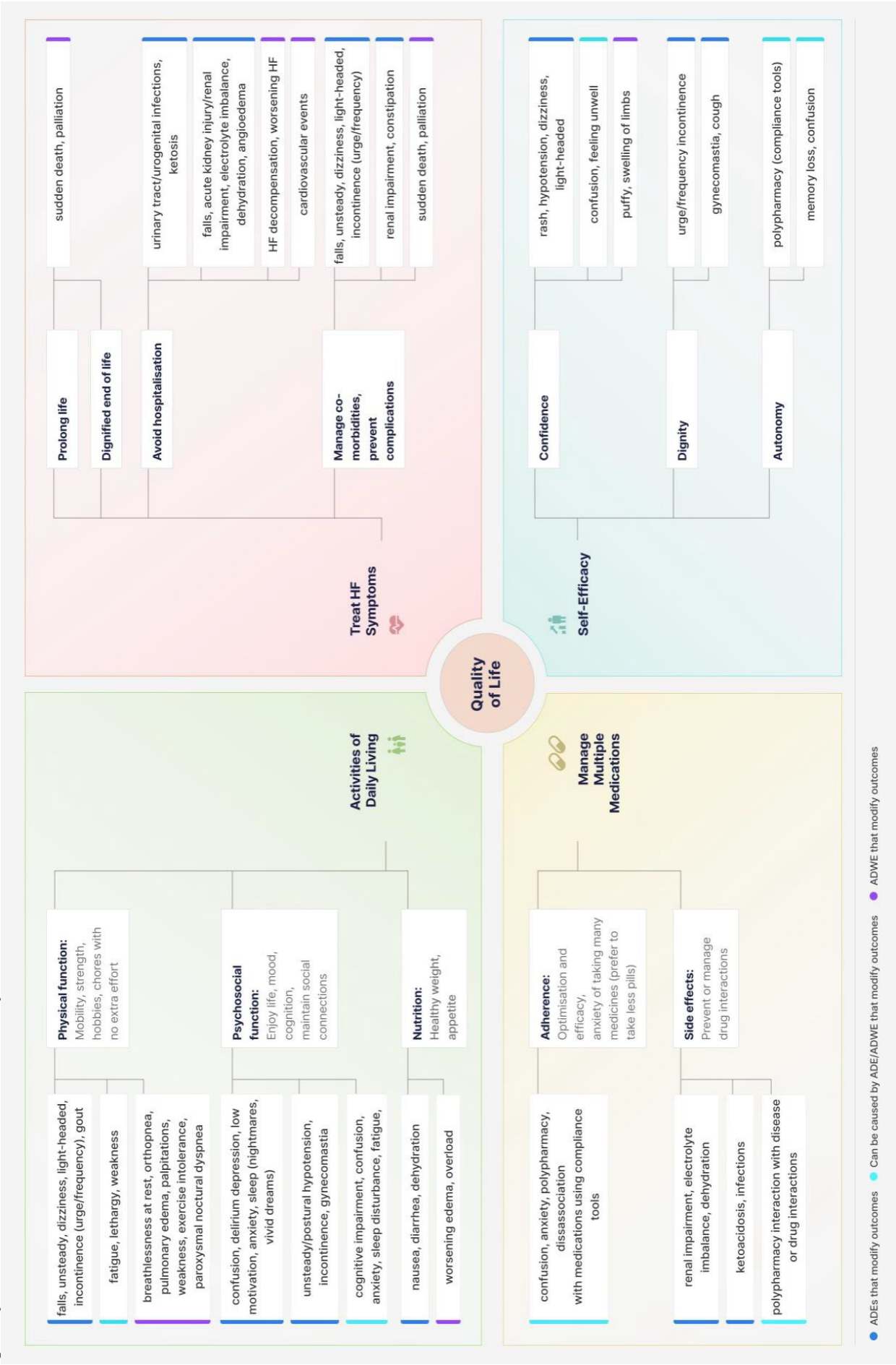
“[To see a cardiologist], do you have to find accommodation somewhere? Most of them don't drive. There is no public transport. People in the [rural] community if they haven't got funds and transport, they would go without an echo, even people who are not frail necessarily. They haven't got the access. We have quite a low socioeconomic population here.” -Pharmacist-4

“Some patients don't have GPs they can get into and/or they need a home visiting GP because they're not mobile and it's not [available]. It's really hard. Part of our role in the community is to check and make sure the GP is getting enough support. The GPs in this area are very overworked. It takes our patients a couple of weeks to get an appointment.” -Nurse-10

Characterisation of clinical outcomes, ADEs and ADWEs

Inductive analysis provided a hypothesis-generating model based on the consensus of prioritising QoL in older people with frailty. The conceptual model shown in Figure 5.1 illustrates overlapping responses from consumers and HCPs using participant descriptions of the most common clinical outcomes (Supplementary-Table S5.1), ADEs by therapeutic class (Supplementary-Table S5.2) and ADWEs (Supplementary-Table S5.3). The model demonstrates the interplay between commonly reported ADEs and ADWEs from HF-pharmacotherapy, that can potentially influence aspects of QoL in people with advanced age and frailty. For example, an outcome can be that patients want to maintain their ADLs, with adequate physical function to be mobile and strong enough to perform the hobbies they enjoy and chores without excessive effort. However, medications can cause dizziness, unsteadiness or incontinence that could lead to increased falls risks that would impact their physical function and confidence. In contrast, the risk of worsening HF symptoms such as breathlessness at rest, orthopnoea, and weakness due to deprescribing may similarly limit their physical function and independence and lead to hospitalisation. Individuals can experience fatigue or weakness because of an ADE, ADWE, frailty and/or comorbidities which can exacerbate current limitations in their physical or cognitive function.

Figure 5.1: Perceptions of the effect of Adverse Drug Events and Adverse Drug Withdrawal Events from heart failure pharmacotherapy on the quality of life of older adults with frailty



5.3.5 Discussion

This study identified consumer and HCP perspectives unique to medication management in older people living with HF and frailty. Consumers and HCPs share similar goals for improving patient QoL, but their approaches to achieving this may differ due to dynamic and complex influences. This novel patient-centred conceptual model proposes how tailoring treatment care plans to consider frailty status can mitigate potential adverse effects during prescribing and deprescribing of HF-pharmacotherapy. This model can be further developed to guide future research and/or customise multi-disciplinary clinical tools tailored to the complex and dynamic priorities of older people with frailty among diverse populations, such as integrating appropriate deprescribing guidance.¹⁵

Findings confirm maintaining QoL is the highest priority for older people with frailty. Participants' descriptions align with the *capability approach*; whereby, wellbeing is valued as what is practically possible for individuals to do in their daily lives.¹⁸ This can be functioning in ADLs that achieve self-respect and social integration, as well as the freedom to accomplish things they value.¹⁹ Management of HF symptoms, ADEs and ADWEs potentially contribute to both improving and worsening individuals' QoL. Participants' reasons for deprescribing were aligned with deprescribing frameworks,¹⁵ mainly due to no indication for all GDMT in HFpEF, ADEs like falls risks outweighed potential benefits to prolong life and were unlikely to be realised because of limited life expectancy. Hesitation to deprescribe was due to uncertainty of evidence to predict recurrence of HF symptoms but participants were less concerned with the lack of evidence on how to taper medications. The STOPP-Frail criteria²⁰ do not specifically address HF treatments. STOPP-Frail reports physiological withdrawal

effects were unlikely in deprescribing angiotensin converting enzyme inhibitors and angiotensin receptor blockers to prevent diabetic nephropathy. Deprescribing clinical trials are required to inform whether this applies to HF and if this precludes the long-term benefits²¹. Future research could explore how the conceptual model could support the deprescribing process in older individuals with HF and frailty to support optimisation of HF-pharmacotherapy.¹⁵

In some instances, optimisation of single-organ/disease specific medications potentially conflicted with other treatment guidelines or global function.²² For example, cardiologists preferred optimisation of HF-GDMT to maximise benefits to treatment, regardless of the blood pressure value, unless the individual demonstrated physical symptoms of hypotension. In contrast, guidelines for hypertension management in people ≥ 65 years take into consideration the risks of frailty and propose target blood pressure between $<130/80\text{mmHg}$ and $<150/90\text{mmHg}$.²³ Similarly, contraindications or dose adjustments for risks associated with renal impairment/failure can create challenges when communicating with multi-disciplinary teams and contradict patient education. Thus, efficacy and safety data from clinical trials involving frail older people, real world observational data on HF treatment and outcomes that objectively measures frailty,²⁴ and guidelines to manage ADEs that interact with global patient function and/or other organ systems is needed.

The widespread uncertainty surrounding decisions to manage ADEs and ADWEs associated with HF-pharmacotherapy in older people with frailty warrants more evidence and practice models to support caring for this population. Older people with frailty have the right to equal access to life-saving HF-pharmacotherapy. But this study raises concerns with the

uncertainty of evidence-based efficacy for people ≥ 75 years with frailty, medication harm, equitable access to treatment and monitoring, and upholding the right to self-determination and/or caregiver decisions in individuals with cognitive impairment.²⁵ Individualising HF management that considers the dynamic interplay of ADEs, ADWEs and frailty according to patient-centred outcomes is consistent with practical tips to adjust pharmacotherapy in advanced HF,²⁶ domain management of HF²⁷ and barriers to deprescribing cardiovascular medications in geriatric patients.²⁸ This study aligns with a call for more country-specific and international research to optimise prescribing in older people with functional challenges.^{24,29} This underpins the need for further development of the person-centred conceptual model to determine how frailty risks and medication reviews can be integrated into HF treatment algorithms, tailored to specific drug classes/combinations, and/or adapted for multi-disciplinary clinical tools.^{3,15}

This qualitative study of consumer and HCP perspectives provides new insights that consider how frailty status of older adults can impact communication and evaluation of ADEs and ADWEs associated with HF-pharmacotherapy. Interview questions were piloted and data analysis involved three independent researchers and reviewed by a multi-disciplinary team. Themes were triangulated with the *capability approach* and reviewed by multiple specialists. The low number interviews with lived experience, reflects recruitment challenges involving older people with HF and frailty living in the community or diverse populations. Participation of older people with HF and frailty demonstrated that more time was needed to interview participants compared to the pilot. The interviews took approximately one hour due to extended time taken for participants to comfortably reflect and describe their responses in relation to their circumstances, provide rich personal stories and include pauses when the individual had difficulty recalling events, which enabled participants the opportunity to respond. Common adverse effects identified for each therapeutic class could be evaluated in clinical trials.

Limitations in this study include sampling bias, due to small sample size and lack of ethnicity reporting in a population predominantly of people of European geographic ancestry, but still reached thematic saturation. Furthermore, frailty was self-reported by participants, not formally assessed nor objectively measured in participants. HF phenotypes were not identified, but similar QoL goals were reported for symptomatic HFrEF and HFpEF.³⁰ Future studies may mitigate the burden on participants using co-design approaches. Researchers may consider conducting interviews according to the 5T's framework of communication and specified strategies to improve evaluation of medications in older adults.^{31,32,33} The generalisability of the findings needs to be confirmed with future studies that include individuals from other countries, health settings and diverse populations. General practitioner, physiotherapist and other allied HCP views were not represented despite invitations to participate in this study; thus, should be considered in future research. Consumer involvement in further development and testing of the conceptual model can reduce the burden on people with frailty by using a co-design approach or creating separate frameworks for consumers and health professionals.

This study explores consumer and HCP perspectives to develop a conceptual model that illustrates how information on ADEs and ADWEs may be used to tailor HF-pharmacotherapy around QoL for people with advanced age and frailty. This may guide discussions about the benefits and harms of HF-pharmacotherapy during shared decision making. This study introduces a paradigm shift from pharmacovigilance reporting, which focuses on HCP responses to adverse events, to characterising whether ADEs and ADWEs impact attributes of an individual's well-being and ability to maintain an acceptable QoL. This model supports an individualised approach to managing ADEs and ADWEs of HF-pharmacotherapy in frail older people during shared decision-making. Evaluation of common ADEs and ADWEs identified in this study can be included in future clinical trials involving

frail older participants. Further research is needed to determine how this information can be applied to support individualised care plans and sustainable models of care.

5.3.6 Funding and Acknowledgements

Mai Duong is funded by the Commonwealth of Australia National Health and Medical Research Council (NHMRC) Postgraduate Scholarship Grant APP1191018 awarded in 2020, HROz Scholarship awarded in 2023-24 and the University of Sydney Postgraduate Research Support Scheme 2022-24. We acknowledge the recruitment support and resources from Heart Research Australia (HROz), Queensland Heart Failure Services, Heart Support Australia and Hearts 4 Hearts. We appreciate the valuable time and insights provided by all participants. We acknowledge Ryan Snow for his graphic design support. We appreciate Kristie Weir and Maureen Bartels for reviewing the pilot questions.

5.3.7 Disclosures

None.

5.3.8 References

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5.4 Supplementary Material

Refer to Appendix D: Chapter 5 Supplementary Materials

5.5 Research Presentations

Preliminary results were presented in oral and poster presentations as:

Conference Oral Presentations

Duong MH, Gnjdjic D, McLachlan A, Kouladjian O Donnell L, Trivedi R, Kozar R, Hilmer S. Adverse drug events and adverse drug withdrawal effects of heart failure pharmacotherapy in frail older people. Australasian Society of Clinical & Experimental Pharmacologists & Toxicologists (ASCEPT) Student and Early Career Researcher Cardiovascular Special Interest Group Symposium. Virtual, 2023.

Duong MH, Gnjdjic D, McLachlan A, Kouladjian O Donnell L, Trivedi R, Kozar R, Hilmer S. Consumer and clinician perspectives of adverse drug events and adverse drug withdrawal effects of heart failure medications in frail older people. International Pharmaceutical Federation (FIP). Health and medicines information section and Australasian Pharmaceutical Science Association (APSA). Brisbane, 2023.

Conference Poster Presentation

Duong MH, Gnjdjic D, McLachlan A, Kouladjian O Donnell L, Trivedi R, Kozor R, Hilmer S. Adverse effects of heart failure pharmacotherapy in frail older people. Toronto-Ottawa Heart Summit. Toronto, Canada, 2023.

Published conference abstracts

Duong MH, Gnjdjic D, McLachlan A, Kouladjian O Donnell L, Trivedi R, Kozar R, Hilmer S. Consumer and clinician perspectives of adverse drug events and adverse drug withdrawal effects of heart failure medications in frail older people. *Pharmacy Education*; 2023. 23(6): 187-187. doi: [10.46542/pe.2023.236.158191](https://doi.org/10.46542/pe.2023.236.158191)

Media Activities

Duong MH. “HROz 2023”. Project summary for Heart Research Australia (HROz) 2023.

Available at <https://www.youtube.com/watch?v=Z6sEriATCRY> (last accessed on August 28, 2024)

Appendix D: NSLHD newsletter November 2023 - Available at the NSLHD e-newsletter, page 6 <https://online.flippingbook.com/view/197927661/6/>

Appendix D: International Pharmaceutical Federation (FIP) Health and Medicines

Information Section Newsletter. “*Mai Duong*”. 10 Nov 2023 - Available at

<https://us18.campaign-archive.com/?u=a6bc44c643480f96b17dc2a1a&id=b37afc63b4> (last accessed on August 28, 2024)



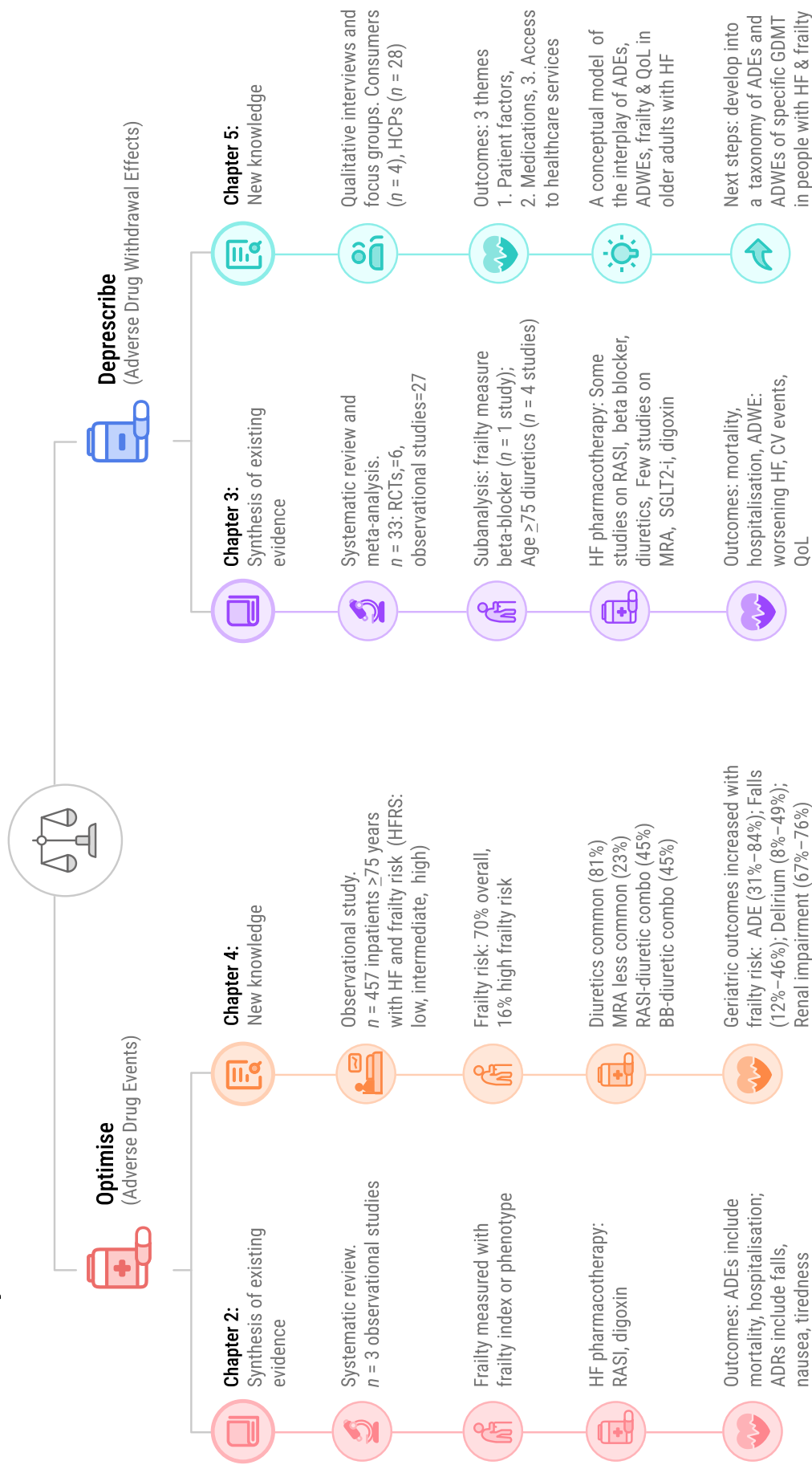
DISCUSSION AND CONCLUSION

DISCUSSION

6.1 Overview

This doctoral work highlights that there is a paucity of evidence describing the prevalence and management of the ADEs and ADWEs associated with HF pharmacotherapy in older people with frailty. Figure 6.1 provides an overview of this thesis. The findings in this thesis address the international research priorities calling for more pharmacotherapy research in older people with cardiovascular disease to optimise prescribing.¹⁻⁴ The key research areas addressed in older people with HF have included characterising the ADEs relating to evidenced-based HF medications with a potential high fall risk, evaluating the effectiveness and outcomes of deprescribing interventions, and linking person-centred outcomes to frailty and HF clinical outcomes.¹ The novel conceptual model developed adds new knowledge relevant to caring for individuals with frailty and functional impairment. This doctoral thesis presents exciting opportunities for future research in this emerging field.

Figure 6.1: Thesis summary.



Evidence Gaps and Limitations

● HF phenotypes not commonly reported. ● Limited evidence for HFpEF, HFmrEF, HFimpEF. ● Frailty is not objectively measured in research and routine clinical practice. ● Mostly report one component of frailty (physical frailty). ● Exclusion of older people with frailty in clinical trials. ● High quality evidence needed. ● Limited sample sizes. Systemic under-reporting of ADRs. ● Availability of data limited for both cardiovascular and geriatric biomarkers and outcomes.

Figure Legend: HF = Heart Failure; HFpEF = HF with Preserved Ejection Fraction; HFmrEF = HF with Mildly-Reduced Ejection Fraction; HFimpEF = HF with Improved Ejection Fraction; ADE = Adverse Drug Event; ADR = Adverse Drug Reaction; ADWE = Adverse Drug Withdrawal Effects; RASI = Renin-Angiotensin System Inhibitor; BB = Beta-Blocker; MRA = Mineralocorticoid Receptor Antagonist; SGLT2-i = Sodium Glucose coTransporter-2 Inhibitor; GDMT = Guideline-Directed Medical Therapy; HFRS = Hospital Frailty Risk Score; QoL = Quality of Life; CV = Cardiovascular; RCT = Randomised Controlled Trial; HCP = Healthcare Professional; CCI = Charlson Comorbidity Index.

6.2 Significance of key findings

6.2.1 Defining significant research gaps

There were insufficient numbers of clinical trials and high-quality observational studies to determine with certainty the risks of the ADRs and ADEs associated with optimisation and the ADWEs associated with deprescribing HF pharmacotherapy in older people with objective frailty measures. The evaluation of the existing literature demonstrated similar challenges in study design and interpretation, particularly in terms of the significant heterogeneity across study participants.^{5,6} Most notably, the demographic characteristics and outcomes lacked reporting and analyses of participants' HF phenotypes and objective frailty measures, and there was a lack of participants aged over 75 years. Studies of specific drug or class interventions are needed to determine causality and associations with outcomes, especially in the presence of multimorbidity and polypharmacy.

The research in this field reflects the current decision-making priorities in clinical practice, whereby multidisciplinary teams often focus on organ-specific outcomes and practice mostly in silos.⁷ The reported research outcomes demonstrate the prioritisation of either HF-specific or geriatric-specific outcomes. For example, HF trials often report mortality, hospitalisation, worsening HF and other cardiovascular (CV) events, whereas geriatric populations also report ADEs, polypharmacy, falls and cognitive impairment. Additionally, diagnostic biomarkers such as B-type natriuretic peptides can be useful in the screening and prognosis of HF in geriatric patients presenting with atypical symptoms and complex comorbidities.⁸ Unfortunately, the integration of these CV and geriatric outcomes and biomarkers are not reported in the results. A general overview of the characteristics

identified in this doctoral work from reviewing the existing literature on HF in Chapter 2 and 3^{5,6} and an analysis of geriatric data captured in hospital routine care in Chapter 4⁹ are synthesised in Table 6.1. Data collection in future clinical trials and database research should consider reporting a combination of these characteristics and outcomes to narrow this knowledge gap.

Table 6.1: A summary of the differences in design and reporting of demographic characteristics, subgroups and outcomes measured for most heart failure and geriatric-specific research.

Characteristics	HF-specific	Geriatric-specific
Demographics	Gender, ethnicity, smoking Routine laboratory values	
	Age (years) ≥ 18 Body mass index (BMI) Physical function Comorbidities Medications (CV/non-CV) CV disease: HF classification and severity HF symptoms HF-specific biomarkers CV biomarkers (e.g. B-type natriuretic peptides) HF-specific biomarkers Implantable cardiac devices CV function Respiratory function	Age (years) (over: 65, 75, 80 or 90) Weight Global function: objective frailty measure Comorbidities, multimorbidity (e.g. Charlson Comorbidity Index) Medications (high falls risks, prescription/OTC) Cognition Polypharmacy Living status (level of independence) Marital status Palliative care Previous adverse drug reactions
Effect modifiers (or subgroups)	HF phenotypes HF presentation (acute/stable chronic) HF drug class or specific drug	Frailty risk according to objective measure Dementia status or cognitive impairment Healthcare setting
Outcomes	All-cause mortality and hospitalisation Quality of life, activities of daily living	
	Mortality (HF/CV) Hospitalisation (HF/CV) Worsening HF CV events	Falls Fractures Delirium Cognition Adverse drug events Healthcare utilisation Nutritional status

Abbreviations: HF = heart failure; CV = cardiovascular; OTC = over-the-counter medications.

In summary, the existing evidence cannot provide strong certainty in predicting the risk of adverse CV and geriatric outcomes of HF pharmacotherapy in people aged over 75 years, particularly for varying classifications of HF and according to objective frailty risk.

The significant gaps in the existing body of knowledge provide a roadmap for important future investigations involving the optimisation and deprescribing of HF pharmacotherapy in older people with objective frailty measures.

6.3 Novelty and implications for clinical practice

6.3.1 Research implications

The steps to addressing the gaps in the literature,^{9,10} as presented in Chapters 4 and 5, involve reporting geriatric outcomes regarding polypharmacy, falls, delirium, renal impairment and QoL according to frailty status among older people with HF across multiple healthcare settings. Chapter 4 provided a snapshot of clinical outcomes captured in routine care during hospitalisation.⁹ Chapter 5 combined the experiences of consumers living independently and healthcare professionals working in the community and nursing homes to understand the considerations for the self-management of ADEs and ADWEs.¹⁰

In Chapter 4, the retrospective analysis of real-world data from a multi-centre hospital population aged over 75 years with HF showed there were more adverse geriatric outcomes (i.e. polypharmacy, ADEs, falls, delirium and renal impairment) with increasing frailty risk. Diuretic use, as monotherapy or in combination with beta-blockers or RASIs, was high among this population. Symptomatic management of acute HF with diuretics is critical in supporting optimisation of GDMT, particularly during GDMT titration, and optimisation of GDMT may reduce the need for diuretics once patients are stabilised. There are clinical scenarios where diuretics should be deprescribed short term such as drug interactions, disease interaction, contraindication, substitution and adverse events.¹¹ However, further research is needed to evaluate the effect of chronic diuretic use and risk of rebound fluid retention or symptoms of worsening HF (e.g. oedema, fatigue, dyspnoea, decompensation) during

withdrawal, as identified in the conceptual model in Chapter 5. Thus, diuretic use in older patients with HF and frailty risk should be prioritised in future interventions to reduce medication burden or potential high-risk drug–drug interactions. This was highlighted by a recent trial of older multimorbid patients, which reported a high incidence and prevalence (50.9%) of drug–drug interactions involving HF pharmacotherapy leading to ADRs, most commonly major serum electrolyte disturbance and falls.¹² Chapter 4 provided a novel contribution to the literature by assessing geriatric outcomes according to frailty status in older people with HF and proposed a framework to promote the critical inclusion of frailty reporting in emerging research.^{3,13}

This approach can be applied to existing and emerging research. For example, a similar study¹⁴ in Spain involving 410 patients hospitalised for acute decompensated heart failure (ADHF) found that reducing the dose of furosemide at discharge was not linked to higher mortality or hospitalisation rates (HR 1.34, 95% CI 0.86–2.06, $P = 0.184$). The risk of death and worsening HF was influenced by fluid overload status. Similar findings were reported in a cohort of Japanese patients hospitalised with ADHF.¹⁵ In contrast, a review of adverse events reported across 17 landmark HFrEF clinical trials and GDMT classes demonstrated no significant differences in adverse events in the intervention group optimising GDMT compared with the placebo arms.¹⁶ The methodology used to report frailty in Chapter 4⁹ could also be applied to these and similar studies of contemporary HF pharmacotherapies, prospectively or retrospectively, to enhance our understanding of these risks in frail older people with diverse ethnicities, if such people have been recruited to the clinical trials.¹⁷ This has been carried out recently for several CV therapies, including HF.¹⁸

There is a need for high-quality clinical trials and prospective studies to clarify the safety of deprescribing interventions, for diuretics and GDMT, as well as contemporary or emerging HF therapies. A recent systematic review demonstrated that there is very low certainty of

evidence describing the feasibility, safety and tolerability of deprescribing the diuretics used for hypertension and HF in adults, thus limiting guideline development until higher-quality studies are available.¹⁹ Sodium-glucose co-transporter 2 inhibitors (SGLT2-i) are increasingly prescribed for older patients with HF and frailty to improve outcomes and renal adverse events, but increases risk of muscle wasting and sarcopenia if patients are not supported with physical rehabilitation.^{20,21,22} Stronger certainty of evidence is needed to evaluate the appropriateness and safety of deprescribing GDMT and chronic diuretic use in older people with frailty. Capturing and reporting frailty at baseline in future studies of older adults with HF is essential. Ideally, this should be extended to include reporting of ADEs and ADWEs, including by pharmaceutical industry funded studies.

6.3.2 Caring for older individuals living with heart failure and frailty in clinical practice

This doctoral work establishes that the limited evidence on the adverse effects associated with the optimisation and deprescribing of HF pharmacotherapy in frail older people is not sufficient for clinicians to confidently discuss the potential risks and benefits of treatment with patients and their carers. Although various clinical ‘practical tips’ to adjust pharmacotherapy in advanced HF exist,²³ these recommendations do not address the concurrent risks and management of frailty. Other models of care, such as domain management of HF in geriatric patients,²⁴ are clinically useful but do not provide specific recommendations on managing ADEs, ADWEs and HF symptoms in older people with frailty.

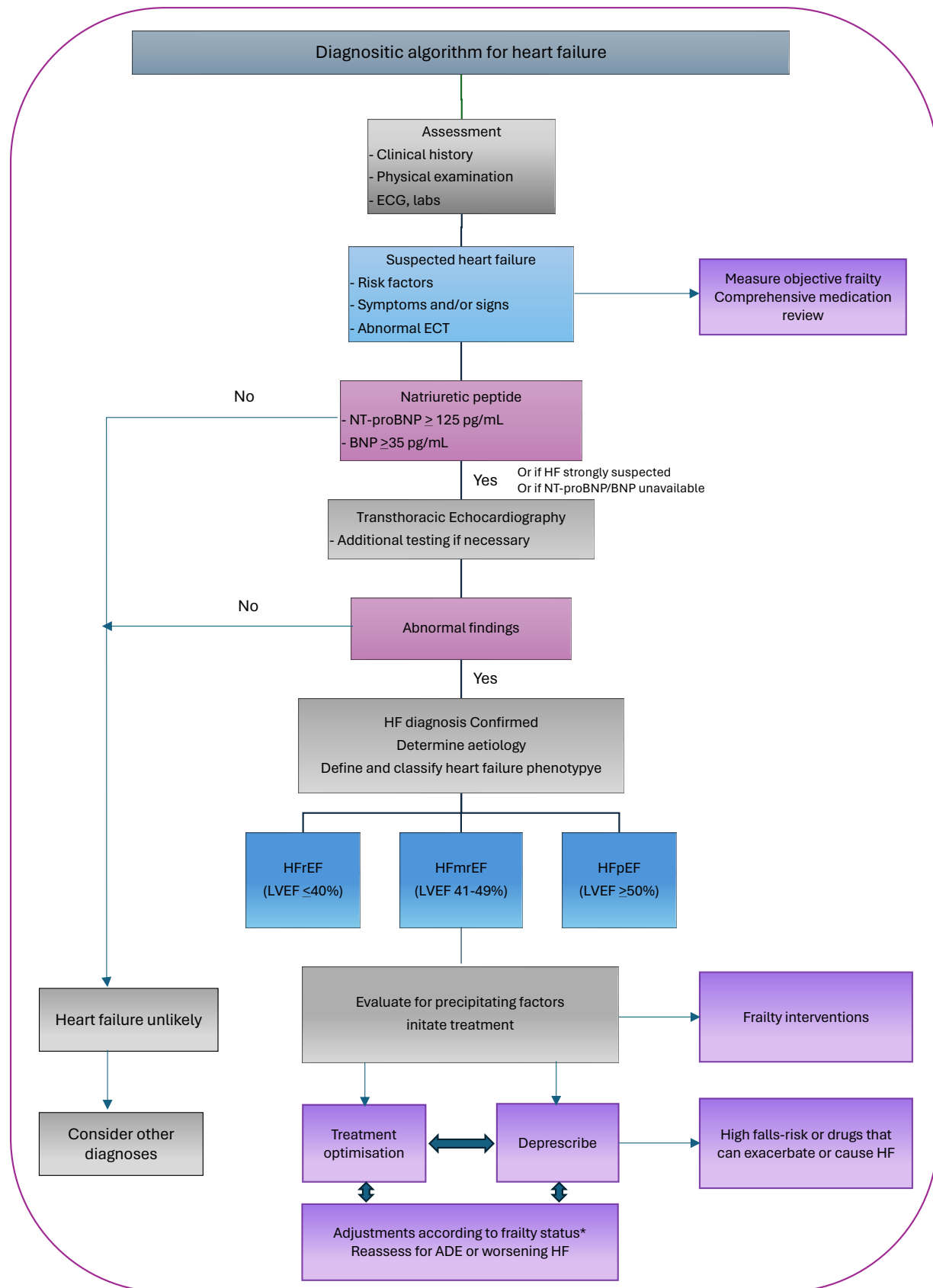
Pharmacological and non-pharmacological management of HF in older people with frailty can be complex, especially in high-risk patients with multimorbidity and polypharmacy. The conceptual model outlined in Chapter 5 offers a new person-centred

strategy for addressing and communicating the potential adverse effects of optimising and deprescribing HF pharmacotherapy for older individuals with frailty and HF.¹⁰ Implementing shared decision-making interventions to enhance medication safety and minimise the use of polypharmacy has proven to be achievable for older adults living in the community with frailty.^{25,26} Future development of this model and research also align with previous research prioritising older adult-specific health outcome goals and care preferences across all care settings to improve clinical outcomes in people with multimorbidity (e.g. the 4Ms framework: what Matters, Medication, Mentation and Mobility).²⁷

The conceptual model for managing the adverse effects associated with HF pharmacotherapy in frail older individuals is a preliminary prototype that could be further developed and tailored to specific drug classes, drug combinations or non-HF high-risk drug interactions. The model could also be used to develop tools for calculating QoL risk scores, similar to existing tools such as the anticoagulation CHADS-VASc.²⁸ Further development of this model could be adapted to clinical research or to support the person-centred communication and monitoring of ADEs, ADWEs, HF symptoms and frailty status with patients, carers and multidisciplinary healthcare providers.²⁹

The data suggest that there is a potential benefit to including frailty measurements in routine care that could be useful in guiding clinical care. Frailty measurements could potentially be routinely integrated into the care of older individuals and included in emerging diagnostic algorithms, as proposed in Figure 6.2, which merit further investigations. This could include approaches to identifying atypical signs and symptoms of HF or those that overlap with frailty, ADEs and pharmacotherapy. In addition to measuring jugular venous pressure in HF patients experiencing ADEs to mitigate misdiagnosis, the use of frailty measures may help distinguish between non-specific adverse symptoms resulting from HF decompensation, frailty or adverse effects from pharmacotherapy.

Figure 6.2: Proposed inclusion of objective frailty measures and comprehensive medication reviews in the diagnosis algorithm for heart failure³³ in older adults.



Footnote:*refers to examples of future research to explore how frailty can be integrated into care, as shown in Table 6.2. Purple boxes represent opportunities to integrate frailty and medication reviews into diagnosis algorithms.

Clinicians may also want to consider the physiological and pharmacological changes unique to older individuals with frailty when optimising pharmacotherapy. Including comprehensive medication reviews, frailty measurements and frailty interventions may influence the appropriateness of indication, pharmacokinetic or pharmacodynamic response warranting dose changes, and interactions and treatment of other comorbidities, as well as monitoring frailty outcomes (e.g. falls, incontinence, delirium) in addition to normal CV monitoring. Further investigation is needed due to limited evidence whether these are effective strategies are effective, such as medication reviews in older people with HF and those with frailty.^{30,31,32} Future research questions could explore ways to optimise HF pharmacotherapy and manage adverse events when frailty is present.

Future research is needed to evaluate the safety and clinical appropriateness of potentially integrating frailty into the care of older people with stable chronic HF during initiation, up- or down-titration of doses and discontinuation of pharmacotherapy, including the examples shown in Table 6.2. These strategies could be adapted according to frailty status and HF phenotypes.

Table 6.2: Examples for future research exploring the potential integration of frailty into the care of older people with heart failure, according to frailty status and heart failure phenotype.

Initiation of HF pharmacotherapy
Initiate and optimize multiple-GDMT and/or additional pharmacotherapy according to titration doses and schedules guided by clinical trials. Concurrently prevent or treat frailty and HF symptoms.
Initiate and optimise single-GDMT according to titration doses and schedules guided by clinical trials. Once optimised, add another GDMT. Concurrently prevent or treat frailty and HF symptoms.
Initiate and up-titrate with very low dose, once daily frequency and wide titration intervals of one single-agent pharmacotherapy, with frequent monitoring or follow-up. Concurrently treat and monitor frailty status and HF symptoms.
Dose changes during optimisation of HF pharmacotherapy
Concurrently treat frailty and increase intervals between up-titration schedules to correspond with frailty status.
Pause optimisation and focus on treatments to improve frailty status, then continue up-titration to target doses as frailty status improves concurrently. Monitor frailty status and HF symptoms.
Evaluate the cause and severity of ADE, or if worsening HF. If the impact of adverse effects on quality of life is deemed intolerable by the individual, discuss with patient and/or carer whether to initiate, up-titrate, down-titrate, withhold temporarily or discontinue permanently. Concurrently treat and monitor frailty status.
Consider deprescribing
Evaluate the cause and severity of ADE, or if worsening HF. If the impact of ADEs on quality of life is deemed intolerable by the individual, discuss with patient and/or carer whether to down-titrate, withhold temporarily or discontinue permanently. Concurrently treat and monitor frailty status and HF symptoms.
End of life. Proceed with discontinuation and acute treatment according to advanced care plan and palliation.

Abbreviations: GDMT = HF-specific guideline-directed medical therapy; HF = heart failure; ADE = adverse drug event. **Footnote:** treatment of frailty refers to multi-domain management, which includes physical rehabilitation and exercise.

6.4 Limitations

It is important to interpret the findings in this thesis with caution, owing to the low number of studies, participants and the quality of evidence, as highlighted in the previous research gaps. This was partly due to the focus on physical frailty and exercise in the cardiology studies (e.g. SBBP, 6MWT),⁵ rather than using global objective frailty measures. This gap reflects the trends in routine clinical practice, as reported in the systematic reviews and meta-analyses,³⁴ showing a lack of consensus on which frailty measure to use. Moreover, there is a lack of documentation detailing the HF phenotypes that are specified and coded by medical and nursing teams during admission and discharge. This creates fragmented care by GPs and allied health workers, which can affect the management of symptoms and the optimisation of titration schedules in primary care.

The small sample size of the observational cohort study⁹ in Chapter 4 limited the statistical power to determine the significance of the findings. These numbers were consistent with other studies of older patients admitted with ADHF.^{14,15,35} This reduced the utility of analysing subgroups and confounders, including pharmacological differences between the outcomes and treatments attributed to sex³⁶ and ethnicity, which are worth exploring because of the higher prevalence of HFpEF in women.³⁷ This thesis did not discuss special populations with HF, such as those with comorbidities, like cardio-oncology, and vulnerable populations, owing to limited evidence. The impact of deprescribing high-risk medications in HFrEF, which are contraindicated, and can exacerbate or cause HF (e.g. sitagliptin, pioglitazone, verapamil, diltiazem and COX-1/COX-2 inhibitors), was not investigated but could be insightful in future research. Although sub-analyses were not performed, they should be considered for evaluation in future research with larger sample sizes. These challenges are common in precision medicine research, in which specific criteria are

narrowed from a more extensive general population, trading the generalisability of results for relevance to a specific high-risk population.^{35,38,39}

The low number of eligible consumer participants in the qualitative study,¹⁰ particularly older individuals living with HF and frailty, as well as the challenges of measuring frailty in these individuals, reflects the challenges of recruiting older people with HF and frailty living in the community. Previous studies that recruited from urban cardiac centres with patients under the care of a cardiology team increased the potential to recruit up to 20 participants with lived experience; however, this increased the risk of biased responses in favour of their direct healthcare provider(s).⁴⁰⁻⁴² Other studies combined participants from previous studies to conduct secondary analyses.⁴³ Although few, repeated themes were provided by these carers and older individuals living independently with frailty and managing HF in the community, which provided unique insights. Importantly, spending limited time and using appropriate language during interviews are needed to respect participants' potential vulnerability to stress, cognitive impairment, mobility and social confidence. These valuable participants were able to share their views on the self-management of ADEs and ADWEs within their current knowledge, as well as access to health care in rural and urban settings.

The challenge of using chronological age to define older populations was demonstrated by the variable ages used in this thesis, reflective of the different populations investigated in the literature. There was limited evidence identified in the systematic reviews despite applying age cutoffs of ≥ 65 years in Chapter 2; and ≥ 50 years in Chapter 3 to include high risk groups or those living in low to middle income countries. The retrospective study of TOHOME was an existing population of people aged ≥ 75 years in Chapter 4. In the qualitative study in Chapter 5, the commonly understood cutoff age ≥ 65 years was used to facilitate recruitment. In addition to ages ≥ 65 years, there is movement towards including patients with HF over 80 years due to higher rates of adverse outcomes and risk of undertreatment.⁴⁴ The wide range of age cutoffs

used in the literature supports the use of objective frailty measures in future research to account for biological age and associated risks.

6.5 Future opportunities

The challenges raised in this doctoral work align with the ‘national agenda for action on frailty in heart failure’ statement made by the Australian Cardiovascular Alliance, which calls for multidisciplinary research and education to perform and apply frailty measures across multiple healthcare settings.⁴ Future multidisciplinary collaborative research and integration into clinical practice will rely heavily on determining how to define and objectively measure frailty and the appropriate outcomes, which are currently not considered routine practice.⁴⁵ Efforts to support and encourage partnerships across specialties and the pharmaceutical industries could also support the identification, reporting and management of adverse effects by establishing consensus on acceptable blood pressure and renal function safety parameters for older populations with frailty to prevent and manage adverse geriatric outcomes.⁴⁶

Future research requirements include an extensive body of work to provide larger sample populations, a higher number of high-quality clinical trials, and prospectively designed databases and national registries that capture CV and geriatric outcomes of older cohorts with specified HF phenotypes and objectively measured frailty. Frailty is dynamic and measurement in longitudinal studies should be tailored to the study setting (e.g. hospital, primary care) at baseline and repeated for subsequent visits using electronic frailty index or data from usual care. With the advances in data science and large linked datasets, there is access to more routinely measured frailty across settings. Depending on the data available, modifications are required and may not always be reproducible.⁴⁷ Some potential methodologies for future studies that could further improve our understanding

include clinical trials and observational studies. Efficacy and deprescribing clinical trials, including n-of-1 trials,⁴⁸ should include the characteristics proposed in Table 6.1 for frail compared with robust individuals. The design of future randomised controlled trials should emulate similar trials in atrial fibrillation to evaluate the impact of frailty on adverse outcomes and ADWEs involving deprescribing single-agent HF pharmacotherapy.^{49,50} Although recently published deprescribing trials were not identified, current trials registered at clinicaltrials.gov mainly included participants over 18 years, and only few were recruiting participants over 75 years; none reported frailty.

This research highlights the need for representative enrolment of diverse populations, including people with HF and frailty at high risk of adverse outcomes, into clinical trials. Recommendations to encourage community engagement and partnerships with communities of diverse populations⁵¹ align with guidance from the US Food and Drug Administration to increase the enrolment of diverse populations in clinical trials.⁵² This also presents an opportunity to engage with the pharmaceutical industry to advocate for inclusion of older people with frailty and report geriatric outcomes in future clinical trials. The limited access to high-risk patients with frailty or more diverse ethnic patient populations⁵³ means that consideration of novel methodologies may also be warranted, such as emulation trials of real-world patients,⁵⁴ propensity-matched cohorts, predictive artificial intelligence simulated models and natural language processing machine learning.

CONCLUSION

This doctoral research lays out the opportunities for pertinent high-quality research to evaluate the impact of frailty, ADEs and ADWEs on CV and geriatric outcomes to support the care of older people with HF. The scarcity of data necessitates a larger body of work with wide multidisciplinary engagement. The next steps to develop this research are in alignment with the emerging multidisciplinary collaborations driven by the Australian Cardiovascular Alliance ‘national agenda for action on frailty in heart failure’, including priorities to optimise medications. These research priorities also align with international strategies and frameworks proposed for future research on older people with HF.^{1,3}

The inclusion of objective frailty measures and comprehensive medication reviews during the optimisation of HF pharmacotherapy can help to individualise treatments in older people with frailty. Further, there are opportunities to develop and validate the novel conceptual model synthesised from the qualitative data to inform future research and clinical practice tools around person-centred priorities. A person-centred approach to developing high-quality evidence can provide individuals with the confidence to self-manage their adverse effects and health, and achieve wellbeing. The findings in this thesis provide a framework to build future research to determine with higher certainty the impact of the ADEs and ADWEs associated with HF pharmacotherapy in older people with frailty.

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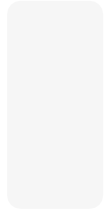
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APPENDICES

APPENDIX A: CHAPTER 2 SUPPLEMENTARY MATERIALS

Supplementary Information (SI):

Drugs and Aging.

The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure Medications in Frail Older Adults: A Systematic Review.

Mai H Duong*, Danijela Gnjjidic, Andrew J McLachlan, Marissa A Sakiris, Parag Goyal, Sarah N Hilmer.

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Table S2.1 Search strategy

ADRs or ADEs; AND	Heart Failure; AND	Elderly; AND	Frailty
adverse drug reaction* OR adverse drug event* OR adverse effect* OR adrs OR adverse drug effect* OR adverse reaction* OR adverse event* OR adverse outcome* OR complication* OR harm* OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR safe OR safety OR adverse drug reaction reporting systems OR drug hypersensitivity OR drug monitoring OR drug toxicity OR adverse outcome OR undesirable event* OR unexpected effect* OR unexpected event* OR abnormalities, drug induced OR long term adverse effects	heart failure OR cardiac failure OR congestive heart failure OR heart decompensation OR cardiac decompensation	Aged OR elderly OR Aging OR older adult* OR older people	Frailty OR Frail Elderly OR frail*

Table S2.2 PRESS validation checklist

TABLE 10: PRESS GUIDELINE ASSESSMENT FORM

PRESS Guideline — Search Submission & Peer Review Assessment

SEARCH SUBMISSION:

Searcher: Mai Duong

Email: mai.duong@sydney.edu.au

Date submitted: Wednesday May 12, 2021

Date requested by: Friday May 14, 2021

Systematic Review Title:

The prevalence of adverse drug reactions or adverse drug events with heart failure management in frail older adults: a systematic review and meta-analysis.

This search strategy is...

X	My PRIMARY (core) database strategy — First time submitting a strategy for search question and database
	My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
	SECONDARY search strategy— First time submitting a strategy for search question and database
	SECONDARY search strategy — NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

Database

CENTRAL, MEDLINE, Embase, Ageline, CINAHL, International Pharmaceutical Abstracts, PsychInfo, and Scopus

Interface

Ovid, EBSCO, Elsevier

Research Question

What is the extent of adverse drug reactions (ADRs) or adverse drug events (ADEs) in frail older adults related to their heart failure (HF) treatment?

- (i) What is the prevalence, type and severity of ADRs or ADEs with HF treatment in frail older adults compared to non-frail older adults?

PICO Format

PICOS: Population (frail older adults), Intervention (heart failure medication treatment), Comparator (non-frail older adults), Outcome (ADRs or ADEs), Study Design (systematic review and meta-analysis)

P I C O S Inclusion Criteria

(List criteria such as age groups, study designs, etc., to be included) [optional]

Include randomised controlled trials (RCTs); controlled before-and-after trials; interrupted time series; or meta-analysis; or observational studies (cohort, case-control or cross sectional studies). Studies measuring ADR or ADE with definitions and/or causality assessment criteria; or studies focused on ADRs or ADEs secondary to a specific medication or pharmacological class; or specific ADR or ADE.

Population:

- (i) Include only people aged 65 years or older or must separately report outcomes for people aged 65 years or older;
- (ii) Include people with a primary diagnosis of HF, with disease severity based on the New York Association (NYHA) classification and included persons with mild to severe functional limitations (NYHA grade II-IV). Studies may include people treated for HF in various settings (e.g. hospitalised with HF, receiving care in a nursing home or living independently in the community);
- (iii) Include studies reporting ADRs or ADEs with definition and/or causality assessment criteria;
- (iv) Include only people described as being frail or must separately report outcomes for people described as frail, with a frailty measurement using objective criteria. The term 'frail' must be justified using systematically defined criteria (e.g. the Cardiovascular Health Study Criteria (Fried 2001), Frailty Index score (Mitnitski 2004), CSHA Clinical Frailty Score (Rockwood 2005), frailty phenotype, difficulty performing specified tasks, require assisted living arrangements (e.g. nursing home resident), or other measures of vulnerability).

Exclusion Criteria

(List criteria such as study designs, date limits, etc., to be excluded) [optional]

Exclude qualitative studies, self-reports, case reports, case series, expert opinion or reviews. Exclude trials of pharmacotherapy with cardiovascular agents for indications other than heart failure (e.g., hypertension, angina, atrial fibrillation, stroke, previous myocardial infarction, liver failure, heart rate control, chronic kidney disease).

Was a search filter applied?

Yes x No ☐

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. [mandatory if YES to previous question — textbox]

The search filters for drug interventions, free texts and index terms used to describe ADRs or ADEs were adapted from a Cochrane RCT filter for adverse effects by Golder S et. al. 2019.

Golder, S., Peryer, G. and Loke, Y.K., 2019. Overview: comprehensive and carefully constructed strategies are required when conducting searches for adverse effects data. *Journal of clinical epidemiology*, 113, pp.36-43.

Other notes or comments you feel would be useful for the peer reviewer? *[optional]*

There are 8 search strategies for review included below. The Scopus strategy includes both the original strategy (1002 results) and followed your truncated recommended strategy (3 results) for comparison.

1. Database: Ovid MEDLINE(R) ALL <1946 to May 10, 2021> Search Strategy:

1 ae.fs. [adverse effects] (1795345)
2 co.fs. [complications] (2031160)
3 de.fs. [drug effects] (3065572)
4 safe.ti,ab. (390361)
5 safety.ti,ab. (549367)
6 undesirable effect*.ti,ab. (3134)
7 treatment emergent.ti,ab. (5485)
8 tolerability.ti,ab. (51701)
9 toxicity.ti,ab. (397618)
10 adrs.ti,ab. (4453)
11 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.(469244)
12 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (555986)
13 abnormalities, drug induced/ (14613)
14 adverse drug reaction reporting systems/ (7885)
15 drug hypersensitivity/ (23972)
16 drug monitoring/ (21789)
17 "Drug-Related Side Effects and Adverse Reactions"/ (33494)
18 long term adverse effects/ (665)
19 safety-based drug withdrawals/ (401)
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (7317665)
21 exp heart failure/ (127020)
22 cardiac failure/ (123841)
23 congestive heart failure.ti,ab. (39034)
24 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (187456)
25 21 or 22 or 23 or 24 (224141)
26 Aged/ (3193985)
27 "Aged, 80 and over"/ (958294)
28 Aging/ (234832)
29 elderly.ti,ab. (255685)
30 26 or 27 or 28 or 29 (3450978)
31 Frailty/ (4024)
32 Frail Elderly/ (12394)
33 frail*.ti,ab. (24904)
34 31 or 32 or 33 (29450)
35 20 and 25 and 30 and 34 (292)
36 limit 35 to (abstracts and english language and humans and yr="1960 - Current") (249)

2. Database: Embase Classic Search Strategy <1947 to 1973>, Embase <1974 to 2021 May 10>:

1 ae.fs. [adverse drug reaction] (1279182)
2 co.fs. [complications] (1762058)
3 complication/ (257660)
4 de.fs. [drug effects] (4641)
5 drug effect/ (777253)
6 safe.ti,ab. (600910)
7 safety.ti,ab. (863531)
8 side-effect*.ti,ab. (405321)
9 undesirable effect*.ti,ab. (4646)
10 treatment emergent.ti,ab. (13119)
11 tolerability.ti,ab. (94657)
12 drug tolerance/ (37525)
13 toxicity.ti,ab. (568321)
14 adrs.ti,ab. (9010)
15 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.(746854)
16 ((adverse or undesirable or harm*) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (793990)
17 Adverse drug reaction/ (256528)
18 drug hypersensitivity/ (52416)
19 drug monitoring/ (55747)
20 drug safety/ (449977)
21 drug surveillance program/ (26572)

22 drug toxicity/ (82463)
 23 side effect/ (341162)
 24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (5961708)
 25 exp heart failure/ (557204)
 26 cardiac failure/ (252983)
 27 congestive heart failure.ti,ab. (58137)
 28 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (322544)29 25 or 26 or 27 or 28 (609709)
 30 Aged/ (3225396)
 31 elderly.ti,ab. (374141)
 32 Aging/ (285761)
 33 (older adj1 (adult* or people)).ti,ab. (149062)34
 30 or 31 or 32 or 33 (3515290)
 35 Frailty/ (15053)
 36 Frail Elderly/ (10791)
 37 frail*.ti,ab. (38640)
 38 35 or 36 or 37 (44117)
 39 24 and 29 and 34 and 38 (742)
 40 limit 39 to (abstracts and human and english language and yr="1960 -Current") (683)

3. Database: EBM Reviews - Cochrane Central Register of Controlled Trials Search Strategy <April 2021>:

 1 ae.fs. [adverse effects] (130832)
 2 co.fs. [complications] (55061)
 3 de.fs. [drug effects] (122139)
 4 safe.ti,ab. (70565)
 5 safety.ti,ab. (233410)
 6 undesirable effect*.ti,ab. (393)
 7 treatment emergent.ti,ab. (8586)
 8 tolerability.ti,ab. (56827)
 9 toxicity.ti,ab. (37922)
 10 adrs.ti,ab. (668)
 11 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.(173281)
 12 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (182109)
 13 abnormalities, drug induced/ (46)
 14 adverse drug reaction reporting systems/ (90)
 15 drug hypersensitivity/ (456)
 16 drug monitoring/ (1842)
 17 "Drug-Related Side Effects and Adverse Reactions"/ (1587)
 18 long term adverse effects/ (38)
 19 safety-based drug withdrawals/ (5)
 20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (576828)
 21 exp heart failure/ (9710)
 22 cardiac failure/ (9456)
 23 congestive heart failure.ti,ab. (5309)
 24 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (29012)
 25 21 or 22 or 23 or 24 (30020)
 26 Aged/ (213960)
 27 "Aged, 80 and over"/ (55094)
 28 Aging/ (3712)
 29 elderly.ti,ab. (46908)
 30 26 or 27 or 28 or 29 (251440)
 31 Frailty/ (168)
 32 Frail Elderly/ (742)
 33 frail*.ti,ab. (3841)
 34 31 or 32 or 33 (4022)
 35 20 and 25 and 30 and 34 (41)
 36 limit 35 to (abstracts and english language and humans and yr="1960 - Current") [Limit not valid; records were retained] (33)

4. Database: International Pharmaceutical Abstracts Search Strategy <1970 to April 2021>:

 1 complication*.mp. (12712)

2 co.fs. [complications] (3)3
 safe.ti,ab. (15069)
 4 safety.ti,ab. (41356)
 5 undesirable effect*.ti,ab. (171)
 6 treatment emergent.ti,ab. (1083)
 7 tolerability.ti,ab. (8831)
 8 toxicity.ti,ab. (24797)
 9 adrs.ti,ab. (1427)
 10 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.(46682)
 11 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (51217)
 12 hypersensitivity.mp. (2331)
 13 (drug adj1 monitoring).mp. (3037)
 14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (121796)
 15 heart failure.mp. (7007)
 16 cardiac failure.mp. (321)
 17 (congestive adj1 heart adj1 failure).mp. (2118)
 18 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (6763)
 19 15 or 16 or 17 or 18 (7221)
 20 Aged.mp. (18831)
 21 senior*.mp. (1100)
 22 geriatric.mp. (2300)
 23 elderly.ti,ab. (9583)
 24 Aging.mp. (2966)
 25 (older adj1 (adult* or people)).ti,ab. (1937)
 26 20 or 21 or 22 or 23 or 24 or 25 (32065)
 27 frailty.mp. (148)
 28 frail*.ti,ab. (337)
 29 (Frail adj1 Elderly).mp. (87)
 30 27 or 28 or 29 (337)
 31 14 and 19 and 26 and 30 (9)

5. Database: APA PsycInfo Search Strategy*** <1806 to April Week 4 2021> (post-validation update 18.05.21):

 1 exp "Side Effects (Drug)"/ (59848)
 2 exp Geriatrics/ (14589)
 3 exp Aging/ (82944)
 4 exp Older Adulthood/ (9084)
 5 exp Geriatric Patients/ (13895)
 6 complication*.mp. (35270)
 7 safe.ti,ab. (35178)
 8 safety.ti,ab. (69507)
 9 undesirable effect*.ti,ab. (375)
 10 treatment emergent.ti,ab. (1370)
 11 tolerability.ti,ab. (7550)
 12 toxicity.ti,ab. (9191)
 13 adrs.ti,ab. (314)
 14 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (42990)
 15 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).ti,ab. (49914)
 16 hypersensitivity.mp. (4769)
 17 (drug adj1 monitoring).mp. (1777)
 18 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (184728)
 19 heart failure.mp. (4454)
 20 cardiac failure.mp. (144)
 21 (congestive adj1 heart adj1 failure).mp. (959)
 22 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (4293)
 23 19 or 20 or 21 or 22 (4597)
 24 Aged.mp. (620776)
 25 senior*.mp. (30626)
 26 geriatric.mp. (39958)
 27 elderly.ti,ab. (59882)
 28 Aging.mp. (114591)
 29 (older adj1 (adult* or people)).ti,ab. (67473)
 30 24 or 25 or 26 or 27 or 28 or 29 (742406)

31 frailty.mp. (2708)
 32 frail*.ti,ab. (5180)
 33 (Frail adj1 Elderly).mp. (2591)
 34 31 or 32 or 33 (6172)
 35 18 and 23 and 30 and 34 (8)
 36 limit 35 to (human and english language and abstracts and yr="1960 -Current") (7)
 37 1 or 18 (232116)
 38 2 or 3 or 4 or 5 or 30 (752758)
 39 23 and 34 and 37 and 38 (7)

****(Use of subject headings and keyword searches applied post-validation to PsychInfo and CINAHL – search strategy was updated May 18, 2021)*

6. EBSCO CINAHL Search***

CINAHL Search Strategy 11.05.21 (post-validation update 18.05.21)

#	Query	Results
S60	S37 AND S44 AND S52 AND S58	85
S59	S37 AND S44 AND S52 AND S58	85
S58	S53 OR S54 OR S55 OR S56 OR S57	17,336
S57	(MH "Frail Elderly")	7,894
S56	(MH "Frailty Syndrome")	2,728
S55	TI frail* OR AB frail*	13,956
S54	TI Frail Elderly OR AB Frail Elderly	2,154
S53	TI Frailty OR AB Frailty	8,610
S52	S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51	1,060,605
S51	(MH "Aged, 80 and Over+")	306,998
S50	(MH "Aged+")	868,914
S49	TI older people OR AB older people	29,655
S48	TI older adult* OR AB older adult*	69,173
S47	TI Aging OR AB Aging	60,990
S46	TI elderly OR AB elderly	94,046
S45	TI Aged OR AB Aged	196,047
S44	S38 OR S39 OR S40 OR S41 OR S42 OR S43	70,616
S43	(MH "Heart Failure+")	44,053
S42	TI cardiac decompensation OR AB cardiac decompensation	173
S41	TI heart decompensation OR AB heart decompensation	171
S40	TI congestive heart failure OR AB congestive heart failure	8,730
S39	TI cardiac failure OR AB cardiac failure	5,533
S38	TI heart failure OR AB heart failure	55,919
S37	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	707,683
S36	(MH "Substance Withdrawal, Controlled")	989
S35	(MH "Drug Monitoring")	8,073
S34	(MH "Drug Hypersensitivity+")	7,131
S33	(MH "Abnormalities, Drug-Induced")	1,220
S32	(MH "Drug Toxicity+")	17,121
S31	(MH "Medication Side Effects (Saba CCC)")	1
S30	(MH "Treatment Complications, Delayed")	2,330
S29	(MH "Adverse Drug Event+")	30,554
S28	(MH "Adverse Health Care Event+")	69,136
S27	TI long term adverse effects OR AB long term adverse effects	1,010
S26	TI abnormalities, drug induced OR AB abnormalities, drug induced	26
S25	TI unexpected event* OR AB unexpected event*	821
S24	TI unexpected effect* OR AB unexpected effect*	561
S23	TI undesirable event* OR AB undesirable event*	116
S22	TI adverse outcome OR AB adverse outcome	26,879
S21	TI drug toxicity OR AB drug toxicity	2,673

S20	TI drug monitoring OR AB drug monitoring	3,994
S19	TI drug hypersensitivity OR AB drug hypersensitivity	534
S18	TI adverse drug reaction reporting systems OR AB adverse drug reaction reporting systems	44
S17	TI safety OR AB safety	191,313
S16	TI safe OR AB safe	104,894
S15	TI toxicity OR AB toxicity	45,064
S14	TI tolerability OR AB tolerability	13,859
S13	TI treatment emergent OR AB treatment emergent	2,277
S12	TI undesirable effect* OR AB undesirable effect*	903
S11	TI side effect* OR AB side effect*	47,054
S10	TI harm* OR AB harm*	58,479
S9	TI complication* OR AB complication*	202,940
S8	TI adverse outcome* OR AB adverse outcome*	29,644
S7	TI adverse event* OR AB adverse event*	67,876
S6	TI adverse reaction* OR AB adverse reaction*	11,763
S5	TI adverse drug effect* OR AB adverse drug effect*	2,673
S4	TI adrs OR AB adrs	1,853
S3	TI adverse effect* OR AB adverse effect*	43,275
S2	TI adverse drug event* OR AB adverse drug event*	4,751
S1	TI adverse drug reaction* OR AB adverse drug reaction*	5,105

****(Use of subject headings and keyword searches applied post-validation to PsychInfo and CINAHL – search strategy was updated May 18, 2021)*

7. EBSCO Ageline Search 11.05.21

#	Query	Results
S41	S22 AND S28 AND S36 AND S40	15
S40	S37 OR S38 OR S39	6,329
S39	frail*	6,329
S38	Frail Elderly	4,250
S37	Frailty	2,443
S36	S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35	161,951
S35	older people	129,446
S34	older adult*	134,359
S33	geriatric*	38,829
S32	senior*	9,336
S31	Aging	75,697
S30	elderly	131,510
S29	Aged	138,398
S28	S23 OR S24 OR S25 OR S26 OR S27	1,266
S27	cardiac decompensation	3
S26	heart decompensation	4
S25	congestive heart failure	970
S24	cardiac failure	697
S23	heart failure	1,253
S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	12,291
S21	long term adverse effects	13
S20	unexpected event*	22
S19	undesirable event*	21
S18	drug toxicity	45
S17	drug monitoring	89
S16	drug hypersensitivity	1
S15	safety	4,983
S14	safe	1,899
S13	treatment emergent	21
S12	undesirable effect*	26
S11	side effect*	1,514
S10	harm*	1,806
S9	complication*	1,532
S8	adverse outcome*	691
S7	adverse event*	818
S6	adverse reaction*	460
S5	adverse drug effect*	120
S4	ADRs	61
S3	adverse effect*	863
S2	adverse drug event*	356
S1	"adverse drug reaction*"	384

8. Elsevier Scopus Search (Original)

1. ADRs and ADEs

Drug intervention filters - (adapted from Golder 2019)

(adverse AND drug AND reaction*) OR (adverse AND drug AND event*) OR (adverse AND effect*) OR adrs OR (adverse AND drug AND effect*) OR (adverse AND reaction*) OR (adverse AND event*) OR (adverse AND outcome*) OR complication* OR harm* OR side-effect* OR (undesirable AND effect*) OR (treatment AND emergent) OR tolerability OR toxicity OR safe OR safety OR (adverse AND drug AND reaction AND reporting AND systems) OR (drug AND hypersensitivity) OR (drug AND monitoring) OR (drug AND toxicity) OR (undesirable AND event*) OR (unexpected AND effect*) OR (unexpected AND event*) OR (abnormalities AND drug AND induced) OR (long AND term AND adverse AND effects)

2. Heart Failure

(heart AND failure) OR (cardiac AND failure) OR (congestive AND heart AND failure) OR (heart AND decompensation) OR (cardiac AND decompensation)

3. Elderly

Aged OR elderly OR Aging OR (older AND adult*) OR (older AND people)

4a. Frailty

Frailty OR (Frail AND Elderly) OR frail*

-1002 document results

(Peer reviewed Truncated recommendations and results)

1. ADRs and ADEs

((adverse OR undesirable OR unexpected) AND (effect* OR event* OR reaction* OR outcome*))OR ADRS OR “adverse drug reaction reporting system*” OR ((drug* OR treatment) AND (hypersensitive* OR hyper-sensitiv* OR monitoring OR toxicity OR tolerability OR safe* OR abnormalit* OR harm* OR side-effect* OR reaction* OR event* OR effect* OR complication* OR emergent*))

2. Heart Failure

((heart OR cardiac) AND (failure OR decompensation))

3. Elderly

Elderly OR Age* OR (older AND (adult* OR people OR person*))

(392 document results retrieved)

4. Frailty

Frailty OR (Frail AND Elderly) OR frail*

(3 document results retrieved)

PEER REVIEW ASSESSMENT: THIS SECTION TO BE FILLED IN BY THE REVIEWER

Reviewer: Dr Yulia Ulyannikova	Email: yulia.ulyannikova@sydney.edu.au	Date completed: 14 May 2021
1. TRANSLATION		
	A. No revisions	☒
	B. Revision(s) suggested	☐
	C. Revision(s) required	☐

If “B” or “C,” please provide an explanation or example:

2. BOOLEAN AND PROXIMITY OPERATORS		
	A. No revisions	☒
	B. Revision(s) suggested	☐
	C. Revision(s) required	☐

If “B” or “C,” please provide an explanation or example:

If “B” or “C,” please provide an explanation or example:

3. SUBJECT HEADINGS		
	A. No revisions	☐
	B. Revision(s) suggested	☐
	C. Revision(s) required	☒

PsycInfo is a database with a thesaurus. Currently the search includes no subject headings.CINAHL

is a database with a thesaurus, currently the search includes no subject headings

4. TEXT WORD SEARCHING		
	A. No revisions	☒
	B. Revision(s) suggested	☐
	C. Revision(s) required	☐

If “B” or “C,” please provide an explanation or example:

5. SPELLING, SYNTAX, AND LINE NUMBERS			
	A. No revisions	☒	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If “B” or “C,” please provide an explanation or example:

6. LIMITS AND FILTERS			
	A. No revisions	☒	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If “B” or “C,” please provide an explanation or example:

7. OVERALL EVALUATION (Note: If one or more “revision required” is noted above, the response below must be “revisions required”.)			
	A. No revisions	☐	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☒	

If “B” or “C,” please provide an explanation or example:

Add subject heading search to PsycInfo and CINAHL search strategies. Use keyword searches with subject headings.

****(Use of subject headings and keyword searches applied post-validation to PsychInfo and CINAHL – search strategy was updated May 18, 2021)*

Table S2.3 Eligible guideline directed heart failure specific medications in search strategy

Drug class	Example of medications
angiotensin-converting enzyme inhibitors (ACEIs)	enalapril
angiotensin-2 receptor antagonists/blockers (ARBs)	candesartan
angiotensin receptor neprilysin inhibitor (ARNI)	sacubitril/valsartan
aldosterone/mineralocorticoid receptor antagonists (MRAs)	spironolactone, eplerenone
renin inhibitor	aliskiren
beta-blockers	bisoprolol
renin inhibitor	aliskiren
diuretics	furosemide
calcium channel blockers (CCBs)	verapamil, diltiazem
cardiac glycosides	digoxin
inotropes/adrenergic agonists	dobutamine, dopamine
I _f channel inhibitors	ivabradine
SGLT-2 inhibitors	dapagliflozin, empagliflozin
vasodilators	nitroglycerin, isosorbide dinitrate, hydralazine

Note: The treatments can be administered alone or in combination; in fixed or titrated (up/down) regimens

Figure S2.4 Risk of bias assessment: ROBINS-I summary for non-randomised intervention studies

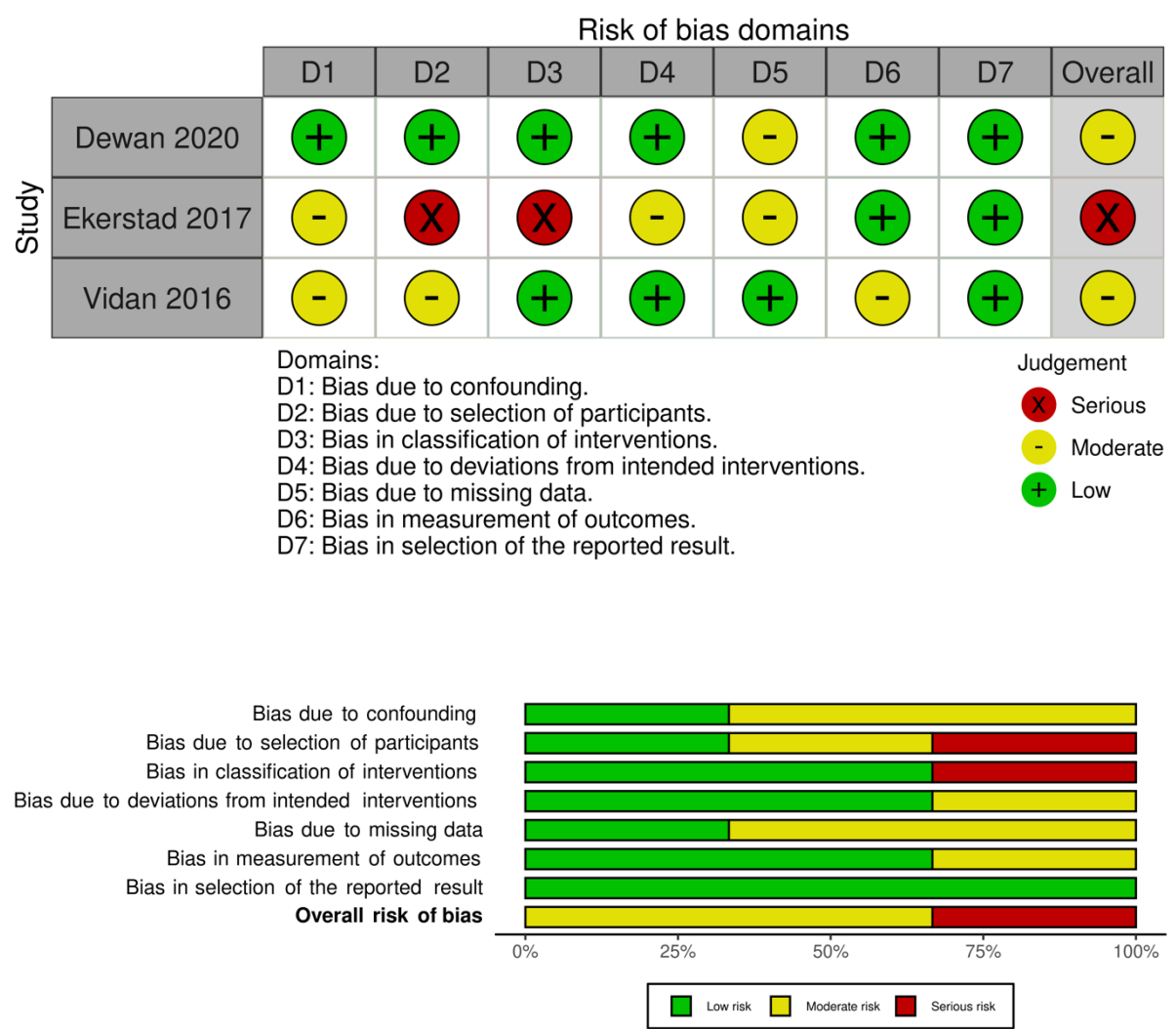


Table S2.5: GRADE criteria and scoring

Table S2.5a: GRADE Assessment Criteria

Each of the domains were assessed from “high” quality evidence and given downgrade or upgrade points accordingly.

	Domain	Description	No downgrade given (0) if:	Downgrade given by one level (-1) if:
Factors that can downgrade the quality of evidence include:				
1	Study design	Randomised controlled trials (0) and observational studies (-1) were included in this review.	Studies were RCTs.	Studies were observational in design.
2	Risk of bias/ study limitation	Study limitations were determined with the Cochrane risk of bias assessment tool ROB-2 for RCTs and ROBINS-I for observational studies.	Studies had “low” overall risk of bias score.	Studies had “moderate” or “high” overall risk of bias score.
3	*Inconsistency	Inconsistency was based on presence of statistical heterogeneity (I^2) but was not performed in this review’s narrative analysis. We did not conduct a meta-analysis. Investigators were unable to determine the differences in underlying treatment effect nor identify a plausible explanation if heterogeneity existed.	Inconsistency was not present.	All outcomes were downgraded since investigators unable to demonstrate if statistical heterogeneity was present.
4	Indirectness	Indirectness was evaluated using the PICO format to determine how well the evidence included in the review answered the research question, including: Population: older age, frailty Intervention: HF specific medication Comparator: non-frail older adults Outcome: ADR or ADE	Indirectness was not observed.	Indirectness was present in either population, intervention comparator or outcomes.
5	Imprecision	Imprecision was evaluated on optimal information size implication and variation in the effect observed from confidence intervals.	There were narrow confidence intervals around the point estimate, if null effect and appreciable harm or benefit were both not included or if confidence interval excludes point estimate.	No point estimate given, if there were wide confidence intervals around the point estimate, or if confidence intervals do not include the null effect but do include appreciable harm or benefit.
6	*Publication bias	Publication bias was a systematic under or over estimate of the underlying effect due to the selective publication of studies or availability of their data. We did not perform a meta-analysis so did not assess publication bias because funnel plots were not generated in a narrative synthesis.	Publication bias was not observed.	All outcomes were downgraded because publication bias is strongly suspected in a very small (scarce) number of studies despite absence of a funnel plot.
Factors that can upgrade the quality of evidence by one level: - if dose-response gradient or relationship was observed in frail compared to non-frail participants, - if demonstrated large or very large effects, - if all plausible residual confounders would reduce a demonstrated effect or suggest a spurious effect if no effect was observed.				

*NA – not applicable since no meta-analysis and subgroup analysis was performed.

Table S2.5b: Definition of grades of evidence ²¹

Score	Rationale for scoring overall quality of evidence
High	further research is very unlikely to change the confidence in the estimate of effect.
Moderate	further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
Low	further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	any estimate of effect is very uncertain.

Table S2.5c. GRADE Scoring

Outcome	Study Design	Risk of Bias	*Inconsistency	Indirectness	Imprecision	*Publication bias	Overall Score
<i>Renin angiotensin system inhibitors (Dewan et al. 2020)</i>							
Mortality	-1	-1	NA	0	0	NA	Low
Hospitalisation	-1	-1	NA	0	0	NA	Low
<i>ACEI/ARB (Vidan et al. 2016)</i>							
Mortality	-1	-1	NA	0	0	NA	Very Low
<i>Digoxin (Ekerstad et al. 2017)</i>							
Falls	-1	-1	NA	-1	-1	NA	Very Low
Tiredness	-1	-1	NA	-1	-1	NA	Very Low
Nausea	-1	-1	NA	-1	-1	NA	Very Low
Hospital readmission	-1	-1	NA	-1	-1	NA	Very Low
No data was available to assess the following clinical outcomes							
Fractures due to falls, worsening renal function, dyspnea, dizziness, syncope, hyper/hypo-kalaemia, cognitive function, oedema, infections, gynecomastia, quality of life, glucose levels, arrhythmias	NA	NA	NA	NA	NA	NA	NA

*NA – not applicable since no meta-analysis and subgroup analysis were performed and downgraded by one level.

Table S2.6 Subgroup of included participants from a secondary analysis of two randomised controlled trials. (Dewan et al. 2020)²⁵

	PARADIGM-HF ²⁶	ATMOSPHERE ²⁷	Dewan -Frailty analysis of PARADIGM-HF and ATMOSPHERE	Dewan- Frailty Subgroup ≥ 75 (n, %)
Total population (n)	8399	7016	15415	2544
Intervention	sacubitril/valsartan (ARNI) (n=4187)	aliskiren + enalapril (n=2340) aliskiren (n=2340)	Sub-analysis of frailty	Subgroup analysis by age
Comparator	enalapril (n=4212)	enalapril (n=2336)	Non frail FI ≤ 0.210 Frail Subgroups: FI 0.211–0.310; FI ≥ 0.311	Non frail FI ≤ 0.210 (n=474) Frail Subgroups: FI 0.211–0.310; (n=795) FI ≥ 0.311 (n=829)
Frailty	No	No	Yes-frailty data available for n=13265/15415	Yes-frailty data available for n=2098/2544
Run-in phase prior to randomization (median, IQR days)	2-part single blind enalapril (15, 14-21) sacubitril/valsartan (29, 26-35)	2-part single blind enalapril (28, 16-39) enalapril + aliskiren (18, 14-24)	NA	NA
Proportion (n,%) of patients with reported adverse events and discontinued run-in phase	enalapril 591/1102, 5.6% sacubitril/valsartan 547/977, 5.8%	enalapril 370/1047, 3.5% aliskiren + enalapril 428/724, 5.9%	NA	NA

Note: The authors calculated frailty from cumulative deficits in a 42-item frailty index (FI) in participants in the PARADIGM-HF and ATMOSPHERE trials. Excluded from analysis were patients with $\geq 20\%$ missing variables. Participants with FI ≤ 0.210 were considered non-frail/robust, and patients with FI > 0.210 were considered frail, and further divided into groups by increments of 0.100 (0.211-0.310 or ≥ 0.311).²⁵

NA: Not provided by authors

Table S2.7 PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page, Line 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1, Lines 76-78
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Lines 78-79
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2, Lines 92-98
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Lines 85-86
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Lines 88-90, Table S2, S3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 106-108
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Lines 108-113
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Lines 98-104
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Lines 92-93
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 117-118, Figure S1
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Lines 113-115
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Lines 92-98
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Lines 94-96
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Lines 101-104, 113-115
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Lines 101-104, 113-115
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Lines 113-115
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Lines 120-121
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Lines 117-113
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Lines 117-113
RESULTS			

Topic	No.	Item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3, Lines 124-127, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1. Section 4, Lines 209-211,
Study characteristics	17	Cite each included study and present its characteristics.	Lines 127, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Lines 148,158, 173, Figure S1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Lines 140-147, Figure 2., Lines 153-157, Lines 162-172
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Lines 148,158, 173, Figure S1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Lines 148,158, 173, Figure S1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Lines 148,158, 174, Table S5, Figure 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4, Lines 179-243
	23b	Discuss any limitations of the evidence included in the review.	Lines 186-229
	23c	Discuss any limitations of the review processes used.	Lines 262-274
	23d	Discuss implications of the results for practice, policy, and future research.	Lines 245-260
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Abstract, Line 49, Section 2, Line 82-83
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 2, Lines 82-83, Reference #13
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Section 2, Line 83
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Lines 296-297
Competing interests	26	Declare any competing interests of review authors.	Lines 299-300
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Lines 304

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes

Topic	No.	Item	Reported?
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

APPENDIX B: CHAPTER 3 SUPPLEMENTARY MATERIALS



BRITISH
PHARMACOLOGICAL
SOCIETY

S3: Publication

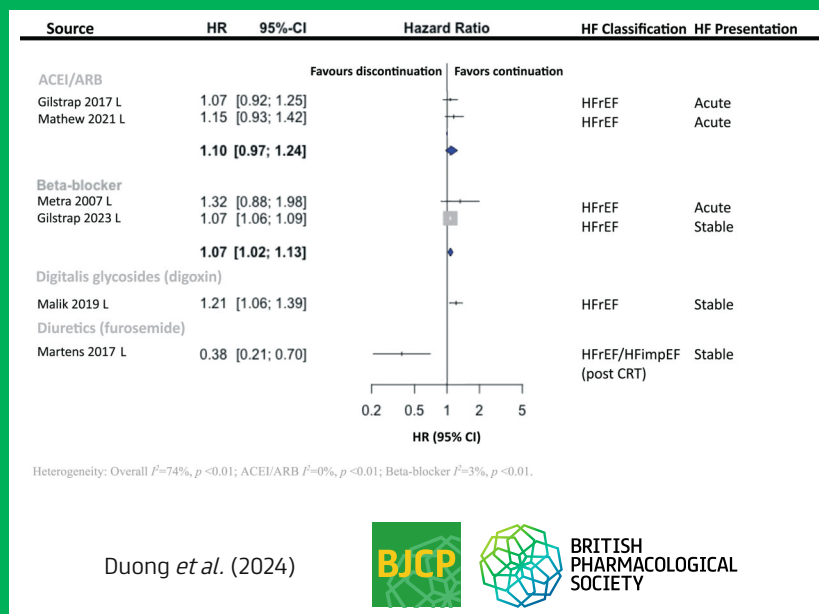
VOLUME 91

NUMBER 1

January 2025

BJCP

British Journal of
Clinical Pharmacology



www.bjcp-journal.com
ISSN 0306-5251 ISSN 1365-2125

WILEY

THEMED ISSUE REVIEW

The effect of down-titration and discontinuation of heart failure pharmacotherapy in older people: A systematic review and meta-analysis

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 Sarah N. Hilmer¹ 

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Funding information

This work was supported by the Commonwealth of Australia National Health and Medical Research Council (NHMRC) Postgraduate Scholarship 2020 (grant APP1191018 to M.H.D.); Heart Research Australia (HROz) Postgraduate Scholarship 2023/2024 to M.H.D.; American Heart Association (grant 20CDA35310455 to PG); National Institute on Aging (grant K76AG064428 to PG), and Junior Investigator Intensive Program of the US Deprescribing Research Network, funded by the National Institute on Aging (R24AG064025) to P.G.

The aim of this study was to investigate whether interventions to discontinue or down-titrate heart failure (HF) pharmacotherapy are feasible and associated with risks in older people. A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines. Electronic databases were searched from inception to 8 March 2023. Randomized controlled trials (RCTs) and observational studies included people with HF, aged ≥ 50 years and who discontinued or down-titrated HF pharmacotherapy. Outcomes were feasibility (whether discontinuation or down-titration of HF pharmacotherapy was sustained at follow-up) and associated risks (mortality, hospitalization, adverse drug withdrawal effects [ADWE]). Random-effects meta-analysis was performed when heterogeneity was not substantial (Higgins $I^2 < 70\%$). Sub-analysis by frailty status was conducted. Six RCTs (536 participants) and 27 observational studies (810 499 participants) across six therapeutic classes were included, for 3–260 weeks follow-up. RCTs were conducted in patients presenting with stable chronic HF. Down-titrating a renin-angiotensin system inhibitor (RASi) in patients with chronic kidney disease was 76% more likely than continuation (risk ratio [RR] 1.76, 95% confidence interval [CI] 1.14–2.73), with no difference in mortality (RR 0.64, 95% CI 0.30–1.64). Discontinuation of beta-blockers were feasible compared to continuation in preserved ejection fraction (RR 1.00, 95% CI 0.68–1.47). Participants were 25% more likely to re-initiate discontinued diuretics (RR 0.75, 95% CI 0.66–0.86). Digoxin discontinuation was associated with 5.5-fold risk of hospitalization compared to continuation. Worsening HF was the most

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common ADWE. One observational study measured frailty but did not report outcomes by frailty status. The appropriateness and associated risks of down-titrating or discontinuing HF pharmacotherapy in people aged ≥ 75 years is uncertain. Evaluation of outcomes by frailty status necessitates investigation.

KEYWORDS

cardiovascular pharmacology, clinical pharmacology, epidemiology, medication safety, evidence-based medicine, geriatrics, geriatric medicine

1 | INTRODUCTION

Medication management in older adults with heart failure (HF) is complex due to disease heterogeneity, multi-morbidities, deficits across multiple health domains, changes in life expectancy and patient priorities.¹ Pharmacological management for stable chronic HF and acute decompensated HF (ADHF) are recommended by international cardiology organizations as guideline-directed medical therapies (GDMT), with strong evidence to reduce hospitalization and improve survival in HF patients.^{2,3} Current guideline recommendations are based on the limited evidence on clinical presentation and drug use in older people and can also lead to increased medication burden. Polypharmacy, a risk factor for adverse drug events (ADEs), is highly prevalent in people living with HF with 95% of patients taking five or more medications at hospital discharge and nearly half taking at least ten medications.⁴ Frailty, prevalent in up to 75% of community-dwelling HF patients,⁵ can reduce the ability to tolerate adverse effects.^{6,7} Up to 91% of HF patients perceived their ADE as a chronic problem.⁸ Persistent intolerance to HF pharmacotherapy can impact quality of life (QoL) associated with 38% likelihood of dose changes or discontinuation.⁹ Older adults report lower adherence and higher medication discontinuation rates.^{10,11}

Deprescribing, defined as the supervised withdrawal of a medication¹² with monitoring for adverse drug withdrawal effects (ADWEs), may be useful when the harms outweigh the benefits of treatment. With increasing recognition of the potential value of deprescribing in select settings involving patients with HF,^{13,14} it is important to understand the evidence regarding feasibility and risks of deprescribing interventions. Such evidence is critical to guide shared decision-making for older adults regarding their medication, a key priority in HF management.¹⁵ This review examined whether HF pharmacotherapy in older adults can be down-titrated or discontinued; and evaluate the effects on mortality, hospitalization, HF symptoms and ADWEs, according to frailty status.

2 | METHODS

This systematic review was registered in PROSPERO (CRD42021285380)¹⁶ and conducted according to the PRISMA 2020 checklist.¹⁷ We searched electronic databases (Cochrane

Central Register of Controlled Trials, MEDLINE, EMBASE, Ageline, CINAHL, PsychInfo, International Pharmaceutical Abstracts) from inception to 8 March 2023 for studies of older adults, who reduced or discontinued HF pharmacotherapy and reported withdrawal effects. The intervention was compared to continuation of optimized maintenance doses as per usual care or placebo (Table S1). The complete search strategy (Table S2) included studies in English and was validated using the Peer Review of Electronic Search Strategies (PRESS) checklist.¹⁸ Manual searches of PROSPERO, clinicaltrials.gov, connectedpapers.com and references of screened manuscripts were performed.

2.1 | Study selection

Search results were screened with Covidence software (Melbourne, Australia). Duplicates were removed using automation and manual identification. Two reviewers (M.H.D. and M.R.R.) independently screened titles, abstracts and full texts. Disagreements were resolved by consensus with a third reviewer (D.G., A.J.M. or S.N.H.). Eligible studies included randomized controlled trials (RCTs), meta-analyses or observational studies. Interventions included discontinuation or dose down-titration of a HF GDMT (Table S1).^{2,3} Participants were aged ≥ 50 years, were diagnosed with HF and from any clinical setting. Older adults were defined with age cut-off ≥ 50 years to avoid unintended exclusion of minority high-risk groups with lower life expectancy or participants from developing countries, based on WHO recommendations for research in older people.¹⁹ Subgroup analysis of individuals ≥ 75 years was conducted. Self-reports, case reports/series, expert opinion, reviews, qualitative and non-human studies were excluded.

2.2 | Outcomes

Outcomes were reported for medicines grouped by therapeutic class (e.g., **beta-blockers**) and prioritized by study design.

Feasibility refers to whether the reduction in dose or cessation occurred and/or was sustained. In RCTs, interventions were “feasible” if there were no statistical differences between study arms or favoured the intervention compared to the control arm, with respect to (i) discontinuation or dose reduction of HF pharmacotherapy;

and/or (ii) sustained discontinuation or dose reduction at follow-up (risk ratio (RR) and 95% confidence intervals (95% CI) were >1). In observational studies consisting of ≥ 1 comparator groups, “feasibility” of interventions was measured as the proportion of participants in whom HF pharmacotherapy was (i) dose-reduced or discontinued and (ii) discontinuation was sustained, compared to the proportion of participants in the comparator group who continued HF pharmacotherapy in usual care. Secondary outcomes were the number of serious adverse events (mortality, hospitalization) and ADWEs (e.g., worsening HF symptoms as defined by the study authors, new cardiovascular [CV] events).

2.3 | Data collection and synthesis

Study and participant characteristics and outcomes were manually recorded into a piloted data form in Microsoft Excel 2014 by M.H.D. (details in PROSPERO [CRD42021285380] protocol).¹⁶ A second reviewer (M.R.R.) validated the accuracy of data extracted from 50% of studies.²⁰ Study authors were contacted to confirm eligibility or obtain missing data. Searched studies were summarized in a PRISMA 2020 flow diagram.¹⁷ Mortality, hospitalization and ADWEs were extracted as number of incidences per participant. ADWEs report the proportion (%) of events in the intervention groups. Follow-up time-points were categorized as short (≤ 30 days), intermediate (5–24 weeks) and long (> 24 weeks), using the last time-point if multiple were provided.

2.4 | Statistical analyses

Analysis was conducted separately for RCTs and observational studies by therapeutic class. Meta-analysis of pooled measures of treatment effect from point estimates (e.g., RR, hazard ratio [HR], and 95% CI) were calculated using meta v7.0 in R/RStudio v4.2.2 (Boston, MA, USA). Meta-analyses were conducted on outcomes using the random effects model, Higgins I^2 , and Hartung-Knapp and maximum-likelihood method to calculate 95% CIs and P -values. Outcome measures were pooled by therapeutic class if the level of heterogeneity was not considerable ($I^2 < 70\%$).²¹ Where substantial heterogeneity was present, narrative synthesis described study design, participant characteristics, feasibility and outcomes. Subgroup analyses were planned according to frailty, as defined by the study authors. Meta-regression was performed for study-level factors: therapeutic class, HF classification,²² HF presentation (stable chronic/acute) and aged ≥ 75 years.

2.5 | Assessment of risk of bias and the certainty of the evidence

Two reviewers (M.H.D. and M.R.R.) independently assessed risk of bias using the Cochrane assessment tools, RoB2 for RCTs and

ROBINS-I for observational studies.^{23,24} Sensitivity analysis on outcomes were conducted removing high risk of bias studies. The quality level of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach (Table S6).⁵⁷ GRADEpro GDT software (Hamilton, Canada) generated the effect and certainty of evidence for each outcome.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24.

3 | RESULTS

Thirty-three studies (participants [n] = 797 690), consisting of six RCTs (n = 532) and 27 observational studies (n = 797 158), were included (Figure S1). Most studies were conducted in Europe (17 studies) and North America (12 studies), three in low-to-middle income countries and both Europe and North America (one study). One observational study reported frailty status. Studies of discontinuation (32 studies) and/or down-titration (five studies) of HF pharmacotherapy had short (seven studies), intermediate (seven studies) and long (19 studies) follow-up time-points (Table 1).

3.1 | Participant characteristics

Studies evaluated patients with HF with reduced ejection fraction (HFrEF) (12 studies, n = 407 492), HF with preserved ejection fraction (HFpEF) (five studies, n = 516) or unspecified (undifferentiated single or combination) HF classifications (16 studies, n = 389 682), which include combinations with HF with mildly reduced ejection fraction (HFmrEF) (two studies, n = 118). Patients with stable chronic HF (23 studies, n = 764 455) were mainly living in or discharged to community settings; while those with ADHF were all in hospital settings (10 observational studies, n = 33 235). In RCTs and observational studies, the mean age (years) was 61–78 and 64–84 (median 67–87), respectively. Four observational studies (n = 12 944) mostly of diuretics, reported outcomes in participants ≥ 75 years (Table S4).

3.2 | Risk of bias and certainty of evidence

Risk of bias was assessed as low in three-studies (9%), moderate in seven studies (21%), high in 14 studies (42%) and serious in nine studies (28%) (Figure S7).^{25,28–30,41,46,53} Ten studies were industry-funded (30%) (Table S3). GRADE quality of evidence was deemed higher for

TABLE 1 Study characteristics.

Study name	Country, setting, prospective (P)	HF classification, presentation	Deprescribing intervention	Sample size (n, %)		Age (years) mean (SD) or *median (IQR)	Female (n, %)	Follow-up (weeks)	Main outcomes	Quality rating
				Intervention	Continue					
Randomized controlled trials (RCTs)										
Guideline-directed medical therapies (GDMT) for heart failure										
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB)										
Pita-Fernandez 2014 ²⁶	Spain, single centre, hospital, P	Unspecified, stable chronic	Reduce	30, 64%	47	78 (8) 74 (6)	30, 64%	52	Mortality, clinical/lab outcomes	1
Beta-blocker										
Palau 2021 ²⁷ (PRESERVE-HR)	Spain, multi centre, hospital outpatient clinic, P	HFpEF (LVEF>50%), stable chronic	Discontinue (tapered)	26, 50%	52	*77(72–80) *73 (68–77)	31, 60%	4.3 25	Exercise HR, peak VO ₂ , VO ₂ %, MMSE, MoCA, MLHFQ, mortality, CV admissions	1
Diuretics										
Van Kraaij 2000 ²⁸	Netherlands, multi-centre, hospital, community, P	HFmrEF/HFpEF, stable chronic	Discontinue	21, 66% 11, 34%	32	75 (4)	17, 53%	12	HF score, HF symptoms, 6MWT, BP, weight, FEV1	1
Walma 1997 ²⁹	Netherlands, single-centre, community, P	Unspecified, stable chronic	Discontinue	102, 50.5% 100, 49.5%	202	76 (1) (≥65)	151, 75%	26	HF symptoms, BP, HR, SOB, oedema, symptoms	1
Other treatments for heart failure:										
Digitalis glycoside (digoxin)										
Packer 1993 ³⁰ (RADIANCE)	USA, Canada, multi centre/setting, P	HFrEF, stable chronic	Discontinue	3, 52.2% 85, 47.8% 19, 90.5%	178	59 (1)	42, 24%	12	Mortality, hospitalization, frequency/reasons, worsening HF, symptoms, ADEs, exercise, NYHA, QoL	1
Taggart 1983 ³¹	Ireland, single centre, aged care, P	Unspecified, stable chronic	Discontinue	21, 100%	21	66 (8)	8, 38.1%	12	MI, HF, digitalis toxicity, tachycardia, NYHA class	1
Observational studies										
GDMT for heart failure										
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB)										
Gilstrap 2017 ³² (GWTF-HF)	USA, single-centre, hospital	HFrEF, ADHF	Discontinue	308, 2% 9572, 60%	16 052	78 (8)	6718, 42%	52	Mortality, readmission, composite (30 days, 90 days, 1 year)	3
Mathew 2021 ³³	USA, multi-centre, hospital	HFrEF, ADHF	Discontinue	717 1715	3652	72 (11) 71 (10)	59, 1.6%	52	Mortality, readmission, worsening renal function	4
Nicholls 1982 ³⁴	New Zealand, single-centre, hospital, P	Unspecified, stable chronic	Discontinue	5, 100%	5	54–73	1, 20%	4	NYHA, haemodynamics, hormones, clinical effects	3
Beta-blocker										
Brouse 2006 ³⁵	USA, single-centre, hospital	HFrEF/HFpEF, ADHF	Discontinue, reduce	21, 28% 19, 25% 26, 34%	76	*67 (57, 83) *67 (59, 82) *67(58, 82)	1, 5%	52	Mortality, arrhythmias, LOS, HF readmission, worsening HF indicators	3

TABLE 1 (Continued)

Study name	Country, setting, prospective (P)	HF classification, presentation	Deprescribing intervention	Sample size (n, %)		Age (years) mean (SD) or *median (IQR)	Female (n, %)	Follow-up (weeks)	Main outcomes	Quality rating
				Intervention	Total					
Fonarow 2008 ²⁵ (OPTIMIZE-HF)	USA, multi-centre, hospital	HFrEF, ADHF	Discontinue	79, 3% 1350, 57%	2364	69 (13)	977, 41%	12	60–90-day mortality, readmission	3
Gilstrap 2023 ³⁶	USA, multi-centre, hospital	HFrEF, stable chronic	Discontinue	73 869, 21% 110 914, 31%	357 030	(all ≥65) 79.2	182 085, 51%	52	90-day, 1 year mortality and readmission, frailty status	3
Metra 2007 ³⁷ (COMET)	Europe, multi-centre, hospital	HFrEF, ADHF	Discontinue, reduce	61, 8% 162, 22% 529, 70%	752	64 (11)	180, 24%	232	All-cause mortality, readmission, predictors	3
Miro 2016 ³⁸ (BETAWIN-AHF)	Spain, multi-centre, hospital	HFrEF/HFrEF, ADHF	Discontinue	1460, 73% 530, 27%	1990	78 (10)	1103, 55%	8	Mortality, rehospitalization	3
Nambiar 2020 ³⁹	USA, single-centre, rehab/cardiac clinic, P	HFrEF, stable chronic	Discontinue, switch	22, 100% 11, 50%	22	77 (8)	16, 73%	52	NT-proBNP	3
Orso 2009 ⁴⁰	Italy, multi-centre, hospital	Unspecified, ADHF	Discontinue	141, 9% 362, 23%	1572	72 (11)	577, 37%	12	All-cause mortality, clinical events, LOS	3
Mineralocorticoid receptor antagonist (MRA)										
Ferreira 2020 ⁴¹ (TOPCAT)	USA, Canada, Brazil, Argentina, multi-centre/setting	HFrEF (LVEF>45%), stable chronic	Discontinue, placebo discontinued subgroup	225, 25% 161, 18%	386	<75 114/1020 (23) >75 111/747 (28) <75 96/1020 (18) >75 65/747 (18)	187, 48%	52	Mortality, hospitalization, hypokalaemia, renal function, BP, QoL	3
Jonsson Holmdahl 2022 ⁴²	Sweden, single-centre, hospital	HFrEF (LVEF<40%), ADHF	Discontinue	297, 52% 275, 48%	572	77 (12) 72 (11)	178, 31%	260	Mortality, frequency of discontinuation and reasons	3
Trivisan 2021 ⁴³ (SCREAM)	Sweden, multi-centre/setting	Unspecified, stable chronic	Discontinue	1519, 30% 2436, 48%	3955	*79 (71.85)	1740, 44%	24	Mortality, CV event, fracture, hyperkalaemia	3
Sodium-glucose cotransporter-2 inhibitor (SGLT2-i)										
Nakagaito 2021 ⁴⁴	Japan, single-centre, hospital, P	HFrEF/HFrEF, HFrEF, ADHF	Discontinue	30, 35% 56, 56%	86	72 (12)	31, 36%	52	Mortality, HF hospitalization, BNP, eGFR, ADEs	2

(Continues)

TABLE 1 (Continued)

Study name	Country, setting, prospective (P)	HF classification, presentation	Deprescribing intervention	Sample size (n, %)		Age (years) mean (SD) or *median (IQR)	Female (n, %)	Follow-up (weeks)	Main outcomes	Quality rating
				Intervention	Total					
Diuretics										
Braunschweig 2002 ³⁶	Sweden, multi-centre/setting, P	HFrEF, stable chronic	Discontinue	4, 100%	4	65 (8)	-	3	6MWT, QoL, Doppler ECG	3
DeVore 2015 ⁴⁶ (ASCEND-HF)	Americas, Europe, Asia Pacific, multi-centre, hospital	HFrEF/HFpEF, ADHF	Discontinue, reduce	213, 4% 583,10% 1912, 31%	6119	*69 (57, 78) *68 (57, 77) *67 (56, 77)	2089, 34%	4	Mortality, 30-day readmission, dyspnoea, dose change post discharge	3
Martens 2017 ⁴⁵	Belgium, single-centre, hospital	HFrEF/HFimpEF, stable chronic (post CRT)	Discontinue, reduce	296, 46% 126,19% 137, 21%	648	71 (11) 73 (10) 73 (11)	214, 33%	36	Mortality, HF readmission, BP, SCr, NYHA, LVEF, LVEDD, successful withdrawal	3
Straand 1993 ⁴⁷	Norway, multi-centre, community, P	HFpEF, stable chronic	Discontinue	18, 55% 15, 45%	33	(all ≥75) *82 (75, 95)	25, 76%	26	Severe ADE, causality of restart/discontinue, severity	3
van Kraaij 1997 ⁴⁹	Netherlands, multi-centre, hospital	Unspecified, stable chronic	Discontinue	74, 28% 186, 72%	260	(all ≥75) *82 (75, 102)	-	52	Diuretic-free after 1-year	3
van Kraaij 1998 ⁵⁰	Netherlands, multi-centre, aged care	unspecified, Stable chronic	discontinue	23, 30% 54, 70%	77	(all ≥75) 84 (6)	62, 80%	52	Mortality, hospitalization	3
Other treatments for heart failure: Digitalis glycoside (digoxin)										
Dall 1970 ⁵¹	Scotland, multi-centre/setting, P	Unspecified, stable chronic	Discontinue	12, 15% HF subgroup	12	*74 (58, 99)	62, 78%	12	HF, respiratory infection, anaemia,	3
Forman 1991 ⁵²	USA, multi-centre, aged care, P	HFpEF, stable chronic	Discontinue	14, 60.9% 9, 39.1%	23	*87 (65, 101)	33, 70%	9	Ejection fraction, sinus rhythm	3
Malik 2019 ⁵³ (OPTIMIZE-HF)	USA, multi-centre, hospital	HFrEF (LVEF<45%), stable chronic	Discontinue	698, 50% 698, 50%	1396	76 (11)	566, 40.5%	208	Mortality, hospitalization	3
Sommers 1981 ⁵⁴	South Africa, single-centre, community, P	HFrEF (LVEF<45%), stable chronic	Discontinue	20, 100%	20	*73 (52, 84)	14, 70%	5	HF, tachycardia, ECG, chest infection, PEP/LVET ratios	3
Combination treatments										
Allen 2018 ⁵⁵ (PINNACLE)	USA, multi-centre, hospital	HFrEF/HFpEF, stable chronic	Discontinue/reduce ACEI/ARB beta-blocker diuretic	241 230, 64% 262 206, 70% 224 748, 60%	374 580	(≥65 subgroup) 77 (8)	175 303, 47%	52	NYHA class, dyspnoea, orthopnoea, signs	4
Garred 2022 ¹⁰		HFrEF, stable chronic	Discontinue ACEI/ARB	- 20 033 13 746	20 033 13 746	(65–79 subgroup)	9862, 33%	260	Mortality, hospitalization, average daily target dose, adherence, discontinuation	3

TABLE 1 (Continued)

Study name	Country, setting, prospective (P)	HF classification, presentation	Deprescribing intervention	Sample size (n, %)		Age (years) mean (SD) or *median (IQR)	Female (n, %)	Follow-up (weeks)	Main outcomes	Quality rating
				Intervention	Continue					
	Denmark, multi-centre, hospital or HF clinic		beta-blocker MRA	6287		*73 (69–76) (≥80 subgroup) *84 (82–87)				
Sammour 2022 ⁵⁶	USA, multi-centre, cardiology clinics	HFrEF, stable chronic	Discontinue ACEI/ARB beta-blocker MRA, SGLT2-I diuretic	5439	-	68 (14)	1849, 34%	52	HF pharmacotherapy initiation or discontinuation	4

Note: Quality rating was adapted from Oxford Centre for Evidence-Based Medicine for ratings of individual studies.

Abbreviations: 6MWT, 6-min walk test; ADEs, adverse drug events; ADHF, acute decompensated heart failure; ADRD, Alzheimer's disease or a related dementia; AHD, atherosclerotic heart disease; BNP, B-type natriuretic peptide; BP, blood pressure; CRT, cardiac resynchronization therapy; CV, cardiovascular; ECG, echocardiogram; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 s; HF, heart failure; HFimpEF, heart failure with improved ejection fraction (improved to LVEF > 40%); HFmrEF, heart failure with mildly reduced ejection fraction (LVEF 41%–49%); HFpEF, heart failure with preserved ejection fraction (LVEF > 50%); HFrEF, heart failure with reduced ejection fraction (LVEF < 40%); HR, heart rate; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PEP/LVET, pre-ejection period/left ventricular ejection time; QoL, quality of life; Scr, serum creatinine; SOB, shortness of breath; VO₂, oxygen consumption attainable during physical exertion.

mortality, hospitalization and worsening HF outcomes; and lower for ADWEs (Table S6c).

3.3 | Outcomes

Feasibility results are summarized for RCTs in Figure 1 and for observational studies in Figures S2 and S3. There were too few RCTs to pool mortality and hospitalization. Risk of hospitalization for people with HFrEF in observational studies are summarized in Figure 2. ADWEs are summarized in Table 2.

3.3.1 | Angiotensin-converting enzyme inhibitor (ACEI)/Angiotensin receptor antagonist (ARB)

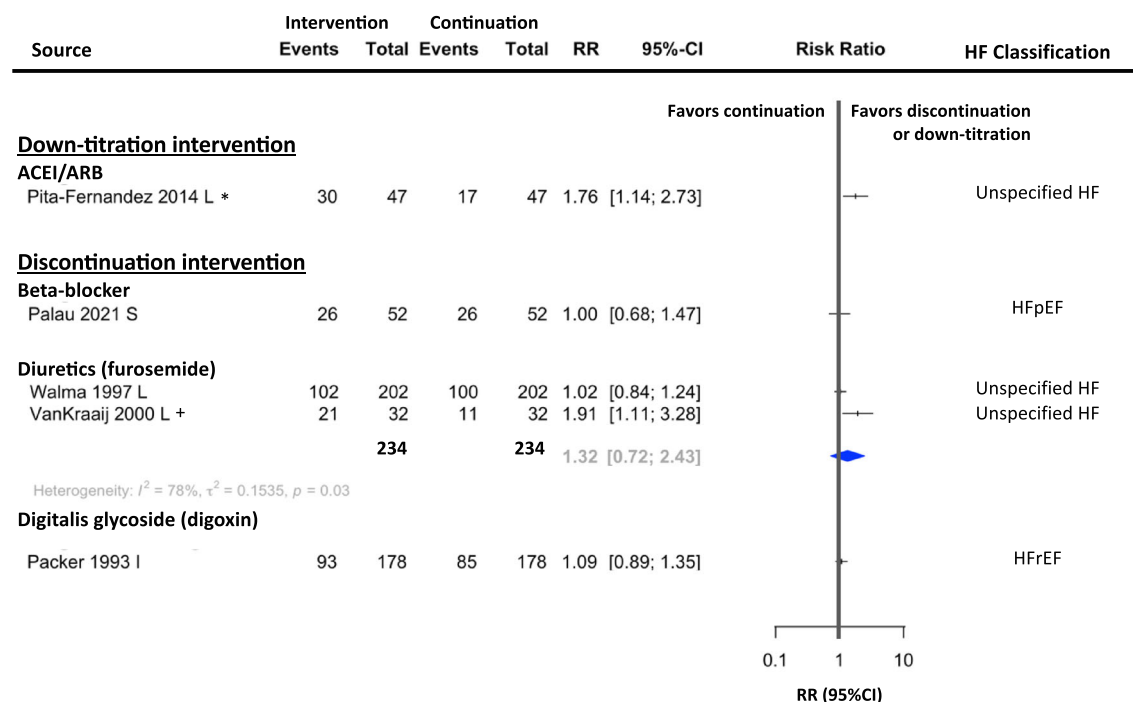
RCTs. A single-centre unblinded RCT²⁶ ($n = 47$) examined down-titrating the dose of **enalapril** or **losartan** by 50% compared to maintaining the optimized dose per usual care. The study included hospitalized patients ≥50 years with unspecified chronic HF, New York Heart Association class I–III, chronic kidney disease (CKD) (creatinine clearance <60 mL/min/1.63 m²) and anaemia. It was feasible to down-titrate the ACEI/ARB. Participants in the intervention group ($n = 30$) were 76% more likely to down-titrate their ACEI/ARB than to continue their optimized dose (RR 1.76, 95% CI 1.14–2.73, one trial). There was no statistical difference in 1-year mortality (RR 0.64, 95% CI 0.30–1.64, one trial, moderate-quality evidence). No participants were hospitalized nor reported worsening HF. No eligible RCT of **angiotensin receptor-neprilysin inhibitor (ARNI)** was identified.

Six **observational studies**^{10,32–34,55,56} ($n = 19\,704$) of ACEI/ARB discontinuation in registry HFrEF patients with ADHF showed no statistical difference in 1-year readmission compared to continuation (HR 1.10, 95% CI 0.97–1.24, two studies, $n = 19\,704$, $I^2 = 0\%$, high-quality evidence, Figure 2).^{32,33} One-year mortality risk was 65% higher in those that discontinued ACEI/ARBs compared to continuation (RR 1.65 95% CI 1.39–1.96, two studies, $I^2 = 65\%$, moderate-quality evidence study, Figure S4b).^{32,33} ADWEs in one registry⁵⁵ ($n = 374\,580$) of ambulatory cardiology care were orthopnoea (16.8%, rate ratio 2.8) and dyspnoea (19.1%, rate ratio 3.4) after discontinuation or down-titration of ACEI/ARBs ($n = 241\,230$) or beta-blockers ($n = 262\,206$).

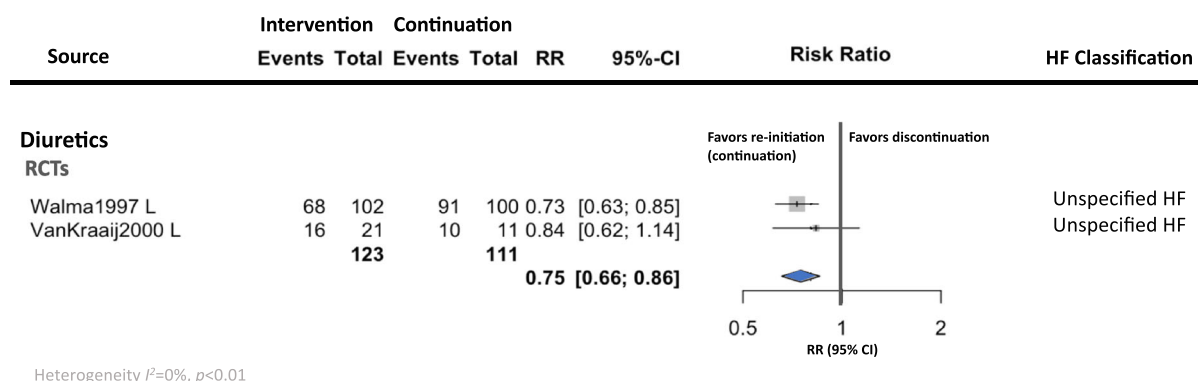
3.3.2 | Beta-blockers

RCTs. A multi-centre unblinded crossover trial²⁷ ($n = 52$) of community-dwelling patients with stable chronic HFpEF and chronotropic incompetence, examined discontinuing beta-blockers compared to maintaining the optimized dose per usual care. It was feasible to taper, then discontinue a beta-blocker for 15 days, with no statistical differences between the proportion in discontinuation and continuation groups (RR 1.00, 95% CI 0.68–1.47, one trial). After completion

(A) Feasibility of down-titration or discontinuation of intervention compared to continuation.



(B) Feasibility of sustained discontinuation of interventions at follow-up.



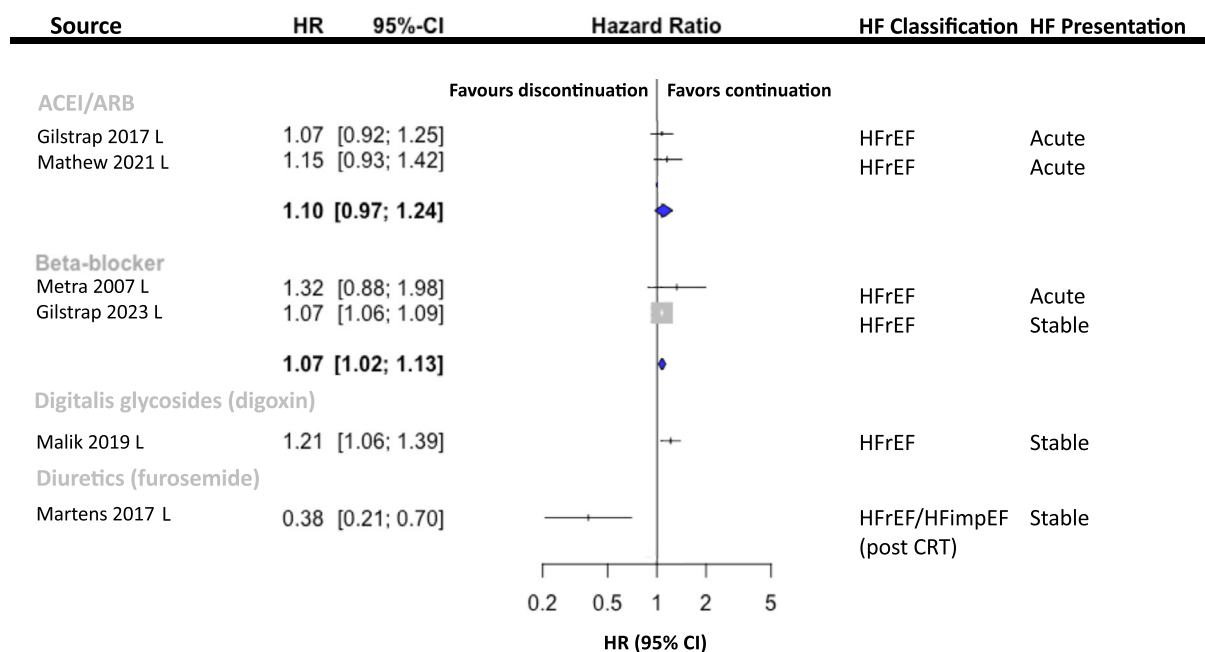
Heterogeneity $I^2=0\%$, $p<0.01$

FIGURE 1 Feasibility of intervention during stable chronic HF presentation in RCTs. 95% CI, 95% confidence interval; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; HF, heart failure; I^2 , heterogeneity statistic; RCT, randomized controlled trial; RR, risk ratio.

of the crossover trial, 88% ($n = 46$) remained on a lower dose or discontinued their beta-blocker due to improved functional capacity during discontinuation. There was no difference in hospitalization during the intervention period. One participant in each intervention arm experienced atrial fibrillation (AF) with rapid ventricular rate (successfully cardioverted) after discontinuation and withdrew from the study (RR 3.00, 95% CI 0.13–70.36, one trial, low-quality evidence). After 6 months, three participants with unspecified CV events were hospitalized; none died.

Ten **observational studies**^{10,25,35–40,56} ($n = 363\,784$) reported similar findings in people with HFpEF³⁹ but increased risk in HFrEF. Discontinuation of beta-blockers in hospitalized HFrEF

patients with ADHF showed two-fold risk of mortality (RR 2.06, 95% CI 1.31–3.24, five studies, $n = 178\,849$, $I^2 = 69\%$, very low-quality evidence, Figure S4b)^{25,35,36,38,40} and 7% increased risk of 1-year readmission compared to continuation (HR 1.07, 95% CI 1.02–1.13, two studies, $n = 357\,782$, $I^2 = 3\%$, moderate-quality evidence, Figure 2)^{36,37} and no statistical difference in risk of 8–52 week hospitalization (RR 1.00, 95% CI 0.84–1.19, four studies, $n = 362\,136$, $I^2 = 69\%$, very low-quality evidence, Figure S6b).^{25,36–38} ADWEs included ventricular arrhythmia ($n = 8$, 5%), AF ($n = 44$, 3%), acute coronary artery syndrome ($n = 12$, 8%) and syncope ($n = 3$, 2%); but no significant change in activities of daily living (ADLs).



Heterogeneity: Overall $I^2=74\%$, $p < 0.01$; ACEI/ARB $I^2=0\%$, $p < 0.01$; Beta-blocker $I^2=3\%$, $p < 0.01$.

FIGURE 2 Hospitalization in HFrEF patients discontinuing HF pharmacotherapy in observational studies. 95% CI, 95% confidence interval; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CRT, cardiovascular resynchronization therapy; HR, hazard ratio; HF, heart failure; HFimpEF, heart failure with improved ejection fraction (baseline LVEF < 40%, > 10-point increase from baseline and second measurement of LVEF > 40%); HFpEF, heart failure with preserved ejection fraction (LVEF > 50%); HFrEF, heart failure with reduced ejection fraction (LVEF < 40%); I^2 , heterogeneity statistic.

Frailty was reported in one observational study³⁶ ($n = 357\ 030$), defined as frailty index >0.25. In hospitalized HFrEF American Medicare patients ≥ 65 years, 23% ($n = 83\ 353$) were frail. Overall, 21% ($n = 73\ 869$) of participants discontinued a beta-blocker. Outcomes were not reported by frailty status.

3.3.3 | Diuretics

RCTs. Two unblinded RCTs ($n = 234$), one single²⁹ and one multi-centred,²⁸ examined discontinuation of furosemide among community-dwelling patients ≥ 65 years with stable chronic unspecified HF classification and HFpEF. The proportion of participants that discontinued vs. continued diuretics could not be pooled ($I^2 = 78\%$). Participants that discontinued a diuretic were 25% likely to re-initiate furosemide within 26 weeks (RR 0.75, 95% CI 0.66–0.86, two trials, $I^2 = 0\%$). No deaths or hospitalizations occurred. There was no statistical difference in worsening HF symptoms between study arms (RR 3.45, 95% CI 0.68–17.46, two trials, $I^2 = 48\%$, moderate-quality evidence).

Eight observational studies^{45–50,55,56} ($n = 237\ 328$) reported similar feasibility and risk of worsening HF. In two before-and-after studies ($n = 37$), 25% (HFrEF)⁴⁵ and 55% (HFpEF)⁴⁸ of participants discontinued and did not re-initiate their diuretic after 3–26 weeks. No hospitalization or death occurred (Table S5). ADWEs included worsening HF symptoms of oedema ($n = 344$, 30%), hypertension

($n = 267$, 8%), myocardial infarction ($n = 33$, 3%), stroke ($n = 33$, 3%), and peripheral oedema ($n = 267$, 7%). One study⁵⁵ ($n = 224\ 748$) reported orthopnoea (8.8%, rate ratio 2.3) and dyspnoea (10.6%, rate ratio 3.0) after reducing or discontinuing a diuretic.

3.3.4 | Digitalis glycosides (digoxin)

RCTs. A blinded multi-centre RCT³⁰ ($n = 178$) examined 12-week discontinuation of digoxin compared to continuation in stable chronic HFrEF (LVEF < 35%) patients with reduced exercise capacity for >3 months on optimized doses of ACEI. There were no statistical differences in the proportion of participants in both study arms (RR 1.09, 95% CI 0.89–1.35, one trial), nor all-cause mortality (RR 0.30, 95% CI 0.03–2.87, one trial, high-quality evidence). Participants that discontinued digoxin had a 5.5-fold risk of hospitalization (RR 5.48, 95% CI 1.26–23.80, one trial, high-quality evidence) and a 5.3-fold risk of worsening HF (RR 5.26, 95% CI 1.89–14.58, one trial, high-quality evidence).

A single-centre double-blind crossover trial³¹ ($n = 21$) of outpatients with stable chronic unspecified HF were randomized to take digoxin and placebo for two consecutive 12-week periods. Fourteen (67%) participants remained off digoxin and seven (33%) failed to complete both treatment periods due to worsening HF (placebo $n = 4$; digoxin $n = 1$), supraventricular tachycardia (placebo $n = 1$) and digoxin toxicity (digoxin $n = 1$). One (5%) participant died from oedema and myocardial infarction (MI). Three (14%) participants

TABLE 2 Summary of adverse drug withdrawal effects (ADWEs) from discontinuing or *down-titrating HF pharmacotherapy in older people.

Adverse drug withdrawal effects (ADWE)	No. of studies	Study design CT [R], non-RCT (NR)]	No. events/sample, proportion (%)				Total sample	Point estimate and 95% CI; or score and P-value	GRADE quality of evidence
			Intervention		Control				
Guideline-directed medical therapies (GDMT) for heart failure									
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB)									
Worsening HF	1	NR	1/5	20%	-	-	5	-	Very low
Beta-blocker									
Worsening HF	1	NR	48/61	79%	475/529	90%	590	RR 0.88 (0.77–1.00)	High
Ventricular arrythmia	2	NR	8/162	5%	27/388	7%	1648	-	Very low
	1*	NR	2/19	11%	2/26	7%	76	-	Very low
Atrial fibrillation with rapid ventricular rate	3	R & NR	45/1674	3%	109/1648	7%	1674	RR 3.00 (0.13–70.36)	Very low to low
	1*	NR	1/19	5%	1/76	1%	76	-	Very low
Acute coronary syndrome	1	NR	12/141	9%	42/362	12%	1572	-	Moderate
Other: Barthel Index for ADLs, syncope, cognition (MMSE, MOCA), MQoLHF	2	NR	ADLs 78.7(25.5) Syncope 3/141, 2% Baseline MMSE 28(2) Baseline MoCA 22(4) Baseline MQoLHF 25(13–35)	ADLs 79.6(23.3) Syncope 16/362, 4% Baseline MMSE 27(3) Baseline MoCA 20(5) Baseline MQoLHF 27(11–40)			1572	- - MMSE 28, P = 0.929 MOCA 23, P = 0.420 Physical 22, RR – 1.8 (–4–0.4), emotional 27 RR-2.4 (–4.7––0.01)	Low to moderate
Sodium-glucose cotransporter-2 inhibitor (SGLT2-i)									
Escalating diuretic	1	NR	-	-	-	-	86	HR 1.17 (1.01–1.32)	Low
Diuretic									
Worsening HF/Oedema	2	R	27/123	22%	5/111	4.5%	234	RR 3.45 (CI 1.99–12.00)	Moderate
	2	NR	26/56	47%	0/87	0%	110	-	Very low
Hypertension	2	R	10/123	8%	5/111	4.5%	234	-	Low
	1	NR	3/33	9%	0/33	0%	33	-	Very low
Myocardial infarction	1	NR	1/33	3%	0/33	0%	33	-	Very low
Stroke	1	NR	1/33	3%	0/33	0%	33	-	Very low
Other									
Oedema (peripheral)	2	R	8/123	7%	1/111	1%	234	-	Low
	1	NR	3/33	9%	0/33	0%	33	-	Very low
Dyspnoea (shortness of breath)	1	R	6/102	6%	0/100	0%	202	-	Moderate
Other: anxiety, malignancy, MQoLHF	1	NR	3/33	3–6%	0/33	0%	33	- MQoLHF: baseline 12, stop 9	Very low
Mineralocorticoid receptor antagonist (MRA)									
Major CV event (composite CV death, MI, stroke and HF)	1	NR	-	-	-	-	3995	HR 1.06 (1.01–1.12)	Moderate
Other									
2-year risk of fracture		1	NR	-	-	-	3995	HR 1.17 (0.97–1.36)	High
Moderate to severe hyperkalaemia		1	NR	-	-	-	3995	HR 0.73 (0.66–0.8)	Moderate

TABLE 2 (Continued)

Additional treatments for heart failure									
Digoxin									
Worsening HF	1	R	23/93	25%	4/85	5%	178	RR 5.26 (1.89–14.58)	High
	3	NR	9/53	17%	-		53	-	Very low
Sinus tachycardia	3	NR	3/131	2%	-		219	-	Very low
Myocardial infarction	1	R	1/111	1%	2/106	2%	217	-	Very low
Atrial fibrillation	2	R	2/111	2%	0/106	0%	217	-	Very low
Unstable angina	1	R	1/93	1%	0/85	0%	178	-	Low
Other									
URTI (including bronchitis)	3	NR	6/131	5%	-		131	-	Very low
Escalating diuretic	1	R	11/93	12%	4/85	5%	178	-	Moderate
Dyspnoea	1	R	22/93	24%	12/85	14%	178	-	Moderate
Fatigue		R	22/93	24%	13/85	15%	178	-	Moderate
MHFQoL improved	1	R	19/93	20%	34/85	40%	178		Moderate
MFHQoL deteriorated			28/93	30%	30/85	35%			
Patient feeling better/unchanged			61/93	66%	30/85	35%			
Patient feeling worse			70/93	75%	13/85	15%			
Other: hyponatremia, thyrotoxicosis, renal carcinoma	3	R & NR	3/103	1–5%	0/105	0%	208	-	Very low to low

Abbreviations: HF, heart failure; RCT, randomized controlled trial; NonRCT, observational study; ADE, adverse drug events; ADWE, adverse drug withdrawal events; CI, confidence interval; “Other”, includes sum of all “other ADWEs” /sum of N or T (not duplicated denominator); * Reduced dose; MQLHF, Minnesota quality of life in heart failure scale; URTI, upper respiratory tract infection; UTI, urinary tract infection; MI, myocardial infarction; CV, cardiovascular; ADL, activities of daily living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

withdrew early from worsening HF during the first treatment phase while taking digoxin ($n = 1$) and placebo ($n = 2$).

Four **observational studies**^{51–54} ($n = 1451$) reported similar feasibility, hospitalization and worsening HF. In aged care residents with HFpEF and hospital patients with HFrEF,^{52,53} it was feasible to discontinue digoxin, with no statistical difference compared to continued use (RR 1.12, 95% CI 0.77–1.64, two studies, $n = 1419$, $I^2 = 50\%$). HFrEF patients⁵³ showed no statistical difference in 4-year mortality (HR 1.09, 95% CI 0.96–1.23, one study, $n = 1396$, high-quality evidence, Figure S6a) and 16% increased hospitalization between those who discontinued and continued digoxin (HR 1.16, 95% CI 1.03–1.30, one study, $n = 1396$, moderate-quality evidence, Figure S6b). ADWEs included worsening HF symptom of oedema ($n = 231$, 22%), sinus tachycardia ($n = 219$, 2%), MI ($n = 199$, 1%), AF ($n = 199$, 2%), unstable angina ($n = 178$, 1%) and upper respiratory tract infection ($n = 32$, 16%); but no significant changes in ADLs.

3.3.5 | Mineralocorticoid receptor antagonists (MRA)

No eligible RCT was identified.

Five **observational studies**^{10,41–43,56} ($n = 30\,385$) on discontinuing **spironolactone** or **eplerenone** in community-dwelling HFpEF and HFrEF patients could not pool feasibility ($I^2 = 99\%$) and mortality ($I^2 = 98\%$). ADWE included 6% increased risk of major CV events

(e.g., CV death, MI, stroke, HF) (HR 1.06, 95% CI 1.01–1.12, one study, $n = 3955$, moderate-quality evidence).⁴³

3.3.6 | Sodium-glucose cotransporter-2 inhibitors (SGLT2-i)

No eligible RCT was identified.

Two **observational studies**^{44,56} ($n = 5525$) on discontinuing SGLT2-i were scarce. In a single-centre study⁴⁴ ($n = 86$) of patients across HF classifications and presentations, participants were 46% more likely to continue than discontinue SGLT2-i (RR 0.54, 95% CI 0.39–0.74), with no statistical difference for re-initiation within 1-year of discontinuation (RR 1.10, 95% CI 0.98–1.24). There was no statistical difference in 1-year mortality (HR 0.71, 95% CI 0.16–3.16, one study, low-quality evidence, Figure S4a) and hospitalization between study arms (RR 1.73, 95% CI 0.94–3.19, one study, low-quality evidence, Figure S5).⁴⁴ ADWE of increasing diuretic dose was 17% more likely in discontinued SGLT2-i compared to continuation (HR 1.17, 95% CI 1.01–1.32, one study, low-quality evidence).⁴⁴

4 | DISCUSSION

In situations where optimization of GDMT is not tolerated, these findings provide a roadmap of the current knowledge on deprescribing HF

pharmacotherapy in adults ≥ 50 years. Outcomes are unknown in frail adults ≥ 75 years, precluding recommendations for this sub-population. During stable chronic HF, evidence from limited RCTs demonstrate down-titration of ACEI/ARBs in patients with CKD and discontinuation of beta-blockers in HFpEF was feasible and not associated with increased risk of 1-year mortality and hospitalization. Decisions to discontinue diuretics or digoxin may want to consider potential risks of worsening HF and hospitalization.

Similar to efficacy trials, the population in this review are mostly younger, more robust and overrepresent HFREF compared to real-world treatment populations with multiple comorbidities, poly-pharmacy, cognitive impairment and variable access to healthcare services.⁵⁸ In single-agent HF trials, up to 85% of participants experience at least one adverse event, but discontinuation rates did not differ from placebo.⁵⁹ Inclusion of frail adults ≥ 75 years, with objective frailty measures in HF trials would help inform the appropriateness to continue or discontinue current and emerging therapies.^{6,60–64} RCTs and larger scale studies are needed to evaluate discontinuation of contemporary HF pharmacotherapies.³

The shift in focus on providing symptomatic relief in HF, improving QoL and daily function, can take priority over longevity in older adults who may not tolerate or achieve target doses recommended from clinical trials.^{65,66} Only half of adults ≥ 80 years reached target doses^{10,11} and as low as 1.68% reached median beta-blocker target doses.⁶⁷ ACEI/ARB adherence is 10% lower (69%) and discontinuation is 10% higher (51%) in adults ≥ 80 years compared to those < 65 years.¹⁰ Reasons to deprescribe can include uncertain benefit, new contraindications, non-tolerable ADEs, nonadherence, interactions with acute/chronic disease, drug interactions, geriatric outcomes or GDMT optimization (e.g., diuretic tapering).⁶⁸ Some patients may prioritize decreasing medication burden over the benefits of HF pharmacotherapy.

Limited RCTs demonstrate a potential role for down-titrating ACEI/ARBs²⁶ and discontinuing beta-blockers²⁷ in select situations. Data suggest that down-titrating ACEI/ARBs in the setting of CKD may improve serum creatinine levels, without much short-term harm. However, existing data cannot address whether reducing doses of ACEI/ARB in people with CKD will ultimately preclude the long-term benefits of high-dose ACEI/ARB. While beta-blockers are not indicated in patients with HFpEF,^{2,3} data on effects of deprescribing beta-blockers after chronic therapy are needed.⁶⁹ Caution must be exercised when deprescribing diuretics and digoxin in frail stable chronic HF patients ≥ 75 years to weigh ADEs (e.g., falls, hospitalization, fatigue) with potential ADWEs (e.g., hospitalization, CV events, worsening HF) that require ongoing monitoring.^{6,70} Discontinuation of beta-blockers in HFREF patients with ADHF is not recommended due to increased risk of mortality and readmission.

4.1 | Strengths and limitations

This novel review evaluates ADWEs and frailty status during deprescribing of HF pharmacotherapy in older adults, which should be

considered with the benefits and adverse effect(s) rationalizing discontinuation.^{6,59,71} Compared to previous works focused on deprescribing of antihypertensive medications in older people in 2020⁷² or of heart failure medications in people with stable chronic HFREF in 2012,⁷³ this review evaluated studies of all HF phenotypes; and also sub-analyses by age ≥ 75 years and frailty. The degree of inclusion of frail people and the impact on clinical outcomes is unknown. The mean study age does not reflect advanced age ≥ 80 years, warranting attention in prospective research. There was limited reporting of QoL and ADLs; and no data on falls and confusion.

Low generalizability and substantial heterogeneity reflect the complexity of individualizing HF pharmacotherapy. Interpretation is particularly limited for drug classes with low number of clinical trials and observational studies such as SGLT2-i, MRAs and ARNIs. This is an area of increasing research focus, and there may be benefit of repeating this review in the near future, when additional trials that are currently registered are completed and published, especially for contemporary and emerging HF treatments (e.g., SGLT2-i, ARNIs, [soluble guanylate cyclase stimulators](#), [inotropes](#)). Moreover, existing research does not distinguish whether outcomes were caused by changes in HF pharmacotherapy or disease progression. HF phenotypes were reported alongside results to mitigate bias of interpretation in this review, particularly for studies with combination HF phenotypes (e.g., HFREF, HFmrEF, HFpEF) where outcomes were not reported separately by authors. Non-adherence, planned deprescribing, tapering regimens or palliative care plans could not be differentiated in observational studies.⁷⁴ Interpretation of data was limited by reporting/selection bias and confounding of exposure time-points/outcomes, education and socioeconomic or health status; and did not discern baseline function between groups.⁷⁵

5 | CONCLUSION

Interventions must be considered within the holistic context of patient needs and priorities; the benefit of the HF pharmacotherapy and risks of underuse will vary between and within patients over time. Few RCTs suggest stable chronic HF patients ≥ 50 years may down-titrate ACEI/ARBs in CKD or discontinue beta-blockers in HFpEF. The effects of deprescribing HF pharmacotherapy remain uncertain in frail adults ≥ 75 years due to the limited number of studies with high quality of evidence. RCTs and longitudinal studies of current and novel HF pharmacotherapies that include objective measures of frailty at baseline are needed to evaluate deprescribing outcomes that are important to older adults, especially among those with frailty.

AUTHOR CONTRIBUTIONS

Mai H. Duong: conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, original manuscript preparation and editing, visualization, project administration, funding acquisition. Danijela Gnjidic: supervision, conceptualization, methodology, validation, manuscript review and editing. Andrew

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ACKNOWLEDGEMENTS

We acknowledge the collaboration of Mr Ryan Snow for graphic design support, librarian Dr Yulia Ulyannikova for technical assistance and PRESS validation, and the technical assistance of Mr Jim Matthews of the Sydney Informatics Hub, a Core Research Facility of the University of Sydney. Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

There are no competing interests to declare. M.H.D., D.G., S.N.H. and S.M. are members of the Australian Deprescribing Network (ADeN) and P.G. is a member of the United States Deprescribing Network (USDEN).

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

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SUPPORTING INFORMATION

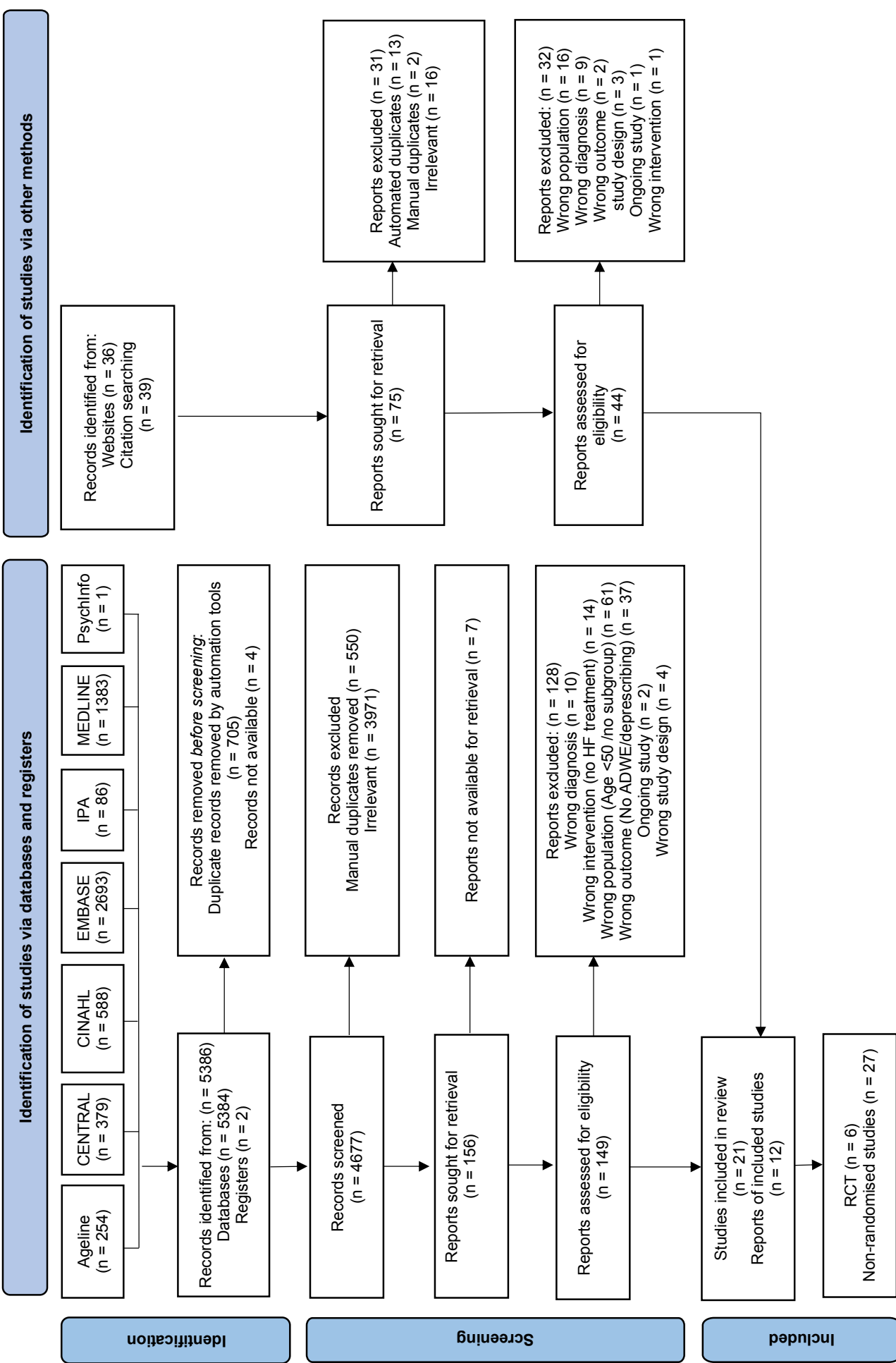
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Duong MH, Gnjidic D, McLachlan AJ, et al. The effect of down-titration and discontinuation of heart failure pharmacotherapy in older people: A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2025;91(1):23-37. doi:[10.1111/bcp.16223](https://doi.org/10.1111/bcp.16223)

ONLINE SUPPLEMENTARY MATERIALS

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Figure S3.1: PRISMA flowchart



Footnote: Interrater reliability showed agreement between reviewers (MHD/MRR) was substantial (Cohen's kappa statistic (k) 0.63) for title-abstract screening and moderate (k 0.54) for full text screen. Abbreviation: HF = heart failure; ADWE = adverse drug withdrawal effect

Table S3.1: Search Strategy

Elderly or Frail; AND	Withdrawal; AND	Medication; AND	Heart Failure; AND	Study design
Aged OR elderly OR Aging OR older adult* OR older people OR middle aged OR geriatric* OR Frailty OR Frail Elderly OR frail* OR Pre-frail* OR Fragility	Deintensification OR Discontinu* OR Deprescrib* OR Reduc* OR Stop* OR Taper* OR Ceased OR Ceasing OR Cessation OR de-escalation	ACEI/ARB, beta blockers, renin inhibitor, diuretics, cardiac glycosides, aldosterone/ mineralocorticoid receptor antagonists (MRAs), vasodilators, nitrates, calcium channel blockers, inotropes/adrenergic agonists, I _f channel inhibitors, SGLT-2 inhibitors, soluble guanylate cyclase stimulator, myotrope	heart failure OR cardiac failure OR congestive heart failure OR heart decompensation OR cardiac decompensation	Randomised controlled trial OR RCT OR observational stud* OR cohort stud* OR cross sectional stud* OR case control stud* OR meta analysis

Table S3.2: Peer Review of Electronic Search Strategies (PRESS) checklist

PRESS Guideline Assessment FORM (2015)-Search Submission & Peer Review Assessment

SEARCH SUBMISSION:

Searcher: MD

Email: [REDACTED]

Date submitted: Wednesday October 13, 2021

Date requested by: Friday October 15, 2021

Systematic Review Title:

Withdrawal of Pharmacological Treatment for Heart Failure in Frail and Non-frail Older People: A Systematic Review and Meta-analysis.

This search strategy is...

X	My PRIMARY (core) database strategy — First time submitting a strategy for search question and database
	My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
	SECONDARY search strategy— First time submitting a strategy for search question and database
	SECONDARY search strategy — NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

Database

MEDLINE, Embase, CENTRAL, International Pharmaceutical Abstracts, PsychInfo, CINAHL, and Ageline

Interface

Ovid, EBSCO

Research Question

1. Is the withdrawal of pharmacological treatment for heart failure (HF) feasible in older people?

- a) In what proportion of older people could a HF treatment be stopped?
- b) Of those that stopped a HF treatment:
 - i) What proportion were restarted or replaced by another treatment?
 - ii) What definition, classification or cause of HF was most commonly reported?

2. What is the clinical impact of withdrawal of pharmacological treatment for heart failure in older people?

- c) Which clinical and laboratory variables were measured during withdrawal of HF treatment?
- d) What impact does reducing or ceasing HF treatment have on clinical and global patient outcomes over time?

3. What data exists on the feasibility and impact of withdrawal of pharmacological treatment for HF in frail older people? What is the analysis of questions 1 and 2 for any participants who were frail according to an objective frailty definition?

PICO Format

PICOS: Population (older adults), Intervention (reduce or cease HF treatment), Comparator (routine medical care), and Outcome (withdrawal effects), Study Design (systematic review and meta-analysis)

P I C O S Inclusion Criteria

(List criteria such as age groups, study designs, etc., to be included) [optional]

We will include studies of withdrawal versus continuation of HF treatments in older adults (defined as 50 years and over). Studies will report the withdrawal (e.g. dose reduction or complete discontinuation) of a HF treatment; Study types will include randomised controlled trials (RCTs) (controlled before-and-after trials; interrupted time series); or meta-analysis; or observational studies (cohort, case-control or cross sectional studies). Study participants can be recruited from residential aged care facilities, based in hospital, clinics or living independently in the community.

Population:

(i) Include only people aged 50 years or older or must separately report outcomes for people aged 50 years or older;

(ii) Studies reported HF as the primary diagnosis for treatment indication in the study (or separately reported). Include people with a diagnosis of HF (e.g. congestive HF (CHF), reduced ejection fraction (HFrEF), preserved ejection fraction (HFpEF)), meets the universal definition or classification of HF, or with disease severity based on the New York Association (NYHA) classification and included persons with mild to severe functional limitations (NYHA grade II-IV).

(iii) Include studies reporting withdrawal (e.g. dose reduction or complete discontinuation) of a pharmacological treatment for HF;

(iv) When available for subgroup analysis, will include studies with people described as being frail or must separately report outcomes for people described as frail, with a frailty measurement using objective criteria and/or justified using systematically defined criteria (e.g. phenotype criteria, frailty index).

Exclusion Criteria

(List criteria such as study designs, date limits, etc., to be excluded) [optional]

We will exclude qualitative studies, self-reports, case reports, case series, expert opinion or reviews. Exclude trials of pharmacotherapy with cardiovascular agents for indications other than HF (e.g., hypertension, angina, atrial fibrillation, stroke, previous myocardial infarction, liver failure, heart rate control, chronic kidney disease).

Was a search filter applied?

Yes ☐ No ☒

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. *[mandatory if YES to previous question — textbox]*

The search filters for drug interventions, free texts and index terms used to describe withdrawal were adapted from a Cochrane RCT filter for adverse effects by Reeve E et. al. 2020.

Reeve E, Jordan V, Thompson W, Sawan M, Todd A, Gammie TM, Hopper I, Hilmer SN, Gnjdjic D. Withdrawal of antihypertensive drugs in older people. Cochrane Database of Systematic Reviews 2020, Issue 6. Art. No.: CD012572

Other notes or comments you feel would be useful for the peer reviewer? *[optional]*

There are 7 search strategies for review included below.

1. Database: Ovid MEDLINE(R) ALL <1946 to March 7, 2023> Search Strategy:

- 1 exp heart failure/ or cardiac failure/ (131550)
- 2 (congestive heart failure or ((heart or cardiac) adj1 (failure* or decompensation or de-compensation))).ti,ab. (193309)
- 3 1 or 2 (230737)
- 4 Aged/ or "Aged, 80 and over"/ or Aging/ or exp geriatrics/ (3477510)
- 5 elderly.ti,ab. (261764)
- 6 Middle Aged/ (4587602)
- 7 Frailty/ or Frail Elderly/ (15964)
- 8 frail*.ti,ab. (26567)
- 9 (fragility or fragil*).ti,ab. (46054)
- 10 (prefrail* or pre-frail*).ti,ab. (1675)
- 11 4 or 5 or 6 or 7 or 8 or 9 or 10 (5608352)
- 12 (withdraw* or taper*).ti,ab. (155161)
- 13 (ceased or ceasing or cessation*).ti,ab. (93596)
- 14 (deprescrib* or discontinu*).ti,ab. (137965)
- 15 ((reduc* or taper* or titrat* or stop* or unnecessary or omission) adj3 (dosage* or dose* or dosing* or drug* or medicat* or medicine* or prescri*)).ti,ab. (112441)
- 16 deprescriptions/ or drug tapering/ (876)
- 17 dose-response relationship, drug/ (414448)
- 18 (deescalat* or de-escalat*).ti,ab. (3332)
- 19 12 or 13 or 14 or 15 or 16 or 17 or 18 (860600)
- 20 (((ceiling or loop) adj diuretic*) or (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*)).ti,ab. (38046)
- 21 exp angiotensin converting enzyme inhibitors/ or angiotensin receptor antagonists/ or angiotensin-converting enzyme inhibitors/ or (((angiotensin converting enzyme inhibit* or ace) adj2 inhibit*) or acei or (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril or perindopril or pivopril or quinapril or ramipril or rentiapril or saralasin or s nitrosocaptopril or spirapril or temocapril or teprotide ortrandolapril or utibapril or zabicipril or zofenopril or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril)).ti,ab. (70255)
- 22 exp Angiotensin Receptor Antagonists/ or (((angiotensin adj3 receptor antagon*) or angiotensin) adj3 receptor block*) or arb or arbs or (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten)).ti,ab. (38237)
- 23 exp calcium channel blockers/ or (calcium adj2 (antagonist* or block* or inhibit*)).ti,ab. or (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).ti,ab. (122091)
- 24 exp adrenergic beta antagonists/ or (beta adj2 (adrenergic* or antagonist* or block* or receptor*)).ti,ab. or (acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iproclorol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthioproprianolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or

sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).ti,ab. (169376)

25 exp Cardiac Glycosides/ or exp Digoxin/ (44175)

26 (renin inhibitor or aliskiren).ti,ab. (1645)

27 exp Mineralocorticoid Receptor Antagonists/ or exp Spironolactone/ or exp Eplerenone/ or (aldosterone antagonists or finerenone).ti,ab. (10354)

28 exp Vasodilator Agents/ or exp Nitroglycerin/ or exp Isosorbide Dinitrate/ or exp hydralazine/ (435896)

29 exp Adrenergic Agonists/ or exp Dobutamine/ or exp Dopamine Agents/ or exp Dopamine/ or exp Dopamine Agonists/ or (inotropes or inotrope agonist).ti,ab. (438979)

30 exp Ivabradine/ (1040)

31 exp Sodium-Glucose Transporter 2 Inhibitors/ or (SGLT2 inhibitors or SGLT2I or dapagliflozin or empagliflozin).ti,ab. (6190)

32 (Soluble guanylate cyclase stimulator or vericiguat).ti,ab. (230)

33 (myotrope or omecamtiv mecarbil).ti,ab. (140)

34 angiotensin receptor neprilysin inhibitor/ or sacubitril plus valsartan/ or ARNI.ti,ab. (357)

35 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (1108499)

36 Randomized Controlled Trials as Topic/ or Meta-Analysis/ or Prospective Studies/ or Retrospective Studies/ or Cohort Studies/ or Cross-Sectional Studies/ or Case-Control Studies/ (2494774)

37 (randomi#ed controlled trial or meta analysis or observational stud* or cohort stud* or cross sectional stud* or case control stud*).mp. (853435)

38 36 or 37 (2786449)

39 3 and 11 and 19 and 35 (2483)

40 3 and 11 and 19 and 35 and 38 (782)

2. Database: Embase Classic+Embase <1947 to 2023 March 07> Search Strategy:

1 exp heart failure/ or cardiac failure/ or Heart Failure, Congestive/ or congestive heart failure/ (569854)

2 (congestive heart failure or ((heart or cardiac) adj1 (failure* or decompensation or de-compensation))).ti,ab. (329595)

3 1 or 2 (623392)

4 Aged/ or very elderly/ or Aging/ or exp geriatrics/ (3488788)

5 (older adj1 (adult* or people)).ti,ab. (154560)

6 elderly.ti,ab. (378523)

7 Middle aged/ (1740716)

8 Frailty/ or Frail Elderly/ (26424)

9 frail*.ti,ab. (40713)

10 (fragility or fragil*).ti,ab. (62094)

11 (prefrail* or pre-frail*).ti,ab. (2529)

12 4 or 5 or 6 or 7 or 8 or 10 or 11 (4662072)

13 (withdraw* or taper*).ti,ab. (228771)

14 (ceased or ceasing or cessation*).ti,ab. (133383)

15 (deprescrib* or discontinu*).ti,ab. (237188)

16 ((reduc* or taper* or titrat* or stop* or unnecessary or omission) adj3 (dosage* or dose* or dosing* or drug* or medicat* or medicine* or prescri*)).ti,ab. (185471)

17 Dose-Response Relationship, Drug/ or drug dose titration/ or Dose response/ (410760)

18 treatment withdrawal/ or drug withdrawal/ or Substance Withdrawal Syndrome/ or drug dose reduction/ (300388)

19 (deescalat* or de-escalat*).ti,ab. (6745)

20 13 or 14 or 15 or 16 or 17 or 18 or 19 (1275773)

21 (((ceiling or loop) adj diuretic*) or (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*)).ti,ab. (52047)

22 exp angiotensin converting enzyme inhibitors/ or angiotensin receptor antagonists/ or angiotensin-converting enzyme inhibitors/ or sodium-glucose transporter 2 inhibitors/ or (((angiotensin converting enzyme inhibit* or ace) adj2 inhibit*) or acei or (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril or perindopril or pivopril or quinapril or

ramipril or rentiapril or saralasin or s nitrosocaptopril or spirapril or temocapril or teprotide or trandolapril or utibapril or zabicipril or zofenopril or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril)).ti,ab. (209068)

23 exp Angiotensin Receptor Antagonists/ or (((angiotensin adj3 receptor antagonist*) or angiotensin) adj3 receptor block*) or arb or arbs or (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten)).ti,ab. (109936)

24 exp calcium channel blockers/ or (calcium adj2 (antagonist* or block* or inhibit*)).ti,ab. or (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).ti,ab. (298374)

25 exp adrenergic beta antagonists/ or (beta adj2 (adrenergic* or antagonist* or block* or receptor*)).ti,ab. or (acebutolol or adimolol or afurolof or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocholol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropiranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).ti,ab. (375408)

26 exp Cardiac Glycosides/ or exp Digoxin/ (97880)

27 (renin inhibitor or aliskiren).ti,ab. (2582)

28 exp Mineralocorticoid Receptor Antagonists/ or exp Spironolactone/ or exp Eplerenone/ or (aldosterone antagonists or finerenone).ti,ab. (48281)

29 exp Vasodilator Agents/ or exp Nitroglycerin/ or exp Isosorbide Dinitrate/ or exp hydralazine/ (735182)

30 exp Adrenergic Agonists/ or exp Dobutamine/ or exp Dopamine Agents/ or exp Dopamine/ or exp Dopamine Agonists/ or (inotropes or inotrope agonist).ti,ab. (681242)

31 angiotensin receptor neprilysin inhibitor/ or sacubitril plus valsartan/ or ARNI.ti,ab. (3515)

32 exp Sodium-Glucose Transporter 2 Inhibitors/ or (SGLT2 inhibitors or SGLT2I).ti,ab. or (dapagliflozin or empagliflozin).ti,ab. (16047)

33 (Soluble guanylate cyclase stimulator or vericiguat).ti,ab. (371)

34 (myotrope or omecamtiv mecarbil).ti,ab. (221)

35 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (1729000)

36 Randomized Controlled Trial/ or Meta-Analysis/ or Prospective Studies/ or Retrospective Studies/ or Cohort Studies/ or Cross-Sectional Studies/ or Case-Control Studies/ (2925768)

37 (randomi#ed controlled trial or meta analysis or observational stud* or cohort stud* or cross sectional stud* or case control stud*).mp. (1182299)

38 36 or 37 (3360395)

39 3 and 12 and 20 and 35 (5857)

40 3 and 12 and 20 and 35 and 38 (1972)

3. Database: EBM Reviews - Cochrane Central Register of Controlled Trials < February 2023>

Search Strategy:

1 exp heart failure/ or cardiac failure/ (10009)

2 (congestive heart failure or ((heart or cardiac) adj1 (failure* or decompensation or de-compensation))).ti,ab. (29971)

3 1 or 2 (31002)

4 Aged/ or "Aged, 80 and over"/ or Aging/ or exp geriatrics/ (219250)

- 5 elderly.ti,ab. (48155)
- 6 Middle Aged/ (331719)
- 7 Frailty/ or Frail Elderly/ (911)
- 8 frail*.ti,ab. (4106)
- 9 (fragility or fragil*).ti,ab. (1846)
- 10 (prefrail* or pre-frail*).ti,ab. (394)
- 11 4 or 5 or 6 or 7 or 8 or 9 or 10 (398361)
- 12 (withdraw* or taper*).ti,ab. (33798)
- 13 (ceased or ceasing or cessation*).ti,ab. (17588)
- 14 (deprescrib* or discontinu*).ti,ab. (41556)
- 15 ((reduc* or taper* or titrat* or stop* or unnecessary or omission) adj3 (dosage* or dose* or dosing* or drug* or medicat* or medicine* or prescri*)).ti,ab. (42190)
- 16 deprescriptions/ or drug tapering/ (44)
- 17 dose-response relationship, drug/ (30961)
- 18 (deescalat* or de-escalat*).ti,ab. (840)
- 19 12 or 13 or 14 or 15 or 16 or 17 or 18 (146556)
- 20 (((ceiling or loop) adj diuretic*) or (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*)).ti,ab. (7555)
- 21 exp angiotensin converting enzyme inhibitors/ or angiotensin receptor antagonists/ or angiotensin-converting enzyme inhibitors/ or (((angiotensin converting enzyme inhibit* or ace) adj2 inhibit*) or acei or (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril or perindopril or pivopril or quinapril or ramipril or rentiapril or saralasin or s nitrosocaptopril or spirapril or temocapril or teprotide or trandolapril or utibapril or zabicipril or zofenopril or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril)).ti,ab. (15372)
- 22 exp Angiotensin Receptor Antagonists/ or (((angiotensin adj3 receptor antagon*) or angiotensin) adj3 receptor block*) or arb or arbs or (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten)).ti,ab. (10941)
- 23 exp calcium channel blockers/ or (calcium adj2 (antagonist* or block* or inhibit*)).ti,ab. or (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nifedipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).ti,ab. (18467)
- 24 exp adrenergic beta antagonists/ or (beta adj2 (adrenergic* or antagonist* or block* or receptor*)).ti,ab. or (acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthioproprianolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).ti,ab. (24649)
- 25 exp Cardiac Glycosides/ or exp Digoxin/ (985)
- 26 (renin inhibitor or aliskiren).ti,ab. (800)
- 27 exp Mineralocorticoid Receptor Antagonists/ or exp Spironolactone/ or exp Eplerenone/ or (aldosterone antagonists or finerenone).ti,ab. (1378)
- 28 exp Vasodilator Agents/ or exp Nitroglycerin/ or exp Isosorbide Dinitrate/ or exp hydralazine/ (24773)

29 exp Adrenergic Agonists/ or exp Dobutamine/ or exp Dopamine Agents/ or exp Dopamine/ or exp Dopamine Agonists/ or (inotropes or inotrope agonist).ti,ab. (32494)
 30 exp Ivabradine/ (0)
 31 exp Sodium-Glucose Transporter 2 Inhibitors/ or (SGLT2 inhibitors or SGLT2I or dapagliflozin or empagliflozin).ti,ab. (2723)
 32 (Soluble guanylate cyclase stimulator or vericiguat).ti,ab. (124)
 33 (myotrope or omecamtiv mecarbil).ti,ab. (53)
 34 angiotensin receptor neprilysin inhibitor/ or sacubitril plus valsartan/ or ARNI.ti,ab. (197)
 35 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (104140)
 36 Randomized Controlled Trials as Topic/ or Meta-Analysis/ or Prospective Studies/ or Retrospective Studies/ or Cohort Studies/ or Cross-Sectional Studies/ or Case-Control Studies/ (124922)
 37 (randomi#ed controlled trial or meta analysis or observational stud* or cohort stud* or cross sectional stud* or case control stud*).mp. (93690)
 38 36 or 37 (209828)
 39 3 and 11 and 19 and 35 (892)
 40 3 and 11 and 19 and 35 and 38 (237)

4. Database: International Pharmaceutical Abstracts <1970 to January 2023> Search Strategy:

 1 (heart failure or cardiac failure).ti,ab. (6861)
 2 (congestive adj1 heart adj1 failure).ti,ab. (2127)
 3 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (6891)
 4 1 or 2 or 3 (6891)
 5 (Aged or Aging).ti,ab. (21403)
 6 (senior* or elderly or geriatric).ti,ab. (11906)
 7 (older adj1 (adult* or people)).ti,ab. (2015)
 8 (Frailty or frail*).ti,ab. (349)
 9 (Frail adj1 Elderly).ti,ab. (88)
 10 (fragility or fragil*).ti,ab. (555)
 11 (prefrail* or pre-frail*).ti,ab. (3)
 12 5 or 6 or 7 or 8 or 9 or 10 or 11 (32707)
 13 withdraw.ti,ab. (189)
 14 (ceased or ceasing or cessation).ti,ab. (3705)
 15 (deprescrib* or discontinu*).ti,ab. (14343)
 16 ((reduc* or taper* or titrat* or stop* or unnecessary or omission) adj3 (dosage* or dose* or dosing* or drug* or medicat* or medicine* or prescri*)).ti,ab. (11663)
 17 (deescalation or descalated or deescalating or de-escalation or de-escalated or de-escalating).ti,ab. (166)
 18 13 or 14 or 15 or 16 or 17 (28313)
 19 (((ceiling or loop) adj diuretic*) or (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*)).ti,ab. (5046)
 20 angiotensin converting enzyme inhibitors/ or angiotensin receptor antagonists/ or angiotensin-converting enzyme inhibitors/ or (((angiotensin converting enzyme inhibit* or ace) adj2 inhibit*) or acei or (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril or perindopril or pivopril or quinapril or ramipril or rentiapril or saralasin or s nitrosocaptopril or spirapril or temocapril or teprotide or trandolapril or utibapril or zabicipril or zofenopril or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril)).ti,ab. (7267)
 21 Angiotensin Receptor Antagonists/ or (((angiotensin adj3 receptor antagon*) or angiotensin) adj3 receptor block*) or arb or arbs or (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten)).ti,ab. (3293)
 22 calcium channel blockers/ or (calcium adj2 (antagonist* or block* or inhibit*)).ti,ab. or (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nifedipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or

nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).ti,ab. (9379)

23 adrenergic beta antagonists/ or (beta adj2 (adrenergic* or antagonist* or block* or receptor*)),ti,ab. or (acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocarolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropiranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).ti,ab. (11708)

24 Cardiac Glycosides/ or Digoxin/ (2606)

25 (renin inhibitor or aliskiren).ti,ab. (186)

26 angiotensin receptor neprilysin inhibitor/ or sacubitril plus valsartan/ or ARNI.ti,ab. (19)

27 Mineralocorticoid Receptor Antagonists/ or Spironolactone/ or Eplerenone/ or (aldosterone antagonists or finerenone).ti,ab. (1088)

28 Vasodilator Agents/ or Nitroglycerin/ or Isosorbide Dinitrate/ or hydralazine/ (1971)

29 Adrenergic Agonists/ or Dobutamine/ or Dopamine Agents/ or Dopamine/ or Dopamine Agonists/ or (inotropes or inotrope agonist).ti,ab. (1284)

30 Ivabradine/ (154)

31 Sodium-Glucose Transporter 2 Inhibitors/ or (SGLT2 inhibitors or SGLT2I or dapagliflozin or empagliflozin).ti,ab. (470)

32 (Soluble guanylate cyclase stimulator or vericiguat).ti,ab. (12)

33 (myotrope or omecamtiv mecarbil).ti,ab. (11)

34 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (35546)

35 4 and 12 and 18 and 34 (50)

36 4 and 12 and 18 (83)

5. Database: APA PsycInfo <1806 to October Week 1 2021> Search Strategy:

1 (heart failure or cardiac failure).ti,ab. (4192)

2 (congestive adj1 heart adj1 failure).ti,ab. (926)

3 ((heart or cardiac) adj1 (failure* or decompensation or de-compensation)).ti,ab. (4221)

4 1 or 2 or 3 (4221)

5 (Aged or Aging).ti,ab. (315247)

6 (senior* or elderly or geriatric).ti,ab. (96214)

7 (older adj1 (adult* or people)).ti,ab. (65981)

8 (Frailty or frail*).ti,ab. (5067)

9 (Frail adj1 Elderly).ti,ab. (858)

10 (fragility or fragil*).ti,ab. (8071)

11 (prefrail* or pre-frail*).ti,ab. (234)

12 5 or 6 or 7 or 8 or 9 or 10 or 11 (425964)

13 withdraw.ti,ab. (2390)

14 (ceased or ceasing or cessation).ti,ab. (23713)

15 (deprescrib* or discontinu*).ti,ab. (22080)

16 ((reduc* or taper* or titrat* or stop* or unnecessary or omission) adj3 (dosage* or dose* or dosing* or drug* or medicat* or medicine* or prescri*)).ti,ab. (12733)

17 (deescalation or descalated or deescalating or de-escalation or de-escalated or de-escalating).ti,ab. (565)

18 13 or 14 or 15 or 16 or 17 (59422)

19 (((ceiling or loop) adj diuretic*) or (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*)).ti,ab. (922)

- 20 angiotensin converting enzyme inhibitors/ or angiotensin receptor antagonists/ or angiotensin-converting enzyme inhibitors/ or (((angiotensin converting enzyme inhibit* or ace) adj2 inhibit*) or acei or (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril or perindopril or pivopril or quinapril or ramipril or rentiapril or saralasin or s nitrosocaptopril or spirapril or temocapril or teprotide or trandolapril or utibapril or zabicipril or zofenopril or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril)).ti,ab. (845)
- 21 Angiotensin Receptor Antagonists/ or (((angiotensin adj3 receptor antagon*) or angiotensin) adj3 receptor block*) or arb or arbs or (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten)).ti,ab. (664)
- 22 calcium channel blockers/ or (calcium adj2 (antagonist* or block* or inhibit*)).ti,ab. or (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).ti,ab. (3213)
- 23 adrenergic beta antagonists/ or (beta adj2 (adrenergic* or antagonist* or block* or receptor*)).ti,ab. or (acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmepipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iproclolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropiranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).ti,ab. (5824)
- 24 Cardiac Glycosides/ or Digoxin/ (76)
- 25 (renin inhibitor or aliskiren).ti,ab. (10)
- 26 angiotensin receptor neprilysin inhibitor/ or sacubitril plus valsartan/ or ARNI.ti,ab. (2)
- 27 Mineralocorticoid Receptor Antagonists/ or Spironolactone/ or Eplerenone/ or (aldosterone antagonists or finerenone).ti,ab. (8)
- 28 Vasodilator Agents/ or Nitroglycerin/ or Isosorbide Dinitrate/ or hydralazine/ (19)
- 29 Adrenergic Agonists/ or Dobutamine/ or Dopamine Agents/ or Dopamine/ or Dopamine Agonists/ or (inotropes or inotrope agonist).ti,ab. (26996)
- 30 Ivabradine.ti,ab. (18)
- 31 Sodium-Glucose Transporter 2 Inhibitors/ or (SGLT2 inhibitors or SGLT2I or dapagliflozin or empagliflozin).ti,ab. (21)
- 32 (Soluble guanylate cyclase stimulator or vericiguat).ti,ab. (3)
- 33 (myotrope or omecamtiv mecarbil).ti,ab. (1)
- 34 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (37442)
- 35 4 and 12 and 18 (20)
- 36 4 and 12 and 18 and 34 (1)
- *****

6. EBSCO Ageline Search 23.03.08

#	Query	Results
S6	S1 AND S4 AND S5	215
S5	S2 OR S3	158,853
S4	withdraw* OR deprescrib* OR discontinu* OR ceased OR ceasing OR cessation* OR reduc* OR taper* OR titrat* OR drug tapering OR deprescription OR descalat* or de-escalat*	21,406
S3	frail* OR Frailty OR Frail Elderly	6,541
S2	Aged OR elderly OR Aging OR older adult* OR older people	158,762
S1	heart failure OR cardiac failure OR congestive heart failure OR heart decompensation OR cardiac decompensation	1,311

7. EBSCO CINAHL Search 23.03.08

#	Query	Results
S18	S3 AND S8 AND S11 AND S14 AND S15	544
S17	S3 AND S8 AND S11 AND S15	846
S16	S3 AND S8 AND S11 AND S13	3,035
S15	(MH "Diuretics+") or "diuretics" or "furosemide" or "metolazone" OR (MH "Angiotensin-Converting Enzyme Inhibitors+") OR "angiotensin converting enzyme inhibitors" OR (MH "Angiotensin II Type I Receptor Blockers+") OR "Angiotensin Receptor Antagonists" OR (MH "Adrenergic Beta-Antagonists+") OR "adrenergic beta antagonists" OR "beta blockers" OR (MH "Cardiac Glycosides+") OR "Cardiac Glycosides or Digoxin" OR "Renin inhibitor or aliskiren" OR (MH "Aldosterone Antagonists+") OR "Mineralocorticoid Receptor Antagonists or Spironolactone or Eplerenone or aldosterone antagonists or finerenone" OR (MH "Isosorbide Dinitrate with Hydralazine") OR (MH "Vasodilator Agents+") OR "Vasodilator Agents or Nitroglycerin or Isosorbide Dinitrate OR hydralazine" OR (MH "Dopamine Agonists+") OR (MH "Adrenergic Agonists+") OR "Adrenergic Agonists or Dobutamine or Dopamine Agents or Dopamine or Dopamine Agonists or inotropes or inotrope agonist" OR (MH "Sodium-Glucose Co-Transporter 2 Inhibitors+") OR "Sodium-Glucose Transporter 2 Inhibitors or SGLT2 inhibitors or SGLT2I or dapagliflozin or empagliflozin"	60,398
S14	S12 OR S13	1,196,247
S13	(MH "Randomized Controlled Trials+") OR (MH "Clinical Trials+") OR (MH "Cochrane Library") OR (MH "Clinical Trial Registry") OR "observational study" OR (MH "Cross Sectional Studies") OR (MH "Quantitative Studies") OR (MH "Prospective Studies+") OR (MH "Case Control Studies+") OR (MH "Controlled Before-After Studies") OR "case control study"	1,068,629
S12	TI (Randomized controlled trial* OR randomised controlled trial* OR RCT OR observational stud* OR cohort stud* OR cross sectional stud* OR case control stud*) OR AB (Randomized controlled trial* OR randomised controlled trial* OR RCT OR observational stud* OR cohort stud* OR cross sectional stud* OR case control stud*)	448,888
S11	S9 OR S10	700,471
S10	TI (withdraw* OR deprescrib* OR discontinu* OR ceased OR ceasing OR cessation* OR reduc* OR taper* OR titrat* OR drug tapering OR deprescription OR descalat* or de-escalat*) OR AB (withdraw* OR deprescrib* OR discontinu* OR ceased OR ceasing OR cessation* OR reduc* OR taper* OR titrat* OR drug tapering OR deprescription OR descalat* or de-escalat*)	697,761
S9	(MH "Drug Tapering") OR (MH "Deprescribing") OR (MH "Substance Withdrawal, Controlled") OR (MH "Substance Withdrawal Syndrome+") OR (MH "Substance Use Treatment: Drug Withdrawal (Iowa NIC)")	7,089
S8	S4 OR S5 OR S6 OR S7	1,093,096
S7	TI (frail* OR Frailty OR Frail Elderly) OR AB (frail* OR Frailty OR Frail Elderly)	14,759
S6	(MH "Frail Elderly") OR (MH "Frailty Syndrome") OR "frail"	18,499
S5	TI (Aged OR elderly OR Aging OR older adult* OR older people) OR AB (Aged OR elderly OR Aging OR older adult* OR older people)	394,507
S4	(MH "Aged+") OR (MH "Aged, 80 and Over+")	889,082
S3	S1 OR S2	72,423
S2	TI (heart failure OR cardiac failure OR congestive heart failure OR heart decompensation OR cardiac decompensation) OR AB (heart failure OR cardiac failure OR congestive heart failure OR heart decompensation OR cardiac decompensation)	59,867
S1	(MH "Heart Failure+") OR "heart failure"	70,040

PEER REVIEW ASSESSMENT: THIS SECTION TO BE FILLED IN BY THE REVIEWER

Reviewer: [REDACTED]	Email: [REDACTED]	Date completed: 14/10/2021
1. TRANSLATION		
	A. No revisions	☒
	B. Revision(s) suggested	☐
	C. Revision(s) required	☐

2. BOOLEAN AND PROXIMITY OPERATORS			
	A. No revisions	☒	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If “B” or “C,” please provide an explanation or example:

If “B” or “C,” please provide an explanation or example:

3. SUBJECT HEADINGS			
	A. No revisions	☒	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If “B” or “C,” please provide an explanation or example:

4. TEXT WORD SEARCHING			
	A. No revisions	☒	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If “B” or “C,” please provide an explanation or example:

5. SPELLING, SYNTAX, AND LINE NUMBERS			
	A. No revisions	☒	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If “B” or “C,” please provide an explanation or example:

6. LIMITS AND FILTERS			
	A. No revisions	☒	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If “B” or “C,” please provide an explanation or example:

7. OVERALL EVALUATION (Note: If one or more "revision required" is noted above, the response below must be "revisions required".)			
	A. No revisions	☒	
	B. Revision(s) suggested	☐	
	C. Revision(s) required	☐	

If "B" or "C," please provide an explanation or example:

Table S3.3: Summary of inclusion and exclusion criteria for individual studies

Study Name	Inclusion criteria	Exclusion criteria	Industry Funding
Angiotensin-converting enzyme inhibitor (ACEI)/Angiotensin receptor antagonist (ARB)			
Pita-Fernandez 2014³²	>50 years, CHF, Hb<12 mg/dl, CrCl<60ml/min/1.63m ² , on ACEI, EudraCT database.	MI, require device/surgery, pericardial disease, acute bleeding, pulmonary embolism, treated with erythropoietin, ultrafiltration, hemodialysis and oncology.	No
Gilstrap 2017³⁴	HF based on GWTG-HF records linked with Medicare claims, 130 155 patients from 339 hospitals Jan 2005-Dec 2013.	LVEF>40% (n=79986), contraindications to ACEI/ARB (n=13268), on inotropes, transplanted, discharged to hospice, placed on comfort measures only, died during admission, left against medical advice, transferred to another short-term hospital, or enrolled in Medicare fee-for-service.	No
Matthew 2021³⁶	Hospital admission in 2016, diagnosed with HFrEF, >48h stay in hospital, eGFR>15mL/min/1.73m ² , not on maintenance hemodialysis at admission.	Patients with an estimated glomerular filtration <15 cm ³ /min/1.73 m ² and those on dialysis.	No
Nicholls 1982³³	CHF due to CAD, NYHA class III-IV, used digoxin, furosemide and vasodilators (prazosin/hydralazine).	Not reported.	No
Beta blockers			
Palau 2021³⁸	1-month stable chronic symptomatic HF (NYHA class >2); HFpEF (symptoms and signs of HF, LVEF>50%, NT-proBNP>125, >1 relevant structural heart disease LVH and/or HAE and diastolic dysfunction); adults >18 yrs; previous admission for acute HF; previous treatment with beta blockers during last 3 months; chronotropic incompetence assessed by CPET (HRmax-HRrest)/220-age-HRrest <0.62 (Authors confirmed only one participant was aged <50 years (47 years) in Arm A)	Unable to perform baseline exercise test; significant primary pulmonary disease (e.g. pulmonary arterial hypertension, chronic thromboembolic pulmonary disease or chronic obstructive pulmonary disease); prior history or LVEF<50%; history of an acute coronary syndrome < 12 months; effort angina or signs of ischemia during CPET; significant primary moderate to severe valvular disease; any other comorbidity with a life expectancy lower < 1 year; chronic treatment with digoxin or calcium channel blockers; HR at rest >75 bpm; uncontrolled blood pressure, defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure>90mmHg.	No
Brouse 2006³⁹	All patients receiving chronic beta blocker therapy admitted to the VANTHCS with primary diagnosis of HF exacerbation (ICD-9 diagnosis code 428) between Jan2000-Dec2002.	Did not have an active β -blocker prescription through the VANTHCS outpatient pharmacy prior to admission or were hospitalised for a reason other than HF exacerbation.	No
Fonarow 2008²⁵ (OPTIMIZE-HF)	HFrEF (LVEF<40%) or moderate-severe systolic dysfunction by qualitative assessment, beta blocker before admission, hospitalised for episodes of new or worsening HF as the primary cause of admission; or if significant HF symptoms developed during hospitalisation for another primary diagnosis, with HF being the primary discharge diagnosis.	Documented contraindications or intolerance to beta blockers including allergy, second- or third-degree heart block without a pacemaker, symptomatic bradycardia, symptomatic hypotension, cardiogenic shock, or reactive airway disease.	Yes
Study Name	Inclusion criteria	Exclusion criteria	Industry Funding
Gilstrap 2023⁴⁴	Patients aged ≥ 65 years, ≥ 1 hospitalisation for HFrEF between	Patients who died during admission, underwent or had prior cardiac transplant, or placement of a durable mechanical circulatory support	No

2008-2018. HFrEF was defined using ICD 9 and 10 codes.

(MCS) device during their index admission and those admitted from or discharged to hospice or with home intravenous inotropes. Patients who remained in post-acute care ≥ 30 days after discharge.

Metra 2007⁴⁰ (COMET)	Symptomatic chronic HF (NYHA class II–IV), LVEF $\leq 35\%$, at least one cardiovascular hospitalisation during the 2 years before trial entry, optimal baseline therapy, including the need for diuretic therapy	Recent change of treatment <2 weeks before randomisation, require IV inotropic therapy, current CCB treatment, amiodarone (>200mg/d), class-I antiarrhythmic drug, or investigational drugs in 30 days; unstable angina MI, coronary revascularisation or stroke <2mos; uncontrolled HTN (SBP>170, DBP>105), hemodynamically significant valve disease, symptomatic and sustained ventricular arrhythmias in <2 months not adequately treated with antiarrhythmic/implantation of defibrillator, pregnancy, women with childbearing potential, drug/alcohol abuse, poor compliance, serious systematic disease that may reduce life expectancy, contraindication to beta blocker (e.g. HR<60bpm, sick sinus syndrome, bivascular block, 2nd/3rd degree atrioventricular block unless pacemaker, sitting SBP<85, history of asthma or COPD, PVD, symptoms at rest, or unstable insulin dependent diabetes mellitus.	Yes
Miro 2016⁴¹ (BETAWIN-AHF)	EAHF registry (168 variables): All consecutive patients admitted for ADHF during periods were included. CHF diagnosis by doctor and supported by medical reports before current index of AHF, based on symptoms of dyspnea, orthopnea, nocturnal paroxysmal dyspnea, and cardiac indicators. All patients were on treatment with chronic BB at home prior to ED admission	MI with ST elevation.	No
Nambiar 2020⁴³	EF>50%, NT-proBNP >300 pg/dL, physician clinical judgement deemed discontinuation of beta blocker safe.	Not reported.	No
Orso 2009⁴²	Treated with beta blocker.	Absolute contraindications or intolerance.	Yes
Mineralocorticoid receptor antagonist (MRA)			
Ferreira 2020³¹ (TOPCAT)	Sub-analysis >75years. ≥ 50 years, LVEF $\geq 45\%$, >1 symptom of HF, hospitalised within 12 mos, proBNP>100/NT-proBNP ≥ 360 .	Severe illness of survival<3yrs, severe renal dysfunction GFR<30ml/min, Scr>2.5mg/dL.	No
Study Name	Inclusion criteria	Exclusion criteria	Industry Funding
Jonsson-Holmdahl 2022⁵⁵	All patients treated with MRA for HF.	Patients with EF>40% died before Jan 1, 2016.	No
Trevisan 2021⁵⁴ (SCREAM)	Developed hyperkalemia after initiation of MRA treatment between Jan2007-Dec2018; new users of MRA (i.e. without any MRA dispensed in the < 12 months); developed a first-detected hyperkalemia after initiation of MRA.	Records of death at the same date as first hyperkalemia; undergoing long-term dialysis or recent kidney transplant; missing data for eGFR at the date of index hyperkalemia and up to 1 year prior; <18 years.	Yes
Sodium-glucose cotransporter-2 inhibitor (SGLT2-i)			

Nakagaito 2021⁵⁶	HbA1c $\geq 6.1\%$ on GDMT (ACEI/ARB, BB, MRA, diuretic). Hospitalised for HF Feb 2016-Mar 2019. Required to be hemodynamically stable (SBP >90 mmHg), no dehydration, no use if IV vasodilators/inotropes <24 hrs prior).	Exclude T1DM, previous use of SGLT2I, ESRF (eGFR <20 ml/min/1.73m ²), mechanical circulatory support, pregnancy, breastfeeding, history of hypersensitivity to SGLT2-I, severe ketosis, diabetic coma/ precoma, or otherwise considered unsuitable.	No
Diuretics			
VanKraaij 2000³⁰	NYHA class I-III, furosemide 20-80mg/d, CHF, >2 prior symptoms (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema), >1 prior sign (jugular distention, rales, pulmonary vascular congestion on x-ray).	SBP >170 /DBP >90 , absence of regular ECG, Symptoms of angina for NYHA $>II$, over congestion.	No
Walma 1997²⁸	≥ 65 years, diuretic ≥ 6 months, no acute HF/HTN.	Acute HF, IV diuretic, <3 months with HF symptoms, HF score >4 , high dose furosemide >80 mg/d, mean BP $>180/100$ mmHG, hypercalciuria, nephrotic syndrome, glaucoma, use of combo therapy of BB, diuretic, vasodilators, HTN, no placebo available for diuretic, non-compliance in run in phase.	No
DeVore 2015²⁹ (ASCEND-HF)	Enrolled < 24 hrs of hospitalisation of HF or < 48 h of diagnosis of acute HF after hospitalisation for another cause. ≥ 1 objective findings of HF (e.g., elevated NTBNP/BNP, evidence of congestion or oedema on chest radiograph).	ESRD requiring chronic or intermittent renal replacement therapy. On any thiazide diuretic at admission or discharge. High risk of hypotension (SBP <100 mmHg or 110 mmHg + IV nitroglycerin), CI for vasodilators, dobutamine (dose >5 ug/kg/min, milrinone/levosimendan < 30 days, persistent uncontrolled HTN, ACS, normal BNP/NT-proBNP, severe pulmonary disease, ESRD during renal replacement therapy, clinically significant anemia. Death before discharge or missing data on diuretic doses at discharge.	Yes
Braunschweig 2002⁴⁵	CHF with implantable hemodynamic monitor Aug 1998-1999 in Chronical trial. Clinically stable and on stable chronic medications.	Refractory HF.	No
Martens 2017⁴⁶	Consecutive HFReEF patients who had CRT implant in single tertiary care center Oct 2008-Aug 2015. Note they may have improved LVEF and HFReEF.	No documented CRT.	No
Study Name	Inclusion criteria	Exclusion criteria	Industry Funding
Straand 1993⁴⁷	≥ 75 yrs, lived at home, seen at GP practice >2 visits, last visit <2 years, on long-term diuretic treatment, no signs of HTN target organ damage, BP $<220/110$ mmHg, no HF, HF NYHA class I-II, BP $<170/100$ mmHg. Re-establishment criteria: follow up >2 symptoms (anginal pain, dyspnea on exertion, orthopnea, discomfort caused by peripheral oedemas), BP $>23/120$ mmHg, HTN target organ damage $180/100$ mmHg $<$ BP $230/120$ mmHg, HF increased NYHA class during follow up.	Increased diuretic dose <6 months, homebound (reasons unrelated to study), SBP >220 mgHg or DBP >110 mmHg, HF NYHA III-IV.	No

vanKraaij 1997⁴⁸	≥75years, first contacts of patients admitted to the inpatient clinic and patients visiting the outpatient clinic from 1990-1993.	Non diuretic use.	No
vanKraaij 1998⁴⁹	>75 years, admitted 240-bed nursing home from 1990-1994, using diuretic indicated for HF, HTN, ankle oedema (with or without HF).	Non diuretic use.	No
Digitalis glycoside (digoxin)			
Packer 1993²⁶ (RADIANCE)	Reduced exercise capacity (i.e., Naughton protocol 2-14min) despite treatment with digoxin, diuretics, and ACEI ≥3 months. Normal sinus rhythm, <18 years old, had conditions of SBP≥160mm Hg or <90mm Hg or DBP >95mm Hg, exercise limited by angina, lung disease, claudication, angina requiring continuous treatment, MI <3months or stroke <12 months, severe primary pulmonary/renal/hepatic disease.	History of SV or sustained V arrhythmias, uncorrected primary valvular disease, active myocarditis, obstructive/hypertrophic/restrictive cardiomyopathy.	Yes
Taggart 1983⁵⁰	Stable HF<3months, plasma digoxin concentration 0.8-2.5 ng/mL (1.03-3.21 nmol/L) with no dose adjustment, no digoxin toxicity, sinus rhythm persistent, no signs of tachyarrhythmia.	Not reported.	No
Dall 1970⁵¹	On maintenance dose of digoxin, stopped due to toxic effect or symptomless.	Not reported.	No
Forman 1991⁵²	≥65 years in urban nursing home. Normal LVEF and normal sinus rhythm. No clinical signs or symptoms of CHF to determine why digoxin therapy was started.	Abnormal LVEF and AF.	Yes
Malik 2019²⁷ (OPTIMIZE-HF)	HFrEF (EF<45%), on digoxin at discharge, propensity matched 50 characteristics (97%).	Not receiving digoxin before admission, and discontinued before discharge, AKI (>0.3mg/dl rise in serum creatinine).	Yes
Study Name	Inclusion criteria	Exclusion criteria	Industry Funding
Sommers 1981⁵³	HFrEF>3 months, in sinus rhythm with no record of previous AF and taking digoxin for >4 months (mean 2.5 years).	Not reported.	No
Combination treatments			
Allen 2018³⁵ (PINNACLE)	Sub-analysis >65 years: aged ≥18 yrs, enrolled in PINNACLE registry with diagnosis code for HF (May2008 - Dec2014), ≥1 pair of ambulatory visits < 1 year apart. Diagnosis of HF was defined using PINNACLE Registry criteria of unusual dyspnea on light exertion, recurrent dyspnea occurring in the supine position, fluid retention, and low cardiac output secondary to cardiac dysfunction; via the description of rales, jugular venous distension, or pulmonary oedema constituted HF; or	Not reported.	No

as a previous hospital admission with primary diagnosis of HF.

Garred 2022¹⁰	First HF presentation (HFrEF) at admission, had both an ACEI/ARB and a BB initiated <120 days from HF presentation, received diagnosis in both hospital admission or specialised HF outpatient clinic, survived for ≥ 120 days after HF presentation.	Emigrated or died <120 days. Censored individuals who received first HF diagnosis during the last 120 days of the study period (i.e., last entry date was Sept 2, 2018). ARNI (sacubitril/valsartan) was not included because very few patients received this treatment at index and after 1 year (<2%).	Yes
Sammour 2022³⁷	Patients with HFrEF ICD-10 diagnosis codes (I50.2, I50.20-23, I50.4, I50.40-43, I42.0, and I25.5) were included regardless of the most recent ejection fraction.	Not reported.	Yes

Abbreviations: HF = heart failure; CHF = Congestive Heart Failure; HFrEF = heart failure with reduced ejection fraction (LVEF<40%), HFpEF = heart failure with preserved ejection fraction (LVEF>50%), HFmrEF = heart failure with mildly-reduced ejection fraction (LVEF 41%-49%); HFimpEF = heart failure with improved ejection fraction (improved to LVEF>40%); ADHF = acute decompensated heart failure; Stable = refers to stable chronic heart failure. HTN = hypertension; AF = Atrial Fibrillation; AKI = acute kidney injury; Hb = hemoglobin; CrCl = creatinine clearance; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor antagonist; ARNI = Angiotensin receptor neprilylin inhibitors; BB = beta blocker; CCB = calcium channel blocker; MI myocardial infarction; LVEF left ventricular ejection fraction; eGFR estimated glomerular filtration rate; CAD coronary artery disease; NYHA = New York Heart Association; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; ECG = electrocardiogram; IV = intravenous; ESRD = end stage renal disease; ESRF = end stage renal failure; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; CRT = cardiac resynchronisation therapy; PVD = peripheral vascular disease; COPD = chronic obstructive pulmonary disease; LVH = left ventricular hypertrophy; HAE = hereditary angioedema; CPET cardiopulmonary exercise testing; ED = emergency department; ICD-10 = international classification of disease, tenth revision.

Table S3.4: Outcomes and characteristics reported in studies of people aged ≥ 75 years

Therapeutic class	Participants (n)	Female (%)	HF classification	HF presentation	Discontinuation (%)	Mortality or hospitalisation (HR, 95%CI)	Other outcomes
Diuretics	33	76	HFpEF ⁴⁷	stable chronic	45	NA	WHF 78%
	260	72	Unspecified ⁴⁸		50	NR for subgroup	NR for subgroup
	77	80	Unspecified ⁴⁹		52	NA	WHF 52%
ACEI/ARB	6,287	34	HFrEF ¹⁰		16%	Mortality 1.65 (1.48-1.83) p<0.001	Adherence 74%
Beta blocker	6,287				12%	1.2 (1.06-1.36, p=0.0004)	69%

Abbreviations: NR = Not Reported; ACEI/ARB = Angiotensin-converting enzyme inhibitor/Angiotensin receptor antagonist; HF = heart failure; HFrEF = heart failure with reduced ejection fraction (LVEF<40%), HFpEF = heart failure with preserved ejection fraction (LVEF>50%), HR = hazards ratio; 95%CI = 95% confidence interval; WHF = worsening heart failure

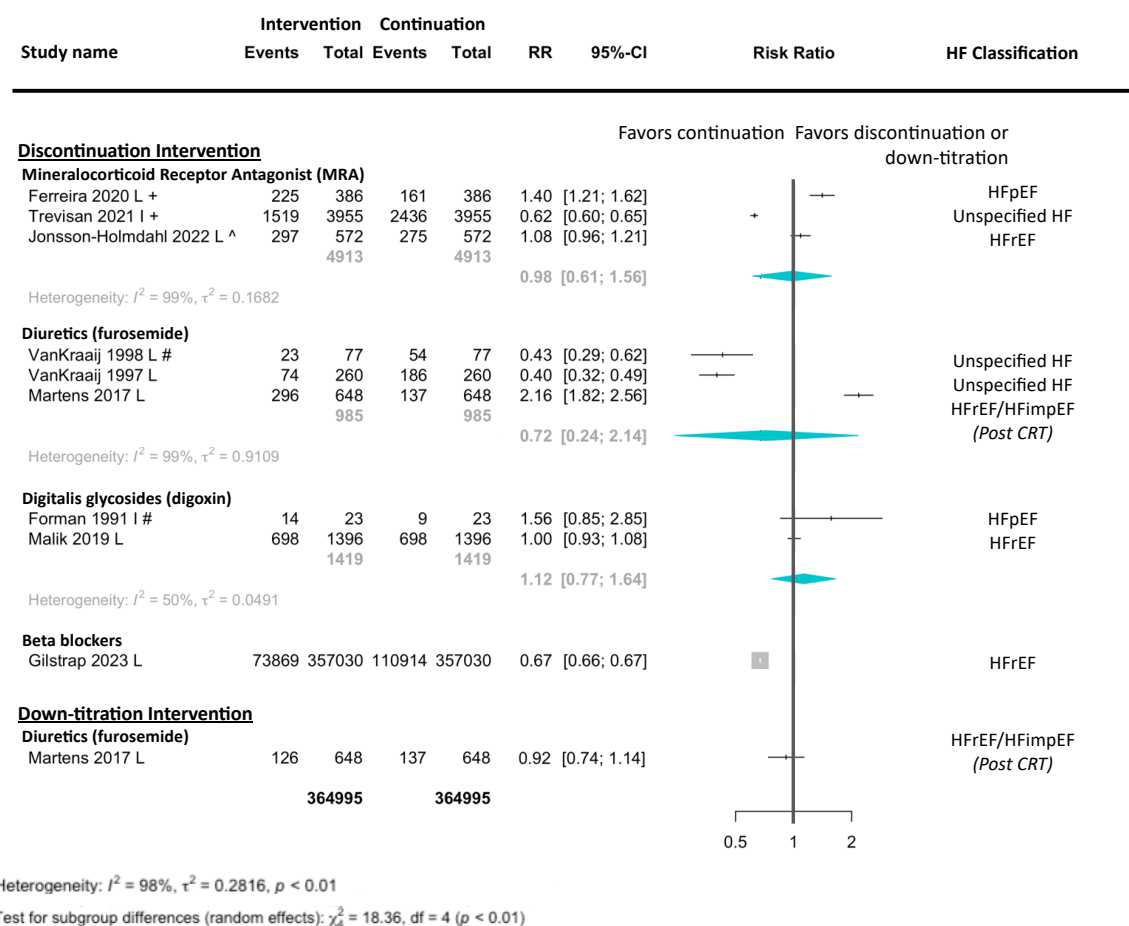
Table S3.5: Summary of studies with one exposure group

Drug class	Study	HF classification	Follow up (weeks)	No. of participants	Proportion successful cessation (%)	Proportion restarted (%)	Mortality	Hospitalisation
ACEI/ARB	Nichols 1982 ³³	Unspecified	4	5	20	80	0	-
Beta-blocker	Nambiar 2020 ⁴³	HFpEF	52	22	50	50	0	0
Diuretic	Straand 1993 ⁴⁷	HFpEF	26	33	55	45	0	-
	Braunschweig 2002 ⁴⁵	HFrEF	3	4	25	75	0	0
Digoxin	Dall 1970 ⁵¹	Unspecified	12	12	67	33	0	0
	Sommers 1981 ⁵³	HFrEF	5	20	90	10	0	0
Total	-	-	-	96	-	-	0	-

Abbreviations: NR = Not Reported; ACEI/ARB Angiotensin-converting enzyme inhibitor/Angiotensin receptor antagonist; HFrEF heart failure with reduced ejection fraction (LVEF<40%), HFpEF heart failure with preserved ejection fraction (LVEF>50%), HR hazards ratio; 95%CI 95% confidence interval; WHF worsening heart failure

Figure S3.2: Feasibility, the proportion of participants in whom HF-pharmacotherapy was down-titrated or discontinued compared to continued at optimised dose during stable chronic HF presentation in observational studies; and the proportion of participants who sustained discontinued HF-pharmacotherapy at follow-up compared to re-initiation at optimised dose.

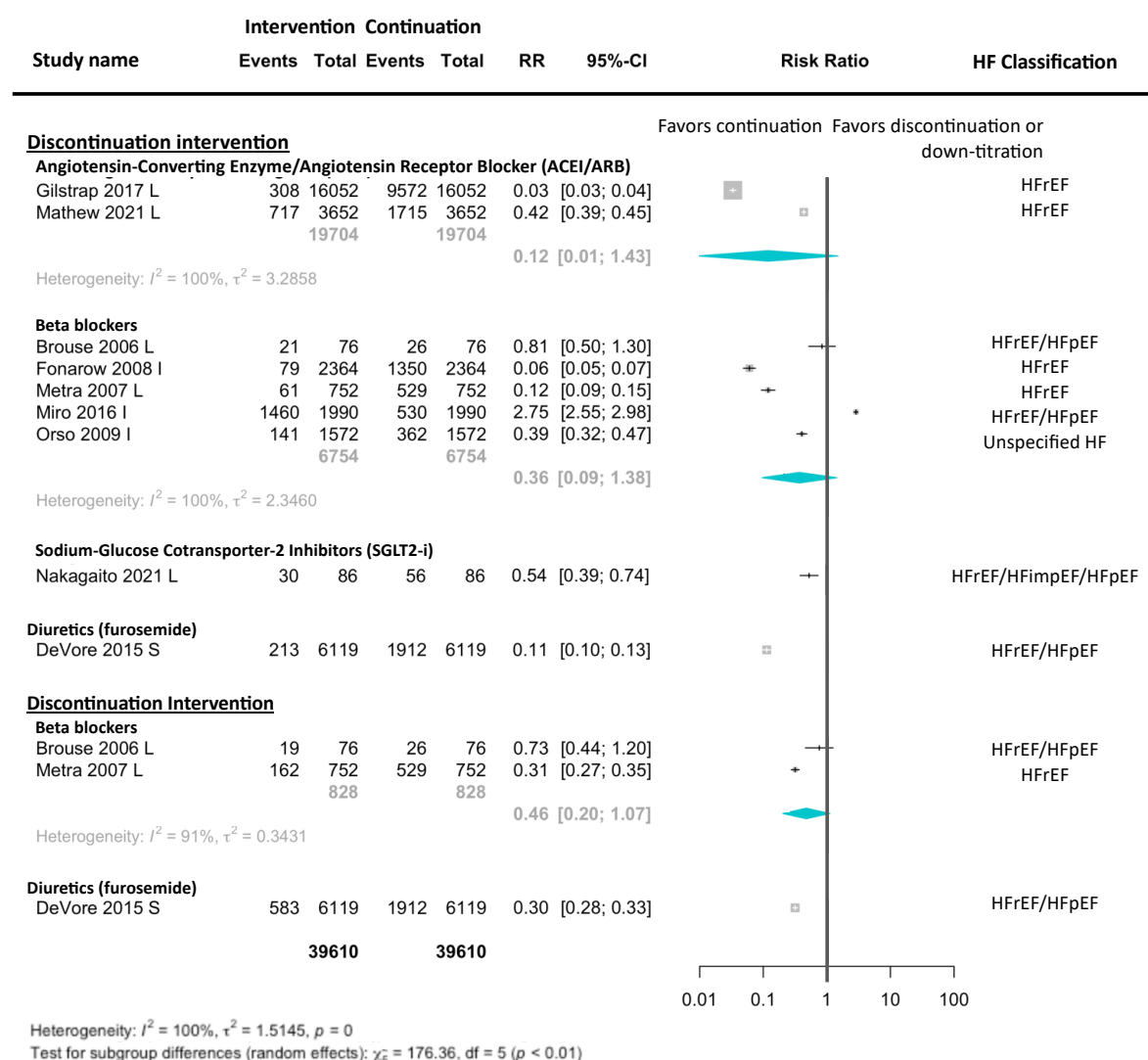
(i) Intervention in patients with stable chronic HF presentation (in hospital or community settings)



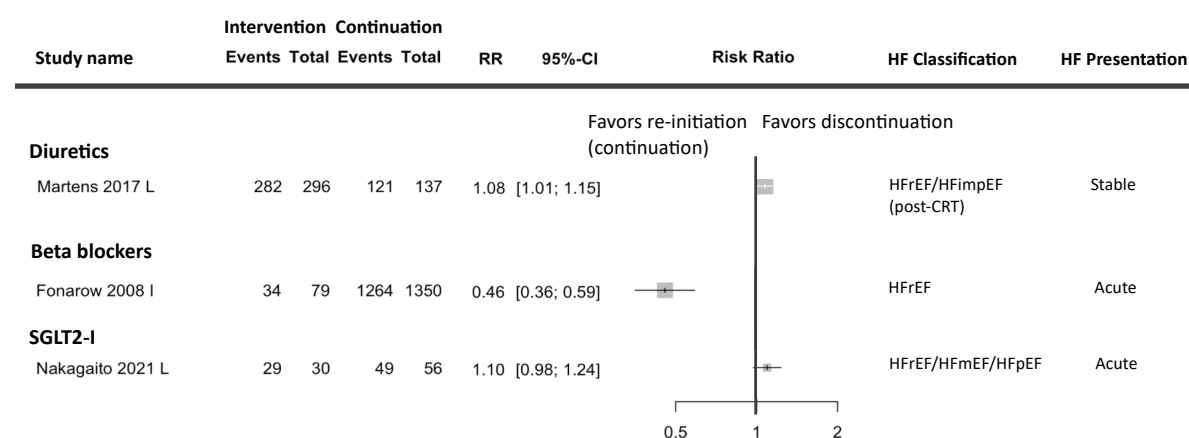
Footnote: Feasibility refers to whether the change in dose was sustained.

Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (> 24 weeks); ^unspecified setting; + discontinued in hospital or outpatient settings; # discontinued in aged care settings; HF heart failure; HFrEF =heart failure with reduced ejection fraction; HFpEF =heart failure with preserved ejection fraction; HFimpEF =heart failure with improved ejection fraction; post-CRT= after cardiac resynchronisation therapy; RR =risk ratio; 95%CI =95% confidence interval.

(ii) Intervention in patients with acute decompensation HF (ADHF) (in hospital)

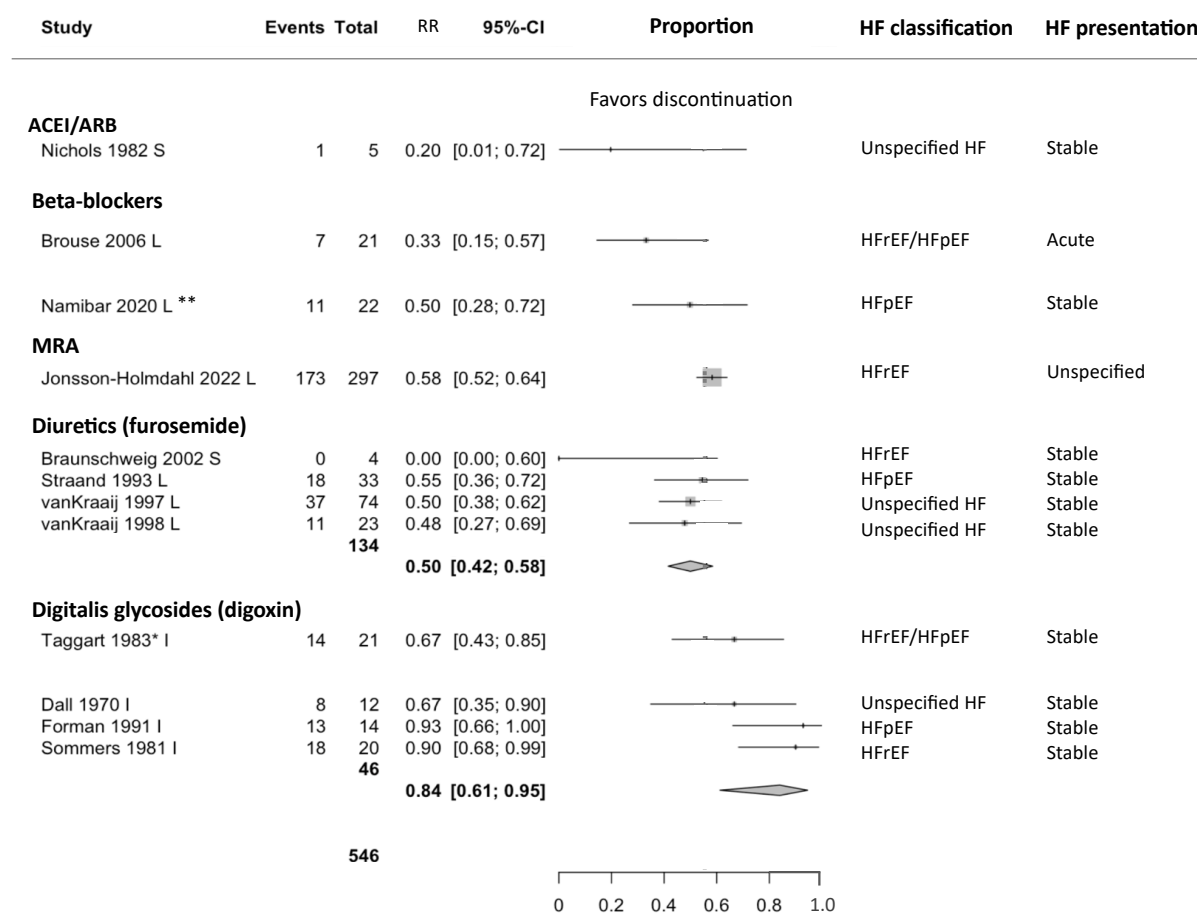


(iii) Proportion who sustained discontinuation intervention at follow-up



Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (> 24 weeks); Stable refers to stable chronic heart failure. HF = heart failure; HFrEF heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFmEF = heart failure with mildly-reduced ejection fraction; HFimpEF = heart failure with improved ejection fraction; post-CRT = after cardiac resynchronisation therapy; RR = risk ratio; 95%CI = 95% confidence interval; Feasibility refers to whether the change in dose was sustained.

Figure S3.3: Feasibility in observational studies with one exposure (discontinuation), proportion of participants that did not re-initiate or switch to an alternative HF-pharmacotherapy

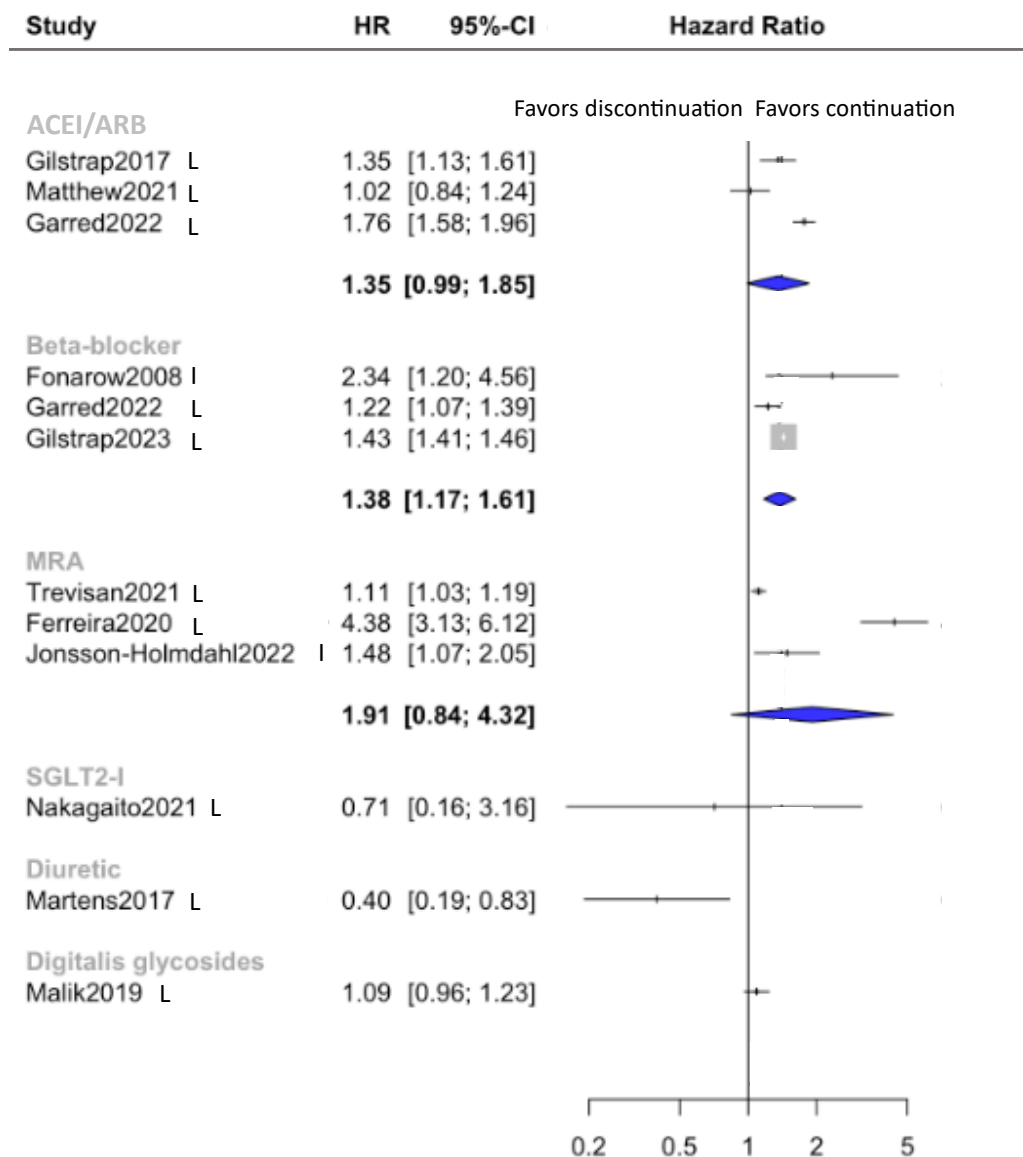


Heterogeneity: digoxin $I^2 = 45\%$, diuretics $I^2 = 0\%$

Footnote: meta-analysis included observational studies with exception of Taggart 1993 ; *crossover RCT); ** discontinued intervention was not re-initiated but switched to an alternative HF-pharmacotherapy; Stable refers to stable chronic heart failure.
Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (>24 weeks).
HF heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction

Figure S3.4: Meta-analysis of mortality in observational studies

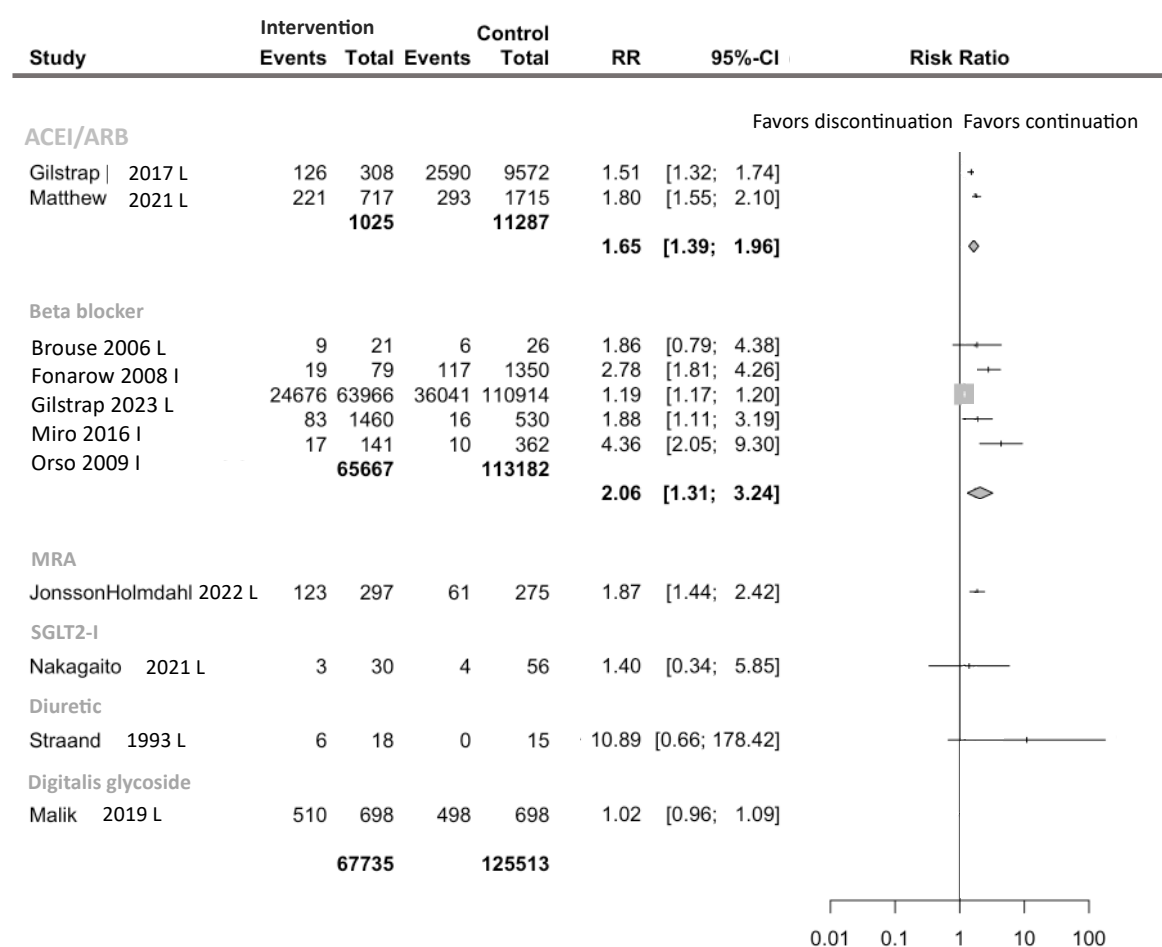
Figure S3.4a: Meta-analysis of mortality risk (hazard ratio (HR)) in observational studies



Overall heterogeneity $I^2=93\%$, $\tau = 0.47$, $p < 0.001$; ACEI/ARB $I^2= 92\%$; Beta blocker $I^2=75\%$; MRA $I^2=98\%$.

Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (>24 weeks); ACEI/ARB = Angiotensin-converting enzyme inhibitor/Angiotensin receptor antagonist; SGLT2-I = sodium-glucose co-transporter-2 inhibitor.

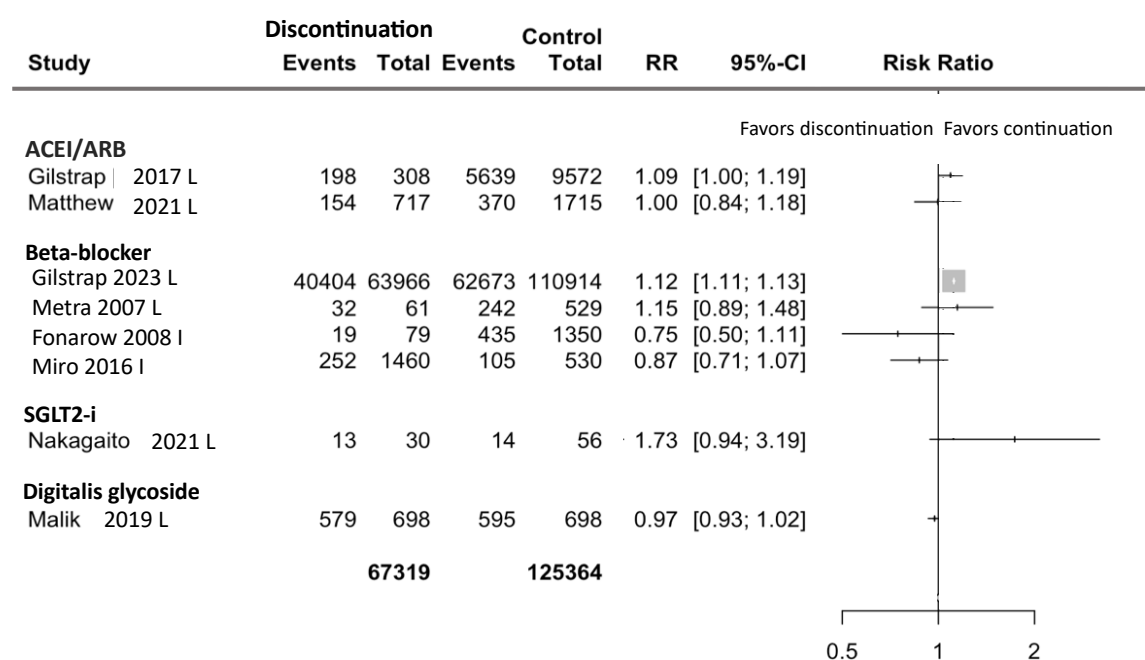
Figure S3.4b: Meta-analysis of mortality risk (events) in observational studies



Overall heterogeneity $I^2=91\%$, $\tau^2=0.113$, $p < 0.01$; ACEI/ARB $I^2=65\%$; beta blocker $I^2=69\%$.

Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (>24 weeks); ACEI/ARB = Angiotensin-converting enzyme inhibitor/Angiotensin receptor antagonist.

Figure S3.5: Meta-analysis of hospital events in observational studies



Overall heterogeneity $I^2=85\%$, $p < 0.01$; ACEI/ARB $I^2= 0\%$; beta blocker $I^2=69\%$.

Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (>24 weeks); ACEI/ARB = Angiotensin-converting enzyme inhibitor/Angiotensin receptor antagonist; SGLT2-i = sodium-glucose co-transporter-2 inhibitor.

Figure S3.6: All-cause mortality and hospitalisation over time in observational studies

Figure S3.6a. All-cause mortality reported over time in observational studies

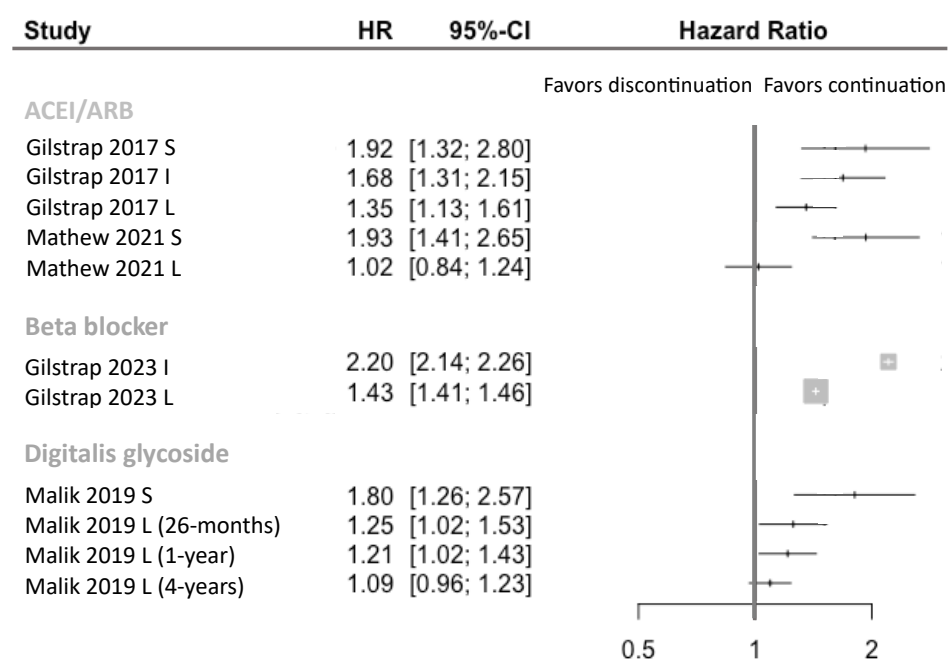
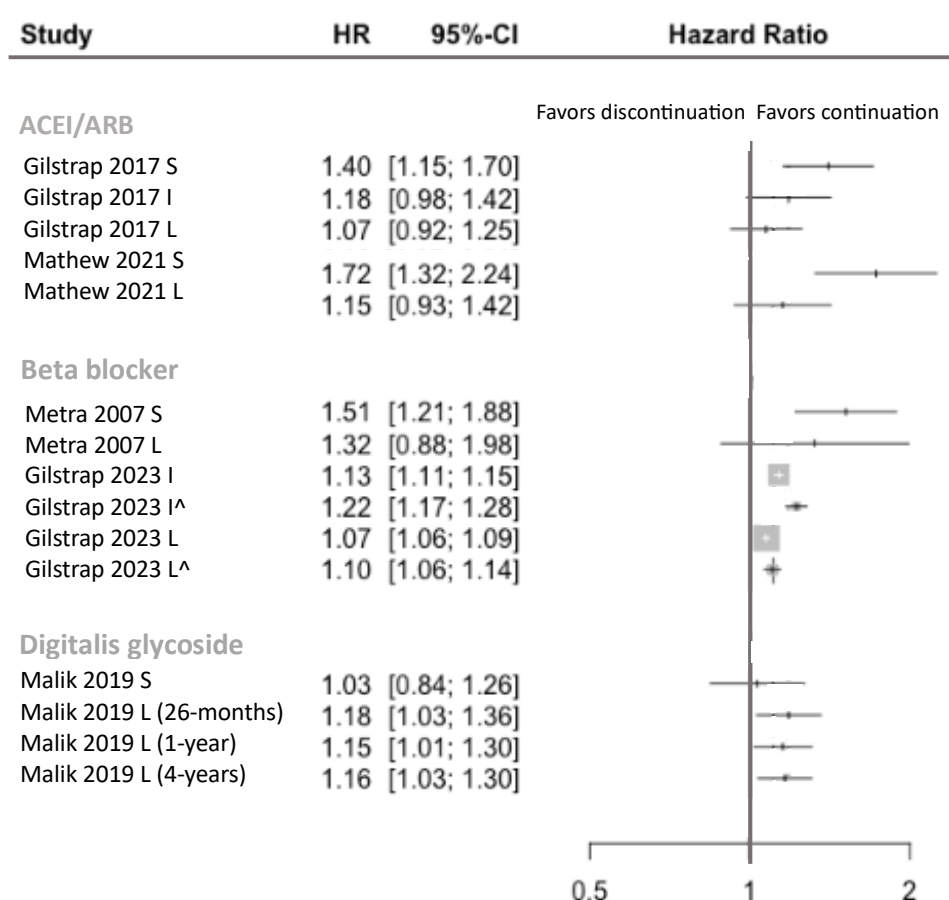


Figure S3.6b. All cause hospitalisation reported over time in observational studies



Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (> 24 weeks); ^ reported for patients with both heart failure with reduced ejection fraction (LVEF $<40\%$) (HFrEF) and Alzheimer's disease or a related dementia (ADRD); ACEI/ARB = Angiotensin-converting enzyme inhibitor/Angiotensin receptor antagonist.

Figure S3.7: Risk of Bias

Figure S3.7a. Risk of bias assessment for RCTs (RoB2)

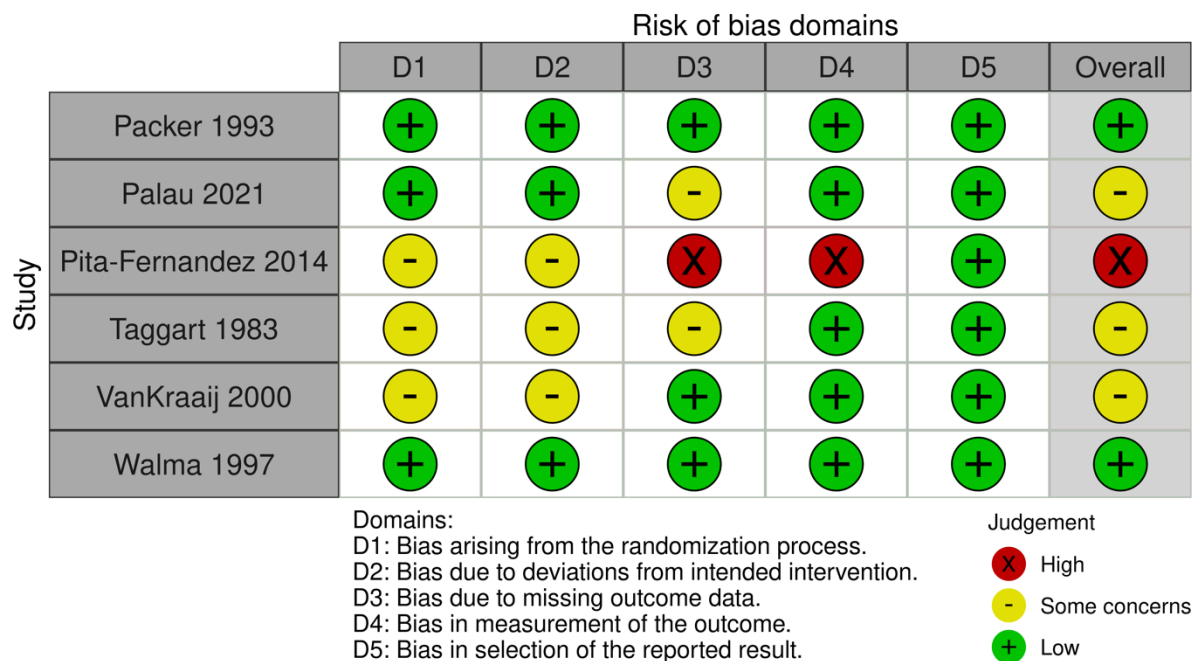
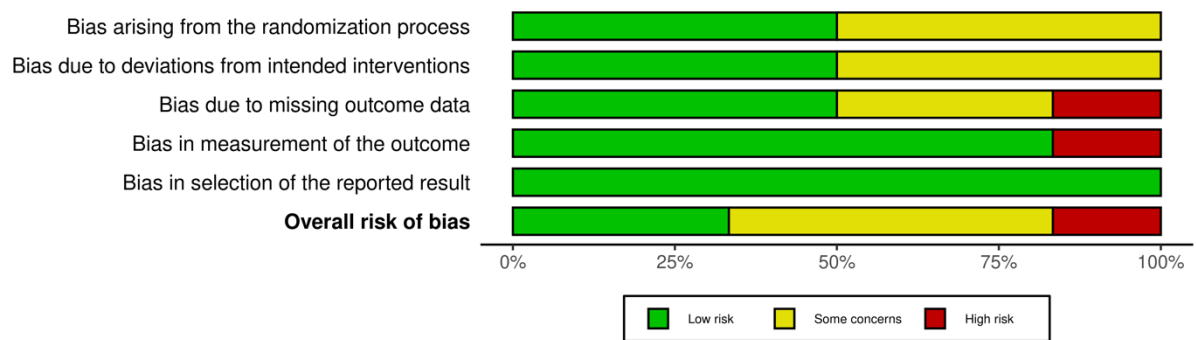
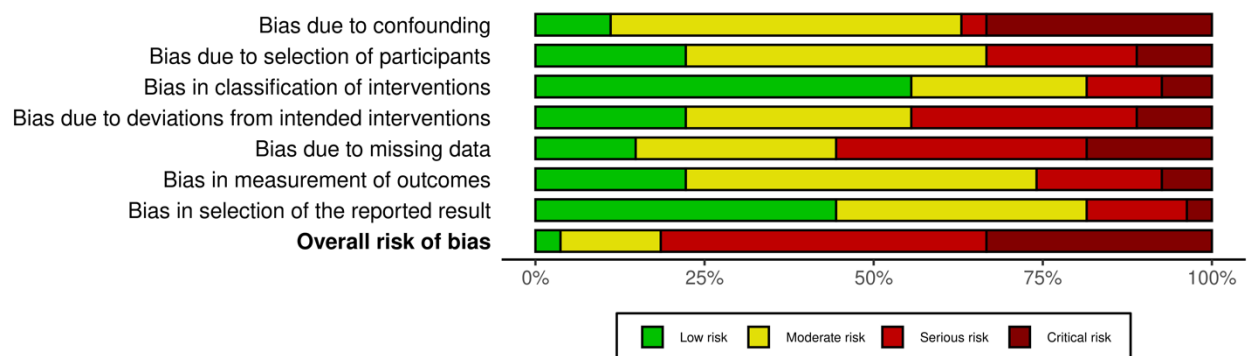


Figure S3.7b: Risk of bias assessment for non-randomised (observational) studies (ROBINS-I)



	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Allen 2018	-	X	+	-	-	-	-	X
Braunschweig 2002	!	X	-	X	+	-	+	!
Brouse 2006	!	X	+	X	-	-	+	!
Dall 1970	!	!	!	!	!	X	X	!
DeVore 2015	-	+	+	+	+	-	+	-
Ferreira 2020	+	+	+	+	+	+	+	+
Fonarow 2008	+	+	+	+	-	-	-	-
Forman 1991	!	X	+	-	X	-	-	!
Gared 2022	-	-	X	-	-	-	+	X
Gilstrap 2017	-	+	+	-	X	+	-	X
Gilstrap 2023	-	-	X	X	X	-	-	X
Jonsson-Holmdahl 2022	-	-	+	-	X	+	+	X
Malik 2019	+	-	+	-	-	+	+	-
Martens 2017	-	-	+	+	X	-	+	X
Matthew 2021	-	+	-	-	-	+	+	-
Metra	-	-	+	-	-	+	X	X
Miro 2016	-	-	-	+	X	-	+	X
Nakagaito 2021	-	-	+	X	X	X	+	X
Nambiar 2020	!	!	!	X	X	!	X	!
Nicholls 1982	!	!	X	!	!	-	-	!
Orso 2009	-	-	-	X	X	-	-	X
Sammour 2022	-	+	-	-	!	-	+	!
Sommers 1981	!	-	+	X	+	X	-	X
Straand 1993	!	-	-	X	!	!	!	!
Trevisan 2021	-	X	+	+	!	-	X	X
vanKraaij 1997	X	-	-	X	X	X	-	X
vanKraaij 1998	!	X	+	!	-	X	-	!

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
! Critical
X Serious
- Moderate
+ Low

Figure S3.7c: Sensitivity Analysis of low to moderate risk of bias studies.

Studies with high or critical risk of bias were excluded.

Drug	Study Name	Timepoint	Risk of Bias	Significant Outcomes
Randomised controlled trials				
Beta blocker	Palau 2021 ³⁸	short	low	(referred to in-text)
Diuretic	Walma 1997 ²⁸	long	low	
	VanKraaij 2000 ³⁰	long	some concerns	
Digoxin	Packer 1993 ²⁶	moderate	low	
	Taggart 1983 ⁵⁰	short	some concerns	
Observational studies				
ACEI/ARB	Mathew 2021 ³⁶	long	Moderate	No significant difference in mortality (HR 1.02, 95%CI 0.84-1.24) and hospitalisation (HR 1.15, 95%CI 0.93-1.42)
Beta Blocker	Fonarow 2008 ²⁵	long	Moderate	3-fold increase (RR 2.78 1.81-4.28) in mortality, but no difference (RR 0.75, 95%CI 0.50-1.11) in hospitalisation compared to continued use
Diuretic	DeVore 2015 ²⁹	short	Moderate	2.4-fold risk (OR 2.38, 95%CI 1.81-3.13) of 30-day mortality and readmission in those with ADHF after discontinuing a diuretic
Digoxin	Malik 2019 ²⁷	long	Moderate	HFrEF inpatients had no difference in risk of mortality (RR 1.02, 95%CI 0.96-1.09, p=0.5) or re-admission (RR 0.97, 95%CI 0.93-1.02) compared to continued digoxin use.
MRA	Ferreira 2020 ³¹	long	Moderate	58% of HFpEF patients discontinued spironolactone

All studies evaluated outcomes for the discontinuation of a HF-pharmacotherapy.

Abbreviations: S=Short-term follow-up (≤ 30 days); I = Intermediate-term follow-up (5-24 weeks); L = Long-term follow-up (>24 weeks); ACEI/ARB = Angiotensin-converting enzyme inhibitor/Angiotensin receptor antagonist.

eTables 3.6: GRADE criteria and scoring

Table S3.6a: Definition of grades of evidence (Atkins 2004²⁴)

Score	Rationale for scoring overall quality of evidence
High	further research is very unlikely to change the confidence in the estimate of effect.
Moderate	further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
Low	further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	any estimate of effect is very uncertain.

Table S3.6b: Assessment Criteria adapted from GRADE

Each of the domains were assessed from “high” quality evidence and given downgrade or upgrade points accordingly.

Domain	Description	No downgrade given (0) if:	Downgrade given by one level (-1) if:	Downgrade given by one level (-2) if:
Factors that can downgrade the quality of evidence include:				
1 Study design	Randomised controlled trials (0) and observational studies (-1) were included in this review.	Studies were RCTs.	Studies were observational in design.	Studies were case reports or qualitative interviews
2 Risk of bias/ study limitation	Study limitations were determined with the Cochrane risk of bias assessment tool ROB-2 for RCTs and ROBINS-I for observational studies.	Studies had “low” overall risk of bias score.	Studies had “unclear”, “moderate” or “high” overall risk of bias score suggesting serious limitations.	Studies had “critical” overall risk of bias score suggesting very serious limitations.
3 Inconsistency	Inconsistency was based on presence of statistical heterogeneity (I^2).	Inconsistency was not present, negligible or moderate ($I^2 \leq 60\%$) and $p > 0.05$.	Outcomes showed substantial heterogeneity (I^2 50-90%) or if investigators reported from narrative analysis) suggesting serious inconsistency.	Outcomes showed considerable heterogeneity (I^2 75-100%) or if investigators reported from narrative analysis) suggesting serious inconsistency.
4 Indirectness	Indirectness was evaluated using the PICO format to determine how well the evidence included in the review answered the research question, including: Population: older age, frailty Intervention: HF specific medication/drug class Comparator: non-frail older adults	Indirectness was not observed	Indirectness was present in either population, intervention comparator or outcomes suggesting serious doubts about directness.	Indirectness was present in either population, intervention comparator or outcomes suggesting very serious doubts about directness.

Outcome: serious adverse event (SAE) or adverse drug withdrawal effect (ADWE).

5	Imprecision	Imprecision was evaluated on optimal information size (OIS) implication and variation in the effect observed from confidence intervals.	There were narrow confidence intervals around the point estimate, if null effect and appreciable harm or benefit were both not included or if confidence interval excludes point estimate. If sample size is >400 and RRR>25%, and significant number of events were reported. OIS is met	1. Small total sample size - n <300 or if does not meet OIS threshold. 2. Number of events expressed (meaningful) 3. Wide CIs & uncertainty about magnitude of effect - No point estimate given, if there were wide confidence intervals around the point estimate, or if confidence intervals do not include the null effect but do include appreciable harm or benefit.	1. Sample size is <100 and RRR≤30% at any control event rate. 2. no events reported 3. very wide CIS and uncertainty
6	*Publication bias	Publication bias was a systematic under or over estimate of the underlying effect due to the selective publication of studies or availability of their data. We did not perform a meta-analysis so did not assess publication bias because funnel plots were not generated in a narrative synthesis.	All outcomes were downgraded because publication bias is strongly suspected in a small (number of studies despite absence of a funnel plot.		

Factors that can upgrade the quality of evidence by one level:

- if dose-response gradient or relationship was observed in frail compared to non-frail participants,
- if demonstrated large or very large effects,
- if all plausible residual confounders would reduce a demonstrated effect or suggest a spurious effect if no effect was observed.

*NA – not applicable when no meta-analysis and subgroup analysis of outcomes included 5- 10 studies.

Table S3.6c: Summary of GRADE Assessment

Discontinuation or *down-titration Angiotensin-converting enzyme inhibitor (ACEI)/Angiotensin receptor antagonist (ARB) compared to continuation in older people with heart failure

Certainty assessment				№ of patients		Effect	Certainty	Importance		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	depresscribing of ACEI/ARB	continuation	Relative (95% CI)	Absolute (95% CI)	
*Mortality (down-titrated, long term follow-up)										
1	randomised trials	serious	not serious	not serious	very serious ^{a,b,c,d}	9/30 (30.0%)	8/17 (47.1%)	RR 0.64 (0.30 to 1.64)	169 fewer per 1,000 (from 329 fewer to 301 more)	⊕⊕⊕○ Moderate IMPORTANT
Mortality (discontinued, long term follow-up)										
3	observational studies	serious	very serious	not serious	serious ^{b,f}	347/1025 (33.9%)	2883/11,287 (25.5%)	HR 1.35 (0.99 to 1.85)	73 more per 1,000 (from 2 fewer to 165 more)	⊕⊕○○ Low IMPORTANT
Mortality (discontinued, long term follow-up, number of Events)										

Certainty assessment				№ of patients		Effect	Certainty	Importance	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of ACEI/ARB	continuation	Relative (95% CI)	Absolute (95% CI)
2	observational studies	serious	not serious	not serious	not serious	347/1025 (33.9%)	2883/11,287 (25.5%)	RR 1.65 (1.39 to 1.96)	166 more per 1,000 (from 100 more to 245 more)
Hospitalisation (discontinued) (long-term follow-up)									
2	observational studies	serious	not serious	not serious ^f	not serious ^b	352/1025 (34.3%)	6009/11,287 (53.2%)	HR 1.10 (0.97 to 1.24)	34 more per 1,000 (from 11 fewer to 79 more)
Mortality or hospitalisation (discontinued, long-term follow-up)									
1	observational studies	serious	not serious	serious	serious ^{a,b}	225/308 (73.1%)	6202/9572 (64.8%)	HR 1.14 (0.96 to 1.35)	48 more per 1,000 (from 15 fewer to 108 more)
Worsening heart failure (discontinued, short-term follow-up)									
1	observational studies	extremely serious	not serious	not serious	extremely serious ^{a,d}	1 of 5 participants (20%) experienced symptoms		⊕○○○ Very low	IMPORTANT

Discontinuation or *down-titration of beta blockers compared to continuation in older people with heart failure

Certainty assessment				№ of patients		Effect	Certainty	Importance	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of beta blocker	continuation	Relative (95% CI)	Absolute (95% CI)
Mortality (intermediate to long-term follow-up, number of Events)									
5	observational studies	very serious	serious	serious	not serious	24,804/65,667 (37.8%)	36,190/113,182 (32.0%)	RR 2.03 (1.31 to 3.24)	329 more per 1,000 (from 99 more to 716 more)
Mortality (intermediate to long-term follow-up)									
3	observational studies	serious	serious	serious	not serious	24,695/64,045 (38.6%)	36,158/112,264 (32.2%)	HR 1.38 (1.17 to 1.61)	93 more per 1,000 (from 43 more to 143 more)
Hospitalisation (short-term follow-up)									
1	randomised trials	serious	not serious	not serious	very serious ^{b,f}	1/26 (3.8%)	2/26 (7.7%)	RR 0.50 (0.05 to 5.18)	38 fewer per 1,000 (from 73 fewer to 322 more)
Hospitalisation long-term follow-up)									

№ of studies	Certainty assessment				№ of patients		Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of beta blocker	continuation	Relative (95% CI)		
2	observational studies	serious	not serious	serious	not serious	40,436/64,027 (63.2%)	62,915/111,443 (56.5%)	HR 1.07 (1.02 to 1.13)	⊕⊕⊕○ Moderate	22 more per 1,000 (from 6 more to 41 more)
Hospitalisation long-term follow-up, number of Events)										
4	observational studies	serious	not serious	serious ^b	serious ^f	40,707/65,566 (62.1%)	63,455/113,232 (56.0%)	RR 1.00 (0.84 to 1.19)	⊕○○○ Very low	0 fewer per 1,000 (from 90 fewer to 106 more)
Mortality or hospitalisation (short to intermediate-term follow-up)										
2	observational studies	serious	not serious	not serious	not serious	465/1539 (30.2%)	616/1880 (32.8%)	HR 1.28 (1.04 to 1.58)	⊕⊕⊕⊕ High	71 more per 1,000 (from 11 more to 138 more)
Worsening heart failure (long-term follow-up)										
1	observational studies	serious	not serious	not serious	not serious ^a	48/61 (78.7%)	475/529 (89.8%)	RR 0.88 (0.77 to 1.00)	⊕⊕⊕⊕ High	108 fewer per 1,000 (from 207 fewer to 0 fewer)

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of beta blocker	continuation	Relative (95% CI)	Absolute (95% CI)	
Acute coronary syndrome (intermediate-term follow-up)										
1	observational studies	serious	not serious	not serious	serious ^a	12/141 (8.5%) participants discontinued beta blocker compared to those that continued therapy.			⊕⊕⊕○ Moderate	IMPORTANT
Ventricular arrhythmia (intermediate to long-term follow-up)										
2	observational studies	extremely serious	serious	not serious	serious	8/162 (4.9%) participants discontinued beta blocker compared to those that continued therapy.			⊕○○○ Very low	IMPORTANT
*Ventricular arrhythmia (down-titrated) (intermediate to long-term follow-up)										
1	observational studies	very serious	not serious	not serious	very serious ^{s,d}	2/19 (10.5%) participants down-titrated beta blocker compared to those that continued therapy.			⊕○○○ Very low	IMPORTANT
Atrial fibrillation (AF) with rapid ventricular rate (short-term follow-up)										
1	randomised trials	serious	not serious	not serious	very serious ^{a,b,f}	1/26 (3.8%)	0 (0.0%)	RR 3.00 (0.13 to 70.36)	⊕⊕○○ Low	IMPORTANT
Atrial fibrillation (AF) or rapid ventricular rate (intermediate to long-term follow-up)										
2	observational studies	extremely serious	serious	not serious	serious	44/1648 (2.7%) participants discontinued beta blocker compared to those that continued therapy.			⊕○○○ Very low	IMPORTANT
*Atrial fibrillation (AF) or rapid ventricular rate (down-titrated) (long-term follow-up)										

№ of studies	Certainty assessment					№ of patients	Effect		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	depressing of beta blocker continuation	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	very serious	not serious	not serious	very serious ^{a,d}	1/19 (5.3%) participants experienced symptoms after down-titrated beta blocker compared to 1/76 (1.3%) in those that continued therapy.			⊕○○○ Very low	IMPORTANT
Syncope (long-term follow-up)										
1	observational studies	serious	not serious	not serious	serious ^a	3/141 (2.1%) participants experienced symptoms after discontinued beta blocker compared to 16/362 (4.4%) in those that continued therapy.			⊕⊕⊕○ Moderate	IMPORTANT
Barthel Index for Activities of Daily Living (long-term follow-up)										
1	observational studies	serious	not serious	not serious	serious ^{a,d}	78.7/100 (78.7%) participants experienced symptoms after discontinued beta blocker compared to 79.6/100 (79.6%) in those that continued therapy.			⊕⊕⊕○ Moderate	IMPORTANT
Quality of Life: Minnesota Quality of Life Living with Heart Failure (MQoLHF) score										
1	Randomised trials	serious	not serious	not serious	very serious ^{a,b,f}	MQoLHF score: discontinued (22.3) compared to continued (27.4) no statistically significant physical change RR -1.80, 95%CI -4 to 0.4, p=0.106; decreased emotional state RR -2.40, 95%CI -4.7 to -0.01, p=0.043			⊕⊕○○ Low	IMPORTANT
Cognition: Mini-mental state examination (MMSE) and Montreal Cognition Assessment (MoCA)										
1	Randomised trials	serious	not serious	not serious	very serious ^{a,b,f}	No significant change in cognition. MMSE change (28, p=0.929), MoCA change (22, p=0.420) – check if change from baseline and specify clearly			⊕⊕○○ Low	IMPORTANT

Discontinuation of mineralocorticoid receptor antagonist (MRA, spironolactone) compared to continuation in older people with heart failure

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing MRA	continuation	Relative (95% CI)	Absolute (95% CI)	
Mortality (long-term follow-up)										
3	observational studies	serious	very serious	serious	serious ^{b,f}	240/522 (46.0%)	178/436 (40.8%)	HR 1.91 (0.84 to 4.32)	255 more per 1,000 (from 52 fewer to 488 more)	⊕○○○ Very low IMPORTANT
Mortality or hospitalisation (long-term follow-up)										
2	observational studies	serious	very serious	serious	serious ^{b,f}	117/225 (52.0%)	117/161 (72.7%)	HR 1.55 (0.74 to 3.22)	139 more per 1,000 (from 110 fewer to 258 more)	⊕○○○ Very low IMPORTANT
Major CV event (intermediate-term follow-up)										
1	observational studies	serious	not serious	not serious	serious ^a	1519 participants	2436 participants	HR 1.06 (1.01 to 1.12)	-	⊕⊕⊕○ Moderate CRITICAL
Hyperkalemia (moderate/severe K+>5.5mmol/L) (intermediate-term follow-up)										
1	observational studies	serious	not serious	not serious	serious ^{a,c}	1519 participants	2436 participants	HR 0.73 (0.66 to 0.80)	-	⊕⊕⊕○ Moderate IMPORTANT

Certainty assessment					№ of patients		Effect	Certainty	Importance		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing MRA	continuation	Relative (95% CI)	Absolute (95% CI)		
2-year risk of fracture (intermediate-term follow-up)											
1	observational studies	serious	not serious	not serious	serious ^{a,b}	1519 participants	2436 participants	HR 1.17 (0.97 to 1.36)	-	⊕⊕⊕○ Moderate	IMPORTANT

Discontinuation of sodium-glucose cotransporter-2 inhibitor (*SGLT2-i*) compared to continuation in older people with heart failure

Certainty assessment				№ of patients	Effect	Certainty	Importance				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing SGLT2-i	continuation	Relative (95% CI)	Absolute (95% CI)		
Mortality (long-term follow-up)											
1	observational studies	serious	not serious	not serious	very serious ^{a,b,c,d}	3/30 (10.0%)	4/56 (7.1%)	HR 0.71 (0.16 to 3.16)	20 fewer per 1,000 (from 60 fewer to 137 more)	⊕⊕○○ Low	IMPORTANT
Hospitalisation (long-term follow-up)											
1	observational studies	serious	not serious	not serious	very serious ^{a,c,d}	13/30 (43.3%)	14/56 (25.0%)	RR 1.73 (0.94 to 3.19)	167 fewer per 1,000 (from 216 fewer to 54 fewer)	⊕⊕○○ Low	IMPORTANT
Escalating diuretic use (long-term follow-up)											
1	observational studies	serious	not serious	not serious	very serious ^{a,d}	30 participants	56 participants	HR 1.17 (1.01 to 1.32)	-	⊕⊕○○ Low	IMPORTANT

Discontinuation of *diuretic* compared to continuation in older people with heart failure

Certainty assessment			№ of patients		Effect	Certainty	Importance				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing diuretic	continuation	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality or hospitalisation (short-term follow-up)											
1	observational studies	serious	not serious	not serious	serious ^a	38/213	0/1912	OR 2.38 (1.81 to 3.13)	-	⊕⊕⊕⊕ High	CRITICAL
Mortality or hospitalisation (long-term follow-up)											
1	observational studies	serious	not serious	not serious ^e	not serious ^{a,c,d}	296 participants	126 participants	HR 0.34 (0.20 to 0.60)	-	⊕⊕⊕⊕ High	CRITICAL
Hospitalisation (long-term follow-up)											
1	observational studies	extremely serious	not serious	not serious	extremely serious ^{a,d}	In a before and after cohort study, 6/33 (18.2%) participants that discontinued diuretics were hospitalised				⊕○○○ Very low	IMPORTANT
Worsening heart failure (intermediate to long-term follow-up)											
2	randomised trials	not serious	not serious	serious	very serious ^d	27/123 (22.0%)	5/111 (4.5%)	RR 3.45 (0.68 to 17.46)	110 more per 1,000 (from 45 more to 495 more)	⊕⊕⊕○ Moderate	IMPORTANT
Worsening heart failure (short to long-term follow-up)											

№ of studies	Certainty assessment				№ of patients	Effect	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing diuretic continuation		
						Relative (95% CI)	Absolute (95% CI)	
2	observational studies	extremely serious	very serious	serious	serious ^d	26/56 (46.4%) participants in the discontinued group and none in the control group experienced symptoms	⊕○○○ Very low	IMPORTANT
Dyspnea or shortness of breath (long-term follow-up)								
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	participants experienced symptoms 6/102 (5.9%) after discontinued diuretic and none 0/100 (0%) in those that continued	⊕⊕○○ Moderate	IMPORTANT
Hypertension (intermediate to long-term follow-up)								
2	randomised trials	not serious	serious	not serious	very serious ^d	participants experienced hypertension 10/123 (8.1%) after discontinued diuretic compared to 5/111 (4.5%) when continued taking diuretics	⊕⊕○○ Low	IMPORTANT
Hypertension (long-term follow-up)								
1	observational studies	extremely serious	not serious	not serious	extremely serious ^{a,d}	participants experienced hypertension 3/33 (9.1%) after discontinued diuretic and none while taking	⊕○○○ Very low	IMPORTANT
Myocardial infarction (long-term follow-up)								
1	observational studies	extremely serious	not serious	not serious	extremely serious ^{a,d}	participants experienced MI 1/33 (3.0%) after discontinued diuretic and none while taking	⊕○○○ Very low	IMPORTANT
Stroke (long-term follow-up)								
1	observational studies	extremely serious	not serious	not serious	extremely serious ^{a,d}	participants experienced stroke 1/33 (3.0%) after discontinued diuretic and none while taking.	⊕○○○ Very low	IMPORTANT
Peripheral oedema (long-term follow-up)								

№ of studies	Certainty assessment					№ of patients	Effect	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing diuretic	continuation		
							Relative (95% CI)	Absolute (95% CI)	
2	randomised trials	not serious	serious	not serious	very serious ^d	participants experienced symptoms after discontinued compared to continued taking diuretics.	8/123 (6.5%) 1/111 (0.9%)	⊕⊕○○ Low	IMPORTANT
Peripheral oedema (long-term follow-up)									
1	observational studies	extremely serious	not serious	not serious	extremely serious ^{a,d}	participants experienced symptoms discontinued diuretic and none while taking	3/33 (9.1%)	⊕○○○ Very low	IMPORTANT
Other: anxiety, malignancy, quality of life (MQoLHF) (intermediate to long-term follow-up)									
2	observational studies	extremely serious	serious	not serious	very serious ^d	participants experienced anxiety: malignancy 1/33 (3%) after discontinued diuretic and none while on diuretic previously	2/33 (6%)	⊕○○○ Very low	IMPORTANT

Discontinuation of *digitalis glycoside (digoxin)* compared to continuation in older people with heart failure

Certainty assessment					№ of patients		Effect	Certainty	Importance		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	depresscribing of digoxin	continuation	Relative (95% CI)	Absolute (95% CI)		
Mortality (intermediate-term follow-up)											
1	randomised trials	not serious	not serious	not serious	very serious ^{a,b,c,d}	1/93 (1.1%)	3/85 (3.5%)	RR 0.30 (0.03 to 2.87)	25 fewer per 1,000 (from 34 fewer to 66 more)	⊕⊕⊕⊕ High	CRITICAL
Mortality (long-term follow-up)											
1	observational studies	serious	not serious	not serious	not serious ^{a,b}	287/698 (41.1%)	251/698 (36.0%)	HR 1.09 (0.96 to 1.23)	25 more per 1,000 (from 12 fewer to 62 more)	⊕⊕⊕⊕ High	CRITICAL
Hospitalisation (intermediate-term follow-up)											

№ of studies	Certainty assessment					№ of patients		Effect	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of digoxin	continuation			
								Relative (95% CI)	Absolute (95% CI)	
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d,f}	12/93 (12.9%)	2/85 (2.4%)	RR 5.48 (1.26 to 23.80)	105 more per 1,000 (from 6 more to 536 more)	⊕⊕⊕⊕ High CRITICAL
All-cause hospitalisation (long-term follow-up)										
1	observational studies	serious	not serious	not serious	serious ^a	407/698 (58.3%)	391/698 (56.0%)	HR 1.16 (1.03 to 1.30)	54 more per 1,000 (from 11 more to 96 more)	⊕⊕⊕○ Moderate IMPORTANT
HF hospitalisation (long-term follow-up)										
1	observational studies	serious	not serious	not serious	serious ^a	579/698 (83.0%)	595/698 (85.2%)	HR 1.21 (1.06 to 1.39)	49 more per 1,000 (from 16 more to 78 more)	⊕⊕⊕○ Moderate IMPORTANT
Worsening heart failure (intermediate-term follow-up)										

Certainty assessment					N° of patients		Effect		Certainty		Importance	
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of digoxin	continuation	Relative (95% CI)	Absolute (95% CI)			
1	randomised trials	not serious	not serious	not serious	serious ^{a,d,f}	23/93 (24.7%)	4/85 (4.7%)	RR 5.26 (1.89 to 14.58)	200 more per 1,000 (from 42 more to 639 more)	⊕⊕⊕⊕ High	CRITICAL	
Worsening heart failure (intermediate-term follow-up)												
2	observational studies	very serious	not serious	not serious	very serious ^d	9/53 (17.0%) participants discontinued digoxin compared to those that continued therapy				⊕○○○ Very low	IMPORTANT	
Myocardial infarction (intermediate-term follow-up)												
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	1/18 (5.6%) participants discontinued digoxin compared to those that continued therapy				⊕⊕⊕○ Moderate	IMPORTANT	
Unstable angina (intermediate-term follow-up)												
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	1/93 (1.1%) participants discontinued digoxin compared to those that continued therapy.				⊕⊕⊕○ Moderate	IMPORTANT	
Atrial fibrillation (intermediate-term follow-up)												

N° of studies	Certainty assessment					N° of patients	Effect	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of digoxin	continuation		
							Relative (95% CI)	Absolute (95% CI)	
2	randomised trials	not serious	serious ^f	not serious	very serious ^{a,d}	2/111 (1.8%) participants discontinued digoxin compared to 0/106 (0%) in those that continued therapy.		⊕⊕○○ Low	IMPORTANT
Sinus tachycardia (intermediate-term follow-up)									
3	observational studies	very serious	serious	not serious	very serious ^d	3/131 (2.3%) participants discontinued digoxin compared to those that continued therapy		⊕○○○ Very low	IMPORTANT
Upper respiratory tract infection (URTI) (intermediate-term follow-up)									
3	observational studies	very serious	serious	not serious	very serious ^d	6/131 (4.6%) participants discontinued digoxin compared to those that continued therapy.		⊕○○○ Very low	IMPORTANT
Escalating diuretic (intermediate-term follow-up)									
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	11/93 (11.8%) participants discontinued digoxin compared to 4/85 (4.7%) in those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT
Dyspnea or Shortness of breath (intermediate-term follow-up)									
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	22/93 (23.7%) participants discontinued digoxin compared to 12/85 (14.1%) in those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT
Fatigue (intermediate-term follow-up)									

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of digoxin	continuation	Relative (95% CI)	Absolute (95% CI)
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	22/93 (23.7%) participants discontinued digoxin compared to those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT
Other:									
Hyponatremia (intermediate-term follow-up)									
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	1/93 (1.1%) participants discontinued digoxin compared to those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT
Thyrotoxicosis (intermediate-term follow-up)									
1	observational studies	very serious ^c	not serious	not serious	very serious ^{a,d}	1/20 (5.0%) participants discontinued digoxin compared to those that were on therapy.		⊕○○○ Very low	IMPORTANT
Renal carcinoma (intermediate-term follow-up)									
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	1/93 (1.1%) participants discontinued digoxin compared to those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT
Quality of Life									
MQoLHF (improved) (intermediate-term follow-up)									

№ of studies	Certainty assessment					№ of patients	Effect	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	deprescribing of digoxin	continuation		
							Relative (95% CI)	Absolute (95% CI)	
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	19/93 (20.4%) participants improved after discontinued digoxin compared to 34/85 (40.0%) in those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT
MQoLHF (deteriorated) (intermediate-term follow-up)									
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	28/93 (30.1%) participants deteriorated after discontinued digoxin compared to 30/85 (35.3%) in those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT
Patient reported feeling better or unchanged (intermediate-term follow-up)									
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	61/93 (65.6%) participants felt better or unchanged after discontinued digoxin compared to 30/85 (35.3%) in those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT
Patient reported feeling worse (intermediate-term follow-up)									
1	randomised trials	not serious	not serious	not serious	very serious ^{a,d}	70/93 (75.3%) participants felt worse after discontinued digoxin compared to 13/85 (15.3%) in those that continued therapy.		⊕⊕⊕○ Moderate	IMPORTANT

Abbreviations: **CI**= confidence interval; **HR**= hazard Ratio; **OR**= odds ratio; **RR**= risk ratio; **MQoLHF** =Minnesota quality of life in heart failure scale; **BI**= Barthel index for activities of daily living (assessed out of 100). **Explanations:** a. Only 1 study; b. 95%CI includes no effect & CI crosses effect size; c. 95%CI includes favors discontinuation effect & RRR >25%; d. small sample size; e. post CRT (HFimpEF) population; f. wide 95%CI. Publications bias, funnel plots could not be constructed due to limited number of studies. **Time intervals:** **Short** (<30 days); **Intermediate** (5-24 weeks); **Long** (>24 week).

Table S3.7. Monitored laboratory outcomes and patient characteristics reported at baseline and/or after deprescribing in included studies in Chapter 3.

Drug Class	Laboratory outcomes monitored		Patient characteristics		Comorbidities; Medications
	Routine blood work	Echocardiogram (ECG)	Characteristics		
ACEI/ARB	BMI, SCr, eGFR, NT-proBNP, BNP, K+	LVEF, HR, SBP, DBP	aetiology, ethnicity		DM, PVD, CAD, AF, renal insufficiency, hyperlipidaemia, smoking
Diuretic	weight, BMI, SCr, eGFR, BNP, NT-proBNP, Na+, blood urea nitrogen	LVEF, LV, SBP, DBP	aetiology, ethnicity, hospitalisation history, NYHA class, 6MWT		DM, CAD, AF, atherosclerosis; ACEI/ARB, BB, MRA
Digoxin	SCr, GFR, haemoglobin, BNP, Na+	LVEF, SBP, DBP, HR, PEP/LVET, E/A ratio	aetiology, ethnicity, hospitalisation history, orthopnoea, oedema		DM, CAD, AF, anaemia, COPD, CRT, hyperlipemia; ACEI/ARB, BB, diuretic, MRA, nitrates, CCB
Beta blocker	weight, BMI, SCr, Na+, K+, BNP, NT-proBNP, haemoglobin	LVEF, systolic/diastolic BP, HR	aetiology, ethnicity, hospitalisation history, NYHA class, oedema		DM, CAD, PVD, AF, arrythmia, CVA, TIA, ICD, CV event, anaemia, dementia, renal failure/insufficiency, COPD, sinus rhythm, dyslipidaemia, pacemaker, smoking, thyroid abnormality; ACEI/ARB, BB, diuretic, MRA, inotropes
MRA	BMI, SBP, eGFR, K+	LVEF	aetiology		DM, PVD, CVD; ACEI/ARB, BB, diuretic
SGLT2-I	weight, BMI, SCr, eGFR, haemoglobin, hematocrit, serum albumin, BNP, HbA1c, Na+, K+	LVEF, SBP, HR	aetiology		AF, ICD, CRT; ACEI/ARB, BB, diuretic, MRA
Abbreviations: ACEI/ARB = angiotensin converting enzyme inhibitor; BB = beta blocker; MRA = Mineralocorticoid receptor antagonist; SGLT2-I = Sodium-Glucose Cotransporter-2 Inhibitor; CCB = calcium channel blockers; BMI = body mass index; SCr = serum creatinine; GFR = glomerular filtration rate; eGFR = estimated glomerular filtration rate; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; K+ = serum potassium; Na+ = serum sodium; 6MWT = 6 minute walk test; LVEF = left ventricular ejection fraction; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; PEP/LVET : E/A ratio = pre-ejection period/left ventricular ejection time; DM = diabetes mellitus; PVD = peripheral vascular disease; CAD = coronary artery disease; AF = atrial fibrillation; CVA = cerebrovascular accident; TIA = trans ischemic attack; ICD = implantable cardioverter defibrillator; CV = cardiovascular; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; NYHA = New York Heart Association					

Table S3.8: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7,8



PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,eFigure7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	eFigure 7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	online supplement
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Table S3.9: MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	5
Hypothesis statement	Yes	5
Description of Study Outcome(s)	Yes	7
Type of exposure or intervention used	Yes	6
Type of study design used	Yes	6
Study population	Yes	6
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	6, eTable 2
Search strategy, including time period included in the synthesis and keywords	Yes	6, eTable 2
Effort to include all available studies, including contact with authors	Yes	6, eTable 2
Databases and registries searched	Yes	6, eTable 2
Search software used, name and version, including special features used (eg, explosion)	Yes	6, eTable 2
Use of hand searching (eg, reference lists of obtained articles)	Yes	6
List of citations located and those excluded, including justification	Yes	eFig1, eTab2
Method for addressing articles published in languages other than English	Yes	6, eTable 2
Method of handling abstracts and unpublished studies	Yes	6, eTable 2
Description of any contact with authors	Yes	7
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	6,7
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	8
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	7,8
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Yes	8

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	8
Assessment of heterogeneity	Yes	8
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	8
Provision of appropriate tables and graphics	Yes	Fig1,2,supple
Reporting of Results		
Table giving descriptive information for each study included	Yes	Table 1
Results of sensitivity testing (eg, subgroup analysis)	Yes	9, supp
Indication of statistical uncertainty of findings	Yes	10
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	19
Justification for exclusion (eg, exclusion of non-English-language citations)	Yes	6, eTable 2
Assessment of quality of included studies	Yes	eFigure 7
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	16-17
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	16-17
Guidelines for future research	Yes	17
Disclosure of funding source	Yes	18

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

APPENDIX C: CHAPTER 4 SUPPLEMENTARY MATERIALS

ORIGINAL ARTICLE

Prevalence of heart failure pharmacotherapy utilisation, frailty and adverse drug events among hospitalised adults older than 75 years: a multicentre cross-sectional study

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Key words

congestive heart failure, polypharmacy, observational study, guideline adherence, drug utilisation, data visualisation.

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Received 12 July 2024; accepted 26 November 2024.

Abstract

Background: Optimal heart failure (HF) pharmacotherapy (guideline-directed medical therapy and diuretics) in older people with frailty is uncertain due to limited evidence.

Aims: To evaluate utilisation of HF pharmacotherapy and prevalence of polypharmacy, adverse drug events (ADEs), falls, delirium, renal impairment and duration of hospitalisation in older inpatients, according to frailty.

Methods: A retrospective cross-sectional study of the TO HOME cohort of 2000 inpatients ≥ 75 years admitted for ≥ 48 h to rehabilitation, geriatric or general medicine from 1 July 2016 to 30 June 2017 across six hospitals in Sydney, Australia. Data were collected from electronic medical records. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification identified HF diagnosis, ADEs and frailty using hospital frailty risk score. Outcomes included utilisation of HF pharmacotherapy; polypharmacy; ADEs, falls, delirium, renal and impairment; and duration of hospitalisation.

Results: Among 439 (22.0% of TO HOME cohort) patients with undifferentiated HF, 284 (69.5%) had intermediate or high risk of frailty, and 412 (94%) took ≥ 1 HF pharmacotherapy, with 357 (81.3%) patients on loop diuretics. Patients with high frailty risk frequently continued beta-blockers (70%) and discontinued renin-angiotensin system inhibitors (57%). Most patients experienced polypharmacy ($n = 426$, 97.0%). Renal impairment prevalence was 67%–76% across frailty groups. Increasing frailty risk (low, intermediate and high) was associated with increasing prevalence of ADEs (31%, 56% and 84%), falls (12%, 25% and 46%) and delirium (8%, 27% and 49%) and longer hospitalisation.

Conclusions: Frailty, HF-pharmacotherapy changes in hospital and ADEs were common among older inpatients with HF. The association of adverse outcomes according to frailty needs further investigation. Poor documentation of HF phenotype may be a barrier to medication optimisation in older inpatients.

Abbreviations: ADE, adverse drug event; ADR, adverse drug reaction; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; CCI, Charlson comorbidity index; eMR, electronic medical record; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction (LVEF $> 50\%$); HFrEF, heart failure with reduced ejection fraction (LVEF $< 40\%$); HFRS, hospital frailty risk score; ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification; LOS, length of stay; MRA,

mineralocorticoid receptor antagonist; OR, odds ratio; RASI, renin-angiotensin system inhibitors; SD, standard deviation; SGLT2-i, sodium-glucose cotransporter 2 inhibitors; TO HOME, Towards Optimising Hospitalised Older adults' Medications

Funding: MHD is funded by the Commonwealth of Australia National Health and Medical Research Council (NHMRC) Postgraduate Scholarship Grant APP1191018 awarded in 2020, HROz Scholarship awarded in 2023–24 and the University of Sydney Postgraduate Research Support Scheme 2022–24.

Conflict of interest: None.

Introduction

Heart failure (HF) is a complex syndrome increasingly prevalent in the ageing population and associated with high risk of hospitalisation and death.¹ Half of HF hospitalisations involve people aged ≥ 75 years.² Frailty, a reversible syndrome involving multisystem deficiencies, affects up to 75% of people living with HF in the community.³ Utilisation and optimisation of HF guideline-directed medical therapies (GDMTs) (i.e. renin-angiotensin system inhibitors (RASIs), HF-specific beta-blockers, mineralocorticoid receptor antagonists (MRAs) and, more recently, sodium-glucose co-transporter-2 inhibitors (SGLT2-i)) have demonstrated reduced mortality and hospitalisation.⁴ Older people report lower tolerance and higher discontinuation rates of HF GDMTs.^{5,6}

Polypharmacy is highly prevalent in patients with HF, especially as their age increases. Ninety-five per cent take ≥ 5 medications and 50% take ≥ 10 medications, increasing the risk of adverse drug reactions (ADRs).⁷ Up to 91% of HF patients report experiencing chronic adverse drug events (ADEs).⁸ Previous studies of hospitalised older adults reported HF in approximately 13% of inpatients,⁹ 40% were affected by frailty and 8.6%–18.4% reported ADRs in hospital.^{10–13} The prevalence of ADRs in people aged < 65 years compared to those ≥ 65 years differed by 30%–60%.¹⁴ Hospitalisation of older patients with HF often occurs under the care of multidisciplinary teams, which may or may not include cardiology specialists.

The management of HF and optimisation of medications in frail older people can be complex due to disease progression, changes in cognition, multimorbidity, life expectancy and changing patient priorities. Frail older people are persistently and widely excluded from HF clinical trials, which measure cardiovascular outcomes rather than geriatric outcomes; thus, evidence on efficacy and safety in this population is limited.^{15,16} Research evaluating geriatric outcomes is needed to fill this knowledge gap to support shared decision-making.

This study aimed to evaluate the utilisation of HF GDMTs and diuretics in hospitalised patients ≥ 75 years with HF, according to frailty risk. Secondary objectives were to determine the duration of hospitalisation and evaluate the prevalence of polypharmacy and geriatric-relevant adverse events in patients with HF on HF GDMTs or diuretics at hospital discharge by frailty risk.

Methods

Data source

This retrospective cross-sectional study included 2000 consecutive patients aged ≥ 75 years admitted for ≥ 48 h

to geriatric, general and rehabilitation medicine between 1 July 2016 and 30 June 2017 across six hospitals in Sydney, Australia. Data were collected from patient electronic medical records (eMRs) in routine care and verified by a research clinician on medications, clinical characteristics and outcomes (e.g. changes in medication utilisation, ADEs, falls, delirium and renal impairment) during admission. Data were obtained from the Towards Optimising Hospitalised Older adults' Medications (TO HOME) dataset, designed to look at overall medication management during routine care in general medical, geriatric and rehabilitation services, previously published methods and characteristics.¹⁷ Patients with HF who present with geriatric syndromes or non-cardiac reasons for admission (e.g. infection, falls), with or without active cardiac diagnosis, are likely to be admitted to general medical and geriatric hospital services for HF or non-HF admissions. This study did not capture data for patients admitted under cardiology service, more likely to be admitted for initial diagnosis of HF, acute treatment of severe HF requiring critical care or HF without other active diagnoses.

Study subjects

Patients were identified using coding of diagnoses during hospital admission with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes. ICD-10-AM coding for HF diagnosis and related cardiomyopathy¹⁸ included undifferentiated HF (U82.2, I50, I50.0, I50.1, I50.9, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–42.9, I43, P29.0, E10.53, E11.53, E13.53, E14.53), heart failure with reduced ejection fraction (HFrEF) (I50.2x, I50.4x) and heart failure with preserved ejection fraction (HFpEF) (I50.3). Demographic characteristics were determined for patients with HF diagnosis compared to those with no HF diagnosis. Previous ADRs were identified from documentation in admission notes and discharge summaries in the eMR.

Frailty measurement

Frailty risk of each patient was calculated with ICD-10-AM codes according to the hospital frailty risk score (HFRS), a numerical score determined by relevant ICD-10-AM codes during admission as previously reported.¹⁹ The HFRS calculates the risk of frailty into three categories: low (< 5 points), intermediate (5–15 points) or high (> 15 points). All outcomes were reported by frailty risk (HFRS categories) to mitigate reporting bias. This study evaluated the prevalence of medication utilisation and highly prevalent outcomes among

geriatric populations with cardiovascular disease, particularly polypharmacy, duration of hospitalisation, ADEs, falls, delirium and renal impairment, according to frailty risk.²⁰

HF pharmacotherapy utilisation

Anatomical Therapeutic Chemical Classification codes for HF-GDMT⁴ include RASIs (C09), beta-blockers (C07), MRAs (C03D, C03DA) and loop diuretics (C03, C03CA, C03CA01). The codes for SGLT2-i (A10BK) were not included in this analysis since they were not recommended in HF guidelines at the time of data collection. RASIs mostly referred to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists as sacubitril/valsartan was not approved in Australia during the entire data collection period. Diuretics include loop diuretics (i.e. furosemide, bumetanide, etacrynic acid) and exclude thiazide diuretics.

The primary outcome measure was HF pharmacotherapy utilisation by individual therapeutic class and combination (i.e. taking at least one GDMT or diuretic). These categorical data are reported as the frequency and proportion of initiation, continuation, uptitration, downtitration, discontinuation and re-initiation of each class of HF pharmacotherapy at discharge. Analysis did not reveal whether individual doses for each HF pharmacotherapy met the criteria for recommended optimised doses in clinical trials. Polypharmacy (the use of ≥ 5 regular medications) and hyperpolypharmacy (the use of ≥ 10 regular medications) at admission and discharge were reported for all HF patients. The frequency of two, three and four HF pharmacotherapy combinations per patient and the prevalence of overall pairwise combinations were reported.

Clinical outcomes

Secondary outcomes were measured as the frequency and proportion of clinical outcomes, reported as ADEs, falls, delirium and renal impairment for patients taking ≥ 1 HF pharmacotherapy at discharge. ADEs are defined as any adverse outcome occurring in people taking a medication.²¹ ADEs were identified with ICD-10-AM codes using Du *et al.*²² published criteria to identify potential ADEs of clinical significance occurring in hospital. Specifically, the combination of ICD-10-AM external cause codes (Y40-59)²³ and previously published ICD-10-AM codes assigned causality ratings (A, B, C and D) estimating the probability that a specific diagnosis was related to an ADR. Falls and delirium were extracted from the free text in the eMR. Renal Impairment (acute or chronic) was defined as glomerular filtration rate < 60 mL/min/1.73 m²

measured at admission.²⁴ Missing data ($n = 1$) for renal impairment identified in one HF patient with intermediate frailty were coded as no renal impairment. Duration of hospitalisation (length of stay (LOS)) was measured as the number of days (mean, standard deviation) between patient initial admission and discharge.

Statistical analysis

A descriptive analysis was performed on the TO HOME cohort, stratified by frailty risk. Sample size was determined by the TO HOME cohort. A retrospective power analysis was conducted. A clinically significant difference in prevalence of ADRs was considered as 10% in patients aged ≥ 65 years in a recent systematic review.^{25,26} Therefore, the study had 0.87 power to detect a 10%–18% difference in ADRs from HF pharmacotherapy when comparing people with low, intermediate and high risk of frailty.^{11,27} Descriptive statistics were applied to calculate frequency and proportions of all outcomes. The mean (standard deviation) was reported for continuous variables, and count (%) was reported for categorical variables, binary groups and frailty risk and graphed. Sociodemographic and hospital admission data in patients with and without HF were compared using the Pearson chi-squared test for categorical variables and the Mann–Whitney *U* test for continuous variables. Differences between patients with HF and no HF diagnosis were deemed statistically significant if the *P*-value was < 0.05 . Subgroup analysis reported outcomes by frailty risk. Patterns between frailty groups were not compared statistically. Instead, weighted utilisation for individual therapeutic classes were grouped by frailty risk using radar plots,^{28,29} and heatmaps of HF pharmacotherapy pairwise combinations per person with annotations of frequency and proportions of ADEs were visualised.³⁰ Data analysis and visualisation were performed in R/Rstudio version 4.2.2 using ggplot2 (version 3.5.0), ggradar (version 0.2) and ComplexHeatmap (version 2.14.0), along with Microsoft Excel 2014.

Results

Demographics

Undifferentiated HF was identified in 439 (22%) patients; no coding reported HFrEF or HFpEF (Fig. 1). Table 1 describes patient characteristics in those with HF compared to no HF diagnosis. The proportion of frailty risk was similar among patients with diagnosis of HF ($n = 305$, 69.5%) and no HF ($n = 1107$, 70.9%). In patients with HF, there was low ($n = 134$, 30.5%), intermediate ($n = 230$, 52.4%) and high ($n = 75$, 17.1%) frailty risk. The mean age was

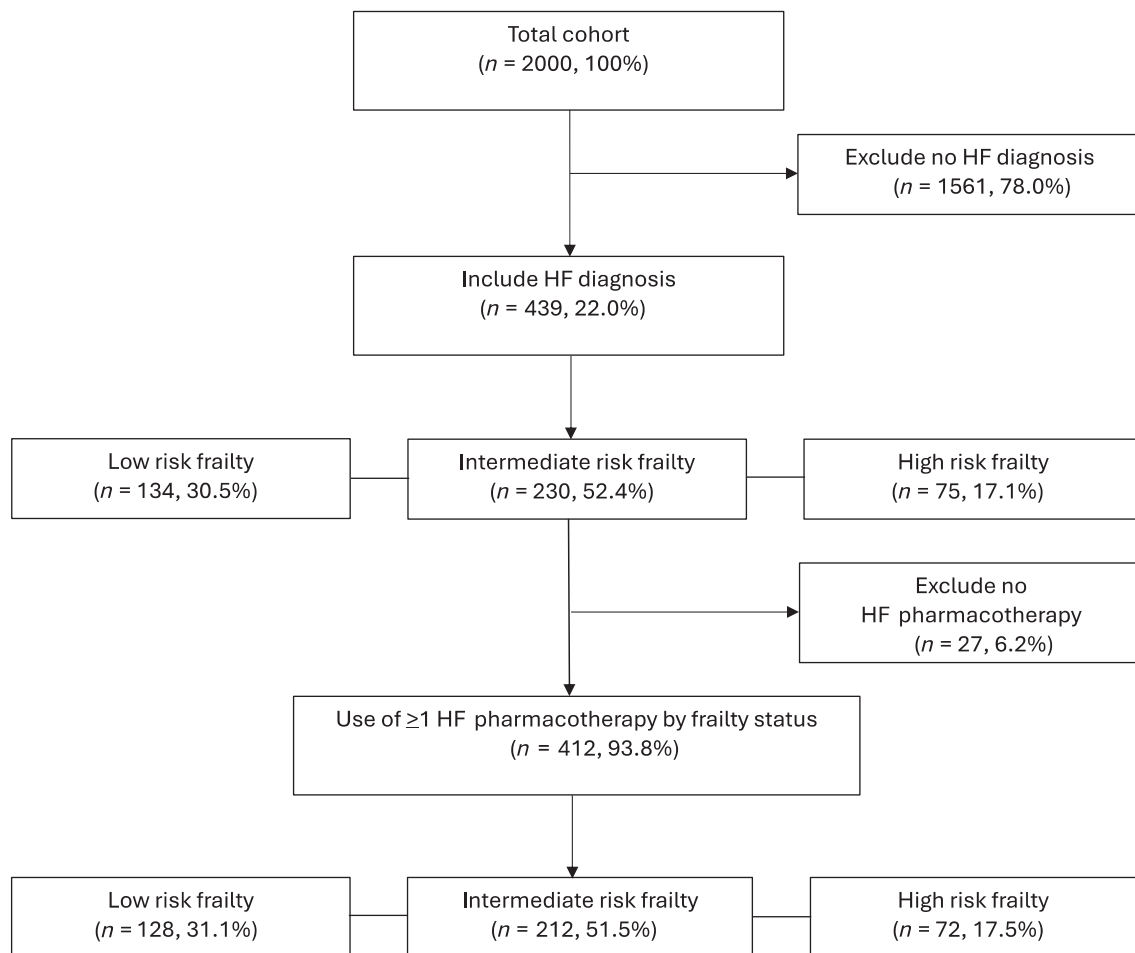


Figure 1 Flow chart of study population selection.

87 (5.6) years, 59.0% ($n = 259$) were female, 15.3% ($n = 90$) had dementia, 7.1% ($n = 42$) had mild cognitive impairment, 134 (30.5%) and 67.2% ($n = 295$) considered English their preferred language. Compared to patients without HF diagnosis, patients with HF had more comorbidities (Charlson comorbidity index ≥ 3)³¹ ($n = 134$, 30.5% HF, $n = 201$, 12.9% without HF), lower prevalence of documented dementia ($n = 90$, 15.3% HF, $n = 427$, 27.4% without HF) and a higher prevalence of a cardiac or circulatory system-related primary reason for admission ($n = 125$, 28.5% HF, $n = 95$, 6.1% without HF). Of those with a diagnosis of HF, HF was the primary reason for admission in 97 (22.1%). Prior to admission, 68.8% ($n = 302$) lived at home and 50.1% ($n = 220$) were discharged home.

HF pharmacotherapy utilisation

The use of at least one HF pharmacotherapy was reported in 412 (94%) patients with a documented

diagnosis of HF. At discharge, HF pharmacotherapy was frequently continued ($n = 289$, 65.8%). HF pharmacotherapy withheld or discontinued during hospital admission was commonly not recommended for re-initiation at discharge, with <1% being recommended for re-initiation if deemed appropriate by their general practitioner (Fig. S1, Table S1). During hospitalisation, patients with HF were frequently prescribed loop diuretics ($n = 357$, 81.3%, predominantly furosemide ($n = 355$, 80.9%)), MRAs were less frequently prescribed ($n = 100$, 22.8%), and half were prescribed RASIs ($n = 218$, 49.7%) and/or beta-blockers ($n = 216$, 49.2%) (Table S2). HF-specific beta-blockers (e.g. excluding atenolol, labetalol, propranolol, sotalol) were reported for 179 (40.8%) patients. Sotalol, which may exacerbate HF, was prescribed for 11 (2.5%) patients diagnosed with HF but not with HF as the primary reason for admission and was continued ($n = 8$, 1.8%), discontinued ($n = 2$, 0.5%) or downtitrated ($n = 1$, 0.2%) during admission.

Table 1 Patient characteristics

Characteristics, <i>n</i> (%)	Total		Heart failure		No heart failure	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Sample size	2000	100%	439	22%	1561	78%
Age (years), mean (SD)	86 (5.8)	—	87 (5.6)	—	86 (5.8)	—
75–79	307	15.4%	44	10%	263	17%
80–89	1116	55.8%	245	56%	871	56%
≥90	577	28.9%	150	34%	427	27%
Sex (female)	1181	59.1%	259	59.0%	922	59.1%
Preferred language spoken at home						
English	1381	69%	295	67.2%	1092	70.0%
Language other than English	613	31%	144	32.8%	469	30.0%
Frailty risk (hospital frailty risk score (HFRS))						
Low (HFRS < 5)	588	29.4%	134	30.5%	454	29.1%
Intermediate (HFRS 5–15)	1087	54.4%	230	52.4%	857	54.9%
High (HFRS > 15)	325	16.3%	75	17.1%	250	16.0%
Number of comorbidities (Charlson Comorbidity Index)‡						
Low: score 0–2	1665	83.2%	305	69.4%	1360	87.1%
High: score 3+	335	16.8%	134	30.5%	201	12.9%
Cognition						
Dementia documented‡	517	26%	90	15.3%	427	27.4%
Mild cognitive impairment	197	10%	42	7.1%	155	9.9%
Primary reason for admission						
Cardiac and circulatory system‡	220	11%	125	28.5%	95	6.1%
Heart failure	97	4.9%	97	22.1%	—	—
Low risk (HFRS < 5)	48	2.4%	48	11%	—	—
Intermediate risk (HFRS 5–15)	43	2.2%	43	10%	—	—
High risk (HFRS > 15)	6	<1%	6	1.4%	—	—
Length of hospital stay (days) mean (SD)	13.4 (15.6)	—	13.5 (12.7)	—	13.4 (16.3)	—
History of a previous ADR† prior to admission	831	41.6%	207	47.2%	624	40.0%
Living status prior to admission						
Home	1458	73%	302	68.8%	1156	74.1%
Residential aged care facility	421	25%	108	24.6%	313	20.1%
Other	121	22%	29	6.6%	92	5.9%
Discharge destination						
Home	1050	53%	220	50.1%	830	53.2%
Residential aged care facility	506	25%	123	28.0%	383	24.5%
Assisted living	78	4%	20	4.6%	58	3.7%
Hospice/palliative care	1	<1%	0	0.0%	1	0.1%
Other	365	18	76	17.3%	289	18.5%

†Participant had documented adverse drug reactions.

‡Difference between HF and no HF was statistically significant ($P < 0.05$).

Deprescribing of HF pharmacotherapy was frequent ($n = 185$, 42.1%) (Table S1). Of the 97 patients admitted with HF as the primary reason for admission, 22 (22.7%) discontinued and 19 (19.6%) downtitrated HF pharmacotherapy. Discontinuation was most prevalent for RASIs ($n = 75$, 17.1%). Loop diuretics were most frequently adjusted during hospitalisation, as doses were initiated ($n = 68$, 15.5%), uptitrated ($n = 74$, 16.9%) and downtitrated ($n = 41$, 9.3%). Continuation of beta-blockers ($n = 160$, 36.4%) and diuretics ($n = 142$, 32.3%) were most prevalent across frailty subgroups (Fig. 2). High-frailty- and risk patients frequently continued beta-blockers ($n = 26$, 70.3%) discontinued

RASIs ($n = 21$, 56.8%), and MRAs were similarly continued ($n = 5$, 38.5%) and discontinued ($n = 5$, 38.5%).

Polypharmacy

Polypharmacy ($n = 411$, 93.6%) and hyperpolypharmacy ($n = 219$, 50.0%) at admission increased at discharge ($n = 426$, 97.0% and $n = 281$, 64.0%, respectively) (Table S2). The proportion of HF patients with hyperpolypharmacy was 10% higher in those with high compared to low frailty risk (high 56.0%, intermediate 50.4%, low 45.5%). Eighty-eight (20.0%) patients with HF had no HF GDMT, of whom 27 (6.2%) were on neither HF GDMT

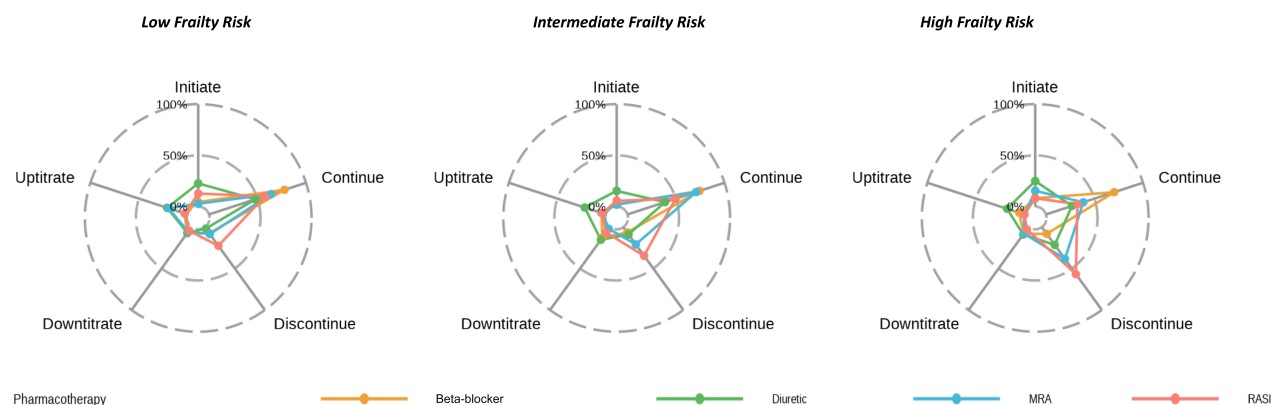


Figure 2 The proportion of heart failure-pharmacotherapy utilisation in hospitalised patients over 75 years with heart failure, by frailty risk.

nor diuretic (Table S2). Monotherapy diuretic use was reported in 61 (13.9%) patients. Multidrug combinations with diuretics were frequent. Use of two ($n = 170$, 41.3%) or three ($n = 118$, 28.6%) HF pharmacotherapies were most frequent, but use of four ($n = 25$, 6.1%) was

uncommon (Table S2). The most frequent pairwise HF pharmacotherapy combinations were diuretic–beta-blocker ($n = 184$, 44.7%), diuretic–RASI ($n = 183$, 44.4%) and beta-blocker–RASI ($n = 112$, 27.2%) combinations, while monotherapies were uncommon (Fig. 3). This pattern of

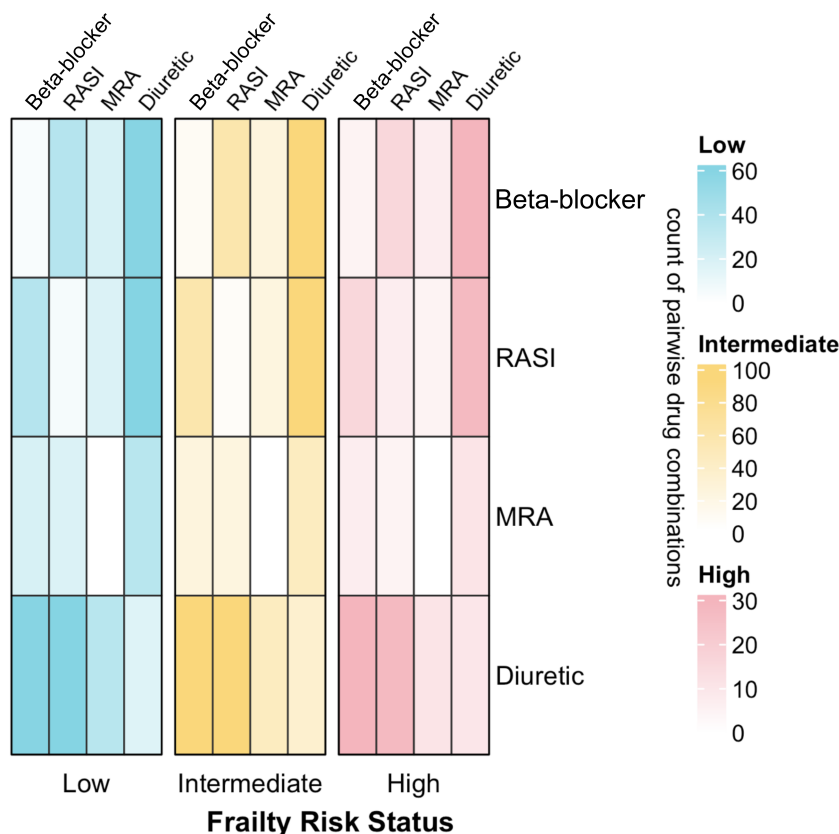


Figure 3 Heatmap displaying frequencies of dual heart failure pharmacotherapy combinations in hospitalised patients aged over 75 years, by frailty risk. Same drug class (diagonals) represents the frequencies of monotherapy and not duplicate therapy. Shaded areas represent the proportion of dual heart failure pharmacotherapy combinations per frailty risk group (low: $n = 134$, intermediate: $n = 230$, high: $n = 75$); MRA, mineralocorticoid receptor antagonist; RASI, renin-angiotensin system inhibitor.

utilisation of dual HF pharmacotherapy combinations is similar across frailty risk groups (Table S3).

Clinical outcomes and adverse drug events

Hospital LOS increased with increasing frailty among HF patients with low (7.8 (6.9) days), intermediate (14.7 (12.9) days) and high (20.3 (15.3) days) frailty risk, and up to 2.6-fold longer in high- compared to low-frailty-risk groups. ADEs were high, occurring in approximately half of patients with HF ($n = 227$, 51.7%). Compared to the proportion in patients with low frailty risk ($n = 40$, 29.9%), the prevalence of ADEs was 1.8-fold higher ($n = 124$, 53.9%) in intermediate- and 2.8-fold higher ($n = 63$, 84.0%) in high-frailty-risk patients (Figs 4, S2, Table S5).

Similar prevalence of falls ($n = 106$, 24.1%) and delirium ($n = 110$, 25.1%) were reported in patients with HF; of whom 25 (6.1%) patients experienced both falls and delirium, but mostly occurred in those with high frailty risk ($n = 17$, 68.0%). Compared to the proportion in patients with low frailty risk ($n = 15$, 11.2%), falls were 2.2-fold higher ($n = 57$, 24.8%) in intermediate and fourfold higher ($n = 34$, 45.3%) in high frailty risk. Compared to the proportion in patients with low frailty risk ($n = 10$, 7.5%), delirium was 3.7-fold higher ($n = 63$, 27.4%) in intermediate and 6.6-fold higher ($n = 37$, 49.3%) in high frailty risk. Renal impairment ($n = 305$, 69.5%) in patients with HF was similar across frailty risk groups, ranging between 66% and 74%, and was often prevalent in patients using ≥ 2 HF-pharmacotherapies (Fig. 4).

In frequent pairwise-combinations, the proportions of ADEs in people with high frailty risk increased by 3.2-fold for diuretic–beta-blocker ($n = 29/30$, 97%; $n = 18/60$, 30%), 2.3-fold for diuretic–RASi ($n = 24/28$, 86%; $n = 23/61$, 38%) and 2.5-fold for beta-blocker–RASi ($n = 14/16$, 88%; $n = 13/37$, 35%) combinations compared to low frailty risk (Fig. 3, Table S4).

Discussion

This study demonstrated that among hospitalised patients over 75 years with HF, most were at risk of frailty; diuretics were frequently continued, uptitrated or initiated during hospitalisation; beta-blockers were mostly continued at discharge; and few were prescribed MRAs. Older patients with HF at high risk of frailty frequently discontinued RASi compared to those with low frailty risk. Polypharmacy, hyperpolypharmacy and combination use of diuretic–beta-blocker and diuretic–RASi were frequent; ADEs were highly prevalent among those with high frailty risk. Prevalence of combination therapy

was lower in patients with high frailty risk, potentially due to reduced tolerance. HF patients with increasing frailty risk reported longer hospitalisation and increasing proportions of ADEs, falls and delirium. Renal impairment was common across all frailty subgroups. Barriers to evaluating evidence-based medication management during changes in hospital were identified.

This study provides new insights on the prevalence of ADEs, falls, delirium and renal impairment in a geriatric hospital population with HF and frailty risk. The adverse clinical outcomes reported in this study can significantly impact the quality of life in people of advanced age with frailty, who may no longer prioritise longevity and have more difficulty tolerating HF pharmacotherapy or recovering from ADEs. A systematic review of ADEs associated with HF pharmacotherapy in older people with HF and frailty reported a twofold increased risk of mortality and hospitalisation in frail compared to robust people on RASi,¹⁵ but overall there were no data for adverse geriatric outcomes. These findings support consideration of global function and patient preference during medication management of HF in people with advanced age and frailty who may prefer to optimise quality of life and avoid hospitalisation. In addition, these patients may benefit from uptake of strategies to reverse frailty risk.

The ADEs and adverse clinical outcomes reported in this study are important to consider within the context of potential benefits of HF pharmacotherapy. Findings showed increased numbers of pharmacotherapies increased the prevalence of ADEs, falls and delirium with increasing frailty risk. A recent study³² conducted in Taiwan ($n = 38\,843$) reported a similar frailty distribution and showed 27.3% of HF patients died of cardiovascular diseases. Compared to robust patients with HF, patients with severe frailty had increased risk of all-cause mortality (adjusted hazard ratio (aHR) 1.16, 95% confidence interval (CI) 1.11–1.21) and all-cause re-admissions (sub-distributional hazard ratio 1.21, 95% CI 1.16–1.25).³² Use of any triple HF pharmacotherapy or more combinations compared to monotherapy was shown to decrease risk of 2-year all-cause re-admissions (adjusted odds ratio (aOR) 0.49, 95% CI 0.44–0.54) across all frailty groups.³² In addition, older patients hospitalised with ADRs often have more comorbidities (mean 6.1) compared to those without ADRs (mean 5.2).¹¹ In the global REPORT-HF study ($n = 18\,553$), patients presenting with acute HF and a higher number (≥ 5) of comorbidities ($n = 4449$, 24%) were more likely to use potentially HF-worsening medications and were less likely to receive HF GDMTs (i.e. RASi, MRA) at discharge.³³ Thus, the benefit and risks of these medications should be personalised for each individual when supporting optimisation in people with HF, multimorbidity and high frailty risk.

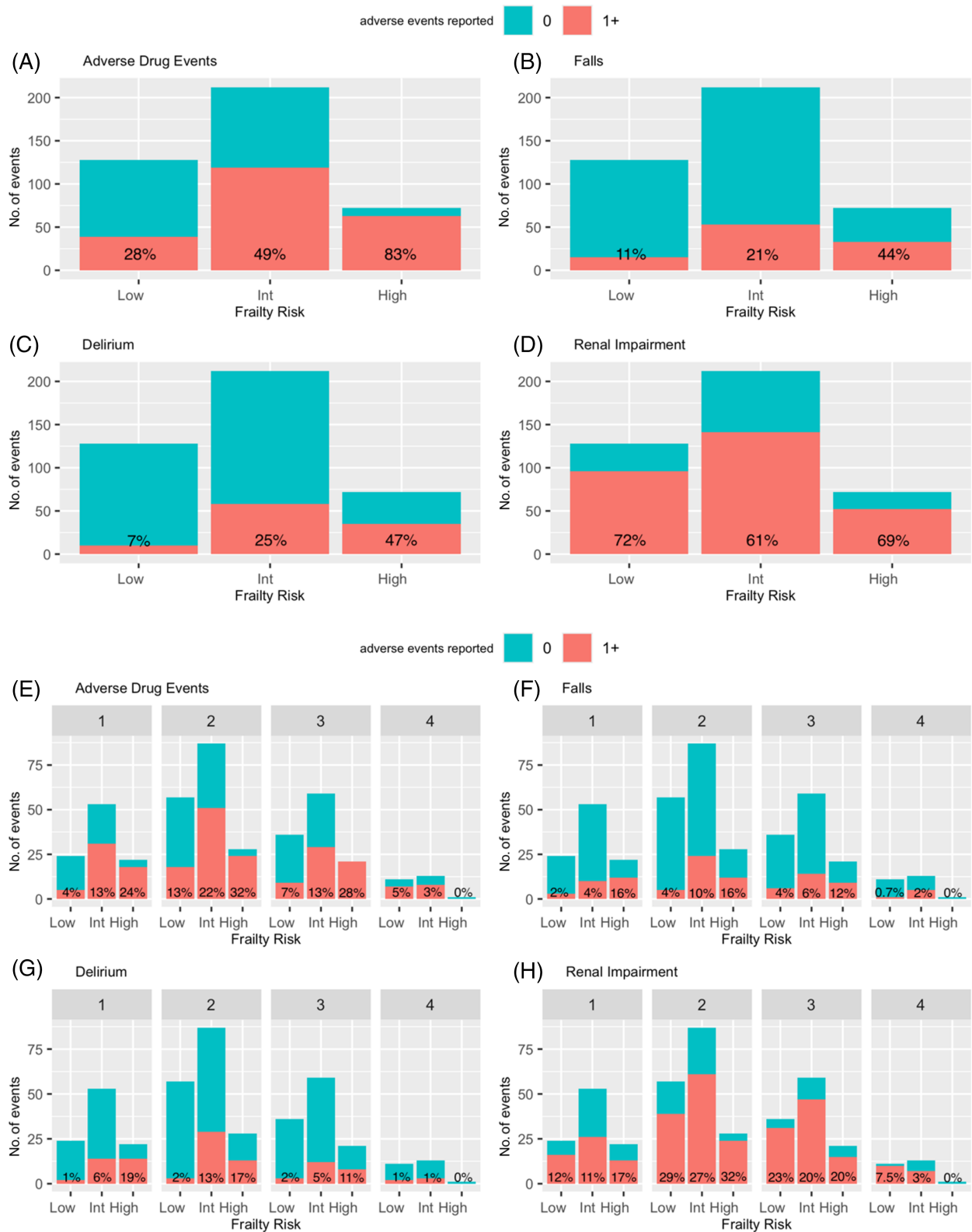


Figure 4 Frequency of adverse drug events and adverse clinical outcomes in hospitalised patients over 75 years on at least one heart failure pharmacotherapy (A–D); and on monotherapy or two, three or four combination heart failure pharmacotherapies (E–H), according to frailty status. Int, intermediate frailty risk. Annotated percentage represents the proportion of adverse events (red) per frailty risk group (low: $n = 134$; intermediate: $n = 230$; high: $n = 75$).

Barriers to evidence-based management of changes during hospitalisation included poor documentation of HF phenotype and rationale for deprescribing. Appropriate medication optimisation could not be evaluated in the absence of accurate HF diagnosis. The frequency of deprescribing (~40%) was similar among patients with acute and chronic stable HF but did not distinguish whether deprescribing was intended to be permanent or if medications were temporarily ceased to manage acute issues. Specific reasons for deprescribing were not captured in this dataset; however, potential reasons include management of hypotension, acute kidney injury, syncope, falls, drug interactions, infections and changes in cognition, for example. Among community aged care residents with dementia, deprescribing of anti-hypertensives (without HF diagnosis) was associated with 16% reduced odds of cognitive decline (OR 0.84, 95% CI 0.72–0.98) compared with continued use in usual care.³⁴ Future investigation is needed to explore safety and rationale for deprescribing HF pharmacotherapy or potentially high-risk medications^{39,35} in this population.

Strengths and limitations

This descriptive study provides novel data on adverse geriatric outcomes in older hospitalised adults with HF and frailty risk that can be applied to the optimisation and management of adverse events by multidisciplinary teams. In a cohort of older people, adverse outcomes were particularly high in patients with high frailty risk, supporting the need to consider not just age but global function in shared decision-making. The proportion of 22% with HF diagnosis in the TO HOME sample is comparable to other geriatric populations internationally.^{36–38} The methodology used in this study can be applied to future investigations of other diseases (e.g. atrial fibrillation) or diverse populations to report geriatric outcomes by frailty risk.

Data were not available to determine causal relationships between medication and adverse reactions, and there was no confirmation on whether adverse outcomes were caused by HF pharmacotherapy, non-specific or related to other potentially inappropriate medications treating comorbidities. The association or causality of underutilisation or optimised HF pharmacotherapy utilisation with adverse outcomes, mortality and re-admission was not investigated. The frequency of ADEs in pairwise combinations was counted per patient, and retrospective ICD-10-AM

diagnosis codes could contribute to both frailty risk and the associated outcomes, specifically for delirium and falls. Evaluation of SGLT2-i and emerging therapies (e.g. vericiguat, omecamtiv mecarbil) and subanalysis of potential confounders (e.g. age, sex, renal function, ethnicity) were not performed due to small sample size. Patients admitted under cardiology service were not included in the TO HOME study. Cardiovascular biomarkers and HF phenotypes were not included at the time of data collection. The small sample size in an urban Australian inpatient population with 25% from residential aged care settings limited the generalisability of the results. Future prospective cohort studies and clinical trials of HF pharmacotherapy utilisation and optimisation in older people should build on our findings by considering the inclusion of these variables and analyses in a larger more diverse population.

Conclusions

This study demonstrated that older adults with HF and frailty risk were frequently prescribed diuretics, diuretic-GDMT combinations and continued beta-blockers during hospitalisation. HF phenotype was not documented, and it is unknown whether it guided therapeutic choices. The reasons for the lack of documentation in this older population should be explored. A higher proportion of people with high frailty risk discontinued RASIs. Polypharmacy and renal impairment were prevalent across all frailty groups. Duration of hospitalisation and reported prevalence of ADEs, falls and delirium increased with increased frailty risk. These findings can be considered when managing cardiovascular outcomes in complex older patients with limited global function. Research reporting adverse outcomes of mortality, hospitalisation, cardiovascular biomarkers, geriatric outcomes and frailty is needed to inform shared decision-making and advanced care planning.

Acknowledgements

The authors acknowledge the collaboration of Associate Professor Patrick Kelly and Professor Rosalie Viney for contributions to the conceptualisation and management of the TO HOME database, statistical advice from Associate Professor Ana Capuano and Dr Kenji Fujita, and technical assistance from Mr Omar Arnaiz of the Sydney Informatics Hub, a Core Research Facility of the University of Sydney.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Data S1 Supporting Information.

Supplementary Online Materials

- Figure S4.1** The proportion of hospitalised patients aged over 75 years with heart failure pharmacotherapy status change, stratified by their risk of frailty.
- Table S4.1** The frequency of heart failure pharmacotherapy utilisation that was initiated, continued, up-titrated, down-titrated, discontinued, and re-initiated at discharge by inpatients over 75 years with heart failure according to frailty status.
- Table S4.2** Polypharmacy and combination heart failure pharmacotherapy use at discharge in older inpatients according to frailty risk.
- Table S4.3** Frequency of pairwise drug class combination use according to frailty status.
- Table S4.4** Frequency of adverse drug events (n) per pairwise drug class combination (N) according to frailty status.
- Figure S4.2** Frequency and proportion of heart failure-pharmacotherapy pairwise-combinations and adverse drug events in hospitalised patients aged over 75 years, by frailty risk status.
- Table S4.5** The frequency of adverse outcomes in adults ≥ 75 years with HF at risk of frailty on GDMT and diuretics

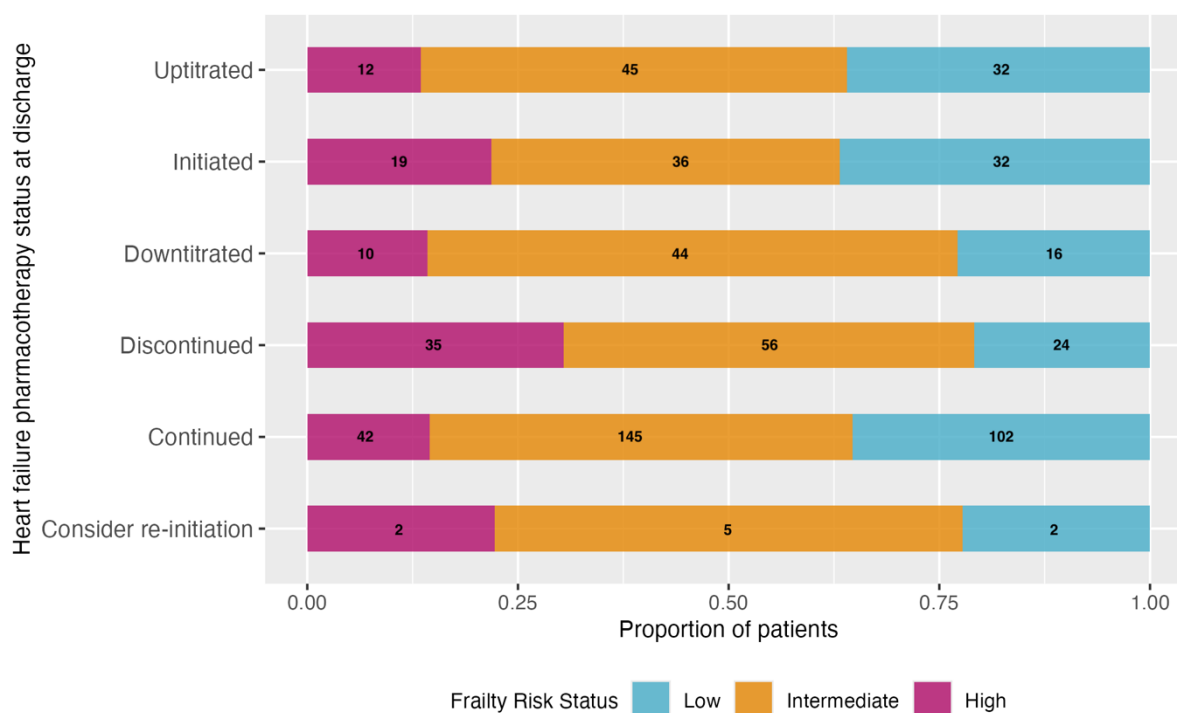


Figure S4.1. The proportion of hospitalised patients over 75 years with heart failure pharmacotherapy status change, stratified by their risk of frailty.

Footnote: annotated numbers represent the number of patients.

	Low Risk Frailty (HFRS<5)		Moderate Risk Frailty (HFRS 5-15)		High Risk Frailty (HFRS>15)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Initiated						
at least 1 GDMT or diuretic	34	8%	37	8%	19	4%
ACEI/ARB	9	2.1%	6	1.4%	3	0.7%
Beta blocker	3	0.7%	2	0.5%	3	0.7%
MRA	1	0.2%	1	0.2%	2	0.5%
Loop diuretic	26	5.9%	28	6.4%	14	3.2%
Continued						
at least 1 GDMT or diuretic	102	23%	145	33%	42	10%
ACEI/ARB	41	9.3%	53	12.1%	12	2.7%
Beta blocker	53	12.1%	81	18.5%	26	5.9%
MRA	23	5.2%	34	7.7%	5	1.1%
Loop diuretic	56	12.8%	71	16.2%	15	3.4%
Up-titrated						
at least 1 GDMT or diuretic	32	7.3%	45	10.3%	12	2.7%
ACEI/ARB	2	0.5%	4	0.9%	0	0.0%
Beta blocker	2	0.5%	5	1.1%	2	0.5%
MRA	7	1.6%	2	0.5%	0	0.0%
Loop diuretic	24	5.5%	40	9.1%	10	2.3%
Down-titrated						
at least 1 GDMT or diuretic	16	3.6%	44	10.0%	10	2.3%
ACEI/ARB	3	0.7%	7	1.6%	1	0.2%
Beta blocker	5	1.1%	14	3.2%	3	0.7%
MRA	2	0.5%	1	0.2%	1	0.2%
Loop diuretic	8	1.8%	28	6.4%	5	1.1%
Discontinued						
at least 1 GDMT or diuretic	24	5.5%	56	12.8%	35	8.0%
ACEI/ARB	17	3.9%	37	8.4%	21	4.8%
Beta blocker	5	1.1%	7	1.6%	3	0.7%
MRA	3	0.7%	10	2.3%	5	1.1%
Loop diuretic	2	0.5%	16	3.6%	12	2.7%
Re-initiated at discharge 0, 0% for all therapeutic classes						
Withheld on admission, GP review before restarting						
at least 1 GDMT or diuretic	2	0.5%	5	1%	2	0.5%
ACEI/ARB	1	0.5%	2	0.7%	0	0.2%
Beta blocker	0	0.0%	1	0.2%	1	0.2%
MRA	0	0.0%	2	0.7%	0	0.0%
Loop diuretic	1	0.2%	0	0.7%	1	0.2%

Table S4.1: The frequency of heart failure pharmacotherapy utilisation that was initiated, continued, up-titrated, down-titrated, discontinued, and re-initiated at discharge by inpatients over 75 years with heart failure according to frailty status.

Abbreviations: GP General Practitioner; GDMT Guideline-Directed Medical Therapy; ACEI angiotensin converting enzyme inhibitor; ARB angiotensin receptor antagonist; MRA Mineralocorticoid Antagonist
Footnote: Initiation includes status coded as "Other" and "New medication".

Total		Low Risk Frailty (HFRS <5)		Moderate Risk Frailty (HFRS 5-15)		High Risk Frailty (HFRS >15)		
<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Sample size	439	100	134	30.5%	230	52.4%	75	17.1%
Medication Class								
Loop diuretic	357	81.3%	115	85.8%	185	80.4%	57	76.0%
Guideline-Directed Medical Therapy (GDMT)*								
ACEI/ARB	218	49.7%	71	53.0%	110	47.8%	37	49.3%
Beta blocker	216	49.2%	68	50.7%	110	47.8%	38	50.7%
Mineralocorticoid Antagonist	100	22.8%	36	26.9%	51	22.2%	13	17.3%
Combinations use of GDMT								
0	88	20.0%	22	5.0%	53	12.1%	13	3.0%
1	196	44.6%	61	13.9%	97	22.1%	38	8.7%
2	127	28.9%	39	8.9%	66	15.0%	22	5.0%
3	28	6.4%	12	2.7%	14	3.2%	2	0.5%
Combinations use heart failure pharmacotherapy (GDMT or diuretic)								
0	27	6.6%	6	4.5%	18	7.8%	3	4.0%
1	99	24.0%	24	17.9%	53	23.0%	22	29.3%
2	170	41.3%	56	41.8%	86	37.4%	28	37.3%
3	118	28.6%	37	27.6%	60	26.1%	21	28.0%
4	25	6.1%	11	8.2%	13	5.7%	1	1.3%
Number of medications at admission								
No Polypharmacy (<5 medications)	28	6.4%	8	6.0%	14	6.1%	6	8.0%
Polypharmacy (≥5 medications)	411	93.6%	126	94.0%	216	93.9%	69	92.0%
Hyperpolypharmacy (≥10 medications)	219	49.9%	61	45.5%	116	50.4%	42	56.0%
Number of medications at discharge								
No Polypharmacy (<5 medications)	13	3.0%	1	0.7%	10	4.3%	2	2.7%
Polypharmacy (≥5 medications)	426	97.0%	133	99.3%	220	95.7%	73	97.3%
Hvperpolypharmacy (>10 medications)	281	64%	74	55.2%	154	67.0%	53	70.7%

Table S4.2: Polypharmacy and combination heart failure pharmacotherapy use at discharge in older inpatients according to frailty risk.

Abbreviation: HFRS Hospital Frailty Risk Score; ACEI angiotensin converting enzyme inhibitor; ARB angiotensin receptor antagonist;

Footnote: Diuretics predominantly refer to furosemide (n=355), etacrynic acid (n=1) and butanamide (n=1).

Low Frailty
(n=134)

	Beta blocker		RAS		MRA	
	(n)	(%)	(n)	(%)	(n)	(%)
Beta blocker	3	2.2%	37	27.6%	20	14.9%
RAS	37	27.6%	5	3.7%	18	13.4%
MRA	20	14.9%	18	13.4%	0	0.0%
Loop diuretic	60	44.8%	61	45.5%	35	26.1%

Intermediate Frailty
(n=230)

Beta blocker	9	3.9%	59	25.7%	25	10.9%
RAS	59	25.7%	7	3.0%	24	10.4%
MRA	25	10.9%	24	10.4%	2	0.9%
Loop diuretic	94	40.9%	94	40.9%	46	20.0%

High Frailty
(n=75)

Beta blocker	5	6.7%	16	21.3%	7	9.3%
RAS	16	21.3%	7	9.3%	5	6.7%
MRA	7	9.3%	5	6.7%	0	0.0%
Loop diuretic	30	40.0%	28	37.3%	11	14.7%

Table S4.3: Frequency of pairwise drug class combination use according to frailty status

Abbreviation: RAS Renin Angiotensin System Inhibitor; MRA Mineralocorticoid Receptor Antagonist

Footnote: Values are reported per drug-class (not per patient), which may be repeated for patients on three of four HF pharmacotherapies

	Beta blocker				RASi				MRA				Loop diuretic			
	(n)	(N)	(%)	(n)	(N)	(%)	(n)	(N)	(N)	(n)	(%)	(N)	(n)	(N)	(%)	(N)
Beta blocker	0	3	0%	13	37	35%	9	20	45%	18	60	30%				
RASi	13	37	35%	1	5	20%	9	18	50%	23	61	38%				
MRA	9	20	45%	9	18	50%	0	0	0%	15	35	43%				
Loop diuretic	18	60	30%	23	61	38%	15	35	43%	0	16	0%				
Low Frailty (n=134)																
Beta blocker	5	9	56%	29	59	49%	13	25	52%	51	94	54%				
RASi	29	59	52%	1	7	14%	14	24	58%	53	94	56%				
MRA	13	25	52%	14	24	58%	1	2	50%	26	46	57%				
Loop diuretic	51	94	54%	53	94	56%	26	46	57%	0	35	0%				
Intermediate Frailty (n=230)																
Beta blocker	5	5	100%	14	16	88%	6	7	86%	29	30	97%				
RASi	14	16	88%	0	7	0%	4	5	80%	24	28	86%				
MRA	6	7	86%	4	5	80%	0	0	0%	10	11	91%				
Loop diuretic	29	30	97%	24	28	86%	10	11	91%	0	10	0%				
High Frailty (n=75)																

Table S4.4: Frequency of adverse drug events (n) per pairwise drug class combination (N) according to frailty status

Abbreviations: RASi Renin Angiotensin System Inhibitor; MRA Mineralocorticoid Receptor Antagonist;
Footnote: Values are reported per drug-class (not per patient), which may be repeated for patients on three of four HF pharmacotherapies; n count of adverse drug events reported; N count of pairwise drug class combinations; % the proportion of adverse drug events per pairwise drug class combinations (n/N*100%)

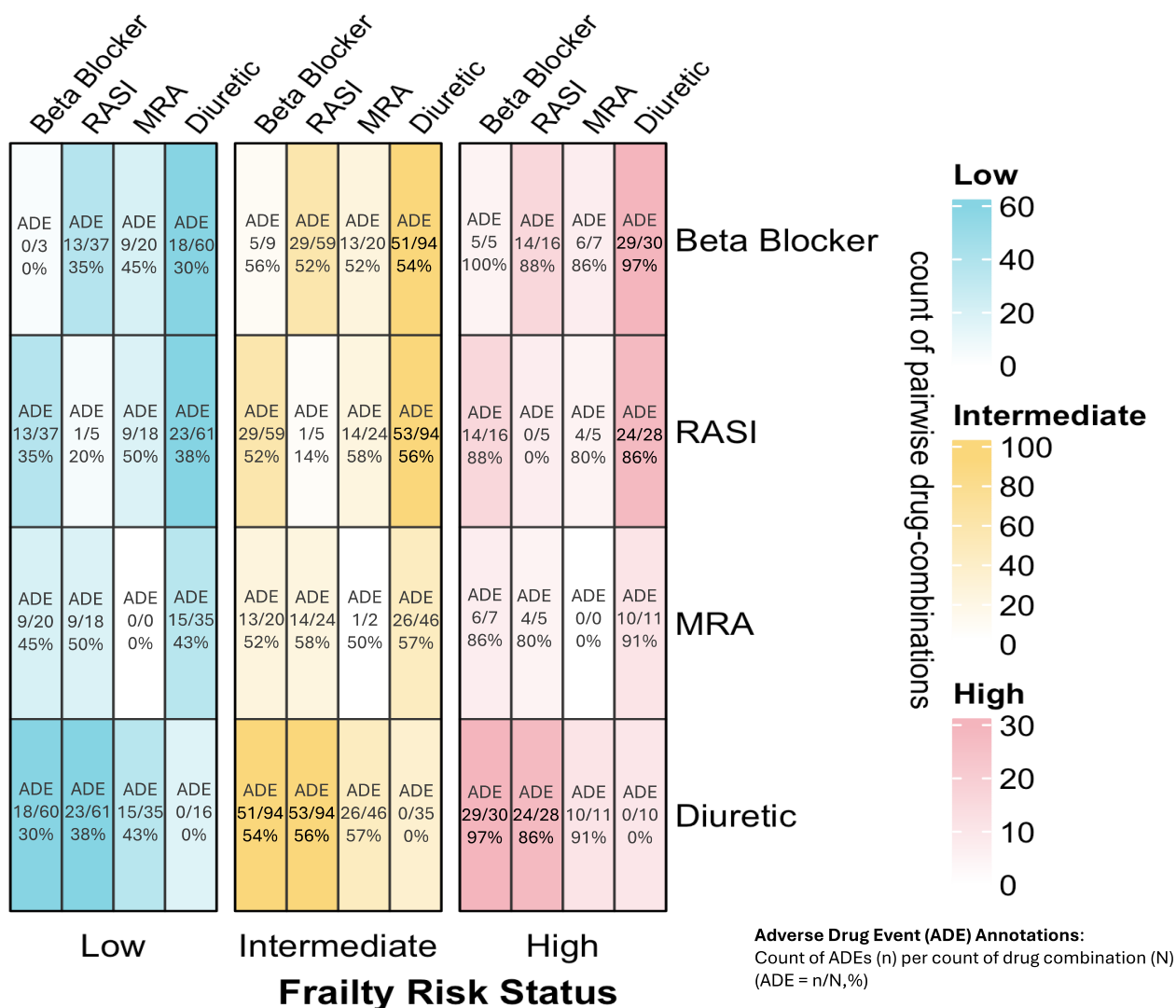


Figure S4.2. Frequency and proportion of adverse drug events in hospitalised patients aged over 75 years with heart failure-pharmacotherapy pairwise-combinations, by frailty risk status.

Footnote: Same drug class (Diagonals) represent the frequencies of monotherapy and not duplicate therapy. Shaded areas represent the proportion of dual heart failure-pharmacotherapy combinations per frailty risk group (Low: n=134, Int: n=230, High: n=75); Annotated percentage represents the proportion of adverse events per frailty risk group (Low: n=134, Int: n=230, High: n=75);

Abbreviations: HF Heart failure; ADE Adverse Drug Event; HF Heart Failure, RASI Renin Angiotensin System Inhibitors; MRA Mineralocorticoid Receptor Antagonists.

	Total HF population			≥1 GDMT or diuretic			HF-Drug Class			
	(n)	(%)	%HF Frailty group	(n)	(%)	%HF Frailty group	Beta blocker	RASI	MRA	Loop Diuretic
	439	22%					216	218	100	357
Low Frailty Risk (HFRS <5)	134	31%	100%	128	29%	96%				
Number of ADEs	40	9%	30%	39	9%	28%	68	71	36	115
Falls	15	3%	11%	15	3%	11%	8	11	2	14
Delirium	10	2%	7%	10	2%	7%	6	6	4	9
Renal Impairment (GFR<60mL/min/1.72m ²)	99	23%	74%	96	22%	72%	55	50	32	79
Moderate Frailty Risk (HFRS 5-15)	230	52%	100%	212	48%	92%				
Number of ADEs	124	28%	54%	119	26%	49%	110	110	51	185
Falls	57	13%	25%	48	11%	21%	28	30	16	46
Delirium	63	14%	27%	58	13%	25%	28	25	13	54
Renal Impairment* (GFR<60mL/min/1.72m ²)	151	34%	66%	141	32%	61%	79	75	35	128
High Frailty Risk (HFRS >15)	75	17%	100%	72	16%	96%				
Number of ADEs	63	14%	84%	63	14%	83%	38	37	13	57
Falls	34	8%	45%	33	8%	44%	17	16	4	26
Delirium	37	8%	49%	35	8%	47%	15	18	3	28
Renal Impairment (GFR<60mL/min/1.72m ²)	55	13%	73%	52	12%	69%	26	29	9	42

Table S4.5: The frequency of adverse outcomes in adults ≥75 years with HF at risk of frailty on GDMT and diuretics.

Abbreviation: HF Heart Failure, GDMT Guideline Directed Medical Therapy; HFRS Hospital Frailty Risk Score; ADE Adverse Drug Event; RASI Renin Angiotensin System Inhibitors; MRA Mineralocorticoid Receptor Antagonists; GFR Glomerular Filtration Rate. Footnote: Falls, delirium, renal impairment were measured according to ICD-10 and considered separate diagnosis from ADEs. *1 person in moderate frailty group was coded as 9999 = missing data coded as no renal impairment.

Characteristics (n, %)	Low Frailty Risk	Intermediate Frailty Risk	High Frailty Risk
Sample size (n)	134	230	75
Age (years), mean (SD)	86.6 (5.5)	87.3 (5.9)	87.8 (4.9)
75-79	14 (10.4%)	25 (10.9%)	5 (6.7%)
80-89	82 (61.2%)	118 (51.3%)	45 (60.0%)
>90	38 (28.3%)	87 (37.8%)	25 (33.3%)
Sex (female)	80 (59.7%)	129 (56.1%)	50 (66.7%)
Preferred language spoken at home			
English	83 (61.9%)	160 (69.6%)	52 (69.3%)
Language other than English	51 (38.1%)	70 (30.4%)	23 (30.7%)
Number of comorbidities (Charlson Comorbidity Index)			
Low: Score 0-2	105 (78.4%)	162 (70.4%)	38 (50.7%)
High: Score 3+	29 (21.6%)	68 (29.6%)	37 (49.3%)
Cognition			
Dementia*	19 (14.2%)	47 (20.4%)	24 (32.0%)
Mild cognitive impairment*	6 (4.5%)	25 (10.9%)	11 (14.7%)
Length of stay (days) mean (SD) **	7.8 (6.9)	14.7 (12.9)	20.3 (15.3)
History of a previous ADR prior to admission	61 (45.5%)	112 (48.7%)	34 (45.3%)
Living status prior to admission*			
Home	98 (73.1%)	157 (68.3%)	47 (62.7%)
Residential aged care facility	27 (20.1%)	54 (23.5%)	27 (36.0%)
Assisted living	9 (6.7%)	19 (8.3%)	1 (1.3%)
Discharge Destination			
Home	82 (61.2%)	111 (48.3%)	27 (36.0%)
Residential aged care facility	27 (20.1%)	64 (27.8%)	32 (42.7%)
Assisted living	8 (6.0%)	12 (5.2%)	0 (0.0%)
Other	25 (18.7%)	55 (23.9%)	16 (21.3%)
Palliative care	8 (6.0%)	12 (5.2%)	6 (8.0%)
Primary Reason for admission			
Cardiac and circulatory system	55 (41.0%)	59 (25.7%)	11 (14.7%)
Heart Failure	48(35.8%)	43 (18.7%)	6 (8.0%)
Respiratory	38 (28.4%)	42 (18.3%)	11 (14.7%)
Musculoskeletal or connective tissue	15 (11.2%)	31 (13.5%)	19 (25.3%)
Neurological	3 (2.2%)	23 (10.0%)	7 (9.3%)
Infection	1 (0.7%)	11 (4.8%)	9 (12.0%)
Dermatological	2 (1.5%)	13 (5.7%)	6 (8.0%)
Genitourinary system	1 (0.7%)	16(7.0%)	7 (9.3%)
Gastrointestinal	5 (3.7%)	13 (5.7%)	1 (1.3%)

Footnote: Comparison between frailty risk groups using Pearson Chi-Squared test and Mann-Whitney U test.

* p<0.05; ** p<0.001.

Supplementary Table S4.6: Sociodemographic characteristics of heart failure patients aged over 75 years according to the hospital frailty risk score.



8 September 2017

Professor Sarah Hilmer
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Level 12, Kolling Building
Royal North Shore Hospital
St Leonards NSW 20165

Dear Professor Hilmer,

NSW Population & Health Services Research Ethics Committee

AU RED Reference: HREC/17/CIPHS/30

Cancer Institute NSW Reference: 2017/HRE0801

Project Title: Towards Optimising Hospitalised Older adults' Medications

Thank you for your correspondence dated 1 September 2017 responding to a request for further information/clarification of the above referenced study, submitted to the NSW Population & Health Services Research Ethics Committee. The Committee has reviewed your response and has agreed that the aforementioned application meets the requirements of the *National Statement on Ethical Conduct in Human Research (2007)*. This approval is for a maximum of five years from the date of this letter, after which time a renewal application will be required if the protocol has not been completed.

The Committee granted a waiver of the usual requirement of consent for the use of re-identifiable information held by NSW agencies, in line with the State Privacy Commissioner's Guidelines for Research and the Health Records and Information Privacy Act 2002 (NSW) and the Guidelines approved under Section 95 of the Privacy Act 1988.

The documents reviewed and approved include:

- Letter of Response, dated 1 September 2017
- Cover Letter, dated 24 July 2017
- Cover Letter, dated 4 August 2017
- NSW National Ethics Application Form, v2.2, submission code AU/1/957F29, dated 21 July 2017
- Protocol version 2, dated 1 September 2017
- CHeReL Technical Feasibility Letter, dated 21 July 2017
- NSW APDC Data Variable Checklist
- NSW EDDC Data Variable Checklist
- APDC & EDDC Data Custodian Sign Off Form, dated 4 August 2017
- NSW RBDM Data Variable Checklist
- NSW COD URF Data Variable Checklist
- NSW RBDM & COD URF Data Custodian Sign Off Form, dated 2 August 2017
- PBS Data Variable Checklist
- MBS Data Variable Checklist

- TO HOME Data Custodian Sign Off Form, dated 1 September 2017
- NSW Privacy Form
- Professor Sarah Hilmer CV
- Confirmation of Peer Review & Funding Letter, dated 29 June 2017
- HSLHD Secure Storage Approval Brief

Approval is now valid for the following sites for unit record data:

- Royal North Shore Hospital, NSW
- Concord Repatriation General Hospital, NSW
- University of Technology Sydney, NSW
- University of Sydney, NSW
- University of Queensland, QLD

Approval is now valid for the following sites for recruitment and data collection:

- Royal North Shore Hospital, NSW
- Concord Repatriation General Hospital, NSW
- Ryde Hospital, NSW
- Hornsby Ku-Ring-Gai Hospital, NSW
- Canterbury Hospital, NSW
- Balmain Hospital, NSW

The NSW Population & Health Services Research Ethics Committee has been accredited by the NSW Ministry of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Ministry of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* and relevant legislation and guidelines.

Please note that ethical approval is valid for **5 years**, conditional on the following:

- Principal investigators will immediately report anything which might warrant a review of ethical approval of the research, including unforeseen events that might affect continued ethical acceptability.
- Proposed amendments to the research proposal or conduct of the research which may affect the ethical acceptability of the research are to be provided to the NSW Population & Health Services Research Ethics Committee for review.
- The NSW Population & Health Services Research Ethics Committee will be notified giving reasons, if the research is discontinued before the expected date of completion.
- The Principal Investigator will provide a progress report to the NSW Population & Health Services Research Ethics Committee annually and at the completion of the study.

Your first progress report will be due on **08/09/2018** and the duration of approval is until **08/09/2022**, after which time a new submission to the Ethics Committee will be required.

You are reminded that this letter constitutes '*ethical approval*' only. This research project must not commence at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. It is your responsibility to forward a copy of this letter together with any approved documents as enumerated above, to all site investigators for submission to the site's Research Governance Officer. Where relevant, copies will also need to be provided to the CHeReL and the data custodian.

For further information about the NSW Population & Health Services Research Ethics Committee, please refer to our website <https://www.cancerinstitute.org.au/Data-research/Research-ethics-committee>.

Should you have any queries about the ethical review of your research proposal, please contact ethics at ethics@cancerinstitute.org.au.

Yours sincerely,

Professor David Roder
Chairperson
NSW Population & Health Services Research Ethics Committee

APPENDIX D: CHAPTER 5 SUPPLEMENTARY MATERIALS

S5.1: Consumer and healthcare professional interview guides

Research Study: The classification of adverse drug reactions and adverse drug events during the optimization of heart failure medications in frail older people: a mixed-methods study

Semi-structured questions – Participant handout (consumer)

1. Please describe your experiences with frail older people with heart failure.

A: Definition of adverse drug effects

2. How do older people and/or their carers identify adverse drug effects, in general?
3. How do older people and/or their carers identify adverse drug effects from medications used to treat heart failure?
4. Which of the following types of adverse drug effects are common in frail older people taking medications for heart failure? Please describe and provide examples.
 - i. dose-related (increasing/decreasing medication)
 - ii. non-dose-related
 - iii. dose-related and time-related (short/long term)
 - iv. time-related (immediate/delayed)
 - v. withdrawal (end of use)
 - vi. failure of therapy
5. What are the most common adverse drug effects from heart failure medications? Which medications/drug classes are involved?
6. Which of these are the most important to patients and why?

B: Impact of adverse drug effects

7. How do older people and/or carers assess the severity of adverse drug effects and how is this measured?
8. What reasons would lead older people and/or carers to consider an adverse drug effect as mild, moderate or severe?
9. What are the most important outcomes patients and/or carers are concerned with following adverse effects from heart failure medications in frail older people?
10. How do older people and/or carers treat symptoms of adverse drug effects if:
 - i. patient doesn't feel any different
 - ii. stay the same (don't change over a few months, years)

iii. worsen over time

11. What kind of challenges are frail older people with heart failure faced with when experiencing adverse drug effects?

C: Causes of adverse drug effects

12. How do patients and/or carers distinguish whether adverse effects could be caused by the condition of heart failure or from a medication?
13. Are symptoms a result of taking many medications? Or a high dose of one medication?
14. Do older people usually know why they're taking the drug(s) related to the adverse effect?

D: Management

15. How do frail older people and/or carers feel about taking many medications to treat heart failure?
16. How do frail older people and/or carers assess the ongoing benefit of HF medications?
17. How do patients and/or carers weigh the harm of adverse effects with the benefits of the medication?
18. In what situations would patients and/or carers approach their healthcare provider to discuss changes to their heart failure medications?
19. Where are adverse drug effects managed (e.g. home, health care setting) and by whom?
20. What are the key considerations around reducing the dose or stopping a medication used to treat heart failure?

Research Study: The classification of adverse drug reactions and adverse drug events during the optimization of heart failure medications in frail older people: a mixed-methods study

Semi-structured questions - Participant handout (clinicians)

1. How do you manage frail older people with heart failure (HF) in your practice?

A: Definition of adverse drug effects

2. How do you identify adverse drug reactions (ADRs) and adverse drug events (ADEs), in general?
3. How do you identify ADRs and ADEs from heart failure medications, including guideline directed medication therapy (GDMT)?
4. How can ADRs and ADEs be measured?
5. Which of the following types of ADRs are commonly reported in frail older people during optimization of heart failure medications? Please describe and provide examples.
 - i. dose-related (up/down-titration)
 - ii. non-dose-related
 - iii. dose-related and time-related (acute/chronic)
 - iv. time-related (immediate/delayed)
 - v. withdrawal (end of use)
 - vi. failure of therapy
6. In your practice, what are the most commonly reported ADRs and ADEs from heart failure medications?
7. Which of these do you see as most important and why?
8. How do patients and caregivers report ADRs and ADEs from heart failure medications?

B: Impact (severity) of adverse drug effects

9. How do you assess/measure the severity of ADRs and ADEs?
10. How would you manage the ADR and ADE if classified as mild, moderate or severe?
11. How do you treat symptoms of ADR and ADEs that are:
 - i. non-existent
 - ii. stable
 - iii. progressive
12. What are the factors (barriers and facilitators) that contribute to the complexities associated with ADRs and ADEs in HF patients?
13. What are the most important clinical outcomes in patients following ADR and ADE from heart failure medications? (e.g. mortality, hospitalization, HF symptoms, QoL, ADLs)

C: Cause of adverse drug effects

14. How do you distinguish whether adverse effects could be caused by progressive heart failure, underlying conditions or medication related?
15. Are symptoms a result of cascade prescribing?
16. Are symptoms due to significant toxicity?
17. Do the drugs related to the ADR have a clear indication? Are there any circumstances that this indication does not apply?
18. What are contraindications that you consider when managing patients on heart failure medications?

D: Management

19. How do you assess the ongoing benefit of heart failure medications?
20. How do you assess the harm of adverse effects with the benefits of the medication?
21. When managing medications, do you consider:
 - a. preventative drugs in any/some/all circumstances?
 - b. If the potential benefit may be realized because of limited life expectancy?
22. Where are ADRs and ADEs managed (e.g. home, health care setting) and by whom?
23. What are the key considerations around down-titrating a GDMT?
 - a. How can we determine if down-titration of a HF medication is appropriate?
 - b. What are the situations where down-titration could be appropriate to consider?
 - c. What would facilitate down-titration or discontinuation of a HF medication?
 - d. What are the barriers and potential risks associated with down-titration?
 - e. What are the situations where down-titration should NOT be considered?

Table S5.1: Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No	Item	Guide questions/description	Reported on page #
Domain 1: Research team and reflexivity			
Personal Characteristics			
1	Interviewer/facilitator	Which author/s conducted the interview or focus group?	6
2	Credentials	What were the researcher's credentials? E.g. PhD, MD	title page, 6
3	Occupation	What was their occupation at the time of the study?	6, 18
4	Gender	Was the researcher male or female?	title page
5	Experience and training	What experience or training did the researcher have?	6
Relationship with participants			
6	Relationship established	Was a relationship established prior to study commencement?	5
7	Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	5, 18
8	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	5, 17
Domain 2: study design			
Theoretical framework			
9	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	6
Participant selection			
10	Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	5
11	Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	5
12	Sample size	How many participants were in the study?	7
13	Non-participation	How many people refused to participate or dropped out? Reasons?	7
Setting			
14	Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	5

15	Presence of non-participants	Was anyone else present besides the participants and researchers?	7
16	Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	7, 25 (Table 1)
Data collection			
17	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Supplementary 1
18	Repeat interviews	Were repeat interviews carried out? If yes, how many?	NA
19	Audio/visual recording	Did the research use audio or visual recording to collect the data?	6
20	Field notes	Were field notes made during and/or after the interview or focus group?	NA
21	Duration	What was the duration of the interviews or focus group?	7, 25 (Table 1)
22	Data saturation	Was data saturation discussed?	5
23	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	6
Domain 3: analysis and findings			
Data analysis			
24	Number of data coders	How many data coders coded the data?	6
25	Description of the coding tree	Did authors provide a description of the coding tree?	26 (Table 2)
26	Derivation of themes	Were themes identified in advance or derived from the data?	6
27	Software	What software, if applicable, was used to manage the data?	6
28	Participant checking	Did participants provide feedback on the findings?	NA
Reporting			
29	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number	6-13
30	Data and findings consistent	Was there consistency between the data presented and the findings?	7-17, 28 (Figure 1)
31	Clarity of major themes	Were major themes clearly presented in the findings?	7, 27-26, (Table 2)
32	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	7-14, 26 (Table 2)

Table S5.2: Goals and clinical outcomes described by participants

Consumer	Cardiologist	Doctor (geriatrician, pharmacologist)	Nurse	Pharmacist
Quality of life (QoL) Do normal activities (ADLs), e.g., going to the shops Joy hobbies social connections Self-efficacy Wellness Dignity confidence autonomy sense of purpose or contribution to society, physically fitter, being informed about decisions	Maintain or improve Quality of life ADLs go out and do normal things Improve/maintain function, mobility maintain physical exercise, rehab, muscle strength improve frailty enjoy living life participate in their hobbies social interactions maintain mood (anxiety, depression) maintain memory good diet improve patient confidence live in a state acceptable to that person and family	Maintain QoL ADLs able to do their normal daily routine frailty status prevent falls changing baseline function maintain social connections and interactions cognitive impairment support patient independence and self-management	Quality of Life ADLs, Function support mental health (anxiety, depression) support changes in cognitive function maintain physical function, mobility, strength weight, diet and fluid management independently and comfortably perform normal daily routines (personal tasks, chores) maintain social interactions/activities maintain or improve sleep Support patient autonomy support self-management at home coordinate access to health services	Improve / maximise QoL recover or maintain ADLs Social connections and engagement emotional well being maximise function (dexterity, disability, mobility) balance prolonging life with living a good life support patient autonomy and preference patient live independently in the community
Healthy weight/appetite Take less pills manage side effects	manage comorbidities prevent other complications (e.g., falls) optimize evidence based medications minimize side effects	medication management optimise medications for symptom management manage adverse drug events patient compliance/adherence reduce medication burden deprescribe if appropriate Individualize and adjust treatment	Manage comorbidities prevent/minimize other complications (falls) Support patient compliance/adherence medication optimization support management of adverse effects of disease/drugs manage medication burden/polypharmacy	accommodate change in cognition manage weight/appetite medication management optimisation of evidence based medications prevent/manage adverse drug effects patient compliance/adherence manage drug interactions

Consumer	Cardiologist	Doctor (geriatrician, pharmacologist)	Nurse	Pharmacist
Treat symptoms breathless when walking feet swell feet oedema and walking Pain free, eat what you want Do chores with no extra effort Prolong life, essential life saving Prevent CV event (AF, stroke) Avoid hospitalization Dignified end of life	Symptom management/benefit prevent decompensation slow cognitive decline Slow disease progression (improve prognosis) longevity/prevent premature mortality (depends on patients) reduce hospitalization reduce morbidity reverse remodeling, improve ejection fraction Reduce risk of CV event (MI) outcomes of single organ systems	Symptomatic management consider global outcomes not just disease progression Reduce mortality adapt treatment to life expectancy prevent re-hospitalization support palliative/end of life care manage comorbidities support mental health (mood, depression, anxiety) maintain physical function measure and manage frailty	Symptomatic management adjustments to changing functional status reduce morbidity Increase length of life, keep people alive longer slow disease progression prevent re-hospitalization Support advanced care planning needs (end of life care)	Symptom management (feel better) stabilize patient prevent future complications slow disease progression (improve prognosis) reduce mortality reduce hospitalization/re-hospitalization improve ejection fraction manage comorbidities improve morbidity
Abbreviations: QoL Quality of Life; ADL Activities of Daily Living; CV cardiovascular; AF atrial fibrillation; MI myocardial infarction				

Table S5.3: Summary of participant reported adverse drug events (ADEs) by drug class

Drug Class	Consumer	Cardiologist	Physician (geriatrician, clinical pharmacologist)	Pharmacist	Nurse
RASI: ACEI/ARB/ARNI	-	decrease renal function angioedema	renal impairment acute kidney injury (AKI) hypotensive (ARNI)	renal impairment, reduced renal function acute kidney injury postural hypotension (high in ARNI) cough (ACEI) electrolyte imbalance diarrhea (ARB)	renal function goes off, impaired renal function (>30% drop in eGFR, flag if 20%) fry the kidneys low blood pressure dizziness cough (ACEI) increased frequency of urination (no UTI) fatigue, lethargic, tiredness, loss of mobility brain fog (ARB)
Beta blocker	-	fatigue feel washed- out nightmares	impotence depression swelling of the ankles (titration too fast)	erectile dysfunction/impotence mood (depression) confusion (fuzziness in the head) vivid dreams/ nightmares tired/fatigue/slow down dizziness hypotension slower heart rate worsen breathing, shortness of breathless (rare) worsen circulatory disorders	sexual dysfunction brain fog, not clear minded, don't feel like themselves vivid dreams falls fatigue constipation bradycardia tachycardia (underdosing)
Drug Class	Consumer	Cardiologist	Physician (geriatrician, clinical pharmacologist)	Pharmacist	Nurse

MRA (spironolactone)	male breasts	gynecomastia sore nipples	gynecomastia hyperkalemia (can cause sudden death)	gynecomastia hyperkalemia nausea dehydration	man boobs (gynecomastia) electrolytes potassium goes up, hyperkalemia cardiac arrest
SGLT2-inhibitors	-	UTI urosepsis euglycemic ketoacidosis, increase ketones	UTI and urinary symptoms diabetic ketoacidosis	UTIs urogenital infections	UTI vaginal or perineal issues ketosis
Diuretics (furosemide)	need to go to the toilet, incontinence risk of dehydration Electrolytes potassium sodium dizzy confusion trouble with memory	urinate frequently confusion and trouble with memory	frequency and urge incontinence sleep disturbance (getting up to go to the toilet) dehydration (very dry) dry mouth dysuria thirst electrolyte abnormalities low potassium low sodium hypotensive dizzy feeling weak	incontinence (urge/frequency) diuresis dehydration hypotension falls electrolyte imbalance hypokalemia, low sodium low magnesium, low calcium,	running to the toilet, makes them pee/wee a ton, frequency/urgency of urination incontinence, wetting their pants, weeing all through the night, get up at night dehydration dry out, dry as a crisp constipation dry mouth, licking the top of their mouth dry, scaly skin really tight legs low blood pressure dizziness, light-headedness foggy feeling
Digitalis Glycoside (digoxin)	-	digoxin toxicity	-	flickering in peripheral vision	-
Drug Class	Consumer	Cardiologist	Physician (geriatrician, clinical pharmacologist)	Pharmacist	Nurse

Calcium Channel Blockers	angioedema	angioedema peripheral oedema	-	ankle oedema vivid dreams dizziness hypotension	-
Other	-	-	-	-	-
Vasodilators	-	-	-	-	-
Hydralazine	-	-	autoimmune function	-	-
Ivabradine	-	-	-	-	sinus rhythm (bradycardia, sinus arrest)
Inotrope (dobutamine)	-	-	-	-	hypotension dizziness
Abbreviations: RASI Renin-Angiotensin System Inhibitor; ACEI Angiotensin-Converting Enzyme Inhibitor; ARB Angiotensin Receptor antagonist/Blocker; ARNI Angiotensin Receptor-Neprilysin Inhibitor; SGLT2-i Sodium-Glucose coTransporter-2 Inhibitors; AKI Acute Kidney Injury; eGFR estimated Glomerular Filtration Rate; UTI Urinary Tract Infection.					

Table S5.4: Summary of participant reported adverse drug withdrawal effects (ADWEs)

Consumer	Cardiologist	Doctor (geriatricians, pharmacologist)	Pharmacist	Nurse
Nonspecific end your life	Nonspecific lose mortality benefit CV events Angina hospitalization Trigger HF episode/exacerbations HF Decompensation	Nonspecific death sudden cardiac death (e.g., stroke risk. MI) Palliation/end of life HF symptoms return breathlessness, JVP, edema HF exacerbation / decompensation Rise in heart rate and blood pressure	Nonspecific HF symptoms return Rise in heart rate and blood pressure HF exacerbation decompensation	Nonspecific Loss of medication benefits (e.g., cardiac remodeling, hospitalization) Heart failure symptoms/exacerbation pulmonary oedema overload, decompensation heart rate, palpitations breathless, fatigue Rise in heart rate and blood pressure ADE not resolved
Beta blocker stroke	RASI: ACEI/ARB/ARNI lose long-term renal protective benefits	-	-	-
Diuretics edema gets worse	-	-	furosemide and thiazides CV event decompensation hospitalization	-
Abbreviations: HF heart failure; CV cardiovascular; ADE adverse drug event; RASI Renin-Angiotensin System Inhibitor; ACEI Angiotensin-Converting Enzyme Inhibitor; ARB Angiotensin Receptor Antagonist/Blocker; ARNI Angiotensin Receptor-Neprilysin Inhibitor; JVP Jugular Venous Pressure.				

Table S5.5: Framework of emerging themes and categories

Theme 1: Individual Factors	Theme 2: Medication	Theme 3: Access to Healthcare
A. Complex patient factors i. Comorbidities ii. Changes in function iii. Patient cognition iv. HF phenotype v. Frailty looks at the whole patient a) impact of changes in a frail person b) change in mood, depression, bereavement c) frailty helps determine "ceiling" of care (patient threshold) d) Equity to access care and benefits of treatment vi. Definition of frailty is complex a) frailty is a measure of function and mobility vii. Health professional understanding of frailty a) resistance to identifying frailty b) objective frailty not measured in routine care so not used c) rank/spectrum or measure severity of frailty (how frail) B. Supporting patients' autonomy i. Dignity a) reliance on others, loss of autonomy b) adjust to societal and social expectations of older people c) patient confidence d) importance of social connections ii. Patient engagement and choice iii. Patient support or advocate iv. Goals of care and patient expectations a) Quality of life (QoL) b) activities of daily living (ADLs) v. Tailored to each person vi. Patient is stable vii. Decisions at end of life	A. Medication management i. Evidence based medicine (guidelines) a) Prioritisation of clinical outcomes vs patient under use of guideline directed medical therapy (GDMT) (ACEI/ARB, BB, MRA, SGLT2-I ii. tolerability (benefits vs risks) a) focus on symptomatic relief of HF iii. Polypharmacy is a separate issue from prioritising clinical outcomes iv. dynamic, when ADE resolved/stable (e.g. BP, renal fxn), rechallenge and up-titrate GDMT again a) aim to stabilise the patient. Change is challenging to manage b) patient prognosis and goals of therapy v. adjustments and limitations of GDMT in frailty a) lower doses/slow up-titration/wider intervals if tolerated/flexible dosing b) single agent vs combination/multiple agents c) One change at a time vi. Gap in the evidence for GDMT a) Lack of tools to rank or score level of risk to optimise pharmacotherapy (e.g. modified Rankin score in thrombolysis) b) identify which frailty phenotype benefit from GDMT in which HF phenotypes c) Research to personalise appropriateness of GDMT according to patient outcomes and "acceptable" quality of life in frail older people d) lack of evidence to treat HFpEF e) absence of frailty measure in clinical trial data is challenging to draw conclusions (gap in evidence) vii. drug interactions viii. time frames or monitoring intervals ix. patient adherence/non-compliance a) medication compliance tools (pros/cons) b) Medication reviews c) patient given enough time to adjust to tolerable changes x. patient attitudes and beliefs about medicines, health, HCPs a) patient anxiety around medications b) polypharmacy, high number of medicines a concern	A. Multidisciplinary approach i. Multiple health care settings a) communication between HCPs b) Sharing of information and decisions across specialties c) leadership/responsibility of overall patients care d) Differing priorities between specialties e) accountability ii. Monitoring and follow up a) Ongoing or continuity of care iii. Need coordinated multidisciplinary expertise to navigate complex frail older people a) Focus on one organ vs whole patient even though considering overall patient status b) Provide advice how to adjust dosing for specific ADEs between settings and health providers B. Patient access to care i. Challenges to accessing care a) Health services and/or medication related costs b) Available support to manage HF and frailty ii. Co-ordination of care a) Physical access or cognitive coordination

	B. Identification and management of ADEs i. Prevention of ADEs during selection and initiation of medication ii. Identify, report, investigate symptoms a) sources of information used to identify ADE b) ADEs a concern raised by patient vs probed by HCP c) symptoms not experienced prior to initiating medication d) Uncertain if symptoms caused by comorbidities or medications e) Validation if stop and see symptoms improve, then restart and observe if ADE returns (rechallenge confirms or maybe something else) iii. Severity of ADEs a) perceived impact of ADE (e.g., impact on function) b) signs ADEs no longer tolerable c) have sick day plans for moderate to serious ADEs iv. Lack of ADE patient knowledge a) unaware which medication is causing ADE v. weigh benefits vs risks a) ADE vs decompensation/worsening HF b) accept chronic ADEs c) patients manage to live with (anticipated) ADEs and make adjustments d) Cascade prescribing e) preference to switch to alternative medication	
	C. Adverse drug withdrawal effects (ADWEs) considerations i. lack of evidence on deprescribing a) hesitancy to deprescribe HF medications b) can cause harm and worsen QoL ii. weigh risks vs benefits of deprescribing a) obvious harm of ADE warrants being stopped b) consider patient stability following deprescribing c) deprescribing a sign of worsening prognosis (treatment stops working) d) deprescribe if improve healthy lifestyle, habits, exercise, diet (reduce need/benefit if not symptoms or reduced risk) iii. Preference/attitudes to deprescribing a) deprescribing dynamic not always permanent b) preference to deprescribe non-HF medications iv. Identification and monitoring of ADWEs a) frequency of ADWEs b) safe, no change in patient after discontinuation	

	D. Patient Education and Information i. balance medication recommendations with QoL a) Communicating about frailty and impact on treatments ii. Navigating evidence of HF medications iii. Communication to patients about medications and ADEs a) limited time for effective communication b) challenges to patient -HCP communication c) Shared decision making	
Abbreviations: HF = heart failure; QoL = quality of life; ADL = activities of daily living; GDMT = guideline directed medical therapy; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2-I = sodium-glucose cotransporter-2 inhibitor; BP = blood pressure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HCP = healthcare professionals; ADE = adverse drug event; ADWE = adverse drug withdrawal effect.		

Table S5.6: Summary and quotes of main themes and subthemes

Theme 1: Individual factors	
1a. Complex patient factors	
Multiple complex issues to consider	<i>“Initially manage the frail older person, rather than isolated heart failure. The first for older frail people is to have the ceiling of care in place. In these frail people, probably the bar needs to set unfortunately a little bit lower compared to the normal healthy younger adults. If it's pre-frail, maybe there's some room for movement, and that medication might help them to become less frail.” Cardiologist 27</i>
Defining frailty status	<i>“Frailty tends to indicate physical function. Under the banner of frailty, you've got dementia, cognitive impairment, and that that's a huge issue when you are prescribing medications. Often their blood pressure and their creatinine and electrolytes don't allow you to treat them with optimal medications. It's a fine line between keeping them upright and having their heart failure treated adequately. We're often treading that line in our patients.” Geriatrician 19</i>
1b. Supporting patients' autonomy	
Patient independence	<i>“I struggle a bit. It's navigating that without actually worrying or hating all of it. All they want to know [is if] you're getting better. Sometimes you're not feeling all good, don't feel much better. It's a tricky path we tread as we get older and with the frail.” Consumer 55</i>
Maintaining social engagements	<i>“From mom and some people in aged care, having friendship, having warmth and comfort and socialization is very important. Is very important because they've left their home. They've lost all their independence. They've often lost their partner, and I think it can be very lonely. I think you can't underestimate that. Your emotional wellbeing”. Consumer 54</i>
Support of carers and advocates	<i>“A lot of people don't like the feel of any vague kind of dizziness in an older person. The fear of falling is big, knowing they can really hurt themselves if they fall. And if they feel a fall, their fall can then trigger lack of confidence, and this cycle of being anxious. I can understand why people don't want to be dizzy and don't want to fall.” Cardiologist 25</i>
Flexible and tailored for limited function and frailty.	<i>“Goals that we talk about, we have made ourselves as healthcare providers. But with frailty, a lot of these patients have lived a very long life. The goals for them are fundamentally different to what we have traditionally thought of as important endpoints in care.” Cardiologist 28</i>
Theme 2: Medications	
2a. Medication management	
Consumers prioritise maintaining their QoL	<i>“The aim of most medications is to make it to old age, not to prolong old age. A lot of my older patients who are frail, say that when their time comes, time comes; they want to feel good until then. But a lot of people say they want to live long as they can. So it's a half-half.” Cardiologist 25</i> <i>“The fact that they can't get off the chair, or they're exhausted, or they feel they're gonna fall over every time they stand up. That would be the thing in my experience that patients would want managed.” Nurse 11</i>

Health professionals prioritise clinical outcomes	<i>“There’s a belief that you should practice evidence-based medicine. You should be on these medications and at the dose that’s proved to be effective. So their starting point is we need to get people to those doses. That’s their paradigm and there’s a logic to that.” Geriatrician 23</i> <i>“The GDMT, although it’s great in theory in people who are otherwise robust and have really good cardiogenic reserve, I think in elderly patients is really challenging because a lot of the guideline directive of medical therapy has side effects that are overlapping with the syndrome that they have come to hospital with.” Cardiologist 28</i>
Optimising GDMT entails dynamic and frequent changes	<i>“I find it really hard sometimes with the hospital [admissions]. We’ll spend all this time in community titrating things and then they just like stop it because they’re a bit hypotensive and things like that, and you’re like, ‘No!’.” Nurse 26</i>
Targets in frail older people different than those from clinical trials and require adjustments.	<i>“We individualised that and went very slowly with him. We did half a tablet of Entresto every couple of weeks. And finally got him up to maximum dose. Even though that’s not guideline, at least he’s got there and he’s feeling better and he’s been safe in that process.” Nurse 11</i> <i>“Sometimes the reduction in frailty through the physical rehabilitation will allow the later up-titration of the medical side of things and you allow them that time for things to come together. You really see that early post-heart failure hospitalization for example.” Cardiologist 12</i>
Under-use of GDMT in frail older people	<i>“The overarching treatment goal for these people is probably the symptom management rather than aiming for the full, reverse remodelling of their heart failure. Rather than choosing [all] therapy of heart failure, you might just pick a couple. That also can help with symptom management. The most recent guideline directed medical therapy, SGLT2-i and Entresto, they actually help decongesting the heart failure. They have the natriuresis side effects [which] also help with symptomatic management. In fact, Entresto actually can give people more energy and help decongestion.” Cardiologist 27</i>
Evidence for optimisation of in very old frail people	<i>“Our aim should be sort of more for the symptom management rather than the aim for prolongation of life. Unless of course they have a very good baseline function and things like that, then we should definitely give them that option. But otherwise it should be less, sort of be more conservative and more patient centre-focused approach.” Cardiologist 27</i>
Absence of frailty measures in clinical trial data	<i>“If there is evidence that the guideline directed medical therapy we’re offering patients who are already very frail, compromises their quality of life, then that’s something we need to address. Because there’s no point living longer in a state of being that is not acceptable to that person or their family.” Cardiologist 28</i>
Anxiety of using multiple medications	<i>“I’m careful how when I take my medications. They do cause digestive problems and anxiety.” Consumer 55</i> <i>“Once a patient’s got an adverse event to a medication, which may be due to an excessive dose, it’s really hard to regain their confidence in it [the medication]. If you do it slowly, then build their confidence in [the medication], they’re less likely to have that [adverse event] and get the anxiety that goes with it. The anxiety can cause adverse events. Six to nine months time to dose up-titrate, we will get the dose up there eventually.” Cardiologist 12</i>

Patients' attitudes and beliefs around medicines.	<i>"Patients who are very good and methodical are able to manage their medications. We encourage them to maintain some control over their medications for as long as they are able, because then they have an understanding of what they're taking and why they're taking it. When it does go into the Webster-pack, they start to lose an association with what is in there and why they're on it. That can make it harder for us as clinicians sometimes to manage the changes as well and for patients to report changes." Nurse 14</i> <i>"In a way, that's a necessary evil, but it also robbed dad of his autonomy as well. For someone like dad who had actually been managing his meds quite well, until the old Webster pack came along and did his head in." Consumer 53</i> <i>"For those who are home alone with some degree of cognitive impairment where we don't think they'll reliably take their medications, they need to be on a once-daily regime, so that if needed, community nursing can go out and administer those medications. Otherwise, there's no point if they are taking the same medication twice and mixing up their medications. Geriatrician 20</i> <i>"[Polypharmacy] is just not a clinical problem that needs a solution. Just figure out the solutions." Pharmacologist 24</i> <i>"Quite often we find patients who have this great medication list, and you look at their medications and they're beautiful and you think, 'this patient's optimized.' They come into hospital and the nurses start giving them the medication as it's been prescribed, and that's nowhere near what they're taking. Five seconds later, their kidneys are terrible. That patient looks like they've got optimized." Nurse 6</i>
2b. Identification and management of ADEs	
Expected adverse effects	<i>"For older people with multiple problems, we will selectively consider nebivolol over other beta blockers because they tend to tolerate blood pressure. If they have multiple hospital admissions or multiple presentation with a lot of urine infections, probably not a good idea to add on the SGLT2-I, similar for MRAs like spironolactone. In frail people, the renal function in advanced age will not be very good." Cardiologist 27</i>
Monitor common adverse effects	<i>"[ADEs] are plentiful, frequent and common. It might be hypotension, renal impairment, or acute kidney injury. That patient may have a fall related to hypotension. Few number of patients complain of incontinence or frequency of urine. But once we've reached a euvolemic state, that settles that symptom. The beta blocker, fatigue would be really quite common, [and] less often patients will report really vivid dreams and sometimes a switch will improve that. We do still see a cough associated with the ACEI. But it's usually kidney, potassium, creatinine and hypotension and potential fall. Nurse 14</i>
Difficulty distinguishing whether symptoms caused	<i>"It's close-up follow-up with the patients and see what they're experiencing in terms of medication side effects, which wasn't pre-existing, previous before the actual medication started. Otherwise, it's hard to stay which is which." Cardiologist 27</i>

by underlying comorbidities or medications.	“I’m always comparing myself to what I was doing, rather than just settling into the moment and working through the bad. It’s not over medication, but it’s just come from all that [has occurred].” Consumer 55 “The adverse effects that I’m most interested in are things that are going to increase the risk of falls, blood pressure, and things that are going to throw the kidneys off.” Pharmacologist 24
Severity of ADEs based on the patients’ symptomatic response.	“I do find that some of the medications I take do give me quite digestional problems. I also feel, and I have talked with my doctor, that I get very anxious and it may also be coming from some of the medications I had to take for atrial fibrillation and enlarged heart.” Consumer 55
Adjusting treatment depends on patient engagement.	“The very frail, silent generation, those born between the wars, they don’t tell you anyway. It’s like, “It’s nothing.” They don’t want to be any bother.” Nurse 10
Consumers awareness of adverse effects	“It’s hard to say what’s important for the patient when they don’t know they’re having an adverse effect.” Nurse 11 “The patients don’t really tell you that they feel dizzy, lightheaded. Especially the aging population, I don’t think they actually know which one of the medications is causing it.” Cardiologist 27
Weighing the benefits and harms of preventing worsening HF with adverse effects.	“Because of the way that it makes them urinate so frequently because of other comorbidities, primarily obesity and osteoarthritis, we’ve seen a lot of patients who have stopped taking medications that make them pee. They come with florid, decompensated congested cardiac failure, like floridly.” Cardiologist 28 “You don’t know whether the medications become stronger because their organ function is getting older. You don’t know whether organ functions go, [and] medications have become stronger because they’re not profusing and everything becomes relatively stronger because the heart’s failing, Or because the heart is failing, and they can no longer keep their blood pressure up.” Pharmacologist 24 “But [the medication will] work and most of the doctors won’t go, ‘okay, we’ll just get rid of that one.’ They’ll try and find something else, another combination. But they may withdraw a drug and say, ‘the side effects are worse than the benefit. So, let’s try this.’” Consumer 54 “Can their renal function take the diuretic, do we dry them out? If it’s clear they’re getting symptomatic benefit, and that the cost of that is a new baseline renal function, then so be it.” Geriatrician 23 “The fatigue is incredible at times, but it’s improving a little bit. I’ve got try and manage it, with public obligations and commitments.” Consumer 55
Self-manage adverse effects to maintain benefits of medications.	Patients themselves, the older ones who really understand their Lasix, will not take it on the days when they’re going to do something. They self-manage the adverse event in that way. Nurse 10

Adjustments are not always manageable	<i>'It depends on the spectrum of how much they're feeling worse, if they're actually worse. A lot of people tolerate medications that make them feel awful, especially in the older age. Cardiologist 25</i>
2c. ADWE considerations	
Identification of common ADWEs	<i>"[Patients] stop taking the medications in the hope that they can stop peeing and stop having to use the bathroom. But then, they decompensate. By that point it's too late, they need to come into hospital. That is a good example of where drug withdrawal, because of maintaining quality of life, has actually come at a cost to the patient. And I think that the answer is not drug withdrawal. It's treating the underlying problem, which is profound obesity, sarcopenia and osteoarthritis in these elderly frail patients." Cardiologist 28</i>
Hesitancy to deprescribe HF-medications.	<i>"Unless they're end of life, any therapy is beneficial to them. If your LVEF is stronger, you are less likely to have a lot of the issues that come with heart failure as a very simple way of looking at it. Unless someone you think is going to die in three months or less, then stopping heart failure therapy for no reason at all doesn't make sense to me." Cardiologist 29</i>
Deprescribing dynamic, particularly during acute illness.	<i>"As long as you can, keep titrating as much as you can, as much time as possible on the maximal optimal doses is the goal. Yes, down-titrate if required, up-titrate again when you can. Really dynamically; even the patients who've sort of entered unequivocally sort of palliative phase, terminal days, even then [I'm] very reluctant to totally eliminate the medications, unless it was for symptoms." Cardiologist 12</i>
Loss of treatment benefit is harmful in patients with HFrEF.	<i>"We're trying to balance things because you don't want to rush to remove anything that's going to be potentially beneficial to the heart function and remodelling of the myocardium. But also, you don't want to be increasing risk of fall and re-hospitalization due to that. That's not an easy question to answer as to when do I rush in to do something." Nurse 14</i>
Potential harm in deprescribing in asymptomatic stable patients.	<i>"I stopped their digoxin. 'This isn't doing anything. You've got CRT, you're on all the medications, it'll be fine.' Ten weeks later; 'I'm quite short of breath.'" She was in terminal decline though I ramped up the hydrochlorothiazide. Her NT-proBNP went from 4,000 to 22,000. She's like, "I'm still really bad. I went to cut my fingernails and I became short of breath." What happened is that digoxin was enough to keep her heart rate down so that her CRT could do its job. When I removed the digoxin, her heart rate went above the level at which the CRT kicked in and she went back to her natural dyssynchronous rhythm. She was dioxin dependent." Pharmacologist 24</i>
Preference to deprescribe non-HF medications.	<i>"Generally, we will be trying to deprescribe. [But] especially not with heart failure specific medications, they are more sacrosanct than a lot of other medicines. We take some of those medications down and taper, hopefully one at a time. In general, heart failure meds would be the last to go. Most of the time we'd be taking other things out and they would be left in until someone was palliative." Pharmacist 4</i>
HFrEF has lack of clinical trials demonstrating clear benefit.	<i>"One other patient we started on, he has HFpEF [and] pulmonary hypertension. We thought could have been some benefit to him, but he didn't feel it made much difference to his symptoms so [we] didn't persist with it." Nurse 14</i>
Obvious harm warrants deprescribing.	<i>"Sometimes we make the decision this is too dangerous for this person. We think we should stop it completely. If someone with a massive prostate, coming with a urosepsis, generally we will probably stop it permanently. If this is</i>

	<i>their second or third episode of urosepsis with the SGLT2 inhibitor. The cost benefit actually doesn't weigh in favor of those patients because they're very close to dying every time they come in."</i> Cardiologist 28 <i>"If I get readmissions to the service, it'll be people with HFpEF who for one reason or another [but] usually quite different, don't respond to medications in the same way. Maybe a bit diuretic resistant. Nurse 11</i> <i>"With both ARBs and beta blockers, people have thought, I just don't feel right. I feel like my brain's in a fog. Then you back off and then they feel better again. I think sometimes the optimal dose we see to maximum tolerated."</i> Nurse 26
Considerations for permanent deprescribing	<i>"A more holistic point of view is really useful. Patients, they don't want to have gout, they do not want to have pulmonary oedema that is much more motivating than lose weight. Look after yourself exercise, they're like, 'Yeah everyone tells me that.' If you say, 'I'm going to give you less diuretics because you haven't got so much fluid on board. You can drink the bath, you're still going to be thirsty. If you drink less, you're going to feel well and you're not going to have a flareup of your gout because I don't need to give you this medication.' They're like, 'oh yeah, I'm in'.</i> Nurse 6
2d. Facilitators and barriers to patient education and information about benefits and harms	
Challenges to communication challenging when discussing balancing ADEs and QoL.	<i>In the acute stages coming out of the hospital, I'd say the benefit outweighs the risks of continuing with the medication, use simple words like, to keep them safe, "This medication is keeping you going, keeping you chugging along. You may be going to the bathroom a lot, but you're less breathless. You're able to walk, you're able to mobilise more. And this is a short-term thing. You might stay on these meds, but it's keeping your heart rested and so you can go for longer."</i> Nurse 15
Facilitating communication repeating the benefits and harms of medications, referencing patients' function and QoL.	<i>"When I'm starting someone and/or titrating an ACEI, I'll say, "This will make you feel a bit woozy for the next three days. That means sit to stand, turn your head suddenly. It doesn't mean you can't drive, you can't do the things that you've been doing. It just means to go gently for the next couple of days. If you're lying on the couch and watching television and someone's at the front door and you jump up to answer it, you're going to fall over. So just go gently."</i> Nurse 6 <i>"For the patients we see, a large proportion do not know what medications they're taking. If they can list their medications, they don't necessarily know the indication. If we were to communicate all of that information, I'm not sure how much of it they would retain."</i> Geriatrician 20
Limited time and opportunity for health professionals to manage ADEs and ADWEs is a barrier	<i>"[Nurses] spend a lot of time explaining. When they see their cardiologist and their GP, there's usually not a lot of time, they just say, 'these will help your heart sort of thing' for 10 minutes and then the [GP] get this letter from me with this list of demands and they need this and this... They're like, 'oh my god.'"</i> Nurse 26 <i>"Especially if you're in a busy pharmacy, you want to call the doctor to explain what's happening and follow up. It's quite rare for that to happen because you need [to consider] the time factor in the community setting."</i> Pharmacist 5

	<i>“Generally, we will sit down with the family and instead of going through all the drugs, we’ll pick the drugs that have either, been complicated this admission or have caused them to come into hospital. And we’ll just lay out the information for the family and our recommendation, to get the family’s point of view. Especially in the patients that have cognitive impairment or dementia.” Cardiologist 28</i>
Theme 3: Access to Healthcare Services	
3a. Multidisciplinary approach	
Care across multiple health settings	<i>“True adverse effects, or the serious ones, don’t come to a clinic so it’s hard. You get the reason why something started was stopped taken out of context, it’s tricky. There’s a lot of role for heart failure specific clinics and nurse practitioner education clinics where someone is dedicated and patients are followed a lot more.” Cardiologist 29</i>
Manage outcomes for single-organ diseases compared to global patient function.	<i>“[Cardiologists] can always advise on those medications, but at the end of the day, their treatment optimization decisions need to be made in conjunction with the geriatrician. Some cardiologists can be very aggressive and will say ‘this treatment [is needed]’ which may not necessarily be suitable for this patient. At the same time, geriatricians will sometimes push us to do certain things that we think is not appropriate for that particular age group. It’s completely individualized, based on the clinician, regardless of their specialty training.” Cardiologist 27</i>
Sharing information and responsibility of patient’s care.	<i>“[Cardiologists] are the most influential people, and they treat the majority of people with heart failure, along with the GPs. Geriatricians, look after that anecdotal subset of people.” Geriatrician 23</i>
Responsibility of managing adverse effects in individuals living at home.	<i>“I’d probably be more inclined to ensure that I check blood in patients who have really any change in regular diuretics. Any big change, any change really in ACE inhibitors or ARB or Entresto. I’d be doing a few more frequent checks for those things. A bit slower probably as well. I must admit as a cardiologist they’re not seeing people that frequently anyway. Sometimes I might, see people kind of probably the most frequently three to six months; and then least frequently about every year. Timelines are a bit different in specialist land cause, you’re not seeing everyone every two weeks or every month like you might in GP world.” Cardiologist 25</i>
Need improved coordinated multidisciplinary expertise to navigate care.	<i>“Furosemide, is often prescribed either from hospital or by the GP as a drug that’s like a get out of jail free card. ‘If you’re putting on weight, you’ve noticed your feet are getting swollen, or you’re becoming a bit more breathless, just start taking some furosemide and see how you go.’ Which often is an indicator that they need to seek care rather than taking furosemide. But on the flip side, a lot of patients have regular furosemide because of how poor their ejection fraction is.” Cardiologist 28</i> <i>“I’ve got much better at deliberately involving the cardiologist in my deprescribing. I’ll send an email straight away. Whereas previously, I just deprescribe. It’s not good patient care cause what’ll happen is you’ll reduce it, [the patient] will then go and see the cardiologist and restart it. And the poor GPs caught in between.” Geriatrician 23</i>
3b. Patient access to care	
Frequent monitoring and access to health services.	<i>“It’s the burden of the treatment. The titrating and the people coming in and out of their life. It’s actually the diuretic and the pill burden and the burden of getting to and from medical appointments and things in the frail, that I think potentially has equal consequences as the tablets.” Nurse 10</i>

Community support to coordinate care	<i>"In the heart failure program, I don't know whether the outreach team takes on very demented or very, very frail people. Geriatrician 20</i>
Access to healthcare services not always possible, further exacerbating health inequities.	<i>"Somebody who is maybe not so wealthy or maybe homeless, they don't have any supports. You've got to take all that into consideration of how the person's dealing with their illness and whether they can afford or take their medications." Nurse 6</i>



Wednesday, 7 December 2022

Prof Sarah Hilmer
Northern Clinical School: Medicine; Faculty of Medicine and Health
Email: [REDACTED]@sydney.edu.au

Dear Sarah,

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

I am pleased to inform you that after consideration of your response, your project has been approved.

Details of the approval are as follows:

Project No.: 2022/811
Project Title: The classification of adverse drug reactions and adverse drug events during optimisation of heart failure medications in frail older people: a mixed-methods study
Authorised Personnel: Hilmer Sarah; McLachlan Andrew; Duong Mai; Gnjdjic Danijela; Kouladjian-O'Donnell Lisa Marie;
Approval Period: 07/12/2022 to 07/12/2026
First Annual Report Due: 07/12/2023

Documents Approved:

Date Uploaded	Version Number	Document Name
21/11/2022		ALL 4 Flyers for consumers and clinicians (clean)
21/11/2022	Version 2	Clinician (focus group)-Participant info statement (clean)
21/11/2022	Version 2	Clinician (survey)- Participant info statement (clean)
21/11/2022	Version 2	Clinician consent form (clean)
21/11/2022	Version 2	Consumer (Focus group) -Participant info statement (clean)
21/11/2022	Version 2	Consumer (survey) -Participant info statement (clean)
21/11/2022	Version 2	Consumer consent form (clean)
21/11/2022	Version 2	Demographic sheet (clean)
21/11/2022	Version 2	study protocol (clean)
21/11/2022	Version 2	Twitter posts (clean)
07/10/2022	Version 1	Clinician interviewer guide
07/10/2022	Version 1	clinician participant handout
07/10/2022	Version 1	consumer interviewer guide
07/10/2022	Version 1	consumer participant handout

Condition/s of Approval

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
 - Serious or unexpected adverse events (which should be reported within 72 hours).
 - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).

- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.
- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.
- The Ethics Office may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

This letter constitutes ethical approval only.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,

Associate Professor Stephen Fuller
Chair
Human Research Ethics Committee (HREC 2)

The University of Sydney of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) [National Statement on Ethical Conduct in Human Research \(2018\)](#) and the NHMRC's [Australian Code for the Responsible Conduct of Research \(2018\)](#)



Dr Rebecca Kozor, Mai Duong, Dr Lisa Kouladjian O'Donnell and Professor Sarah Hilmer

AWARDS HIGHLIGHT THE IMPACT OF DRUGS ON FRAIL OLDER PEOPLE WITH HEART FAILURE

One of our up-and-coming researchers within the Kolling's Ageing and Pharmacology Lab has taken out two prestigious awards.

Pharmacist and PhD student Mai Duong received the initial award at the International Pharmaceutical Federation World Congress in Brisbane.

The APSA awarded Mai the Outstanding Oral Presentation in Pharmacy Practice prize for her discussion on the different perspectives of adverse drug events with heart failure medications in frail older people.

She also took out an award for her presentation at the Cardiovascular Symposium hosted by the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists.

Mai's research has greatly benefitted from a new collaboration within the Kolling Institute involving researchers from the Ageing and Pharmacology Lab including Professor Sarah Hilmer and Dr Lisa Kouladjian O'Donnell and A/Professor Rebecca Kozor from the Cardiology Department.

She said her work has highlighted the contrasting consumer and clinician views on clinical outcomes, patient priorities and

medication management of frail older people with heart failure.

"We know that heart failure is becoming more common in the ageing population, leading to frequent hospital visits and claiming lives," she said.

"Patients report that the big problem for them is the number of medications they're on and the possible interactions.

"We are seeing that some medications for heart failure can cause falls, dizziness, renal impairment and other adverse events.

"We know that optimising heart failure medication can be complex, but we hope that following our research there will be a greater focus on frailty and quality of life when these medications are prescribed.

"We found that clinicians recognised that frailty status was important, but it was not routinely measured or included in medication management plans.

"Backed by our research, we would like to see frailty measures considered when prescribing these medications, so that clinicians can tailor their approach for each patient for the best outcome."



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2023 Australasian Pharmaceutical Science Association (APSA) “Outstanding Oral Presentation in Pharmacy Practice” Prize

Mai Duong

Northern Clinical School, University of Sydney

Ageing and Pharmacology Laboratory, Kolling Institute, Royal North Shore Hospital, Sydney, Australia

I am a registered pharmacist practicing in aged care and community settings in Canada and conduct research in hospital settings in Australia. Prior to my PhD, I was the project pharmacist on a translational research project, led by Professor Sarah Hilmer, to develop several multi-disciplinary hospital electronic decision support tools to support reducing inappropriate polypharmacy in older people. My PhD research is on developing taxonomies of adverse drug events (ADEs) and adverse drug withdrawal effects (ADWEs) to support optimisation and deprescribing of heart failure medications in older people living with frailty.



Pictured (from left to right):

A/Prof Danijela Gnjidic, Ms Mai Duong, and Prof. Andrew McLachlan

At this year's 81st FIP World Congress in Brisbane, I was honoured and grateful for my abstract, selected for a HaMIS oral presentation, to be awarded the Australasian Pharmaceutical Science Association (APSA) “Outstanding Oral Presentation in Pharmacy Practice” Prize. My presentation, “Consumer and clinician perspectives on ADEs and ADWEs of heart failure medications in frail older people”, is part of my PhD research at the Northern Clinical School, University of Sydney; and Ageing and Pharmacology Laboratory at the Kolling Institute, Royal North Shore Hospital in Sydney, Australia.

My findings demonstrate that objective frailty measures can support clinicians to individualise medication management care plans to support patients and/or their caregivers to optimise outcomes important to them. Automated measurement of frailty status can facilitate use in pharmacy practice, but more research is needed to determine how this can be applied within sustainable models of care.

My research has been possible through collaborations and resources across pharmacy practice, geriatric medicine, pharmacology, and cardiology networks; under the supervision of Professor Sarah Hilmer, Associate Professor Danijela Gnjidic and Professor Andrew McLachlan. I am funded by the National Health and Medical Research Council (NHMRC) and Heart Research Australia (HROz) Post-graduate Scholarships. My travel to the FIP Congress in Brisbane was supported by the APSA student travel award.

To read more, the conference abstract can be accessed [here](#) (p 186-7).

CONFERENCE ABSTRACTS

FIP Brisbane 2023

81st FIP World Congress of Pharmacy and Pharmaceutical Sciences in Brisbane, Australia,
 24 to 28 September 2023

Health and medicines information

Development of practice recommendations for potential drug disease interactions in patients with pulmonary hypertension

Mrs Emma De Ruiter¹, Mrs S Gipmans², Mrs MME Diesveld¹, Mrs. B Koch², Mr. A van Dijk³, Mr SD Borgsteede¹

¹Health Base Foundation, Houten , Netherlands, ²Royal Dutch Pharmacists Association (KNMP), The Hague, Netherlands, ³Radboud University Medical Centre , Nijmegen, Netherlands

Posters Monday, September 25, 2023, 12:30 PM - 2:30 PM

Introduction: Pulmonary hypertension is characterized by increased pressure in the pulmonary artery. It can be caused primarily by a vasculopathy in the small lung arteries (pulmonary arterial hypertension, World Health organization (WHO) group 1) and obstruction (chronic thrombo-embolic pulmonary hypertension, WHO group 4) or secondary by heart failure (WHO group 2), lung disease (WHO group 3) or miscellaneous and unclear etiologies (WHO group 5). Because of the complexity of the disease, patients with pulmonary hypertension are treated by multidisciplinary teams in expertise centres in the Netherlands.

Regulatory agencies identified pulmonary hypertension as a contraindication in 2020 in the Netherlands. Therefore, recommendations for potential clinically relevant drug-disease interactions (DDSI) with pulmonary hypertension were evaluated.

Purpose: The purpose of this study was to evaluate drugs with a potential clinically relevant DDSI with pulmonary hypertension.

Methods: We used a previously developed six-step plan, which combines literature and expert opinion to generate practical recommendations. The scope was defined to identify which sub forms of pulmonary hypertension should be included and which outcomes were clinically relevant. Next, a systematic literature search was performed for drugs that were suspected to worsen pulmonary hypertension,

based on the list of contraindicated drugs with pulmonary hypertension in European Society of Cardiology Guideline of pulmonary hypertension and expert opinion. The results of the literature search were combined with expert opinion of two cardiologists specialized in pulmonary hypertension to assess clinical relevancy of each drug. Five drug(group)s were evaluated in this study, seven other drug(group)s still need to be assessed.

Results: Primary pulmonary hypertension group 1 and 4 were classified as relevant for the DDSIs, since in the case of secondary hypertension treatment is focused on the underlying disease rather than pulmonary hypertension. Clinically relevant outcomes were WHO functional class, six minute walking distance and the right ventricular function.

Dopamine and the calcium antagonists diltiazem and verapamil were classified as drugs with a relevant DDSI. Dopamine-induced pulmonary vasoconstriction cannot be compensated in pulmonary hypertension patients due to lack of cardiac reserves. Diltiazem and verapamil are negative inotropic drugs that can lead to cardiac effects as hypotension and cardiac arrest. Both drug(group)s should be avoided.

Pulmonary vasoconstriction may occur with tyrosine kinase inhibitors (TKIs) dasatinib, ponatinib and bosutinib, hence hemodynamic checks are indicated during treatment. In the Netherlands, an alert in electronic prescribing systems was not considered necessary as these checks are already performed according to protocols that guide TKI-management. Additionally, no convincing evidence was found for the interaction between beta-blockers and pulmonary hypertension. Lastly, the concomitant use of nitrates and phosphodiesterase inhibitors can lead to severe hypotension, which is signalled as an interaction and beyond the scope of this DDSI.

Conclusion: So far, two drug(group)s can clinically-relevantly worsen pulmonary hypertension (especially WHO 1 and 4). These DDSIs will be implemented in clinical decision support systems to support health care

cases), hospitalization (1643 cases) and other serious events (1164 cases).

Conclusion The data mining of FAERS suggested an association between VTE and antipsychotic drugs which reminds medical workers to pay attention to the serious adverse drug effects of antipsychotic drugs leading to venous thromboembolism

Creation of the ew meds list-A comprehensive list of poor tasting liquid medications

Dr Amy Kruger Howard¹, Dr Jill Ann Morgan¹

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Posters Wednesday, September 27, 2023, 12:30 PM - 2:30 PM

Infants demonstrate a preference for sweetness and umami flavors, as well as a strong dislike of bitterness from shortly after birth. Most oral dosage forms, like capsules and tablets, are specifically designed to minimize taste perception of the active pharmaceutical ingredient and avoid concerns about medication palatability. However, young kids often struggle to take solid dosage forms. Furthermore, masking techniques available for liquid formulations often fall short, making them more likely to have poor palatability. The direct link between poor palatability and non-adherence is well documented. Palatability, as a key component of acceptability, has been incorporated into the European Medicines Agency's evaluation in the approval process for new pediatric drug formulations. Therefore, it is essential to assess which medications are known to be poorly tolerated because of taste, find alternatives that may be more favorable, and highlight home taste-masking interventions to mitigate poor palatability. As pharmacists, we can make medications more manageable for kids. To increase awareness about medication palatability, we created the Ew Meds List® - a comprehensive list of poor-tasting liquid medications and evidence-based recommendations to mask poor palatability.

A PubMed and EMBASE search was conducted using the terms child, bitter, flavor, masking, palatability, and adherence. The search was limited to human randomized control trials and systematic reviews from 1980-2021. Articles containing scored taste perception for medications were used to rank medications to assess eligibility for the Ew Meds List. All scales were aligned to a 5-point Likert score with 1 being dislike it very much and 5 being like it very much. The lowest score was used for any medication appearing in multiple publications. Any medication scoring less than 2.5 met criteria to be added to the Ew Meds List®. Those medications with a score of 2.5 and above were added to "Better Tasting Medications". Studies with taste-masking evidence related to specific medications were used to create evidence-based taste-masking recommendations. The project objective was to identify and compile palatability information into a single resource to expand prescriber and pharmacist awareness about poor-tasting

medications and provide tangible suggestions of alternate medication selections or taste-masking recommendations.

The search yielded 452 abstracts. Upon review, 65 studies were deemed appropriate for inclusion in the analysis. Sixteen articles contained ranked taste perceptions of 30 specific medications. Of those medications, 16 met the criteria for the Ew Meds List® and 14 for the better-tasting meds, and the majority of medications studied were anti-infectives. There were evidence-based recommendations for masking 10 specific medications. Pharmaceuticals literature provided general flavoring recommendations to mask basic taste properties such as bitter or sour.

The scoring threshold for better-tasting liquid medications should be higher and work needs to be focused on medications used in chronic illnesses. Knowing the link between acceptability and adherence, there needs to be more emphasis placed on improving new formulations and identifying evidence-based taste-masking techniques to help improve adherence for Ew Meds. We applaud the efforts of government agencies working to increase the focus on taste perception in pediatric medications.

Consumer and clinician perspectives on adverse drug events and adverse drug withdrawal effects of heart failure medications in frail older people

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RFMO-02 - Rapid Fire Session Monday, P1-P2, September 25, 2023, 11:00 AM - 12:30 PM

Background: Heart failure (HF) is increasingly prevalent in the ageing population and associated with high mortality and hospitalisation, particularly in people aged over 75 years. Frailty is defined as a reversible syndrome involving multi-system deficiencies. Optimising HF medications in frail older people can be complex due to multi-morbidities, polypharmacy (>5 medications), deficits in multiple health domains and changes in life expectancy, cognition and patient priorities. Older HF patients living in the community are mostly frail and experience at least one adverse drug event (ADE) from their HF medications; yet are poorly represented in clinical trials and observational studies.

Purpose: To examine consumer and clinician perspectives of ADEs and adverse drug withdrawal effects (ADWEs) from HF medications in frail older people.

Methods: Qualitative interviews and focus groups were conducted with consumers (carers, advocates or older individuals living with HF and frailty) and clinicians (pharmacists, nurses, geriatricians, specialist physicians) involved in caring for frail older patients with HF. Semi-structured interview questions were informed by the literature and piloted with clinicians. Recruitment of a purposive sample of participants involved electronic distribution of advertisements through professional and community networks and invited to respond; or contacted directly through snowballing in acute, aged care and community settings across Australia. Interviews were conducted by a pharmacist researcher via videoconference or phone, audio-recorded, transcribed and de-identified. A general inductive content analysis approach was used to identify themes to address the aims.

Results: To date, 24 participants (2 consumers, 4 geriatricians and cardiologists, 7 nurses and 11 pharmacists) have participated in interviews and focus groups. Preliminary analyses identified eight themes relating to characteristics and management of ADEs and ADWEs experienced by frail older people. Participants acknowledged the importance of addressing individuals' physical and emotional function to support individual goals and ability to live independently. Clinicians recognised frailty status was important but not routinely measured nor included in medication management plans. Complex patient factors, medication management and identification of common ADEs could be supported with patient education and communication of the benefits and adverse effects of HF medications across multiple clinical outcomes. Participants described ongoing challenges of multi-disciplinary collaboration, particularly during transitions of care.

Common ADEs identified by participants included hypotension (e.g. falls, dizziness, light-headed) and renal impairment, which warranted clinician intervention. Diuretics (furosemide) frequently caused urinary incontinence which was mostly patient self-managed to balance social and emotional disruption. Common ADWEs included cardiovascular events (e.g., worsening HF symptoms). A participant described, "the big problem is the number of medications that they're on and potential interactions. One of our big issues is patients falling down with hypotensive drugs. With [furosemide], needing to get to the bathroom quickly [can be a] falls concern" [nurse 013].

Conclusion: Based on results so far, this study identified several perspectives unique to medication management in frail older patients with HF. Findings revealed treatment priorities and opportunities to include frailty status in medication management plans. Future observational studies are needed to determine how this information can be applied to support individualised care plans.

Characteristics, content and language of deprescribing recommendations in clinical practice guidelines: A scoping review

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RFMO-02 - Rapid Fire Session Monday, P1-P2, September 25, 2023, 11:00 AM - 12:30 PM

Background: Adherence to prescribing recommendations in clinical practice guidelines may contribute to inappropriate polypharmacy. Healthcare professionals, including pharmacists, require evidence-based recommendations to ensure safe and effective prescribing and deprescribing (medication dose reduction or cessation). The extent to which deprescribing recommendations are included in clinical practice guidelines is unclear.

Purpose: To determine the proportion and characteristics of clinical practice guidelines that contain deprescribing recommendations, and to explore the content and language of these recommendations.

Method: A random 10% sample of all clinical practice guidelines published in the past five years from four international guideline registries (Guidelines International Network [GIN], Canadian Medical Association Infobase [CPG infobase], MAGICapp, and GuidelineCentral) were screened in duplicate to determine the proportion of guidelines containing one or more deprescribing recommendations. Additionally, three databases (Medline, EMBASE and CINAHL Plus) and Google were searched for guidelines published in the last ten years containing one or more deprescribing recommendations. We included guidelines which met the Institute of Medicines definition and criteria of a clinical practice guideline and excluded guidelines focussing on acute treatment only (e.g. related to surgery or interventional investigations, or medicines prescribed short term for an acute condition). Guideline characteristics were extracted, including year and country of development, total number of recommendations, number of deprescribing recommendations, and whether or not a consumer was involved in guideline development. The content and language of recommendations were examined using a conventional content analysis, with two independent reviewers applying the coding framework. The SheLL Health