Understanding outcomes and improving research methodologies for older patients with chronic kidney disease

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Statement of originality

This is to certify that, to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any other degree or other purposes.

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.

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Authorship attribution

This thesis contains work carried out by the author under the supervision of Professor Martin Gallagher, Professor Alan Cass and Professor Meg Jardine.

For all chapters that have been submitted or published, the author made substantial contributions to the conception and design of the studies, planned the research, collected, analysed and interpreted the data, drafted the manuscripts, coordinated submissions, revised manuscripts after peer-review, and wrote and compiled this thesis.

Chapter 2: AS is a leading member of the national steering committee for the Elderly Advanced CKD Program. AS conducts, oversees and coordinates the studies in this program. For this chapter, AS, CF, MG, NG and YM conceived the Program and formulated protocols for the study components. AS drafted the manuscript, and all authors contributed to critical review and revisions of the manuscript.

Chapter 3: AS and MJ conceived the review. AS drafted the manuscript, and AS, BS and MJ contributed to writing, appraisal and manuscript review.

Chapter 4: AS, MG and NG conceived this analysis. AS analysed the data, interpreted results and drafted the manuscript. All authors contributed to critical review and revisions of the manuscript.

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Chapter 6: AS, BN, LB, CA and VP contributed to the conceptualisation, data curation and data interpretation. AS and LB performed the formal analysis. AS wrote the original draft of the manuscript, and all authors were involved in the review and editing of the manuscript.

Chapter 7: AS conceived study design, conducted the literature search, data extraction, risk of bias assessment, data analysis, drafting and preparing of the manuscript. DK contributed to the literature search, data extraction and risk of bias assessment. BN contributed to the study design, interpretation of results and preparing of the manuscript. All authors were involved in critical review and revisions of the manuscript.

Chapter 8: AS, RM, BS and MB conceived study design. AS and AH collected the data. AS analysed the data, and AS, RM, BS and MB interpreted results. AS drafted the manuscript. All authors were involved in critical review and revisions of the manuscript.

Attesting authorship statement

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

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Abstract

Background: As the global population ages, there has been a dramatic increase in the prevalence of chronic kidney disease (CKD) among older individuals. In turn, older individuals represent the largest group progressing to the most advanced form of CKD, kidney failure. The current and future health care implications that these trends pose are immense. There is a need to identify and implement evidence-based measures to slow progression to kidney failure for older patients, align treatment approaches with patient values and preferences, and involve patients, carers and clinicians in well-informed shared decision-making processes.

In practice, however, older patients are underrepresented in randomised clinical trials (RCTs), and high quality prospective observational studies assessing important patient outcomes, such as comparing survival and other patient-reported outcomes across different treatment pathways for kidney failure, are few and frequently confounded by methodological biases. As a result, there is a high degree of uncertainty and variability in the understanding of outcomes, decision-making processes and management of CKD and kidney failure in older patients.

Methods: This thesis has taken a systematic approach to increase understanding on important clinical outcomes and management approaches for older patients with CKD and kidney failure. It utilises review methodologies, novel research designs, and observational and RCT data in older patients. *Chapter 1* introduces the thesis, summarising the

epidemiology of CKD in older individuals and principles of management. *Chapter 2* reports on the study design of the Elderly Advanced CKD Program, a suite of studies that includes a multi-centre, prospective observational cohort study with nested sub-studies and linked qualitative research. This ongoing study program was designed to derive outcome data on older patients ≥75 years as they undertake different kidney failure treatment pathways (dialysis and conservative kidney management). *Chapter 3* reviews national, regional and international guidelines on utilising waiver of consent in low-risk clinical research, a study design feature that is central to the Elderly Advanced CKD Program. *Chapter 4* is an interim analysis of the OUTcomes of Older patients with Kidney failure (OUTLOOK) study, the primary study component of the Elderly Advanced CKD Program. Baseline characteristics of presently enrolled OUTLOOK participants are compared with characteristics of incident kidney replacement therapy (KRT) patients aged ≥75 years in the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). *Chapter 5* presents an analytical review of the application of CKD risk prediction models to older patient populations and how these can be utilised in shared decision-making discussions. *Chapters 6 and 7* evaluate the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors, now considered a pillar in CKD therapy, among older patient populations. A pooled secondary analysis of patient-level trial data from the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial is presented in *Chapter 6*, to examine the efficacy and safety of SGLT2 inhibitor therapy across the spectrum of age. A systematic review and meta-analysis of SGLT2 inhibitors according to frailty status is presented in *Chapter 7*. *Chapter 8* explores health-related quality of life in dialysis patients, an outcome now considered central in the design of dialysis RCTs and a particularly important patient-reported outcome for older patients. This

chapter utilises anchor-based and distribution-based statistical approaches and is the first study to estimate a minimal important difference (MID) for the EQ-5D-5L utility index in dialysis patients. The final chapter, *Chapter 9*, discusses the implications of this thesis, explores future directions for the Elderly Advanced CKD Program and explores remaining research questions pertaining to outcomes for older patients with CKD.

Results: The Elderly Advanced CKD Program is enrolling patients ≥75 years with kidney failure (defined as estimated glomerular filtration rate, eGFR, <15 mL/min/1.73m^2) across 8 Australian sites. To date, 529 patients have been enrolled in the largest study component, OUTLOOK. High-quality, prospective Australian data on survival, patient-reported outcomes and healthcare utilisation in older patients are novel and will support patients with kidney failure, carers and clinicians as they make personalised treatment pathway decisions. Review of waiver of consent guidelines provides an ethical framework for the use of this consent model in low-risk studies such as OUTLOOK, in order to facilitate inclusive, large and feasible enrolment of older patients in clinical studies. Compared with 5339 incident KRT patients aged ≥75 years in ANZDATA, baseline characteristics of the 529 currently enrolled participants in OUTLOOK identify an older, comorbid, predominantly community-dwelling cohort, with a high proportion opting for conservative kidney management as the chosen pathway of kidney failure management. This analysis highlights that OUTLOOK is deriving valuable prospective outcome data on an older Australian kidney failure cohort that is not otherwise being captured in national registries.

To support shared decision-making discussions for older patients with CKD, analytical review of CKD risk prediction models in older patients identifies limitations of existing

models but that a combined approach of using the Kidney Failure Risk Equation (KFRE) and Mortality Risk Equation for Kidney disease (MREK) holds the highest clinical utility for kidney failure and mortality prediction in this patient population.

Strategies to mitigate progression of CKD to kidney failure in older patients are essential, and pooled analysis from the CANVAS Program and CREDENCE trials and meta-analysis across major SGLT2 inhibitor trials indicate that these agents provide cardiovascular, kidney and mortality benefits across the spectrum of age and among frail individuals, without significant additional safety concerns.

Finally, health-related quality of life, as measured by the EQ-5D-5L utility index, is an important patient-reported outcome among older patients, is lower among kidney failure patients compared with general population norms and decrements over time. Anchor-based and distribution-based approaches provide EQ-5D-5L utility index MID estimates ranging from 0.034 to 0.134, and are of value for endpoint, power and sample size calculations in the design of future dialysis clinical trials.

Conclusion: This thesis identifies that high-quality and well-designed studies among older patients with CKD and kidney failure are feasible and essential in generating evidence to guide older patients, carers and clinicians as they make life-impacting CKD treatment decisions. By utilising novel study designs, multicentre enrolment and national collaboration, the Elderly Advanced CKD Program which forms the largest component of this thesis, is generating much-needed prospective data regarding older patients across kidney failure treatment pathways. Furthermore, important new insights on risk prediction, efficacy and

safety of SGLT2 inhibitor therapy and health-related quality life in older patients with CKD have been delineated in this thesis and provide guidance for prognostication, decision-making and management approaches in this patient population. The work presented, identification of ongoing evidence gaps and future directions discussed in this thesis are important steps towards generating high-quality and much-needed evidence to guide the management of older patients with CKD and kidney failure.

Ethical clearances

Chapter 2: Ethics approval was obtained for each study in the Elderly Advanced CKD Program through the Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783).

Chapter 4: Ethics approval for the OUTLOOK study was obtained through the Sydney Local Health District Human Research Ethics Committee (2019/ETH07718). Ethics approval for this analysis comparing OUTLOOK participants with incident patients in ANZDATA was obtained through the Northern Sydney Local Health District Human Research Ethics Committee (2024/ETH00995).

Chapter 6: This is a secondary analysis of the CANVAS Program and CREDENCE trial. For these trials, ethical clearance was obtained from respective human ethics committees within each participating country.

Chapter 8: Ethics approval for this study was obtained from South Easter Sydney Human Research Ethics Committee (2020/ETH01670).

Chapters 3, 5 and 7 did not require ethics approval.

Publications arising from this thesis (included in Appendix A)

This thesis is a 'thesis with publications'. Chapters 2 and 8 have been published in peer reviewed journals. Chapters 3, 5 and 6 are under journal review for publication. Chapters 4 and 7 are planned for journal submission.

Chapter 2:

Siriwardana A, Gray NA, Makris A, Li CK, Yong K, Mehta Y, Ramos J, Di Tanna GL, Gianacas C, Addo IY, Roxburgh S, Naganathan V, Foote C, Gallagher M. Treatment decision-making and care among older adults with kidney failure: protocol for a multicentre, prospective observational cohort study with nested substudies and linked qualitative research (the Elderly Advanced CKD Programme). *BMJ Open*. 2022; 12(12):e066156.

Chapter 3:

Siriwardana A, Smyth B, Jardine M, On behalf of the RESOLVE Study Global Team. Waiver of informed consent in clinical research: A review of contemporary guidelines. Under review July 2024 in *BMJ Open*.

Chapter 4:

Siriwardana A, Gray NA, Makris A, Li CK, Yong K, Ramos J, Gianacas C, Addo IY, Roxburgh S, Clayton J, Ducharlet K, Chou A, Naganathan V, Foote C, Gallagher M, On behalf of the Elderly Advanced CKD Program. Comparison of baseline characteristics of participants in the

OUTLOOK study with older patients in the ANZDATA Registry. Planned for submission in October 2024 to *Nephrol Dial Transplant*.

Chapter 5:

Siriwardana A, Tangri N, Neuen B, Jardine M, Foote C, Gallagher M. Utilising risk prediction models for older patients with chronic kidney disease. Under review September 2024 in *Lancet Healthy Longev*.

Chapter 6:

Siriwardana A, Buizen L, Jun M, Kotwal S, Arnott C, Jardine M, Levin A, Heerspink H JL, Charytan D, Pollock C, Perkovic V, Neuen B. Cardiovascular, kidney and safety outcomes with canagliflozin in older adults: A combined analysis from the CANVAS Program and CREDENCE trial. Under review September 2024 in *Diabetes Obes Metab*.

Chapter 7:

Siriwardana A, Kim D, Chan B, Jun M, Smyth B, Arnott C, Jardine M, Perkovic V, Neuen B. Efficacy and safety of SGLT2 inhibitors according to frailty status: A systematic review and meta-analysis. Planned for submission in October 2024 in *Lancet Healthy Longev*.

Chapter 8:

Siriwardana A, Hoffman A, Morton R, Smyth B, Brown M. Estimating a minimal important difference for the EQ-5D-5L utility index in dialysis patients. *Value Health*. 2024; 27(4):469-477.

Conference presentations arising from this thesis

Oral presentations

Siriwardana A, Hoffman A, Morton R, Smyth B & Brown M. Estimating a minimum clinically important difference for the EQ-5D utility index in dialysis patients. Australian Health Economics Society Conference. Brisbane, 20 September 2022.

Siriwardana A, Gray N, Makris A, Li C, Yong K, Mehta Y, Ramos J, Di Tanna G, Gianacas C, Addo I, Roxburgh S, Naganathan V, Foote C & Gallagher M. The Elderly Advanced CKD Program: Methods & baseline characteristics of a study program investigating treatment Decision-making and care among older adults with kidney failure. Australia and New Zealand Society of Nephrology 57th Annual Scientific Meeting. Sydney, 17 October 2022.

Siriwardana A, Hoffman A, Morton R, Smyth B & Brown M. Estimating a minimum clinically important difference for the EQ-5D utility index in dialysis patients. Australia and New Zealand Society of Nephrology 57th Annual Scientific Meeting. Sydney, 17 October 2022.

Siriwardana A, Smyth B, Jardine M. Waiver of informed consent in clinical research: A review of contemporary guidelines. Kidney Disease Clinical Trialists Workshop. Washington DC, 15 March 2024.

Siriwardana A, Jardine M, Perkovic V, Jun M, Kotwal S, Arnott C, Neuen B. Cardiovascular, kidney and safety outcomes with canagliflozin in older adults: A combined analysis from the

CANVAS Program and CREDENCE trial. American Society of Nephrology Kidney Week 2024. San Diego, 24 October 2024 (upcoming).

Conference abstracts under review

Siriwardana A, Gray N, Roxburgh S, Naganathan V, Clayton J, Foote C, Gallagher M, On behalf of the Elderly Advanced CKD Program Investigators. Comparison of baseline characteristics of participants in the OUTLOOK study with older patients in the Australia and New Zealand Dialysis and Transplant Registry. World Congress of Nephrology 2025. New Delhi, 6-9 February 2025.

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(included in Appendix B)

Publications

Siriwardana A, Hoffman A, Brennan F, Li K, Brown M. Impact of Renal Supportive Care on symptom burden in dialysis patients: A prospective observational cohort study. *J Pain Symptom Manage.* 2020; 60(4):725-736.

Dahwa R, Rutsito L, **Siriwardana A,** Kumar N, Gallagher M. Dialysis prevalence in Zimbabwe: A cross-sectional descriptive study. *Am J Kidney Dis.* 2022; 80(6):813-816.

Published conference abstracts

Dawha R, Rutsito L, **Siriwardana A**, Kumar N, Gallagher M. Mortality in incident dialysis patients in Zimbabwe. *Kidney Int. Rep.* 2021; 6(4):S107.

Dawha R, Rutsito L, **Siriwardana A**, Kumar N, Gallagher M. Outcomes in patients with acute kidney injury requiring dialysis in Zimbabwe. *Kidney Int. Rep*. 2024; 9(4):S539.

Conference abstracts under review

Jeyaruban A, Bose B, Lee V, Jardine M, Mallawarchchi A, Ritchie A, Wong MG, Makris A, Badve S, **Siriwardana A,** Yong K, Perkovic V, Kotwal S. Glomerular disease registry and biobank (GRIT) – design and baseline results. World Congress of Nephrology 2025. New Delhi, 6-9 February 2025.

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Abbreviations

AKI	Acute kidney injury
ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
CANVAS	Canagliflozin Cardiovascular Assessment Study
CI	Confidence interval
CKD	Chronic kidney disease
CKM	Conservative kidney management
Co-TIMELY	Caregivers of The InfirM ElderLY with end stage kidney disease
CONTEND	CONsumer views of Treatment options for Elderly patieNts with kiDney failure
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
FI	Frailty index
GLP-1RA	Glucagon-like peptide 1 receptor agonist
HD	Haemodialysis
HF	Heart failure
HR	Hazard ratio
HRQOL	Health-related quality of life
KDIGO	Kidney Disease Improving Global Outcomes
KFRE	Kidney Failure Risk Equation
KRT	Kidney replacement therapy

MACE	Major adverse cardiovascular events
MID	Minimal important difference
MREK	Mortality Risk Equation for Kidney disease model
nsMRA	Non-steroidal mineralocorticoid receptor antagonist
OUTLOOK	OUTcomes Of Older patients with Kidney failure
RAS	Renin angiotensin system
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter-2
T2DM	Type 2 diabetes
TIMELY	Treatment modalities for the InfirM ElderLY with end stage kidney disease
UK	United Kingdom
US	United States

CHAPTER 1

Thesis introduction

INTRODUCTION

The global population is facing an unprecedented rate of ageing. In 2020, the world's population aged over 60 years exceeded that of children aged under 5 years. By 2030, it is projected that one in six people will be over 60 years, and between 2015 and 2050 the proportion of the global population aged over 60 years will almost double from 12% to 22%.[1] These trends are associated with dramatic increases in the burden of chronic diseases, frailty and disability, and significant impacts on current and future healthcare systems.

Chronic kidney disease (CKD) is among the conditions being critically driven by population ageing. CKD is defined as a reduction in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73m^2 or the presence of markers of kidney damage for a minimum of three months. The most advanced form of CKD, kidney failure, is defined as an eGFR that declines below 15 mL/min/1.73m^2.[2] The Global Burden of Disease (GBD) Study which assessed global health data from 1990 to 2017 provides the most comprehensive overview of global CKD trends.[3, 4] This data reveals clear increases in CKD burden from 1990 to 2017, with crude global CKD prevalence increasing by one-third over this time period. Importantly, however, age-standardised global CKD prevalence has remained relatively stable over this time period, suggesting that population ageing is the primary driver of increases in global CKD prevalence.[3] As a result, without widespread mitigation strategies and novel treatments, it is estimated that CKD will be the fifth leading cause of death worldwide by 2040,[5] and that the prevalence of the most severe forms of CKD (categories G3-G5 encompassing eGFR values ≤59 mL/min/1.73m^2) will exceed 10% in many regions of the world by 2050.[6] These trends are particularly pertinent to high-income countries where populations already have a

preponderance of older age-groups. In Australia, CKD currently affects 22% of adults aged 65-74 years and 45% over 75 years,[7] and CKD affects 34% of adults aged over 65 years in the United States.[8]

As the severity of CKD increases the risk of adverse outcomes for patients' increases, with older patients who commence renal replacement therapies (such as dialysis and transplantation) having 1-year mortality rates of 20-30% and 5-year mortality rates exceeding 75% in high income countries such as Australia and the United States.[9, 10] Beyond poor outcomes for older patients, treatments for severe CKD such as dialysis are burdensome and expensive, with their use having ramifications for patients, their families, health systems and the wider economy.

With this burgeoning CKD burden among older populations, there is a need to understand how ageing and CKD interact, to identify and implement interventions to mitigate progression of CKD to kidney failure in older individuals, to understand older patient priorities as they undertake shared decision-making processes in choosing treatment pathways, and to ensure provision of evidence-based therapies and treatment pathways within healthcare systems. This chapter introduces and provides background to these needs.

INTERACTIONS BETWEEN AGEING, THE KIDNEYS AND CKD

Kidney volume and functional nephron number decline with age. This is driven by a number of molecular and haemodynamic changes, including oxidative stress, decreased expression

of anti-ageing factors such as klotho, impairment of cell autophagy, defects in DNA damage repair and mitochondrial function, declines in effective renal plasma flow, intimal and medial thickening of renal microvasculature, and alterations in tubular sodium reabsorption and fluid balance regulation.[11-13] These changes culminate in age-related annual decreases in eGFR ranging from 0.4 to 2.6 mL/min/1.73m^2.[11] This eGFR decline is much less than the degree of nephron loss, owing to hypertrophy and functional compensation of remnant nephrons ameliorating substantial declines in kidney function.[14] However, these changes reduce renal functional reserve and increase the susceptibility to acute kidney injury (AKI) and CKD in older individuals.[13, 14]

These risks to kidney function are compounded by the increasing comorbidity of advancing age. Diabetes and hypertension are predominantly conditions of older individuals, with 59% of Australians with type 2 diabetes aged ≥65 years, and nearly half of all adults aged >75 years in Australia having hypertension.[15] Additionally, cardiovascular diseases, including coronary artery disease, heart failure and stroke, affect over 50% of adults aged >75 years in high-income countries.[6] Cardiovascular diseases have a bidirectional relationship with CKD, with CKD also accelerating vascular calcification and stiffness, and the development of left ventricular hypertrophy.[16] As a result, CKD, particularly in older people, is strongly associated with an increased risk of heart failure, cardiovascular death and all-cause mortality,[11, 16] and most individuals with CKD die due to cardiovascular disease before reaching kidney failure.[6] Effective treatments, such as lifestyle and pharmacological interventions, to modify the impact of diabetes, hypertension and cardiovascular disease risk are therefore among the highest priorities in mitigating the wave of CKD and its health consequences in older individuals world-wide.

CKD AND FRAILTY

Frailty is a multi-dimensional construct resulting in a cumulative decline in physiological systems and greater vulnerability to physical stressors.[17] Frailty is related to, but distinct from, chronological ageing, though frailty disproportionately affects older adults. Its prevalence is high among patients with CKD and increases with CKD progression, with 48% of patients with advanced CKD considered frail.[18] In turn, frailty is associated with adverse outcomes in CKD patients, including reduced quality of life, increased hospitalisations, progression to kidney failure, and higher risk of mortality.[19, 20] Although the clinical implications of frailty in CKD populations are high, targeted frailty intervention studies among CKD patients are few and understanding the extent to which the efficacy and safety of established CKD therapies extends to frail CKD populations are research priorities.[21]

MANAGING CKD IN OLDER PATIENTS

Treatment of CKD in older individuals aims to prevent CKD-associated cardiovascular events, premature mortality and progression to more advanced stages of CKD including kidney failure. Traditional approaches to management include healthy lifestyle modification such as smoking cessation, regular exercise and maintaining healthy dietary intake. These lifestyle interventions are also established strategies to reduce the development of CKD risk factors such as hypertension, diabetes, cardiovascular disease and obesity.[2] Evidence for the benefits of these interventions extends to older patients, with findings from the LIFE trial conducted in 8 sites in the United States demonstrating that a daily moderate-intensity

exercise intervention in older community-dwelling individuals aged 70-89 years slowed eGFR decline by 0.96 mL/min/1.73m^2 over the 2 year trial period.[22] In practice, however, widespread implementation of lifestyle interventions such as these require multi-level stakeholder engagement and are challenging to implement in older patient populations with high rates of comorbidity and burdens of treatment.[12]

Pharmacological management of risk factors for CKD including diabetes and hypertension are critical in slowing CKD progression and reducing cardiovascular risk. However, optimal treatment targets in older individuals remain controversial. The STEP trial, which randomised older patients aged 60 to 80 years with hypertension to intensive blood pressure lowering with a target systolic blood pressure of 110-129 mmHg versus standard blood pressure lowering to a systolic blood pressure of 130-149 mmHg, demonstrated a reduction in the risk of cardiovascular events in the intensive target arm though at the expense of an increased risk of hypotension events.[23] Notably, however, less than 3% of patients in the STEP trial had CKD at baseline. Kidney Disease Improving Global Outcomes (KDIGO) 2024 guidelines provide broad recommendations of 'less intensive BP-lowering in people with frailty, high risk of falls and fractures, very limited life expectancy, or symptomatic postural hypotension'.[2] Similarly broad targets exist with for glycaemic control in older patients with diabetes and CKD. The ADVANCE trial, which randomised patients with type 2 diabetes to intensive glucose control (HbA1c ≤6.5%) versus standard glucose control, demonstrated reductions in the risk of cardiovascular events and new or worsening nephropathy, with no effect modification according to baseline age.[24] However, subsequent trials and meta-analyses have demonstrated varied impacts of tight glucose control on cardiovascular events and little or no improvement in all-cause mortality and progression to

kidney failure.[25] Additionally, the benefits of tight glycaemic control are likely to manifest over many years of treatment, which may make them less relevant to older patients at high risk.[26, 27] As a result, guidelines on the management of diabetes in CKD patients recommend individualised glycaemic targets, particularly for older adults, based on age, comorbidities, hypoglycaemia risk, life expectancy and patient preferences.[27]

Beyond traditional lifestyle approaches and optimal control of CKD risk factors, significant advances have been made in the development of targeted CKD therapies in recent decades. Renin-angiotensin system (RAS) blockade with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) form the pillar of CKD therapy, having been extensively shown to reduce the risk of CKD progression, kidney failure and all-cause mortality in patients with diabetic CKD and proteinuric non-diabetic CKD.[28-30] However, it is important to recognise that most studies investigating ACE inhibitors and ARBs in CKD had very limited representation of participants over the age of 70 years. Other trials of ACE inhibitors and ARBs in older populations but not specifically with CKD have demonstrated reduced cardiovascular events and cardiovascular mortality, thus offering support for the use of these agents in older patient groups.[31-33]

The drug class of sodium-glucose cotransporter-2 (SGLT2) inhibitors inhibit glucose reabsorption in the proximal tubule of the kidney and thereby result in glycosuria and natriuresis.[34] While originally developed as glucose-lowering agents, the cardiovascular, kidney and mortality benefits of SGLT2 inhibitors among adults with type 2 diabetes, with and without CKD, have now been extensively demonstrated in several large cardiovascular and kidney outcome trials. [35-47] Notably, these effects are independent of glucose-lowering.

While representation of older patients in major SGLT2 inhibitor trials was limited, initial analyses suggest that the efficacy of SGLT2 inhibitors are likely to extend across the spectrum of age,[48-51] but further reporting on older subgroups from these trials are needed. Other newer agents including glucagon-like peptide 1 receptor agonists (GLP-1RAs) and non-steroidal mineralocorticoid receptor antagonists (nsMRAs) have been more recently shown to reduce kidney, cardiovascular and mortality events in patients with type 2 diabetes and varying degrees of CKD, however dedicated analyses on how the efficacy and safety profile of these agents extends to older patients are awaited.[52-54]

SGLT2 inhibitors, GLP-1RAs and nsMRAs herald a promising new era of CKD therapies. However, the limited and post hoc nature of the analyses of these agents in older age subgroups means that conclusions for older patients are largely exploratory. There is a need to better understand how these clinical benefits and safety profiles translate, particularly to the very elderly and frail, in order to better inform individualised risk-benefit decisions on CKD therapies in older patients.

TREATMENT OPTIONS FOR KIDNEY FAILURE IN OLDER PATIENTS

The management of older patients approaching and with established kidney failure (eGFR <15 mL/min/1.73m^2) broadly falls into two approaches:

- Preparation for, and initiation of, kidney replacement therapy (KRT) using either kidney transplantation or a form of dialysis, or

- Conservative kidney management (CKM), a range of interventions to alleviate uraemic symptoms, improve quality of life, delay progression and manage complications, without the use of KRT.[55]

The KRT option in older patients is almost exclusively a form of dialysis, as very few patients aged ≥75 years with kidney failure are medically suitable for transplantation and the societal gain from allocating such a scarce resource to older patients is small. Older patients who undergo transplantation experience inferior graft outcomes and poorer patient survival compared with younger counterparts, and hence transplantation in the elderly requires very careful patient selection.[56] As a result, choosing between dialysis and CKM is the predominant form of decision-making faced by older patients with kidney failure and their families.

Kidney failure in older patients, regardless of treatment pathway, results in a significant reduction in life expectancy compared with the comparative age-matched general population. Australian registry data indicates that the 1-year mortality rate after dialysis initiation for individuals ≥75 years exceeds 20% and 5-year mortality is over 75%.[9] Comparisons in survival between dialysis and CKM among older patients are challenging due to the limited number of robust prospective survival estimates for CKM patients and methodological biases that arise from differing definitions for calculating survival time.[57] Current evidence suggests dialysis may prolong life in some older individuals, however this survival advantage is lost in older patients with high comorbidity (particularly cardiovascular disease), poor performance status or extreme age (≥80 years).[57, 58] Additionally, dialysis may result in unacceptable physical and psychological impacts for many patients. Prior systematic reviews have identified that CKM may yield similar quality of life and have advantages over

dialysis for some patients in terms of symptom burden, hospitalisation rates and alignment of end-of-life care with preferred place of death, however the heterogeneity and quality of studies prevents meta-analyses and quantitative estimation of these differences.[58, 59] Thus, while an understanding of expected outcomes is essential to shared decision-making processes for older patients with kidney failure, data limitations and evidence gaps make such discussions challenging and highly variable. For patients who opt for CKM in Australia, this is increasingly being supported through formal CKM programs with multi-disciplinary nephrology and palliative care clinicians. There is, however, great variability in access to these services across Australia and internationally.[55, 60] Greater understanding of kidney failure outcomes, particularly for patients on a CKM pathway, are needed in order to understand which patients are likely to derive the greatest benefits from this treatment pathway, to better inform the needs of CKM patients and to understand how these services are best provided.

RESEARCH METHODOLOGY IN INVESTIGATING OLDER PATIENTS WITH CKD AND KIDNEY FAILURE

Representation, generally, of older people in clinical trials is poor, limiting the ability to make evidence-informed treatment decisions. This is particularly true in older patients with CKD, where prospective observational studies and randomised controlled trials (RCTs) are rare.[61, 62] Robust prospective cohort studies and specifically powered RCTs for older populations are essential to better understand outcomes, identify effective interventions to delay disease progression in this population, and to guide treatment decision-making, however they are

lacking. Reasons for this are multifaceted,[61-65] though there are potential strategies to overcome these. These are summarised in Table 1.

Table 1. Perceived barriers and challenges to the design and enrolment of older patients with CKD and kidney failure in observational studies and randomised controlled trials (RCTs) and potential solutions.

Barrier/challenge	Potential solutions
Arbitrary upper age limits in RCTs	Elimination of chronological upper age limits as an eligibility criteria in RCTs
Highly prevalent conditions in older patients frequently considered as exclusion criteria in observational studies and RCTs (including multimorbidity, short life expectancy, polypharmacy/concomitant medications and frailty)	Broadening of study inclusion criteria Targeted support for older patients and their carers to facilitate study participation despite comorbid conditions (such as transport support, home visits, and telephone visits)
Efficacy and safety outcomes not directly relevant to older patient populations	Design of dedicated studies in older patient populations powered to detect relevant clinical outcomes
High prevalence of cognitive impairment which poses challenges to informed consent processes	Utilisation of ethically appropriate waiver of consent models, particularly for low-risk routine-care studies
High cost of conducting RCTs in older patients	Greater utilisation of well-designed observational studies which can achieve high inclusivity, external validity and feasibility Design of pragmatic and routine-care studies with lower costs and higher generalisability
Lack of understanding of the importance of participation in clinical research among older patients and carers, and perceptions that participation will be burdensome	Increased attempts at engaging older patients in research opportunities Simplification of study processes, including consent, study visits and methods of data collection

SUMMARY

CKD and its most advanced form, kidney failure, are conditions strongly interlinked with age and their growing prevalence present significant challenges to current and future global

healthcare. In high-income countries such as Australia which already have a predominance towards older age-groups, these impacts are current. The lack of high-quality evidence on effective treatments that may reduce morbidity and mortality in this patient population is profound, and a more detailed understanding of various clinical outcomes so that older patients, carers and clinicians are better informed as they make life-impacting treatment decisions is essential. Addressing these needs requires collaborative, well-planned and novel research designs. This thesis aims to take a systematic approach to increase understanding on important clinical outcomes and management approaches for older patients with CKD and kidney failure.

OBJECTIVES

The specific objectives of this thesis are:

1. To summarise evidence gaps in the understanding of clinical outcomes in older patients with kidney failure, and to report on the design of the Elderly Advanced CKD Program which aims to address these (Chapter 2)
2. To report on ethical guidelines for the use of waiver of informed consent in clinical research and how this consent model may be appropriately utilised in research involving older persons (Chapter 3)
3. To compare prospective observational and registry-based data on Australian patients aged ≥75 years with kidney failure (Chapter 4)
4. To examine how risk prediction tools can be used to guide treatment decision-making discussions in older patients with CKD (Chapter 5)

5. To examine the efficacy and safety of SGLT2 inhibitor therapy across the spectrum of age (Chapter 6)
6. To examine the efficacy and safety of SGLT2 inhibitor therapy in frail individuals (Chapter 7)
7. To evaluate longitudinal metrics of health-related quality of life in dialysis patients and how these may be used to guide design of dialysis randomised clinical trials involving older patients (Chapter 8).

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CHAPTER 2

Treatment decision-making and care among older adults with kidney failure: protocol for a multicentre, prospective observational cohort study with nested substudies and linked qualitative research (the Elderly Advanced CKD Program)

CHAPTER OVERVIEW

Greater understanding of core outcomes for older patients with kidney failure is essential to support shared decision-making between patients, carers and clinicians as they decide between kidney failure treatment pathways. This chapter addresses the first objective of this thesis, to summarise evidence gaps in the understanding of clinical outcomes in older patients with kidney failure. These outcomes include survival as well as patient-reported outcomes valued highly by older patients, including health-related quality of life, symptom burden, hospitalisations and caregiver burden. This chapter then reports on the design of the Elderly Advanced CKD Program, a collection of studies which systematically aim to address these evidence gaps. This chapter also discusses a key aim of the Elderly Advanced CKD Program, which is to formulate a risk prediction model that can be used to guide prognostic discussions for older patients.

PUBLICATION DETAILS

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AUTHOR CONTRIBUTIONS

AS is a leading member of the national steering committee for the Elderly Advanced CKD Program. AS conducts, oversees and coordinates the studies in this program. For this chapter, AS, CF, MG, NG and YM conceived the Program and formulated protocols for the

study components. AS drafted the manuscript, and all authors contributed to critical review and revisions of the manuscript.

ABSTRACT

Introduction: Shared treatment decision-making and planning of care are fundamental in advanced chronic kidney disease (CKD) management. There is limited data on several key outcomes for the elderly population including survival, quality-of-life, symptom burden, changes in physical functioning, and experienced burden of healthcare. Patients, caregivers and clinicians consequently face significant uncertainty when making life-impacting treatment decisions. The Elderly Advanced CKD Program includes quantitative and qualitative studies to better address challenges in treatment decision-making and planning of care among this increasingly prevalent elderly cohort.

Methods and analysis: The primary component is OUTLOOK, a multi-centre prospective observational cohort study that will enrol 800 patients ≥75 years with kidney failure (estimated glomerular filtration rate ≤15mL/min/1.73m^2) across a minimum of 8 sites in Australia. Patients entered are in the decision-making phase or have recently made a decision on preferred treatment (dialysis, conservative kidney management or undecided). Patients will be prospectively followed until death or a maximum of 4 years, with the primary outcome being survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry, and end-of-life care characteristics. Data will be used to formulate a risk prediction tool applicable for use in the decision-making phase. The nested sub-studies TIMELY and Co-TIMELY will longitudinally assess quality-of-life, symptom burden, and caregiver burden among 150 patients and 100 caregivers, respectively. CONTEND is an additional qualitative study that will enrol a minimum of 20 patients and 20 caregivers to explore experiences of treatment decision-making and care.

Ethics and dissemination: Ethics approval was obtained through Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). OUTLOOK is approved to have waiver of individual patient consent. TIMELY, Co-TIMELY and CONTEND participants will provide written informed consent. Final results will be disseminated through peer-reviewed journals and presented at scientific meetings.

Strengths and limitations of this study program

- Prospective study design with multi-centre enrolment, broad representation and ease of data collection.
- Clinical outcome data collection to allow formulation of a risk prediction tool for use in the treatment decision-making phase.
- Nested sub-studies using a combination of quantitative and qualitative methodologies to provide wide-ranging assessment of important clinical outcomes for older patients with kidney failure, including survival, quality of life, symptom burden, receipt of dialysis, receipt of conservative kidney management, caregiver experiences, and end-of-life care.
- The study program is conducted across multiple sites in Australia and extrapolation of findings to other healthcare settings may not be applicable.

INTRODUCTION

Background

Chronic kidney disease (CKD) has risen from the 17th to the 12th leading cause of death globally over the last 25 years. Increasing numbers of individuals are progressing to the most advanced form of the disease, kidney failure (defined as an estimated glomerular filtration rate 15 mL/min/1.73 m^2 or lower).[1] For the increasing proportion of these patients with advanced age and multi-morbidity, complex decisions need to be made about treatment with kidney replacement therapy (KRT, with dialysis or kidney transplantation) or conservative kidney management (CKM). CKM involves a range of interventions to manage symptoms, improve quality of life, delay progression and manage complications, without the use of KRT.[2]

In Australia, the prevalent dialysis population increased from 337 to 549 per million population between 2000 to 2019, with over half of prevalent patients aged ≥65 years and 26% aged ≥75 years.[3] Whilst dialysis registries in many countries measure entry onto dialysis well, it is more challenging to quantify and understand the characteristics and outcomes of older patients with kidney failure who do not enter dialysis programs. A retrospective data linkage analysis combined deaths ascribed to kidney failure from the Australian National Death Index with the Australia and New Zealand Dialysis and Transplant Registry and identified 21,370 patients with death due to kidney failure over a 4-year period.[4] Roughly half of the patients studied received dialysis (n=10,949) and a similar proportion died without ever receiving dialysis (n=10,421). The majority of the patients who did not receive

dialysis were aged ≥75 years, the age group which also has the highest rate of incident dialysis in Australia and other developed countries.

For older patients with advanced CKD, the processes of decision-making between treatment pathways differ from that of younger patients, where there are clear differences in survival between treatment options. The greatest uncertainty occurs for patients aged 75 years or older, where few patients are medically suitable for transplantation, and there is limited data to inform decision-making, especially around the relative burden of dialysis and CKM and the outcomes they deliver for an older patient group. In turn, there are few tools to assist clinicians and patients in making decisions between these treatment pathways.[5-10] Best practice approaches to decision-making should be timely, well-informed and individualised.[11] Timely decisions are essential, as patients who commence dialysis in an unplanned manner have increased mortality,[12, 13] reduced quality of life,[14] and significantly higher healthcare costs.[15] Ideally, an understanding of the various health outcomes important to older patients, including survival, quality of life, symptom burden, and experienced burden of healthcare should be at the centre of discussions.[16-18] Furthermore, patients express a desire for frank, detailed prognostic information,[19-21] but, in practice, there is little data to inform such prognostication. Real-world decision-making is thus challenging and highly variable.

Current knowledge of outcomes

Prospective clinical data collection is difficult in older patients, most notably seen in their under-representation in randomised clinical trials.[22, 23] This reflects their high burden of comorbidities, frailty and cognitive impairment, and high experienced burden of

treatment.[24] Well-designed observational studies can achieve high inclusivity, external validity, and feasibility, and hold significant applicability for evaluating outcomes among older advanced CKD patients. A scoping review of published observational literature reporting outcomes relevant to shared decision-making for older patients with kidney failure identified 248 publications, the majority from high-income English-speaking countries (USA, UK, Canada and Australia) and published in the last 10 years.[7] However, 77% of studies exclusively pertained to dialysis patients,[7] similar to that seen in reported meta-analyses[25, 26] and highlights the limited published literature on CKM.[10]

A meta-analysis of patient survival among elderly patients with kidney failure from studies between 1976 to 2014 reported similar 1-year survival rates between dialysis and CKM (73.0-78.4% and 70.6%, respectively).[25] However, survival estimates for CKM patients were derived from only 12 of the total 89 studies and accounted for much fewer patients (724 vs. 294,196 for CKM and dialysis, respectively). There was also considerable residual heterogeneity for survival estimates within each treatment group, which may reflect changes in patterns of referral, acceptance onto dialysis programs and components of CKM provided by centres over the long period of the review. Other recent observational studies have been inconsistent, with some suggesting a survival advantage with dialysis compared to CKM,[27, 28] and others suggesting limited or no survival advantage from dialysis in those patients with severe comorbidity, poor performance status or extreme age.[29-31]

Many survival comparisons are also confounded by methodological issues, such as; lead-time bias, immortal time bias, and indication bias.[25, 32] Lead-time bias arises from variability in defining a distinct starting point for CKM. This may result in a perceived survival

advantage with CKM if survival time is calculated from an earlier starting point not equivalent to when dialysis would have been initiated. Conversely, immortal time bias occurs mainly in analysis of retrospective cohorts, when an index starting point is defined and patients go on to start dialysis much later (or not at all), giving rise to a perceived survival advantage ascribed to dialysis treatment. Indication bias is inherent to analysing survival in elderly kidney failure cohorts where there is expected referral of healthier patients for dialysis, and referral of older and frailer patients for CKM. Incorporating baseline covariates such as frailty and functional status into adjusted survival analyses aims to account for this, however such data is frequently not collected or available. These biases are magnified in retrospective analyses conducted after treatment decisions have been made, and notably 71 of the 89 included studies in Foote et al.'s systematic review were retrospective.[25]

As identified in qualitative and discrete choice studies, a range of other outcomes are important to older patients, caregivers and clinicians in decision making, including quality of life, symptom burden, functional independence, experienced burden of healthcare and caregiver burden.[33-36] Existing literature suggests that the health-related quality of life of older patients on dialysis, compared to CKM, is broadly similar,[37] that some older advanced CKD patients would 'trade-off' survival time in preference for maintaining functional independence,[33-35] and that dialysis initiation is associated with high rates of deterioration of physical functioning among patients and high caregiver burden.[38-40] Additionally, Canadian and UK studies suggest older dialysis patients spend significantly more time in hospital than CKM patients.[27, 41] However, there are notable limitations to this data, as few studies have broad and systematic data collection, resulting in high risk of selection bias and limited adjustment for other variables.[37] The majority of published studies are cross-sectional, and

longitudinal data across either treatment pathway are lacking. Furthermore, patient outcomes, burden of healthcare and caregiver experiences are markedly dependent on healthcare structures. There is a need to assess these outcomes widely, including in the Australian context.

Program aims

In response to these limitations in data, we describe a program of work, the Elderly Advanced CKD Program, designed to explore decision-making and planning of care for older patients (defined in this program as age ≥75 years) with kidney failure. This includes addressing deficiencies in outcome data, broadening understanding of outcomes that are a priority to patients and caregivers, and applying this evidence to better support real-world decision-making processes. The aims of this study program are:

(a) To quantify survival in a cohort of older patients with kidney failure followed from estimated glomerular filtration rate (eGFR) ≤15mL/min/1.73m^2,

(b) To formulate a risk prediction tool for mortality applicable to patients at the time of treatment decision-making,

(c) To quantify other key patient outcomes among older patients with kidney failure in a prospective and longitudinal fashion, including quality of life, symptom burden, burden of planned and unplanned hospitalisations, and caregiver burden,

(d) To qualitatively explore patient and caregiver experiences of shared decision-making processes, planning of care, CKM and, ultimately, end-of-life care.

METHODS AND ANALYSIS

Program design

The program consists of 4 components (*Figure 1* and *Table 1*); a prospective observational cohort study with 3 components (including a small qualitative component), and a purely qualitative study examining patient and caregiver experiences:

1. OUTcomes Of Older patients with Kidney failure (OUTLOOK),
2. Treatment modalities for the InfirM ElderLY with end stage kidney disease (TIMELY),
3. Caregivers of The InfirM ElderLY with end stage kidney disease (Co-TIMELY), including a small qualitative component, and
4. CONsumer views of Treatment options for Elderly patieNts with kiDney failure (CONTEND).

Study design

OUTLOOK is a multi-centre prospective observational cohort study that aims to enrol 800 older patients with kidney failure (age ≥75 years and eGFR ≤15mL/min/1.73m^2) across a minimum of 8 sites in Australia. The study is ethically approved with a waiver of the need for individual patient consent. TIMELY is a nested cohort study that aims to enrol a subset of 150 patients within OUTLOOK, which requires individual patient consent for additional data collection relating to quality of life, symptom burden and functional status over time. The Co-TIMELY study aims to enrol 100 caregivers of older patients to prospectively examine caregiver responsibilities, quality of life and caregiver burden.

Study population and recruitment

Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY are shown in *Table* 2. Patients are enrolled into OUTLOOK by study investigators if they meet the inclusion criteria, which are broad to minimise selection bias, maximise recruitment and increase external validity of the study. An eGFR ≤15mL/min/1.73m^2 at study entry, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula, was chosen to define kidney failure, as it reflects a point at which patients and clinicians would be expected to be making decisions regarding planning for dialysis or CKM.[5] This uniform definition provides an index date from which survival time will be determined for all participants, regardless of treatment pathway, aiming to mitigate lead-time bias and immortal time bias.

All patients enrolled into OUTLOOK will be screened for potential participation in TIMELY, with the only additional exclusion criteria for patient participation being extreme infirmity, significant cognitive impairment or insufficient English language skills (see *Table 2*), all of which would preclude participation in patient-reported outcome questionnaires. Potential TIMELY participants will be approached, and if willing to participate, will be asked to provide written informed consent. For the Co-TIMELY study, patients who consent to participate in TIMELY will be asked to nominate a primary caregiver. This caregiver will be screened against inclusion/exclusion criteria (see *Table 2*) and, if eligible, will be approached for participation with a view to provide written informed consent.

Study period

Patients enrolled into OUTLOOK have baseline data collection and will be prospectively followed until death or for a maximum of 4 years, with follow-up occurring at 6-monthly intervals. Similarly, participants enrolled into TIMELY will be followed until death or for a

maximum of 4 years, with follow-up questionnaires completed by participants at 12-monthly intervals. Caregivers enrolled into Co-TIMELY will be followed prospectively until either caregiver death, until 6 months after death of the corresponding care-recipient, or for a maximum of 4 years.

Measurement of baseline characteristics

Baseline data collection schedules for OUTLOOK, TIMELY and Co-TIMELY are shown in *Table* 3. OUTLOOK will only collect data from patient medical records and from healthcare providers involved in patient care (including from public/private hospitals, general practitioners, specialist records, and pathology providers). At enrolment, site investigators will review records and discuss with the treating team to determine the patient's planned treatment pathway (dialysis, CKM, or undecided) and the approximate timing of this decision.

Other baseline data collection incorporates wide-ranging measurement of patient characteristics that, based on prior literature, may influence the study's primary outcome of survival. These include patient demographics, medical history, medications, baseline pathology measurements, measures of functional status, and treatment plans. Baseline medical history will be used to derive a modified Charlson comorbidity score, a validated predictor of mortality in kidney failure patients, with a theoretical maximum score of 37.[42, 43] Baseline pathology measurements include serum creatinine, eGFR, albumin, haemoglobin, parathyroid hormone, and proteinuria (albumin:creatinine ratio or protein:creatinine ratio), all of which are markers of kidney disease progression.[18] Measures of functional status are the Clinical Frailty Scale,[44] Karnofsky performance score,[45] and mobility status. The Clinical

Frailty Scale is a 9-point scale that was chosen for its feasibility and its prior use in advanced CKD research showing an association with mortality.[46] The Karnofsky functional performance score assesses functional status on a scale of 0 to 100, and it is the most widely used measure of functional impairment in chronic disease states including kidney failure.[47] Additional treatment-related questions at baseline address the use of advance care planning, appointment of an enduring guardian, and the 'surprise question', which asks the treating nephrologist if they would be surprised if the patient died in the next 12 months and has demonstrated predictive ability for mortality in advanced CKD.[48]

For TIMELY participants, two additional cognitive and nutritional baseline components will be collected during face-to-face visits. The mini-mental state examination[49] is a validated tool for assessment of cognition in the general population,[50] and cognitive impairment (score of <24 out of a maximum score of 30) is associated with adverse health outcomes in advanced CKD.[47] The subjective global assessment tool[51] assesses gastrointestinal symptoms, weight change, functional capacity and visual evaluation of subcutaneous tissue and muscle mass. It is the most commonly used nutritional assessment tool in Australian nephrology units, with higher rating scores associated with increased mortality in dialysis patients.[52]

For caregivers participating in Co-TIMELY, baseline data includes caregiver demographics, caregiver characteristics (including relationship to the care-recipient and duration of caregiving), and caregiver responsibilities.

Primary and secondary outcomes

The primary outcome of OUTLOOK is survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry (including serum creatinine and eGFR), and characteristics of end-of-life care (including date, location, and primary cause of death).

In the nested sub-study TIMELY, additional outcomes are changes in health-related quality of life, changes in symptom burden, and patient-reported hospitalisations in the preceding 12 months. Health-related quality of life is assessed at baseline and in annual follow-up by the EuroQol-5 Dimension 3-Level (EQ-5D-3L) questionnaire and the Satisfaction with Life Scale (SWLS). The EQ-5D-3L is a generic quality of life measure assessing 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[53] These responses can be compared against an Australian EQ-5D value set[54] to derive a single utility score ranging from less than 0 to 1 (with 0 representing death, negative values representing utilities worse than death and 1 representing perfect health). The SWLS is a 5-item scale with questions relating to ideal life, conditions of life, and satisfaction with present and past life.[55] It has been used in various disease states including advanced CKD.[37] Symptom burden is assessed with the Integrated Palliative Care Outcome Scale (iPOS-Renal), an inventory modified for use in advanced CKD populations.[37, 56] It asks the responder about the impact of 15 kidney disease-specific physical symptoms and further emotional symptoms (each rated on a 5-point scale from 0, no impact, to 4, overwhelming impact) in the preceding week.

In the caregiver study Co-TIMELY, primary outcomes are changes in caregiver quality of life and changes in caregiver burden. Varied tools have been used to assess caregiver quality of life in prior CKD studies and the optimal tool is unclear.[57] Baseline and annual caregiver

quality of life is assessed in Co-TIMELY with the EQ-5D and SWLS as these are generic measures and they align with the TIMELY study. Caregiver burden is assessed at baseline and annual follow-up using the Zarit Burden Interview, a 12-question tool relating to feelings of personal strain from the caregiving role, with 5 responses for each question ranging from 0 (never) to 4 (almost always).[58] This tool is the most commonly used measure of subjective caregiver burden in advanced CKD studies.[57]

Following study completion, study datasets will be linked to the National Death Index, Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), Admitted Patient Data Collection (APDC), and Medicare and Pharmaceutical Benefits Schedules (MBS, PBS), using relevant national and state-based data linkage entities. Data linkage will be used to assess inpatient and non-inpatient healthcare usage and costs, dialysis characteristics and end-of-life care characteristics across treatment pathways.

Data analysis plan

From OUTLOOK, differences in survival between treatment groups will be analysed using Kaplan-Meier survival analysis and log-rank tests. A multivariable Cox proportional hazards model will be constructed using prespecified covariates based on clinical plausibility, including age, gender, comorbidity score, frailty score and functional performance score, with the aim of selecting a parsimonious model. Primary analyses will be a complete case analyses, however a multiple imputation approach for missing values of predictors will be assessed according to the proportion and patterns of missingness. Model performance will be assessed using standard metrics including discrimination (C-statistic) and calibration

(Hosmer-Lemeshow statistic), and internal validation will be performed with bootstrap resampling.

Bayesian networks allow a more flexible modelling approach, are more reliable when there are high correlations between predictor variables and allow a more efficient method to handle missing data, so an additional Bayesian network will be formulated using data from OUTLOOK. This model will consist of a target variable (mortality), multiple random variables (nodes), probabilistic dependencies between variables, and conditional probability tables that describe the direction and degree of influence between variables. The Bayesian model's performance will be assessed using the area under the curve-receiver operating characteristic (AUCROC), which is analogous to the C-statistic derived from the multivariate Cox proportional hazards model. Prediction models will be reported according to transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.[59]

Further data from TIMELY and Co-TIMELY including longitudinal changes in patient and caregiver quality of life, symptom burden, caregiver burden, and additional data from data linkage for end-of-life care characteristics, healthcare usage and costs will be analysed using a hierarchical modelling approach, which accounts for within- and between-patient variability for continuous outcomes, and Chi-square tests and logistic regression for categorical outcomes.

Sample size calculation

To guide sample size calculations in OUTLOOK, we estimated 40-50% 2-year mortality in patients who go on to dialysis and 60% for CKM patients.[12] A minimum of 10 events per candidate variable is used as a benchmark for sample size calculations in model development studies. It is anticipated that 6-10 variables will be included in our final models based upon prior advanced CKD risk prediction models.[60-63] However, larger sample sizes mitigate the risk of model overfitting, improve precision and performance of models, and enhance clinical utility.[64] Accordingly, a sample size of 800 patients in OUTLOOK is targeted. A subsidiary sample of 150 patients is targeted for TIMELY and 100 caregivers are targeted for Co-TIMELY.

Qualitative methodology

Caregivers in Co-TIMELY whose care-recipient is specifically receiving CKM will be asked to participate in a qualitative component. Minimum sample size is 20 caregivers and maximum sample size will be determined from data saturation, whereby no new themes are emerging from participant interviews. Single-encounter interviews will be conducted face-to-face or via teleconferencing for 30-60 minutes. These will be semi-structured using an interview guide, with participants asked to discuss their experiences of the planning of care, daily roles as a caregiver of a patient receiving CKM, and the impact being a caregiver has had on their life. Caregivers of patients who die during the study, who indicated on their consent that they are willing participate in a post-death interview, will be approached no sooner than 3 months and no later than 6 months after their care-recipient's death to participate in a second semi-structured interview exploring end-of-life care. Target sample size for this end-of-life care component is 10 caregivers. Questions will be based on the Quality of Dying and Death (QoDD) tool.[65, 66] Example interview questions include whether their care recipient

was comfortable, how often end-of-life symptoms were controlled, whether they were at peace with dying, where they died, and what support was offered to the caregiver.

CONTEND is the final qualitative component of the program and involves single-encounter interviews with patients ≥70 years with kidney failure (eGFR ≤15mL/min/1.73m^2) and their caregivers. Eligible patients must have had a discussion about treatment pathways with their nephrologist and they are about to decide or have made a treatment decision within the last 2 years (ie. patients can be on dialysis or a CKM pathway initiated within 2 years). Patients and caregivers will be purposefully recruited during routine outpatient visits. The focus of CONTEND is upon shared decision-making, with a broad interview guide including questions on what information was provided to facilitate decision-making, experiences of the decision-making process, barriers/enablers of decision-making, and experiences of end-of-life care planning. This component aims for a minimum of 20 patients and 20 caregivers and maximum sample size determined from data saturation.

Transcripts from the Co-TIMELY qualitative component and from CONTEND will be thematically analysed using grounded theory, where data will be coded using NVivo software and abstract categories are constructed inductively to identify themes and relationships between themes. Data will be reported according to the consolidated criteria for reporting qualitative research (COREQ).[67]

Patient and public involvement statement

The design of this research program is shaped by prior literature on older patient priorities when making advanced CKD treatment decisions.[5] The program began as pilot studies in

2017, with initial enrolment at 3 hospital sites. Informed by feedback from patients and caregivers, small changes to study design have been made to improve feasibility. The study design and participant information sheets for these studies will continue to receive regular feedback from the George Institute for Global Health Consumer Engagement Panel, consisting of patients with kidney disease and their caregivers.

ETHICS AND DISSEMINATION

Ethics approval for this study program has been obtained through the Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). OUTLOOK is approved as a waiver of individual patient consent study in accordance with the 2018 National Health and Medical Research Council National Statement on Ethical Conduct in Human Research.[68] All other study components in this program involve direct patient contact and data collection beyond routine care, and accordingly involve written and informed consent. All study data is stored through a dedicated electronic data capture tool only accessible to site and central investigators. All data is managed confidentially and anonymously, and will be stored for a minimum of 15 years in accordance with national guidelines.[68] The results of this research are intended to be disseminated through peer-reviewed journals and presented at scientific meetings.

DISCUSSION

While there will always be some degree of prognostic uncertainty in patient care,[69] the Elderly Advanced CKD Program aims to provide clinicians, patients and caregivers with accurate data and tools to reduce the extent of this uncertainty in the planning and provision of care for older patients with kidney failure. To our knowledge, this is the first study to prospectively follow an older kidney failure cohort to produce a risk prediction model for survival for use in the treatment decision-making phase. The nested work with patients and caregivers will provide detailed and longitudinal insights on important patient-reported outcomes such as quality of life and experienced burden of healthcare.

In the context of the exponential increase in elderly patients progressing to kidney failure in developed countries, this study program holds high clinical relevance. The program is currently enrolling across 8 sites in Australia, with the intention of further expansion to achieve national representation and enrolment targets for all studies by 2026. Baseline data from the 529 patients currently enrolled in OUTLOOK has found the following characteristics: mean age 83 years (range 75-99 years), predominantly community-dwelling (89%) and functionally independent (56%), with a high prevalence of frailty (47%). This is the population group in whom there is greatest equipoise regarding whether dialysis compared with CKM offers greater benefits. This work will thus generate valuable outcome data and ensure that the developed risk prediction tool will have direct clinical application. However, we acknowledge that such quantitative data alone will not overcome all challenges in complex decision-making. Accordingly, this research program incorporates qualitative work,

to broaden the focus and encompass perspectives of patients and their families on treatment decision-making processes, experiences of CKM and end-of-life care.

Large multi-centre cohorts prospectively investigating outcomes in older patients with kidney failure are few. To date, there are two comparative studies. The European QUALity study (EQUAL) is an ongoing study recruiting patients ≥65 years with eGFR ≤20mL/min/1.73m^2 in 5 European countries, with prospective follow-up for 4 years.[70] EQUAL aims to evaluate optimal timing of dialysis initiation among older patients, with additional insights regarding survival and longitudinal changes in patient-reported outcomes. Over 1500 of the targeted 3500 participants have been enrolled. The focus is on dialysis planning and the investigators have stated that patients on a CKM pathway will not be captured.[71] The Canadian Frailty Observation and Interventions Trial (CanFIT) is a multi-centre observational cohort study which has enrolled 603 adult patients between 2012-2018 with eGFR <30mL/min who have had baseline frailty assessments and are being prospectively followed.[72] CanFIT aims to examine the longitudinal trajectory of frailty and its associations with morbidity, mortality and patient-reported outcomes, but is capturing patients with less advanced kidney disease compared with those in the Australian Elderly Advanced CKD Program. Nonetheless, both EQUAL and CanFIT complement the large-scale, robust and prospective aims of the OUTLOOK study. The collective aims of these studies, particularly those of the Elderly Advanced CKD Program, are to better inform discussions and decision-making processes for older patients with advanced kidney disease.

This work has limitations. Given the observational methodology, there is the potential for confounding from measured and unmeasured variables in the quantitative components of

this program. For example, socioeconomic status has not been objectively measured and may be a confounder in survival and quality of life analyses. While the study design aims to minimise the impact of lead-time, immortal time and indication bias, complete elimination of these biases is not possible. Furthermore, while the study program aims to achieve multi-centre national representation, application of findings beyond Australia will have limitations.

Decision-making between treatment pathways is highly complex for older patients with kidney failure, their caregivers and clinicians. Challenges include accurate outcome predictions, communicating meaningful prognostic information, communicating associated uncertainty, and using this information to undertake systematic processes of shared decision-making and planning of care. The Elderly Advanced CKD Program is a large-scale multi-centre research program designed to address modifiable factors relating to each of these challenges by producing prospective, longitudinal, and robust data on survival, patient-reported outcomes and caregiver-reported outcomes, collected efficiently at a national level; to derive the necessary tools for patients, caregivers and clinicians; and, to understand patient and caregiver preferences for care. Such work is novel, practice-informing and much needed as we face a growing population of elderly, frail and comorbid kidney failure patients.

COLLABORATORS

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COMPETING INTERESTS

None declared.

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FIGURES AND TABLES

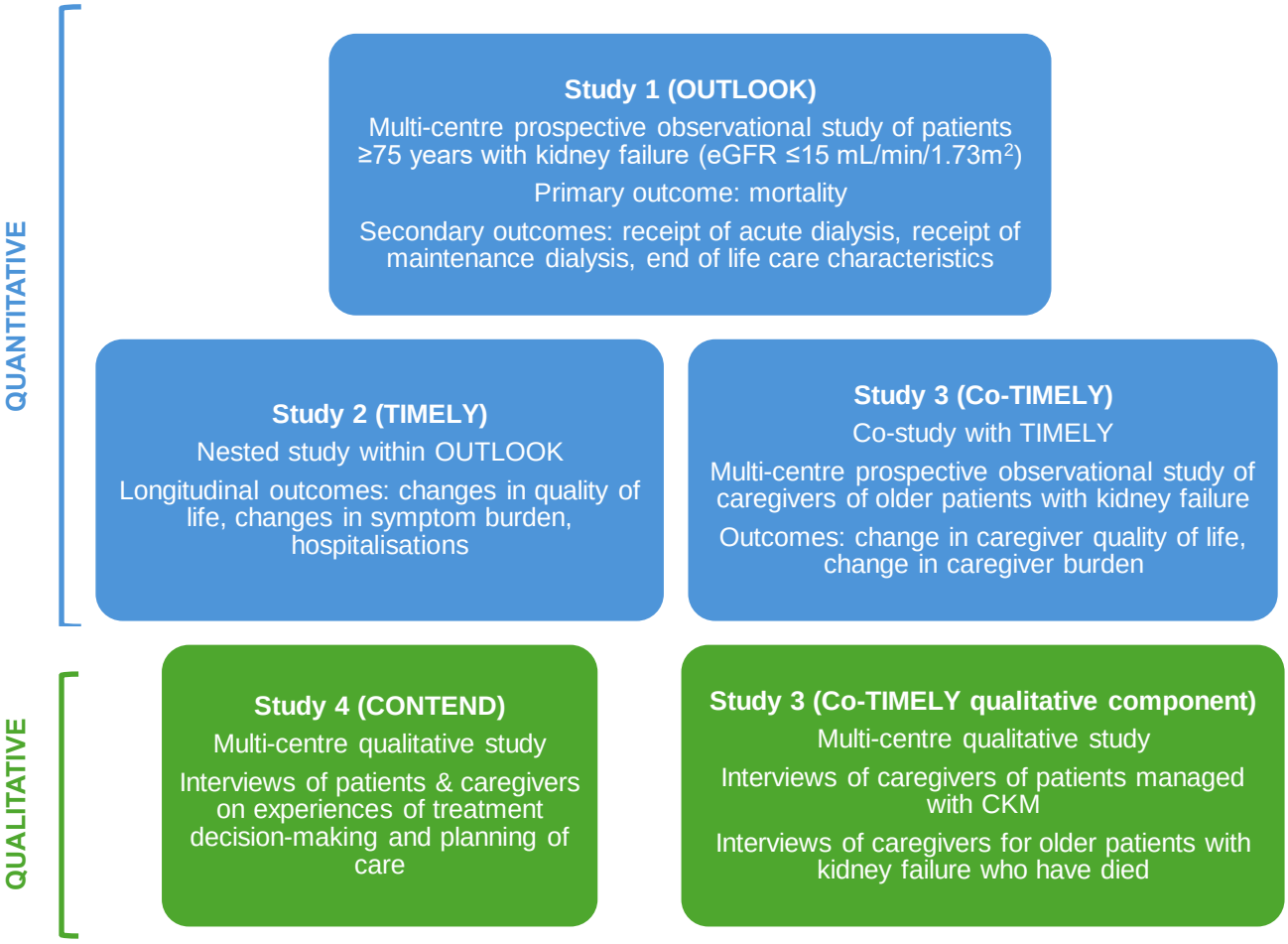

Figure 1. Components of the Elderly Advanced CKD Program.

eGFR, estimated glomerular filtration rate; CKM, conservative kidney management; OUTLOOK, OUTcomes of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CONTEND, CONsumer views of Treatment options for Elderly patieNts with kiDney failure.

Table 1. Summary of the Elderly Advanced CKD Program components.

	OUTLOOK	TIMELY	Co-TIMELY	Co-TIMELY (qualitative component)	CONTEND
Study type	Prospective observational cohort study	Prospective observational cohort study	Prospective observational cohort study	Qualitative study	Qualitative study
Target population for recruitment	Patients aged ≥75 years with kidney failure (eGFR ≤15 mL/min/1.73m^2)	Patients aged ≥75 years with kidney failure (eGFR ≤15 mL/min/1.73m^2)	Caregivers of patients enrolled in TIMELY	Caregivers of patients enrolled in TIMELY who are receiving CKM, caregivers of patients enrolled in TIMELY whose care-recipient has died	Patients ≥70 years with kidney failure and their caregivers
Targeted sample size	800	150	100	20 caregivers of CKM patients, 10 caregivers whose care-recipient has died	20 patients, 20 caregivers
Primary outcome	Mortality	EQ-5D	EQ-5D	Caregiver experiences of CKM, caregiver experiences of end-of-life care for their care-recipient	Experiences of shared decision-making for kidney failure treatment
Secondary outcomes	Receipt of acute dialysis, receipt of long-term maintenance dialysis, end-of-life care characteristics	Satisfaction with life, symptom burden, living situation, hospitalisations	Satisfaction with life, caregiver responsibilities, caregiver burden	-	-
Frequency of follow-up	6 months	12 months	12 months	-	-
Study period	4 years	4 years	4 years	Single encounter interviews	Single encounter interviews

OUTLOOK, OUTcomes of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CONTEND, CONsumer views of Treatment options for Elderly patieNts with kiDney failure, eGFR, estimated glomerular filtration rate; CKM, conservative kidney management; EQ-5D, Euroqol-5 Dimension.

Table 2. Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY.

Inclusion criteria	Exclusion criteria
Patient age ≥ 75 years	Patient is receiving dialysis at the time of initial screening
Patient eGFR ≤ 15mL/min/1.73m^2	Patient not expected to survive 3 months beyond enrolment
Additional caregiver criteria for Co-TIMELY: - Nominated by the patient as a primary caregiver	Additional exclusion criteria for patients in TIMELY and for caregivers in Co-TIMELY: - Extreme infirmity (as assessed study team) - Significant cognitive impairment (inability to complete questionnaires as assessed by the treating nephrologist or study team, with a guiding lower threshold of ≤18 on mini-mental state examination) - English language skills insufficient to participate in questionnaires

eGFR, estimated glomerular filtration rate; OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease.

Table 3. Study schedule for data collection. 'O' denotes data collection for both OUTLOOK & TIMELY, 'T' denotes data collection for TIMELY only, and 'C' denotes data collection for Co-TIMELY only.

	Timeline based on individual date of enrolment								
Data collection	**Baseline**	**6 mths**	**1 yr**	**18 mths**	**2 yrs**	**30 mths**	**3 yrs**	**42 mths**	**4 yrs**
Demographics (age, gender, ethnicity, primary language, marital status, residential status)	O								
Medical history (Charlson comorbidity score, medications)	O								
Functional status (Clinical Frailty Scale, Karnofsky Performance Score, mobility)	O								
Treatment pathway decision (dialysis, CKM, undecided), advance care planning status, surprise question	O								
Biochemistry	O	O	O	O	O	O	O	O	O
Survival status (including date, location and cause of death)		O	O	O	O	O	O	O	O
Receipt of dialysis		O	O	O	O	O	O	O	O
Cognitive assessment (MMSE)	T								
Nutritional status (SGA)	T								
Patient questionnaires: - Quality of life (EQ-5D, SWLS) - Symptom burden (iPOS-Renal)	T		T		T		T		T
Patient-reported changes in living situation, mobility and functional status	T		T		T		T		T
Patient-reported hospitalisations	T		T		T		T		T
Caregiver demographics (age, gender, ethnicity, primary language, education level)	C								
Caregiver characteristics (relationship to care recipient, duration of caregiving)	C								
Caregiver responsibilities	C		C		C		C		C
Caregiver questionnaires: - Quality of life (EQ-5D) - Caregiver burden (Zarit Burden Interview)	C		C		C		C		C
Data linkage (National Death Index, ANZDATA, Admitted Patient Data Collection, MBS, PBS)									O

OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease; Co-TIMELY, Caregivers of The InfirM ElderLY with end stage kidney disease; CKM, conservative kidney management; MMSE, mini-mental state examination; SGA, subjective global assessment; EQ-5D, Euroqol-5 Dimension; SWLS, Satisfaction with Life Scale; ANZDATA, Australian and New Zealand Dialysis and Transplant Registry; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme.

CHAPTER 3

Waiver of informed consent in clinical research: A review of contemporary guidelines

CHAPTER OVERVIEW

Numerous study design barriers contribute to the underrepresentation of older patients with CKD and kidney failure in observational studies and randomised controlled trials. Novel and ethically appropriate design features may facilitate greater research involvement of older individuals. This chapter addresses the second objective of this thesis, to review ethical guidelines for the use of waiver of informed consent in clinical research. National, regional and international ethical guidelines are reviewed and collated in this manuscript.

The original stimulus for this paper came from the authors' experience as researchers undertaking a multicentre international pragmatic cluster-randomised trial evaluating real-world comparative effectiveness of two default sodium dialysate concentrations in haemodialysis patients (the RESOLVE trial). A waiver of consent model was essential to the design of this pragmatic trial, however there was a frequent need to provide ethics committees and institutional review boards with relevant national statements on waiver of consent guidelines, underscoring the limited dissemination of these documents. A similar experience was encountered with ethics submissions for the OUTLOOK study, the primary component of the Elderly Advanced CKD Program. OUTLOOK is a routine-care observational study that prospectively follows older kidney failure patients and involves no additional data collection outside that collected for standard patient care. The justification for the use of a waiver of consent in this study is methodological. It is essential to mitigating selection bias, with high rates of cognitive impairment and comorbidity in the older patient population being studied posing direct barriers to more traditional models of consent. Additionally, it is a low-risk study of routine care. A waiver of consent in OUTLOOK facilitates broad recruitment, minimises selection bias and is a feasible study design.

This consent model is particularly relevant to routine-care clinical research involving older patients and provides opportunities to feasibly improve evidence in this population. This manuscript aims to collate ethical guidelines on waiver of consent to allow its use as a reference paper for the design of future studies.

PUBLICATION DETAILS

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AUTHOR CONTRIBUTIONS

AS and MJ conceived the review. AS drafted the manuscript, and AS, BS and MJ contributed to writing, appraisal and manuscript review.

ABSTRACT

Learning health system research, quality assurance activities and comparative effectiveness studies using routinely collected clinical data are methods of embedding clinical research within routine practice to generate generalisable evidence. Individual written informed consent may present a barrier to the feasibility and inclusiveness of such pragmatic clinical research. Within an overarching moral and ethical framework, the form and requirements of consent vary in both clinical practice and research settings according to the context and level of risk. In low-risk research settings, waiver of consent may be appropriate. Given the growing importance of routine-care embedded research activity, we sought to describe contemporary national and international English-language guidelines pertaining to the use and oversight of waiver of consent in clinical research. We identify 14 guidelines including 1 international, 1 regional (European Union) and 12 national statements, and summarise the principles in each for circumstances in which a waiver of consent is appropriate. We conclude that while complete international harmonisation of policy may be neither realistic nor necessary, there are numerous unifying concordances suggesting a broad consensus on the approach to waiver of consent research.

INTRODUCTION

Learning health systems embed research processes within routine practice.[1] Learning health system research is conducted in real-world settings and seeks to evaluate effectiveness in all participants exposed to a practice or intervention. Examples include comparative effectiveness pragmatic randomised controlled trials (RCTs), which act within areas of existing variation in clinical practice that are not justified by high-quality evidence or local conditions.[2, 3] These quality assurance studies replace arbitrary treatment selection with randomised selection and are essential to improving patient outcomes, especially with respect to institutional or health system practices that are determined outside of, or prior to, individual clinician-patient treatment decisions.

Randomised study populations have historically differed substantially from the broader patient population,[4-7] yet comparative effectiveness studies and evaluations of health-service interventions will naturally lead to changes in practice that affect all patients. It is essential that such studies include generalisable populations, are sufficiently large and minimise bias. Given the barriers that traditional written informed consent models pose to inclusion of a representative patient population, such studies of practices where patient consent is not sought in *clinical practice* will benefit from a similar waiver of *research* consent to minimise selection and other biases.[8-10] The benefits of aligning consent requirements for practice evaluation with those for the conduct of clinical practice have long been recognised. In 1987 Chalmers et al. posited that in the face of uncertainty in clinical research and clinical care, the consent processes required for rigorously conducted real-world studies compared with the lack of such requirements for clinical decision-making was

an ethical discordance that impeded practice improvement.[11, 12] Recommendations for facilitating research and clinical practice integration are through the anchoring of consent requirements in a real-world study with those of the equivalent routine clinical practice setting.[13-15] In line with this, utilisation of waiver of consent in low-risk learning health system research and comparative effectiveness studies has gained increasing relevance and is detailed in various consent guidelines. To date, these guidelines have not been collated and compared.

This analysis examines current international, regional and national English-language guidelines on 'waiver of consent'. 'Waiver of consent' was defined as situations where investigators are not required to inform or request permission from research subjects prior to participation.[16] Specifically, waiver of consent guidelines for non-emergency clinical research were examined.

INTERNATIONAL, REGIONAL AND NATIONAL GUIDELINES ON WAIVER OF CONSENT

In collaboration with the World Health Organisation (WHO), the Council for International Organisations of Medical Sciences (CIOMS) released the *International Ethical Guidelines for Health-related Research Involving Humans* in 2016, replacing the 2002 guidelines.[17] Guideline 10 pertains to waiver of consent. In addition to this international guideline, we identified thirteen national/regional guidelines, applicable in 39 countries (*Figure 1*). These documents and their intended scope are detailed in *Table 1*.

Within the CIOMS international guidelines, three essential criteria for using waiver of consent are described:

a. The research would not otherwise be feasible or practicable,
b. The research has important social value, and
c. The research poses no more than minimal risk.

In addition to these criteria within the CIOMS guideline, other criteria were identified within national and regional guidelines for the use of waiver of consent and are summarised in *Table 2*. Among these international, regional and national guidelines, we identified seven recurring principles which are discussed below.

REVIEW OF INDIVIDUAL PRINCIPLES

1. Would not otherwise be feasible or practicable

Research being 'not otherwise feasible or practicable' was a universal criterion within all guidelines examined.[16-29] 'Unfeasible' and 'impracticable' are specifically defined in some,[17, 18] with a consensus towards a lack of scientific or logistical feasibility and onerousness that wholly jeopardises study conduct; mere inconvenience is not a sufficient justification.[17, 30]

This criterion is the central theme underpinning waiver of consent research, with particular emphasis that informed consent should remain the standard where it is practicable or feasible to obtain consent regardless of whether other criteria are met for waiver of

consent.[31] Specific descriptions for this criterion within the examined guidelines are outlined in *Table 3*.

2. Important social value and 'risk-value' assessment

The 'important social value' criterion is founded upon beneficence ideals, with justification for carrying out the research being for the benefit of subjects, the community and society at large.[32, 33]

This criterion is included, though variably worded, in several guidelines (*Table 3*).[17, 18, 21, 24] In guidelines without a specific social value criterion for waiver of consent, social value is often stipulated as a broader requirement of *all* clinical research.[16, 20, 23, 25, 26, 28, 29] Linked to this social value criterion is also the concept of balancing potential risks to participants against anticipated social value ('risk-value' assessment) which is expressed in some guidelines.[18, 20, 29, 32]

3. No more than minimal risk

The requirement of 'no more than minimal risk' aims to uphold non-maleficence principles.[30] 'Minimal risk' is specifically defined in twelve guidelines, with unifying concepts being that the anticipated probability and magnitude of harm is small and there is no or minimal *additional* risk by participation in the research relative to not participating.[16, 18-26, 28, 29]

The 'no more than minimal risk' criterion is contained within all guidelines examined (*Table 3*).[16-29] Four of the guidelines explicitly define 'minimal risk' as relating to both

interventions/treatments *and* any associated tests/monitoring from conducting the research.[19, 25, 27, 29] Two of the guidelines explicitly refer to the testing of treatments currently available within clinical practice.[19, 29] The UK guidance document also comments on individual equipoise within cluster-determined interventions, stating that 'healthcare professionals have the option of using an intervention other than the one assigned if they believe doing so is important for a particular patient', relating to situations where clinician judgement deems neither clinical equipoise nor minimal risk apply.[19]

4. Protection of welfare and rights

The 'protection of participant welfare' criterion closely relates to 'minimal risk' and broader principles of non-maleficence.[30] 'Welfare' is discussed in seven guidelines (*Table 3*).[16, 18, 19, 21, 23-25]

The condition of a subject's 'rights' not being adversely affected by the research is complex and raises the question of *which* rights are most relevant. Respect for individual autonomy may be thought to include the right to participate in research, choose between interventions and be informed throughout.[30] However, Chalmers and Truog argue standard clinical care includes many low-risk decisions in which patients are neither involved in nor formally consented.[11, 34] Comparative effectiveness research and cluster randomised trials are frequently conducted in these usual care settings, and hence it may be argued that participation need not involve any additional level of disclosure and consent.[30] Additionally, routine-care observational research involves no direct patient contact and no direct impacts of conducting the research upon the individuals being studied, rather involves following cohorts in real-world settings. Chalmers and Truog argue that the need to obtain patient

consent in these routine-care observational research settings on the basis of individual rights is a particular malalignment of research and clinical practice standards.[11, 34]

Acknowledging these contentions, the term 'rights' is detailed in US, UK, Philippines and Indian guidelines in conjunction with participant welfare[19, 23, 25, 35] and in the Malawian NHSRC guidelines which stipulate the 'waiver is consistent with individual's rights'.[27] Furthermore, the UK draft guidance document requires that the 'patient has not expressed a strong preference for any particular treatment'[19] and Australian NHMRC guidelines stipulate 'there is no known or likely reason for thinking that participants would not have consented',[20] both of which pertain to maintenance of autonomy and individual rights.

5. Protection of privacy and confidentiality

Maintaining patient privacy and confidentiality is an expected feature of all clinical research.[17] This is specifically detailed in two waiver of consent guidelines (*Table 3*).[20, 21]

6. Provision of information

Provision of pertinent information after research participation is founded upon the ethical principle of respect,[36] and it is detailed in nine guideline documents (*Table 3*).[18, 20, 23, 24, 26-29, 35] Provision of such information after participation acknowledges that while these low risk studies may have scientific justification for waiver of consent at the time of conducting the research, that patients remain the primary stakeholders and there is a responsibility to maintain public confidence and accessibility of the research process.

Several documents also discuss provision of information on a community level prior to conducting the research, including Canadian Tri-Council guidelines which, in relation to population and public health research, state that 'researchers should… seek community engagement prior to data collection',[18] Japanese MHLW guidelines state that measures be taken 'to make announcement for the population to which the research subjects etc. belong'[24] and Ethiopian MoST guidelines state that 'it is the responsibility of the investigator and the sponsor to publicise such a study to the community before commencement'.[26]

7. Legal and financial obligations

Reference to legal obligations, which closely relates to the principles of beneficence and non-maleficence, is discussed in two guidelines (*Table 3*).[20, 29] Australian NHMRC guidelines also discuss financial obligations in reference to waiver of consent research, requiring that 'the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled'.[20]

IMPLICATIONS OF WAIVER OF CONSENT POLICY

The CIOMS guidelines and their adoption within national/regional guidelines provide a framework for understanding situations where waiver of consent may be appropriate in study design. Importantly, these guidelines are not designed to alleviate researcher inconveniences; rather, they aim to provide a model for conducting ethically-founded research and improving health outcomes that would otherwise not occur if other, more traditional, consent models are required.[34] In the face of uncertainty and variations in

practice, requiring a higher threshold for conducting a formal evaluation of treatments in randomised controlled trials and real-world observational research than for making clinical treatment decisions will result in a paucity of evidence-based practice with no gain for patient autonomy. An equally important consideration is that in situations of true clinical equipoise where practice variability lacks consensus rather than reflecting good individualised decision-making, preventing research that could not otherwise be carried out without a waiver of consent will lead to continued treatment variability that poses at least the same risk to current and future patients as random treatment assignment.

Historically, participants in RCTs across a variety of specialities are poorly representative of the real-world patient population for which the intervention is intended and this reflects strict eligibility criteria, volunteer bias and likely other biases.[4-7] These are typically trials of novel agents where the effects of the agents on human health, including risks, are largely unknown. By contrast, low-risk pragmatic RCTs, cluster randomised studies and real-world observational studies are conducted in situations where all patients already receive one of several potential treatments, the relative benefits and risks of which are uncertain but the decision on which treatment to use is not based on high quality, direct evidence. These studies can utilise broad inclusion criteria, reflect real-world clinical situations and generate evidence clearly generalisable to a wider patient population [37]. Waiver of consent is of value in these situations where the research would not otherwise be feasible for methodological reasons (eg. interventions with cluster-level participation or cluster-level outcomes, or high rates of cognitive impairment in low-risk observational studies where requirements for consent would result in extreme selection bias), where there is no or minimal risk, and

where there is anticipated to be significant individual, community and/or societal value and real-world evidence from the research being conducted.

CONCLUSIONS

National, regional and international frameworks exist for the utilisation of waiver of consent in low-risk studies that closely resemble usual practice under the oversight of designated ethical bodies. These frameworks have a clear unifying basis consistent with the 2016 CIOMS guidelines. These frameworks facilitate learning health system environments that can provide rigorous assessments of the relative effectiveness of variations in clinical practice and lead to improved outcomes through the evidence-based identification of optimal practices.

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FIGURES AND TABLES

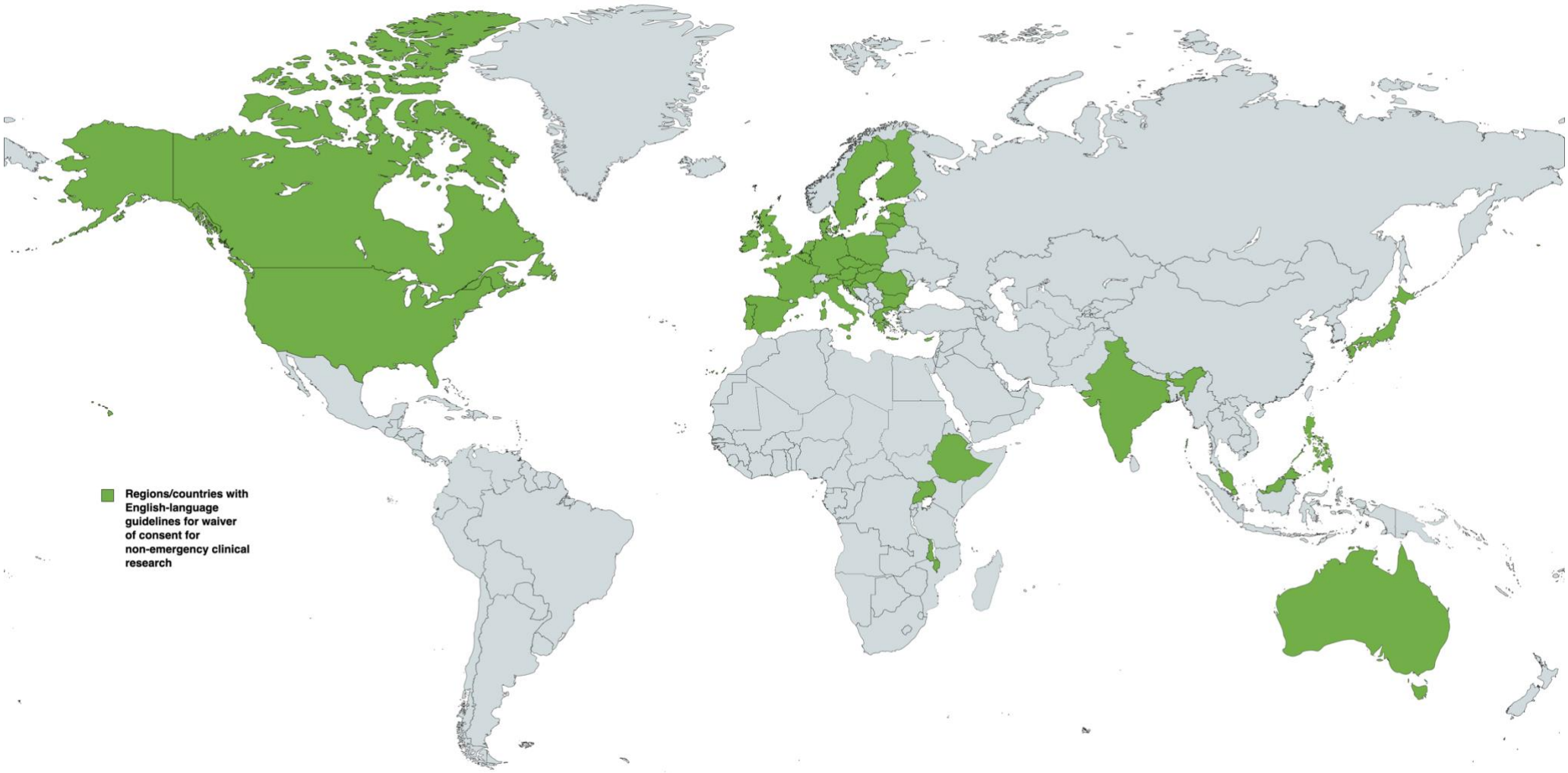

Figure 1. Countries with regional or national guidelines for 'waiver of consent' in non-emergency clinical research.

Figure sourced from MapChart and modified with permission.

Table 1. International, regional and national guidelines included for review within this paper with 'waiver of consent' guidelines for non-emergency clinical research.

Governing organisation(s) (region/country)	Guideline	Year of publication	'Waiver of consent' subsection	Scope of waiver of consent guideline
Council for International Organisations of Medical Sciences, CIOMS (International)	*International Ethical Guidelines for Health-related Research Involving Humans* [17]	2016	Guideline 10	Applies to all clinical research, including 'health-related research', 'studies [which] involve identifiable data or biological specimens', 'when data or biological specimens are not personally identifiable', 'studies [which] analyse existing data from health-related registries… for example, cancer registries and databanks of genetic or other anomalies', and 'when the participants are children, adolescents, and individuals not capable of giving informed consent'
U.S. Department of Health & Human Services (United States)	*Code of Federal Regulations (CFR)* [16]	2019	Title 45: Public Welfare Part 46: Protection of Human Subjects (45 CFR 46) (Human research policy was initially defined in 1991 in 45 CFR 46 ('The Common Rule'). The *IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects* was released in 2017 as an additional guideline for immediate implementation [35]. This 2017 guideline was then included as a statutory change in the CFR, referred to as the 'revised Common Rule' and effective as of 21 January 2019 [16])	Applies to all 'clinical investigations'
Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and	*Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* [18]	2018	Articles 3.7A and 3.7B	Applies to all clinical research, with particular reference to 'social sciences research', use of 'data and/or human biological materials', 'participants in vulnerable circumstances', and 'population and public health research'

Humanities Research Council of Canada (Canada)				
European Parliament and Council (European Union)	*Regulation No 536/2014 On Clinical Trials on Medicinal Products for Human Use* [29]	2014	Paragraph 33 and Article 30	Specifically for cluster randomised trials, where 'the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products'
Health Research Authority, HRA (United Kingdom)	*Seeking informed consent for simple and efficient trials in the NHS (Draft guidance: For comment)* [19]	2014	Section 2.6 (Although this remains a draft document, when put up for public and professional commentary, majority of the 103 respondents supported the principles detailed in section 2.6 [38])	Applies to all clinical trials, with particular reference to pragmatic trials and cluster randomised trials
National Health and Medical Research Council, NHMRC (Australia)	*National Statement on Ethical Conduct in Human Research* [20]	2018	Chapter 2.3.10	Applies to all clinical research using 'personal information' or 'personal health information'
Bioethics Advisory Committee, BAC (Singapore)	*Ethics Guidelines for Human Biomedical Research* [21]	2015	Paragraph 3.29	Applies to all 'research done in the public interest', with particular reference to 'epidemiological or public health research carried out with medical records or with data from national registries'
Medical Review & Ethics Committee, MREC (Malaysia)	*Guidelines for Ethical Review of Clinical Research or Research Involving Human Subjects* [22]	2006	Guideline 2	Applies to all clinical research
Philippine Health Research Ethics Board, PHREB (Philippines)	*National Ethical Guidelines for Health and Health-related Research* [23]	2017	Paragraphs 15-17	Applies to all clinical research
Ministry of Health, Labour and Welfare, MHLW (Japan)	*Ethical Guidelines for Medical and Health Research Involving*	2017	Chapter 5 Part 12 Paragraph 7	Applies to all clinical research

	Human Subjects (English Edition) [24]			
Indian Council of Medical Research, ICMR (India)	*National Ethical Guidelines for Biomedical and Health Research Involving Human Participants* [25]	2017	Definitions of social value and minimal risk (sections 1 and 2) and criteria for waiver of consent research (section 5.7)	Numerous research examples listed, including 'retrospective studies, where the participants are de-identified or cannot be contacted', 'research on anonymised biological samples', 'public health studies/surveillance programmes/programme evaluation studies', and 'research on data available in the public domain'
Ministry of Science and Technology, MoST (Ethiopia)	*National Research Ethics Review Guideline (5th Edition)* [26]	2014	Article 6.15	Applies to all clinical research
National Health Sciences Research Committee, NHSRC (Malawi)	*General Guidelines on Health Research* [27]	2007	Article 7.4	Applies to all clinical research
National Council for Science and Technology, UNCST (Uganda)	*National Guidelines for Research Involving Humans as Research Participants* [28]	2014	Section 5.5	Applies to all clinical research

Table 2. Individual criteria for waiver of consent in non-emergency clinical research within international, regional and national guidelines.

Criterion	CIOMS (International)	CFR (US)	Tri-Council (Canada)	European Parliament & Council (EU)	HRA (UK)	NHMRC (Australia)	BAC (Singapore)	MREC (Malaysia)	PHREB (Philippines)	MHLW (Japan)	ICMR (India)	MoST (Ethiopia)	NHSRC (Malawi)	UNCST (Uganda)
Research not otherwise feasible/practicable	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Research has important social value	+	Δ	+	Δ		Δ	+		Δ	+	Δ	Δ		Δ
Research poses no more than minimal risk	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Benefits from research justify any risks of harm associated with not seeking informed consent			+	+		+								
Intervention used in accordance with marketing and/or published scientific evidence				+	+									
Comparison between standard treatments				+	+									
Healthcare professionals can override the assigned intervention					+									
Protection of rights and welfare of subjects		+	+		+		+		+	+	+		+	
Participant has not expressed a preference for any particular treatment					+									
No reason to think participants would not have consented if asked						+								

Protection of privacy and confidentiality of subjects						+	+							
Provision of information after participation, where practicable, including potential to withdraw use of data where practicable		+	+	+		+			+	+		+	+	+
Involvement of community representatives prior to commencement, where practicable			+							+		+		
Subjects not deprived of financial benefits with commercial use of data						+								
Waiver is not prohibited by state, federal, or international law				+		+								

Boxes in grey indicate criteria deemed essential in the 2016 CIOMS *International Ethical Guidelines for Health-related Research Involving Humans* guidelines. Use of '+' denotes inclusion of a criterion within a country or region's specific waiver of consent policy. Use of 'Δ' denotes inclusion of the 'research of important social value' criterion within a country or region's broad clinical research policy though not specifically relating to waiver of consent research.

CIOMS, Council for International Organisations of Medical Sciences; CFR, Code of Federal Regulations; US, United States; EU, European Union; HRA, Health Research Authority; UK, United Kingdom; NHMRC, National Health and Medical Research Council; BAC, Bioethics Advisory Committee; MREC, Medical Review & Ethics Committee; PHREB, Philippine Health Research Ethics Board; MHLW, Ministry of Health, Labour and Welfare; ICMR, Indian Council of Medical Research; MoST, Ministry of Science and Technology; NHSRC, National Health Sciences Research Committee; UNCST, National Council for Science and Technology.

Table 3. Detailed description of wording used for individual criteria contained within each international, regional and national guideline.

1. Would not otherwise be feasible or practicable	
CIOMS (International)	'the research would not be feasible or practicable to carry out without the waiver or modification' [17]
CFR (US)	'research could not practicably be carried out without the requested waiver' [16]
Tri-Council (Canada)	'it is impossible or impracticable to carry out the research question properly, given the research design, if the prior consent of participants is required' [18]
HRA (UK)	'following the normal consent process would place a disproportionate burden in terms of time and resources' [19]
NHMRC (Australia)	'impracticable to obtain consent' [20]
BAC (Singapore)	'the research could not practicably proceed without the waiver' [21]
MREC (Malaysia)	'individual informed consent would make the conduct of the research impracticable' [22]
PHREB (Philippines)	'the research cannot be practicably carried out without the waiver or alteration' [23]
MHLW (Japan)	'if [informed consent procedures] are not omitted, it will be difficult to implement the research or the value of the said research will be significantly undermined' [24]
ICMR (India)	'research cannot practically be carried out without the waiver and the waiver is scientifically justified' [25]
MoST (Ethiopia)	'the research project could not practically be carried out without the waiver or alteration' [26]
NHSRC (Malawi)	'the research could not practically be carried out without the consent waiver and obtaining informed consent is not practicable' [27]
UNCST (Uganda)	'the research project could not practicably be carried out without the waiver or alteration' [28]
European Parliament & Council (EU) (in reference to cluster randomised trials only)	'it is appropriate to allow that informed consent be obtained by simplified means for certain clinical trials where the methodology of the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products' [29]
2. Important social value and 'risk-value' assessment	
2a. Social value	
CIOMS (International)	'the research has important social value' [17]

Tri-Council (Canada)	'the potential benefits to be considered include benefits to the participants themselves, to the group they represent and/or to society more generally' [18]
BAC (Singapore)	'research done in the public interest' [21]
MHLW (Japan)	'the research to be implemented is recognised as being of socially high significance' [24]
CFR (US) (in reference to *all* clinical research)	'research [is]… designed to develop or contribute to generalisable knowledge' [16]
European Parliament & Council (EU) (in reference to *all* clinical research)	'low-intervention clinical trials are often of crucial importance … thereby optimising use of medicinal products and thus contributing to a high level of public health' [29]
NHMRC (Australia) (in reference to *all* clinical research)	'research that has merit is justifiable by its potential benefit, which may include its contribution to knowledge and understanding, to improved social welfare and individual well-being, and to the skill and expertise of researchers' [20]
PHREB (Philippines) (in reference to *all* clinical research)	'participation of human beings in research can only be justified if the study has social value' [23]
ICMR (India) (in reference to *all* clinical research)	'research on human participants [is] … aimed at developing generalisable knowledge that improves health, increases understanding of disease and is ethically justified by its social value' [25]
MoST (Ethiopia) (in reference to *all* clinical research)	'enhance health or generalisable knowledge, and benefit individuals and the community where the research is conducted' [26]
UNCST (Uganda) (in reference to *all* clinical research)	'demonstrate value in terms of new knowledge added and probably improvement in health care provision and general social wellbeing' [28]
2b. Balancing potential risks to participants against anticipated social value ('risk-value' assessment)	
Tri-Council (Canada)	'the nature of the research may justify some alteration(s) to consent requirements if the potential benefits outweigh the foreseeable risks' [18]
NHMRC (Australia)	'the benefits from the research justify any risks of harm associated with not seeking consent' [20]
European Parliament & Council (EU) (in reference to cluster randomised trials only)	'the protocol justifies the reasons for obtaining informed consent with simplified means' [29]

3. No more than minimal risk	
3a. Minimal risk	
CIOMS (International)	'the research poses no more than minimal risks to participants' [17]
CFR (US)	'the research involves no more than minimal risk to the subjects' [16]
Tri-Council (Canada)	'the research involves no more than minimal risk to the subjects' [18]
European Parliament & Council (EU) (in reference to cluster randomised trials only)	'low-intervention clinical trials' which 'do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice' [29]
HRA (UK)	'the study involves little or no deviation from usual care' and 'research risks are no greater than those involved in standard care/not greater than minimal' [19]
NHMRC (Australia)	'involvement in the research carries no more than low risk' [20]
BAC (Singapore)	'the research … poses no more than minimal risk to research participants' [21]
MREC (Malaysia)	'subjects would be exposed to no more than minimal risk' [22]
PHREB (Philippines)	'the research represents no more than minimal risk' [23]
MHLW (Japan)	'the research to be implemented does not involve invasiveness (not including minor invasiveness)' [24]
ICMR (India)	'the research involves less than minimal risk to participants' [25]
MoST (Ethiopia)	'the research project carries no more than minimal risk' [26]
NHSRC (Malawi)	'the research presents no more than a minimal risk of harm to the subjects' [27]
UNCST (Uganda)	'the research project carries no more than minimal risk, that is, risk that is no more than the risks encountered in normal daily life in a stable society' [28]
3b. Interventions available within current practice	
European Parliament & Council (EU) (in reference to cluster randomised trials only)	'there are no interventions other than the standard treatment of the subjects concerned' and 'the investigational medicinal products are used in accordance with the terms of the marketing authorisation' [29]
HRA (UK)	'the study addresses a clinical question where there is uncertainty regarding the relative merits of relevant interventions', 'all medicines used in the trial are in routine use and within the terms of licence' and 'all interventions/diagnostic tests are in routine use within the NHS' [19]

4. Protection of welfare and rights	
CFR (US)	'the waiver or alteration will not adversely affect the rights or welfare of the subjects' [16]
Tri-Council (Canada)	'alteration to consent requirements [must be] unlikely to adversely affect the welfare of participants' [18]
HRA (UK)	'use of simplified means to obtain consent does not adversely affect the rights or welfare of study participants' [19]
BAC (Singapore)	'the waiver will not adversely affect the welfare and interests of research participants' [21]
PHREB (Philippines)	'the waiver or alteration will not adversely affect the rights and welfare of the participants' [23]
ICMR (India)	'the waiver will not adversely affect the rights and welfare of the participants' [25]
MHLW (Japan)	'the omission of procedures… is not against the research subjects' interests' [24]
NHSRC (Malawi)	'waiver is consistent with individual's rights' [27]
HRA (UK)	'patient has not expressed a strong preference for any particular treatment' [19]
NHMRC (Australia)	'there is no known or likely reason for thinking that participants would not have consented' [20]
5. Protection of privacy and confidentiality	
NHMRC (Australia)	'there is sufficient protection of [participants'] privacy' and that 'there is an adequate plan to protect the confidentiality of the data' [20]
BAC (Singapore)	'individual privacy and confidentiality of the personal information are assured' [21].
6. Provision of information	
6a. Provision of information after research participation	
CFR (US)	'whenever appropriate, the subjects will be provided with additional pertinent information after participation' [35]
Tri-Council (Canada)	'debriefing must be part of all research involving an alteration to consent… whenever it is possible, practicable and appropriate' and 'participants in such research must have the opportunity to refuse consent and request withdrawal of their data and/or human biological materials whenever possible, practicable and appropriate' [18]
European Parliament & Council (EU) (in reference to cluster randomised trials only)	'describes the scope of information provided to the subjects, as well as the ways of providing information' [29]
NHMRC (Australia)	'there is, where practicable, a plan for making information arising from the research available to [participants]' [20]

PHREB (Philippines)	'participants will be provided with additional pertinent information after their participation (whenever appropriate)' [23]
MHLW (Japan)	'to offer an ex-post explanation to the research subject etc. promptly' [24]
MoST (Ethiopia)	'whenever appropriate the research participants will be provided with additional pertinent information after participation' [26]
NHSRC (Malawi)	'in lieu of a signed consent form, the NHSRC may require the investigator to provide subjects with a written statement regarding the research' [27]
UNCST (Uganda)	'whenever appropriate the research participants will be provided with additional pertinent information after participation' [28]
6b. Involvement of community before research participation	
Tri-Council (Canada)	'researchers should… seek community engagement prior to data collection' [18]
MHLW (Japan)	'make announcement for the population to which the research subjects etc. belong' [24]
MoST (Ethiopia)	'it is the responsibility of the investigator and the sponsor to publicise such a study to the community before commencement' [26]
7. Legal and financial obligations	
European Parliament & Council (EU) (in reference to cluster randomised trials only)	'the simplified means for obtaining informed consent [does] not contradict national law in the Member State concerned' [29]
NHMRC (Australia)	'the waiver is not prohibited by State, federal or international law' and 'the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled' [20]

CHAPTER 4

Comparison of baseline characteristics of participants in the OUTLOOK study with older patients in the ANZDATA Registry

CHAPTER OVERVIEW

The OUTcomes Of Older patients with Kidney failure (OUTLOOK) study is the central component of the Elderly Advanced CKD Program and is prospectively enrolling patients Australian patients ≥75 years with kidney failure (estimated glomerular filtration rate ≤15 mL/min/1.73 m^2). The study is ongoing and is capturing patients who are choosing either a dialysis pathway, conservative kidney management (CKM) pathway, or are undecided. The latter two groups are a unique feature of OUTLOOK which distinguishes it from data collected in kidney replacement therapy registries.

This chapter addresses the third objective of this thesis, to compare the characteristics of OUTLOOK with registry-based data on Australian patients aged ≥75 years with kidney failure. This comparison of baseline characteristics aims to highlight the valuable prospective data that OUTLOOK will provide.

PUBLICATION DETAILS

Amanda Siriwardana [1, 2, 3], Nicholas Gray [4, 5], Angela Makris [6, 7, 8], Chenlei K Li [9], Kenneth Yong [10, 11], Jannel Ramos [2], Chris Gianacas [2], Isaac Y Addo [12], Sarah Roxburgh [1, 3], Vasi Naganathan [1, 13], Josephine Clayton [1, 14], Kathryn Ducharlet [15, 16, 17, 18], Angela Chou [19], Celine Foote [20], Martin P Gallagher [2, 6, 7], On behalf of the Elderly Advanced CKD Program Investigators. Comparison of baseline characteristics of participants in the OUTLOOK study with older patients in the ANZDATA Registry. Planned for submission in October 2024 to *Nephrol Dial Transplant*.

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AUTHOR CONTRIBUTIONS

AS is a leading member of the national steering committee for the Elderly Advanced CKD Program. AS conducts, oversees and coordinates the studies in this program. For this chapter, AS, MG and NG conceived this analysis. AS analysed the data, interpreted results and drafted the manuscript. All authors contributed to critical review and revisions of the manuscript.

ABSTRACT

Background: Deciding between treatment pathways for older patients with kidney failure is challenging, in part due to limited high-quality outcome data. The OUTcomes Of Older patients with Kidney failure (OUTLOOK) study is an ongoing prospective observational cohort study enrolling Australian patients ≥75 years with kidney failure (estimated glomerular filtration rate ≤15 mL/min/1.73 m^2). Patients are in the decision-making phase or have recently decided between kidney replacement therapy (KRT) or conservative kidney management (CKM). This analysis compares the OUTLOOK population with incident KRT patients aged ≥75 years in the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).

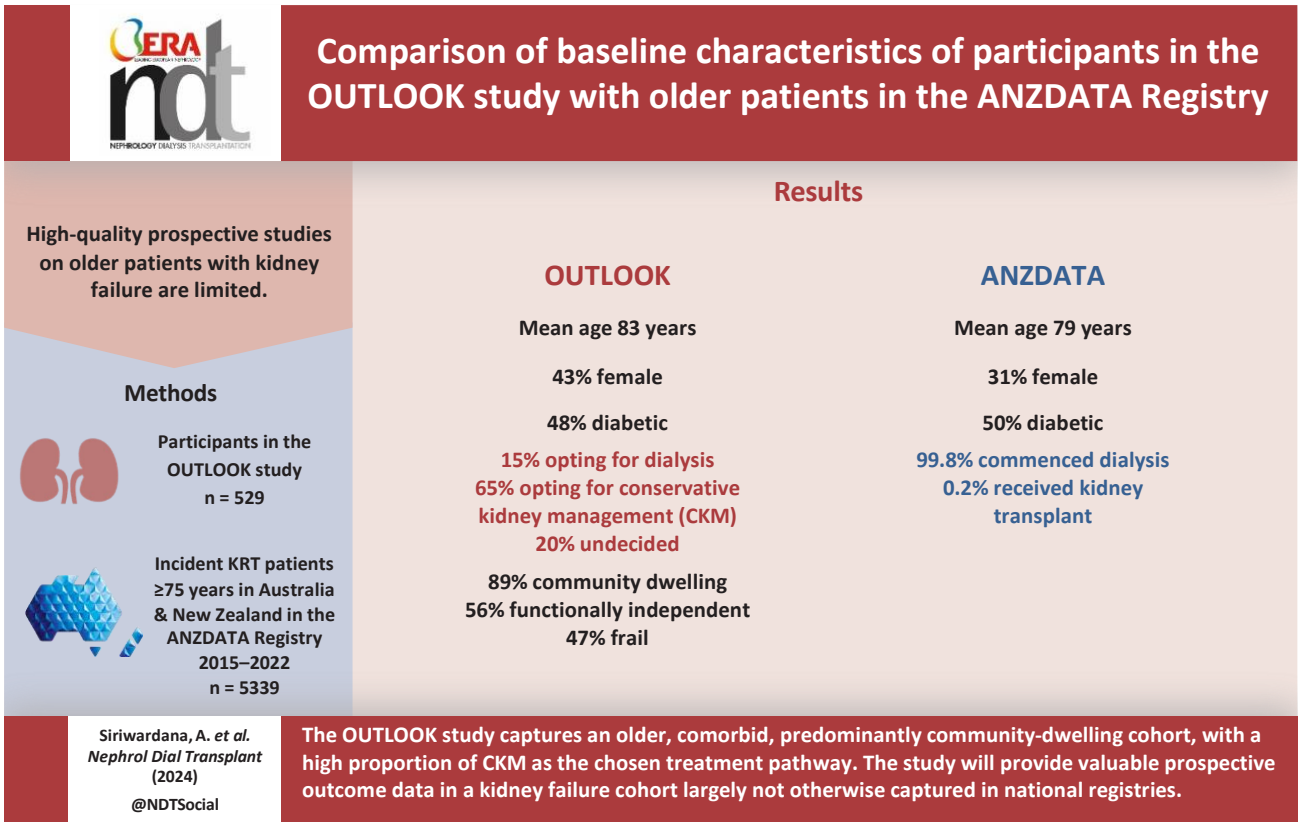
Methods: Baseline characteristics of currently enrolled participants in OUTLOOK are compared with incident KRT patients aged ≥75 years who entered the ANZDATA between January 2015 and December 2022.

Results: 529 patients from a targeted 800 patients have been enrolled in OUTLOOK, and 5339 incident patients aged ≥75 years commenced KRT and entered onto ANZDATA in the study period. OUTLOOK patients were older (mean age 83.0 vs. 79.4 years, standardised difference [d]=0.81, P<0.001), had higher female representation (43.1% vs. 30.6%, d=0.26, P<0.001), similar rates of diabetes (48.0% vs. 50.3%, d=–0.05, P=0.87), and a higher proportion of unknown aetiology of kidney failure (24.2% vs. 1.3%, d=0.82, P<0.001). OUTLOOK patients were predominantly community-dwelling (89.2%) and functionally independent (56.3%), with a high prevalence of frailty (47.4%). 14.9% of OUTLOOK patients opted for a dialysis pathway, 65.4% for a CKM pathway, and 19.7% undecided, compared

with 99.8% of the ANZDATA cohort undergoing dialysis and 0.2% undergoing kidney transplantation at KRT entry.

Conclusions: Compared with the ≥75 years incident KRT population from ANZDATA, OUTLOOK capture an older, comorbid, predominantly community-dwelling cohort, with a high proportion of CKM as the chosen pathway of kidney failure management. OUTLOOK will therefore provide valuable prospective outcome data for an older Australian kidney failure cohort not otherwise captured in national registries.

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- For older patients with kidney failure, deciding between the treatment pathways of kidney replacement therapy (KRT) and conservative kidney management (CKM) is challenging. There is limited data to guide these decisions.
- Methodological challenges and statistical biases need to be carefully considered when examining survival comparisons across kidney failure treatment pathways.

This study adds:

- Comparison of characteristics from the OUTcomes Of Older patients with Kidney failure (OUTLOOK) study with older KRT patients in the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) highlights that novel insights will be gained on a population of older patients not otherwise well captured in national registries.
- Prospective data collection across multiple centres and utilising simple study design are central features of the OUTLOOK study and demonstrate the feasibility of examining this study population through high-quality observational study design.

Potential impact (on practice or understanding):

- The ongoing OUTLOOK study will report on the survival and other secondary outcomes of a large prospective cohort of older patients with kidney failure.
- OUTLOOK is collecting novel covariates (including functional status, modified Charlson comorbidity index, and a frailty assessment), all of which are associated

with outcomes in kidney failure patients and are likely to result in improved prognostication.

- These findings will complement outcome data on KRT patients from ANZDATA, in order to provide more applicable prognostic estimates for older patients with kidney failure.

INTRODUCTION

The burden of chronic kidney disease (CKD) rapidly increases with age, affecting 22% of Australians aged 65-74 years and 45% over 75 years.[1] In turn, older Australians represent the most prevalent population group to progress to kidney failure (defined as estimated glomerular filtration rate, eGFR, ≤15mL/min/1.73m^2). For these patients, decisions between the treatment options of kidney replacement therapy (KRT, either with kidney transplantation or dialysis) or conservative kidney management (CKM) are required. Few older patients are medically suitable for kidney transplantation due to excessive perioperative and immunosuppression risk; hence treatment decisions are largely between dialysis and CKM. CKM involves a range of interventions to manage symptoms, optimise quality of life, delay progression and manage complications, without the use of KRT.[2]

The number of older patients with kidney failure who are making treatment decisions between pathways is unclear. Entry and survival on KRT programs are captured well in national registries. Data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) indicates that Australia's prevalent dialysis population increased from 337 to 597 per million population between 2000 to 2022, and over half of these prevalent dialysis patients are aged ≥65 years and 26% aged ≥75 years.[3] The number of individuals on a CKM pathway is less clear. A data linkage analysis between deaths in the National Death Index and patients receiving KRT in ANZDATA identified 21,370 incident cases of individuals who died with kidney failure in Australia from 2003 to 2007, of which roughly half had received KRT (n=10,949) and a similar proportion died without receiving KRT (n=10,421).[4] Most patients who did not receive KRT were aged ≥75 years. This analysis was conducted over two decades

ago, and beyond approximate quantification, little is known about the decision-making process, type of care received, or survival time of those patients who do not receive KRT.

For older patients with kidney failure, decisions between treatment pathways requires careful consideration of individual risks and benefits. These decisions should be timely, as older patients who initiate dialysis in an unplanned manner have increased mortality,[5] reduced quality of life,[6] and higher healthcare costs.[7] In practice, however, shared decision-making for older individuals and their families is challenging and highly variable.[8, 9] Contributing factors are the lack of high-quality prospective data to guide discussions on the relative outcomes and burdens associated with dialysis and CKM for an older patient group, and the variability of information provided by clinicians to patients and families.[9-12]

Predicted survival time is among the primary outcome considerations prioritised by older patients with kidney failure.[13, 14] A meta-analysis among older kidney failure patients identified similar 1-year survival rates between dialysis and CKM (73.0%–78.4% and 70.6%, respectively).[15] However, survival estimates for CKM patients were derived from only 12 of the total 89 studies and much fewer patients (294,196 vs. 724 for dialysis and CKM, respectively). Other recent analyses suggest a survival advantage with dialysis compared with CKM,[16, 17] while some suggest limited or no survival advantage from dialysis in patients with severe comorbidity, poor performance status or the oldest age-groups (≥80 years).[18-20] These comparisons are heavily confounded by retrospective analyses and methodological biases, including lead-time bias and immortal time bias due to inconsistencies in defining a distinct starting point for survival time calculations.[15, 21] Interpreting and using this data to

guide real-world decision-making is therefore complex and challenging for both clinicians and patients.

It is in this context that the OUTcomes Of Older patients with Kidney failure (OUTLOOK) study was designed. OUTLOOK is an observational cohort study enrolling older patients with kidney failure across 8 sites in Australia. Patients are enrolled at eGFR ≤15 mL/min/1.73m^2 which is usually a time of treatment decision-making, so OUTLOOK captures both those patients entering a CKM pathway as well as those intending to commence dialysis. The primary outcome of OUTLOOK is survival, with the intent of deriving a risk prediction model for survival to support prognostic discussions. Secondary outcomes including hospitalisation burden, changes in biochemistry and end-of-life care characteristics are also being assessed. The OUTLOOK study is ongoing with a target sample size of 800 patients. In the present analysis, we compare the baseline characteristics of patients currently enrolled in OUTLOOK with those of incident patients aged ≥75 years receiving KRT registered with ANZDATA over the corresponding period. The primary aims of this analysis were to characterise the OUTLOOK population and gain insights into what additional clinical outcomes the OUTLOOK study will provide on older patients with kidney failure relative to the ANZDATA Registry.

MATERIALS AND METHODS

Study design

This analysis compares (a) patients currently enrolled in the OUTLOOK study with (b) a contemporary cohort of incident patients aged ≥75 years who commenced KRT and entered

the ANZDATA Registry. Ethics approval for this analysis was obtained through the Northern Sydney Local Health District Human Research Ethics Committee (2024/ETH00995). This analysis was conducted in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[22]

Study populations

OUTLOOK is an ongoing multi-centre prospective observational study which began enrolment in July 2015. The methods for OUTLOOK have been previously published.[23] In brief, selection criteria for the study are purposefully broad and includes patients aged ≥75 years, with kidney failure (eGFR ≤15 mL/min/1.73m^2) and expected to survive 3 months beyond enrolment. Patients can be in the treatment decision-making phase or have recently made a treatment decision between CKM or dialysis, but not yet commenced onto dialysis. OUTLOOK is a non-interventional routine care study with no additional data collection outside that of standard patient care. It is ethically approved with a waiver of the need for individual patient consent, meeting National Health and Medical Research Council[24] and Council for International Organisations of Medical Sciences[25] criteria for low-risk clinical research with a waiver of consent. Patients are enrolled and followed prospectively until death or for a maximum of 4 years, with follow-up data entry at 6-monthly intervals. The primary outcome is survival, and secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry, hospitalisations and characteristics of end-of-life care. Ethics approval for OUTLOOK was obtained through the Sydney Local Health District Human Research Ethics Committee (2019/ETH07718). For the present analysis, all patients enrolled from study commencement to 27 July 2024 were included.

ANZDATA is a binational registry that collects data for clinical quality purposes on all dialysis patients anticipated to require long-term maintenance treatment and all kidney transplant recipients. Data is collected from all Australia and New Zealand nephrology units and reported annually by calendar year. Last completed data was up to 31 December 2022. For the present analysis, all incident KRT patients aged ≥75 years who entered onto ANZDATA from 1 January 2015 to 31 December 2022 were included.

The selection criteria for OUTLOOK and the ANZDATA cohort in this analysis are summarised in *Table 1.*

Data variables

Baseline data collected in the OUTLOOK study and from the comparator ANZDATA cohort included age, gender, ethnicity, primary cause of kidney failure, late referral to a nephrologist (defined as <3 months before study entry in OUTLOOK, and <3 months before KRT initiation in ANZDATA), and medical comorbidities (including diabetes, coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic lung disease, and history of solid organ malignancy). Of note, coronary artery disease was defined in OUTLOOK as previous acute myocardial infarct, and defined in ANZDATA as any known coronary artery disease in the opinion of the treating nephrologist. Baseline pathology results (including serum creatinine, eGFR, haemoglobin and serum phosphate) were recorded from within 3 months of entry onto OUTLOOK. In ANZDATA, serum creatinine and eGFR are recorded at KRT entry, while other pathology results are reported from the end of the first calendar year of KRT. Additional baseline data collected in OUTLOOK included a measure of overall

comorbidity burden with the Modified Charlson Comorbidity Score,[26] sociodemographic features (including marital status and residential situation), functional characteristics (including mobility status, Karnofsky functional performance score,[27] and the Rockwood Clinical Frailty Scale[28]), planned kidney failure treatment choice (dialysis, CKM or undecided), care planning decisions including advance care planning (defined as a plan about resuscitation, intensive care or intubation) and enduring guardianship (defined as appointment of someone to make medical decisions on behalf of the patient if they are in a situation of lacking capacity), and the 'surprise question' which asks the treating nephrologist if they would be surprised if their patient died in the next 12 months.[29]

Statistical analysis

Characteristics of each cohort are presented as frequencies and percentages for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for not normally distributed continuous variables. Differences in characteristics between groups are compared using Chi-square tests, independent *t*-tests and Wilcoxon rank-sum tests, for categorical variables, normally distributed continuous variables, and not normally distributed continuous variables, respectively. Differences between groups are quantified with standardised difference scores (d), calculated as differences in means or proportions divided by standard error. Differences of 0.2, 0.5 and 0.8 represent small, medium and large effect sizes, respectively.[30] Standardised difference scores greater than 1 are theoretically possible and indicate very large differences between groups. *P* values of <0.05 were considered statistically significant. All analyses were performed using R Statistical Software (version 4.4.1).

RESULTS

At the time of this analysis, 529 patients were enrolled into OUTLOOK across 8 Australian sites. 14.9% of participants nominated dialysis as their chosen kidney failure treatment pathway, 65.4% opted for a CKM pathway, and 19.7% were undecided (*Table 2*). Comparatively, 5339 incident patients aged ≥75 years commenced KRT and were entered onto ANZDATA. Of these, 99.8% commenced dialysis and 0.2% (10 patients) received a kidney transplant at KRT entry (*Table 2*). A further 12 patients in the ANZDATA cohort who commenced dialysis went on to receive a kidney transplant during the analysis period (0.2%).

Demographic and clinical characteristics

Baseline demographic and clinical characteristics are shown in *Table 2*. Patients in OUTLOOK were older than the ANZDATA cohort (mean ± SD, 83.0 ± 5.2 vs. 79.4 ± 3.7 years, d=0.81, P<0.001). The spread of age was greater in OUTLOOK where over two-third (67.5%) were aged 75-85 years, while the ANZDATA cohort was more heavily concentrated (66.8%) between 75-80 years (*Figure 1*). Females had lower representation in both cohorts, with OUTLOOK having a higher female proportion than in the ANZDATA cohort (43.1% vs. 30.6%, d=0.26, P<0.001). There were differences in ethnicity between the cohorts (d=0.32, P<0.001), with OUTLOOK having a greater proportion of Asian or Pacific background patients (22.1% vs. 12.9%). In OUTLOOK, there was no difference in the proportion of females and males planning for a CKM pathway (66.7% vs. 64.5%, P=0.61), and similarly no difference between those of Asian or Pacific background compared with White or European background planning for a CKM pathway (67.5% vs. 64.8%, P=0.90).

There were differences in primary cause of kidney failure between OUTLOOK and the ANZDATA cohort (d=0.82, P<0.001), with diabetic kidney disease, hypertension and renal vascular disease being the leading causes in both cohorts but a higher proportion of unknown cause of kidney failure in the OUTLOOK cohort (24.2% vs. 1.3%). There was a lower rate of coronary artery disease in OUTLOOK (20.8% vs. 49.5%, d=–0.63, P<0.001), however this may reflect different definitions for coronary artery disease between the cohorts. There were no differences in diabetes prevalence (48.0% vs. 50.3%, d=–0.05, P=0.32). Overall comorbidity burden was high in the OUTLOOK cohort, with mean Modified Charlson Comorbidity Score of 8.1 ($\pm$ 1.9).

Pathology results

Serum creatinine was lower and eGFR higher at entry for patients in OUTLOOK compared with the ANZDATA cohort (mean $\pm$ SD, serum creatinine 383.1 $\pm$ 117.1 vs. 560.8 $\pm$ 208.9 μmol/L, d=–1.05, P<0.001; eGFR 11.3 $\pm$ 2.9 vs. 8.3 $\pm$ 4.3 mL/min/1.73m^2, *Figure 2*). Other pathology results were similar between the two cohorts (*Table 2*).

Additional sociodemographic and functional characteristics in OUTLOOK

Additional baseline sociodemographic and functional characteristics among the OUTLOOK cohort are shown in *Table 3*. Majority (89.2%) of OUTLOOK patients at baseline were community-dwelling, and 9.8% were living in a retirement village, hostel or nursing home. Just over half (56.0%) mobilised independently, and 40.6% required some form of mobility aid. 56.3% of patients had a baseline Karnofsky functional performance score above 70 (indicating functional independence). Close to half (47.4%) had some degree of frailty.

Care plan characteristics in OUTLOOK

Nephrologist response to the surprise question was 'no' in close to two-third (59.5%) of OUTLOOK patients. At baseline, 28.0% of patients had a verbal or written advance care plan, and 25.5% had verbal or written appointment of an enduring guardian. Patients in whom nephrologists answered 'no' to the surprise question were significantly more likely than those with a surprise question response of 'yes' to have an advance care plan (35.6% vs. 17.4%, P<0.001), or enduring guardianship plan (31.4% vs. 18.5%, P=0.006).

DISCUSSION

In this analysis of baseline characteristics of presently enrolled participants in the OUTLOOK study compared with incident patients aged ≥75 years who commenced KRT and entered the ANZDATA Registry over the corresponding time period, important differences were identified. OUTLOOK participants were older, highly comorbid, predominantly community-dwelling, and had a high proportion of CKM as their chosen kidney failure treatment pathway. This comparison highlights that the OUTLOOK study will provide valuable prospective outcome data on a large cohort of older patients with kidney failure who would not otherwise be captured in national KRT registries.

OUTLOOK is following a cohort of older patients with a mean age of 83 years and wider age range than the comparative ANZDATA cohort in this analysis (*Figure 1*). Despite this advanced age and having a high prevalence of frailty, the OUTLOOK cohort is predominantly community-dwelling and functionally independent. While some studies have suggested that

severe comorbidity, poor performance status and very advanced age (≥80 years) are associated with no differences in survival between dialysis and CKM pathways,[18-20] there is greater uncertainty for independent older patients with more robust performance statuses.[15] There is a higher degree of equipoise about which pathway they will derive the most benefit from, and there is limited high-quality outcome data on these patients to guide prognostication and support treatment decision-making. It is for this population, in particular, that the OUTLOOK study will provide novel, prospective and clinically relevant outcome data. Although over one-third of incident KRT patients in the ANZDATA cohort in our analysis were aged ≥80 years at KRT initiation, evaluating outcome data from these patients in isolation does not take into account those patients who opt for, or who are deemed medically more suitable for, a CKM pathway.[31, 32] The OUTLOOK study is following patients from a time of treatment decision-making, incorporates those opting for dialysis or a CKM pathway thereby overcoming some of the selection bias of KRT registries, and complements the outcome data on KRT pathway patients derived from national registries.

In addition to differences in age and chosen treatment pathway, we identified other differences between OUTLOOK participants and older patients in the ANZDATA cohort. Firstly, the OUTLOOK cohort had higher female representation and secondly, a greater proportion of Asian or Pacific background individuals. We did not observe that these population groups were more likely to preference a CKM pathway. The reasons for these differences between OUTLOOK and ANZDATA are unclear and may relate to the 8 OUTLOOK sites being metropolitan, whilst ANZDATA contains metropolitan, regional and rural patients. Thirdly, although diabetic kidney disease, hypertension and renal vascular disease were the leading causes of kidney failure in both cohorts, there was a higher proportion of unknown

cause of kidney failure in the OUTLOOK cohort. Again, it is difficult to postulate the reasons for this difference though it may represent a lower kidney biopsy rate and therefore higher uncertainty on kidney failure aetiology among the older cohort captured in OUTLOOK, as well as the nature of data collection in OUTLOOK relying upon available documentation in medical records.

OUTLOOK is enrolling patients from eGFR ≤15mL/min/1.73m^2 and results from our analysis identify an earlier mean eGFR at entry onto OUTLOOK compared with entry onto ANZDATA. This difference is expected, with the aim of OUTLOOK being to capture older patients at or shortly after treatment decision-making, while eGFR at entry onto ANZDATA reflects timing of KRT commencement. The latter is guided by trial results[33] and clinical trends, and prior ANZDATA studies have shown that older patients ≥75 years tend to commence dialysis at a higher eGFR than younger patients.[34] Differences in eGFR at entry between OUTLOOK patients and the ANZDATA cohort in our analysis highlight considerations of lead-time bias and immortal time bias when comparing survival time between the two treatment groups.[15, 21] Lead-time bias arises from variability in defining a distinct starting point for CKM, and may result in a perceived survival advantage with CKM if survival time is calculated from an earlier starting point not equivalent to when dialysis would have been initiated. Conversely, immortal time bias occurs primarily in retrospective data when an index starting point is defined and patients go on to start dialysis much later (or not at all), giving rise to a perceived survival advantage ascribed to dialysis treatment. OUTLOOK was designed to follow patients prospectively and all patients (regardless of their chosen treatment pathway) will have survival calculated from the index starting point of eGFR ≤15mL/min/1.73m^2, with this time point chosen as it reflects a point at which patients and clinicians would be

expected to be making decisions regarding a plan for dialysis or CKM.[8] Lead-time bias and immortal time bias will therefore be mitigated in survival comparisons between the treatment pathway groups within the OUTLOOK study. However, these biases will remain and require careful consideration when making external survival comparisons between OUTLOOK study patients and other cohorts such as registry populations. Consistent handling of these biases is among the difficulties in conducting and collating survival comparisons between kidney failure treatment pathways in older patients.[15]

Prospective data collection is challenging in older patients, most notably seen in their under-representation in randomised clinical trials (RCTs).[35] This reflects higher rates of comorbidity, frailty, cognitive impairment and experienced burden of treatment, compared with younger counterparts.[36] The Prepare for Kidney Care trial is an RCT being conducted in the United Kingdom. Patients with kidney failure (eGFR ≤15mL/min/1.73m^2) who are aged ≥80 years, or ≥65 years with high comorbidity burden or poor performance status, and in whom their treating team has equipoise regarding whether dialysis or CKM will derive greater benefit, are randomised to receive either preparation for dialysis or preparation for CKM.[37] The primary outcome is change in quality-adjusted life years (QALY) between the two groups, and secondary outcome measures include survival. The trial is ongoing and targeting a sample size of 512 patients. While results of this trial are eagerly awaited, its feasibility and reproducibility may be challenging in light of high rates of patient and clinician reluctance to participate in a trial where complete equipoise in the judgement that one treatment arm is equally suitable for a patient than the other may be easily undermined by various recruiter, patient and discussion-related factors.[37]

Where randomisation is scientifically challenging or not feasible, well-designed observational studies that address and adjust for differences in baseline characteristics between treatment groups can achieve high inclusivity, external validity and feasibility, and are particularly relevant for evaluating outcomes among kidney failure patients entering different treatment pathways.[38] Indication bias is an inherent feature of assessing survival in older patients with kidney failure, where there is expected referral of healthier patients for dialysis, and referral of older and frailer patients for CKM. Incorporating baseline covariates such as frailty and functional status into adjusted observational survival analysis aims to account for this. The OUTLOOK study is large, prospective, recruiting from multiple centres, and collecting data on various covariates that have known associations with survival such as frailty and performance status, all of which are features that will result in high-quality outcome data with thorough accountability for confounding factors. Furthermore, OUTLOOK is ethically approved with a waiver of informed consent and requires no additional data collection outside of that collected for routine patient care, in order to maximise enrolment, minimise bias and achieve high feasibility. Rigid requirements for informed consent, particularly in low-risk pragmatic research settings, are known to hamper enrolment and reduce the validity of results from observational studies.[39] Considered use of a waiver of informed consent is an ethically and scientifically supported feature of the OUTLOOK study, is integral to the study's conduct, and demonstrates avenues to use novel study design to generate evidence to guide the care of older patients.

This analysis has some limitations. Firstly, despite comprehensive review of data definitions in OUTLOOK and ANZDATA and pre-specified inclusion of variables with reasonable alignment across both sources, it is possible that findings were influenced by varying

definitions across the cohorts. Secondly, comparisons between the two cohorts were limited by variables collected in ANZDATA, with some factors relevant to older patients that are included in the OUTLOOK study such as overall comorbidity burden, residential situation, mobility, functional status, and frailty not able to be compared. Thirdly, ANZDATA reports annually by calendar year, resulting in the time frames for the OUTLOOK and ANZDATA cohorts for this analysis only approximately corresponding. Fourthly, both OUTLOOK and ANZDATA are capturing older patients with kidney failure who are referred to nephrology services, and older kidney failure patients who may be managed in primary care alone are not represented. Finally, it should be acknowledged that some patients in the OUTLOOK cohort who opted for a dialysis pathway may have commenced KRT within the time frame of this analysis and subsequently will have also been included in the ANZDATA cohort.

CONCLUSIONS

Compared with incident patients aged ≥75 years in ANZDATA, the ongoing OUTLOOK study is capturing a population of older patients with kidney failure who are comorbid, predominantly community-dwelling, functionally independent and have high rates of frailty. These patients are being followed prospectively from the time of treatment decision-making, and a large proportion have opted for a CKM pathway. Older patients with kidney failure, their families and clinicians require more detailed prognostic information to guide treatment pathway decisions. The OUTLOOK study will provide novel, prospective and clinically relevant outcome data for a population group that is not otherwise well represented in registry data.

DATA AVAILABILITY STATEMENT

Data from the OUTLOOK study may be available from the corresponding author upon reasonable request, subject to relevant approvals and permissions. Patient-level data from the ANZDATA Registry is not publicly available due to data access agreements and ethical oversight, though can be requested upon application to the ANZDATA Registry Executive.

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FIGURES AND TABLES

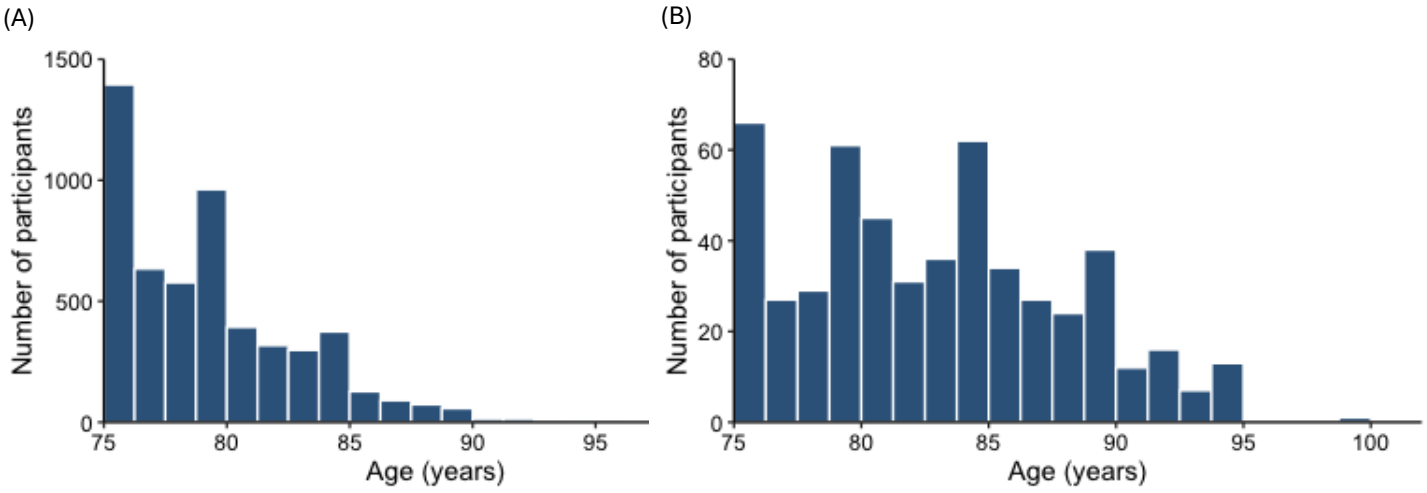

Figure 1. Age at entry into (A) ANZDATA and (B) the OUTLOOK study.

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; OUTLOOK, OUTcomes Of Older patients with Kidney failure.

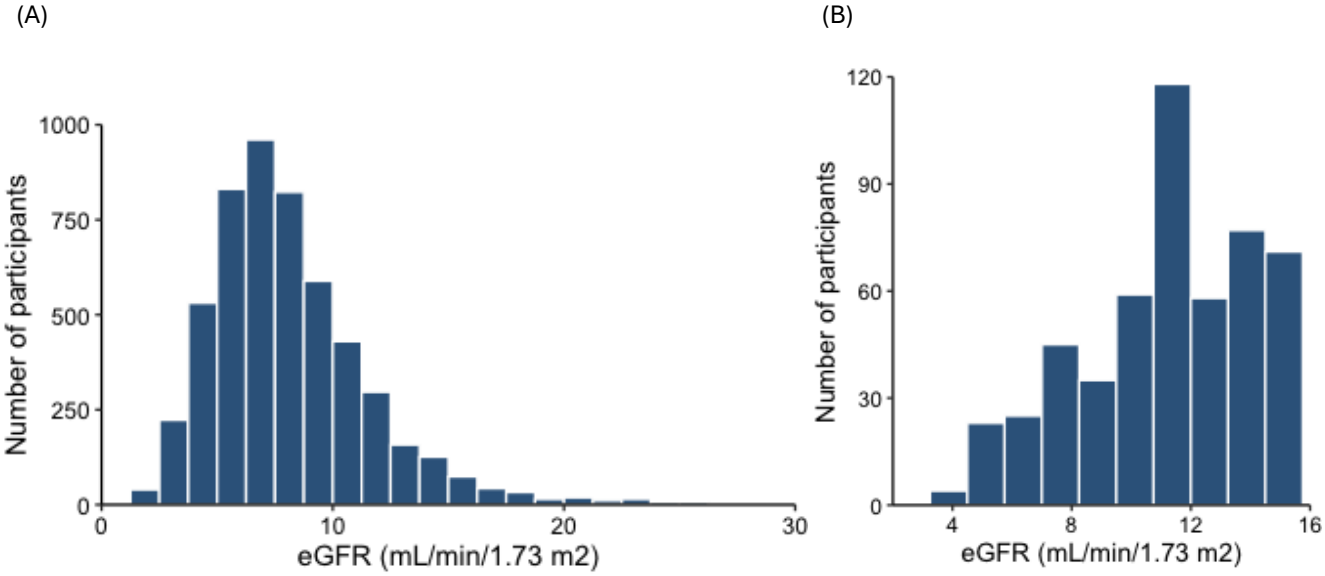

Figure 2. eGFR at entry into (A) ANZDATA and (B) the OUTLOOK study.

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; OUTLOOK, OUTcomes Of Older patients with Kidney failure.

Table 1. Selection criteria for OUTLOOK and ANZDATA cohorts in this analysis.

OUTLOOK	ANZDATA
Enrolled in OUTLOOK between 1 July 2015 to 27 July 2024	Commenced KRT between 1 January 2015 and 31 December 2022 and entered onto the ANZDATA Registry
Age ≥75 years at study entry	Age ≥75 years at commencement of KRT
eGFR ≤15mL/min/1.73m^2 at study entry	Patient expected to require long-term maintenance KRT
Not receiving dialysis at the time of initial screening	
Patient expected to survive at least 3 months beyond enrolment	

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy (dialysis or kidney transplantation); OUTLOOK, OUTcomes Of Older patients with Kidney failure.

Table 2. Baseline characteristics of OUTLOOK study participants compared with incident patients aged ≥75 years receiving KRT registered with ANZDATA over the corresponding time period.

Characteristic	ANZDATA (N = 5339)	OUTLOOK (N = 529)	Standardised difference (OUTLOOK – ANZDATA)[a]	*P* value
Age (years)				
Mean (SD)	79.4 (3.7)	83.0 (5.2)	0.81	<0.001
Median (IQR)	79 (76–82)	83 (79–87)		<0.001
Gender				
Female	1635 (30.6%)	228 (43.1%)	0.26	<0.001
Ethnicity			0.32	<0.001
White or European	4133 (77.4%)	378 (71.5%)		
Australian Aboriginal/Torres Strait Islander	72 (1.3%)	4 (0.8%)		
New Zealand Māori	89 (1.7%)	0		
Asian or Pacific	687 (12.9%)	117 (22.1%)		
Arabic or Middle Eastern	156 (2.9%)	18 (3.4%)		
Other	55 (1.0%)	5 (0.9%)		
Unknown	147 (2.8%)	7 (1.3%)		
Primary language			-	-
English	NA	321 (60.7%)		
Cantonese or Mandarin	NA	64 (12.1%)		
Arabic	NA	14 (2.6%)		
Other	NA	125 (23.6%)		
Unknown	NA	5 (0.9%)		
Primary cause of kidney failure			0.82	<0.001
Diabetic kidney disease	1736 (32.5%)	148 (28.0%)		
Hypertension/Renal vascular disease	1387 (26.0%)	118 (22.3%)		
Glomerulonephritis	627 (11.7%)	53 (10.0%)		
Familial / hereditary kidney diseases	181 (3.4%)	12 (2.3%)		
Other systemic diseases affecting the kidney	171 (3.2%)	17 (3.2%)		
Tubulointerstitial disease	415 (7.8%)	3 (0.6%)		
Other	750 (14.0%)	50 (9.5%)		
Unknown	72 (1.3%)	128 (24.2%)		
Coronary artery disease [b]	2643 (49.5%)	110 (20.8%)	–0.63	<0.001
Peripheral vascular disease	1255 (23.5%)	80 (15.1%)	–0.21	<0.001
Cerebrovascular disease	751 (14.1%)	73 (13.8%)	–0.008	0.87
Chronic lung disease	918 (17.2%)	51 (9.6%)	–0.22	<0.001
Diabetes	2685 (50.3%)	254 (48.0%)	–0.05	0.32
History of any cancer	1493 (28.0%)	105 (19.8%)	–0.19	<0.001
Modified Charlson comorbidity index, mean (SD)	NA	8.1 (1.9)		
Late referral to nephrologist [c]			0.40	<0.001
No	4463 (83.6%)	504 (95.3%)		
Yes	794 (14.9%)	19 (3.6%)		
Unknown	82 (1.5%)	6 (1.1%)		
Treatment pathway at entry [d, e]			-	-
Haemodialysis	4093 (76.7%)	35 (6.6%)		
Peritoneal dialysis	1236 (23.2%)	36 (6.8%)		
Dialysis (type undecided)	-	8 (1.5%)		
Kidney transplant	10 (0.2%)	0		
Conservative kidney management	-	346 (65.4%)		
Undecided	-	104 (19.7%)		
Blood results at entry [f]				
Serum creatinine (μmol/L), mean (SD)	560.8 (208.9)	383.1 (117.1)	–1.05	<0.001
eGFR (mL/min/1.73m^2), mean (SD)	8.3 (4.3)	11.3 (2.9)	0.83	<0.001
Serum albumin (g/L), mean (SD)	NA	36.4 (5.5)		

Serum uncorrected calcium (mmol/L), mean (SD)	2.2 (0.2)	2.3 (0.2)	0.12	0.02
Serum phosphate (mmol/L), mean (SD)	1.6 (0.5)	1.6 (0.5)	–0.07	0.18
Haemoglobin (g/L), mean (SD)	107.9 (15.0)	107.6 (14.4)	–0.02	0.66

[a] Standardised difference = differences in means or proportions divided by standard error. Differences of 0.2, 0.5 and 0.8 represent small, medium and large effect sizes, respectively [30].

[b] Coronary artery disease defined in OUTLOOK as previous acute myocardial infarct, and defined in ANZDATA as any known coronary artery disease.

[c] Late referral defined in OUTLOOK as referral to nephrologist ≤3 months prior to study enrolment, and defined in ANZDATA Registry as referral to nephrologist ≤3 months prior to KRT commencement.

[d] Treatment pathway refers to planned treatment pathway for OUTLOOK cohort, and actual KRT treatment pathway at entry for ANZDATA Registry cohort.

[e] Standardised difference between OUTLOOK and ANZDATA for treatment pathway categories not calculated due to inherent differences in definition.

[f] Blood results were within 3 months of entry into study for OUTLOOK, at KRT commencement for serum creatinine and eGFR in the ANZDATA cohort, and at the end of the first calendar year of KRT for serum uncorrected calcium, serum phosphate and haemoglobin in the ANZDATA cohort.

ANZDATA, Australia and New Zealand Dialysis and Transplant; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KRT, kidney replacement therapy (dialysis or kidney transplantation); NA, not available; OUTLOOK, OUTcomes Of Older patients with Kidney failure; SD, standard deviation.

Table 3. Baseline sociodemographic and functional characteristics of OUTLOOK study participants.

Characteristic	OUTLOOK (N = 529)
Marital status	
Married	302 (57.1%)
Separated/single	64 (12.1%)
Widowed	157 (29.7%)
Unknown	6 (1.1%)
Residential situation	
Living with family or friends	300 (56.7%)
Alone with no supports	84 (15.9%)
Alone with nearby family/friends support	56 (10.6%)
Alone with support services	32 (6.0%)
Retirement village/hostel/nursing home	52 (9.8%)
Unknown	5 (0.9%)
Mobility status	
Independent	296 (56.0%)
Walking stick	94 (17.8%)
4-wheel walker	88 (16.6%)
Wheelchair	33 (6.2%)
Unknown	18 (3.4%)
Karnofsky functional performance score	
100 – Normal activity with no symptoms/signs of disease	17 (3.2%)
90 – Normal activity with minor symptoms/signs of disease	104 (19.7%)
80 – Normal activity with some difficulty and symptoms/signs of disease	111 (21.0%)
70 – Cares for self but not capable of normal activities	66 (12.5%)
60 – Requires some help but able to shower/dress/toilet	109 (20.6%)
50 – Requires considerable help and frequent medical care	72 (13.6%)
40 – Disabled/requires special care	11 (2.1%)
Unknown	39 (7.4%)
Rockwood Clinical Frailty Scale (rated 1 – 9)	
1 – Very fit	4 (0.8%)
2 – Well	40 (7.6%)
3 – Managing well	88 (16.6%)
4 – Vulnerable	90 (17.0%)
5 – Mildly frail	102 (19.3%)
6 – Moderately frail	98 (18.5%)
7 – Severely frail	43 (8.1%)
8 – Very severely frail	8 (1.5%)
9 – Terminally ill	0
Unknown	56 (10.6%)

OUTLOOK, OUTcomes Of Older patients with Kidney failure.

Table 4. Care plan characteristics and clinician surprise question responses of OUTLOOK study participants.

Characteristic	OUTLOOK (N = 529)
Verbal or written advance care plan [a]	
Yes	148 (28.0%)
No	232 (43.9%)
Unknown	149 (28.2%)
Verbal or written enduring guardianship plan [b]	
Yes	135 (25.5%)
No	175 (33.1%)
Unknown	219 (41.4%)
Clinician surprise question response [c]	
Yes	184 (34.8%)
No	315 (59.5%)
Unknown	30 (5.7%)

[a] Advance care plan defined as a plan about resuscitation, intensive care or intubation.

[b] Enduring guardianship plan defined as appointment of someone to make medical decisions on behalf of the patient if they are in a situation of lacking capacity.

[c] Surprise question refers to response of the patient's nephrologist to the question 'Would you be surprised if this patient died within the next year?'

OUTLOOK, OUTcomes Of Older patients with Kidney failure.

CHAPTER 5

Utilising risk prediction models for older patients with chronic kidney disease: A comprehensive review

CHAPTER OVERVIEW

Strategies to facilitate timely decision-making between treatment pathways for chronic kidney disease are essential. This is particularly relevant to older patients where decision-making can be challenging and resource intensive, and in whom initiation of unplanned treatments results in significantly poorer outcomes.

It is now a grade 1A Kidney Disease Improving Global Outcomes (KDIGO) recommendation that an externally validated risk prediction tool be used in all patients with chronic kidney disease to guide prognostic discussions and treatment decisions. As a result, there is enormous interest in chronic kidney disease prediction models, and several have been published and validated in recent years. There are however unique considerations and limitations that need to be evaluated when looking to apply these models to older patient populations. This chapter addresses the fourth objective of this thesis, to examine how risk prediction tools can be used to guide treatment decision-making discussions in older patients with CKD.

PUBLICATION DETAILS

Amanda Siriwardana [1, 2, 3], Navdeep Tangri [4, 5], Brendon Neuen [1, 2, 3], Meg Jardine [2, 6, 7], Celine Foote [7], Martin Gallagher [2, 8, 9]. Utilising risk prediction models for older patients with chronic kidney disease. Under review September 2024 in *Lancet Healthy Longev*.

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AUTHOR CONTRIBUTIONS

AS conceptualised and wrote the original draft of the manuscript. NT, BN, MJ, CF and MG were involved in critical review and editing of the manuscript.

ABSTRACT

Older patients represent the most rapidly growing age-group presenting with kidney failure. Despite this high incidence, the rate of progression to kidney failure tends to be slower in older adults, and the competing risk of death before the development of kidney failure is a more significant consideration in older patients compared with younger counterparts. Incorporating these concepts of risk are challenging in shared decision-making discussions between clinicians, older patients and their families. Risk prediction models are rapidly increasing in nephrology and have the potential to provide personalised absolute risk prediction for patients with advanced chronic kidney disease (CKD), however there are several considerations of these models relevant to older patient populations. This review discusses metrics for assessing risk prediction models, examines key models for predicting kidney failure and mortality risk in older patients with advanced CKD, and provides guidance for how best to interpret and utilise these models to support personalised decision-making processes with older patients.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified through a search of PubMed using the search terms (‘kidney failure’ or ‘chronic renal failure’ or ‘chronic kidney failure’ or ‘ESKD’ or ‘ESRD’ or ‘CKD’ or ‘chronic kidney disease’) and (‘predictive model’ or ‘prediction model’ or ‘prediction’ or ‘predictive’ or ‘predicting’ or ‘predict’ or ‘prognostic model’ or ‘risk score’). Articles in English were specified. Searches were specified from 1 January 1995 to 1 May 2024 to reflect outcome studies and prediction models relevant to contemporary chronic kidney disease patients. Articles were analysed and included in this review based on their applicability to chronic kidney disease and older patient populations.

INTRODUCTION

The prevalence of chronic kidney disease (CKD) increases with age, affecting 34% of adults aged over 65 years in the United States.[1] In turn, individuals over 65 years represent the largest group progressing to the most advanced form of CKD, kidney failure (defined as an estimated glomerular filtration rate, eGFR, ≤15mL/min/1.73m^2). Kidney failure is managed through kidney replacement therapy (either with kidney transplantation or dialysis) or conservative kidney management (CKM). It is recommended that patients with advanced CKD (CKD G4-G5, eGFR ≤29mL/min/1.73m^2) have clinician-led discussions regarding kidney failure treatment options to facilitate timely decision-making and planning of care.[2]

For older patients, making decisions between treatment pathways is challenging due to several factors. Firstly, although prevalence of advanced CKD is high in older people, rate of progression tends to be slow.[3, 4] Secondly, death is an important competing risk in such patients, with patients aged 70 years or older with advanced CKD being 3 to 10 times more likely to die, particularly due to cardiovascular causes, before developing kidney failure.[5] Furthermore, among very elderly patients and those with significant comorbidity, dialysis may yield little or no survival benefit, and is associated with significantly poorer functional and cognitive capabilities, greater hospitalisations and reduced quality of life.[6-11] Balancing these concepts of risk and benefit in shared decision-making discussions with older patients and their families is complex and challenging.

The Kidney Disease Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guidelines for the Evaluation and Management of CKD provides updated ‘heat maps’ with colour-coded

relative risk estimates for mortality, cardiovascular and adverse kidney outcomes based on the two input variables of creatinine-based eGFR and urine albumin:creatinine ratio (ACR).[2] However, for any two individuals in the same risk category there can be a wide range of absolute risks for various adverse outcomes, with variability of up to 4000% for the risk of kidney failure.[12] This variability arises from the impact of additional risk factors such as age and sex, comorbid conditions, aetiology of CKD, nutrition, socioeconomic status and lifestyle factors upon absolute risk. Risk prediction models which incorporate additional predictive variables can provide more individualised absolute risk prediction and support personalised decision-making processes. Current CKD guidelines recommend that an externally validated risk prediction tool be used in all patients with an eGFR ≤59mL/min/1.73m^2 (CKD G3-G5).[2] There are considerations and limitations of these models that are relevant to older patients. The present review discusses the characteristics of risk prediction models, examines key models applicable to older patients with advanced CKD, and provides guidance of how best to use these tools in this patient population.

CHARACTERISTICS OF RISK PREDICTION MODELS

Clinical risk prediction models are equations that use multiple predictor variables such as demographics, comorbidities and laboratory parameters to estimate an individual's probability of a health outcome.[13] They are developed using various statistical methods, including logistic regression, Cox proportional hazards regression and, increasingly, machine learning.

Key characteristics of risk prediction models are summarised in *Table 1*. The performance of a prediction model in being able to accurately predict an outcome is assessed by calibration and discrimination.[14, 15] Calibration is the agreement between observed and predicted event rates. It is visualised using a calibration plot of observed versus predicted values, and quantified using a calibration slope or with other model-specific measures (such as the Hosmer-Lemeshow test for logistic regression models).[15, 16] Discrimination refers to how well a model distinguishes between individuals who will develop the outcome of interest from those who will not. The concordance statistic (C-statistic) is the most used discrimination measure, representing the probability that the model will assign a higher risk to a random case than to a random non-case. C-statistics range between 0.5 and 1, with 0.7 considered reasonable discrimination, 0.8 considered good discrimination and 1 representing perfect discrimination.[13, 15, 16] The C-statistic does however have limitations, including that it can be insensitive to the addition of new predictors and that it provides a summary statistic lacking clinical relevance.[17] For models derived with logistic regression, the C-statistic is equivalent to the area under the receiver operating characteristic curve (AUROC), which when plotted has the advantage of visually providing sensitivity (true positive rate) against 1 – specificity (false positive rate) for consecutive combinations of the probability of an outcome and thereby greater clinical relevance.[15-17]

Predictive models require internal and external validation processes to assess how well they work across different patient populations. Internal validation involves using new data from the same source as that used for model development. Internal validation methods depend on the size of available data, and include split-sampling where the dataset is randomly split into two parts (usually 2:1) with the first portion used to derive the model and the second to

assess predictive accuracy.[13, 18] Newer methods that permit data re-use, such as cross validation and bootstrapping, are preferred as they reduce risk of model overfitting.[18]

Performance of a prediction model is generally lower in new populations compared with the population in which the model was developed.[19] This may be due to derivation data not reflecting the target population in whom the model is intended, inadequate sample size of the derivation cohort, and inadequate handling of missing predictor data.[13] External validation studies in patients with the same disease from a different source population are critically important in demonstrating the generalisability of a model and are strongly recommended in the Transparent Reporting of a multivariable model for Individual Prognosis or Diagnosis (TRIPOD) Statement for reporting prediction models.[20] In practice, however, few kidney failure prediction models have been externally validated in clinically relevant populations.[21, 22]

Clinical utility of a prediction model refers to the extent predicted risks from a model affect decisions.[15] Decision curve analysis is one statistical approach to assessing utility. It involves defining the minimum threshold for when decision-makers (clinicians and patients) would opt for an intervention, taking into account the harm:benefit profile of the intervention for an individual patient. Although a highly clinically relevant measure, decision curve analysis is also rarely reported for kidney failure prediction models.[21]

RISK PREDICTION MODELS FOR OLDER PATIENTS WITH ADVANCED CKD

A systematic review from 2019 identified 47 derivation and validation studies for risk prediction models for progression of CKD to kidney failure,[21] and this is likely to have substantially increased since the time of the review.[22, 23] The suitability of these models to older patients is variable and warrants consideration. Major kidney failure prediction models applicable to older patient populations are summarised in *Table 2* and *Figure 1*.

Kidney Failure Risk Equation (KFRE)

While not specifically derived from an older patient cohort, the Kidney Failure Risk Equation (KFRE) is the most established tool to predict kidney failure among patients with an eGFR ≤59mL/min/1.73m^2 (CKD G3-G5).[24] It was developed and validated in 2011 using 8391 adults in 2 Canadian provinces, and over two-thirds of patients in both the derivation and validation cohorts were aged ≥65 years.[24] It was derived using multivariate Cox proportional hazards regression models and uses either 4 variables (age, sex, eGFR and urine ACR) or 8 variables (with the addition of serum calcium, phosphate, bicarbonate and albumin) to predict 2- and 5-year kidney failure risk, with a small improvement in performance with the 8-variable equation if this data is available in clinical practice.[25] The KFRE has been externally validated in 721,357 individuals from over 30 countries, with excellent discrimination (C-statistics of >0.80 in 28/30 cohorts) and good calibration.[25] However, the KFRE was developed using death before kidney failure as a censoring rather than competing event. In less elderly and less frail populations and across shorter-term predictions, the impact of censoring death is minimal due to the competing risk being infrequent, and sensitivity analyses using the entire derivation cohort from the original KFRE study with competing risk

approaches did not significantly change predicted probabilities.[24] However, the competing risk of death is particularly important in older populations and across longer follow-up durations, where the competing event of death occurs more frequently.[26, 27] While the 2-year KFRE reasonably predicts short-term kidney failure risk in older patients, external validation studies indicate that censoring of death with the KFRE may overestimate true 5-year risk of kidney failure by 18% in older patients,[27] and by close to 25% in the very elderly aged ≥80 years.[26] This overestimation has important clinical implications for shared decision-making discussions and can result in earlier and potentially unnecessary referral of older patients to nephrology services based on 5-year risk. However, when a model based on the original KFRE with additional incorporation of the competing risk of mortality was applied to a large multinational analysis of over 300,000 adults, for the subgroup of patients ≥65 years there were some improvements in calibration though still overprediction of 5-year kidney failure risk in half of the validation cohorts.[28] Thus, although the competing risk of mortality has clear relevance to older populations, addition of competing risk analysis to the KFRE does not meaningfully improve longer term risk prediction in this patient population.

Grams Model

The newer CKD G4+ risk calculator (referred to as the Grams model) was published in 2018 and was derived from 264,296 patients from 30 countries who had more advanced CKD (eGFR <30mL/min/1.73m^2, CKD G4-G5) than the KFRE derivation cohort.[29] As with the KFRE, this tool was not derived from a specifically older cohort, however mean age was 72 years. The Grams model was formulated using competing risk regression, random effects models and Markov simulations, and incorporates 9 demographic and clinical variables (age, sex, race, eGFR, urine ACR, systolic blood pressure, smoking status, diabetes mellitus and history

of cardiovascular disease) to predict 2- and 4-year risk of the individual outcomes of kidney failure, non-fatal cardiovascular events and death in any possible sequence; for instance, both death without kidney failure and death after kidney failure are predicted and there are a total of 9 mutually exclusive outcome trajectories including 'no event'. The original Grams model achieves good discrimination for kidney failure (C-statistics of 0.81 and 0.78 for 2- and 4-year risk models, respectively) and good calibration, comparable to that of the KFRE.[27, 29] Given extensive validation of the KFRE, the authors of the Grams model recommend use of the KFRE in patients with eGFR ≤59mL/min/1.73m^2 in the whom the primary event of interest is kidney failure, and in patients with eGFR <30mL/min/1.73m^2 in whom there is an interest in other outcomes including cardiovascular events or death or the sequence of these events in relation to kidney failure timing, the Grams model may provide more refined risk prediction.[29] While older patients predominantly fall into the latter category, applying the Grams model to older patients requires careful consideration. External validation of the Grams model is significantly more challenging due to its complex derivation and large number of possible outcomes, as event rates for each of the 9 outcome trajectories may be low in potential validation cohorts.[30] Using an older European cohort of 1517 patients with CKD G4, all aged ≥65 years and mean age 76 years, Ramspek *et al.* conducted an external validation study of the Grams model.[31] The study found reasonable discrimination for predicting kidney failure (2- and 4-year C-statistics of 0.74 and 0.73, respectively), however poorer discrimination for predicting death before kidney failure (2- and 4-year C-statistics of 0.62 and 0.64, respectively) and overall risk of death (2- and 4-year C-statistics of 0·61 and 0.62, respectively). Ramspek *et al.* employed decision curve analysis to demonstrate that using thresholds from the Grams model of 2-year kidney failure risk >20% at low harm:benefit ratios (eg. in less frail and less comorbid patients) and 2-year kidney failure risk

>40% at high harm:benefit ratios (eg. in more frail and more comorbid patients) was more effective than using an eGFR threshold alone in reducing the rate of unused dialysis access. A US study of 3418 CKD patients identified that 33% of patients aged ≥70 years underwent dialysis access creation but did not initiate dialysis within 2 years, and 15% underwent access creation and died before ever initiating dialysis,[32] hence the ability to better tailor referral for access creation in older patients has clear clinical relevance. Acknowledging the limitations of the Grams model for older populations, particularly its poorer discriminative ability for predicting death compared with kidney failure, it may offer some decisional support related to dialysis access placement.

Mortality Risk Equation for Kidney Disease (MREK)

The Mortality Risk Equation for Kidney disease (MREK) model was published by Bansal *et al.* in 2015.[33] It was specifically derived from an older cohort of 828 community-dwelling older adults with mean age 80 years and mean eGFR 47mL/min/1.73m^2. It predicts 5-year risk of mortality in older patients with CKD. Cox proportional hazards models were used, with the final model containing 9 variables (age, sex, race, eGFR, urine ACR, smoking status, diabetes mellitus, heart failure and previous stroke). The model had reasonable discriminative ability in predicting 5-year mortality in the derivation cohort (C-statistic 0.72) and good calibration, though slightly lower discrimination with subsequent external validation in an independent older cohort (C-statistic 0.69).[33, 34] A key limitation of the MREK model, however, is that frailer non-community dwelling adults were not included, limiting application to these patients. Additionally, very few patients in the derivation and external validation cohorts had advanced CKD (CKD G4-G5), meaning that kidney failure events were very low and competing risk analysis for kidney failure was not conducted. Using the MREK in isolation,

therefore, has restricted clinical utility as it does not identify those patients who will develop kidney failure before death.

Combined use of the KFRE and MREK

Perhaps the most relevant external validation study for older patients with advanced CKD was that published by Hallan *et al.* in 2019.[35] This study assessed the performance of a combined approach of using both the KFRE in predicting 5-year kidney failure risk and the MREK in predicting 5-year mortality risk in the same population concurrently. The validation cohort consisted of 1188 Norwegian patients with a mean age of 80 years and mean eGFR 36mL/min/1.73m^2 with a follow-up period of 5 years. The study demonstrated that both the KFRE and MREK independently had reasonable diagnostic accuracy (C-statistics of 0.93 and 0.71, respectively) and good calibration when externally validated in the older cohort, with 3.5% progressing to kidney failure within 5 years versus a 5-year predicted kidney failure risk of 4.9% based on the KFRE and 38.9% of patients dying versus a predicted 5-year mortality of 30.1% based on the MREK. It confirmed that the risk of death was much higher than risk of kidney failure in an older community-dwelling cohort (at a ratio of 10:1) despite moderate to severe CKD at baseline. When used jointly, only 2.6% of patients had a 5-year kidney failure risk higher than their 5-year risk of mortality. However, among those high-risk patients, most truly experienced kidney failure rather than death during follow-up. The authors used decision curve analysis to demonstrate how both equations may be used concurrently in the same patient to guide when treatment planning (*Figure 2*). For example, for an older patient without significant frailty or comorbidities in whom both the patient and clinician feel the harm:benefit ratio of treatment planning is low (eg. harm:benefit ratio 1:4), referral for treatment planning when eGFR is <25mL/min/1.73m^2 if the patient is aged <80

years has the highest clinical utility. For more comorbid older patients in whom the harm:benefit ratio is equivocal (eg. harm:benefit ratio 1:1), deferring treatment planning for when predicted 5-year kidney failure risk (using the KFRE) exceeds predicted 5-year mortality risk (using the MREK) has the highest clinical utility. However, it should be noted that at a harm:benefit of 1:1, other thresholds such as when '5-year kidney failure risk exceeds 5-year mortality risk provided the patient is not frail' or '5-year kidney failure risk >50%' all yielded slightly lower but similar clinical utility (*Figure 2*). Thus, in the 'average' patient with a harm:benefit ratio of 1:1, any of these three clinical utility algorithms (when 'kidney failure risk > mortality risk', 'kidney failure risk > mortality risk provided the patient is not frail', or 'kidney failure risk >50%') may be appropriate.[36] Hallan *et al.*'s clinical utility algorithm takes into account the spectrum of patient and clinician harm:benefit perceptions in addition to validated prediction tools, thus providing a more individualised approach to guide shared decision-making discussions.

RISK PREDICTION MODELS IN THE TREATMENT DECISION-MAKING PHASE

It is important to note that the aforementioned models for predicting kidney failure risk define kidney failure as initiation of dialysis or kidney transplantation, and their derivation cohorts did not account for patients with eGFR ≤15mL/min/1.73m^2 who were on a CKM pathway and hence had no initiation of dialysis.[36] This is predominantly due to data limitations, whereby the outcome of kidney failure managed without dialysis was not a readily accessible or recorded outcome in the derivation cohorts.[27] Up to 14-29% of patients with kidney failure in developed countries do not plan to enter onto dialysis,[37-39] and the

lack of CKM patients within the derivation cohorts of the risk prediction tools described may result in underestimation of the risk of kidney failure for older patients.[27]

A Dutch model by Ramspek *et al.* in 2020 directly addresses these issues of kidney failure definition.[40] This model was derived from a cohort of 366 older patients aged ≥70 years who were followed from eGFR ≤20mL/min/1.73m^2 and once a treatment decision for either dialysis or CKM had been made. The study contained 240 patients intending to start dialysis and 126 patients electing a CKM pathway. For each sub-cohort, a risk prediction model for the outcome of 2-year mortality was derived using logistic regression. Each model used the same predictors (age, eGFR, active malignancy, diabetes mellitus and cardiovascular disease), with the aim that the models could be used in the same patient at the time of treatment decision-making to predict mortality risk with dialysis or CKM pathway. With internal validation, discrimination for predicting 2-year mortality ranged from C-statistics of 0.68 to 0.75 for the dialysis model and 0.68 to 0.73 for the CKM model. These discriminative abilities are moderate, and there are several other limitations to these models including their derivation from a single-centre population with small sample size (which increases the risk of overfitting and poor performance in other populations) and the lack of external validation. Furthermore, the premise of using these models in the same patient to predict mortality risk with a dialysis versus CKM pathway at the time of treatment decision-making assumes that differences in prognosis are due to treatment choice, and does not account for fundamental differences between the dialysis and CKM derivation cohorts such as differences in comorbidities. Although this concept of counterfactual prediction (how a patient might fare on alternative treatment plans) may have a role in older patients for whom there is a high degree of equipoise about whether they will derive the most benefit

from a dialysis versus CKM pathway, more work is needed to overcome methodological challenges of confounding factors.[22, 40]

The more recent machine learning KDpredict tool reported by Liu *et al*. in 2024 offers a novel modelling approach and addresses issues surrounding kidney failure definitions.[41] This tool was derived using a cohort of 67,942 Canadian patients with median age 78 years and eGFR ≤45mL/min/1.73m^2 at baseline, who were followed for the outcomes of kidney failure and mortality. Importantly, kidney failure was defined as initiation of KRT or eGFR ≤10mL/min/1.73m^2 for more than 90 days, thus incorporating a larger proportion of patients opting for CKM. A super learner machine learning approach was used to predict future kidney failure risk and all-cause mortality risk each year up to five years. For any one individual, the super learner method uses cross-validation to choose the best performing algorithm from a vast suite of prespecified regression models and machine learning algorithms (known as learners), based on their ability to minimise prediction error (as assessed by the Brier score, a measure of the discrepancy between the expected risk of an outcome and the observed risk in validation datasets).[42] Input predictors are age, sex, eGFR, urine ACR, diabetes mellitus and cardiovascular disease, and the final algorithm used for an individual's prediction of risk varies according to inputs. External validation was performed using a 17,538 Danish cohort and a 7740 Scottish cohort and compared to the KFRE, with KDpredict outperforming the KFRE in predicting kidney failure risk (5-year predictive accuracy for kidney failure of 28% with KDpredict versus 18% with KFRE in the Danish cohort, and 31% versus 14% respectively in the Scottish cohort).[41] The authors postulate reasons for this superior performance, including that the KDpredict tool was derived from an older population (median age 77 years versus 70 years) and included patients with more

advanced CKD (eGFR ≤45mL/min/1.73m^2 versus ≤59mL/min/1.73m^2), thus had higher outcome event rates. Secondly, KDpredict accounts for the competing risk of death and predicts both death and kidney failure risk (including those not managed with KRT), in contrast to the KFRE which does not account for the competing risk of death and may overestimate kidney failure risk in older patients. Thirdly, KDpredict uses real-time machine learning methodology that lets the data select the best performing model from a library of models without imposing restrictions. Limitations of KDpredict, however, should be acknowledged. Machine learning approaches are novel in the kidney failure prediction field, require widespread availability of internet access and smart devices, and require much greater external validation in diverse settings to garner the generalisability of the KFRE.[42] Additionally, although KDpredict demonstrates good predictive accuracy for 5-year kidney failure risk, discrimination for mortality risk prediction was lower and comparable to that of the MREK. Furthermore, KDpredict was derived and validated for patients with eGFR ≤45 mL/1.73m^2, which operationally poses challenges to clinicians regarding which risk prediction tool to use in patients with stage 3 CKD, where both KFRE and KDpredict appear reasonable.[2] Nonetheless, KDpredict is a promising decision support tool that predicts both 5-year kidney failure and mortality risk with strong applicability to older patients, and it is likely that this model will change the landscape of kidney failure risk prediction tools in coming years.

CLINICAL IMPLICATIONS FOR TREATMENT DECISION-MAKING WITH OLDER PATIENTS

Each of the risk prediction models discussed have led to incremental steps in bringing risk-based care to nephrology, however challenges and unmet needs for their application to older patients with advanced CKD remain. Acknowledging these challenges, an approach for how best to employ currently available tools may best be conceptualised with three key questions.[43]

Firstly, how well does the risk prediction model predict the outcome(s) of interest in the study population it was developed? This is primarily assessed by discrimination (eg. C-statistics) and differs from statistical significance. For example, a number of variables in an observational study may be statistically significant in predicting an outcome but when incorporated into a risk prediction tool the summary C-statistic may be poor (<0.7), indicating that much of the variation of the outcome in the population examined is determined by unmeasured factors. In the setting of older patients with advanced CKD, factors such as frailty and functional status are likely to be strong predictors of outcomes and are worthy of consideration in future risk prediction models.[44]

Secondly, how well does the risk prediction model predict outcomes in individual patients? This reflects the external validity of a risk prediction model and is challenging to assess in the absence of diverse external validity studies. One approach to this is to broadly consider how a clinician's own patient and setting compares to the population in which the prediction model was developed. In the United Kingdom and Australia, for instance, it is predicted that there are high rates of older patients on a CKM pathway,[45] and thus the generalisability of

models derived from largely North American populations that did not account for CKM patients may be limited. It is here that the KDpredict tool (which had greater accountability for CKM patients) has promise, though it requires further external validation.

And thirdly, does the risk prediction tool make a meaningful contribution to the decision-making process for clinicians and their patients? Most prediction models are opportunistically derived from large data sets developed for other purposes, and on their own do not take into account individual patient factors such as patient preference or individual harm:benefit profiles. Quantifiable measures of clinical utility such as decision curve analysis are a useful and relatable means of incorporating these concepts into assessment of how best to use a risk prediction model in the decision-making process.

Taking into account these three questions, while further external validation studies of the KDpredict tool are awaited, the concurrent method of using the KFRE in combination with the MREK that was externally validated by Hallan *et al*. in an older patient cohort is an approach that likely has the greatest merit.[35] Particularly for patients with an equivocal harm:benefit profile (eg. 1:1, which could be considered the 'average' older patient with CKD), using the threshold of when predicted 5-year kidney failure risk (using the KFRE) exceeds predicted 5-year mortality risk (using the MREK) to guide referral for when to initiate dialysis access planning is a threshold with good discriminative ability and clinical utility. However, for older patients with much higher harm:benefit profiles (eg. 4:1) who may be more likely to enter onto a CKM pathway, the applicability of the combined method proposed by Hallan *et al*. is less clear. Ideally, a clinical impact trial that randomises clinicians and patients to the use of different prediction models to assist decision-making would

provide the greatest insights into the clinical utility of various risk prediction models in an older advanced CKD population.

CONCLUSIONS

Risk prediction modelling has rapidly increased in nephrology and holds promise in supporting individualised decision-making processes for older patients with advanced CKD. However, several limitations remain including currently available risk prediction models largely being developed from general CKD cohorts rather than specifically older age cohorts, varying accountability for the competing risk of death, limited accountability for patients who develop kidney failure and opt for a CKM pathway, and the lack of diverse external validation studies. While a combined approach of using the KFRE and MREK may have the highest clinical utility, further work is needed to bridge the gap between prediction research and patient care, in order to understand how best to integrate these models into shared decision-making processes for older adults with advanced CKD.

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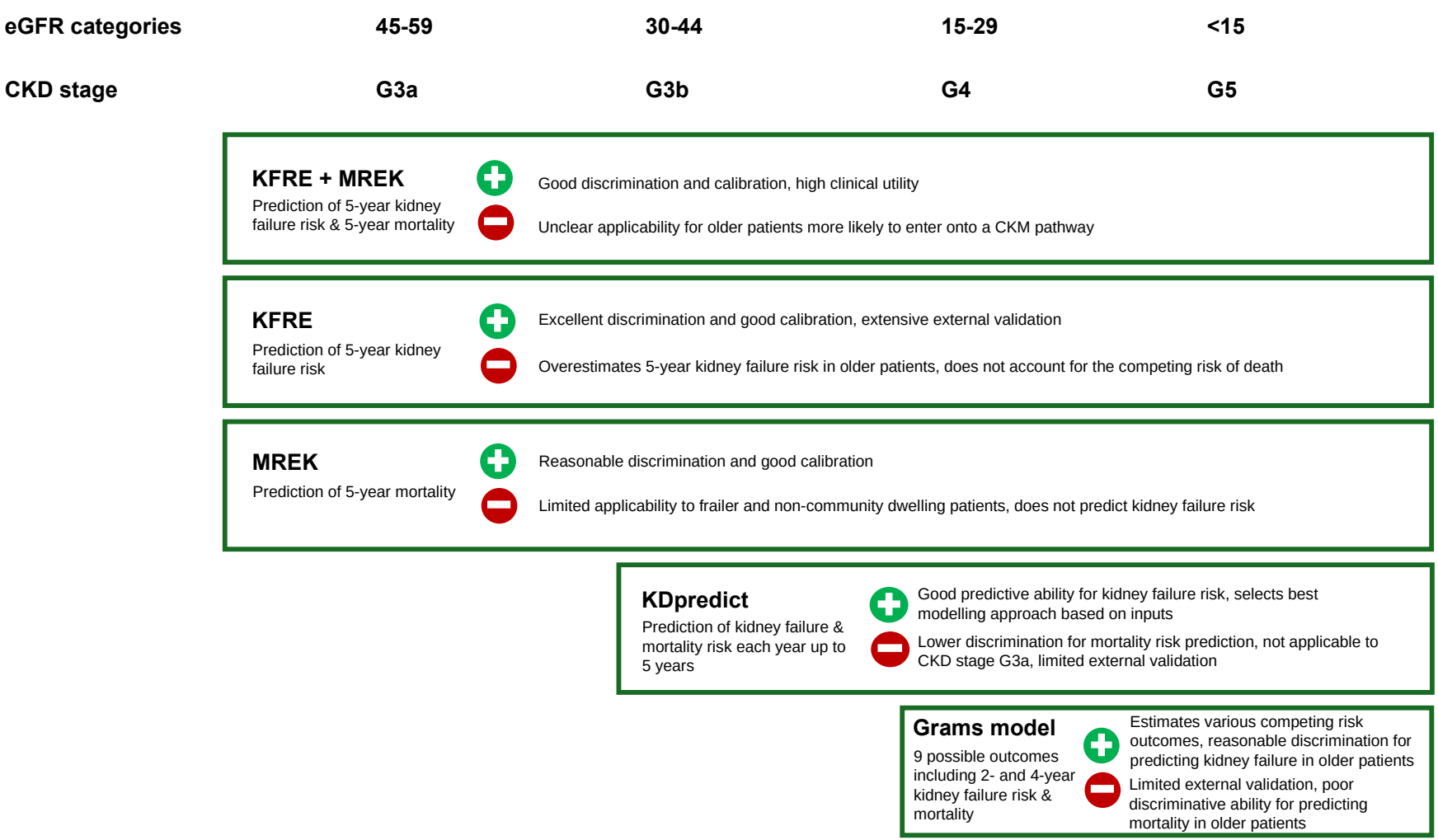

Figure 1. Major risk prediction models applicable to older patients across the spectrum of eGFR ≤59 mL/min/1·73m^2 (CKD G3-G5), and their respective strengths and limitations.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KFRE, Kidney Failure Risk Equation; MREK, Mortality Risk Equation for Kidney disease.

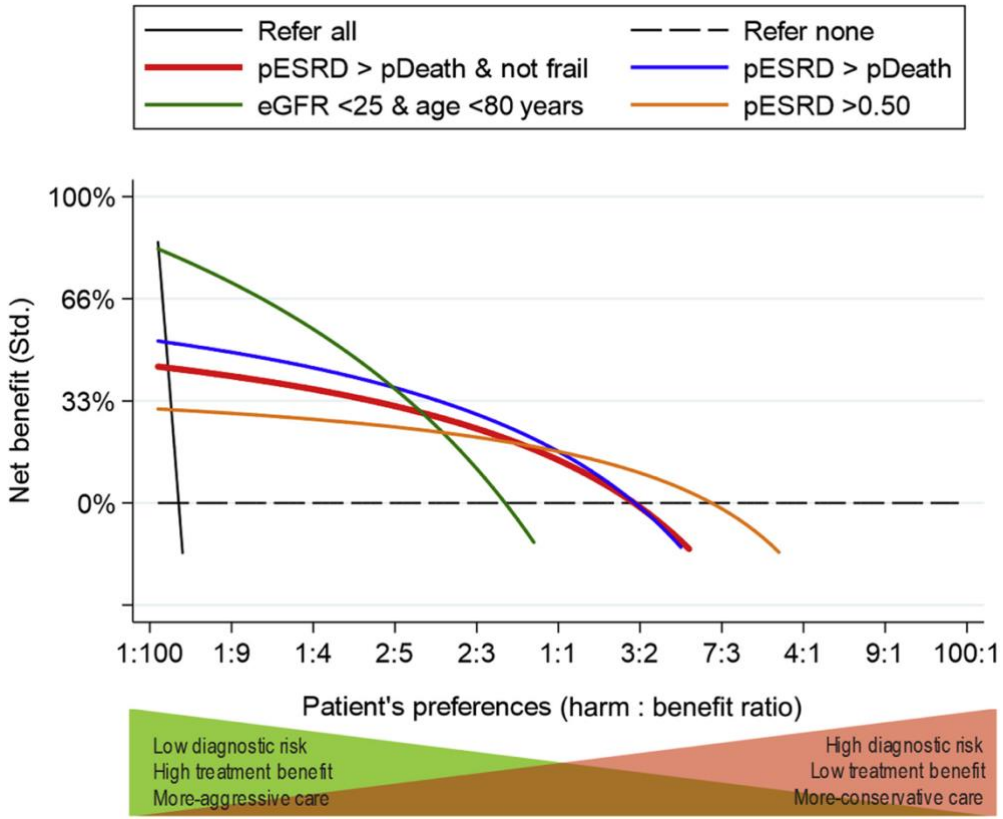

Figure 2. Decision curve analysis by Hallan et al. for highest clinical utility for referral for kidney failure treatment planning relative to valuation of harm versus benefit.

Best clinical utility (also known as net benefit) is represented by the highest level on the y-axis, and harm:benefit ratio is represented on the x-axis. 'Benefit' refers to timely preparation for KRT in those who ultimately experience kidney failure as their first event, and 'harm' refers to the same interventions in those who experience death as their first event. Harm:benefit ratio broadly reflects patient frailty and comorbidities and patient and clinician perceptions of when there is likely to be treatment benefit versus harm. For example, for an older patient without significant frailty or comorbidities in whom both the patient and clinician feel that the harm:benefit ratio of treatment

planning is low (eg. 1:4), referral for treatment planning when eGFR is <25mL/min/1·73m^2 if the patient is aged <80 years has the highest clinical utility. For more comorbid older patients with an equivocal harm:benefit ratio (eg. 1:1), deferring treatment planning for when predicted kidney failure risk using the KFRE exceeds predicted morality risk using the MREK has the highest clinical utility.

KRT, kidney replacement therapy; eGFR, estimated glomerular filtration rate; KFRE, Kidney Failure Risk Equation; MREK, Mortality Risk Equation for Kidney disease.

Source: Hallan et al. *Kidney Int* 2019; 96(3): 728-37.[35]

Table 1. Key characteristics of risk prediction model performance.

Characteristic	Description	Methods of assessment
Calibration	The degree of agreement between observed event rates and predicted event rates	Calibration plot (perfect calibration lies at 45^{o}) Calibration slope (perfect calibration is equivalent to a slope of 1) Hosmer-Lemeshow test
Discrimination	How well the predictions from a model differentiate between those with and those without the outcome	C-statistic (ranging from 0.5 to 1) Area under the receiver operating characteristic (AUROC) curve
Internal validation	Assessment of model performance using new data from the same source as the data used to develop the model	Split-sample validation Cross validation Bootstrapping
External validation	Assessment of model performance in a different sample of data to that used to develop the model	Evaluation in external datasets representative of the development population Evaluation in external datasets intentionally different to the development population
Clinical utility	Assessment of how a model affects clinical decisions	Decision curve analysis

Table 2. Major risk prediction models relevant to older patients with advanced CKD.

Model (Year of publication)	Variables	Development population	Outcome(s)	Modelling technique	Discrimination/ calibration in development cohort	External validation	Clinical usefulness assessment for older patient populations
KFRE (2011)[24] www.kidneyfailurerisk.com	Age, sex, eGFR, urine ACR (4 variables) + calcium, phosphate, bicarbonate and albumin (8 variables)	8391 Canadian patients (mean age 70 years, eGFR ≤59 mL/min/1·73m^2)	2- and 5-year kidney failure risk (defined as initiation of dialysis or transplantation, and censored for mortality before kidney failure)	Cox proportional hazards regression	Excellent/good	721,357 patients in >30 countries, including older patient cohorts [26, 27]	Overestimates 5-year kidney failure risk in older patients
Grams model (2018)[29] http://ckdpcrisk.org/lowgfrevents	Age, sex, race, eGFR, urine ACR, systolic blood pressure, smoking status, diabetes mellitus, history of cardiovascular disease	264,296 patients across 30 countries (mean age 72 years, eGFR <30 mL/min/1·73m^2)	2- and 4-year risk of kidney failure, non-fatal cardiovascular events and death in any possible sequence (total of 9 mutually exclusive outcome trajectories including 'no event')	Competing risk regression, random effects models and Markov simulations	Excellent/good	Less extensively externally validated due to complexities with large number of possible outcomes, has been validated in an older patient cohort [31]	Reasonable predictive ability for kidney failure risk in an older patient cohort, poorer discriminative ability for predicting death
MREK (2015)[33]	Age, sex race, eGFR, urine ACR, smoking status, diabetes mellitus, history of heart failure, history of stroke	828 community-dwelling US patients (mean age 80 years, mean eGFR 47 mL/min/1·73m^2)	5-year mortality risk	Cox proportional hazards regression	Reasonable/good	Validated in 789 patients	Limited applicability to frailer and non-community dwelling older patients, and does not predict risk of kidney failure
Concurrent KFRE + MREK (2019)[35] Calculator linked to online version of paper at www.kidney-international.org	4-variable KFRE and 9-variable MREK	1188 Norwegian patients (mean age 80 years, mean eGFR 36 mL/min/1·73m^2)	5-year kidney failure and 5-year mortality risk	External validation and decision curve analysis	Excellent/good for KFRE, good/good for MREK	-	High clinical utility for using the threshold of kidney failure risk > mortality risk to guide dialysis planning in older patients with equivocal harm:benefit ratio (eg. 1:1)

KDpredict (2024)[41] http://kdpredict.com	Age, sex, eGFR, urine ACR, diabetes mellitus, history of cardiovascular disease	67,942 Canadian patients (median age 78 years, eGFR ≤45 mL/min/1·73m^2)	Kidney failure and all-cause mortality risk each year up to 5 years	Super learner machine learning algorithm	Excellent/good	17,538 Danish patients and 7740 Scottish patients	Outperforms KFRE in predicting 5-year kidney failure risk in the Danish and Scottish cohorts, though requires greater external validation

ACR, albumin:creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KFRE, Kidney Failure Risk Equation; MREK, Mortality Risk Equation for Kidney disease.

CHAPTER 6

Cardiovascular, kidney and safety outcomes with canagliflozin in older adults: A combined analysis from the CANVAS Program and CREDENCE trial

CHAPTER OVERVIEW

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to have cardiovascular, kidney and mortality benefits among individuals with type 2 diabetes, with and without chronic kidney disease (CKD). Given the growing prevalence of these conditions in older adults, there is significant research and clinical interest in how the results of SGLT2 inhibitor trials translate to older patients. This chapter aims to address the fifth objective of this thesis, to use post-hoc secondary analyses of trial data to examine the efficacy and safety of the SGLT2 inhibitor canagliflozin across the spectrum of age. The efficacy and safety of this drug class in older individuals offers dramatic potential to mitigate some of the impacts of growing CKD and diabetes prevalence in older patient populations.

PUBLICATION DETAILS

Amanda Siriwardana [1, 2, 3], Luke Buizen [2], Min Jun [2], Sradha Kotwal [2, 4], Clare Arnott [2, 5], Meg Jardine [2, 6, 7], Adeera Levin [8], Hiddo JL Heerspink [9], David Charytan [10], Carol Pollock [3, 11], Vlado Perkovic [2, 12], Brendon L Neuen [1, 2, 3]. Cardiovascular, kidney and safety outcomes with canagliflozin in older adults: A combined analysis from the CANVAS Program and CREDENCE trial. Under review September 2024 in *Diabetes Obes Metab*.

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AUTHOR CONTRIBUTIONS

AS, BN, LB, CA and VP contributed to the conceptualisation, data curation and data interpretation. AS and LB performed the formal analysis. AS wrote the original draft of the manuscript, and all authors were involved in the review and editing of the manuscript.

ABSTRACT

Aim: SGLT2 inhibitors may be underused in older adults with type 2 diabetes due to concerns about safety and tolerability. This pooled analysis of the CANVAS Program and CREDENCE trial examined the efficacy and safety of canagliflozin according to age.

Methods: Pooled individual participant data from the CANVAS Program (n=10,142) and CREDENCE trial (n=4,401) were analysed by baseline age (<65 years, 65 to <75 years, and ≥75 years). Main outcomes of interest were: major adverse cardiovascular events (MACE, a composite of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death), cardiovascular death, hospitalisation for heart failure, all-cause mortality, composite kidney outcome (doubling of serum creatinine, kidney failure or death due to kidney disease), cardiorenal composite (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular disease), and safety outcomes. Cox proportional hazards models and Fine and Gray competing risk analysis were used.

Results: Among the 14,543 participants, 7,927 (54.5%) were <65 years, 5,281 (36.3%) were 65 to <75 years, and 1,335 (9.2%) were ≥75 years. Older participants had higher rates of atherosclerotic cardiovascular disease and heart failure, longer diabetes duration, and lower mean eGFR. Reductions in cardiovascular and kidney outcomes with canagliflozin were consistent across age categories (all *P* trend >0.10), although there was some evidence that effects on cardiovascular death and all-cause death were attenuated with older age (*P* trend=0.02 and 0.03, respectively). Although the incidence of adverse events increased with age, effects of canagliflozin on safety outcomes including acute kidney injury, volume depletion, urinary tract infections and hypoglycaemia, were not modified age (all *P* trend >0.10).

Conclusions: In this pooled CANVAS and CREDENCE analysis of T2DM patients with varying degrees of kidney function, canagliflozin reduced cardiovascular and kidney outcomes, regardless of age, with no additional safety concerns identified in older patients.

INTRODUCTION

The distribution of the world's population is undergoing a dramatic shift towards older age groups.[1] With this comes the growing burden of chronic diseases including type 2 diabetes (T2DM), which pose a significant current and future public health challenge. The prevalence of diabetes among older adults aged ≥65 years in the United States is estimated at 29.2%, a prevalence rate more than double that for the overall adult population aged ≥18 years.[2]

Management of T2DM among older adults has unique considerations, including high rates of coexisting medical conditions, frailty, cognitive impairment and polypharmacy. It is therefore crucial to understand the efficacy and safety of treatments for T2DM among older adults when making evidence-based benefit-risk decisions in this population.

The cardiovascular, kidney and mortality benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors among adults with T2DM have been demonstrated in several cardiovascular and kidney outcome trials.[3-15] To better understand the effects of SGLT2 inhibition in older adults, we conducted a pooled individual participant data analysis of the CANVAS Program and CREDENCE trial to evaluate the efficacy and safety of canagliflozin across a broad range of age and cardiorenal risk.

METHODS

Trial design and populations

This post-hoc study analysed individual participant data from the CANVAS Program, consisting of the CANVAS and CANVAS-Renal (CANVAS-R) trials (ClinicalTrials.gov registration numbers NCT01032629 and NCT01989754), and the CREDENCE trial (ClinicalTrials.gov registration number NCT02065791). The study design and main results of these trials have been published previously.[16-18]

In brief, all were randomized, double-blind, placebo-controlled, multicentre trials. The CANVAS Program enrolled individuals with T2DM and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m^2, who were either aged ≥30 years with a history of symptomatic atherosclerotic cardiovascular disease or aged ≥50 years with ≥2 cardiovascular disease risk factors. Participants in the CANVAS trial were randomised in a 1:1:1 allocation to 100mg canagliflozin, 300mg canagliflozin, or placebo. Participants in the CANVAS-R trial were randomised in a 1:1 allocation to 100mg canagliflozin, with optional uptitration to 300mg at week 13, or placebo. The CREDENCE trial enrolled individuals aged ≥30 years with T2DM and CKD, defined as an eGFR of ≥30 to <90 mL/min/1.73m^2 and a urine albumin:creatinine ratio (UACR) of >300 to ≤5000 mg/g. CREDENCE participants were randomised on a 1:1 allocation to 100mg canagliflozin or placebo. There was no upper age limit for the CANVAS Program or CREDENCE trial. Other therapy for glycaemic control, cardiovascular management and kidney management was continued or instituted in accordance with best practice care for all trials. Ethics approval was obtained from all participating centres and all participants provided written informed consent.

Participant categorisation

For this analysis, the CANVAS Program and CREDENCE populations were pooled and analysed by baseline age (<65 years, 65 to <75 years, and ≥75 years).

Outcomes

All cardiovascular and kidney outcomes in the CANVAS Program and CREDENCE trial were independently adjudicated by blinded clinical endpoint committees.

For this analysis, the main efficacy outcomes of interest were major adverse cardiovascular events (MACE, defined as a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death), cardiovascular death, hospitalisation for heart failure, a composite of hospitalisation for heart failure or cardiovascular death, all-cause mortality, composite kidney outcome (doubling of serum creatinine, kidney failure or death due to kidney disease), and a cardiorenal composite (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular disease).

Adverse events, both serious and non-serious, were collected in the CANVAS trial until early 2014 in accordance with regulatory requirements. After this time, only serious adverse events, adverse events leading to drug discontinuation, and selected adverse events of interest were collected in the CANVAS trial. These latter three criteria for adverse event data collection were used for the entirety of the CANVAS-R trial. For the CREDENCE trial, both serious and non-serious adverse events were recorded. To ensure consistency of definitions for the present analysis, safety outcomes included in this pooled analysis were any serious adverse events, serious and non-serious hypoglycaemia, serious volume depletion, serious

acute kidney injury, serious and non-serious male genital mycotic infections, serious and non-serious female genital mycotic infections, and serious urinary tract infections.

Statistical analysis

Baseline characteristics were compared across age subgroups using Chi-squared and ANOVA or Kruskal-Wallis tests for categorical and continuous variables, respectively.

All analyses were conducted according to the intention-to-treat principle. Cox proportional hazards models were used to obtain treatment effects, expressed as hazard ratios (HRs) and 95% confidence intervals (CIs), with stratification according to trial. The proportional hazards assumption was assessed by testing of Schoenfeld residuals. Heterogeneity of the treatment effect across age subgroups was assessed by including a subgroup-by-treatment group interaction term in the relevant model. *P* trend values across subgroups were obtained using the likelihood ratio test with no adjustment for multiple comparisons. Sensitivity analysis adjusting for competing risk of death were performed for efficacy outcomes using the Fine and Gray method.[19]

As pre-specified in each of the trials, safety outcomes were assessed in the pooled on-treatment population, with events considered for participants who had a safety outcome while receiving canagliflozin or placebo, or within 30 days of discontinuation of study medication. Effects on safety outcomes were evaluated using Cox proportional hazards models as previously described.

All analyses were performed using Stata version 18 (StataCorp LLC).

RESULTS

Baseline characteristics

This analysis consisted of 14,543 participants pooled from the CANVAS Program (n=10,142) and CREDENCE trial (n=4,401). Mean age at baseline was 63.7 years (±8.5 years). 7,927 (54.5%) participants were <65 years, 5,281 (36.3%) were 65 to <75 years, and 1,335 (9.2%) were ≥75 years, with the oldest participant aged 90.6 years (*Figure S1*). Older participants were more likely to be white, and have coronary artery disease, heart failure and longer diabetes duration (all *P* <0.001; *Table 1*). They were also more likely to have lower eGFR, higher UACR, higher SBP and lower HbA1c (all *P* <0.001; *Table 1*). Baseline use of renin-angiotensin system blocking agents was high overall and in each age category (*P* = 0.75, *Table 1*). Older patients were less likely to receive insulin and metformin, and more likely to be treated with diuretic therapy, statins and anti-thrombotic agents (*P* ≤0.01 for all, *Table* 1). Baseline characteristics across age categories by treatment group are shown in *Table S1*.

Cardiovascular outcomes

Effects of canagliflozin on cardiovascular and kidney outcomes across age groups are displayed in *Figure 1*. In the overall pooled population, canagliflozin reduced the risk of MACE (HR 0.84, 95% CI 0.76 to 0.93), with consistent effects across age subgroups (*P* trend = 0.66; *Figure 1*). Canagliflozin showed consistent relative benefits across age subgroups in reducing the risk of hospitalisation for heart failure (*P* trend = 0.68; *Figure 1*) and for the composite of hospitalisation for heart failure or cardiovascular death (*P* trend = 0.15; *Figure 1*). While canagliflozin reduced the risk of cardiovascular death in the overall pooled population (HR 0.84, 95% CI 0.72 to 0.98), there was some evidence of attenuated effect

with increasing age (<65 years: HR 0.66, 95% CI 0.52 to 0.83; 65-<75 years: HR 0.97, 95% CI 0.77 to 1.22; ≥75 years: HR 1.11, 95% CI 0.74 to 1.65; *P* trend = 0.02). Similarly, canagliflozin reduced all-cause mortality in the overall pooled population (HR 0.85, 95% CI 0.75 to 0.97), with some evidence of heterogeneity across age groups (<65 years: HR 0.72, 95% CI 0.59 to 0.86; 65-<75 years: HR 1.00, 95% CI 0.82 to 1.21; ≥75 years: HR 0.88, 95% CI 0.64 to 1.21; *P* trend = 0.03; *Figure 1*). These findings were similar in a sensitivity analysis adjusting for the competing risk of death (*Table S2*).

Kidney outcomes

In the overall pooled population, canagliflozin reduced the risk of the composite kidney outcome (HR 0.63, 95% CI 0.53 to 0.77), with consistent benefits across age groups (*P* trend = 0.14; Figure 1). Canagliflozin also reduced the risk of the composite cardiorenal outcome (HR 0.75, 95% CI 0.66 to 0.84), although again there was some evidence of heterogeneity with the addition of cardiovascular death to the composite kidney outcome (<65 years: HR 0.66, 95% CI 0.56 to 0.78; 65-<75 years: HR 0.81, 95% CI 0.66 to 0.99; ≥75 years: HR 0.92, 95% CI 0.64 to 1.31; *P* trend = 0.01; *Figure 1*).

Safety outcomes

The effects of canagliflozin on key safety outcomes are summarised in *Figure 2*. The overall frequency of serious adverse events increased with age in both treatment arms. However, the relative effects of canagliflozin compared with placebo on safety outcomes were largely consistent regardless of age, including for serious adverse events, hypoglycaemia, serious volume depletion, serious acute kidney injury, and serious urinary tract infections (all *P* trend >0.10, *Figure 2*).

DISCUSSION

In this large, pooled analysis from the CANVAS Program and CREDENCE trial of 14,543 participants with T2DM at high cardiovascular risk or with CKD, canagliflozin consistently reduced cardiovascular and kidney outcomes across the spectrum of age. While the overall incidence of safety outcomes increased with older age, relative effects of canagliflozin on safety outcomes were largely consistent across age categories including in the oldest age group of ≥75 years, indicating no additional safety concerns in older adults.

Due to population ageing and a greater absolute increase in the prevalence of T2DM in older adults compared with younger adults, it is expected that individuals aged ≥65 years will make up most of the diabetic population in the United States by 2050.[20] In turn, older individuals with T2DM have higher absolute risks of cardiovascular events, particularly heart failure-related events, and kidney complications.[21, 22] The cardiovascular, kidney and mortality benefits of SGLT2 inhibitors in patients with T2DM have been demonstrated in several cardiovascular and kidney outcome trials,[3-15] and the relatively short times to benefit of these agents renders them a particularly appealing treatment class for older patients. Despite this, real-world uptake of SGLT2 inhibitors among older age groups is among the lowest of all patient groups.[23-26] Concerns regarding polypharmacy, potential adverse effects and unclear safety data due to historical underrepresentation of older and frailer patients in clinical trials are likely to be major contributors to these low uptake rates of SGLT2 inhibitors in older adults.[23, 26] Addressing these evidence gaps and clinical inertia in the prescribing for older adults with T2DM are both important and timely.

With over one-third of participants aged 65 to <74 years at baseline and close to 10% aged ≥75 years, the CANVAS Program and CREDENCE trial populations provide an important opportunity to assess the efficacy and safety of SGLT2 inhibition across the spectrum of age and cardiorenal risk in T2DM. The findings from this analysis extend upon previous age subgroup analyses of other large outcome-driven SGLT2 inhibitor trials. In cardiovascular outcome trials among patients with T2DM, post-hoc analyses of the EMPA-REG OUTCOME, DECLARE-TIMI 58 and VERTIS-CV trials demonstrated consistent risk reduction in cardiovascular and kidney outcomes irrespective of age.[27-29] Among dedicated kidney outcome trials, post-hoc analysis from the DAPA-CKD trial showed consistent reductions in the risk of CKD progression, hospitalisation for heart failure or cardiovascular death, and all-cause mortality across the spectrum of age.[30] Taken together, the data presented in the current analysis and that of other outcome-driven SGLT2 inhibitor trials suggests clear extension of the cardiorenal benefits of SGLT2 therapy to older individuals.

We observed some heterogeneity in the effects on mortality outcomes with canagliflozin versus placebo when analysed by age, with similar results observed in competing risk analyses. However, these findings should be interpreted as hypothesis generating due to the post-hoc nature of this study with no adjustment for multiplicity. The findings from major heart failure SGLT2 inhibitor trials, which enrolled significantly older patient populations at high risk of mortality, offer important context for these findings. Post-hoc analyses from DAPA-HF, EMPEROR-Preserved, EMPEROR-Reduced and DELIVER demonstrated consistent cardiovascular benefits with no effect modification by age.[31-34] Nevertheless, further assessment of the effects of SGLT2 inhibitors in the elderly would be of benefit. GOLDEN-AGE is an ongoing pragmatic intraclass open-label trial comparing glycaemic and safety

outcomes with three SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) in patients aged 70-90 years in Italy (ClinicalTrials.gov Identifier: NCT04796428).

Importantly, no additional safety concerns were identified for elderly patients. Consistent with what is known about the SGLT2 inhibitor class, there were higher risk genital mycotic infections with canagliflozin compared with placebo, though majority of these infections were minor, with no consistent evidence that the effect on genital mycotic infections was modified by age. Similarly, while there was a modest increase in risk of serious volume depletion in canagliflozin treated participants, this effect was not impacted by age. Importantly, canagliflozin did not increase the risk of serious urinary tract infections, either overall or across subgroups of age, and there were no treatment-by-age interactions observed for all other safety outcomes. These findings should engender confidence amongst clinicians and patients regarding the use of canagliflozin in older adults.

The findings from this study should be interpreted in light of some important limitations. Firstly, this was a pooled post-hoc analysis and the CANVAS, CANVAS-R and CREDENCE trials were not designed to evaluate treatment effects in specific age subgroups. The *P* trend values were not corrected for multiple comparisons and should be interpreted as exploratory given the number of tests performed. Secondly, because of the CANVAS Program and CREDENCE trial were enriched for patients at high cardiorenal risk, generalising these age-related findings to T2DM populations with lower baseline risk should be done cautiously. Finally, there were fewer patients in the very elderly category of this analysis.

CONCLUSIONS

This pooled analysis of the CANVAS Program and CREDENCE trial demonstrates that the cardiovascular and kidney benefits of canagliflozin are broadly consistent across the spectrum of age, with a consistent safety profile in older adults. These findings provide strong support for the therapeutic potential of SGLT2 inhibitors among older patients with T2DM with high cardiovascular risk and/or chronic kidney disease.

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DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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FIGURES AND TABLES

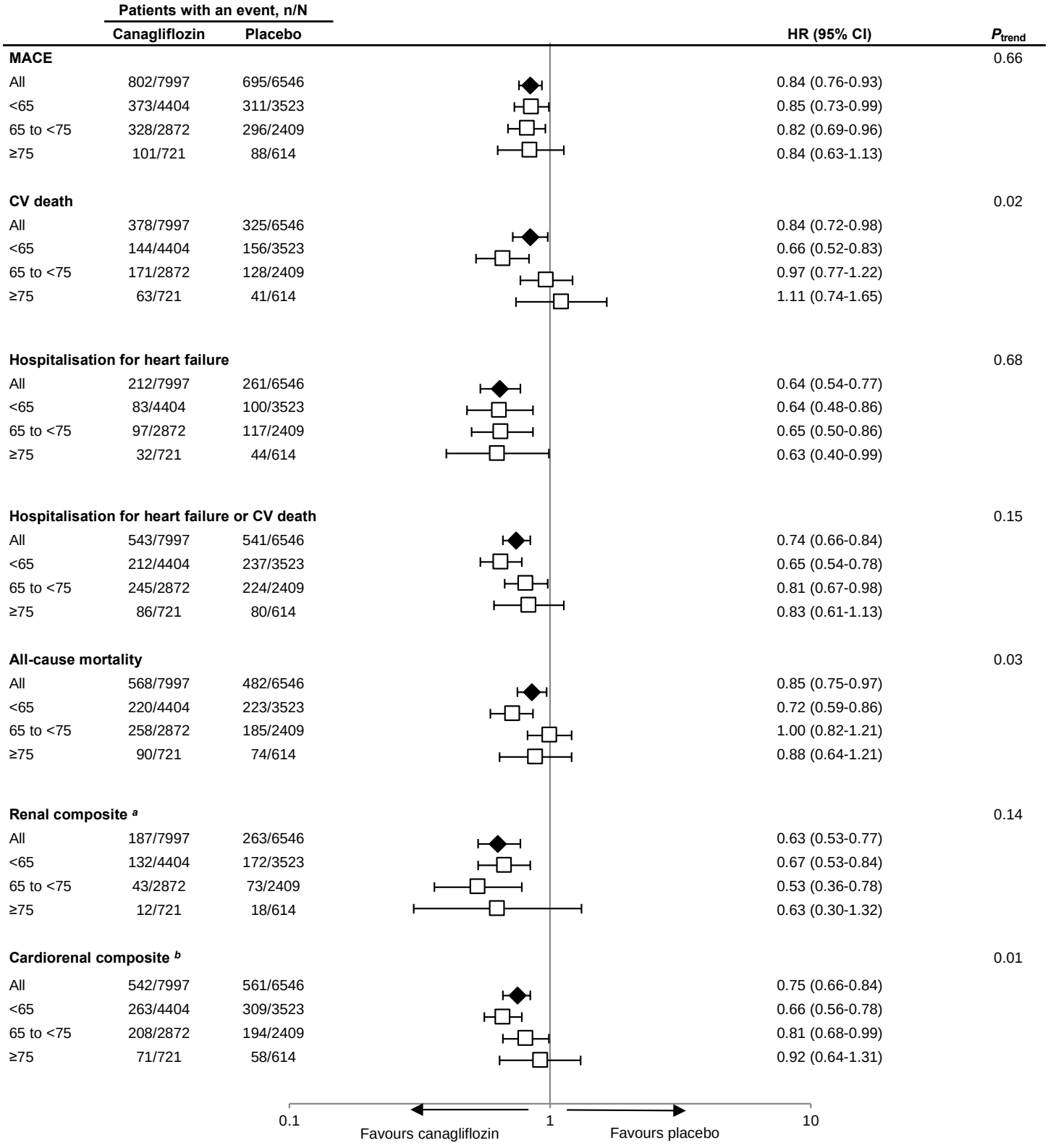

Figure 1. Effects of canagliflozin versus placebo on cardiovascular and kidney outcomes by age group.

[a] Defined as doubling of serum creatinine, kidney failure or death due to kidney disease.

[b] Defined as doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular disease.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event.

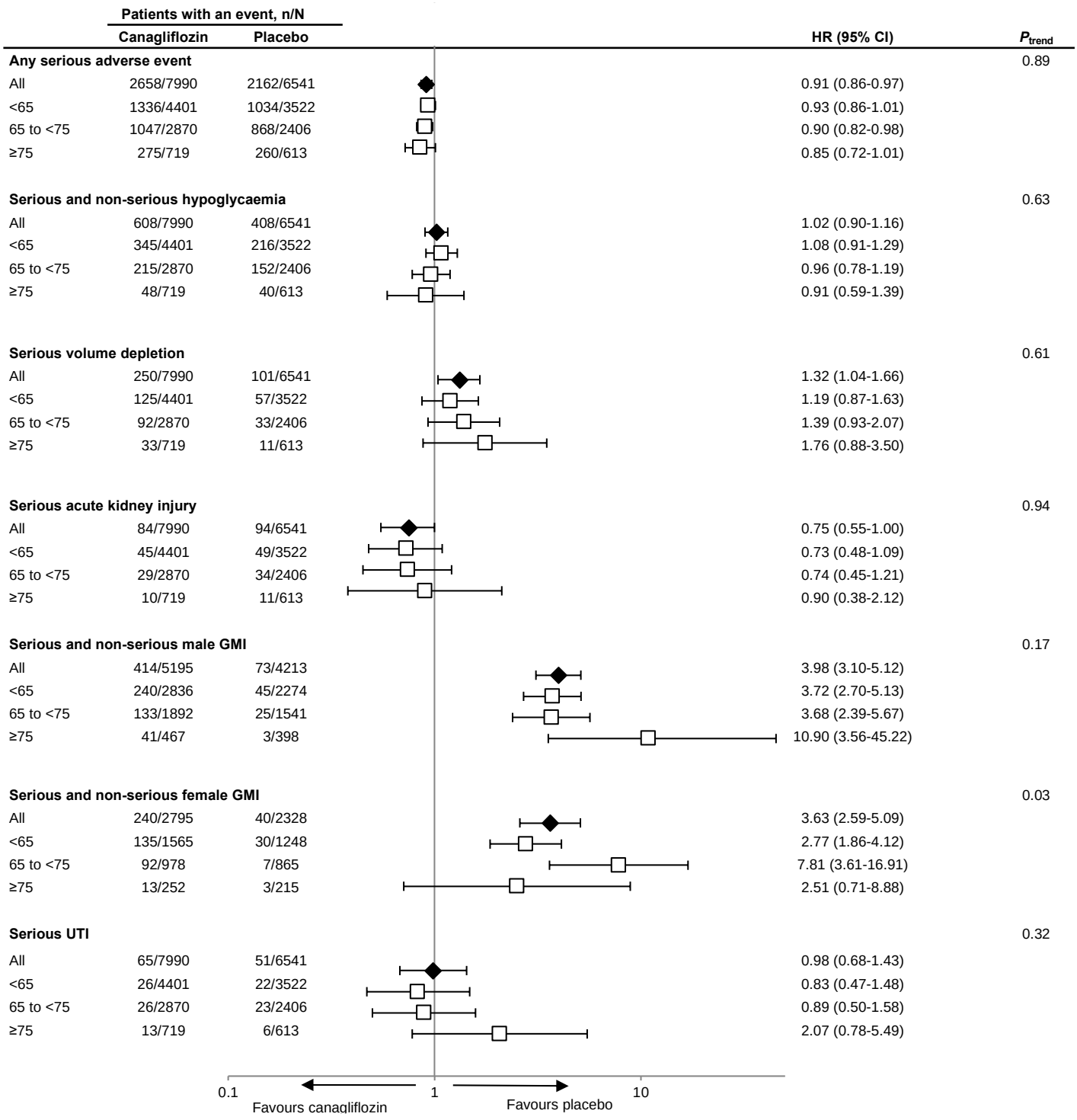

Figure 2. Safety outcomes of canagliflozin versus placebo by age group.

CI, confidence interval; HR, hazard ratio.

Table 1. Baseline characteristics of participants in the pooled CANVAS Program and CREDENCE trial by baseline age group.

Characteristics	Age <65 years (n=7927)	Age 65 – <75 years (n=5281)	Age ≥75 years (n=1335)	*P* value
Trial, n (%)				<0.001
CANVAS	2603 (32.8)	1438 (27.2)	289 (21.6)	
CANVAS-R	2980 (37.6)	2230 (42.2)	602 (45.1)	
CREDENCE	2344 (29.6)	1613 (30.5)	444 (33.3)	
Age (years), mean (SD)	57.5 (5.6)	693 (2.8)	78.4 (2.9)	<0.001
Sex (female), n (%)	2814 (35.5)	1845 (34.9)	468 (35.1)	0.79
Race, n (%)				<0.001
Asian	1432 (18.1)	615 (11.6)	114 (8.5)	
Black	366 (4.6)	148 (2.8)	46 (3.4)	
White	5564 (70.2)	4214 (79.8)	1097 (82.2)	
Other	565 (7.1)	304 (5.8)	78 (5.8)	
Current smoker, n (%)	1,697 (21.4)	645 (12.2)	103 (7.7)	<0.001
Hypertension, n (%)	7,170 (90.5)	4,945 (93.6)	1,270 (95.1)	<0.001
Heart failure, n (%)	1075 (13.6)	813 (15.4)	225 (16.9)	0.0006
Atherosclerotic vascular disease, n (%)				
Coronary	3,470 (43.8)	2,804 (53.1)	760 (56.9)	<0.001
Cerebrovascular	1,306 (16.5)	1,040 (19.7)	312 (23.4)	<0.001
Peripheral	1,586 (20.0)	1,211 (22.9)	362 (27.1)	<0.001
Diabetes duration (years), mean (SD)	12.7 (7.2)	15.7 (8.3)	17.8 (9.7)	<0.001
HbA1c (%), mean (SD)	8.4 (1.1)	8.2 (1.0)	8.0 (1.0)	<0.001
SBP (mmHg), mean (SD)	136.2 (15.7)	139.2 (15.5)	140.3 (16.4)	<0.001
DBP (mmHg), mean (SD)	79.5 (9.2)	76.4 (9.6)	74.1 (9.6)	<0.001
BMI (kg/m^2), mean (SD)	32.3 (6.4)	31.4 (5.6)	30.0 (4.9)	<0.001
eGFR ($mL/min/1.73m^2$), mean (SD)	75.0 (22.8)	66.3 (19.4)	58.9 (18.3)	<0.001
UACR (mg/g), median (IQR)	29.1 (8.0, 541.2)	35.1 (8.7, 508.0)	62.0 (10.8, 498.0)	<0.001
Drug therapy, n (%)				
Insulin	4,319 (54.5)	2,966 (56.2)	694 (52.0)	0.01
Metformin	5,861 (73.9)	3,706 (70.2)	803 (60.2)	<0.001
GLP-1 receptor agonists	347 (4.4)	200 (3.8)	43 (3.2)	0.06
RAAS inhibitor	6,809 (85.9)	4,558 (86.3)	1,144 (85.7)	0.75
Diuretic	3,304 (41.7)	2,564 (48.6)	679 (50.9)	<0.001
Statin	5,657 (71.4)	3,970 (75.2)	1,009 (75.6)	<0.001
Antithrombotic agent	5,170 (65.2)	3,906 (74.0)	1,019 (76.3)	<0.001

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; IQR, interquartile range; n, number; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SD, standard deviation; UACR, urine albumin:creatinine ratio.

Supplementary Material – Cardiovascular, kidney and safety outcomes with canagliflozin in older adults: A combined analysis from the CANVAS Program and CREDENCE trial

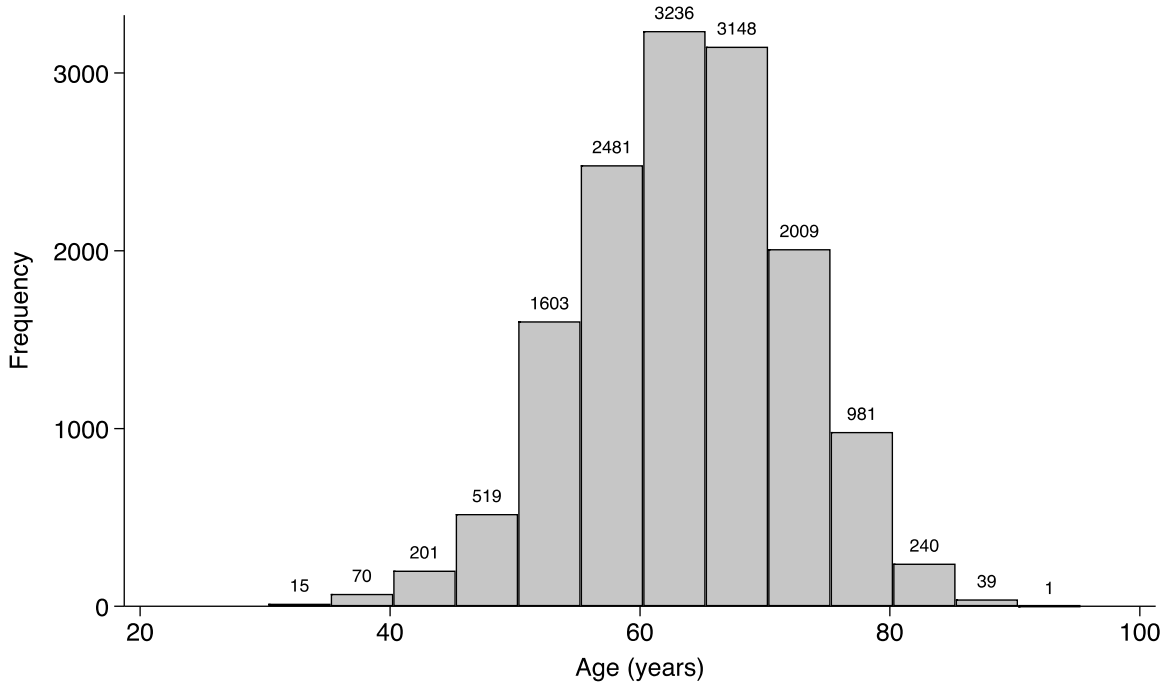

Figure S1. Age distribution across the pooled CANVAS and CREDENCE cohort.

Table S1. Baseline characteristics of canagliflozin and placebo-treated participants by baseline age group.

Characteristics	Age <65 years		Age 65 – <75 years		Age ≥75 years	
	Canagliflozin (n=4404)	Placebo (n=3523)	Canagliflozin (n=2872)	Placebo (n=2409)	Canagliflozin (n=721)	Placebo (n=614)
Trial, n (%)						
CANVAS	1713 (38.9)	890 (25.3)	979 (34.1)	459 (19.1)	196 (27.2)	93 (15.1)
CANVAS-R	1498 (34.0)	1482 (42.1)	1100 (38.3)	1130 (46.9)	309 (42.9)	293 (47.7)
CREDENCE	1193 (27.1)	1151 (32.7)	793 (27.6)	820 (34.0)	216 (30.0)	228 (37.1)
Age (years), mean (SD)	57.5 (5.7)	57.5 (5.6)	69.3 (2.8)	69.4 (2.8)	78.3 (2.8)	78.4 (2.9)
Sex (female), n (%)	1566 (35.6)	1248 (35.4)	979 (34.1)	866 (35.9)	253 (35.1)	215 (35.0)
Race, n (%)						
Asian	831 (18.9)	601 (17.1)	307 (10.7)	308 (12.8)	64 (8.9)	50 (8.1)
Black	184 (4.2)	182 (5.2)	80 (2.8)	68 (2.8)	24 (3.3)	22 (3.6)
White	3091 (70.2)	2473 (70.2)	2318 (80.7)	1896 (78.7)	586 (81.3)	511 (83.2)
Other	298 (6.8)	267 (7.6)	167 (5.8)	137 (5.7)	47 (6.5%)	31 (5.0%)
Current smoker, n (%)	948 (21.5)	749 (21.3)	359 (12.5)	286 (11.9)	54 (7.5)	49 (8.0)
Hypertension, n (%)	3,964 (90.0)	3,206 (91.0)	2,670 (93.0)	2,275 (94.4)	685 (95.0)	585 (95.3)
Heart failure, n (%)	573 (13.0)	502 (14.2)	436 (15.2)	377 (15.6)	123 (17.1)	102 (16.6)
Atherosclerotic vascular disease, n (%)						
Coronary	1,953 (44.4)	1,517 (43.1)	1,521 (53.0)	1,283 (53.3)	413 (57.3)	347 (56.5)
Cerebrovascular	741 (16.8)	565 (16.0)	555 (19.3)	485 (20.1)	159 (22.1)	153 (24.9)
Peripheral	877 (19.9)	709 (20.1)	638 (22.2)	573 (23.8)	192 (26.6)	170 (27.7)
Diabetes duration (years), mean (SD)	12.6 (7.2)	12.8 (7.3)	15.5 (8.4)	15.9 (8.2)	17.3 (9.6)	18.3 (9.9)
HbA1c (%), mean (SD)	8.4 (1.1)	8.3 (1.1)	8.2 (1.0)	8.2 (1.0)	8.0 (0.9)	8.0 (1.0)
SBP (mmHg), mean (SD)	136.0 (15.8)	136.4 (15.5)	139.0 (15.4)	139.5 (15.7)	139.5 (16.4)	141.2 (16.5)
DBP (mmHg), mean (SD)	79.4 (9.2)	79.7 (9.2)	76.4 (9.6)	76.4 (9.6)	73.8 (9.4)	74.4 (9.9)
BMI (kg/m^2), mean (SD)	32.3 (6.4)	32.3 (6.4)	31.5 (5.6)	31.4 (5.6)	30.2 (4.8)	29.8 (5.1)
eGFR ($mL/min/1.73m^2$), mean (SD)	75.6 (22.5)	74.1 (23.2)	67.0 (19.2)	65.3 (19.5)	59.4 (18.3)	58.4 (18.3)
UACR (mg/g), median (IQR)	25.2 (7.9, 459.0)	36.9 (8.1, 659.0)	29.9 (8.5, 425.0)	45.1 (9.0, 636.0)	42.2 (9.5, 446.0)	90.2 (12.5, 580.2)
Drug therapy, n (%)						
Insulin	2,382 (54.1)	1,937 (55.0)	1,588 (55.3)	1,378 (57.2)	372 (51.6)	322 (52.4)
Metformin	3,266 (74.2)	2,595 (73.7)	2,031 (70.7)	1,675 (69.5)	426 (59.1)	377 (61.4)
GLP-1 receptor agonists	181 (4.1)	166 (4.7)	108 (3.8)	92 (3.8)	22 (3.1)	21 (3.4)
RAAS inhibitor	3,755 (85.3)	3,054 (86.7)	2,477 (86.3)	2,081 (86.4)	614 (85.2)	530 (86.3)
Diuretic	1,806 (41.0)	1,498 (42.5)	1,372 (47.8)	1,192 (49.5)	384 (53.3)	295 (48.1)
Statin	3,144 (71.4)	2,513 (71.3)	2,157 (75.1)	1,813 (75.3)	567 (78.6)	442 (72.0)

Antithrombotic agent	2,908 (66.0)	2,262 (64.2)	2,109 (73.4)	1,797 (74.6)	560 (77.7)	459 (74.8)

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; IQR, interquartile range; n, number; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SD, standard deviation; UACR, urine albumin:creatinine ratio.

Table S2. Effect of canagliflozin on cardiovascular and kidney outcomes by age group adjusted for competing risk of death.

	Canagliflozin			Placebo				
	N censored	N event	N death	N censored	N event	N death	HR (95% CI)	P_{trend}
MACE								0.80
All	7,038	802	157	5,734	695	117	0.84 (0.76, 0.93)	
<65	3,967	373	64	3,161	311	51	0.85 (0.73, 0.99)	
65 to <75	2,473	328	71	2,072	296	41	0.82 (0.69, 0.96)	
≥75	598	101	22	501	88	25	0.85 (0.64, 1.14)	
CV death								0.007
All	7,429	378	190	6,064	325	157	0.84 (0.72, 0.98)	
<65	4,184	144	76	3,300	156	67	0.66 (0.53, 0.83)	
65 to <75	2,614	171	87	2,224	128	57	0.97 (0.77, 1.22)	
≥75	631	63	27	540	41	33	1.12 (0.75, 1.67)	
Hospitalisation for heart failure								0.96
All	7,319	212	466	5,907	261	378	0.65 (0.54, 0.78)	
<65	4,133	83	188	3,242	100	181	0.64 (0.48, 0.86)	
65 to <75	2,565	97	210	2,153	117	139	0.65 (0.50, 0.86)	
≥75	621	32	68	512	44	58	0.63 (0.40, 1.00)	
Hospitalisation for heart failure or CV death								0.11
All	7,297	543	157	5,879	541	126	0.75 (0.66, 0.84)	
<65	4,126	212	66	3,230	237	56	0.65 (0.54, 0.78)	
65 to <75	2,557	245	70	2,141	224	44	0.81 (0.67, 0.97)	
≥75	614	86	21	508	80	26	0.83 (0.61, 1.13)	
Renal composite [a]								0.68
All	7,326	187	484	5,893	263	390	0.63 (0.52, 0.77)	
<65	4,090	132	182	3,174	172	177	0.67 (0.54, 0.84)	
65 to <75	2,603	43	226	2,185	73	151	0.54 (0.36, 0.79)	
≥75	633	12	76	534	18	62	0.65 (0.30, 1.40)	
Cardiorenal composite [b]								0.01
All	7,301	542	154	5,863	561	122	0.75 (0.66, 0.84)	
<65	4,081	263	60	3,161	309	53	0.66 (0.56, 0.78)	
65 to <75	2,594	208	70	2,172	194	43	0.81 (0.66, 0.99)	
≥75	626	71	24	530	58	26	0.92 (0.65, 1.32)	

[a] Defined as doubling of serum creatinine, kidney failure or death due to kidney disease.

[b] Defined as doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular disease.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event.

CHAPTER 7

Efficacy and safety of SGLT2 inhibitors according to frailty status: A systematic review and meta-analysis

CHAPTER OVERVIEW

Frailty is common among chronic disease populations and is independently associated with poorer outcomes for patients with type 2 diabetes, heart failure and chronic kidney disease. Although frailty is distinct from ageing, it disproportionately affects older individuals. It is highly clinically relevant to understand how the effects and safety profiles of therapies translate to frail chronic disease populations. This chapter aims to address the sixth objective of this thesis, to examine the efficacy and safety of SGLT2 inhibitor therapy in frail individuals, to provide greater guidance for the use of these agents among frail populations.

PUBLICATION DETAILS

Amanda Siriwardana [1, 2, 3], Dana Kim [1, 2], Bernard Chan [1, 4], Min Jun [2], Brendan Smyth [5, 6], Clare Arnott [2, 7], Meg Jardine [2, 5, 8], Vlado Perkovic [2, 9], Brendon Neuen [2, 3]. Efficacy and safety of SGLT2 inhibitors according to frailty status: A systematic review and meta-analysis. Planned for submission in October 2024 to *Lancet Healthy Longev.*

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AUTHOR CONTRIBUTIONS

AS conceived study design, conducted the literature search, data extraction, risk of bias assessment, data analysis, drafting and preparing of the manuscript. DK contributed to the literature search, data extraction and risk of bias assessment. BN contributed to the study design, interpretation of results and preparing of the manuscript. All authors were involved in critical review and revisions of the manuscript.

ABSTRACT

Aim: Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce cardiovascular and kidney outcomes in individuals with type 2 diabetes (T2DM), chronic kidney disease (CKD) and heart failure (HF). Despite this, frailty may be a concern among clinicians in the prescription of SGLT2 inhibitor therapy. This systematic review and meta-analysis aimed to assess the efficacy and safety of SGLT2 inhibitors in patients with T2DM, CKD or HF according to frailty status.

Methods: We conducted a systematic review and meta-analysis of randomised, controlled, cardiovascular and kidney outcome trials of SGLT2 inhibitors in adults with T2DM, CKD or HF with subgroup analyses stratified by frailty status. We searched MEDLINE, EMBASE and the Cochrane Register from database inception to 7 July 2024 to identify eligible trials, and contacted study sponsors/investigators to obtain additional trial-level data. The primary outcome was a composite of hospitalisation for HF or cardiovascular mortality. A range of other secondary cardiovascular, kidney and safety outcomes were assessed. Random-effects meta-analysis models were used to obtain summary relative risks (RRs) with 95% confidence intervals (CI) for frail and not frail subgroups.

Results: Seven studies enrolling 42,443 participants met inclusion criteria. Six studies used the Rockwood cumulative deficit approach to define frailty, and one study (EMPA-KIDNEY) used a trial-specific model based on predicted risk of hospitalisation as a surrogate for frailty. The prevalence of frailty ranged from 49.6% in DAPA-HF to 74.7% in EMPEROR-Preserved. SGLT2 inhibitors reduced the risk of hospitalisation for HF or cardiovascular mortality by 19% (RR 0.81, 95% CI 0.76-0.86), an effect consistent regardless of frailty status (I^2=0%, P-heterogeneity=0.50). Reductions in other cardiovascular, mortality and kidney outcomes

were consistent irrespective of frailty status (all P-heterogeneity>0.10). Although the incidences of adverse events were higher in frail individuals, the relative effects of SGLT2 inhibitors on all adverse events were similar in frail and not frail participants (all P-heterogeneity>0.10).

Conclusions: SGLT2 inhibitors consistently reduced cardiovascular, mortality and kidney outcomes, regardless of frailty, with a comparable safety profile in frail and non-frail adults. These findings support use of SGLT2 inhibitor therapy in frail populations.

INTRODUCTION

Frailty is a multi-dimensional construct resulting in a cumulative decline in physiological systems and greater vulnerability to physical stressors.[1] It is associated with an increased risk of various adverse health outcomes, including falls, hospitalisations, disability, requirement for long-term care, and mortality.[2, 3] Although physiological reserves decline with age, frailty is related to, but distinct from, chronological ageing and is an important independent consideration in clinical and therapeutic decision-making.[4]

Frailty is highly prevalent among patients with chronic diseases. In developed countries, the prevalence of frailty among individuals with type 2 diabetes mellitus (T2DM) over the age of 60 years is estimated to be 10-25%.[5] Among patients with chronic kidney disease (CKD), frailty prevalence is high and increases with CKD progression, with 7-14% of patients with CKD stages G1-G4 and up to 48% of patients with more advanced CKD considered frail.[6, 7] In turn, frailty is associated with worse outcomes for patients with CKD including progression to kidney failure and death.[8, 9] Similarly, patients with heart failure (HF) are up to 6 times more likely to be frail than the general population, HF may accelerate the development of frailty, and patients with HF and frailty have poorer outcomes than non-frail HF patients.[10, 11]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a class of glucose-lowering drugs that increase urinary glucose excretion via inhibition of SGLT2 in the proximal renal tubules, and have been shown to have multiple clinical benefits beyond glucose lowering. They are now an established therapy in T2DM, with several large clinical trials demonstrating cardiovascular and mortality benefits.[12-15] Among patients with CKD and HF, SGLT2 inhibitors

have demonstrated cardiovascular, kidney and mortality benefits, irrespective of diabetes status.[16-24] Given the high prevalence of frailty among T2DM, CKD and HF populations, understanding the extent to which the efficacy and safety profile of SGLT2 inhibitors differs in frail and non-frail patients is of major clinical relevance.

We therefore conducted a systemic review and meta-analysis to assess the efficacy and safety of SGLT2 inhibitors according to frailty status in patients with T2DM, CKD and HF, in order to summarise the benefit-risk considerations for these agents across the spectrum of frailty and to provide guidance for their use among frail individuals.

METHODS

Search strategy and selection criteria

We searched MEDLINE via Ovid, EMBASE via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception to 7 July 2024, for English-language publications using search terms including 'sodium-glucose transporter 2' and related phrases, names of individual SGLT2 inhibitor drugs, and terms related to randomised clinical trials. The search strategy used for each database is detailed in *Table S1*. We included all English language, randomised, event-driven, cardiovascular or kidney outcome trials of SGLT2 inhibitors versus active or placebo control in patients with or without T2DM, with available subgroup analyses stratified by frailty status. Frailty status could be classified according to any frailty index as chosen by the study authors. Trials in patients with type 1 diabetes mellitus or patients less than 18 years of age were excluded. Observational studies

and case series were excluded. In addition to database searches, study sponsors and investigators were contacted to obtain additional trial-level data. Two authors (AS and DK) independently screened article titles and abstracts, and then reviewed full-text manuscripts to identify relevant studies. A third author (BN) adjudicated any discrepancies between authors regarding eligibility of studies.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was used to guide conduct and reporting of this systematic review and meta-analysis.[25] The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) before data extraction (PROSPERO registration number CRD42024560932).

Data extraction

Data extraction and risk of bias assessments were independently conducted by two authors (AS and DK) using a standardised data extraction form. A third author (BN) adjudicated any discrepancies between authors regarding data extraction and bias assessments. For each RCT that met eligibility criteria, number of events, number of at-risk patients, hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes of interest were extracted according to the following frailty risk groups: 'not frail' and 'frail'. If study authors reported further subgroups (such as 'more frail' and 'most frail'), we pooled estimates of these subgroups to derive the 'frail' category effect estimate and to remain consistent with other reported frailty subgroup categories. Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias Tool (Rob2) for RCTs.[26] Risk of bias was rated as 'low risk', 'some concerns' and 'high risk', for the domains of bias arising from the randomisation process, deviations from

intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Overall risk of bias was deemed low if all domains were at low risk, high if any domain was at high risk, and some concerns in any other case.

Outcomes

The primary outcome was a composite of hospitalisation for HF or cardiovascular death. Secondary efficacy outcomes included: hospitalisation for HF, cardiovascular death, all-cause mortality, a composite kidney outcome (substantial loss of kidney function, kidney failure or death due to kidney disease), and a composite cardiorenal outcome (substantial loss of kidney function, kidney failure, death due to kidney disease or death due to cardiovascular causes). Substantial loss of kidney function was defined as a sustained decrease from baseline estimated glomerular filtration rate (eGFR) of ≥40% or ≥50%, as reported by study authors. Onset of kidney failure was defined as commencement of maintenance dialysis or kidney transplantation, or sustained eGFR <15 mL/min/1.73m^2 or eGFR <10 mL/min/1.73m^2, as reported by study authors.

Safety outcomes of interest included serious adverse events (AEs), discontinuation of study drug due to an AE, volume depletion, serious hypoglycaemia, diabetic ketoacidosis, kidney adverse events, urinary tract infections, genital mycotic infections, fracture, and amputation. Volume depletion included definitions of symptomatic hypotension and symptomatic dehydration, as reported in individual studies. Amputations included all amputations or lower limb amputations, as reported in individual studies.

Data analysis

In order of preference, we pooled hazard ratios (HR), incidence rate ratios (events per patient-years), and risk ratios (events per number of participants), to maximise the use of trial-level data from included studies. Individual trial results were quantitatively synthesised using a random effects model with inverse-variance weighting for each outcome and for frailty subgroups to generate pooled estimates for the effect of SGLT2 inhibitors compared with placebo. Because of differing definitions for determining frailty in the included trials, we performed a sensitivity analysis based on frailty definition to assess the vulnerability of findings to definitions of frailty.

P-heterogeneity values of <0.05 from random effects models were considered to reflect a high likelihood of difference beyond that expected by chance. Constancy of effects was also evaluated using the I^2 statistic, with I^2 ≤25% representing low likelihood of differences between studies, 25-75% representing moderate likelihood, and ≥75% representing high likelihood.

All analyses were conducted using Stata version 18 (StataCorp LLC).

RESULTS

Search results

9768 reports were retrieved from electronic database searches. After removal of duplicates, records were screened for eligibility. 68 full-text articles were assessed against pre-specified

selection criteria, with 5 articles from 5 trials meeting eligibility (*Figure S1*). An unpublished secondary analysis according to frailty status using pooled data from the CANVAS Program and CREDENCE trial was identified through contact with the study authors.

Study characteristics and risk of bias assessment

A total of 42,443 patients from the seven trials were included in this meta-analysis. All trials compared an oral SGLT2 inhibitor with matching placebo. Three were HF outcome trials: DAPA-HF[16, 27] (n=4744) tested the effects of dapagliflozin in patients with HF with reduced ejection fraction, DELIVER[19, 28] (n=6263) tested the effects of dapagliflozin in patients with mildly reduced or preserved ejection fraction, and EMPEROR-Preserved[18, 29] (n=5988) tested the effects of empagliflozin in patients with preserved ejection fraction. There was one cardiovascular outcome trial: the CANVAS Program[15] (n=10,142) evaluated the effects of canagliflozin in patients with T2DM and high cardiovascular risk. Three primary kidney-outcome trials were included: CREDENCE[21] (n=4401) tested the effects of canagliflozin in patients with T2DM and albuminuric CKD, DAPA-CKD[23, 30] (n=4304) tested the effects of dapagliflozin in patients with albuminuric CKD (with and without T2DM), and EMPA-KIDNEY[24, 31] (n=6609) tested the effects of empagliflozin in patients with either advanced CKD or less severe CKD with albuminuria. Risk of bias in all indicators was low for all studies (*Table S2*).

Selected baseline characteristics for the included studies are presented in *Table 1.* Median follow-up time ranged from 1.5 years in DAPA-HF to 2.6 years in CREDENCE. The mean age across the studies ranged from 61.8 to 71.9 years, 15,276 (36.0%) participants were female, and 29,968 (70.6%) were of white race. Overall, 28,372 (66.8%) of patients had T2DM,

20,234 (47.7%) had HF, and 21,659 (51.0%) had established atherosclerotic cardiovascular disease. Mean eGFR across the studies ranged from 37.4 mL/min/1.73m^2 in EMPA-KIDNEY to 76.5 mL/min/1.73m^2 in the CANVAS Program. There were high rates of RAAS inhibitor use across all studies, particularly in the CKD trials. Use of mineralocorticoid receptor antagonists, any diuretic therapy and beta blockers were highest in the HF trials.

The prevalence of frailty across the studies included in this meta-analysis ranged from 49.6% in DAPA-HF to 74.7% in EMPEROR-Preserved. Six out of seven studies used the Rockwood cumulative deficit approach[32] to define frailty status of participants at baseline. This approach involves creation of a multi-item scoring system containing a minimum of 30 items and each item must be associated with health and not be a part of normal ageing. These items may include a history of specific medical conditions, vital signs, laboratory data, quality of life measures and functional status. Each individual item is scored as absent (0) or present (1). Individual item scores are summated and divided by the total number of variables to determine an overall Frailty Index (FI) ranging from 0 to 1. A FI ≥0.21-0.25 is typically considered the cutoff to define frailty,[33] and this threshold was used across the trials that implemented the Rockwood cumulative deficit approach in this meta-analysis. EMPA-KIDNEY used a logistic regression model to predict baseline risk of hospitalisation. A >20% risk of hospitalisation was used as a surrogate for frailty status, based on the established association of clinical frailty with hospitalisation.[34, 35]

Cardiovascular and mortality outcomes

The incidence of the primary composite outcome of hospitalisation for HF or cardiovascular death was higher in frail compared to non-frail patients. Treatment with an SGLT2 inhibitor

reduced the risk of the primary outcome by 19% (RR 0.81, 95% CI 0.76-0.86; *Figure 1*), an effect consistent regardless of frailty status (RR 0.77, 95% CI 0.64-0.92 and RR 0.82, 95% CI 0.77-0.88 respectively, P-heterogeneity=0.50). Results were similarly consistent irrespective of frailty for hospitalisation for HF (RR 0.76, 95% CI 0.69-0.82; P-heterogeneity=0.47; *Figure 2*) and for CV death (RR 0.86, 95% CI 0.79-0.93; P-heterogeneity=0.47; *Figure 2*), SGLT2 inhibitors reduced the risk of all-cause mortality by 11% (RR 0.89, 95% CI 0.82-0.95; *Figure 3*), an effect consistent across frailty subgroups (RR 0.87, 95% CI 0.77-0.98 and RR 0.88, 95% CI 0.79-0.98 respectively, P-heterogeneity=0.61). Findings were similar in a sensitivity analysis restricted to trials which used the Rockwood FI to define frailty (*Table S3*).

Kidney outcomes

The overall incidence of CKD progression was higher in frail compared with non-frail participants. SGLT2 inhibitor treatment reduced the risk of the composite kidney outcome (RR 0.72, 95% CI 0.61-0.86; *Figure 4*) and the composite cardiorenal outcome (RR 0.71, 95% CI 0.62-0.81; *Figure 4*), and these effects were consistent irrespective of frailty status (P-heterogeneity=0.34 and 0.53, respectively).

Safety outcomes

Treatment with an SGLT2 inhibitor had no effect on the risk of serious AEs (RR 0.96, 95% CI 0.89-1.02; *Figure 5*) or discontinuation of study drug due to an AE (RR 0.99, 95% CI 0.88-1.11; *Figure 5*), a finding that was consistent across frailty subgroups (P-heterogeneity>0.10 for both). Other safety outcomes are presented in *Figures S2-S5.* SGLT2 inhibitor treatment increased the likelihood of some safety outcomes including volume depletion (RR 1.29, 95% CI 1.17-1.41), diabetic ketoacidosis (RR 2.88, 95% CI 1.38-6.00) and genital mycotic infections

(RR 4.28, 95% CI 3.21-5.71), with no heterogeneity by baseline frailty (all P-heterogeneity>0.10). There was no impact of treatment or differences across frailty subgroups for other safety outcomes including serious hypoglycaemia and amputations.

DISCUSSION

In this systematic review and meta-analysis of 42,443 patients from seven randomised, double-blind, placebo-controlled trials, the prevalence of frailty was high. SGLT2 inhibitors consistently reduced the risk of hospitalisation for HF or cardiovascular death in frail and not frail adults. Relative risk reductions for a broad range of other cardiovascular, mortality and kidney outcomes were similarly consistent across the spectrum of frailty. Importantly, the safety profile of SGLT2 inhibitor therapy was consistent in frail and not frail adults, indicating no additional safety concerns with the use of SGLT2 inhibitors in frail populations.

The differences between older age and frailty, particularly when applied to therapeutic decision-making, are important to distinguish. Older age is typically defined in clinical trials as ≥65 years, and such a definition incorporates a proportion of functionally independent and mobile individuals without significant multi-morbidity. A large proportion of older adults are not frail, and it is recommended that biologically fit older adults with T2DM be treated similar to younger counterparts.[36] This is supported by secondary analyses from several SGLT2 inhibitor cardiovascular and kidney outcome trials which demonstrated consistent benefits without a relative increase in safety concerns with the use of SGLT2 inhibitors in older adults.[37-44] While frailty is related to ageing, it is a distinct entity that is independently

associated with poorer outcomes in T2DM, HF and CKD. Management of frail adults with chronic diseases is challenging, in part due to concerns regarding reduced efficacy of therapies, increased risk of adverse events due to decreased physiological reserves, polypharmacy, high rates of cognitive impairment and poorer adherence to therapies. The importance of understanding the benefit-risk considerations of SGLT2 inhibitors in frail, rather than older, adults is therefore a different and clinically relevant question which this systematic review and meta-analysis sought to answer.

We observed a very high prevalence of frailty in our meta-analysis population, with at least 50% of patients considered frail in each trial cohort and as high as 74.7% in EMPEROR-Preserved. In keeping with what is known about the impact of frailty on chronic disease populations, frailty was associated with an increased absolute risk of cardiovascular, mortality and kidney clinical endpoints including the primary outcome of hospitalisation for HF or cardiovascular mortality. We identified that the relative benefits of SGLT2 inhibitor therapy in lowering the risk of all cardiovascular, mortality and kidney outcomes were clear and consistent across frail and not frail categories. Real-world studies indicate that frailty is associated with a significantly lower rate of SGLT2 inhibitor initiation.[45] A lack of summarised evidence and specific guidelines for their use in frail populations are likely to have contributed to this reduced uptake. The efficacy findings of this meta-analysis address this need and offer strong support for the use of SGLT2 inhibitors in frail adults with T2DM, HF or CKD, population groups who are at the highest risk of poor outcomes.

The optimal method for assessing frailty in chronic disease populations, particularly CKD, is unclear.[9] Several methods have been proposed and six out of the seven trials included in this

meta-analysis used the Rockwood cumulative deficit approach to define frailty. This approach requires assessment of a minimum of 30 items across multiple systems and these are summated to provide an overall assessment of cumulative deficits across systems. While this approach may not be feasible to implement in clinical practice, it offers a detailed and validated definition for comparing frailty across clinical trials. The EMPA-KIDNEY trial developed a trial-specific approach to define frailty, formulating a logistic regression model to predict a >20% risk of hospitalisation in patients at baseline as a surrogate definition for frailty. A sensitivity analysis excluding EMPA-KIDNEY yielded results that were virtually identical to the main findings, supporting the robustness of the overall conclusions.

As with efficacy endpoints, we observed that the incidence of adverse safety events was increased in frail patients irrespective of treatment allocation, but that the relative effects of SGLT2 inhibitor therapy on safety outcomes were consistent among frail and not frail patients. There was a higher risk of volume depletion, diabetic ketoacidosis and genital mycotic infections with SGLT2 inhibitor therapy, however there was no evidence to suggest these effects were more likely in frail individuals. There is a high degree of reticence in prescribing new therapies to frail patient populations due to concerns about tolerability and increased vulnerability to adverse events. The safety outcome findings of this meta-analysis should allay some of these concerns and indicate a comparable safety profile of SGLT2 inhibitors in both frail and not frail individuals.

Data on the efficacy of guideline-directed therapy in T2DM, CKD and HF according to frailty status are limited. This systematic review and meta-analysis offers quantitative synthesis of a large number of SGLT2 inhibitor randomised trials and provides detailed efficacy and safety

evaluations. However, there are important limitations that should be considered. Firstly, although we accounted for different methods of defining frailty in sensitivity analyses, slight differences in the Rockwood Frailty Index threshold used between trials (ranging from FI ≥0.21-0.25) may have contributed to some variations in outcomes. Secondly, we analysed frailty status as a binary construct (frail versus not frail) which does not account for the severity of frailty. Extrapolating findings to severely frail individuals should be done with caution, as these individuals may be less well represented in the included trials. Finally, while detailed data according to frailty status was available for most cardiovascular, mortality and safety outcomes, this was reported less for the kidney outcomes, and hence meta-analysed data for these outcomes was more limited.

CONCLUSIONS

SGLT2 inhibitors offer comparable cardiovascular, mortality and kidney outcome in frail and non-frail patients with T2DM, HF and CKD, with no additional safety concerns for frail individuals. Given the high prevalence of frailty in chronic disease populations and the much poorer outcomes experienced by these individuals, the findings of this systematic review and meta-analysis offer clinically relevant guidance for the use of SGLT2 inhibitors to improve outcomes among frail patients.

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FIGURES AND TABLES

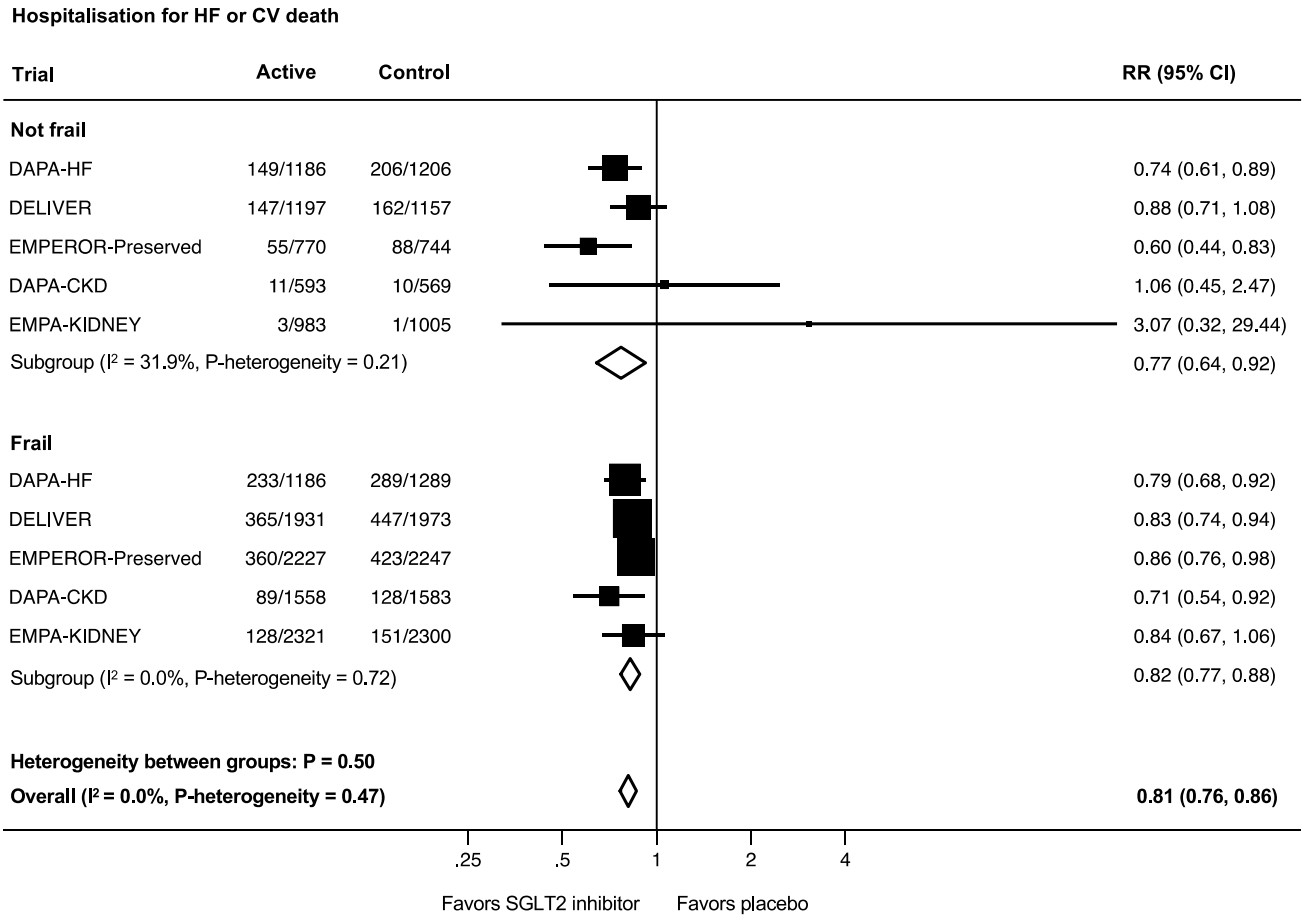


Figure 1. Effect of SGLT2 inhibitors on hospitalisation for heart failure or cardiovascular death according to frailty status.

CI, confidence interval; CV, cardiovascular; HF, heart failure; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.

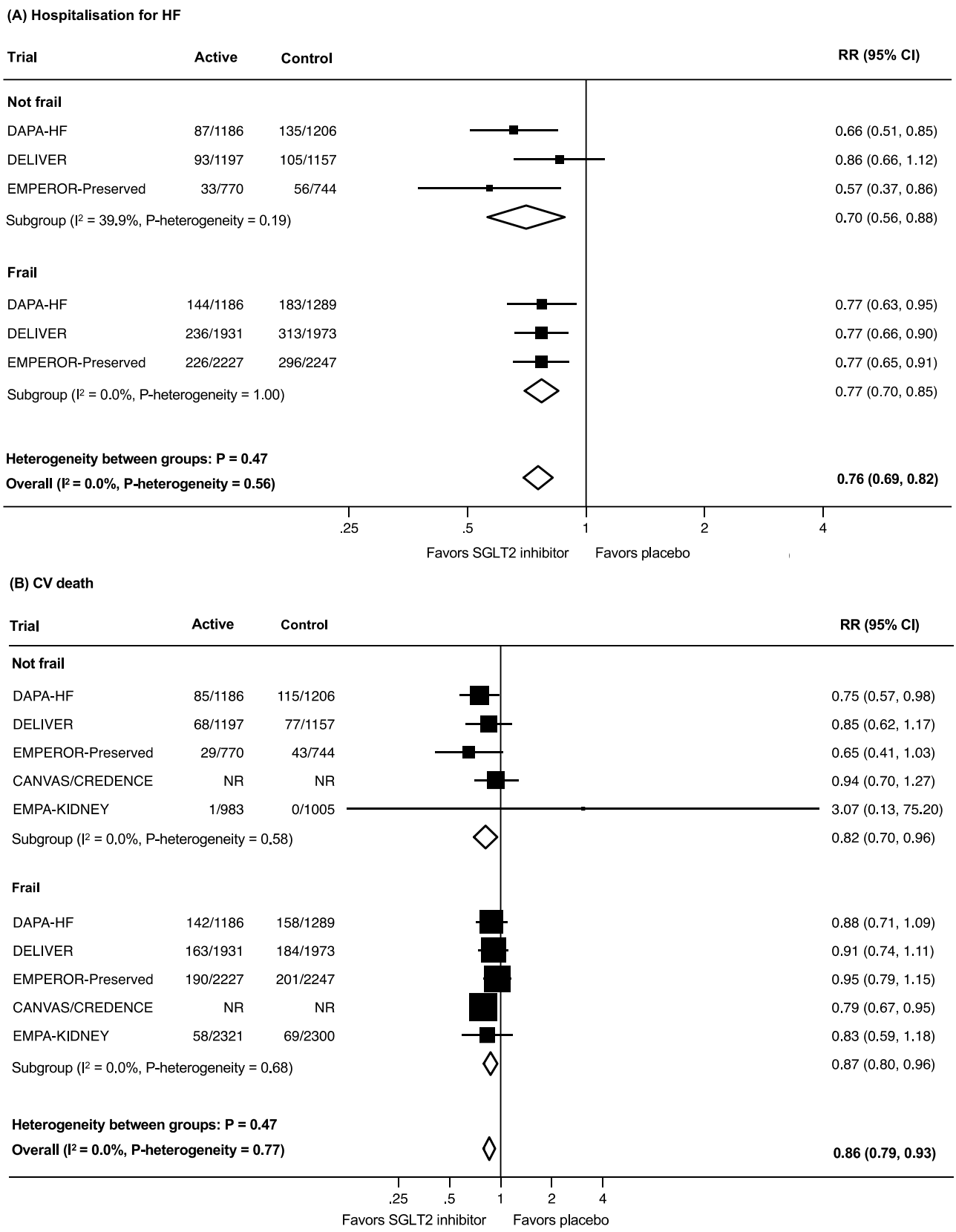


Figure 2. Effect of SGLT2 inhibitors on (A) hospitalisation for heart failure and (B) cardiovascular death according to frailty status.

CI, confidence interval; CV, cardiovascular; HF, heart failure; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.

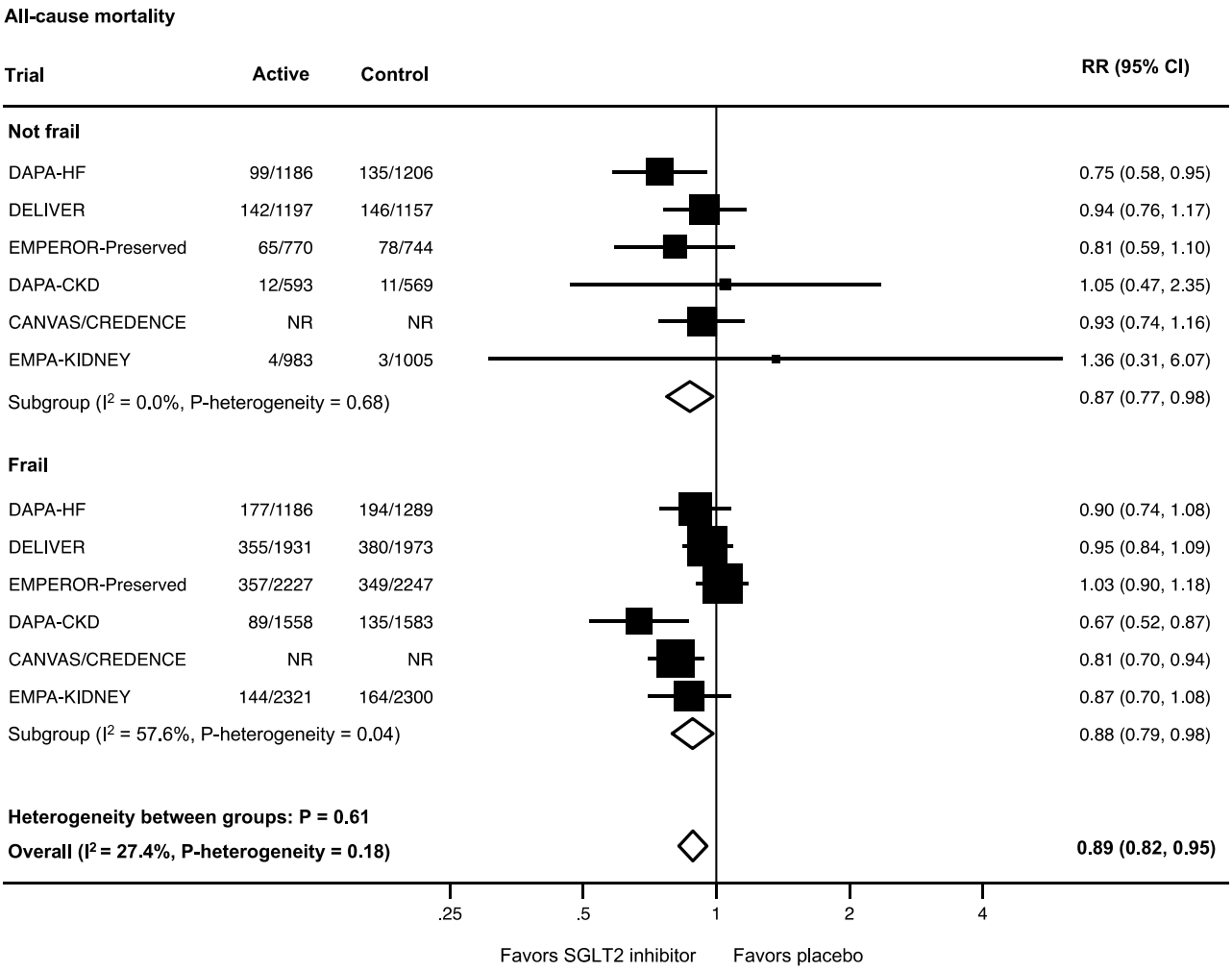


Figure 3. Effect of SGLT2 inhibitors on all-cause mortality according to frailty status.

CI, confidence interval; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.

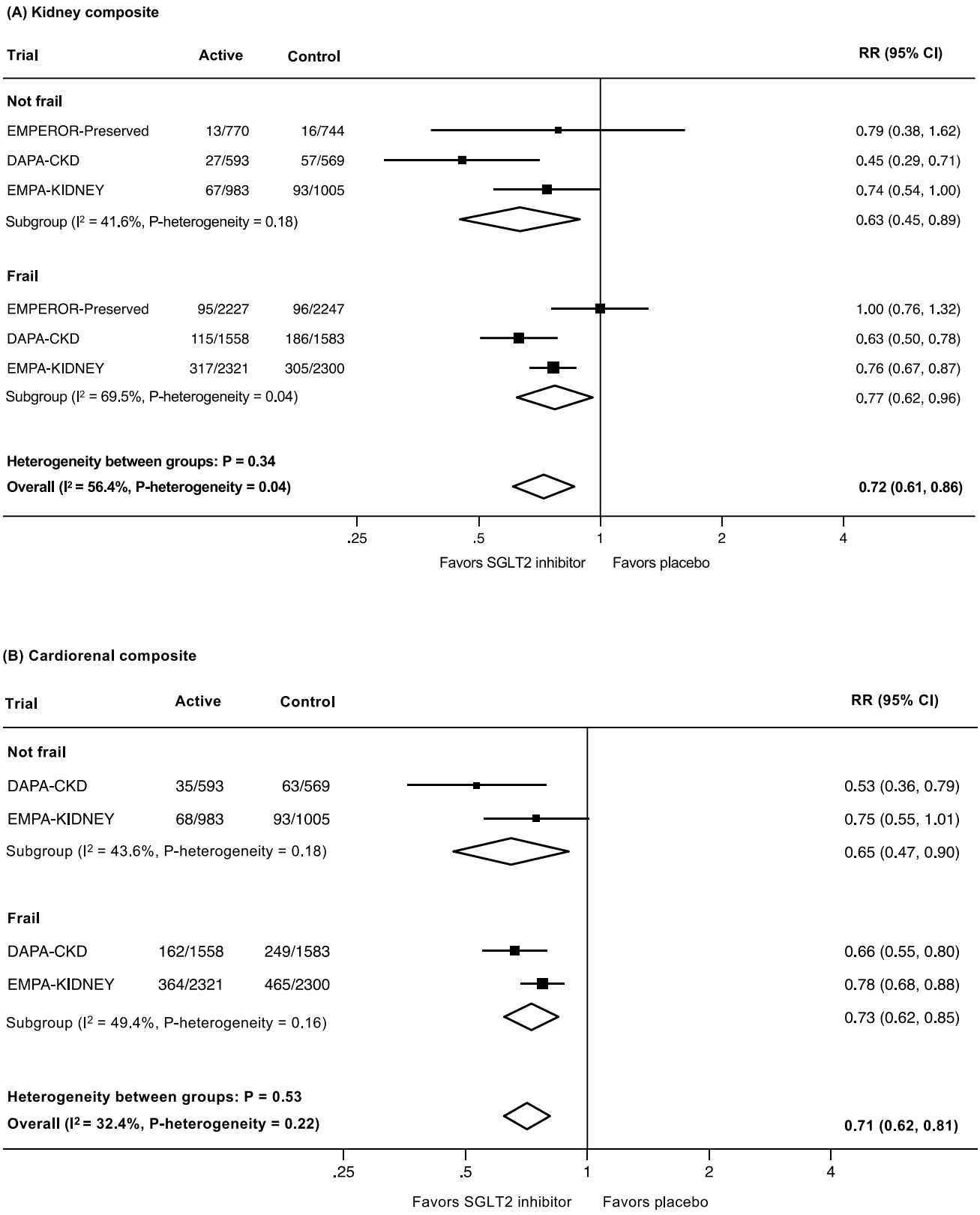


Figure 4. Effect of SGLT2 inhibitors on (A) composite kidney outcome and (B) composite cardiorenal outcome according to frailty status.

Composite kidney outcome defined as substantial loss of kidney function, kidney failure or death due to kidney disease. Composite cardiorenal outcome defined as substantial loss of kidney function, kidney failure, death

due to kidney disease or death due to cardiovascular causes. In EMPEROR-Preserved, substantial loss of kidney function defined as sustained reduction of ≥40% of baseline eGFR, and onset of kidney failure defined as commencement of maintenance dialysis or kidney transplantation, sustained eGFR <15 mL/min for patients with baseline eGFR ≥30 mL/min or sustained eGFR <10 mL/min for patients with baseline eGFR <30 mL/min. In DAPA-CKD, substantial loss of kidney function defined as sustained reduction of ≥50% of baseline eGFR, and onset of kidney failure defined as commencement of maintenance dialysis or kidney transplantation or sustained eGFR <15 mL/min. In EMPA-KIDNEY, substantial loss of kidney function defined as sustained reduction of ≥40% of baseline eGFR, and onset of kidney failure defined as commencement of maintenance dialysis or kidney transplantation or sustained eGFR <10 mL/min.

CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.

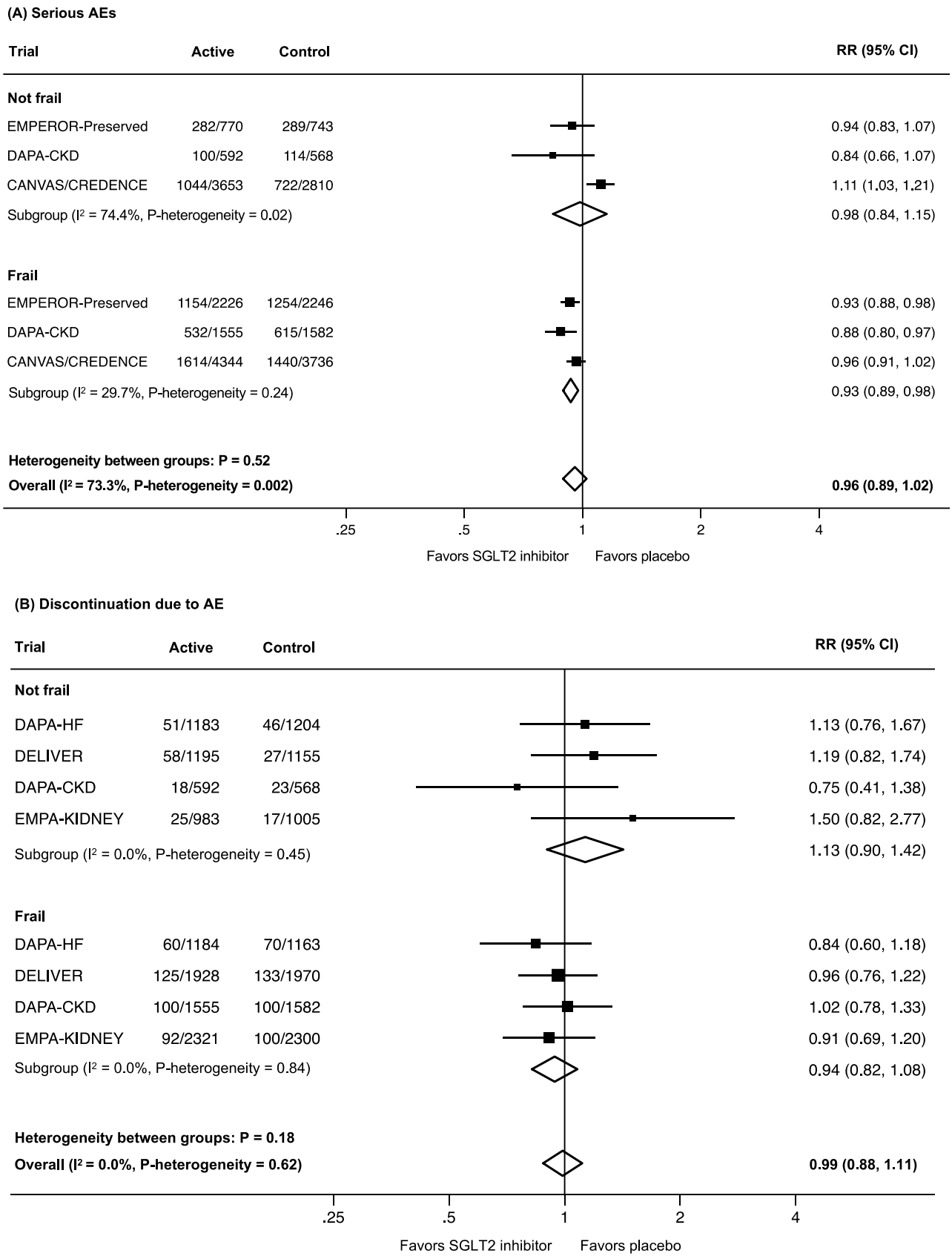


Figure 5. Effect of SGLT2 inhibitors on (A) serious AEs and (B) discontinuation of study drug due to an AE according to frailty status.

AE, adverse event; CI, confidence interval; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.

Table 1. Baseline characteristics of included studies.

Characteristics	T2DM with high cardiovascular risk trial	Heart failure trials			CKD trials		
	CANVAS Program [15]	DAPA-HF [16, 27]	DELIVER [19, 28]	EMPEROR-Preserved [18, 29]	CREDENCE [21]	DAPA-CKD [23, 30]	EMPA-KIDNEY [24, 31]
Trial characteristics							
SGLT2 inhibitor	Canagliflozin	Dapagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin	Dapagliflozin	Empagliflozin
Dose (mg)	100 and 300	10	10	10	100	10	10
Participants, n	10142	4744	6263	5988	4401	4304	6609
Enrolment period	2009-2017	2017-2018	2018-2020	2017-2020	2014-2017	2017-2018	2019-2021
Median follow-up, years	2.4	1.5	2.3	2.2	2.6	2.4	2.0
Method for defining frailty[a]	Rockwood FI >0.25	Rockwood FI ≥0.211	Rockwood FI ≥0.211	Rockwood FI ≥0.21	Rockwood FI >0.25	Rockwood FI ≥0.211	Predicted hospitalisation risk >20%
Participant characteristics							
Age (years), mean (SD)	63.3 (8.3)	66.3 (10.9)	71.7 (9.6)	71.9 (9.6)	63.0 (9.2)	61.8 (12.1)	63.8 (13.9)
Sex (female), n (%)	3633 (35.8)	1109 (23.4)	2747 (43.9)	2676 (44.7)	1494 (33.9)	1425 (33.1)	2192 (33.2)
Race, n (%)							
White	7944 (78.3)	3333 (70.3)	4439 (70.9)	4542 (75.9)	2931 (66.6)	2920 (67.8)	3859 (58.4)
Asian	1284 (12.7)	1116 (23.5)	1274 (20.3)	824 (13.8)	877 (19.9)	1467 (34.1)	2393 (36.2)
Black	336 (3.3)	226 (4.8)	159 (2.5)	258 (4.3)	224 (5.1)	191 (4.4)	262 (4.0)
Other	578 (5.7)	69 (1.5)	391 (6.2)	364 (6.1)	369 (8.4)	356 (8.2)	95 (1.4)
Diabetes, n (%)	10142 (100)	2139 (45.1)	2806 (44.8)	2938 (49.1)	4401 (100)	2906 (67.5)	3040 (46.0)
Established ASCVD, n (%)	6656 (65.6)	3042 (64.1)	3598 (57.4)	3320 (55.4)	2220 (50.4)	1329 (30.9)	1494 (22.6)

Heart failure, n (%)	1461 (14.4)	4744 (100)	6263 (100)	5988 (100)	652 (14.8)	468 (11.0)	658 (10.0)
eGFR (mL/min/1.73m^2), mean (SD)	76.5 (20.5)	65.8 (19.4)	61.0 (19.1)	60.6 (19.9)	56.2 (18.2)	43.1 (12.3)	37.4 (14.5)
UACR (mg/g), median (IQR)	12 (7-42)	NR	NR	21 (8-72)	927 (463-1833)	949 (477-1885)	329 (49-1069)
Drug therapy, n (%)							
RAAS inhibitor	8116 (80.0)	4476 (94.4)	4868 (77.7)	4832 (80.7)	4395 (99.9)	4174 (97.0)	5628 (85.2)
MRA	192 (1.9)	3370 (71.0)	2665 (42.6)	2244 (37.5)	35 (0.8)	229 (5.3)	473 (7.2)
Beta blocker	5421 (53.5)	4558 (96.1)	5177 (82.7)	5167 (86.3)	1770 (40.2)	1680 (39.0)	2759 (41.7)
Diuretic	4490 (44.3)	4433 (93.4)	5580 (89.1)	4636 (77.4)	2057 (46.7)	1882 (43.7)	2776 (42.0)
Insulin	5095 (50.2)	540 (11.4)	845 (13.5)	861 (14.4)	2884 (65.5)	1598 (37.1)	1663 (25.2)
Metformin	7825 (77.2)	1016 (21.4)	1666 (26.6)	1595 (26.6)	2545 (57.8)	1244 (28.9)	668 (10.1)
GLP-1 receptor agonist	407 (4.0)	21 (0.4)	61 (1.0)	59 (1.0)	183 (4.2)	122 (2.8)	315 (4.8)
Frailty prevalence, n (%)[a]	8080 (55.6)[b]	2350 (49.6)	3904 (62.4)	4744 (74.7)	8080 (55.6)[b]	3141 (73.0)	4621 (69.9)

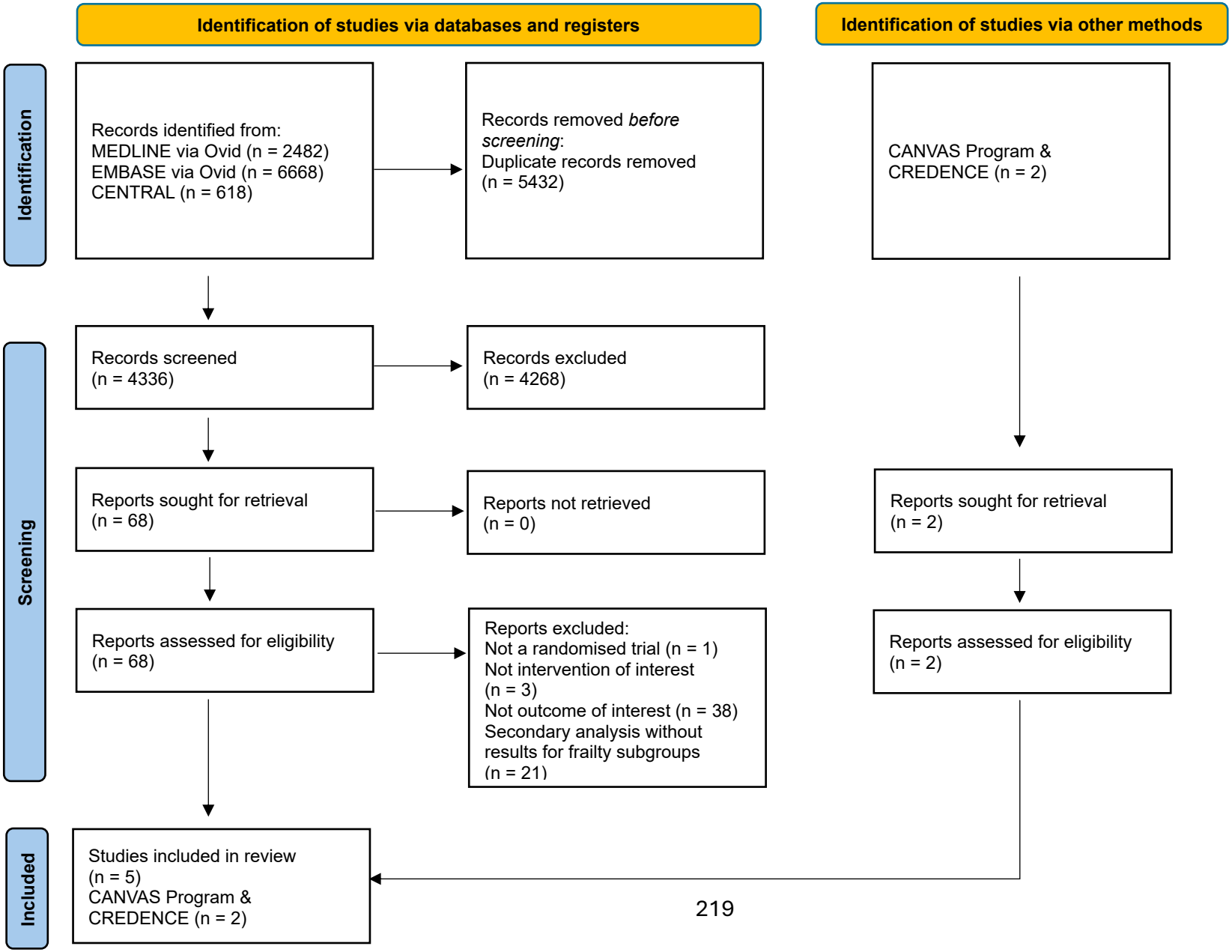
[a] Definition of frailty was specified by study authors. For all trials except EMPA-KIDNEY, frailty was defined using the Rockwood cumulative deficit approach. A Rockwood Frailty Index (FI) of ≥0.21-0.25 was used as a cutoff threshold to define frailty. EMPA-KIDNEY used a logistic regression model to predict baseline risk of hospitalisation, with a risk ≥20% used to define frailty status on the basis of the established association of clinical frailty with hospitalisation.

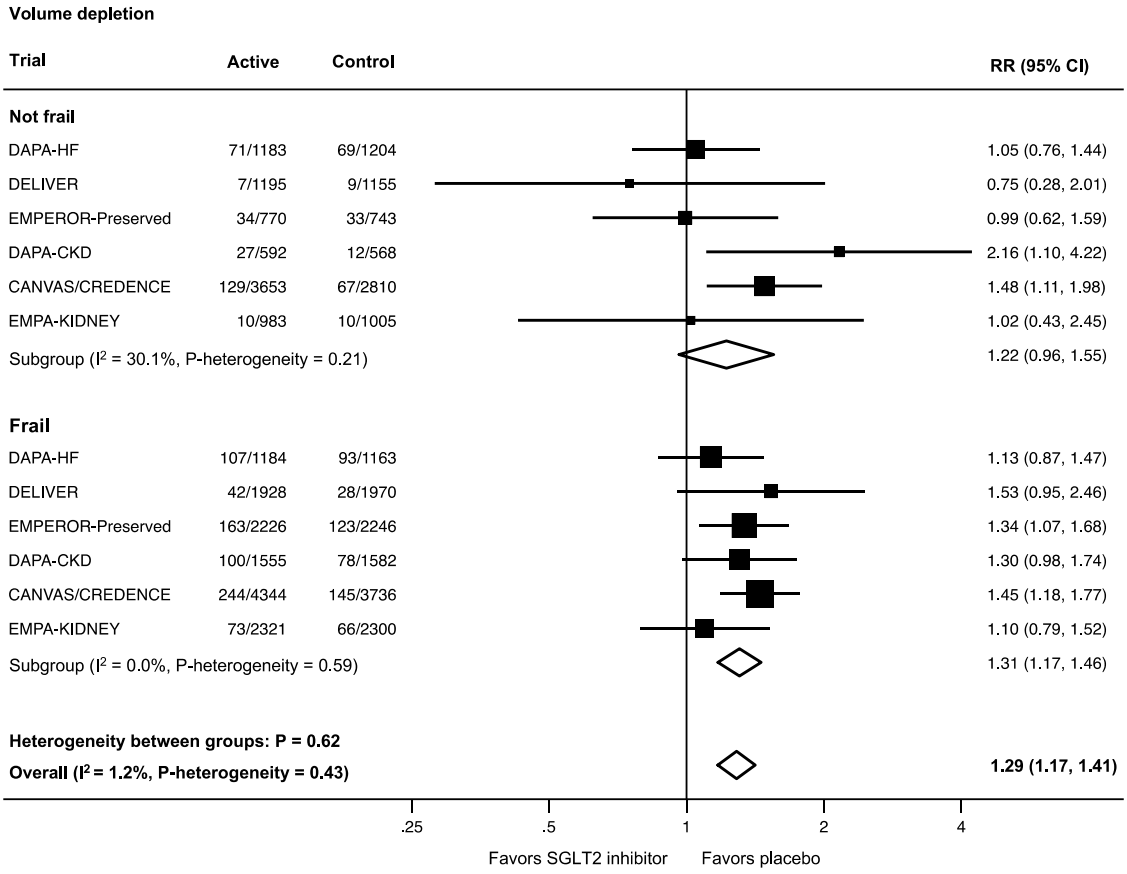
[b] Frailty prevalence presented for the CANVAS Program and CREDENCE trial reflects the combined prevalence pooled across both trial programs.

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FI, frailty index; GLP-1, glucagon-like peptide 1; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NR; not reported; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes; UACR, urine albumin:creatinine ratio.

Supplementary Material – Efficacy and safety of SGLT2 inhibitors according to frailty status: A systematic review and meta-analysis

Figure S1. PRISMA flow diagram of identification of eligible studies





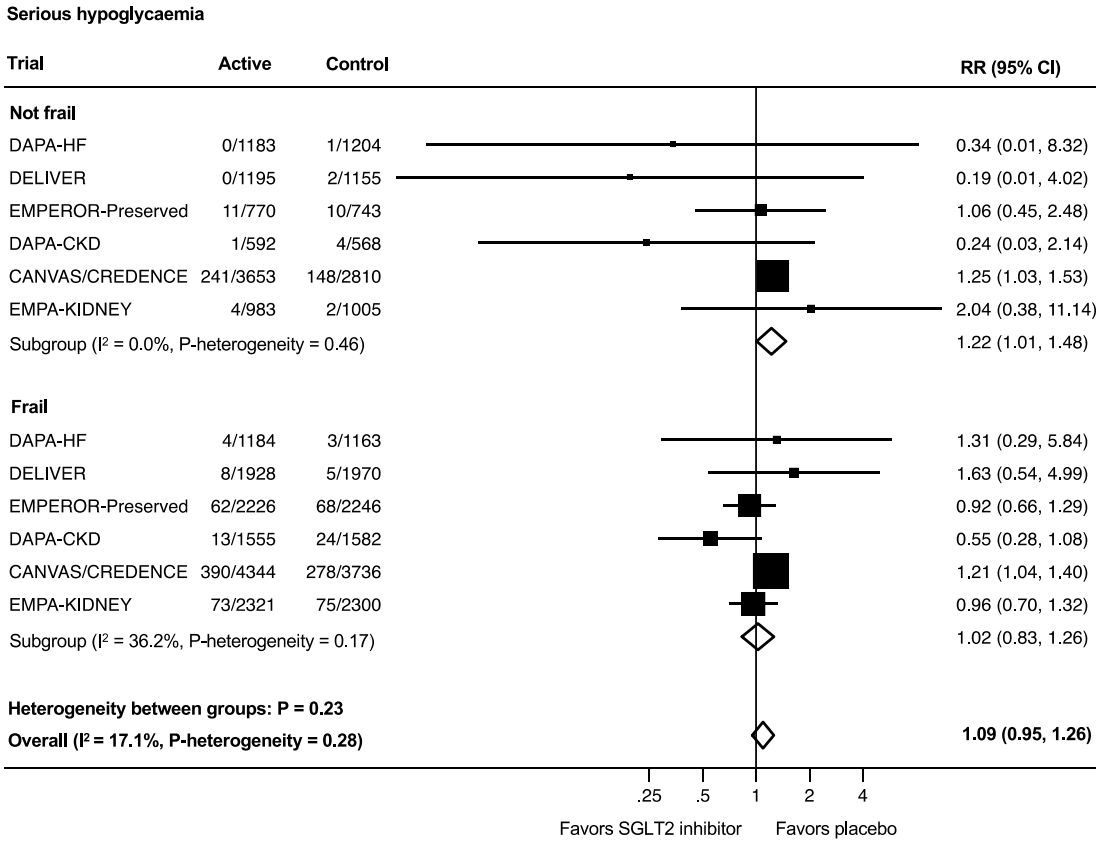


Figure S2. Effect of SGLT2 inhibitors on (A) volume depletion and (B) serious hypoglycaemia according to frailty status.

CI, confidence interval; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.

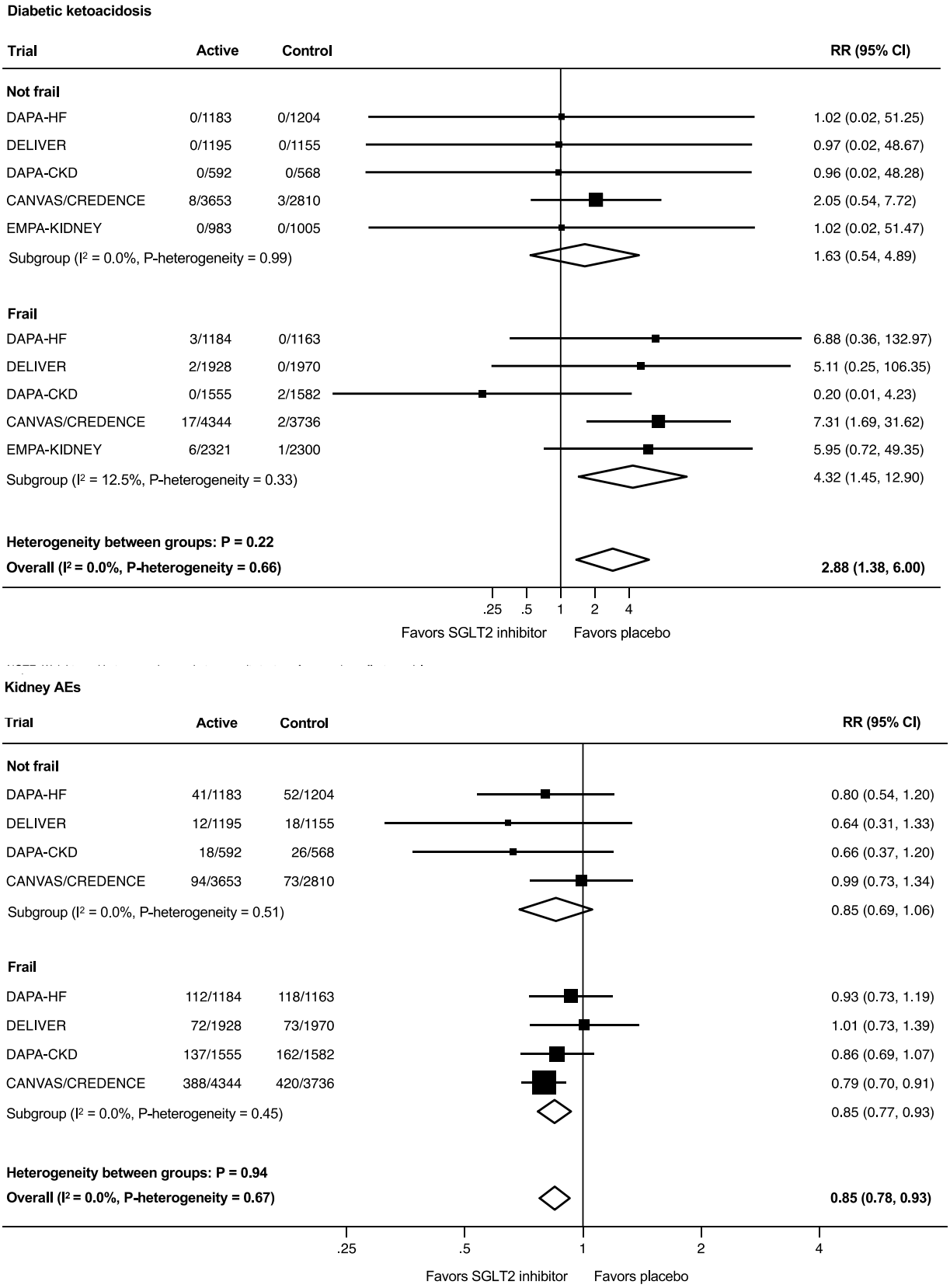
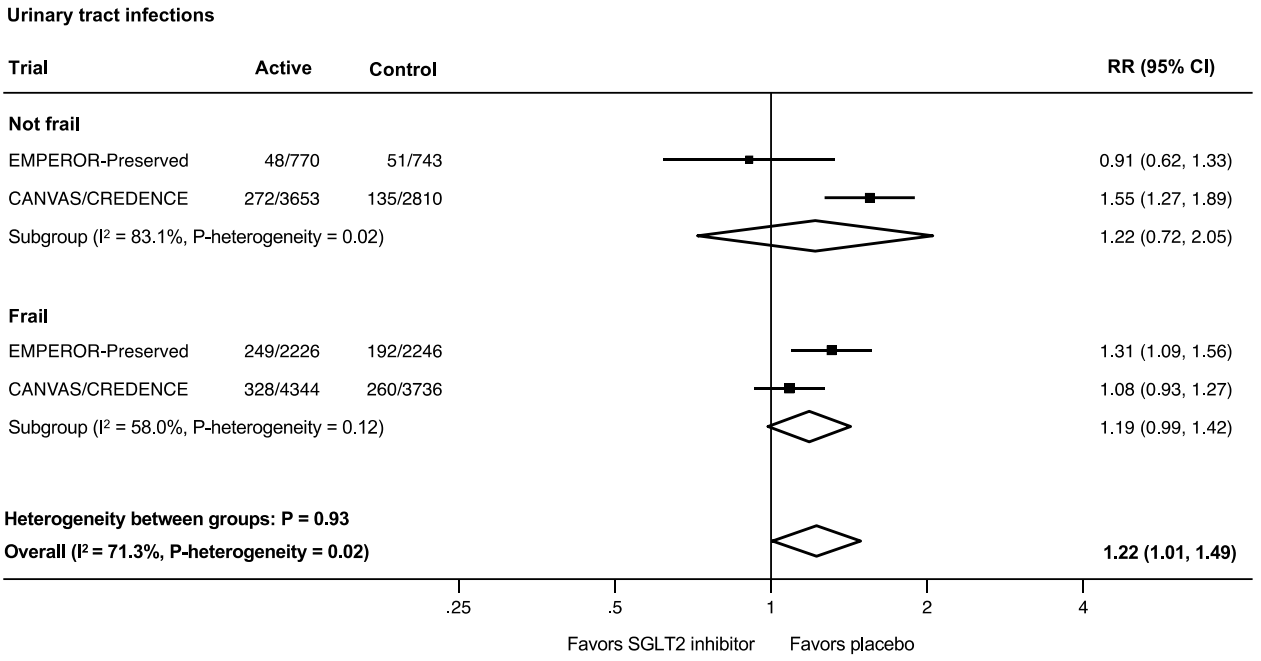


Figure S3. Effect of SGLT2 inhibitors on (A) diabetic ketoacidosis and (B) kidney AEs according to frailty status.

AE, adverse event; CI, confidence interval; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.



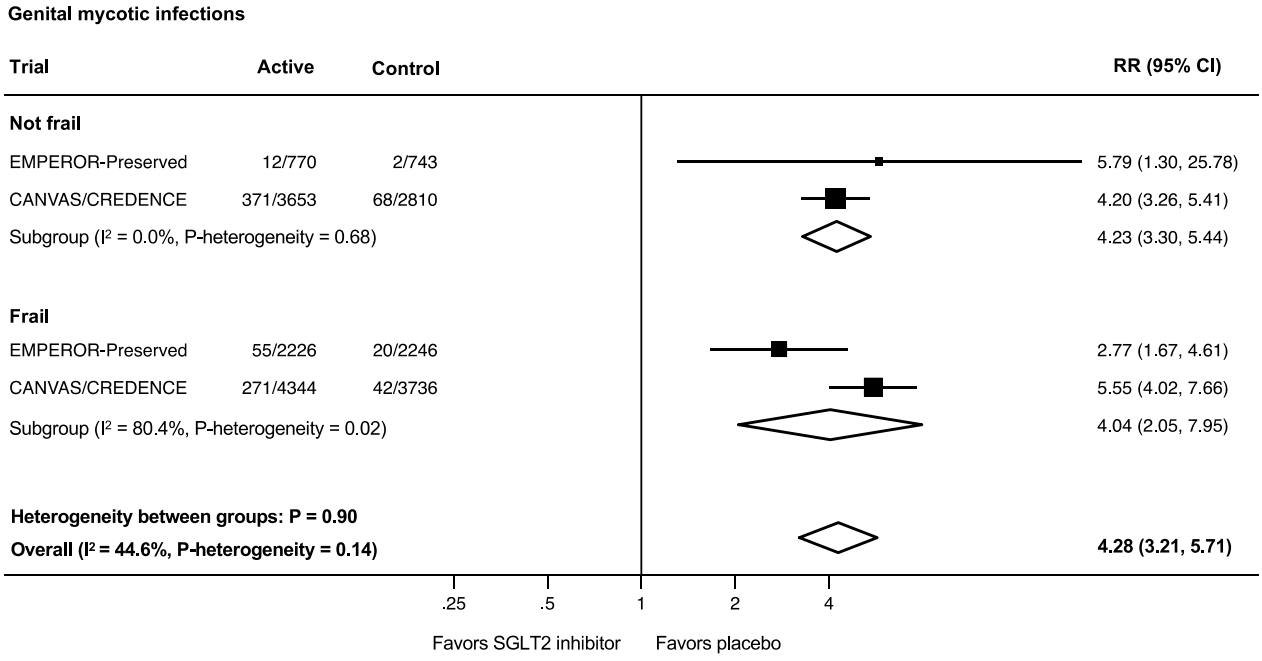
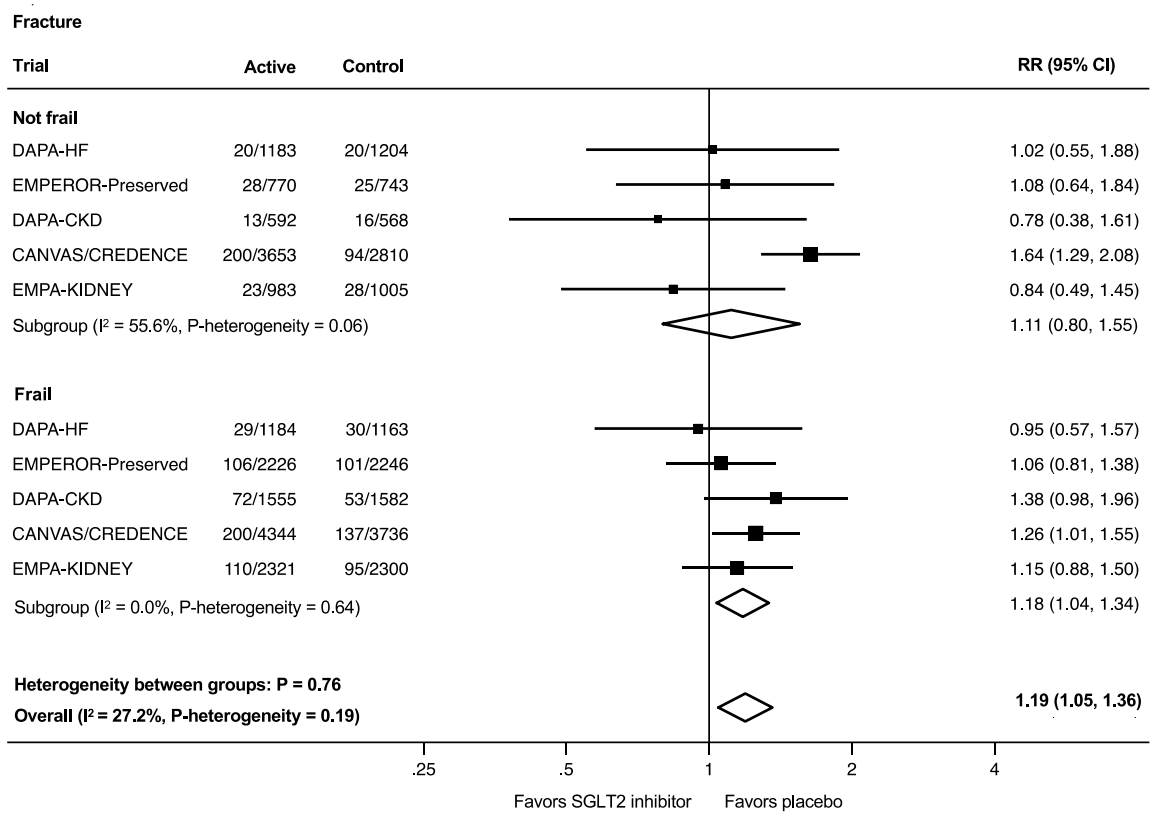


Figure S4. Effect of SGLT2 inhibitors on (A) urinary tract infections and (B) genital mycotic infections according to frailty status.

CI, confidence interval; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.



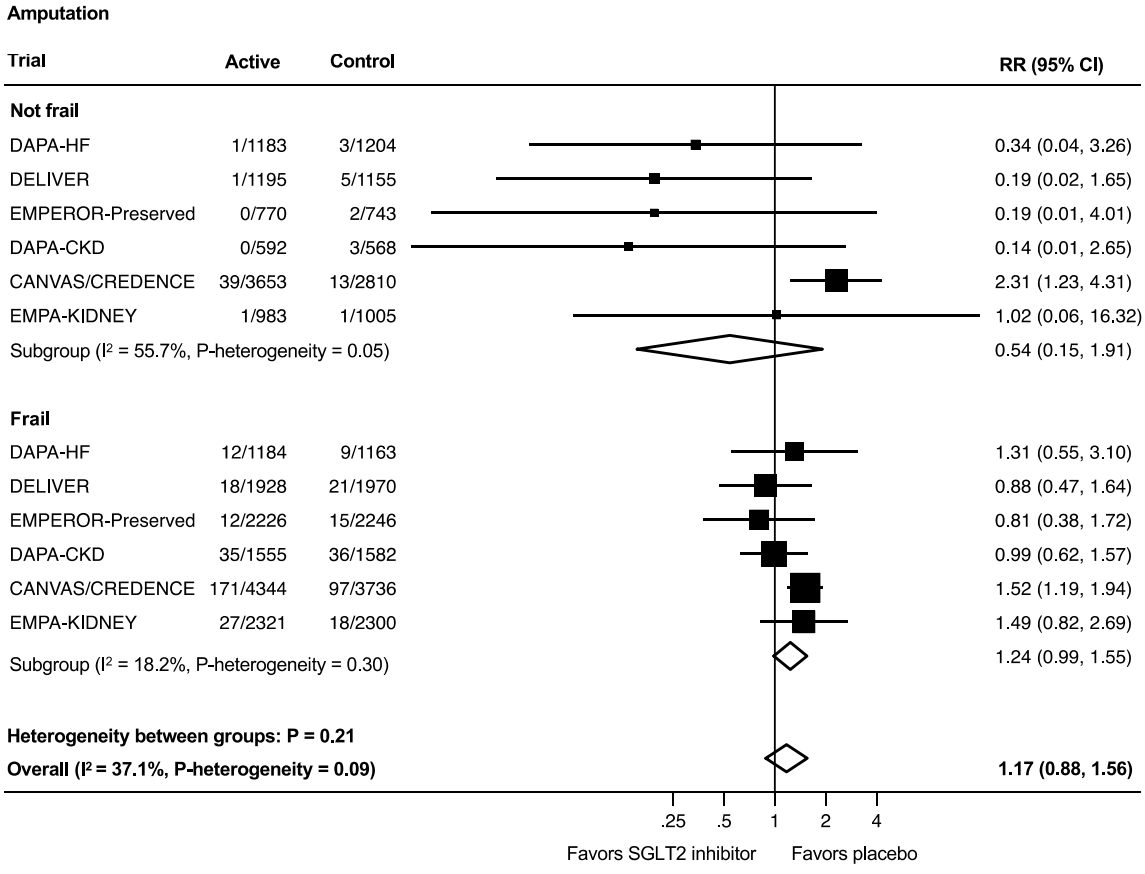


Figure S5. Effect of SGLT2 inhibitors on (A) fracture and (B) amputation according to frailty status.

CI, confidence interval; RR, relative risk; SGLT2, sodium-glucose cotransporter 2.

Table S1. Search strategy.

MEDLINE via Ovid
1. exp sodium-glucose transporter 2/
2. sodium-glucose transporter$.mp.
3. sodium-glucose co-transporter$.mp.
4. SGLT2.mp.
5. SGLT-2.mp.
6. sodium-dependent glucose cotransporter$.mp.
7. (canagliflozin$ or dapagliflozin$ or empagliflozin$ or ertugliflozin$ or ipragliflozin$ or tofogliflozin$ or sergliflozin$ or remogliflozin$ or luseogliflozin$ or sotagliflozin$).mp.
8. or/1-7
9. exp clinical trial/
10. exp random allocation/
11. exp single blind method/
12. exp double blind method/
13. (random$ adj5 trial$).tw.
14. (random$ adj5 allocation$).tw.
15. (blind$ adj5 method$).tw.
16. or/9-15
17. 8 and 16
18. Limit 17 to (English language and humans)
EMBASE via Ovid
1. exp sodium-glucose transporter 2/
2. sodium-glucose transporter$.mp.
3. sodium-glucose co-transporter$.mp.
4. SGLT2.mp.
5. SGLT-2.mp.
6. sodium-dependent glucose cotransporter$.mp.

7. (canagliflozin$ or dapagliflozin$ or empagliflozin$ or ertugliflozin$ or ipragliflozin$ or tofogliflozin$ or sergliflozin$ or remogliflozin$ or luseogliflozin$ or sotagliflozin$).mp.
8. or/1-7
9. exp clinical trial/
10. exp random allocation/
11. exp single blind method/
12. exp double blind method/
13. (random$ adj5 trial$).tw.
14. (random$ adj5 allocation$).tw.
15. (blind$ adj5 method$).tw.
16. or/9-15
17. 8 and 16
18. Limit 17 to (English language and humans)
Cochrane Central Register of Controlled Trials (CENTRAL)
1. MeSH descriptor: [Sodium-Glucose Transporter 2] explode all trees
2. (sodium-glucose transporter$):ti,ab,kw
3. (sodium-glucose co-transporter$):ti,ab,kw
4. (SGLT2):ti,ab,kw
5. (SGLT-2):ti,ab,kw
6. (sodium-dependent glucose cotransporter$):ti,ab,kw
7. (canagliflozin$ or dapagliflozin$ or empagliflozin$ or ertugliflozin$ or ipragliflozin$ or tofogliflozin$ or sergliflozin$ or remogliflozin$ or luseogliflozin$ or sotagliflozin$):ti,ab,kw
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. MeSH descriptor: [Clinical Trial] explode all trees
10. MeSH descriptor: [Random Allocation] explode all trees
11. MeSH descriptor: [Single-Blind Method] explode all trees
12. MeSH descriptor: [Double-Blind Method] explode all trees
13. (random$ NEAR/5 trial$):ti,ab,kw

14. (random$ NEAR/5 allocation$):ti,ab,kw
15. (blind$ NEAR/5 method$):ti,ab,kw
16. #9 or #10 or #11 or #12 or #13 or #14 or #15
17. #8 and #16

Table S2. Risk of bias assessment.

	D1	D2	D3	D4	D5	Overall
DAPA-HF	+	+	+	+	+	+
DELIVER	+	+	+	+	+	+
EMPEROR-Preserved	+	+	+	+	+	+
CANVAS	+	+	+	+	+	+
CREDENCE	+	+	+	+	+	+
DAPA-CKD	+	+	+	+	+	+
EMPA-KIDNEY	+	+	+	+	+	+

Domains:

D1: Bias due to randomisation process

D2: Bias due to deviations from intended intervention

D3: Bias due to missing outcome data

D4: Bias due to outcome measurement

D5: Bias due to selection of reported results

Legend:

× High

\- Some concerns

\+ Low

Table S3. Sensitivity analysis of efficacy outcomes including only trials which used the Rockwood frailty index to define frailty.

Outcome	Number of trials	Frailty subgroup	RR	95% CI	P-heterogeneity	I^2
HHF or CV death	4	All patients	0.81	0.76-0.86	0.44	3.3%
		Not frail	0.76	0.64-0.91		
		Frail	0.82	0.76-0.88		
HHF	3	All patients	0.76	0.69-0.82	0.47	0.0%
		Not frail	0.70	0.56-0.88		
		Frail	0.77	0.70-0.85		
CV death	5	All patients	0.86	0.79-0.93	0.43	0.0%
		Not frail	0.81	0.69-0.95		
		Frail	0.88	0.80-0.96		
All-cause mortality	6	All patients	0.88	0.81-0.96	0.85	39.1%
		Not frail	0.87	0.77-0.98		
		Frail	0.88	0.78-1.00		
Kidney composite	2	All patients	0.69	0.49-0.98	0.31	72.6%
		Not frail	0.55	0.33-0.92		
		Frail	0.79	0.50-1.24		
Cardiorenal composite	1	All patients	0.63	0.53-0.75	0.60	-
		Not frail	0.53	0.36-0.79		
		Frail	0.66	0.55-0.80		

Trials which used the Rockwood frailty index to define frailty: DAPA-HF, DELIVER, EMPEROR-Preserved, DAPA-CKD, CANVAS/CREDENCE.

Trials which did not sue the Rockwood frailty index (excluded from sensitivity analysis): EMPA-KIDNEY.

CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; RR; relative risk.

CHAPTER 8

Estimating a minimal important difference for the EQ-5D-5L utility index in dialysis patients: A health utility cohort study

CHAPTER OVERVIEW

Health-related quality of life (HRQOL) is a highly relevant clinical outcome for older patients with kidney failure, with a systematic review of qualitative studies suggesting that many patients value preservation of this outcome higher than longevity or survival. As a result, EQ-5D-5L utility, a measure of HRQOL, is increasingly being used as a primary or secondary endpoint in several completed and currently recruiting dialysis trials. However, there have been no published minimal important difference (MID) estimates for the EQ-5D-5L utility index in dialysis patients, and hence there is little clarity as to what constitutes a meaningful treatment effect for this population.

This chapter addresses the seventh objective of this thesis, to evaluate longitudinal metrics of HRQOL in an older cohort of dialysis patients (mean age 69 years) to establish MID estimates for the EQ-5D-5L utility index in this population. Such data will strongly guide design of dialysis randomised clinical trials, particularly those involving older patients where HRQOL is a high patient priority.

PUBLICATION DETAILS

Amanda Siriwardana [1, 2, 3], Anna Hoffman [4], Rachael Morton [5], Brendan Smyth [4, 5], Mark Brown [4, 6]. Estimating a minimal important difference for the EQ-5D-5L utility index in dialysis patients. *Value Health*. 2024; 27(4):469-477.

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AUTHOR CONTRIBUTIONS

AS, RM, BS and MB conceived study design. AS and AH collected the data. AS analysed the data, and AS, RM, BS and MB interpreted results. AS drafted the manuscript. All authors were involved in critical review and revisions of the manuscript.

ABSTRACT

Objectives: The EQ-5D-5L is a commonly used health-related quality of life instrument for evaluating interventions in individuals receiving dialysis, however the minimal important difference (MID) that constitutes a meaningful treatment effect for this population has not been established. This study aims to estimate the MID for the EQ-5D-5L utility index in dialysis patients.

Methods: 6-monthly EQ-5D-5L measurements were collected from adult dialysis patients between April 2017-November 2020 at a renal network in Sydney, Australia. EQ-VAS and Integrated Palliative care Outcome Scale Renal (IPOS-Renal) symptom burden scores were collected simultaneously and used as anchors. MID estimates for the EQ-5D-5L utility index were derived using anchor-based and distribution-based methods.

Results: 352 patients with ≥1 EQ-5D-5L observation were included, constituting 1127 observations. Mean EQ-5D-5L utility index at baseline was 0.719 (SD ±0.267), and mean EQ-5D-5L utility decreased over time by -0.017 per year (95% CI -0.029 to -0.006, p=0.004). Using cross-sectional anchor-based methods, MID estimates ranged from 0.073 to 0.107. Using longitudinal anchor-based methods, MID for improvement and deterioration ranged from 0.046 to 0.079 and -0.111 to -0.048, respectively. Using receiver operating characteristic curves, MID for improvement and deterioration ranged from 0.037 to 0.122 and -0.074 to -0.063, respectively. MID estimates from distribution-based methods were consistent with anchor-based estimates.

Conclusions: Anchor-based and distribution-based approaches provided EQ-5D-5L utility index MID estimates ranging from 0.034 to 0.134. These estimates can inform the target difference or 'effect size' calculations for clinical trial design among dialysis populations.

HIGHLIGHTS

- The minimal important difference (MID) for an outcome in a particular disease state is the threshold for meaningful treatment effect that would warrant a change in a patient's management. The MID for the EQ-5D-5L utility index in dialysis patients has not yet been established.
- This study utilises a variety of anchor-based and distribution-based methods to estimate the MID for the EQ-5D-5L utility index in dialysis patients, with estimates ranging from 0.034 to 0.134.
- There is increasing emphasis on evaluating patient-reported outcomes such as health-related quality of life in clinical trials involving interventions among dialysis patients, particularly for older patients who value this clinical outcome highly. The EQ-5D-5L utility index MID estimates derived from this study are of value in understanding quality of life trajectories among dialysis patients and for guiding endpoint, power and sample size calculations in dialysis trial design.

KEYWORDS

Health-related quality of life, EQ-5D-5L, Renal Dialysis, Patient Outcome Assessment, Minimal Important Difference

INTRODUCTION

Patient-reported outcomes measures such as health-related quality of life (HRQOL) are of high clinical and economic importance in assessing the impact of medical interventions, with 27% of clinical trials registered with ClinicalTrials.gov (2007-2013) and 45% of trials registered with the Australian New Zealand Clinical Trials Registry (2005-2017) utilising these measures as primary or secondary endpoints.[1, 2] Furthermore, patient-reported outcomes are now recommended for consideration of drug approval by the US Food and Drug Administration (FDA).[3] While incorporation of these outcomes into kidney failure trials has lagged,[4, 5] there is now an increasing emphasis on evaluating outcomes in kidney failure trials that are of importance to patients.[6, 7]

HRQOL is a multi-dimensional concept of a patient's perceived health state.[8] Measurement can be through generic instruments such as the EQ-5D[9] or disease-specific instruments such as the Kidney Disease Quality of Life (KDQOL).[10] Generic HRQOL measures are advantageous in allowing clinical decision-makers, policy-makers and funders to make comparisons between treatments and across disease states.[11] Generic utility-based HRQOL measures consist of a set of items covering different HRQOL dimensions and each dimension has multiple response categories. Together, the responses describe a multidimensional health state, to which value (or utility) can be attached using data obtained from general population surveys indicating relative preferences for different health states. Utilities are typically on a scale of 0 to 1, with 0 representing a health state equivalent to death and 1 representing full health. Some measures allow negative utilities (values less than 0) to be derived, representing health states perceived as worse than death.[8] Utilities can be

combined with survival estimates to calculate quality-adjusted life years (QALYs), which capture the impact of an intervention on both quantity and quality of life and are the most widely used outcome measure in cost-effectiveness analysis.

Critical to using generic utility-based HRQOL measures in clinical trials is not just determining whether an intervention results in a statistically significant change, but also whether that change is clinically meaningful. The minimal important difference (MID) represents the smallest change that is perceived as beneficial and would, in the absence of troublesome side effects or excessive cost, warrant a change in a patient's management.[12] MID estimates for a given outcome in a specific population are determined from prior literature and several approaches have been developed, broadly divided into anchor-based and distribution-based methods.[13-15] Anchor-based methods examine the relationship between the outcome measure of interest with respect to another measure of clinical change (the 'anchor'). Anchors may be objective clinical outcomes (such as laboratory values, disease stage or a physical performance score), or another patient-reported outcome measure (such as a patient's global health rating). Anchor-based methods can be used with either cross-sectional or longitudinal data of the anchor and of the outcome measure of interest. In contrast, distribution-based methods use statistical characteristics, particularly between-patient variability, of the obtained sample. Examples include calculation of a one-half standard deviation estimate, Cohen's effect size or a standard error of measurement. There are relative merits and limitations between anchor-based and distribution-based methods in determining the MID for HRQOL measures, and hence an integrated approach combining both is recommended.[13]

The EQ-5D is among the most widely used generic utility-based HRQOL measures. EQ-5D utility MID estimates have been established for oncology, myeloma, chronic obstructive pulmonary disease, autoimmune diseases and other disease states.[16-23] Despite change in EQ-5D utility being used as a primary or secondary endpoint in several recently completed and currently recruiting kidney failure trials[24-30] and a pre-specified change in EQ-5D being used to calculate target sample size for some trials,[24, 25] a MID for dialysis patients has not been established. Therefore, the aim of this analysis was to use anchor-based and distribution-based methods to estimate the EQ-5D MID from a cohort of dialysis patients.

METHODS

Study population

EQ-5D and EQ-VAS measures[9] have been prospectively assessed twice per year since April 2017 for all dialysis patients across two hospital sites in Sydney, Australia. These sites comprise of one in-centre haemodialysis unit, two satellite haemodialysis units, and a home therapy unit (with home haemodialysis and peritoneal dialysis patients). Symptom assessment using the Integrated Palliative care Outcomes Scale Renal (IPOS-Renal)[31] were collected at the same time points as EQ-5D and EQ-VAS questionnaires. These questionnaires have been used to identify troubling symptom and quality of life burden that may go unnoticed in routine care,[32, 33] and to institute management approaches. All questionnaires were completed during in-centre haemodialysis sessions, or mailed to home haemodialysis and peritoneal dialysis patients. Inclusion criteria for this analysis were adult dialysis patients with ≥1 EQ-5D measure between April 2017 to November 2020 who had no

missing EQ-5D response data at baseline such that a baseline EQ-5D utility score could be derived. The study was approved by the South Eastern Sydney Human Research Ethics Committee (2020/ETH01670).

EQ-5D-5L measures

The EQ-5D is a generic preference-based HRQOL measure with five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[9] The English-language EQ-5D 5-level version (EQ-5D-5L) was used. Each dimension has five response categories (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, 5=extreme problems), giving rise to 3125 distinct health states. Patient's health states were converted to a utility score through comparison with a value set from a general population valuation study in England (an Australian value set has not yet been developed and the English value set was thought to be closely representative).[34] This EQ-5D-5L utility score can be regarded as a continuous outcome on a scale from -0.285 (extreme problems in all dimensions and considered to be worse than death) up to 1 (no problems in all dimensions and considered full and complete health).

Anchor measures

The EQ-VAS[9] is a secondary component completed with the EQ-5D-5L and provides a global self-rated measure of health state. Current health state is rated on a continuous scale of 0 to 100, with 0 equating to 'worst imaginable health state' and 100 equating to 'best imaginable health state'.

The IPOS-Renal symptom inventory[31] is a validated tool for assessing symptom burden in advanced chronic kidney disease (CKD) and dialysis patients.[35] It has been shown to correlate well with EQ-5D scores in dialysis patients.[36] It comprises 15 CKD-related physical symptoms (pain, shortness of breath, weakness/lack of energy, nausea, vomiting, poor appetite, constipation, sore or dry mouth, drowsiness, poor mobility, itching, difficulty sleeping, restless legs, changes in skin, and diarrhea) and additional emotional symptoms (feeling anxious or worried, and feeling depressed). Responders rate the degree each symptom affected them in the 7 days prior to survey completion using an ordinal 5-point scale. The 15 physical symptom scores in addition to anxiety and depression scores were summated to derive a global symptom score, ranging from a minimum of 0 (no symptom burden) to a maximum of 68.

Other measures

Demographic, clinical and dialysis characteristics were obtained from medical records, including baseline age, sex, body mass index, comorbidities, dialysis modality and years on dialysis. Modified Charlson comorbidity index was calculated using baseline age and comorbidities, with a theoretical maximum score of 37.[37]

Analysis

Description of sample

Patient characteristics are reported as frequencies (n, %), means (± standard deviation, SD) and medians (interquartile range, IQR) for categorical, continuous and skewed continuous variables, respectively. Rate of change per year in utility-based HRQOL across the cohort was determined using a linear mixed effects model with a correlated structure and with random

intercepts and random slopes, which account for repeated measures and variable follow-up time points. A multivariable mixed effects model was created using stepwise backwards elimination.

Anchor-based cross-sectional methods

Anchors need to have a proven association with the outcome measure of interest and a minimum correlation of $r \geq |0.30|$ is recommended.[14] Pearson correlation analyses between candidate anchors and baseline EQ-5D-5L index values were used to select anchors ($r \geq |0.30|$), expecting that IPOS-Renal global symptom score and EQ-VAS would have the highest correlations as patients completed symptom assessment simultaneously with the EQ-5D-5L and symptom burden is among the strongest predictors of HRQOL in dialysis patients,[38-40] and EQ-VAS is a global assessment of health state that was also completed simultaneously with the EQ-5D-5L.

Using baseline IPOS-Renal global symptom score as a cross-sectional anchor, a linear regression method was employed. 5 points has been reported as a moderate effect size threshold for the generic IPOS from prior literature, and this was used as an anchor threshold.[41] An unadjusted linear regression model was fitted between baseline IPOS-Renal global symptom scores and baseline EQ-5D-5L index scores, and the EQ-5D-5L MID estimate was extracted using a 5-point change in IPOS-Renal global symptom score as meaningful. Adjustment for independent variables that may influence the outcome of interest is recommended to assess stability of the derived MID estimate,[42] hence analysis was repeated with a multivariable model developed from stepwise backwards elimination (final model

was adjusted for baseline age, sex, modified Charlson comorbidity index and dialysis vintage).

The same cross-sectional linear regression method was used with baseline EQ-VAS scores as an anchor. An EQ-VAS MID ranging from 4.2-14.8 has been estimated in other disease states,[16, 19-22, 43] and we used an EQ-VAS MID of 10 as an anchor threshold based on that derived from oncology populations.[16] An unadjusted linear regression model was fitted between baseline EQ-VAS and baseline EQ-5D-5L index scores, and the EQ-5D-5L MID estimate was extracted using a 10-point change in EQ-VAS score as meaningful. Analysis was repeated with an adjusted model.

Anchor-based longitudinal methods

Longitudinal anchors allow estimation of different EQ-5D MID values for improvement and deterioration, which is recommended as these values are often asymmetrical.[14] Using IPOS-Renal global symptom scores and EQ-VAS scores as longitudinal anchors, a several-measure mixed models approach was used. As patients completed a variable number of EQ-5D-5L, IPOS-Renal and EQ-VAS questionnaires, mixed models allow use of data across all time points.

Firstly, within-patient changes in IPOS-Renal global symptom scores between baseline to each assessment were categorised as 'improved' (≥5 point decrease), 'about the same' (0-4 increase or decrease), or 'deteriorated' (≥5 point increase). A time-varying mixed effects model with random intercepts and random slopes was then used, with time as a continuous variable and change in global symptom scores centred to the patient's baseline included as a

time-varying categorical variable. The coefficients for 'improvement' and 'deterioration' were extracted from this mixed model, and analysis was repeated with an adjusted model. The same method was applied to EQ-VAS scores, with within-patient changes in EQ-VAS scores categorised as 'improved' (≥10 point increase), 'about the same' (0-9 increase or decrease), or 'deteriorated' (≥10 point decrease), and coefficients for 'improvement' and 'deterioration' were extracted from unadjusted and adjusted mixed effects models.

Anchor-based receiver operating characteristic (ROC) methods

ROC curve methods were used to identify the optimum sensitivity and specificity of change in EQ-5D-5L index scores in 'predicting' clinically significant changes in the anchors between 0 and 6 months. The MID for improvement was identified from the ROC curve as the EQ-5D-5L change score that best discriminated between patients who improved their IPOS-Renal global symptom burden status (≥5 point decrease) or EQ-VAS score (≥10 point increase) compared with those who did not improve, with the optimum score having the highest Youden's index (sensitivity + specificity – 1).[15] Analyses were repeated to identify the MID for deterioration, defined as the EQ-5D-5L change score that best discriminated those patients who deteriorated in IPOS-Renal global symptom burden status (≥5 point increase) or EQ-VAS score (≥10 point decrease) compared with those who did not deteriorate. The area under the ROC curve (AUC) represents the probability that the derived MID correctly discriminates between groups, with an AUC ≥0.7 considered acceptable. 95% confidence intervals (CIs) for AUCs were derived using bootstrapping with 2000 replicates.

Distribution-based methods

3 distribution-based methods were used. First, 0.5 of the SD for EQ-5D-5L utility scores were calculated at baseline and 6 months. This is a measure of sample variability at each time point and has been suggested as a consistent estimation of the MID for HRQOL measures.[44] Second, the standard error of measurement (SEM) for EQ-5D-5L utility scores were calculated at baseline and 6 months. The SEM is the variation in scores that is attributed to instrument unreliability and a change smaller than the SEM is likely due to measurement error rather than true change. It is defined as SD x √1 – r, where r is the test-retest reliability of the measure.[13] Test-retest reliability is measured by the intraclass correlation coefficient (ICC) and has been reported as 0.85 for the EQ-5D-5L in a United Kingdom reliability study.[45] Third, standardised effect size was calculated as the mean difference between EQ-5D-5L utility scores at baseline and 6 months divided by SD at baseline. Cohen defined an effect size of 0.2 for 'small' effects and 0.5 for 'moderate' effects,[46] with 'small' effects considered representative of the MID.[47]

Level of significance was defined as p-value <0.05 for all analyses. Tukey corrections were used for pairwise comparisons. Assumptions of normality, homoscedascity and linearity were assessed graphically for all models. Analyses were performed using R Statistical Software (version 4.0.0).

RESULTS

Patient characteristics

355 patients had ≥1 EQ-5D-5L observation over the study period, of which 3 had missing data in one or more EQ-5D-5L response categories at baseline and were excluded from analysis. 352 patients with ≥1 EQ-5D-5L observations were included, constituting a total of 1127 observations. 263 patients had ≥2 observations for use in longitudinal analyses. Median follow-up time was 12 months (range 6-44 months). Baseline characteristics of the study population are summarised in *Table 1*. *Figure S1* shows the distribution of EQ-5D-5L responses at baseline, from which baseline utility index was derived.

Utility-based HRQOL over time

Mean EQ-5D-5L utility at baseline was 0.719 (±0.267). In both unadjusted and adjusted mixed effects models (adjusted for age, sex, modified Charlson comorbidity index and dialysis vintage), EQ-5D-5L utility showed a slight decrement over time (unadjusted: -0.019 per year, 95% CI -0.030 to -0.008, p=0.002; adjusted: -0.017 per year, 95% CI -0.029 to -0.006, p=0.004) (*Figure S2*).

Correlation between possible anchors and EQ-5D-5L

Table 1 describes the relationships between baseline characteristics that are continuous variables and baseline EQ-5D-5L utility score. There were significant but weak correlations ($r < 0.30$) for baseline EQ-5D-5L utility with age and modified Charlson comorbidity index. There were strong correlations between baseline EQ-5D-5L utility and IPOS-Renal global symptom score ($r = -0.71$), and baseline EQ-5D-5L utility and EQ-VAS score ($r = 0.58$) (*Figure*

1). IPOS-Renal global symptom score and EQ-VAS score were therefore deemed appropriate anchors for anchor-based MID estimation.

Anchor-based MID estimation

Using linear regression, MID estimates for the EQ-5D-5D utility index were 0.103 (unadjusted) and 0.107 (adjusted) using a 5-point threshold in IPOS-Renal global symptom score as an anchor and, and 0.075 (unadjusted) and 0.073 (adjusted) using a 10-point threshold in EQ-VAS score as an anchor (*Table 2*).

Results of the longitudinal anchor-based methods are summarised in *Table 3*. Using several-measure mixed models with longitudinal IPOS-Renal global symptom scores, the MID for improvement in an adjusted model was 0.076 and the MID for deterioration was -0.109. Using several-measure mixed models with longitudinal EQ-VAS scores, the MID for improvement was 0.046 and the MID for deterioration was -0.048.

Results of the ROC curve methods are summarised in *Figure 2*. From ROC curves with IPOS-Renal global symptom score as an anchor, the optimal EQ-5D-5L change score that best discriminated between patients who had a ≥5 point decrease in symptom score from baseline to 6 months (ie. MID for improvement) was 0.122 (AUC 0.76, 95% CI 0.65 to 0.85), and the optimal EQ-5D-5L change score that best discriminated between patients with a ≥5 point increase in IPOS-Renal global symptom score (ie. MID for deterioration) was -0.063 (AUC 0.69, 95% CI 0.59 to 0.78). From ROC curves with EQ-VAS scores as an anchor, the optimal EQ-5D-DL change score that best discriminated between patients who had a ≥10 point increase in EQ-VAS score from baseline and 6 months (ie. MID for improvement) was

0.037 (AUC 0.66, 95% CI 0.56 to 0.74), and the optimal EQ-5D-5L change score that best discriminated between patients with a ≥10 point decrease in EQ-VAS score (ie. MID for deterioration) was -0.074 (AUC 0.66, 95% CI 0.58 to 0.75).

Distribution-based MID estimation

MID estimates from distribution-based methods are summarised in *Table 4*. Using 0.5 SD, MID estimates ranged from 0.108 to 0.134. Using SEM, MID estimates ranged from 0.084 to 0.104. Using Cohen's definitions, 0.2 standardised effect size ('small' effects) for change in EQ-5D-5L utility scores between baseline and 6 months was 0.034 and 0.5 standardised effect size ('moderate' effects) was 0.084.

DISCUSSION

HRQOL in dialysis patients, as measured by the 5Q-5D-5L utility index in this study, was lower than general population norms and showed slight decrement over time. This is the first study to estimate the MID for the EQ-5D-5L utility index in dialysis patients, with anchor-based and distribution-based approaches providing MID estimates ranging from 0.034 to 0.134, with some variation depending on the MID calculation technique used.

Utility-based HRQOL is known to be poor among dialysis patients compared with general population norms and kidney transplant recipients, with a large Australian general population survey reporting a mean EQ-5D-5L utility index score of 0.91[48] and a prior meta-analysis reporting mean utility-based HRQOL of 0.70 and 0.82 among dialysis and kidney

transplant patients, respectively.[49] These utility-based HRQOL estimates in dialysis patients are comparable to that of oncology patients.[50] Further, poorer HRQOL is a predictor of other adverse clinical outcomes including mortality and hospitalisations among dialysis patients.[51-53] Given these disparities and implications, HRQOL is an increasingly important consideration, and pre-dialysis and dialysis patients, particularly those in older age-groups, place high priority on this patient-reported outcome.[54-56] Among a cohort whose demographic profile is typical of high-income country dialysis populations (mean age 68.6 years, mean modified Charlson comorbidity index 6.4, 49% with diabetes mellitus), our study identified a mean baseline EQ-5D-5L utility index of 0.719 consistent with prior studies. Outside clinical trials of novel interventions,[25] longitudinal data on utility-based HRQOL among dialysis populations are sparse.[49] In our population, there was a small though statistically significant decline in EQ-5D-5L utility by -0.017 per year. This contrasts with the utility trajectories of kidney transplant recipients which have shown increase or stable values in previous studies.[49]

The MID of HRQOL measures is a property relevant to multiple stakeholders. Rather than basing treatment, policy and funding decisions purely on statistical significance, the MID allows such decisions to incorporate an understanding of clinical relevance. To our knowledge, this is the first study to estimate the MID for the EQ-5D-5L utility index in dialysis patients. We utilised patient-reported outcome data collected on patients every 6 months, rendering a large patient and observation sample size when compared with other MID studies.[57] MID estimates in our population ranged from 0.034 to 0.134. EQ-5D utility MID estimates of 0.09-0.12 have been reported for oncology patients,[16] 0.08-0.10 for myeloma patients,[17] and a pooled EQ-5D utility MID estimate of 0.074 (range 0-0.139) from 11 studies

among various chronic disease patient groups.[23] While differences in MID estimates across disease states are expected, it should be noted that there is great variation in the computation methods, value sets, anchors and handling of missing data across MID studies.[57] Hence, making comparisons between EQ-5D-5L MID estimates across different disease states and different countries requires great caution and emphasises the importance of deriving disease-specific and population-specific estimates.

As there is no consensus for the optimal MID estimation method, we used a combination of anchor-based and distribution-based methods, utilising both cross-sectional and longitudinal data. Estimates in our study showed some variation across methods which has been reported in other MID studies.[58] Anchor-based MID estimates derived by using change in IPOS-Renal global symptom score as a clinical anchor produced larger estimates than those using change in EQ-VAS as an anchor. Although both anchors showed strong correlations with EQ-5D-5L utility, these variations in MID estimates could be explained by the respective thresholds of meaningful change for the anchors used which were based on established MID estimates for the IPOS and EQ-VAS in other disease states. The mixed models approach is advantageous in that these models account for within-patient correlation of repeated measures, adjust for regression to the mean, and utilise multiple measurements across multiple time points which enhances estimate precision. As such, they are argued as a more flexible and appropriate approach to MID estimation.[59] While the thresholds identified using ROC curve analysis were consistent with those derived from longitudinal anchor-based models, these curves utilised data from two time-points only (baseline and 6 months) and AUCs ranged from 0.66 to 0.76, rendering some analyses just below the 0.70 threshold for acceptable discrimination.

Distribution-based methods rely purely upon the distribution of the cohort, with no valuation of clinical relevance. They are therefore thought to be less reliable as stand-alone MID estimates. The distribution-based MID estimates from our study do, however, show agreement with those derived from anchor-based methods. Revicki et al. proposed a process of triangulation; using various anchor-based methods, then examining distribution-based estimates to support anchor-based estimates, to converge on a range of MID values rather than a single estimate.[14] More recently, Wang et al. devised a step-wise approach to selecting an optimal MID from multiple anchor-based estimates.[60] This approach places greatest importance on methodological rigor, with assessment of each estimate against 'credibility criteria' and then deriving usable median values from the selected estimates. From our study, anchor-based mixed models and ROC curves meet highest credibility criteria and give rise to a median MID for improvement of 0.061 and median MID for deterioration of -0.069. We would suggest that these MID estimates are likely to have greatest relevance in guiding clinical trial design.

Both haemodialysis and peritoneal dialysis are intensive and invasive treatments, and while there has been substantial research investment in dialysis over the past two decades, gains in survival have been modest.[61] The importance of including HRQOL as a core domain in dialysis trials cannot be overstated.[6] This is particularly relevant in the growing era of learning healthcare systems and real-world comparative effectiveness trials, whose goal are to perform studies relevant to patients and decision-makers.[62, 63] Ideally, clinical trials should be powered to detect the MID of the primary outcome measure. In practice, dialysis trials using patient-reported outcome measures are often powered to detect group differences

based on MID estimates in other disease states.[64] The EQ-5D-5L utility MID estimates derived from our study thus offer useful insights for clinical trial design in dialysis populations, particularly regarding power and sample size calculations. There is a clear need for further dialysis MID studies to better understand the clinical meaningfulness of HRQOL changes and to potentially narrow the range of estimates derived in our study. However, it should also be acknowledged that the MID is a statistical concept that, while useful in clinical trial design, does not supersede the importance of considering individual patient trajectories. Any change in a patient's EQ-5D-5L utility over time, regardless of how small, is important and reflects their perspective of change. As the key stakeholder in treatment decision-making, an individual's perception of change rather than an aggregated threshold such as the MID should be at the centre of clinical decisions.

This study has some limitations. Firstly, patients were censored at the time of kidney transplantation and death, which may introduce some selection bias of longitudinal data. However, majority of dialysis trials include heterogenous cohorts of transplant waitlisted and non-waitlisted patients, thus supporting the generalisability of our estimates. Secondly, while attempts were made by nursing staff and family members to support frailer, visually impaired and non-English speaking patients with questionnaire completion, it is likely that these groups were underrepresented in data collection. Thirdly, while the 5-level version of the EQ-5D has reduced floor and ceiling effects compared with the preceding 3-level version,[65] these effects are not completely negated and limit the ability to pick up further change in patients with extreme values at baseline. Finally, we categorised anchors into three categories; 'improved', 'no change' and 'deteriorated', rather than multiple categorisation such as 'slightly improved' and 'much improved'. It is argued that

categorisation into fewer groups can result in grouping of individuals with change beyond minimally important, thus resulting in overestimation of MID values. However, this issue is not encountered in ROC methods which identify the optimal cut-off between 'improved' and 'no change'/'deteriorated', and MID estimates from ROC methods were largely consistent with other anchor-based methods in our study.

CONCLUSIONS

EQ-5D-5L utility index MID estimates determined from this study are the first among a dialysis cohort. Derivation of this data is critically important, given the high priority dialysis patients, particularly in older age-groups, place upon HRQOL as a clinical outcome. The range of MID estimates derived provide insight into variability of quality of life trajectories among dialysis patients, and are of value for endpoint, power and sample size calculations in the design of dialysis clinical trials. This study encourages further MID studies in this patient population. Such studies are needed to determine the reproducibility of these results and potentially narrow the EQ-5D-5L utility MID estimate range.

CONFLICT OF INTEREST DISCLOSURES

The authors report no conflicts of interest.

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FIGURES AND TABLES

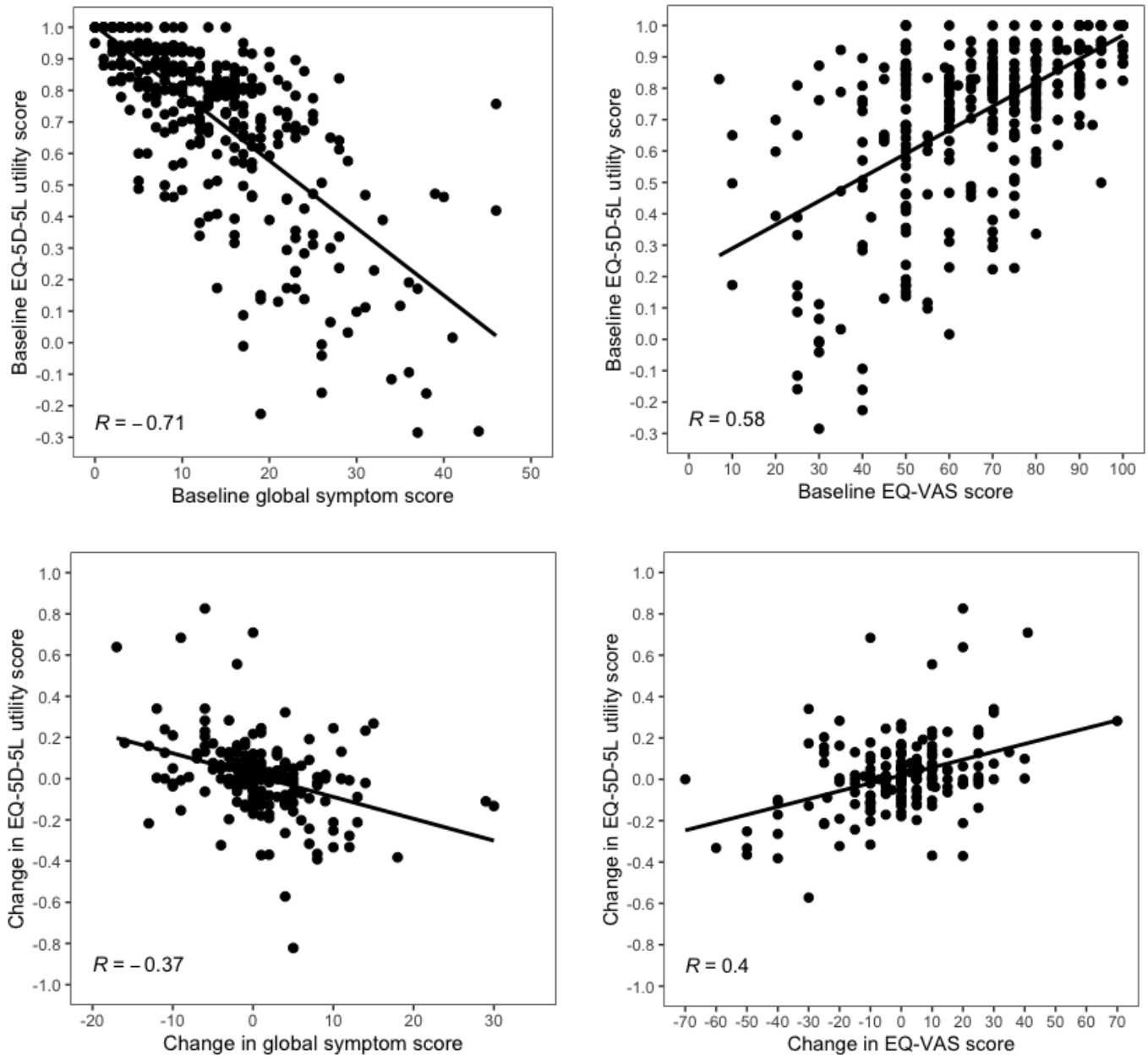

Figure 1. Correlation between baseline EQ-5D-5L utility score with IPOS-Renal global symptom score (top left) and EQ-VAS score (top right), and correlation between change in EQ-5D-5L utility score from 0-6 months with change in IPOS-Renal global symptom score (bottom left) and change in EQ-VAS score (bottom right).

r = -0.71, *r* = 0.58, r = -0.37 and r=0.40 respectively, p <0.001 for all.

IPOS-Renal, Integrated Palliative care Outcomes Scale Renal.

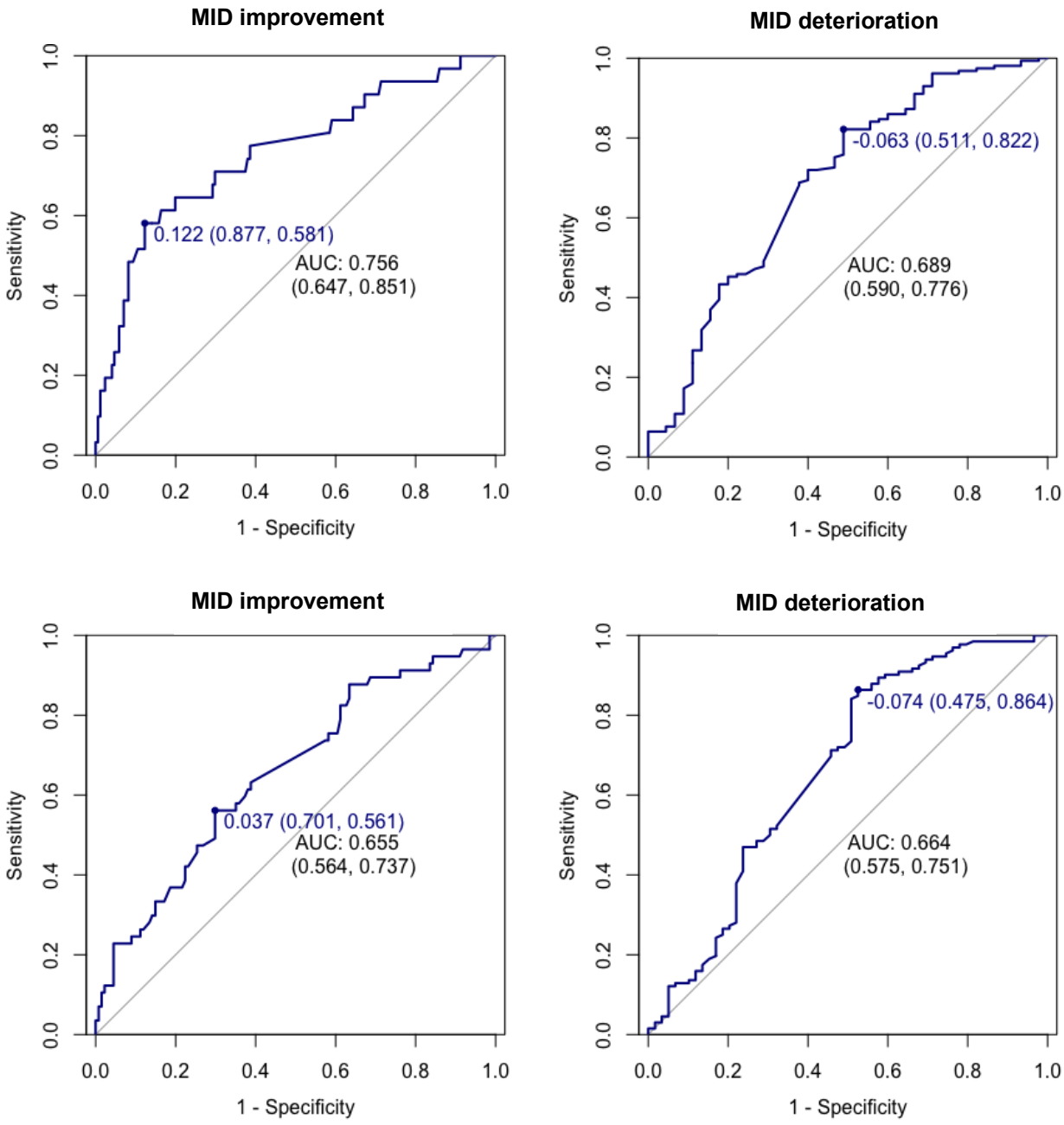

Figure 2. EQ-5D-5L utility index MID estimates from ROC curves: MID for improvement using ≥5 point decrease in global symptom burden score between 0 and 6 months as anchor (top left), MID for deterioration using ≥5 point increase in global symptom burden score between 0 and 6 months as anchor (top right), MID for improvement using ≥10 point increase in EQ-VAS score between 0 and 6 months as anchor (bottom left), and MID for

deterioration using ≥10 point decrease in EQ-VAS score between 0 and 6 months as anchor (bottom right).

Cut-off points in blue with specificity and sensitivity in brackets represent the best discriminatory threshold using Youden's index. AUC with 95% confidence intervals for AUC presented in brackets.
AUC, area under the ROC curve; MID, minimal important difference; ROC, receiver operating characteristic.

Table 1. Baseline patient characteristics and Pearson's correlation coefficients with baseline EQ-5D-5L utility score.

		Pearson's correlation coefficient with baseline EQ-5D-5L utility score	
	All patients (n = 352)	***r***	**p value**
Mean age, years (± SD)	68.6 (12.9)	-0.19	<0.001
Female sex, n (%)	132 (38)	-	-
Mean BMI, kg/m^2 (± SD) [a]	29.8 (6.6)	-0.04	0.46
Known diabetes mellitus, n (%)	173 (49)	-	-
Mean mCCI (± SD)	6.4 (2.3)	-0.19	<0.001
Median dialysis vintage, years (IQR)	1.9 (0.4, 5.6)	-0.15	0.004
Dialysis modality, n (%)			
Hospital HD	257 (73)	-	-
Home HD	33 (9)	-	-
PD	62 (18)	-	-
Mean baseline EQ-5D-5L utility score (± SD)	0.719 (0.267)	-	-
Mean baseline IPOS-Renal global symptom score (± SD)	13.3 (8.9)	-0.71	<0.001
Mean baseline EQ-VAS score (± SD)	67.2 (20.3)	0.58	<0.001

[a] BMI data available for 292 patients.

BMI, body mass index; HD, haemodialysis; IPOS-Renal, Integrated Palliative care Outcomes Scale Renal; IQR, interquartile range; mCCI, modified Charlson comorbidity index; n, number; PD, peritoneal dialysis; SD, standard deviation.

Table 2. EQ-5D-5L utility index MID estimates from anchor-based cross-sectional methods.

Anchor	Method	MID estimate (95% CI)	p value
IPOS-Renal global symptom score			
5-point threshold	Linear regression (unadjusted model)	0.107 (0.096, 0.118)	<0.001
5-point threshold	Linear regression (adjusted model) [a]	0.103 (0.092, 0.114)	<0.001
EQ-VAS score			
10-point threshold	Linear regression (unadjusted model)	0.075 (0.064, 0.087)	<0.001
10-point threshold	Linear regression (adjusted model) [a]	0.073 (0.062, 0.084)	<0.001

[a] Adjusted for age, sex, modified Charlson comorbidity index and dialysis vintage.

CI, confidence interval; IPOS-Renal, Integrated Palliative care Outcomes Scale Renal; MID, minimal important difference.

Table 3. EQ-5D-5L utility index MID estimates from anchor-based longitudinal methods.

Several-measure mixed models performed using all time points for each patient, with within-patient changes in IPOS-Renal global symptom scores and EQ-VAS scores at each time point compared with baseline.

		MID estimate for improvement		MID estimate for deterioration	
Anchor	**Method**	**Estimate (95% CI)**	**p value**	**Estimate (95% CI)**	**p value**
IPOS-Renal global symptom score					
≥ 5-point change	Several-measure mixed model (unadjusted model)	0.079 (0.047, 0.112)	<0.001	-0.111 (-0.139, -0.084)	<0.001
≥ 5-point change	Several-measure mixed model (adjusted model) [a]	0.076 (0.044, 0.109)	<0.001	-0.109 (-0.136, -0.081)	<0.001
EQ-VAS score					
≥ 10-point change	Several-measure mixed model (unadjusted model)	0.048 (0.018, 0.077)	0.005	-0.053 (-0.083, -0.023)	0.002
≥ 10-point change	Several-measure mixed model (adjusted model) [a]	0.046 (0.017, 0.076)	0.006	-0.048 (-0.078, -0.018)	0.005

[a] Adjusted for age, sex, modified Charlson comorbidity index and dialysis vintage.

CI, confidence interval; IPOS-Renal, Integrated Palliative care Outcomes Scale Renal; MID, minimal important difference.

Table 4. EQ-5D-5L utility index MID estimates from distribution-based methods.

EQ-5D-5L utility score time point	Distribution-based criteria			
	0.5 SD	SEM	0.2 Effect size	0.5 Effect size
Baseline	0.134	0.104	-	-
6 months	0.108	0.084	-	-
Change from baseline to 6 months	-	-	0.034	0.084

MID, minimal important difference; SD, standard deviation; SEM, standard error of measurement.

Supplementary Material – Estimating a minimal important difference for the EQ-5D-5L utility index in dialysis patients

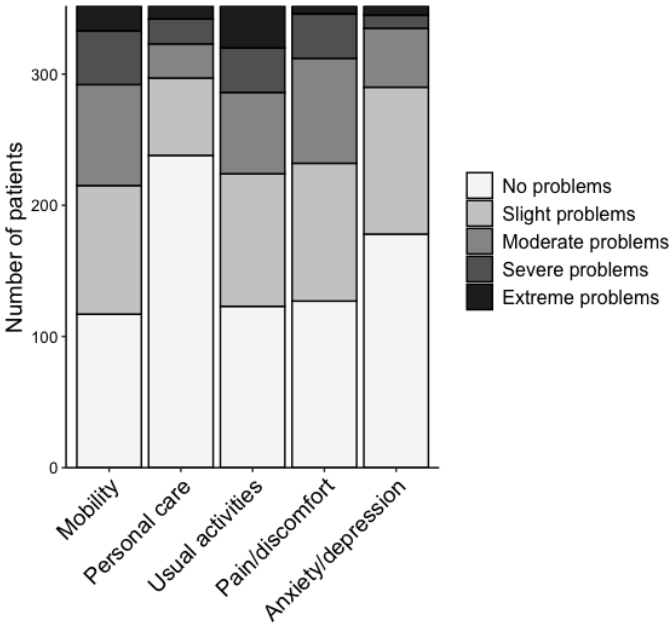

Figure S1. Distribution of baseline EQ-5D-5L responses.

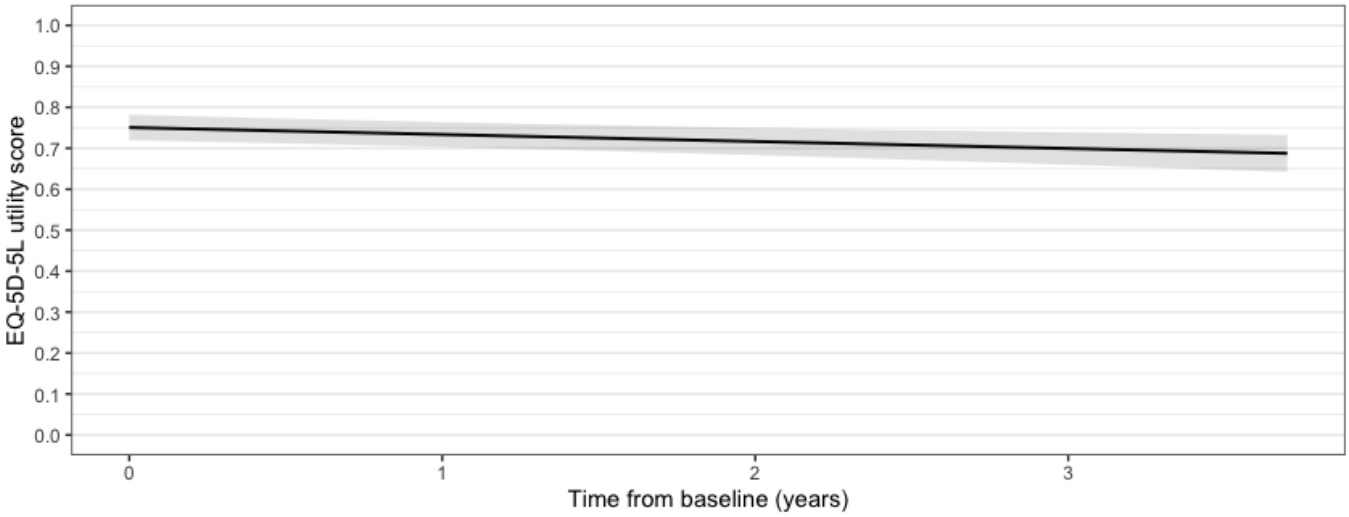

Figure S2. Adjusted mixed effects model of utility-based HRQOL over time.

Model adjusted for age, sex, modified Charlson comorbidity index and dialysis vintage (-0.017 decline per year, 95% CI -0.029 to -0.006, p=0.004).

CHAPTER 9

Thesis discussion & future directions

SYNTHESIS & IMPLICATIONS OF THESIS FINDINGS

As global population ageing gives rise to dramatic increases in the prevalence of older age-groups, the current and projected burden of chronic diseases including CKD are set to reach unprecedented levels. CKD is estimated to be the fifth leading cause of death worldwide by 2024,[1] and the prevalence of CKD categories G3-G5 (eGFR ≤59 mL/min/1.73m^2) will exceed 10% in many regions of the world by 2050.[2] These projections warrant critical action for older individuals with kidney disease; specifically, to identify and implement interventions to mitigate CKD progression in this population, to better understand outcomes in older CKD patients including survival and patient-reported outcomes, and to utilise this information to support shared decision-making processes as older patients, their families and clinicians make important decisions about care. Given the challenges and historical underrepresentation of older patients in kidney disease studies [3, 4] and limited high-quality data regarding outcomes for older kidney failure patients,[5-7] addressing these needs requires collaborative, well-planned and novel research designs.

In this thesis, I have taken a systematic approach in working towards these objectives and utilised a combination of research methodologies, including:

- Design and conduct of a research program including observational cohort studies and qualitative studies,
- Cross-sectional comparison of observational and registry-based data,
- Review methodology,
- Analysis of RCT data,
- Systematic review and meta-analysis of published RCTs, and

- Cross-sectional and longitudinal analysis of patient-reported outcome data.

The chapters of this thesis provide important insights into research methodologies, various clinical outcomes, and targeted management approaches aimed at addressing the wave of ageing-related CKD growth, as discussed below.

Overcoming methodological challenges in investigating older patients with CKD and kidney failure

Participation of older patients with CKD and kidney failure in observational studies and RCTs has been hampered by numerous factors, including highly prevalent conditions in older patients frequently considered as study exclusion criteria (such as multimorbidity, frailty, and polypharmacy), historical setting of arbitrary upper age limits in RCTs, the high prevalence of cognitive impairment in older populations posing challenges to traditional informed consent processes, patient, carer and clinician perceptions that participation will be burdensome, and a high reliance upon retrospective study designs that introduce methodological biases.[3, 4, 8-10] Furthermore, efficacy and safety outcomes in various CKD and kidney failure studies are often not directly relevant to or powered to detect changes in older patient populations,[3] and conducting RCTs specifically in older patients are restricted by cost and feasibility. Well-designed prospective observational studies that collect data on important baseline characteristics and adjust for differences in these baseline characteristics between treatment groups can achieve high inclusivity, feasibility and external validity. There is a clear role for utilising this study design in the older kidney failure population to better understand patient outcomes across treatment pathways.

It is in response to these needs that the Elderly Advanced CKD Program was designed. In Chapter 2, I reported on the design considerations of this study program. Its primary component, OUTLOOK, is a large prospective observational cohort study aiming to enrol 800 older patients with kidney failure (aged ≥75 years and eGFR ≤15mL/min/1.73m^2), in order to robustly quantify differences in survival, receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry (including serum creatinine and eGFR), hospitalisation burden and characteristics of end-of-life care for older patients across kidney failure treatment pathways (dialysis compared with CKM). Large-scale prospective data of this sort is novel, and the key outcomes are of critical importance to both older patients and clinicians. The nature of this study being routine-care, utilising a waiver of consent model and involving no direct patient contact are carefully considered design features that have yielded a feasible, collaborative and nationally representative study. Secondary studies in this program include longitudinal measurement of patient-reported outcomes including quality of life and symptom burden (in the TIMELY study), and carer outcomes such as carer quality of life and carer burden (in the Co-TIMELY study). Longitudinal data of this sort, particularly involving carers, have been rarely reported on.[11] However, decision-making between kidney failure treatment pathways for older patients is complex and quantitative data alone will not overcome all of the challenges involved. Qualitative work to understand the perspective of patients and their families on treatment decision-making processes, experiences of CKM and end-of-life care are therefore fundamental components of this study program (in the Co-TIMELY qualitative study and CONTEND study). The qualitative CONTEND study involves single-encounter interviews with patients and carers, is minimally burdensome, and interviews can be conducted remotely, again highlighting direct strategies in study design to feasibly engage the population being studied.

The Elderly Advanced CKD Program has, however, not been without its challenges. The COVID-19 pandemic had widespread impacts on workflow, staffing and resource allocation for all sites involved, and resulted in a significant increase in clinical workload for myself and other clinicians leading this program. Despite this, the program has maintained momentum, which is a testament to the research methodology being used and the quality of engagement of multiple sites in a national program with direct relevance to clinical practice. At the time of analysis in Chapter 4, 529 patients had been in enrolled into OUTLOOK, and at the time of submission of this thesis OUTLOOK enrolment has further increased to close to 600 patients. Similarly, the CONTEND qualitative study has achieved close to half of its targeted sample size. However, recruitment into the patient- and carer-reported outcome components of the program (TIMELY and Co-TIMELY) have been slower. These studies involve direct patient and carer contact and involve longitudinal completion of study surveys. Slower recruitment into these components likely reflects the greater demands upon patients and carers, necessitating strategies to reduce participant burden such as reducing survey frequency from 6-monthly to 12-monthly. It is still expected that valuable longitudinal insights will be gained from these study components, however they illustrate some of the aforementioned challenges of consent and engagement in clinical research with older patient/carer populations who have high rates of cognitive impairment, comorbidity and existing high burdens of treatment.

In response to our experiences with justifying the ethical and scientific rationale for a waiver of consent model in the OUTLOOK study, Chapter 3 of this thesis synthesised national, regional and international ethical guidelines on the use of waiver of consent in low-risk clinical research. The primary aim of this manuscript was to serve as a reference tool for

researchers designing studies that may warrant a waiver of consent and for ethical boards who are called upon to weigh up the suitability of this consent model. This manuscript concludes that while the situations for using a waiver of consent in clinical research must meet stringent criteria, there is broad international consensus on the ethical principles underlying its use. The applicability of this consent model to low-risk routine-care research involving older patients with kidney disease is evidenced by the OUTLOOK study, whereby large-scale, generalisable and low-risk observational research is being generated that would not otherwise be feasible if traditional consent models were necessitated. Waiver of consent models are also increasingly being utilised in nephrology in pragmatic RCTs such as cluster randomised trials, whereby study participation is at the cluster level, individual patient consent prior to cluster randomisation is not methodologically feasible, and hence a waiver of consent is justified.[12] These trials are considered low-risk and are typically assessing real-world effectiveness of already well-studied interventions, comparative effectiveness of interventions for which there is significant equipoise and arbitrary decision-making in clinical practice, and implementation strategies.[13, 14] This study design holds great potential for older patient populations with CKD, such as assessing approaches to deliver kidney failure treatment pathway education, strategies to embed frailty assessment in decision-making processes, and strategies to identify and address polypharmacy. While there is much more work to be done to expand this trial design to older CKD populations, the review of waiver of consent guidelines presented in Chapter 3 of this thesis provides important methodological guidance going forward.

Chapter 8 of this thesis is a statistical and health outcomes manuscript aimed at supporting study design in older individuals with kidney failure. Using HRQOL and patient-reported

outcome data from a cohort whose demographic characteristics are typical of high-income country dialysis populations (with a mean age of 68.6 years and mean modified Charlson comorbidity index of 6.4), anchor-based and distribution-based methods were used to estimate a minimal important difference (MID) range for the EQ-5D-5L utility index in dialysis patients of 0.034 to 0.134. This is the first study to estimate a MID for the EQ-5D-5L utility index in dialysis patients. Maintenance of HRQOL is a heavily prioritised outcome for older patients with kidney failure, and qualitative and discrete choice studies indicate that some older patients preference HRQOL above survival.[15-17] Accordingly, change in EQ-5D utility is increasingly being used as a primary or secondary endpoint in kidney failure trials, and there is a need to understand what constitutes a meaningful treatment effect in this population.[18-24] The findings from this study are therefore of value for endpoint, power and sample size calculations in the design of dialysis trials, particularly those involving older populations where HRQOL is a priority. This study serves as a forerunner for others to potentially narrow the EQ-5D-5L utility MID estimate range in dialysis patients and to assess the applicability of these estimates to kidney failure populations managed with CKM.

Outcome data for older patients with kidney failure

As detailed in Chapter 2, the Elderly Advanced CKD Program is generating high-quality prospective outcome data for older patients with kidney failure who are opting for either a dialysis or CKM pathway. While the program is ongoing and final results are awaited, Chapter 4 of this thesis presented an interim analysis comparing baseline characteristics of the 529 presently enrolled patients in OUTLOOK, the main study component of the Elderly Advanced CKD Program, with 5339 incident patients aged ≥75 years who commenced kidney replacement therapy (KRT) and entered onto the Australia and New Zealand Dialysis and

Transplant Registry (ANZDATA) between January 2015 and December 2022. These cohorts are inherently different, with OUTLOOK capturing patients ≥75 years with kidney failure (eGFR ≤15 mL/min/1.73m^2) who are in the decision-making phase or have recently made a decision on preferred treatment (dialysis, CKM or undecided), and ANZDATA capturing patients who have opted for and commenced a KRT pathway. KRT registry data in most high-income countries, including Australia and New Zealand, is robust. However, the purpose of the comparison presented in Chapter 4 is to highlight the selectivity of registry data in only capturing those patients who go on to KRT. In contrast, OUTLOOK is capturing an older (age range 75 to 99 years), comorbid (mean modified Charlson comorbidity index 8.1), predominantly community-dwelling cohort (89.2%) with a high prevalence of frailty (47.4%), who are deciding between kidney failure treatment pathways. While some studies have suggested that severe comorbidity, poor performance status and very advanced age (≥80 years) are associated with no differences in survival between dialysis and CKM pathways,[25-27] there is much greater uncertainty for community-dwelling older patients who are independent and have more robust performance statuses.[5] Thus, the comparison presented in Chapter 4 highlights the unique survival data that will be derived from the OUTLOOK study on an older kidney failure population for which, in clinical practice, there is a high degree of equipoise about which treatment pathway they will derive most benefit from. In particular, OUTLOOK has a high proportion of patients with CKM as the chosen pathway of kidney failure management (65.4%), and large-scale prospective data collection on survival among CKM patients is a major strength of the study.

Robust outcome data and prognostic tools are essential to shared decision-making processes, and older patients with CKD express a desire for frank, detailed prognostic

information.[28-30] It is now a grade 1A Kidney Disease Improving Global Outcomes (KDIGO) recommendation that an externally validated risk prediction tool be used in all patients with CKD to guide prognostic discussions and treatment decisions. Although several validated models exist, most were not specifically designed for older patient populations and require careful interpretation. Chapter 5 of this thesis presented a comprehensive review of the use of risk prediction models in older patients with CKD and provides practical guidance on how these models may be best applied by clinicians caring for older patients. While a combined approach using two validated tools, the Kidney Failure Risk Equation (KFRE) and the Mortality Risk Equation for Kidney disease (MREK) model, may have the highest clinical utility for older patients with advanced CKD, [31-33] there is a need to better account for older patients, particularly those who go on to a CKM pathway, in the derivation of CKD risk prediction models. As such, one of the fundamental aims of the OUTLOOK study in the Elderly Advanced CKD Program is to apply various risk prediction methodologies (Cox proportional hazards, Bayesian network modelling and machine learning modelling) to the large prospective survival data collected in the study, in order to generate an applicable risk prediction model for survival among older patients with advanced CKD. Such a model is promising, though will require further external validation in other older patient populations to ascertain its generalisability.

Applicability of CKD therapies to older patient populations

The past two decades have heralded a promising landscape of CKD therapies to slow CKD progression and to improve cardiovascular and mortality outcomes in CKD patients. These therapies include sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1RAs) and non-steroidal mineralocorticoid receptor antagonists

(nsMRAs). These agents have high efficacy and relatively short times to benefit, thus are appealing treatment classes for older patients. While the evidence for GLP-1RA and nsMRA agents in CKD patients is relatively recent,[34-36] the evidence for renal, cardiovascular and mortality benefits with SGLT2 inhibitors has been extensively established.[37-49] Despite this, real-world uptake of SGLT2 inhibitors in older patient groups are among the lowest of all patient groups.[50-53]

In response to this low uptake, Chapters 6 and 7 utilised trial data with the aim of offering detailed insights into the efficacy and safety of SGLT2 inhibitors in older and frail patient populations. A large pooled analysis of patient-level data from the CANVAS Program and CREDENCE trial of 14,543 participants with T2DM, high cardiovascular risk and varying degrees of kidney function is presented in Chapter 6. In this analysis, the SGLT2 inhibitor canagliflozin consistently reduced major adverse cardiovascular events (MACE), non-fatal cardiovascular outcomes and composite kidney events across age subgroups (<65 years, 65 to <75 years, and ≥75 years, *P* trend >0.10). While there was some suggestion of attenuation of effect for mortality-driven outcomes including cardiovascular death and all-cause mortality (*P* trend <0.10 for both), the post-hoc nature of this analysis with multiple comparisons means these findings should be interpreted as exploratory. In particular, an unusual pattern of effect was observed for all-cause mortality with increasing age categories having divergent hazard ratios, which suggests this is most likely a chance finding. Nonetheless, further studies assessing the efficacy of SGLT2 inhibitors specifically in older patients such as in the ongoing pragmatic intraclass GOLDEN-AGE trial will be of value (ClinicalTrials.gov Identifier: NCT04796428). The relative effects of canagliflozin on safety outcomes were consistent across age categories in the pooled analysis presented in Chapter

6 including in the oldest age group of ≥75 years, indicating no additional safety concerns in older adults. Given that this pooled cohort had over one-third of participants aged 65 to <74 years and close to 10% aged ≥75 years, the findings from this analysis offer strong support for the use of SGLT2 inhibitors to improve outcomes in older patient populations.

To offer further insights into SGLT2 inhibitor therapy relevant to older patient populations, Chapter 7 presented a systematic review and meta-analysis of SGLT2 inhibitors according to frailty status, analysing the efficacy and safety outcomes from 7 large cardiovascular- and kidney-outcome RCTs. A strength of this analysis is that it utilised data from all trials with available frailty subgroup analyses, constituting 42,443 participants. Most trials used a validated method of assessing frailty through the Rockwood cumulative deficit approach.[54, 55] This approach uses at least 30 items across a range of body systems, and these items must be associated with health and should not be a part of normal ageing (though the constructed index will generally increase with age). Although the exact items used in deriving this index may differ slightly, this approach yields a cumulative frailty index that can be compared across studies and populations. Notably, the prevalence of frailty in the SGLT2 inhibitor trials included in the meta-analysis in Chapter 7 was high with at least 50% of patients in each trial considered frail. This meta-analysis identified consistent benefits in cardiovascular and mortality outcomes with SGLT2 inhibitors across frail and not frail populations, without an increase in the risk of adverse events. As such, these findings suggest a strongly favourable benefit:risk ratio for SGLT2 inhibitors among frail patient populations. The prevalence of frailty is high among CKD patients and increases with CKD progression, with 48% of patients with advanced CKD considered frail,[56] hence there is high real-world relevance to these findings.

Despite the work in Chapters 6 and 7 providing detailed insights into the benefits of SGLT2 inhibitor therapy in older and frail patients, undoubtedly the greatest challenges lie in implementation. In an Australian study derived from primary care data with a mean age of 71.4 to 74.4 years across the study cohorts, close to 45% of patients with CKD met eligibility criteria for an SGLT2 inhibitor, though only 4.1% were receiving one.[57] Similarly, data from the United States and United Kingdom indicate that despite proven cardiorenal benefits and the larger absolute benefits of these agents in CKD patients, individuals with CKD are paradoxically less likely to be prescribed them.[58, 59] Strategies to translate the proven benefits of SGLT2 inhibitors, including in older and frail patient groups, are urgently needed to ensure that those patients who will derive benefit from this treatment are able to receive it. COORDINATE-Diabetes was a cluster randomised trial conducted in 43 cardiology clinics in the United States.[60] This trial demonstrated that, compared with usual care, a multicomponent intervention of identifying local barriers, clinician education and real-time feedback improved prescription of three guideline-based therapies (SGLT2 inhibitors, GLP-1RAs and statins) in patients with type 2 diabetes and atherosclerotic cardiovascular disease. This trial is an important and novel example of applying implementation science to improve patient outcomes, an approach that is worthy of consideration to increase the uptake of effective therapies in the growing older CKD population.

FUTURE DIRECTIONS

The findings of this thesis and the persisting evidence gaps discussed in this chapter provide ongoing opportunities to continue research beyond this thesis into older patients with CKD

and kidney failure. Chiefly, my post-doctoral work will involve ongoing leadership and oversight of the Elderly Advanced CKD Program as it finalises recruitment over the coming years and moves into the analysis phase. Each of the four study components are novel opportunities to generate practice-informing findings. Firstly, the OUTLOOK study will report on survival outcomes across treatment pathways for a large cohort of older patients with kidney failure and will derive a risk prediction model with high applicability to this patient population. Beyond this, however, the opportunities for secondary analysis of this high-quality prospective dataset are vast. For instance, there is an opportunity to apply this cohort to assess the external validity of other risk prediction models for mortality that were discussed in Chapter 5 (such as the MREK and KDpredict), to determine how well these models apply to an older advanced CKD cohort with a high proportion of patients opting for a CKM pathway. For the other components of the Elderly Advanced CKD Program, an interim analysis of the CONTEND study is planned this year. This qualitative work has utilised semi-structured interviews to explore older patient and carer experiences of treatment decision-making in kidney failure, the barriers/enables to decision-making, and experiences of end-of-life care planning. An interim analysis will identify core themes and may signify data saturation, as has been anecdotally indicated in the process of conducting these interviews. Depending on the proportion of dialysis versus CKM patients and the timing of interviews conducted within the '2 year from treatment decision' timeframe, the CONTEND study may also raise discussion regarding confirmation and survivor bias if there is a high proportion of participants already on dialysis. The opportunity to deliver findings on older patient and carer perspectives of shared decision-making in kidney failure from the CONTEND study is therefore an eagerly anticipated aspect of this study program that will require careful consideration and analysis. Finally, once completed, the Elderly Advanced CKD Program is

planned for data linkage to datasets including the National Death Index, ANZDATA, Admitted Patient Data Collection (APDC), and Medicare and Pharmaceutical Benefits Schedules (MBS, PBS), using relevant national and state-based data linkage entities. Having not used data linkage in this thesis, I look forward to extending my research methodologies to assess inpatient and outpatient healthcare usage, healthcare costs, dialysis characteristics and end-of-life care characteristics across treatment pathways, all of which are of high clinical relevance to the older kidney failure patient population as they make treatment decisions.

CONCLUSION

The implications of the growing global burden of CKD and kidney failure among older individuals are immense. The findings of this thesis indicate that high-quality and well-designed studies are feasible and essential to identifying and implementing evidence-based measures to slow CKD progression and improve cardiovascular and mortality outcomes in older patients, and to better understand clinical outcomes such that older patients, carers and clinicians are well-informed as they make life-impacting treatment decisions about kidney failure care. Most notably, this thesis has utilised novel study designs, multicentre enrolment and national collaboration to lead a large prospective study program. The work presented, identification of ongoing evidence gaps and future directions of this work are important steps towards improving the care of older patients with CKD and kidney failure.

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APPENDIX A

Publications arising from this thesis

BMJ Open

Treatment decision-making and care among older adults with kidney failure: protocol for a multicentre, prospective observational cohort study with nested substudies and linked qualitative research (the Elderly Advanced CKD Programme)

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ABSTRACT

Introduction Shared treatment decision-making and planning of care are fundamental in advanced chronic kidney disease (CKD) management. There are limited data on several key outcomes for the elderly population including survival, quality of life, symptom burden, changes in physical functioning and experienced burden of healthcare. Patients, caregivers and clinicians consequently face significant uncertainty when making life-impacting treatment decisions. The Elderly Advanced CKD Programme includes quantitative and qualitative studies to better address challenges in treatment decision-making and planning of care among this increasingly prevalent elderly cohort.

Methods and analysis The primary component is OUTcomes of Older patients with Kidney failure (OUTLOOK), a multicentre prospective observational cohort study that will enrol 800 patients ≥75 years with kidney failure (estimated glomerular filtration rate ≤15 mL/min/1.73 m^2) across a minimum of six sites in Australia. Patients entered are in the decision-making phase or have recently made a decision on preferred treatment (dialysis, conservative kidney management or undecided). Patients will be prospectively followed until death or a maximum of 4 years, with the primary outcome being survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry and end-of-life care characteristics. Data will be used to formulate a risk prediction tool applicable for use in the decision-making phase. The nested substudies Treatment modalities for the InfirM ElderLY with end stage kidney disease (TIMELY) and Caregivers of The InfirM ElderLY with end stage kidney disease (Co-TIMELY) will longitudinally assess quality of life, symptom burden and caregiver burden among 150 patients and 100 caregivers, respectively. CONsumer views of Treatment options for Elderly patieNts with kiDney failure (CONTEND) is an additional qualitative study that will enrol a minimum of 20 patients and 20 caregivers to explore experiences of treatment decision-making and care.

Ethics and dissemination Ethics approval was obtained through Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). OUTLOOK is approved to have waiver of individual patient consent. TIMELY, Co-TIMELY and CONTEND participants will provide written informed consent. Final results will be disseminated through peer-reviewed journals and presented at scientific meetings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective study design with multicentre enrolment, broad representation and ease of data collection.
⇒ Clinical outcome data collection to allow formulation of a risk prediction tool for use in the treatment decision-making phase.
⇒ Nested substudies using a combination of quantitative and qualitative methodologies to provide wide-ranging assessment of important clinical outcomes for older patients with kidney failure, including survival, quality of life, symptom burden, receipt of dialysis, receipt of conservative kidney management, caregiver experiences and end-of-life care.
⇒ The study programme is conducted across multiple sites in Australia and extrapolation of findings to other healthcare settings may not be applicable.

INTRODUCTION

Background

Chronic kidney disease (CKD) has risen from 17th to 12th leading cause of death globally over the last 25 years. Increasing numbers of individuals are progressing to the most advanced form of the disease, kidney failure (defined as an estimated glomerular filtration rate (eGFR) 15 mL/min/1.73 m^2 or lower).[1] For the increasing proportion of these patients with advanced age and multimorbidity, complex decisions need to be made about treatment with kidney replacement therapy (KRT, with dialysis or kidney transplantation) or conservative kidney management (CKM). CKM involves a range of interventions to manage symptoms, improve quality of life, delay progression and manage complications, without the use of KRT.

In Australia, the prevalent dialysis population increased from 337 to 549 per million population between 2000 and 2019, with over half of prevalent patients aged ≥65 years and 26% aged ≥75 years.[2] While dialysis registries in many countries measure entry onto dialysis well, it is more challenging to quantify and understand the characteristics and outcomes of older patients with kidney failure who do not enter dialysis programmes. A retrospective data linkage analysis combined deaths ascribed to kidney failure from the Australian National Death Index with the Australia and New Zealand Dialysis and Transplant Registry and identified 21 370 patients with death due to kidney failure over a 4-year period. Roughly half of the patients studied received dialysis (n=10 949) and a similar proportion died without ever receiving dialysis (n=10 421). The majority of the patients who did not receive dialysis were aged ≥75 years,[3] the age group which also has the highest rate of incident dialysis in Australia and other developed countries.

For older patients with advanced CKD, the processes of decision-making between treatment pathways differ from that of younger patients, where there are clear differences in survival between treatment options. The greatest uncertainty occurs for patients aged 75 years or older, where few patients are medically suitable for transplantation, and there is limited data to inform decision-making, especially around the relative burden of dialysis and CKM and the outcomes they deliver for an older patient group. In turn, there are few tools to assist clinicians and patients in making decisions between these treatment pathways.[4–9] Best practice approaches to decision-making should be timely, well-informed and individualised.[10] Timely decisions are essential, as patients who commence dialysis in an unplanned manner have increased mortality,[11 12] reduced quality of life[13] and significantly higher healthcare costs.[14] Ideally, an understanding of the various health outcomes important to older patients, including survival, quality of life, symptom burden and experienced burden of healthcare should be at the centre of discussions.[15–17] Furthermore, patients express a desire for frank, detailed prognostic information[18–20] but, in practice, there are little data to inform such prognostication. Real-world decision-making is thus challenging and highly variable.

Current knowledge of outcomes

Prospective clinical data collection is difficult in older patients, most notably seen in their under-representation in randomised clinical trials.[21 22] This reflects their high burden of comorbidities, frailty and cognitive impairment, and high experienced burden of treatment.[23] Well-designed observational studies can achieve high inclusivity, external validity and feasibility, and hold significant applicability for evaluating outcomes among older advanced patients with CKD. A scoping review of published observational literature reporting outcomes relevant to shared decision-making for older patients with kidney failure identified 248 publications, the majority from high-income English-speaking countries (USA, UK, Canada and Australia) and published in the last 10 years.[6] However, 77% of studies exclusively pertained to dialysis patients,[6] similar to that seen in reported meta-analyses[24 25] and highlights the limited published literature on CKM.[9]

A meta-analysis of patient survival among elderly patients with kidney failure from studies between 1976 and 2014 reported similar 1-year survival rates between dialysis and CKM (73.0%–78.4% and 70.6%, respectively).[24] However, survival estimates for CKM patients were derived from only 12 of the total 89 studies and accounted for much fewer patients (724 vs 294196 for CKM and dialysis, respectively). There was also considerable residual heterogeneity for survival estimates within each treatment group, which may reflect changes in patterns of referral, acceptance onto dialysis programmes and components of CKM provided by centres over the long period of the review. Other recent observational studies have been inconsistent, with some suggesting a survival advantage with dialysis compared with CKM,[26 27] and others suggesting limited or no survival advantage from dialysis in those patients with severe comorbidity, poor performance status or extreme age.[28–30]

Many survival comparisons are also confounded by methodological issues[24 31] such as; lead-time bias, immortal time bias and indication bias. Lead-time bias arises from variability in defining a distinct starting point for CKM. This may result in a perceived survival advantage with CKM if survival time is calculated from an earlier starting point not equivalent to when dialysis would have been initiated. Conversely, immortal time bias occurs mainly in analysis of retrospective cohorts, when an index starting point is defined and patients go on to start dialysis much later (or not at all), giving rise to a perceived survival advantage ascribed to dialysis treatment. Indication bias is inherent to analysing survival in elderly kidney failure cohorts where there is expected referral of healthier patients for dialysis, and referral of older and frailer patients for CKM. Incorporating baseline covariates such as frailty and functional status into adjusted survival analyses aims to account for this, however, such

data are frequently not collected or available. These biases are magnified in retrospective analyses conducted after treatment decisions have been made, and notably 71 of the 89 included studies in Foote *et al*'s systematic review were retrospective.[24]

As identified in qualitative and discrete choice studies, a range of other outcomes are important to older patients, caregivers and clinicians in decision-making, including quality of life, symptom burden, functional independence, experienced burden of healthcare and caregiver burden.[32–35] Existing literature suggests that the health-related quality of life of older patients on dialysis, compared with CKM, is broadly similar,[36] that some older patients with advanced CKD would 'trade-off' survival time in preference for maintaining functional independence,[32–34] and that dialysis initiation is associated with high rates of deterioration of physical functioning among patients and high caregiver burden.[37–39] Additionally, Canadian and UK studies suggest older dialysis patients spend significantly more time in hospital than CKM patients.[26 40] However, there are notable limitations to this data, as few studies have broad and systematic data collection, resulting in high risk of selection bias and limited adjustment for other variables.[36] The majority of published studies are cross-sectional, and longitudinal data across either treatment pathway are lacking. Furthermore, patient outcomes, burden of healthcare and caregiver experiences are markedly dependent on healthcare structures. There is a need to assess these outcomes widely, including in the Australian context.

Programme aims

In response to these limitations in data, we describe a programme of work, the Elderly Advanced CKD Programme, designed to explore decision-making and planning of care for older patients (defined in this programme as age ≥75 years) with kidney failure. This includes addressing deficiencies in outcome data, broadening understanding of outcomes that are a priority to patients and caregivers, and applying this evidence to better support real-world decision-making processes. The aims of this study programme are as follows:

1. To quantify survival in a cohort of older patients with kidney failure followed from eGFR ≤15 mL/min/1.73 m^2.
2. To formulate a risk prediction tool for mortality applicable to patients at the time of treatment decision-making.
3. To quantify other key patient outcomes among older patients with kidney failure in a prospective and longitudinal fashion, including quality of life, symptom burden, burden of planned and unplanned hospitalisations, and caregiver burden.
4. To qualitatively explore patient and caregiver experiences of shared decision-making processes, planning of care, CKM and, ultimately, end-of-life care.

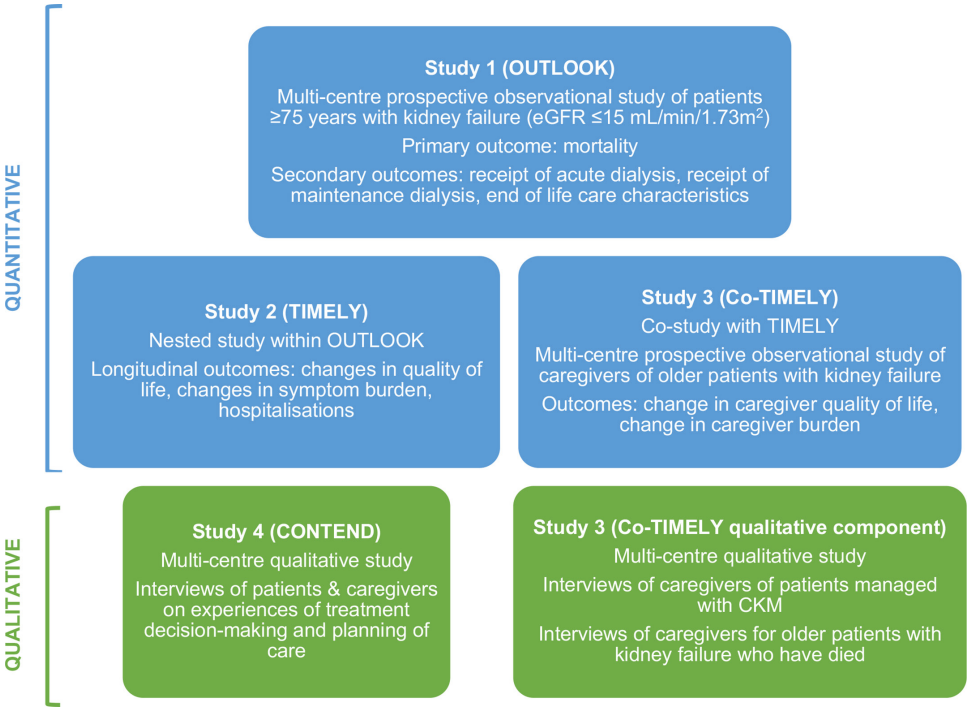

Figure 1 Components of the elderly advanced CKD Programme. CKM, conservative kidney management; CONTEND, CONsumer views of Treatment options for Elderly patieNts with kiDney failure; Co-TIMELY, Caregivers of The InfirM ElderLY; EGFR, estimated glomerular filtration rate; OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease.

Table 1 Summary of the elderly advanced CKD Programme components

	OUTLOOK	TIMELY	Co-TIMELY	Co-TIMELY (qualitative component)	CONTEND
Study type	Prospective observational cohort study	Prospective observational cohort study	Prospective observational cohort study	Qualitative study	Qualitative study
Target population for recruitment	Patients aged ≥75 years with kidney failure (eGFR ≤15 mL/min/1.73 m^2)	Patients aged ≥75 years with kidney failure (eGFR ≤15 mL/min/1.73 m^2)	Caregivers of patients enrolled in TIMELY	Caregivers of patients enrolled in TIMELY who are receiving CKM, caregivers of patients enrolled in TIMELY whose care-recipient has died	Patients ≥70 years with kidney failure and their caregivers
Targeted sample size	800	150	100	20 caregivers of CKM patients, 10 caregivers whose care-recipient has died	20 patients, 20 caregivers
Primary outcome	Mortality	EQ-5D	EQ-5D	Caregiver experiences of CKM, caregiver experiences of end-of-life care for their care-recipient	Experiences of shared decision-making for kidney failure treatment
Secondary outcomes	Receipt of acute dialysis, receipt of long-term maintenance dialysis, end-of-life care characteristics	Satisfaction with life, symptom burden, living situation, hospitalisations	Satisfaction with life, caregiver responsibilities, caregiver burden	–	–
Frequency of follow-up	6 months	12 months	12 months	–	–
Study period	4 years	4 years	4 years	Single encounter interviews	Single encounter interviews

CKD, chronic kidney disease; CKM, conservative kidney management; CONTEND, CONsumer views of Treatment options for Elderly patieNts with kiDney failure; Co-TIMELY, Caregivers of TIMELY; eGFR, estimated glomerular filtration rate; EQ-5D, Euroqol-5 Dimension; OUTLOOK, OUTcomes of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease.

METHODS AND ANALYSIS

Program design

The programme consists of four components (figure 1 and table 1); a prospective observational cohort study with three components (including a small qualitative component), and a purely qualitative study examining patient and caregiver experiences:

1. OUTcomes Of Older patients with Kidney failure (OUTLOOK).
2. Treatment modalities for the InfirM ElderLY with end stage kidney disease (TIMELY).
3. Caregivers of TIMELY with end-stage kidney disease (Co-TIMELY), including a small qualitative component.
4. CONsumer views of Treatment options for Elderly patieNts with kiDney failure (CONTEND).

Study design

OUTLOOK is a multicentre prospective observational cohort study that aims to enrol 800 older patients with kidney failure (age ≥75 years and eGFR ≤15 mL/min/1.73 m^2) across a minimum of 6 sites in Australia. The study is ethically approved with a waiver of the need for individual patient consent. TIMELY is a nested cohort study that aims to enrol a subset of 150 patients within OUTLOOK, which requires individual patient consent for additional data collection relating to quality of life, symptom burden and functional status over time. The Co-TIMELY study aims to enrol 100 caregivers of older patients to prospectively examine caregiver responsibilities, quality of life and caregiver burden.

Study population and recruitment

Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY are shown in table 2. Patients are enrolled into OUTLOOK by study investigators if they meet the inclusion criteria, which are broad to minimise selection bias, maximise recruitment and increase external validity of the study. An eGFR ≤15 mL/min/1.73 m^2, as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula, was chosen to define kidney failure, as it reflects a point at which patients and clinicians would be expected to be making decisions regarding planning for dialysis or CKM.[4] This uniform definition provides an

Table 2 Inclusion and exclusion criteria for OUTLOOK, TIMELY and Co-TIMELY

Inclusion criteria	Exclusion criteria
Patient age ≥75 years	Patient is receiving dialysis at the time of initial screening
Patient eGFR ≤15 mL/min/1.73 m^2	Patient not expected to survive 3 months beyond enrolment
Additional caregiver criteria for Co-TIMELY: - Nominated by the patient as a primary caregiver	Additional exclusion criteria for patients in TIMELY and for caregivers in Co-TIMELY: ► Extreme infirmity (as assessed by study team). ► Significant cognitive impairment (inability to complete questionnaires as assessed by the treating nephrologist or study team, with a guiding lower threshold of ≤18 on Mini-Mental State Examination). ► English language skills insufficient to participate in questionnaires.

Co-TIMELY, Caregivers of TIMELY; eGFR, estimated glomerular filtration rate; OUTLOOK, OUTcomes Of Older patients with Kidney failure; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease.

index date from which survival time will be determined for all participants, regardless of treatment pathway, aiming to mitigate lead-time bias and immortal time bias.

All patients enrolled into OUTLOOK will be screened for potential participation in TIMELY, with the only additional exclusion criteria for patient participation being extreme infirmity, significant cognitive impairment or insufficient English language skills (see table 2), all of which would preclude participation in patient-reported outcome questionnaires. Potential TIMELY participants will be approached, and if willing to participate, will be asked to provide written informed consent. For the Co-TIMELY study, patients who consent to participate in TIMELY will be asked to nominate a primary caregiver. This caregiver will be screened against inclusion/exclusion criteria (see table 2) and, if eligible, will be approached for participation with a view to provide written informed consent.

Study period

Patients enrolled into OUTLOOK have baseline data collection and will be prospectively followed until death or for a maximum of 4 years, with follow-up occurring at 6-monthly intervals. Similarly, participants enrolled into TIMELY will be followed until death or for a maximum of 4 years, with follow-up questionnaires completed by participants at 12-monthly intervals. Caregivers enrolled into Co-TIMELY will be followed prospectively until either caregiver death, until 6 months after death of the corresponding care-recipient, or for a maximum of 4 years.

Measurement of baseline characteristics

Baseline data collection schedules for OUTLOOK, TIMELY and Co-TIMELY are shown in table 3. OUTLOOK will only collect data from patient medical records and from healthcare providers involved in patient care (including from public/private hospitals, general practitioners, specialist records and pathology providers). At enrolment, site investigators will review records and discuss with the treating team to determine the patient's planned treatment pathway (dialysis, CKM or undecided) and the approximate timing of this decision.

Other baseline data collection incorporates wide-ranging measurement of patient characteristics that, based on prior literature, may influence the study's primary outcome of survival. These include patient demographics, medical history, medications, baseline pathology measurements, measures of functional status and treatment plans. Baseline medical history will be used to derive a modified Charlson Comorbidity Score, a validated predictor of mortality in kidney failure patients, with a theoretical maximum score of 37.[41 42] Baseline pathology measurements include serum creatinine, eGFR, albumin, haemoglobin, parathyroid hormone and proteinuria (albumin:creatinine ratio or protein:creatinine ratio), all of which are markers of kidney disease progression.[17] Measures of functional status are the Clinical Frailty Scale,[43] Karnofsky performance score[44] and mobility status. The Clinical Frailty Scale is a 9-point scale that was chosen for its feasibility and its prior use in advanced CKD research showing an association with mortality.[45] The Karnofsky functional performance score assesses functional status on a scale of 0–100, and it is the most widely used measure of functional impairment in chronic disease states, including kidney failure.[46] Additional treatment-related questions at baseline address the use of advance care planning, appointment of an enduring guardian and the 'surprise question', which asks the treating nephrologist if they would be surprised if the patient died in the next 12 months and has demonstrated predictive ability for mortality in advanced CKD.[47]

For TIMELY participants, two additional cognitive and nutritional baseline components will be collected during face-to-face visits. The Mini-Mental State Examination[48] is a validated tool for assessment of cognition in the general population,[49] and cognitive impairment (score of <24 out of a maximum score of 30) is associated with adverse health outcomes in advanced CKD.[46] The subjective global assessment tool[50] assesses gastrointestinal symptoms, weight change, functional capacity and visual evaluation of subcutaneous tissue and muscle mass. It is the most commonly used nutritional assessment tool in Australian nephrology units, with higher rating scores associated with increased mortality in dialysis patients.[51]

For caregivers participating in Co-TIMELY, baseline data include caregiver demographics, caregiver characteristics (including relationship to the care-recipient and duration of caregiving) and caregiver responsibilities.

Table 3 Study schedule for data collection

	Timeline based on individual date of enrolment								
Data collection	**Baseline**	**6 months**	**1 year**	**18 months**	**2 years**	**30 months**	**3 years**	**42 months**	**4 years**
Demographics (age, gender, ethnicity, primary language, marital status, residential status)	O								
Medical history (Charlson Comorbidity Score, medications)	O								
Functional status (Clinical Frailty Scale, Karnofsky Performance Score, mobility)	O								
Treatment pathway decision (dialysis, CKM, undecided), advance care planning status, surprise question	O								
Biochemistry	O	O	O	O	O	O	O	O	O
Survival status (including date, location and cause of death)		O	O	O	O	O	O	O	O
Receipt of dialysis		O	O	O	O	O	O	O	O
Cognitive assessment (MMSE)	T								
Nutritional status (SGA)	T								
Patient questionnaires: ► Quality of life (EQ-5D, SWLS) ► Symptom burden (iPOS-Renal)	T		T		T		T		T
Patient-reported changes in living situation, mobility and functional status	T		T		T		T		T
Patient-reported hospitalisations	T		T		T		T		T
Caregiver demographics (age, gender, ethnicity, primary language, education level)	C								
Caregiver characteristics (relationship to care recipient, duration of caregiving)	C								
Caregiver responsibilities	C		C		C		C		C
Caregiver questionnaires: ► Quality of life (EQ-5D) ► Caregiver burden (Zarit Burden Interview)	C		C		C		C		C
Data linkage (National Death Index, ANZDATA, Admitted Patient Data Collection, MBS, PBS)									O/T

*O' denotes data collection for both OUTLOOK and TIMELY, 'T' denotes data collection for TIMELY only, and 'C' denotes data collection for Co-TIMELY only.
ANZDATA, Australian and New Zealand Dialysis and Transplant Registry; CKM, conservative kidney management; Co-TIMELY, Caregivers of TIMELY; EQ-5D, Euroqol-5 Dimension; iPOS, Integrated Palliative Care Outcome Scale; MBS, Medicare Benefits Schedule; MMSE, Mini-Mental State Examination; OUTLOOK, OUTcomes Of Older patients with Kidney failure; PBS, Pharmaceutical Benefits Scheme; SGA, subjective global assessment; SWLS, Satisfaction with Life Scale; TIMELY, Treatment modalities for the InfirM ElderLY with end stage kidney disease.

Primary and secondary outcomes

The primary outcome of OUTLOOK is survival. Secondary outcomes are receipt of short-term acute dialysis, receipt of long-term maintenance dialysis, changes in biochemistry (including serum creatinine and eGFR) and characteristics of end-of-life care (including date, location and primary cause of death).

In the nested substudy TIMELY, additional outcomes are changes in health-related quality of life, changes in symptom burden and patient-reported hospitalisations in the preceding 12 months. Health-related quality of life is assessed at baseline and in annual follow-up by the EuroQol-5 Dimension 3-Level (EQ-5D-3L) questionnaire and the Satisfaction with Life Scale (SWLS). The EQ-5D-3L is a generic quality of life measure assessing five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[52] These responses can be compared against an Australian EQ-5D value set[53] to derive a single utility score ranging from less than 0 to 1 (with 0 representing death, negative values representing utilities worse than death and 1 representing perfect health). The SWLS is a five-item scale with questions relating to ideal life, conditions of life and satisfaction with present and past life.[54] It has been used in various disease states, including advanced CKD.[36] Symptom burden is assessed with the Integrated Palliative Care Outcome Scale-Renal, an inventory modified for use in advanced CKD populations.[36 55] It asks the responder about the impact of 15 kidney disease-specific physical symptoms and further emotional symptoms (each rated on a 5-point scale from 0, no impact, to 4, overwhelming impact) in the preceding week.

In the caregiver study Co-TIMELY, primary outcomes are changes in caregiver quality of life and changes in caregiver burden. Varied tools have been used to assess caregiver quality of life in prior CKD studies and the optimal tool is unclear.[56] Baseline and annual caregiver quality of life is assessed in Co-TIMELY with the EQ-5D and SWLS as these are generic measures and they align with the TIMELY study. Caregiver burden is assessed at baseline and annual follow-up using the Zarit Burden Interview, a 12-question tool relating to feelings of personal strain from the caregiving role, with 5 responses for each question ranging from 0 (never) to 4 (almost always).[57] This tool is the most commonly used measure of subjective caregiver burden in advanced CKD studies.[56]

Following study completion, study datasets will be linked to the National Death Index, Australian and New Zealand Dialysis and Transplant Registry, Admitted Patient Data Collection and Medicare and Pharmaceutical Benefits Schedule, using relevant national and state-based data linkage entities. Data linkage will be used to assess inpatient and non-inpatient healthcare usage and costs, dialysis characteristics and end-of-life care characteristics across treatment pathways.

Data analysis plan

From OUTLOOK, differences in survival between treatment groups will be analysed using Kaplan-Meier survival analysis and log-rank tests. A multivariable Cox proportional hazards model will be constructed using prespecified covariates based on clinical plausibility, including age, gender, comorbidity score, frailty score and functional performance score, with the aim of selecting a parsimonious model. Primary analyses will be a complete case analyses, however, a multiple imputation approach for missing values of predictors will be assessed according to the proportion and patterns of missingness. Model performance will be assessed using standard metrics including discrimination (C-statistic) and calibration (Hosmer-Lemeshow statistic), and internal validation will be performed with bootstrap resampling.

Bayesian networks allow a more flexible modelling approach, are more reliable when there are high correlations between predictor variables and allow a more efficient method to handle missing data, so an additional Bayesian network will be formulated using data from OUTLOOK. This model will consist of a target variable (mortality), multiple random variables (nodes), probabilistic dependencies between variables and conditional probability tables that describe the direction and degree of influence between variables. The Bayesian model's performance will be assessed using the area under the curve receiver operating characteristic, which is analogous to the C-statistic derived from the multivariate Cox proportional hazards model. Prediction models will be reported according to Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[58]

Further data from TIMELY and Co-TIMELY including longitudinal changes in patient and caregiver quality of life, symptom burden, caregiver burden and additional data from data linkage for end-of-life care characteristics, healthcare usage and costs will be analysed using a hierarchical modelling approach, which accounts for within-patient and between-patient variability for continuous outcomes, and χ^2 tests and logistic regression for categorical outcomes.

Sample size calculation

To guide sample size calculations in OUTLOOK, we estimated 40%–50% 2-year mortality in patients who go on to dialysis and 60% for CKM patients.[11] A minimum of 10 events per candidate variable is used as a benchmark for sample size calculations in model development studies. It is anticipated that 6–10 variables will be included in our final models based on prior advanced CKD risk prediction models.[59–62] However, larger sample sizes mitigate the risk of model overfitting, improve precision and performance of models and enhance clinical utility.[63] Accordingly, a sample size of 800 patients in OUTLOOK is targeted, with a target of 150 patients participating in TIMELY and 100 caregivers participating in Co-TIMELY.

Qualitative methodology

Caregivers in Co-TIMELY whose care-recipient is specifically receiving CKM will be asked to participate in a

qualitative component. Minimum sample size is 20 caregivers and maximum sample size will be determined from data saturation, whereby no new themes are emerging from participant interviews. Single-encounter interviews will be conducted face-to-face or via teleconferencing for 30–60 min. These will be semistructured using an interview guide, with participants asked to discuss their experiences of the planning of care, daily roles as a caregiver of a patient receiving CKM, and the impact being a caregiver has had on their life. Caregivers of patients who die during the study, who indicated on their consent that they are willing participate in a postdeath interview, will be approached no sooner than 3 months and no later than 6 months after their care-recipient's death to participate in a second semistructured interview exploring end-of-life care. Target sample size for this end-of-life care component is 10 caregivers. Questions will be based on the Quality of Dying and Death tool.[64 65] Example interview questions include whether their care recipient was comfortable, how often end-of-life symptoms were controlled, whether they were at peace with dying, where they died, and what support was offered to the caregiver.

CONTEND is the final qualitative component of the programme and involves single-encounter interviews with patients ≥70 years with kidney failure (eGFR ≤15 mL/min/1.73 m^2) and their caregivers. Eligible patients must have had a discussion about treatment pathways with their nephrologist and they are about to decide or have made a treatment decision within the last 2 years (ie, patients can be on dialysis or a CKM pathway initiated within 2 years). Patients and caregivers will be purposefully recruited during routine outpatient visits. The focus of CONTEND is on shared decision-making, with a broad interview guide including questions on what information was provided to facilitate decision-making, experiences of the decision-making process, barriers/enablers of decision-making and experiences of end-of-life care planning. This component aims for a minimum of 20 patients and 20 caregivers and maximum sample size determined from data saturation.

Transcripts from the Co-TIMELY qualitative component and from CONTEND will be thematically analysed using grounded theory, where data will be coded using NVivo software and abstract categories are constructed inductively to identify themes and relationships between themes. Data will be reported according to the consolidated criteria for reporting qualitative research.[66]

Patient and public involvement

The design of this research programme is shaped by prior literature on older patient priorities when making advanced CKD treatment decisions.[4] The programme began as pilot studies in 2017, with initial enrolment at three hospital sites. Informed by feedback from patients and caregivers, small changes to study design have been made to improve feasibility. The study design and participant information sheets for these studies will continue to receive regular feedback from the George Institute for Global Health Consumer Engagement Panel, consisting of patients with kidney disease and their caregivers.

ETHICS AND DISSEMINATION

Ethics approval for this study programme has been obtained through the Sydney Local Health District Human Research Ethics Committee (2019/ETH07718, 2020/ETH02226, 2021/ETH01020, 2019/ETH07783). OUTLOOK is approved as a waiver of individual patient consent study in accordance with the 2018 National Health and Medical Research Council National Statement on Ethical Conduct in Human Research.[67] All other study components in this programme involve direct patient contact and data collection beyond routine care, and accordingly involve written and informed consent. All study data are stored through a dedicated electronic data capture tool only accessible to site and central investigators. All data are managed confidentially and anonymously, and will be stored for a minimum of 15 years in accordance with national guidelines.[67] The results of this research are intended to be disseminated through peer-reviewed journals and presented at scientific meetings.

DISCUSSION

While there will always be some degree of prognostic uncertainty in patient care,[68] the Elderly Advanced CKD Programme aims to provide clinicians, patients and caregivers with accurate data and tools to reduce the extent of this uncertainty in the planning and provision of care for older patients with kidney failure. To our knowledge, this is the first study to prospectively follow an older kidney failure cohort to produce a risk prediction model for survival for use in the treatment decision-making phase. The nested work with patients and caregivers will provide detailed and longitudinal insights on important patient-reported outcomes such as quality of life and experienced burden of healthcare.

In the context of the exponential increase in elderly patients progressing to kidney failure in developed countries, this study programme holds high clinical relevance. The programme is currently enrolling across six sites in Australia, with the intention of further expansion to achieve national representation and enrolment targets for all studies by 2026. Baseline data from the 316 patients currently enrolled in OUTLOOK has found the following characteristics: mean age mean 83.5 years (range 75–95 years), predominantly community-dwelling (88%), and high prevalence of frailty (58%) and functional impairment (46% requiring a mobility aid). This is the population group in whom there is the greatest equipoise regarding whether dialysis compared with CKM offers greater benefits. This work will thus generate valuable outcome data and ensure that the developed risk prediction tool will have direct clinical application. However, we acknowledge that such quantitative data alone will not overcome all challenges in complex decision-making.

Accordingly, this research programme incorporates qualitative work, to broaden the focus and encompass perspectives of patients and their families on treatment decision-making processes, experiences of CKM and end-of-life care.

Large, multicentre cohorts prospectively investigating outcomes in older patients with kidney failure are few. To date, there are two comparative studies. The European QUALity study (EQUAL) is an ongoing study recruiting patients ≥65 years with eGFR ≤20 mL/min/1.73 m^2 in 5 European countries, with prospective follow-up for 4 years.[69] EQUAL aims to evaluate optimal timing of dialysis initiation among older patients, with additional insights regarding survival and longitudinal changes in patient-reported outcomes. Over 1500 of the targeted 3500 participants have been enrolled. The focus is on dialysis planning and the investigators have stated that patients on a CKM pathway will not be captured.[70] The Canadian Frailty Observation and Interventions Trial (CanFIT) is a multicentre observational cohort study which has enrolled 603 adult patients between 2012 and 2018 with eGFR <30 mL/min who have had baseline frailty assessments and are being prospectively followed. CanFIT aims to examine the longitudinal trajectory of frailty and its associations with morbidity, mortality and patient-reported outcomes, but is capturing patients with less advanced kidney disease compared with those in the Australian Elderly Advanced CKD Programme. Nonetheless, both EQUAL and CanFIT complement the large-scale, robust and prospective aims of the OUTLOOK study. The collective aims of these studies, particularly those of the Elderly Advanced CKD Programme, are to better inform discussions and decision-making processes for older patients with advanced kidney disease.

This work has some limitations. Given the observational methodology, there is the potential for confounding from measured and unmeasured variables in the quantitative components of this programme. For example, socioeconomic status has not been objectively measured and may be a confounder in survival and quality of life analyses. While the study design aims to minimise the impact of lead-time, immortal time and indication bias, complete elimination of these biases is not possible. Furthermore, while the study programme aims to achieve multicentre national representation, application of findings beyond Australia will have limitations.

Decision-making between treatment pathways is highly complex for older patients with kidney failure, their caregivers and clinicians. Challenges include accurate outcome predictions, communicating meaningful prognostic information, communicating associated uncertainty, and using this information to undertake systematic processes of shared decision-making and planning of care. The Elderly Advanced CKD Programme is a large-scale multicentre research programme designed to address modifiable factors relating to each of these challenges by producing prospective, longitudinal and robust data on survival, patient-reported outcomes and caregiver-reported outcomes, collected efficiently at a national level; to derive the necessary tools for patients, caregivers and clinicians; and, to understand patient and caregiver preferences for care. Such work is novel, practice-informing and much needed, as we face a growing population of elderly, frail and comorbid kidney failure patients.

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Contributors CF, MG, AS, NAG and YM conceived the Elderly Advanced CKD Programme and formulated protocols for study components. AS drafted the protocol manuscript, and NAG, AM, CKL, KY, YM, JR, GLDT, CG, IYA, SR, VN, CF and MG contributed to critical review and revisions of the manuscript.

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Patient-Reported Outcomes

Estimating a Minimal Important Difference for the EQ-5D-5L Utility Index in Dialysis Patients

Amanda N. Siriwardana, MBBS, Anna T. Hoffman, Rachael L. Morton, PhD, Brendan Smyth, PhD, Mark A. Brown, MBBS, MD

ABSTRACT

Objectives: The EQ-5D-5L is a commonly used health-related quality of life instrument for evaluating interventions in patients receiving dialysis; however, the minimal important difference (MID) that constitutes a meaningful treatment effect for this population has not been established. This study aims to estimate the MID for the EQ-5D-5L utility index in dialysis patients.

Methods: 6-monthly EQ-5D-5L measurements were collected from adult dialysis patients between April 2017 and November 2020 at a renal network in Sydney, Australia. EQ-VAS and Integrated Palliative care Outcome Scale Renal symptom burden scores were collected simultaneously and used as anchors. MID estimates for the EQ-5D-5L utility index were derived using anchor-based and distribution-based methods.

Results: A total of 352 patients with ≥1 EQ-5D-5L observation were included, constituting 1127 observations. Mean EQ-5D-5L utility index at baseline was 0.719 (SD ± 0.267), and mean EQ-5D-5L utility decreased over time by −0.017 per year (95% CI −0.029 to −0.006, P = .004). Using cross-sectional anchor-based methods, MID estimates ranged from 0.073 to 0.107. Using longitudinal anchor-based methods, MID for improvement and deterioration ranged from 0.046 to 0.079 and −0.111 to −0.048, respectively. Using receiver operating characteristic curves, MID for improvement and deterioration ranged from 0.037 to 0.122 and −0.074 to −0.063, respectively. MID estimates from distribution-based methods were consistent with anchor-based estimates.

Conclusions: Anchor-based and distribution-based approaches provided EQ-5D-5L utility index MID estimates ranging from 0.034 to 0.134. These estimates can inform the target difference or "effect size" for clinical trial design among dialysis populations.

Keywords: EQ-5D-5L, health-related quality of life, minimal important difference, patient outcome assessment, renal dialysis.

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Introduction

Patient-reported outcomes measures such as health-related quality of life (HRQOL) are of high clinical and economic importance in assessing the impact of medical interventions, with 27% of clinical trials registered with ClinicalTrials.gov (2007-2013) and 45% of trials registered with the Australian New Zealand Clinical Trials Registry (2005-2017) utilizing these measures as primary or secondary endpoints.[1,2] Furthermore, patient-reported outcomes are now recommended for consideration of drug approval by the US Food and Drug Administration.[3] Although incorporation of these outcomes into end-stage kidney disease (ESKD) trials has lagged,[4,5] there is now an increasing emphasis on evaluating outcomes in ESKD trials that are of importance to patients.[6,7]

HRQOL is a multidimensional concept of a patient's perceived health state.[8] Measurement can be through generic instruments, such as the EQ-5D,[9] or disease-specific instruments, such as the Kidney Disease Quality of Life.[10] Generic HRQOL measures are advantageous in allowing clinical decision makers, policy makers, and funders to make comparisons between treatments and across disease states.[11] Generic utility-based HRQOL measures consist of a set of items covering different HRQOL dimensions, and each dimension has multiple response categories. Together, the responses describe a multidimensional health state, to which value (or utility) can be attached using data obtained from general population surveys, indicating relative preferences for different health states. Utilities are typically on a scale of 0 to 1, with 0 representing a health state equivalent to death and 1 representing full health. Some measures allow negative utilities (values <0) to be derived, representing health states perceived as worse than death.[8] Utilities can be combined with survival estimates to calculate quality-adjusted life-years, which capture the impact of an intervention on both quantity and quality of life and are the most widely used outcome measure in cost-effectiveness analysis.

Critical to using generic utility-based HRQOL measures in clinical trials is not just determining whether an intervention results in a statistically significant change but also whether that change is clinically meaningful. The minimal important difference

(MID) represents the smallest change that is perceived as beneficial and would, in the absence of troublesome side effects or excessive cost, warrant a change in a patient's management.[12] MID estimates for a given outcome in a specific population are determined from prior literature and several approaches have been developed, broadly divided into anchor-based and distribution-based methods.[13-15] Anchor-based methods examine the relationship between the outcome measure of interest with respect to another measure of clinical change (the "anchor"). Anchors may be objective clinical outcomes (such as laboratory values, disease stage, or a physical performance score), or another patient-reported outcome measure (such as a patient's global health rating). Anchor-based methods can be used with either cross-sectional or longitudinal data of the anchor and of the outcome measure of interest. In contrast, distribution-based methods use statistical characteristics, particularly between-patient variability, of the obtained sample. Examples include calculation of a one-half SD estimate, Cohen's effect size or a standard error of measurement. There are relative merits and limitations between anchor-based and distribution-based methods in determining the MID for HRQOL measures, and hence an integrated approach combining both is recommended.[13]

The EQ-5D is among the most widely used generic utility-based HRQOL measure. EQ-5D utility MID estimates have been established for oncology, myeloma, chronic obstructive pulmonary disease, autoimmune diseases, and other disease states.[16-23] Despite change in EQ-5D utility being used as a primary or secondary endpoint in several recently completed and currently recruiting ESKD trials[24-30] and a pre-specified change in EQ-5D being used to calculate target sample size for some trials,[24,25] a MID for dialysis patients has not been established. Therefore, the aim of this analysis was to use anchor-based and distribution-based methods to estimate the EQ-5D MID from a cohort of dialysis patients.

Methods

Study Population

EQ-5D and EQ-VAS measures[9] have been prospectively assessed twice per year since April 2017 for all dialysis patients across 2 hospital sites in Sydney, Australia. These sites comprise of 1 in-center hemodialysis unit, 2 satellite hemodialysis units, and a home therapy unit (with home hemodialysis and peritoneal dialysis patients). Symptom assessment using the Integrated Palliative care Outcomes Scale Renal (IPOS-Renal)[31] were collected at the same time points as EQ-5D and EQ-VAS questionnaires. These questionnaires have been used to identify troubling symptom and quality-of-life burden that may go unnoticed in routine care[32,33] and to institute management approaches. All questionnaires were completed during in-center hemodialysis sessions or mailed to home hemodialysis and peritoneal dialysis patients. Inclusion criteria for this analysis were adult dialysis patients with ≥1 EQ-5D measure between April 2017 to November 2020 who had no missing EQ-5D response data at baseline such that a baseline EQ-5D utility score could be derived. The study was approved by the South Eastern Sydney Human Research Ethics Committee.

EQ-5D-5L Measures

The EQ-5D is a generic preference-based HRQOL measure with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[9] The English-language EQ-5D 5-level version (EQ-5D-5L) was used. Each dimension has 5 response categories (1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, 5 = extreme problems), giving rise to 3125 distinct health states. Patient's health states were converted to a utility score through comparison with a value set from a general population valuation study in England (an Australian value set has not yet been developed and the English value set was thought to be closely representative).[34] This EQ-5D-5L utility score can be regarded as a continuous outcome on a scale from −0.285 (extreme problems in all dimensions and considered to be worse than death) up to 1 (no problems in all dimensions and considered full and complete health).

Anchor Measures

The EQ-VAS[9] is a secondary component completed with the EQ-5D-5L and provides a global self-rated measure of health state. Current health state is rated on a continuous scale of 0 to 100, with 0 equating to "worst imaginable health state" and 100 equating to "best imaginable health state."

The IPOS-Renal symptom inventory[31] is a validated tool for assessing symptom burden in advanced chronic kidney disease and dialysis patients.[35] It has been shown to correlate well with EQ-5D scores in dialysis patients.[36] It comprises 15 chronic kidney disease-related physical symptoms (pain, shortness of breath, weakness/lack of energy, nausea, vomiting, poor appetite, constipation, sore or dry mouth, drowsiness, poor mobility, itching, difficulty sleeping, restless legs, changes in skin, and diarrhea) and additional emotional symptoms (feeling anxious or worried and feeling depressed). Responders rate the degree each symptom affected them in the 7 days before survey completion using an ordinal 5-point scale. The 15 physical symptom scores in addition to anxiety and depression scores were summated to derive a global symptom score, ranging from a minimum of 0 (no symptom burden) to a maximum of 68.

Other Measures

Demographic, clinical, and dialysis characteristics were obtained from medical records, including baseline age, sex, body mass index, comorbidities, dialysis modality, and years on dialysis. Modified Charlson comorbidity index was calculated using baseline age and comorbidities, with a theoretical maximum score of 37.[37]

Analysis

Description of sample

Patient characteristics are reported as frequencies (n, %), means (±SD and medians (interquartile range) for categorical, continuous, and skewed continuous variables, respectively. Rate of change per year in utility-based HRQOL across the cohort was determined using a linear mixed effects model with a correlated structure and with random intercepts and random slopes, which account for repeated measures and variable follow-up time points. A multivariable mixed effects model was created using stepwise backward elimination.

Anchor-based cross-sectional methods

Anchors need to have a proven association with the outcome measure of interest and a minimum correlation of $r \geq |0.30|$ is recommended.[14] Pearson correlation analyses between candidate anchors and baseline EQ-5D-5L index values were used to select anchors ($r \geq |0.30|$), expecting that IPOS-Renal global symptom score and EQ-VAS would have the highest correlations as patients completed symptom assessment simultaneously with the EQ-5D-5L and symptom burden is among the strongest predictors of HRQOL in dialysis patients,[38-40] and EQ-VAS is a global assessment

of health state that was also completed simultaneously with the EQ-5D-5L.

Using baseline IPOS-Renal global symptom score as a cross-sectional anchor, a linear regression method was used. 5 points has been reported as a moderate effect size threshold for the generic IPOS from prior literature, and this was used as an anchor threshold.[41] An unadjusted linear regression model was fitted between baseline IPOS-Renal global symptom scores and baseline EQ-5D-5L index scores, and the EQ-5D-5L MID estimate was extracted using a 5-point change in IPOS-Renal global symptom score as meaningful. Adjustment for independent variables that may influence the outcome of interest is recommended to assess stability of the derived MID estimate[42]; hence, analysis was repeated with a multivariable model developed from stepwise backward elimination (final model was adjusted for baseline age, sex, modified Charlson comorbidity index, and dialysis vintage).

The same cross-sectional linear regression method was used with baseline EQ-VAS scores as an anchor. An EQ-VAS MID ranging from 4.2 to 14.8 has been estimated in other disease states,[16,19-22,43] and we used an EQ-VAS MID of 10 as an anchor threshold based on that derived from oncology populations.[16] An unadjusted linear regression model was fitted between baseline EQ-VAS and baseline EQ-5D-5L index scores, and the EQ-5D-5L MID estimate was extracted using a 10-point change in EQ-VAS score as meaningful. Analysis was repeated with an adjusted model.

Anchor-based longitudinal methods

Longitudinal anchors allow estimation of different EQ-5D MID values for improvement and deterioration, which is recommended as these values are often asymmetrical.[14] Using IPOS-Renal global symptom scores and EQ-VAS scores as longitudinal anchors, a several-measure mixed models approach was used. As patients completed a variable number of EQ-5D-5L, IPOS-Renal and EQ-VAS questionnaires, mixed models allow use of data across all time points.

First, within-patient changes in IPOS-Renal global symptom scores between baseline to each assessment were categorized as "improved" (≥5 point decrease), "about the same" (0-4 increase or decrease), or "deteriorated" (≥5 point increase). A time-varying mixed effects model with random intercepts and random slopes was then used, with time as a continuous variable and change in global symptom scores centered to the patient's baseline included as a time-varying categorical variable. The coefficients for "improvement" and "deterioration" were extracted from this mixed model, and analysis was repeated with an adjusted model. The same method was applied to EQ-VAS scores, with within-patient changes in EQ-VAS scores categorized as "improved" (≥10 point increase), "about the same" (0-9 increase or decrease), or "deteriorated" (≥10 point decrease), and coefficients for "improvement" and "deterioration" were extracted from unadjusted and adjusted mixed effects models.

Anchor-based receiver operating characteristic methods

Receiver operating characteristic (ROC) curve methods were used to identify the optimum sensitivity and specificity of change in EQ-5D-5L index scores in "predicting" clinically significant changes in the anchors between 0 and 6 months. The MID for improvement was identified from the ROC curve as the EQ-5D-5L change score that best discriminated between patients who improved their IPOS-Renal global symptom burden status (≥5 point decrease) or EQ-VAS score (≥10 point increase) compared with those who did not improve, with the optimum score having the highest Youden's index (sensitivity + specificity − 1).[15] Analyses were repeated to identify the MID for deterioration, defined as the EQ-5D-5L change score that best discriminated those patients who deteriorated in IPOS-Renal global symptom burden status (≥5 point increase) or EQ-VAS score (≥10 point decrease) compared with those who did not deteriorate. The area under the ROC curve (AUC) represents the probability that the derived MID correctly discriminates between groups, with an AUC ≥0.7 considered acceptable. 95% CIs for AUCs were derived using bootstrapping with 2000 replicates.

Distribution-based methods

3 distribution-based methods were used. First, 0.5 of the SD for EQ-5D-5L utility scores were calculated at baseline and 6 months. This is a measure of sample variability at each time point and has been suggested as a consistent estimation of the MID for HRQOL measures.[44] Second, the standard error of measurement (SEM) for EQ-5D-5L utility scores were calculated at baseline and 6 months. The SEM is the variation in scores that is attributed to instrument unreliability and a change smaller than the SEM is likely due to measurement error rather than true change. It is defined as SD x $\sqrt{1 - r}$, where r is the test-retest reliability of the measure.[13] Test-retest reliability is measured by the intraclass correlation coefficient and has been reported as 0.85 for the EQ-5D-5L in a UK reliability study.[45] Third, standardized effect size was calculated as the mean difference between EQ-5D-5L utility scores at baseline and 6 months divided by SD at baseline. Cohen defined an effect size of 0.2 for "small" effects and 0.5 for "moderate" effects,[46] with "small" effects considered representative of the MID.[47]

Level of significance was defined as P value $< .05$ for all analyses. Tukey corrections were used for pairwise comparisons. Assumptions of normality, homoscedascity and linearity were assessed graphically for all models. Analyses were performed using R Statistical Software (version 4.0.0).

Results

Patient Characteristics

355 patients had ≥1 EQ-5D-5L observation over the study period, of which 3 had missing data in 1 or more EQ-5D-5L response categories at baseline and were excluded from analysis. 352 patients with ≥1 EQ-5D-5L observations were included, constituting a total of 1127 observations. 263 patients had ≥2 observations for use in longitudinal analyses. Median follow-up time was 12 months (range 6-44 months). Baseline characteristics of the study population are summarized in Table 1. Appendix Figure 1 in Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.011 shows the distribution of EQ-5D-5L responses at baseline, from which baseline utility index was derived.

Utility-based HRQOL Over Time

Mean EQ-5D-5L utility at baseline was 0.719 (±0.267). In both unadjusted and adjusted mixed effects models (adjusted for age, sex, modified Charlson comorbidity index, and dialysis vintage), EQ-5D-5L utility showed a slight decrement over time (unadjusted: −0.019 per year, 95% CI −0.030 to −0.008, P = .002; adjusted: −0.017 per year, 95% CI −0.029 to −0.006, P = 0.004) (Appendix Fig. 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.01.011).

Correlation Between Possible Anchors and EQ-5D-5L

Table 1 describes the relationships between baseline characteristics that are continuous variables and baseline EQ-5D-5L

Table 1. Baseline patient characteristics and Pearson's correlation coefficients with baseline EQ-5D-5L utility score.

Patient characteristics	All patients (N = 352)	Pearson's correlation coefficient with baseline EQ-5D-5L utility score	
		r	*P* value
Mean age, years (± SD)	68.6 (12.9)	−0.19	<.001
Female sex, n (%)	132 (38)	-	-
Mean BMI, kg/m^2 (± SD)*	29.8 (6.6)	−0.04	.46
Known diabetes mellitus, n (%)	173 (49)	-	-
Mean mCCI (± SD)	6.4 (2.3)	−0.19	<.001
Median dialysis vintage, years (IQR)	1.9 (0.4, 5.6)	−0.15	.004
Dialysis modality, n (%)			
Hospital HD	257 (73)	-	-
Home HD	33 (9)	-	-
PD	62 (18)	-	-
Mean baseline EQ-5D-5L utility score (±SD)	0.719 (0.267)	-	-
Mean baseline IPOS-Renal global symptom score (±SD)	13.3 (8.9)	−0.71	<.001
Mean baseline EQ-VAS score (±SD)	67.2 (20.3)	0.58	<.001

BMI indicates body mass index; HD, hemodialysis; IPOS-Renal, Integrated Palliative care Outcomes Scale Renal; IQR, interquartile range; mCCI, modified Charlson comorbidity index; PD, peritoneal dialysis.
*BMI data available for 292 patients.

utility score. There were significant but weak correlations ($r < 0.30$) for baseline EQ-5D-5L utility with age and modified Charlson comorbidity index. There were strong correlations between baseline EQ-5D-5L utility and IPOS-Renal global symptom score ($r = -0.71$), and baseline EQ-5D-5L utility and EQ-VAS score ($r = 0.58$) (Fig. 1). IPOS-Renal global symptom score and EQ-VAS score were therefore deemed appropriate anchors for anchor-based MID estimation.

Anchor-based MID Estimation

Using linear regression, MID estimates for the EQ-5D-5D utility index were 0.103 (unadjusted) and 0.107 (adjusted) using a 5-point threshold in IPOS-Renal global symptom score as an anchor and, and 0.075 (unadjusted) and 0.073 (adjusted) using a 10-point threshold in EQ-VAS score as an anchor (Table 2).

Results of the longitudinal anchor-based methods are summarized in Table 3. Using several-measure mixed models with longitudinal IPOS-Renal global symptom scores, the MID for improvement in an adjusted model was 0.076 and the MID for deterioration was −0.109. Using several-measure mixed models with longitudinal EQ-VAS scores, the MID for improvement was 0.046 and the MID for deterioration was −0.048.

Results of the ROC curve methods are summarized in Figure 2. From ROC curves with IPOS-Renal global symptom score as an anchor, the optimal EQ-5D-5L change score that best discriminated between patients who had a ≥5 point decrease in symptom score from baseline to 6 months (ie, MID for improvement) was 0.122 (AUC 0.76, 95% CI 0.65 to 0.85), and the optimal EQ-5D-5L change score that best discriminated between patients with a ≥5 point increase in IPOS-Renal global symptom score (ie, MID for deterioration) was −0.063 (AUC 0.69, 95% CI 0.59 to 0.78). From ROC curves with EQ-VAS scores as an anchor, the optimal EQ-5D-DL change score that best discriminated between patients who had a ≥10 point decrease in EQ-VAS score from baseline and 6 months (ie, MID for improvement) was 0.037 (AUC 0.66, 95% CI 0.56 to 0.74), and the optimal EQ-5D-5L change score that best discriminated between patients with a ≥10 point decrease in EQ-VAS score (ie, MID for deterioration) was −0.074 (AUC 0.66, 95% CI 0.58 to 0.75).

Distribution-based MID Estimation

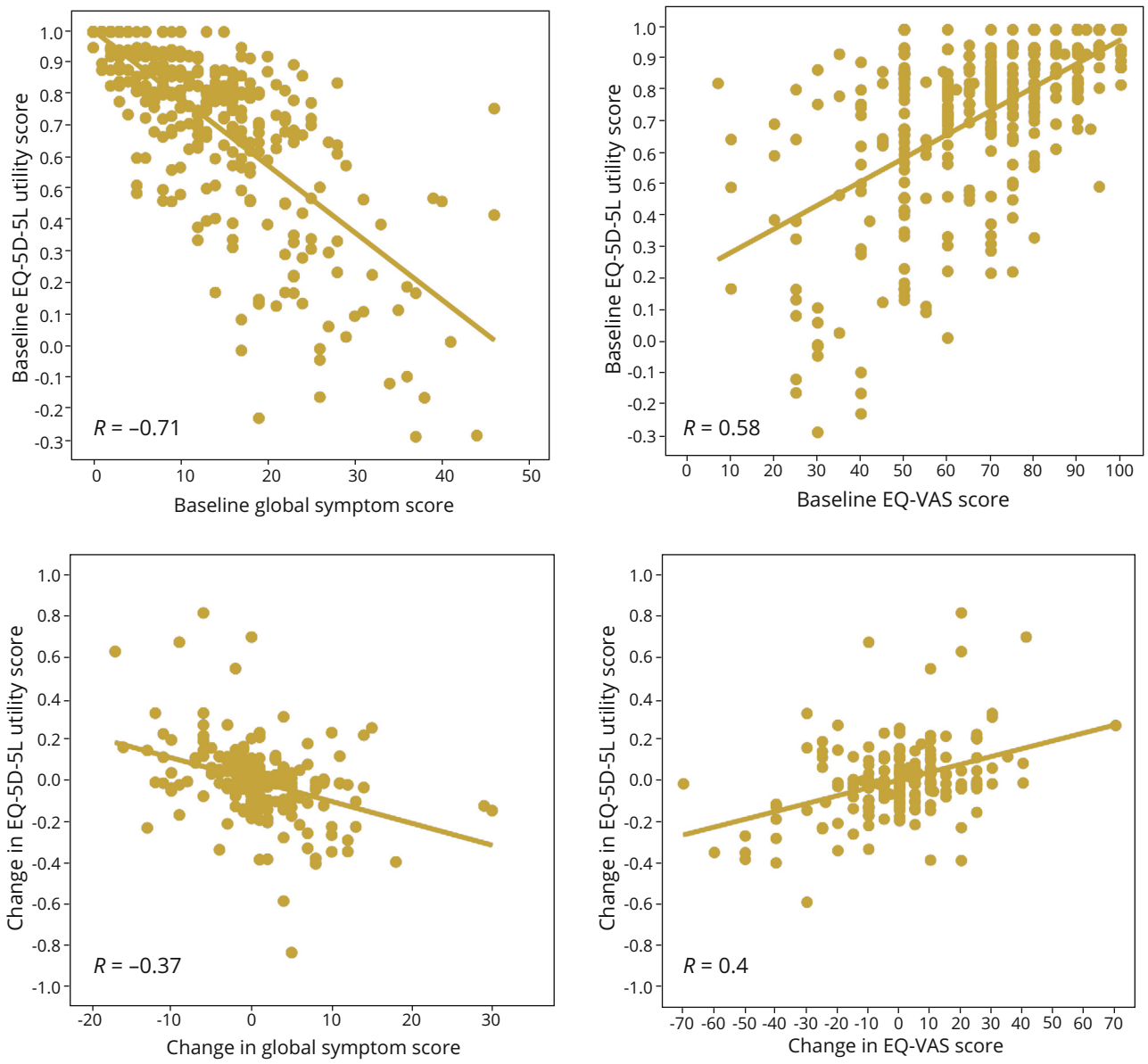
MID estimates from distribution-based methods are summarized in Table 4. Using 0.5 SD, MID estimates ranged from 0.108 to 0.134. Using SEM, MID estimates ranged from 0.084 to 0.104. Using Cohen's definitions, 0.2 standardized effect size ("small" effects) for change in EQ-5D-5L utility scores between baseline and 6 months was 0.034 and 0.5 standardized effect size ("moderate" effects) was 0.084.

Discussion

HRQOL in dialysis patients, as measured by the 5Q-5D-5L utility index in this study, was lower than general population norms and showed slight decrement over time. This is the first study to estimate the MID for the EQ-5D-5L utility index in dialysis patients, with anchor-based and distribution-based approaches providing MID estimates ranging from 0.034 to 0.134, with some variation depending on the MID calculation technique used.

Utility-based HRQOL is known to be poor among dialysis patients compared with general population norms and kidney transplant recipients, with a large Australian general population survey reporting a mean EQ-5D-5L utility index score of 0.91[48] and a prior meta-analysis reporting mean utility-based HRQOL of 0.70 and 0.82 among dialysis and kidney transplant patients, respectively.[49] These utility-based HRQOL estimates in dialysis patients are comparable to that of oncology patients.[50] Further, poorer HRQOL is a predictor of other adverse clinical outcomes including mortality and hospitalizations among dialysis patients.[51-53] Given these disparities and implications, HRQOL is an

Figure 1. Correlation between baseline EQ-5D-5L utility score with IPOS-Renal global symptom score (top left) and EQ-VAS score (top right), and correlation between change in EQ-5D-5L utility score from 0-6 months with change in IPOS-Renal global symptom score (bottom left) and change in EQ-VAS score (bottom right). $r = -0.71$, $r = 0.58$, $r = -0.37$ and $r = 0.40$ respectively, $P < 0.001$ for all.



IPOS-Renal indicates Integrated Palliative care Outcomes Scale Renal.

Table 2. EQ-5D-5L utility index MID estimates from anchor-based cross-sectional methods.

Anchor	Method	MID estimate (95% CI)	*P* value
IPOS-Renal global symptom score			
5-point threshold	Linear regression (unadjusted model)	0.107 (0.096, 0.118)	<.001
5-point threshold	Linear regression (adjusted model)*	0.103 (0.092, 0.114)	<.001
EQ-VAS score			
10-point threshold	Linear regression (unadjusted model)	0.075 (0.064, 0.087)	<.001
10-point threshold	Linear regression (adjusted model)*	0.073 (0.062, 0.084)	<.001

CI indicates confidence interval; IPOS-Renal, Integrated Palliative care Outcomes Scale Renal; MID, minimal important difference.
*Adjusted for age, sex, modified Charlson comorbidity index and dialysis vintage.

Table 3. EQ-5D-5L utility index MID estimates from anchor-based longitudinal methods.

Anchor	Method	MID estimate for improvement		MID estimate for deterioration	
		Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
IPOS-Renal global symptom score					
≥5-point change	Several-measure mixed model (unadjusted model)	0.079 (0.047, 0.112)	<.001	−0.111 (−0.139, −0.084)	<.001
≥5-point change	Several-measure mixed model (adjusted model)*	0.076 (0.044, 0.109)	<.001	−0.109 (−0.136, −0.081)	<.001
EQ-VAS score					
≥10-point change	Several-measure mixed model (unadjusted model)	0.048 (0.018, 0.077)	.005	−0.053 (−0.083, −0.023)	.002
≥10-point change	Several-measure mixed model (adjusted model)*	0.046 (0.017, 0.076)	.006	−0.048 (−0.078, −0.018)	.005

Note. Several-measure mixed models performed using all time points for each patient, with within-patient changes in IPOS-Renal global symptom scores and EQ-VAS scores at each time point compared with baseline. CI indicates confidence interval; IPOS-Renal; MID, minimal important difference.
*Adjusted for age, sex, modified Charlson comorbidity index, and dialysis vintage.

increasingly important consideration, and pre-dialysis and dialysis patients, particularly those in older age-groups, place high priority on this patient-reported outcome.[54-56] Among a cohort whose demographic profile is typical of high-income country dialysis populations (mean age 68.6 years, mean modified Charlson comorbidity index 6.4, 49% with diabetes mellitus), our study identified a mean baseline EQ-5D-5L utility index of 0.719 consistent with prior studies. Outside clinical trials of novel interventions,[25] longitudinal data on utility-based HRQOL among dialysis populations are sparse.[49] In our population, there was a small though statistically significant decline in EQ-5D-5L utility by -0.017 per year. This contrasts with the utility trajectories of kidney transplant recipients, which have shown increase or stable values in previous studies.[49]

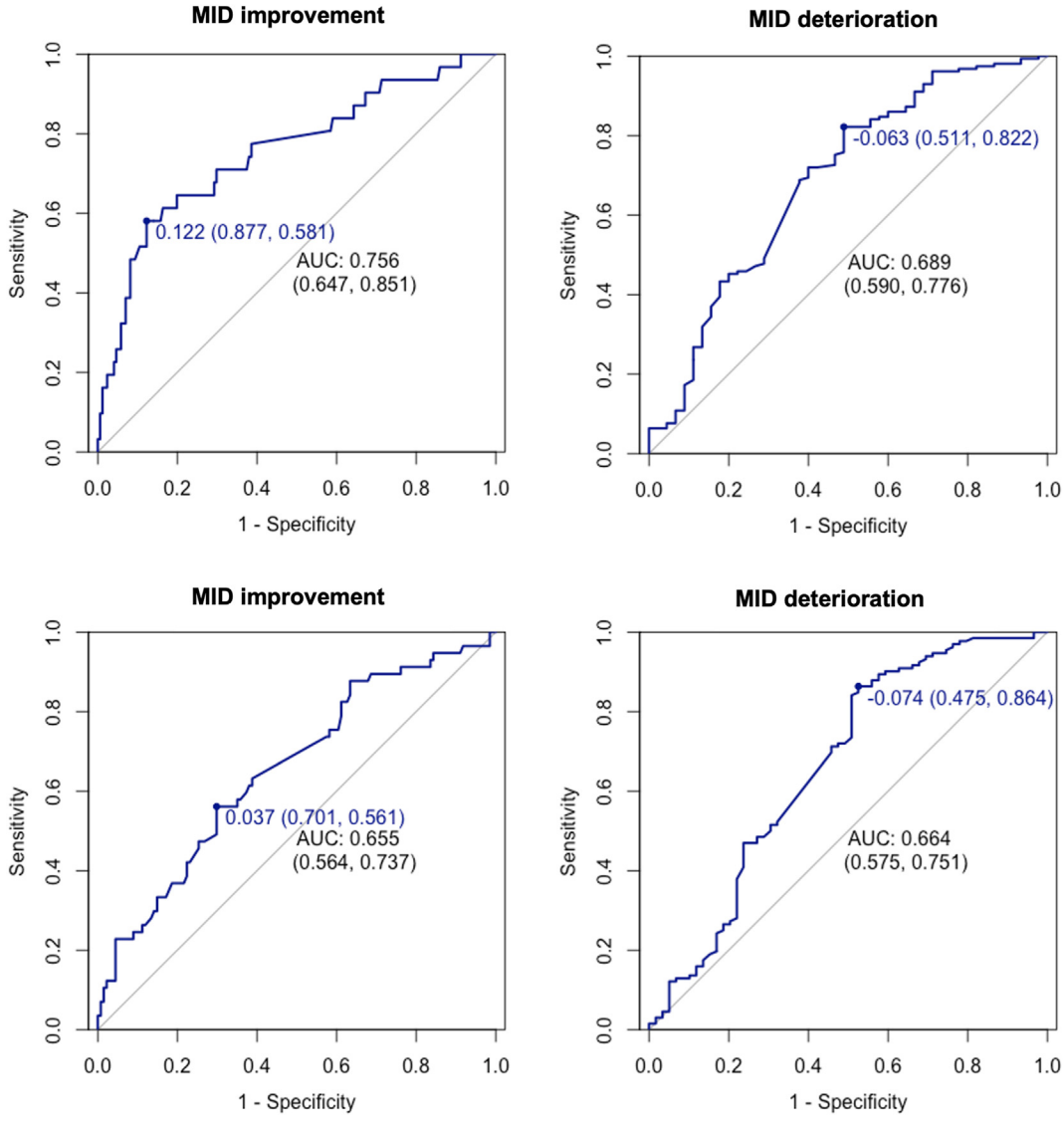
The MID of HRQOL measures is a property relevant to multiple stakeholders. Rather than basing treatment, policy, and funding decisions purely on statistical significance, the MID allows such decisions to incorporate an understanding of clinical relevance. To our knowledge, this is the first study to estimate the MID for the EQ-5D-5L utility index in dialysis patients. We utilized patient-reported outcome data collected on patients every 6 months, rendering a large patient and observation sample size when compared with other MID studies.[57] MID estimates in our population ranged from 0.034 to 0.134. EQ-5D utility MID estimates of 0.09 to 0.12 have been reported for oncology patients,[16] 0.08 to 0.10 for myeloma patients,[17] and a pooled EQ-5D utility MID estimate of 0.074 (range 0-0.139) from 11 studies among various chronic disease patient groups.[23] Although differences in MID estimates across disease states are expected, it should be noted that there is great variation in the computation methods, value sets, anchors, and handling of missing data across MID studies.[57] Hence, making comparisons between EQ-5D-5L MID estimates across different disease states and different countries requires great caution and emphasizes the importance of deriving disease-specific and population-specific estimates.

Because there is no consensus for the optimal MID estimation method, we used a combination of anchor-based and distribution-based methods, utilizing both cross-sectional and longitudinal data. Estimates in our study showed some variation across methods, which has been reported in other MID studies.[58] Anchor-based MID estimates derived by using change in IPOS-Renal global symptom score as a clinical anchor produced larger estimates than those using change in EQ-VAS as an anchor. Although both anchors showed strong correlations with EQ-5D-5L utility, these variations in MID estimates could be explained by the respective thresholds of meaningful change for the anchors used, which were based on established MID estimates for the IPOS and EQ-VAS in other disease states. The mixed models approach is advantageous in that these models account for within-patient correlation of repeated measures, adjust for regression to the mean, and utilize multiple measurements across multiple time points, which enhances estimate precision. As such, they are argued as a more flexible and appropriate approach to MID estimation.[59] Although the thresholds identified using ROC curve analysis were consistent with those derived from longitudinal anchor-based models, these curves utilized data from 2 time points only (baseline and 6 months) and AUCs ranged from 0.66 to 0.76, rendering some analyses just below the 0.70 threshold for acceptable discrimination.

Distribution-based methods rely purely upon the distribution of the cohort, with no valuation of clinical relevance. They are therefore thought to be less reliable as stand-alone MID estimates. The distribution-based MID estimates from our study do, however, show agreement with those derived from anchor-based methods. Revicki et al[14] proposed a process of triangulation; using various anchor-based methods, then examining distribution-based estimates to support anchor-based estimates, to converge on a range of MID values rather than a single estimate. More recently, Wang et al[60] devised a stepwise approach to selecting an optimal MID from multiple anchor-based estimates. This approach places greatest importance on methodological rigor, with assessment of each estimate against "credibility criteria" and then deriving usable median values from the selected estimates. From our study, anchor-based mixed models and ROC curves meet highest credibility criteria and give rise to a median MID for improvement of 0.061 and median MID for deterioration of −0.069. We would suggest that these MID estimates have greatest relevance in guiding clinical trial design.

Both hemodialysis and peritoneal dialysis are intensive and invasive treatments, and although there has been substantial research investment in dialysis over the past 2 decades, gains in mortality have been modest.[61] The importance of including HRQOL as a core domain in dialysis trials cannot be overstated.[6] This is particularly relevant in the growing era of learning healthcare systems and real-world comparative effectiveness trials, whose goal are to perform studies relevant to patients and decision makers.[62,63] Ideally, clinical trials should be powered to detect the MID of the primary outcome measure. In practice,

Figure 2. EQ-5D-5L utility index MID estimates from ROC curves: MID for improvement using ≥5 point decrease in global symptom burden score between 0 and 6 months as anchor (top left), MID for deterioration using ≥5 point increase in global symptom burden score between 0 and 6 months as anchor (top right), MID for improvement using ≥10 point increase in EQ-VAS score between 0 and 6 months as anchor (bottom left), and MID for deterioration using ≥10 point decrease in EQ-VAS score between 0 and 6 months as anchor (bottom right). Cutoff points in blue with specificity and sensitivity in brackets represent the best discriminatory threshold using Youden's index. AUC with 95% confidence intervals for AUC presented in brackets. $r = -0.71$, $r = 0.58$, $r = -0.37$ and $r = 0.40$ respectively, $P < 0.001$ for all.



AUC indicates area under the ROC curve; MID, minimal important difference; ROC, receiver operating characteristic.

Table 4. EQ-5D-5L utility index MID estimates from distribution-based methods.

EQ-5D-5L utility score time point	Distribution-based criteria			
	0.5 SD	SEM	0.2 Effect size	0.5 Effect size
Baseline	0.134	0.104	-	-
6 months	0.108	0.084	-	-
Change from baseline to 6 months	-	-	0.034	0.084

MID indicates minimal important difference; SEM, standard error of measurement.

dialysis trials using patient-reported outcome measures are often powered to detect group differences based on MID estimates in other disease states.[64] The EQ-5D-5L utility MID estimates derived from our study thus offer useful insights for clinical trial design in dialysis populations, particularly regarding power and sample size calculations. There is a clear need for further dialysis MID studies to better understand the clinical meaningfulness of HRQOL changes and to potentially narrow the range of estimates derived in our study. However, it should also be acknowledged that the MID is a statistical concept that, although useful in clinical trial design, does not supersede the importance of considering individual patient trajectories. Any change in a patient's EQ-5D-5L utility over time, regardless of how small, is important and reflects their perspective of change. As the key stakeholder in treatment decision making, an individual's perception of change rather than an aggregated threshold, such as the MID, should be at the center of clinical decisions.

This study has some limitations. First, patients were censored at the time of kidney transplantation and death, which may introduce some selection bias of longitudinal data. However, majority of dialysis trials include heterogenous cohorts of transplant waitlisted and non-waitlisted patients, thus supporting the generalizability of our estimates. Second, although attempts were made by nursing staff and family members to support frailer, visually impaired, and non-English speaking patients with questionnaire completion, it is likely that these groups were underrepresented in data collection. Third, although the 5-level version of the EQ-5D has reduced floor and ceiling effects compared with the preceding 3-level version,[65] these effects are not completely negated and limit the ability to pick up further change in patients with extreme values at baseline. Finally, we categorized anchors into 3 categories; "improved," "no change," and "deteriorated," rather than multiple categorization, such as "slightly improved" and "much improved." It is argued that categorization into fewer groups can result in grouping of individuals with change beyond minimally important, thus resulting in overestimation of MID values. However, this issue is not encountered in ROC methods that identify the optimal cutoff between "improved" and "no change"/"deteriorated," and MID estimates from ROC methods were largely consistent with other anchor-based methods in our study.

Conclusion

EQ-5D-5L utility index MID estimates determined from this study are the first among a dialysis cohort. The range of MID estimates derived provide insight into variability of quality-of-life trajectories among dialysis patients and are of value for endpoint, power, and sample size calculations in the design of dialysis clinical trials. This study encourages further MID studies in this patient population. Such studies are needed to determine the reproducibility of these results and potentially narrow the EQ-5D-5L utility MID estimate range.

Author Disclosures

Links to the disclosure forms provided by the authors are available here.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2024.01.011.

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APPENDIX B

Publications during candidature external to this thesis

Original Article

Impact of Renal Supportive Care on Symptom Burden in Dialysis Patients: A Prospective Observational Cohort Study

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Abstract

Context. Symptom burden is a strong predictor of reduced health-related quality of life and survival in patients with end-stage kidney disease. Renal supportive care (RSC) is a comprehensive approach shown to benefit symptoms in nondialysis conservatively managed patients, although its role in dialysis patients has not been reported.

Objectives. This study aimed to investigate the impacts of RSC intervention on symptoms in dialysis patients.

Methods. Dialysis patients who were referred to an RSC clinic for symptom control between April 2010 and December 2017 were followed prospectively. Symptoms were scored using the Integrated Palliative care Outcomes Scale-Renal Inventory. Change in symptoms was analyzed at three visits and at final RSC visit within the study period. Correlation and linear regression were used to assess for effect modifiers.

Results. A total of 127 dialysis patients attended the RSC clinic for symptom management. Median age was 74 years, 62% males, median dialysis vintage was 2.2 years, and median-modified Charlson Comorbidity Index was 7. Mean combined physical and emotional symptom score at baseline was 17.5 (SD 9.6), the most overwhelming/severe symptoms being difficulty sleeping (35%), pain (31%), lack of energy (31%), poor mobility (24%), and itch (22%). Eighty patients had follow-up to at least three RSC visits (median 3.1 months). There was significant improvement in combined physical and emotional symptom score during three clinic visits (18.1 vs. 14.2; mean change −3.8; 95% CI −5.7 to −1.9; $P < 0.001$), with greatest improvement in symptom scores for the five most severe symptoms (each $P < 0.001$). Follow-up of these 80 patients to final RSC visit (median 13.0 months) showed sustained reduction in mean combined physical and emotional symptom score (18.1 vs. 14.4; mean change −3.7; 95% CI −5.6 to −1.7; $P < 0.001$). These changes occurred without change in dialysis delivery.

Conclusion. RSC intervention that focuses on symptom control and patient-centered care is associated with improved total and individual symptom burden in dialysis patients. This supports a role for RSC as a management adjunct in these patients. J Pain Symptom Manage 2020;60:725−736.

Key Words

ESKD, dialysis, symptoms, supportive care

Key Message

This prospective cohort study investigated renal supportive care as an approach to managing symptom burden in a dialysis cohort. The results demonstrated that this program is effective in reducing global and individual symptom scores from baseline to three months, with sustained reductions to final follow-up (median 13.0 months).

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Introduction

The prevalence of end-stage kidney disease in developed countries is rising, with dialysis rates in the U.S. increasing from 1018 per million population (pmp) in 2000 to 1582 pmp in 2016 and increasing in Australia from 337 pmp in 2000 to 536 pmp in 2018.[1,2] It is often underappreciated that maintenance dialysis patients have high symptom and depression rates, comparable to that experienced by patients with advanced malignancies.[3–5] Furthermore, heavy symptom burden is among the greatest predictors of reduced health-related quality of life (HRQOL) in this population.[6–9] This disparate burden is multifactorial and likely relates to the combination of advanced renal disease, comorbid conditions, time lost on dialysis, post-treatment fatigue, and treatment-related complications.[10] Elderly, frail, functionally impaired, and highly comorbid dialysis patients are particularly affected, which has strong relevance given that 46% of U.S. dialysis patients and 52% of Australian dialysis patients are 65 years or older.[1,2]

This heavy physical and emotional symptom burden is observed despite provision of adequate dialysis as assessed by measures of solute clearance and occurs despite standard nephrology care and optimization of comorbid conditions. To date, no therapeutic interventions beyond standard nephrology care have shown success in sustainably reducing symptom burden in this cohort.[11,12]

Renal supportive care (RSC) is the integration of specialist palliative care with nephrology to manage difficult symptoms, maintain quality of life, provide emotional and family support, facilitate advance care planning, and ultimately, provide end-of-life care for patients with chronic kidney disease (CKD).[13,14] It is used in combination with standard nephrology care, and it prioritizes patient-centered and family centered management through an interdisciplinary approach (nephrology, palliative care, nutritional support, social work, and nursing).[15] The role of RSC in reducing overall symptoms at six and 12 months in patients on a nondialysis conservative management pathway (also referred to as comprehensive conservative care and active medical management without dialysis) has been demonstrated.[16] The effectiveness of RSC in a dialysis population has, however, not been studied. Specifically, impacts of an RSC team approach on symptom control have not been examined.

This prospective observational study was undertaken to examine the impact of an RSC team intervention, in addition to standard nephrology care, on symptom burden in dialysis patients specifically referred for symptom management.

Materials and Methods

Study Population

This is a single-center prospective study of chronic dialysis patients at St George Hospital, Sydney, Australia, where all in-center hemodialysis (HD) patients undergo routine six-monthly symptom assessments using the renal version of the Integrated Palliative care Outcomes Scale (IPOS-Renal).[17] Those identified with high symptom burden (scoring either severe or overwhelming in any physical symptom) are referred by their nephrologist or dialysis nursing staff to the RSC clinic. Other dialysis patients were referred at their nephrologist's discretion (e.g., patients with troubling symptom clusters that may not reach severe or overwhelming on IPOS-Renal assessment). Patients were recruited between April 20, 2010 and December 31, 2017. Inclusion criteria were maintenance dialysis (in-center HD, home HD, or peritoneal dialysis (PD) patients who remained dialysis-dependent for a minimum of three months) and patients aged 18 years and older. Study protocol was approved as quality assurance/improvement by the South Eastern Sydney Human Research Ethics Committee.

Study Intervention

The RSC multidisciplinary clinic is staffed by a palliative care specialist, nephrology senior trainee, senior renal-palliative care nurse, dietician, and social worker. The RSC clinic service is separate and in addition to routine nephrologist clinics. Each RSC clinic visit was similarly structured, beginning with formal symptom assessment using the IPOS-Renal inventory, followed by palliative care physician review for symptom management. Patients may also see other members of the RSC team depending on needs. The approach to symptom management was systematic, involving prioritization of maximally distressing physical and emotional symptoms, implementation of evidence-based symptom interventions, nutritional support, psychosocial counseling, and family support. Interventions were based on evidence-based RSC symptom management guidelines,[14,15] with a particular focus on pharmacological and nonpharmacological strategies for commonly experienced symptoms, including pain, itch, poor mobility, lack of energy, and drowsiness.[15,18,19] Frequency and duration of follow-up for each patient was individualized and dependent on symptom burden and treatments implemented. Follow-up was conducted in the RSC clinic, although brief RSC nurse reviews occurred during dialysis attendance or via phone for some patients; IPOS-Renal inventories were not completed on these occasions, and hence, these episodes were not included in analysis.

Demographic and Clinical Data Collection

Baseline characteristics at first RSC clinic were obtained from patient history, medical records, and nephrologist diagnoses, including age, sex, body mass index, and comorbidities. We used the modified Charlson comorbidity score as a measure of comorbid conditions, as this score has been shown to predict health outcomes and costs in dialysis patients.[20–22]

Baseline biochemical and hematological parameters were obtained from medical records, including serum creatinine, urea, hemoglobin, and serum albumin. For HD patients, blood tests were taken at the beginning of dialysis sessions. For PD patients, timing of blood tests was variable.

Baseline dialysis parameters were obtained from dialysis records, including dialysis modality, years on dialysis, dialysis prescriptions, and dialysis adequacy measures within six months of first RSC attendance (Kt/V). For PD patients, Kt/V was a composite of dialysis Kt/V and residual Kt/V calculated from 24-hour spent dialysate and urine collections, and for HD patients, Kt/V was either obtained from real-time online clearance monitoring or manually calculated using the single-pool Kt/V formula by Daugirdas.[23]

Symptom Data Collection

The IPOS questionnaires are a series of patient-reported outcome measures (PROMs) used in various chronic disease populations.[17] The IPOS-Renal inventory is modified for CKD and dialysis populations and has been shown to hold several key instrument characteristics, including validity (i.e., accuracy of measuring the desired concepts, studied as content validity and construct validity), reliability (i.e., consistency of the measure, studied as test-retest reliability and internal consistency), and sensitivity to change and practicality.[24–26] The IPOS-Renal comprises 15 CKD-related physical symptoms: pain, shortness of breath, weakness/lack of energy, nausea, vomiting, poor appetite, constipation, sore or dry mouth, drowsiness, poor mobility, itching, difficulty sleeping, restless legs, changes in skin, and diarrhea. Patients are asked to rate the degree each symptom affected them during the seven days before survey completion using a five-point scale: zero representing not at all, one slightly, two moderately, three severely, and four overwhelming. Emotional symptoms, including feeling anxious or worried and feeling depressed in addition to carer anxiety, adequate communication, and other practical issues, are assessed using the same scale.

Patients completed an IPOS-Renal inventory on arrival to each RSC clinic visit individually, with staff member assistance, or with an interpreter if of non-English-speaking background. Missing responses (less than 1% of all data points) were omitted from analysis. For analysis, we defined total physical symptom score as a summation of the 15 physical symptom scores, ranging from 0 (no symptoms) to a maximum of 60. We defined combined physical and emotional symptom score as a summation of the 15 physical symptom scores in addition to depression and anxiety scores, ranging from 0 to a maximum of 68. Other nonsymptom-based components of the IPOS-Renal Inventory such as carer anxiety and adequate communication were not included in this combined physical and emotional symptom score. For this study, symptoms were analyzed at baseline, three visits (this was chosen as it was felt to be a minimum time point at which improvements in symptom scores would be clinically expected), and at final visit within the study period.

Statistical Analyses

Baseline characteristics are reported as frequencies (n, %), means (±SD), and medians (interquartile range [IQR]) for categorical, continuous, and skewed continuous variables, respectively. Baseline total and individual symptom scores are reported as means (±SD). Changes in total and individual symptom scores between first and third visits and between first and last visits were compared using paired t-tests and reported as mean change (mean Δ) with 95% CI. Changes in symptoms between first and third RSC visits were characterized as stable, improved, or worse (no change, improvement by ≥1 point, and deterioration by ≥1 point, respectively) and compared using Chi-squared tests. Univariable and multivariable linear regression analyses and correlation were used to assess the effects of independent baseline factors on changes in symptom burden, including age, comorbidity, dialysis years, dialysis adequacy ,and baseline biochemical parameters. Level of significance was defined as $P < 0.05$. Analyses were performed using SPSS, Version 24 (IBM Corp, Armonk, NY).

Results

Study Population

A total of 127 patients receiving maintenance dialysis were enrolled (Table 1), of whom 97 were receiving hospital HD, six home HD, and 24 PD. Seventy-nine (62%) were males, median age at first RSC clinic was 74 years (IQR 15), and median dialysis vintage was 2.2 years (IQR 4.3). Patients were heavily comorbid with a median Charlson score of 7 (IQR 3). Hemoglobin, biochemical parameters, and dialysis

Table 1
Baseline Characteristics at First RSC Clinic Visit

Baseline Characteristics	All Patients ($n = 127$)
Dialysis modality; *n* (%)	
Hospital HD	97 (76)
Home HD	6 (5)
PD	24 (19)
Age at first appointment (yrs); median (IQR)	73.7 (14.7)
Male; *n* (%)	79 (62)
Body mass index (kg/m^2); median (IQR)	27.2 (8.1)[a]
Duration on dialysis (months); median (IQR)	26.5 (53.1)
Kt/V at baseline; median (IQR)[b]	
Hospital HD	1.38 (0.33)
Home HD	1.46 (0.53)
PD	1.92 (0.68)
Laboratory parameters; mean (SD)	
Creatinine, mg/dL	7.1 (2.5)
Blood urea nitrogen, mg/dL	53.0 (17.9)
Hemoglobin, g/L	110 (14)
Albumin, g/L	30 (5)
Number of comorbidities; median (IQR)	3 (3)
Charlson Comorbidity Index; median (IQR)	7 (3)
Major comorbidities; *n* (%)	
Diabetes mellitus	73 (57.5)
Ischemic heart disease	68 (53.5)
Peripheral vascular disease	32 (25.2)
COPD	32 (25.2)
Dementia	8 (6.3)

RSC = renal supportive care; HD = hemodialysis; PD = peritoneal dialysis; IQR = interquartile range; COPD = chronic obstructive pulmonary disease.
[a]Body mass index available for 122 patients.
[b]Kt/V available for 119 patients.

adequacy were within optimal target ranges at baseline (Table 1).

Baseline Symptom Burden

Patients experienced a median of nine (IQR 5) symptoms at baseline. One hundred fourteen (90%) had four or more symptoms, and 53 (42%) had 10 or more symptoms at baseline. Patients experienced a median of two severe/overwhelming symptoms (IQR 3). Thirty-five patients (28%) experienced four or more severe/overwhelming symptoms, and three patients (2%) experienced 10 or more severe/overwhelming symptoms.

Mean physical symptom score at baseline was 15.4 (SD 8.3). Mean combined physical and emotional symptom score was 17.5 (SD 9.6).

Most frequently reported physical symptoms were lack of energy (84%), poor mobility (72%), pain (69%), drowsiness (69%), difficulty sleeping (67%), and itching (63%). Feeling depressed was reported in 53% and feeling anxious in 54%. Fig. 1 compares our cohort's baseline symptom prevalence rates with those reported in systematic reviews by Murtagh et al.[3] (59 studies in dialysis patients and one study in patients discontinuing dialysis) and Almutary et al.[4] (14 studies in dialysis patients).

Severity of baseline symptoms is shown in Fig. 2. The five symptoms most frequently rated as severe or overwhelming at baseline were difficulty sleeping (35%), pain (31%), lack of energy (31%), poor mobility (24%), and itching (22%).

Changes in Total Symptom Burden After RSC Intervention

Eighty patients had follow-up to three RSC visits, and there were no significant differences in baseline characteristics compared with the original cohort of 127 patients (Table 2). Median follow-up between first and third RSC visits in this group was 3.1 months (IQR 3.3). There was significant improvement in mean physical symptom score during three clinic visits (15.8 vs. 12.4; mean Δ −3.4; 95% CI −5.1 to −1.7; $P < 0.001$) and mean combined physical and emotional symptom score during three clinic visits (18.1 vs. 14.2; mean Δ −3.8; 95% CI −5.7 to −1.9; $P < 0.001$). When categorized as improved, stable, or worse, 61% of patients experienced improvement in physical symptom score ($P < 0.001$), and 63% experienced improvement in combined physical and emotional symptom score ($P < 0.001$) (Fig. 3).

When patients were followed out to their last follow-up within the study period (median 13.0 months; IQR 20.3 months), comparison between baseline and final visit showed sustained improvement in mean physical symptom score (15.8 vs. 12.7; mean Δ −3.1; 95% CI −4.9 to −1.4; $P < 0.001$) and mean combined physical and emotional symptom score (18.1 vs. 14.4; mean Δ −3.7; 95% CI −5.6 to −1.7; $P < 0.001$) (Fig. 4).

Changes in Individual Symptoms After RSC Intervention

Mean severity scores for all individual physical symptoms significantly improved (Table 3), with greatest improvement in diarrhea, vomiting, nausea, mouth problems, and itching. Although still significant, the smallest improvements were seen in poor appetite, poor mobility, drowsiness, and shortness of breath. For emotional symptoms, there was significant improvement in depression (−0.8; $P = 0.001$) but not anxiety (−0.5; $P = 0.051$). Symptoms with improvement in the greatest number of patients were lack of energy (51%), difficulty sleeping (44%), itching (40%), pain (40%), and changes in skin (34%) (Fig. 3). The five most troubling symptoms rated as severe/overwhelming at baseline showed large and significant improvements, with the greatest improvement in severe/overwhelming itching (Table 4).

Dialysis Adequacy Over Time

During the first to third RSC follow-up period, there was no significant change in mean dialysis adequacy for all 60 hospital HD patients (1.36 vs. 1.41; $P = 0.45$) and five home HD patients (1.35 vs. 1.40;

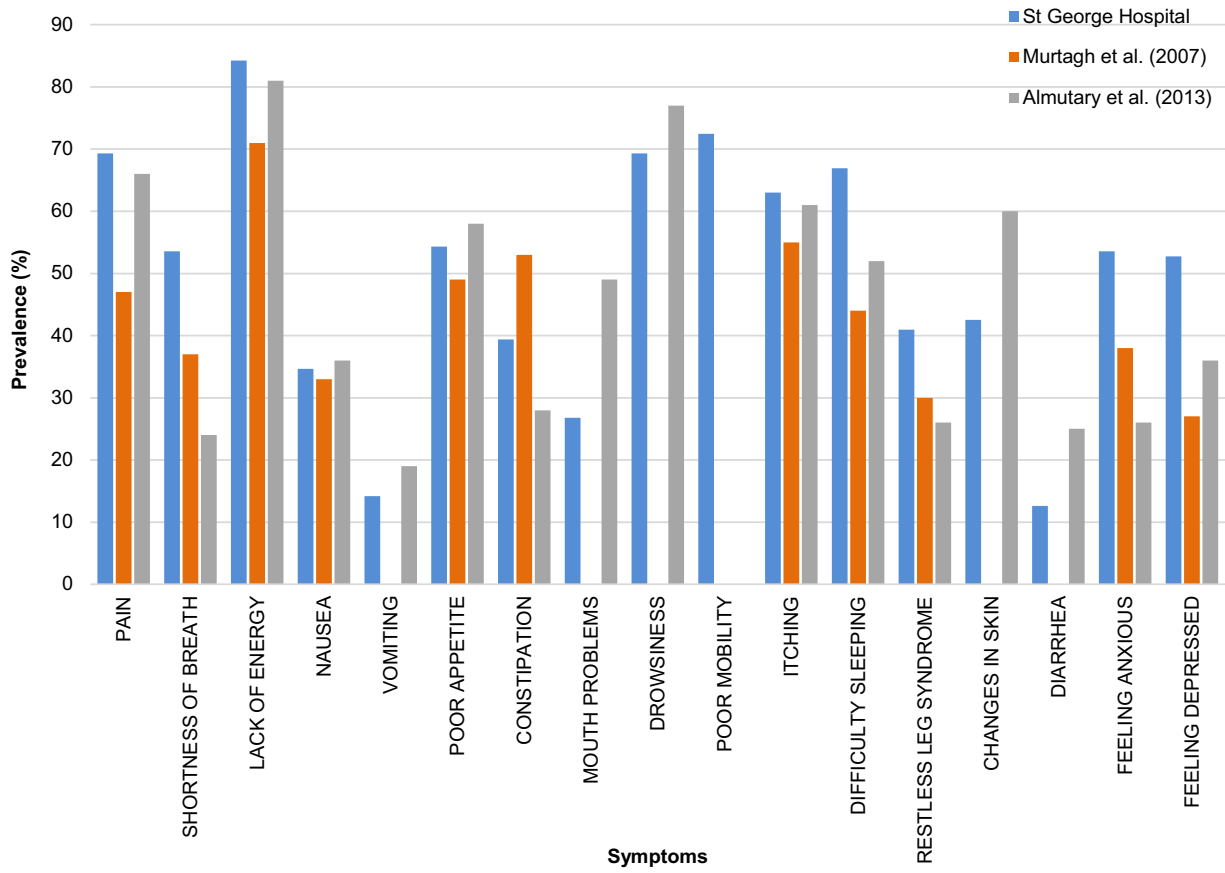

Fig. 1. Prevalence of individual symptoms at baseline. Prevalence of individual symptoms at baseline among 127 patients in St George Hospital cohort (blue) graphed against the weighted mean prevalence of individual symptoms reported by Murtagh et al.[3] (orange) and Almutary et al.[4] (gray) in their respective systematic reviews. Symptoms not reported in either systematic review are represented as blank bars. There were slight variations in symptom wording between our study and those reported in the systematic reviews; we assumed lack of energy in our study to be equivalent to fatigue/tiredness in the review by Murtagh et al. and fatigue or lack of energy in the review by Almutary et al., poor appetite in our study to be equivalent to anorexia in the review by Murtagh et al. and decreased appetite in the study by Almutary et al., mouth problems in our study to be equivalent to dry mouth in the review by Almutary et al., difficulty sleeping in our study to be equivalent to sleep disturbance in the review by Murtagh et al., change in skin in our study to be equivalent to dry skin in the review by Almutary et al., and feeling depressed in our study as being equivalent to feeling sad in the review by Almutary et al. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

$P = 0.90$). Serial adequacy was not performed for the PD patients within the three-visit period, although dialysis prescriptions were unchanged during this time.

Predictors of Change in Symptom Scores

Univariate analysis showed weak negative correlation between increased age and lower baseline combined physical and emotional symptom score ($r = -0.24$; $P = 0.03$). There were otherwise no associations between baseline characteristics (including baseline hemoglobin, blood urea nitrogen, ischemic heart disease, comorbidity count, and dialysis vintage) and baseline combined physical and emotional symptom score.

Univariate analyses showed no statistically significant associations with any baseline demographics and change in combined physical and emotional symptom score. There was strong association between higher baseline symptom score and magnitude of change in total score across three visits ($r = -0.71$; $P < 0.001$) and to final visit ($r = -0.61$; $P < 0.001$) and moderate association between higher baseline symptom count and magnitude of change in total score across three visits ($r = -0.60$; $P < 0.001$) and to final visit ($r = -0.50$; $P < 0.001$) (Fig. 5).

Discussion

This prospective observational study confirms a heavy symptom burden among dialysis patients specifically referred to an RSC service and shows that a structured RSC program is associated with improvement in

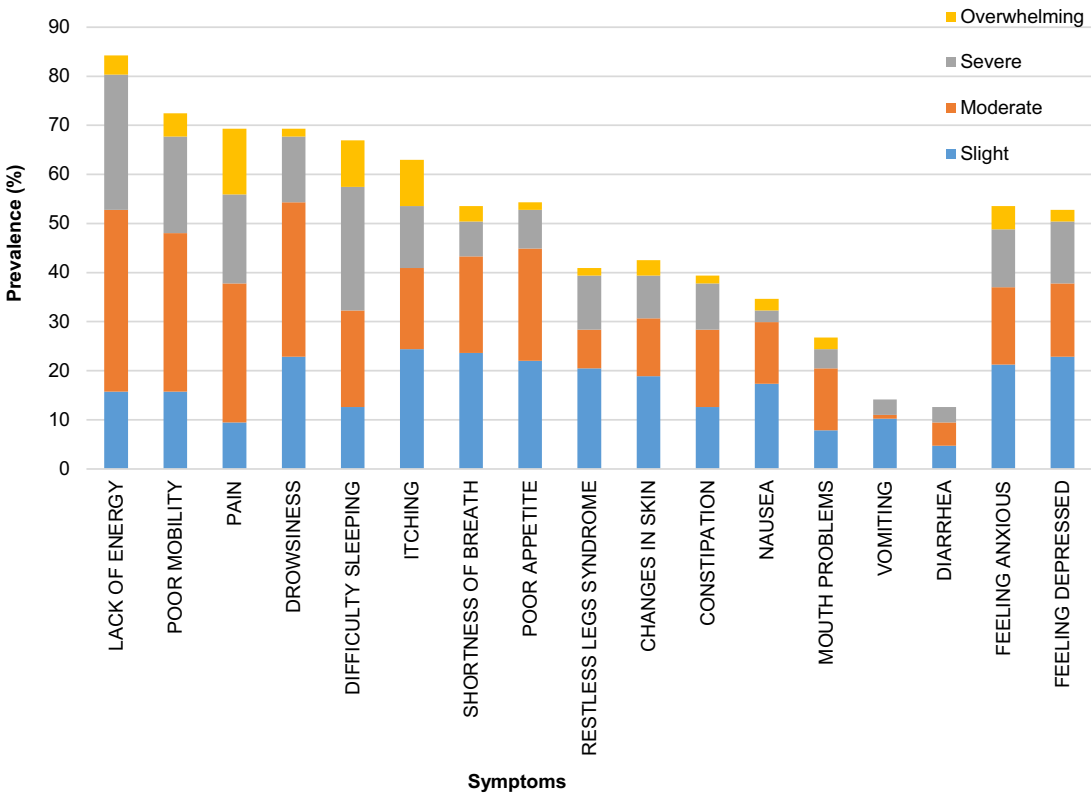

Fig. 2. Prevalence and severity of individual symptoms at baseline.

these symptoms in close to two-thirds of patients. This occurs alongside an improvement in depression but not anxiety and occurs independent of changes in dialysis delivery. To the best of our knowledge, this is the first study to examine the role of RSC as an adjunct for symptom control in dialysis patients.

Baseline Symptoms

Our selective patient cohort were those detected by routine assessment or perceived by their nephrologist or dialysis nurses to have distressing symptom burden, a group that is often difficult to treat. They had a median of nine baseline symptoms, including two severe/

Table 2
Baseline Characteristics of 80 Patients With Three or More RSC Clinic Visits

Baseline Demographics	All Patients	Hospital HD	Home HD	PD
Dialysis modality; *n* (%)	80	60 (75)	5 (6)	15 (19)
Age at first appointment (yrs); median (IQR)	73.9 (16.9)	73.2 (17.3)	63.1 (25.8)	76.1 (10.7)
Male; *n* (%)	51 (64)	37 (62)	3 (60)	11 (73)
Body mass index (kg/m^2); median (IQR)	27.8 (7.6)	28.0 (8.3)	28.0 (12.8)	27.7 (2.9)
Duration on dialysis (months); median (IQR)	26.5 (54.0)	23.0 (53.0)	71.0 (90.0)	26.0 (56.0)
Kt/V at baseline; median (IQR)	1.40 (0.53)[a]	1.36 (0.33)	1.39 (0.62)	1.92 (0.58)
Laboratory parameters; mean (SD)				
Creatinine, mg/dL	7.2 (2.3)	7.1 (2.3)	8.0 (4.7)	7.5 (2.0)
Blood urea nitrogen, mg/dL	53.5 (17.2)	54.8 (16.7)	38.4 (25.7)	52.0 (15.8)
Hemoglobin, g/L	110 (14)	109 (14)	121 (3)	110 (16)
Albumin, g/L	30 (5)	30 (4)	32 (3)	28 (6)
Number of comorbidities; median (IQR)	3 (2)	3 (2)	2 (2)	4 (2)
Charlson score; median (IQR)	7 (2)	7 (2)	6 (2)	7 (2)
Major comorbidities; *n* (%)				
Diabetes mellitus	47 (59)	36 (60)	2 (40)	9 (60)
Ischemic heart disease	36 (45)	25 (42)	1 (20)	10 (67)
Peripheral vascular disease	18 (23)	16 (27)	0	2 (13)
COPD	17 (21)	10 (17)	2 (40)	5 (33)
Dementia	7 (9)	7 (12)	0	0

RSC = renal supportive care; HD = hemodialysis; PD = peritoneal dialysis; IQR = interquartile range; COPD = chronic obstructive pulmonary disease.
[a]Kt/V available for 79 patients.

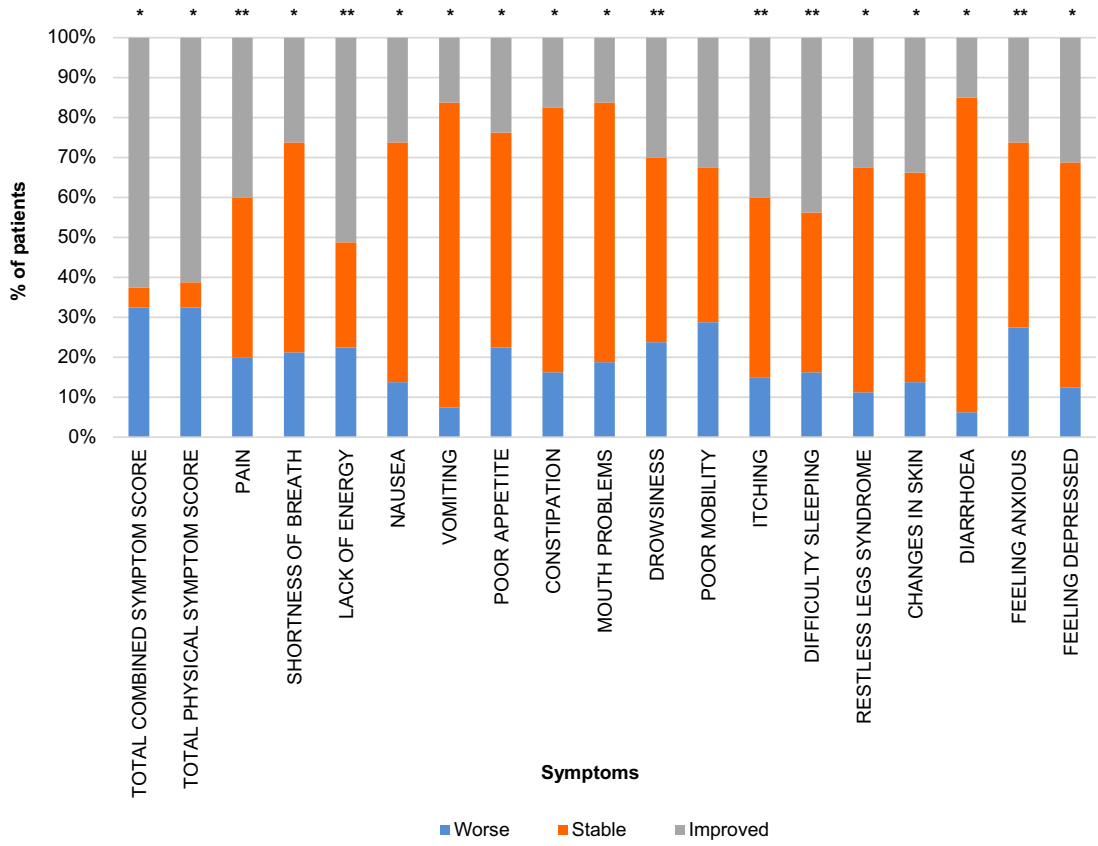

Fig. 3. Change in total and individual symptom scores from first to third clinic visits. $^{*}P \leq 0.001$; $^{**}P < 0.05$.

overwhelming symptoms. More than 90% experienced four or more symptoms at baseline, and more than one-third experienced 10 or more symptoms, an extent of problems that may go underappreciated in usual dialysis follow-up. Previous Australian and U.S. literature has shown that standard consultations pertain poor sensitivity to patients' symptom experiences, hence emphasizing the role of PROMs in symptom assessment.[27,28] Encouragingly, a number of randomized controlled trials assessing formal use of PROMs and feedback to nephrologists in routine dialysis care are currently in process globally.[29,30]

Our cohort was elderly, highly comorbid, and referred to RSC because of symptom burden, and their combined physical and emotional symptom score (mean 17.5 and median 18.0 at baseline) was higher than the median of 12.0 reported by Lowney et al.[31] in their younger cohort of 893 HD patients in England and Ireland (mean age 64 years). However, despite advanced age, comorbidity burden, and preselection, baseline symptom rates in our patients share several concordances with those reported in all-comer dialysis patients in other studies. For instance, Almutary et al.[4] reported a mean of 6–20 symptoms per patient across 10 studies, and Davison et al.[6] reported a mean of 7.5 symptoms among 507 dialysis patients. Individual symptom prevalence rates were also similar to those reported by Almutary et al.; among the most frequently reported symptoms in our study were lack of energy (84%), drowsiness (69%), and pain (69%), compared with 81%, 77%, and 66%, respectively, in the review by Almutary et al.[4] Notably, however, depression and anxiety rates in our cohort (53% and 54%, respectively) far exceeded those in previous reviews. Reasons for this may reflect our cohort's advanced dialysis vintage and comorbidity burden, both of which correlate with depressive symptoms,[32] as does high symptom burden.[11,33,34]

Trajectory of Symptoms in Dialysis Patients

Few studies have analyzed longitudinal symptom trajectory in dialysis patients. In the cohort of Davison and Jhangri[7] of 591 HD patients with a mean dialysis vintage of 3.3 years, mean Edmonton Symptom Assessment System score increased by 20.9 points (SD 15.4) during six months of follow-up. In the review by Novak et al.,[35] of 45 PD patients followed during the first 12 months after dialysis commencement, median Pittsburgh Symptom Score initially improved from 12 to 8 by three months although there was no further improvement to 12 months. These studies suggest

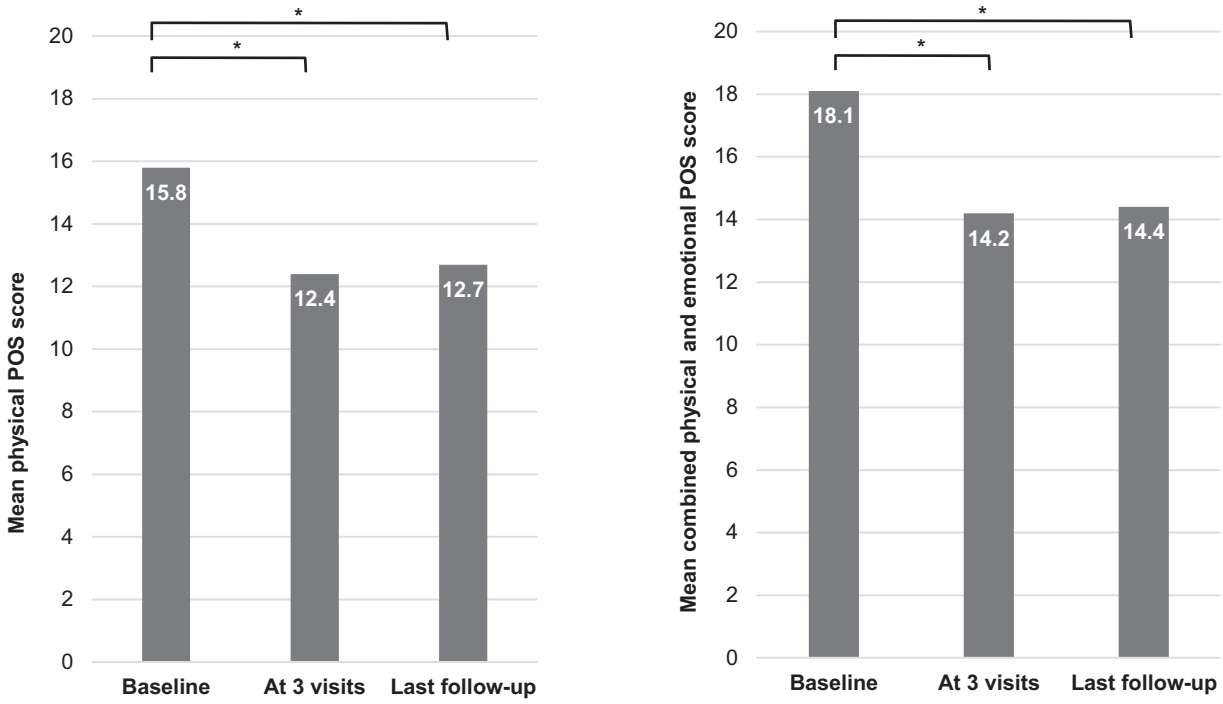

Fig. 4. Change in total symptom scores to three visits (median 3.1 months) and to final visit in study period (median 13.0 months); $^{*}P < 0.001$. There was improvement of mean physical score between baseline and three visits (mean Δ −3.4; 95% CI −5.1 to −1.7; $P < 0.001$) and between baseline and last follow-up (mean Δ −3.1; 95% CI −4.9 to −1.4; $P < 0.001$). There was also improvement in mean combined physical and emotional score between baseline and three visits (mean Δ −3.8; 95% CI −5.7 to −1.9; $P < 0.001$) and between baseline and last follow-up (mean Δ −3.7; 95% CI −5.6 to −1.7; $P < 0.001$).

that among established dialysis patients, ongoing symptom burden is not improved, and perhaps even worsened, over time.

Impact of RSC

RSC has been proposed as a means of curtailing symptom trajectory among dialysis patients, but to the best of our knowledge, no studies have examined effectiveness. We were able to demonstrate that a systematic approach of formally assessing and managing symptoms by a multidisciplinary RSC team is associated with improved symptoms in dialysis patients. Across a median of 3.1 months, combined physical and emotional symptom scores significantly improved, and an improvement was experienced by nearly two-thirds of patients. In particular, those patients with higher baseline symptom scores or higher total symptom count experienced the greatest magnitude of benefit, which has the important clinical implication of identifying these as potential triggers for RSC referral.

Our patients experienced a significant improvement in all individual physical symptoms, and not unexpectedly, greatest improvements were in physical symptoms with established evidence-based treatments, such as nausea, vomiting, diarrhea, itch, and mouth problems. Symptoms with smaller, although still significant, improvements included shortness of breath, poor appetite, drowsiness, and poor mobility, all of which are acknowledged as more challenging symptoms.

One of our key findings was that RSC is particularly effective in addressing severe and overwhelming symptoms that may be poorly addressed by standard nephrology care. For instance, in the Dialysis Outcomes and Practice Patterns Study of 18,801 HD patients, moderate or severe pruritus was reported in 42%, and composite mental and physical quality of life scores were 3.1−8.6 points lower than in patients with no or mild pruritus.[36] Severe or overwhelming pruritus was experienced by 21% of our patients. Through stepwise implementation of strategies,[15,18] mean pruritus severity among these patients in our study reduced from 3.7 to 1.4. Similarly, specialist palliative care approaches in severe/overwhelming pain management and multidisciplinary and allied health involvement in mobility management are all unique aspects of RSC that are likely to have facilitated improvement in these severe/overwhelming symptoms compared with standard nephrology care alone. Randomized trials and prospective observational studies in the fields of oncology, heart failure, and

Table 3
Change in Individual Symptom Scores During Three Clinic Visits

Symptom	*n*	Mean Symptom Score		Mean Δ in Symptom Score Between First and Third Visits (95% CI)	*P*
		Visit 1	Visit 3		
Pain	55	2.7	1.9	−0.8 (−1.2 to −0.5)	<0.001
Shortness of breath	43	1.8	1.2	−0.6 (−0.9 to −0.2)	0.002
Lack of energy	67	2.3	1.6	−0.7 (−1.0 to −0.4)	<0.001
Nausea	26	1.9	0.7	−1.1 (−1.5 to −0.7)	<0.001
Vomiting	14	1.8	0.5	−1.3 (−1.8 to −0.8)	<0.001
Poor appetite	40	1.8	1.3	−0.5 (−0.8 to −0.1)	0.03
Constipation	30	2.2	1.6	−0.7 (−1.2 to −0.2)	0.01
Mouth problems	18	1.9	0.8	−1.1 (−1.7 to −0.5)	0.001
Drowsiness	53	1.9	1.4	−0.6 (−0.9 to −0.3)	<0.001
Poor mobility	55	2.2	1.6	−0.5 (−0.9 to −0.2)	0.002
Itching	53	2.2	1.1	−1.0 (−1.4 to −0.6)	<0.001
Difficulty sleeping	57	2.4	1.6	−0.9 (−1.2 to −0.5)	<0.001
Restless legs syndrome	37	1.9	1.0	−0.9 (−1.2 to −0.5)	<0.001
Changes in skin	36	2.1	1.0	−1.1 (−1.5 to −0.7)	<0.001
Diarrhea	13	1.9	0.3	−1.5 (−2.1 to −1.0)	<0.001
Feeling anxious	42	2.0	1.5	−0.5 (−1.1 to 0)	0.051
Feeling depressed	46	2.0	1.2	−0.8 (−1.3 to −0.3)	0.001

others have shown improvements in HRQOL, symptom burden, depression, and anxiety in patients treated with specialist palliative care in addition to standard specialty care.[37,38] Evidence for this in dialysis patients outside the dialysis withdrawal context has thus far been limited; in this regard, our study provides important support for the role of specialist palliative care in the management of symptoms in dialysis patients.

Individual symptom assessment and subsequent implementation of targeted treatments in dialysis patients has been demonstrated in previous studies. In a cohort by Weisbord et al.,[39] 220 HD patients underwent monthly pain, erectile dysfunction, and depression assessments. They were then randomized to either feedback, where their nephrologist was simply informed of their symptom scores, or management, where trained nurses implemented specific treatment recommendations. Both approaches had small, although statistically significant, symptom improvements compared with usual care. Similarly, Barakzoy and Moss[40] evaluated Short-Form McGill Pain Questionnaire scores in 45 HD patients, implemented stepwise World Health Organization analgesic ladder recommendations, and evaluated pain scores weekly for four weeks. They demonstrated a significant decrease in mean pain scores from 7.8 to 1.6. Both these studies demonstrated that symptom identification and subsequent implementation of targeted management improve symptom burden in chronic dialysis patients. Our study complements this literature, although is unique in highlighting the role of symptom identification and implementation of appropriate interventions in a structured, holistic, and longitudinal RSC care setting.

Strengths and Weaknesses

There are limitations to this analysis. First, our patient population were those identified as having a high symptom burden routinely or referred to the RSC clinic by their nephrologist or dialysis nursing staff; hence; this may limit generalizability to all dialysis patients. Second, the IPOS-Renal was mostly completed when patients attended the RSC clinic rather than during dialysis, and it is possible that patients experience more symptoms at the time of their treatment. This inventory asks patients to recall their symptom experience during the past week, such that

Table 4
Change in the Top Five Troubling Symptoms Initially Rated Severe/Overwhelming During Three Clinic Visits

Symptom	*n*	Mean Symptom Score		Mean Δ in Symptom Score Between First and Third Visits (95% CI)	*P*
		Visit 1	Visit 3		
Difficulty sleeping	30	3.2	2.1	−1.1 (−1.6 to −0.7)	<0.001
Pain	28	3.5	2.1	−1.4 (−1.9 to −0.9)	<0.001
Lack of energy	27	3.1	1.7	−1.4 (−1.7 to −1.1)	<0.001
Poor mobility	18	3.2	1.6	−1.6 (−2.1 to −1.0)	<0.001
Itching	17	3.7	1.4	−2.3 (−3.1 to −1.5)	<0.001

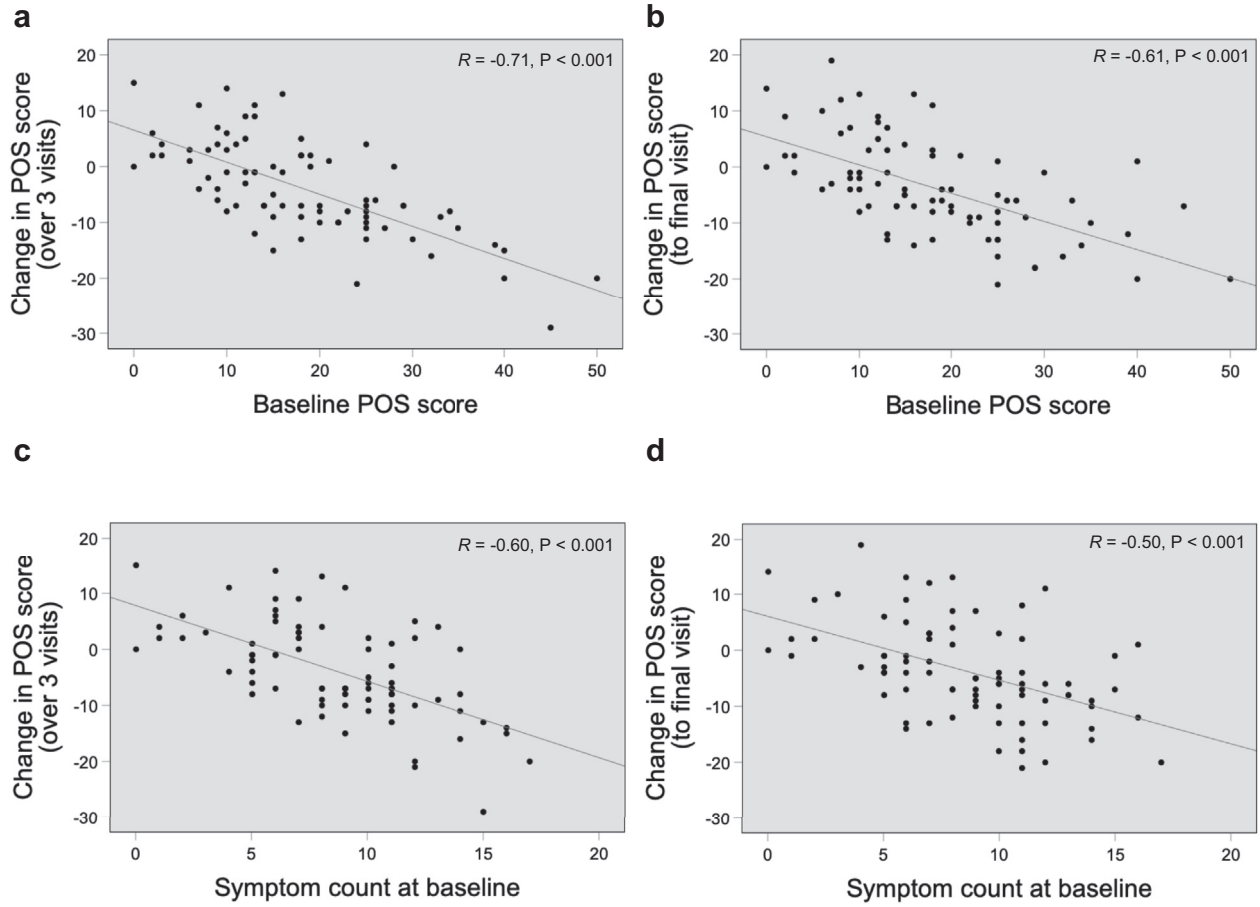

Fig. 5. Correlation between baseline combined physical and emotional IPOS score and change in IPOS score across a) three visits and b) to final visit, and correlation between baseline symptom count and change in IPOS score across c) three visits and d) to final visit. IPOS = Integrated Palliative care Outcomes Scale.

patients ideally integrate their experiences both on and off dialysis in their responses. Although the IPOS-Renal is known to have low respondent burden and good test-retest reliability, internal consistency, and convergent validity,[24–26] the potential for recall bias must always be acknowledged. Third, the IPOS-Renal asks patients to describe how a symptom has affected them during the previous seven days; it does not specifically differentiate symptom intensity from symptom frequency. Although this is a deliberate patient-centered feature of the IPOS-Renal to capture overall symptom experience, these dimensions are likely to play varying roles in overall symptom distress and may have implications for management. Fourth, although symptom burden has been shown to predict HRQOL, our study did not directly measure HRQOL. Finally, we (deliberately) did not have a control group to determine whether symptom improvements may have occurred spontaneously, although this would not be expected given previously described symptom trajectories in dialysis patients.

The strengths of our study include the standardized approach to management by the same clinical team throughout the study, objective symptom assessments at each visit using a validated symptom inventory, and capturing of dialysis adequacy data to show that symptom changes were not associated with changes in dialysis delivery.

Conclusions

Symptom burden among chronic dialysis patients is high, despite provision of adequate dialysis. Utilization of a PROM to assess symptom burden, referral to a multiprofessional RSC clinic, implementation of targeted management approaches, and longitudinal follow-up are effective in reducing total and individual symptom burden, with the most striking impact being among patients experiencing symptoms that are severe or overwhelming. In dialysis patients, who have symptom rates far exceeding that of population norms and even that of most cancers, this study supports incorporation of RSC in their management. There is a further role for future research to explore how symptom management through a systematic RSC program impacts on HRQOL in this patient population.

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Dialysis Prevalence in Zimbabwe: A Cross-sectional Descriptive Study

To the Editor:

The contribution of chronic kidney disease (CKD) to the global burden of disease is growing, accounting for an estimated 1.2 million deaths worldwide in 2017.[1,2] In the low- and lower-middle-income countries of sub-Saharan Africa, such as Zimbabwe, the burden of CKD is poorly understood, with little data on even the most severe form, kidney failure. This poverty of data was highlighted by the recent Assessment of Global Kidney Health Atlas being unable to report a prevalence of treated kidney failure across most of Africa, including Zimbabwe.[3]

The Dialysis in Zimbabwe (DIAZ) project was designed to collect and report on prevalence, incidence, characteristics, and outcomes of treated kidney failure patients. All dialysis patients in Zimbabwe were approached for participation in February 2018, with participants providing written informed consent. The study had an observational cohort design and used World Bank population estimates for the year 2018 as the denominator in describing prevalence (Item S1). Ethics approval was granted by the Medical Research Council of Zimbabwe (approval number MRCZ/A/2202).

The 16 participating dialysis units are located across Zimbabwe's major cities (Fig 1, Table S1), with the majority in the capital, Harare. Peritoneal dialysis (PD)

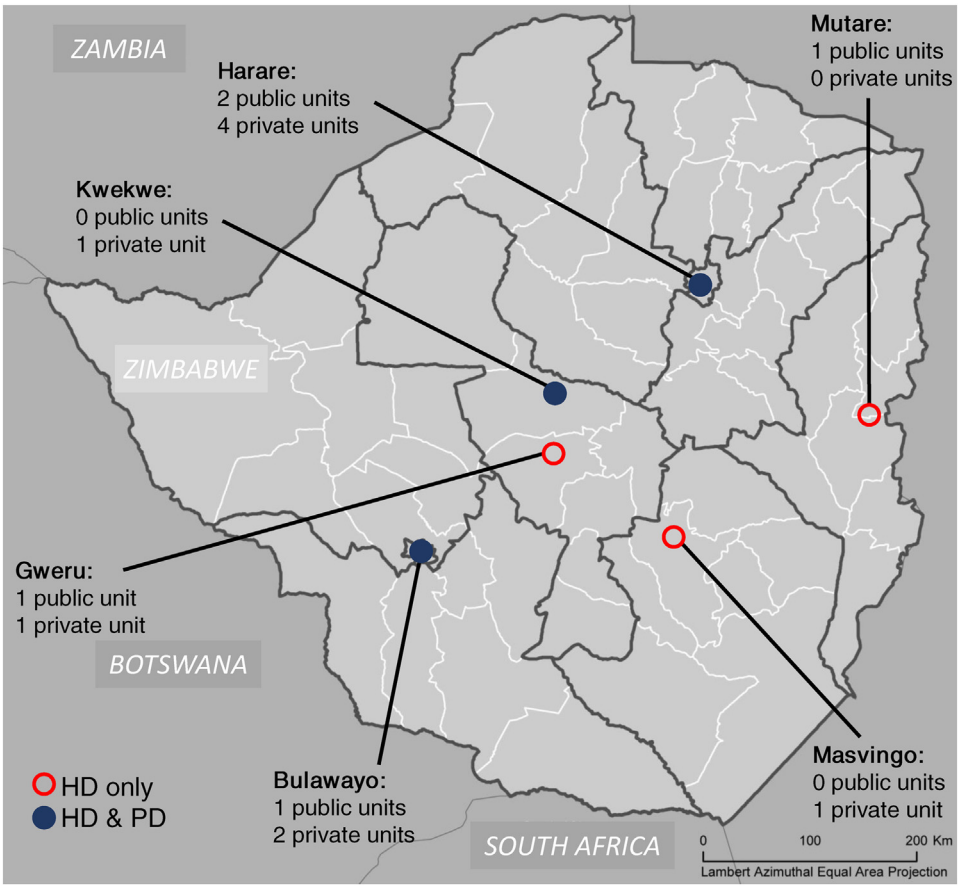

Figure 1. Geographical distribution of dialysis treatment across Zimbabwe. Adapted under a CC BY 3.0 license from the Center for International Earth Science Information Network, Columbia University; original graphic ©2005 The Trustees of Columbia University.

training occurs in a single public unit in Harare, with PD supplies available from Harare and Bulawayo. Most patients, however, access government-funded supplies in Harare, requiring travel distances of 5-272 kilometers. At the time of this study, dialysis was not publicly subsidized, and all patients were required to pay for dialysis through health insurance or direct payment.

A total of 482 prevalent dialysis patients were identified in February 2018 (hemodialysis [HD]: 457; PD: 25), equating to a crude national prevalence rate of 33.4 patients per million population (pmp) and an estimated dialysis prevalence of 46.0 and 21.8 pmp for male and female persons, respectively. Consent for data collection was obtained from 367 of the prevalent patients (HD: 354; PD: 13), representing 76% of Zimbabwe's prevalent dialysis population.

Most HD patients were male (66.7%) while most PD patients were female (62%); patients' mean age and dialysis vintage were 53.2 and 1.7 years for HD and 50.1 and 0.7 years for PD (Tables 1 and S2). HD patients mostly dialyzed in private units (69.5%), for 2 sessions per week of 5 hours each, and predominantly through tunneled central venous catheters (72.6%) (Table S3). All PD patients were on continuous ambulatory peritoneal dialysis, with 2-4 exchanges per day (Table S4). Demographics of private and public dialysis patients were similar, though in the private setting a higher proportion had diabetes (Table S5). Most patients reported a monthly family income of ≤US$1,000, and most used health insurance to pay for dialysis.

Etiology of kidney disease (as attributed by patients) was dominated by hypertension (HD: 71.8%; PD: 85%) and diabetes (HD: 34.5%; PD: 31%), with HIV-related kidney disease uncommon (Fig S1). The lack of access to kidney biopsy limits our ability to precisely assign etiology; however, the high prevalence of hypertension and diabetes, and the rarity of glomerulonephritis, raises the possibility that targeted use of preventative treatments may mitigate the future burden of kidney failure.

These data provide a valuable insight into dialysis prevalence in Zimbabwe, and the sub-Saharan region generally, home to over 1 billion people.[4] Our results are consistent with prior modeling estimates, based upon life expectancy and gross national income, of a dialysis prevalence of <50 pmp.[4] This compares with a prevalence of 190 pmp in South Africa and more than 1,000 pmp in high-income countries,[5,6] although these rates include transplantation, a treatment modality not accessible in

Table 1. Clinical and sociodemographic characteristics of study population

	HD (n = 354)	PD (n = 13)
Male sex	236 (66.7%)	5 (39%)
Age at enrollment	53.2 ± 13.5	50.1 ± 11.5
<20 y	2 (0.6%)	0
20-39 y	57 (16.1%)	3 (23%)
40-59 y	180 (50.8%)	7 (54%)
≥60 y	115 (32.5%)	3 (23%)
Monthly family income category[a]		
Not available	39 (11.0%)	0
0-500 USD	203 (57.3%)	5 (39%)
500-1,000 USD	54 (15.3%)	6 (46%)
1,000-1,500 USD	27 (7.6%)	0
1,500-2,000 USD	8 (2.3%)	0
>2,000 USD	23 (6.5%)	2 (15%)
Dialysis payment source		
Health insurance	283 (79.9%)	13 (100%)
Self	16 (4.5%)	0
Relative in Zimbabwe or abroad	44 (12.4%)	0
Other	11 (3.1%)	0
Time since CKD diagnosis, y	4.0 (2.0-5.0)	3.0 (2.0-5.0)
Duration of dialysis, y	1.7 (0.7-3.7)	0.7 (0.4-1.8)
Known diabetes	134 (37.9%)	5 (39%)
Duration, y[b]	15.0 (9.8-23.0)	20.0 (5.0-20.0)
Known hypertension	313 (88.4%)	12 (92%)
Duration, y[c]	9.0 (4.0-18.0)	8.5 (5.0-18.0)
Known ischemic heart disease	26 (7.3%)	0
Duration, y	1.0 (1.0-3.5)	–
Infection status		
HBV surface antigen positive	21 (5.9%)	1 (8%)
Hepatitis C virus positive	6 (1.7%)	0
HIV positive	56 (15.8%)	1 (8%)
Renal medication use		
Erythropoietin in last 3 months	251 (70.9%)	4 (31%)
Iron sucrose in last 3 months	204 (57.6%)	3 (23%)
Current phosphate binder use	95 (26.8%)	0

Values given as number (%), mean ± SD, or median (IQR). Abbreviations: CKD, chronic kidney disease; HBV, hepatitis B virus; USD, US dollars.
[a]The World Bank reports the purchasing power parity conversion factor for Zimbabwe as 0.5 per US dollar for 2020.[8] GDP per capita was reported as USD1,239 in 2020.[9]
[b]Duration of diabetes not available for 2 patients.
[c]Duration of hypertension not available for 4 patients.

Zimbabwe. Our study also highlights a very low rate of PD, which likely has multifactorial origins, including the high cost of supplies (equivalent to the cost of twice-weekly HD), concerns about peritonitis, and the lack of PD catheter insertion and training outside of Harare.

Our results confirm modeling that conservatively estimated less than 10% of patients in Zimbabwe that would benefit from kidney failure treatment are currently receiving it.[4] Introduction of public dialysis support by the Zimbabwean government in July 2018 is likely to assist in addressing undertreatment, but gaps in funding, trained staff, and infrastructure are sizeable and will take some time to remedy.[7]

In conclusion, this project provides comprehensive data on the nature and prevalence of dialysis in Zimbabwe, highlighting low access to dialysis and the underuse of PD as a treatment modality. Importantly, our findings provide an insight into the sub-Saharan region, show the feasibility of such measurement, and point to possible approaches that may reduce the future burden of kidney failure.

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Supplementary Material

Supplementary File (PDF)

Figure S1; Item S1; Tables S1-S5.

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