Ivabradine for the treatment of ACS: a systematic review (/meta-analysis) (Protocol)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the benefit and harms of Ivabradine in the treatment of Acute Coronary Syndrome (ACS).

BACKGROUND

Description of the condition

Acute Coronary Syndrome (ACS) is a collective term used for a range of conditions resulting from an acute reduction or even total occlusion of blood-supply to the heart, more precisely the coronary vessels. Common to all ACS-patients is the leading symptom of chest pain and the underlying occlusion of coronary arteries. Based on the patients' ECG, the conditions are subdivided into ST-elevation ACS and non-ST-elevation ACS (NSTE-ACS) (Ibanez *et al.*, 2018, Roffi *et al.*, 2016).

ACS is widespread and carries a considerable medical and socioeconomic burden. Nowadays, being a major part of the ischemic heart diseases, it is the most common cause of death worldwide, especially in the developed parts of the world. Nonetheless, there has been a trend in mortality reduction due to ischemic heart disease in Europe over the last decades (Hartley *et al.*, 2016). Still, there have been 1.8 million annual deaths, meaning that 20% of all deaths in Europe are attributable to this disease spectrum (Townsend *et al.*, 2016).

In females, ischemic heart disease develops 7 to 10 years later than in males. Nevertheless, ACS is still a leading cause of death in women, especially after the age of 75. Below the age of 60, men are 3 to 4 times more frequently affected by the ACS (EUGenMed *et al.*, 2016).

Studies have shown that mortality can be influenced by many factors, such as age, previous history of myocardial infarction, diabetes mellitus or renal failure, the number of affected coronary arteries and factors related to its appropriate management. Not only does the presence of emergency medical system-based STEMI networks and the time delay to treatment play a crucial role in survival and sequels, but so does the treatment strategy as well. The use of modern antithrombotic therapy, reperfusion therapy, primary percutaneous coronary intervention and secondary prevention, as highlighted in recent studies, are considered as mortality reducing therapies (Gale *et al.*, 2014, Puymirat *et al.*, 2012, Townsend *et al.*, 2016). However, regardless of the successes in mortality reduction there is still need for finding further improvements in the management of this widespread syndrome. One such promising improvement could be the observation that early use of Ivabradine reduces mortality in patients suffering from ACS (Niccoli *et al.*, 2017).

Description of the intervention

Originally approved as an anti-anginal agent, Ivabradine is still a novel cardiovascular drug used primarily in the treatment of selected heart failure and stable angina patients (Perings et al., 2016, Petite et al., 2018, Ponikowski et al., 2016a, Ponikowski et al., 2016b). In terms of heart failure, current guideline-directed indication for Ivabradine use, according to European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure, is somewhat narrow and includes symptomatic patients with left-ventricular ejection fraction (LVEF) ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with evidence-based therapy such as maximally tolerated dose of beta blockers, ACE inhibitors (or ARBs), and an MRA (or ARB) (Ponikowski et al., 2016a). In terms of stable coronary artery disease (CAD) with normal left ventricular function, Ivabradine has a favorable effect in reducing anginal symptoms either alone or on top of beta-blockers (Fox *et al.*, 2006, Montalescot *et al.*, 2013). Ivabradine has unique pharmacodynamic effect in sense that it is a selective I_f-current blocker, which makes it a pure heart-rate lowering medication without any direct influence on blood pressure and coronary vasomotion (Kaski *et al.*, 2018). Based on its heart rate-reducing properties, there is a possibility that Ivabradine might be beneficial alternative therapy or an adjunct therapy to beta-blockers and Ca^{2+}-channel blockers in various off-label conditions of the heart, e.g. in ACS, as well (Niccoli *et al.*, 2017, Oliphant *et al.*, 2016). In fact there have been more and more evidence showing that Ivabradine may improve treatment outcomes and reduce mortality in patients suffering from ACS (Bonadei *et al.*, 2014, Camici *et al.*, 2016, Heusch and Kleinbongard, 2016, Petite *et al.*, 2018, Soukoulis *et al.*, 2014). Furthermore, Ivabradine might confer beneficial cardioprotective effects by exerting pleiotropic pharmacodynamic actions independent of heart rate-lowering (Heusch, 2008, Kleinbongard *et al.*, 2015, Rohm *et al.*, 2016).

How the intervention might work

Ivabradine is a heart rate lowering agent acting selectively and specifically by inhibiting I_f-current, the leading regulatory mechanism of spontaneous diastolic depolarization in the SA-node. There is no direct effect on intraatrial, atrioventricular or intraventricular conduction, as well as on contractility or ventricular repolarization (Heusch and Kleinbongard, 2016). The dose-dependent heart rate-lowering action leads to a decrease in work and therefore diminished oxygen-consumption of the myocardium, without the negative inotropic effects nor effects on ventricular repolarization, as is the case in other pharmacological interventions. (Heusch and Kleinbongard, 2016, Kleinbongard *et al.*, 2015) The outcome is a possible cardioprotective effect in conditions where there is a diminished supply of blood and therefore oxygen and nutrients to the heart. As there is no negative effect on LVEF it is biologically plausible that Ivabradine might even be used in patients with a left ventricular dysfunction (Fasullo *et al.*, 2009).

Why it is important to do this review

The proposed systematic review will provide the best available evidence on the benefits and harms of the use of Ivabradine for acute coronary syndrome. This is particularly important because acute coronary syndrome is a disease that affects large segments of the population and presents a significant economic burden to society. For example, acute myocardial infarction (AMI) and ischemic heart disease (IHD), both part of the ACS-spectrum, comprise two of the ten most expensive conditions treated in the US in 2013, summing up to 12.1 billion US$ and 9.0 billion US$, respectively (Torio and Moore, 2006-2016 May). Furthermore, IHD is the most prominent single cause of mortality and loss of disability-adjusted life years (DALYs) worldwide, encompassing approximately 7 million deaths and 129 million DALYS per year (Lozano *et al.*, 2012, Murray *et al.*, 2012, Vedanthan *et al.*, 2014). Although there is a decreasing trend in the prevalence of ACS over the past decade, it is still one of the leading causes of mortality and morbidity in the world

(Benjamin *et al.*, 2018). Utilization of novel interventions and improvement in the management of this condition would not only be a benefit to socioeconomic disease burden, but would also decrease overall morbidity and mortality in general population. Ivabradine, therefore, presents a promising novel therapeutic option in the pharmacological management of ACS.

OBJECTIVES

To evaluate the effectiveness, in terms of benefit and harms, of Ivabradine either used alone or in combination with usual treatment (β-blocker), as compared to the usual care in the treatment of Acute Coronary Syndrome on mortality, myocardial infarction, unstable angina or cardiac arrest, as well as heart rate reduction.

METHODS

The search strategy, study selection, data extraction, and analysis will be performed according to this predefined protocol. The protocol will be registered at PROSPERO database (PROSPERO: International prospective register of systematic reviews.) Data reporting will be performed according to the PRISMA statement (Liberati *et al.*, 2009).

Criteria for considering studies for this review

Types of studies

We will search for randomized controlled trials (RCT) (full reports in a peer-reviewed journal and conference abstracts) including cluster randomized trials and cross-over designs. Studies in which randomization is not used or not indicated will be excluded. Studies published in any language, irrespective of publication type, publication status and publication date will be considered for inclusion. We will either handle non-English studies internally (i.e. by the authors of this review) or enlist external experts skilled in the given language. We will report any external sources of data extraction used in the review. For multi-arm trials, we will use only those treatment arms relevant to our review.

Types of participants

We will include studies enrolling adults, i.e. participants 18 years of age or older with a diagnosis of acute coronary syndrome (according to the definition of the trialists) in sinus rhythm, with heart rate (HR) ≥60 beats per minute on a resting standard 12-lead ECG. Studies will be included regardless of participants' race, gender, socioeconomic status, geographical location or setting.

Types of interventions

We will include trials comparing:

1. The usual care (β-blocker) with placebo versus usual care with ivabradine; or

2. The usual care (β-blocker) versus usual care with additional ivabradine for the management of acute coronary syndrome. We will combine the possible comparators (placebo, no treatment) into a single comparison.

Ivabradine and/or control treatment should have been administered within 48 h of hospital admission, without percutaneous coronary intervention (PCI) or within 8 hours after PCI, with Ivabradine dose of at least 10 mg once daily or 5 mg twice daily, administered either orally (PO) or intravenously (IV).

All trial lengths will be included, and will be categorized into 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

No core outcome set for clinical studies investigating interventions in acute coronary syndrome patients is available. In fact we have chosen the list of outcomes based on outcome measures from potentially eligible studies that have been regarded as meaningful and prominent in majority of studies, and which we consider to be the most clinically relevant and biologically plausible. For each of the outcomes we provide the relevant time points that we plan to include in the analyses. The time points are based on the time points used in primary studies, and are judged as clinically meaningful.

Major outcomes

1. All-cause mortality;
2. Incidence of cardiac mortality (defined by the trialists);
3. Incidence of MACE – composite outcome of: death, nonfatal, myocardial infarction, unstable angina, cardiac arrest;

The one-month, three months and six months (or nearest) time points will be included in the analysis of all-cause mortality, cardiac mortality and incidence of MACE.

4. Major arrhythmia events (ventricular fibrillation, ventricular, tachycardia, cardiac arrest), measured at 30 days (or nearest) time point;
5. Heart rate (HR) reduction (in beats per minute, in terms of delta – change from the baseline)
6. Systolic blood pressure (SBP) change (in mmHg, in terms of delta – change from the baseline)

Both, HR and SBP will be analysed at following time points:

i. At 24 hours or within one day after IVA administration
ii. At hospital discharge compared to baseline
iii. At 30 days, and three to six months (or nearest) time points after hospital discharge

7. Incidence of adverse effects as defined by study investigators

Minor outcomes

1. Levels of inflammation markers (high-sensitivity C-reactive protein, hs-CRP or similar) assessed after 24h, seven days or one month (or nearest) time points after IVA administration;
2. LVEF (left-ventricular ejection fraction, %), measured at 30 days and/or 3 to six months after index hospitalization.

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 the identification of studies

In order to identify potentially eligible studies for inclusion, the following databases will be searched:

Electronic searches

We will systematically search the following electronic databases, unrestricted by date, language or publication status:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (via OVID 1946 to present);
2. MEDLINE (via OVID 1946 to present);
3. Web of Science Core Collection (via Web of Science platform 1996 to present);
4. EMBASE (via OVID, from 1996 to present)

The search strategy we have developed for MEDLINE (Appendix 1) will be adapted appropriately for identifying trials in other databases. We will not perform a separate search for adverse effects of interventions used for the treatment of Acute Coronary Syndrome. We will consider adverse effects described in included studies only.

Searching other resources

We will identify additional trials from the reference lists of all included studies and any relevant systematic reviews (*backward search*). Citation databases like Web of Science (WoS) will be searched in order to find studies that cited our included studies (*forward search*). We will also examine any relevant retraction statements and errata for included studies. We will contact authors for missing data and ongoing trials. Drug companies will also be contacted for ongoing or unpublished trials.
Conference proceedings and abstracts will be searched using the ZETOC (from 1980 to present) and the ISI Web of Science Conference Proceedings (from 1990 to present).

Trial registries

We will search for ongoing studies in the following trial registries.

- ClinicalTrials.Gov (www.clinicaltrials.gov)
- metaRegister of Controlled Trials (mRCT), available at www.controlled-trials.com
- WHO International Clinical Trials Registry Platform (ICTRP) (http:// apps.who.int/trialsearch/), which includes the following registries:
    - Australian New Zealand Clinical Trials Registry
    - ClinicalTrials.gov
    - EU Clinical Trials Register (EU-CTR)
    - ISRCTN
    - Brazilian Clinical Trials Registry (ReBec)
    - Chinese Clinical Trial Registry
    - Clinical Trials Registry - India
    - Clinical Research Information Service - Republic of Korea
    - Cuban Public Registry of Clinical Trials
    - German Clinical Trials Register
    - Iranian Registry of Clinical Trials
    - Japan Primary Registries Network
    - Pan African Clinical Trial Registry
    - Sri Lanka Clinical Trials Registry
    - The Netherlands National Trial Register

Unpublished studies

For unpublished but completed studies, we will contact the responsible researcher indicated in the registry.

Grey literature will be searched in grey literature databases like the OpenGrey library, via customized Google search engines, and by consultation with contact experts.

Data collection and analysis

Selection of studies

Two members of the review team (JAB, MK) will independently screen results of the search consisting of titles with or without abstracts, and will make independent decisions about study eligibility and the need for consequent retrieval of full texts of study reports. They will do so by coding the search results as 'retrieve' (eligible,

potentially eligible, or unclear), or 'do not retrieve'. If there will be any disagreements, a third author will be consulted (JB). We will obtain a full copy of all possibly or definitely relevant studies for further assessment. The two review authors (JAB and MK) will independently screen the retrieved full texts and identify trials eligible for inclusion in the systematic review. We will report reasons for exclusion of the ineligible studies. All discrepancies in judgments regarding trial eligibility will be resolved by discussion and consensus, or if required, we will consult a third author. In cases of unclear or missing data, we will contact authors of the included studies for clarification or for additional data. Studies will be translated into English when necessary. We will identify and exclude duplicates and collate multiple reports of the same trial so that each trial, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail using the PRISMA flow diagram and will report excluded studies with reasons for exclusion in the 'Characteristics of excluded studies' tables.

Data extraction and management

Two members of the review team (JAB, TPP), one of them a methodologist and the other a topic area specialist, both not blinded to the authors, interventions or results obtained in the included studies, will independently extract relevant outcome data from the included studies according to the inclusion criteria. Possible doubts and disagreements will be discussed and, if they cannot be resolved, we will contact the authors of the original articles for clarification. A purposely-developed data collection form will be used, but first piloted on several eligible trials to minimize errors. For each included study we will extract patient and study characteristics, intervention, and outcome data. We will extract the raw data (means and standard deviations for continuous outcomes and number of events and participants for dichotomous outcomes) for the outcomes of interest.
The following data will be extracted:

1. Methods: trial design duration of the trial, details of any 'run-in' period, number of study centers and location, study setting, withdrawals, and date of publication.

2. Participants: number randomized, number analyzed, number lost to follow up/withdrawn, mean age, age range, gender, and inclusion and exclusion criteria.

3. Interventions: generic and trade name of the experimental intervention, the type of control used, dosage and frequency, duration of treatment, concomitant medications, and excluded medications.

4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.

5. Notes: source of financial support, notable conflicts of interest of trial authors and publication status.

A priori decision rules for the selection of which data to extract in the event of multiple outcome reporting, are the following:

- if both final values and change from baseline values are reported for the same outcome, we will extract both; present the change scores as one subgroup, and the final values as another subgroup, and then combine the two in an overall analysis;
- if both unadjusted and adjusted values for the same outcome are reported, we will extract both and include adjusted values in the meta-analysis;
- if data are analyzed based on an intention-to-treat (ITT) sample and another sample (e.g. per-protocol, as treated), we will extract both, regardless of whether the outcomes assess benefits or harms; and use intention-to-treat data in analyses.

When necessary, we will approximate means and measures of dispersion from the figures in the reports. Whenever possible, we will use results from an intention-to-treat analysis. 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 will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (JB, TPP) will independently assess risk of bias for all included studies using The Cochrane Collaboration's tool for assessing risk of bias tool (Higgins and Green, 2011). The tool addresses seven domains: 1) random sequence generation (selection bias), 2) allocation concealment (selection bias), 3) blinding of participants and researchers (performance bias), 4) blinding of outcome assessment (detection bias), 5) incomplete outcome data (attrition bias), 6) selective reporting (reporting bias) and 7) other potential sources of bias (Higgins and Green, 2011). In case of lack of important study information, we will contact authors to obtain the information needed, using open-ended questions. To determine the risk of bias of a study, for each domain we will evaluate the presence of sufficient information and the likelihood of potential bias. We will judge the level of risk of bias for each domain as low risk of bias, high risk of bias or unclear risk of bias, and will provide clear explanation for every judgment of every domain, preferably by using quotes from the original article. Any disagreements among the review authors will be discussed and resolved during discussion meetings. If consensus cannot be reached, a third review author will make the final decision. Risk of bias will be presented in tables, and will also be summarized graphically.

Measures of treatment effect

For incidence of mortality, incidence of MACE, and for arrhythmia events the outcome measures will be presented using dichotomous data, therefore Risk Ratios together with 95% confidence intervals (CI) will be used to combine dichotomous data.
The HR reduction, the systolic blood pressure change, the level of inflammation markers and the LVEF, all of which continuous outcomes, will be presented using means and standard deviations, therefore mean difference together with the corresponding 95% CI will be the effect measure used for these outcomes.

As for the incidence of adverse effects, we plan to calculate Odds Ratio (OR) with the 95% CI.
Data will be entered into the Review Manager (RevMan) software, and will be analyzed using the generic inverse variance meta-analysis method. Alternatively, Mantel-Haenszel method will be used for meta-analysis for dichotomous outcomes of small studies with few events.

Unit of analysis issues

Unit of analysis is a single patient.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to 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 using a sensitivity analysis. A common problem is missing summary data, such as standard deviations for continuous outcomes, or separate sample sizes for each intervention group. Missing summary data will not be a reason to exclude a study from the review and methods outlined in section 16.1.3 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) will be used for imputing missing standard deviations.
If for some reason data on individuals will be missing from the results, we will contact the study authors to ask them for more information.
We will make explicit assumptions about the reasons why we think the data are missing. For the data that we judge to be 'missing at random', meaning that their being missing is not related to the actual values of the data, we will consider those as non important. The analyses will include only the available data, ignoring the missing data. However, if we consider the data not to be missing at random, than we will perform a sensitivity analysis in order to explore the impact it could have on the results. Potential impact that the missing data could have on the overall findings of the review will be discussed in the text of the review. The problem of missing whole studies will be addressed in the 'Assessment of reporting biases' section in this protocol.

Assessment of heterogeneity

Assessment of clinical homogeneity of included studies, including judgments on whether studies are similar and comparable with respect to type of intervention, control group and the outcomes, will be performed before statistical analysis. Clinically heterogeneous studies will not be combined in meta-analysis, and will be described separately. Among clinically homogenous studies that will be combined in meta-analysis. Heterogeneity will be tested using the Chi^2 test for identification of heterogeneity. Chi^2 test with a P value less than 0,10 will be considered a significant heterogeneity. The the I^2 statistics will be used for quantifying the possible magnitude of heterogeneity, with the following rough guide for interpretation of the level of heterogeneity: 0% to 40% might not be important heterogeneity; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity.

Assessment of reporting biases

Reporting biases will be considered on two levels, within study and between studies. Reporting biases within included studies will be analyzed through the incomplete outcome data and the selective reporting domains as part of the Risk of bias assessment. We will try and find protocols of included studies and compare the methods outlined in the protocols with those reported in full publications. Also, we will compare outcomes listed in the methods sections of included studies with outcomes reported in the Results of published articles. If we find signs of selective or incomplete reporting, we shall contact study authors for more information.
In order to investigate the possibility of publication bias, provided there will be at least ten studies in the meta-analysis, a funnel plot will be created, analyzing effect estimates against their standard errors. If we find an asymmetry of the funnel plot, either by inspection or statistical tests, we will consider all possible explanations and will take them into account in the interpretation of the overall estimates. We will interpret the results from tests for funnel plot asymmetry cautiously. When there is evidence of small study effects, we will consider publication bias as only one of a number of possible explanations. In these circumstances, we will attempt to understand the source of small study effects and consider their implication in sensitivity analyses. If there will be less than 10 studies included in meta-analysis, we will assess reporting bias qualitatively, based on the characteristics of the included studies.

Data synthesis

Meta-analysis will include only clinically homogenous studies, i.e. studies reporting the same outcomes, provided there are at least two studies eligible for meta-analysis. Weighted mean differences will be used for combining continuous data. For binary data, overall risk ratios (with 95% CI) will be calculated. For illustrative purposes, when overall results will be shown as significant, we will calculate the absolute risk reduction (ARR) and the number needed to treat (NNT), as appropriate. As we expect the effect of IVA to be consistent in most patients, a fixed effect meta-analysis will be used as a primary model of meta-analysis to assess the summary effect for outcomes related to effectiveness and safety. However, if for some reason, we observe significant heterogeneity, with the value of I^2 statistics more than 40%, random effects meta-analysis will be performed instead.

Subgroup analysis and investigation of heterogeneity

The following subgroup analysis will be performed based on different clinical entities of the ACS among participants, therefore subgroups of participants that will be analyzed as follows:

1. Myocardial infarction with a ST-elevation, STEMI-ACS;
2. Myocardial infarction without ST-elevation, NSTEMI-ACS;
3. Unstable angina pectoris - AP

Sensitivity analysis

Primary meta-analysis will include all eligible studies. Sensitivity analysis will exclude studies at high risk of bias to assess how the results of meta-analysis might be affected if studies at high risk of bias were included. If the analysis of heterogeneity finds one or two outlying studies with results that conflict with the rest of the studies, sensitivity analysis will be performed to assess their effect on the results of meta-analysis. Sensitivity analysis will be performed taking into account sources of funding of the included studies, as well. The results of primary analysis will be compared to the results of sensitivity analysis for all mentioned issues: the high risk of bias, outlying studies, and funding sources. Sensitivity analysis will also be performed to test how the different assumptions about the missing data may affect the results. Sensitivity analysis will take into account areas of bias that could considerably affect the results of the overall treatment effects.

'Summary of findings' table

We will present the seven most relevant outcomes of the review in a 'Summary of findings' table, which we will develop using the GRADEpro software before writing the results and conclusions of our review. We have included a template 'Summary of findings' table in Appendix II. This table will provide key information concerning the quality of the evidence, the magnitude of effect of the intervention examined and the sum of available data on the main outcomes. The table will include an overall grading of the evidence related to each of the main outcomes using the GRADE approach, as indicated in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Two review authors (JAB, TTP) will independently assess the quality of the evidence, with disagreements resolved by discussion or involving a third author (JB). They will justify, document, and incorporate their judgments into the reporting of results for each outcome.

The important outcomes that could be included in the 'Summary of findings' tables are:

1. Incidence of cardiac mortality
2. Incidence of MACE
3. Major arrhythmia events
4. HR reduction
5. Incidence of adverse effects
6. Levels of inflammation markers (hs-CRP or similar)
7. LVEF

In the 'Comments' column of the 'Summary of findings' table, we will provide the absolute percent difference, the relative percent change from baseline and the number needed to treat to benefit (NNTB). The NNT will be provided only when the outcome shows a statistically significant difference.

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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APPENDICES

Appendix 1. Full search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to June 2018> Search strategy:

1. Ivabradine.af.
2. Procoralan.af.
3. Corlanor.af.
4. S 16257-2.af.
5. S-16257-2.af.
6. S-16260-2.af.
7. S 16260-2.af.
8. S 16257.af.
9. S-16257.af.
10. or/1-9
11. exp Acute Coronary Syndrome/
12. exp Myocardial Infarction/
13. exp Coronary Thrombosis/
14. coronary thrombosis.tw.
15. acute coronary.tw.
16. exp Angina, Unstable/
17. myocardial infarct*. tw.
18. heart infarct*.tw.
19. acs.tw.
20. ami.tw.
21. (coronary adj3 syndrome*).tw.
22. acute angina.tw.
23. (unstable adj3 angina).tw.
24. unstable coronary.tw.
25. or/11-24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab.
30. drug therapy.fs.
31. randomly.ab.
32. trial.ab.
33. groups.ab.
34. or/26-33
35. exp animals/ not humans.sh.
36. 34 not 35
37. 10 and 25 and 36

Appendix II. Summary of findings tables

Summary of findings table 1:

Ivabradine compared to placebo, usual care, or no treatment for patients with Acute Coronary Syndrome (Major Outcomes)

Patient or population: patients with Acute Coronary Syndrome (Major Outcomes)
Setting: hospital 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**				
Cardiac mortality	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	
Incidence of MACE	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	
Major arrhythmia	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	

***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

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

Summary of findings table 2:

Ivabradine compared to placebo, usual care, or no treatment for patients with Acute Coronary Syndrome (Minor Outcomes)

Patient or population: patients with Acute Coronary Syndrome (Minor Outcomes)
Setting: hospital or outpatient
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**				
Heart rate	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	
Advesre effects	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	
Inflammation markers	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	
LVEF	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	

***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

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

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- Designing search strategies and undertaking searches: MK

- Screening search results and retrieved papers against inclusion criteria: JAB, MK
- Appraising quality of papers: JAB, MK, JB, TPP
- Extracting data from papers: TPP, JAB, JB
- Writing to authors of papers for additional information: JAB, MK
- Data management for the review and entering data into RevMan: TTP
- Analysis and interpretation of data: JAB, MK, JB, TTP
- Providing research perspective: JAB, MK, JB, TTP
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DECLARATIONS OF INTEREST

JAB: none known.

MK: none known.

JB: none known.

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