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# Coronary Computed Tomography Angiography vs Functional Stress Testing for Patients With Suspected Coronary Artery Disease
## A Systematic Review and Meta-analysis

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**IMPORTANCE** Coronary computed tomography angiography (CCTA) is a new approach for the diagnosis of anatomical coronary artery disease (CAD), but it is unclear how CCTA performs compared with the standard approach of functional stress testing.

**OBJECTIVE** To compare the clinical effectiveness of CCTA with that of functional stress testing for patients with suspected CAD.

**DATA SOURCES** A systematic literature search was conducted in PubMed and MEDLINE for English-language randomized clinical trials of CCTA published from January 1, 2000, to July 10, 2016.

**STUDY SELECTION** Researchers selected randomized clinical trials that compared a primary strategy of CCTA with that of functional stress testing for patients with suspected CAD and reported data on patient clinical events and changes in therapy.

**DATA EXTRACTION AND SYNTHESIS** Two reviewers independently extracted data from and assessed the quality of the trials. This analysis followed the PRISMA statement for reporting systematic reviews and meta-analyses and used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. The Mantel-Haenszel method was used to conduct the primary analysis. Summary relative risks were calculated with a random-effects model.

**MAIN OUTCOMES AND MEASURES** The outcomes of interest were all-cause mortality, cardiac hospitalization, myocardial infarction, invasive coronary angiography, coronary revascularization, new CAD diagnoses, and change in prescription for aspirin and statins.

**RESULTS** Thirteen trials were included, with 10 315 patients in the CCTA arm and 9777 patients in the functional stress testing arm who were followed up for a mean duration of 18 months. There were no statistically significant differences between CCTA and functional stress testing in death (1.0% vs 1.1%; risk ratio [RR], 0.93; 95% CI, 0.71-1.21) or cardiac hospitalization (2.7% vs 2.7%; RR, 0.98; 95% CI, 0.79-1.21), but CCTA was associated with a reduction in the incidence of myocardial infarction (0.7% vs 1.1%; RR, 0.71; 95% CI, 0.53-0.96). Patients undergoing CCTA were significantly more likely to undergo invasive coronary angiography (11.7% vs 9.1%; RR, 1.33; 95% CI, 1.12-1.59) and revascularization (7.2% vs 4.5%; RR, 1.86; 95% CI, 1.43-2.43). They were also more likely to receive a diagnosis of new CAD and to have initiated aspirin or statin therapy.

**CONCLUSIONS AND RELEVANCE** Compared with functional stress testing, CCTA is associated with a reduced incidence of myocardial infarction but an increased incidence of invasive coronary angiography, revascularization, CAD diagnoses, and new prescriptions for aspirin and statins. Despite these differences, CCTA is not associated with a reduction in mortality or cardiac hospitalizations.

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Coronary computed tomography angiography (CCTA) images coronary artery anatomy, whereas functional stress testing assesses for inducible cardiac ischemia. Coronary computed tomography angiography has higher diagnostic accuracy for coronary artery disease (CAD) when using invasive coronary angiography as the reference standard.[1] Several studies have concluded that CCTA is safe and expedites the triage of patients in the emergency department with acute chest pain compared with standard care.[2,3] United States and European cardiology guidelines include the use of CCTA for patients with suspected CAD.[4]

Whether CCTA improves clinical outcomes compared with traditional functional stress testing for patients with suspected CAD remains unclear. Meta-analyses comparing CCTA vs stress testing have reached different conclusions using a limited number of trials and have not assessed the effect on new diagnoses of CAD and changes to cardiac medication.[5-8] Because the value of diagnostic tests lies in their ability to affect clinical management and improve patient outcomes, we performed a systematic review and meta-analysis of randomized clinical trials (RCTs) for CCTA vs functional stress testing to examine subsequent patient management and cardiovascular outcomes for patients with both acute and stable chest pain.

### Key Points

**Question** For patients with suspected coronary artery disease, what is the effect on clinical outcomes of coronary computed tomography angiography compared with functional stress testing?

**Findings** This systematic review and meta-analysis of randomized clinical trials found that, compared with functional stress testing, coronary computed tomography angiography may reduce the incidence of myocardial infarction, but not death or cardiac hospitalizations. Coronary computed tomography angiography increased the downstream rates of invasive coronary angiography and coronary revascularization, as well as new coronary artery disease diagnoses and new prescriptions for aspirin and statin medications.

**Meaning** Compared with functional stress testing, coronary computed tomography angiography is associated with a decreased incidence of myocardial infarction in patients with suspected coronary artery disease, as well as an increase in detection of coronary artery disease and use of secondary prevention medications; tradeoffs involve an increase in downstream invasive procedures, many of which may be unnecessary.

## Methods

### Data Sources

We followed the PRISMA statement for reporting systematic reviews and meta-analyses.[9] A systematic search of MEDLINE and PubMed for English-language RCTs of CCTA was performed. Search terms corresponding to *coronary computed tomography angiography* limited to RCTs conducted for adults from January 1, 2000, to July 10, 2016, were used. We also searched the references of all articles retrieved (eAppendix in the Supplement). We identified all RCTs of CCTA vs functional stress testing for patients with suspected CAD that included information on downstream cardiovascular events and patient management with at least 1 month of follow-up. This study used deidentified, trial level data from published trials. The data publicly available at the time our study was performed; thus, institutional review board approval was not sought, nor was it necessary.

### Study Selection

Two of us (A.J.F. and B.P.) independently performed the following steps to screen studies identified in the database search and to extract data. Any disagreements were resolved by consensus. First, all titles were reviewed to exclude studies that were observational, that performed the wrong test (eg, lower extremity CTA), or that addressed the wrong question (eg, comparing diagnostic accuracy or comparing different CCTA techniques), followed by reviewing abstracts of the remaining studies using the same exclusion criteria.

### Data Extraction

Two of us (A.J.F. and B.P.) independently reviewed all studies meeting the inclusion criteria and performed standardized data extraction of the following study characteristics: patient population (eg, acute vs stable chest pain), setting (eg, emergency department, inpatient, or outpatient), design (eg, intervention and comparator arms), primary end point (s), duration of follow-up, patient characteristics, and patient outcomes (all-cause death, myocardial infarction [MI], cardiac hospitalization, invasive coronary angiography, coronary revascularization including percutaneous coronary intervention or coronary artery bypass graft surgery, new CAD diagnosis, new medication change for aspirin, and new medication change for statin therapy). New CAD was diagnosed when patients had either angiographic evidence of obstructive CAD on a CCTA (ie, >50% obstruction) and/or angiographic evidence of obstructive CAD on an invasive coronary angiogram (ie, >50% obstruction). If these data were not provided, new CAD was diagnosed if any of the following diagnoses were explicitly stated: acute coronary syndrome, stable angina, or CAD.

### Data Synthesis

The Mantel-Haenszel method was used to conduct the primary analysis. Each clinical outcome was organized into a 2 × 2 table and analyzed on the log relative scale using a random-effects model. A prespecified subgroup analysis was performed based on whether patients were being evaluated for acute vs stable chest pain. Trials that did not report the clinical end point of interest were removed from the denominator and not factored into the analysis. Trials in which the end point of interest was reported but no events occurred in either arm were included in the analyses using a fixed-count correction method, where a value of 1 was added to all cell counts. Trials in which the end point of interest was reported but events occurred in only 1 arm were included without the need for correction. Examination of heterogeneity was performed using $Q$ statistics and $I^2$. Heterogeneity was assessed for all studies



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combined and between subgroups. A sensitivity analysis was performed for each end point by excluding individual studies. Examination of publication bias was performed visually using funnel plots.

### Quality of Trials

Two of us (A.J.F. and S.S.D.) independently assessed the quality of the trials using Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[10] Any disagreements were resolved by consensus.

### Statistical Analysis

All statistical analyses were performed with Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration). *P* values were 2 sided, with $P < .05$ considered statistically significant.

## Results

### Qualitative Synthesis

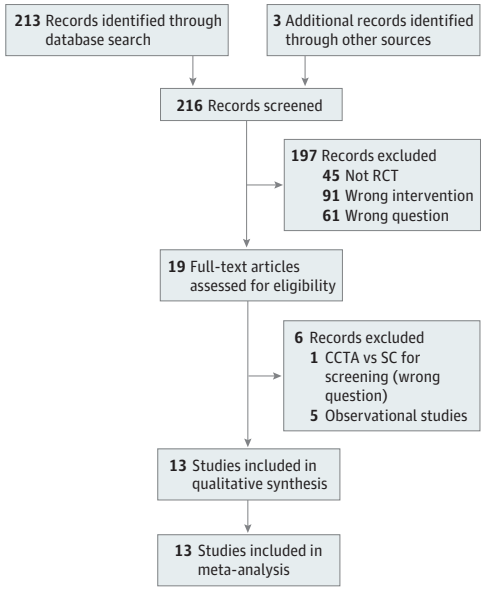
We screened 216 records and 19 full-text articles (**Figure 1**), from which 13 RCTs that randomized 20 092 patients were included: 10 315 patients were assigned to the CCTA arm and 9777 were assigned to the functional stress testing arm.[2,3,11-21] Mean participant age was 58 years, and 9845 were women (49.0%). Patients in the acute chest pain subgroup were significantly younger than those in the stable chest pain subgroup (53 vs 59 years; eTable 1 in the Supplement). The mean duration of follow-up was 18 months; follow-up was longer in the stable chest pain subgroup than in the acute chest pain subgroup (23 vs 5 months; **Table 1**).

The CCTA strategy used in the intervention arm differed across studies, and most of the RCTs did not follow prespecified protocols for handling indeterminate stenosis identified on a CCTA. In 2 trials, there were prespecified plans to follow up all cases of intermediate stenosis with myocardial perfusion imaging,[11,12] and in 1 trial (SCOT-HEART [Scottish Computed Tomography of the Heart Trial]), 85% of patients received functional stress testing in both arms.[21]

The stress testing arms varied among trials, with multiple modalities, including no testing, used in 4 trials (31%), myocardial perfusion imaging used in 4 trials (31%), exercise treadmill or bike electrocardiography testing used in 3 trials (23%), and stress echocardiography used in 1 trial (8%); the modality was not specified in 1 trial (8%). In 2 studies in which multiple modalities were used that involved patients with acute chest pain, 42% of patients in one trial and 26% of patients in the other trial did not undergo any functional stress testing in the control arms.[2,3]

Nine trials involved patients who presented to the emergency department with symptoms concerning for acute coronary syndrome and who underwent testing prior to or shortly following hospital discharge.[2,3,11-13,15-17,20] Eight trials required initially normal serum troponin level test results and nonischemic electrocardiogram results,[2,3,11-13,15,16,20] while 1 trial enrolled patients admitted with suspected acute coronary syndrome who were thought to be at intermediate risk based on elevated troponin levels, electrocardiographic changes, or clinical signs or symptoms.[17] Four trials involved patients who underwent testing in the outpatient setting for symptoms of stable chest pain.[14,18,19,21]

Figure 1. PRISMA Diagram




CCTA indicates coronary computed tomography angiography; RCT, randomized clinical trial; and SC, standard care (stress testing in all or most patients in the control group).

There was significant variation in the quality of the trials based on the Cochrane Collaboration's tool for bias assessment (eTable 2 in the Supplement). The overall quality of evidence was judged to be moderate, with 45 of 98 domains (46%) judged to be at high or questionable risk for bias. In all studies, at least 2 domains were potentially susceptible to bias. Lack of blinding patients and personnel was noted in all trials. Only 3 trials explicitly used blinded outcome assessment,[12,18,21] and only 5 trials explicitly stated their technique for allocation concealment in the publications.[2,11,15,16,21] The SCOT-HEART was assigned a high risk of other bias because its design included functional stress testing for 85% of patients in the CCTA arm.[21] The funding source was noted as a possible risk of other bias in 3 trials because industry-sponsored trials are nearly 4 times more likely to report positive results than are non–industry-sponsored studies.[11,12,14,22]

### Quantitative Results

#### All-Cause Mortality

There was no difference between CCTA and functional stress testing in mortality overall (1.0% vs 1.1%; risk ratio [RR], 0.93; 95% CI, 0.71-1.21) or in patients with acute (0.3% vs 0.6%; RR, 0.66; 95% CI, 0.27-1.59) or stable chest pain (1.3% vs 1.3%; RR, 0.96; 95% CI, 0.72-1.27) (**Table 2** and eFigure 1 in the Supplement). No deaths occurred in 7 trials, and zero event handling was used.[2,3,11-14,20] There was no significant heteroge-



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Table 1. Description of Trials

| Trial | Setting | Intervention Arm | Comparator Arm | Primary End Point(s) | Follow-up, mo | Location |
|---|---|---|---|---|---|---|
| Goldstein et al,[11] 2007 | ED | CCTA with MPI for all indeterminate stenoses | MPI, 100% | Not specified | 6 | United States |
| Goldstein et al (CT-STAT),[12] 2011 | ED | CCTA with MPI for all indeterminate stenoses | MPI, 100% | Time to diagnosis | 6 | United States |
| Miller et al,[13] 2011 | ED | CCTA | Not specified | Total resource use | 3 | United States |
| Min et al,[14] 2012 | Outpatient | CCTA | MPI, 100% | Near-term angina-specific health status | 2 | United States |
| ACRIN/PA,[2] 2012 | ED | CCTA | Stress test with imaging, 56%; ETT, 2%; no test, 42% | Absence of MI and cardiac death during first 30 d in subgroup with negative CCTA | 1 | United States |
| Hoffman et al (ROMICAT-II),[3] 2012 | ED | CCTA | MPI, 25%; SE, 20%; ETT, 29%; no test, 26% | Length of stay in the hospital | 1 | United States |
| Linde et al (CATCH),[15] 2013 | Outpatient following ED visit | CCTA | EBT,76%; MPI, 22% | Referral rate for ICA, positive predictive value for CAD and subsequent revascularizations | 4 | Denmark |
| Hamilton-Craig et al (CT-COMPARE),[16] 2014 | ED | CCTA | ETT, 100% | Diagnostic performance for ACS | 12 | Australia |
| PROSPECT,[17] 2015 | Inpatient | CCTA | MPI, 100% | Cardiac catheterization not leading to revascularization | 12 | United States |
| Douglas et al (PROMISE),[18] 2015 | Outpatient | CCTA | MPI, 67%; SE, 23%; ETT, 10% | Composite of death, MI, hospitalization for UA, or major procedural complication | 25 | North America |
| SCOT-HEART,[21] 2015 | Outpatient | CCTA and functional stress testing (ETT) for all eligible patients (85%) | ETT, 85% | Certainty of angina due to coronary heart disease at 6 wk | 20 | Scotland |
| McKavanagh et al (CAPP),[19] 2015 | Outpatient | CCTA | ETT, 100% | Change in Seattle Angina Questionnaire score from baseline to 3 mo | 12 | Ireland |
| Uretsky et al (PERFECT),[20] 2016 | Inpatient | CCTA | SE, 88%; MPI, 4% | No difference found in time to discharge, change in medication use, downstream testing, and cardiovascular rehospitalizations | 12 | United States |

Abbreviations: ACRIN/PA, American College of Radiology Imaging Network/Pennsylvania Department of Health; ACS, acute coronary syndrome; CAD, coronary artery disease; CAPP, Cardiac CT for the Assessment of Pain and Plaque; CATCH, Cardiac CT in the Treatment of Acute Chest Pain; CCTA, coronary computed tomography angiography; CT-COMPARE, CT Coronary Angiography Compared to Exercise ECG; CT-STAT, Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patient to Treatment; EBT, exercise bicycle test; ED, emergency department; ETT, exercise treadmill test; ICA, invasive coronary angiography; MI, myocardial infarction; MPI, myocardial perfusion imaging; PERFECT, Prospective First Evaluation in Chest Pain; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; PROSPECT, Prospective Randomized Outcome Trial Comparing Radionuclide Stress Myocardial Perfusion Imaging and ECG-Gated Coronary CT Angiography; ROMICAT-II, Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography–II; SCOT-HEART, Scottish Computed Tomography of the Heart Trial; SE, stress echocardiography; UA, unstable angina.

neity between trials ($\chi^2$ = 2.74; $P$ = .95; eFigure 1 in the Supplement). The overall effect estimate is not sensitive to the inclusion or exclusion of any individual trial. There was no significant interaction noted between the acute and stable chest pain subgroups ($\chi^2$ = 0.64; $P$ = .99). There is mild visual asymmetry in the funnel plot in eFigure 2 in the Supplement in favor of CCTA related to PROSPECT (Prospective Randomized Outcome Trial Comparing Radionuclide Stress Myocardial Perfusion Imaging and ECG-Gated Coronary CT Angiography).[17] Removal of this trial did not lead to a significant difference in the overall effect estimate.

### Myocardial Infarction

Coronary computed tomography angiography was associated with a reduction in MIs overall (0.7% vs 1.1%; RR, 0.71; 95% CI, 0.53-0.96) and for patients with stable chest pain but not those with acute chest pain (Table 2 and **Figure 2**). No MIs occurred in 4 trials, and zero event handling was used.[11-14] There was only a modest amount of heterogeneity between trials, which was not statistically significant ($\chi^2$ = 0.31; $P$ = .58; Figure 2). The overall effect estimate is sensitive to the exclusion of the SCOT-HEART trial, which assigned most patients in the CCTA arm to undergo functional stress testing.[21] Its removal leads to a 17% increase in the relative risk estimate that is no longer statistically significant (RR, 0.88; 95% CI, 0.70-1.21). The relative risk reduction was greater for patients with stable chest pain (RR, 0.68; 95% CI, 0.49-0.95) than for patients with acute chest pain (RR, 0.84; 95% CI 0.44-1.61) (Table 2), but there was no significant interaction between groups ($\chi^2$ = 0.31; $P$ = .58). There is no visual asymmetry in the funnel plot in eFigure 3 in the Supplement.



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Table 2. Summary of Findings[a]

| Outcome | Illustrative Comparative Risks, No. per 1000[b] | | RR (95% CI) | No. of Participants (No. of Studies) | Quality of Evidence[c] |
|---|---|---|---|---|---|
| | Assumed Risk (SC) | Corresponding Risk (CCTA) (95% CI) | | | |
| Death | 11 | 10 (8-14) | 0.93 (0.71-1.21) | 20 092 (13) | Moderate |
| Acute chest pain subgroup | 3 | 2 (1-5) | 0.66 (0.27-1.59) | 5275 (9) | Moderate |
| Stable chest pain subgroup | 13 | 12 (9-17) | 0.96 (0.72-1.27) | 14 817 (4) | Moderate |
| Myocardial infarction | 11 | 8 (6-11) | 0.71 (0.53-0.96) | 20 092 (13) | Moderate |
| Acute chest pain subgroup | 8 | 7 (4-13) | 0.84 (0.44-1.61) | 5275 (9) | Moderate |
| Stable chest pain subgroup | 11 | 7 (5-10) | 0.68 (0.49-0.95) | 14 817 (4) | Moderate |
| Cardiac hospitalization | 27 | 27 (21-33) | 0.98 (0.79-1.21) | 19 401 (12) | Moderate |
| Acute chest pain subgroup | 63 | 52 (42-66) | 0.83 (0.66-1.04) | 4584 (8) | Moderate |
| Stable chest pain subgroup | 17 | 21 (16-26) | 1.21 (0.96-1.53) | 14 821 (4) | Moderate |
| Invasive coronary angiography | 91 | 121 (102-155) | 1.33 (1.12-1.59) | 20 092 (13) | Moderate |
| Acute chest pain subgroup | 72 | 100 (79-127) | 1.39 (1.10-1.76) | 5275 (9) | Moderate |
| Stable chest pain subgroup | 98 | 125 (94-167) | 1.27 (0.96-1.70) | 14 817 (4) | Moderate |
| Revascularization | 45 | 84 (64-109) | 1.86 (1.43-2.43) | 20 092 (13) | High |
| Acute chest pain subgroup | 28 | 55 (41-74) | 1.96 (1.45-2.65) | 5275 (9) | High |
| Stable chest pain subgroup | 51 | 87 (57-133) | 1.70 (1.12-2.60) | 14 817 (4) | Moderate |
| Coronary artery disease diagnosis | 83 | 232 (169-321) | 2.80 (2.03-3.87) | 8793 (9) | High |
| Acute chest pain subgroup | 50 | 169 (96-295) | 3.37 (1.92-5.89) | 3979 (6) | High |
| Stable chest pain subgroup | 107 | 251 (162-392) | 2.35 (1.51-3.66) | 4814 (3) | High |
| Therapeutic change—aspirin | 82 | 181 (98-331) | 2.21 (1.20-4.04) | 5625 (5) | Low |
| Acute chest pain subgroup | 249 | 316 (247-401) | 1.27 (0.99-1.61) | 811 (2) | Low |
| Stable chest pain subgroup | 54 | 189 (145-245) | 3.50 (2.69-4.54) | 4814 (3) | Low |
| Therapeutic change—statin | 73 | 148 (80-275) | 2.03 (1.09-3.76) | 5625 (5) | Low |
| Acute chest pain subgroup | 190 | 230 (177-300) | 1.21 (0.93-1.58) | 811 (2) | Low |
| Stable chest pain subgroup | 53 | 184 (139-244) | 3.48 (2.63-4.61) | 4814 (3) | Low |

Abbreviations: CCTA, coronary computed tomography angiography; RR, risk ratio; SC, standard care.

[a] Must allow for minor discrepancy based on how data from table are calculated in the "corresponding risk" group. Both are technically correct.

[b] The basis for the assumed risk is based on the risk in the functional stress testing groups. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[c] High quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate; very low quality, we are very uncertain about the estimate.

### Cardiac Hospitalization

There was no statistically significant difference between CCTA and functional stress testing in cardiac hospitalizations overall (2.7% vs 2.7%; RR 0.98; 95% CI 0.79-1.21) or for patients with acute (4.8% vs 6.3%; RR, 0.83; 95% CI, 0.66-1.04) or stable chest pain (2.0% vs 1.7%; RR, 1.21; 95% CI, 0.96-1.53) (Table 2 and eFigure 4 in the Supplement). There was only a modest amount of heterogeneity between trials, which was not statistically significant ($\chi^2$ = 14.26; $P$ = .22; eFigure 4 in the Supplement), and the overall effect estimate is not sensitive to the inclusion or exclusion of any individual trial. An important interaction was found between the acute and stable chest pain groups ($\chi^2$ = 5.15; $P$ = .02; eFigure 4 in the Supplement). Coronary computed tomography angiography led to a nonstatistically significant reduction in cardiac hospitalizations of patients with acute chest pain (RR, 0.83; 95% CI, 0.66-1.04) but a nonstatistically significant increase in cardiac hospitalizations of patients with stable chest pain (RR 1.21; 95 CI, 0.96-1.53). There is no visual asymmetry in the funnel plot in eFigure 5 in the Supplement.

### Invasive Coronary Angiography

Coronary computed tomography angiography was associated with an increase in invasive coronary angiography procedures overall (11.7% vs 9.1%; RR, 1.33; 95% CI, 1.12-1.59) and in both the acute (9.2% vs 7.2%; RR, 1.39; 95% CI, 1.10-1.76) and stable chest pain (12.7% vs 9.8%; RR, 1.27; 95% CI, 0.96-1.70) subgroups (Table 2 and eFigure 6 in the Supplement). The overall effect estimate is not sensitive to the inclusion or exclusion of any individual trial. There was significant heterogeneity found between trials ($\chi^2$ = 29.29; $P$ = .004). The main source of heterogeneity is the SCOT-HEART trial.[21] When it is excluded, there is no significant heterogeneity ($\chi^2$ = 12.59; $P$ = .32). There was no significant interaction identified between the acute and stable chest pain subgroups ($\chi^2$ = 0.22; $P$ = .64). There is mild visual asymmetry in the funnel plot in eFigure 7 in the Supplement associated with the PERFECT (Prospective First Evaluation in Chest Pain) trial.[20] Removal of this trial did not lead to a significant difference in the overall effect estimate.



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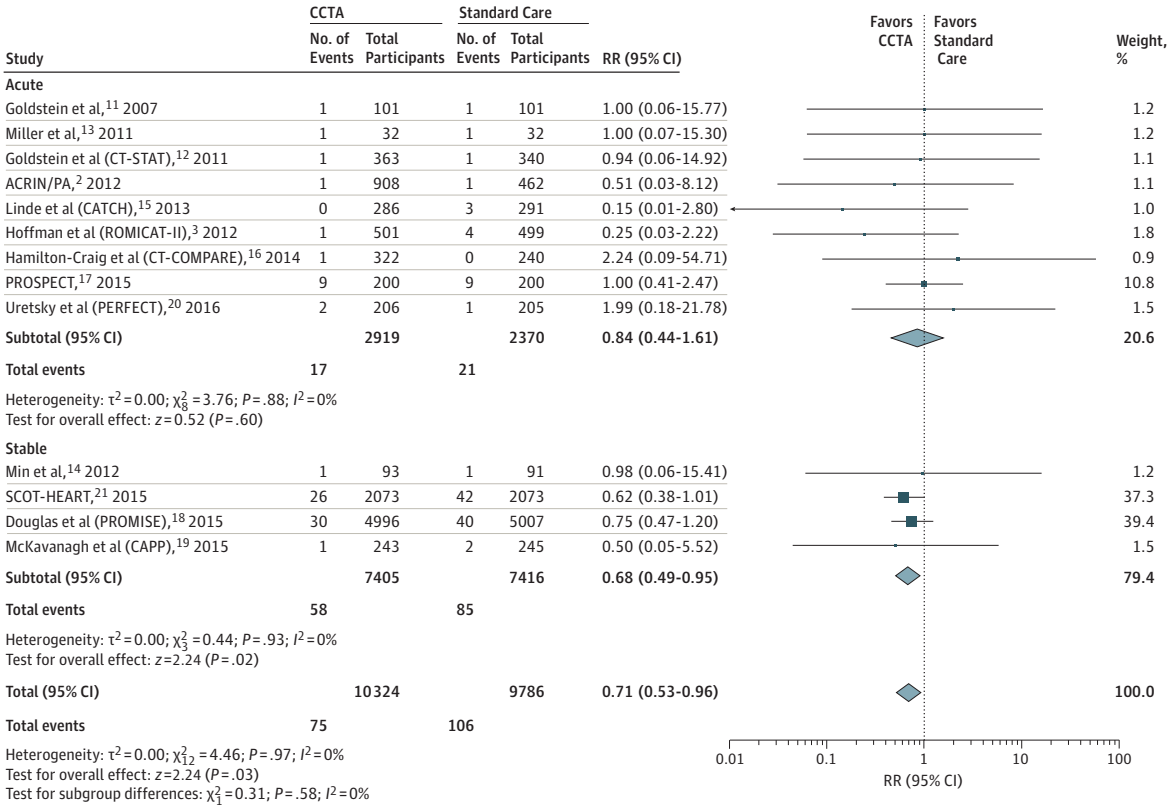
Figure 2. Forest Plot for Myocardial Infarction




Risk ratios (RRs) were determined by the Mantel-Haenszel method with a random-effects model. Square data markers represent RRs; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. ACRIN/PA indicates American College of Radiology Imaging Network/Pennsylvania Department of Health; CAPP, Cardiac CT for the Assessment of Pain and Plaque; CATCH, Cardiac CT in the Treatment of Acute Chest pain; CCTA, coronary computed tomography angiography; CT-COMPARE, CT Coronary Angiography Compared to Exercise ECG; CT-STAT, Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patient to Treatment; PERFECT, Prospective First Evaluation in Chest Pain; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; PROSPECT, Prospective Randomized Outcome Trial Comparing Radionuclide Stress Myocardial Perfusion Imaging and ECG-Gated Coronary CT Angiography; ROMICAT-II, Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography–II; and SCOT-HEART, Scottish Computed Tomography of the Heart Trial.

### Revascularization

Coronary computed tomography angiography was associated with an increase in revascularizations overall (7.2% vs 4.5%; RR, 1.86; 95% CI, 1.43-2.43) and in both the acute (5.2% vs 2.8%; RR, 1.96; 95% CI, 1.45-2.65) and stable chest pain (7.9% vs 5.1%; RR, 1.70; 95% CI, 1.12-2.60) subgroups (Table 2 and **Figure 3**). The overall effect estimate is not sensitive to the inclusion or exclusion of any individual trial. There was significant heterogeneity between trials ($\chi^2$ = 29.87; $P$ = .003). The main source of heterogeneity is the SCOT-HEART trial.[21] When it is excluded, there is no significant heterogeneity. There is mild visual asymmetry in the funnel plot related to the SCOT-HEART and PERFECT trials (eFigure 8 in the Supplement).[20,21] Removal of these trials did not lead to a significant difference in the overall effect estimate.

### New CAD Diagnoses

Coronary computed tomography angiography was associated with an increase in new diagnoses of CAD overall (18.3% vs 8.3%; RR, 2.80; 95% CI, 2.03-3.87) and in both the acute (12.5% vs 5.0%; RR, 3.37; 95% CI, 1.92-5.89) and stable chest pain (23.8% vs 10.7%; RR, 2.35; 95% CI, 1.51-3.66) subgroups (Table 2 and eFigure 9 in the Supplement). The overall effect estimate is not sensitive to the inclusion or exclusion of any individual trial. There was significant heterogeneity found between the 9 trials that allowed for adjudication of this end point ($\chi^2$ = 27.31; $P$ < .001).[2,3,13-17,19-21] There was no significant interaction between the acute and stable chest pain groups ($\chi^2$ = 0.97; $P$ = .32). There is mild visual asymmetry in the funnel plot related to 2 small trials (eFigure 10 in the Supplement).[13,14] Removal of these trials did not lead to a significant difference in the overall effect estimate.

### Medication Change: Aspirin and Statins

Coronary computed tomography angiography was associated with a significant increase in the use of aspirin (21.6% vs 8.2%; RR 2.21; 95% CI, 1.20-4.04) and statin prescribing overall (20.0% vs 7.3%; RR, 2.03; 95% CI, 1.09-3.76) and in the stable



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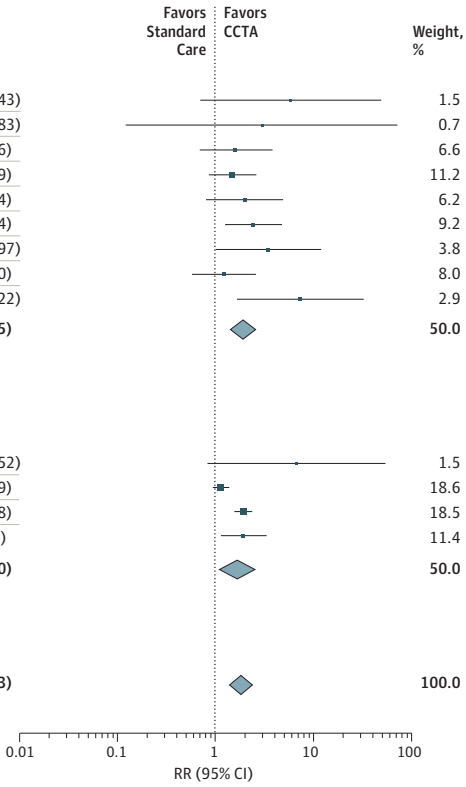
Figure 3. Forest Plot for Revascularization

| Study | CCTA No. of Events | CCTA Total Participants | Standard Care No. of Events | Standard Care Total Participants | RR (95% CI) | Weight, % |
|---|---|---|---|---|---|---|
| **Acute** | | | | | | |
| Goldstein et al,[11] 2007 | 6 | 99 | 1 | 98 | 5.94 (0.73-48.43) | 1.5 |
| Miller et al,[13] 2011 | 1 | 30 | 0 | 30 | 3.00 (0.13-70.83) | 0.7 |
| Goldstein et al (CT-STAT),[12] 2011 | 14 | 361 | 8 | 338 | 1.64 (0.70-3.86) | 6.6 |
| Hoffman et al (ROMICAT-II),[3] 2012 | 32 | 501 | 21 | 499 | 1.52 (0.89-2.59) | 11.2 |
| ACRIN/PA,[2] 2012 | 24 | 908 | 6 | 462 | 2.04 (0.84-4.94) | 6.2 |
| Linde et al (CATCH),[15] 2013 | 29 | 285 | 12 | 291 | 2.47 (1.28-4.74) | 9.2 |
| Hamilton-Craig et al (CT-COMPARE),[16] 2014 | 14 | 322 | 3 | 240 | 3.48 (1.01-11.97) | 3.8 |
| PROSPECT,[17] 2015 | 15 | 200 | 12 | 200 | 1.25 (0.60-2.60) | 8.0 |
| Uretsky et al (PERFECT),[20] 2016 | 15 | 206 | 2 | 205 | 7.46 (1.73-32.22) | 2.9 |
| **Subtotal (95% CI)** | | **2912** | | **2363** | **1.96 (1.45-2.65)** | **50.0** |
| **Total events** | **150** | | **65** | | | |
| Heterogeneity: $\tau^2 = 0.01$; $\chi^2_8 = 8.30$; $P = .40$; $I^2 = 4\%$<br>Test for overall effect: $z = 4.38$ ($P < .001$) | | | | | | |
| **Stable** | | | | | | |
| Min et al,[14] 2012 | 7 | 91 | 1 | 89 | 6.85 (0.86-54.52) | 1.5 |
| SCOT-HEART,[21] 2015 | 233 | 2073 | 201 | 2073 | 1.16 (0.97-1.39) | 18.6 |
| Douglas et al (PROMISE),[18] 2015 | 311 | 4996 | 158 | 5007 | 1.97 (1.64-2.38) | 18.5 |
| McKavanagh et al (CAPP),[19] 2015 | 37 | 243 | 19 | 245 | 1.96 1.16-3.32) | 11.4 |
| **Subtotal (95% CI)** | | **7403** | | **7414** | **1.70 (1.12-2.60)** | **50.0** |
| **Total events** | **588** | | **379** | | | |
| Heterogeneity: $\tau^2 = 0.12$; $\chi^2_3 = 19.30$; $P < .001$; $I^2 = 84\%$<br>Test for overall effect: $z = 2.47$ ($P = .01$) | | | | | | |
| **Total (95% CI)** | | **10315** | | **9777** | **1.86 (1.43-2.43)** | **100.0** |
| **Total events** | **738** | | **444** | | | |
| Heterogeneity: $\tau^2 = 0.09$; $\chi^2_{12} = 29.87$; $P = .003$; $I^2 = 60\%$<br>Test for overall effect: $z = 4.57$ ($P < .001$)<br>Test for subgroup differences: $\chi^2_1 = 0.28$; $P = .60$; $I^2 = 0\%$ | | | | | | |




Risk ratios (RRs) were determined by the Mantel-Haenszel method with a random-effects model. Square data markers represent RRs; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. ACRIN/PA indicates American College of Radiology Imaging Network/Pennsylvania Department of Health; CAPP, Cardiac CT for the Assessment of Pain and Plaque; CATCH, Cardiac CT in the Treatment of Acute Chest pain; CCTA, coronary computed tomography angiography; CT-COMPARE, CT Coronary Angiography Compared to Exercise ECG; CT-STAT, Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patient to Treatment; PERFECT, Prospective First Evaluation in Chest Pain; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; PROSPECT, Prospective Randomized Outcome Trial Comparing Radionuclide Stress Myocardial Perfusion Imaging and ECG-Gated Coronary CT Angiography; ROMICAT-II, Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography–II; and SCOT-HEART, Scottish Computed Tomography of the Heart Trial.

(aspirin: 19.9% vs 5.4%; RR, 3.50; 95% CI, 2.69-4.54; statins: 19.6% vs 5.3%; RR, 3.48; 95% CI, 2.63-4.61) but not acute chest pain (aspirin: 31.6% vs 24.9%; RR, 1.27; 95% CI, 0.99-1.61; statins: 23.0% vs 19.0%; RR, 1.21; 95% CI, 0.93-1.58) subgroup in the 5 trials that allowed adjudication of these end points (Table 2 and eFigures 11 and 12 in the Supplement).[14,17,19-21] There was significant heterogeneity between trials for aspirin ($\chi^2$ = 60.60; $P$ < .001) and statins ($\chi^2$ = 48.29; $P$ < .001). There were also significant interactions between the acute and stable chest pain groups. Funnel plots were limited by the small number of trials (eFigures 13 and 14 in the Supplement).

## Discussion

This systematic review and meta-analysis of RCTs comparing outcomes in patients undergoing CCTA vs functional stress testing for suspected CAD found no difference in mortality or cardiac hospitalization; however, CCTA was associated with a reduction in MIs and an increase in invasive coronary angiography procedures, revascularizations, new CAD diagnoses, and aspirin use and statin prescribing.

Four meta-analyses have addressed the efficacy of CCTA vs stress testing and reached different conclusions.[5-8] The 3 analyses conducted for patients with acute chest pain have relied on 4 RCTs each, and new trials have been conducted since then; 1 included observational data.[5-7] To our knowledge, only 1 meta-analysis has been conducted for outpatients with stable chest pain.[8] None of the meta-analyses assessed the outcomes of new CAD diagnoses and medication changes between trial arms.[5-8] Combining data from trials of both patients with acute chest pain and patients with stable chest pain increases the sample size of this analysis. In addition, testing for interactions between patients with acute chest pain and those with stable chest pain better informs how clinical scenarios may affect the efficacy of CCTA compared with func-



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tional stress testing. For example, CCTA lowered the risk of MI when including all trials, but the difference was only statistically significant in the stable chest pain subgroup. However, the lack of an interaction effect between the subgroups suggests that patients with acute chest pain may also benefit in terms of MI reduction. Based on our results, 250 patients with suspected CAD need to undergo CCTA rather than functional stress testing to prevent 1 MI (number needed to treat, 250).

There are several reasons to view this reduction in MI cautiously. The SCOT-HEART, which drove this finding, compared CCTA plus functional stress testing with functional stress testing alone and thus did not directly compare a CCTA strategy with a functional stress testing strategy.[21] Patients in the CCTA arm in SCOT-HEART experienced a lower rate of excess revascularization compared with those in the CCTA arm in all other trials, which may be because patients with stenosis detected by CCTA who did not have ischemia detected by functional testing did not get referred for revascularization. Less revascularization means lower rates of periprocedural MI and cardiac events associated with in-stent thrombosis and restenosis.

Coronary computed tomography angiography was not associated with an overall reduction in mortality or cardiac hospitalizations. This finding may be due to a lack of power to detect a reduction in mortality; however, a lack of power is unlikely to account for the cardiac hospitalization finding because there were more than twice as many cardiac hospitalizations as MIs, and the difference in MIs was statistically significant. In fact, patients with stable chest pain had a borderline statistically significant increase in cardiac hospitalizations in the CCTA arm (RR, 1.21; 95% CI, 0.96-1.53), despite the reduction in MIs in this subgroup (RR, 0.68; 95% CI, 0.49-0.95). One possible explanation is that the MI reduction for patients in the CCTA arm is offset by downstream cardiac hospitalizations due to complications after a percutaneous coronary intervention such as in-stent restenosis because these patients had higher rates of revascularization. Another possible reason is that the MIs prevented are small and would not be associated with significant morbidity; future investigations should investigate this possibility.

This analysis corroborates prior meta-analyses showing that CCTA compared with functional stress testing is associated with increased invasive coronary angiography and revascularization procedures.[5-8] For every 37 patients who undergo CCTA, there will be 1 excess revascularization procedure. We hypothesize that at least some of these additional procedures are associated with the finding of incidental CAD that is not causing symptomatic ischemia and would not have been detected with functional stress testing alone. Results from SCOT-HEART support this contention.[21] Eighty-five percent of patients in the CCTA arm of SCOT-HEART underwent functional stress testing, and this arm had a nonsignificant excess rate of revascularization (RR, 1.16; 95% CI, 0.97-1.39) that was significantly lower than that of all other trials combined, excluding SCOT-HEART (RR, 1.98; 95% CI, 1.70-2.30).[21]

A novel finding from our meta-analysis is that CCTA was associated with an increase in new CAD diagnoses, based on a criterion of obstructive stenosis of more than 50%, at 18.3% for CCTA vs 8.3% for functional stress testing alone. This increase in CAD diagnoses likely drove the associated increase in aspirin and statin use and might explain the reduction in MIs. However, a randomized clinical trial of CCTA screening vs standard care for asymptomatic patients with diabetes failed to show that more CCTA-related CAD diagnoses plus the resulting intensified care improved clinical outcomes.[23]

### Limitations

Limitations to this meta-analysis include the use of trial-level data rather than patient-level data. Thus, we are unable to assess for heterogeneous effects associated with CCTA that may be present based on age, sex, baseline risk, and comparator test used. However, patient-level data are unavailable. Our search was also limited to PubMed and English-language studies. Furthermore, we did not analyze end points of time to hospital discharge and cost for patients in the emergency department with acute chest pain.[6] We also did not assess for differences in radiation exposure, an end point dependent on the functional stress test modality used in the comparator arms.

## Conclusions

There were no significant differences between CCTA and functional stress testing in the end points of mortality and cardiac hospitalization. Coronary computed tomography angiography was associated with a reduction in MIs but an increase in invasive coronary angiography procedures, revascularizations, new CAD diagnoses, and aspirin and statin prescriptions. Although these results may apply to patients with both acute and stable chest pain and suspected CAD, important gaps in the medical evidence remain. These gaps include (1) the presence of heterogeneous effects for CCTA compared with functional stress testing related to the variables of age, sex, baseline risk, and comparator test used; (2) the risk of adverse events associated with excess invasive procedures; and (3) whether information gained from CCTA improves patient management and long-term clinical outcomes compared with functional stress testing alone when patients in both groups are managed using systematic protocols.

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*Study concept and design:* Foy, Dhruva, Morgan, Redberg.
*Acquisition, analysis, or interpretation of data:* Foy, Dhruva, Peterson, Mandrola.
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Invited Commentary

# Coronary Computed Tomographic Angiography—The First Test for Evaluating Patients With Chest Pain?

Todd C. Villines, MD; Leslee J. Shaw, PhD

**In November 2016,** the National Institute for Health and Care Excellence (NICE), the evidence-based organization that provides authoritative national guidance to improve health care quality in the United Kingdom (UK), updated its clinical guideline on the evaluation of patients with chest pain of recent onset.[1] On the basis of a thorough literature review, NICE updated the guideline to recommend coronary computed tomographic angiography (CCTA) as the initial test for all patients without known coronary artery disease (CAD) who present with atypical and typical angina, and for those with nonanginal chest pain who have an abnormal resting electrocardiogram. This dramatic change to national health care policy in the UK resonated across the Atlantic, where office-based single-photon emission computed tomography (SPECT) has served for decades as the dominant noninvasive test for CAD in the United States.

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Why did NICE make such a drastic change? Over the past 15 years, CCTA certainly has undergone dramatic technologi-



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