Diagnostic Strategies for Patients with Suspected Coronary Artery Disease: A Network Meta-analysis of Diagnostic Randomized Controlled Trials

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The following protocol has been written according to the template for a Cochrane intervention review that compares multiple interventions (available in http://cmim.cochrane.org/sites/cmim.cochrane.org/files/uploads/Protocol%20for%20Cochrane%20Reviews%20with%20Multiple%20Interventions.pdf).
Description of the condition

Chest pain is one of the most frequent clinical presentations for ambulatory consultations and leads to several million emergency department visits and hospitalizations yearly. History, physical examination and electrocardiographic investigation at rest are frequently supplemented with noninvasive cardiac imaging procedures although evidence for outcome benefits and their relative diagnostic yield is limited. Despite the use of clinical decision rules and the improved sensitivity of cardiac biomarkers, many patients who are admitted to the hospital in order to exclude acute coronary syndromes (ACS), are ultimately found not to suffer from a cardiac cause responsible for their symptoms. Conversely, patients diagnosed with non-cardiac chest pain account for one third of patients who subsequently die from cardiovascular disease or experience ACS during 5 years of follow-up. Therefore, improved diagnostic accuracy and risk stratification is needed, especially in younger patients to advance our understanding of the disease and choose appropriate therapies.

The choice of noninvasive imaging modalities in patients with suspected CAD is a major focus for comparative effectiveness research. Exercise-induced symptoms and functional capacity are predictors for the presence of obstructive coronary artery disease and are used in clinical practice to guide referral for invasive coronary angiography (CA). Invasive CA is the last step in the diagnostic work-up of patients with suspected CAD, often on the basis of results of non-invasive stress testing (functional or anatomical) under different clinical settings. Support for this practice as recommended in current practice guidelines is derived from data on the prognostic value of functional capacity and extent of ischemia, as well as investigations performed more than 15 years ago to evaluate the comparative effectiveness of direct referral to invasive coronary angiography versus selective referral on the basis of stress test findings. Of
note, there is substantial heterogeneity in the use of functional testing before invasive CA (15). Moreover, the frequency of invasive assessment (16) and the appropriateness of invasive CA show geographical variation that is independent of hospital location, teaching status, or availability of revascularization.

Although guidelines recommend the use of stress testing, recent audits in large number of patients showed only a modest impact on subsequent diagnostic findings. (17) Patients with positive tests were only moderately more likely to show obstructive coronary disease. In the CathPCI survey, (18) the difference in the proportion of testing among patients with obstructive and non-obstructive disease was small, although abnormal noninvasive test results improved the identification of individuals with anatomically obstructive CAD. Fewer individuals with non-obstructive CAD—who are at risk of incident myocardial infarction and mortality—are recognized with a selective referral strategy on the basis of functional testing than with coronary imaging (invasive CA).

Another diagnostic tool that has recently gained popularity is coronary computed tomographic angiography (CCTA) as it has been suggested to overcome limitations of functional testing. (19,20) The growth of CCTA has been supported by comparative prognostic evidence of CCTA versus functional testing, radiation dose reduction, as well as the incremental value added to clinical scoring systems and CAD risk factors both in stable CAD (21-23) and in the evaluation of low risk, possible ACS. (23)

The assessment of decision making after the results of functional testing suggests that it is rarely performed on the basis of risk (24) and that this problem may be even more pronounced with CCTA. In a comparative analysis of outcomes after CCTA and stress testing in a large Medicare population, the availability of coronary anatomy data with CCTA was associated with increased use of subsequent cardiac catheterization, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery compared with nuclear myocardial perfusion imaging, and consequently resulted in higher costs. (25) At the same time, CCTA use was associated with a slightly lower likelihood of hospitalization for acute myocardial infarction (AMI), but there was no difference in overall mortality. Further concerns about CCTA remain, including false
positive results leading to unnecessary invasive testing (26,27), radiation exposure (28,29) and increased downstream resource utilization (25,30). In addition, much of the prospective evidence on CCTA stems from studies with relatively low-risk populations and short follow-up (28,31-33). Thus, equipoise exists regarding the utility of CCTA as an evaluation strategy in routine clinical practice.

**Description of the interventions**

A number of different functional- and anatomical-based imaging tools has been investigated, including exercise electrocardiogram (ECG), stress echocardiography, single-photon emission computed tomography - myocardial perfusion imaging (SPECT-MPI), CCTA, stress myocardial computed tomography perfusion (CTP), cardiac magnetic resonance (CMR) (including stress imaging), and positron emission tomography (PET).

1. **Exercise ECG**

   The exercise ECG stress testing is done by exercise on a treadmill or bicycle under continuous electrocardiographic monitoring and blood pressure recording.

2. **Stress echocardiography**

   A stress test may be accompanied by echocardiography. The echocardiography is performed both before and after the stress (exercise or pharmacologic) so that structural differences can be compared. A resting echocardiogram is always obtained prior to stress. The images obtained are similar to the ones obtained during a full surface echocardiogram, commonly referred to as transthoracic echocardiogram. After the target heart rate is achieved, 'stress' echocardiogram images are obtained. The two sets of echocardiographic images (rest and stress) are then compared to assess for any abnormalities in wall motion of the heart. The basic concept of stress echocardiography is the detection of ischemia through the development of new regional wall motion abnormalities or worsening of pre-existing regional wall motion abnormalities. Stress echocardiography is used to
risk stratify patients in the assessment of CAD, localize ischemia in patients with previously known CAD and also assess myocardial viability.

3. **Single-photon emission computed tomography - myocardial perfusion imaging (SPECT-MPI)**

Radionuclide myocardial perfusion imaging involves the visualization of a radiopharmaceutical agent (most commonly thallium-201 and technetium-99) that is distributed throughout the myocardium in proportion to coronary blood flow, thereby permitting the determination of relative blood flow in various regions of the heart. Regional coronary blood flow (delivery) determines the amount of tracer activity within a specific area. Perfusion imaging is dependent upon the physical properties of the radiolabeled tracer, its delivery, and its extraction and retention by the myocyte. Both cell membrane integrity and energy utilization are necessary for intracellular extraction and retention of tracer. Thus, retained tracer activity is synonymous with myocyte viability.

4. **Coronary computed tomographic angiography (CCTA)**

CCTA is a noninvasive means of assessing coronary anatomy and coronary lesions. The patient is injected with iodinated intravenous dye and the heart is scanned using a multislice CT scanner, allowing the assessment of coronary anatomy and at the same time quantitative detection of coronary artery calcium. The presence and extent of coronary artery calcium can predict the presence of coronary artery stenoses, but in general it is a better marker of the extent of coronary atherosclerosis than the severity of stenosis.

5. **Stress myocardial computed tomography perfusion (CTP)**

Stress myocardial computed tomography perfusion (CTP) is a novel examination that provides both anatomic and physiological information (i.e., myocardial perfusion). Myocardial CTP protocols allow for the simultaneous acquisition of coronary anatomy and myocardial perfusion, and a combined CCTA/CTP protocol has been shown to have better diagnostic characteristics than CCTA alone.
6. **Cardiac magnetic resonance (CMR)**

Magnetic resonance imaging is a noninvasive method for visualization of the heart anatomy and function. Technical advantages are the potential for three-dimensional imaging, the free choice of tomographic planes, and the lack of ionizing radiation. The use of magnetic resonance imaging in coronary artery disease falls into four main categories: (1) evaluation of acute myocardial ischemia and infarction, (2) assessment of the sequelae of myocardial infarction, (3) evaluation of coronary artery bypass grafts, and (4) visualization of the coronary arteries.

7. **Positron emission tomography (PET)**

PET is a non-invasive method of evaluating myocardial perfusion and viability. This technique has the advantage of being able to assess both perfusion and metabolism. PET requires the use of positron-emitting isotopes (such as oxygen-15, carbon-11, nitrogen-13, and fluorine-18), which are cyclotron-produced. Ischemia shifts myocyte metabolism preferentially to glucose from fatty acids. Thus, uptake of a glucose analog, fluorine-18 labeled deoxyglucose (FDG) by myocytes in an area of dysfunctional myocardium indicates metabolic activity and thus, viability. Regional perfusion can also be assessed with an agent that remains in the vascular space and demonstrates the distribution of blood flow (such as nitrogen n-13 ammonia or rubidium rb-82). As a result, PET imaging has the potential to differentiate between normal, stunned, hibernating, and scarred myocardium. The presence of enhanced FDG uptake in regions of decreased blood flow (known as a "PET mismatch") defines hibernating myocardium by PET imaging, while a concordant reduction in both metabolism and flow ("PET match") is thought to represent predominantly necrotic myocardium.
**How the intervention might work**

The different noninvasive imaging strategies (functional and anatomical) discussed above aim to appropriately risk-stratify patients presenting with symptoms suggestive of flow-limiting, obstructive coronary artery disease under different clinical settings. They have been proposed as effective “gatekeepers” prior to referral of patients for invasive evaluation, resulting in fewer inappropriate referrals, better use of medical sources, and improved clinical outcomes. They have been also used to identify asymptomatic individuals who are at high risk of having CAD and subsequently they are in risk of cardiac events.

**Why it is important to do this review**

Diagnostic tests are critical components of an effective health care system. Clinicians largely rely on information of diagnostic accuracy to decide on the usefulness of a test (34); whereas the net patient benefit derived by different diagnostic strategies is difficult to measure (35,36). Since the diagnostic accuracy may not necessarily translate into patient benefits (37,38), the impact of a diagnostic test on patient-oriented outcomes needs to be subsequently quantified. One would anticipate that a good diagnostic test will appropriately and effectively guide further testing and selection of treatments, but it is not always clear whether the increase or decrease of downstream diagnostic or therapeutic interventions translates into improved clinical outcomes. Therefore, when studying patient outcomes in medical research, the use of randomized comparisons comes into perspective. The most conclusive evidence regarding patient outcomes can be derived from diagnostic randomized controlled trials (D-RCTs), in which participants are randomized to a new diagnostic test versus a control (the “gold standard method” or “usual care”) or no test (39-42). Performing such trials is challenging (43), but D-RCTs represent a rigorous approach to diagnostic test evaluation (38,44).

Regarding the risk stratification of patients suspected to have CAD, physicians seek guidance as to whether a non-invasive anatomical or functional testing strategy would provide the most favorable outcomes compared to invasive
CA. However, the choice between testing strategies in D-RCTs remains inconclusive mainly due to the limited power of the current evidence to identify any meaningful difference in clinical outcomes following different diagnostic strategies.\(^{(45,46)}\) The relative impact of information derived from such anatomical and/or functional testing on subsequent management and clinical outcomes is not known; in addition, head-to-head comparisons for most diagnostic strategies of interest in D-RCTs are limited which creates uncertainty for decision makers.

**Objectives**

Our aim is to evaluate the relative efficacy of the different diagnostic strategies (functional or anatomical) for detection of CAD in patients with or without symptoms suggestive of CAD under diverse settings (acute, stable, or asymptomatic). To this end we will summarize the available evidence derived from relevant D-RCTs.
METHODS

Criteria for considering studies for this review

Type of studies to be included
Diagnostic randomized controlled trials (D-RCTs) examining the safety and efficacy of different anatomical or functional non-invasive imaging strategies for the detection of CAD in patients with or without symptoms suggestive of CAD in various settings will be identified through a broad systematic literature search. We will include trials that investigate any anatomical imaging- or functional-based diagnostic strategy for the detection of CAD. Trials with 2 or more arms of interventions, or with a control arm of “usual care” (irrespective of the applied strategy) will be also eligible. We will also include trials that allowed in the same arm of intervention any diagnostic test of the same testing-group (i.e. functional or anatomical testing). Trials with multiple arms for which a subset of interventions satisfy the inclusion criteria will be kept in the analysis as long as there are at least two eligible interventions only. Potentially eligible D-RCTs that are available only as conference abstracts will be included if data for the primary outcome of interest will be available. We will exclude D-RCTs that included an arm of invasive diagnostic intervention (invasive coronary angiography). No language or year restrictions will be applied. From our systematic review, we will exclude studies that were not completed at the time of our search.

Types of participants
Patients with suspected stable CAD, or acute coronary syndromes (ACS) with initial negative troponin which not require immediate invasive assessment, or asymptomatic patients considered to be at high risk of CAD who were randomized to different diagnostic strategies will be deemed eligible.
Types of interventions
We will consider D-RCTs that compare two or more of the following diagnostic strategies for the detection of CAD: exercise-ECG test, stress echocardiography, SPECT-MPI, CCTA, CTP, CMR, and/or cardiac PET. We will also consider studies comparing any of the above interventions to a “usual care” arm as defined by the investigators in each study. All possible comparisons are illustrated in the network plot in Figure 1. Nodes refer to interventions and edges between nodes refer to the fact that there are studies directly comparing the interventions defined by the nodes. Any interventions other than the pre-specified diagnostic strategies that will be identified through our search will be also considered for inclusion in our network after assessing their comparability with the pre-specified set of competing strategies.(47) As a condition, we assume that any patient that meets the inclusion criteria is, in principle, equally likely to be randomized to any of the eligible above-mentioned diagnostic approaches.

Types of outcome measures
We will focus on outcomes directly related to the index care episode and clinical outcomes related to the longest available follow up period. The eligible trials will be scrutinised for information on the following outcomes:

Primary outcomes:
- Subsequent referral to invasive coronary angiography (CA)
- Any coronary revascularization (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG))

Secondary outcomes:
- Death from any cause
- Cardiac death
- Myocardial infarction
- Time to diagnosis (applicable to patients suspected of ACS - time from presentation in the emergency department until the first test that led to the diagnosis)
- Cumulative radiation exposure (mSv, mSv/patient)
- Length of hospitalisation during the index care of episode
- Rehospitalisation for cardiac reason
- Downstream testing (including the number of additional non-invasive and invasive tests following the indexed intervention)

In case of missing outcomes in the main and subsequent publications of the included trials, we will contact the principal investigator to provide additional unpublished outcome data.

**Search methods for identification of studies**

D-RCTs comparing any eligible strategy (anatomical or functional) for the detection of CAD will be identified through a systematic literature search of the following databases: Medline, Medline in process, Embase, Cochrane Library for clinical trials, Pubmed (for online first and non MEDLINE records), Web of Science, SCOPUS, WHO International Clinical Trials Registry Platform (ICTRP), and Clinicaltrials.gov. A modified search algorithm will be developed and adapted for each database with a combination of relevant text terms and key words. We will scrutinize for additional eligible studies the reference lists of the retrieved publications, and relevant meta-analyses in the field. No language or sample size restrictions will be applied to our searches.

**Data collection and analysis**

**Selection of studies**

The aforementioned search strategy will be performed for each database separately and a summary list (after removing duplicate records) of the retrieved items will be prepared for the first stages of a systematic review. Two investigators (GCMS, KCS) will scrutinize in duplicate all the items for eligibility in title and abstract level.
Data extraction and management

Two investigators (GCMS, KCS) will perform study identification, data abstraction, and risk of bias assessment independently. Any discrepancies will be resolved by consensus and arbitration by a third investigator.

We will review the main report, subsequent publications of each trial and any supplementary material of the included trials and extract the following data:

- **Trial characteristics:** first author, study acronym, year of publication, interventions (diagnostic strategies) of interest, number of study arms, number of patients randomised to each arm, number of completers, the sponsor of the study, number of centers (single or multicentre trial), area of origin (Europe, USA, or other), imputation methods and number of imputations.

- **Patients characteristics:** age, gender, cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, family history of CAD), renal function, clinical indication for diagnostic assessment (suspicion for stable angina, ACS, or asymptomatic), any given baseline risk estimation based on risk prediction models for having CAD (summary estimates in each arm and the respective used prediction model will be extracted).

- **Diagnostic tests characteristics:** specific characteristics for each applied test will be summarised: anatomical vs. functional, and further details on the specific test.

- **Clinical outcomes:** the above listed clinical outcomes will be searched in each trial fulfilling our pre-specified eligibility criteria and arm-level data will be extracted accordingly for the longest available follow-up period. The number of events and total number of patients or mean score values and standard deviations in a measurement scale in each arm of intervention of interest will be summarised as appropriate.
Assessment of risk of bias in included studies
We will investigate study limitations using the Cochrane risk of bias tool to evaluate the internal validity and conduct of included studies. (48) Two authors will independently assess the risk of bias for each included study using the risk of bias assessment tool. We will resolve any disagreements with discussion and involvement of a third author. Each item will be described as being at low, high or unclear risk of bias. The areas that will be evaluated are:

- **random sequence generation**: Was there adequate sequence generation (selection bias)?
- **allocation concealment**: Was allocation adequately concealed (selection bias)?
- **blinding**: Was knowledge of the allocated intervention adequately prevented during the study (detection bias)?
  - participants and personnel
  - outcome assessors
- **incomplete outcome data**: Were incomplete outcome data adequately addressed (attrition bias)?
- **selective outcome reporting**: Are reports of the study free of possible selective outcome reporting (reporting bias)?

We will evaluate the aforementioned items for each study and we will summarize our judgements across pairwise comparisons.(49) We will classify each direct evidence in the network as pertaining to low, moderate, or high risk of bias. A trial will be considered to be in “high-risk of bias” overall if at least one of the individual bias assessment domains listed above is judged to be at high risk. In case of all individual bias domains will be judged to be at low risk, a study will be considered “low-risk of bias” overall. If one or more individual bias assessment domains will be judged to be of unclear risk of bias, the overall trial risk of bias will be considered “moderate-risk of bias”.(48)
Measures of treatment effect

Relative treatment effects

We will estimate the pairwise relative treatment effects of the competing interventions (diagnostic strategies) using mean differences (MD) if the same metric is given and standardized mean differences (SMD) if different metrics were used for the continuous outcomes of interest; whereas we will estimate odds ratios (OR) for dichotomous outcomes.

Unit of analysis issues

In case of a cluster RCT that randomize group of people rather than individuals, we will check if results have been reported from appropriate statistical methods that adjust for clustering (e.g. multilevel analysis, random effect models). If the cluster adjustment has not been made appropriately we will extract the relevant information (intra-cluster correlation, event rate, average cluster size) from the original paper to estimate the effect size. If this information is not available, we will contact the authors of the study.

Dealing with missing data

Missing data and dropouts will be assessed in all included studies for the primary outcome of interest of referral to invasive coronary angiography. Details and characteristics of dropouts will be investigated and reported. We will explore if reasons for missing data are related to the actual outcome(s) and if missing data are balanced in the intervention arms. If any of these is true, this would be an indication that data are not missing at random and a complete case analysis may be biased. In that case, we will consider the study to be at high risk of bias. We will extract if authors accounted for missing data and which method they used to do so. If the authors have used naïve imputation methods (best/worst case scenarios, mean imputation), we will consider the study to be at high risk of bias whereas if they have used methods that take into account the fact that data have been imputed using statistical methods that take uncertainty in the imputed values into account (e.g. multiple imputation) we will consider the study to be at low risk of bias. If we have the number of non-completers in each arm, we will
use a pattern mixture model to evaluate how robust results are to departures from the missing at random assumption.\(^{(50,51)}\)

**Assessment of reporting biases**
For each pairwise comparison that includes at least 10 trials we will draw funnel plots to test visually and statistically for small-study effects. For these comparisons we will draw contour-enhanced funnel plots to disentangle small study effects from publication bias.\(^{(52)}\) We will also draw a comparison-adjusted funnel plot to explore for small study effects assuming that small study effects favour the novel treatment.\(^{(53,54,55)}\)

**Assessment of clinical and methodological heterogeneity within interventions comparisons**
To evaluate the presence of clinical heterogeneity we will generate descriptive statistics for trial and study population characteristics as mentioned below across all eligible trials that compare each pair of interventions. We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing these characteristics. We will assess methodological heterogeneity by evaluating the design of the studies.

**Assessment of transitivity across interventions comparisons**
Although participants are randomized within a study, diagnostic strategy comparisons are not randomized across studies. We assume that an intervention is missing from a trial for reasons not associated with its relative effectiveness and any patient that meets the inclusion criteria is, in principle, equally likely to be randomized to any of the eligible diagnostic strategies.\(^{(56,57)}\) This is a key assumption in network meta-analysis called transitivity. It states that we can genuinely learn about the relative effectiveness between two interventions via an indirect route. We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers across the different pairwise comparisons. We expect that year of study publication, number of participating centers (single center vs. multicenter trials), funding (industry-related vs. non-
industry-related), and mean age of participants can be effect modifiers and we will explore if the distribution of these differs across diagnostic strategies comparisons.

**Data synthesis**
The available trials will be grouped into three categories based on the type of included patients (patients suspected of stable CAD, ACS, or asymptomatic individuals at high risk of CAD). We will perform the predefined analyses in separate for each group and for each outcome of interest.

**Methods for direct diagnostic interventions comparisons**
First, we will conduct a standard pairwise meta-analysis by synthesizing at least two studies that compare the same diagnostic strategies using a random-effects model (58) in Stata 13. A random-effects model assumes that different studies assessed different yet related treatment effects. For the primary analysis we will consider each diagnostic strategy separately as applied in each D-RCT but we will also estimate grouped effects for anatomical interventions (i.e. CCTA) against functional interventions (i.e. stress echocardiography).

**Methods for indirect and mixed comparisons**
We will use network meta-analysis to compare different diagnostic strategies for identifications of patients with CAD under different clinical settings. Network meta-analysis synthesizes both direct and indirect evidence, estimates the relative effectiveness between pair of interventions even if these interventions have never been compared directly in RCTs and provides a ranking of interventions.(59-62) For a comparison, for example stress echocardiography vs. CCTA, direct evidence is provided by trials directly comparing these two interventions whereas indirect evidence is provided if there is an indirect path linking these two tests (e.g., if both stress echocardiography and CCTA are compared to SPECT).(63) By combining direct and indirect evidence we obtain estimates with increased precision. We will perform network meta-analysis in
Stata using the `mvmeta` command (64) and collection of Stata routines. (53) We will illustrate the assessments of risk of bias in the network plot for the primary outcomes with coloured edges according to the estimated risk of bias. (53) Finally, we will produce the contribution matrix which gives the percentage contribution of each direct estimate to the network meta-analysis estimates. (65) This will help to delineate the contribution of direct and indirect evidence to each network meta-analysis estimate.

We will also estimate the ranking probabilities for all strategies of being at each possible rank for each diagnostic intervention using the `sucra` command in Stata and obtain a hierarchy of the competing strategies using rankograms. (66)

**Assessment of statistical heterogeneity**

*Assumptions when estimating the heterogeneity*

We expect that we will find a small number of studies per comparison. When conducting the network meta-analysis, we will assume that heterogeneity is the same for all treatment comparisons with an aim to get a better estimate for heterogeneity. We will estimate heterogeneity using restricted maximum likelihood both in pairwise and network meta-analysis.

*Measures and tests for heterogeneity*

We will assess statistical heterogeneity visually by inspecting the forest plot for each pairwise comparison. The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter ($\tau^2$) estimated from the network meta-analysis models. For dichotomous outcomes magnitude of heterogeneity variance will be compared with the empirical distribution as derived by Turner. (67) We will also compute the $I^2$ and its 95% confidence interval that shows the percentage of variation that is not attributed to random error both in pairwise and network meta-analysis.

**Assessment of statistical inconsistency**

*Local approaches for evaluating inconsistency*
To evaluate the presence of inconsistency locally we will use the loop-specific approach using the \textit{ifplot} command in Stata.\cite{53,63} This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). We will also estimate the inconsistency factors by contrasting the direct evidence to the indirect evidence as estimated from the entire network.\cite{68} Then, the magnitude of the inconsistency factors and their 95\% confidence intervals can be used to infer about the presence of inconsistency.

**Global approaches for evaluating inconsistency**

To check the assumption of consistency in the entire network we will use the “design-by treatment” model as described by Higgins and colleagues.\cite{69} This method accounts for different source of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we will infer about the presence of inconsistency from any source in the entire network based on a chi-square test. The design-by-treatment model will be performed in Stata using the \textit{network} command.\cite{70}

**Investigation of heterogeneity and inconsistency**

If we find important heterogeneity or/and inconsistency, we will explore the possible sources. If sufficient studies are available, we will perform meta-regression subgroup analyses for the primary outcome by using the following effect modifiers as possible sources of inconsistency and or heterogeneity: year of study publication, number of participating centers (single center vs. multicenter trials), funding (industry-related vs. non-industry-related), sample size of the trial, and mean age of participants.

**Sensitivity analyses**

For our main analysis we define the nodes as presented in “Description of interventions Section” and Figure 1. However, some tests present important
similarities and could be considered to form a common node. Figure 2 presents an alternative network that we will analyze for the primary outcomes. In this network exercise ECG, stress echocardiography, and/or SPECT-MPI form a common node called “functional tests”. This merging of tests is expected to increase the power of the analysis.
**Figure 1:** Network-plot showing possible comparisons across the available diagnostic strategies.

Abbreviations: exercise ECG, exercise electrocardiogram; stress echo, stress echocardiography; SPECT-MPI, single-photon emission computed tomography - myocardial perfusion imaging; CCTA, coronary computed tomographic angiography; CTP, computed tomography perfusion; CMR, cardiac magnetic resonance; PET, positron emission tomography.
**Figure 2:** Network-plot showing possible comparisons across the available diagnostic strategies, by considering exercise ECG, stress echocardiography, and SPECT-MPI in the same group of diagnostic modalities of “Functional testing”.

Abbreviations: exercise ECG, exercise electrocardiogram; stress echo, stress echocardiography; SPECT-MPI, single-photon emission computed tomography - myocardial perfusion imaging; CCTA, coronary computed tomographic angiography; CTP, computed tomography perfusion; CMR, cardiac magnetic resonance; PET, positron emission tomography.
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