Author's response to reviews

Title: Validity of Electron Beam Computed Tomography for Coronary Artery Disease: A Systematic Review and Meta-analysis

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Author's response to reviews: see over
To:
The Editor-in-Chief,
BMC Medicine

Dear Dr. Norton,

We would like to thank the reviewers for their thoughtful comments on our article. We believe we have addressed all comments as explained in detail in the attached pages.

Please do not hesitate to contact me if you need any further information.

Sincerely,
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Response to Brahmajee Nallamothu:

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Comment 1. The authors correctly point out that coronary artery calcification scores need to be interpreted in light of age- and gender-predicted values and few studies report such stratified values. They also mention the inability of their analysis to comment on the utility of EBCT scores beyond traditional risk factors which also implications for the management of patients. For these reasons, we believe that the authors should consider tempering their conclusions somewhat.

In the Abstract, for example, their conclusions for asymptomatic patients in the High category and symptomatic patients in the Low category seem too firm (despite the qualifying phrase “can perhaps”). The authors themselves point out in the discussion that their results should not be used for “individual risk stratification” but reflect differences between populations.

Both in the abstract and in the discussion we have changed the tone of our conclusions and reiterate that our results cannot be used to decide the course of action for an individual patient based on the calcium score.

Comment 2. The authors suggest directions for future EBCT research in the discussion. We agree with all these points. However, we recommend that the authors also mention the role of MDCT (at least briefly). MDCT has become a key tool for assessing coronary artery calcification scores in real world settings, essentially supplanting EBCT which is still restricted to a few research centers. Much additional research on coronary artery calcification will be performed with MDCT, which should be acknowledged in the paper.

We now mention in the introduction to the paper that MDCT is widely being used to measure coronary artery calcium and state that our meta-analysis is limited to EBCT.

Comment 3. This study compared the ratios of positive predictive value (PPV) and negative predictive values (NPV) between groups. We understand the statistical reasons for pooling results in this manner but worry about its interpretability for clinicians. What exactly does it mean that “a symptomatic subject with a Low score has approximately one quarter the risk of having significant angiographic coronary stenosis than the Moderate/High categories”? Wouldn’t it be valuable to place these findings in the context of their absolute risk of an event? Also, how should we interpret the finding that the ratios of negative predictive values were consistent across risk categories of asymptomatic patients? Couldn’t the negative predictive values all be “similar” but inadequate?

We now use the median risk of CAD among Moderate+High categories in studies of symptomatic patients (80%) to illustrate the meaning of the statement above.
As we have mentioned in the discussion, the high negative predictive values among the asymptomatic patients are not of much use as they do not help distinguish between Low, Moderate and High categories.

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**Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)**

4. The authors write that “among symptomatic patients, those with EBCT scores in the low category can perhaps, at least temporarily, avoid invasive coronary angiography.” We are somewhat concerned with this statement. Symptoms used for inclusion in the various studies that were considered for this paper are not clearly defined. In patients with unstable or high-risk symptoms, urgent cardiac catheterization may be indicated despite the findings of the EBCT (or other clinical tools), especially since vulnerable and ruptured plaques may be associated with little or no coronary calcium. This issue is strongly related to Point 1 above, which also cautions about patient-level recommendations based on these findings.

As mentioned in response to Comment 1 we have altered our language to underline that our results cannot be used to determine the course of treatment for an individual patient.

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**Discretionary Revisions (which the author can choose to ignore)**

Comment 1. For Tables 1 and 2, couldn’t much of the “value” column be eliminated with individual cells directly reporting “yes,” “no”, and “NR” (not reported)? This may make the Tables easier to read.

Many of the “value” column entries are not as simple as “Yes”, “No” and “NR” so we felt it was best to leave these tables as such. However, we would be willing to modify them as the reviewer still feels his suggestion would make them easier to read.

Comment 2. Figure 2 demonstrates the low PPVs and significant overlap between moderate and high risk categories in asymptomatic patients. This may deserve more mention in the discussion.

We have now added a mention of this in the discussion.
Response to Zhongua Sun:

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Comment 1. The question posed by the authors is not new, as the MSCT is another useful and less-invasive technique for calcium scoring and diagnosis of CAD.

We now mention in the introduction to the paper that MDCT is widely being used to measure coronary artery calcium and state that our meta-analysis is limited to EBCT.

Comment 2. The methods of the study are appropriate, and well described. I feel like the section of statistical analysis on page 4 is a little bit weak and more detailed description about the methodology should be provided here as this is a systematic review and meta-analysis.

We have added a couple more sentences to the statistical analysis section describing the fitting of the hierarchical model. We will be glad to share the WinBUGS program with the interested reader.

Comment 3a. Data selection and extraction are sound and well-controlled. However, there are a few points which need to be clarified a. EBCT protocol on page 5, the exact number of studies following the Agatston method for scoring should be provided;

The exact number of studies following the Agatston method of scoring is now given.

Comment 3b. EBCT protocol on page 5, 2nd line, suggesting changing “a signal of greater than 130 HU..” to “a threshold of greater than 130 HU..”;

We now use the suggested language.

Comment 3c. EBCT protocol on page, 5th line, suggest change “the scan time per slice was…” to “the scan time per rotation was…”.

We now use the suggested language.

Comment 5. General discussion is fine. I am concerned about the discussion or statements made in the 2nd and 3rd paragraphs on page 9, as the results were based on analysis of a number of studies which lack of uniform criteria. The validity of the study findings would be questioned.
We now temper our conclusions to underline the fact that our results apply only to the aggregate patient and cannot be used to determine the course of action for an individual patient.

**Additional comments:**

*Comment:* Some references are missing and were not listed in the references, e.g., Raggi (2000), Baumgart (1997), Yao (2000), Knez (2004).

We apologize for this oversight. These references have now been added to the article.

*Comment:* References in tables 3-5 need to be revised in order to locate them easily in the reference list. Suggest changing the numbers in front of the references to the numbers cited in the text.

In tables 3-6 we have now inserted the reference number of each article in brackets next to the first author’s name.
Response to Alexander Becker:

Comment: The meta analysis focused on the diagnosis of coronary artery disease, which is hampered by a reduced specificity. As shown in different studies, an increase in specificity can be achieved by using age adjusted percentiles, which of course is not possible in this meta analysis. Still in all age groups the exclusion of coronary calcification is associated with a very high negative predictive value. This is also true for symptomatic patients, making the calcium score a valuable tool for the exclusion of coronary artery disease helping to reduce the number of invasive examinations. Even if the group of patients with score O is not a separate group in this meta analysis I would suggest to give the sampled negative predictive value of these patients in the studies with symptomatic patients as this illustrates the possible use of coronary calcium. As already mentioned in the meta analysis the specificity in symptomatic patients is not adequate in some score groups for a reliable diagnosis.

We have now added a sentence to the results section where we mention the range of negative predictive values of the Low EBCT category across studies of symptomatic patients.

Comment: Due to technical progress today usually the volume score determined by multislice CT is used to assess coronary calcifications. I would mention, that this technique can be used equivalent to EBCT and Agatston score.

We now mention this in the introduction.