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Screening for Coronary Artery Disease in type 2 Diabetic Patients: A Meta-analysis and Trial Sequential Analysis

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STRUCTURED ABSTRACT (252)

Objective: Evaluate the efficacy of coronary artery disease screening in asymptomatic patients with type 2 diabetes and assess the statistical reliability of the findings.

Methods: Electronic databases (MEDLINE, EMBASE, Cochrane Library and clinicaltrials.org) were reviewed up to July 2016. Randomized controlled trials evaluating coronary artery disease screening in asymptomatic type 2 diabetic patients and reporting cardiovascular events and/or mortality were included. Data was summarized with Mantel-Haenszel relative risk. Trial sequential analysis (TSA) was used to evaluate the optimal sample size to detect a 40% reduction in outcomes. Main outcomes were all-cause mortality and cardiac events (non-fatal myocardial infarction and cardiovascular death); secondary outcomes were non-fatal myocardial infarction, myocardial revascularizations and heart failure. PROSPERO: CRD42015026627.

Results: One hundred thirty-dive references were identified and 5 studies fulfilled the inclusion criteria and totalized 3315 patients, 117 all-cause deaths and 100 cardiac events. Screening for coronary artery disease was not associated with decrease in risk for all-cause deaths all-cause deaths (RR 0.95 [95% CI 0.66 to 1.35]) or cardiac events (RR 0.72 [95% CI 0.49 to 1.06]). TSA shows that futility boundaries were reached for all-cause mortality and a relative risk reduction of 40% between treatments could be discarded. However, there is not enough information for firm conclusions for cardiac events. For secondary outcomes no benefit or harm was identified; optimal sample sizes were not reached.

Conclusion: Current available data do not support screening type 2 diabetic patients for coronary artery for preventing fatal events. Further studies are needed to assess the effects on cardiac events.

KEYWORDS: Cardiovascular disease screening; type 2 diabetes; systematic review; meta-analysis; trial sequential analysis.

ARTICLE SUMMARY

Strengths and limitations of this study

- Electronic databases were reviewed to identify randomized controlled trials evaluating screening for coronary artery disease in type 2 diabetes.
- Results from individual studies were combined and summarized with Mantel-Haenszel relative risk.
- Trial sequential analysis was used to assess the optimal sample size for the outcomes.
- The results should be interpreted with caution as different screening methods were combined.

INTRODUCTION

Diabetes mellitus is a well-known risk factor for atherosclerosis and asymptomatic coronary disease is frequent and associated with increased mortality.[1] Intensive medical treatment with antiplatelet agents, statins, as well as blood pressure and glycemic control decrease the number of cardiovascular events in patients with established coronary artery disease.[2] It is expected that early detection and treatment of myocardial ischemia would lead to similar benefits.

Coronary artery bypass grafting reduces mortality by 40% in patients with diabetes and established multivessel coronary disease.[3] However, percutaneous coronary intervention (PCI) does not appear to influence mortality in patients with asymptomatic and stable coronary artery disease (with or without diabetes) when compared to intensive medical therapy alone.[4] BARI 2D study results showed no benefit of early revascularization in patients with type 2 diabetes. On the other hand, it suggested that coronary artery bypass grafting (CABG) might be better than medical therapy alone, but this finding must be interpreted with caution, as the allocation to PCI or CABG was not randomized.[5] Moreover, patients with diabetes and high-risk coronary lesions do benefit from CABG.[3] In summary, the goal of a screening strategy for coronary artery disease in type 2 diabetic patients would be the identification of subjects with high-risk coronary lesions (multivessel), who would be eligible for CABG and might benefit from this intervention by reducing coronary events and mortality.

Some trials directly evaluated the effects of screening for coronary artery disease vs. usual care and found no benefit for mortality or coronary events.[6 7] These trials were performed with adequate designs but in most cases have limited conclusions due to lack of power.[6 7] Meta-analysis is a valuable tool in this situation, as it combines studies in a

single analysis, which increases the sample size. Furthermore, trial sequential analysis (TSA) enables the assessment of sample size power and the need for further studies.[8 9] Therefore, our objective was to assess the efficacy of screening for asymptomatic coronary artery disease in type 2 diabetic patients compared to no screening in reducing cardiac events (non-fatal myocardial infarction and cardiovascular mortality) and all-cause mortality. Furthermore, we aimed to evaluate the statistical reliability (sample size power) of the results.

RESEARCH DESIGN AND METHODS

This study follows the PRISMA statement for reporting systematic reviews and meta-analysis.[10] The present review was registered in the PROSPERO registry under number CRD42015026627.

To perform the present study, we searched for randomized controlled trials evaluating the effects of screening for coronary artery disease in type 2 diabetic patients reporting any of the outcomes of interest, which were non-fatal myocardial infarction, cardiovascular and all-cause mortality, myocardial revascularizations and heart failure events. Pubmed, EMBASE, Cochrane library and clinicaltrials.org databases were searched from inception through July 2016 using the following terms: type 2 diabetes, screening of coronary heart disease and randomized clinical trial. No restrictions were made regarding study length, publication year or language. The full search terms for Pubmed were: *(screening AND coronary artery disease) AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract]) AND "Diabetes Mellitus, Type 2"[Mesh]*. We also searched the references lists of main publications on the topic manually.

Two authors (DVR and LCP) performed the study selection independently. We included any randomized controlled trial which included type 2 diabetic patients and that evaluated the effects of any coronary artery disease screening method on the incidence of non-fatal myocardial infarction, cardiovascular or all-cause mortality. We excluded studies that were not randomized and that compared two different screening methods. Initially, titles and abstracts were reviewed for potentially eligible studies. These studies were then evaluated in full-text and those reporting any of the selected outcomes were considered for the final review and meta-analysis.

The following information was extracted with a standardized form: first author´s name; study name and year of publication; screening method; study registry; baseline HbA_{1c} and age; number of men; number of patients in each group; follow-up time; number of events: non-fatal myocardial infarction, cardiovascular and all-cause deaths, revascularizations and heart failure events. We defined cardiac events as a composite of non-fatal myocardial infarctions and cardiovascular deaths.

We evaluated the risk of bias at the study level with the Cochrane Collaboration tool;[11] for the "other bias" item we evaluated the presence of a trial registry as low risk of bias and lack of registry as high-risk. We defined no pre-specified analysis based on the risk of bias of the individual studies. The overall quality of the evidence of each meta-analysis was classified as 'high', 'moderate', 'low' or 'very low' based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE).[12]

The outcomes of interest were summarized as relative risk (RR) of screening vs. no screening and they were combined using the Mantel-Haenszel RR. The heterogeneity was assessed using the Cochran Q and the I^2 tests ($P < 0.1$ and $I^2 > 50\%$ indicating high heterogeneity, respectively). We evaluated the risk of small study bias with the contour-

enhanced funnel plot and asymmetry with the Begg and Egger's tests; we considered a significant small study bias if P <0.1 and, if appropriate, the trim-and-fill computation was performed to evaluate the potential effect of non-published data.

One of the aims of our study was to assessed the reliability of the results – that is, to evaluate the ideal sample size to establish firm conclusions about the findings.[9] To accomplish this we performed TSA of the data. Interim analysis of a single randomized trial avoids type I error by creating monitoring boundaries for an estimated difference between groups, so if the estimated difference is reached the trial could be terminated. TSA uses a similar accurate method to create monitoring boundaries and estimate the optimal sample size in meta-analyses.[8 9] TSA performs a cumulative meta-analysis with the results of the available studies (represented by the Z-curve): as each new study is included, significance is tested and confidence intervals are estimated. It also creates adjusted boundaries for benefit, harm and futility and estimates the optimal sample size for a given difference between treatment arms, so that a smaller estimated difference would result in wider boundaries and a greater optimal sample size.[8] Because cumulative meta-analyses may lead to false positive results due to repetitive testing, this evaluation is adjusted to control for repeated analyses, while maintaining type I error at 5% and the power at 80%.[8] It is also adjusted for the variability between trials and for the amount of available evidence. If one of the boundaries (benefit, risk or futility) or if the optimal sample size is reached, firm conclusions might be made (for that predefined difference) and further studies are deemed unnecessary; instead, if no boundaries are reached, further studies are needed to settle the question.[8] For the present analysis, we performed a TSA for a relative difference (relative risk reduction – RRR) between groups of 40%. This value was chosen based on the expected benefit of

revascularization in the mortality rate demonstrated by previous studies.[3] An additional TSA analysis was also performed using a RRR of 20%.

The risk of bias graph was generated with RevMan software version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). The meta-analyses were performed with Stata version 12.0 (Stata Inc., College Station, Texas, USA) and the TSA and graphics were generated using TSA software version 0.9 [beta] (Copenhagen Trial Unit, Copenhagen, Denmark).

RESULTS

The search in electronic databases and the manual review retrieved 135 studies for the evaluation of titles and abstracts. After screening, 7 studies were evaluated in full-text and 5 fulfilled the inclusion and exclusion criteria.[6 7 13-15] The study flowchart is depicted in supplementary material (Supplemental Material, Figure 1).

The included studies comprised patients with a mean age of 61 years, with a mean HbA_{1c} of 7.6 % and the mean follow-up was 4.1 years. Additional characteristics are presented in Table 1. Most studies performed screening with stress testing along with electrocardiography, echocardiography or scintigraphy monitoring; one study performed coronary computed tomography angiography with measurement of coronary calcium. The studies totalized 3315 patients with 117 all-cause deaths and 100 cardiac events.

Table 1. Included study characteristics

Study Name	First author	Publication year	Screening method	Management recommendation
--	Faglia E[13]	2005	Exercise electrocardiogram and stress echocardiography	Yes
			No screening	No
DIAD	Young LH[7]	2009	Stress scintigraphy	No
			No screening	No
DYNAMIT	Lièvre MM[14]	2011	Bicycle exercise test or stress scintigraphy	No
			No screening	No
FACTOR-64	Muhlestein JB[6]	2014	Coronary computed tomography angiography	Yes
			No screening	No
DADDY-D	Turrini F[15]	2015	Exercise electrocardiogram	Yes
			No screening	No

Table 1. Included study characteristics (continued)

Patients (n)	Age (years)	HbA1c (%)	Blood pressure (mmHg)	Smoking (%)	Statin use (%)	Aspirin use (%)	Registry
71	58.7 ± 8.3	8.6 ± 2.3	143/85	46	28	9	No
70	61.5 ± 8.1	8.4 ± 1.9	141/84	55	21	12	
561	60.7 ± 6.7	7.2 ± 1.6	133/80	10	37	43	Yes
562	60.8 ± 6.4	7 ± 1.5	132/79	9	41	46	
316	64.1 ± 6.4	8.6 ± 2.2	N.R.	17	33	39	Yes
315	63.7 ± 6.4	8.7 ± 2	N.R.	14	36	24	
452	61.5 ± 7.9	7.4 ± 1.4	129/74	16	76	43	Yes
448	61.6 ± 8.3	7.5 ± 1.4	130/74	15	72	40	
262	61.9 ± 4.8	7.7 ± 1.4	140/81	40	39	29	Yes
258	62 ± 5.1	7.8 ± 1.3	141/81	37	44	25	

Data showed no difference between patients in coronary artery disease screening and control groups for all-cause death incidence (Figure 1a): RR 0.95 (95% CI 0.66 to 1.35). There was low heterogeneity (I^2 = 0% and p = 0.615). TSA for all-cause mortality events indicates that the futility boundary was reached, so a difference of 40% between groups is firmly discarded and no further studies are required (Figure 1b). For the RRR of 20% the optimal sample size (19548 patients) nor the futility boundary were reached. There was also no difference in cardiac events (Figure 2a): RR 0.72 (95% CI 0.49 to 1.06; I^2 = 38.5% and p = 0.181). For this outcome, TSA shows that the optimal sample size is 6645 patients, which is larger than the current sample. Furthermore, neither the benefit nor the futility boundaries were reached (Figure 2b). The analysis with the (RRR

of 20% showed similar results, but with a much larger optimal sample size (29763 patients).

Additional outcome analyses are presented in Table 2: the coronary artery disease screening group was similar to the control group for non-fatal myocardial infarction (RR 0.65 [95% CI 0.41 to 1.02]), heart failure (RR 0.60 [95% CI 0.33 to 1.10]) and myocardial revascularizations (PCI and CABG) (RR 1.08 [95% CI 0.83 to 1.41]). None of these outcomes reached the optimal sample size or the boundaries for futility.

Table 2. Results for myocardial infarction, revascularization and heart failure of screening versus no screening

Outcome	RR (95% CI)	Accrued Population	Optimal Sample Size (RRR = 40 %)	Optimal Sample Size (RRR = 20 %)
Non-fatal Myocardial Infarction	0.65 (0.41 - 1.02)	3315	6154	17495
Heart Failure	0.60 (0.33 - 1.10)	3174	10990	49352
Revascularizations	1.08 (0.83 - 1.41)	3174	10598	47339

Overall, the study quality was high according to the Cochrane Collaboration tool (Supplemental Material, Figures 2 and 3).[11] It must be stressed that none of the studies was blinded, but this was not considered a limitation because blinding of participants (patients and clinicians) was not feasible due to the type of intervention (screening). On the other hand, blinding of outcome assessment was reported in only one study. According to GRADE,[16] quality of evidence was judged as high quality for both main outcomes (all-cause mortality and cardiac events).

The funnel plot and Begg and Egger's tests showed small study bias for the cardiac events outcome, but the correction with trim-and-fill computation did not change the results; for the all-cause mortality outcome no significant risk of small study bias was identified.

DISCUSSION

In the present study we identified no benefit of screening for asymptomatic coronary artery disease for all-cause mortality in patients with type 2 diabetes. This conclusion is supported by a sufficient number of patients, as shown by TSA. Although we found no benefit for the other outcomes evaluated, such as cardiovascular events, these results are not definitive, as they are not supported by an adequate number of patients, and further studies are still required.

A relevant point of our analysis is the trend for statistically significant difference found in cardiac events and non-fatal myocardial infarction favoring the screening group. This finding seems to be driven by the study of Faglia et al.,[13] which was the smallest and oldest study included in our analysis. Moreover, patients in this study had an unfavorable clinical profile, represented by the worst glycemic control, the highest blood pressure, the greatest prevalence of smoking and the lowest use of statins and aspirin in comparison with the others studies. Despite this trend, TSA shows that there is insufficient data to perform firm conclusion about cardiac events and myocardial infarction. Whether this is a real effect or not further studies are needed to firm conclusion on effects of screening for these outcomes.

Some limitations of this review must be acknowledged. First, the trials performed different screening tests with different specificity and sensitivity[2] and combining them

may be questionable. Despite this, current guidelines do not define a preferable strategy for the diagnosis of coronary artery disease, [2] and a clinical trial support this position.[17] Therefore, we believe these tests may be aggregated in a meta-analysis, as they all aim to identify high-risk patients with greater chance to benefit from CABG. [3 5 18] We cannot rule out the possibility that a test with higher sensitivity (coronary computed tomography angiography)[19] would be beneficial.[2] However, as discussed above, the potential benefit we identified in this review seems to be derived from only one study[13] that used tests with low to moderate sensitivity.

The second limitation was the somewhat choice of a relative difference of 40% between treatment arms. It was based on the benefits of CABG for patients with severe coronary artery disease.[3] Even though this evidence was published in the 90s, it is still largely used by guidelines to recommend revascularization for stable coronary artery disease. In addition, recent studies and meta-analysis have shown that CABG is superior to PCI for subjects with or without diabetes and multivessel coronary disease.[5 18 20] As only CABG is capable to reduce mortality and major cardiac events, a screening intervention aimed to identify patients with multivessel coronary artery disease assumes that patients would benefit from CABG. Therefore, a clear clinical benefit must be evident to justify the risks and costs from screening and the potential procedures resulting from it.

The analysis with a RRR of 20% showed that for cardiac events, myocardial infarction, heart failure and revascularizations the results from TSA also showed that the number of patients included was not enough. In addition, for all-cause mortality the RRR of 20% analysis also lacked power and it would be required an increase in the number of patients by a factor of five, which is unlikely to happen.

Another potential source for heterogeneity in our study is the inclusion of patients with type 1 diabetes in FACTOR – 64 study.[6] We believe this is not a major issue, as they represent only 10% of the sample in the original study, and 3% of the systematic review sample.

Some strengths of our study must be pointed out. We performed a comprehensive database search and identified all randomized trials evaluating the effects of a screening strategy for coronary artery disease in type 2 diabetic patients. Furthermore, the trials included are of high quality. As mentioned, there are some methodological differences between the studies, but the statistical heterogeneity was low or absent in the analyses. We also performed detailed analyses of the data and through TSA we could discard a significant difference between treatment arms for all-cause mortality. Unfortunately, we cannot make the same firm conclusions for the cardiac events, myocardial infarction, heart failure, and revascularization outcomes.

In conclusion, the present study supports the idea that type 2 diabetic patients without symptoms of coronary artery disease do not need to be screened for asymptomatic disease and that non-invasive coronary exams should be reserved for symptomatic patients. This would avoid unnecessary risks, patient distress and costs for asymptomatic patients.

Acknowledgment

We would like to thank Dr. Fabrizio Turrini for sharing additional data on his study (DADDY-D study).

Data sharing: no additional data available.

The criteria from the International Committee of Medical Journal Editors for authorship were followed and the final version of the manuscript has been approved for submission by all authors. This manuscript has not been published before, and is not being considered for publication in any other journal. DVR was responsible for study design, data acquisition, analysis, interpretation and drafting of the manuscript. LCP contributed to study design, reference selection and data acquisition and analysis. CBL contributed to study design, data analysis and interpretation and drafting of the manuscript. JLG contributed to study design, data analysis and interpretation and drafting of the manuscript. All authors have read and approved the final manuscript. Drs. Dimitris Varvaki Rados and Jorge Luiz Gross are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Dimitris Varvaki Rados is the corresponding author.

Ethical Approval

Not needed.

Role of the funding source

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Conflict of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that no support was received from any organization for the submitted work; JLG reports grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico, during the conduct of the study; grants and other from Eli Lilly, grants from Bristol-Myers Squibb, grants and other from Boehringer Ingelheim, grants from GlaxoSmithKline, grants and other from Novo Nordisk, grants from Janssen, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work are reported.

ABBREVIATION LIST

CABG: Coronary artery bypass grafting

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

PCI: Percutaneous coronary intervention

RR: Relative risk

RRR: Relative risk reduction

TSA: Trial sequential analysis

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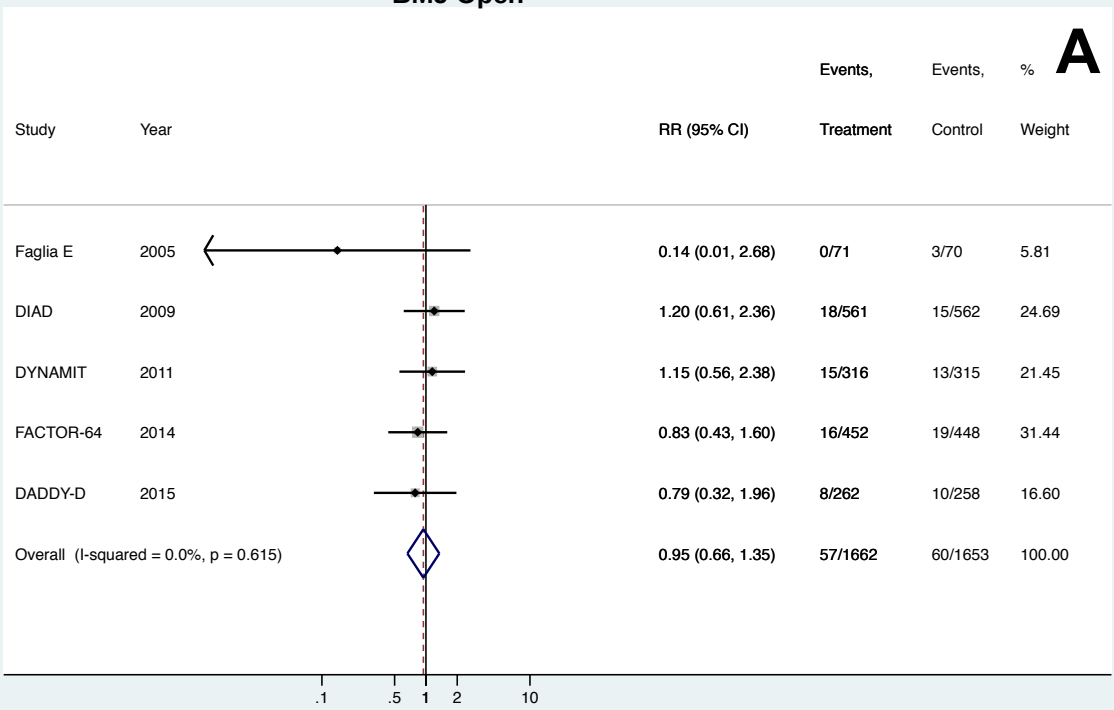
Figure 1. Forest plot and TSA of screening versus no screening for all-cause mortality outcome

A) Forest plot for all-cause mortality. B) TSA for a relative risk reduction of 40%. The continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The continuous black lines represent the conventional confidence intervals.

Figure 2. Forest plot and TSA of screening versus no screening for cardiac events outcome

A) Forest plot for all-cause mortality. B) TSA for a relative risk reduction of 40%. The continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The continuous black lines represent the conventional confidence intervals.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Study
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Events, Treatment
Events, Control
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Faglia E 2005 0.14 (0.01, 2.68) 0/71 3/70 5.81
DIAD 2009 1.20 (0.61, 2.36) 18/561 15/562 24.69
DYNAMIT 2011 1.15 (0.56, 2.38) 15/316 13/315 21.45
FACTOR-64 2014 0.83 (0.43, 1.60) 16/452 19/448 31.44
DADDY-D 2015 0.79 (0.32, 1.96) 8/262 10/258 16.60
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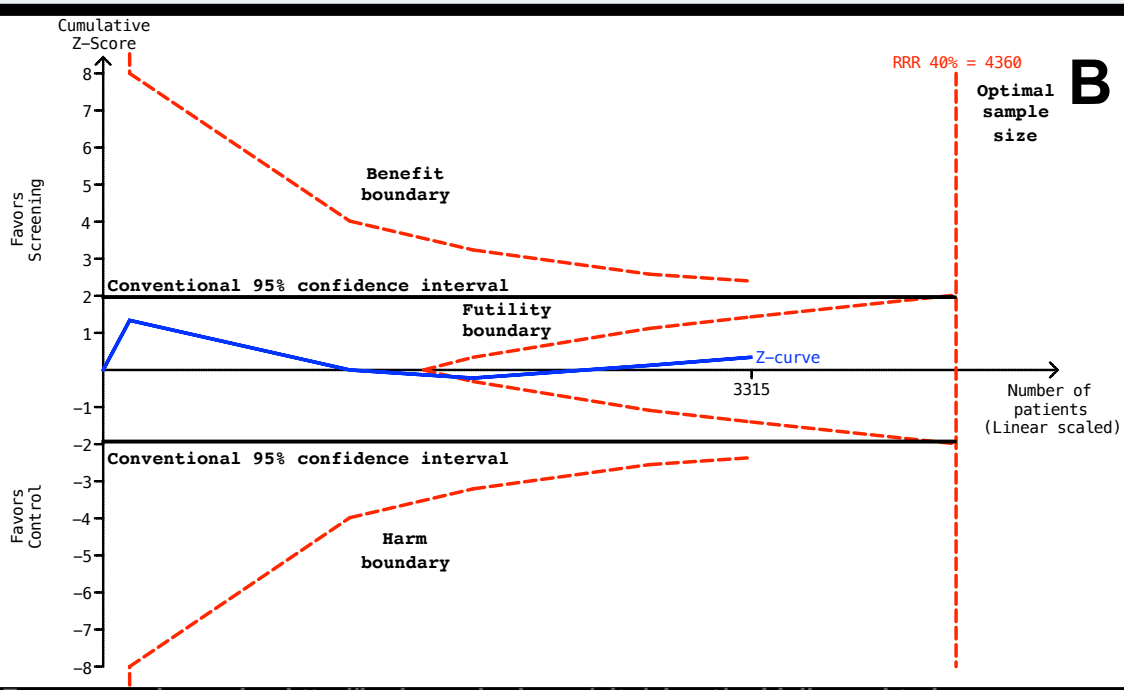
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Cumulative Z-Score
RRR 40% = 4360
Optimal sample size
Benefit boundary
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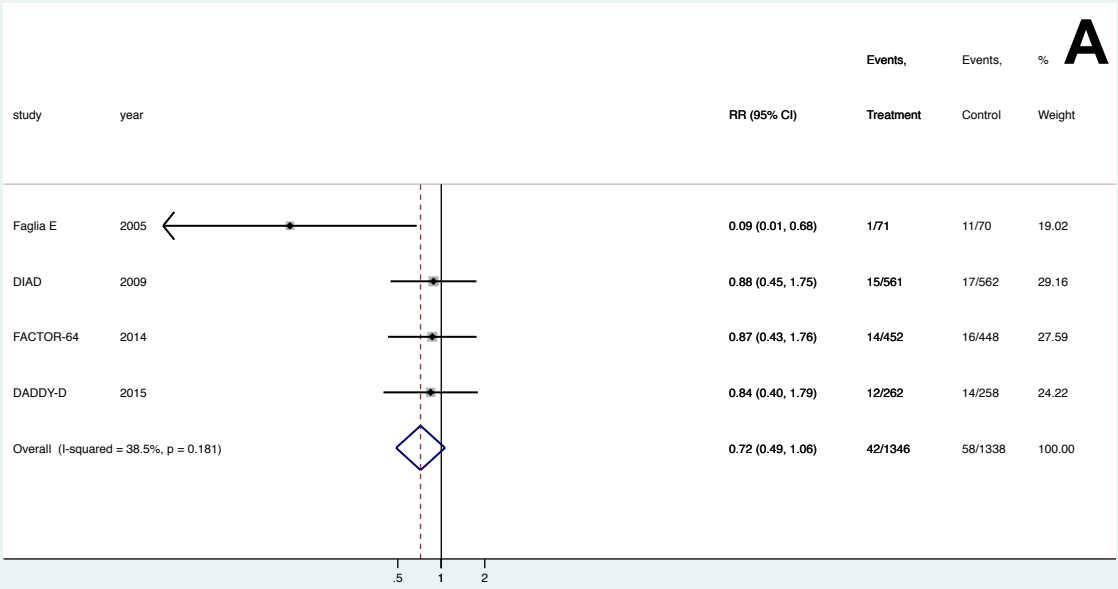


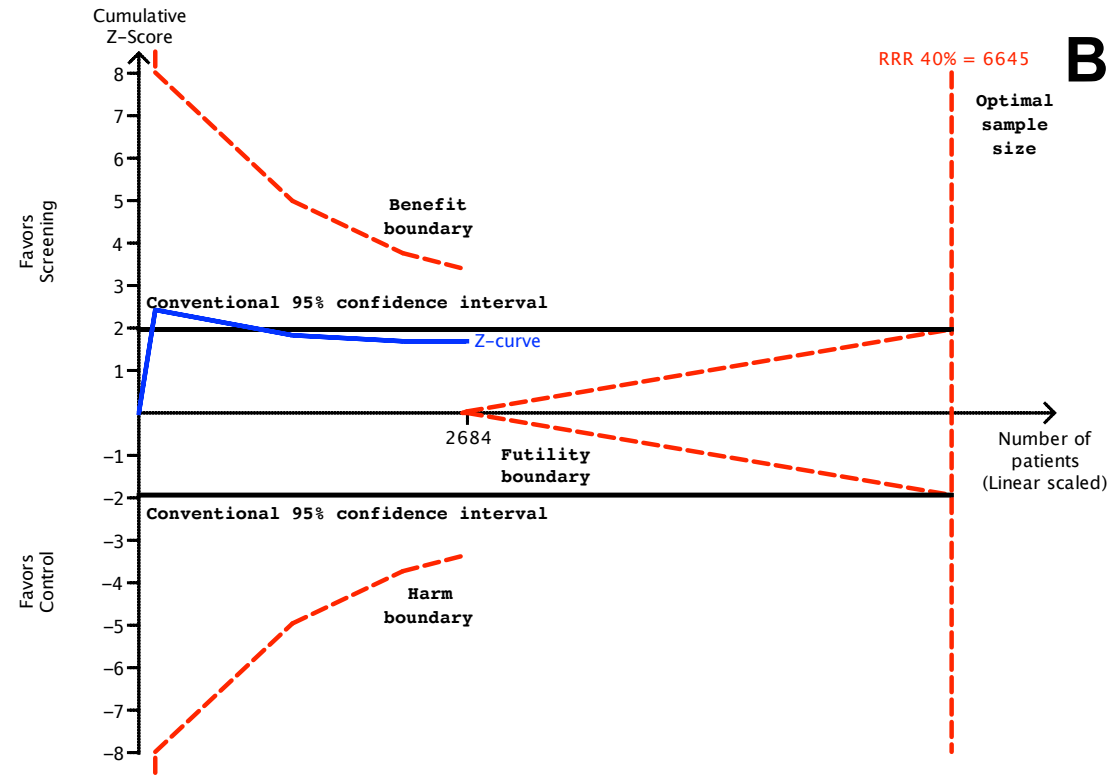


Figure 1. Study flowchart.

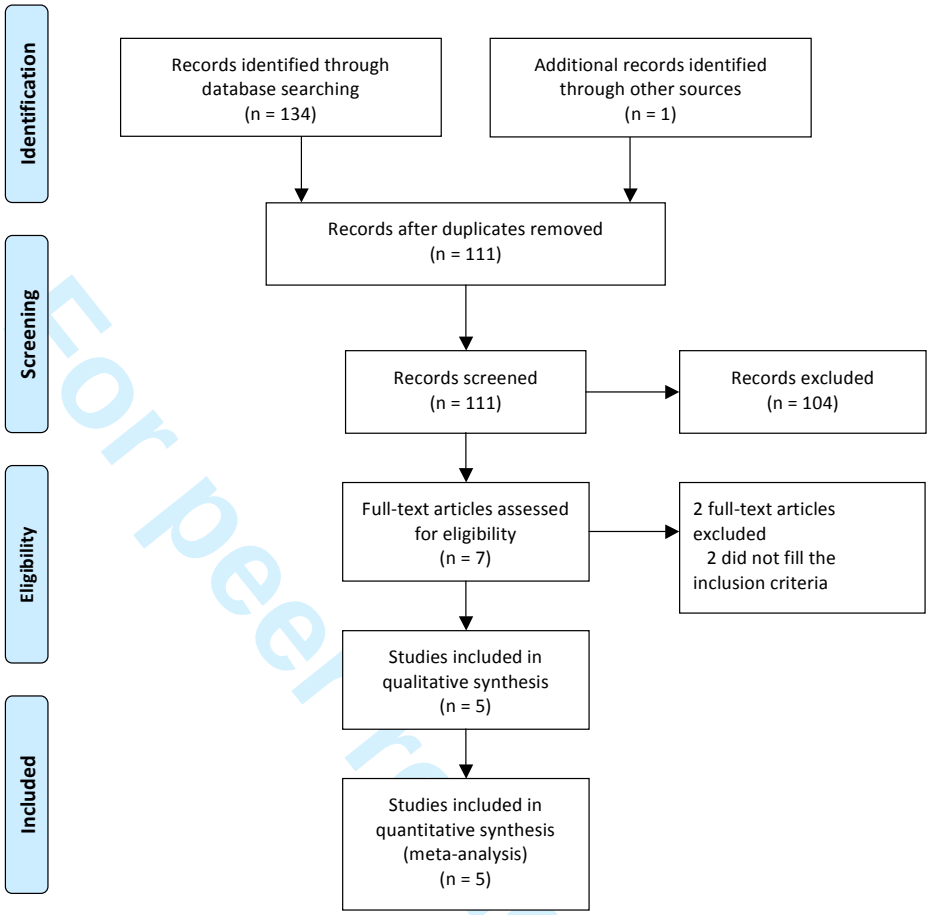


Figure 2. Risk of bias across studies.

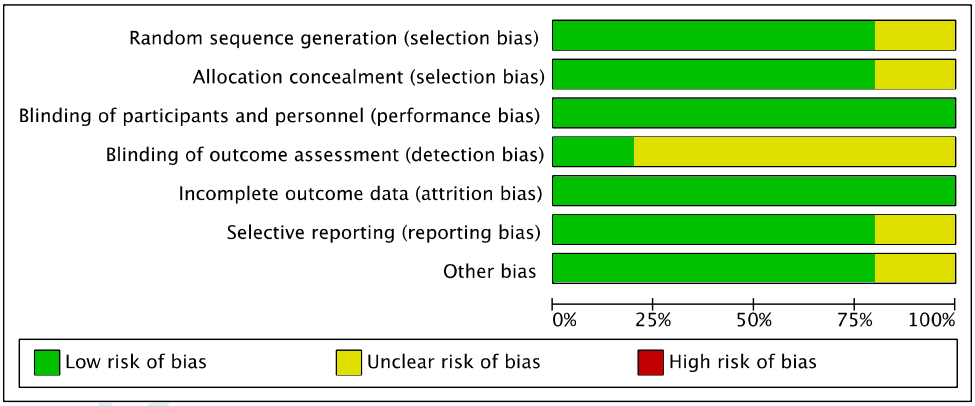
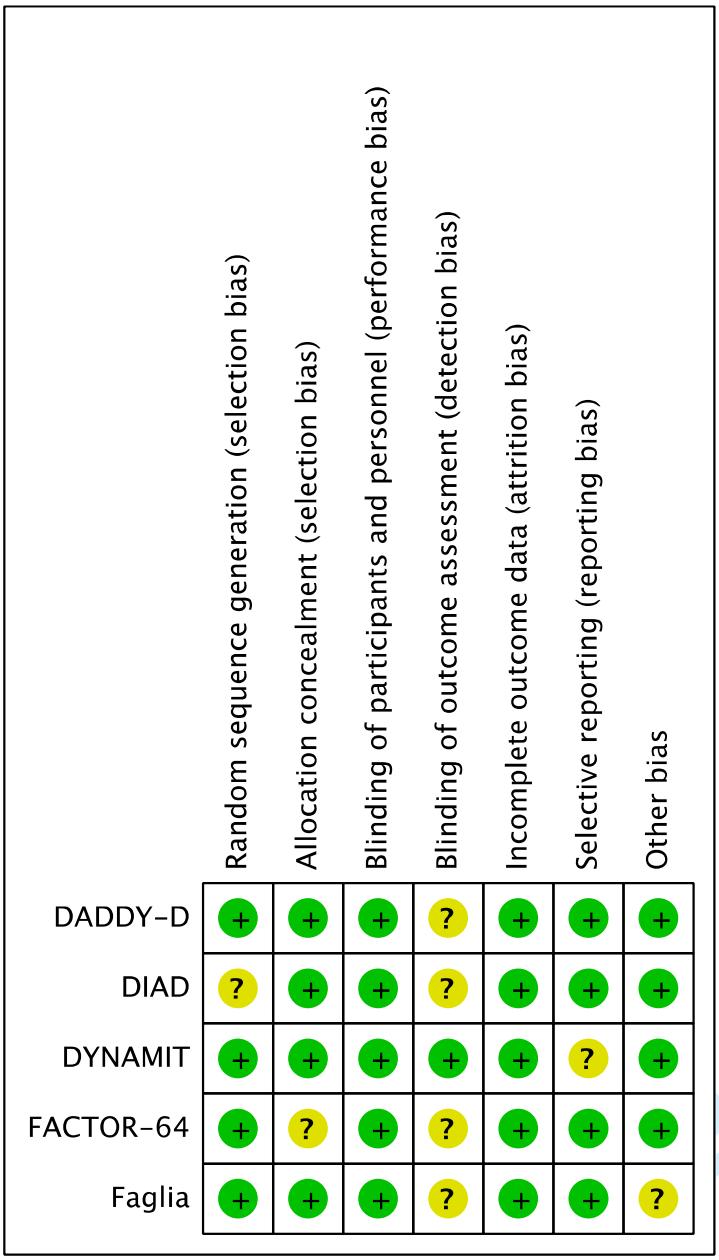


Figure 3. Risk of bias for individual studies.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 and eFigure1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	eFigure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9 and Figure 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	eFigure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9 and Figures 1 and 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

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Screening for Coronary Artery Disease in type 2 Diabetic Patients: A Meta-analysis and Trial Sequential Analysis

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Screening for Coronary Artery Disease in type 2 Diabetic Patients: A Meta-analysis and Trial Sequential Analysis

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STRUCTURED ABSTRACT (252)

Objective: To evaluate the efficacy of coronary artery disease screening in asymptomatic patients with type 2 diabetes and assess the statistical reliability of the findings.

Methods: Electronic databases (MEDLINE, EMBASE, Cochrane Library and clinicaltrials.org) were reviewed up to July 2016. Randomized controlled trials evaluating coronary artery disease screening in asymptomatic type 2 diabetic patients and reporting cardiovascular events and/or mortality were included. Data was summarized with Mantel-Haenszel relative risk. Trial sequential analysis (TSA) was used to evaluate the optimal sample size to detect a 40% reduction in outcomes. Main outcomes were all-cause mortality and cardiac events (non-fatal myocardial infarction and cardiovascular death); secondary outcomes were non-fatal myocardial infarction, myocardial revascularizations and heart failure.

Results: One hundred thirty five references were identified and 5 studies fulfilled the inclusion criteria and totalized 3315 patients, 117 all-cause deaths and 100 cardiac events. Screening for coronary artery disease was not associated with decrease in risk for all-cause deaths (RR 0.95 [95% CI 0.66 to 1.35]) or cardiac events (RR 0.72 [95% CI 0.49 to 1.06]). TSA shows that futility boundaries were reached for all-cause mortality and a relative risk reduction of 40% between treatments could be discarded. However, there is not enough information for firm conclusions for cardiac events. For secondary outcomes no benefit or harm was identified; optimal sample sizes were not reached.

Conclusion: Current available data do not support screening type 2 diabetic patients for coronary artery for preventing fatal events. Further studies are needed to assess the effects on cardiac events.

PROSPERO: CRD42015026627.

KEYWORDS: Cardiovascular disease screening; type 2 diabetes; systematic review; meta-analysis; trial sequential analysis.

ARTICLE SUMMARY

Strengths and limitations of this study

- Electronic databases were reviewed to identify randomized controlled trials evaluating screening for coronary artery disease in type 2 diabetes.
- Results from individual studies were combined and summarized with Mantel-Haenszel relative risk.
- Trial sequential analysis was used to assess the optimal sample size for the outcomes.
- The results should be interpreted with caution as different screening methods were combined.

INTRODUCTION

Diabetes mellitus is a well-known risk factor for atherosclerosis and asymptomatic coronary disease is frequent and associated with increased mortality.[1] Intensive medical treatment with antiplatelet agents, statins, as well as blood pressure and glycemic control decrease the number of cardiovascular events in patients with established coronary artery disease.[2] It is expected that early detection and treatment of myocardial ischemia would lead to similar benefits.

Coronary artery bypass grafting reduces mortality by 40% in patients with diabetes and established multivessel coronary disease.[3] However, percutaneous coronary intervention (PCI) does not appear to influence mortality in patients with asymptomatic and stable coronary artery disease (with or without diabetes) when compared to intensive medical therapy alone.[4] BARI 2D study results showed no benefit of early revascularization in patients with type 2 diabetes. On the other hand, it suggested that coronary artery bypass grafting (CABG) might be better than medical therapy alone, but this finding must be interpreted with caution, as the allocation to PCI or CABG was not randomized.[5] Moreover, patients with diabetes and high-risk coronary lesions do benefit from CABG.[3] In summary, the goal of a screening strategy for coronary artery disease in type 2 diabetic patients would be the identification of subjects with high-risk coronary lesions (multivessel), who would be eligible for CABG and might benefit from this intervention by reducing coronary events and mortality.

Some trials directly evaluated the effects of screening for coronary artery disease vs. usual care and found no benefit for mortality or coronary events.[6 7] These trials were performed with adequate designs but in most cases have limited conclusions due to lack of power.[6 7] Meta-analysis is a valuable tool in this situation, as it combines studies in a

single analysis, which increases the sample size. Furthermore, trial sequential analysis (TSA) enables the assessment of sample size power and the need for further studies.[8 9] Therefore, our objective was to assess the efficacy of screening for asymptomatic coronary artery disease in type 2 diabetic patients compared to no screening in reducing cardiac events (non-fatal myocardial infarction and cardiovascular mortality) and all-cause mortality. Furthermore, we aimed to evaluate the statistical reliability (sample size power) of the results.

RESEARCH DESIGN AND METHODS

This study follows the PRISMA statement for reporting systematic reviews and meta-analysis.[10] The present review was registered in the PROSPERO registry under number CRD42015026627.

Search strategy

To perform the present study, we searched for randomized controlled trials evaluating the effects of screening for coronary artery disease in type 2 diabetic patients reporting any of the outcomes of interest, which were non-fatal myocardial infarction, cardiovascular and all-cause mortality, myocardial revascularizations and heart failure events. Pubmed, EMBASE, Cochrane library and clinicaltrials.org databases were searched from inception through July 2016 using the following terms: type 2 diabetes, screening of coronary heart disease and randomized clinical trial. No restrictions were made regarding study length, publication year or language. The full search terms for Pubmed were: *(screening AND coronary artery disease) AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract])*

AND "Diabetes Mellitus, Type 2"[Mesh]. We also searched the references lists of main publications on the topic manually.

Study selection

Two authors (DVR and LCP) performed the study selection independently. We included any randomized controlled trial which included type 2 diabetic patients and that evaluated the effects of any coronary artery disease screening method on the incidence of non-fatal myocardial infarction, cardiovascular or all-cause mortality. We excluded studies that were not randomized and that compared two different screening methods. Initially, titles and abstracts were reviewed for potentially eligible studies. These studies were then evaluated in full-text and those reporting any of the selected outcomes were considered for the final review and meta-analysis.

Data extraction

The following information was extracted with a standardized form: first author´s name; study name and year of publication; screening method; study registry; baseline HbA_{1c} and age; number of men; number of patients in each group; follow-up time; number of events: non-fatal myocardial infarction, cardiovascular and all-cause deaths, revascularizations and heart failure events. We defined cardiac events as a composite of non-fatal myocardial infarctions and cardiovascular deaths.

Appraisal of study quality

We evaluated the risk of bias at the study level with the Cochrane Collaboration tool;[11] for the “other bias” item we evaluated the presence of a trial registry as low risk of bias

and lack of registry as high-risk. We defined no pre-specified analysis based on the risk of bias of the individual studies. The overall quality of the evidence of each meta-analysis was classified as 'high', 'moderate', 'low' or 'very low' based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE).[12]

Data analysis

The outcomes of interest were summarized as relative risk (RR) of screening vs. no screening and they were combined using the Mantel-Haenszel RR. The heterogeneity was assessed using the I^2 tests (I^2 >50% indicating high heterogeneity).

One of the aims of our study was to assess the reliability of the results – that is, to evaluate the ideal sample size to establish firm conclusions about the findings.[9] To accomplish this we performed TSA of the data. Interim analysis of a single randomized trial avoids type I error by creating monitoring boundaries for an estimated difference between groups, so if the estimated difference is reached the trial could be terminated. TSA uses a similar accurate method to create monitoring boundaries and estimate the optimal sample size in meta-analyses.[8 9] TSA performs a cumulative meta-analysis with the results of the available studies (represented by the Z-curve): as each new study is included, significance is tested and confidence intervals are estimated. It also creates adjusted boundaries for benefit, harm and futility and estimates the optimal sample size for a given difference between treatment arms, so that a smaller estimated difference would result in wider boundaries and a greater optimal sample size.[8] Because cumulative meta-analyses may lead to false positive results due to repetitive testing, this evaluation is adjusted to control for repeated analyses, while maintaining type I error at 5% and the power at 80%.[8] It is also adjusted for the variability between trials and for

the amount of available evidence. If one of the boundaries (benefit, risk or futility) or if the optimal sample size is reached, firm conclusions might be made (for that predefined difference) and further studies are deemed unnecessary; instead, if no boundaries are reached, further studies are needed to settle the question.[8] For the present analysis, we performed a TSA for a relative difference (relative risk reduction – RRR) between groups of 40% and considered as control group event rate the incidence observed in the control group for each outcome. The RRR value was chosen based on the expected benefit of revascularization in the mortality rate demonstrated by previous studies.[3] An additional TSA analysis was also performed using a RRR of 20%.

The risk of bias graph was generated with RevMan software version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). The meta-analyses were performed with Stata version 12.0 (Stata Inc., College Station, Texas, USA) and the TSA and graphics were generated using TSA software version 0.9 [beta] (Copenhagen Trial Unit, Copenhagen, Denmark).

RESULTS

The search in electronic databases and the manual review retrieved 135 studies for the evaluation of titles and abstracts. After screening, 7 studies were evaluated in full-text and 5 fulfilled the inclusion and exclusion criteria.[6 7 13-15] The study flowchart is depicted in supplementary material (Supplemental Material, Figure 1).

The included studies comprised patients with a mean age of 61 years, with a mean HbA_{1c} of 7.6 % and the mean follow-up was 4.1 years. Additional characteristics are presented in Table 1. Most studies performed screening with stress testing along with electrocardiography, echocardiography or scintigraphy monitoring; one study performed coronary computed tomography angiography with measurement of coronary

calcium. The studies totalized 3315 patients with 117 all-cause deaths and 100 cardiac events.

Table 1. Included study characteristics

Study Name	First author	Publication year	Screening method	Management recommendation
--	Faglia E[13]	2005	Exercise electrocardiogram and stress echocardiography	Yes
			No screening	No
DIAD	Young LH[7]	2009	Stress scintigraphy	No
			No screening	No
DYNAMIT	Lièvre MM[14]	2011	Bicycle exercise test or stress scintigraphy	No
			No screening	No
FACTOR-64	Muhlestein JB[6]	2014	Coronary computed tomography angiography	Yes
			No screening	No
DADDY-D	Turrini F[15]	2015	Exercise electrocardiogram	Yes
			No screening	No

Table 1. Included study characteristics (continued)

Patients (n)	Age (years)	HbA1c (%)	Blood pressure (mmHg)	Smoking (%)	Statin use (%)	Aspirin use (%)	Mean Follow-up (years)	Registry
71	58.7 ± 8.3	8.6 ± 2.3	143/85	46	28	9	4.4	No
70	61.5 ± 8.1	8.4 ± 1.9	141/84	55	21	12		
561	60.7 ± 6.7	7.2 ± 1.6	133/80	10	37	43	4.8	Yes
562	60.8 ± 6.4	7 ± 1.5	132/79	9	41	46		
316	64.1 ± 6.4	8.6 ± 2.2	N.R.	17	33	39	3.5	Yes
315	63.7 ± 6.4	8.7 ± 2	N.R.	14	36	24		
452	61.5 ± 7.9	7.4 ± 1.4	129/74	16	76	43	4.0	Yes
448	61.6 ± 8.3	7.5 ± 1.4	130/74	15	72	40		
262	61.9 ± 4.8	7.7 ± 1.4	140/81	40	39	29	3.6	Yes
258	62 ± 5.1	7.8 ± 1.3	141/81	37	44	25		

Data showed no difference between patients in coronary artery disease screening and control groups for all-cause death incidence (Figure 1a): RR 0.95 (95% CI 0.66 to 1.35). There was low heterogeneity (I^2 = 0% and p = 0.615). TSA for all-cause mortality events indicates that the futility boundary was reached, so a difference of 40% between groups is firmly discarded and no further studies are required (Figure 1b). For the RRR of 20% neither the optimal sample size (19548 patients) nor the futility boundary were reached.

There was also no difference in cardiac events (Figure 2a): RR 0.72 (95% CI 0.49 to 1.06; I^2 = 38.5% and p = 0.181). For this outcome, TSA shows that the optimal sample size is 6645 patients, which is larger than the current sample. Furthermore, neither the

benefit nor the futility boundaries were reached (Figure 2b). The analysis with the (RRR of 20% showed similar results, but with a much larger optimal sample size (29763 patients).

Additional outcome analyses are presented in Table 2: the coronary artery disease screening group was similar to the control group for non-fatal myocardial infarction (RR 0.65 [95% CI 0.41 to 1.02]), heart failure (RR 0.60 [95% CI 0.33 to 1.10]) and myocardial revascularizations (PCI and CABG) (RR 1.08 [95% CI 0.83 to 1.41]). None of these outcomes reached the optimal sample size or the boundaries for futility.

Table 2. Results for myocardial infarction, revascularization and heart failure of screening versus no screening

Outcome	RR (95% CI)	Accrued Population	Optimal Sample Size (RRR = 40 %)	Optimal Sample Size (RRR = 20 %)
Non-fatal Myocardial Infarction	0.65 (0.41 - 1.02)	3315	6154	17495
Heart Failure	0.60 (0.33 - 1.10)	3174	10990	49352
Revascularizations	1.08 (0.83 - 1.41)	3174	10598	47339

Overall, the study quality was high according to the Cochrane Collaboration tool (Supplemental Material, Figures 2 and 3).[11] It must be stressed that none of the studies was blinded, but this was not considered a limitation because blinding of participants (patients and clinicians) was not feasible due to the type of intervention (screening). On the other hand, blinding of outcome assessment was reported in only one study.

According to GRADE,[16] quality of evidence was judged as high quality for both main outcomes (all-cause mortality and cardiac events).

DISCUSSION

In the present study we identified no benefit of screening for asymptomatic coronary artery disease for all-cause mortality in patients with type 2 diabetes. This conclusion is supported by a sufficient number of patients, as shown by TSA. Although we found no benefit for the other outcomes evaluated, such as cardiovascular events, these results are not definitive, as they are not supported by an adequate number of patients. This review shows that further studies evaluating coronary artery disease screening in type 2 diabetes are required before definitive recommendations on this topic can be made.

A relevant point of our analysis is the trend for statistically significant difference found in cardiac events and non-fatal myocardial infarction favouring the screening group. This finding seems to be driven by the study of Faglia et al.,[13] which was the smallest and oldest study included in our analysis. Moreover, patients in this study had an unfavourable clinical profile, represented by the worst glycemic control, the highest blood pressure, the greatest prevalence of smoking and the lowest use of statins and aspirin in comparison with the others studies. Despite this trend, TSA shows that there is insufficient data to perform firm conclusion about cardiac events and myocardial infarction. Therefore, further studies are needed to investigate the effects of screening for coronary artery disease in these outcomes.

Some limitations of this review must be acknowledged. First, the trials performed different screening tests with different specificity and sensitivity. [2] This generate two potential problems: studies using technics with lower accuracy might compromise the benefit of other technics, and combining these different tests may be questionable.

Despite this, current guidelines do not define a preferable strategy for the diagnosis of coronary artery disease, [2] and a clinical trial support this position.[17] Therefore, we believe these tests may be aggregated in a meta-analysis, as they all aim to identify high-risk patients with greater chance to benefit from CABG. [3 5 18] We cannot rule out the possibility that a test with higher sensitivity (coronary computed tomography angiography)[19] would be beneficial.[2] However the individual results of the FACTOR-64 which used a highly accurate method do not support this conclusion,[6] and, as discussed above, the potential benefit we identified in this review seems to be derived from only one study[13] that used tests with low to moderate sensitivity.

The second limitation was the somewhat choice of a relative difference of 40% between treatment arms. It was based on the benefits of CABG for patients with severe coronary artery disease.[3] Even though this evidence was published in the 90s, it is still largely used by guidelines to recommend revascularization for stable coronary artery disease. In addition, recent studies and meta-analysis have shown that CABG is superior to PCI for subjects with or without diabetes and multivessel coronary disease.[5 18 20] As only CABG is capable to reduce mortality and major cardiac events, a screening intervention aimed to identify patients with multivessel coronary artery disease assumes that patients would benefit from CABG. Therefore, a clear clinical benefit must be evident to justify the risks and costs from screening and the potential procedures resulting from it.

The analysis with a RRR of 20% showed that for cardiac events, myocardial infarction, heart failure and revascularizations the results from TSA also showed that the number of patients included was not enough. In addition, for all-cause mortality the RRR of 20% analysis also lacked power and it would be required an increase in the number of patients by a factor of five, which is unlikely to happen.

Another potential source for heterogeneity in our study is the inclusion of patients with different basal cardiovascular risk due to comorbidities and risk factors. As discussed above, this might be the case of Faglia et al. study, [13] which had older patients with an unfavorable clinical profile and found reduced risk of myocardial screening with the screening. Due to the limited number of studies, subgroup analyses could not be performed. FACTOR – 64 study included some patients with type 1 diabetes,[6] but this seems minor issue, as they represent only 10% of the sample in the original study, and 3% of the systematic review sample. Finally, the results of this systematic review are restricted to patients with characteristics comparable to the included patients in the individual studies. So these conclusions are not applicable to some higher risk populations, such as chronic kidney injury patients.

Some strengths of our study must be pointed out. We performed a comprehensive database search and identified all randomized trials evaluating the effects of a screening strategy for coronary artery disease in type 2 diabetic patients. Furthermore, the trials included are of high quality. As mentioned, there are some methodological differences between the studies, but the statistical heterogeneity was low or absent in the analyses. We also performed detailed analyses of the data and through TSA we could discard a significant difference between treatment arms for all-cause mortality. Unfortunately, we cannot make the same firm conclusions for the cardiac events, myocardial infarction, heart failure, and revascularization outcomes.

In conclusion, the present study supports the idea that type 2 diabetic patients without symptoms of coronary artery disease do not need to be screened for asymptomatic disease and that non-invasive coronary exams should be reserved for symptomatic patients. This would avoid unnecessary risks, patient distress and costs for

asymptomatic patients. For other events new studies are still needed before definitive recommendations can be made.

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Data sharing: no additional data available.

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Ethical Approval

Not needed.

Role of the funding source

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Conflict of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that no support was received from any organization for the submitted work; JLG reports grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico, during the conduct of the study; grants and other from Eli Lilly, grants from Bristol-Myers Squibb, grants and other from Boehringer Ingelheim, grants from GlaxoSmithKline, grants and other from Novo Nordisk, grants from Janssen, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work are reported.

ABBREVIATION LIST

CABG: Coronary artery bypass grafting

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

PCI: Percutaneous coronary intervention

RR: Relative risk

RRR: Relative risk reduction

TSA: Trial sequential analysis

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Figure 1. Forest plot and TSA of screening versus no screening for all-cause mortality outcome

A) Forest plot for all-cause mortality. B) TSA for a relative risk reduction of 40%. The continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The continuous black lines represent the conventional confidence intervals.

Figure 2. Forest plot and TSA of screening versus no screening for cardiac events outcome

A) Forest plot for all-cause mortality. B) TSA for a relative risk reduction of 40%. The continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The continuous black lines represent the conventional confidence intervals.

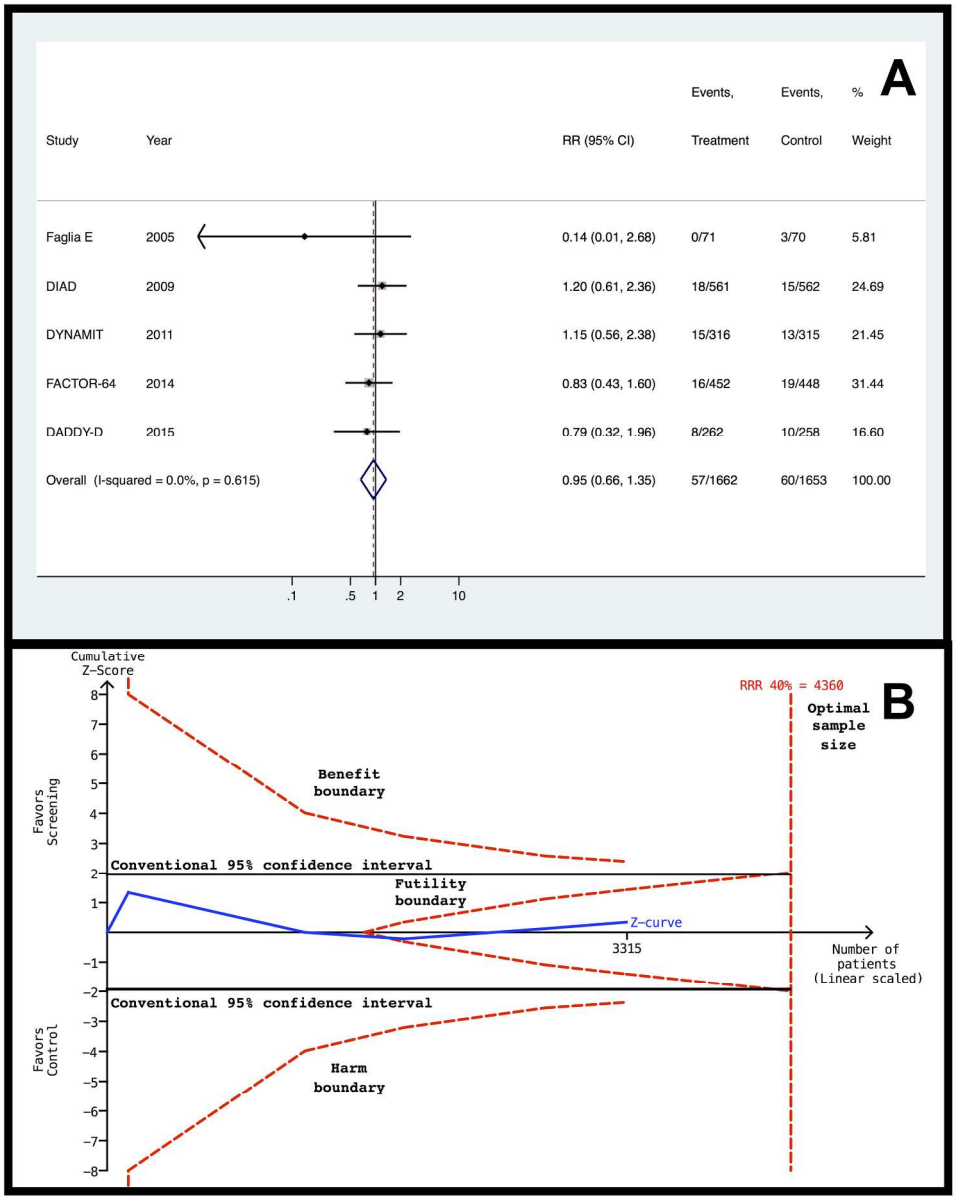

Figure 1. Forest plot and TSA of screening versus no screening for all-cause mortality outcome. A) Forest plot for all-cause mortality. B) TSA for a relative risk reduction of 40%. The continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The continuous black lines represent the conventional confidence intervals.

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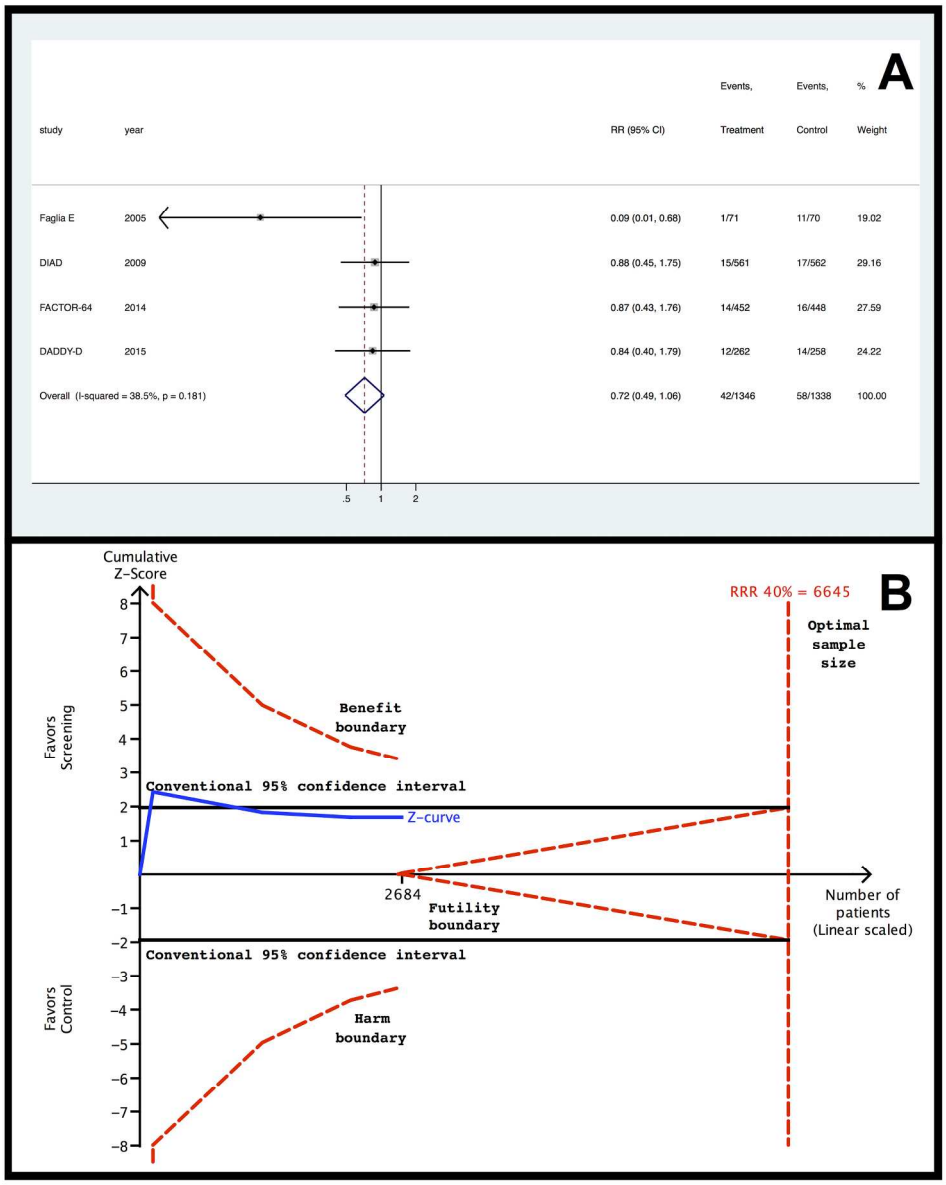

Figure 2. Forest plot and TSA of screening versus no screening for cardiac events outcome† A) Forest plot for all-cause mortality. B) TSA for a relative risk reduction of 40%. The continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The continuous black lines represent the conventional confidence intervals.

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Figure 1. Study flowchart.

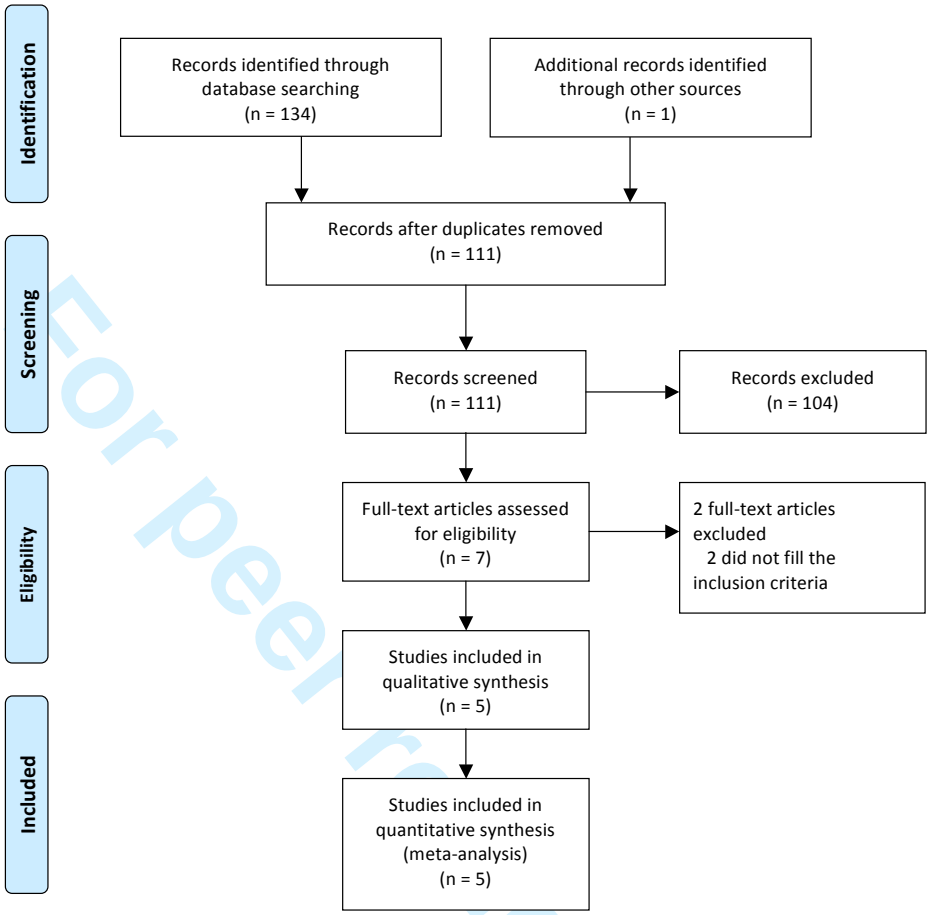


Figure 2. Risk of bias across studies.

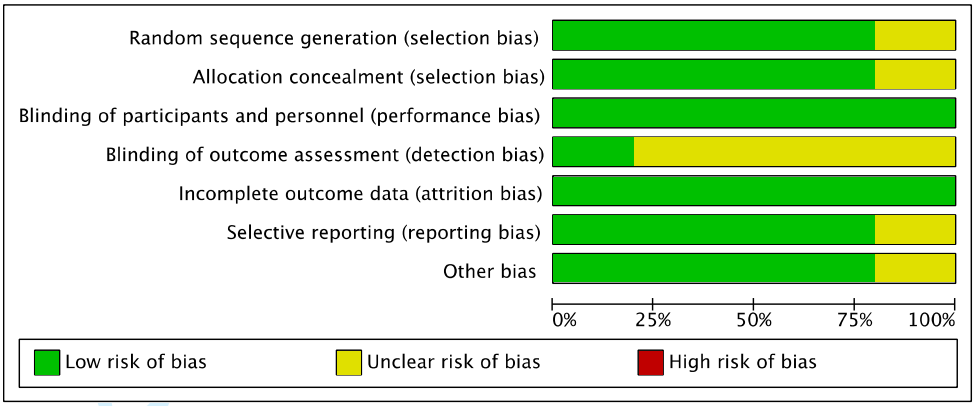
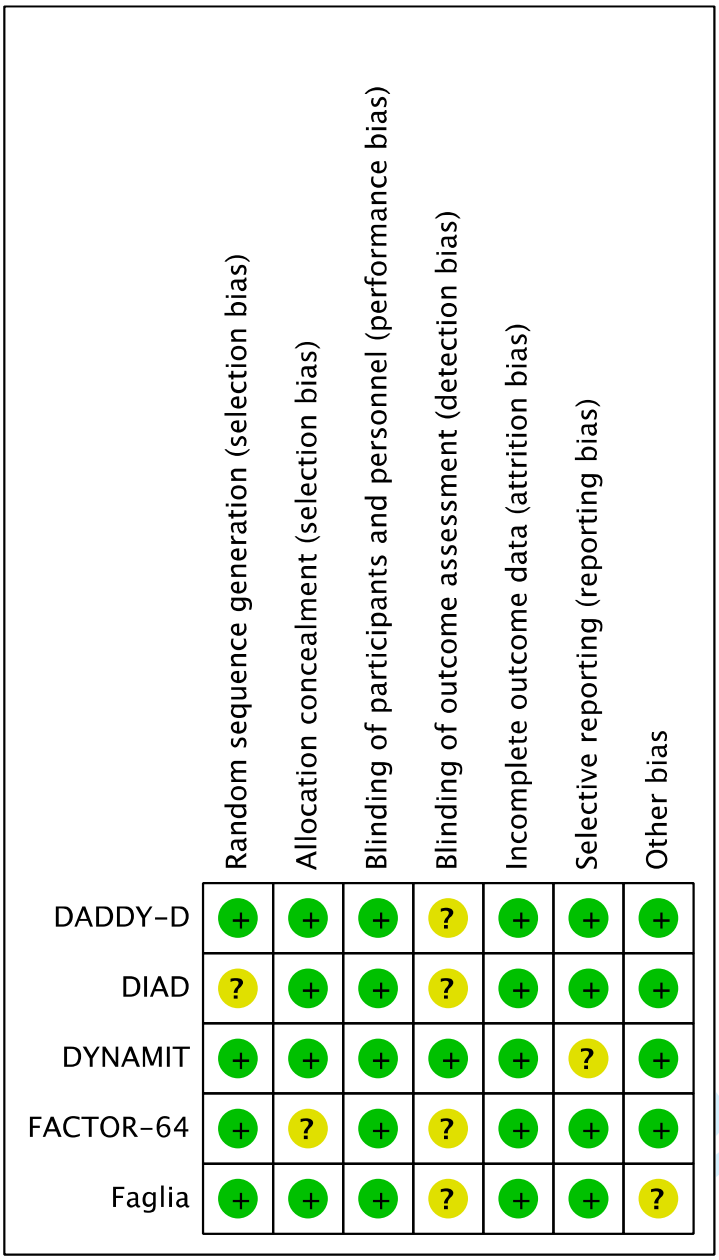


Figure 3. Risk of bias for individual studies.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 and eFigure1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	eFigure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9 and Figure 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	eFigure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9 and Figures 1 and 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

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