

## Clinical Outcomes After Evaluation of Stable Chest Pain by Coronary Computed Tomographic Angiography Versus Usual Care A Meta-Analysis

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**Background**—Limited data exist on how noninvasive testing options compare for evaluating patients with suspected stable coronary artery disease. In this study, we have performed a meta-analysis of randomized controlled trials comparing the use of coronary computed tomographic angiography (CTA) with usual care.

**Methods and Results**—We systematically searched databases for randomized clinical trials comparing coronary CTA with usual care for the evaluation of stable chest pain with follow-up for cardiovascular outcomes. The primary outcomes were myocardial infarction and all-cause mortality. We identified 4 randomized clinical trials, including a total of 7403 patients undergoing coronary CTA and 7414 patients undergoing usual care with various functional testing approaches. When compared with usual care, the use of coronary CTA was associated with a significant reduction in the annual rate of myocardial infarction (rate ratio, 0.69; 95% confidence interval, 0.49–0.98;  $P=0.038$ ), but no difference was found in all-cause mortality. There was a trend toward more invasive coronary angiographies among patients undergoing coronary CTA (odds ratio, 1.33; 95% confidence interval, 0.95–1.84;  $P=0.09$ ) and higher use of coronary revascularizations (odds ratio, 1.77; 95% confidence interval, 1.14–2.75). Significant heterogeneity for invasive coronary angiography and revascularization was noted, which was attributable to the Scottish Computed Tomography of the HEART (SCOT-HEART) study. We found no difference in the rate of admission for cardiac chest pain (rate ratio, 1.21; 95% confidence interval, 0.95–1.54).

**Conclusions**—In comparison to usual care, an initial investigation of suspected stable coronary artery disease using coronary CTA resulted in a significant reduction in myocardial infarction, an increased incidence of coronary revascularization, and no effect in all-cause mortality. Future studies should further define whether the potential reduction in myocardial infarction identified justifies the increased resource utilization associated with coronary CTA. (*Circ Cardiovasc Imaging*. 2016;9:e004419. DOI: 10.1161/CIRCIMAGING.115.004419.)

**Key Words:** angina, stable ■ chest pain ■ coronary angiography ■ coronary artery disease ■ myocardial infarction

Individuals who have symptoms suggestive of stable coronary artery disease (CAD) can be investigated by various noninvasive techniques, including functional (eg, nuclear myocardial perfusion imaging, stress echocardiography, exercise treadmill testing (ETT), or cardiac magnetic resonance imaging) and anatomic (eg, coronary computed tomographic angiography [CTA]) approaches. However, the optimal role for each test, including which subgroups are most likely to benefit from each strategy, has not been fully elucidated. Improved testing strategy selection may reduce the need for

additional downstream testing,<sup>1</sup> enhance the yield of detecting disease,<sup>2,3</sup> and increase the prognostic value of test results.<sup>4</sup>

### See Editorial by Nieman See Clinical Perspective

In addition to accurately identifying obstructive CAD,<sup>5</sup> coronary CTA provides prognostic information related to the presence and extent of nonobstructive plaque.<sup>6,7</sup> Because the presence of nonobstructive plaque is less likely to be identified by functional testing techniques, it has been proposed that the

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use of CTA might be associated with a higher use of downstream preventive therapies<sup>8–10</sup> and improved risk factor control, consequently leading to improved outcomes.<sup>11,12</sup> Nevertheless, the effect of testing on preventive therapies is more modest in clinical practice,<sup>9</sup> and thus, it remains unclear whether the use of CTA may lead to improved outcomes. In addition, there is concern that by identifying more CAD, CTA may lead to a higher use of invasive angiography and coronary revascularizations of uncertain benefit.<sup>13</sup>

Recognizing these issues, 3 recent studies have evaluated the role of coronary CTA compared with usual care (UC) for the investigation of stable CAD and did not find any difference in clinical outcomes.<sup>14–16</sup> Although 2 studies were not powered to detect a difference in major adverse cardiovascular events,<sup>15,16</sup> one of them demonstrated a nonsignificant trend toward reduction of cardiovascular mortality and myocardial infarction (MI).<sup>16</sup> Although a third study was designed to evaluate a composite clinical outcome, this study had reduced power because of a lower than expected rate of events (ie, observed rate of 3% versus expected rate of 8%).<sup>14</sup> Therefore, in the present meta-analysis, we sought to evaluate randomized controlled trials (RCTs) conducted among patients with stable chest pain and compare coronary CTA with UC for the incidence of death, MI, downstream invasive coronary angiography (ICA), coronary revascularization, and recurrent angina or cardiac chest pain (CCP) admissions.

## Methods

### Literature Search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and the PRISMA checklist is presented in the Data Supplement.<sup>17</sup> We systematically searched PubMed, EMBASE, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials for RCT of coronary CTA for stable chest pain with at least 1-month follow-up post randomization and published from January 1, 1998, to March 30, 2015. We searched for all randomized trials of coronary/cardiac CTA studies, including individuals with stable chest pain or equivalent symptoms, excluding those performed in the emergency care setting (full syntax example is presented in the Data Supplement). We did not limit by language. We additionally searched the references of all articles retrieved. Two studies were only abstracts and were excluded because of missing data.<sup>18,19</sup> We also excluded observational studies and studies that did not randomize patients to a control arm of UC.

### Data Extraction

Two investigators (M.S.B. and E.A.H.) independently abstracted data using a standardized form, including study characteristics (design, inclusion, and exclusion criteria), characteristics of the intervention (CT technology, UC testing, and post-test management), patient characteristics (age, sex, cardiac risk factors, symptoms at presentation, and baseline medications when available), and outcomes.

For the outcomes, we defined a priori the primary outcomes of nonfatal MI and all-cause death. Secondary outcomes defined a priori included ICA, revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), and chest pain or unstable angina (UA) requiring admission to the hospital. All outcomes were adjudicated in all studies using standardized definitions for MI. Although Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) and Cardiac CT for the Assessment of Patients With Pain and Plaque (CAPP) studies evaluated UA as part of the end points, the Scottish Computed Tomography of the HEART (SCOT-HEART) study and the study by Min et al<sup>19</sup> only included the outcome of CCP requiring admission.

Recognizing this difference, we performed a pooled analysis of any UA/CCP symptoms requiring admission. For all outcomes, the actual number of events was available in all studies.

### Data Synthesis

For the primary analysis, the absolute number of events and annualized event rates were collected, and the data were pooled using a random effects model. For all-cause death, MI, and UA/CCP symptoms requiring admission, the data were pooled as annualized rates of events and presented as rate ratios (RRs) between groups. For ICA, revascularizations, PCI, and CABG, the data were pooled as the absolute number of events and presented as proportion of individuals undergoing those procedures and odds ratio (OR) between groups.

### Sensitivity Analysis

Examination of heterogeneity was performed visually using Labbe plots and statistically using  $Q$  statistics and  $I^2$ . The  $I^2$  statistic provides an estimate of the variance because of heterogeneity rather than chance and is based on the traditional measure of variance, the Cochrane  $Q$  statistic. To investigate further a potential source of heterogeneity, we performed additional analysis with the systematically exclusion of each study. In particular, we have consistently reported the data with the exclusion of SCOT-HEART as this study had a significant difference in design. The reason for this a priori strategy is that in the SCOT-HEART study, the majority of patients in both arms underwent ETT, and coronary CTA was added after the ETT. We assessed for small study effects by the method of Peters.<sup>20</sup>

### Quality Assessment

Two investigators (M.S.B. and E.A.H.) independently assessed study quality using a 0 to 8 scale based on the Jadad criteria for RCT reporting.<sup>21</sup> Two investigators (M.S.B. and E.A.H.) evaluated studies also using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.<sup>22</sup> Disagreements were resolved by consensus.

### Statistics

All statistics were performed with Stata version 13.1 (College Station, TX) using the metan commands.  $P$  values were 2-sided with an  $\alpha$  of 0.05.

## Results

### Study Population

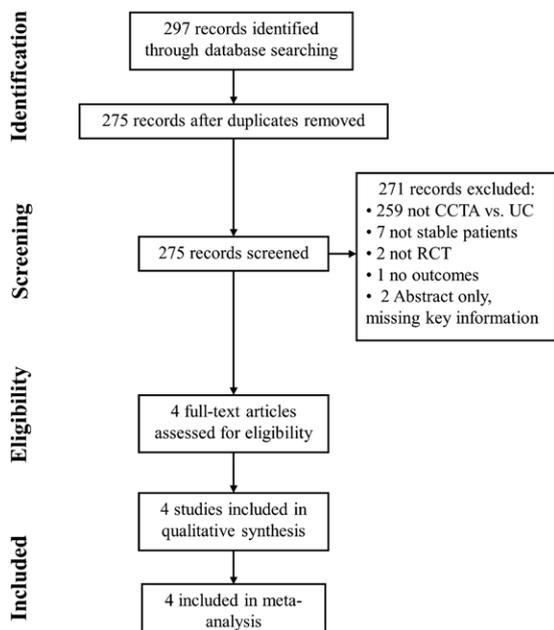
Results of the literature search are presented Figure 1. Four RCT were included representing 14817 patients; of those, 7403 were evaluated by coronary CTA and 7414 were evaluated by UC.<sup>23</sup>

Baseline demographics are listed in Table 1. The mean age of the population was 60±9 years in both groups, with 51% men in the CTA arms and 49% men in the UC arms. There were no differences in baseline characteristics between the CTA and the UC arms.

All studies had similar inclusion criteria, except for the age range (Table 2). However, the differences in mean age across studies were minimal. Other differences in inclusion criteria were exclusion of known CAD in the PROMISE study and the study by Min et al<sup>19</sup> but not in SCOT-HEART and CAPP studies. A history of previous CAD was reported in 9% of patients in the SCOT-HEART study and not reported in the CAPP study.

### Use of Risk Scores

The studies used different scores to define the clinical pretest probability of disease and risk of future events. Thus, risk score data could not be pooled although most studies reported



**Figure 1.** Results of literature search. RCT indicates randomized clinical trial; and UC, usual care.

an intermediate probability of obstructive CAD, with a mean Diamond–Forester classification pretest probability of obstructive CAD of  $53 \pm 21\%$  in the PROMISE study and  $46 \pm 30\%$  in the CAPP study. In the study by Min et al,<sup>19</sup> the mean values were not reported, but most patients (65%) were categorized as having an intermediate Diamond–Forester pretest probability. The pretest probability was not reported in the SCOT-HEART study, but physicians’ baseline diagnosis of CAD was  $\approx 47\%$ , with 36% presenting with angina caused by CAD according to physician impression. Only 2 studies reported the risk of future cardiovascular events: the risk was  $\approx 18\%$  in the study by Min et al<sup>19</sup> using the Framingham risk score and 17% in the SCOT-HEART study using the Assessing Cardiovascular Risk Using SIGN score, which is a Scottish score using traditional cardiovascular risk factors and social information to predict cardiovascular events. It was developed and calibrated for the Scottish population.<sup>24</sup>

### Testing Strategy Used in UC

There were significant differences in the type of testing used as part of UC across all studies. The UC arm in the PROMISE study included various stress testing options (68% nuclear stress test, 22% stress echocardiography, and 10% treadmill test), whereas Min et al<sup>19</sup> included only nuclear stress tests and CAPP included only ETT. By comparison, in the SCOT-HEART study, the majority of participants (85%) underwent an ETT before randomization, and the frequency of ETT use was similar in both arms. For all studies, additional noninvasive and invasive testing, as well as medical management, was performed at the discretion of the referring physician.

### Test Results

The overall incidence of positive tests was low in all studies despite the reported intermediate pretest probability. In the PROMISE study, the incidence of obstructive CAD (defined as  $\geq 50\%$  stenosis in at least 1 vessel) was 10.7% in the coronary

CTA arm and the incidence of abnormal functional test (defined as an abnormal stress ECG, stress echo, or stress nuclear perfusion test) was 11.7% in the UC group. In the CAPP study, the incidence of obstructive CAD (defined as  $\geq 50\%$  stenosis) was 30% in the coronary CTA arm and the incidence of abnormal ETT was 19% in the UC. In the study by Min et al,<sup>23</sup> the coronary CTA was abnormal (defined as  $\geq 50\%$  stenosis) in 29% of the patients, whereas the nuclear stress perfusion was abnormal in 36% of the patients in the UC arm. In the SCOT-HEART study, no test was mandated in the UC arm, but the incidence of abnormal ETT in those patients who underwent this test was 15% in both arms, whereas obstructive CAD defined by  $\geq 50\%$  stenosis was 42%, and obstructive CAD defined as  $\geq 70\%$  stenosis was diagnosed by coronary CTA in 25%.

### Clinical Outcomes

The number of all-cause deaths, MIs, UA or CCP admissions, ICA procedures (ICA), revascularization procedures, and the combined event rates, stratified by UC and CTA, as well as the corresponding pooled weighted RRs, or ORs, are reported in Table 3.

### Death and Nonfatal MI

The annualized pooled incidence of MI was significantly lower in the coronary CTA arm (3.78 events per 1000 patient-years) when compared with the UC arm (5.56 events per 1000 patient-years) with an RR of 0.69 (95% confidence interval [CI], 0.49–0.98;  $P=0.038$ ) as illustrated in Figure 2A. The absolute reduction in MI rates would be 1.8 events per 1000 patient-years undergoing a coronary CTA. The incidence of all-cause death was not significantly different between the groups (Table 3; Figure 2). No significant heterogeneity was noted for MI ( $I^2=0\%$ ;  $P=0.857$ ; Figure I in the Data Supplement) or death ( $I^2=0\%$ ;  $P=0.919$ ; Figure II in the Data Supplement). The exclusion of each individual study resulted in minimal changes in the RR estimation for both outcomes although removal resulted in a nonsignificant  $P$  values because of decreased power.

### Referral for ICA After Coronary CTA Versus UC

The pooled weighted incidence of ICA was 12.7% after coronary CTA versus 9.8% after UC (OR, 1.33; 95% CI, 0.95–1.84;  $P=0.09$ ; Table 3; Figure 3A). There was significant heterogeneity between the studies ( $I^2=83\%$ ;  $P<0.001$ ; Figure III in the Data Supplement), which was mainly driven by the results of the SCOT-HEART study. Once this study was excluded, the OR increased to 1.56 (95% CI, 1.38–1.78), and the difference reached statistical significance ( $P<0.001$ ). The exclusion of each of the other studies did not significantly change the effect size although removal resulted in a nonsignificant  $P$  value because of decreased power.

### Coronary Revascularization After Coronary CTA Versus UC

The pooled weighted incidence of any coronary revascularization was 7.9% for coronary CTA and 5.1% for UC ( $P<0.001$ ). When compared with UC, the absolute increase in coronary revascularization was 28 procedures per 1000 patients undergoing a coronary CTA (95% CI, 18.9–38.6).

The odds of revascularization was higher in the coronary CTA arm with an OR of 1.77 (95% CI, 1.14–2.75) when

**Table 1. Baseline Demographic Characteristics of the Populations Included in Each Study, According to Randomization**

	PROMISE, <sup>14</sup> n=10 003		SCOT-HEART, <sup>16</sup> n=4146		CAPP, <sup>15</sup> n=488		Min et al, <sup>23</sup> n=180		Summary, n=14 817	
	CTA	UC	CTA	UC	CTA	UC	CTA	UC	CTA	UC
Sample size	4996	5007	2073	2073	243	245	91	89	7403	7414
Age, y (SD)	60.7±8.3	60.9±8.3	57.1±9.7	57.0±9.7	57.8±10.0	58.9±10.2	55.9±10.0	58.9±9.5	59.7±8.8	59.8±8.8
Men, n (%)	2401 (48)	2332 (47)	1162 (56)	1163 (56)	138 (57)	131 (53)	53 (58)	38 (43)	3754 (51)	3664 (49)
BMI, kg/m <sup>2</sup> (SD)	30.5±6.1	30.5±6.1	29.7±5.8	29.8±5.8	27.8±3.6	28.0±3.6	...	...	29.8±5.9	29.9±5.9
Hypertension (%)	3247 (65)	3254 (65)	712 (34)	683 (33)	77 (32)	73 (30)	56 (32)	61 (59)	4092 (55)	4071 (55)
Hyperlipidemia (%)	3365 (67)	3402 (68)	1099 (53)	1077 (52)	...	...	48 (53)	54 (61)	4512 (63)	4533 (63)
Diabetes mellitus, n (%)	1065 (21)	1079 (22)	223 (11)	221 (11)	14 (6)	12 (5)	21 (23)	19 (21)	1323 (18)	1331 (18)
Family history (%)	1624 (33)	1578 (32)	887 (43)	829 (40)	...	...	37 (41)	43 (48)	2548 (36)	2450 (34)
Smoking (%)	2533 (51)	2571 (51)	1095 (53)	1090 (53)	46 (19)	47 (19)	53 (58)	38 (44)	3727 (50)	3746 (51)
Aspirin/antiplatelets (%)	2164 (45)	2116 (44)	1009 (49)	984 (48)	...	...	40 (44)	32 (35)	3213 (45)	3132 (44)
Statin (%)	2215 (46)	2174 (45)	902 (44)	884 (43)	...	...	31 (34)	35 (40)	3148 (44)	3093 (43)
β-blocker (%)	1205 (25)	1194 (25)	685 (33)	672 (32)	...	...	15 (17)	22 (25)	1905 (27)	1888 (26)
ACEi or ARB (%)	2089 (44)	2105 (44)	341 (16)	344 (17)	...	...	32 (37)	36 (41)	2462 (34)	2485 (35)
<b>Chest pain</b>										
Typical	590 (12)	576 (12)	737 (36)	725 (35)	84 (35)	68 (28)	29 (32)	20 (23)	1440 (19)	1389 (19)
Atypical	3873 (78)	3900 (78)	502 (24)	486 (23)	16 (7)	20 (8)	21 (23)	22 (25)	4412 (60)	4428 (60)
Nonanginal	533 (11)	531 (11)	833 (40)	859 (41)	143 (58)	156 (64)	25 (28)	22 (25)	1534 (21)	1568 (21)
Pre-test probability (%)	53.2	53.4	...	...	47.8±31.7	44.9±30.2	...	...		
Median follow-up, mo	25		21		12		2			

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BMI, body mass index; CAPP, Cardiac CT for the Assessment of Patients With Pain and Plaque; CTA, computed tomographic angiography; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; SCOT-HEART, Scottish Computed Tomography of the HEART; and UC, usual care/standard of care.

compared with UC (Figure 4A). There was evidence of significant heterogeneity ( $I^2=84%$ ;  $P<0.001$ ; Figure IV in the Data Supplement). The exclusion of single studies did not result in a significant change in the results. A similar pattern was noted for both PCI and CABG procedures (Figure 4B and 4C).

### UA and Recurrent Admission for CCP

For the outcome of UA/CCP, the annualized pooled weighted incidence was not significantly different between the 2 arms (18.70 events per 1000 patient-years in the coronary CTA arm versus 16.32 events per 1000 patient-years in the UC arm) with an RR of 1.21 (95% CI, 0.95–1.54;  $P=0.12$ ; Figures V and VI in the Data Supplement).

### Assessment of Quality of Reporting and Risk of Bias

Assessment of reporting quality and risk of bias is presented in Table I in the Data Supplement. All studies were rated as high quality (median Jadad score,  $\geq 5$  of 8). Because of the

impracticability of blinding imaging tests, no study used a “double-blinded” model that would be considered the gold-standard experimental design as neither patients nor investigators were not blinded to the assignment of coronary CTA or UC. Blinding to the study group was performed during event adjudication. Blinded core laboratory read of all coronary CTA or UC studies was generally not performed although local centers were certified by a core laboratory before study initiation in PROMISE and SCOT-HEART studies. Using the Cochrane tool for risk of bias, no evidence of high risk of bias was noted.

### Small Study Effects

There was no statistical evidence for small study effects (publication bias) for the primary analysis by Peters test for MI ( $P=0.71$ ), ICA ( $P=0.19$ ), revascularization ( $P=0.35$ ), PCI (0.96), or CABG ( $P=0.48$ ). There was evidence of publication bias only for the outcome of death ( $P=0.01$ ) although no significant difference in this outcome was noted.

**Table 2. Inclusion and Exclusion Criteria for Each Study**

Study	Inclusion and Exclusion Criteria	Exclusion Criteria
PROMISE <sup>14</sup>	Symptomatic, nonurgent noninvasive CV testing necessary for suspected CAD indicated, age >54 y in men and >64 y in women or between 45 and 54 y plus ≥1 risk factors in men and between 55 and 64 y plus ≥1 risk factors in women	Previous CAD, previous evaluation for CAD in the last 12 mo or other cardiac abnormality or contraindication to any test in any arm
SCOT-HEART <sup>16</sup>	Symptomatic stable chest pain evaluation, age between 18 and 75 y for both sexes	Contraindication to coronary CTA
CAPP <sup>15</sup>	Symptomatic stable chest pain evaluation, no age range defined.	Contraindication to coronary CTA or treadmill test
Min et al <sup>23</sup>	Symptomatic stable chest pain evaluation, nonurgent noninvasive CV testing necessary for suspected CAD indicated, age ≥ 40 y for both sexes	Previous CAD, contraindication to either arm or a class I indication for invasive angiography

CAD indicates coronary artery disease; CAPP, Cardiac CT for the Assessment of Patients With Pain and Plaque; CTA, computed tomography angiography; CV, cardiovascular; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; and SCOT-HEART, Scottish Computed Tomography of the HEART.

## Discussion

The present meta-analysis comparing coronary CTA with UC in the evaluation of stable CAD has novel important findings. First, the overall incidence of future adverse cardiovascular

events in this population is consistently low across studies regardless of which testing strategy was used. Second, despite this overall low incidence of events, when compared with functional testing approaches, an evaluation using coronary CTA was associated with a significant 31% relative risk reduction in the incidence of MI compared with UC. On the other hand, the use of coronary CTA testing was associated with a 77% relative increase in the odds downstream coronary revascularization, with increased rates of both PCI and CABG.

Because none of the trials mandated any particular tests or treatment strategies based on CTA or UC findings, the outcomes observed in our analysis were likely influenced by how clinicians interpreted and acted on the test results. Previous studies have suggested that coronary CTA findings may influence physicians' choice for both medical<sup>10,11</sup> and surgical treatment,<sup>25</sup> and such treatments may have significant effect on outcomes.<sup>11,25</sup> However, the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease registry revealed a more modest effect of CTA and nuclear testing on preventive therapies.<sup>9</sup> Thus, the true potential for changes in medical therapy after diagnostic testing to reduce MI remains speculative, and future studies are needed to identify the effect of noninvasive testing on medical treatments and outcomes.

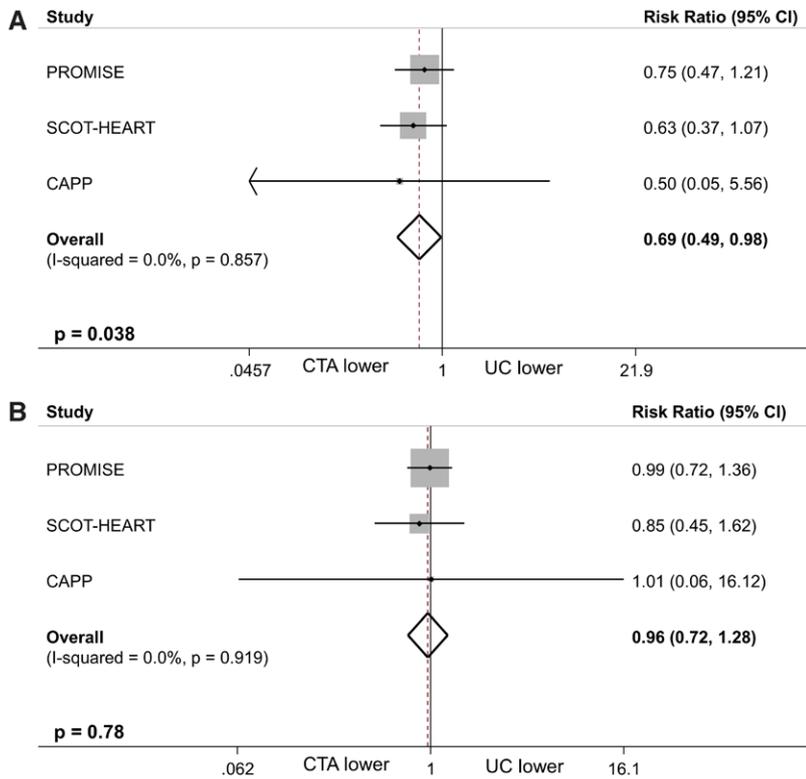
The increase in revascularizations in the coronary CTA arm was consistent among the individual studies. In the PROMISE study, this finding was interpreted as a potential overuse of unnecessary diagnostic and therapeutic strategies as the study failed to demonstrate any improvement in its primary or secondary outcomes during a median follow-up of 25 months. On the other hand, despite the lack of statistical significance ( $P=0.05$ ), the SCOT-HEART findings suggested a potential reduction of cardiovascular death or MI after CTA occurring in association with increased revascularizations. However, differences in outcomes could have been driven by other differences

**Table 3. Outcomes of Death, Nonfatal Myocardial Infarction, Angina, and Coronary Revascularization During Follow-Up**

	PROMISE, <sup>14</sup> n=10 003		SCOT-HEART, <sup>16</sup> n=4146		CAPP, <sup>15</sup> n=488		Min et al, <sup>23</sup> n=180		Pooled, n=14 817		Pooled Weighted Ratio*	P Values
	CTA	UC	CTA	UC	CTA	UC	CTA	UC	CTA	UC		
Sample size	4996	5007	2073	2073	243	245	91	89	7403	7414		
Death	74 (7.1)	75 (7.2)	17 (4.7)	20 (5.5)	1 (4.1)	1 (4.1)	0 (0)	0 (0)	92 (6.3)	96 (6.5)	0.96	0.78
Myocardial infarction	30 (2.9)	40 (3.8)	22 (6.1)	35 (9.6)	1 (4.1)	2 (8.2)	0 (0)	0 (0)	53 (3.8)	77 (5.6)	0.69	0.038
Angina/cardiac chest pain admission	61 (5.9)	41 (3.9)	76 (21.0)	69 (19.0)	1 (4.1)	3 (12.3)	11 (711.1)	10 (660.9)	149 (18.7)	123 (16.3)	1.21	0.12
Invasive angiography	609 (58.6)	406 (39.0)	255 (70.3)	260 (71.7)	66 (271.6)	51 (208.2)	12 (778.7)	7 (462.6)	942 (77.7)	724 (58.8)	1.33	0.09
Revascularizations	311 (29.9)	158 (15.2)	233 (64.2)	201 (55.4)	37 (152.3)	19 (77.6)	7 (452.5)	1 (66.1)	588 (48.7)	379 (29.1)	1.77	0.01
PCI	239 (23.0)	120 (11.5)	184 (50.7)	160 (44.1)	29 (119.34)	12 (49.0)	...	...	452 (34.1)	292 (22.0)	1.74	0.02
CABG	72 (6.9)	38 (3.7)	54 (14.9)	45 (12.4)	8 (32.9)	7 (28.6)	...	...	134 (10.1)	90 (7.0)	1.48	0.02

CABG indicates coronary artery bypass graft; CAPP, Cardiac CT for the Assessment of Patients With Pain and Plaque; CTA, computed tomography angiography; PCI, percutaneous coronary intervention; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; SCOT-HEART, Scottish Computed Tomography of the HEART; and UC, usual care/standard of care.

\*The results are presented as risk ratio for all-cause death, myocardial infarction, and angina/cardiac chest pain admission and as odds ratio for invasive angiography, revascularizations, PCI, and CABG.



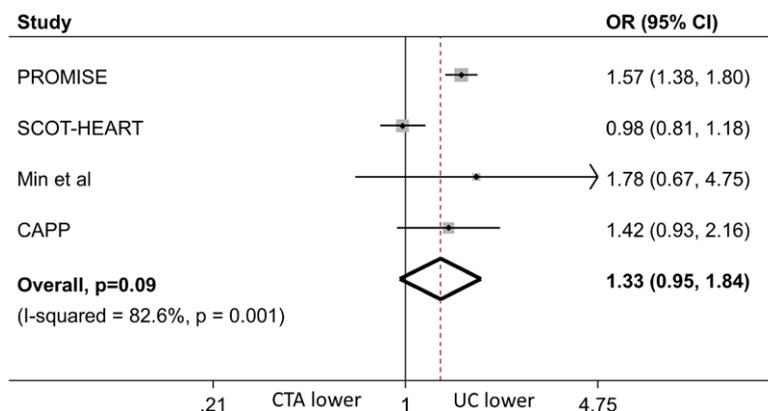
**Figure 2. A**, Forest plot of the pooled weighted annualized incidence rate ratio for myocardial infarction. **B**, Forest plot of the pooled weighted annualized incidence rate ratio for all-cause death.<sup>14–16,23</sup> CAPP indicates Cardiac CT for the Assessment of Patients With Pain and Plaque; CI, confidence interval; CTA, computed tomographic angiography; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; SCOT-HEART, Scottish Computed Tomography of the HEART; and UC, usual care.

in management, such as downstream medical management, and not revascularizations. In fact, randomized trials of revascularization versus medical management in patients with stable CAD have failed to show any reduction in events with revascularizations even in patients with documented ischemia.<sup>26</sup> One possible explanation for these differences in the use of downstream coronary revascularizations could be the fact that although most studies were a head-to-head comparison of anatomic (coronary CTA) versus a functional testing, in the SCOT-HEART study, 85% of the individuals underwent regular ETT before randomization. However, although the present data suggest that combining both anatomic and functional data may be useful in some patients, the incremental benefit of adding functional testing by ETT to coronary CTA may not be applicable to all patient populations.

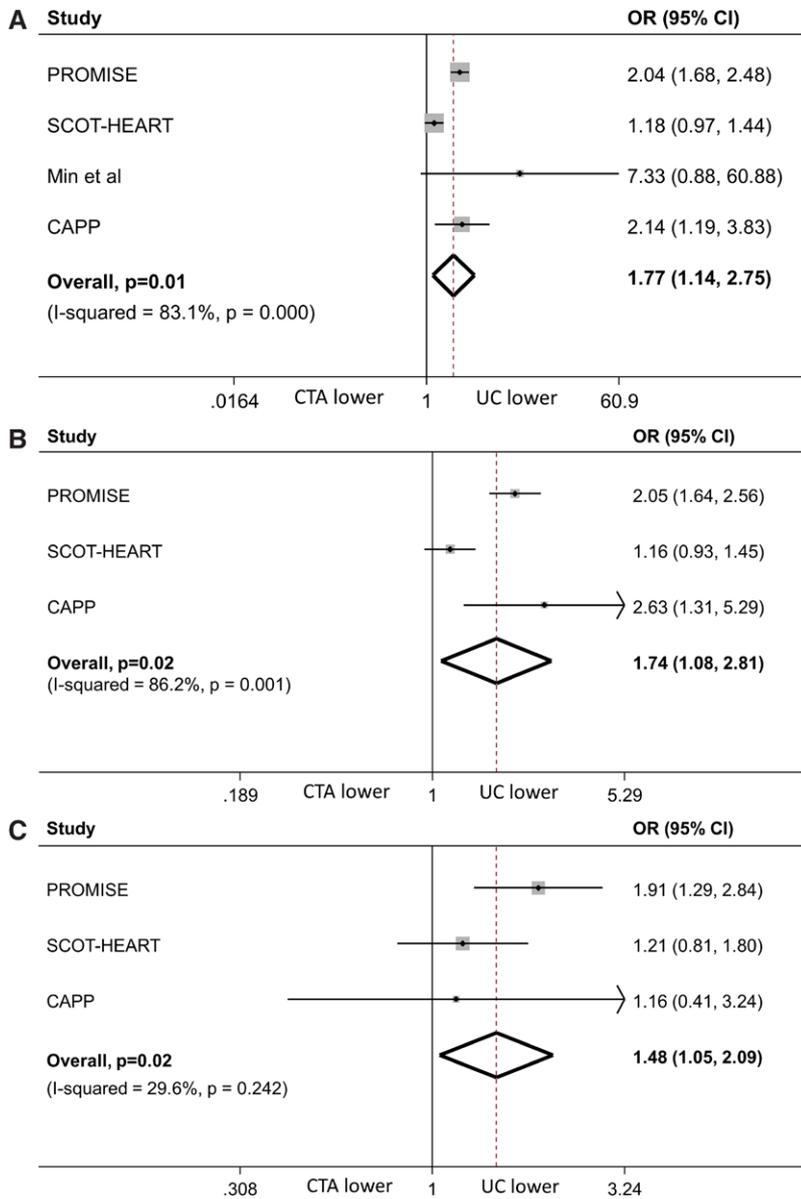
Although all other studies found an ~50% higher use of ICA in the coronary CTA arm, the referral to ICA was identical in the 2 groups in the SCOT-HEART study (OR, 0.98).

Moreover, although the incidence of revascularizations in the other 3 trials was almost twice as high in the coronary CTA arm as in UC, the observed rate in the SCOT-HEART study was only 20% higher than in the UC arm. A possible explanation for these findings is that the additional information provided by the ETT results in the SCOT-HEART study may have improved the ability to select candidates for ICA. However, other known and unknown confounders could have influenced the use of downstream invasive procedures and revascularization, such as regional differences in practice between the United States and Scotland or other differences in patient population.

This potential overuse of ICA in individuals who may not benefit from coronary revascularizations is particularly important and points to the known low-positive predictive value of using coronary anatomy (whether via CTA<sup>27</sup> or invasive angiography<sup>28</sup>) to identify ischemia. The increased use of invasive angiography after CTA has previously been reported in other coronary CTA studies.<sup>13,29</sup> One approach to avoid the unnecessary use of ICA



**Figure 3.** Forest plot of the pooled weighted odds ratio (OR) for invasive coronary angiography.<sup>14–16,23</sup> CAPP indicates Cardiac CT for the Assessment of Patients With Pain and Plaque; CI, confidence interval; CTA, computed tomographic angiography; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; SCOT-HEART, Scottish Computed Tomography of the HEART; and UC, usual care.



**Figure 4.** **A**, Forest plot of the pooled weighted odds ratio (OR) for coronary revascularization. **B**, Forest plot of the pooled weighted OR for percutaneous coronary intervention (PCI). **C**, Forest plot of the pooled weighted OR for coronary artery bypass graft (CABG) surgery. The study by Min et al<sup>23</sup> was excluded from the analysis on PCI and CABG as data on the type of revascularization were not provided.<sup>14–16,23</sup> CAPP indicates Cardiac CT for the Assessment of Patients With Pain and Plaque; CI, confidence interval; CTA, computed tomographic angiography; PROMISE, Prospective Multicenter Imaging Study for Evaluation of Chest Pain; SCOT-HEART, Scottish Computed Tomography of the HEART; and UC, usual care.

in this scenario is to evaluate the presence (and ideally severity) of ischemia after coronary CTA. This can be accomplished with techniques ranging from ETT<sup>30</sup> (as performed in the SCOT-HEART study) to using various imaging stress tests. Alternatively, an evaluation of ischemia could be performed based on the rest coronary CTA with the estimation of coronary fractional flow reserve by coronary CTA (FFR<sub>CT</sub>)<sup>31</sup> or by performing CT myocardial perfusion imaging using vasodilator-induced stress.<sup>32,33</sup> The role of FFR<sub>CT</sub> as a gatekeeper has recently been evaluated in the Prospective Longitudinal Trial of FFRCT Outcome and Resource Impacts (PLATFORM) trial and was found to effectively reduce the number of candidates referred to ICA by 61%. However, it is noteworthy that none of the aforementioned CT-based approaches are currently used in clinical practice.<sup>34</sup>

One of the advantages of performing this meta-analysis of trials comparing CTA with UC is that individual studies did not have sufficient power to examine for differences across any of the individual end points. As a result, all studies included composite end points, which raises several important

considerations. For example, in the PROMISE study, the reduction in the incidence of MI in patients undergoing CTA was offset by an increase in hospitalizations for UA. As coronary CTA identifies any evidence of CAD, it would not be surprising that its use would lead to more hospitalizations once patients and their providers know that they have CAD. Another limitation of composite end points used in the current clinical setting is that they provide a similar weight to all outcomes, whereas a lethal MI is clearly more ominous than a hospitalization for UA.

The current findings, as well as the individual results of each trial, may have important implications on outpatient care of stable chest pain patients. First, downstream management after either strategy seems safe and effective in patients with stable symptoms. Second, although the use of testing to confirm or exclude disease is often required,<sup>34</sup> given the low event rates observed in these trials, future studies are needed to better identify subgroups of patients in whom testing can be avoided. Third, given the findings that anatomic testing increases revascularization revascularization procedures, functional testing (noninvasively or by

invasive FFR) should remain an integral component in deciding on the need for coronary revascularization.

Our analysis has several limitations that need to be acknowledged. In addition to the aforementioned differences in inclusion criteria, the studies have differential follow-up. Second, the baseline risk was variable, with a higher risk group in the SCOT-HEART trial. This is noted by the higher prevalence of obstructive CAD ( $\geq 50\%$  stenosis) in the coronary CTA arm, which was  $\approx 12\%$  in PROMISE,  $30\%$  in CAPP, and  $42\%$  in SCOT-HEART trials. Similarly, the proportion of patients who underwent revascularizations or who experienced MI was also higher in the SCOT-HEART trial. Thus, the current results may be less applicable to lower risk populations. Third, most studies did not include core laboratory reads. Although this may represent an imperfect use of each testing modality, it more closely represents how these tests are used in routine clinical practice. In addition, patients and clinicians were not blinded to the type of test performed or results. Death, MI, and revascularizations were one of the several safety end-points in the SCOT-HEART trial and not the primary outcome of the study. Although the use of several outcomes may lead to false-positive results because of multiple testing, the consistency of those results across all studies makes this possibility unlikely. None of the studies mandated any particular treatments based on test results; the effect of the test findings on outcomes was largely dependent on the referring physicians' interpretation of how the test results should be used in patient management. Nevertheless, the consistency of the results across different studies, each representing different clinical and geographical settings, suggests that the current results are externally generalizable.

### Conclusions

When compared with UC, the use of coronary CTA in the evaluation of patients with stable symptoms suggestive of CAD resulted in a significant reduction in the incidence of MI, with no difference in the rate of all-cause mortality over a median follow-up of 2 years. Conversely, the use of CTA resulted in a significant increase in downstream coronary revascularizations and a trend toward increased ICA in the CTA group. Additional studies should further investigate the mechanism underlying the possible reduction in MI incidence and whether the apparent lower rate of MI after CTA is consistently seen in low-risk populations. Future studies should also define whether the potential reduction in MI identified by this study justifies the increased resource utilization associated with coronary CTA.

### Disclosures

The opinions and assertions herein are the authors' alone and do not represent those of the Department of Defense or the US Government. The authors report no conflicts.

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## CLINICAL PERSPECTIVE

Contemporary clinicians intensely debate the relative merits of anatomic (coronary computed tomographic angiography) versus functional noninvasive cardiovascular testing for the initial evaluation of patients with stable chest pain of suspected ischemic origin. To add to our understanding of the limited previous research, 2 landmark randomized controlled trials (Prospective Multicenter Imaging Study for Evaluation of Chest Pain [PROMISE] and Scottish Computed Tomography of the HEART [SCOT-HEART]) have recently deemed either strategy to be a safe and acceptable diagnostic option. However, individual trials lack statistical power to evaluate for differences between anatomic versus functional imaging for important clinical end points, such as myocardial infarction, cardiovascular death, or coronary revascularization. In the present meta-analysis, we pool the PROMISE and SCOT-HEART clinical outcomes with 2 smaller trials. In so doing, we demonstrate that the strategy of an initial evaluation using an anatomic strategy resulted in a 31% relative risk reduction in the rate of myocardial infarction. A 77% increase in the odds of coronary revascularization procedures (percutaneous and surgical) was also noted, although only a non-significant trend for increase in the rate of invasive angiography was noted. Comparative cost-effectiveness studies are needed to clarify whether the myocardial infarction reduction justifies the increased revascularization procedures.