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MEDICINE
MASTER THESIS

Non-acute percutaneous coronary intervention versus medical therapy in patients with ischaemic heart disease: a Cochrane systematic review with meta-analysis and Trial Sequential Analysis

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Dansk titel

Ikke-akut perkutan coronar intervention sammenlignet med medicinsk behandling til behandling af iskæmisk hjertesygdom: et Cochrane systematisk litteratur gennemgang med meta-analyse og Trial Sequential Analysis

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Dansk resumé

Baggrund

En ud af tre dødsfald I patienter over 35 år skyldes iskæmisk hjertesygdom, og ikke-akut PCI er en af de essentielle behandlinger som bruges til behandling af iskæmisk hjertesygdom. Ingen tidligere systematiske litteraturgennemgang har set på effekten af ikke-akut PCI sammenlignet med medicinsk behandling. Formålet med denne litteraturgennemgang var at undersøge fordele og ulemper ved ikke-akut PCI sammenlignet med medicinsk behandling til behandling af patienter med iskæmisk hjertesygdom.

Metode

Vi udførte en Cochrane systematisk litteratur gennemgang med meta-analyse og Trial Sequential Analysis. Vi søgte Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, Science Citation Index Expanded databaser, og tidligere ikke-systematiske litteraturgennemgange publiceret indtil april 2016. Derudover søgte vi efter ikke publicerede studier. Vi inkluderede randomiserede kliniske forsøg der undersøgte effekten af ikke-akut PCI sammenlignet med medicinsk behandling til voksne patienter med iskæmisk hjertesygdom. Forsøgene blev inkluderet uanset type, status, dato og sprog.

Resultater

Vi inkluderede 25 randomiserede kliniske forsøg, med i alt 14.568 patienter. Alle forsøg og resultater var vurderet til at være i høj risiko for systematiske fejl ('bias'). Meta-analyserne viste at ikke-akut PCI sammenlignet med medicinsk behandling ikke havde nogen signifikant effekt ved 3 måneder efter randomisering på risikoen for at dø (RR 1,02; 95% CI 0,90 to 1,16; P = 0.76; I^2 = 0%), på risikoen for en alvorlig kardiovaskulær hændelse (RR 1,01; 95% CI 0,83 to 1,23; P = 0,93; I^2 = 39%) og på risikoen for en alvorlig uønsket hændelse (RR 1,06; 95% CI 0,92 to 1,22; P = 0,42; I^2 = 29%). Resultaterne af Trial Sequential Analysis viste at vi ikke havde nok information til at bekræfte eller afvise en relativ risiko reduktion på 10% på dødelighed. Trial Sequential Analysis viste at vi havde nok information til at afvise en relative risiko reduktion på 15% for alvorlige kardiovaskulær hændelse, og 20% for alvorlige uønskede hændelser. Ikke-akut PCI viste en statistisk signifikant effekt på General Health domænet af SF-36. Kun tre forsøg brugte dette effektmål. Bias som følge af manglende data fra forsøgene alene kunne forklare resultatet. Angina som et kontinuert effektmål kunne ikke meta-analyseres da der ikke var to forsøg eller mere som bruge den samme skala. Ikke-akut PCI viste en signifikant gavnlig effekt på risikoen for at have angina set som et dikotomt effektmål.

Konklusion

Ikke-akut PCI sammenlignet med medicinsk behandling alene ser ikke ud til at have en signifikant effekt på risikoen for at dø, risikoen for en alvorlig kardiovaskulær hændelse og risikoen for en alvorlig skadelig hændelse. Ikke-akut PCI viste en lille men signifikant effekt på General Health domænet af SF-36. Angina som et kontinuert effektmål kunne ikke meta-analyseres.

English abstract

Background

One third of all deaths in patients over 35 years are caused by ischaemic heart disease and non-acute percutaneous coronary intervention (PCI) is considered as one of the most essential intervention for ischaemic heart disease. No systematic reviews have previously assessed the effects of non-acute PCI versus medical therapy, and previous non-systematic reviews have shown conflicting results. Our objective was to assess the benefits and harms of non-acute PCI versus medical therapy in patients with ischaemic heart disease.

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, and former reviews until April 2016. Additionally, we searched for unpublished trials. We included randomised clinical trials assessing the effects of non-acute PCI versus medical therapy for adult participants (≥18 years) with ischaemic heart disease. Trials were included irrespective of publication type, status, date, and language. Non-acute PCI included both sub-acute and elective PCI.

Findings

We included 25 trials randomising 14,568 participants. All trials and outcome results were at high risk of bias and the quality of the evidence per GRADE was of very low quality. Meta-analyses showed that non-acute PCI versus medical therapy did not seem to have any significant effects at three months after randomisation on the risk of all-cause mortality (RR 1.02, 95% CI 0.90 to 1.16, P = 0.76, I2 = 0%), major adverse cardiovascular events (RR 1.01, 95% CI 0.83 to 1.23, P = 0.93, I2 = 39%), and serious adverse events (RR 1.06, 95% CI 0.92 to 1.22, P = 0.42, I2 = 29%). The results of Trial Sequential Analysis showed that we did not have sufficient information to confirm or reject our anticipated risk ratio reduction of 10% on all-cause mortality. Trial Sequential Analysis confirmed that non-acute PCI did not reduce the risk ratio of major adverse cardiovascular events by 15% and serious adverse events by 20%. Non-acute PCI showed a statistically significant effect on the General Health domain of the SF-36 but only three trials assessed this outcome. Incomplete outcome data bias alone could account for the beneficial effect seen. Angina as a continuous outcome could not be meta-analysed. PCI showed significant beneficial effects on angina when assessed as a dichotomised outcome, but results based on dichotomised continuous outcomes should be interpreted with caution.

Interpretations

Non-acute PCI compared with medical therapy does not seem to have any significant beneficial effects on the risk of all-cause mortality, major adverse cardiovascular events, or serious adverse events. Non-acute PCI showed a small but statistically significant effect on the General Health domain of the SF-36. Angina as a continuous outcome could not be meta-analysed.

Background:

Cardiovascular disease is considered the leading cause of death globally [1-3]. According to the World Health Organisation (WHO), 7.4 million people died from ischaemic heart disease in 2012, representing 15% of all global deaths [4]. Ischaemic heart disease is generally divided into stable ischaemic heart disease and acute coronary syndrome (ACS) [5]. Stable ischaemic heart disease is defined as episodes of reversible myocardial demand/supply mismatch, related to ischemia or hypoxia of the heart muscle commonly associated with transient chest discomfort, precipitated by activity such as walking, emotion, or stress, with none to minimal symptoms at rest and symptom relief with the administration of sublingual nitro-glycerin[6]. Acute coronary syndrome presents as three different forms: (1) Chest pain during rest (unstable angina pectoris, minor infarction); (2) acute non-ST-elevation myocardial infarction (NSTEMI); and (3) acute ST-elevation myocardial infarction (STEMI)[5]. The symptom of chest pain (angina) is usually because of a blockage of a great coronary artery resulting in ischemia of the myocardium.

Percutaneous coronary intervention (PCI) is performed by inserting a catheter into an artery (most often the femoral artery or the radial artery), which is then guided by x-ray up through the blood vessels to the coronary arteries to the location of the blockage. The first PCI was performed by inflating a balloon at the blockage of the coronary artery to dilate the artery ('balloon angioplasty'). Then came different kinds of stents inserted into the coronary artery to permanently keep the lumen open after dilation[7,8].

Non-acute PCI includes both sub-acute PCI and elective PCI. Sub-acute PCI is generally performed in patients with unstable angina pectoris and NSTEMI patients who are not candidates for primary PCI because they are haemodynamically stable with medical therapy [5]. Elective PCI is performed in patients where coronary artery bypass grafting is not indicated, and also in patients who are dissatisfied with their quality of life because of symptoms related to ischaemic heart disease or with adverse events due to their medical treatment [9].

Previous meta-analyses [10-15] have shown conflicting results and no systematic review has used Cochrane methodology to assess the effects of non-acute PCI versus medical therapy. The present review will be the first to: (1) take full account of the risk of systematic errors ('bias'), design errors, and risks of random errors ('play of chance')[16-20] (2) include trials irrespective of outcome, follow-up duration, and number of participants; and (3) assess outcomes at several time points and take into account the variability of the follow-up period.

Methods:

We have published a protocol with a detailed description of the methods used [21]. Here, we summarise the methodology. The methodology is 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, and Science Citation Index Expanded, from conception till February 2016. In addition, we searched: 1) the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp); clinicaltrials.gov; Turning Research

Into Practice (TRIP); Google Scholar; and BIOSIS; 2) the bibliographies of review articles and already identified trials. The search strategies can be found in our protocol [21]. Two review authors (EEN, JF) independently screened the initial searches. Four review authors (EEN, JF, NJS, SS) independently screened the full-text in pairs. If the two authors disagreed, a third author (JCJ) resolved the issue. Non-English papers were 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 non-acute PCI versus medical therapy for adult participants (≥18 years) with ischaemic heart disease. Trials were included irrespective of publication type, status, date, and language. Non-acute PCI included both sub-acute and elective PCI. We included any type of non-acute PCI, either without stents (balloon angioplasty) or with stents (bare-metal stents, first generation drug-eluting stents (paclitaxel-eluting stents, sirolimus-eluting stents, zotarolimus-eluting stent), second-generation drug-eluting stents (everolimus-eluting stent and zotarolimus stent, biodegradable stents, or any polymer-free drug-eluting stents). We included any type of medical therapy as the control intervention, such as anti-anginal therapies (e.g., beta-blockers, calcium-antagonist, short-acting nitrates, and long-acting nitrates), vitamin K antagonists (warfarin), and antiplatelet therapies (e.g., aspirin or clopidogrel). We accepted any type of medical therapy as co-intervention to non-acute PCI.

Outcomes:

We assessed all dichotomous and continuous outcomes at three time points:

- closest to one month.
- closest to three months (this was the time point of primary interest).
- maximal follow-up.

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 [22].

Our secondary outcomes were quality of life, severe bleeding, angina, and non-serious adverse events.

All outcomes, except quality of life or angina, 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 [23-25]. 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 [26,27]. 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 closest to three months with low risk of bias in all domains except 'blinding of participants'. We used three primary outcomes and, therefore, we considered a P value of 0.025 or less as statistically significant. We used an eight-step procedure to assess if the thresholds for statistical and clinical significance were crossed [17].

Traditional meta-analysis runs the risk of random errors due to. Therefore, we performed Trial Sequential Analysis[19,25] 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[19,20,29-32]. We estimated the required information size based on the proportion of participants with an event in the control group, an alpha of 2.5%, and a beta of 20%. The relative risk reductions (RRR) were based on the maximum realistic intervention effect estimates based on former studies, trials and meta-analyses (10% for all-cause mortality, 15% for major adverse cardiovascular events, 20% for serious adverse events).

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[33].

Results:

We identified a total of 69,745 potentially relevant references. 181 full text publications were assessed for eligibility. We included 103 publications reporting results of 27 trials. Two of these trials were ongoing trials with no available data yet. Accordingly, 25 trials could be included in our analyses[34-58]. Flowchart can be found in **Figure 1**.

Included studies:

The 25 trials were conducted at sites in 31 different countries, and randomised a total of 14,568 participants. The number of participants in each trial ranged from 44 to 3339, the mean age was 59.8, and the mean proportion of women was 18.2%. The mean proportion of participants with a former myocardial infarction was 26.4%. We included 8 trials where all participants had one-vessel disease, 1 trial with two-vessel disease, 15 trials with mixed vessel disease, and 1 trial where it was unclear. The overall mean proportion of participants with one vessel disease was 69.4%, while the proportion of participants with two vessel disease was 21.3%, and the proportion of participants with three vessel disease was 9.3%. We included 19 trials where the experimental intervention was elective PCI, 4 trials where the experimental intervention was subacute PCI, 1 trial where the experimental intervention was both elective and subacute PCI, and 1 trial where it was unclear whether it was elective or subacute PCI. We included 22 trials where a significant stenosis was located by coronary angiography before randomisation, and 3 trials where the participants were randomised before coronary angiography.We included 19 trials where the control group only

received a co-intervention which was also planned to be delivered similarly in the experimental group. In the remaining 6 trials, the control group received additional medical therapy (3 trials with anti-angina therapy, 1 trial with anti-angina therapy and anti-ischaemic therapy, 1 trial with atorvastatin, and 1 trial with additional medical therapy described as standard medical therapy) in addition to co-intervention.

Table 1

Trial Name	No. of patients	Mean age	Men (%)	One vessel disease (%)	Two vessel disease (%)	Three vessel disease (%)	Prior MI (%)	Type of PCI
ACME-1[34]	212	62.5	100	100	0	0	28.8	Elective
ACME-2[35]	101	60	100	0	100	0	45.6	Elective
ALKK[36]	300	57.9	86.7	100	0	0	3.7	Elective
APRICOT-3[37]	49	59	83.7	NR	NR	NR	NR	Sub-acute
AVERT[38]	341	58.5	84.2	56.6	43.4	0	NR	Elective
BARI-2D[39]	1605	62	67.8	NR	NR	20.3	30.1	Elective
COSTA-RICA[40]	100	63.5	85	100	0	0	100	Elective
COURAGE[41]	2287	61.6	85.1	30.1	38.7	30.4	38.3	Elective
Dakik[42]	44	53.4	54.5	43.9	41.5	14.6	17.1	Elective
DECOPI[43]	212	57	84.9	66.7	26.2	7.1	NR	Mixed
FAME-II[44]	888	63.7	78.2	57.7	34	8.3	37.5	Elective
JSAP[45]	384	64.4	74.2	66.7	32	0	13.8	Elective
Legutko[46]	94	57.1	65.9	NR	NR	NR	100	Unclear
MASS[47]	144	56.7	81	100	0	0	0	Elective
MASS-II[48]	408	60	85	0	41.4	58.6	26.4	Elective
OAT[49]	2166	58.7	79.3	82.3	17.7	0	11.2	Sub-acute
RITA-2[50]	1018	58	82	60	33.2	6.8	46.2	Elective
SWISS-II[51]	201	55.3	87.6	NR	NR	NR	100	Elective
TIMI IIB[52]	3339	56.8	80.1	100	0	0	100	Sub-acute
TOAT[53]	66	58.3	80.3	100	0	0	NR	Elective
TOOMIS[54]	44	58	70.5	100	0	0	NR	Elective
TOPS[55]	87	57	83.9	NR	NR	NR	21.8	Elective
Van den Brand[56]	224	55.5	86.6	54.8	28.1	17.1	4.6	Sub-acute
VELETI[57]	57	69	89.5	100	0	0	61.4	Elective
Won[58]	182	78.1	48.4	46.3	53.7 had multivessel		5.6	Elective

Excluded studies:

We excluded 29 publications after full-text assessment based on our inclusion and exclusion criteria[59-87]. 10 trials had PCI as a planned part of the control group, 7 trials used only acute PCI, 5 trials did not assess PCI as experimental intervention, 1 trial assessed participants with stenosis in femoral artery, 5 trials were not randomised, and 1 trial was quasi-randomised.

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. Many trials were judged to be at unclear risk of bias in several domains, and additional information could not be obtained from the authors when we contacted them. No trials were at low risk of bias in the domain blinding of participants and personnel (**Figure 2)**.

Primary outcomes

All-cause mortality:

24 out of 25 trials with a total of 14,289 participants reported all-cause mortality at the time point closest to three months. A total of 427/7163 (5.96%) PCI participants died versus 420/7126 (5.89%) control participants. Random-effects meta-analysis showed that non-acute PCI did not significantly affect the risk of all-cause mortality at the time point closest to three months (RR 1.02, 95% CI 0.90 to 1.16, P = 0.76, I2 = 0%, 14,289 participants, 24 trials, very low quality of evidence, **Figure 3**) and at maximum follow-up with a mean follow-up of 42 months (RR 0.94, 95% CI 0.85 to 1.04, P = 0.25, I2 = 0%, 14,196 participants, 24 trials, very low quality of evidence). Trial Sequential Analysis showed that there was not enough information to confirm or reject that non-acute PCI versus medical therapy has a RRR of 10% on all-cause mortality at closest to three months (**Figure 4**) and at maximum follow-up.

Major adverse cardiovascular events:

23 out of 25 trials with a total of 14,218 participants reported major adverse cardiovascular events (defined as cardiovascular death or myocardial infarction) at the time point closest to three months. A total of 559/7126 (7.84%) PCI participants had a major adverse cardiovascular event versus 527/7092 (7.43%) control participants. Random-effects meta-analysis showed that non-acute PCI did not significantly affect the risk of major adverse cardiovascular events the time point closest to three months (RR 1.01, 95% CI 0.83 to 1.23, P = 0.93, I^2 = 39%, 14,218 participants, 23 trials, very low quality of evidence, **Figure 5**) and at maximum follow-up with a mean follow-up of 44.5 months (RR 0.92, 95% CI 0.79 to 1.09, P = 0.35, I2 = 42%, 14,122 participants, 23 trials, very low quality of evidence). Trial Sequential Analysis showed that the Z-curve crossed the boundary for futility. Hence, there is firm evidence that non-acute PCI versus medical therapy do not reduce or increase the relative risk of major adverse cardiovascular events by 15% or more at closest to three months (**Figure 6**) and at maximum follow-up.

We assessed each component cardiovascular mortality and myocardial infarction of the composite outcome major adverse cardiovascular events separately.

Non-acute PCI versus medical therapy did not significantly affect the risk of cardiovascular mortality at closest to three months (RR 0.96, 95% CI 0.78 to 1.18, P = 0.69, I^2 = 34%, 10,130 participants, 16 trials, very low quality of evidence) nor at maximum follow-up (RR 0.78, 95% CI 0.60 to 1.02, P = 0.07, I^2 = 29%, 10,146 participants, 16 trials, very low quality of evidence).

Non-acute PCI versus medical therapy did not significantly affect the risk of myocardial infarction at the time point closest to three months (RR 1.03, 95% CI 0.83 to 1.26, P = 0.81, I^2 = 37%, 14,118 participants, 22 trials, very low quality of evidence), nor at maximum follow-up (RR 0.99, 95% CI 0.84 to 1.17, P = 0.99, I^2 = 32%, 13,957 participants, 22 trials, very low quality of evidence).

Serious adverse events:

25 out of 25 trials with a total of 14,358 participants reported serious adverse events at the time point closest to three months. A total of 863/7196 (11.99%) PCI participants had a serious adverse event versus 805/7162 (11.23%) control participants. Random-effects meta-analysis showed that non-acute PCI did not significantly affect the risk of serious adverse events the time point closest to three months (RR 1.06, 95% CI 0.92 to 1.22, P = 0.42, I2 = 29%, 14,358 participants, 25 trials, very low quality of evidence, Figure 7) nor at maximum follow-up with a mean follow-up of 42 months (RR 1.00, 95% CI 0.90 to 1.11, P = 0.95, I2 = 22%, 14,217 participants, 25 trials, very low quality of evidence). Trial Sequential Analysis with a RRR of 20% showed that the Z-curve crossed the boundary for futility at closest to three months (**Figure 8**), and at maximum follow-up. A post-hoc Trial Sequential Analysis showed that we had sufficient information to confirm that non-acute PCI versus medical therapy do not reduce or increase the relative risk of serious adverse events by as low as 13% or more at the time point closest to three months.

Heterogeneity

Both major adverse cardiovascular events and serious adverse events showed significant heterogeneity both visually and per statistical tests for statistical heterogeneity with an I^2 of 39% and 29% respectively. However, when investigating the forest plots the SWISS-II trial[51] seemed to have an extreme result compared to the remaining trials. When removing this trial from the analyses, heterogeneity was removed both visually and by the test for statistical heterogeneity (I^2= 0%). A post hoc sensitivity analysis showed that after removing the SWISS-II trial[51] from the analysis the meta-analysis result indicated that PCI versus medical therapy significantly increased the risk of a serious adverse event at closest to three months (RR 1.13, 95% CI 1.01 to 1.27, P = 0.04, I^2 = 0%, 14,026 participants, 22 trials).

Subgroup analyses

None of the planned tests for subgroup differences found significant differences in subgroups analyses on all-cause mortality, major adverse cardiovascular events, or serious adverse events at closest to three months according to (1) stent type, (2) number of vessels affected, (3) age above or below 75 years, (4) length of time point use, (5) similar/different medical intervention, and (6) timing of PCI (elective or subacute).

When comparing trials using different types of stents for major adverse cardiovascular events at maximum follow-up, test for subgroup difference showed a significant result (P = 0.03). When each group of trials, each using one specific type of stents, were analysed separately only the group of trials using bare-metal stents had a significant effect on major adverse cardiovascular events (RR 0.68, 95% CI 0.52 to 0.89, P = 0.005, I^2 = 0%, 601 participants, 3 trials, very low quality of evidence). All remaining test for subgroup differences in Review Manager found no significant statistical difference.

Risk of bias and sensitivity analyses

The best-worst and worst-best case meta-analyses showed that incomplete outcome data bias alone do not have the potential to influence the results for all primary outcomes as closest to three months. However, the analyses showed that incomplete outcome data bias alone do have the potential to influence the results at maximum 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.
We performed meta-regression for all primary outcomes using age as a covariate. We found no significant effect of age.

Secondary outcomes

Quality of life

Nine trials reported quality of life at the time point closest to three months[34,35,38,39,41,48-50,53]. Few trials used similar quality of life questionnaires and only data from the SF-36 could be used in a meta-analysis.
Three trials reported quality of life at the time point closest to three months using the SF-36 questionnaire[41,48,50]. All three trials reported the 8 separate domains of the SF-36. Meta-analysis of these trial results found a significant beneficial effect of non-acute PCI on general health at closest to three months (random-effects MD 4.98, 95% CI 3.39 to 6.58, P < 0.00001, 3094 participants, 3 trials, very low quality of evidence), and at maximum follow-up (random-effects MD 3.04, 95% CI 1.18 to 4.90, P = 0.001, 2239 participants, 3 trials, very low quality of evidence). The best-worst and worst-best case meta-analyses (using one SD)[21] showed that incomplete outcome data bias alone had the potential to influence the results both at closest to three months and at maximum follow-up. The remaining six trials assessing quality of life used different scales and it was, therefore, not possible to meta-analyse the results of these trials.

Angina

Twelve trials reported angina [34,35,39,41,44,45,47-50,55,56]. Only the COURAGE trial[41] reported angina using a continuous scale (the Seattle Angina Questionnaire). It found a statistically significant benefit of non-acute PCI in addition to medical therapy compared with medical therapy alone at three months on angina stability (MD 4.00 points 95% CI 1.40 to 6.60, P = 0.003, 1720 participants, 1 trial, very low quality evidence). It also found a statistically significant benefit of non-acute PCI in addition to medical therapy compared with medical therapy alone on angina frequency (MD 5.00,

95% CI 2.89 to 7.11, P < 0.00001, 1742 participants, 1 trial, very low quality evidence). There were no statistically significant effects at maximum follow-up (at 36 months).

We performed a meta-analysis of 5 trials that randomised 2907 participants reporting on the proportion of participants with angina [34,35,41,47,48]. A total of 520/1454 (35.76%) PCI participants were with angina compared with 694/1453 (47.76%) control participants. Fixed-effects meta-analysis showed that non-acute PCI significantly reduced the risk of being with angina at the time point closest to three months (RR 0.75 95% CI 0.69 to 0.82, P < 0.00001, I^2 = 77%, 2907 participants, 5 trials, very low quality of evidence), and at maximum follow-up with a mean follow-up of 36.7 months (RR 0.72, 95% CI 0.64 to 0.82, P < 0.00001, I^2 = 79%, 1678 participants, 5 trials, very low quality of evidence).

Two trials [44,50] randomised 1891 participants and reported on the proportion of participants with angina with Canadian Cardiovascular Society angina class two or worse. A total of 131/943 (13.89%) randomised to non-acute PCI had a score of 2 or more versus 265/948 (27.95%) participants randomised to the control group. Fixed-effects meta-analysis showed that non-acute PCI significantly had a beneficial effect on the risk of having Canadian Cardiovascular Society angina class of two or worse (RR 0.50, 95% CI 0.42 to 0.60, P < 0.00001, I^2 = 39%, 1891 participants, 2 trials, very low quality evidence).

The remaining trials reported angina using either different questionnaires or in such ways that meta-analysis was not appropriate. The pre-planned Trial Sequential Analysis of angina was based on a continuous scale; however, we performed a post-hoc Trial Sequential Analysis on the dichotomous outcome risk of being with angina. The Trial Sequential Analysis was based on a RRR of 20% showed that the Z-curve crossed the boundary for benefit. Hence, non-acute PCI compared to medical therapy does seem to reduce the risk of being with angina. However, this result should be interpreted with caution. See '**Discussion**'.

Time point closest to one month

We also assessed our outcomes at the time point closest to one month. In this outcome, we included data only if the trials reported data at a time point before three months; otherwise the results were used in our primary analysis (time point closest to three months). Data resulting from assessments at three months or thereafter are therefore not included in the following analyses.

Only six trials reported outcomes at closest to one month[41,44,45,49,52,56]. No significant effect was found on all-cause mortality, major adverse cardiovascular events, and serious adverse events. Only one trial assessed quality of life and found a significant effect (P <0.001)[41]. Three trials assessed angina, and no data could be meta-analysed. Only one of these trials used angina as a continuous outcome and a found a beneficial effect (RR 0.39, 95% CI 0.28 to 0.53, P < 0.001)[41].

Our main results are summarised in the '**Table 2 - Summary of findings table**'.

Discussion:

We included 25 trials randomising 14,568 participants. All trials and outcome results were at high risk of bias and the quality of the evidence per GRADE was of very low quality. Non-acute PCI compared with medical therapy does not seem to have any significant beneficial effects on the risk of all-cause mortality, major adverse cardiovascular events, or serious adverse events. Non-acute PCI showed a small but statistically significant effect on the General Health domain of the SF-36. Angina as a continuous outcome could not be meta-analysed.

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, 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[21], and we conducted the review using the methods recommended by The Cochrane Collaboration and findings from additional methodological studies[16]. We assessed the statistical heterogeneity in the planned primary analyses as low to moderate. After removing the SWISS trial[51] with an extreme result from major adverse cardiovascular events and serious adverse events, the heterogeneity was very low (I^2= 0%).

We also performed Trial Sequential Analyses 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 with sensitivity analyses (best-worst, worst-best, no-event trials, and for missing SDs). Our Trial Sequential Analysis results showed that we had sufficient information to reject or confirm our anticipated intervention effects, when we analysed all dichotomous outcomes, except all-cause mortality. Hence, there is low risk of random errors causing these results.

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., that there is a great risk that our results overestimate benefit and underestimate harms of non-acute PCI[17,88-94]. This is the primary limitation of our review. As predicted, no trials used blinding of participants and personnel, due to the nature of the PCI-procedure. The severity of the potential bias of this domain is worse in trials reporting subjective outcomes [94]. Therefore, the results of angina and quality of life should especially be interpreted with caution.

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[95]. This might bias the results of these composite

outcomes[95]. 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[95].

We included angina as a continuous outcome. However, only few trials reported angina on a continuous scale. Several trials assessed angina as a dichotomous outcome. However, these dichotomised results should be interpreted with great caution for a number of reasons: 1) several of the trials did not specify how 'free of angina' was assessed or defined; 2) often the trialists dichotomised a continuous angina scale and information is then lost and the analysis results can be greatly influenced by the distribution of data and the choice of an arbitrary cut-point[16,96-98]; 3) even though a larger proportion of participants cross the cut-point in one of the compared groups, the effect measured might still be limited to a few point (e.g. on the Seattle Angina Questionnaire); and 4) by only focusing on how many patients crossed a line for benefit, investigators ignore how many patients are deteriorating at the same time. If e.g. half of the patient benefit but the other half deteriorates then the dichotomised results will only show benefit.

The medical therapy used in the different trials differed. Even though our results showed limited sign of statistical heterogeneity, this is a limitation of our review because the subsequent transferability into a specific clinical context may be impaired.

Conclusions

Non-acute PCI compared with medical therapy does not seem to have any significant effects on the risk of all-cause mortality, major adverse cardiovascular events, or serious adverse events. Non-acute PCI did seem to result in a small but statistically significant increase on the General Health domain of the SF-36, however, this result was at high risk of bias, and incomplete outcome data bias alone could account for the effect seen. Angina as a continuous outcome could not be meta-analysed. Most trials assessed angina as a dichotomous outcome, which has several methodological limitations, and such results should be interpreted with great caution. All the trials and all the outcome results were at high risk of bias so there is a great risk that out results overestimate benefits and underestimate harms of non-acute PCI. No subgroup differences were seen regarding timing of PCI (subacute or elective), vessel disease, or medical intervention. The lack of effect on outcomes such as mortality, major adverse cardiovascular events, and serious adverse events should be taken into consideration when deciding whether a patient should undergo non-acute PCI.

Future randomised clinical trials assessing non-acute PCI should especially focus on assessing mortality, quality of life, and angina as a continuous outcome, as it seems we have enough data on serious adverse events and major adverse cardiovascular events to rule out beneficial and harmful effects. Such trials should be conducted with low risk of design, low risk of random errors, and focus on minimising the risk of bias preferably by blinding the participants to the intervention by using sham-PCI. This would increase the validity of patient-reported outcomes such as quality of life and angina. Such trials ought to be designed and reported according to the SPIRIT and CONSORT guidelines[99,100].

Appendix

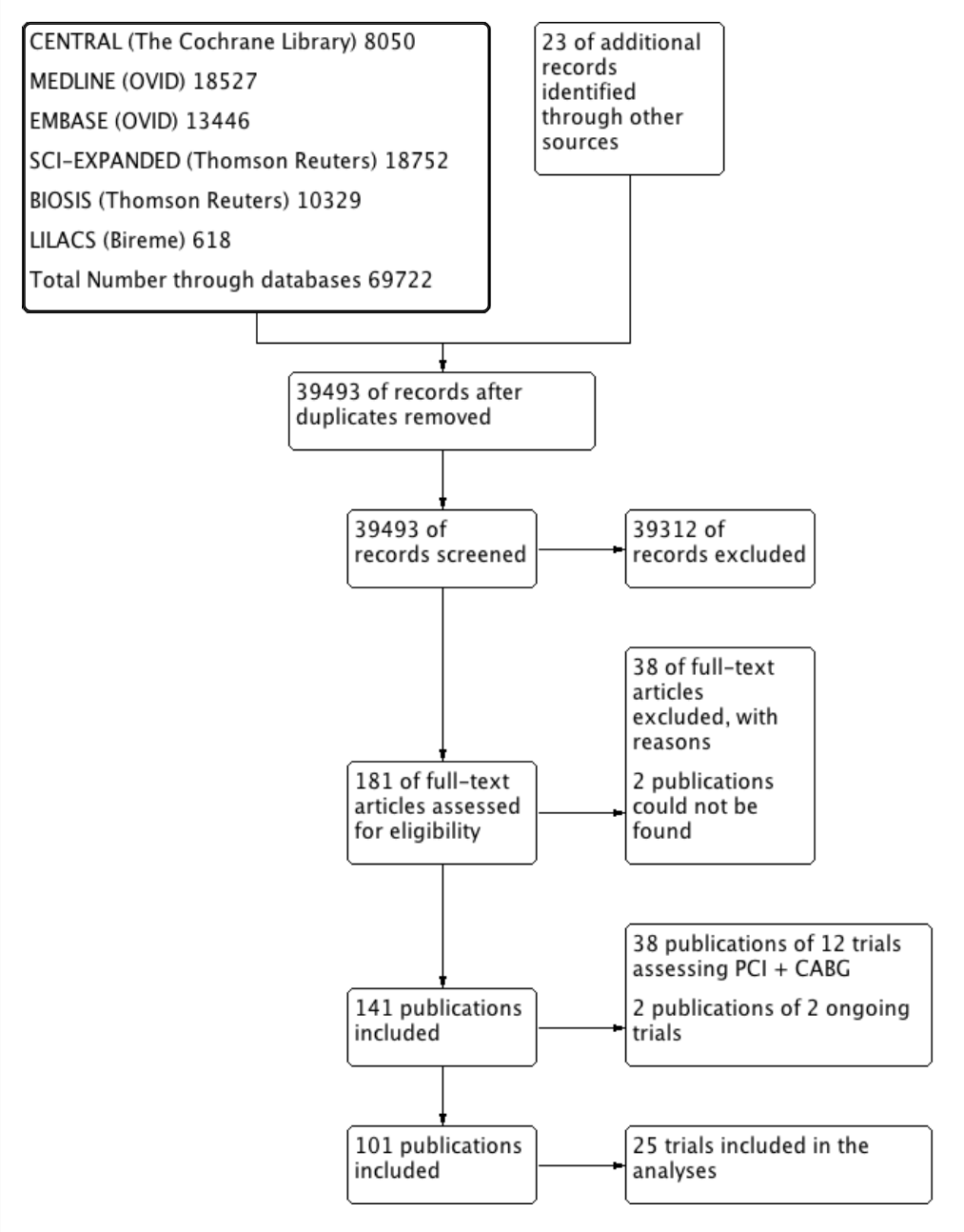

Figure 1 - Flow chart

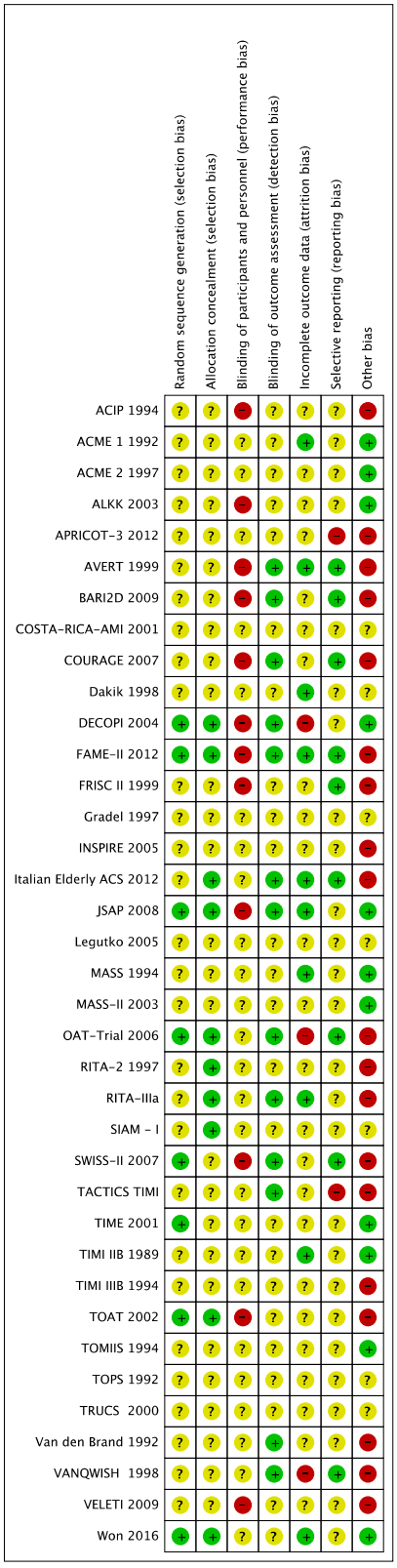

Figure 2 - Bias risk summary according to Cochrane Handbook. Green = low risk of bias, yellow = unclear risk of bias, red = high risk of bias

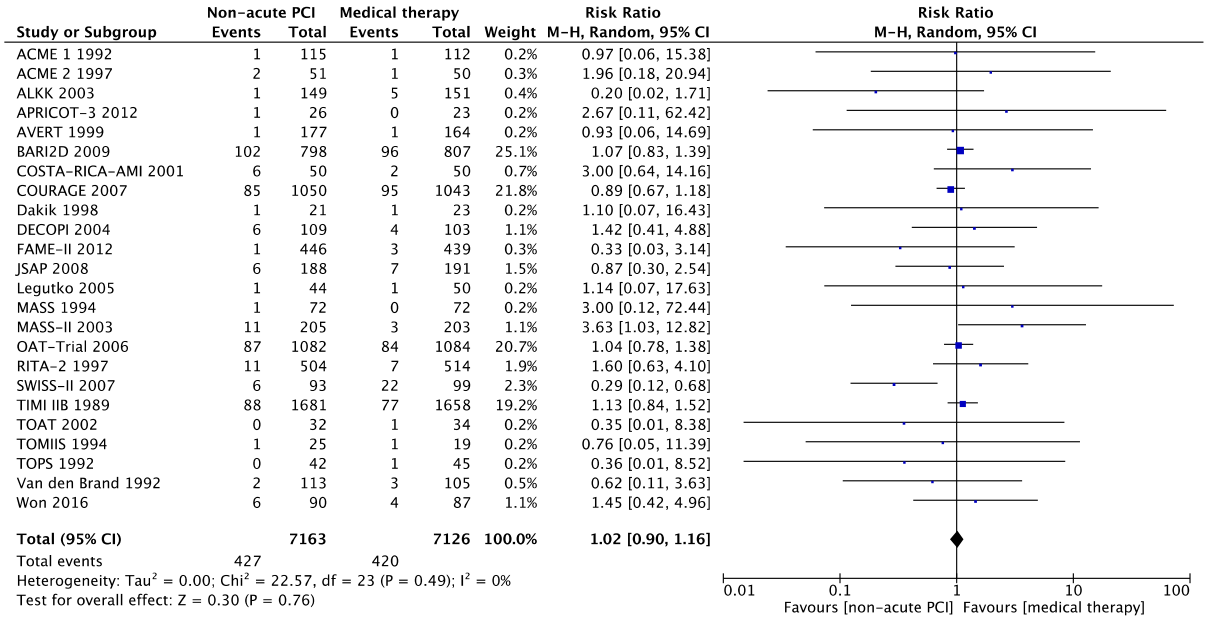

Figure 3 - Forest plot. Non-acute percutaneous coronary intervention versus medical therapy at closest to three months - all-cause mortality

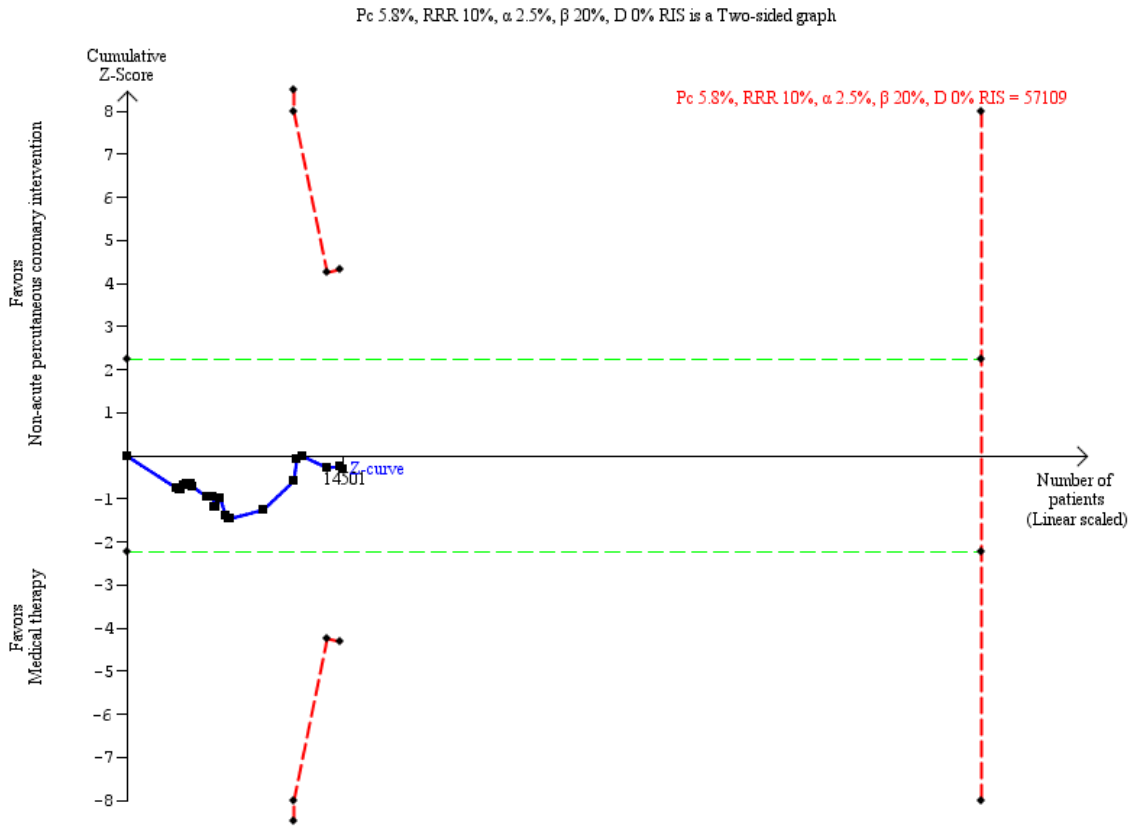

Figure 4 - Trial Sequential Analysis of non-acute percutaneous coronary intervention versus medical therapy on all-cause mortality closest to three months in 24 trials. The diversity-adjusted required information size (RIS) was calculated based on mortality in the control group of 5.8%; risk ratio reduction of 10% in the experimental group; type I error of 2.5%; and type II error of 20% (80% power). No diversity was noted. The required information size was 57109 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 crossed the inner-wedge futility line (the inner-wedge futility could not be calculated due to too low information). Additionally, the cumulative Z-score did not cross the RIS. The green dotted line shows conventional boundaries (2.5%).

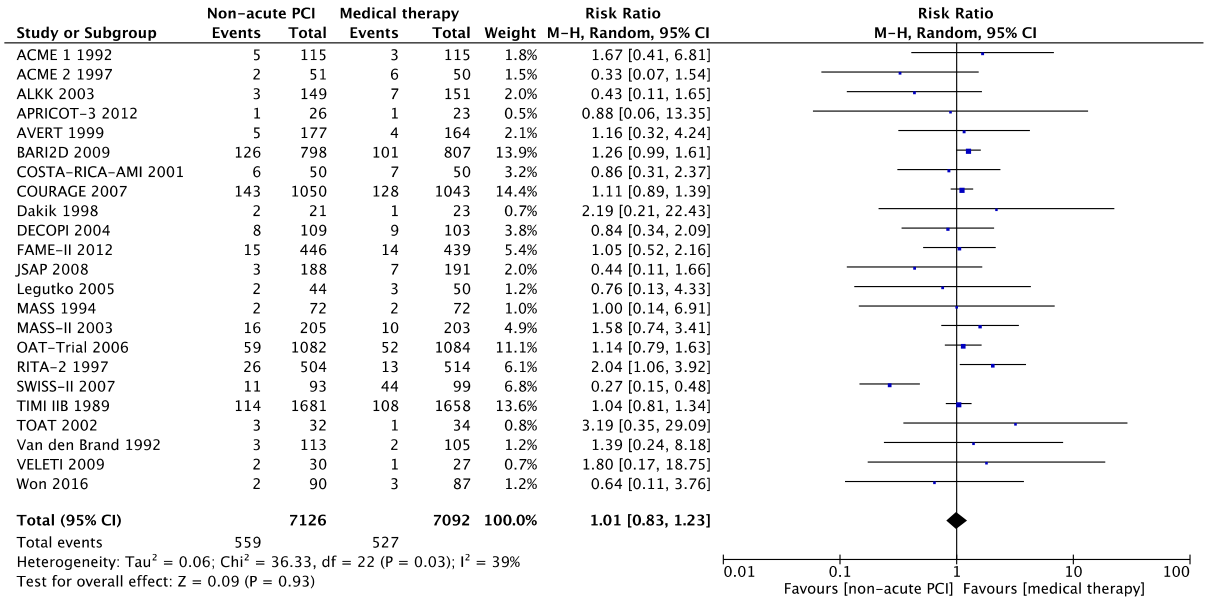

Figure 5 - Forest plot - Major adverse cardiovascular events at closest to three months

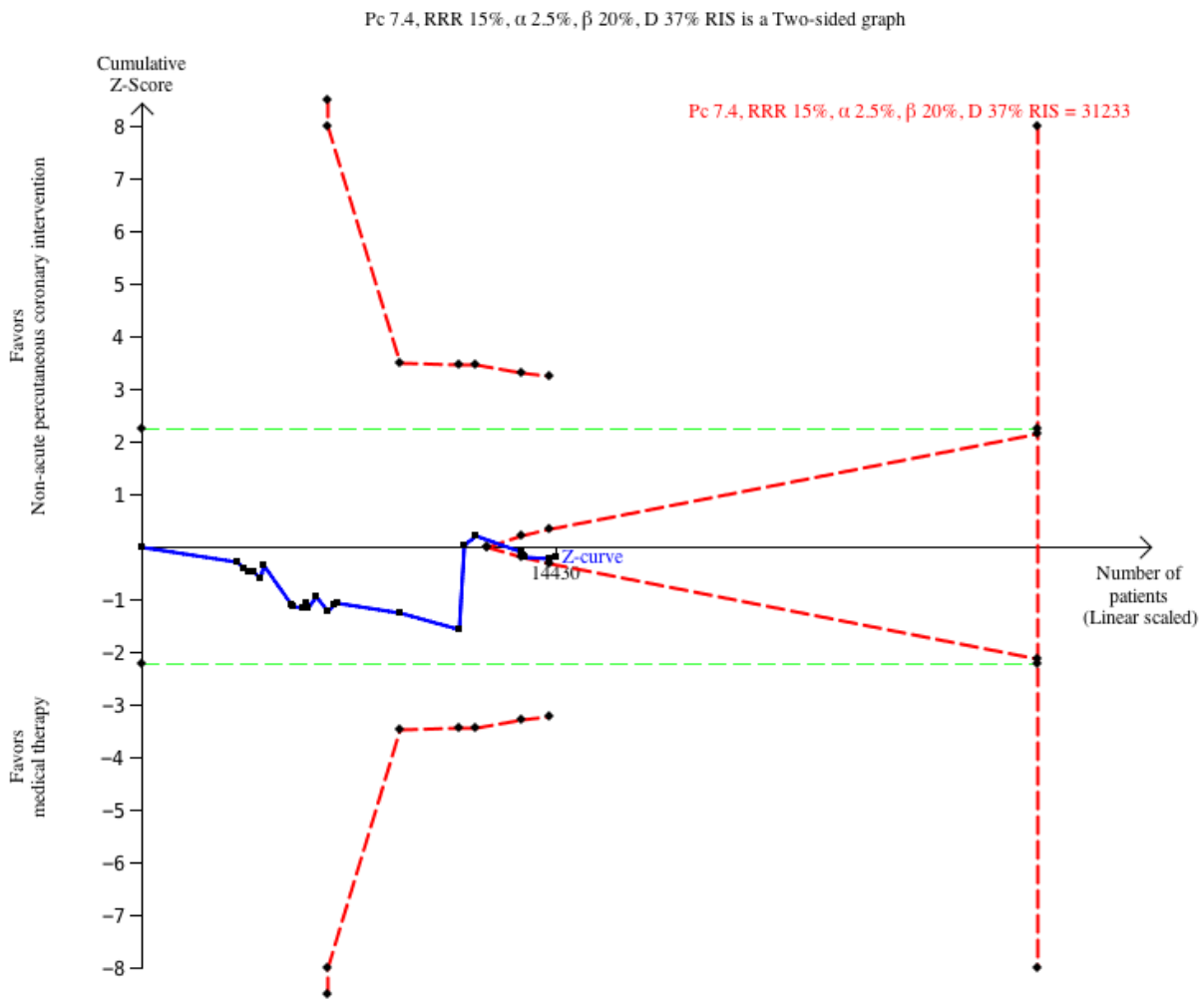

Figure 6 - Trial Sequential Analysis of non-acute percutaneous coronary intervention versus medical therapy on major adverse cardiovascular events closest to three months in 23 trials. The diversity-adjusted required information size (RIS) was calculated based on event rate in the control group of 7.4%; risk ratio reduction of 15% in the experimental group; type I error of 2.5%; type II error of 20% (80% power); and diversity of 37%. The required information size was 31233 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 RIS. However, the cumulative Z-curve crossed the inner-wedge futility line (red outward sloping lines). The green dotted line shows conventional boundaries (2.5%).

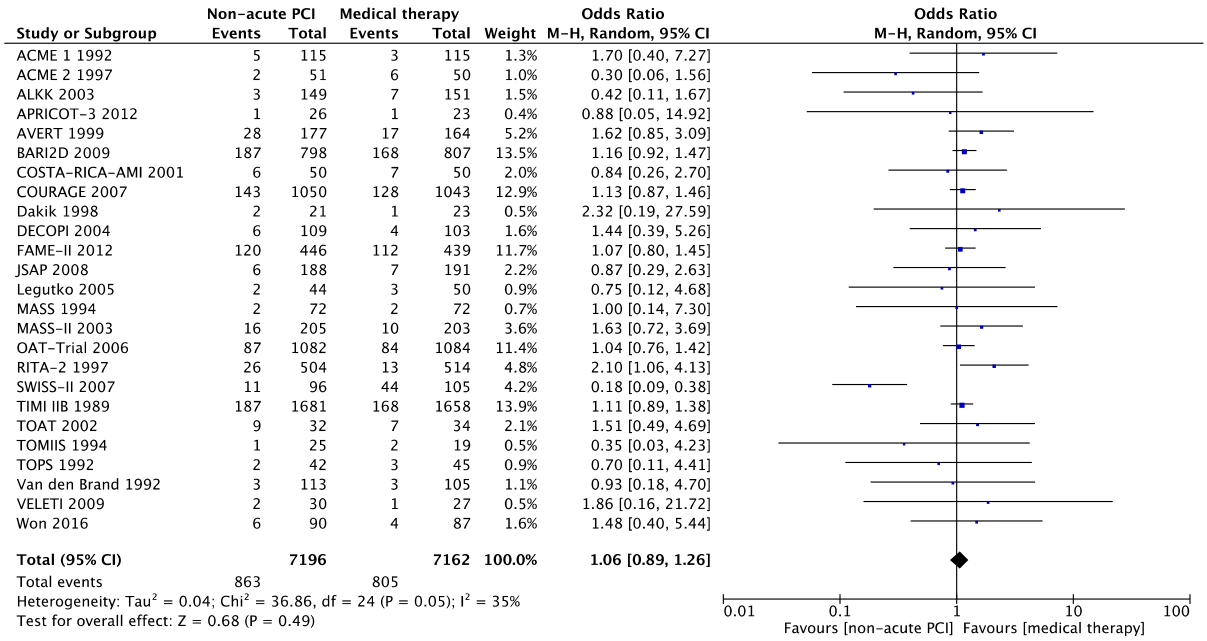

Figure 7 - Forest plot - Serious adverse events at closest to three months

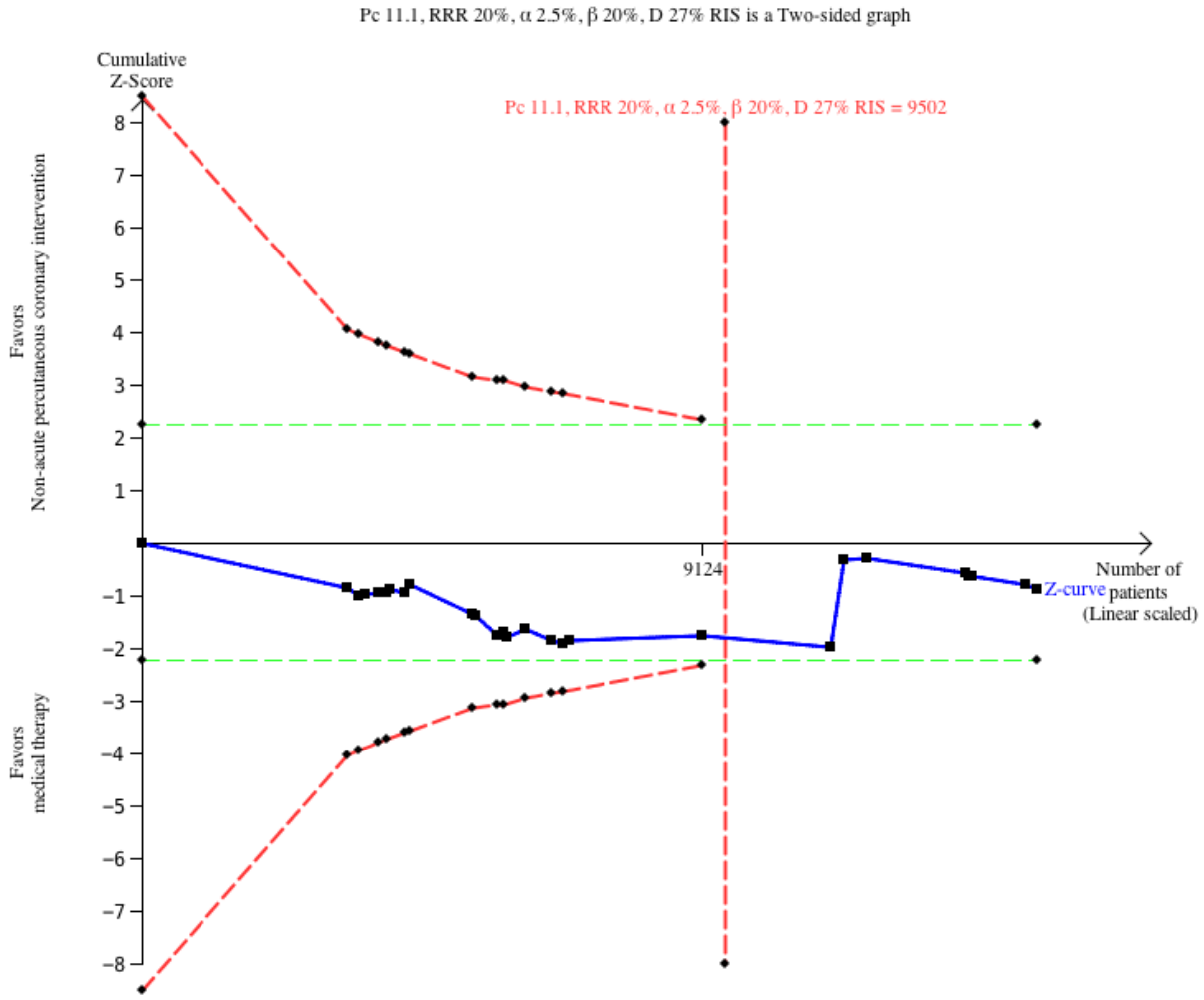

Figure 8 - Trial Sequential Analysis of non-acute percutaneous coronary intervention versus medical therapy on serious adverse events closest to three months in 25 trials. The diversity-adjusted required information size (RIS) was calculated based on event rate in the control group of 11.1%; risk ratio reduction of 20% in the experimental group; type I error of 2.5%; type II error of 20% (80% power); and diversity of 27%. The required information size was 9502 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 crossed the RIS. The green dotted line shows conventional boundaries (2.5%).

Tables

Summary of findings:

Non-acute percutaneous coronary intervention compared to medical therapy for patients with ischaemic heart disease

Patient or population: patients with ischaemic heart disease
Setting: any setting
Intervention: non-acute percutaneous coronary intervention
Comparison: medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with medical therapy	Risk with non-acute percutaneous coronary intervention				
All-cause mortality at closest to three months	59 per 1.000	**60 per 1.000** (53 to 68)	**RR 1.02** (0.90 to 1.16)	14289 (24 RCTs)	⨁◯◯◯ VERY LOW [a,b]	
Major adverse cardiovascular event at closest to three months	74 per 1.000	**75 per 1.000** (62 to 91)	**RR 1.01** (0.83 to 1.23)	14218 (23 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	
Serious adverse events at closest to three months	112 per 1.000	**119 per 1.000** (100 to 142)	**RR 1.06** (0.89 to 1.26)	14358 (25 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	
Quality of life at closest to three months	Quality of life showed an significant effect of non-acute PCI on the General Health domain of SF36 at closest to three months (MD 4.98, 95% CI 3.39 to 6.58). However only 3 trials reported this outcome, and our sensitivity best-worst/worst-best analyses, showed that both results had the potential alone to be caused by incomplete outcome data. The remaining six trials describing quality of life, used a variety of different scales. One trial found a significant effect on quality of life, while four trials did not			(9 RCTs)	-	
Angina at closest to three months	Only one trial reported angina as a continuous outcome and showed a beneficial effect on both angina frequency and stability at closest to three months, but not at maximum follow-up. We found a significant effect of non-acute PCI reducing the risk of being with angina. However, our sensitivity best-worst/worst-best analyses showed that both results had the potential alone to be caused by incomplete outcome data. Additionally, we found an significant effect of non-acute PCI reducing the risk of having Canadian Cardiovascular Society angina class two or worse. The remaining five trials describing angina, used a variety of different scales. All five trials found a significant effect on angina			(12 RCTs)	-	

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

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Downgraded 2 levels because of very serious risk of bias
b. Downgraded 1 level because of serious risk of indirectness
c. Downgraded 2 levels because of very serious inconsistency

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Table 2: Summary of findings table

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