PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Prevalence of Coronary Artery Calcification in a Non-Specific Chest Pain Population in Emergency and Cardiology Departments compared to the Background Population – a Prospective Cohort Study in Southern Denmark with 12-month Follow-up of Cardiac Endpoints.
AUTHORS	Ilangkovan, Nivethitha; Mogensen, Christian; Mickley, Hans; Lassen, Annmarie; Lambrechtsen, Jess; Sand, Niels Peter; Albiniussen, Rasmus; Byg, Jorgen; Hald, Flemming; Grønhøj, Mette; Diederichsen, Axel

VERSION 1 – REVIEW

REVIEWER	U. Joseph Schoepf Medical University of South Carolina Heart & Vascular Center, Ashley River Tower 25 Courtenay Drive, MSC 226, Charleston, SC 29425 United States of America
REVIEW RETURNED	14-Jul-2017

GENERAL COMMENTS	Synopsis: The study described in this manuscript aimed to examine the prevalence of coronary artery calcification and frequency of cardiac events in a cohort of non-specific chest pain (NSCP) patients (an acute admission for chest pain and discharged without an obvious reason for the chest pain) compared with a background control population. It was designed as a double-blinded prospective study that included 229 NSCP patients and 722 control subjects who underwent non-contrast CT scans with a CAC score. They found no significant difference between the prevalence of CAC and a good prognosis for NSCP patients during a one year follow up period. General comments: Although the authors describe an interesting topic, overall, this manuscript lacks proper structure and a linguistic review is recommended. Major Strengths: Large sample size from multiple centers. Interesting topic. Major Weaknesses: Different data gathering methods were used in both populations. It uses only absolute values for CAC and does not include any information about risk categories and risk stratification groups. The data on CAC score in different subgroups is not corrected for

	confounders. Not all statements from different sections of the manuscript support each other. Specific Comments Introduction: Clear and compact introduction. However, the introduction is clearly focused on European data. Perhaps adding prevalence values and findings from US studies would strengthen the importance. Materials and Methods: Page 14,l4-In the introduction, it is mentioned that up to 20% of CAD patients do not have any traditional risk factors, however, one of the inclusion criterion is: known with one risk factor of CAD. Why not include patients without risk factors? Page 14,l14- It seems like it would be more logical to exclude any patients with a previous history of CAD. Page 14,l41- More information about previous smoking history would be interesting. For example, if you have the appropriate information, current smoker vs. past smoker, pack years, etc. Page 15, l30- "reference til Agatston score," is this a missing reference? If not, please re-phrase. Page 15, l32- "correlation was 99%." What sort of correlation? What is the correlation coefficient? Does 99% reflects the observer agreement rather than correlation? Page 16, l45- "age was non-parametric" should be changed to "age was not normally distributed." Please revise the statistical analysis paragraph, it is cluttered and difficult to read. Line 35-40 and line 50-51 are similar other than the fact that they are for different groups. Please merge these statements. Analyzing calcium score per factor between the two populations is not relevant, it says nothing about the influence of a combination of factors on the CAC score (table 3). Patients in the age group of 60-70 years have a higher calcium score, however, they may also have a higher prevalence of risk factors such as HTN or HLD. If you want to address anything regarding association, please use an appropriate statistical model. I would also recommend adding data about the actual risk stratification and risk groups in comparison to using only absolute values of CAC. Results: In addition to table 3, an overview table with overall CAC scores per group would be appreciated. Rather than comparing absolute values of CAC, why not compare risk categories and differences in risk stratifications, as this can actually have a clinical impact? Indeed, performing a regression analysis to correct for different factors is appropriate; however, it would be interesting to test which of the factors have the most influence on the CAC. Rather than reporting the CAC per individual factor (table 1), an overview regarding the general impact of specific combinations of factors/the attribution of age on the difference in CAC score between the two populations would be interesting. Please be consistent in naming the populations. Currently, it switches between NSCP/study population and background/DanRisk population. Please provide data regarding the radiation dose given to the patient

	by the CT acquisition. Discussion: Page 24, l42; This sentence lacks a conclusion, please add. Page 25, l12; It is mentioned that both patients have more than one risk factor. Why is this not taken into consideration during your statistical analysis? If you perform a multivariate logistic regression, give the beta values for each factor and add whether a combination of factors has an influence. If you insist on reporting CAC scores for each factor separately, I would recommend adding the number of risk factors as a factor in this list. Page 25, l27- "However, the higher prevalence of CAC in the NSCP population…." In the results and conclusion, you state that CAC prevalence does not differ between the NSCP population and the background population. Page 25, l32- What is the consequence of the referenced study and the connection to the results reported in this manuscript? Page 25, l48- It is mentioned that patients without risk factors are excluded in order to exclude very low risk patients. However, as correctly stated in the introduction, 20% of CAD patients do not have any risk factors. Inclusion of this group of very low risk patients could add extra value to your conclusions. Page 25, l53; It is mentioned that one of the limitations to the study is the age selection criteria. Please explain why a comparable age range between the DanRisk and the NSCP population was not chosen. Why do you conclude that CAC in an older population is not useful? Please add some references about the accuracy of self-reported data as used in the NSCP population and what the expected effect is on the study results. Please add information addressing the effect of different scanners and different scan protocols used by the different centers. Please add information about the effect of the added radiation dose. Also, it would be interesting to see if there were any incidental findings in the NSCP population. References: OK Tables and Figures: I recommend switching the order of figure 1 and figure 2 and table 2. Table 1: caption: proporiotions□ proportion Add a caption to table 4 to help further explain the results. Table 5: I'm assuming the study population is the included NSCP population? Again, please be consistent in naming the populations. I would recommend deleting this table because all the information is already in the text and other tables.

REVIEWER	A/Prof Christian Hamilton-Craig Heart & Lung Institute, Prince Charles Hospital University of Queensland, Brisban
REVIEW RETURNED	10-Aug-2017

GENERAL COMMENTS	Prospective cohort study of patients discharged from ED with non-specific (ie undifferentiated) chest pain. The title I find potentially misleading

	"Non contrast cardiac CT scan as a risk stratification tool in non-specific chest pain patients" implies that the non-contrast CAC score was used to risk-stratify patients presenting with chest pain. This is not the case; the score was used after the discharge, and this study investigates the prevalence of coronary artery calcification in patients with NSCP discharged from ED. It does not "risk stratify" them at either the index admission, or longterm as the event rates and numbers are insufficiently powered to draw any conclusions (see MESA trial for numbers needed to screen to show outcomes with CAC scoring over 10 years). Therefore, the title should be amended to reflect the observations in the study. Importantly, the discussion correctly identifies that "The use of cardiac CT scan for CAC appears to be of limited value in the setting of patients with NSCP" . This is a more potent finding, and merits rethinking how the Title and Abstract are worded, particularly given the original NICE CG95 guidlines which recommended CAC scoring in chest pain patient (with no evidence to support this claim). This is a strong negative finding, and the authors could make more of this, which would make the manuscript more relevant and publishable. Consider a title such as "Negative contribution of con-contrast coronary calcium scoring in chest pain presentations - a prospective cohort study" , or something similar. The Abstract conclusion does not represent this finding at all, and should be reworded to reflect the main finding of this paper that CAC does NOT add value in NSCP - this is a useful finding! "Conclusion: The prevalence of CAC is comparable with the background population, and the prognosis for NSCP patients during one year follow up is excellent" is not really supported by the data, and authors should consider rewording to focus on the important message that CAC does NOT help in NSCP. The main manuscript conclusion should also be altered to re-focus the "take home message" of this study. inclusion criteria should specify "high sensitivity troponin" , as discussed later. For patients imaged using Siemens FLASH the scan mode needs to be specified - was it high pitch Flash scanning, or sequential prospective axial scan? High pitch (3.4) may over-estimate CAC. The clinical endpoints of " cardiac death, ventricular tachycardia (VT), non-fatal MI, coronary revascularization and unstable angina" are expected to be low in undifferentiated CP with negative hsTn,and therefore the study is underpowered to show any differences in events. Thus, it could be reframed as an observational study on the prevalence of CAC in patients discharged with undifferentiated CP; this does provide additional information, as these patients are not usually offered athersclerosis imaging (and this provides opportunity for downstream medical therapy and risk mitigation) The Sample Size calculation does not really make sense; the description is calculating the expected prevalence (vs what was observed in the study), the expected power of 80% was to detect what?

	Results are analysed on CAC>0. Whilst this is of interest, the majority of risk with CAC is in CAC>100; the number of patients with CAC>100 should be shown. Both events in follow up were CAC>100 (349 and 2595) Table 2 " blod pressure" should be "blood pressure" HDL cholesterolmmol/L should be HDL cholesterol mmol/L Overall I think this is a useful study, but the authors should be encouraged to "reframe" the main thrust of the paper (both in abstract and main body) to be show the negative contribution of CAC in NSCP patients, and reinforce the message (as in SCCT guidelines) that chest pain in ER should receive contrast CCTA and that CAC alone does not risk reclassify these patients adequately. (incidentally our institution has recently had a series of CAC=0 patients with significant obstructive non-calcified plaque presenting to ED and receiving CTCA; this occurrence avery real phenomenon, and demonstrates the pressing need to image the coronary lumen as well as calcium in chest pain patients, not just CAC alone which can falsely reassure; the CAC=0 with stenosis >70% should be discussed in this manuscript also)

REVIEWER	Florian Andre University of Heidelberg, Department of Cardiology, Angiology and Pneumology, Germany
REVIEW RETURNED	29-Aug-2017

GENERAL COMMENTS	In the reviewed manuscript, the authors assess the prevalence of coronary calcifications and adverse events in patients with non-specific chest pain. The comparison groups are a reference population of the Danish Risk Score study and a group of patients who were directly referred to cardiac imaging testing after the discharge. The topic of the study is of clinical interest, the study design is sound and the manuscript is well written. Yet, we would like the authors to address several issues prior to publication. The crucial point of this interesting study is the definition of the NSCP group. Thus, I would like the authors to explain more in detail, how this population was drawn. Several points might be helpful: - How were chest pain and non-specific chest pain defined? This is of importance since patients with obvious reasons for chest pain were excluded. Did the NSCP patients have pain which might resemble a cardiovascular origin or was in mostly atypical chest pain (e.g. suggestive for musculoskeletal origin)? - Where any other tests than ECG and biomarkers applied in the ED and CD (e.g. chest x-ray, echocardiography, treadmill test)? - Furthermore, it is of great interest on which basis patients were directly referred to cardiac imaging testing after discharge. Although this point is addressed in the limitation parts, I would ask the authors to provide further information if possible. Otherwise, it may be difficult to understand what kind of patients form the NSCP group. Minor points - The title of the manuscript is a little bit misleading since cardiac CT was not applied as a risk stratification tool in this study. - In the introduction, the authors state, that a significant proportion of

	patients with CAD do not have any traditional risk factors. Yet, the inclusion criteria requested at least one risk factor. I would like the authors to explain why this inclusion criterion was chosen (e.g. radiation savings, low pretest probability). - The inclusion criteria include normal troponin values and the cutoff for troponin I is given with <30 ng/ml. However, the decision limit for myocardial infarction was set at ≥25 ng/l. I would like the authors to comment on that. Furthermore, it is unclear, of only one troponin value was obtained or if serial measurements as recommended in the current ESC guidelines for most of the cases were done. - I suppose, the upper reference limit for troponin T using Roche elecsys is 14 pg/ml and not 14 ng/ml as given in the inclusion criteria. - In the inclusion criteria, smoking is defined as present or former smoker. However, the definition part states "smoking was defined as current smoker". Please clarify this discrepancy. - Why did the authors define a positive family history without consideration of age? - I would like the authors to give a more detailed explanation on the calcium score measurements. Which software was used and which threshold value was applied? Did they take the different slices thicknesses (0.5 mm vs. 2.5 mm vs 3.0 mm) into consideration? Were any iterative reconstruction algorithms (e.g. AIDR3D or ADMIRE) applied which might have influenced the measurements? - The correlation between the first author and the radiographers with respect to calcium scoring measurements should be rather given in the results than in the methods part. In addition, I would like the authors to explain how the correlation was assessed (number of subjects, statistical test). - The authors give the manufacturer details for the dual-source CT scanners. I would ask the authors to do the same for the GE and Toshiba scanners. - The sample size calculation resulted in a number of 238 patients and the enrollment number in the clinical trial form is 240 patients. Yet, the study population consisted of only 229 patients. I would like the authors to comment on that. - The statistical analysis part might be a shortened by just stating which test was used for which statistical question. Please give the test used for the assessment of normal distribution. - Why did the authors assess the differences between the participating hospitals in tables 3 and 4? - I would ask the authors to give the p-values for table 5. - Do the authors have any information on further cardiac testing in the NSCP population which was initiated by third parties (e.g. general practitioners)? - Although it may be beyond the scope of this manuscript, I wonder, if the calcium scoring scans revealed any non-coronary pathologies which could be accounted for the chest pain. - The authors state, that the two subjects with adverse events had high Agatston scores. I would like the authors to give the respective percentiles. - There are several typing, grammatical and formatting errors (e.g. page 2 line 17: "cohort"; page 3 line 47: "criteria […] is"; page 6 line 48: "compromised"; page 7 line 43: "p=0.0.001", figure 1: "moykardie"). Thus, I would recommend revising the manuscript thoroughly. - Please give the full term before using abbreviations (e.g. IHD).

VERSION 1 – AUTHOR RESPONSE

BMJ Open access

Manuscript ID bmjopen-2017-018391

Dear Editor,

Thank you for giving us the opportunity to revise our manuscript. Below you will find a response to each of the suggested revisions and changes made. All changes in the manuscript are highlighted with yellow markings.

On behalf of the authors, Nivethitha Ilangkovan.

Editorial Requirements:
- Please revise your title to state the research question, study design, and setting (location). This is the preferred format for the journal.
The title has been changed according to the requirements mentioned above.

- Please ensure that each bullet point in the Strengths and Limitations section is a full sentence.
This has been done.

Reviewer: 1
Reviewer Name: U. Joseph Schoepf
Institution and Country: Medical University of South Carolina, Heart & Vascular Center, Ashley River Tower
25 Courtenay Drive, MSC 226, Charleston, SC 29425, United States of America
Please state any competing interests: Dr. U. Joseph Schoepf is a consultant for and/or receives institutional research support from Astellas, Bayer, GE, Guerbet, and Siemens Healthineers

Please leave your comments for the authors below
Synopsis:
The study described in this manuscript aimed to examine the prevalence of coronary artery calcification and frequency of cardiac events in a cohort of non-specific chest pain (NSCP) patients (an acute admission for chest pain and discharged without an obvious reason for the chest pain) compared with a background control population. It was designed as a double-blinded prospective study that included 229 NSCP patients and 722 control subjects who underwent non-contrast CT scans with a CAC score. They found no significant difference between the prevalence of CAC and a good prognosis for NSCP patients during a one year follow up period.

General comments:
Although the authors describe an interesting topic, overall, this manuscript lacks proper structure and a linguistic review is recommended.

Major Strengths:
Large sample size from multiple centers. Interesting topic.

Major Weaknesses:
Different data gathering methods were used in both populations. It uses only absolute values for CAC and does not include any information about risk categories and risk stratification groups. The data on

CAC score in different subgroups is not corrected for confounders. Not all statements from different sections of the manuscript support each other.
We agree, and have made significant changes in the manuscript.

Specific Comments

Introduction:
Clear and compact introduction. However, the introduction is clearly focused on European data. Perhaps adding prevalence values and findings from US studies would strengthen the importance.
We have included references in the introduction which are based on US studies. Page 3.

Materials and Methods:
Page 14,l4-In the introduction, it is mentioned that up to 20% of CAD patients do not have any traditional risk factors, however, one of the inclusion criterion is: known with one risk factor of CAD. Why not include patients without risk factors?
This is certainly a good idea. However due to ethical consideration and logistic problems we had to have this inclusion criteria. The inclusion criterion does increase the pretest probability for presence of CAC and an event at follow-up, thus we believe we are able to answer the question: is CAC score useful to risk stratify NSCP patients compared with the background population.

Page 14,l14- It seems like it would be more logical to exclude any patients with a previous history of CAD.
We apologize, the clumpsy wording in this paragraph. We excluded everyone with MI, previous percutaneous intervention and coronary bypass grafting. Page 5.

Page 14,l41- More information about previous smoking history would be interesting. For example, if you have the appropriate information, current smoker vs. past smoker, pack years, etc.
Unfortunately, we do not know pack year, but smoking status has been further elaborated in Table 2 according to present smoker, previous smoker and non smoker.

Page 15, l30- "reference til Agatston score," is this a missing reference? If not, please re-phrase.
Sorry, this was a missing reference and has been added. P. 6.

Page 15, l32- "correlation was 99%." What sort of correlation? What is the correlation coefficient? Does 99% reflects the observer agreement rather than correlation?
We used the Pearson's correlation coefficient. The manuscript has been rephrased accordingly. P.7.

Page 16, l45- "age was non-parametric" should be changed to "age was not normally distributed."
The statistical paragraph has been changed significantly.

Please revise the statistical analysis paragraph, it is cluttered and difficult to read. Line 35-40 and line 50-51 are similar other than the fact that they are for different groups. Please merge these statements.
Analyzing calcium score per factor between the two populations is not relevant, it says nothing about the influence of a combination of factors on the CAC score (table 3). Patients in the age group of 60-70 years have a higher calcium score, however, they may also have a higher prevalence of risk factors such as HTN or HLD. If you want to address anything regarding association, please use an appropriate statistical model.
I would also recommend adding data about the actual risk stratification and risk groups in comparison to using only absolute values of CAC.
We apologies for this clumsy statistical paragraph, and it now been prepare thoroughly.

Concerning Table 3, we do agree. Association between risk factors and CAC scores is not the topic, and accordingly the table is omitted from the current manuscript. Instead we have added the CAC score categories to Table 2.

Results:
In addition to table 3, an overview table with overall CAC scores per group would be appreciated. Rather than comparing absolute values of CAC, why not compare risk categories and differences in risk stratifications, as this can actually have a clinical impact? Indeed, performing a regression analysis to correct for different factors is appropriate; however, it would be interesting to test which of the factors have the most influence on the CAC. Rather than reporting the CAC per individual factor (table 1), an overview regarding the general impact of specific combinations of factors/the attribution of age on the difference in CAC score between the two populations would be interesting.
As mentioned above, we have omitted Table 3, and added the CAC score categories to Table 2. Additionally, we have performed a supplementary regression analysis to test which of the risk factors have the most influence on CAC. All of the traditionally risk factors are of importance, and this is accordance with the general view.
We analysed the CAC prevalence with a multi logistic regression as suggested and gave consideration to all risk factors (gender, age, smoking, hypertension, hypercholesterolemia, diabetes mellitus, body mass index and family history of cardiovascular disease). As we adjusted for several more risk factors this has changed the odds ratio to 0.9. However, the odds ratio for the prevelance of CAC (0 Au versus >0AU) is still non-significant. We conducted the same analysis for <100 AU vs >=100 AU. In this case the odds ratio was 1.0 (95% CI: 0.6-1.5) p value=0.826. Finally, we did an analysis with CAC as a categorical variable (CAC=0, 1-99 and >=100 AU respectively). The odds ratio for NSCP patients was 0.9 (95% CI: 0.7-1.3) p value=0.675 compared to the background population. Although the aim of this manuscript was to compare the prevalence of CAC (CAC= 0AU vs CAC>0AU), we have added the results of CAC <100 versus >=100.

Multiple logistic regression for CAC prevalence in NSCP patients compared to background population

CAC	OR	p-value	95% CI
>0AU	0.9	0.546	0.6-1.3
>100 AU	1.0	0.826	0.6-1.5

P.9.

Please be consistent in naming the populations. Currently, it switches between NSCP/study population and background/DanRisk population.
We do agree, and we have corrected accordingly.

Please provide data regarding the radiation dose given to the patient by the CT acquisition.
Unfortunately, we don't know the exact radiation dose for study patients. However, we have the data from the DanRisk study, and here the dose length product (DLP) was from 15 to 303. The mean was 68 DLP, equivalent to 1 mSV. We used similar CT protocols for this study and hence estimate the same radiation dose.

Discussion:
Page 24, l42; This sentence lacks a conclusion, please add.
We have added a period.

Page 25, l12; It is mentioned that both patients have more than one risk factor. Why is this not taken into consideration during your statistical analysis? If you perform a multivariate logistic regression, give the beta values for each factor and add whether a combination of factors has an influence. If you insist on reporting CAC scores for each factor separately, I would recommend adding the number of risk factors as a factor in this list.

We do agree, but the study is too small to conclude on the value of the individually risk factors and the CAC score on events. What we can conclude is that there seems to be no difference among NSCP patients and the background population. Additionally as suggested by the review'er, we have made major revisions of the statistical paragraph and the result section.

Page 25, l27- "However, the higher prevalence of CAC in the NSCP population…." In the results and conclusion, you state that CAC prevalence does not differ between the NSCP population and the background population.
Sorry about this mistake, you are right. We found a non-significant higher prevalence. Also after stratification there were no difference, thus we have deleted this confusing sentence.

Page 25, l32- What is the consequence of the referenced study and the connection to the results reported in this manuscript?
We have chosen to delete this reference. Even though, it was interesting, we can see it lacks association with the rest of the discussion section.

Page 25, l48- It is mentioned that patients without risk factors are excluded in order to exclude very low risk patients. However, as correctly stated in the introduction, 20% of CAD patients do not have any risk factors. Inclusion of this group of very low risk patients could add extra value to your conclusions.
As outlined above, we understand this perspective and agree that it could have added useful information. However, at this point we cannot change the criteria we used during the inclusion.

Page 25, l53; It is mentioned that one of the limitations to the study is the age selection criteria. Please explain why a comparable age range between the DanRisk and the NSCP population was not chosen. Why do you conclude that CAC in an older population is not useful?
Our focus were from the very beginning the middle-aged, since in this age range the calcifications are developing. After reconsidering we have deleted this sentence, since we don't find this as an important limitation. Concerning the different ages in the two cohorts we were limited that the DanRisk study only included 50 and 60 years old people.

Please add some references about the accuracy of self-reported data as used in the NSCP population and what the expected effect is on the study results.
This has been done. P.11.

Please add information addressing the effect of different scanners and different scan protocols used by the different centers.
This has been done. P.12.

Please add information about the effect of the added radiation dose. Also, it would be interesting to see if there were any incidental findings in the NSCP population.
Unfortunately, we don't know the exact radiation dose for study patients. However, the background population dose is known to be 15 .303 dose length product (DLP). Mean 68 DLP and equivalent to 1 mSV. We used similar CT protocols for this study and hence estimate the same radiation dose.

References:
OK

Tables and Figures:
I recommend switching the order of figure 1 and figure 2 and table 2.
We understand your point; currently we did not change anything.

Table 1: caption: proporiotions proportion
This has been changed, and the entire manuscript has been corrected by a translator

Add a caption to table 4 to help further explain the results.
Table 5: I'm assuming the study population is the included NSCP population? Again, please be consistent in naming the populations. I would recommend deleting this table because all the information is already in the text and other tables.
Tables 4 and 5 have been deleted and the content included in result section. P.9.

Reviewer: 2
Reviewer Name: A/Prof Christian Hamilton-Craig
Institution and Country: Heart & Lung Institute, Prince Charles Hospital, University of Queensland, Brisbane, Australia
Chair, SCCT IRC Australia-NZ.
Please state any competing interests: None declared

Please leave your comments for the authors below
Prospective cohort study of patients discharged from ED with non-specific (I e undifferentiated) chest pain.

The title I find potentially misleading
"Non contrast cardiac CT scan as a risk stratification tool in non-specific chest pain patients" implies that the non-contrast CAC score was used to risk-stratify patients presenting with chest pain. This is not the case; the score was used after the discharge, and this study investigates the prevalence of coronary artery calcification in patients with NSCP discharged from ED. It does not "risk stratify" them at either the index admission, or longterm as the event rates and numbers are insufficiently powered to draw any conclusions (see MESA trial for numbers needed to screen to show outcomes with CAC scoring over 10 years).
Therefore, the title should be amended to reflect the observations in the study. Importantly, the discussion correctly identifies that "The use of cardiac CT scan for CAC appears to be of limited value in the setting of patients with NSCP". This is a more potent finding, and merits rethinking how the Title and Abstract are worded, particularly given the original NICE CG95 guidelines which recommended CAC scoring in chest pain patient (with no evidence to support this claim). This is a strong negative finding, and the authors could make more of this, which would make the manuscript more relevant and publishable.
Consider a title such as
"Negative contribution of con-contrast coronary calcium scoring in chest pain presentations - a prospective cohort study" , or something similar.
We agree, the title could be misleading, and according to the comments from the Editor, the title has been changed to provide information about the research question, study design and setting.

The Abstract conclusion does not represent this finding at all, and should be reworded to reflect the main finding of this paper that CAC does NOT add value in NSCP - this is a useful finding!
"Conclusion: The prevalence of CAC is comparable with the background population, and the prognosis for NSCP patients during one year follow up is excellent" is not really supported by the data, and authors should consider rewording to focus on the important message that CAC does NOT help in NSCP.
The main manuscript conclusion should also be altered to re-focus the "take home message" of this study.
Conclusions in both abstract and main manuscript have been altered as suggested.

Inclusion criteria should specify "high sensitivity troponin" , as discussed later.

This has been corrected p.4.

For patients imaged using Siemens FLASH the scan mode needs to be specified - was it high pitch Flash scanning, or sequential prospective axial scan? High pitch (3.4) may over-estimate CAC.
At all sites we performed a sequential prospective scan. This has been added. P.6.

The clinical endpoints of " cardiac death, ventricular tachycardia (VT), non-fatal MI, coronary revascularization and unstable angina" are expected to be low in undifferentiated CP with negative hsTn, and therefore the study is underpowered to show any differences in events. Thus, it could be reframed as an observational study on the prevalence of CAC in patients discharged with undifferentiated CP; this does provide additional information, as these patients are not usually offered athersclerosis imaging (and this provides opportunity for downstream medical therapy and risk mitigation)
We agree, and this has been added to the Limitation section. P.11.

The Sample Size calculation does not really make sense; the description is calculating the expected prevalence (vs what was observed in the study), the expected power of 80% was to detect what?
We agree, and this section has been revised and added information. P.7.

Results are analysed on CAC>0. Whilst this is of interest, the majority of risk with CAC is in CAC>100; the number of patients with CAC>100 should be shown.
Both events in follow up were CAC>100 (349 and 2595)
We have included further information of the prevalence of CAC >100 AU.

Table 2 " blod pressure" should be "blood pressure"
OK

HDL cholesterolmmol/L should be HDL cholesterol mmol/L
OK

Overall I think this is a useful study, but the authors should be encouraged to "reframe" the main thrust of the paper (both in abstract and main body) to be show the negative contribution of CAC in NSCP patients, and reinforce the message (as in SCCT guidelines) that chest pain in ER should receive contrast CCTA and that CAC alone does not risk reclassify these patients adequately. (incidentally our institution has recently had a series of CAC=0 patients with significant obstructive non-calcified plaque presenting to ED and receiving CTCA; this occurrence avery real phenomenon, and demonstrates the pressing need to image the coronary lumen as well as calcium in chest pain patients, not just CAC alone which can falsely reassure; the CAC=0 with stenosis >70% should be discussed in this manuscript also
This is very interesting and important knowledge. However, it is outside the scope of the topic as we did not compare CAC vs. contrast CCTA. Hence, this statement might be beyond what this study demonstrates.

Reviewer: 3
Reviewer Name: Florian Andre
Institution and Country: University of Heidelberg, Department of Cardiology, Angiology and Pneumology, Germany
Please state any competing interests: None declared.

Please leave your comments for the authors below
In the reviewed manuscript, the authors assess the prevalence of coronary calcifications and adverse events in patients with non-specific chest pain. The comparison groups are a reference population of

the Danish Risk Score study and a group of patients who were directly referred to cardiac imaging testing after the discharge.
The topic of the study is of clinical interest, the study design is sound and the manuscript is well written. Yet, we would like the authors to address several issues prior to publication.

The crucial point of this interesting study is the definition of the NSCP group. Thus, I would like the authors to explain more in detail, how this population was drawn. Several points might be helpful:
- How were chest pain and non-specific chest pain defined? This is of importance since patients with obvious reasons for chest pain were excluded. Did the NSCP patients have pain which might resemble a cardiovascular origin or was in mostly atypical chest pain (e.g. suggestive for musculoskeletal origin)?
We included all patients with any kind of chest pain, and an acute contact to emergency department and with the following discharge diagnosis codes ICD codes: DR072/DR073/DR034/DR035.

- Where any other tests than ECG and biomarkers applied in the ED and CD (e.g. chest x-ray, echocardiography, treadmill test)?
Chest x-ray, CT scans, echocardiography and other diagnostic test during the admission were applied at the sole discretion of the attending physician, but not used in this study. This has been added to manuscript. P.4.

- Furthermore, it is of great interest on which basis patients were directly referred to cardiac imaging testing after discharge. Although this point is addressed in the limitation parts, I would ask the authors to provide further information if possible. Otherwise, it may be difficult to understand what kind of patients form the NSCP group.
This has been further elaborated in the manuscript in the study design section. P.4

Minor points
- The title of the manuscript is a little bit misleading since cardiac CT was not applied as a risk stratification tool in this study.
The title has been changed to provide information about the research question, study design and setting.

- In the introduction, the authors state, that a significant proportion of patients with CAD do not have any traditional risk factors. Yet, the inclusion criteria requested at least one risk factor. I would like the authors to explain why this inclusion criterion was chosen (e.g. radiation savings, low pretest probability).
Even though, 20% of patients with CAD do not have any traditional risk factors, the risk of a clinical event is more likely in a population with risk factors than without as previous studies have shown. However, we would like to include patients without risk factors, but we had to due to ethical consideration and logistic problems.

- The inclusion criteria include normal troponin values and the cutoff for troponin I is given with <30 ng/ml. However, the decision limit for myocardial infarction was set at ≥25 ng/l. I would like the authors to comment on that. Furthermore, it is unclear, of only one troponin value was obtained or if serial measurements as recommended in the current ESC guidelines for most of the cases were done.
This was a typing error and has been corrected to 25 ng/L.
Some patients had a single troponin measurement while others had serial. This was an individual assessment by the treating physician. We chose to exclude everyone with an increased troponin measured above the cut- off point.

- I suppose, the upper reference limit for troponin T using Roche elecsys is 14 pg/ml and not 14 ng/ml as given in the inclusion criteria.
This has been corrected to ng/L. Thank you.

- In the inclusion criteria, smoking is defined as present or former smoker. However, the definition part states “smoking was defined as current smoker”. Please clarify this discrepancy.
Unfortunately, we do not know pack year, but smoking status has been further elaborated in Table 2 according to present smoker, previous smoker and non smoker.

- Why did the authors define a positive family history without consideration of age?
This was a mistake we performed in the very beginning of the study, however presently we are unable to make adjustments. This is a limitation, and had been described in the Limitation section.

- I would like the authors to give a more detailed explanation on the calcium score measurements. Which software was used and which threshold value was applied? Did they take the different slices thicknesses (0.5 mm vs. 2.5 mm vs 3.0 mm) into consideration? Were any iterative reconstruction algorithms (e.g. AIDR3D or ADMIRE) applied which might have influenced the measurements?
We used the vendors standard software accompanied with the CT scanner, and the threshold was 130 Hounsfield Units, as recommended by Agatston. We have previously tested different slice thicknesses, and we found minor differences (unpublished data), but in this study we did not make an effort to analyze this subject. More importantly is the tube voltage, and this was kept uniform.

- The correlation between the first author and the radiographers with respect to calcium scoring measurements should be rather given in the results than in the methods part. In addition, I would like the authors to explain how the correlation was assessed (number of subjects, statistical test).
We used the Pearson’s correlation coefficient and compared CAC in 52 subjects. The sentence has been moved and the missing information has been added as suggested. P.9.

- The authors give the manufacturer details for the dual-source CT scanners. I would ask the authors to do the same for the GE and Toshiba scanners.
We apologize if we don’t understand the question, but we believe the required information is in the manuscript. P.6

- The sample size calculation resulted in a number of 238 patients and the enrollment number in the clinical trial form is 240 patients. Yet, the study population consisted of only 229 patients. I would like the authors to comment on that.
Unfortunately, we had to exclude some of the patients after they had been through the CT scan due to presence of exclusion criteria like: missing information and referred for further testing at the index admission.

- The statistical analysis part might be a shortened by just stating which test was used for which statistical question. Please give the test used for the assessment of normal distribution.
We have rewritten the statistical paragraph, and included the extra information. P.7

- Why did the authors assess the differences between the participating hospitals in tables 3 and 4?
This has been removed as we understand this was unnecessary information.

- I would ask the authors to give the p-values for table 5.
We have removed the tables from the manuscript, and added the results including p-values to the manuscript

- Do the authors have any information on further cardiac testing in the NSCP population which was initiated by third parties (e.g. general practitioners)?
Unfortunately we do not.

- Although it may be beyond the scope of this manuscript, I wonder, if the calcium scoring scans revealed any non-coronary pathologies which could be accounted for the chest pain.
Interesting subject, but the scans were not written by radiologists.

- The authors state, that the two subjects with adverse events had high Agatston scores. I would like the authors to give the respective percentiles.
The female patient aged 64 years had a CAC score at 349, and this is at the percentile 94%, while the male patient aged 60 had a CAC score at 2595, and this is at the percentile 99%. This was based on MESA CAC calculator (https://www.mesa-nhlbi.org/calcium/input.aspx).

- There are several typing, grammatical and formatting errors (e.g. page 2 line 17: “cohort”; page 3 line 47: “criteria […] is”; page 6 line 48: “compromised”; page 7 line 43: “p=0.0.001”, figure 1: “moykardie”). Thus, I would recommend revising the manuscript thoroughly.
- Please give the full term before using abbreviations (e.g. IHD).
We apologise and the manuscript has been corrected by a translator.

VERSION 2 – REVIEW

REVIEWER	U. Joseph Schoepf Medical University of South Carolina
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	Synopsis: The study described in this manuscript aimed to examine the prevalence of coronary artery calcification and frequency of cardiac events in a cohort of non-specific chest pain (NSCP) patients (an acute admission for chest pain and discharged without an obvious reason for the chest pain) compared with a background control population. It was designed as a double-blinded prospective study that included 229 NSCP patients and 722 control subjects who underwent non-contrast CT scans with a CAC score. They found no significant difference between the prevalence of CAC and a good prognosis for NSCP patients during a one year follow up period. Title: please correct the spelling error in the title- on-specific should be non-specific. Materials and Methods: The statistical paragraph has undergone significant changes. An expected prevalence of 62% was stated based on a symptomatic population with a prevalence of 79%. Is the 62% based on other studies or a pilot study? If not, is this number just randomly chosen? Why not do an ad-hoc sample size calculation? Results: Please add a table with the B coefficients of each variable tested in the multivariate logistic regression - could be in the supplements. In regression analysis, the regression coefficient for an explanatory variable indicates how much the average value of the outcome variable varies with each unit change in the explanatory variable. The B coefficient, is an estimate and should be accompanied by a confidence interval. Was univariate analysis used to select the appropriate explanatory variables?

	Tables and Figures: Figure legend: fir should be for, please change.

REVIEWER	Florian Andre University of Heidelberg Department of Cardiology, Angiology and Pneumology
REVIEW RETURNED	22-Oct-2017

GENERAL COMMENTS	The authors provide a revised version of their manuscript on the prevalence of CAC in a NSCP population. Especially the focus was shifted from cardiac CT as a risk stratification tool to the assessment of the CAC of NSCP patients compared to a background population. As stated by the authors, the risk stratification at the index contact was very efficient. Thus, the NSCP population is quite similar to the asymptomatic background population with regard to cardiovascular risk factors and shows a low incidence of cardiovascular endpoints. As the CAC score was not different between patients and controls, calcium scoring might not improve risk stratification in this low-risk population. As I noted in the first review, the composition of the NSCP group is a crucial point. Unfortunately, only little data on the initial risk stratification was available since diagnostic tests aside from troponin tests were applied at the discretion of the attending physician. Thus, it remains unclear, based on which factors patients were referred directly to coronary angiography or other non-invasive tests. Nevertheless, the study is of clinical interest as it may reduce useless CT examinations in NSCP patients. I really appreciate the effort of the authors to address the multiple comments of the reviewers and providing a substantially improved manuscript. Thus, there are only a few points to be addressed. In the introduction, the authors state, that the importance of CAC in patients with acute chest pain without MI remains to be investigated, I consider the phrasing a little bit imprecise since the CAC scans were done after the acute presentation of the patients. The authors state, that the wished to examine the frequency of clinical events related to CAC in NSCP patients (p. 3). However, presumably due to the low number of events, the correlation between CAC and endpoints was not statistically assessed in the present study. The ICD codes of the NSCP patients are given. Yet, I assume that a Danish version of the ICD codes was used. I would like to ask the authors to provide the international ICD codes or to specify the diagnoses in the text. As the authors state correctly, the 99th percentile of high-sensitivity troponin T measured by the Roche elecsys system is 14 ng/L. Thus, a value of 14 ng/L is still regarded as normal. I would like to ask the authors, why the decision limit for MI includes the 99th percentile (≥14 ng/L, p. 6). I would like to apologize for the imprecise request regarding the manufacturer details. I just wanted the authors to give place and country for GE and Toshiba as they did for Siemens (Forchheim, Germany).

	As proposed in the first review, I would like to ask the authors to remove the results of the CAC interobserver correlation from the Statistical analysis part (p. 7). The authors give the mean age of the participants and none-participants. As the IQR is given as well, I assume that they give rather the median age (p. 8). The legend of Table 1 states "Values are n (%) or mean ± SD". Yet, the table includes only categorical variable and age which is given with IQR. Furthermore, the "%" letter in the heading might be removed. In Table 2 the p-value regarding the CAC score is given with 0.230. In the text, it is 0.229. I would like the authors to correct one of the values. I assume that in addition to age, gender and cardiovascular risk factors the patient groups (NSCP vs. controls) were applied as independent variables in the multivariate logistic regression model whereas the binary CAC classification was the dependent variable. Is this assumption correct or was the model constructed in another way? Did the authors ensure that the model was not underpowered for the number of independent variables? Furthermore, I would recommend including the results of the supplementary regression analysis (answer to reviewer 1). If the authors do not want to enlarge the results part, they might provide a supplementary table showing the results. The SCCT guideline recommends a CT angiography whereas only a calcium scoring was performed in this study (p. 11). I would recommend to emphasizes this point since the sensitivity and specificity of both techniques differ. Although the manuscript was corrected by a translator, there are several typing and grammatical errors (e.g. on-specific (title), United State (p. 3), measurement … were included (p. 4), slice Thickness (p. 6), compromise vs. comprise (pp. 11 and 12)). Thus, I would ask the authors to perform a thorough review.

VERSION 2 – AUTHOR RESPONSE

Editorial Requirements:
- Please include the study location in the title.
We have added Southern Denmark to the title

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: U. Joseph Schoepf
Institution and Country: Medical University of South Carolina
Please state any competing interests: Dr. U. Joseph Schoepf is a consultant for and/or receives institutional research support from Astellas, Bayer, GE, Guerbet, and Siemens Healthineers.

Please leave your comments for the authors below

Synopsis:
The study described in this manuscript aimed to examine the prevalence of coronary artery calcification and frequency of cardiac events in a cohort of non-specific chest pain (NSCP) patients (an acute admission for chest pain and discharged without an obvious reason for the chest pain) compared with a background control population. It was designed as a double-blinded prospective study that included 229 NSCP patients and 722 control subjects who underwent non-contrast CT scans with a CAC score. They found no significant difference between the prevalence of CAC and a good prognosis for NSCP patients during a one year follow up period.

Title: please correct the spelling error in the title- on-specific should be non-specific.
This has been corrected.

Materials and Methods:
The statistical paragraph has undergone significant changes. An expected prevalence of 62% was stated based on a symptomatic population with a prevalence of 79%. Is the 62% based on other studies or a pilot study? If not, is this number just randomly chosen? Why not do an ad-hoc sample size calculation?
We knew from The DanRisk study (reference 17) that the prevalence in an asymptomatic population was 44%. In a symptomatic population it was demonstrated to be 79%. We expected that the NSCP population would carry a risk profile that was in between a symptomatic higher risk population and the asymptomatic background population. Accordingly we estimated that the prevalence of CAC in the NSCP population would be 62%.

Results:
Please add a table with the B coefficients of each variable tested in the multivariate logistic regression - could be in the supplements. In regression analysis, the regression coefficient for an explanatory variable indicates how much the average value of the outcome variable varies with each unit change in the explanatory variable. The B coefficient, is an estimate and should be accompanied by a confidence interval.
We have performed the supplementary tables.

Was univariate analysis used to select the appropriate explanatory variables?
No, we adjusted for all the traditionally risk factors (gender, age, smoking, hypertension, hypercholesterolemia, diabetes mellitus, body mass index and family history of cardiovascular disease) in the multivariate analysis.

Tables and Figures:
Figure legend: fir should be for, please change.
This has been changed.

Reviewer: 3
Reviewer Name: Florian Andre
Institution and Country: University of Heidelberg, Department of Cardiology, Angiology and Pneumology
Please state any competing interests: None

Please leave your comments for the authors below

The authors provide a revised version of their manuscript on the prevalence of CAC in a NSCP population. Especially the focus was shifted from cardiac CT as a risk stratification tool to the assessment of the CAC of NSCP patients compared to a background population.

As stated by the authors, the risk stratification at the index contact was very efficient. Thus, the NSCP population is quite similar to the asymptomatic background population with regard to cardiovascular risk factors and shows a low incidence of cardiovascular endpoints. As the CAC score was not different between patients and controls, calcium scoring might not improve risk stratification in this low-risk population. As I noted in the first review, the composition of the NSCP group is a crucial point. Unfortunately, only little data on the initial risk stratification was available since diagnostic tests aside from troponin tests were applied at the discretion of the attending physician. Thus, it remains unclear, based on which factors patients were referred directly to coronary angiography or other non-invasive tests. Nevertheless, the study is of clinical interest as it may reduce useless CT examinations in NSCP patients.

I really appreciate the effort of the authors to address the multiple comments of the reviewers and providing a substantially improved manuscript. Thus, there are only a few points to be addressed.

In the introduction, the authors state, that the importance of CAC in patients with acute chest pain without MI remains to be investigated, I consider the phrasing a little bit imprecise since the CAC scans were done after the acute presentation of the patients.
We have changed this sentence to "the clinical importance of CAC in patients with NSCP remains to be investigated."

The authors state, that the wished to examine the frequency of clinical events related to CAC in NSCP patients (p. 3). However, presumably due to the low number of events, the correlation between CAC and endpoints was not statistically assessed in the present study.
We agree, and have rephrased that sentence to "we wished to examine the frequency of clinical cardiac events in NSCP patients during a 12 months follow-up period, and compare these data with the results from the asymptomatic background."

The ICD codes of the NSCP patients are given. Yet, I assume that a Danish version of the ICD codes was used. I would like to ask the authors to provide the international ICD codes or to specify the diagnoses in the text.
We used the International Statistical Classification of Diseases and Related Health Problems 10th Revision (http://apps.who.int/classifications/icd10/browse/2016/en). That has been added to the manuscript.

As the authors state correctly, the 99th percentile of high-sensitivity troponin T measured by the Roche elecsys system is 14 ng/L. Thus, a value of 14 ng/L is still regarded as normal. I would like to ask the authors, why the decision limit for MI includes the 99th percentile (≥14 ng/L, p. 6).
This is a typing error, a Troponin above 14 is considered as the decision limit according to our biochemical departments.

I would like to apologize for the imprecise request regarding the manufacturer details. I just wanted the authors to give place and country for GE and Toshiba as they did for Siemens (Forchheim, Germany).
This has been added

As proposed in the first review, I would like to ask the authors to remove the results of the CAC interobserver correlation from the Statistical analysis part (p. 7).
This has been done.

The authors give the mean age of the participants and none-participants. As the IQR is given as well, I assume that they give rather the median age (p. 8).
We apologies for the confusion. IQR has been changed to 95% CI.

The legend of Table 1 states “Values are n (%) or mean ± SD”. Yet, the table includes only categorical variable and age which is given with IQR. Furthermore, the “%” letter in the heading might be removed.
This has been changed

In Table 2 the p-value regarding the CAC score is given with 0.230. In the text, it is 0.229. I would like the authors to correct one of the values.
This has been done

I assume that in addition to age, gender and cardiovascular risk factors the patient groups (NSCP vs. controls) were applied as independent variables in the multivariate logistic regression model whereas the binary CAC classification was the dependent variable. Is this assumption correct or was the model constructed in another way?
Yes this assumption is correct, and has been clarified in the statistical section.

Did the authors ensure that the model was not underpowered for the number of independent variables? Furthermore, I would recommend including the results of the supplementary regression analysis (answer to reviewer 1). If the authors do not want to enlarge the results part, they might provide a supplementary table showing the results.
As requested by Review’er 1, we have provided a supplementary table with the Beta coefficients

The SCCT guideline recommends a CT angiography whereas only a calcium scoring was performed in this study (p. 11). I would recommend to emphasizes this point since the sensitivity and specificity of both techniques differ.
This has been done.

Although the manuscript was corrected by a translator, there are several typing and grammatical errors (e.g. on-specific (title), United State (p. 3), measurement … were included (p. 4), slice Thickness (p. 6), compromise vs. comprise (pp. 11 and 12)).
Thus, I would ask the authors to perform a thorough review.
The manuscript has been through a thorough review as recommended.

VERSION 3 – REVIEW

REVIEWER	U. Joseph Schoepf, MD Medical University of South Carolina United States
REVIEW RETURNED	05-Jan-2018

GENERAL COMMENTS	All previous comments and recommendations have been addressed accordingly.

REVIEWER	Florian Andre University of Heidelberg, Department of Cardiology, Angiology an Pneumology

REVIEW RETURNED	14-Jan-2018

GENERAL COMMENTS	I would like to thank the authors for the thorough revision of the manuscript. The interoberserver correlation is given twice (Methods and Results). This point should not prolongate the review process and, thus, could be changed during the editorial process.