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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	2
OBJECTIVES	4
METHODS	4
ACKNOWLEDGEMENTS	7
REFERENCES	8
ADDITIONAL TABLES	11
APPENDICES	11
CONTRIBUTIONS OF AUTHORS	12
DECLARATIONS OF INTEREST	12
SOURCES OF SUPPORT	12

[Intervention Protocol]

LCZ696 (sacubitril/valsartan) for patients with heart failure

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess benefits and harms of first-in-class angiotensin receptor-neprilysin inhibitor sacubitril/valsartan (LCZ696) as compared to angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in chronic heart failure (HF) patients with either reduced, mid-range, or preserved ejection fraction.

BACKGROUND

Description of the condition

Heart failure (HF) is a leading cause of morbidity and mortality worldwide (Ponikowski 2016; Bleumink 2004; Ho 1993). Despite the effectiveness of preventive measures and better control of risk factors, especially in younger patients, morbidity is still increasing (Guha 2013). Advanced device-based therapies have prolonged survival in patients with HF; however, optimisation of pharmacological treatment remains the principal means of management. HF is not one distinct disease but a clinical syndrome characterised by typical signs and symptoms (Ponikowski 2016). Currently, three types of HF are defined by left ventricular ejection fraction (LVEF): HF with reduced LVEF (< 40%; HFrEF), HF with mid-range LVEF (40% to 49%; HFmrEF), and HF with preserved LVEF (≥ 50%; HFpEF) (Ponikowski 2016). The current American College of Cardiology Foundation/American Heart Association (ACC/AHA) guidelines state that characteristics, treatment options and outcomes in patients with HFmrEF are similar to those of patients with HFpEF (Yancy 2013). There are still ongoing studies with the aim of recognising the underlying characteristics, pathophysiology, treatment and differences between types of HF patients (Rickenbacher 2017). In the USA, prevalence of chronic heart failure (CHF) is over 5.7 million, with 670,000 new cases yearly and a cost of about USD 32 billion annually in treatment expenditures and lost productivity (Van Nuys 2018). The prevalence of HF is approximately 1% to 2% of the adults in developed countries, and 10% or more among people over 70 years of age. The lifetime risk of HF at age 55 years is 33% for men and 28% for women (Ponikowski 2016; Bleumink 2004). Farré and colleagues found that 8.8% of HF patients had an HF hospitalisation at 1-year follow-up; however about 30% had an all-cause hospitalisation (Farré 2017). CHF hospitalisation rates are about 1% to 2% of all hospitalisations yearly and it is the leading cause of hospital stay in patients over 65 years of age (Mahmood 2013). Despite optimisation of therapy according to current guidelines, including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), beta-blockers, ivabradine, loop diuretics and mineralocorticoid receptor antagonists for chronic systolic HF, this disease remains a leading cause of morbidity, mortality, and health care costs (Farré 2017).

Description of the intervention

The suspected therapeutic success of the augmentation of neurohumoral systems with the use of natriuretic peptides did not have positive results (Bevan 1992). The introduction of synthetic natriuretic peptides into HF management has not improved outcomes in acute HF but modulation of the natriuretic system through inhibition of neprilysin, the enzyme that degrades natriuretic peptides (NP), has been successful (Bevan 1992). Inhibition of neprilysin increases the levels of these substances and also decreases vasoconstriction, abnormal growth, sodium retention and remodelling (McMurray 2014). High levels of circulating A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) exert their physiologic effects through binding to receptors for NP and stimulating the production of cyclic guanosine monophosphate (cGMP), thereby enhancing natriuresis and diuresis, and consequently myocardial relaxation and anti-remodelling effects (Matsuo 2019). ANP and BNP are also able to inhibit secretion of renin and aldosterone (Matsuo 2019). Angiotensin II is a substrate of neprilysin, however.

Thus, the addition of an ARB to the neprilysin inhibitor is necessary to prevent activation of the renin-angiotensin-aldosterone system (RAAS). Neprilysin inhibition alone raises natriuretic peptide levels but also increases angiotensin II levels, potentially counteracting the actions of the former peptides (Jhund 2016). A dual neprilysin-angiotensin converting enzyme (ACE) inhibition did not show benefits in the primary end point — death from any-cause or HF hospitalisations (Packer 2002). However, the Prospective comparison of angiotensin receptor neprilysin inhibitor (ARNI) with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial demonstrated improved morbidity and mortality with the combination of neprilysin inhibitor/angiotensin receptor blocker sacubitril/valsartan (formerly known as LCZ696) (Bevan 1992; Solomon 2012; Srivastava 2018). In the PARADIGM-HF trial, the long-term effects of sacubitril/valsartan 200 mg twice daily compared with enalapril 10 mg twice daily in patients with HFrEF was assessed. To be considered for trial inclusion, patients were required to tolerate a stable dose of a beta blocker and an ACE inhibitor or ARB equivalent of at least 10 mg of enalapril daily for at least four weeks prior to trial screening and to have systolic blood pressure of at least 100 mmHg (McMurray 2014). In comparison to enalapril, sacubitril/valsartan reduced the occurrence of the primary outcome (cardiovascular death or hospitalisation for HF) by 20% and delivered a 16% reduction in all-cause mortality (Desai 2015).

How the intervention might work

Myocardial wall stress is the main stimulus for increased BNP and NT-probrain natriuretic peptide (NT-proBNP) synthesis and secretion. Vasoconstriction and sodium and water retention caused by activation of RAAS, activity of vasopressin and the sympathetic nervous system in HF patients lead to elevated wall stress and increased ventricular preload and afterload which in turn lead to production of pre-pro BNP which is cleaved to BNP and N-terminal proBNP (NT-proBNP) (Daniels 2007; Jhund 2016; Marques da Silva 2017). Also, other neurohormones such as angiotensin II and endothelin A may influence the release of NP (Rademaker 2004). The pre-pro ANP has similar biological properties to BNP and NT-proBNP and is produced as a response to atrial stretching (Daniels 2007). The physiological effects of BNP comprise natriuresis/diuresis, peripheral vasodilatation, and inhibition of RAAS and the sympathetic nervous system. ANP plays a pivotal role in modulation of vascular function.

The first attempt to improve outcomes in HFrEF via modulation of the above physiological pathways was the administration of exogenous natriuretic peptides. Nesiritide, a recombinant human BNP, initially showed promising beneficial effects on haemodynamics and natriuresis in patients with HFrEF (Schulz-Knappe 1988). However, in a large-scale randomised controlled trial, nesiritide therapy was not associated with an increase or a decrease in the rate of death and rehospitalisation (it had a small, nonsignificant effect on dyspnoea when used in combination with other therapies but it was associated with an increase in rates of hypotension) (O'Connor 2011). The recombinant ANP-carperotide is used as a treatment for acute HF in Japan but there is no evidence supporting this practice (Matsue 2015).

The second option was to inhibit the breakdown of natriuretic peptides as we know that natriuretic peptides are cleaved and inactivated by a membrane-bound endopeptidase, neprilysin.

However there were no benefits after attempts at inhibiting neprilysin using oral and intravenous formulations (Bevan 1992). This might be explained by the finding that neprilysin also breaks down angiotensin II (Ferro 1998). Therefore inhibiting neprilysin may simultaneously increase the level of angiotensin II and other substrates such as endothelin, vasopressin, bradykinin, etc. potentially counteracting the actions of the natriuretic peptides. The resolution for such process should be omapatrilat — the combination of ACE and neprilysin inhibitor which in a large randomised controlled trial against enalapril 10 mg twice daily (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial; Packer 2002) showed a reduction of mortality and hospitalisation in chronic HF; it was, however, no more effective than ACE inhibition alone. An additional problem with this drug was connected with an unintended excessive level of bradykinin and high rates of serious angio-oedema. Both ACEI and neprilysin break down bradykinin; and omapatrilat also inhibits aminopeptidase P, which also catabolises bradykinin. The results of OVERTURE led to the discontinuation of the clinical development of this drug (Packer 2002). Scientists concluded that combining ARB and a neprilysin inhibitor may resolve the problem encountered with omapatrilat. The ARNI sacubitril/valsartan was designed to inhibit neprilysin while blocking the adverse effects of RAAS and reducing bradykinin potentiation (Hegde 2011; Jhund 2016; Marques da Silva 2017). Inhibition of neprilysin increases the levels of natriuretic peptides, bradykinin, and substance P and in this way decreases vasoconstriction, sodium retention, abnormal growth, and remodelling (McMurray 2014). However, angiotensin II is also a substrate of neprilysin. Thus, the addition of an ARB to the neprilysin prevents the activation of the RAAS. Sacubitril (LBQ657), an active metabolite of sacubitril, does not inhibit aminopeptidase P so the risk of angio-oedema was expected to be lower than with omapatrilat (Hegde 2011; Jhund 2016; Marques da Silva 2017). Given twice daily, sacubitril/valsartan causes neprilysin and RAAS inhibition over a 24-hour period (McMurray 2013). The systemic exposure delivered by sacubitril/valsartan 97 mg/103 mg (200 mg LCZ696) is equivalent to 160 mg of valsartan and after this dosage neprilysin is almost completely inhibited for up to 12 hours (Hegde 2011; Jhund 2016; Marques da Silva 2017).

Why it is important to do this review

Inhibition of chronically activated neurohormonal pathways (RAAS and sympathetic nervous system (SNS)) is now a basis of chronic HFrEF treatment (Marques da Silva 2017). Positive effects of natriuretic peptides on cardiovascular system and renal function in HF may bring additional benefits to HF patients as therapy complements to RAAS and SNS blockade (Marques da Silva 2017). Sacubitril/valsartan represents a novel form of pharmacotherapy that acts by enhancing the natriuretic peptides system via inhibition of neprilysin and by suppressing the RAAS via AT1 receptor blockade, thereby producing more effective neurohormonal modulation than can be achieved with RAAS inhibition alone (Jhund 2016; Marques da Silva 2017). In PARADIGM-HF, a multicentre trial performed in 47 countries (8399 patients randomised), patients with HFrEF treated with sacubitril/valsartan had 20% lower risk of cardiovascular death or hospitalisation due to HF, 20% lower risk of cardiovascular death, 21% lower risk of first hospitalisation due to HF, and 16% lower risk of death from any cause, compared with enalapril (all $P < 0.001$) (Simpson 2015). In this trial, the sacubitril/valsartan group had a higher proportions of

patients with hypotension (< 0.001) but lower number of patients with renal impairment with serum creatinine (≥ 2.5 mg/dL, $P = 0.007$), hyperkalaemia (> 6 mmol/L, $P = 0.007$), and cough ($P < 0.001$) compared with the enalapril group. In the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fraction (PARAMOUNT) trial, 301 patients with HFpEF were randomised to valsartan alone or sacubitril/valsartan (Solomon 2012). In this study the concentration of NT-proBNP fell in the sacubitril/valsartan group, and reductions in HF aggravation according to New York Heart Association (NYHA) classification and reductions of left atrial volumes were also observed. The results of the large multicentre PARAGON-HF trial of sacubitril/valsartan versus valsartan in HFpEF showed a nonsignificantly lower rate of total hospitalisations for heart failure or death from cardiovascular causes among patients with heart failure and an ejection fraction of 45% or higher (690 total hospitalisations for heart failure in the sacubitril/valsartan group and 797 in the valsartan group; risk ratio (RR) 0.85, 95% confidence interval (CI) 0.72 to 1.00; 8.5% and 8.9% of deaths from cardiovascular causes with HR 0.95, 95% CI 0.79 to 1.16, respectively) (Solomon 2018; Solomon 2019). The primary composite outcome of hospitalisations for heart failure and death from cardiovascular causes showed a modest nonsignificant 13% relative reduction, which was driven mainly by a reduction in first and recurrent HF hospitalisations. The use of an ARB as an active comparator in PARAGON-HF may have attenuated the overall treatment effect. Secondary analyses included improvement in symptoms, renal function, and quality of life with the use of sacubitril/valsartan compared with valsartan alone (Solomon 2019). Sacubitril/valsartan is recommended to replace ACEIs in ambulatory HFrEF patients who remain symptomatic despite optimal therapy and is also recommended in symptomatic HFrEF patients with ventricular arrhythmia according to the 2016 European Society of Cardiology (ESC) chronic heart failure guidelines (Ponikowski 2016). The benefits and harms of sacubitril/valsartan in HFrEF, HFmrEF and HFpEF have not been formally evaluated in a systematic review.

Neprilysin inhibition is a confirmed therapeutic strategy in treating chronic heart failure with reduced LVEF and preliminary data suggested a potential role for the use of ARNI in a broader spectrum of cardiovascular diseases like post-acute myocardial infarction, heart failure with preserved ejection fraction, hypertension, arrhythmias, and chronic kidney diseases (Haynes 2018; Riddell 2017).

Gaps in evidence in recent ESC heart failure guidelines indicate the need for further studies of therapies for HFmrEF or HFpEF including ARNIs as well as a better understanding of pathophysiology and potential treatments in specific HF populations, including the very elderly, young patients, diabetic patients, cardiotoxic chemotherapy-induced HF, cachexia and depression (Ponikowski 2016). According to current 2017 ACC/AHA/HFSA guidelines for the management of heart failure (Yancy 2017), the clinical strategy of inhibition of the RAAS with ARNI (Level of Evidence: B-R) in conjunction with beta blockers and aldosterone antagonists in selected patients is recommended for patients with chronic HFrEF to reduce morbidity and mortality. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality in ESC guidelines (Yancy 2017), and LCZ696 is recommended for HFrEF patients NYHA II-IV (Ponikowski 2016). There are still no head-to-head comparisons of an ARB versus

ARNI, so for those patients for whom an ACE inhibitor or ARNI is inappropriate, use of an ARB remains advised. To facilitate initiation and titration, the approved ARNI is available in three doses that include a dose that was not tested in the HF trial; the target dose used in the trial was 97/103 mg twice daily. Clinical studies and meta-analyses are needed to provide further information about the effect of doses different from the assessed 97/103 mg twice daily, about optimal titration and tolerability of ARNI, particularly regarding to blood pressure, and adjustment of concomitant HF medications. There are also gaps in evidence in US guidelines about effects of ARNI in NYHA class I and IV patients and patients with HFmrEF and HFpEF. Use of an ARNI is associated with hypotension and a low incidence of angio-oedema. We need further research to assess safety of ARNI in heart failure patients (Yancy 2017).

The recently finished EVALUATE-HF trial evaluated sacubitril/valsartan versus enalapril in HFrEF; investigators did not find significant reductions of central aortic stiffness. Authors found significant effects on myocardial remodelling and wall stress, however (Desai 2019; NCT02874794).

PIONEER-HF trial was performed at 129 sites in the USA and enrolled 881 patients with HFrEF who were hospitalised for acute decompensated heart failure. The initiation of LCZ696 therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy. Rates of worsening renal function, hyperkalaemia, symptomatic hypotension, and angio-oedema did not differ significantly between the sacubitril/valsartan and enalapril groups in this study (NCT02554890; Velazquez 2019).

Another recently published single-arm study, PROVE-HF, evaluated patients with HFrEF treated with sacubitril/valsartan; the reduction in NT-proBNP concentration was weakly yet significantly correlated with improvements in markers of cardiac volume and function at 12 months. The observed reversed cardiac remodelling may provide a mechanistic explanation for the effects of sacubitril/valsartan in patients with HFrEF (Januzzi 2019).

The ongoing LIFE trial may determine whether in patients with symptomatic, advanced heart failure due to left ventricular systolic dysfunction, treatment with sacubitril/valsartan for 24 weeks will improve NT-proBNP levels, which reflect haemodynamic and clinical status, compared to treatment with valsartan in NYHA IV class patients (NCT02816736).

There are also several finished and ongoing studies with sacubitril/valsartan in HF patients to assess potential new indications such as reduction of ventricular arrhythmias, reversing ventricular remodelling (Martens 2018; Martens 2019), reducing secondary mitral regurgitation (Kang 2019; Mullens 2019), or improving function and structure of myocardium in cancer-therapy-induced cardiomyopathy (Martín-García 2019).

A systematic review and meta-analysis of these studies will improve our knowledge on overall effects of sacubitril/valsartan and on effects in some specific heart failure populations (e.g. HFrEF vs HFpEF, hypertensive, diabetic, elderly and chronic kidney disease).

OBJECTIVES

To assess benefits and harms of first-in-class angiotensin receptor-neprilysin inhibitor sacubitril/valsartan (LCZ696) as compared to angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II

receptor blockers (ARB) in chronic heart failure (HF) patients with either reduced, mid-range, or preserved ejection fraction.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel-arm, phase 2, 3 and 4 randomised controlled trials (RCTs). We will include published and unpublished studies. We do not anticipate having published or ongoing cluster randomised or cross-over trials in this area. During switching from ACEI to ARNI, 36 hours is needed without ACEI as safe period to start with ARNI. The potential wash-out period of usually about two weeks typical in cross-over trials is not ethically proper in patients with HF who need the treatment with blockade of RAAS, so cross-over trials are not feasible in this area.

Types of participants

Patients (18 years of age or older) with a diagnosis of heart failure, both chronic and acute, are eligible.

The exclusion criteria in relevant sacubitril/valsartan trials are also exclusion criteria for our review: known history of angio-oedema (Balmforth 2019); requirement of treatment with both ACEIs and ARBs (Balmforth 2019; Solomon 2018); serum potassium greater than 5.2 mmol/L (Balmforth 2019); eGFR less than 15 mL/min/1.73m² (www.ema.europa.eu/en/documents/product-information/entresto-epar-product-information_en.pdf); and hypersensitivity or allergy to any study drugs, drugs of similar chemical classes, and known contraindications or suspected contraindications to study drugs (Balmforth 2019; Solomon 2018).

To deal with trials that include some participants that are eligible and some that are not, we will contact trial authors to obtain the data for the subset of interest. If this fails, we plan to include trials with up to 10% of ineligible participants. We will then perform sensitivity analysis without the trials that include ineligible participants.

Types of interventions

Comparisons of interest are:

- sacubitril/valsartan (LCZ696) vs any ACE-I (all pooled together as one comparator); and
- sacubitril/valsartan (LCZ696) vs any ARBs (all pooled together as one comparator).

Types of outcome measures

We will use trial definitions for all outcomes. We will report the longest available follow-up data and note whether or not it is an intention-to-treat (ITT) population.

Reporting one or more of the outcomes listed here in the trial is not an inclusion criterion for the review. Where a published study does not appear to report these outcomes, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. We will include relevant trials which measured these outcomes but did not report the data at all, or not in a usable format, in the review as part of the narrative.

Primary outcomes

1. Heart failure hospitalisations (assessed as participants with at least one event and time to first event during follow-up)
2. Cardiovascular mortality

Secondary outcomes

1. All-cause mortality
2. All-cause hospitalisation (assessed as participants with at least one event and time to first event during follow-up)
3. Cognitive function measured with Montreal Cognitive Assessment (MoCA) (Nasreddine 2005) or similar
4. Kidney function measured with eGFR
5. Myocardial dysfunction, which will be treated as a dichotomous outcome and measured by several methods such as increased BNP or NT-proBNP levels (e.g. > 100 pg/mL or > 400 pg/mL, respectively), decreased LVEF (e.g. < 25%), increased early mitral filling velocity (E)/early diastolic mitral annular velocity (E') ratio (E/E') (e.g. > 15), and decreased global longitudinal strain (e.g. < 16%)
6. Quality of life (QoL) assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (Joseph 2013); Minnesota Living with Heart Failure Questionnaire (MLHFQ) (Rector 1994); Left Ventricular Disease Questionnaire (LVDQ) (O'Leary 2000); or the Chronic Heart Failure Questionnaire (CHFQ) (Guyatt 1989)
7. Economic costs
8. Systolic blood pressure
9. Diastolic blood pressure
10. Serious adverse events (SAE) defined according to the FDA (www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event) as any undesirable experience associated with the use of a medical product in a patient. The event is serious when the patient outcome is: death if it is suspected that the death was an outcome of the adverse event; life-threatening event if use or continued use of medical product might have resulted in the death of the patient; hospitalisation (initial or prolonged) as a result of the adverse event; disability or permanent damage if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions; or congenital anomaly/birth defect.
11. Adverse events
 - a. worsening renal function (elevated creatinine ≥ 2 mg/dL)
 - b. hyperkalaemia (serum K ≥ 5.5 mmol/L)
 - c. symptomatic hypotension (SBP < 100 mmHg)
 - d. angio-oedema

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE (Ovid)
- Embase (Ovid)
- Scopus
- Web of Science

We will adapt the preliminary search strategy for MEDLINE (Ovid) (Appendix 1) for use in the other databases. We will apply the Cochrane sensitivity-maximising RCT filter to MEDLINE (Ovid) (Lefebvre 2011); and adaptations of it to the other databases, except CENTRAL.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch) for ongoing or unpublished trials.

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status. We will not perform a separate search for adverse effects of sacubitril/valsartan. We will consider adverse effects described in included trials only.

Searching other resources

We will check reference lists of all included studies and any relevant systematic reviews identified for additional references to trials. We will also examine any relevant retraction statements and errata for included studies. We are going to contact trial authors for missing data.

Data collection and analysis

Selection of studies

Two review authors (ABD and AVH) will independently screen titles and abstracts for inclusion of all the potential studies and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, we will consult a third author (MB). We will retrieve full texts and the same two authors (ABD and AVH) will independently screen them; the authors will identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (MB). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We will use a pre-specified data collection form which has been piloted on at least one study in the review.

Two review authors (ABD, VP) will independently extract outcome data from included studies. We will resolve disagreements by involving a third person (MB) to reach consensus. One review author (ABD) will transfer data into the Review Manager 5 (RevMan 5) file (Review Manager 2014). We will double-check that data is entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (AVH) will spot-check study characteristics for accuracy against the trial report.

We will extract the following study characteristics.

1. Trial characteristics: first author last name, year of publication, trial phase, type of trial (parallel vs cross-over), total duration of study in months, details of any 'run in' period, number of study

centres, countries, study setting, inclusion criteria, exclusion criteria.

2. Participant characteristics: number randomised, number lost to follow-up/withdrawn, number analysed, baseline characteristics (mean age, age range, %male, %hypertension, %diabetes, %smoking, %CAD, %CKD4-5, %HFrEF, lung function).
3. Interventions: intervention (dose, frequency, duration), control (dose, frequency, duration), concomitant medications.
4. Outcomes: primary and secondary, and time of follow-up per outcome.
5. Other: funding for trial, conflicts of interest of trial authors.

Assessment of risk of bias in included studies

Two authors (ABD, VP) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will resolve any disagreements by discussion or by involving a third author (AVH). We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

Measures of treatment effect

Measures of treatment effects will be risk ratio (RR) or hazard ratio (HR) with their 95% confidence intervals (95% CIs) for dichotomous outcomes, and mean difference (MD) or standardised mean difference (SMD) with their 95% CIs for continuous outcomes. We will prefer HR to RR when follow-up time for RCTs is longer than six months. When continuous outcomes were measured using different scales, then we will use SMD; otherwise the effect measure will be MD. We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

If there are more than two groups per trial we will combine groups to create a single pairwise comparison; or if not possible, we will split the shared group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons.

Dealing with missing data

We will contact investigators in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where

possible, we will use the RevMan 5 calculator to calculate missing standard deviations using other data from the trial, such as confidence intervals. Where this is not possible, and we think that the absence of data introduces serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis (Egger 1997).

Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. Presence of heterogeneity is defined as P less than 0.10 in the χ^2 test (Xu 2008). We will use the I^2 statistic to measure statistical heterogeneity per outcome across trials; substantial heterogeneity is defined as I^2 greater than 60% (Xu 2008). There is uncertainty in the value of I^2 when there is only a small number of studies.

Assessment of reporting biases

We will evaluate small-study effects for all outcomes with information in at least 10 trials (Page 2019). This evaluation includes creating funnel plots and testing for asymmetry of the funnel plot with the Egger's test.

Data synthesis

We will undertake meta-analyses only where this is meaningful: that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will use random-effects models as we expect heterogeneity of effects among trials; and the DerSimonian and Laird method for calculating between-study variance (τ^2).

We will create a 'Summary of findings' table using the following outcomes: all-cause mortality, cardiovascular mortality, all-cause hospitalisations, cardiovascular hospitalisations, severe harms, cognitive function, and kidney function. We will use the five GRADE considerations (study limitations; consistency of effect; imprecision; indirectness; and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), using GRADEpro software (GRADEpro GDT). We will provide a separate 'Summary of findings' table for each comparison of sacubitril/valsartan versus control. We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid readers' understanding of the review where necessary. A template 'Summary of findings' table is included as Table 1.

Two review authors (ABD, AVH) working independently will make judgements about quality of evidence, with disagreements resolved by discussion or by involving a third author (MB). We will justify judgements, and document and incorporate them into reporting of results for each outcome.

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses, if possible.

1. By type of heart failure (chronic and acute).
2. By hypertension (yes vs no). Hypertension is defined as office SBP values ≥ 140 mmHg or diastolic blood pressure (DBP) values ≥ 90 mmHg (or both) in two different measurements ([Williams 2018](#)).
3. By severe chronic kidney disease (yes vs no). Chronic kidney disease (CKD) is defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² for 3 months or more, irrespective of cause. Severe CKD means eGFR < 30 mL/min/1.73 m²; subsequently designated as Stage G4+ ([Levey 2005](#)).
4. By diabetes (yes versus no).
5. By age (> 75 years versus ≤ 75 years).
6. By type of heart failure (aetiology: ischemic versus non-ischemic; according to LVEF: HFpEF, HFmrEF, HFrEF).
7. By race.

We will use all outcomes for subgroup analyses. The interaction test will be used to assess subgroup differences ([Review Manager 2014](#)).

Sensitivity analysis

We plan to carry out the following sensitivity analyses for primary outcomes, to test whether key methodological factors or decisions have affected the main results.

1. Only including studies with a low risk of bias.
2. Use of fixed-effect models.
3. Use of Paule-Mandel estimator for Tau², and Hartung-Knapp adjustment of the CI adjustment.

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ADDITIONAL TABLES

Table 1. 'Summary of findings' table – draft

Sacubitril/valsartan vs enalapril for the treatment of chronic heart failure					
Patient or population: adults with chronic heart failure Setting: community Intervention: sacubitril/valsartan Comparison: enalapril					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with treatment			
All-cause mortality					
Cardiovascular mortality					
All-cause hospitalisation					
Cardiovascular hospitalisation					
Severe harms					
Cognitive function					
Kidney function					
<p>*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval</p>					
<p>GRADE Working Group grades of evidence</p> <p>High certainty: we are very confident that the true effect lies close to that of the estimate of the effect</p> <p>Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</p> <p>Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect</p> <p>Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect</p>					

APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1 Neprilysin/ and inhibitor*.tw. (1557)

2 (Neprilysin adj2 inhibitor*).tw. (432)

- 3 (sacubitril adj2 valsartan).tw. (512)
- 4 ARNI*.tw. (690)
- 5 (LCZ696 or LCZ 696).tw. (218)
- 6 1 or 2 or 3 or 4 or 5 (2676)
- 7 exp Heart Failure/ (115855)
- 8 ((heart* or cardiac* or myocard*) adj2 (fail* or insuff*)).tw. (175228)
- 9 (heart* adj2 decomp*).tw. (3910)
- 10 (chf or hf).tw. (54551)
- 11 7 or 8 or 9 or 10 (231101)
- 12 6 and 11 (788)
- 13 randomized controlled trial.pt. (490235)
- 14 controlled clinical trial.pt. (93274)
- 15 randomized.ab. (455427)
- 16 placebo.ab. (200896)
- 17 drug therapy.fs. (2142784)
- 18 randomly.ab. (318651)
- 19 trial.ab. (477492)
- 20 groups.ab. (1957144)
- 21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (4531291)
- 22 exp animals/ not humans.sh. (4619723)
- 23 21 not 22 (3923002)
- 24 12 and 23 (487)

CONTRIBUTIONS OF AUTHORS

Agata M Bielecka-Dabrowa and Adrian V Hernandez designed the protocol. Agata M Bielecka-Dabrowa wrote the first draft of the protocol. Adrian V Hernandez, Vinay Pasupuleti, and Maciej Banach revised and improved the whole protocol. All authors approved the final version of the protocol and its revisions.

DECLARATIONS OF INTEREST

AVH: none known

VP: none known

MB: none known

AMBD: none known

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