Journal Pre-proof

Impact of design characteristics among studies comparing coronary computed tomography angiography to noninvasive functional testing in chronic coronary syndromes.

Alessandro Spirito , Alessandro Sticchi , Fabien Praz , Christoph Gräni , Franz Messerli , George CM Siontis

PII: S0002-8703(22)00291-5
DOI: https://doi.org/10.1016/j.ahj.2022.10.087
Reference: YMHJ 6660

To appear in: *American Heart Journal*

Received date: March 12, 2022
Accepted date: October 13, 2022

Please cite this article as: Alessandro Spirito , Alessandro Sticchi , Fabien Praz , Christoph Gräni , Franz Messerli , George CM Siontis , Impact of design characteristics among studies comparing coronary computed tomography angiography to noninvasive functional testing in chronic coronary syndromes., *American Heart Journal* (2022), doi: https://doi.org/10.1016/j.ahj.2022.10.087

Impact of design characteristics among studies comparing coronary computed tomography angiography to noninvasive functional testing in chronic coronary syndromes.

Short title: Differential effects of study characteristics in CCTA vs. functional testing

Alessandro Spirito[1]; Alessandro Sticchi[2]; Fabien Praz[2]; Christoph Gräni[2]; Franz Messerli[2]; George CM Siontis[2,*]

[1] Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York NY

[2] Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland.

Am Heart J section: Clinical Investigations

***Corresponding author:**
George CM Siontis, MD, PhD
Department of Cardiology
Bern University Hospital, Inselspital
CH-3010 Bern
Switzerland
Email: georgios.siontis@insel.ch

ABSTRACT

Background: Coronary computed tomography angiography (CCTA) is widely adopted to detect obstructive coronary artery disease (CAD) in patients with chronic coronary syndromes (CCS). However, it is unknown to which extent study-specific characteristics yield different conclusions.

Methods: We summarized non-randomized and randomized studies comparing CCTA and noninvasive functional testing for CCS with information on the outcome of myocardial infarction (MI). We evaluated the differential effect according to study characteristics using random-effect meta-analysis with Hartung-Knapp-Sidik-Jonkman adjustments.

Results: Fifteen studies (8 non-randomized, 7 randomized) were included. CCTA was associated with decrease in relative (odds ratio (OR) 0.54, 95%CI 0.47 to 0.62, $p<0.001$) and absolute MI risk (risk difference (RD) -0.4%, 95%CI -0.6 to -0.1, $p=0.005$). The results remained consistent among the non-randomized (RD -0.4%, 95%CI -0.7 to -0.1, $p=0.029$), but not among the randomized trials where there was no difference in the observed risk (RD 0.2%, 95%CI -0.6 to 0.1, $p=0.158$). CCTA was not associated with MI reduction in studies with clinical outcome definition (OR 0.77, 95%CI 0.41 to 1.44, $p=0.212$), research driven follow-up (OR 0.54, 95%CI 0.24 to 1.21, $p=0.090$), central event assessment (OR 0.63, 95%CI 0.21 to 1.86, $p=0.207$), outcome adjudication (OR 0.74, 95%CI 0.24 to 2.23, $p=0.178$), or at low-risk of bias (OR 0.74, 95%CI 0.24 to 2.23, $p=0.178$).

Conclusions: Among studies of any design, CCTA was associated with lower risk of MI in CCS compared to noninvasive functional testing. This benefit was diminished among studies with clinical outcome definition, central outcome assessment/adjudication or at low-risk of bias.

Keywords: coronary computed tomography angiography; functional testing; outcomes ascertainment; electronic health records; randomized clinical trials; myocardial infarction

HIGHLIGHTS

- CCTA is one of the preferred initial tests to detect coronary artery disease in patients presented with chronic coronary syndromes (CCS).
- In patients with CCS, the risk of myocardial infarction following initial testing with CCTA versus functional testing varies across studies.
- CCTA compared to functional testing decreased the risk of myocardial infarction among studies of any design, considering non-randomized and randomized studies.
- This benefit was driven by studies using electronic health records for outcome definition.
- This benefit was diminished in randomized studies with central outcome assessment.

INTRODUCTION

Randomized controlled trials (RCTs) represent the gold standard methodological study design for the evaluation of any type of interventions since they provide more robust effects compared to the respective non-randomized studies (1). Nonetheless, RCTs are subjected to different types of biases (2) and standardized reporting (3) is encouraged to allow correct interpretation of the results. Methods of outcomes ascertainment and assessment affect the trial findings and have been well identified as potential source of bias (4). Routinely collected health data (RCHD), such as data from electronic health records or administrative claims, have been broadly used in nonrandomized studies over the last years, and are increasingly employed in RCTs. Their reliability compared to an active, prospective, research-driven data collection has been questioned, especially for non-fatal outcomes (5-9). Beside the risk of underestimation of event rates (8), RCHD are potentially affected by outcome assessment errors. Traditionally study endpoints have required a standardized and independent adjudication by a clinical events committee (CEC). This approach, which has been shown to be more accurate than the assessment performed by a single on-site investigator (10-12) or health-care professionals in routine clinical activity (8,9), is seldom used in studies based on RCHD; indeed, it requires additional sources and costs.

Coronary computed tomography angiography (CCTA) is increasingly used in the diagnostic pathway for patients suspected of chronic coronary syndromes (CCS) and is currently recommended by several major cardiology societies (13-16) as one of the preferred initial test to detect coronary artery disease (CAD). CCTA as compared to noninvasive functional tests (eg. exercise electrocardiogram (exercise-ECG), stress-echocardiography, single-photon emission computed tomography (SPECT), cardiac magnetic resonance (CMR), positron emission tomography (PET)) has a higher diagnostic accuracy in ruling out significant CAD and in detecting subclinical coronary atherosclerosis, especially in patients

with low to intermediate pre-test likelihood of obstructive CAD (15). Use of CCTA has been associated with a significant reduction of non-fatal myocardial infarction (MI) as compared to routine testing in a recent landmark RCT (17). This association was not found in a previous landmark RCT (18) or subsequent meta-analyses (19,20) with shorter follow-up.

Against this background, we aimed to evaluate how studies comparing the impact of CCTA with noninvasive functional testing on clinical outcomes in patients suspected of CCS can result in different findings due to differences in study design and characteristics, methods of outcome ascertainment and assessment.

METHODS

This study was performed based on a protocol previously available in PROSPERO (CRD42021220153). We followed established guidelines for reporting and conducting qualitative research by using a rigorous and systematic approach in accordance to Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) (21) and Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) statements (22). Items of both statements have been considered as applicable.

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

Search strategies and study selection criteria

We performed literature searches in Pubmed, Embase, Cochrane Library Central Register of Controlled Trials (CENTRAL) and we concluded them on February 18th 2021. Screening was performed in two stages via two investigators (AS and AS) working independently and in

duplicate against previously defined eligibility criteria. The detailed search algorithms applied to each database are available in **Supplementary Table 1**.

Peer-reviewed reports of non-randomized and randomized clinical trials evaluating the impact on MI occurrence of CCTA compared to noninvasive functional testing (exercise-ECG, stress echocardiography, SPECT, CMR, PET) or any other non-invasive strategy to detect obstructive CAD in patients with clinical suspicion of CCS were included. We did not include conference abstracts because of missing information of interest, and studies without a comparator group or in which all included patients underwent both CCTA and noninvasive functional testing. Moreover, studies investigating CCTA for the detection of CAD in preoperative setting, in diabetic patients without symptoms, or in patients presenting in emergency setting were not considered.

Studies classification, data extraction, and outcomes of interest

Studies were classified according to their design into non-randomized and randomized clinical trials (non-RCT and RCT respectively). We summarized s*tudy design characteristics:* year of publication, study design (non-RCT, RCT), geographical region, number of sites, enrollment period, funding source, control intervention (standard of care, exercise-ECG, stress-echocardiography, SPECT, CMR, cardiac PET), primary outcome and whether this was a single or a composite endpoint, available follow-up timepoints; *study population characteristics in study-arm level:* inclusion and exclusion patients' criteria, number of patients for each modality, sex, age, body mass index, race/ethnicity, cardiovascular risk factors, symptoms at presentation, pre-test likelihood of CAD and method of risk assessment, downstream health-care costs, changes in antiplatelet and statin use, symptoms and quality of life after initial testing or at follow-up; *outcome of interest:* myocardial infarction as defined individual studies and the respective definition, number of

events and the provided metric (point estimate and the corresponding 95% confidence interval [CI]) for each available timepoint of follow-up with preference to adjusted estimates, over unadjusted; *items related to outcomes ascertainment/assessment and blinding:* method of outcome ascertainment (research driven follow-up or RCHD [including electronic health records or administrative claims]), assessor(s) of the outcome as analyzed in the main analysis, assessment based on provided definitions and if any blinding of outcome assessors was applied. Data extraction was performed by one reviewer and verification was carried out by a second reviewer. Data extraction related to outcomes, number of events and effect metrics were performed in duplicate independently by 2 investigators. Disagreements among reviewers were resolved through consensus or third-party adjudication.

Risk-of-bias assessment

We assessed the risk of bias in the results of non-RCTs and RCTs that compared the effect of CCTA to other non-invasive imaging strategies by using the dedicated tools of Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) (23) and of Risk of Bias (RoB) 2 (4), respectively.

Data analysis

Descriptive characteristics of the studies were summarized. We calculated odds ratios (ORs) for each study with the harm-related outcome coded so that ORs less than 1 corresponded to beneficial effect for CCTA intervention. We also computed the absolute risk differences (RD) to describe the actual difference in the observed risk of MI between those individuals undergoing CCTA compared to noninvasive functional testing. We used random effect meta-analysis with Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustments, due to the relatively small number and heterogeneous studies. This method results in more robust estimates of variance

(24,25). We performed sensitivity analyses by removing from the main analysis the 2 landmark RCTs and 2 largest non-RCTs. The estimator for τ^2 in the random effect model was based on Restricted Maximum-Likelihood (26). Estimates for τ^2 around 0.04, 0.16, and 0.36 can be considered to represent a low, moderate, and high degree of heterogeneity, respectively (26,27). We performed stratified meta-analyses to evaluate the impact of studies' and patients' characteristics on the outcome of interest. We also explored the results assuming either an independent or common estimate of τ^2 to evaluate potential excess variability in the subgroups, since the heterogeneity in the subgroups may not be equal. Finally, we explored the direction of disagreement among different subgroups and the magnitude of the different effect estimates (CCTA versus noninvasive functional testing approach) by computing the ratio of odds ratios (ROR) (28). RORs less than 1 indicated greater (beneficial) treatment effect favoring CCTA compared to the reference group (28). Analyses were performed in R version 4.0.

RESULTS

Eligible studies

We screened 12,449 unique citations in title level and 256 items were screened in abstract level. Forty-five articles were scrutinized in full-text for potential eligibility. Finally, 15 reports of unique non-RCTs (n=7) and RCTs (n=8) fulfilled the inclusion criteria and considered in our evaluation (17,18,29-41) (**Supplementary Figure 1**).

Study and population characteristics

Eligible reports were published over a period of 12 years (between 2008 and 2020). The majority of studies were conducted in Europe or North America, in two or more centers and were supported by funding sources other than industry (**Table 1, Supplementary table 2**).

Among non-RCTs and RCTs the most common control noninvasive diagnostic modality was SPECT or the option of any functional test. Follow-up duration varied between 6 to 43 months in non-RCTs and between 2 to 58 months in RCTs. In all but 2 non-RCTs the recruitment period terminated before 2010, while in all but one RCTs patients were enrolled after 2010 (**Table 1**, **Table 2**).

A total of 383,885 patients were included in non-RCT and 17,420 in RCTs studies. Detailed population characteristics in study level and patients excluded after randomization or lost from follow-up are reported in **Supplementary table 3** and **4** respectively**.**

In two out of 6 studies reporting this information, the proportion of patients taking aspirin at follow-up was higher in the CCTA than in the control group in an extent ranging between 5% to 22% (**Supplementary table 5**); in all studies statin intake at follow-up was higher in the CCTA group (range 3.9% to 9.1%) (**Supplementary table 6**). Reporting of some other key variables, such as prognostic relevant patient's comorbidities, quality of life, antiplatelet or lipid lowering medications was generally poor. Quality of life at follow-up was collected in none non-RCTs and 4 out of 8 RCTs (50%), angina symptoms using different scales across studies, preventing a meta-analysis of the results (**Supplementary table 7**).

Risk of bias in non-RCTs and RCTs

According to ROBINS-I (19) assessment tool, the risk of bias for the outcome of MI across non-RCTs was moderate in 3 studies (43%) and high in 4 studies (57%). Among RCTs, 3 studies (37.5%) had a low risk of bias and 5 (62.5%) moderate risk according to RoB 2 (2) (**Table 1** and **Supplementary table 8**).

Definition, ascertainment and assessment of myocardial infarction

A definition of MI was provided in 4 (57%) non-RCTs and corresponded to codes of International Classification of Disease (ICD). Among RCTs, 6 (75%) reported the definition used, which was clinical (either standard or study specific) in all but one study. The outcome of MI was ascertained through RCHD in 6 out of 7 non-RCTs (86%) and in 2 out of 8 RCTs (25%), whereas in the remaining studies, research driven follow-up was performed. Among studies having a clinical outcome as primary endpoint (**Table 1**), 2 (31,39) out of 4 non-RCTs and 1 (17) out of 4 RCTs claimed benefit of CCTA compared to functional testing for MI and all of them used RCHD for outcome ascertainment. A central event committee (CEC) verified whether the reported MIs fulfilled the definition for this outcome adopted in the study in none non-RCT and in two RCTs. In all other studies, MIs reported by care providers were considered events without further assessment (**Table 1** and **Table 2**). Adjusted estimate for the outcome of MI was provided only in one study (**Supplementary table 7**).

CCTA vs. functional testing: Relative and absolute differences for myocardial infarction

Overall, 372 out of 54,567 patients in the CCTA group and 2,045 out of 346,738 in the functional test group suffered from a MI. The use of CCTA was associated with a significant relative decrease (OR 0.54, 95%CI 0.47 to 0.62, p<0.001, τ^2=0.004) and absolute MI risk decrease (RD -0.4%, 95%CI -0.6 to -0.1, p=0.005, τ^2 <0.001) (**Figure 1** and **2**).

Among the 7 non-RCTs, 293 out of 45,794 patients and 1,923 out of 338,091 patients in CCTA and functional test group, respectively, had a MI, with a relative (OR 0.51, 95%CI 0.45 to 0.58, p<0.001, τ^2<0.001) and absolute risk (RD -0.4%, 95% CI -0.7 to -0.1, p<0.005, τ^2<0.001) favoring CCTA. Among the 8 RCTs, MI occurred in 79 out of 8,773 patients in the CCTA group and 122 out of 8,647 in the control group; the use of CCTA was associated with a lower relative risk (OR 0.64, 95%CI 0.47 to 0.88, p<0.001, τ^2<0.001) but a similar absolute

risk (RD 0.2%, 95% CI -0.6 to 0.1, p=0.158, τ^2<0.001) compared to a functional testing (**Figure 1**).

After removing the 2 landmark RCTs (PROMISE (18) and SCOT-HEART (17) and the 2 largest non-RCTs (31,39), even though the magnitude of the effect direction remained the same, there was no formally statistical significant difference for any group of studies and the risk differences were closed to zero (**Supplementary Table 9**).

Subgroup analysis

The results of subgroup analysis considering all studies and in separate for non-RCTs and RCTs are reported in **Figure 2** and **Table 3,** respectively.

Among studies of any design (15 studies), we did not detect subgroup differences in the risk of MI between CCTA and functional testing with respect to the number of study sites, funding sources, number of control functional test, follow-up duration, percentage of female population and patients with diabetes (**Figure 2** and **Supplementary Figures 2-14**), and all estimates were in favor of CCTA. The risk of MI did not differ for the two noninvasive imaging strategies in studies with clinical outcome definition (OR 0.77, 95%CI 0.41 to 1.44, p=0.212), research driven follow-up (OR 0.54, 95%CI 0.24 to 1.21, p=0.09), central event assessment (OR 0.63, 95%CI 0.21 to 1.86, p=0.207), outcome adjudication (OR 0.74, 95%CI 0.24 to 2.23, p=0.178), or at low-risk of bias (OR 0.74, 95%CI 0.24 to 2.23, p=0.178); the differences were significant between most of the respective subgroups (**Figure 2**). CCTA was associated with MI reduction in studies with outcome ascertainment through RCHD only (OR 0.52, 95%CI 0.46 to 0.50, p<0.001), in which outcomes were assessed by care providers or local investigators (OR 0.52, 95% CI 0.46 to 0.59, p<0.001), without events adjudication (OR 0.52, 95% CI 0.46 to 0.58, p<0.001) or studies using a ICD code to define MI events (OR 0.52, 95%CI 0.46 to 0.60, p<0.001). RORs are shown in **Figure 2**. As reported in **Table**

2, evaluators were blinded in the same two studies in which events were assessed by a CEC. Therefore, the effect of blinding on CCTA vs functional test corresponds to that of events assessment by a CEC.

The magnitude of the effects differed considerably for some of the subgroups (**Figure 2**). However, among all subgroups, the individual effect estimates pointed out the same direction without systematic disagreement on the direction of the effect, but the confidence intervals were wide (**Figure 2**).

DISCUSSION

Main findings

Our systematic evaluation of studies of different designs (non-RCTs and RCTs) comparing CCTA and functional testing for CAD in patients with CCS suggests that the effect among the two imaging modalities on MI may vary according to study characteristics. The main results can be summarized as follow:

1) CCTA compared to noninvasive functional testing was associated with a lower relative risk of MI among non-RCTs and RCTs, but the absolute risk difference did not differ among RCTs.
2) CCTA showed a similar risk of future MI compared to non-invasive functional testing when studies with clinical outcome definition, research driven follow-up, central outcome assessment/adjudication or at low-risk of bias were considered, with significant differences between the respective subgroups.

CCTA is currently recommended by several major cardiology societies as one of the preferred initial test to rule out obstructive CAD in patients suspected of CCS with low to intermediate pre-test likelihood given its high diagnostic accuracy in detecting CAD and high-risk plaque features (13,14,16,17,42). Additionally, CCTA has been related with a

significant reduction of non-fatal MI as compared to routine testing in some studies(17,19,20). However, this association was not consistent with the findings of other studies, resulting in ongoing debate and open questions (18,37).

Our analysis showed that the heterogeneous effects of CCTA on MI reduction across studies may be related to different design and methods of outcome ascertainment and assessment. The overall significant MI reduction in the CCTA group was largely driven by non-RCTs, particularly by two large reports (31,39) and one RCT (SCOT-HEART) (17). On the other hand, the PROMISE trial (18) was the largest report showing a similar effect on MI rate of CCTA compared to functional testing. These four studies together accounted for 96% of the patients and events and 91% of the weight in the current meta-analysis. The two large non-RCTs (31,39) and SCOT-HEART (17) had some important similarities, such as the high prevalence of exercise-ECG in the control group (ranging between 79 and 100%), the use of RCHD, ICD-code based MI definitions and the absence of event adjudication. In addition, the non-RCT of Jorgensen et al. (31) and SCOT-HEART trial (17) had a long follow-up (median 43 and 58 months, respectively). In the landmark SCOT-HEART trial the addition of CCTA to standard of care and not CCTA alone was compared to standard of care. However, standard-of-care included a functional test, which was stress-ECG in 85% of the cases and stress imaging in 9% (17). On the contrary, in the PROMISE trial (18), 90% of patients in the control group underwent either SPECT or stress echocardiography, the follow-up was research-driven and events were adjudicated by a CEC based on clinical definition of MI. When only studies with these latter design characteristics were considered, CCTA did not confer any advantage on MI reduction compared to functional testing.

The mechanism with which CCTA would decrease the subsequent risk of MI is not clear (43). The investigators of SCOT-HEART hypothesized an improved preventive treatment and patient's adherence based on coronary CCTA findings. According to the authors, this

effect could be detected because the follow-up was longer (median 4.8 years) than in previous studies, such as PROMISE (median follow-up 2 years) (44). Nonetheless in SCOT-HEART the increases in the use of statins and aspirin in the CCTA compared to the control group were modest (10%) and unlikely to account for a 40% MI risk reduction. The early revascularization in the CCTA arm may have contributed to "stabilize" unstable plaques and prevent subsequent MI; nonetheless, the overall revascularization rate was similar between CCTA and functional testing group, making this procedure an unlikely explanation for the MI reduction (43,44).

It is well known that study design may have a major impact on study results (1,45-47). Previous empirical evidence suggests that randomized and non-randomized studies on the same topic can result in considerable differences in the effect magnitude, highlighting the need of careful interpretation (1,48). Our meta-analysis confirms the tendency of non-RCTs to increase the intervention effect (1). Randomization prevents bias due to noncomparability between groups; masking of trial participants and personnel prevents differences in treatment adherence or clinician care during follow-up (2) and abolishes bias in outcomes assessment. This is especially important when endpoints can potentially be influenced by clinician judgement, such as MI (49). Nonetheless, also RCTs are subject to biases (2) and these can also arise from specific methods of outcomes ascertainment and assessment. As a rule, in RCTs, such as PROMISE trial (18), outcomes are ascertained through a research-driven follow-up and assessed by an independent CEC using standardized definitions. On the other hand, pragmatic RCTs, conceived to lower trial costs, complexity and therefore to answer to the growing need for evidence (50), such as SCOT-HEART trial (17), rely on events ascertainment through RCHD without further adjudication. However, the up to 10 times costs reduction related to these pragmatic approaches may come at detriment of data quality and

challenges in results interpretation especially for outcomes as MI that often are not reliably collected in clinical practice, due to underreporting or misdiagnosis (51).

When RCHD are used, MI rate can be underestimated (8,52) in reason of events outside the catchment area or miscoding and linkage errors (53). Moreover, MIs obtained through RCHD without further assessment showed a modest or even low concordance with MIs adjudicated by a CEC (5,6,9,10,30,52). At variance with all-cause death, MI may be not reliably assessed in routine clinical practice, where MI ascertainment and assessment is left at discretion of treating physician and systematic and homogenous application of standardized definitions is typically missing (10). Our analysis suggests that using RCHD can be one of the major factors affecting the results in study-level. Considering the generally weak concordance between events assessed by care givers or investigators and CEC, outcomes adjudication is recommended in trials assessing the effects of new interventions on non-fatal cardiovascular outcomes, such as MI (10). Nevertheless, RCHD remains a useful tool and attractive approach to assess the effect of interventions in larger and unselected population, in a real world setting or at extended follow-up with considerably less costs (6,7). If RCHD are used to assess non-fatal outcomes, bias can be reduced by applying optimized algorithms for cardiovascular events definition, by linking electronic data with other data sources and select some events for which adjudication by CEC is needed (54). Further research is needed to refine strategies for the quality improvement of data obtained from electronic sources (54). CCTA remains one of the preferred tests to detect CAD in CCS patients, irrespective of the magnitude of its impact on MI reduction. The present analysis puts forward the strengths and limitations of using pragmatic instead of traditional approaches and highlights the need of appropriate design for the next generation clinical trials in this area (5).

Limitations

The study had several limitations. First, the generally low rate of MI and the possible confounding effect of other study characteristics, such as different follow-up duration, may limit the interpretation of the results. Given the absence of patient level data we tried to address this limitation with meta-analyses stratified according to key studies characteristics. Second, whether or not MI alone is the most appropriate endpoint to assess the value of CCTA versus functional testing is open to discussion. Of note, MI was included in the primary composite outcome of all the largest RCTs. However, as reported in Table 2, slightly different definitions of MI were used across studies and in some reports the definition included both fatal and non-fatal MI. Third, the control group among the included studies included noninvasive functional tests with different characteristics and diagnostic accuracies. The study-level analysis did not allow us to compare CCTA with a single functional test. Finally, we were not able to assess the impact of some study features that were sparsely reported at study level, such as pretest probability of CAD or intensity of preventive treatment. Nonetheless, our results were consistent with previous reports and provide a plausible explanation. Given these limitations, the findings of our analysis must be considered exploratory and hypothesis generating.

Conclusions

Among studies of any design, CCTA was associated with lower risk of MI compared to noninvasive functional testing in patients with CCS. This benefit was diminished among studies with clinical outcome definition, central outcome assessment/adjudication or at low-risk of bias. The absolute difference in risk was similar for the two strategies among the randomized trials. Methods of outcomes ascertainment and assessment may impact conclusions and result in contradictory findings among studies.

ACKNOWLEGEMENTS

None.

SOURCE OF FUNDING

No specific funding was obtained for this study.

DISCLOSURES

Dr. Spirito received a research grant from the Swiss National Science Foundation. Dr. Gräni receives funding from Swiss National Science foundation, InnoSuisse and of the CAIM - Center for Artificial Intelligence in Medicine, University Bern outside of the submitted work. The other authors have nothing relevant to disclose.

Sample CRediT author statement

Alessandro Spirito: Investigation, Validation, Data Curation, Writing – Original Draft, Visualization; **Alessandro Sticchi:** Investigation, Validation, Review & Editing**; Fabien Praz:** Review & Editing; **Christoph Gräni:** Review & Editing; **Franz Messerli:** Review & Editing**; George CM Siontis:** Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Review & Editing, Visualization, Supervision.

REFERENCES

1. Ioannidis JP, Haidich AB, Pappa M et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. Jama 2001;286:821-30.
2. Mansournia MA, Higgins JP, Sterne JA, Hernan MA. Biases in Randomized Trials: A Conversation Between Trialists and Epidemiologists. Epidemiology 2017;28:54-59.
3. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC medicine 2010;8:18.
4. Sterne JAC, Savovic J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj 2019;366:l4898.
5. Ahmad FS, Chan C, Rosenman MB et al. Validity of Cardiovascular Data From Electronic Sources: The Multi-Ethnic Study of Atherosclerosis and HealthLNK. Circulation 2017;136:1207-1216.
6. Faridi KF, Tamez H, Butala NM et al. Comparability of Event Adjudication Versus Administrative Billing Claims for Outcome Ascertainment in the DAPT Study: Findings From the EXTEND-DAPT Study. Circulation Cardiovascular quality and outcomes 2021;14:e006589.
7. Mc Cord KA, Ewald H, Agarwal A et al. Treatment effects in randomised trials using routinely collected data for outcome assessment versus traditional trials: meta-research study. Bmj 2021;372:n450.
8. Psaty BM, Delaney JA, Arnold AM et al. Study of Cardiovascular Health Outcomes in the Era of Claims Data: The Cardiovascular Health Study. Circulation 2016;133:156-64.
9. Rodrigues C. OA, Patel S., Agarwal A., Roza da Costa B., Lin E., Yeh R.W., Jüni P., Goodman S. G., Farkouh M. E., Udell J. A. Accuracy of Cardiovascular Trial Outcome Ascertainment and Treatment Effect Estimates from Routine Health Data: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes 2021;14.
10. Leonardi S, Branca M, Franzone A et al. Comparison of Investigator-Reported and Clinical Event Committee-Adjudicated Outcome Events in GLASSY. Circulation Cardiovascular quality and outcomes 2021;14:e006581.
11. Ndounga Diakou LA, Trinquart L, Hrobjartsson A et al. Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates. The Cochrane database of systematic reviews 2016;3:MR000043.
12. Olivier CB, Bhatt DL, Leonardi S et al. Central Adjudication Identified Additional and Prognostically Important Myocardial Infarctions in Patients Undergoing Percutaneous Coronary Intervention. Circulation Cardiovascular interventions 2019;12:e007342.
13. https://www.nice.org.uk/guidance/cg95.
14. Gulati M, Levy PD, Mukherjee D et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;144:e368-e454.
15. Knuuti J, Wijns W, Saraste A et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European heart journal 2020;41:407-477.
16. Poon M, Lesser JR, Biga C et al. Current Evidence and Recommendations for Coronary CTA First in Evaluation of Stable Coronary Artery Disease. Journal of the American College of Cardiology 2020;76:1358-1362.

17. Investigators S-H, Newby DE, Adamson PD et al. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. The New England journal of medicine 2018;379:924-933.
18. Douglas PS, Hoffmann U, Patel MR et al. Outcomes of anatomical versus functional testing for coronary artery disease. The New England journal of medicine 2015;372:1291-300.
19. Cantoni V, Green R, Acampa W et al. Long-term prognostic value of stress myocardial perfusion imaging and coronary computed tomography angiography: A meta-analysis. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2016;23:185-97.
20. Siontis GC, Mavridis D, Greenwood JP et al. Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: network meta-analysis of diagnostic randomised controlled trials. Bmj 2018;360:k504.
21. Shamseer L, Moher D, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj 2015;350:g7647.
22. Tricco AC, Lillie E, Zarin W et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Annals of internal medicine 2018;169:467-473.
23. Sterne JA, Hernan MA, Reeves BC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Bmj 2016;355:i4919.
24. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC medical research methodology 2014;14:25.
25. Rover C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. BMC medical research methodology 2015;15:99.
26. Langan D, Higgins JPT, Jackson D et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. Research synthesis methods 2019;10:83-98.
27. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. European heart journal 2014;35:3336-45.
28. Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Statistics in medicine 2002;21:1513-24.
29. Cheezum MK, Hulten EA, Taylor AJ et al. Cardiac CT angiography compared with myocardial perfusion stress testing on downstream resource utilization. J Cardiovasc Comput Tomogr 2011;5:101-9.
30. Hlatky MA, Ray RM, Burwen DR et al. Use of Medicare data to identify coronary heart disease outcomes in the Women's Health Initiative. Circulation Cardiovascular quality and outcomes 2014;7:157-62.
31. Jorgensen ME, Andersson C, Norgaard BL et al. Functional Testing or Coronary Computed Tomography Angiography in Patients With Stable Coronary Artery Disease. Journal of the American College of Cardiology 2017;69:1761-1770.
32. Karthikeyan G, Guzic Salobir B, Jug B et al. Functional compared to anatomical imaging in the initial evaluation of patients with suspected coronary artery disease: An international, multi-center, randomized controlled trial (IAEA-SPECT/CTA study). Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2017;24:507-517.

33. Lee SP, Seo JK, Hwang IC et al. Coronary computed tomography angiography vs. myocardial single photon emission computed tomography in patients with intermediate risk chest pain: a randomized clinical trial for cost-effectiveness comparison based on real-world cost. Eur Heart J Cardiovasc Imaging 2019;20:417-425.
34. Lubbers M, Dedic A, Coenen A et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. European heart journal 2016;37:1232-43.
35. McKavanagh P, Lusk L, Ball PA et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. Eur Heart J Cardiovasc Imaging 2015;16:441-8.
36. Min JK, Koduru S, Dunning AM et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. J Cardiovasc Comput Tomogr 2012;6:274-83.
37. Min JK, Shaw LJ, Berman DS, Gilmore A, Kang N. Costs and clinical outcomes in individuals without known coronary artery disease undergoing coronary computed tomographic angiography from an analysis of Medicare category III transaction codes. Am J Cardiol 2008;102:672-8.
38. Nielsen LH, Olsen J, Markenvard J, Jensen JM, Norgaard BL. Effects on costs of frontline diagnostic evaluation in patients suspected of angina: coronary computed tomography angiography vs. conventional ischaemia testing. Eur Heart J Cardiovasc Imaging 2013;14:449-55.
39. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. Jama 2011;306:2128-36.
40. Stillman AE, Gatsonis C, Lima JAC et al. Coronary Computed Tomography Angiography Compared With Single Photon Emission Computed Tomography Myocardial Perfusion Imaging as a Guide to Optimal Medical Therapy in Patients Presenting With Stable Angina: The RESCUE Trial. J Am Heart Assoc 2020;9:e017993.
41. Vamvakidou A, Danylenko O, Pradhan J et al. Relative clinical value of coronary computed tomography and stress echocardiography-guided management of stable chest pain patients: a propensity-matched analysis. Eur Heart J Cardiovasc Imaging 2020.
42. Siontis GCM, Raber L. Letter by Siontis and Raber Regarding Article, "Low-Attenuation Noncalcified Plaque on Coronary Computed Tomography Angiography Predicts Myocardial Infarction: Results From the Multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART)". Circulation 2020;142:e240-e241.
43. Hoffmann U, Udelson JE. Imaging Coronary Anatomy and Reducing Myocardial Infarction. The New England journal of medicine 2018;379:977-978.
44. Williams MC, Adamson PD, Newby DE. Coronary CT Angiography and Subsequent Risk of Myocardial Infarction. The New England journal of medicine 2019;380:300.
45. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Annals of internal medicine 2011;155:39-51.

46. Furlan AD, Tomlinson G, Jadad AA, Bombardier C. Methodological quality and homogeneity influenced agreement between randomized trials and nonrandomized studies of the same intervention for back pain. J Clin Epidemiol 2008;61:209-31.
47. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of internal medicine 2001;135:982-9.
48. Papanikolaou PN, Christidi GD, Ioannidis JP. Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. CMAJ 2006;174:635-41.
49. Savovic J, Jones HE, Altman DG et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Annals of internal medicine 2012;157:429-38.
50. Jones WS, Roe MT, Antman EM et al. The Changing Landscape of Randomized Clinical Trials in Cardiovascular Disease. Journal of the American College of Cardiology 2016;68:1898-1907.
51. Mentz RJ, Hernandez AF, Berdan LG et al. Good Clinical Practice Guidance and Pragmatic Clinical Trials: Balancing the Best of Both Worlds. Circulation 2016;133:872-80.
52. Guimaraes PO, Krishnamoorthy A, Kaltenbach LA et al. Accuracy of Medical Claims for Identifying Cardiovascular and Bleeding Events After Myocardial Infarction : A Secondary Analysis of the TRANSLATE-ACS Study. JAMA Cardiol 2017;2:750-757.
53. Barry SJ, Dinnett E, Kean S, Gaw A, Ford I. Are routinely collected NHS administrative records suitable for endpoint identification in clinical trials? Evidence from the West of Scotland Coronary Prevention Study. PLoS One 2013;8:e75379.
54. Maddox TM, Albert NM, Borden WB et al. The Learning Healthcare System and Cardiovascular Care: A Scientific Statement From the American Heart Association. Circulation 2017;135:e826-e857.

Table 1. Characteristics of the included studies stratified according to the study design.

	Total (n=15)	Non-RCTs (n=7)	RCTs (n=8)
STUDY DESIGN			
Geographic area			
North-America	7 (46)	4 (57)	3 (38)
Europe	6 (40)	3 (43)	3 (38)
Asia	1 (7)	0	1 (12)
Global	1 (7)	0	1 (12)
Study sites			
Single center	2 (13)	2 (29)	0
Multicenter	13 (86)	5 (71)	8 (100)
Funding			
Non-industry	11 (73)	4 (57)	7 (88)
Industry related	1 (7)	0	1 (12)
None declared	3 (20)	3 (43)	0
Control group			
SPECT	7 (46)	3 (43)	4 (50)
Exercise-ECG	2 (13)	1 (14)	1 (12)
Stress echocardiography	1 (7)	1 (14)	0
Multiple tests	5 (34)	2 (29)	3 (38)
Primary outcome			
Cardiovascular events	8 (53)	4 (57)	4 (50)
Downstream testing/health-related costs	4 (27)	3 (43)	1 (12)
Symptoms at follow-up	3 (20)	0	3 (38)
Follow-up period			
Median (IQR)	12 (12-24)	24 (9-30)	12 (12-20)
Minimum	2	6	2
Maximum	58	43	58
STUDY POPULATION			
Sample size			
≤1000	7 (46)	2 (29)	5 (72)
>1000	8 (54)	5 (71)	3 (38)
Female population			
<50%	7 (46)	3 (43)	4 (50)
≥ 50%	8 (54)	4 (57)	4 (50)
Mean age			
<60 years	9 (60)	5 (71)	4 (50)
≥60 years	6 (40)	2 (29)	4 (50)
Individuals with diabetes			
<20%	9 (60)	5 (71)	4 (50)
≥20%	6 (40)	2 (29)	4 (50)
OUTCOME			
MI definition			
Not provided	5 (33)	3 (43)	2 (25)
ICD code	6 (40)	4 (57)	2 (25)
Clinical definition	4 (26)	0	4 (50)
Outcome ascertainment			
RCHD	8 (53)	6 (86)	2 (25)
Research driven follow-up	7 (47)	1 (14)	6 (75)
Outcome assessment			
Care providers/local investigators	11 (73)	6 (85)	5 (62)
Central investigator	2 (13)	0	2 (25)
Not reported	2 (13)	1 (15)	1 (13)
Event adjudication			
Yes	3 (20)	1 (14)	2 (25)
No	12 (80)	6 (86)	6 (75)
Risk of bias for outcome MI†			
Low	3 (20)	0	3 (38)
Moderate	9 (60)	4 (57)	5 (62)
High	3 (20)	3*(43)	0

ECG=electrocardiogram; ICD=international classification of disease;.IQR=interquartile range; MI=myocardial infarction; RCHD=routinely collected health data; RCT=randomized controlled trial; SPECT=Single-photon emission computed tomography;
†ROBINS-I for observational studies and ROB-2 for randomized controlled trials *Includes serious to critical risk of bias

Table 2. Study-level characteristics and methods of outcomes' ascertainment and assessment.

First Author, Year of publication	Sample size	Control group	Exercise-ECG Control group(%)	Follow-up duration (months)	Outcome ascertainment	Outcome assessment	Number of observer	Adjudication	Blinding care provider	Blinding evaluators	MI definition	Fatal MI included
Non-RCT												
Cheezum et al., 2011	493	SPECT	0	30	RCHD	local investigator	>1	Yes	not specified	not specified	Not reported	No
Hlatky et al., 2014	1703	SPECT	0	24	Research-driven follow-up	not specified	not specified	unclear	not specified	not specified	Not reported	No
Jorgensen et al., 2017	86705	exercise-ECG or SPECT	79.4	43	RCHD	care providers	not specified	No	No	not specified	ICD codes	Yes
Min et al., 2008	9690	SPECT	0	9	RCHD	care providers	not specified	No	No	No	ICD codes	Not specified
Nielsen et al., 2013	498	exercise-ECG	100	12	RCHD	care providers	not specified	No	No	No	ICD codes	No
Shreibati et al., 2011	282830	functional test[#]	22.3	6	RCHD	care providers	not specified	No	No	No	ICD codes	Not specified
Vamvakidou et al., 2020	1980	stress-echo	0	24	RCHD	care providers	not specified	No	No	No	Not reported	Yes
RCT												
Douglas et al., 2015	10003	functional test[#]	9.5	24	Research-driven follow-up	CEC	>1	Yes	not specified	Yes	Universal definition	No
Karthikeyan et al., 2017	303	SPECT	0	12	not reported	not reported	not specified	No	not specified	not specified	Clinical definition[†]	No
Lee et al., 2019	903	SPECT	0	12	Research-driven follow-up	care providers	not specified	No	not specified	not specified	ICD codes	No
Lubbers et al., 2016	350	functional test[#]	Most of patients	12	Research-driven follow-up	CEC	>1	Yes	No	Yes	Clinical definition[†]	No
McKavanagh et al., 2015	488	exercise-ECG	100	12	RCHD	care providers	not specified	No	-	-	Clinical definition[†]	Not specified
Min et al., 2012	180	SPECT	0	2	Research-driven follow-up	care providers	not specified	No	No	No	Not reported	No
Newby et al., 2018[§]	4146	functional test[#]	86	58	RCHD	care providers	not specified	No*	No	No	ICD codes	No
Stillman et al., 2020	1050	SPECT	0	16.2	Research-driven follow-up	care providers	not specified	No	No	No	Not reported	No

CEC= central event committee; ECG= electrocardiogram; ICD = International Classification of Disease; MI= myocardial infarction; RCHD = Routine collected health data (electronic health records or administrative claims); RCT= randomized controlled trial

SPECT= single-photon emission computerized tomography
*only in selected case of uncertainty assessment performed by 1 observer
[#]X-ECG or SPECT or stress-echo
†study specific
§the experimental group was CCTA+standard of care, the control group standard of care alone

Table 3. Random effect meta-analysis estimates of CCTA versus noninvasive functional testing for non-RCTs and RCTs in separate and stratified according to study characteristics.

	Non-RCTs (n=7)				RCTs (n=8)			
	OR (95%CI)	***p*-value**	**τ^2**	***p* for comparison**	**OR (95%CI)**	***p*-value**	**τ^2**	***p* for comparison**
Overall	0.51 (0.45 – 0.58)	<0.001	<0.001	na	0.64 (0.47 – 0.88)	<0.001	<0.001	na
Study sites								
Single center	0.14 (0.01-2.70)	0.192	na	0.389	na	na	na	na
Multicenter	0.51 (0.45-0.59)	<0.001	<0.001		0.64 (0.47-0.88)	0.018	<0.001	
Funding								
Non-industry	0.50 (0.42-0.60)	0.004	<0.001	0.264	0.64 (0.47-0.88)	0.018	<0.001	na
Industry/None declared	0.66 (0.24-1.83)	0.221	<0.001		na	na	na	
Control test								
Single test	0.63 (0.28-1.39)	0.158	<0.001	0.395	0.62 (0.00-9.9*10^{-3})	0.697	<0.001	0.956
Multiple tests	0.51 (0.45-0.58)	0.005	<0.001		0.65 (0.45-0.93)	0.036	0.802	
Follow-up								
≤12 months	0.56 (0.26-1.20)	0.081	<0.001	0.611	1.06 (0-1.4*10^{-3})	0.953	<0.001	0.501
>12 months	0.51 (0.40-0.64)	0.007	<0.001		0.63 (0.36-1.11)	0.072	<0.001	
Sample size								
≤1000	0.14 (0.01-2.70)	0.192	na	0.389	1.06 (0-1.4*10^{-4})	0.953	<0.001	0.501
>1000	0.51 (0.45-0.59)	<0.001	<0.001		0.63 (0.36-1.11)	0.072	<0.001	
Female population								
<50%	0.61 (0-6.0*10^{-2})	0.528	0.185	0.737	0.59 (0.28-1.25)	0.094	<0.001	0.243
≥50%	0.51 (0.44-0.58)	<0.001	<0.001		0.74 (0.24-2.23)	0.178	<0.001	
Age (mean)								
<60	0.51 (0.42-0.63)	0.002	<0.001	0.760	0.57 (0.35-0.94)	0.040	<0.001	0.157
≥60	0.49 (0.06-4.18)	0.147	<0.001		0.78 (0.07-8.55)	0.411	<0.001	
Diabetes								
<20%	0.51 (0.42-0.63)	0.002	<0.001	0.760	0.61 (0.34-1.09)	0.067	<0.001	0.902
≥20%	0.49 (0.06-4.18)	0.147	<0.001		0.64 (0.01-59.22)	0.427	0.0947	
MI definition								

Not provided	0.56 (0.00-214)	0.420	0.074	0.855	0.29 (0.06-1.41)	0.125	na	0.323
ICD codes	0.51 (0.43-0.60)	<0.001	<0.001		0.59 (0.41-0.87)	0.007	na	
Clinical definition	na	na	na		0.77 (0.41-1.44)	0.212	<0.001	
Outcome ascertainment								
RCHD	0.51 (0.45-0.59)	<0.001	<0.001	0.447	0.61 (0.06-6.71)	0.233	<0.001	0.795
Research driven follow-up	0.29 (0.06-1.28)	0.102	na		0.66 (0.26-1.70)	0.199	0.0332	
Outcome assessment								
Care providers/local investigators	0.51 (0.45-0.59)	<0.001	<0.001	0.447	0.59 (0.28-1.25)	0.178	<0.001	0.244
Central investigators	0.29 (0.06-1.28)	0.102	na		0.74 (0.24-2.23)	0.094	<0.001	
Event adjudication								
Yes	na	na	na	na	0.74 (0.24-2.23)	0.178	<0.001	0.244
No	0.51 (0.45-0.58)	<0.001	<0.001		0.59 (0.28-1.25)	0.094	<0.001	
Risk of bias								
Low	na	na	na	0.611	0.74 (0.24-2.23)	0.178	<0.001	0.244
Moderate	0.51 (0.40-0.64)	0.007	<0.001		0.59 (0.28-1.25)	0.094	0.410	
High	0.56 (0.26-1.20)	0.081	<0.001		na		na	

OR=odds ratio, CI=confidence interval, NA=not applicable, MI=myocardial infarction, ICD=international classification of diseases, RCHD=routinely collected health data.
τ^2 are not reported when 2 studies or less (with events in at least one of the arms) contributed to the meta-analysis.

FIGURES LEGENDS

Figure 1. Odds Ratio (A) and Risk difference (B) from random effect meta-analysis of CCTA versus functional testing stratified according to study design (non-randomized versus randomized clinical trials).
Studies with 0 events in both arms did not contribute to the effect estimate shown in panel A, but they are shown for consistency with panel B.

Figure 2. Random effect meta-analyses of CCTA versus functional testing stratified according to study design and other characteristics.

*Studies with absence of events in both arms did not contribute to the effect estimate.
†For MI definition the RORs are ordered as "not provided vs. ICD codes", "ICD codes vs. clinical definition", "not provided vs. clinical definition".
‡For Risk of bias the RORs are ordered as "low vs. moderate", "moderate vs. high", "low vs. high

Figure 1.

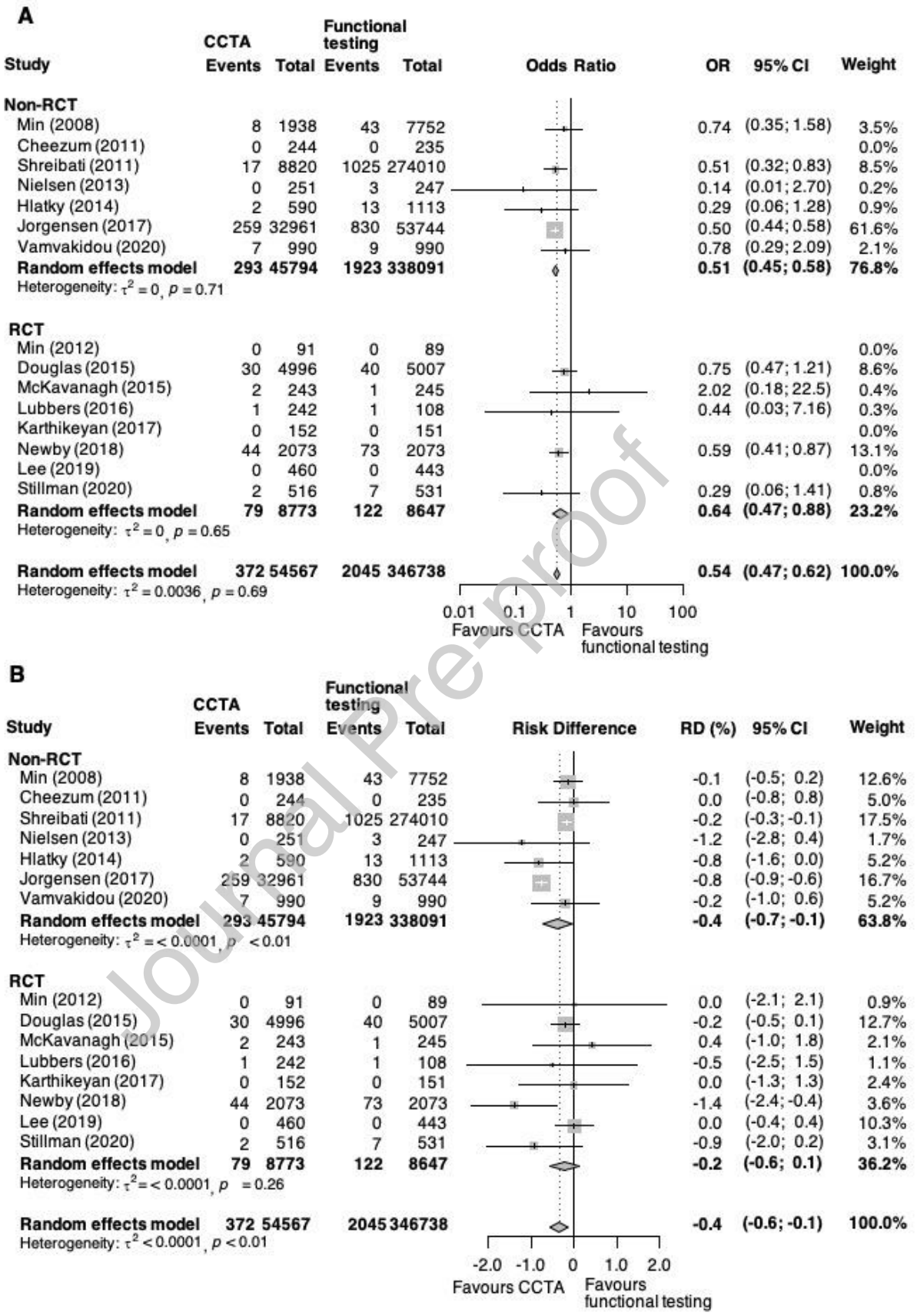
A
Study
CCTA Events Total
Functional testing Events Total
Odds Ratio
OR 95% CI Weight
Non-RCT
Min (2008) 8 1938 43 7752 0.74 (0.35; 1.58) 3.5%
Cheezum (2011) 0 244 0 235 0.0%
Shreibati (2011) 17 8820 1025 274010 0.51 (0.32; 0.83) 8.5%
Nielsen (2013) 0 251 3 247 0.14 (0.01; 2.70) 0.2%
Hlatky (2014) 2 590 13 1113 0.29 (0.06; 1.28) 0.9%
Jorgensen (2017) 259 32961 830 53744 0.50 (0.44; 0.58) 61.6%
Vamvakidou (2020) 7 990 9 990 0.78 (0.29; 2.09) 2.1%
Random effects model 293 45794 1923 338091 0.51 (0.45; 0.58) 76.8%
Heterogeneity: $\tau^2 = 0$, $p = 0.71$
RCT
Min (2012) 0 91 0 89 0.0%
Douglas (2015) 30 4996 40 5007 0.75 (0.47; 1.21) 8.6%
McKavanagh (2015) 2 243 1 245 2.02 (0.18; 22.5) 0.4%
Lubbers (2016) 1 242 1 108 0.44 (0.03; 7.16) 0.3%
Karthikeyan (2017) 0 152 0 151 0.0%
Newby (2018) 44 2073 73 2073 0.59 (0.41; 0.87) 13.1%
Lee (2019) 0 460 0 443 0.0%
Stillman (2020) 2 516 7 531 0.29 (0.06; 1.41) 0.8%
Random effects model 79 8773 122 8647 0.64 (0.47; 0.88) 23.2%
Heterogeneity: $\tau^2 = 0$, $p = 0.65$
Random effects model 372 54567 2045 346738 0.54 (0.47; 0.62) 100.0%
Heterogeneity: $\tau^2 = 0.0036$, $p = 0.69$
0.01 0.1 1 10 100
Favours CCTA
Favours functional testing
B
Study
CCTA Events Total
Functional testing Events Total
Risk Difference
RD (%) 95% CI Weight
Non-RCT
Min (2008) 8 1938 43 7752 -0.1 (-0.5; 0.2) 12.6%
Cheezum (2011) 0 244 0 235 0.0 (-0.8; 0.8) 5.0%
Shreibati (2011) 17 8820 1025 274010 -0.2 (-0.3; -0.1) 17.5%
Nielsen (2013) 0 251 3 247 -1.2 (-2.8; 0.4) 1.7%
Hlatky (2014) 2 590 13 1113 -0.8 (-1.6; 0.0) 5.2%
Jorgensen (2017) 259 32961 830 53744 -0.8 (-0.9; -0.6) 16.7%
Vamvakidou (2020) 7 990 9 990 -0.2 (-1.0; 0.6) 5.2%
Random effects model 293 45794 1923 338091 -0.4 (-0.7; -0.1) 63.8%
Heterogeneity: $\tau^2 = < 0.0001$, $p = < 0.01$
RCT
Min (2012) 0 91 0 89 0.0 (-2.1; 2.1) 0.9%
Douglas (2015) 30 4996 40 5007 -0.2 (-0.5; 0.1) 12.7%
McKavanagh (2015) 2 243 1 245 0.4 (-1.0; 1.8) 2.1%
Lubbers (2016) 1 242 1 108 -0.5 (-2.5; 1.5) 1.1%
Karthikeyan (2017) 0 152 0 151 0.0 (-1.3; 1.3) 2.4%
Newby (2018) 44 2073 73 2073 -1.4 (-2.4; -0.4) 3.6%
Lee (2019) 0 460 0 443 0.0 (-0.4; 0.4) 10.3%
Stillman (2020) 2 516 7 531 -0.9 (-2.0; 0.2) 3.1%
Random effects model 79 8773 122 8647 -0.2 (-0.6; 0.1) 36.2%
Heterogeneity: $\tau^2 = < 0.0001$, $p = 0.26$
Random effects model 372 54567 2045 346738 -0.4 (-0.6; -0.1) 100.0%
Heterogeneity: $\tau^2 < 0.0001$, $p < 0.01$
-2.0 -1.0 0 1.0 2.0
Favours CCTA
Favours functional testing

Figure 2.