Individual patient data meta-analysis for the clinical assessment of coronary computed tomography angiography: protocol of the Collaborative Meta-Analysis of Cardiac CT (CoMe-CCT)

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Abstract

Background: Coronary computed tomography angiography has become the foremost noninvasive imaging modality of the coronary arteries and is used as an alternative to the reference standard, conventional coronary angiography, for direct visualization and detection of coronary artery stenoses in patients with suspected coronary artery disease. Nevertheless, there is considerable debate regarding the optimal target population to maximize clinical performance and patient benefit. The most obvious indication for noninvasive coronary computed tomography angiography in patients with suspected coronary artery disease would be to reliably exclude significant stenosis and, thus, avoid unnecessary invasive conventional coronary angiography. To do this, a test should have, at clinically appropriate pretest likelihoods, minimal false-negative outcomes resulting in a high negative predictive value. However, little is known about the influence of patient characteristics on the clinical predictive values of coronary computed tomography angiography. Previous regular systematic reviews and meta-analyses had to rely on limited summary patient cohort data offered by primary studies. Performing an individual patient data meta-analysis will enable a much more detailed and powerful analysis and thus increase representativeness and generalizability of the results. The individual patient data meta-analysis is registered with the PROSPERO database (CoMe-CCT, CRD42012002780).

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Methods/Design: The analysis will include individual patient data from published and unpublished prospective diagnostic accuracy studies comparing coronary computed tomography angiography with conventional coronary angiography. These studies will be identified performing a systematic search in several electronic databases. Corresponding authors will be contacted and asked to provide obligatory and additional data. Risk factors, previous test results and symptoms of individual patients will be used to estimate the pretest likelihood of coronary artery disease. A bivariate random-effects model will be used to calculate pooled mean negative and positive predictive values as well as sensitivity and specificity. The primary outcome of interest will be positive and negative predictive values of coronary computed tomography angiography for the presence of coronary artery disease as a function of pretest likelihood of coronary artery disease, analyzed by meta-regression. As a secondary endpoint, factors that may influence the diagnostic performance and clinical value of computed tomography, such as heart rate and body mass index of patients, number of detector rows, and administration of beta blockade and nitroglycerin, will be investigated by integrating them as further covariates into the bivariate random-effects model.

Discussion: This collaborative individual patient data meta-analysis should provide answers to the pivotal question of which patients benefit most from noninvasive coronary computed tomography angiography and thus help to adequately select the right patients for this test.

Keywords: Collaborative meta-analysis on cardiac CT, CoMe-CCT, Coronary CT angiography, Individual patient data meta-analysis, IPD, Positive and negative predictive value, Pretest likelihood, Sensitivity and specificity, Study protocol

Background
Coronary artery disease (CAD) is the main cause of death in industrialized countries [1]. To allow early detection as well as accurately ruling out CAD, a reliable noninvasive test would have important advantages. To reliably exclude disease, a diagnostic test with a minimal proportion of false-negative results and thus a relatively high sensitivity should be used [2]. Coronary computed tomography (CT) angiography has already been evaluated comprehensively concerning its diagnostic accuracy potentials by single studies and meta-analyses. However, the influence of the clinical presentation, risk factors and prior test results of patients, which can be used to estimate the influence of the pretest likelihood of CAD on the positive and negative predictive values of coronary CT angiography, are not fully understood. A few single-center studies have been published dealing with the influence of the pretest likelihood of CAD on the diagnostic performance of CT. Meijboom et al. demonstrated in 254 symptomatic patients that the accuracy of coronary CT angiography was greatest in patients with low-to-intermediate pretest likelihood whereas the negative predictive value was substantially reduced in patients with high pretest likelihood [3]. This reduction of the negative predictive values in patients with high disease prevalence was also shown in a comparable study by Husmann et al. comprising 88 patients [4]. In 90 patients, Leber et al. also demonstrated that CT allows CAD to be accurately ruled out if an intermediate pretest likelihood is present [5]. Applying Bayesian analysis, Dewey et al. [6] confirmed that the diagnostic performance of both CT and magnetic resonance coronary angiography was influenced by the pretest likelihood. Pretest likelihood of CAD can be estimated according to clinical presentation and risk factors applying several tabulation tools [7-11] and the appropriateness of further testing may be estimated based on their results. Establishing and further elucidating the potential of pretest likelihood estimations to ensure the appropriateness of CT is an important aim of cardiovascular medicine. In a meta-regression analysis using disease prevalence as a surrogate marker for pretest likelihood, Schlattmann et al. further specified the boundaries of low-to-intermediate pretest likelihood for patients in whom coronary CT angiography can be applied as a reliable rule-out test [12] (Figure 1).

The analysis is based on summary patient collective data from primary study articles aggregated in a regular meta-analysis [13] and, thus, further specific patient-level information for more detailed subanalyses were not available.

The purpose and main aim of this project is thus to summarize the published and unpublished evidence on coronary CT angiography using IPD in a collaborative meta-analysis to draw more reliable and generalizable conclusions [14] concerning the appropriateness of CT in patients with varying presentations and thus pretest likelihoods [15]. The results should enable us to determine which patients benefit most from noninvasive coronary angiography and those less suited to undergo CT.

Moreover, the influence of additional patient and acquisition characteristics will also be summarized in our collaborative meta-analysis to allow us to draw important conclusions concerning the eligibility of patients for coronary CT angiography and the importance of specific technical requirements and methods of preparation.
Among these factors being discussed or having previously been shown to influence the diagnostic performance of coronary CT angiography is the heart rate of the patients during scanning, which may lead to motion artifacts, and the body mass index, which, if severely increased, can result in rather noisy nondiagnostic test results [16-18]. Also, technical factors such as the number of simultaneous CT detector rows and the administration of beta blockade to reduce heart rate and nitroglycerin to dilate the vessels have been shown in single-center studies to alter the diagnostic performance and image quality of coronary CT angiography [19-24]. In detail, subanalyses will be performed to investigate the following questions:

- Is there a decrease in diagnostic accuracy of coronary CT angiography in patients with a body mass index >30?
- Does heart rate control (heart rate <60 beats per minute) lead to an increase of accuracy?
- Does the use of ≥64-row CTs lead to an increase of diagnostic accuracy?
- Is there a difference in diagnostic accuracy between men and women after adjusting for differences in pretest likelihood?
- Is diagnostic accuracy higher in patients >70 years of age or younger patients after adjusting for differences in calcium score?
- Is a certain Agatston calcium score threshold a good universal predictor for coronary artery disease?
- Is diagnostic accuracy of CT different in patients with atypical or typical chest pain?

This IPD meta-analysis will enable us to perform the main and secondary analyses on an individual per-patient basis, the clinically most relevant level of analysis. The results may have relevant clinical implications because conventional coronary angiography (CCA) exposes the patients to infrequent yet considerable risks, such as myocardial infarction, coronary artery dissection and ventricular tachycardia [25,26], which might be avoided using CT in selected patient populations with suspected CAD. In addition, there are also economic considerations because CT might also be more cost effective [27].

**Methods/Design**

This is a study protocol for the collaborative IPD meta-analysis on coronary CT angiography in comparison to
conventional angiography as the gold standard, called Collaborative Meta-Analysis of Cardiac CT (CoMe-CCT). It was registered with the PROSPERO database [28,29] (registration number: CRD42012002780). This collaborative IPD meta-analysis is exempt from ethical approval as the analysis as well as the results for publication only involve de-identified data and all individual studies that will be summarized have received local ethics approval.

Identifying eligible studies for CoMe-CCT
Valid published and unpublished studies will be retrieved by directly contacting all corresponding authors from published studies on coronary CT versus CCA in patients with suspected CAD. This will be achieved by including the primary studies of a recent regular systematic review and meta-analysis by our working group [13], and performing an update of this review to identify most recent studies. A sensitive search strategy using the particular thesaurus terms of the specific databases in combination with free text word synonyms [2] will be used to search MEDLINE (via PubMed), EMBASE (via Ovid) and ISI Web of Science databases for updating the article pool of relevant studies (suggested search strategies for all databases are provided in Additional file 1). We will also search bibliographies of retrieved studies, systematic reviews and meta-analyses, and include results of abstracts presented at most recent congresses as suggested by clinical experts.

Key inclusion criteria are a prospective study design; use of a contemporary CT scanner with at least 12 simultaneous detector rows; use of ≥50% diameter reduction as the cut-off criterion for significant coronary artery stenoses in CT and CCA; application of CCA in all patients, regardless of the results of CT; provision of individual patient results for CT and CCA (positive, negative, and nondiagnostic), which allow calculation of 2×2 (excluding nondiagnostic results) or 3×2 (including nondiagnostic results) tables [30]; articles published in English or German; and provision of basic patient characteristics (age, gender, angina type, heart rate).

Studies with the following characteristics will be excluded: retrospective study design; overlap with other studies as indicated by the corresponding author.

Study screening and selection will be performed by two independent investigators. Retrieved articles will be searched after duplicate papers (from MEDLINE, EMBASE and ISI Web of Science) are identified and eliminated. In a first phase, titles and abstracts will be scanned and, in accordance with the inclusion and exclusion criteria, either discarded or retained for further investigation. In a second phase, the remaining potentially eligible articles will be reassessed in depth using the full text.

Methodological quality assessment
Two investigators will independently carry out the data extraction (including quality assessment) from all the retrieved published studies based on the full text articles. Discrepancies will be resolved in a consensus meeting, or, if agreement cannot be reached, they will be resolved in consensus with a third investigator. To assess and quantify the inter-rater agreement between the two investigators in evaluating methodological quality using the QUADAS tool [31], we will calculate the kappa statistics. The data extracted will be: general and detailed methodological study characteristics, characteristics of the study population, details of the CT technology used, and detailed reference standard (CCA) specifications.

Collection of individual patient data
An international steering committee of renowned experts from the field of noninvasive coronary CT angiography has been established to lead, oversee and represent the CoMe-CCT project. The steering committee consists of four clinical experts for cardiac CT: Stephan Achenbach, Erlangen, Germany; Matthew Budoff, Los Angeles, CA, USA; Mario J Garcia, New York, NY, USA; Marc Dewey, Berlin, Germany, and one clinical expert for CCA: Michael Laule, Berlin, Germany. The steering committee is completed by the project’s statistician Peter Schlattmann, Jena, Germany.

Corresponding authors of identified eligible published studies will be contacted using mail including a cover letter detailing the objectives of the collaborative meta-analysis, background information on IPD meta-analysis, and a CD containing a data collection file for input of individual patient results for the project. The details of the obligatory and additional patient and study characteristics are shown in Tables 1 and 2. The filled out data templates will be send back to us by either mail on CD or, more conveniently, by email. Further communication will mainly be performed by email or phone. Corresponding authors will also be contacted about unpublished data that will be eligible for inclusion in the collaborative meta-analysis if the inclusion criteria are met. To further enlarge the clinical data pool, authors will additionally be asked to provide data from registries. These data will not be included in the primary analyses, which are only based on data from the prospective studies.

Data management, security and validation
The same two investigators who will perform the electronic database search and identify published eligible studies for the regular review will also collect and assemble the IPD provided by the investigators of published and unpublished studies. Data will be sent as email attachments to the coordinating investigator of CoMe-CCT in an anonymized and de-identified way (without directly identifying information, that is, record numbers, names, addresses and so on will be removed). Data will be accepted in any kind of electronic format...
Table 1 Obligatory computed tomography technology and patient characteristics requested in the data file

| Computed tomography characteristics | Patient and conventional coronary angiography characteristics |
|------------------------------------|-------------------------------------------------------------|
| Publication from which the data is derived | Age and gender, type of symptoms (typical angina pectoris, atypical angina pectoris, chest pain, no pain, pain unknown) |
| Results of CT (positive, negative, nondiagnostic). Comment and explanation for nondiagnostic patients | Results of conventional coronary angiography (positive, negative, nondiagnostic). Comment and explanation for nondiagnostic patients |

*At least one ≥50% stenosis in one vessel; no stenosis in any vessel and at least one vessel not fully evaluable.

Table 2 Additional computed tomography technology and patient characteristics requested in the data file

| Additional computed tomography characteristics | Patient characteristics and additional tests |
|-----------------------------------------------|---------------------------------------------|
| Effective radiation dose | Weight and height |
| Type of electrocardiographic gating | Derived body mass index |
| Number of detector rows used | Calcium score, heart rate during scanning, presence of cardiac risk factors (hypertension, diabetes, hyperlipidemia, current or former smoker, positive family history, prior myocardial infarction) |
| Beta blockade (type, route, dosage) | Results of rest electrocardiography |
| Nitroglycerin (type, dosage) | Results of stress electrocardiography |
| Contrast agent (type, concentration, flow, amount) | Results of stress echocardiography |
| Breath hold duration | Results of stress scintigraphy |
also use WinBUGS [39]. If necessary, macros will be written to facilitate the use of three-level generalized linear mixed-effects models.

Based on the model described above, mean logit sensitivity and specificity with their standard error and 95% confidence intervals, estimates of the between-study variability in logit sensitivity and specificity, and the covariance between them will be estimated. These quantities will be back-transformed to the original ROC (Receiver Operating Characteristic) scale to obtain summary sensitivity, specificity and the diagnostic odds ratios. The derived logit estimates of sensitivity, specificity and respective variances are then used to construct a hierarchical summary ROC curve for CT with summary operating points for sensitivity and specificity on the curves and a 95% confidence contour ellipsoid.

Here the individual patient-specific covariates such as type and severity of symptoms, body mass index, beta blockade and sublingual nitroglycerin will be used in the regression analysis. This serves as tool to identify spectrum bias and clinically relevant influential factors.

For performing sensitivity analysis, the analysis will be redone by leaving out one study. The generalized linear mixed model is known to be sensitive to starting values. Thus an additional analysis with Bayesian methods using PROC MCMC, SAS 9.2 will be performed.

Discussion
We believe that this collaborative multi-centric and multi-continental IPD meta-analysis will have an important impact on the clinical management of patients with suspected CAD as it should provide an answer to the question of which patients benefit most from coronary CT angiography. Furthermore, additional factors that influence the diagnostic performance of CT in comparison to CCA can be identified in this meta-analysis. This IPD meta-analysis also holds the potential to analyze and compare the predictive value of cardiac CT and CCA for subsequent major adverse cardiovascular events. Finally, the CoMe-CCT may facilitate the adequate selection of patients for cardiac CT by estimating the pretest likelihood for disease and predicting the diagnostic performance for individual patients that should ultimately help to avoid unnecessary examinations and thus decrease the use of scarce health care resources in the future [40].

Trial status
Currently, in the course of performance of the IPD meta-analysis, we are in the state of data collection and data validation. No statistical analysis has yet been performed. The update search still has to be performed to be able to identify most recent articles and to contact the corresponding authors. At the time of study protocol submission, 54 single data sets from 40 authors and including more than 5,500 IPD comparing CT and CCA have been acquired.

Additional file

Additional file 1: Search Strategies for MEDLINE, EMBASE and ISI Web of Science.

Competing interests
PS and MD are supported by a grant of the German Federal Ministry of Education and Research (BMBF) for meta-analyses as part of the joint program “clinical trials” of the BMBF and the German Research Foundation (DFG). PS is also supported by another grant of the DFG (Schl 3–1) and has received lecture fees from Bayer-Scherding. MD has received grant support from Heisenberg Program of the DFG for a professorship (DE 1361/14-1), European Regional Development Fund (2007/2013/2 020/2007/2013 2/48), German Heart Foundation/German Foundation of Heart Research (F/23/08, F/27/10), Joint program from the DFG and the BMBF for meta-analyses for performing sensitivity analysis, the analysis will be redone by leaving out one study. The generalized linear mixed model is known to be sensitive to starting values. Thus an additional analysis with Bayesian methods using PROC MCMC, SAS 9.2 will be performed.

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including meta-analytic methods. PS is author of the book Medical Applications of Finite Mixture Models.

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MB (MD) is a cardiologist who has over 20 years’ experience with early detection of coronary artery disease using both coronary artery calcium scoring and CT angiography. He has published four books on the topic of cardiac CT and published over 450 MEDLINE-indexed articles on cardiovascular CT. He is past president of both the Society of Atherosclerosis Imaging and Prevention and Society of Cardiovascular Computed Tomography. He is currently a professor of medicine at the David Geffen School of Medicine at UCLA, and program director of Cardiology at Harbor-UCLA Medical Center.

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HA (MD, MPH, EBCR) is an associate professor and senior radiologist. He is a board certified radiologist and board certified neuroradiologist. His main research interests are body CT, emergency radiology and abdominal imaging.

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2013,
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SMMI (MD, MRC(R), BSc(Ions)) gained her degrees in Science and Medicine from the University of Glasgow in 2000 and 2002 respectively. She subsequently underwent clinical training in medicine and cardiology and, following research in the field of cardiac imaging, was awarded a postgraduate Doctor of Medicine degree in 2011, again conferred by the University of Glasgow. She has worked as a specialist registrar in clinical cardiology since 2008 and her subspecialty interests, research and publications are focused on cardiac imaging and heart failure.

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KN is a cardiologist whose clinical and research interests include noninvasive cardiac imaging and acute cardiac care.

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KN is a full professor of radiology, vice chair of the Department of Clinical Radiology, and section chief of MRI. His research interests include cardiovascular CT, dual energy CT, cardiovascular MRI, imaging of atherosclerosis, thoracic imaging and molecular imaging. KN has published more than 160 scientific papers, one book, and more than 20 book chapters. He also serves as a reviewer for numerous journals, including the American Journal of Radiology, Circulation, AJACC Imaging, European Journal of Radiology, Investigative Radiology, International Journal of Cardiovascular Imaging, Journal of Computer Assisted Tomography, Journal of the American College of Cardiology, Magnetic Resonance in Medicine, and others.

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MD is a radiologist and researcher with vast experience in the field of diagnostic imaging and chief consultant. MD has published over 120 MEDLINE-indexed articles including works on cardiovascular imaging, claustrophobia, cost-effectiveness, meta-analyses, radiation and patient safety. He is an associate editor of Radiology and European Radiology and the editor of the books Coronary CT Angiography and Cardiac CT. He is also president of the 1898-founded Rontgen Society of Berlin and Brandenburg.

PS, SA, MB, MG, ML and MD are members of the steering committee of CoMe-CCT.

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