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MEDICINE
BACHELOR THESIS

Beta-blockers in patients without heart failure after myocardial infarction: a Cochrane systematic review with meta-analysis and Trial Sequential Analysis

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Dansk titel

Beta-blokkere til patienter uden hjertesvigt efter et myokardieinfarkt: en Cochrane systematisk litteratur gennemgang med meta-analyse og Trial Sequential Analysis

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Dansk resumé

Baggrund

Hjertekar sygdomme er den hyppigste årsag til død globalt. Ifølge WHO døde 7.4 million mennesker af iskæmiske hjertesygdomme i 2012 og disse udgjorde dermed 15% af alle dødsårsager. Beta-blokkere anbefales til patienter med hjertesvigt efter akut myokardieinfarkt. Det er dog uklart, hvorvidt beta-blokkere burde blive brugt til patienter uden hjertesvigt efter akut myokardieinfarkt. Tidligere meta-analyser har vist modstridende resultater. Formålet med dette review var at undersøge evidensen for brug af beta-blocker til behandling af patienter uden hjertesvigt efter et myokardieinfarkt.

Metode

Vi udførte et Cochrane systematisk review med meta-analyse og Trial Sequential Analysis. Vi søgte Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, Science Citation Index Expanded databaser, BIOSIS Citation Index, the WHO International Clinical Trials Registry Platform, European Medicines Agency, the Food and Drug Administration, ClinicalTrials.gov, Turning Research into Practice og Google Scholar indtil februar 2017. Vi søgte endvidere efter upublicerede forsøg. Vi inkluderede randomiserede kliniske forsøg, der undersøgte effekten af beta-blokkere sammenlignet med placebo/ingen intervention til voksne patienter uden hjertesvigt efter akut myokardieinfarkt. Forsøgene blev inkluderet uanset type, status, dato og sprog.

Resultater

Vi inkluderede 25 randomiserede kliniske forsøg med 21.732 patienter (gennemsnitsalder 56.9 år). Alle forsøg og resultater var vurderet til at være i høj risiko for systematiske fejl ('bias') og kvaliteten af evidensen var lav til meget lav for alle resultater. Meta-analyser viste at beta-blokkere sammenlignet med placebo/ingen intervention havde gavnlig effekt på mortalitet (RR 0.80, 95% CI (konfidens interval) 0.72 to 0.89, P < 0.0001, I^2 = 25%), på risikoen for en alvorlig kardiovaskulær hændelse (RR 0.78, 95% CI 0.70 to 0.87, P < 0.0001, I^2 = 26%), på risikoen for en alvorlig uønsket hændelse (RR 0.81, 95% CI 0.74 to 0.89; P < 0.00001, I^2 = 21%) og på risikoen for et nyt myokardieinfarkt (RR 0.75, 95% CI 0.68 to 0.84, P < 0.0001, I^2 = 0%). Trial Sequential Analyserne bekræftede resultaterne. Den gavnlige effekt fundet ved meta-analyse af kardiovaskulær mortalitet (RR 0.75, 95% CI 0.64 to 0.88, P = 0.0003, I^2 = 49%) blev ikke bekræftet af Trial Sequential Analysis. Beta-blokkere viste ingen gavnlig effekt på angina som et dikotomt effektmål. Ingen data kunne opsamles på livskvalitet.

Konklusion

Beta-blokkere sammenlignet med placebo/ingen intervention ser ud til at have en gavnlig effekt på mortalitet, risikoen for en alvorlig kardiovaskulær hændelse, risikoen for en alvorlig skadelig hændelse og risikoen for et nyt myokardieinfarkt til patienter uden hjertesvigt efter et myokardieinfarkt. Beta-blokkere viste ingen gavnlig effekt på angina som et dikotomt effektmål, og ingen data kunne opsamles på livskvalitet.

English abstract

Cardiovascular disease is the number one cause of death globally. According to the WHO, 7.4 million people died from ischaemic heart diseases in 2012 constituting 15% of all deaths. Beta-blockers are recommended and often used in patients with heart failure after acute myocardial infarction. However, it is currently unclear whether beta-blockers should be used in patients without heart failure after acute myocardial infarction. Previous meta-analyses on the topic have shown conflicting results. No previous systematic review using Cochrane methodology has assessed the effects of beta-blockers in patients without heart failure after acute myocardial infarction.

Methods

We conducted a Cochrane systematic review with meta-analysis and Trial Sequential Analysis. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, Science Citation Index Expanded, BIOSIS Citation Index, the WHO International Clinical Trials Registry Platform, European Medicines Agency, the Food and Drug Administration, ClinicalTrials.gov, Turning Research into Practice, and Google Scholar from their inception to February 2017. Additionally, we searched for unpublished trials. We included randomised clinical trials assessing the effects of beta-blockers versus control (placebo or no treatment) in patients without heart failure after myocardial infarction. Trials were included irrespective of publication type, status, date, and language. We excluded trials randomising participants with diagnosed heart failure at the time of randomisation.

Findings

We included 25 trials randomising 21,732 participants (mean age 56.9 years). All trials and outcomes were at high risk of bias and the quality of the evidence was low to very low for all outcomes. Meta-analyses at maximum follow-on suggested beneficial effects of beta-blockers versus control when assessing all-cause mortality (RR 0.80, 95% CI 0.72 to 0.89, $P < 0.0001$, $I^2 = 25\%$), major cardiovascular events (RR 0.78, 95% CI 0.70 to 0.87, $P < 0.0001$, $I^2 = 26\%$), serious adverse events (RR 0.81, 95% CI 0.74 to 0.89; $P < 0.00001$, $I^2 = 21\%$), and myocardial reinfarction (RR 0.75, 95% CI 0.68 to 0.84, $P < 0.0001$, $I^2 = 0\%$). Trial Sequential Analyses confirmed these meta-analyses results. When assessing cardiovascular mortality, the beneficial effect found by the meta-analyses (RR 0.75, 95% CI 0.64 to 0.88, $P = 0.0003$, $I^2 = 49\%$) was not confirmed by Trial Sequential Analysis. Beta-blockers showed no beneficial effects on angina when assessed as a dichotomised outcome, but results based on dichotomised continuous outcomes should be interpreted with caution. No data was obtained on quality of life.

Interpretations

Beta-blockers compared with placebo/no intervention may reduce the risk of all-cause mortality, major cardiovascular events, serious adverse events, and myocardial reinfarction in patients without heart failure after myocardial infarction. However, these findings should be interpreted with caution since all trials and outcomes were at high risk of bias and the quality of the evidence was low to very low for all outcomes**.** Beta-blockers showed no beneficial effects on angina when assessed as a dichotomised outcome and no data could be obtained on quality of life.

Background:

Cardiovascular disease is the number one cause of death globally[1,2-5]. Ischaemic heart disease accounts for almost 50% of the disease burden of the cardiovascular diseases [6]. According to the World Health Organization (WHO), 7.4 million people died from ischaemic heart disease in 2012 [7].

Ischaemic heart disease is caused by different underlying mechanisms: (1) atherosclerotic plaque-related obstruction of the coronary arteries; (2) focal or diffuse spasms of normal or plaque-diseased arteries; (3) microvascular dysfunction; and (4) left ventricular dysfunction caused by acute myocardial necrosis or ischaemic cardiomyopathy [8]. Ischaemic heart disease increases the risk of stable angina pectoris and acute coronary syndrome.

Acute coronary syndrome is a collective term for: (1) unstable angina pectoris (chest pain during rest related to ischaemia or hypoxia of the heart muscle [9]); (2) non-ST-elevation myocardial infarction (NSTEMI); or (3) ST-elevation myocardial infarction (STEMI) [9,10]. Myocardial infarction is caused by death of cardiac myocytes (myocardial necrosis) due to ischaemia [10,11]. The clinical definition of myocardial infarction is elevated serum levels of cardiac biomarkers (cardiac-specific troponins and the myocardial band (MB) isoenzyme of creatine kinase (CK-MB) among others) and changes of the ST-segment on an electrocardiogram (ECG) (STEMI and NSTEMI) or symptoms of cardiac ischaemia [9,10].

The diagnosis of myocardial infarction is dependent on an elevation of the serum levels of cardiac-specific troponin I, troponin T, or CK-MB , among others [9,10]. However, these enzymes will often not be detectable before 8 to 24 hours after the first symptoms of the myocardial infarction occur. Beta-blockers may accordingly be commenced as an intervention in people with suspected myocardial infarction or may be commenced as an intervention for people with a confirmed diagnosis of myocardial infarction at a later time.

Beta-blockers are classified as non-selective beta-blockers or selective beta-blockers according to their selectivity for one of the three subtypes of beta-receptors ($beta_1$-, $beta_2$- and $beta_3$-receptor) [12]. Three different classes of beta-blockers exist:

- The first generation non-selective beta-blockers (e.g. propranolol, oxprenolol, sotalol, timolol), affecting all beta receptors.
- The second generation selective beta-blockers (e.g. metoprolol, bisoprolol, acebutolol, atenolol, esmolol), mainly affecting the heart.
- The third generation beta-blockers, which have combined non-selective beta-blocking effects and alpha-blocking effects (e.g. carvedilol), affecting all beta-receptors plus alpha receptors in the vessels lowering the blood pressure [12].

Beta-blockers may be administered both intravenously and orally. Oral beta-blockers may be used in the non-acute phase of myocardial infarction as secondary prevention [13].

The role of non-acute treatment with beta-blockers in people with myocardial infarction rests on their inhibition of the chronotropic and inotropic effects of the beta-receptor. This may result in a reduction in heart rate, contractility, and blood pressure thereby decreasing the oxygen demand of the heart and consequently reducing ischaemic chest pain [14]. Additionally, this inhibition of the beta-receptor is thought to decrease recurrent ischaemia and might decrease the risk of life-threatening ventricular arrhythmias and other complications associated with myocardial infarction [9,10].

However, international guidelines differ in their recommendations for the use of beta-blockers in patients without heart failure after a myocardial infarction [9-11,15]. The European Society of Cardiology (ESC) guidelines recommend that beta-blockers should be considered for all STEMI patients without contraindications and NTEMI patients with heart failure with no suggestions for patients without a heart failure. This is in contrast with the current American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines, which suggests that oral beta-blocker therapy should be initiated within the first 24 hours and continued thereafter in all STEMI and non-ST-elevation patients without any signs of heart failure and with normal left ventricular function [11,15]. The ACCF/AHA guidelines for STEMI patients further recommends a 3-year treatment course of beta-blocker therapy as non-acute secondary prevention in all STEMI patients without heart failure (normal left ventricular function) who have had myocardial infarction [11,13]. Former meta-analyses have shown conflicting results and no former reviews have used Cochrane methodology to systematically assess the effects of beta-blockers in people without heart failure after myocardial infarction [16]. The present systematic review will be the first to take fully into account the risk of systematic errors ('bias'), design errors, and risks of random errors ('play of chance') [16-19]; and include trials irrespective of outcome, duration of follow-up, number of participants, language, and publication status.

Methods:

We have published a protocol with a detailed description of the methods used [20]. Here, we summarise the methodology. The methodology was based on The Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for meta-analyses of interventional studies [16]. We used meta-analysis and Trial Sequential Analysis when relevant.

Search strategy:

We searched for trials in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, Science Citation Index Expanded, and BIOSIS, from conception till 28th February 2017. In addition, we searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch), US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), the Food and Drug Administration (FDA) (www.fda.gov), Turning Research Into Practice (TRIP), Google Scholar, and Scisearch in February 2017 for finished trials as well as ongoing trials. The search strategies can be found in our protocol [20]. Two review authors (SS, NJS) independently screened the initial searches. Two review authors (SS, NJS) independently screened the full-text in pairs. If the two authors disagreed, a third author (JCJ) resolved the issue. One Russian trial was translated to English.

Risk of bias of each included trial was assessed according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* [16] consisting of 7 domains: 1) allocation sequence generation, 2) allocation sequence concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other biases (including for-profit bias). Trials with low risk of bias in all domains were classified as overall low risk of bias, while trials with unclear or high risk in one domain were classified as overall high risk of bias.

Types of studies:

We included randomised clinical trials assessing the effects of beta-blockers versus placebo/no intervention for patients without heart failure after a myocardial infarction. Trials were included irrespective of publication type, status, date, and language. We included any type of beta-blocker as experimental intervention (non-selective beta-blockers (e.g. propanolol, oxprenolol, sotalol, timolol), selective beta$_1$-blockers (e.g. metoprolol, bisoprolol, acebutolol, atenolol, esmolol), and beta-blockers which are combined alpha- and non-selective beta-blockers (e.g. carvedilol) either compared with placebo, added to a co-intervention or compared with no intervention. We accepted any type of co-intervention provided they were planned to be delivered similarly to the experimental group and the control group.

Outcomes:

We assessed all outcomes at two different time points:

- outcomes assessed at maximum follow-up (this was our outcome of primary interest);
- outcomes assessed at the time point closest to 12 months after randomisation (varying from 6 to 18 months)

Our primary outcomes were: 1) all-cause mortality; 2) major cardiovascular events defined as a composite outcome consisting of either cardiovascular mortality (defined by trialists) or myocardial infarction (defined by trialists); and 3) serious adverse events defined as any untoward medical occurrence that resulted in death, was life threatening, was persistent, led to significant disability, prolonged hospitalisation or jeopardised the participant [21].
Our secondary outcomes were quality of life, angina, cardiovascular mortality, and myocardial reinfarction.
All outcomes, except quality of life, were analysed as proportions of participants in each group.

Data synthesis:

We performed the analyses using Review Manager 5, STATA 14, and Trial Sequential Analysis [19,22-24]. We used visual inspection of forest plots to look for signs of statistical heterogeneity. We also assessed the presence of statistical heterogeneity using the Chi^2 test with significance set at P value <0.10 and measured the quantities of heterogeneity using the I^2 statistic [25,26]. We followed the recommendations for threshold in the *Cochrane Handbook for Systematic Reviews of Interventions* [27]. We used a funnel plot to assess reporting bias if 10 or more trials were included in the analysis. To assess the potential impact of the missing data for dichotomous outcomes, we performed 'best-worst-case' scenario and 'worst-best- case' scenario sensitivity analyses [28].
We planned on basing our primary conclusions on our primary outcomes assessed at maximum follow-up with low risk of bias in all domains. We used three primary outcomes and, therefore, we considered a P value of 0.025 or less as statistically significant [17]. We assessed four secondary outcomes, and we therefore considered a P value less than $P \leq 0.02$ as statistically significant for the secondary outcomes [17]. We used an eight-step procedure to assess if the thresholds for statistical and clinical significance were crossed [17].
Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data [16,29-34]. Therefore, we performed Trial Sequential Analysis [19,24,35] on the outcomes in order to calculate the required information size (that is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) can be calculated in order to minimise random errors [30,33,35-41]. We estimated the required information size based on the proportion of participants with an event in the control group, a relative risk reduction (RRR) of 10%, an alpha of

2.5% for primary outcomes and 2% for secondary outcomes, and a beta of 10% and a variance suggested by the trials in a random-effects meta-analysis (diversity-adjusted required information size [17,34,37,40] .

We used the GRADE system to assess the quality of the body of evidence associated with each of the primary outcome, as well as quality of life and angina in our review, constructing 'Summary of findings' (SoF) tables using the GRADEpro software [42].

Results:

We identified a total of 11.087 potentially relevant references. 6,433 duplicates were excluded and 231 studies were deemed relevant and full texts were obtained for further evaluation. We then excluded 66 studies based on full text articles. The remaining 165 full text articles reported on 25 completed randomised clinical trials, which were included according to our predefined inclusion criteria and exclusion criteria. Flowchart can be found in **Figure 1**.

Included studies:

The 25 trials were conducted at sites in 17 different countries and randomised a total of 21.732 participants. The number of participants in each trial ranged from 24 to 3.837, the mean age was 56.9 (range 50 to 63 years), and the mean proportion of women was 17.3%. 16 trials excluded participants with heart failure while 9 trials were equivocal and specifically excluded participants with heart failure but reported some participants with prior heart failure in the baseline table [43-51]. One trial [52] was a multi-arm study, and contributed two different comparisons to the review. Data available for analysis were reported in 21 trials. 10 different beta-blockers were assessed in the included trials: 5 with metoprolol, 5 with propranolol, 2 with alprenolol, 3 with oxprenolol, and 1 each with acebutolol, atenolol, pindolol, practolol, sotalol, or timolol. We included 21 trials where the control group received placebo, and 4 trials where the control group received no intervention other than the co-intervention or usual care. 14 out of the 24 trials did not describe any co-intervention. 7 trials received standard medical therapy as co-intervention consisting of digitalis, diuretics, vasodilators, antiarrhythmics, anticoagulants, nitrates, and aspirin. Two trials described the co-intervention as conventional therapy without further specification, one trial added tranquilliser, potassium, antihypertensive, dipyridamole, insulin, hormonal, oral hypoglycaemic, sulphinpyrazone, and lipid-lowering drugs to the standard medical therapy as co-intervention, and participants in one trial received long-acting nitrates and nifedipine as co-intervention, when needed. As stated, the trials were not offering statins or invasive cardiology interventions.

Excluded studies:

We excluded 66 trials after full-text assessment based on our inclusion and exclusion criteria. 62 of these trials included only participants in the acute phase of myocardial infarction and were therefore excluded from this review. One trial was excluded as patients with heart failure were included [53]. One trial was excluded as the patients did not receive any intervention with beta-blockers [54]. One trial was excluded as the majority of the included patients had a history of stable angina pectoris and not myocardial infarction [55]. One trial was excluded as it was a cluster randomised trial [56].

Risk of bias

Based on the information that we collected from the published reports and information from authors, all 25 trials were considered at high risk of bias. A majority of trials were judged to be at unclear risk of bias in several domains, and

additional information could not be obtained from the authors when contacted. Additional information can be found in the risk of bias summary (see **Figure 2)**.

Primary outcomes

All-cause mortality:

21 out of 25 trials with a total of 21,732 participants and a mean follow-up of 23.4 months (range 9 to 60 months) reported all-cause mortality at maximum follow-up. A total of 958/10,942 (8.8%) participants receiving beta-blockers died versus 1169/10,566 (11.1%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus control when assessing all-cause mortality at maximum follow-up (RR 0.80, 95% CI 0.72 to 0.89; P < 0.0001; I^2 = 25%; 21,508 participants; 21 trials; low quality evidence; **Figure 3**). The point estimate of the meta-analysis result corresponds to 88 out of 1000 beta-blocker patients dying compared with 111 out of 1000 control participants or a NNT (numbers needed to treat) of 44 (see **Table 1**). Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.68 to 0.95 showed that the cumulative Z-curve crossed the boundary for benefit (see **Figure 4**).

15 out of 25 trials with a total of 14,303 participants and a mean follow-up of 13 months (range 9 to 18 months) reported all-cause mortality at the time point closest to 12 months. A total of 459/7162 (6.4%) participants receiving beta-blockers died versus 574/6938 (8.3%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus control when assessing all-cause mortality at the time point closest to 12 months (RR 0.78, 95% CI 0.66 to 0.93; P = 0.005; I^2 = 41%; 14,100 participants; 15 trials; very low-quality evidence; **Figure 5**). However, Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.38 to 1.59 showed that the cumulative Z-curve did not cross the boundaries for benefit or harm nor reached the diversity-adjusted required information size (DARIS) or the inner-wedge futility lines (see **Figure 6**).

Major adverse cardiovascular events:

21 out of 25 trials with a total of 21,732 participants and a mean follow-up of 19 months (range 9 to 48 months) reported major cardiovascular events (composite outcome of cardiovascular mortality and reinfarction) at maximum follow-up. A total of 818/10,940 (7.5%) participants receiving beta-blockers had a major cardiovascular event versus 995/10,554 (9.4%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus control when assessing major cardiovascular events at maximum follow-up (RR 0.78, 95% CI 0.70 to 0.87; P < 0.0001; I^2 = 26%; 21,494 participants; 21 trials; low quality evidence; **Figure 7**). The point estimate of the meta-analysis result corresponds to 75 out of 1000 beta-blocker patients dying compared with 94 out of 1000 control participants or a NNT of 53 (see **Table 1**). Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.67 to 0.91 showed that the cumulative Z-curve crossed the boundary for benefit (see **Figure 8**).

15 out of 25 trials with a total of 14,303 participants and a mean follow-up of 13 months (range 9 to 18 months) reported major cardiovascular events (composite outcome of cardiovascular mortality or reinfarction) at the time point closest to 12 months. A total of 448/7145 (6.3%) participants receiving beta-blockers had a major cardiovascular event versus 548/6920 (7.9%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus

control when assessing major cardiovascular events at the time point closest to 12 months (RR 0.80, 95% CI 0.68 to 0.94; P = 0.006; I^2 = 29%; 14,065 participants; 15 trials; very low-quality evidence; **Figure 9**). However, Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.42 to 1.54 showed that the cumulative Z-curve did not cross the boundaries for benefit or harm nor reached the diversity-adjusted required information size (DARIS) or the inner-wedge futility lines (see **Figure 10**).

Serious adverse events:

21 out of 25 trials with a total of 21,732 participants and a mean follow-up of 23.4 months (range 9 to 60 months) reported serious adverse events at maximum follow-up. A total of 1085/10,942 (9.9%) participants receiving beta-blockers had a serious adverse event versus 1294/10,566 (12.2%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus control when assessing serious adverse events at maximum follow-up (RR 0.81, 95% CI 0.74 to 0.89; P < 0.00001; I^2 = 21%; 21,508 participants; 21 trials; low quality evidence; **Figure 11**). The point estimate of the meta-analysis result corresponds to 99 out of 1000 beta-blocker patients dying compared with 122 out of 1000 control participants or a NNT of 44 (see **Table 1**). Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.68 to 0.96 showed that the cumulative Z-curve crossed the boundary for benefit (see **Figure 12**).

15 out of 25 trials with a total of 14,303 participants and a mean follow-up of 13 months (range 9 to 18 months) reported serious adverse events at the time point closest to 12 months. A total of 494/7162 (6.9%) participants receiving beta-blockers had a serious adverse event versus 596/6938 (8.6%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus control when assessing serious adverse events at the time point closest to 12 months (RR 0.82, 95% CI 0.70 to 0.95, P = 0.01; I^2 = 33%; 14,100 participants; 15 trials; very low-quality evidence; **Figure 13**). However, Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.43 to 1.54 showed that the cumulative Z-curve did not cross the boundaries for benefit or harm nor reached the diversity-adjusted required information size (DARIS) or the inner-wedge futility lines (see **Figure 14**).

Heterogeneity

None of the primary outcomes at maximum follow-up showed any sign of significant heterogeneity. However, all-cause mortality and serious adverse events at closest to 12 months follow-up showed signs of moderate heterogeneity both visually and per statistical tests for statistical heterogeneity with an I^2 = 41% and I^2 = 33%, respectively.

Subgroup analyses

None of the planned tests for subgroup differences found significant differences in subgroup analyses on all-cause mortality and serious adverse events at maximum follow-up according to 1) different types of beta-blockers administered, 2) different follow-up periods, 3) and clinical registration status. The remaining tests for subgroup differences were not possible due to lack of data: reperfusion or no reperfusion; different age of participants; men compared to women; and different types of acute coronary syndrome (NSTEMI, STEMI, or UAP). However, when comparing trials according to different follow-up periods for major cardiovascular events, test for subgroup difference showed a significant result (P = 0.02). When each different follow-up period were analyzed separately, the group of trials where the participants were observed for a maximum of 12 months showed no evidence of a difference (RR 0.94, 95%

CI 0.77 to 1.15, P = 0.58; I^2 = 0%; 5249 participants; 7 trials), while trials where the participants were observed for either 1 to 3 years (RR 0.78, 95% CI 0.70 to 0.88, P < 0.0001; I^2 = 6%; 13,754 participants; 12 trials) or 3 years or more (RR 0.57, 95% CI 0.42 to 0.78, P = 0.0004; I^2 = 19%; 2491 participants; 2 trials) showed evidence of a beneficial effect of beta-blockers. Subgroup analysis assessing different follow-up periods for all-cause mortality, serious adverse events, and cardiovascular mortality showed no evidence of a difference when participants were observed for a maximum of 12 months but showed evidence of a beneficial effect of beta-blockers when participants were observed for 1 to 3 years at the time point closest to 12 months.

In our protocol we planned to exclude trials specifically randomising participants with heart failure. However, several trials specifically excluded heart failure participants but reported some percentage of participants with heart failure in the baseline table. We chose to include these trials but decided to perform a post hoc subgroup analysis comparing trials specifically excluding heart failure participants to trials specifically excluding heart failure participants but likely not adhering to it. Test for subgroup differences showed no evidence of a difference when comparing these two subgroups for any of the outcomes.

Risk of bias and sensitivity analyses

The risk of bias of the outcome result was assessed as high risk of bias for all outcomes.

The best-worst and worst-best case meta-analyses showed that incomplete outcome data bias alone had the potential to influence the results for all primary outcomes at maximum follow-up and at closest to 12 months follow-up. Visual inspection of the funnel plots showed no signs of asymmetry. Based on the visual inspection of the funnel plot, we assessed the risk of publication bias as low.

Secondary outcomes

Cardiovascular mortality

16 out of 25 trials with a total of 20,197 participants and a mean follow-up of 18.4 months (range 9 to 48 months) reported cardiovascular mortality at maximum follow-up. A total of 646/10,307 (6.3%) participants receiving beta-blockers died because of a cardiovascular event versus 820/9883 (8.3%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus control when assessing cardiovascular mortality at maximum follow-up (RR 0.75, 95% CI 0.64 to 0.88; P = 0.0003; I^2 = 49%; 20,190 participants; 16 trials; very low-quality evidence). However, Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.40 to 1.42 showed that the cumulative Z-curve did not cross the boundaries for benefit or harm nor reached the diversity-adjusted required information size (DARIS) or the inner-wedge futility lines.

11 out of 25 trials with a total of 12,998 participants and a mean follow-up of 13.2 months (range 9 to 18 months) reported cardiovascular mortality at the time point closest to 12 months. A total of 378/6626 (5.7%) participants receiving beta-blockers died because of a cardiovascular event versus 475/6365 (7.5%) control participants. Meta-analysis showed no evidence of a difference of beta-blockers versus control when assessing cardiovascular mortality at the time point closest to 12 months (RR 0.78, 95% CI 0.63 to 0.97; P = 0.03; I^2 = 54%; 12,991 participants; 11 trials; very low-quality evidence. Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.32 to 1.90 showed that the cumulative Z-

curve did not cross the boundaries for benefit or harm nor reached the diversity-adjusted required information size (DARIS) or the inner-wedge futility lines.

Myocardial reinfarction

19 out of 25 trials with a total of 19,029 participants and a mean follow-up of 19.5 months (range 9 to 48 months) reported myocardial reinfarction at maximum follow-up. A total of 567/9709 (5.8%) participants receiving beta-blockers had a reinfarction versus 724/9320 (7.8%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus control when assessing myocardial reinfarction at maximum follow-up (RR 0.75, 95% CI 0.68 to 0.84; P < 0.0001; I^2 = 0%; 19,029 participants; 19 trials; low quality evidence). Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.63 to 0.90 showed that the cumulative Z-curve crossed the boundary for benefit.

13 out of 25 trials with a total of 11,600 participants and a mean follow-up of 16.8 months (range 9 to 18 months) reported myocardial reinfarction at the time point closest to 12 months. A total of 324/5914 (5.5%) participants receiving beta-blockers had a reinfarction versus 430/5686 (7.6%) control participants. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus control when assessing myocardial reinfarction at the time point closest to 12 months (RR 0.74, 95% CI 0.64 to 0.85; P < 0.0001; I^2 = 0%; 11,600 participants; 13 trials; very low-quality evidence). However, Trial Sequential Analysis with a RRR of 10% and a TSA-adjusted CI 0.42 to 1.30 showed that the cumulative Z-curve did not cross the boundaries for benefit or harm nor reached the diversity-adjusted required information size (DARIS) or the inner-wedge futility lines.

Quality of life

No trials reported quality of life on a continuous or any other scale at any time point.

Angina

Four trials, randomising a total of 6,321 participants, reported angina on as a dichotomous outcome with a mean follow-up of 18.3 months (range 12 to 25 months) at maximum follow-up [44,47,48,57]. None of the trials reported angina using a continuous scale. A total of 930/3132 (29.7%) participants receiving beta-blockers were with angina compared with 917/3189 (28.8%) control participants. Meta-analysis showed no evidence of a difference of beta-blockers versus control when assessing angina at maximum follow-up (RR 1.03, 95% CI 0.96 to 1.11; TSA-adjusted CI 0.91 to 1.17, P = 0.3452; I^2 = 0%; 6321 participants; 4 trials; very low quality of evidence) nor at closest to 12 months follow-up (RR 1.1, 95% CI 0.94 to 1.29; P = 0.22; I^2 = 0%; 2493 participants; 3 trials; very low quality of evidence). Trial Sequential Analysis with a RRR of 10% showed that the cumulative Z-curve did not cross the boundaries for benefit or harm nor reached the diversity-adjusted required information size (DARIS) or the inner-wedge futility lines. Hence, there was not sufficient information to confirm or reject that beta-blockers versus control reduce the risk of angina. Our main results are summarised in '**Table 1 - Summary of findings table**'.

Discussion:

We included 25 trials randomising a total of 21,732 participants. All trials and outcome results were at high risk of bias and the quality of the evidence according to GRADE was of low to very low quality for all outcome results. Hence, there

is a risk that our results overestimate benefits and underestimate harms of beta-blockers. We included all participants without heart failure after myocardial infarction irrespective of age, sex, type of beta-blocker used, and type of control group intervention (placebo or no intervention). We found no to moderate signs of statistical heterogeneity which indicates that the pooling of these diverse participants and interventions were appropriate.

Meta-analysis and Trial Sequential Analyses showed evidence of a beneficial effect of beta-blockers versus placebo or no treatment when assessing all-cause mortality, major cardiovascular events, serious adverse events, and myocardial reinfarction at maximum follow-up. Meta-analysis showed evidence of a beneficial effect of beta-blockers versus placebo or no treatment when assessing cardiovascular mortality, however, Trial Sequential Analysis did not support this finding. Meta-analysis and Trial Sequential Analysis showed no evidence of a difference on the effect of beta-blockers versus placebo or no treatment on the risk of angina. Meta-analyses at the time point closest to 12 months follow-up showed evidence of a beneficial effect of beta-blockers versus placebo or no treatment when assessing all outcomes except for angina but Trial Sequential Analyses did not confirm these meta-analyses result. No data were provided on quality of life. Subgroup analysis assessing all-cause mortality, serious adverse events, cardiovascular mortality (at 12 months follow-up), and major cardiovascular events (at maximum follow-up) according to different follow-up periods, showed no evidence of a difference when participants were observed for a maximum of 12 months but showed evidence of a beneficial effect when participants were observed for 1 to 3 years or 3 years or more.

All remaining tests for subgroup differences showed no evidence of a difference. Tests for subgroup differences were not possible for reperfusion or no reperfusion; different age of participants; men compared to women; and different types of acute coronary syndrome (NSTEMI, STEMI, or UAP).

Strengths

Our review has several strengths. We included trials regardless of language of publication and whether they reported data on the outcomes we had planned to assess. We contacted all relevant authors if additional information was needed. We included more participants than any previous systematic review on this topic which gives us increased power and precision to detect any significant differences between the intervention and control group. We followed our peer reviewed protocol which was published before the literature search began [20], and we conducted the review using the methods recommended by Cochrane and findings from additional methodological studies [16]. Data were double-extracted by two independent authors, minimising the risk of inaccurate data-extraction, and we assessed the risk of bias in all trials according to the *Cochrane Handbook for Systematic Reviews of Interventions* and Lundh 2017[61]. We also conducted Trial Sequential Analyses to assess the risks of random errors and used an eight step procedure to assess if the thresholds for statistical and clinical significance were crossed [17]. This adds further robustness to our results and conclusions. We also tested the robustness of our results by using GRADE to assess the quality of evidence and sensitivity analyses (best-worst, worst-best, no-event trials, and for missing SDs) to test the potential impact of incomplete outcome data bias. Hence, this review considered both risks of random errors and risks of systematic errors which adds further robustness to our results and conclusions.

Limitations

Our systematic review has several limitations. Our findings, interpretations, and conclusions are affected by the quality and quantity of the trials we included. Our bias risk assessment showed that all trials were at high risk of bias. It is, therefore, highly probable that our review results are also biased, i.e., there is a great risk that our results overestimate benefit and underestimate harms of Beta-Blockers [62-69]. This is the primary limitation of our review.

The majority of the included trials were from the 1980s with the latest trial from 1999. This may suggest that the effects of beta-blockers in patients without heart failure after a myocardial infarction is no longer an active research area. The conduct and reporting of trials has immensely improved over the last two decades and new trials may influence the results of this review.

Since a large proportion of the trials were older trials performed more than 30 years ago, one might argue, that the trialists may not have approached or reported the incomplete outcome data properly, why our best-worst and worst-best sensitivity analyses might highly underestimate the potential impact of missing data because we used the trial data available even if the number of included participants in the assessment was unclear based on the publication. Incomplete outcome data bias might potentially have a greater bias impact than our best-worst/worst best-case scenarios show, i.e. the 'true' difference between the actually observed cases and the intention-to-treat population might be larger than our data suggest.

It is a limitation of our review that the trialists generally just stated that they excluded participants with heart failure without specifying how the diagnosis of heart failure was made. Some of the trials might have included participants with reduced ejection fraction but without clinical overt heart failure, other trials might have included participants with clinical overt heart failure but with estimated normal ejection fraction etc.

The beta-blockers used in the experimental group and the co-interventions used in the different trials differed. Theoretically, different types of beta-blockers have different effects. We systematically assessed the degree of heterogeneity in all meta-analyses and we carefully planned subgroup analyses comparing the effects of the different types of beta-blockers. Even though our results showed limited signs of statistical heterogeneity, this is a limitation of our review because the subsequent transferability into a specific clinical context may be impaired.

To increase the statistical power, we chose to use two composite outcomes 'major adverse cardiovascular events' and 'serious adverse events'. A potential limitation when using composite outcomes is that each component of composite outcomes will not necessarily have similar degrees of severity[70]. This might bias the results of these composite outcomes[70]. For example, if certain more severe serious adverse events occur in one of the intervention groups and other less severe serious adverse events occur in the other intervention group, then there is a risk of overlooking actual severity differences between the compared groups on these composite outcomes[70].

We included quality of life and angina on any valid scale. However, no trials reported data on quality of life and there was only limited data on angina. This is of great limitation as we have insufficient information on important subjective patient related outcomes.

Conclusions

Beta-blockers may reduce the risk of all-cause mortality, major cardiovascular events, serious adverse events, and myocardial reinfarction in patients without heart failure after myocardial infarction at maximum follow-up. All trials and outcomes were at high risk of bias and incomplete outcome data bias alone could account for the effect seen. Hence,

there is a great risk that our results overestimate benefits and underestimate harms of Beta-blockers. The effects of beta-blockers on cardiovascular mortality and angina are unclear. No data was obtained on quality of life. We recommend future high quality randomised clinical trials to assess these outcomes and especially quality of life and angina. Future trials ought to assess the effects of beta-blockers in older patients (e.g. 75 years and over). Such trials should be conducted with low risk of systematic error and low risk of random errors [17]. Such trials ought to be designed and reported according to the SPIRIT and CONSORT guidelines[71,72]. In regard to blinding, the effects of beta-blockers on pulse rate make these trials difficult to blind and blinded outcome assessors should be widely involved. Future trials should use standard high-quality measures to exclude heart failure before randomisation. Furthermore, the guidelines recommending beta-blockers to patients without heart failure ought to be updated according to the newest valid evidence on this area.

Appendix

Figure 1 - Flow chart

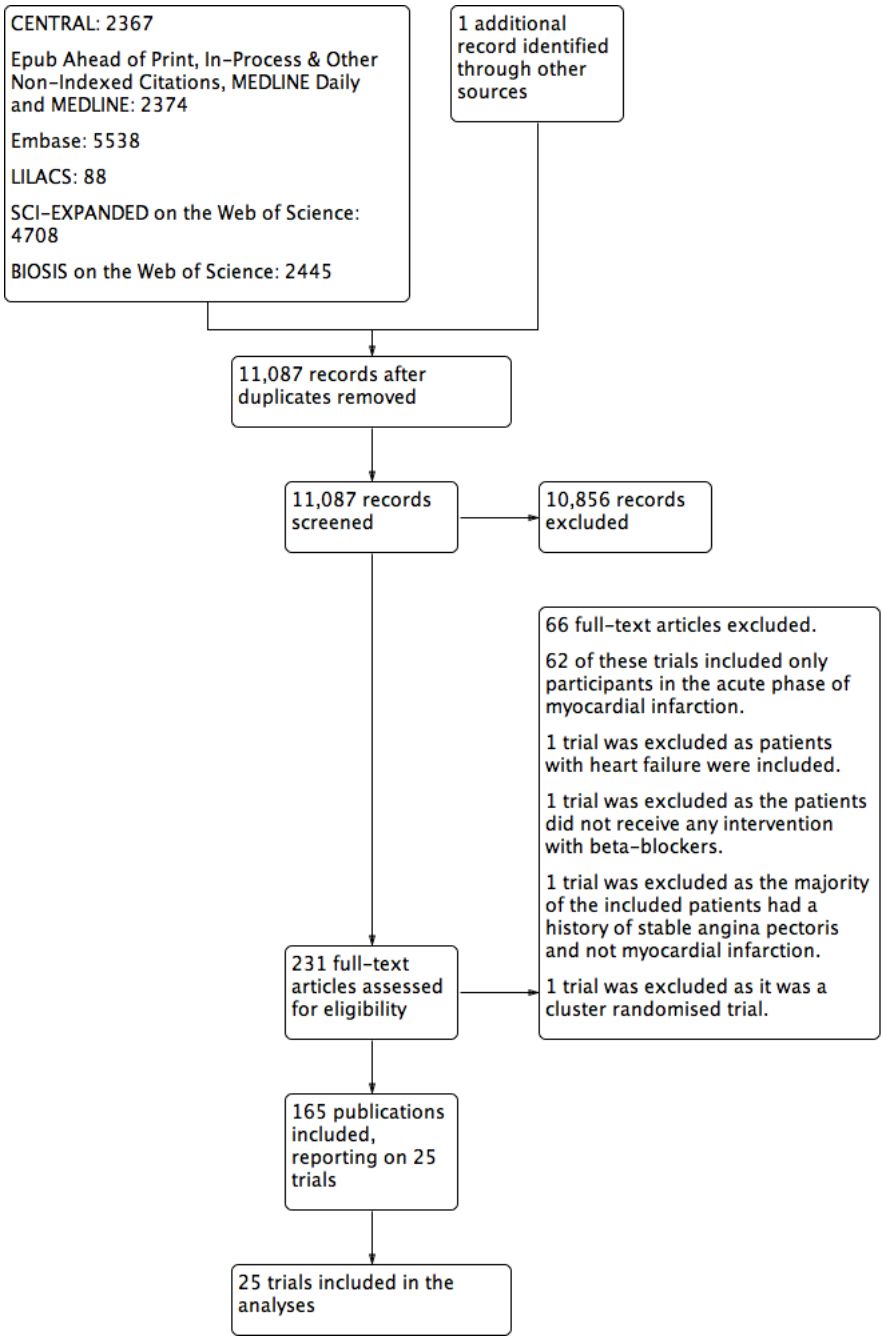

Figure 2 - Bias risk summary according to Cochrane Handbook. Green = low risk of bias, yellow = unclear risk of bias, red = high risk of bias

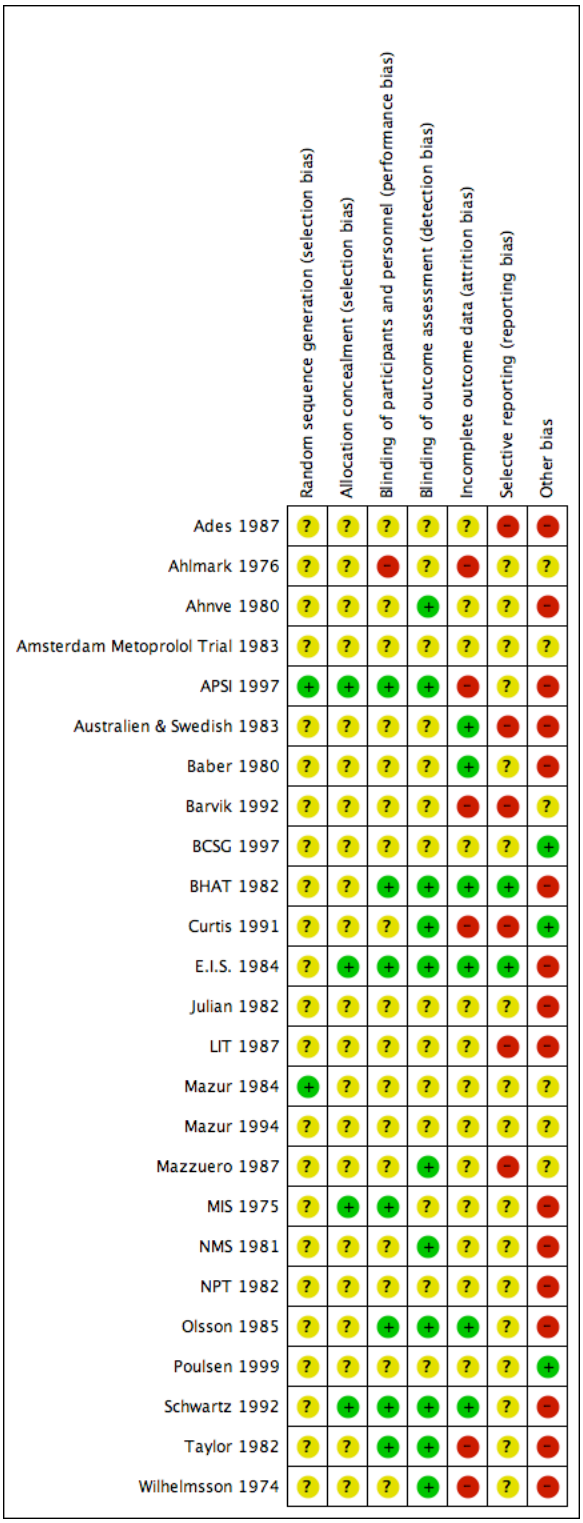

Figure 3 - Forest plot - All-cause mortality at maximum follow-up

Study or Subgroup	Beta-blockers Events	Total	Placebo/no intervention Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahlmark 1976	22	86	29	111	3.9%	0.98 [0.61, 1.58]
Ahnve 1980	4	59	6	52	0.7%	0.59 [0.18, 1.97]
Amsterdam Metoprolol Trial 1983	9	291	16	293	1.6%	0.57 [0.25, 1.26]
APSI 1997	74	283	96	303	9.5%	0.83 [0.64, 1.07]
Australien & Swedish 1983	45	263	47	266	5.8%	0.97 [0.67, 1.40]
Baber 1980	28	355	27	365	3.5%	1.07 [0.64, 1.77]
BCSG 1997	7	385	15	372	1.3%	0.45 [0.19, 1.09]
BHAT 1982	138	1916	188	1921	11.7%	0.74 [0.60, 0.91]
E.I.S. 1984	57	858	45	883	5.6%	1.30 [0.89, 1.91]
Julian 1982	64	873	52	583	6.3%	0.82 [0.58, 1.17]
LIT 1987	86	1192	93	1196	8.4%	0.93 [0.70, 1.23]
Mazur 1984	5	101	11	103	1.0%	0.46 [0.17, 1.29]
Mazur 1994	2	100	11	117	0.5%	0.21 [0.05, 0.94]
MIS 1975	54	1533	83	1520	6.7%	0.65 [0.46, 0.90]
NMS 1981	227	945	280	939	15.4%	0.81 [0.69, 0.94]
NPT 1982	25	278	37	282	3.9%	0.69 [0.42, 1.11]
Olsson 1985	25	154	31	147	3.9%	0.77 [0.48, 1.24]
Poulsen 1999	2	39	1	38	0.2%	1.95 [0.18, 20.61]
Schwartz 1992	17	485	39	488	3.0%	0.44 [0.25, 0.76]
Taylor 1982	60	632	48	471	6.0%	0.93 [0.65, 1.34]
Wilhelmsson 1974	7	114	14	116	1.3%	0.51 [0.21, 1.21]
Total (95% CI)		**10942**		**10566**	**100.0%**	**0.80 [0.72, 0.89]**
Total events	958		1169			

Heterogeneity: Tau² = 0.01; Chi² = 26.57, df = 20 (P = 0.15); I² = 25%
Test for overall effect: Z = 4.18 (P < 0.0001)

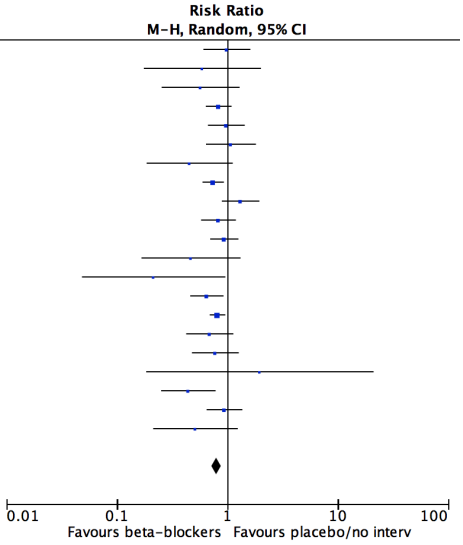

Figure 4. Trial Sequential Analysis of beta-blockers versus placebo/no intervention on all-cause mortality at maximum follow-up based on 21 trials. The diversity-adjusted required information size (DARIS) was calculated based on event rate in the control group of 11.1%; risk ratio reduction of 10% in the experimental group; type I error of 2.5%; type II error of 10% (90% power); and diversity of 41.46%. The green dotted line shows conventional boundaries (2.5%). The required information size was 64,927 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundaries for benefit (red inward sloping lines). The RR 0.80 and the TSA-adjusted CI is 0.68 to 0.95, P < 0.0001.

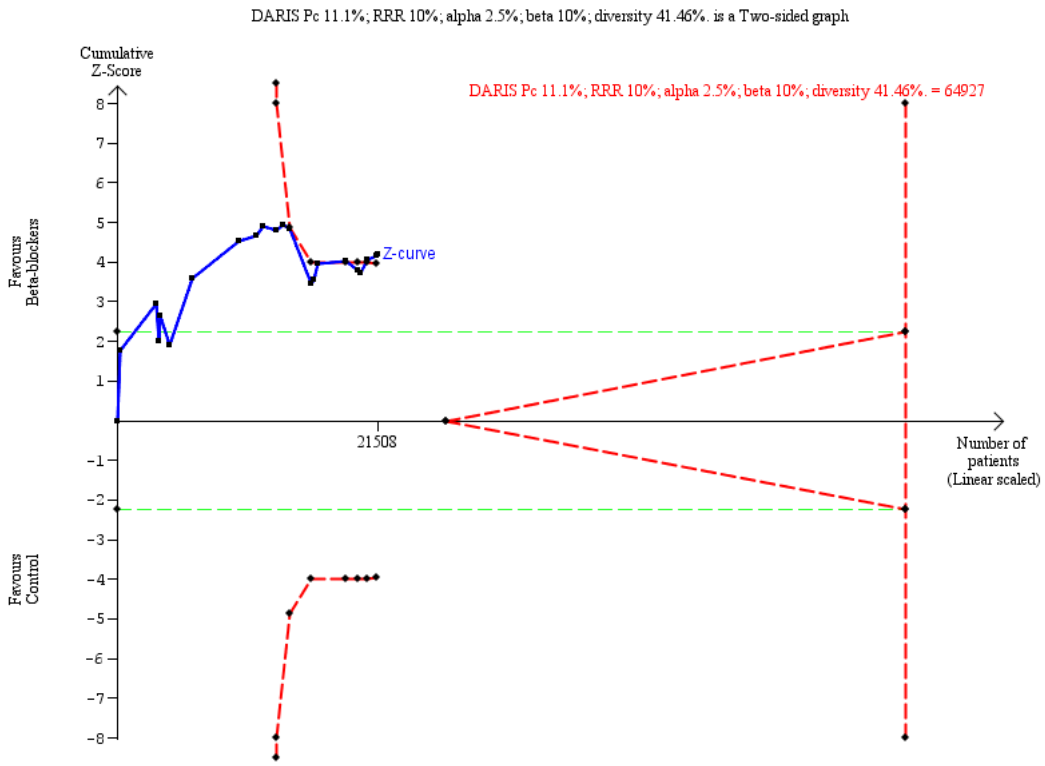

Figure 4 - Forest plot - All-cause mortality at closest to 12 months follow-up

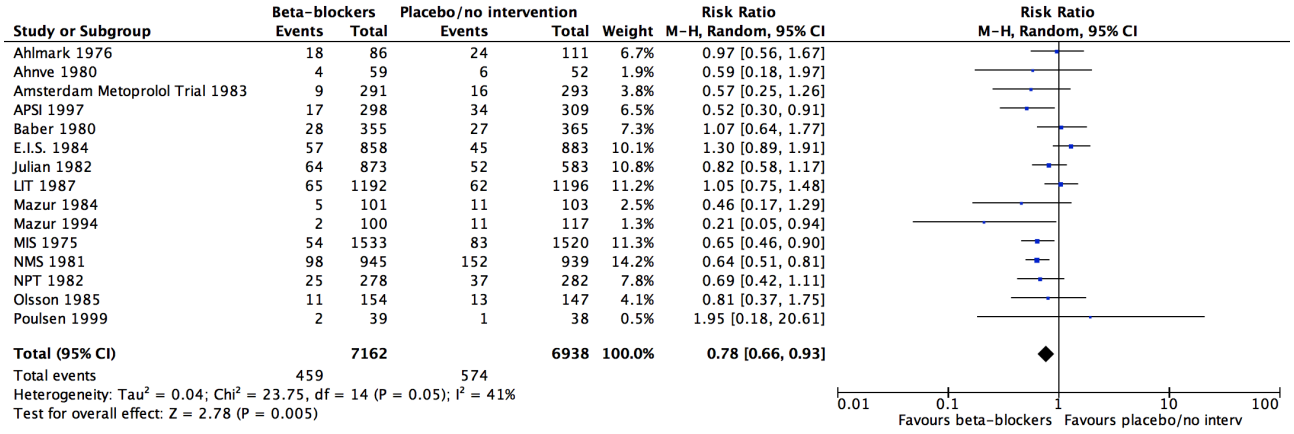

Figure 6. Trial Sequential Analysis of beta-blockers versus placebo on all-cause mortality at the time point closest to 12 months based on 15 trials. The diversity-adjusted required information size (DARIS) was calculated based on event rate in the control group of 8.3%; risk ratio reduction of 10% in the experimental group; type I error of 2.5%; type II error of 10% (90% power); and diversity of 53.61%. The green dotted line shows conventional boundaries (2.5%). The required information size was 112,822 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for benefit or harm (red inward sloping lines). The cumulative Z-curve did not cross the diversity-adjusted required information size (DARIS) nor the inner-wedge futility line (red outward sloping lines). The RR 0.76 and the TSA-adjusted CI is 0.38 to 1.59, P = 0.0055.

Figure 5 - Forest plot – Major cardiovascular events at maximum follow-up

Study or Subgroup	Beta-blockers Events	Total	Placebo/no intervention Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahlmark 1976	4	69	15	93	1.1%	0.36 [0.12, 1.04]
Ahnve 1980	4	59	5	52	0.8%	0.71 [0.20, 2.49]
Amsterdam Metoprolol Trial 1983	16	291	20	293	2.7%	0.81 [0.43, 1.52]
APSI 1997	12	298	30	309	2.6%	0.41 [0.22, 0.79]
Australien & Swedish 1983	40	263	43	266	5.8%	0.94 [0.63, 1.40]
Baber 1980	25	355	25	365	3.6%	1.03 [0.60, 1.76]
BCSG 1997	12	385	15	372	2.0%	0.77 [0.37, 1.63]
BHAT 1982	127	1916	171	1921	11.6%	0.74 [0.60, 0.93]
E.I.S. 1984	51	858	40	883	5.7%	1.31 [0.88, 1.96]
Julian 1982	62	873	50	583	6.7%	0.83 [0.58, 1.18]
LIT 1987	78	1192	80	1196	8.4%	0.98 [0.72, 1.32]
Mazur 1984	5	101	7	103	1.0%	0.73 [0.24, 2.22]
Mazur 1994	5	100	9	117	1.1%	0.65 [0.23, 1.88]
MIS 1975	75	1533	97	1520	8.7%	0.77 [0.57, 1.03]
NMS 1981	88	945	142	939	10.3%	0.62 [0.48, 0.79]
NPT 1982	27	278	35	282	4.4%	0.78 [0.49, 1.26]
Olsson 1985	31	154	49	147	6.0%	0.60 [0.41, 0.89]
Poulsen 1999	2	39	1	38	0.2%	1.95 [0.18, 20.61]
Schwartz 1992	19	485	41	488	3.7%	0.47 [0.27, 0.79]
Taylor 1982	119	632	102	471	10.9%	0.87 [0.69, 1.10]
Wilhelmsson 1974	16	114	18	116	2.8%	0.90 [0.49, 1.68]
Total (95% CI)		**10940**		**10554**	**100.0%**	**0.78 [0.70, 0.87]**
Total events	818		995			

Heterogeneity: Tau² = 0.02; Chi² = 26.93, df = 20 (P = 0.14); I² = 26%
Test for overall effect: Z = 4.37 (P < 0.0001)

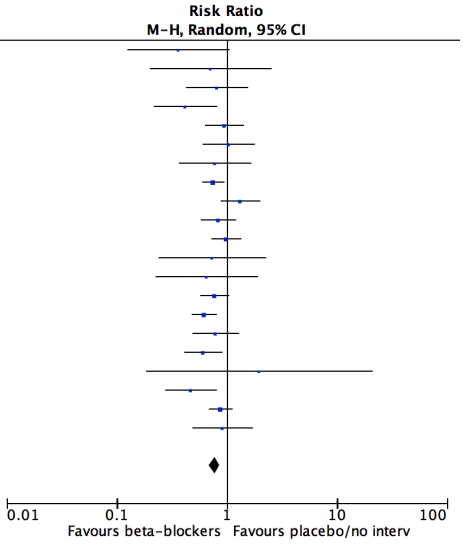

Figure 8. Trial Sequential Analysis of beta-blockers versus placebo on major adverse cardiovascular events at maximum follow-up based on 21 trials. The diversity-adjusted required information size (DARIS) was calculated based on event rate in the control group of 9.4%; risk ratio reduction of 10% in the experimental group; type I error of 2.5%; type II error of 10% (90% power); and diversity of 37.95%. The green dotted line shows conventional boundaries (2.5%). The required information size was 73,636 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundaries for benefit (red inward sloping lines). The RR 0.78 and the TSA-adjusted CI 0.67 to 0.91, P < 0.0001.

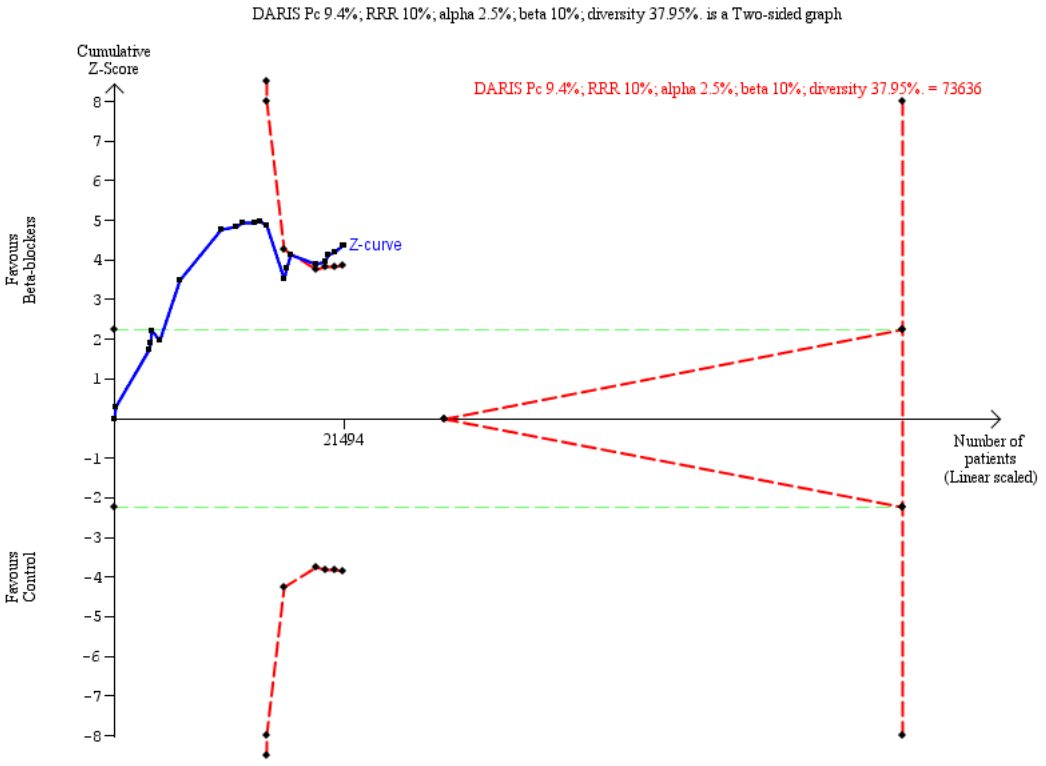

Figure 9 – Forest plot - Major cardiovascular events at closest to 12 months

Study or Subgroup	Beta-blockers Events	Total	Placebo/no intervention Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahlmark 1976	4	69	15	93	2.1%	0.36 [0.12, 1.04]
Ahnve 1980	4	59	5	52	1.5%	0.71 [0.20, 2.49]
Amsterdam Metoprolol Trial 1983	16	291	20	293	5.1%	0.81 [0.43, 1.52]
APSI 1997	12	298	30	309	4.9%	0.41 [0.22, 0.79]
Baber 1980	25	355	25	365	6.7%	1.03 [0.60, 1.76]
E.I.S. 1984	51	858	40	883	9.9%	1.31 [0.88, 1.96]
Julian 1982	62	873	50	583	11.4%	0.83 [0.58, 1.18]
LIT 1987	59	1192	59	1196	11.6%	1.00 [0.71, 1.43]
Mazur 1984	5	101	7	103	1.9%	0.73 [0.24, 2.22]
Mazur 1994	5	100	9	117	2.1%	0.65 [0.23, 1.88]
MIS 1975	75	1533	97	1520	14.1%	0.77 [0.57, 1.03]
NMS 1981	88	945	142	939	16.2%	0.62 [0.48, 0.79]
NPT 1982	27	278	35	282	8.0%	0.78 [0.49, 1.26]
Olsson 1985	13	154	13	147	4.0%	0.95 [0.46, 1.99]
Poulsen 1999	2	39	1	38	0.5%	1.95 [0.18, 20.61]
Total (95% CI)		**7145**		**6920**	**100.0%**	**0.80 [0.68, 0.94]**
Total events	448		548			

Heterogeneity: Tau² = 0.02; Chi² = 19.62, df = 14 (P = 0.14); I² = 29%
Test for overall effect: Z = 2.73 (P = 0.006)

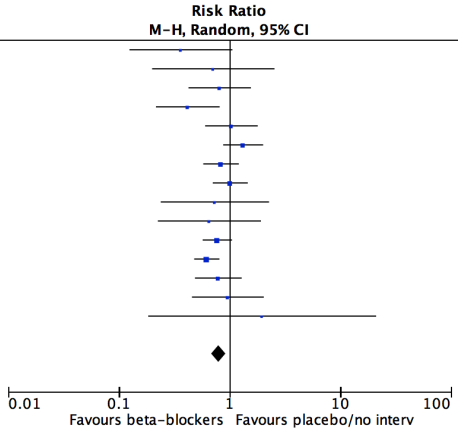

Figure 10. Trial Sequential Analysis of beta-blockers versus placebo on major adverse cardiovascular events at the time point closest to 12 months based on 15 trials. The diversity-adjusted required information size (DARIS) was calculated based on event rate in the control group of 7.9%; risk ratio reduction of 10% in the experimental group; type I error of 2.5%; type II error of 10% (90% power); and diversity of 42.18%. The green dotted line shows conventional boundaries (2.5%). The required information size was 95,502 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for benefit or harm (red inward sloping lines). The cumulative Z-curve did not cross the diversity-adjusted required information size (DARIS) nor the inner-wedge futility line (red outward sloping lines). The RR 0.80 and the TSA-adjusted CI is 0.42 to 1.54, P = 0.0063.

Figure 11 – Forest plot – Serious adverse events at maximum follow-up

Study or Subgroup	Beta-blockers Events	Total	Placebo/no intervention Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahlmark 1976	22	86	29	111	3.2%	0.98 [0.61, 1.58]
Ahnve 1980	4	59	6	52	0.6%	0.59 [0.18, 1.97]
Amsterdam Metoprolol Trial 1983	16	291	20	293	1.9%	0.81 [0.43, 1.52]
APSI 1997	74	283	96	303	8.5%	0.83 [0.64, 1.07]
Australien & Swedish 1983	45	263	47	266	4.9%	0.97 [0.67, 1.40]
Baber 1980	28	355	27	365	2.9%	1.07 [0.64, 1.77]
BCSG 1997	12	385	15	372	1.4%	0.77 [0.37, 1.63]
BHAT 1982	138	1916	188	1921	10.9%	0.74 [0.60, 0.91]
E.I.S. 1984	57	858	45	883	4.7%	1.30 [0.89, 1.91]
Julian 1982	64	873	52	583	5.4%	0.82 [0.58, 1.17]
LIT 1987	86	1192	93	1196	7.5%	0.93 [0.70, 1.23]
Mazur 1984	5	101	11	103	0.8%	0.46 [0.17, 1.29]
Mazur 1994	4	100	14	117	0.7%	0.33 [0.11, 0.98]
MIS 1975	75	1533	97	1520	7.1%	0.77 [0.57, 1.03]
NMS 1981	227	945	280	939	15.3%	0.81 [0.69, 0.94]
NPT 1982	27	278	37	282	3.3%	0.74 [0.46, 1.18]
Olsson 1985	42	154	64	147	6.3%	0.63 [0.46, 0.86]
Poulsen 1999	3	39	2	38	0.3%	1.46 [0.26, 8.26]
Schwartz 1992	21	485	51	488	3.0%	0.41 [0.25, 0.68]
Taylor 1982	119	632	102	471	9.5%	0.87 [0.69, 1.10]
Wilhelmsson 1974	16	114	18	116	2.0%	0.90 [0.49, 1.68]
Total (95% CI)		**10942**		**10566**	**100.0%**	**0.81 [0.74, 0.89]**
Total events	1085		1294			

Heterogeneity: Tau² = 0.01; Chi² = 25.25, df = 20 (P = 0.19); I² = 21%
Test for overall effect: Z = 4.51 (P < 0.00001)

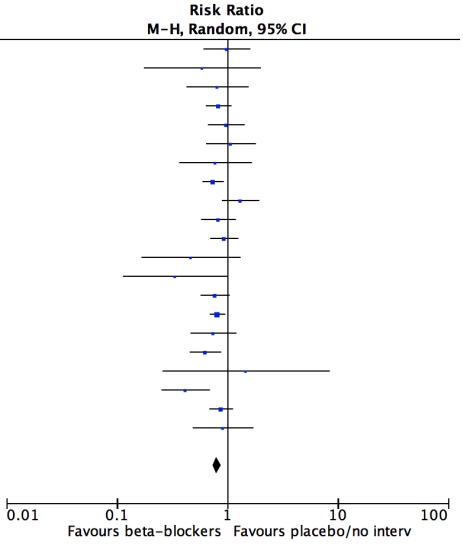

Figure 12. Trial Sequential Analysis of beta-blockers versus placebo on serious adverse events at maximum follow-up based on 21 trials. The diversity-adjusted required information size (DARIS) was calculated based on event rate in the control group of 12.2%; risk ratio reduction of 10% in the experimental group; type I error of 2.5%; type II error of 10% (90% power); and diversity of 34.54%. The green dotted line shows conventional boundaries (2.5%). The required information size was 52,200 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundaries for benefit (red inward sloping lines). The RR 0.81 and the TSA-adjusted CI is 0.68 to 0.96, P < 0.0001.

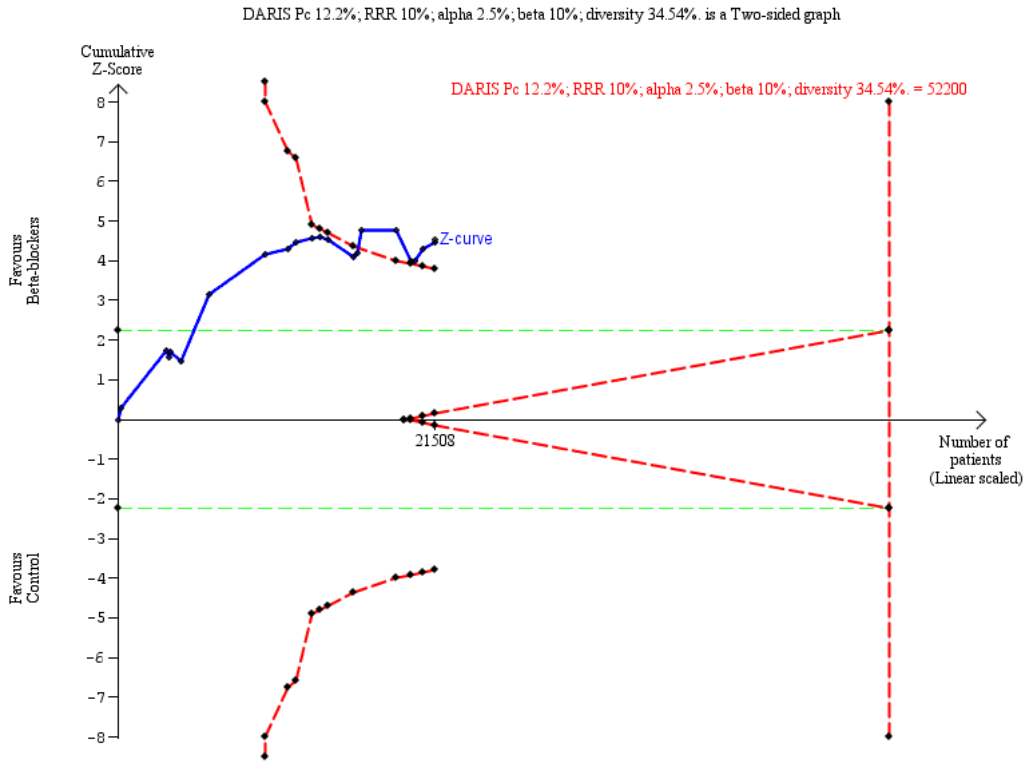

Figure 13 – Forest plot – Serious adverse events at closest to 12 months follow-up

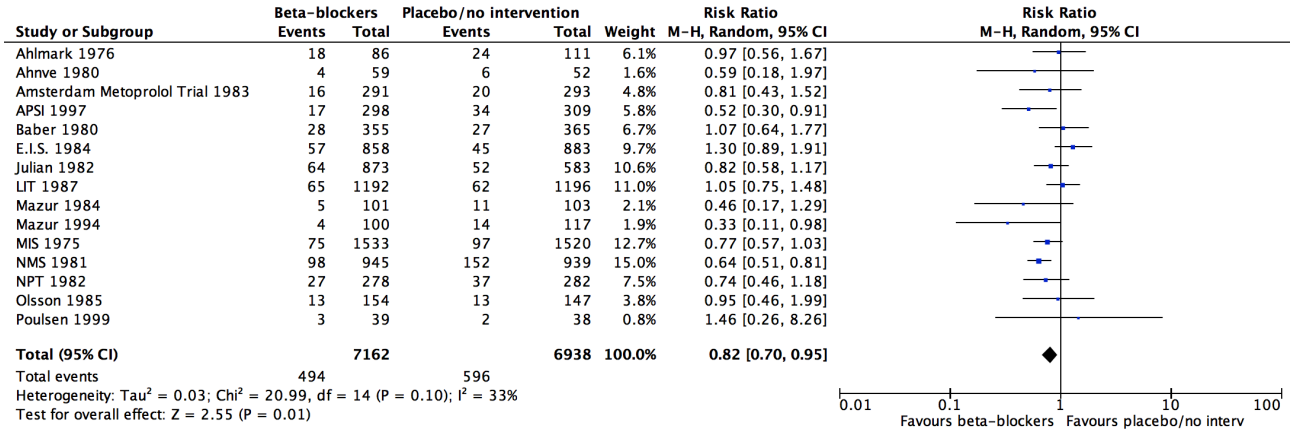

Figure 14. Trial Sequential Analysis of beta-blockers versus placebo on serious adverse events at the time point closest to 12 months based on 15 trials. The diversity-adjusted required information size (DARIS) was calculated based on event rate in the control group of 8.6%; risk ratio reduction of 10% in the experimental group; type I error of 2.5%; type II error of 10% (90% power); and diversity of 45.46%. The green dotted line shows conventional boundaries (2.5%). The required information size was 92,342 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for benefit or harm (red inward sloping lines). The cumulative Z-curve did not cross the diversity-adjusted required information size (DARIS) nor the inner-wedge futility line (red outward sloping lines). The RR 0.82 and the TSA-adjusted CI is 0.43 to 1.54, P = 0.0108.

Tables

Table 1: Summary of Findings Table

Beta-blockers compared with placebo or no intervention for patients without heart failure after an acute myocardial infarction Patient or population: patients without heart failure Settings: any setting Intervention: beta-blockers Comparison: placebo or no intervention						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Risk with Placebo/no intervention	**Risk with Beta-blockers**				
All-cause mortality at maximum follow up (mean follow-up of 23.4 months; range 9 to 60 months)	111 per 1000	88 per 1000 (79 to 96)	RR 0.80 (0.72 to 0.89)	21,732 (21 RCTs)	⨁⊖⊖⊖[1] low	Trial Sequential Analysis for a RRR of 10% and a TSA-adjusted CI 0.68 to 0.95 showed that the boundary for benefit was reached, hence the risk of imprecision of the outcome result is low.
Major cardiovascular events (death or reinfarction) at maximum follow up (mean follow-up of 19 months; range 9 to 48 months)	94 per 1000	75 per 1000 (66 to 82)	RR 0.78 (0.70 to 0.87)	21,732 (21 RCTs)	⨁⨁⊖⊖[1] low	Trial Sequential Analysis for a RRR of 10% and a TSA-adjusted CI 0.67 to 0.91 showed that the boundary for benefit was reached, hence the risk of imprecision of the outcome result is low.
Serious adverse events at maximum follow up (mean follow-up of 23.4 months; range 9 to 60 months)	121 per 1000	97 per 1000 (88 to 106)	RR 0.81 (0.74 to 0.89)	21,732 (21 RCTs)	⨁⨁⊖⊖[1] low	Trial Sequential Analysis for a RRR of 10% and a TSA-adjusted CI 0.68 to 0.96 showed that the boundary for benefit was reached, hence the risk of imprecision of the outcome result is low.
Cardiovascular mortality at maximum follow up (mean follow-up of 18.4 months; range 9 to 48 months)	83 per 1000	62 per 1000 (53 to 73)	RR 0.75 (0.64 to 0.88)	20,190 (16 RCTs)	⨁⊖⊖⊖[1 2 3] very low	Trial Sequential Analysis for a RRR of 10% and a TSA-adjusted CI 0.40 to 1.42 showed that neither the boundary for futility, benefit or harm were reached hence the risk of imprecision of the outcome result is high.
Myocardial infarction at maximum follow up (mean follow-up of 19.5 months; range 9 to 48 months)	78 per 1000	58 per 1000 (53 to 65)	RR 0.75 (0.68 to 0.84)	19,029 (19 RCTs)	⨁⨁⊖⊖[1] low	Trial Sequential Analysis for a RRR of 10% and a TSA-adjusted CI 0.63 to 0.90 showed that the boundary for benefit was reached, hence the risk of imprecision of the outcome result is low.
Angina pectoris at maximum	288 per 1000	296 per 1000 (276 to 319)	RR 1.03 (0.96 to 1.11)	6321 (4 RCTs)	⨁⊖⊖⊖[1 3] very low	Trial Sequential Analysis for a RRR of 10% and a TSA-adjusted CI 0.91 to 1.17 showed that

follow up (mean follow-up of 18.3 months; range 12 to 25 months)						neither the boundary for futility, benefit or harm were reached hence the risk of imprecision of the outcome result is high.
***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (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.**						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

Footnotes

[1] Downgraded by 2 levels due to serious risk of bias. All the included trials were at high risk of bias due to either unclear or high risk in several bias domains.

[2] Downgraded by 1 level because of serious risk of inconsistency due to heterogeneity.

[3] Downgraded by 1 level due to a serious imprecision. Trial Sequential Analysis showed that we did not have enough information to assess a 10% RRR at closest to one month follow-up resulting in a downgrade for imprecision for this outcome.

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