

BMJ - Decision on
Manuscript ID
BMJ.2017.041016

Body:

29-Nov-2017

Dear Prof. Windecker

Manuscript ID BMJ.2017.041016 entitled "Outcomes of Non-invasive Diagnostic Modalities for the Detection of Coronary Artery Disease: A Network Meta-analysis of Diagnostic Randomized Controlled Trials"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Kristina Fišter
kfister@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Wim Weber (chair), Tim Cole (stats), Elizabeth Loder, John Fletcher, Georg Roggla, Tiago Villanueva, Rubin Minhas, Kristina Fišter.

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

* How novel are the recommendations you draw? Is this not already done in many hospital settings? The findings look confirmatory to the 2012 AHA guidelines for the diagnosis and management of patients with stable ischemic heart disease (Circulation. 2012;126:e354).

* General readers will appreciate fewer acronyms and better explanation of phrases like "functional testing" and "downstream testing". We suggest a rewrite, with a general reader in mind. All of the acronyms should be spelled out.

* Please provide, early on in the introduction, a list/description of functional and anatomical tests used for the non-invasive diagnosis of CAD. Also, please provide a box describing the key features of each.

* Although this is a review of diagnostic testing it is not answering a question of diagnostic accuracy. It's probably worth making that clear by presenting the sensitivity and specificity values for the tests you are comparing using references to a large study or review. This would clear the reader's mind and refocus it on the question addressed here. In addition, it would be useful to more explicitly mention the outcomes studied here (referral for ICA/ number of revascularisations etc.).

* The included RCTs are in a separate reference list, which is not helpful. Please include in the main reference list.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

Outcomes of Non-invasive Diagnostic Modalities for the Detection of Coronary Artery Disease: A Network Metaanalysis of Diagnostic Randomized Controlled Trials

Sionitis et al performed an impressive and important metaanalysis on the role of functional and anatomical imaging in patients with suspected low-risk acute coronary syndromes (ACS) and stable coronary artery disease (CAD). The 3 most important findings are:

- 1) In suspected ACS, functional testing reduces ICA, revascularization and costs.
- 2) In suspected stable CAD, functional testing reduces ICA and revascularization.
- 3) "...the geometry of our networks of trials suggests that each technological innovation became the standard for trials of future innovations (i.e. CCTA), although no clear advantage in terms of clinical outcomes had been shown compared with previous diagnostic strategies."

My suggestions to improve the manuscript for the general reader are as follows: The British Medical Journal is read by physicians from many different specialties, not just experts in statistics or metaanalyses. The abstract and certain parts of the manuscript are difficult to read. Therefore, I would suggest to keep definitions and conclusions precise and simple. For example, according to the title of the manuscript, the goal of the current study is to assess outcome related to the results of a certain imaging test which detects or excludes ischemia/stenosis. Thus, the goal of the study would be "outcome in terms of the number of invasive coronary angiographies, death, myocardial infarction after a positive or negative test result"

and not "efficacy of modalities for detection of coronary artery disease (significant =hemodynamically relevant stenosis?) " The latter would require a gold standard such as FFR.

The abstract is difficult to read:

1) relative efficacy. As described above, what is meant by this term? Efficacy to diagnose "obstructive CAD"? Then there would be a need for a gold standard within each study included. The number of ICA following the initial test? The safety regarding outcome? Please give a clear definition for a general reader.

2) downstream testing favored a diagnostic strategy with stress echo. What is meant by downstream testing is favoring something? ICA after an initial SPECT is downstream testing or a CT after initial exercise-ECG is downstream testing. This second testing favored a certain first test?

3) the estimates cannot rule out a significant impact on clinical outcomes associated with individual tests. Please simplify this sentence. In addition, it is more a result than a conclusion. It is somehow contradictory to the conclusion section of the manuscript which states the same risk in ACS-patients for functional or anatomical.

4) Please state what types of imaging tests were included/assessed: SPECT, MR, echo, X-ECG, CT.

5) Eligibility criteria: instead of under "different clinical settings" "under two different clinical settings"

Please make changes accordingly in the manuscript.

Introduction/Objective:

Needs clarifying. Please state with simple words what the study aims and objectives were. What was the idea behind the manuscript initially before the results were available? E.g. anatomical testing is not better than functional? In case of stable CAD, the promise-trial already showed no difference between functional and anatomical testing.

Please explain again what is meant by relative efficacy.

Methods:

What is the definition of low-risk ACS in the manuscript (I might got lost somewhere between the impressive 207 pages of the total manuscript.)? It seems to be defined only in the discussion section as patients with suspected ACS without relevant ECG-changes and negative biomarkers. However, there has been a shift of paradigm at least during the last 5 years in ACS since the introduction of high sensitive troponine T assays: A negative high sensitive troponine T means that there is no ACS and subsequent imaging or exercise-ECG are not required anymore. A positive hsTNT, however, does not necessarily say it is always a coronary problem (Tachycardia, low blood pressure/perfusion, renal function impairment etc. may result in elevated levels of hsTNT). In this group of patients with non-diagnostic ECG and positive hsTNT imaging could reduce the number of unnecessary ICA. Please define ACS in the method section and discuss whether imaging in ACS and the findings of the manuscript for ACS are still relevant in the era of hsTNT.

The study with the largest number of patients from Lim et aliter seemed to include mostly patients without ACS since all patients with positive troponines or slight ECG-changes were excluded ("Only participants who had a negative 6-hour observation received their randomly assigned protocol.").

Results

Exercise-ECG needs to be mentioned in abstract and it's results and role more described in the manuscript (results, discussion) since it is the most often performed test in many countries.

Discussion

The main questions seem to be whether

1) the presence of non-obstructive coronary artery disease - which could only be detected by CT and not by MR / SPECT / PET / stress-echo / exercise ECG - leads to an impaired prognosis if not treated with medication. In a single randomized study, this question already has been answered by the large Promise-trial (N Engl J Med 2015; 372:1291) showing no difference between CT and the other modalities.

2) the investigation of low risk groups leads to measurable differences between different imaging modalities.

Please also discuss the endpoints: ICA and revascularization are potentially physician-driven outcome parameters whereas death and myocardial infarction are not.

What are the suggestions of the authors regarding a potential significant impact on clinical outcomes? It seems to be irrelevant? If so, perform exercise ECG in all patients able to exercise (The number of downstream tests after exercise ECG is mostly driven by the number of non-diagnostic tests due to inability to exercise?)?

* Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references.

Yes

1) In suspected ACS, functional testing reduces ICA, revascularization and costs.

2) In suspected stable CAD, functional testing reduces ICA and revascularization.

3) "...the geometry of our networks of trials suggests that each technological innovation became the standard for trials of future innovations (i.e. CCTA), although no clear advantage in terms of clinical outcomes had been shown compared with previous diagnostic strategies."

* Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it? Not in its current version: this needs to be improved by a revision.

* Scientific reliability

Research Question - clearly defined and appropriately answered?

Yes

Overall design of study - adequate ?

Yes

Participants studied - adequately described and their conditions defined?

A better definition of ACS is needed.

Low risk-groups were studied.

Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ?

Yes

Results - answer the research question? Credible? Well presented?

Credible.

?Research question not fully answered: No impact on risk of myocardial infarction, but estimates were imprecise?

Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear?

Yes

References - up to date and relevant? Any glaring omissions?

hsTNT paradigm shift in ACS-patients is missing

Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?

Abstract and objectives need clarifying. The abstract is difficult to read.

Reviewers advise the editors, who are responsible for the final decision to accept or reject a manuscript.

Advice: accept after revision

Lost sentences:

P5, line 48.

P21, line 44.

Additional Questions:

Please enter your name: Simon Schalla

Job Title: cardiologist

Institution: Maastricht University Medical Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?:

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy)

please declare them here:

Reviewer: 2

Recommendation:

Comments:

In the present study the authors performed a comprehensive meta-analysis of RCTs evaluating the use of non-invasive testing for the assessment of CAD and its relationship with patient outcomes.

The subject is of great clinical relevance and the manuscript is well written. However, there are several issues that are reason for concern and, therefore, requires further discussing.

1- The main issue is related to the general message conveyed by the paper. Even though the authors did exercise some care when they phrased the conclusion of the

manuscript, the general message of the paper could be summarized as follows: (a) The CCTA strategy is associated with higher rates of ICA referrals and revascularizations; (b) However, it is not associated with lower rates of MI and/or death; (c) Hence, the "excess" ICAs and revascularizations associated with the CCTA strategy are not beneficial and represented, at the least, a waste of resources; (d) Therefore, the strategy of using CCTA is worse than the strategies based on functional assessment modalities.

This general message can be exemplified by the following segments of the Discussion Section:

"A functional testing strategy may provide important cost benefits owing to fewer referrals for ICA and revascularization and lower radiation and contrast agent exposure while resulting in similar clinical outcomes" (page 20).

and

"For outpatients with suspected stable angina, our comprehensive synthesis of D-RCTs indicates that an initial strategy based on functional testing may be valuable in the diagnostic work-up, resulting in fewer referrals for ICA and revascularization" (page 20).

and

"US guidelines published in 2012, recommend functional testing as the initial strategy... Our results are in agreement with these guidelines but in contradiction with the recently updated National Institute for Health and Care Excellence (NICE) guidelines, which advise an anatomical based-approach (CCTA) as first line diagnostic strategy..." (page 21).

I do not agree with this way of interpreting the data that was presented. Ultimately, for this rationale to make sense, the fundamental premise is that the CCTA strategy is not associated with lower rates of MI and/or death. So let's look into that in greater detail.

In the present study the authors state that "None of the diagnostic strategies had an impact on the subsequent risk of myocardial infarction, although estimates were imprecise". However, as also mentioned by the authors, a previous meta-analysis (Bittencourt et al. *Circ Cardiovasc Imaging*. 2016 Apr;9(4)) and a very large cohort study (Jorgensen et al. *J Am Coll Cardiol* 2017;69:1761-70) demonstrated a significant reduction of MI rates with the CCTA strategy in patients with stable CAD. So, are the results of the present study in agreement or in contrast with these previous reports? The general message conveyed by the authors assumes that their findings are in contrast with the abovementioned previous studies. I do not see it that way.

The present study clearly showed a trend towards MI reduction with the CCTA strategy among patients with suspected stable CAD. Indeed, the point estimate of the present study comparing CCTA versus functional testing (0.74 [0.48-1.15]) was very similar to the point estimates of the previous meta-analysis by Bittencourt et al. (0.69 [0.49-0.98]) and the previous study by Jorgensen et al. (0.71 [0.61-0.82]). The difference is that in the present study the CIs were wider and, therefore, the p-values were statistically non-significant. The reason for the wider CIs is most likely the fact that the present meta-analysis included a larger number of RCTs that were more different from one another. This resulted in a higher degree of heterogeneity (not only heterogeneity that is statistically quantifiable, but equally as important, conceptual heterogeneity) and, as a consequence, a higher degree of imprecision (Mills et al. *BMJ* 2013;346:f2914), which is mentioned several times throughout the manuscript. Therefore, by using a network meta-analysis that included a larger number of RCTs the authors gained the advantage of being able to look at a bigger picture regarding the use of non-invasive testing for the assessment of stable CAD. However, this advantage was obtained at the expense of study precision (resulting in wider CIs).

So, when we put the findings of the present study into context, taking into consideration the results of the abovementioned previous studies, it seems much more reasonable to conclude that there is robust evidence that the CCTA strategy is, in fact, associated with lower rates of MI in patients with stable CAD. I believe the authors put too much emphasis on the statistically non-significant p-value instead of looking into the bigger picture.

2- Moreover, if we consider that there is robust evidence that CCTA strategy is associated with lower rates of MI, then the authors would have to review their interpretation regarding the outcomes of ICA referrals and revascularization. As mentioned previously, the general message of the paper is based on the concept that these are "negative" outcomes. However, based on the previous discussion, this is most likely not the case. If the CCTA strategy results in lower rates of MI, then it would make more sense to consider the possibility that the higher rates of ICA and revascularizations were, in fact, "positive" outcomes that contributed to the lower rates of MI.

In this context, it would be very informative if the authors could provide data that could help us determine whether these ICAs and revascularization referrals were "appropriately" indicated or not. For example, it would allow us to get a clearer picture about this issue if the authors could provide data regarding the proportion of ICAs showing normal coronary arteries or only non-significant (<50%) CAD within each non-invasive test modality.

3- At this point, it is important to recognize that a diagnostic test will not reduce the rates of MI and/or death by itself. It will depend on the management decisions that are based on the test results. Moreover, "management" (or "treatment") is not limited to coronary revascularization; it also includes use/adherence of CAD preventive pharmacotherapy and the adoption of positive lifestyle modifications. Indeed, there is evidence that the presence of non-obstructive CAD is associated with increased risk of adverse events, which could be potentially prevented by more aggressive medical therapy (Bittencourt et al. *Circ Cardiovasc Imaging*. 2014;7:282-291 and Hulten et al. *Circ Cardiovasc Imaging*. 2014;7:629-638). Moreover, in a sub-study of the SCOT-HEART trial, Williams et al demonstrated that CCTA "lead to more appropriate use of invasive angiography and alterations in preventive therapies that were associated with a halving of fatal and non-fatal myocardial infarction" (*J Am Coll Cardiol* 2016;67:1759-68).

4- Another important issue is the novelty of the information provided by the present study.

4.1- In the beginning of the Discussion Section the authors state:

"This study is the first to assess the available evidence derived from D-RCTs of diagnostic strategies for the detection of CAD in such a systematic and comprehensive way in different clinical settings".

It is widely recognized in the literature that the diagnostic investigation and the therapeutic management are significantly different in patients with suspected low-risk ACS and those with suspected stable CAD. These represent two very different clinical scenarios. Accordingly, in the present study, the authors performed completely separate analyses for these two different clinical settings. In fact, in my opinion, the two analyses could even have been presented in two different papers. I do not see any advantage in putting them together into the same paper.

Having said that, I do not agree that including the analyses of both clinical scenarios into the same paper represent novel information. As we will discuss below, there are several previous meta-analyses investigating these two clinical settings separately.

4.2- The authors also state:

"Among patients with low-risk ACS not required to undergo early invasive assessment, an initial functional diagnostic strategy using stress echocardiography

or CMR was most strongly associated with a reduction in referrals for downstream ICA and revascularization procedures compared with anatomical testing using CCTA”.

Here again, the additional novel information is somewhat limited. A previous meta-analysis by Hulten et al (J Am Coll Cardiol 2013;61(8):880-892) demonstrated that CCTA was associated with higher rates of ICA and revascularizations when compared with SOC among low-risk patients with suspected ACS. Another meta-analysis (D’Ascenzo et al. Eur Heart J Cardiovasc Imaging 2013;14:782–789) also demonstrated that CCTA was associated with higher rates of revascularizations. At this point, I would like to express my concern regarding this particular conclusion. Given that it is based on the comparison of CMR/Echo with CCTA, this conclusion should be interpreted with great caution. First because both CMR and Echo are underrepresented in the network meta-analyses. Second, and most importantly, because there are no direct (head to head) comparisons between either CMR or Echo against CCTA. The comparisons are based exclusively on indirect analyses.

4.3- Finally, the authors also state:

“Among patients with symptoms suggestive of stable CAD, no clear discrimination was obtained across individual diagnostic strategies for the primary outcome of ICA referrals, mainly because of the limited number of trials contributing to each comparison. Stress echocardiography and SPECT-MPI resulted in less overall downstream testing compared to CCTA. After grouping of widely available functional tests, a functional-testing approach yielded fewer referrals for ICA and subsequent revascularizations than anatomical testing”.

Once again, this conclusion does not represent novel information. There are two previous meta-analyses that demonstrated that CCTA strategy is associated with higher rates of ICA and revascularization referrals (Bittencourt et al. Circ Cardiovasc Imaging. 2016 Apr;9(4)) and (Nielsen et al. Eur Heart J Cardiovasc Imaging 2014;15:961–971). This was also demonstrated in the large cohort study by Jorgensen et al. (J Am Coll Cardiol 2017;69:1761–70).

It is important to recognize, however, that the present study does provide interesting novel information. As previously mentioned, the present network meta-analysis included a broader range of RCTs investigating the most frequently used non-invasive diagnostic tests in contemporary cardiology. Therefore, they were able to provide a wider picture about the use of non-invasive testing in both acute and chronic CAD assessment, including stress Echo and, particularly, CMR (rarely contemplated in previous meta-analyses).

5- Regarding the ACS analyses, the authors do not report on ED cost and length of stay. I believe that these constitute relevant outcome parameters, particularly in this clinical setting. Therefore, I would suggest the authors report it for the different diagnostic strategies used in the ER.

Additional Questions:

Please enter your name: Clerio Francisco de Azevedo Filho

Job Title: Assistant Professor, Cardiology

Institution: Rio de Janeiro State University School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A
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lists/declaration-competing-interests'target='_new'> (please see BMJ policy)
please declare them here: I do not have any competing interests.

Reviewer: 3

Recommendation:

Comments:

The present manuscript represents an enormous effort by the authors to compile and to use the most advance techniques available to summarise the evidence of these different diagnostic techniques for detecting Coronary Artery Disease.

The message is as simple as can be made while maintaining a level of uncertainty required given the evidence available. It might be possible to simplify slightly (as one of the reviewers suggests) although this might make it more difficult to reply to the other reviewer challenge of how the authors have interpreted the finding of less invasive assessments and revascularizations as a positive outcome.

In terms of methods, the authors are experts in the N-MA field and it shows. The level of reporting and methods used are at the cutting edge in this area. As a minor note, it might be desirable (as part of the simplification process) to provide figures (as part of the full paper or as extra material) of the diagnostic pathways tested. This might help in the Introduction and certainly in the Discussion.

Additional Questions:

Please enter your name: Rafael Perera

Job Title: Professor of Medical Statistics

Institution: University of Oxford

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A

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please declare them here: I was paid consulting fees to evaluate the role of CCTA as part of an optimal strategy for patients with stable angina (Medical Evaluation Technology Assessment for the EU).

Our conclusions then were that there was no reliable evidence for effect on patient outcome and that diagnostic accuracy estimates were more likely biased.