Reviewer's report

Title: Measurement of Coronary Calcium Scores or Exercise Testing as Initial Screening Tool in Asymptomatic Subjects at Risk for Coronary Artery Disease: an Evaluation Study

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Reviewer: Stefan Möhlenkamp

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General
The present work assesses the predictive value of CAC scoring versus exercise testing from a PREVEND-study subgroup including 149 asymptomatic persons with ST/T-segment changes (i.e. 2.2% from a cohort of 6805 subjects in the PREVEND-trial) on the resting ECG. Based on the CAC score and subsequent bicycle stress tests, participants were stratified to either myocardial perfusion scintigraphy (MPS) or coronary angiography (CAG). The primary endpoint was an angiographic lesion >50%. The secondary endpoint was revascularization.

This study is relevant in that it addresses the clinical work-up of asymptomatic subjects with ST/T-segment changes in the resting ECG. In these, it is important to exclude functionally and prognostically relevant ischemic CAD.

This reviewer suggests some prudence on the strength of the statement regarding the "better test". The question is: better for what? The authors show that CAC scoring may be better than stress-testing to identify >50% angiographic lesions. But is this indeed better for the patient? The "CAC first" approach may lead to an "overtreatment of anatomy", which may not always be necessary with respect to LV function improvement and event reduction. In asymptomatic subjects, aggressive risk factor modification should generally be the treatment of choice in those with relevant plaque burden. In very high CAC scores, stress-testing may detect clinically silent ischemia (see DS Berman et al., JACC 2004;44:923ff). In this sense, both tests may be complementary. CAC may be used as a filter prior to stress-testing to select those individuals who have the highest likelihood to detect ischemia among those with ST/T-segment changes on the resting ECG.

Current guidelines recommend not to use CAC burden alone as an indication for revascularization in asymptomatic persons. Asymptomatic subjects with ST/T-segment changes may indeed differ from other asymptomatic persons in that they may have higher event rates, especially if ST/T-segment changes are accompanied by evidence of LVH. The authors have appropriately revascularized only those with reduced FFR. However, the lack of differences in ROC curve areas regarding the secondary endpoint, suggests that the strong wording in the conclusion should be modified.

Specific comments:

Title: The authors may want to consider modifying the title. ST/T-segment changes constitute an important inclusion criterion in this subgroup of asymptomatic persons, e.g. "Coronary Calcium Scoring or Exercise Testing to Identify CAD in Asymptomatic Subjects with ST/T-segment changes on the Resting ECG".

Cohort: Are any other clinical criteria available, e.g. how many had signs of LV-hypertrophy on their resting ECG? Was there any valvular heart disease? What about LV-function? If available, the rate of known and previously established arterial hypertension should be stated, as many are on antihypertensive medication. How many subjects had LVH with strain on the resting ECG? These may be the ones with highest CAC scores. If data are not available, this could be included in the limitations section.

Although the title suggests that the cohort is "at risk", the authors state that this was a low risk cohort. This is supported by the lack of hard events during follow-up. However, at least 10% of subjects had a CAD-risk equivalent, i.e. diabetes, and some (additional?) persons had PAD or a cerebro-vascular event history. It would be helpful to provide Framingham risk scores, NCEP/ATP III-scores, or European SCORE-values for men and women. How many were low-, intermediate-, and high risk subjects?

Endpoints:
As 76 subjects had a CAC < 10 and had a non-diagnostic or negative stress-test, outcome seems to be assessable in only 73 subjects (see flow chart). Or did the authors assume a negative MPS and CAG in these? If so, this should be stated.

It is of note, that all but one subject with CAC < 100 had absence of significant CAD. Yet the only subject who did, also had a positive stress-test. It would be interesting to describe the clinical background of this one individual who had a primary and secondary endpoint despite a CAC < 10. Was he/she truly asymptomatic or did he/she have atypical symptoms? Did he/she have a risk equivalent? Was this a young active smoker?

Myocardial Perfusion Scintigraphy (MPS):
The clinical definition of a positive MPS-study could be specified. Were there no inconclusive findings as in the bicycle stress-tests? What about "patchy patterns" and evidence for microvascular dysfunction, as frequently observed in hypertensive hearts?

Coronary angiography (CAG) & FFR:
To better understand the functional severity of lesions, it might be helpful to report average FFRs in those subjects that were revascularized.

Stress-ECG:
Does the predictive accuracy of the stress-ECG change when the Duke-Score is utilized? Was it possible to calculate ST/T-hysteresis? Such information may improve sensitivity of stress-testing. If these data are not available, this could be included in the limitations section.

Fig. 1:
Figure 1 - as is - does not fully match the protocol in the text. What happened to subjects with intermediate stress-tests? Persons with a CAC score between 10 and 100 were first recommended to undergo MPS before CAG. Those with a score >100 were initially / immediately referred to CAG. This is not clear from the flow chart. The stress-test in subjects with CAC >10 is missing in the flow chart. It would be helpful to include numbers of subjects in each clinical path in the diagram.

References:
Some additional references should be considered:
1) Budoff MJ et al. AHA scientific statement, Circulation 2006
2) Greenland et al. ACCF/AHA scientific statement, JACC 2007
3) ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging, JACC 2006
The authors may want to reduce the numbers of references (n=5) that support the use and value of FFR.

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.