Author's response to reviews

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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Author's response to reviews: see over
We appreciate all the reviewers’ efforts in discussing and criticizing our manuscript. We feel that the comments have contributed to the quality of the manuscript. Below, we have answered to each of the questions and comments. In the manuscript, all changes have been underlined.

Q1 **Reviewer:** Shuichi Hamasaki  
**Reviewer’s report:**
**General**
This is a good and well-conducted study, which adds information in the literature concerning the usefulness of measurement of coronary calcium scores as initial non-invasive test. However, the following questions have arisen during reading the manuscript; Several points that must be addressed are the following:
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**Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)**

There is no remarks about that the patients on beta-blocker or nitrates or Ca-antagonists can be underestimated on exercise testing.

A1 Please see Limitations section, page 12, last alinea:
“Thirty-two patients (21.5%) used betablockers or calcium antagonists at the time of exercise testing. These medications may affect the maximal exercise heart rate [51]. This may have contributed to a non-interpretable result found in one case (0.7%).”

Q2 It is not uncertain why high calcium scores identified a high number of subjects with an indication for a revascularization procedure. Calcium scores may be representative of coronary anatomical information but not coronary vascular function. Is there any data which shows the relation of calcium scores with coronary vascular function?

A2 We comment on this issue in the discussion section, page 11, second alinea:
“However, several arguments favor an invasive strategy in subjects with high calcium scores. A clear association has been demonstrated between calcium scores and the amount of myocardial ischemia [47-49] as well as the severity of CAD [33,34,36], which are the principle components of guideline recommendations for a revascularization procedure [27-29].”
Coronary artery calcium is associated with atherosclerotic plaque development, but the presence or absence of calcium does not allow for reliable distinction between unstable vs stable plaque. Is there any possibility that calcium scores can be underestimated in patients with unstable plaque?

We comment this issue in the Discussion section, page 10, second alinea: “Coronary calcifications parallel the development of atherosclerosis, with higher values present in men and in the elderly [35]. Higher amounts of coronary calcium have been associated with more severe CAD [33,34,36,37]. Coronary calcifications have been associated with hard as well as with soft plaques [38]. In ultrasound studies the sensitivity for the detection of soft plaques is lower than for hard plaques [38]. However, since the absence of coronary calcium has been associated with a negative predictive value of >95% for future coronary events [39,40], (soft) plaques maybe missed by EBCT have a limited clinical importance [5].”
Q1  
**Ref. 2**

**Reviewer:** Roger S. Blumenthal  
**Reviewer's report:**  
General  
Shorten the long paragraphs

A1  
We have shortened the following paragraphs:  
- Methods, myocardial perfusion scintigraphy  
- Endpoints  
- Discussion, general comments

Q2  
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached) Comment more on the persons with CAC of 100-300.

A2  
Please see page 12, second alinea:  
“Twenty-nine subjects had a calcium score between 100-399. When compared to subjects with calcium scores ≥400, less subjects had a primary endpoint (41% vs 68%) or an indication for a revascularization procedure (17% vs 63%). This finding is in line with previous findings on the increasing number of abnormal stress tests in case of higher calcium scores, namely in 18-60% of subjects with calcium scores ≥400, compared to 7-23% of subjects with calcium cores of 100-399 [47-49]. Since the finding of myocardial ischemia in asymptomatic subjects with calcium scores >100 affects clinical outcome [49], non-invasive stress testing is warranted. This may be followed by an invasive strategy in case of abnormal test results, in addition to appropriate medical treatment. Further studies with larger numbers of patients are needed to evaluate these issues.”

Q3  
“The authors need to make it clearer that coronary calcification is atherosclerosis. They also need to emphasize more that while nearly all men >50 have CAC, that the % score for one's age and gender is the most important factor.
We discuss this issue on page 10, lines 11-15 and 20-21:

“Coronary calcifications are highly specific for atherosclerosis and a strong correlation with total plaque burden has been demonstrated [33,34]. Coronary calcifications parallel the development of atherosclerosis, with higher values present in men and in the elderly [35]. Higher amounts of coronary calcium have been associated with more severe CAD [33,34,36,37].”

“Absolute coronary calcium scores, as well as age- sex- specific percentiles, have been associated with the occurrence of future coronary events [35,39-41].”

They also need to better define intermediate risk. Should it be a 6-20% 10-year hard event rate or a 10-20% 10-year Framingham risk.

We comment this issue in the following alinea:

Please see page 10, last sentence, and page 11, first alinea:

“This is of clinical importance since many subjects at intermediate risk (a probability of a coronary event between 1-2% per year due to the presence of at least one high risk characteristic or based on Framingham scores [4,5]) do not have CAD [42-44].”

The current study population was derived from the PREVEND population of subjects without previous documented coronary heart disease, which can be regarded as a low risk population since 3.3% experienced a first coronary event during 5.5 years of follow up [57]. The presence of ST-T changes on the resting ECG is a clear additional high risk characteristic, and therefore our population can be classified as intermediate risk [13-18]. The prevalence of coronary calcium scores, in particular with regard to the 30-50% of subjects having calcium scores <10, was comparable to other asymptomatic populations with at least one risk
factor [42,43]. Our results are therefore applicable in asymptomatic populations, who are candidates for risk stratification, based on the presence of ≥1 high risk characteristic.”

Q5 Why were bicycle stress tests done instead of treadmill stress test?
A5 Since the Dutch are used to cycling, bicycle tests are routinely performed in the Netherlands.

Page 5, third alinea:
“As is common practice in the Netherlands, all exercise tests were performed on a bicycle.”

Q6 The authors should comment more on the much larger group of women and men who have on CAC scores of 100-300.’
A6 Please see A2

Q7 The authors need to make the point that revascularization should only be done in persons with a high CAC score who have at least moderate ischemia on a good medical regimen.

A7 Please see page 11 and 12:
“Although high risk criteria on stress testing in asymptomatic subjects are accepted as indications for CAG [12], direct referral to CAG based on high calcium scores is generally believed to be inappropriate [12,46]. However, several arguments favor an invasive strategy in subjects with high calcium scores. A clear association has been demonstrated between calcium scores and the amount of myocardial ischemia [47-49] as well as the severity of CAD [33,34,36], which are the principle components of guideline recommendations for a revascularization procedure [27-29]. In addition, event free survival was decreased in asymptomatic subjects with high calcium scores and an abnormal myocardial perfusion test [49]. Clearly, all subjects with high calcium scores require aggressive secondary
prevention, including treatment with cholesterol lowering, antihypertensive medications and aspirin. Our research protocol recommended performance of CAG in case of calcium scores ≥400 or positive exercise test result. The decision to perform a revascularization procedure when a non-invasive stress test had not been performed prior to CAG, was guided by fractional flow reserve measurement during CAG [12,30,31]. Alternative diagnostic strategies may be the performance of CAG only after documentation of myocardial ischemia by non-invasive stress testing [46], or in combination with current generation CT-angiography. We agree that an invasive strategy is associated with a risk of complications and inappropriate revascularizations. The recent COURAGE trial has shown that some patients with stable CAD can be managed conservatively [50], and future guidelines may therefore be adapted. Our multidisciplinary study was based on the former ESC and ACC/AHA guidelines for PCI and CABG [27-29], and identified a substantial number of subjects with a class I or IIa indication for a revascularization procedure.”
The authors compared the predictive power of exercise testing and coronary calcium scores to detect significant CAD (primary endpoint) and the need for revascularisation procedures (secondary endpoint) in asymptomatic patients with ST-T abnormalities in the resting ECG. They found that in 11/16 patients revealing Scores >400 and in 13/33 patients with an abnormal stress test the primary endpoint was present. They concluded that a calcium score >400 reveal a higher diagnostic yield to detect significant CAD than exercise testing.

Negative aspects:
The study population is rather small with only 24 patients who showed significant CAD.

The study is significantly affected by a preselection bias as only asymptomatic patients with ST-T abnormalities in the resting ECG were included. These ECG changes already suggest a relatively high pretest likelihood for significant CAD. Therefore the results cannot be translated to a general asymptomatic patient population and I disagree to the conclusion drawn by the authors, that CAG is indicated in patients with scores>400. The high specificity for high calcium scores to detect significant CAD in the present patient cohort is similar to studies comparing calcium scoring and invasive angiography in symptomatic patients. This underscores the fact that due to the inclusion criteria asymptomatic patients with a relatively high likelihood (similar to that of symptomatic patients) for significant CAD were investigated. This needs to be discussed.

We agree with the reviewer that the high number of subjects with significant CAD in subjects with high calcium scores is comparable to symptomatic populations. We feel that our study population can be regarded as an intermediate risk population, please also see the second Reviewer, A4/Q4.

We comment this issues on page 12, last alinea and page 13, first alinea. “The specificity for high calcium scores to detect significant CAD in our study
population is similar to studies comparing calcium scoring and CAG in symptomatic patients [36,37]. This observation implies that the association between calcium scores and severity of CAD at CAG may be extendable to asymptomatic populations. The current study population was derived from the PREVEND population of subjects without previous documented coronary heart disease, which can be regarded as a low risk population since 3.3% experienced a first coronary event during 5.5 years of follow up [57]. The presence of ST-T changes on the resting ECG is a clear additional high risk characteristic, and therefore our population can be classified as intermediate risk [13-18]. The prevalence of coronary calcium scores, in particular with regard to the 30-50% of subjects having calcium scores <10, was comparable to other asymptomatic populations with at least one risk factor [42,43]. Our results are therefore applicable in asymptomatic populations, who are candidates for risk stratification, based on the presence of ≥1 high risk characteristic.”

Q3 No study has yet demonstrated that PCI or CABG improve the long term prognosis compared to conservative medical treatment even in stable symptomatic patients. Moreover the rate of hospitalisations and intervention related complications is higher in patients treated by PCI or CABG. So I doubt that PCI will improve prognosis in asymptomatic patients and thus invasive testing should be seriously questioned. The authors should point out that in patients with scores> 400 aggressive secondary prevention strategies should be applied in order to improve prognosis rather than recommending an invasive test.

A3 Please see page 11 and 12:
“Although high risk criteria on stress testing in asymptomatic subjects are accepted as indications for CAG [12], direct referral to CAG based on high calcium scores is generally believed to be inappropriate [12,46]. However, several
arguments favor an invasive strategy in subjects with high calcium scores. A clear association has been demonstrated between calcium scores and the amount of myocardial ischemia [47-49] as well as the severity of CAD [33,34,36], which are the principle components of guideline recommendations for a revascularization procedure [27-29]. In addition, event free survival was decreased in asymptomatic subjects with high calcium scores and an abnormal myocardial perfusion test [49]. Clearly, all subjects with high calcium scores require aggressive secondary prevention, including treatment with cholesterol lowering, antihypertensive medications and aspirin. …… We agree that an invasive strategy is associated with a risk of complications and inappropriate revascularizations. The recent COURAGE trial has shown that some patients with stable CAD can be managed conservatively [50], and future guidelines may therefore be adapted. Our multidisciplinary study was based on the former ESC and ACC/AHA guidelines for PCI and CABG [27-29], and identified a substantial number of subjects with a class I or IIa indication for a revascularization procedure.”

Q4 Positive aspects:
1. To best of my knowledge the approach to compare stress testing and calcium scoring to identify significant CAD is unique and not yet investigated and therefore of high clinical relevance.
2. The findings question the current recommendations concerning the interpretation of positive stress tests, however the results presented here are significantly discrepant to well published accuracy studies concerning bicycle exercise ecg-testing. This needs to be discussed.

A4 We comment this issue on page 12, last alinea:
“The sensitivity of the exercise test was somewhat lower than expected from large symptomatic populations undergoing exercise testing and coronary angiography [53]. However, the test characteristics of our study were very comparable to the studies including only asymptomatic subjects [7,54-56].”

3. The fact that FFR was done to determine the functional relevance of a coronary stenosis is an obvious strength of the paper.
Reviewer: Stefan Möhlenkamp

Reviewer's report:

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.

We comment this issue on page 11 and 12:

"In asymptomatic populations, guidelines traditionally focus on long-term risk assessment and prevention of future manifestations of coronary disease, while the role of invasive diagnostic and therapeutic procedures is hardly discussed [8,45]. Although high risk criteria on stress testing in asymptomatic subjects are accepted as indications for CAG [12], direct referral to CAG based on high calcium scores is generally believed to be inappropriate [12,46]. However, several
arguments favor an invasive strategy in subjects with high calcium scores. A clear association has been demonstrated between calcium scores and the amount of myocardial ischemia [47-49] as well as the severity of CAD [33,34,36], which are the principle components of guideline recommendations for a revascularization procedure [27-29]. In addition, event free survival was decreased in asymptomatic subjects with high calcium scores and an abnormal myocardial perfusion test [49]. Clearly, all subjects with high calcium scores require aggressive secondary prevention, including treatment with cholesterol lowering, antihypertensive medications and aspirin. Our research protocol recommended performance of CAG in case of calcium scores ≥400 or positive exercise test result. The decision to perform a revascularization procedure when a non-invasive stress test had not been performed prior to CAG, was guided by fractional flow reserve measurement during CAG [12,30,31]. Alternative diagnostic strategies may be the performance of CAG only after documentation of myocardial ischemia by non-invasive stress testing [46], or in combination with current generation CT-angiography. We agree that an invasive strategy is associated with a risk of complications and inappropriate revascularizations. The recent COURAGE trial has shown that some patients with stable CAD can be managed conservatively [50], and future guidelines may therefore be adapted. Our multidisciplinary study was based on the former ESC and ACC/AHA guidelines for PCI and CABG [27-29], and identified a substantial number of subjects with a class I or IIa indication for a revascularization procedure.

Q2 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.

A2 We changed our conclusion in line with your comment:
Please see abstract, page 2, conclusion:
“Measurement of coronary calcium scores is an appropriate initial non-invasive
test in asymptomatic subjects at increased coronary risk.”

Discussion, page 15, last alinea:
“Measurement of coronary calcium scores is an appropriate initial non-invasive
test in asymptomatic subjects at increased coronary risk.”

Q3 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".

A3 We have changed the title accordingly.
“Measurement of Coronary Calcium Scores or Exercise Testing as Initial Screening Tool in Asymptomatic Subjects With ST-T Changes on the Resting ECG: an Evaluation Study”

Q4 Cohort:
Are any other clinical criteria available, e.g. how many had signs of LV-hypertrophy on their resting ECG?

A4 Please see page 7 last alinea:
‘Left ventricular hypertrophy on the ECG was defined according to the Cornell voltage-duration product [19].”

And table 1.: Eleven subjects (7%) fulfilled the ECG criteria for LVH.

Q5 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.

A5 Information on LV function is not available.
Please see page 7, last alinea:

“Hypertension was defined as a systolic blood pressure >140 mmHg and/or diastolic >90 mmHg or use of antihypertensive medications.”

The number of patients with hypertension was 49%, please see table 1. There were no patients with a history of valvular heart disease, please see table 1.

Q6 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.

A6 Subjects with LVH criteria on the ECG had the following calcium scores, please see page 8, first alinea:

“Of the 11 subjects with ECG criteria for LVH, 5 had calcium scores of 0 and 6 between 16 and 1313.”

Q7 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?

A7 We comment this issue on page 7, last alinea:

“Framingham risk estimations were calculated according to Wilson et al [30]. Since HDL cholesterol was not measured during the second visit, HDL cholesterol data of the first visit were used for the Framingham risk estimations.”

And on page 8, first alinea:

“The 10-year estimated Framingham risk was <10% in 56%, 10-20% in 26% and >20% in 19% of subjects.”
And on page 13:
“The current study population was derived from the PREVEND population of subjects without previous documented coronary heart disease, which can be regarded as a low risk population since 3.3% experienced a first coronary event during 5.5 years of follow up [57]. The presence of ST-T changes on the resting ECG is a clear additional high risk characteristic, and therefore our population can be classified as intermediate risk [13-18]. The prevalence of coronary calcium scores, in particular with regard to the 30-50% of subjects having calcium scores <10, was comparable to other asymptomatic populations with at least one risk factor [42,43]. Our results are therefore applicable in asymptomatic populations, who are candidates for risk stratification, based on the presence of ≥1 high risk characteristic.”

Q8 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.

A8 Indeed, no endpoint was assumed in these subjects, please see page 7. “For the ROC analysis, subjects with calcium scores <10 and a negative or nondiagnostic exercise test and in whom MPS or CAG was not performed, were assumed to have no endpoints.”

Q9 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?

A9 Please see page 9, second alinea:
“The subject with calcium scores <10, a positive exercise test and obstructive CAD was a non-diabetic, male 56-year old subject, a past smoker, who underwent a revascularization procedure for a left main stenosis.”

Q10 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?

A10 There were no inconclusive findings.

Q11 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.

A11 Unfortunatly, FFRs were not systematically registered.

Page 7, first alinea:
“Decisions to perform a revascularization procedure were taken by the Thoraxcenter multidisciplinary heart team. In case of obstructive CAD (≥50% luminal stenosis), either MPS, or fractional flow reserve (FFR) measurement [30,31] was performed to guide the decision for a revascularization procedure. An FFR <0.75 was an indication for a revascularization procedure.”

Page 12, remarks and limitations section:
“Unfortunately, individual FFR values were not registered.”

Q12 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.

A12 Please see Limitations section, on page 12:

“With regard to the exercise test, information on the Duke score and ST-T hysteresis were not measured.”

Q13 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.

A13 Figure 1 is changed accordingly in the revised manuscript.

Q14 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.

A14 We have changed the references according to your suggestions.