PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Screening for Coronary Artery Disease in type 2 Diabetic Patients: A Meta-analysis and Trial Sequential Analysis
AUTHORS	Rados, Dimitris; Catani Pinto, Lana; Leitão, Cristiane; Gross, Jorge

VERSION 1 - REVIEW

REVIEWER	Andrea Fontana Unit of Biostatistics – IRCCS "Casa Sollievo della Sofferenza" – Hospital – San Giovanni Rotondo (Italy)
REVIEW RETURNED	29-Nov-2016

GENERAL COMMENTS	The authors performed meta-analyses of 5 randomized controlled clinical trials to investigate the effect of screening for coronary artery disease both on all-cause mortality and on the onset of composite cardiac events, in type II diabetic patients. Interestingly, the authors not only performed such meta-analyses according to the classical framework but also performed interim analyses for a group sequential trial (i.e. trial sequential analysis) to evaluate whether the accumulated evidence was sufficient to establish firmly decisions even in absence of an adequate sample size, calculated on the basis of a desired statistical power which was referred to an a priori pre-specified effect size. The latter approach undoubtedly represents the main strength of this work. Indeed, critical values generated from the sequential design (i.e. the boundaries) permit to establish whether further studies are needed to update the meta-analysis (until reaching the optimal sample size) or whether sufficient evidence has been achieved to declare a benefit, a risk or a futility, warning the analyst from possible spurious detected associations. Trial sequential analysis methodology is increasing its popularity and it provides its valuable contribution, especially in presence of negative findings. The authors have done a good job: the aim is clear, methods are clearly detailed, results are well described (and easily reproducible) and limitations are properly mentioned. However, I have some very minor suggestions which could be taken into account to further improve paper's quality: 1) As recommended by Sterne and Ioannidis (please see references below), a test for publication bias (i.e. Begg and Egger's tests) is not needed when meta-analysis is constituted by small number of studies (fewer than ten), especially in presence of between-study heterogeneity. Indeed, even though the heterogeneity found in meta-analysis for cardiac events outcome was not substantial (i.e. I2>50%), this could be however considered slightly moderate (I2=38.5), although not statistically significant. Therefore, I would suggest to simplify both the methods and results removing the

	following sentences: “We evaluated the risk of small study bias…trim-and-fill computation was performed to evaluate the potential effect of non-published data” and : “The final plot and Begg and Egger’s tests showed….no significant risk of small study bias was identified” at pages 7-8 and 13, respectively. Moreover, for sake of simplicity, as the I2 test is a derivation of the Cochrane Q test and as the authors never mention the latter both in the results and in Figures, please simplify the sentence: “The heterogeneity was assessed using the Cochrane Q and I2 tests” with: “The heterogeneity was assessed using I2 test”. References: -Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials. BMJ 2011; 343:d4002. -Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ 2007; 176:1091-1096. 2) Trial Sequential Analysis: the authors declared that the computation of the optimal sample was performed having controlled for a type I error at 5%, a statistical power at 80%, and having chosen an expected relative risk reduction (effect size) of 40%. However, this is not sufficient as they should also declare the assumed event rate in the control arm, which should be around 3.5% and 4% (according to my calculations) for all-cause deaths and cardiac events, respectively. Please further include these specifications at the end of Research Design and Methods section. 3) Please include the mean follow-up time of each included trial into Table 1.

REVIEWER	Rosa Sicari Institute of Clinical Physiology, Italy
REVIEW RETURNED	01-Dec-2016

GENERAL COMMENTS	In the present meta-analysis, Authors try to evaluate the efficacy of coronary artery disease screening in asymptomatic patients with type 2 diabetes. They conclude that current available data do not support screening type 2 diabetic patients for coronary artery for preventing fatal events. This is a very relevant and highly controversial issue: available guidelines are not consistent and different indications are given. However, diabetic patients have an incidence rate of events which is higher than that of non-diabetic asymptomatic patients. The study is well conducted and methodology is sound. However, there are some issues that need to be addressed: 1. the main study limitation is due to the non-invasive techniques used: by lumping together exercise ecg, stress echo, perfusion techniques and CT we may have very different results due to the different accuracy. 2. The other factor that should be weighed in the analysis is co-morbidities and other risk factors. A diabetic patient with renal insufficiency, although asymptomatic for chest pain is very different

	from a patient with normal function. 3. The samples under investigation are very dishomogeneous and this may have accounted for the lack of statistical significance. 4. The discussion should be less focused on these findings but on the lack of evidence and on the need to fill this gap of knowledge. In clinical practice there is no coherent screening policy of these high risk patients.

VERSION 1 – AUTHOR RESPONSE

Answers to reviewer #1 comments:

1) As recommended by Sterne and Ioannidis (please see references below), a test for publication bias (i.e. Begg and Egger's tests) is not needed when meta-analysis is constituted by small number of studies (fewer than ten), especially in presence of between-study heterogeneity. Indeed, even though the heterogeneity found in meta-analysis for cardiac events outcome was not substantial (i.e. I2>50%), this could be however considered slightly moderate (I2=38.5), although not statistically significant. Therefore, I would suggest to simplify both the methods and results removing the following sentences: "We evaluated the risk of small study bias…trim-and-fill computation was performed to evaluate the potential effect of non-published data" and : "The final plot and Begg and Egger's tests showed….no significant risk of small study bias was identified" at pages 7-8 and 13, respectively. Moreover, for sake of simplicity, as the I2 test is a derivation of the Cochrane Q test and as the authors never mention the latter both in the results and in Figures, please simplify the sentence: "The heterogeneity was assessed using the Cochrane Q and I2 tests" with: "The heterogeneity was assessed using I2 test".

Answer: Thank you for the careful review and the valuable comment. We excluded the small study bias analyses. We also simplified the description of the heterogeneity assessment methods.

2) Trial Sequential Analysis: the authors declared that the computation of the optimal sample was performed having controlled for a type I error at 5%, a statistical power at 80%, and having chosen an expected relative risk reduction (effect size) of 40%. However, this is not sufficient as they should also declare the assumed event rate in the control arm, which should be around 3.5% and 4% (according to my calculations) for all-cause deaths and cardiac events, respectively. Please further include these specifications at the end of Research Design and Methods section.

Answer: Thank you for your comment. To perform TSA calculations, it is needed to define the "expected control event proportion". As you observed, we assumed it as the observed event rate in the control group in our review. This information is now presented in the Methods, under Data analysis section.

3) Please include the mean follow-up time of each included trial into Table 1.

Answer: Thank you for your advice. The Follow-up times were included.

Answers to reviewer #2 comments:

1) the main study limitation is due to the non-invasive techniques used: by lumping together exercise ecg, stress echo, perfusion techniques and CT we may have very different results due to the different accuracy.

Answer: Thank you for your review. We agree that this is the main limitation of our meta-analysis. This topic was already discussed in the original manuscript and now we expanded it in the reviewed

version of the manuscript.

2) The other factor that should be weighed in the analysis is co-morbidities and other risk factors. A diabetic patient with renal insufficiency, although asymptomatic for chest pain is very different from a patient with normal function.

Answer: We agree with your comment. Differences in the basal risk of the included population may influence the results and some populations are not represented (such as chronic kidney injury patients). We acknowledged this issue in the revised version of the manuscript.

3) The samples under investigation are very dishomogeneous and this may have accounted for the lack of statistical significance.

Answer: Thank you for your comment. As the previous (2) topic, we expanded this discussion in the reviewed manuscript.

4) The discussion should be less focused on these findings but on the lack of evidence and on the need to fill this gap of knowledge. In clinical practice there is no coherent screening policy of these high risk patients.

Answer: We agree with this topic, as one of the uses of TSA is identifying knowledge gaps. We clarified this topic in the conclusions of the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Andrea Fontana Unit of Biostatistics; IRCCS “Casa Sollievo della Sofferenza”, San Giovanni Rotondo (FG) - Italy
REVIEW RETURNED	16-Dec-2016

GENERAL COMMENTS	The authors have done a good job and all statistical concerns have been resolved

REVIEWER	Rosa Sicari Institute of Clinical Physiology, National Research Council of Italy
REVIEW RETURNED	19-Dec-2016

GENERAL COMMENTS	Authors have addressed all the issues raised by this reviewer.