BANDAID^2 – An evidence based mnemonic for the treatment of systolic heart failure

Mr Noel Chia[1,2,*], Dr Jordan Fulcher[1,2,3*], Professor Anthony Keech[1,2,3]

*Co-first authors

Affiliations:

1. NHMRC Clinical Trials Centre, University of Sydney, NSW Australia
2. Sydney Medical School, University of Sydney, NSW Australia
3. Royal Prince Alfred Hospital, Camperdown, NSW Australia

Positions:

Noel Chia – Medical student, UNSW

Jordan Fulcher – BSc (Med) MBBS FRACP ; Cardiologist ; PhD student

Anthony Keech – MBBS MSc(Epi) FRACP FCSANZ FAAHMS ; Consultant Cardiologist ; Professor of Medicine, Cardiology and Epidemiology, University of Sydney ; Deputy Director, NHMRC CTC

Correspondence to:

Dr Jordan Fulcher

National Health and Medical Research Council (NHMRC) Clinical Trials Centre

Level 6 Medical Foundation Building

92-94 Parramatta Rd, Camperdown, NSW 2050, Australia

Email: jordan.fulcher@ctc.usyd.edu.au

Phone: +61295625234 ; Fax: +61280721343

Word counts: Abstract: 192 ; Main text: 3500

Abstract

Heart failure causes significant morbidity and mortality, with recognised underutilisation rates of guideline based therapies. Our aim was to review current evidence for heart failure treatments and derive a mnemonic summarising best practice which might assist physicians in patient care. Treatments were identified for review from multinational society guidelines and recent randomised trials, with a primary aim of examining their effects in systolic heart failure patients on mortality, hospitalisation rates and symptoms. Secondary aims were to consider other clinical benefits. MEDLINE and EMBASE were searched using a structured keyword strategy and the retrieved articles were evaluated methodically to produce an optimised reference list for each treatment. We devised the mnemonic **BANDAID^2**, standing for **B**eta-blocker, **A**CE inhibitor/**A**RB, Hydralazine-Isosorbide Di**N**itrate (or potentially **N**eprilysin inhibitor), **D**iuretics, **A**ldosterone antagonist, **I**vabradine, **D**evices (AICD, CRT or both) and **D**igoxin as a representation of treatments with strong evidence for their use in systolic heart failure. Treatment with omega-3 fatty acids, statins or anti-thrombotic therapies has limited benefits in a general heart failure population. Adoption of this mnemonic for current evidence based treatments for heart failure may help improve prescribing rates and patient outcomes in this debilitating, high mortality condition.

Introduction

Heart failure is a chronic disease with significant morbidity and mortality. In Australia, its prevalence rises from 1% at age 50 years to over 50% at 85 years or older and it is one of the most common reasons for physician consultation and hospital admission in people over 70.[1] Between 20-30% of patients with mild-moderate heart failure and 50% of patients with severe heart failure die within a year.[2] Several evidence based treatments exist that provide both symptomatic and mortality benefits. However, treatment rates are substantially lower than expected rates of intolerance or contraindication – for example, observational data on patient discharges from a regional New South Wales hospital found ACE inhibitors or ARBs were prescribed in only 65% of heart failure patients.[3] In time pressured environments of patient care, simple strategies aimed at improving guideline based prescribing rates are well placed to improve outcomes. Mnemonics are frequently adopted in medical education to recall lists of causes and treatments. The aim of this review was to systematically examine the current evidence base for chronic heart failure treatments in order to derive a contemporary mnemonic for best practice therapies to assist clinicians in their patient care.

Methods

The primary search aim was to identify treatments that provide mortality, hospitalisation or symptomatic benefits, in comparison to placebo, in chronic systolic heart failure patients. A starting list of treatments (pharmacological and device-based) was obtained after reviewing the most recent AHA/ACCF Guidelines (2013),[4] ESC Chronic Heart Failure Guidelines (2012)[5] and Australian National Heart Failure Guidelines (2011).[1] For the purpose of this review, highly specialised therapies such as ventricular assist devices and cardiac transplantation were not included. Both MEDLINE and EMBASE databases were used to obtain reference lists based on a structured search strategy (supplementary appendix, p1). Titles and abstracts were screened to exclude duplicates and unsuitable articles producing a list of studies in which the full text was assessed using PRISMA guidelines to further

determine suitability.[6] Meta-analyses of individual patient data from randomised trials were identified as representative of the highest level of evidence. If these were not available, meta-analyses of published trial data were used, providing the baseline trial populations were considered equivalent. If meta-analyses were not available or suitable, individual randomised controlled trials were sought. Additional factors considered in article selection included the date of publication, the potential for publication bias in meta-analyses, and randomised controlled trial evidence published subsequent to previous meta-analyses. Two co-authors independently performed a literature search and results were jointly reviewed to derive an optimised reference list for each medication.

Results

The search strategy was performed for beta-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), neprilysin inhibitors, hydralazine + isosorbide mononitrate (H-ISDN), diuretics, aldosterone antagonists, ivabradine, implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT), digoxin, omega-3 fatty acids, antithrombotic therapies and HMG-CoA reductase inhibitors (statins). The literature search identified 2527 primary articles after removing duplicates. Of these, 609 manuscripts were selected for full-text review. (Figure 1)

Beta-blockers

Long acting beta-blockers (carvedilol, metoprolol succinate, bisoprolol, bucindolol, nebivolol and atenolol) have a large body of evidence supporting their efficacy in symptomatic heart failure with reduced ejection fraction (≤40%). A meta-analysis of 22 trials involving over 10,000 patients found that beta-blockers (prescribed in addition to ACE inhibitors) reduced the odds of all-cause mortality by 35% (OR 0.65, 95% CI [0.53-0.80]) and hospitalisation for heart failure by 36%, compared to placebo.[7] While individual randomised controlled trials for bucindolol, nebivolol and atenolol have not shown independently significant mortality reductions, a network meta-analysis including these

trials concluded there is no significant difference between individual beta blockers, and that the benefits of beta blockers in heart failure are a class effect.[8] Recently, a large meta-analysis of individual patient data suggested heart failure patients with atrial fibrillation, compared to those in sinus rhythm, may not benefit from mortality reductions with beta-blockers (interaction p<0.0001).[9] Although a highly significant interaction, this has not been a prespecified outcome finding of any randomised controlled trial. Several baseline population differences exist between heart failure patients in sinus rhythm and atrial fibrillation which may have influenced these findings.

Beta-blockers are safest in symptomatic heart failure when initiated at the lowest possible dose and doubled at regular intervals of two weeks, helping to avoid common adverse effects such as worsening heart failure, hypotension and bradycardia.[10] To manage symptomatic hypotension at low doses, the ESC Chronic Heart Failure Guidelines 2012 recommend switching between beta-blockers before reducing the dose of other hypotensive agents such as ACE inhibitors, diuretics or nitrates.[5] Although patients with chronic airway disease were excluded in most clinical trials, cardioselective beta-blockers have demonstrated to be generally safe in the short term, although long term trials are lacking.[11]

Angiotensin Converting Enzyme Inhibitors

A systematic review of randomised controlled trials in moderate-severe heart failure patients (EF ≤35% or ≤40%) showed ACE inhibitors reduce the odds of all-cause mortality by 23% (OR 0.77, 95% CI [0.67-0.88] P<0.001) and readmissions for heart failure by 35%, compared to placebo.[12] Mortality reductions from ongoing therapy have been demonstrated out to twelve years of follow up.[13] The risk of developing atrial fibrillation also appears reduced by ACE inhibitors (or ARBs) in heart failure.[14] In patients with ischaemic heart failure ACE inhibitors also reduce the risk of recurrent myocardial infarction, compared to placebo, by 21%.[15] Overall treatment effects of ACE inhibitors have been shown to be consistent regardless of gender, race and diabetic status,[16] and are additive to beta blocker therapy.

Adverse effects associated with ACE inhibitors include cough, hypotension, hyperkalaemia and renal dysfunction.[15] However, even in most patients with advanced chronic kidney disease they can be used effectively. In the minority of situations where adverse effects have required treatment cessation, such side effects are reversible.

Angiotensin Receptor Blockers

A Cochrane review of 17,900 pooled trial participants with EF≤40% showed that ARBs, compared to placebo, reduced the risk of all-cause mortality by 13% (RR 0.87, 95% CI [0.76-1.00] P=0.05) and readmissions for heart failure by 29%.[17] Compared to ACE inhibitors, ARBs provide similar benefits in terms of reducing the risk of all-cause mortality, total hospitalisations and, in ischaemic heart failure, recurrent myocardial infarction (MI), and have similar side effects, except cough.[17] When used in combination with ACE inhibitors, ARBs further reduce the risk of readmission for heart failure by 19%, but there is no additional reduction in the risk of all-cause mortality or total hospitalisations.[17] Moreover, compared to ACE inhibitor therapy alone, combination therapy is associated with a much greater risk of renal dysfunction (91% higher risk), hyperkalaemia (95%) and symptomatic hypotension (57%).[18]

Hydralazine and Isosorbide Dinitrate (H-ISDN)

H-ISDN have been trialed in combination in heart failure based on their separate and theoretically complementary mechanisms of action - ISDN reduces preload and hydralazine reduces afterload.[19] Together they have been shown to provide mortality benefits and symptomatic relief in systolic heart failure. V-HeFT I demonstrated a 25% lower risk of all-cause mortality and improved exercise capacity with H-ISDN compared to placebo in heart failure patients already receiving digoxin and diuretics.[20] However V-HeFT II, comparing H-ISDN to enalapril, showed a significantly lower all-cause mortality rate with enalapril at 2 years (ARR 5.4%, p=0.02), with a similar but non-significant result at the 2.5 year trial end (ARR 5.4%, p=0.08).[21]

Some preliminary evidence has suggested African Americans may derive greater benefits from H-ISDN than ACE inhibitors, whilst in Caucasians the reverse appears true, but no statistically significant heterogeneity between race and treatment effect for either of these medications has been convincingly demonstrated.[22] Headaches and dizziness (~30%) are common side effects of this therapy.[20, 21] The evidence for using H-ISDN with an ACE inhibitor (or ARB) is sparse (with the exception of use in African Americans), but when the latter are contraindicated, H-ISDN appears a reasonable, possibly less efficacious alternative.

Diuretics

Although diuretics have used for decades to treat volume overload in heart failure, their efficacy is supported by mainly small and dated randomised controlled trials. A Cochrane review comprised of both randomised controlled trials and withdrawal studies found that diuretics reduced the odds of all-cause mortality by 76% (OR 0.24, 95% CI (0.07-0.83), p=0.02) and readmission for heart failure by 93%, while improving exercise capacity compared to placebo.[23] This meta-analysis excluded trials of aldosterone antagonists on the basis that they are not “conventional diuretics”, and hence results reflect trials of mainly loop and hydrochlorothiazide diuretics. Adverse effects of diuretics can include electrolyte and renal function abnormalities.

Aldosterone antagonists

The addition of an aldosterone antagonist (eplerenone or spironolactone) to ACE inhibitor, beta-blocker and other diuretic therapy is a more recently established core component of the standard therapeutic regimen in severe heart failure (EF≤35%). A meta-analysis of 8 randomised controlled trials showed that compared to placebo, aldosterone antagonists reduced the odds of all-cause mortality by 26% (OR 0.74, 95% CI [0.63-0.86] P<0.001), driven mostly by reductions in sudden cardiac deaths (23%).[24] Another meta-analysis showed significant reductions in the odds of all-cause hospitalisation (27%) and improvements in NYHA functional class and ejection fraction (~3%) with aldosterone blockade compared to placebo.[25]

Hyperkalaemia and renal impairment are well known risks for these medications and as a result patients with hyperkalaemia (serum K≥5.0mmol/L) or renal impairment (eGFR<30mL/min/1.73m^2 or serum creatinine >221 µmol/L) were excluded from the large randomised trials. Endocrine side effects from spironolactone include gynaecomastia, decreased libido and, in women, menstrual irregularities. These can be avoided with eplerenone due to greater drug target specificity, which is currently PBS subsidised in Australia for early ischaemic heart failure but not for other aetiologies.

Ivabradine

Ivabradine reduces heart rate by specific inhibition of funny channels (I_f) in the sinus node. A meta-analysis of individual patient data from two large randomised controlled trials in ~12000 patients with a reduced ejection fraction (≤35% or ≤40%) and heart rate ≥70bpm, found ivabradine did not reduce the overall risk of all-cause and cardiovascular mortality but did reduce readmissions for heart failure by 19% and the risk of MI by 23% compared to placebo.[26] In a pre-specified subgroup with baseline heart rate ≥75bpm, the risks of both all-cause mortality (HR 0.89, 95% CI [0.80-1.00] P=0.048) and cardiovascular mortality (HR 0.88, 95% CI [0.78-1.00] P=0.049) were significantly reduced.[26] The treatment effects of ivabradine were independent of NYHA class status and beta-blocker doses.[26]

Ivabradine is generally well-tolerated but adverse effects can include symptomatic bradycardia (4%) and the development of phosphenes (false sensations of seeing lights, 3%).[26] These adverse effects rarely caused withdrawal from treatment in the randomised trials and are reversible when the drug is withdrawn.

Current ESC Chronic Heart Failure Guidelines (2012) and Australian Heart Foundation Guidelines (2011) recommend considering ivabradine in symptomatic heart failure patients (EF ≤35%) with sinus rhythm and HR≥70bpm,[1, 5] noting that PBS authority in Australia restricts subsidies to people with baseline HR>77bpm, which was the subgroup in the SHIFT trial demonstrating mortality benefits.

Devices

AICD

Automatic Implantable Cardioverter Defibrillators (AICDs) are used for the primary prevention of ventricular arrhythmias and sudden cardiac death in heart failure patients. In a meta-analysis of randomised controlled trials of NYHA II-III patients with sinus rhythm and EF ≤35%, AICDs reduced the risk of all-cause mortality by 26% (RR 0.74, 95% CI [0.67-0.83], P<0.00001) compared to medical therapy alone.[27] A mortality benefit was not seen in patients who started therapy within 40 days of having a myocardial infarction,[28] and existing AHA/ACCF guidelines recommend implantation according to an ejection fraction determined more than 40 days post-MI.[4] The same guidelines also recommend AICD implantation in NYHA I ischaemic heart failure patients with a lower ejection fraction (≤30%).[4] There is a lack of evidence for AICDs in NYHA class IV patients which mainly reflects the poor prognosis and typical exclusion of such patients from these trials. The current consensus is that patients should have a prognosis of at least 12 months to warrant AICD insertion.[5]

CRT

Cardiac resynchronisation therapy (CRT) provides an individually optimised pacing of both ventricles to improve pump performance. An individual patient data meta-analysis examined randomised controlled trials of NYHA II-IV participants with sinus rhythm, EF≤35%, increased QRS duration (≥120ms) and optimal medical therapy. It found CRT, compared to control (AICD/pacemaker/optimal medical therapy) was associated with a reduced risk of all-cause mortality by 34% (HR 0.66, 95% CI [0.57-0.77]) and a reduced risk of the combined endpoint of all-cause mortality and hospitalisation for heart failure.[29] Benefits were independent of AICD presence, aetiology of heart failure and QRS morphology, noting the vast majority of subjects had LBBB.

Analyses according to QRS duration have identified greater clinical benefits with longer durations, starting from QRS duration ≥140ms.[29] Conversely a small meta-analysis found a higher mortality risk

for CRT in patients with QRS<130ms compared to medical therapy (RR 1.63, 95% CI [1.07-2.47] P=0.023), despite echocardiographic evidence of dyssynchrony in most patients.[30]

QRS morphology also appears to influence prognosis. A meta-analysis of four CRT trials (n=5356) found CRT significantly reduced composite clinical events in LBBB patients but had no benefits in non-LBBB patients.[31] Long term follow up of the MADIT-CRT trial identified significant reductions in the risk of all-cause mortality (41%) and non-fatal heart failure events (62%) out to seven years in patients with LBBB, but *increased* risks of both outcomes with CRT in patients without LBBB.[32] More data for outcomes in patients with non-LBBB conduction abnormalities are required to help clarify these findings.

CRT and AICD share similar adverse effects including lead problems, infection and mechanical complications. AICDs also risk inappropriate shocks, the psychological stress from which can sometimes significantly impair quality of life.

Currently, major guidelines recommend CRT for NYHA III-IV patients with EF≤35%, sinus rhythm, LBBB and QRS duration ≥120ms. For patients without LBBB, the AHA/ACCF Guidelines (2013) and ESC Chronic Heart Failure Guidelines (2012) recommend CRT at QRS duration (≥150ms). For NYHA II patients international guidelines differ slightly, and the notably harmful findings from long term MADIT-CRT follow up in non LBBB patients suggests the appropriateness of CRT may be limited to more symptomatic patients.[32] Only AHA/ACCF Guidelines (2013) include CRT for NYHA I patients, suggesting consideration in patients with severe ischaemic EF impairment (≤30%), LBBB and a broad QRS (>150ms).

Digoxin

Digoxin has traditionally been used in the setting of atrial fibrillation and advanced heart failure. A Cochrane review showed that digoxin did not reduce all-cause and heart failure mortality but did reduce heart failure symptoms and readmissions for heart failure by 32% (OR 0.68, 95% CI [0.61-

0.75], p<0.00001).[33] Benefits appeared greater in patients with severely reduced ejection fraction (≤25%) or NYHA III-IV functional class.[34] Post-hoc subgroup analyses by serum digoxin concentrations (SDC) found patients within the range 0.5-0.8 ng/mL had their risk of all-cause mortality reduced by 20% (HR 0.80, 95% CI [0.68-0.94] P=0.005). Increased arrhythmic complications have been identified in patients with SDC concentrations ≥1.2 ng/mL.[35] If used in the context of any renal impairment, digoxin requires very careful dose and level monitoring to prevent toxicity.

Drugs with limited evidence

Omega-3 fatty acids

Evidence for fish oil supplementation in heart failure patients is limited but modestly supportive. One randomised controlled trial found that 1g (850-882mg of DHA and EPA in 1.5:1) of omega-3 fatty acids per day, compared to placebo, reduced the risk of all-cause mortality by 9% (HR 0.91, 95% CI [0.833-0.998] P=0.041) at 2 years but did not affect rates of hospitalisation.[36] A meta-analysis of prospective observational studies examining incident heart failure according to fish oil intake demonstrated a linear protective association, with a 5% lower risk per 15g of fish consumed daily.[37] Nausea is the most common side effect but typically does not prompt drug discontinuation.

Antithrombotic therapy in sinus rhythm

Left ventricular systolic dysfunction is associated with an increased risk of thromboembolism in patients with sinus rhythm but the evidence for benefit from antithrombotic therapy is not definitive. In a Cochrane review of trials including heart failure patients in sinus rhythm, warfarin non-significantly reduced the risk of all-cause mortality (OR 0.66, 95% CI [0.36-1.18] P=0.16) compared to placebo.[38] Other larger randomised trials of heart failure have shown no difference between warfarin, aspirin and clopidogrel for mortality risk and reported conflicting findings regarding heart failure readmissions.[39, 40] Warfarin has been shown in heart failure patients to reduce the risk of ischaemic stroke by 48% compared to aspirin[39] and the risk of any stroke compared to either aspirin or clopidogrel.[40]

Factored against these benefits, the risk of major haemorrhage is significantly increased with warfarin use compared to placebo (OR 5.98, 95% CI [1.71-20.93] P=0.0052),[38] aspirin (OR 2.21, 95% CI [1.42-3.47], p<0.001)[39] or clopidogrel (RR 2.48, CI not presented, p=0.007).[40]

Statins

Statins (HMG-CoA reductase inhibitors) are widely used to treat ischaemic heart disease but there is limited evidence for their use in all heart failure patients. A meta-analysis of 10 randomised controlled trials with symptomatic heart failure and standard baseline therapies showed no significant effects with statin therapy vs placebo on the risk of all-cause mortality (OR 0.89, 95% CI [0.72-1.10], p=0.27) or hospitalisations for heart failure, without any excess in adverse events.[41] Current evidence suggests statin prescription should not routinely be given to these patients unless they have other indications such as ischaemic heart or cerebrovascular disease.

ARB and Neprilysin inhibitor combination

LCZ696 (valsartan and sacubitril) is a promising novel combination therapy based on results from a large single phase III randomised controlled trial. The recently published trial included NYHA II-IV patients with reduced ejection fraction (≤40%) and baseline treatment with beta-blockers, diuretics, digoxin and aldosterone antagonists. It found that compared to ACE inhibitor therapy, LCZ696 reduced the risk of all-cause mortality by 16% (HR 0.84; 95% CI, 0.76 to 0.93; P<0.001) and hospitalisation for heart failure by 21%.[42] Whilst data is preliminary and continues to accrue, results are encouraging.

Discussion

Heart failure is a condition with substantial morbidity and mortality and there is an acknowledged deficiency between evidence-based recommended treatments and everyday prescribing patterns. Mnemonics represent a simple way to assist clinicians in their treatment of patients, and in this manuscript we have sought to review the contemporary evidence base for systolic heart failure treatments to devise a mnemonic summarising these treatments. Based on this review we propose use of the mnemonic BANDAID[2] - representing **B**eta-blocker, **A**CE inhibitor/**A**ngiotensin Receptor Blocker, **N**itrates-Hydralazine (or potentially **N**eprilysin inhibitor in the future), **D**iuretics, **A**ldosterone Antagonist, **I**vabradine, **D**evices and **D**igoxin in approaching the treatment of systolic heart failure.

There is strong evidence to support the use of beta-blockers, ACE inhibitors and ARBs in systolic heart failure, noting a choice of either ACE inhibitor or ARB is generally preferable to the use of both. Treatment with H-ISDN is effective but inferior to ACE inhibitors (and to ARBs by indirect comparison) in the general population. The novel combination therapy LCZ696 (valsartan and sacubitril (a neprilysin inhibitor)) has promising preliminary results but more research is required. The evidence for diuretics is limited but supports a mortality reduction and their symptomatic benefits in treating fluid overload are undisputed. Aldosterone antagonists significantly reduce mortality and hospitalisations in heart failure patients. Ivabradine reduces hospitalisations for heart failure in sinus rhythm patients with HR≥70bpm and, in patients with resting heart rate ≥75bpm, reduces both all-cause and cardiovascular mortality. However beta blockers should be used prior to ivabradine, when possible, on account of more definitive mortality benefits. AICDs reduce the risk of sudden cardiac death in medically stabilised, NYHA II-III patients with EF≤35% in sinus rhythm, noting some recommendations for use in NYHA I ischaemic heart failure patients. CRT-D reduces mortality amongst NYHA III-IV patients with EF≤35% in sinus rhythm, with recommendations according to QRS morphology and duration – for LBBB ≥120ms and for non-LBBB >150ms, noting use amongst NHYA II

and I patients is more controversial due to evidence of harm in some non-LBBB settings. Recommendations for digoxin are less definitive because of a lack of clear mortality benefit despite reductions in hospitalisations. Most guidelines therefore recommend digoxin as the last line of treatment for heart failure, irrespective of rhythm.

Importantly, most of these medications or device interventions were trialed in patients receiving existing standards of care of the time for heart failure. This provides reassurance that risk reductions from treatments should in most instances be additive when used in combination in appropriately selected patients. (Figure 2)

An area not examined in this review is the critical role of heart failure outpatient services in providing the frequent monitoring and consultation patients with advanced heart failure require. Prevention of hospitalisations and associated morbidity can successfully be achieved by titrating medication doses, particularly diuretics, early in the course of deteriorating symptoms or increasing weight. Similarly, advances in remote ICD/PPM monitoring allow expedited responses to rhythm, rate and other physiological changes which can effectively prevent patient deteriorations. Beyond achieving standards in pharmacological and device therapeutics, the importance of frequent monitoring and review in heart failure patients cannot be overstated.

Conclusion

It is essential that patients are prescribed optimal evidence-based therapies in both hospital and community settings, as effective management of heart failure can substantially reduce morbidity and mortality. Consideration of BANDAID^2, representing a current evidence based treatment mnemonic for patients with systolic heart failure, could improve prescribing rates and therefore patient outcomes in this complex chronic disease.

Funding

This work was supported by funding from the Sydney Medical School and NHMRC Clinical Trials Centre, University of Sydney, NSW, Australia. The sponsors played no role in study design, data collection, data analysis, manuscript preparation or manuscript submission.

References

1. Krum H, Jelinek MV, Stewart S, Sindone A, Atherton JJ. 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Med J Aust. 2011; **194**(8): 405-9.
2. National Heart Foundation of Australia. A systematic approach to chronic heart failure care: a consensus statement. Melbourne: National Heart Foundation of Australia; 2013.
3. Yao D-K, Wang L-X, Curran S, Ball P. Adherence to treatment guidelines in the pharmacological management of chronic heart failure in an Australian population. Journal of geriatric cardiology: JGC. 2011; **8**(2): 88.
4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013; **128**(16): e240-327.
5. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur J Heart Fail. 2012; **14**(8): 803-69.
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009; **151**(4): 264-9.
7. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. Ann Intern Med. 2001; **134**(7): 550-60.
8. Chatterjee S, Biondi-Zoccai G, Abbate A, et al. Benefits of (beta) blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. BMJ. 2013; **346**.
9. Kotecha D, Holmes J, Krum H, et al. Efficacy of (beta) blockers in patients with heart failure plus atrial fibrillation: An individual-patient data meta-analysis. The Lancet. 2014; **384**(9961): 2235-43.
10. Gottlieb SS, Fisher ML, Kjekshus J, et al. Tolerability of β-Blocker Initiation and Titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Circulation. 2002; **105**(10): 1182-8.
11. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005; **4**.
12. Garg R, Yusuf S, Bussmann W, et al. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA. 1995; **273**(18): 1450-6.
13. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet. 2003; **361**(9372): 1843-8.
14. Zhang Y, Zhang P, Mu Y, et al. The role of renin-angiotensin system blockade therapy in the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. Clin Pharmacol Ther. 2010; **88**(4): 521-31.
15. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet. 2000; **355**(9215): 1575-81.
16. Shekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol. 2003; **41**(9): 1529-38.
17. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. Cochrane Database Syst Rev. 2012; (4).
18. Kuenzli A, Bucher HC, Anand I, et al. Meta-analysis of combined therapy with angiotensin receptor antagonists versus ACE inhibitors alone in patients with heart failure. PLoS ONE. 2010; **5**(4): e9946.

19. Cole RT, Kalogeropoulos AP, Georgiopoulou VV, et al. Hydralazine and Isosorbide Dinitrate in Heart Failure: Historical Perspective, Mechanisms, and Future Directions. Circulation. 2011; **123**(21): 2414-22.
20. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986; **314**(24): 1547-52.
21. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991; **325**(5): 303-10.
22. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. J Card Fail. 1999; **5**(3): 178-87.
23. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev. 2012; **2**: CD003838.
24. Bapoje SR, Bahia A, Hokanson JE, et al. The Effects of Mineralocorticoid Receptor Antagonists on the Risk of Sudden Cardiac Death in Patients with Left Ventricular Systolic Dysfunction: A Meta-analysis of Randomized Controlled Trials. Circulation: Heart Failure. 2013; **6**(2): 166-73.
25. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. Eur Heart J. 2009; **30**(4): 469-77.
26. Fox K, Komajda M, Ford I, et al. Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. Eur Heart J. 2013; **34**(29): 2263-70.
27. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. J Am Coll Cardiol. 2004; **44**(11): 2166-72.
28. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic Use of an Implantable Cardioverter–Defibrillator after Acute Myocardial Infarction. N Engl J Med. 2004; **351**(24): 2481-8.
29. Cleland JG, Abraham WT, Linde C, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013; **34**(46): 3547-56.
30. Shah RM, Patel D, Molnar J, Ellenbogen KA, Koneru JN. Cardiac-resynchronization therapy in patients with systolic heart failure and QRS interval≤ 130 ms: insights from a meta-analysis. EP Europace. 2014.
31. Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J. 2012; **163**(2): 260-7. e3.
32. Goldenberg I, Kutyifa V, Klein HU, et al. Survival with Cardiac-Resynchronization Therapy in Mild Heart Failure. N Engl J Med. 2014; **370**(18): 1694-701.
33. Hood WB, Jr., Dans AL, Guyatt GH, Jaeschke R, McMurray JJ. Digitalis for treatment of heart failure in patients in sinus rhythm. Cochrane Database Syst Rev. 2014; **4**: CD002901.
34. Digitalis Investigation G. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997; **336**(8): 525-33.
35. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2003; **289**(7): 871-8.
36. Gissi-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008; **372**(9645): 1223-30.
37. Djousse L, Akinkuolie AO, Wu JHY, Ding EL, Gaziano JM. Fish consumption, omega-3 fatty acids and risk of heart failure: A meta-analysis. Clin Nutr. 2012; **31**(6): 846-53.
38. Lip GY, Shantsila E. Anticoagulation versus placebo for heart failure in sinus rhythm. Cochrane Database Syst Rev. 2014; **3**: CD003336.

39. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012; **366**(20): 1859-69.
40. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation. 2009; **119**(12): 1616-24.
41. Lipinski MJ, Cauthen CA, Biondi-Zoccai GGL, et al. Meta-analysis of randomized controlled trials of statins versus placebo in patients with heart failure. The American journal of cardiology. 2009; **104**(12): 1708-16.
42. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014; **371**(11): 993-1004.

Figure Legends

Figure 1. PRISMA flow diagram for search strategy results.

Figure 2. Effects on total mortality in patients with systolic heart failure, by treatment allocation compared to placebo.

OR=odd ratio; HR=hazard ratio; RR=risk ratio

*Combination pharmacotherapy represents a broad estimate of the potential clinical benefits from combining treatments marked with an asterisk. The effect of diuretics has not been included due to a broad confidence interval.

†Trial result comparing ARB+Neprilysin inhibitor to ACE inhibitor.

Table 1. Effects of systolic heart failure treatments included in the BANDAID[2] mnemonic on total mortality and hospitalisation rates.

Drug	Comparison	Trial type	End points	HR/RR/OR	ARR for Mortality
Beta-blockers	Placebo [7]	Meta-analysis	Total mortality (22 RCTs, n=10,135)	OR 0.65, 95% CI [0.53-0.80]	4.4% at 1 year
			Hospitalisation for HF (22 RCTs, n= 10,076)	OR 0.64, 95% CI [0.53-0.79]	
ACEI	Placebo [12]	Meta-analysis	Total mortality (32 RCTs, n=7105)	OR 0.77, 95% CI [0.67-0.88], P<0.001	≤3 months: 5.4% 3 months to 4 years: 5.8%
			Total mortality or hospitalisation for HF (30 RCTs, n=6988)	OR 0.65, 95% CI [0.57-0.74], P<0.001	
ARB	Placebo [17]	Meta-analysis	Total mortality (9 RCTs, n=4643)	RR 0.87, 95% CI [0.76-1.00], P=0.05	7.1% at 1.3 years
			Hospitalisation for HF (3 RCTs, n=2590)	RR 0.71, 95% CI [0.61-0.82] P<0.00001	
	ACEI [17]	Meta-analysis	Total mortality (8 RCTs, n=5201)	RR 1.05, 95% CI [0.91-1.22], P=0.48	NA
			Hospitalisation for HF (3 RCTs, n=4310)	RR 0.96, 95% CI [0.83-1.11], P=0.58	
ARB+ACEI	ACEI [17]		Total mortality (7 RCTs, n=8260)	RR 0.98, 95% CI [0.90-1.06], P=0.60	NA
			Hospitalisation for HF (4 RCTs, n=8108)	RR 0.81, 95% CI [0.74-0.89], P<0.00001	
H-ISDN	Placebo [20]	RCT	Total mortality (n=642)	RR 0.66, 95% CI [0.46-0.96], P<0.028	5.3% at 2 years
	ACEI [21]	RCT	Total mortality (n=804)	RR 1.39 (CI not stated), P=0.016	-5.4% at 2 years
LCZ696 (ARB + Neprilysin inhibitor)	ACEI [42]	RCT,	Total mortality (n=10521)	HR 0.84, 95% CI [0.76-0.93], P<0.001	4.7% at 2.3 years
			Hospitalisation for HF (n=10521)	HR 0.79, 95% CI [0.71-0.89], P<0.001	

Diuretics	Placebo [23]	Meta-analysis	Total mortality (3 studies (1 RCT), n=202)	OR 0.24, 95% CI [0.07-0.83], P=0.02	8% at ~6months
			Hospitalisation for HF 2 withdrawal studies, n=169	OR 0.07, 95% CI [0.01-0.52], P=0.01	
Aldosterone antagonist	Placebo	Meta-analysis	Total mortality [24] (7 RCTs, n=11,826)	OR 0.74, 95% CI [0.63-0.86], P<0.001	10.4% at 2.2 years
		Meta-analysis	All-cause hospitalisation [25] (7 RCTs, n=8699)	RR 0.73, 95% CI [0.63-0.84], P<0.0001	
Ivabradine	Placebo [26]	Meta-analysis	Total mortality (2 RCTs, n=7632)	HR 0.96, 95% CI 0.87-1.05, p=NS (Overall population) HR 0.89, 95% CI [0.80-1.00], P=0.048 (HR≥75bpm subgroup)	NA 2% at 1.8 years
			Hospitalisation for HF (2 RCTs, n=7632)	HR 0.78, 95% CI [0.70-0.87] P<0.0001	
AICD	Medical therapy [27]	Meta-analysis	Total mortality (7 RCTs, n=4981)	RR 0.74, 95% CI [0.67-0.83], P<0.00001	6.5% at 2 years
CRT	AICD or medical therapy [29]	Meta-analysis	Total mortality (5 RCTs, n=3872)	HR 0.66, 95% CI [0.57-0.77]	2.9% at 1 year
			Total mortality or hospitalisation for HF (5 RCTs, n=3872)	HR 0.65, 95% CI [0.58–0.74]	
Digoxin	Placebo [33]	Meta-analysis	Total mortality (8 RCTs, n=7755)	OR 0.98, 95% CI [0.89-1.09], P=0.76	NA at 3 years
			Hospitalisation for HF (4 RCTs, n=7262)	OR 0.68, 95% CI [0.61-0.75], P<0.00001	
			Improved clinical status 12 studies, n=1234	OR 0.31, 95% CI [0.21-0.43], P<0.00001	

HR=hazard ratio; RR=risk ratio; OR=odds ratio. These methods give similar estimates when event rates are relatively low.

ARR=absolute risk reduction.

Table 2. Indications, contraindications and major society recommendations for systolic heart failure treatments.

Treatment	Indications	Level of Evidence	Class/Grade of Recommendation	Contraindications	
				Relative	**Absolute**
Beta-blocker	▪ NYHA II-IV ▪ EF ≤40%	ESC: A ACCF/AHA: A	ESC: I ACCF/AHA: I NHF: A	▪ Conduction disease ▪ Symptomatic hypotension or bradycardia ▪ Reversible airways disease	▪ Hypersensitivity ▪ Decompensated heart failure
ACE inhibitor/ARB	▪ NYHA I-IV ▪ EF ≤40%	ESC: A ACCF/AHA: A	ESC: I ACCF/AHA: I NHF: A	▪ Renal dysfunction ▪ Hypotension	▪ Hypersensitivity ▪ Pregnancy
Nitrate-Hydralazine	▪ Alternative to ACEI/ARB (General population) OR ▪ Addition to ACEI (African Americans) ▪ NYHA III-IV ▪ EF ≤35%	ESC: B ACCF/AHA: B (ACCF/AHA: A for African Americans)	ESC: IIb ACCF/AHA: IIa NHF: B (ACCF/AHA: I for African Americans)	▪ Hypotension ▪ Intolerable headache	▪ Hypersensitivity
Diuretics	▪ Volume overload	ESC: N/A ACCF/AHA: C	ESC: I ACCF/AHA: I NHF: D	▪ Hyponatraemia ▪ Hypokalemia ▪ Hypotension	▪ Hypersensitivity
Aldosterone antagonist	▪ NYHA II-IV ▪ EF ≤35%	ESC: A ACCF/AHA: A	ESC: I ACCF/AHA: I NHF: B	▪ Hyperkalemia (>5.0 mmol/L) ▪ Stage 1-2 CKD	▪ Hypersensitivity ▪ Stage 3+ CKD
Ivabradine[i]	▪ NYHA II-IV ▪ EF ≤35% ▪ Sinus rhythm ▪ HR ≥70bpm ▪ Maximum	ESC: B ACCF/AHA: N/A	ESC: IIa ACCF/AHA: N/A NHF: B	▪ Hypotension ▪ Moderate-severe hepatic failure ▪ End stage renal failure ▪ Combination with	▪ Hypersensitivity ▪ Sick sinus syndrome ▪ AV or SA block ▪ HR<50

		tolerable BB dose			cytochrome P450 3A4 inhibitors	
Devices	AICD	▪ NYHA II-III ▪ EF ≤35% ▪ Sinus rhythm ▪ Medical therapy ≥3 months ▪ Prognosis ≥1 year	ESC: A[ii] ACCF/AHA: A	ESC: I ACCF/AHA: I NHF: A	▪ Incessant VT/VF ▪ Severe psychiatric conditions ▪ Poor prognosis ▪ Extensive lateral LV wall scarring (CRT)	▪ Uncontrolled systemic infection ▪ Unsuitable vascular anatomy
	CRT	▪ QRS ≥120ms ▪ Refer to specific criteria for each NYHA class in guidelines	ESC: A ACCF/AHA: A	ESC: I ACCF/AHA: I NHF: A		
Digoxin		▪ Last line therapy for symptomatic relief	ESC: B ACCF/AHA: B	ESC: IIb ACCF/AHA: IIa NHF:B	▪ Renal dysfunction	▪ Hypersensitivity

[i] Ivabradine is recommended for HR ≥70bpm in Australian National Heart Foundation Guidelines (2011) but PBS subsidies are only provided for HR≥77bpm.
[ii] Level B for non-ischaemic causes of heart failure
[iii] Level of evidence and class of recommendation varies according to criteria
[iv] Class IIa for non-LBBB QRS morphology

Figure 1. PRISMA flow diagram for search strategy results.

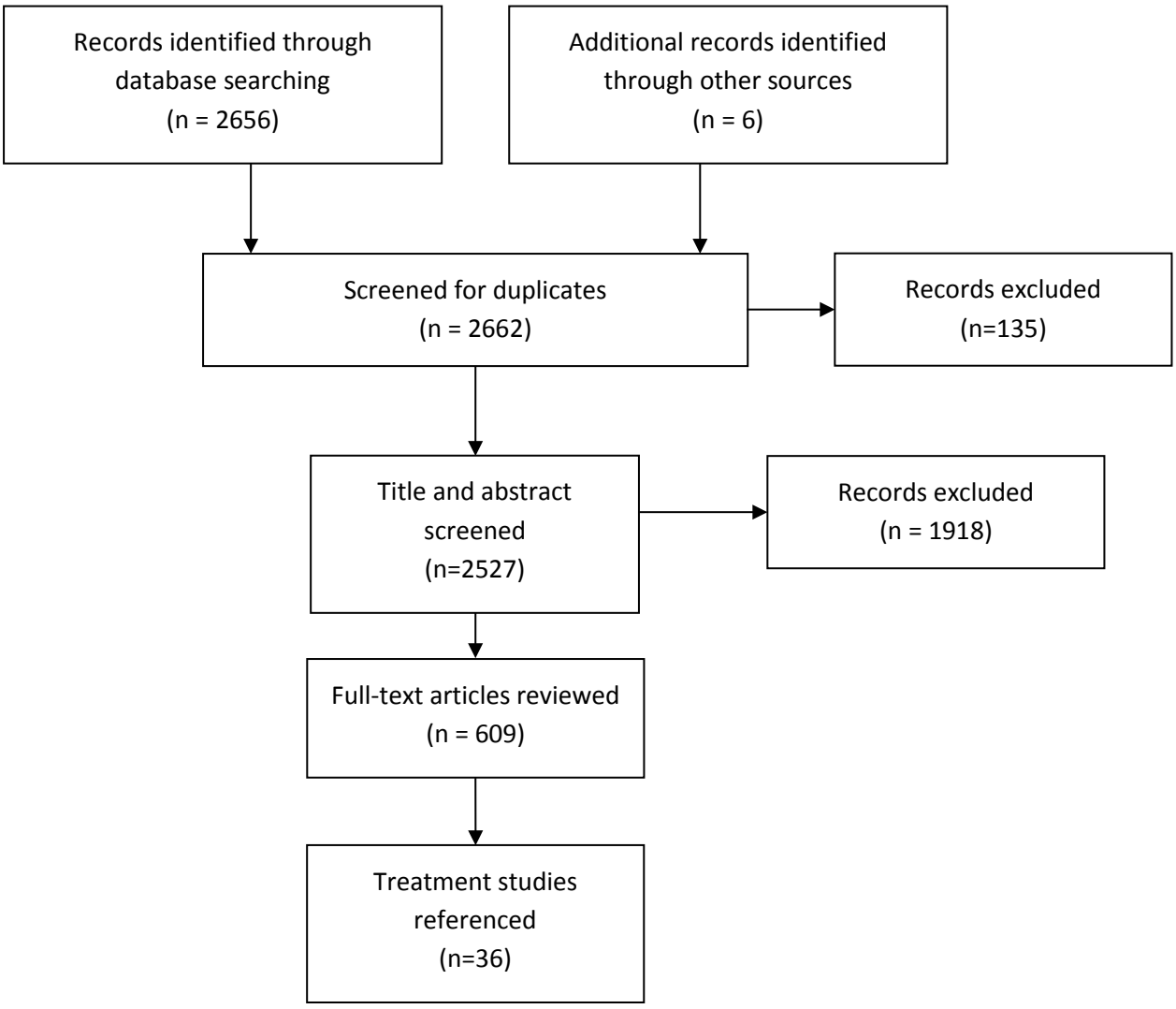
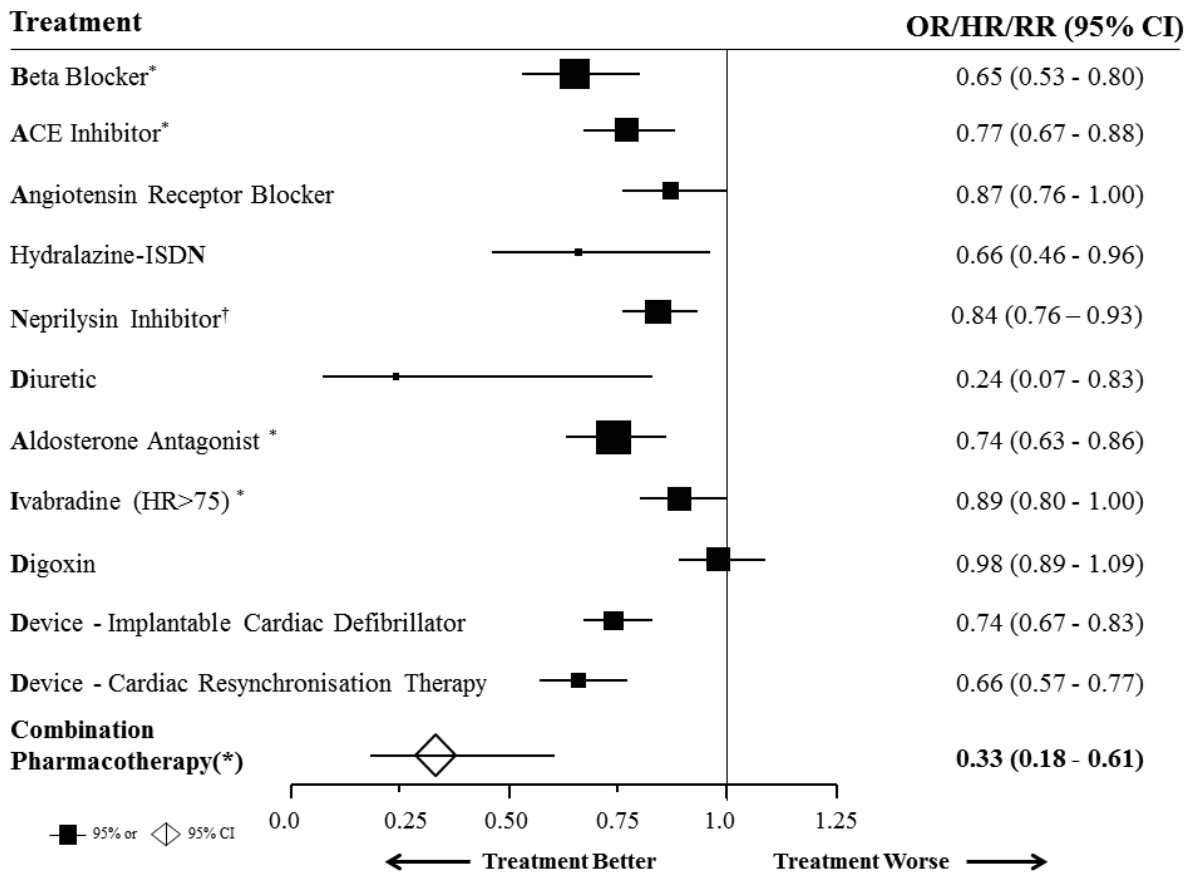


Figure 2. Effects on total mortality in patients with systolic heart failure, by treatment allocation compared to placebo.



OR=odd ratio; HR=hazard ratio; RR=risk ratio

*Combination pharmacotherapy represents a broad estimate of the potential clinical benefits from combining treatments marked with an asterisk. The effect of diuretics has not been included due to a broad confidence interval.

†Trial result comparing ARB+Neprilysin inhibitor to ACE inhibitor.

Supplementary Appendix

Search strategy

Keyword searches were performed in Medline and Embase as described below, for the following treatments:

“angiotensin-converting enzyme inhibitors”, “angiotensin receptor antagonists”, “adrenergic beta-antagonists” (Medline) or “beta adrenergic receptor blocking agent” (Embase), diuretics (Medline) or “diuretic agent” (Embase), “mineralocorticoid receptor antagonists” (Medline) or “aldosterone antagonist” (Embase), “ivabradine”, “defibrillators, implantable” (Medline) or “'implantable cardioverter defibrillator” (Embase), “cardiac resynchronization therapy”, “digoxin”, [“isosorbide dinitrate” or “hydralazine”], “fatty acids, omega-3” (Medline) or “omega 3 fatty acid” (Embase), [“Anticoagulants” or “Warfarin” or “Platelet Aggregation Inhibitors” or “Aspirin” or “Purinergic P2Y Receptor Antagonists”] (Medline) or [“anticoagulant agent” or “antithrombocytic agent”] (Embase), “hydroxymethylglutaryl-CoA reductase inhibitors” (Medline) or “'hydroxymethylglutaryl coenzyme a reductase inhibitor” (Embase), “neprilysin inhibitor” (Medline) or “enkephalinase inhibitor” (Embase)

MEDLINE:

1. “meta-analysis or systematic review or randomised controlled trial or randomized controlled trial”[Publication Type], 2. “(heart failure or ventricular dysfunction)”[Subject Heading], 3. 1 & 2, 4. Limit 3 to “core clinical journals (aim)” and “English language”, 5. “(drug name)”[Subject Heading], 6. 4 & 5.

EMBASE:

1.'heart failure'/mj OR 'ventricular dysfunction'/mj AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim) AND [humans]/lim AND [english]/lim 2.'drug name'/mj 3.1 & 2.