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Ivabradine as adjuvant treatment for chronic heart failure (Protocol)

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[Intervention Protocol]

Ivabradine as adjuvant treatment for chronic heart failure

Carina Benstoem[1], Christian Stoppe[1], Thomas Breuer[1], Nicole Heussen[2,3], Vincent Brandenburg[4], Rudiger Autschbach[5], Andreas Goetzenich[6]

[1]Department of Intensive Care Medicine, Medical Faculty, RWTH Aachen University, Aachen, Germany. [2]Department of Medical Statistics, Medical Faculty RWTH Aachen University, Aachen, Germany. [3]Center of Biostatistic and Epidemiology, Medical School, Sigmund Freud Private University, Vienna, Austria. [4]Department of Cardiology, Medical Faculty, University Hospital RWTH Aachen, Aachen, Germany. [5]Department of Cardiothoracic Surgery, Medical Faculty, RWTH Aachen University, Aachen, Germany. [6]Aachen, Germany

Contact address: Carina Benstoem, Department of Intensive Care Medicine, Medical Faculty, RWTH Aachen University, Pauwelsstrasse 30, Aachen, North Rhine Westphalia, 52074, Germany. cbenstoem@ukaachen.de.

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ABSTRACT

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

To assess the effectiveness and safety of ivabradine in patients with chronic heart failure.

BACKGROUND

Description of the condition

Heart failure is defined as 'a complex clinical syndrome in which abnormal heart function results in, or increases the subsequent risk of, clinical symptoms and signs of reduced cardiac output, pulmonary or systemic congestion, or a combination, at rest or with stress' (Ponikowski 2016). Patients who have had heart failure for some time are often said to have chronic heart failure (Ponikowski 2016). Subsequently, this leads to peripheral vasoconstriction, the increase of extracellular fluid volume that is accompanied by an increase in the end-diastolic preload of the heart, and thus, the inadequate adaptation of the cardiac output and inadequate systemic perfusion. Chronic heart failure, with its age-dependent prevalence and incidence, is one of the most common medical conditions (Roger 2013). One commonly used method to classify the severity of heart failure is the New York Heart Association (NYHA) classification, which describes the functional status and the symptoms of patients (Ezekowitz 2017; German Society for Cardiology 2013; Ponikowski 2016; Table 1). In addition, the terminology used to describe the severity of heart failure is based on measurements of the left ventricular ejection fraction (LVEF; Ponikowski 2016):

1. Heart failure with a reduced ejection fraction (HErEF) applies to patients with a LVEF less than 40%;
2. Heart failure with a preserved ejection fraction (HFpEF) applies to patients with a LVEF 50% or higher; and
3. Heart failure with a mid-range ejection fraction (HFmrEF) applies to patients with a LVEF between 40% and 49%.

Demographic changes and medical progress have contributed significantly to an increased prevalence of chronic heart failure; there-

fore, heart failure is a first-rate medical, social, and economic problem of our society. By 2013, more than 23 million patients were diagnosed with heart failure worldwide (Roger 2013). The prevalence of heart failure depends on the definition applied, but approximately 1% to 2% of the population in developed countries suffer from chronic heart failure, with the prevalence increasing to 10% or higher of the population aged over 70 years (Laribi 2012; Mozaffarian 2016). The lifetime risk of heart failure at an age of 55 years is 33% for men and 28% for women (Bleumink 2004). Nearly three quarters (74%) of heart failure patients suffer from at least one accompanying morbidity, which is most likely to worsen patients' overall health status (van Deursen 2014). Over the last 50 years, age-specific cardiovascular disease-related mortality has fallen by about two-thirds in industrialised countries. However, heart failure is a notable exception in this respect: in the United States, the rate of hospitalisation has increased steadily since 1975, up to 1.9 million cases per year (Centers for Disease Control and Prevention 2017). Today, heart failure is the fourth most frequent cause of death in Germany (Statistisches Bundesamt 2017), and about half of the people who suffer from heart failure die within five years of diagnosis (Mozaffarian 2016). By 2030, the number of people with heart failure is expected to rise by 46% (Benjamin 2017). Reasons for this include an aging population and a growing number of heart attack survivors, who are at increased risk for heart failure.

Therapy goals for chronic HFrEF are the improvement of individual quality of life, prolonged survival, a reduction of signs and symptoms, and the prevention of hospitalisation (German Society for Cardiology 2013). In principle, therapeutic approaches (operative or medicinal) specific to the cause should be sought. According to the European Society of Cardiology (ESC) *Clinical Practice Guideline on Acute and Chronic Heart Failure,* optimal medical pharmacotherapy for chronic HFrEF involves the use of ACE inhibitors and beta-blockers. Patients with persistent symptoms should also receive a mineralocorticoid receptor antagonists (MRA) if the ejection fraction (EF) is 35% or less (Ponikowski 2016). The additional therapeutic value of selective mineralocorticoid-receptor antagonists, like eplerenone, has been shown by the reduction of morbidity and mortality in patients after acute myocardial infarction, systolic heart failure, and left ventricular systolic dysfunction (Pitt 2005; Zannad 2011). In summary, optimal medical pharmacotherapy for HFrEF includes: ACE inhibitors plus beta-blockers plus MRA. These therapy recommendations are in line with the recommendations made by the American Heart Association (Yancy 2013), and the Canadian Cardiovascular Society (Ezekowitz 2017). These drugs have a decisive influence on morbidity and mortality, as they have a positive effect on left ventricular function. This benefit appears to be partly due to a negative chronotropic effect (Lechat 2001; McAlister 2009). However, even with the best medical treatment, the prognosis of HFrEF is still poor, especially in patients with an increased resting pulse (70 to 75 beats per minute, or higher).

Heart failure adds significantly to the overall socioeconomic burden of disease, and will continue to do so in the future. For the USA, costs are quantified at $30.7 billion each year, which includes the cost of healthcare services, medications to treat heart failure, and missed days of work (Heidenreich 2011). The annual global economic cost of heart failure in 2012 was estimated at $108 billion (Cook 2014). Heart failure costs are especially driven by repeated and prolonged hospitalisation, which accounts for 1% to 3% (approximately 1 million in total) of all USA and European hospital admissions per year (Ambrosy 2014). Global registries on hospitalised heart failure show that the median length of stay ranges from 4 to 20 days (Ambrosy 2014). In addition, almost one out of four hospitalised patients (24%) is re-hospitalised for heart failure within the 30-day post-discharge period, and nearly one out of two patients (46%) is re-hospitalised for heart failure within 60-days after discharge (O'Connor 2010).

Description of the intervention

Ivabradine, which is also known by the trade names Bradia (India), Coralan (Hong Kong, Singapore), Coraxan (Russia, Serbia), Corlanor (USA), Corlentor (Armenia, Spain, Italy, Romania), Ivabid (India), Lancora (Canada), Procoralan (worldwide), is used as an adjuvant oral medication for the symptomatic treatment of chronic heart failure. One film-coated tablet contains 5 mg (equivalent to 5.390 mg) or 7.5 mg (equivalent to 8.085 mg) ivabradine as hydrochloride. Ivabradine is approved for the symptomatic treatment of chronic heart failure in NYHA class II to IV with systolic dysfunction, and in patients with sinus rhythm with heart rate 75 beats per minute or higher, in combination with optimal medical pharmacotherapy (ACE inhibitors plus beta-blockers plus MRA), or when beta-blocker therapy is contraindicated, or not tolerated. The European Medicines Agency states: The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if the resting heart rate is persistently above 60 beats per minute, or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if the resting heart rate is persistently below 50 beats per minute, or in case of symptoms related to bradycardia, such as dizziness, fatigue, or hypotension. If the heart rate is between 50 and 60 beats per minute, the dose of 5 mg twice daily should be maintained. If, during treatment, the heart rate decreases and remains below 50 beats per minute at rest, or the patient experiences symptoms related to bradycardia, the dose must be titrated down to the next dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If the heart rate increases and remains above 60 beats per minute at rest, the dose can be titrated up to the next dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. Treatment must be discontinued if heart rate remains below 50 beats per minute, or symptoms of bradycardia persist (European Medicines Agency 2017).

How the intervention might work

The cardiac effects of ivabradine are sinus node-specific, and have no influence on the intra-atrial, the atrioventricular, or the intraventricular stimulus conduction. Myocardial contractility and ventricular repolarization remain unchanged. Ivabradine reduces the myocardial oxygen demand by reducing the heart rate, which makes the use of ivabradine interesting in patients with chronic heart failure. Ivabradine is an active substance with only heart rate lowering effects. It acts as an I_f-channel inhibitor to the heart, selectively inhibiting the I_f-ionic current, which controls the spontaneous diastolic depolarization in the sinus node, thereby regulating the heart rate. As a result, the haemodynamic parameters remain constant, while at the same time, the myocardial oxygen demand is reduced. The main pharmacodynamic property of ivabradine is a specific dose-dependent reduction in heart rate. At the recommended dosage, the heart rate is lowered by about ten beats per minute, both at rest and under load. Randomised controlled trials (RCTs) showed that when added to standard treatment, ivabradine significantly reduced the rate of a combined endpoint, consisting of cardiovascular death and hospitalisation due to acute myocardial infarction, or hospitalisation due to new or worsening heart failure. It also reduced the incidence of death due to cardiac insufficiency, hospitalisation for any reason, or cardiovascular-based hospitalisation (Servier Deutschland GmbH 2016). These aspects make the use of ivabradine very promising in patients with chronic HFrEF.

Why it is important to do this review

Despite current intensive multidrug therapy, people with heart failure are frequently admitted to hospital. Even with the best medical treatment, the prognosis of heart failure remains poor. Patients with NYHA stages II and III, under therapy with ACE inhibitors, show a one-year mortality of 9% to 12%, patients with end-stage heart failure without therapy, have a one-year mortality of 52% (Bauriedel 2005). The continuous development of therapeutic approaches for the treatment of this disease — in particular with regard to drugs with heart rate-lowering properties — is of crucial importance, and we hope to add to this knowledge with our proposed systematic review.

Although there are obvious promising characteristics, we want to highlight that the relevant national and international experts only rated the quality of the evidence as IIa (B) for the therapeutic use of ivabradine in corresponding guidelines (Ponikowski 2016). It is also important to highlight that to date, the effects of ivabradine have been based mainly on results from industry-initiated studies (Fox 2008; Swedberg 2010); the review of these results in science-initiated studies is still pending. In summary, considering all aspects raised, it is anticipated that our proposed Cochrane review will have an impact on future clinical trials in this area.

Two systematic reviews on this topic are available, however, both reviews have several limitations, with a significant impact on the conclusions (Fox 2013; Mizzaci 2017). Fox 2013 only considered two industry-sponsored trials, for one of which, he was the principle investigator (Fox 2008; Swedberg 2010). Mizzaci 2017 was retracted in January 2017 on the request of several editors, as it contained numerous data inaccuracies (e.g. cited incorrect death rates), which made the conclusions unreliable (International Journal of Cardiology 2017). Our preliminary literature search identified at least five more relevant studies (Cavusoglu 2015; Kanorski¡ 2011; Sarullo 2010; Sisakian 2016; Tsutsui 2016).

Our preliminary literature search has identified more than 10 studies (N > 18,000 participants) that fulfil the inclusion criteria for this review. There is a need to assess this evidence systematically and combine results across trials. This Cochrane review will close this gap in research, providing the basis for future randomised controlled trials and clinical guidelines on the management of heart failure.

OBJECTIVES

To assess the effectiveness and safety of ivabradine in patients with chronic heart failure.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (individual, cross-over, and cluster-randomised trials) irrespective of publication type, publication status, publication date, and language. For multi-arm trials, we will use only those treatment arms relevant to our review.

Types of participants

We will include adults (≥18 years of age) with a diagnosis of chronic heart failure. We will contact trialists if the age of participants is not stated clearly, or to obtain data for a subgroup of participants.

Types of interventions

We will include trials comparing:

1. Usual care with placebo versus usual care with ivabradine; or
2. Usual care versus usual care with additional ivabradine

for the management of chronic heart failure. We will combine the possible comparators (placebo, no treatment) into a single comparison.

We will distinguish between the following follow-up times:

1. Short-term treatment (< 6 months) with ivabradine;
2. Long-term treatment (≥6 months) with ivabradine.

Types of outcome measures

As no core outcome set for clinical studies investigating interventions in chronic heart failure patients is available, the list of outcomes chosen is based on outcome measures from potentially eligible studies for inclusion in our review that are most meaningful to patients, clinicians, and policy makers.

Primary outcomes

1. Mortality from cardiovascular causes (as defined by trial authors).
2. Quality of life (QoL) measured using validated scales, e.g. the Short Form Health Survey (SF-36; (Ware 1992)).
3. Time to first hospitalisation for heart failure.
4. Number of days spent in hospital due to heart failure during follow-up.

Secondary outcomes

1. Adverse events (as defined by trial authors, e.g. number of overall adverse events).
2. Exercise capacity measured using validated scales, e.g. the 6-minute-walk-test (6MWT; (American Thoracic Society 2002)).
3. Economic costs (narrative report).

Reporting one or more of these outcomes in the trial is not an inclusion criterion for the review. Where a published report does not appear to report one of 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 measure these outcomes but do not report the data at all, or not in a usable format, as part of the narrative.

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, current issue;
2. MEDLINE Ovid (1946 to present);
3. Embase Ovid (1980 to present);
4. Conference Proceedings citation index-science (CPCI-S) Web of Science Thomson Reuters (1990 to present).

We will adapt the preliminary search strategy for identifying trials in MEDLINE Ovid for use in the other databases (Appendix 1).

We will apply the Cochrane sensitivity-maximising RCT filter to MEDLINE Ovid, and adapt it for the other databases, except CENTRAL (Lefebvre 2011).

We will search ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://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 interventions used for the treatment of chronic heart failure. We will consider adverse effects described in included studies only.

We will identify economic evaluation studies through systematic searches of the following bibliographic databases:

1. NHS Economic Evaluation Database (inception to 31 March 2015, when it stopped being updated);
2. MEDLINE Ovid (2015 to present);
3. Embase Ovid (2015 to present).

We will adapt the preliminary search strategy for identifying economic evaluation studies in MEDLINE Ovid for use in the other databases (Appendix 2). We will apply the NHS EED filter to MEDLINE Ovid and Embase Ovid (Centre for Reviews and Dissemination 2017).

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 will contact authors for missing data and ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (CB, TB) will independently screen titles and abstracts of all the potential studies we identify as a result of the search, and code them as 'retrieve' (eligible, potentially eligible, or unclear), or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate (AG or CS). We will retrieve the full-text study reports or publications. Two review authors (CB, TB) will independently screen the full-text, 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 (AG or CS). 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 purposely-developed data collection form for study characteristics and outcome data, which we will pilot with at least one study in the review. Two review authors (CB, TB) will extract the following study characteristics from included studies.

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 randomised, N lost to follow-up or withdrawn, N analysed, mean age, age range, gender, severity of condition (NYHA class), ejection fraction, pre-existing heart-disease, optimal medical pharmacotherapy according to guideline recommendations, inclusion and exclusion criteria, reported differences between intervention and comparison groups.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (CB, TB) will independently extract outcome data from included studies to check each other's work. We will resolve disagreements by consensus or by involving a third person (AG or CS). One review author (CB) will transfer data into the Review Manager 5 file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review to the data extraction form. A second review author (TB) will spot-check study characteristics for accuracy against the trial report.

We will also include a commentary on economic aspects of the use of ivabradine. This information is of special interest to policy makers and end-users of this systematic review. We intend to address the economic burden of chronic heart failure, resource inputs, resource consequences, and issues of cost-effectiveness. This narrative summary will report on the main characteristics and results of included economic studies, including resource use measures, cost, and cost-effectiveness. We will follow the recommendations provided by the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 15 (Higgins 2011).

Assessment of risk of bias in included studies

Two review authors (CB, TB) 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 (AG). 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 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 risk ratios (RR) with 95% confidence intervals (CI).

For continuous data, we will use the mean difference with 95% CI for outcomes measured in the same way between trials. We will use the standardised mean difference (SMD) with 95% CI to combine data where the same outcome was measured with different scales. We will enter data presented as a scale with a consistent direction of effect.

We will assess time-to-event outcomes with a hazard ratio.

We will describe data reported as medians and interquartile ranges narratively, since we presume their distribution will be skewed.

We will report economic aspects of the use of ivabradine narratively.

Unit of analysis issues

If we are able to include any cross-over trials in our review, we will only include data from the first treatment phase (Elbourne 2002). If trials compare more than two intervention arms that should be included in the same meta-analysis, we will divide the participants in the control arm accordingly to avoid double-counting of participants. If we are able to include individual and cluster-randomised trials, we will analyse the results separately, as we cannot guarantee accurate adjustment for baseline imbalances between clusters, and because participants within clusters tend to react similarly, so their data can no longer be regarded as independent (Higgins 2011; Whiting-O'Keefe 1984).

Dealing with missing data

We will contact investigators or study sponsors 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.

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analyses.

Continuous data

We will not impute missing values for any outcomes in our primary analyses. If studies do not include standard deviations (SD) in their report, we will calculate them using data from the trial, if possible.

Assessment of heterogeneity

We will start by inspecting forest plots visually to gauge likely levels of heterogeneity. Then, we will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity we will report it and explore possible causes by prespecified subgroup analysis. We will regard heterogeneity as substantial if:

1. the I^2 value is high (exceeding 30%); and
2. there is inconsistency between trials in the direction or magnitude of effects (judged visually), or $P < 0.10$ in the Chi^2 test for heterogeneity.

We will interpret the I^2, taking into consideration the magnitude and direction of the treatment effects and the strength of the evidence for heterogeneity.

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, by assessing funnel plot asymmetry visually and by using formal tests. If asymmetry is detected, we will perform exploratory analyses to investigate it. If there are fewer than 10 studies included in the meta-analysis, we will assess reporting bias qualitatively, based on the characteristics of the included studies.

Data synthesis

We will undertake meta-analyses only when this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

Given the clinical heterogeneity across trials on chronic heart failure patients, and their differences in comorbidities and co-medications, we will use a random-effects model to produce an overall summary of average treatment effect across trials. We will treat the random-effects summary as the average range of possible treatment effects. We will present results as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2.
For data synthesis of effect estimates from a paired t-test of continuous outcomes from a cross-over trial, we will use the generic inverse variance method in Review Manager 5 (RevMan 2014).

Summary of findings table

We will create a 'Summary of findings' table for the following outcomes:

1. Mortality from cardiovascular causes,
2. Quality of life,
3. Time to first hospitalisation for heart failure,
4. Number of days spent in hospital due to heart failure,
5. Adverse events.

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 GDT software (GRADEpro GDT).
We will justify all decisions to downgrade the quality of evidence using footnotes, and we will make comments to aid reader's understanding of the review where necessary.
Two review authors (CB, AG) will independently assess the quality of the evidence, with disagreements resolved by discussion or involving a third author (CS). They will justify, document, and incorporate their judgments into the reporting of results for each outcome.
We plan to extract study data, format them into data tables, and prepare a 'Summary of findings' table before writing the results and conclusions of our review. We have included a template 'Summary of findings' table in Table 2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it by using subgroup and sensitivity analyses. We will consider whether an overall summary is meaningful. We plan to carry out the following subgroup analyses:

1. Dosage of ivabradine (e.g. limited to starting dosage of 5 mg or increased dosage, based on resting heart rate).
2. Severity of heart failure (e.g. we will distinguish between studies that included patients diagnosed with heart failure with reduced ejection fraction (HFrEF), or patients diagnosed with

heart failure with preserved ejection fraction (HFpEF) with a mid-range ejection fraction (HFmrEF) diagnosed with heart failure. For this subgroup analysis, we will adopt the definitions provided by the European Society of Cardiology, and base the level of heart failure on the left ventricular ejection fraction (LVEF): a) HFrEF applies to patients with a LVEF < 40%; b) HFpEF applies to patients with a LVEF ≥ 50%; and c) HFmrEF applies to patients with a LVEF between 40% and 49% (Ponikowski 2016).

3. Optimal or sub-optimal medical therapy for chronic heart failure (e.g. we will also distinguish between patients receiving optimal or sub-optimal medical therapy for chronic heart failure as recommended: ACE inhibitors plus beta-blockers plus MRA).

4. Duration of ivabradine treatment (short-term (< 6 months) or long-term treatment (≥ 6 months)).

Where subgroup analyses are performed, we will restrict them to the primary outcomes. We will use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

To assess the potential impact of bias, we will perform a sensitivity analysis by limiting analyses to studies at low risk of bias, by excluding studies judged at high or unclear risk of bias for sequence generation, allocation concealment, and incomplete outcome data. We will also assess the impact of missing data.

To assess the potential impact of the missing data for dichotomous outcomes, we will perform the following sensitivity analyses:

1. 'Best-worst case' scenario: we will assume that all participants lost to follow-up in the ivabradine group survived, had no serious adverse event, were not hospitalised for heart failure, and had improved quality of life, defined as the group mean plus both one and two standard deviations of the group mean; and we will assume that all those with missing outcomes in the control group died, had a serious adverse event, were hospitalised for heart failure, and had reduced quality of life, defined as the group mean plus both one and two standard deviations of the group mean (Jakobson 2014).

2. Worst-best case' scenario: we will assume that all those with missing outcomes in the control group died, had a serious adverse event, were hospitalised for heart failure, and had reduced quality of life, defined as the group mean plus both one and two standard deviations of the group mean; and we will assume that all participants lost to follow-up in the ivabradine group survived, had no serious adverse event, were not hospitalised for heart failure, and had improved quality of life, defined as the group mean plus both one and two standard deviations of the group mean (Jakobson 2014).

We will present the results from both analyses in our review.

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analyses: where SDs are missing and not possible to calculate, we will impute SDs from trials with similar populations and a low risk of bias. If no such trials can be found, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all included trials.

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 the remaining uncertainties in the area.

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None.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. NYHA Classification

Class	Definition	Other descriptor
I	No symptoms	Asymptomatic
II	Symptoms with ordinary activity	Mild symptoms
III	Symptoms with less than ordinary activity	Moderate symptoms
IV	Symptoms at rest or with any minimal activity	Severe symptoms

Table 2. Ivabradine compared to placebo, usual care or no treatment

Ivabradine compared to placebo, usual care or no treatment						
Patient or population: adults (≥18 years of age) with a diagnosis of chronic heart failure **Setting: h**ospital or outpatient care **Intervention:** ivabradine **Comparison:** placebo, usual care, or no treatment						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo, usual care or no treatment	**Risk with ivabradine**				
Mortality from cardiovascular causes	Study population		not estimable	(RCTs)	-	
	0 per 1000	0 per 1000 (0 to 0)				
Quality of life	Study population		not estimable	(RCTs)	-	
	0 per 1000	0 per 1000 (0 to 0)				
Time to first hospitalisation for heart failure	Study population		not estimable	(RCTs)	-	
	0 per 1000	0 per 1000 (0 to 0)				

Table 2. Ivabradine compared to placebo, usual care or no treatment (*Continued*)

Number of days spent in hospital due to heart failure	Study population		not estimable	(RCTs)	-	
	0 per 1000	0 per 1000 (0 to 0)				
Adverse events	Study population		not estimable	(RCTs)	-	
	0 per 1000	0 per 1000 (0 to 0)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
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
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
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

APPENDICES

Appendix 1. Preliminary MEDLINE Ovid search strategy (to identify trials)

1. Ivabradine.tw.
2. Procoralan.tw.
3. Corlanor.tw.
4. 1 or 2 or 3
5. exp Heart Failure/
6. ((heart or cardiac or myocard*) adj2 (fail* or insufficien* or decomp*)).tw.
7. 5 or 6
8. 4 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. drug therapy.fs.
14. randomly.ab.
15. trial.ab.
16. groups.ab.

17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp animals/ not humans.sh.
19. 17 not 18
20. 8 and 19
The Cochrane sensitivity-maximising RCT filter has been applied (Lefebvre 2011).

Appendix 2. Preliminary MEDLINE Ovid search strategy (to identify economic evaluation studies)

1. Ivabradine.tw.
2. Procoralan.tw.
3. Corlanor.tw.
4. 1 or 2 or 3
5. exp Heart Failure/
6. ((heart or cardiac or myocard*) adj2 (fail* or insufficien* or decomp*)).tw.
7. 5 or 6
8. 4 and 7
9. Economics/
10. exp "costs and cost analysis"/
11. Economics, Dental/
12. exp economics, hospital/
13. Economics, Medical/
14. Economics, Nursing/
15. Economics, Pharmaceutical/
16. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
17. (expenditure$ not energy).ti,ab.
18. value for money.ti,ab.
19. budget$.ti,ab.
20. or/9-19
21. ((energy or oxygen) adj cost).ti,ab.
22. (metabolic adj cost).ti,ab.
23. ((energy or oxygen) adj expenditure).ti,ab.
24. or/21-23
25. 20 not 24
26. letter.pt.
27. editorial.pt.
28. historical article.pt.
29. or/26-28
30. 25 not 29
31. exp animals/ not humans/
32. 30 not 31
33. bmj.jn.
34. "cochrane database of systematic reviews".jn.
35. health technology assessment winchester england.jn.
36. or/33-35
37. 32 not 36
The NHS EED filter has been applied (Centre for Reviews and Dissemination 2017).

CONTRIBUTIONS OF AUTHORS

CB is the primary contact author for this protocol. CB coordinated the protocol.

CB, CS, and AG led the conception, design, and drafting of this protocol.

TB, NH, VB, and RA contributed methodological expertise to the design and drafting of the protocol.

All authors contributed important content to the drafting of this protocol and approved the final protocol.

DECLARATIONS OF INTEREST

CB: none known.

CS: none known.

TB: none known.

NH: none known.

VB: none known.

RA: none known.

AG: none known.

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