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Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction (Protocol)

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[Intervention Protocol]

Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction

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ABSTRACT

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

To evaluate the safety and efficacy of beta-blockers (BBs), angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor antagonists (ARBs), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor neprilysin inhibitors (ARNIs) for the treatment of patients with heart failure (HF) with preserved ejection fraction (HFpEF).

BACKGROUND

Description of the condition

Heart failure (HF) is a clinical syndrome characterised by breathlessness and fatigue that results when abnormalities of cardiac structure and function lead to inadequate cardiac output, and/or elevated ventricular filling pressures (Ponikowski 2016). The prevalence of HF is estimated between 1% to 2% of the adult population in developed countries and is projected to increase with population aging and improved survival from cardiovascular disease (Roger 2013). HF represents a significant public health problem accounting for 5% of emergency hospital admissions in the UK, and is associated with significant mortality with five-year survival estimated at 50% (NICE 2010). HF is classified according to the left ventricular ejection fraction (LVEF) into HF with reduced ejection fraction (HFrEF, typically considered as LVEF < 40%), and HF with preserved ejection fraction (HFpEF, typically LVEF $\geq$ 40%); more recently, a third category of HF with mid-range ejection fraction (HFmrEF, LVEF 40% to 49%) has also been proposed (Ponikowski 2016). HFpEF accounts for approximately half of all cases of heart failure and mortality outcomes are similar to those for HFrEF (Gerber 2015).

Description of the intervention

Neurohumoral inhibition with beta-blockers (BBs), angiotensin converting enzyme inhibitors (ACEIs), and mineralocorticoid receptor antagonists (MRAs) leads to improved survival and a reduction in hospitalisations for heart failure in patients with HFrEF (CIBIS Investigators 1999; Consensus Trial Study Group 1987; Flather 2005; Hjalmarson 2000; Kotecha 2014; MERIT-HF Study Group 1999; Packer 1999; Packer 2002; Packer 2001; Pitt 1999; Ponikowski 2016; SOLVD Investigators 1991; SOLVD Investigators 1992; Zannad 2011). Where ACEI or MRA are contraindicated or not tolerated, angiotensin receptor antagonists ARBs) are recommended as an alternative, although evidence is limited (Granger 2003). Angiotensin receptor neprilysin inhibitors (ARNIs) are recommended as a replacement for ACEI with superior efficacy in HFrEF patients who remain symptomatic despite optimal therapy (McMurray 2014). Although neurohumoral activation is observed in HFpEF (Hogg 2005), comparatively fewer clinical trials of neurohumoral inhibitor therapies have been performed in this population. The existing evidence from individual trials of ACEIs, ARBs or MRAs in HFpEF does not support a reduction in mortality with these treatments (Ponikowski 2016), however limited evidence indicates that candesartan (Yusuf 2003) and spironolactone (Pitt 2014) may be effective at reducing hospitalisations with HF. This review seeks to determine whether neurohumoral inhibition with therapies that improve mortality and morbidity in HFrEF (beta-blockers, ACEIs, ARBs, and MRAs) have similar benefit in patients with HFpEF.

How the intervention might work

In HFpEF, inadequate cardiac function triggers compensatory neurohumoral responses similar to those observed in HFrEF (Hogg 2005). Activation of the renin-angiotensin aldosterone system (RAAS) and increased tone of the sympathetic nervous system may be adaptive in the short term, however chronic activation is likely to be detrimental; pre-clinical disease models of HFpEF suggest that RAAS activation leads to maladaptive hypertrophy and fibrosis (Sharma 2014). ACEIs, ARBs or MRAs inhibit components of the RAAS system to counter the over activation that occurs in HF. ARNIs combine inhibition of RAAS through an ARB (valsartan) with augmentation of the natriuretic peptide system by inhibition of neprilysin (salcubitril). Neprilysin is a neutral endopeptidase that degrades a number of endogenous vasoactive peptides that serve to counteract some of the effects of RAAS activation (McMurray 2014). The beneficial effects of beta-blocker therapy in HFrEF are likely to be mediated by a reduction in the detrimental effects of increased sympathetic tone that may include, increased heart rate, adverse myocardial energetics, stimulation of RAAS (Sackner-Bernstein 1995). These mechanisms may also be important in HFpEF and the effects of beta-blockers to increase diastolic filling time may be particularly important (Sharma 2014). The HFpEF patient population is heterogeneous, both with respect to disease aetiology and co-morbidity, however it is possible that neurohumoral activation represents a common pathophysiological mechanism that could be successfully targeted to improve clinical outcomes across the spectrum of LVEF.

Why it is important to do this review

It is uncertain whether beta-blockers or RAAS inhibitors are beneficial in HFpEF with respect to mortality, hospitalisation for HF and quality of life measures. Guidelines offer no specific treatment recommendations regarding use these therapies beyond the management of co-morbidities, aside from a recommendation for the use of ARBs to reduce hospitalisations (IIb recommendation, Yancy 2013); NICE highlights a review of the evidence as a research priority (NICE 2010). A recent, combined meta-analysis of RAAS inhibitors (ACEI, ARB and MRA) in HF reported an overall reduction in hospitalisation, but not mortality in patients with preserved ejection fraction (Emdin 2015). This review seeks to assess the role of beta-blockers and individual classes of RAAS inhibitors for efficacy in HFpEF, including an evaluation of their effect on quality of life measures. A successful synthesis may inform new guideline recommendations and highlight the need for further clinical trials.

OBJECTIVES

To evaluate the safety and efficacy of beta-blockers (BBs), angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor antagonists (ARBs), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor neprilysin inhibitors (ARNIs) for the treatment of patients with heart failure (HF) with preserved ejection fraction (HFpEF).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with parallel group design. We will include studies reported as full-text, those published as abstract only, and unpublished data.

Types of participants

We will include adult patients (≥18 years) with symptomatic heart failure (New York Heart Association (NYHA) >1) and preserved ejection fraction (LVEF ≥ 40%). It is recognised that there may be heterogeneity amongst the study populations relating to the disease definition; a narrative summary of any differences will be included in the discussion. For studies with a mixed population with respect to ejection fraction, we will contact authors to obtain data on the subgroup of interest.

Types of interventions

We will perform separate, meta-analyses of trials which compare drugs from the following classes, (1) BBs; (2) ACEIs or ARBs; (3) ARNIs; and (4) MRAs, in addition to standard care, with placebo or no treatment control.

Types of outcome measures

Primary outcomes

1. Cardiovascular mortality
2. Heart failure hospitalisation
3. Withdrawal due to adverse event (hypotension, hyperkalaemia or renal impairment)

Secondary outcomes

1. All-cause mortality
2. Quality of life (Minnesota Living With Heart Failure Questionnaire or Kansas City Cardiomyopathy Questionnaire)
3. Hyperkalaemia

Reporting one of more of the outcomes listed here in the trial is not an inclusion criterion for the review. We will assess outcomes at the longest reported follow-up.

Search methods for identification of studies

Electronic searches

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

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Wiley)
2. MEDLINE (Ovid)
3. Embase (embase.com)

The preliminary search strategy for MEDLINE (Ovid) (Appendix 1) will be adapted for use in the other databases. The Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) will be applied to MEDLINE (Ovid). For Embase, we will use the multi-term Embase filter with the best optimisation of sensitivity and specificity (Wong 2006) translated from Ovid to embase.com syntax. We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will also search ClinicalTrials.gov (https://clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/) to identify ongoing and unpublished trials. Search terms for the trials registers are listed in Appendix 1.

We will check reference lists of all primary studies and review articles for additional references.

Data collection and analysis

Selection of studies

Two review authors (KM and NM/ JN) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate (TL). We will retrieve the full-text study reports/publication and two review authors (KM/ NM and TL) will independently screen the full-text and identify studies for inclusion, and 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 (JN). 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.

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (NM) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, inclusion criteria, exclusion criteria, systolic blood pressure, heart rate, body mass index, serum creatinine, B-type natriuretic peptide, NT pro B-type. natriuretic peptide, left ventricular ejection fraction, NYHA Class, co-morbidity (hypertension, diabetes,

atrial fibrillation, hospitalisation for heart failure, myocardial infarction, stroke).

3. Interventions: intervention, comparison, concomitant medications (diuretic, digoxin, beta-blocker, ACEI, ARB, MRA).

4. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (KJ/ NM and TL) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person (JN). One review author (NM) will transfer data into the Review Manager (RevMan 2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (KJ) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (NM/KM and TL) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (JN). 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. (e.g. industry funding).

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 judgment 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.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios or risk ratios with 95% confidence intervals and continuous data as mean difference or standardised mean difference with 95% confidence intervals. We will enter data presented as a scale with a consistent direction of effect.

We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

We do not anticipate unit of analysis issues due to inclusion of parallel RCTs only.

Dealing with missing data

We will contact investigators or study sponsors 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 this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity ($I^2 \geq 50\%$) we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small-study biases for the primary outcomes.

Data synthesis

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will use a fixed-effect model in the absence of substantial heterogeneity ($I^2 < 50\%$) and a random-effects model when substantial heterogeneity is present ($I^2 \geq 50\%$).

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: cardiovascular mortality, heart failure hospitalisation, withdrawal due to adverse events, all-cause mortality, quality of life (Minnesota Living With Heart Failure Questionnaire or Kansas City Cardiomyopathy Questionnaire). 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 Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software. At least two review authors will assess the quality of evidence (TL and CD). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Age
2. Sex
3. HFmrEF LVEF 40% to 49%, preserved LVEF≥ 50%
4. Length of follow-up < 12 months, ≥ 12 months

We will use the following outcomes in subgroup analyses.

1. Cardiovascular mortality
2. Heart failure hospitalisation

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

1. Only including studies with a low risk of bias (where at least four of the six domains for bias assessment are judged to be low risk and no domain is at high risk of bias).

Reaching conclusions

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.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Preliminary search strategies

Database Search Strategies

MEDLINE (Ovid)

1. exp Heart Failure/
2. ((heart or cardia* or myocardial) adj3 (failure or insufficienc* or decompensat*)).tw.
3. 1 or 2
4. exp Ventricular Dysfunction/
5. exp Ventricular Function/
6. ((preserved or normal or greater) adj5 (ejection fraction or EF or LVEF)).tw.
7. (preserved systolic function or normal systolic function or HFpEF or HF-pEF or HFnEF or HF-nEF or DHF or diastolic*).tw.
8. 4 or 5 or 6 or 7
9. 3 and 8
10. exp Adrenergic beta-Antagonists/
11. (beta adj2 (antagonist* or block* or receptor*)).tw.
12. (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone or cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol or Betapace or Blocadren or Bystolic or Cartrol or Coreg or Corgard or Inderal or Kerlone or Levatol or Lopressor or Normodyne or Sectral or Tenormin or Toprol or Trandate or Visken or Zebeta).mp.
13. exp Angiotensin-Converting Enzyme Inhibitors/
14. ((angiotensin* or dipeptidyl* or kininase ii) adj3 (convert* or enzyme or inhibit* or recept* or block*)).tw.
15. (ace adj inhibit*).tw.
16. acei.tw.
17. (alacepril or altiopril or ancovenin or benazepril* or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril* or epicaptopril or fasidotril* or fosinopril or foroxymithine or gemopatrilat or idrapril or ilepatril or imidapril* or indolapril or libenzapril or lisinopril or moexipril* or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or sampatrilat or saralasin or s nitrosocaptopril or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril* or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).mp.
18. exp Angiotensin Receptor Antagonists/
19. (angiotensin adj3 (receptor antagonist* or receptor block*)).tw.
20. (arb or arbs).tw.
21. (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or fimasartan or fonsartan or forasartan or irbesartan or KT3-671 or losartan or milfasartan or olmesartan or pomisartan or pratosartan or ripisartan or saprisartan or sparsentan or tasosartan or telmisartan or valsartan or zolasartan or Edarbi or Blopress or Atacand or Amias or Ratacand or Eprozar or Aprovel or Karvea or Avapro or Cozaar or Benicar or Olmecip or Micardis or Diovan).mp.
22. Neprilysin/ai [Antagonists & Inhibitors]
23. (neprilysin adj (inhibit* or antagonist*)).tw.
24. arni.tw.
25. (Sacubitril or "ahu 377" or ahu377 or Sacubitrilat or lbq657 or "lbq 657" or ahu377 or "ahu 377" or Entresto or lcz696 or "lcz 696").mp.
26. exp Mineralocorticoid Receptor Antagonists/

27. ((mineralocorticoid or aldosterone) adj3 (antagonist* or block* or inhibit*)).tw.
28. (canrenoic acid or canrenone or eplerenone or finerenone or oxprenoate potassium or spironolactone or Aldactone or Contaren or Inspra or Luvion or Phanurane or Spiroletan).mp.
29. or/10-28
30. 9 and 29
31. randomized controlled trial.pt.
32. controlled clinical trial.pt.
33. randomized.ab.
34. placebo.ab.
35. drug therapy.fs.
36. randomly.ab.
37. trial.ab.
38. groups.ab.
39. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. exp animals/ not humans.sh.
41. 39 not 40
42. 30 and 41

Clinical Trials Registers Search Strategies

ClinicalTrials.gov

Advanced Search--Limited to study type: interventional studies
("heart failure" AND ("preserved ejection fraction" OR "normal ejection fraction" OR "preserved systolic function" OR "normal systolic function")) OR "diastolic heart failure" OR "HFpEF" OR "HF-pEF" OR "HFnEF" OR "HF-nEF" OR "DHF"

WHO International Clinical Trials Registry Platform (ICTRP) Search Portal

Standard Search
heart failure AND preserved ejection fraction OR heart failure AND normal ejection fraction OR
heart failure AND preserved systolic function OR heart failure AND normal systolic function OR
diastolic heart failure OR HFpEF OR HF-pEF OR HFnEF OR HF-nEF OR DHF

CONTRIBUTIONS OF AUTHORS

TL: drafted the protocol and approved final version.

NM: drafted the protocol and approved final version.

KM: drafted the protocol and approved final version.

JN: drafted the protocol and approved final version.

JT: drafted the protocol and approved final version.

JPC: drafted the protocol and approved final version.

CD: drafted the protocol and approved final version.

DECLARATIONS OF INTEREST

TL: has received research grants from Pfizer and has served as an unpaid consultant to GSK.

NM: none known.

KM: none known.

JN: none known.

JT: none known.

JPC: none known.

CD: has received sponsorship from Servier, Roche and Novartis to attend cardiology conferences, payment from GE Healthcare to give lectures on heart failure, and has served as a paid consultant to Servier and Vifor.

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