Author's response to reviews

Title: Differential association between metabolic syndrome and coronary artery disease evaluated with cardiac computed tomography according to the presence of diabetes in a symptomatic Korean population

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Author's response to reviews: see over
On behalf of all the authors, I would like to thank you and the reviewers of *BMC Cardiovascular Disorders* for taking the time and effort to review our manuscript. The invaluable suggestions of the reviewers were well-taken by all of the authors. After going over the reviewers’ comments, my colleagues and I revised the manuscript as recommended. Thus, we are submitting our revised manuscript; the revised parts are marked in red text.
Dear Prof. Niels Wiinberg

Thank you for your invaluable comments.

This interesting study concerning the association between MetS and CAD using non-obstructive and obstructive plaque, and coronary artery calcium score (CACS) >100 according to diabetes status in 2,869 Korean subjects with low to medium a priori probability of ischemic heart, who underwent cardiac CT angiography.

Conclusions: MetS was independently associated with the presence and severity of CAD only in the nondiabetic subjects among the symptomatic Korean population. The subject is of importance and the paper is well written and clear in message. The study was well designed and performed, using state of the art methods.

Specific comments:

Did you use dose modulation?
Did you use Breath Hold?
What was the mean dose of radiation?
In figure 1 and 2, there are missing legends on the y-axis

RE:

Thank you for the good advice.

a) We added the detailed information related to dose modulation, breath hold, and mean dose of radiation in the paragraph regarding MDCT protocol as follow:

Subjects with an initial heart rate ≥65 beats/min before MDCT examination received a single oral dose of 50 mg metoprolol tartrate (Betaloc, Yuhan, Seoul, South Korea) 1 h before CT examination unless beta-adrenergic blocking agents were contraindicated owing to overt heart failure, atrioventricular conduction abnormalities, and bronchial asthma. In patients with atrial fibrillation, patients with a mean heart rate >100
beats/min received beta-adrenergic blocking agents orally 1 h before cCTA. If the mean heart rate remained >100 beats/min at the time of scanning, we withdraw the scan. A contrast-enhanced volume data set was acquired with retrospective electrocardiogram gating without using tube current modulation to allow reconstructions during all phases of the cardiac cycle. In subjects with a mild allergy to the contrast material such as drug eruption or urticaria, we used a prophylactic IV steroid. However, we did not allow a scan for the patients with severe allergic reactions such as shock or laryngeal edema.

Imaging was performed for all the subjects using a 64-slice CT scanner (Sensation 64; Siemens Medical System, Forchheim, Germany). All CT examinations were performed during breath holding in inspiration. Initially, a non-enhanced prospective electrocardiogram-gated scan to evaluate CACS was performed with the following parameters: rotation time of 330 ms, slice collimation of 0.6 mm, slice width of 3.0 mm, tube voltage of 100–120 kV, tube current of 50 mA, and table feed/scan of 18 mm. Thereafter, cCTA was performed using retrospective electrocardiographic gating with the following scan parameters: rotation time of 330 ms, slice collimation of 64 × 0.6 mm, tube voltage of 100–120 kV, tube current of 400–800 mA (depending on patient size), table feed/scan of 3.8 mm, and pitch factor of 0.2. ECG-based tube current modulation was applied to 65% of the R–R interval. A real-time bolus-tracking technique was applied to trigger scan initiation. The total estimated average radiation dose for the multislice CT protocol was 8.8 ± 1.6 mSv. Contrast enhancement was achieved with 60 mL iopamidol (370 mg/mL iodine, Iopamiro; Bracco, Milan, Italy) injected at 5 mL/s, followed by an injection of 30 mL of diluted contrast medium (saline-to-contrast agent ratio, 7:3) and then 30 mL saline at 5 mL/s, with a power injector (Envision CT; Medrad, Indianola, PA) via an antecubital vein. The estimated volume CT dose index (CTDIvol) was recorded for each patient. The product of CTDIvol and scanning length (dose–length product, mGy × cm) was calculated, and effective dose was estimated using a normalization factor for the adult chest (0.017 mSv × mGy⁻¹ × cm⁻¹). Image reconstruction was performed in the scanner workstation using commercially available software (Wizard, Siemens Medical Solutions). Axial images were reconstructed retrospectively at 65% of the R–R interval for each cardiac cycle. If artifacts were present, additional data sets were obtained for various points of the cardiac cycle, and the data set with the minimum artifact was selected for further analysis. The reconstructed image data sets were transferred to an off-line workstation (Aquari-ous Workstation, TeraRecon, Inc., San Mateo, CA). Each lesion identified was examined using maximum intensity projection and multiplanar reconstruction techniques on a short axis and along multiple longitudinal axes. Lesions were classified by the maximal stenosis of luminal diameter observed on any plane.
b) We added legends for the y-axis in Figure 1 and 2.
Reviewer: Thomas B Christophersen

Dear Prof. Thomas B Christophersen

Thank you for your invaluable comments.

Comment No. 1

Background: The background shortly summarizes the underlying issues the authors wish to elucidate and in paragraph 4 the aim of the study is presented. The paragraph starting “Therefore, we evaluated...” could probably be more presentive of the aim, along the line of “In this study, we aim to evaluate the presence.....” in order to more clearly define the aim to the reader. No hypotheses are presented, as this is a descriptive study. (Discretionary Revision)

RE:

We corrected the sentence as follows:

In this study, we aim to evaluate the association between MetS, individual MetS components, and coronary atherosclerosis according to the presence of diabetes in symptomatic Korean subjects who underwent cardiac computed tomographic angiography.

Comment No. 2

Methods-Study Population: The study was a cross-sectional study of 2,869 consecutive patients at a Single Centre in a defined period of time. The patients had a mixture of symptoms potentially cardiac related: typical angina, atypical angina, dyspnea and fatigue. As some, if not all of these symptoms, may be of different genesis (pulmonary, gastrointestinal), it would be helpful in Table 1 to present relevant co-morbidity or alternately to mention this in the discussion. (Discretionary Revision). Exclusion criteriae are presented, however no actual presentation of the number of referred/screened patients as well as the number of patients being excluded, is
reported. If this data is available, then it should be presented. If it is not available, then the three exclusion criteria is not really relevant. What about patients with atrial fibrillation or known allergy to contrast agents? (Major Compulsory Revision).

RE:

Thank you for your detailed advice.

a) All participants had at least one potential cardiac symptom. Thus, we performed cardiac CT examination to identify whether these symptoms were caused by significant coronary problems according to the recommended strategy of coronary artery disease (CAD) evaluation. There might be a number of extra-cardiac problems that also caused these symptoms. However, we did not have the exact and objective information from the extra-cardiac examinations. Thus, we did not provide data on relevant co-morbidities.

b) We revised the paragraph regarding study population as follow:

This was a cross-sectional study analyzing single-center data collected from 3,159 consecutive symptomatic South Korean subjects who underwent cCTA evaluation with 64-slice multidetector computed tomography (MDCT) at Yonsei Cardiovascular Hospital between January 2005 and April 2009. All participants were referred for evaluation of CAD who had at least one of the symptoms, including typical angina, atypical angina, dyspnea, and excessive fatigue, but were not patients with acute coronary syndrome who required emergent coronary intervention or surgery. Subjects who were younger than 30 years (n = 26), or had an estimated modification of diet in renal disease (MDRD) glomerular filtration rate (GFR) <60 mL/min/1.73m² (n = 264) were excluded from the present study according to the study protocol. As a result, 2,869 participants were finally included. All patients provided written informed consent, and ethical approval was obtained from the Institutional Review Board of Severance Hospital, Yonsei University Health System.

c) We added the detailed information on the study protocol relating to patients with atrial fibrillation or known allergy to contrast agents as follow:

In patients with atrial fibrillation, patients with a mean heart rate >100 beats/min received beta-adrenergic blocking agents orally 1 h before cCTA. If the mean heart rate remained >100 beats/min at the time of scanning, we withdraw the scan. A contrast-enhanced volume data set was acquired with retrospective electrocardiogram gating without using tube current modulation to allow reconstructions during all phases of the cardiac cycle. In subjects with a mild allergy to the contrast material such as drug eruption or urticaria, we used a prophylactic IV
steroid. However, we did not allow a scan for the patients with severe allergic reactions such as shock or laryngeal edema.

Comment No. 3

Methods-MDCT protocol and Measurement of coronary parameters: The cardiac CT protocol was well established, starting with a prospectively gated non-contrast scan to evaluated calcium score followed by a contrast enhance scan using retrospective ECG-gating to reconstruct images. Subsequent off-line analyses are well described. The presence of any plaque, presence of any obstructive plaque, and presence of calcium score (using standard Agatston method) was the primary outcome analyzed, secondarily the discrimination between noncalcified and calcified/mixed plaque. The cut-off for calciumscore of >100 for severe calcification was justified by ethnic differences. The cardiac scans were evaluated by 2 experienced cardiac radiologists. However, it is not reported whether or not all scan were evaluated by both readers, independently, and a consensus was reached in case of discrepancies, or the cardiac scans were only described by one of the two available readers. If the later is the case, then some presentation of inter-reader reproducibility should be made in the article. Especially with regards to presence/absence of obstructive disease, but also the presence/absence of non-calcified plaque, this may be problematic (Major Compulsory Revision)

RE:

Thank you for your advice. All cardiac CT images were evaluated by 2 experienced cardiac radiologists (Y.J.K. and B.W.C., who respectively had 6 and 9 years of experience in cardiac CT). According to the protocol of the Department of Radiology in Yonsei Cardiovascular Hospital, cardiac radiologists attend regular conferences to discuss complex or problematic coronary images in order to ensure the most accurate report. If there was disagreement on a case, a joint reading was performed to reach a consensus. We revised the paragraph regarding the measurement of coronary parameters as follow:

All cCTA were evaluated by 2 experienced cardiac radiologists (Y.J.K. and B.W.C., who respectively had 6 and 9 years of experience in cardiac CT). In case of disagreement, a joint reading was performed to reach a consensus.
Comment No. 4

Methods-Statistical Analyses: Standard methods using Student t-test for continuous variables. Were the distribution of these variables Normal? Or would a nonparametric test be more appropriate? (Minor Essential Revision). For the binary/categorical variables chi-square is fine. Univariate and multivariate logistical regression were used to analyse the presence/absence of individual components of metabolic syndrome with regards to the presence/absence of coronary artery disease outcomes individually (presence of plaque, presence of obstructive plaque, calciumscore>100). This is a valid analysis and the sample size is sufficient to support the number of covariates. However, the analysis of the number of MeTS-components (with a numerical range of 1-5) cannot be analysed using a standard logistical regression. Was a more complex model, like a proportional odds model used? And how were the model assumptions checked (Major Compulsory Revision). With regards to the stratification of patient with/without diabetes there may be issues of variable independence and confounding. It is unproblematic when analysing individual MeTS-components association to the outcome, but problems may arise when analysing the presence/absence of MeTS with regards to the outcome variables in the stratified analyses in the presence/absence of diabetes as diabetes is both a stratifying variables as well as a part of the definition of the explanatory variable. What about interaction? This also relates to the subsequent presentation of data in Figure 2 and Figure 3 and Table 3 (Major Compulsory Revision)

RE:

Thank you for the detailed advice. All statistical methods and models used in the writing of this manuscript were selected in consultation with a statistician of Graduate School of Health and Welfare CHA University, Prof. Jimin Sung, who is the co-author in this manuscript, and in consideration of the objectives of this study. After receiving your comments, we consulted the Department of Statistics, Yonsei University College of Medicine, to see whether there were more suitable statistical methods we could employ. And, we were told that it is acceptable to use the present statistical methods considering the purpose of this study, and that clarifying the objectives of this study may be necessary rather than changing the methods of statistical analysis. As such, we respond to your invaluable comments from the point of view of the clinical significance of this study.
Initially, we were planning to analyze the association between MetS, individual MetS components, and coronary atherosclerotic parameters according to the presence of diabetes in terms of three distinct aspects. First, the main purpose of our manuscript is to identify the association between MetS and coronary atherosclerotic parameters including plaque, obstructive plaque, and CACS >100 according to diabetes status because the WHO has strongly recommended that the concept of MetS not be applied in established diabetic patients.

Second, MetS is defined according to the number of metabolic abnormalities ($\geq 3$ MetS components) regardless of the individual MetS components. Thus, we performed the analysis to identify the association between individual MetS components and coronary parameters according to diabetes status, and the condition of MetS is not considered in this analysis.

Third, all individual MetS components have equal value for the diagnosis of MetS according to National Cholesterol Education Program–Adult Treatment Panel (NCEP–ATP) III definition. It is well-known that the number of MetS components is strongly associated with the progression of subclinical atherosclerosis as reflected in carotid intima-media thickness and pulse wave velocity. Differential association between the number of MetS components and subclinical atherosclerosis according to the presence of diabetes is also well known. However, the association between the number of MetS components and coronary atherosclerotic parameters is unknown, especially when analyzed according to diabetes status. Thus, we endeavored to identify the increase of risk for plaque, obstructive plaque, and CACS >100 with each increase in the number of MetS component in both non-diabetic and diabetic subjects.

To respond to your queries regarding the appropriateness of the statistical tests, we send some opinions that have been suggested by our Department of Statistics.

a) Nonparametric test is not necessary because the sample size of this study is sufficient and the continuous variables showed normal distribution.

b) In performing multivariate logistic regression analysis, if ① individual MetS component have different value for the diagnosis of MetS, ② dependent (outcome) variables are categorized more than 3 ordinal variables, or ③ MetS and the number of MetS components are simultaneously considered in one logistic model, a more complex statistical model would be necessary. However, according to the NCEP–ATP III
definition, individual MetS component have equal value for the diagnosis of MetS. All dependent variables, including plaque, obstructive plaque, and CACS >100, are binary variables. And, MetS and the number of MetS components are separately analyzed after adjusting confounding risk factors in the present study. Thus, standard logistic regression analysis should be acceptable to analyze the association between the number of MetS and individual coronary parameters. As the reviewer noted, the number of MetS components has a numerical range from 0 to 5. However, because this study intended to identify the increase of risk for coronary parameters that are all binary variable with each increase in the number of MetS component according to the presence of diabetes, and individual MetS component have equal value for the diagnosis of MetS, standard logistic regression should be possible. Moreover, there is a strong tendency that each increase in the number of MetS components may be associated with the increased incidence of coronary parameters. The results related to the incidence of plaque, obstructive plaque, and CACS >100 according to the number of MetS components support the necessity of this analysis.

c) It is possible to identify the interaction using statistical analysis. However, considering that the main purpose of this study is to identify the validity of the WHO recommendation related to the application of MetS using coronary atherosclerotic parameters in an era of widespread coronary artery disease, we feel there might be some discrepancy between the main purpose of this study and the suggested analysis.

I hope you understand that I and my colleagues endeavor to do our best to reflect your invaluable opinion in our revisions. We have added the information related to the incidence of plaque, obstructive plaque, and CACS >100 according to the number of MetS components in supplementary file: Table S1. In addition, we revised the paragraph regarding Statistical Analysis to clarify our statistical methods with regard to the purpose of this study, as follow:

Clinical, biochemical, and coronary characteristics are described according to the presence of MetS and diabetes. Values are expressed as mean ± SD or n (%). Continuous variables were compared using the Student t-test, and categorical variables were compared using the χ² test. The associations between the individual MetS components and the coronary parameters, namely plaque, obstructive plaque, and CACS >100, were analyzed in the subjects with and without diabetes after adjusting for confounding risk factors. Univariate and multivariate logistic regression analyses for identifying the association between MetS and coronary parameters were performed according to diabetes status. These analyses were also performed to identify the association between the increase in number of MetS components (MetSN) and coronary parameters according to diabetes status. The
covariate-adjusted odds ratios (OR) and 95% confidence intervals (CI) for each coronary parameter were calculated. Statistical Package for the Social Sciences version 18 (SPSS Inc., Chicago, IL) was used for all the analyses. All the statistical tests were 2-tailed, and P < 0.05 was considered significant.

Comment No. 5

Results: The results are presented in 3 sections of the paper, 3 tables, 3 figures and 1 additional table. There are some discrepancies in the number of patients presented in the tables. The total number of patients was 2,869 (2,308 non-diabetes and 561 diabetes patient). This is presented in table 1. However, in tables 2 and S1 only 2,053 non-diabetic patient and all 561 diabetic patients are included. Please provide the reason for this? (Major Compulsory Revision)

RE:

We apologize for the major mistakes related to the expression of the number of non-diabetic subjects according to the individual MetS components in Table 2 and Table S2 (previous Table S1 was changed to Table S2 because Table S1 is newly added). We identified that this error had no impact on the results of statistical analyses of Table 2 and Table S2. We have revised the tables after identifying the exact number of non-diabetic subjects according to individual MetS components.

Comment No. 6

Results: Please provide a report of the patient radiation dose in mSv (Minor Essential Revision)

RE:

We added the information on radiation dose in the paragraph regarding MDCT protocol as follow:

The total estimated average radiation dose for the multislice CT protocol was 8.8 ± 1.6 mSv.

Comment No. 7
Discussion: The discussion is well written and highlights the overall results, discussing them in context to other reports. Generally, the sections about non-calcified and calcified-mixed plaque are less well described in this report and appear to be a more recent addition? It is less clear in the study aim, why this analysis, specifically, is of interest. Would benefit from clarification. (Discretionary Revision)

RE:

Thank you for your good advice. Our study primarily focused on the association between MetS and the coronary parameters of plaque, obstructive plaque, and CACS >100 according to diabetes status in a symptomatic population considering the WHO recommendation that the concept of MetS should be applied to subjects without established diabetes. The issue related to the impact of MetS and individual MetS components on coronary plaque subtype, especially non-calcified plaque (NCP) and obstructive NCP, might be important in clinical practice. However, the incidence of NCP and obstructive NCP was too low to identify the impact of MetS and its individual component on these coronary parameters in the present study. Thus, we presented the results of analyses related to this issue in supplementary file of Table S2. Further investigation with a larger sample might be necessary to clarify this issue. We added the following in the paragraph regarding study limitations:

Third, although we analyzed the association between MetS, individual MetS components, and plaque subtype, the incidence of NCP and obstructive NCP was too low to identify the impact of MetS and its individual component on these coronary parameters.