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Outcomes After Coronary Computed Tomography Angiography in the Emergency Department

A Systematic Review and Meta-Analysis of Randomized, Controlled Trials

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Objectives The aim of the study was to systematically review and perform a meta-analysis of randomized, controlled trials of coronary computed tomography angiography (CCTA) versus usual care (UC) triage of acute chest pain in the emergency department (ED).

Background CCTA allows rapid evaluation of patients presenting to the ED with acute chest pain syndromes; however, the impact of such testing on patient management and downstream testing has emerged as a concern.

Methods We systematically searched for randomized, controlled trials of CCTA in the ED and performed a meta-analysis of clinical outcomes.

Results Four randomized, controlled trials were included, with 1,869 patients undergoing CCTA and 1,397 undergoing UC. There were no deaths and no difference in the incidence of myocardial infarction, post-discharge ED visits, or rehospitalizations. Four studies reported decreased length of stay with CCTA and 3 reported cost savings; 8.4% of patients undergoing CCTA versus 6.3% of those receiving UC underwent invasive coronary angiography (ICA), whereas 4.6% of patients undergoing CCTA versus 2.6% of those receiving UC underwent coronary revascularization. The odds ratio of ICA for CCTA patients versus UC patients was 1.36 (95% confidence interval [CI]: 1.03 to 1.80, $p = 0.030$), and for revascularization, it was 1.81 (95% CI: 1.20 to 2.72, $p = 0.004$). The absolute increase in ICA after CCTA was 21 per 1,000 CCTA patients (95% CI: 1.8 to 44.9), and the number needed to scan was 48. The absolute increase in revascularization after CCTA was 20 per 1,000 patients (95% CI: 5.0 to 41.4); the number needed to scan was 50. Both percutaneous coronary intervention and coronary artery bypass graft surgery independently contributed to the significant increase in revascularization.

Conclusions Compared with UC, the use of CCTA in the ED is associated with decreased ED cost and length of stay but increased ICA and revascularization. (J Am Coll Cardiol 2013;61:880–92) © 2013 by the American College of Cardiology Foundation

Acute chest pain is the second most frequent reason for patient visits to the emergency department (ED) in the United States (1); however, only a small minority of those patients ultimately receive a diagnosis of acute coronary syndrome (ACS) (2). To improve diagnostic accuracy and cost-effectiveness, various strategies including chest pain units, novel cardiac biomarkers, and noninvasive cardiac imaging have been proposed (3). Recent guidelines have highlighted that the primary goal of this approach is exclusion of ACS and other serious conditions rather than detection of coronary artery disease (CAD) (3).

The routine evaluation of acute chest pain in most centers in the United States includes admission to a hospital or chest pain unit to rule out ACS with the use of serial electrocardiography and cardiac biomarkers. In selected patients, stress testing with or without imaging may be used for further risk stratification (4). Such an approach may

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avoid the inadvertent discharge of a patient who has ACS, but is time-consuming and costly and is associated with a prolonged length of stay (LOS) (4).

Previous studies demonstrated that coronary computed tomography angiography (CCTA) is a rapid and accurate technique to exclude the presence of CAD (5,6). Furthermore, the immediate and future likelihood of cardiac events in patients with no or minimal CAD is extremely low for patients with nonacute chest pain (7,8). In light of these favorable test characteristics, several single-center (9–18) and, more recently, multicenter (19–21) studies have demonstrated the feasibility, safety, and accuracy of CCTA in the ED.

Due to the rapidly expanding literature in this field, 3 recent meta-analyses evaluated the diagnostic accuracy of CCTA in the acute setting (22–24). A major limitation of these investigations was their reliance, by necessity, on observational studies due to the limited data published at that time. Moreover, the majority of these studies did not include any of the currently available multicenter trials. Although the data consistently show the high negative predictive value of CCTA, only recently have sufficient randomized studies been published to investigate post-test outcomes and downstream testing.

Therefore, the objective of the present meta-analysis was to evaluate randomized, controlled trials (RCTs) of ED triage of acute chest pain and compare CCTA and usual care (UC) for the incidence of invasive coronary angiography (ICA), coronary revascularization, death, nonfatal myocardial infarction (MI), repeat ED evaluations for chest pain, re-admission to the hospital for ACS, LOS, and cost.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
CCTA = coronary computed tomography angiography
CI = confidence interval
ED = emergency department
ICA = invasive coronary angiography
LOS = length of stay
MI = myocardial infarction
NNS = number needed to scan
OR = odds ratio
PCI = percutaneous coronary intervention
RCT = randomized, controlled trial
UC = usual care

Methods

Literature search. We followed the PRISMA statement (25). A study protocol is not published but is available on request. We systematically searched PubMed, EMBASE, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials for RCTs of CCTA in the ED enrolling at least 100 patients with at least 1 month of follow-up post-CCTA and published from January 1, 1996, to July 27, 2012. We used the search terms and corresponding MeSH headings for "emergency cardiac computed tomography" limited to adult human RCTs from 1996 through July 27, 2012 (see the Online Appendix for full syntax). We did not limit by language. We additionally searched the references of all articles retrieved. One author was contacted and provided additional data for analysis.

We excluded observational studies and studies that did not randomize patients with chest pain to a control arm of UC, which would be provided if CCTA was not available. We included RCTs that reported clinical outcomes for both in-hospital and downstream events.

Data extraction. Two authors (E.H. and C.P.) independently abstracted data using a standardized data extraction form including study characteristics (design, inclusion and exclusion criteria), characteristics of the intervention (at least 64-slice computed tomography, use and timing of cardiac enzymes relative to CCTA, follow-up duration), patient characteristics (age, sex, cardiac risk factors, and baseline Thrombolysis In Myocardial Infarction risk when available), and outcomes (death, nonfatal MI, repeat ED chest pain evaluation, repeat hospitalization for ACS, ICA, revascularization by percutaneous coronary intervention [PCI]/coronary artery bypass graft [CABG], LOS, and cost.

Data synthesis. For the primary analysis, we evaluated absolute incidence of each clinical outcome. Outcomes were organized into 2×2 tables and pooled using a fixed-effects model for the primary analysis of ICA and revascularization by PCI/CABG.

Sensitivity analysis. Examination of heterogeneity was performed visually using Galbraith plots and statistically using Q statistics and I^2. The I^2 statistic provides an estimate of the variance due to heterogeneity rather than chance and is based on the traditional measure of variance, the Cochrane Q statistic (26). We performed stratified analysis by follow-up duration, ACS prevalence, and management of significant stenosis (i.e., if lesions on CCTA with ≥70% stenosis must undergo ICA vs. allowance for a primary team to manage CCTA findings). We assessed for small study effects by the method of Peters (27).

Quality assessment. Two authors (E.H. and C.P.) independently assessed study quality using a scale of 0 to 8 based on the Jadad criteria for RCT reporting (28). E.H. and C.P. evaluated studies also using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (29). Disagreements were resolved by consensus.

Statistical analysis. All statistical analyses were performed with STATA version 12.1 (StataCorp, College Station, Texas) using the *metan* commands. The p values were 2-sided, with an alpha value of 0.05 considered statistically significant.

Results

Results of the literature search are presented in Figure 1. Four RCTs of 3,266 patients were included (18–21): 1,869 undergoing CCTA and 1,397 evaluated by UC.

The baseline patient demographic characteristics are listed in Table 1. The mean age of the population was 51 years. There were 1,547 males (47%). Baseline risk factors did not differ between CCTA and UC as reported within

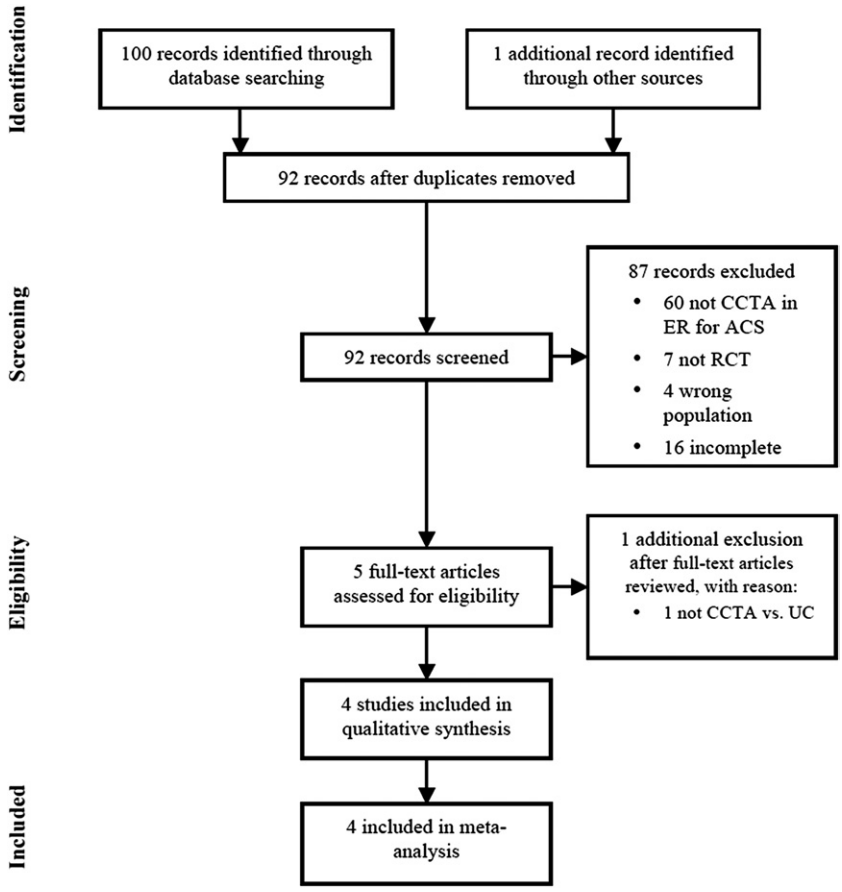


Figure 1 Results of a Literature Search

ACS = acute coronary syndromes; CCTA = cardiac computed tomography angiography; ER = emergency room; RCT = randomized, controlled trial; UC = usual care.

each study and are shown by study in Table 1. Studies had similar patient eligibility (Table 2), although the ACRIN-PA (American College of Radiology Imaging Network/Pennsylvania Department of Health) trial allowed patients with cocaine exposure, known previous CAD, and positive biomarkers. The ROMICAT II (Rule Out Myocardial Ischemia/Infarction Using Computer Assisted Tomography II) trial sought to enroll higher risk patients who were randomized earlier in the triage process.

Absolute incidences of clinical outcomes for each of the individual studies and the combined incidence stratified by UC and CCTA with corresponding pooled weighted odds ratio (OR) are reported in Table 3. For each outcome, events during the index hospitalization, during follow-up, and for the combined duration (index hospitalization + follow-up) are displayed.

Death and nonfatal MI. There were no deaths. There were few MIs, and most occurred during the index hospitalization, not allowing for a meaningful pooled analysis of MI as a safety endpoint, as the type of diagnostic test and MI were not causally related.

Referral for ICA after CCTA versus UC. The pooled weighted incidence of ICA was 8.4% after CCTA versus 6.3% ($p = 0.030$) after UC. Figure 2 depicts the index hospitalization and downstream rates of referral for ICA. The pooled OR of ICA for CCTA versus UC was 1.36 (95% confidence interval [CI]: 1.03 to 1.80, $p = 0.030$). The absolute increase for ICA after CCTA was 21 ICA per 1,000 CCTA patients (95% CI: 1.8 to 44.9) for a number needed to scan (NNS) of 48 patients for 1 additional ICA. There was no evidence of heterogeneity by I^2 ($I^2 = 0\%$, $p = 0.75$) or visual inspection of Galbraith or Labbe plots (Online Fig. 1). Systematically excluding each study from the analysis did not significantly change the effect size, although removal of studies resulted in a nonsignificant p value due to decreased power (Fig. 3).

Coronary revascularization by PCI or CABG after CCTA versus UC. The pooled weighted incidence of PCI/CABG was 4.6% after CCTA versus 2.6% ($p = 0.004$) after UC. The absolute increase for PCI/CABG after CCTA was 20 per 1,000 patients (95% CI: 5.4 to 42.2) for an NNS of 50 CCTA for 1 additional PCI/CABG. Figure 2 depicts the index hospitalization and downstream rates of PCI/CABG. The pooled OR (Fig. 4) comparing these rate differences was 1.81 (95% CI: 1.20 to 2.72, $p = 0.004$).

Table 1 Demographic Characteristics

	Goldstein et al. (18)		CT-STAT (19)		ACRIN-PA (21)		ROMICAT II (20)		Pooled	
	n	SD/%	n	SD/%	n	SD/%	n	SD/%	n	SD/%
n	197		699		1,370		1,000		3,266	
UC, n	98	50	338	48	462	34	499	50	1,397	43
CCTA, n	99	50	361	52	908	66	501	50	1,869	57
Age, yrs	50	12	50	10	49	9.0	54	8.0	51	9.1
Male, n	98	50	322	46	645	47	531	53	1,596	49
BMI, kg/m^2	29	5.0	28	5.0			29	5.1	29	5.0
Hypertension	75	38	259	37	695	51	541	54	1,570	48
Hyperlipidemia	70	36	234	33	367	27	454	45	1,125	34
Diabetes	20	10	48	6.9	194	14	173	17	435	13
Family history of premature CAD	82	42	212	30	394	29	271	27	959	29
Current smoking	35	18	157	22	447	33	492	49	1,131	35
Aspirin in past 7 days	52	26	193	28					245	27
Chest pain in past 24 h	139	71	353	51					492	55
TIMI risk score	1.29	0.80	1.01	0.85					1.06	0.8
ACS	10	5.1	12	1.7	48	3.5	75	7.5	145	4.4
UA	10	5.1	6	0.9	35	2.6	52	5.2	103	3.2
MI	0	0	6	0.9	13	0.9	23	2.3	42	1.3
No testing	0	0	0	0	167	12.2	118	11.8	285	12.1
Follow-up, months	6		6		1		1			
CCTA >70%	11	11	13	3.6	28	3.1			52	4.2

ACS = acute coronary syndrome; BMI = body mass index; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; ICA = invasive coronary angiography; MI = myocardial infarction; SD = standard deviation; TIMI = Thrombolysis In Myocardial Infarction; UC = usual care; UA = unstable angina.

There was no statistically significant evidence of heterogeneity by I^2 (I^2 = 0%, p = 0.64), although the first study by Goldstein et al. was a visual outlier for revascularization by Galbraith plot (Online Fig. 1). Stratified analysis and meta-regression did not identify a statistically significant cause of the heterogeneity. Systematically excluding this outlier and other studies did not change the result (Fig. 3). Both PCI and CABG independently contributed to the significant increase in revascularization (Fig. 4).

A stratified analysis by protocol recommendation of ICA for ≥70% CCTA stenosis showed that the increase in ICA and PCI/CABG is consistent also in studies that allow for primary team management discretion after CCTA (Fig. 5).

Table 2 Exclusion Criteria by Study

Study	Exclusion Criteria
Goldstein et al. (18)	Age <25 yrs, known CAD, +Trp, ischemic ECG changes, BMI >39 kg/m^2, unable to undergo contrast CT, LVEF <45%, >12 h without symptoms
CT-STAT (19)	Age <25 yrs, known CAD, +Trp, ischemic ECG changes, BMI >39 kg/m^2, unable to undergo contrast CT, LVEF <45%, >12 h since arrival at ED, >12 h from symptom onset to ED arrival
ACRIN-PA (21)	Age <30 yrs, ischemic ECG changes, TIMI risk score >2, normal CCTA within 1 yr, unable to undergo contrast CT, other major comorbidity requiring admission
ROMICAT II (20)	Age <40 or >75 yrs, known CAD, +Trp, ischemic ECG changes, BMI >40, unable to undergo contrast CT, >6 h since arrival at ED, cocaine, shock

CAD = coronary artery disease; CT = computed tomography; ECG = electrocardiogram; ED = emergency department; LVEF = left ventricular ejection fraction; +Trp = positive troponin; other abbreviations as in Table 1.

Post-discharge ED visits for recurrent chest pain. The pooled weighted incidence of post-discharge ED visits was 4.2% after CCTA versus 4.5% after UC (p = 0.70). The number of follow-up ED visits avoided per 1,000 patients scanned with CCTA is 3 (95% CI: −13.1 to 14.5), for an NNS of 359. The pooled OR (Fig. 6, top) comparing these incidences was 0.94 (95% CI: 0.67 to 1.31, p = 0.70). There was no statistically significant evidence of heterogeneity by I^2 (I^2 = 0%, p = 0.68). Stratifying by months of follow-up did not significantly change the outcome: the OR for 6-month follow-up was 0.77 (95% CI: 0.297 to 1.99, p = 0.6).

Post-discharge hospitalizations for ACS. Post-discharge hospitalizations were rare. The pooled weighted incidence was 1.5% after CCTA versus 1.3% after UC (p = 0.5). The number of post-discharge hospitalizations increased per 1,000 patients scanned with CCTA is 3 (95% CI: −4.2 to 14.5) for an NNS of 388. The pooled OR (Fig. 6, bottom) comparing these incidences was 1.20 (95% CI: 0.67 to 2.2, p = 0.54). There was no statistically significant evidence of heterogeneity by I^2 (I^2 = 0%, p = 0.68). When stratified by months of follow-up, all events occurred in the 2 studies with 1-month follow-up. There were no events in the 6-month-follow up trials.

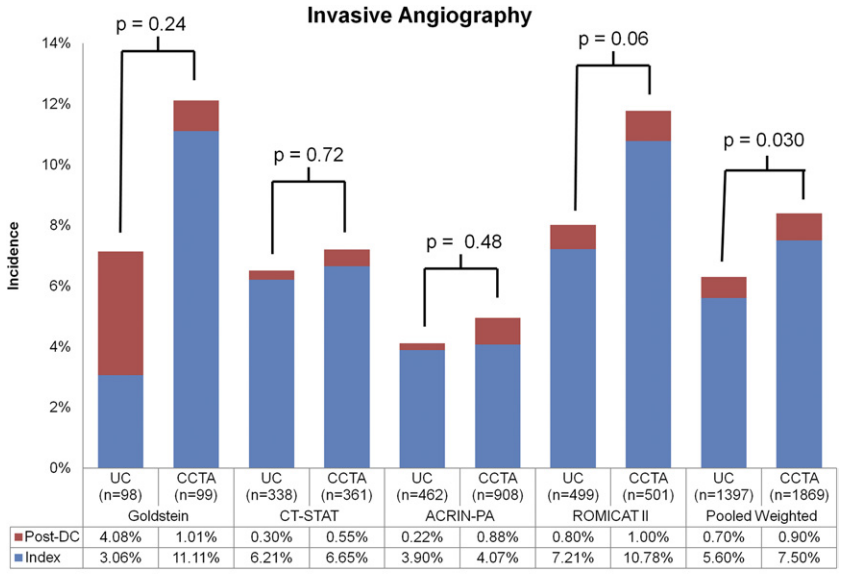
LOS and cost assessment. Studies enrolled patients at different times in their hospital course (e.g., ROMICAT II <6 h vs. other studies <12 h) and reported differing LOSs (e.g., ED stay or total hospital stay). A pooled analysis was not considered reasonable due to this clinical heterogeneity. All studies reported a significant reduction in LOS in the CCTA group. Likewise, studies included differing cost components, defined costs differently, and included differing

Table 3 Death, Nonfatal Myocardial Infarction, and Coronary Revascularization by PCI or CABG Occuring During Index Hospitalization, Post-Discharge, or Combined

	Goldstein et al.				CT-STAT				ACRIN-PA				ROMICAT II				POOLED					
	UC		CCTA		UC		CCTA		UC		CCTA		UC		CCTA		UC		CCTA			
	n = 98		n = 99		n = 338		n = 361		n = 462		n = 908		n = 499		n = 501		n = 1,397		n = 1,869		Pooled Weighted Odds Ratio (Range)	p Value
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
Combined																						
Death	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	N/A	
MI	0	0.0	0	0.0	5	1.5	1	0.3	5	1.1	10	1.1	19	3.8	9	1.8	29	2.1	20	1.1	0.54 (0.30–0.97)	0.038
ICA	7	7.1	12	12	22	6.5	26	7.2	19	4.1	45	5.0	40	8.0	59	12	88	6.3	142	7.6	1.36 (1.03–1.80)	0.030
Revasc	1	1.0	6	6.1	8	2.4	14	3.9	6	1.3	24	2.6	21	4.2	32	6.4	36	2.6	76	4.1	1.81 (1.21–2.71)	0.004
PCI	1	1.0	4	4.0	8	2.4	10	2.8	6	1.3	21	2.3	17	3.4	27	5.4	32	2.3	62	3.3	1.62 (1.05–2.52)	0.030
CABG	0	0.0	2	2.0	0	0.0	4	1.1	0	0.0	3	0.3	4	0.8	5	1.0	4	0.3	14	0.7	2.51 (0.94–6.74)	0.068
Index																						
Death	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	N/A	
MI	0	0.0	0	0.0	5	1.5	1	0.3	4	0.9	9	1.0	15	3.0	8	1.6	24	1.7	18	1.0	0.58 (0.31–1.10)	0.096
ICA	3	3.1	11	11	21	6.2	24	6.6	18	3.9	37	4.1	36	7.2	54	11	78	5.6	126	6.7	1.36 (1.02–1.83)	0.038
Revasc	1	1.0	5	5.1	8	2.4	13	3.6	4	0.9	23	2.5	18	3.6	29	5.8	31	2.2	70	3.7	1.95 (1.26–3.01)	0.003
PCI	1	1.0	3	3.0	8	2.4	9	2.5	4	0.9	20	2.2	14	2.8	24	4.8	27	1.9	56	3.0	1.75 (1.09–2.80)	0.021
CABG	0	0.0	2	2.0	0	0.0	4	1.1	0	0.0	3	0.3	4	0.8	5	1.0	4	0.3	14	0.7	2.51 (0.94–6.74)	0.068
Post-discharge																						
Death	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	N/A	
MI	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1	4	0.8	1	0.2	5	0.4	2	0.1	0.31 (0.058–1.69)	0.18
ICA	4	4.1	1	1.0	1	0.3	2	0.6	1	0.2	8	0.9	4	0.8	5	1.0	10	0.7	16	0.9	1.29 (0.57–2.92)	0.55
Revasc	0	0.0	1	1.0	0	0.0	1	0.3	2	0.4	1	0.1	3	0.6	3	0.6	5	0.4	6	0.3	0.99 (0.34–2.91)	0.99
PCI	0	0.0	1	1.0	0	0.0	1	0.3	2	0.4	1	0.1	3	0.6	3	0.6	5	0.4	6	0.3	0.99 (0.34–2.91)	0.99
CABG	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	N/A	
ER	6	6.1	6	6.1	4	1.2	2	0.6	34	7.4	71	7.8	19	3.8	14	2.8	63	4.5	93	5.0	0.94 (0.67–1.31)	0.70
Admit	0	0	0	0	0	0	0	0	11	2.4	28	3.1	7	1.4	7	1.4	18	1.3	35	1.9	1.20 (0.67–2.16)	0.54

Absolute incidences are reported and differ slightly from pooled weighted incidences in Figure 4.

CABG = coronary artery bypass graft surgery; ICA = invasive coronary angiography; MI = myocardial infarction; N/A = not available; PCI = percutaneous coronary intervention; Revasc = coronary revascularization by PCI or CABG; other abbreviations as in Tables 1 and 2.



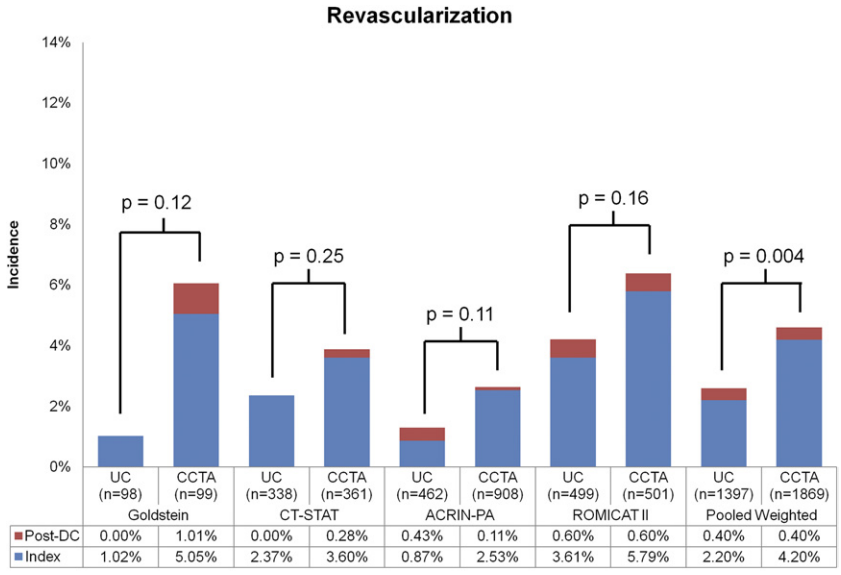


Figure 2 **Invasive Angiography and Coronary Revascularization After CCTA or UC**

Stratified bar graph of index hospitalization and post-discharge invasive coronary angiography **(top)** and revascularization by percutaneous coronary intervention/coronary artery bypass graft surgery **(bottom)**. Pooled weighted incidences are reported and differ slightly due to weighting of meta-analysis from the absolute incidences shown in Table 3. DC = discharge; other abbreviations as in Figure 1.

durations. Similar to the length of stay outcome, a pooled analysis of cost was also not performed due to clinical heterogeneity. Three studies reported cost savings in the CCTA group, and 1 reported no difference. LOS and costs are summarized in Table 4.

Assessment of quality of reporting and risk of bias. Assessment of reporting quality and risk for bias are presented in Online Table 1. All studies were rated as high quality (median Jadad score ≥5 of 8). Due to the impracticability of blinding imaging tests, no study used a double-blinded model that would be considered the gold-standard experimental design; patients and investigators were not blinded to assignment of CCTA or UC. Blinding to study group was generally performed during event adjudication. CCTA studies were read by investigators blinded to patient history or after anonymization in a blinded core laboratory. No blinded assessment or core laboratory interpretation of UC was reported. Using the Cochrane tool for risk of bias, the Goldstein et al. and CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trials (18,19) were also considered to have an "unclear" risk of "other problems" that

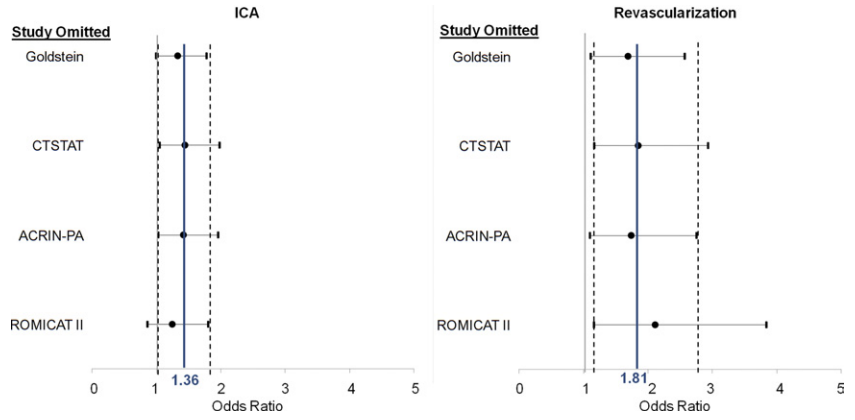


Figure 3 **Assessment for Influence of Individual Studies**

Systematic exclusion of each study (**black dots**; 95% confidence interval represented by error bars) did not affect the pooled estimates for invasive coronary angiography (ICA) (**left:** odds ratio of 1.36 shown as **dark blue line**; 95% confidence interval [1.03 to 1.80] represented by **dashed lines**) or the pooled estimate for percutaneous coronary intervention/coronary artery bypass graft surgery (**right**: odds ratio of 1.81 shown as **dark blue line**; 95% confidence interval [1.20 to 2.72] represented by **dashed lines**) Although the Goldstein et al. study had the highest percutaneous coronary intervention/coronary artery bypass graft surgery rate because of its small sample size, it did not significantly affect the pooled estimate. Removal of trials reduced power for significant difference in ICA, but with a similar odds ratio effect size.

could lead to potential bias due to the treatment recommendation of immediate ICA for those with ≥70% CCTA stenosis. This was not concluded to be "high" risk of bias because an independent primary team would likely perform ICA for those with ≥70% CCTA stenosis.

Small study effects. There was no statistical evidence of small study effects (publication bias) for the primary analysis by the Peters test (p = 0.53 for ICA; p = 0.14 for PCI/CABG).

Discussion

There are several important findings in this first meta-analysis of RCT evaluating the impact of CCTA versus

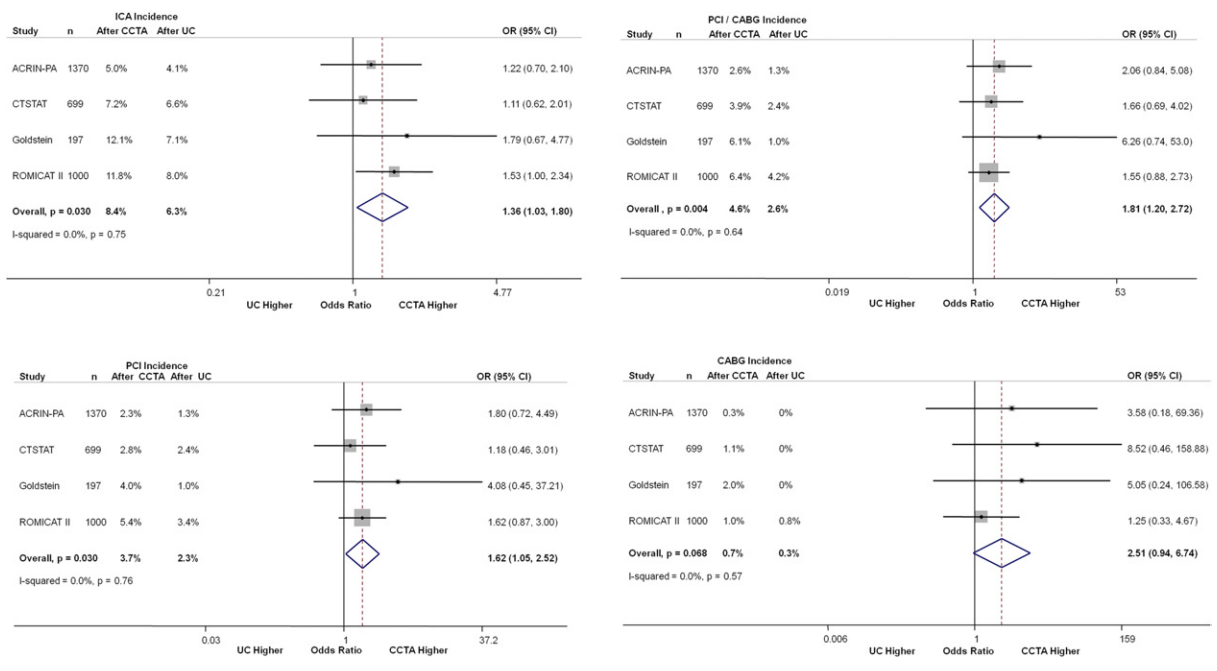


Figure 4 **OR for ICA and Revascularization by PCI/CABG**

Pooled weighted incidences are reported and differ slightly due to weighting of meta-analysis from the absolute incidences shown in Table 3. CABG = coronary artery bypass graft surgery; CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention; other abbreviations as in Figures 1 and 3.

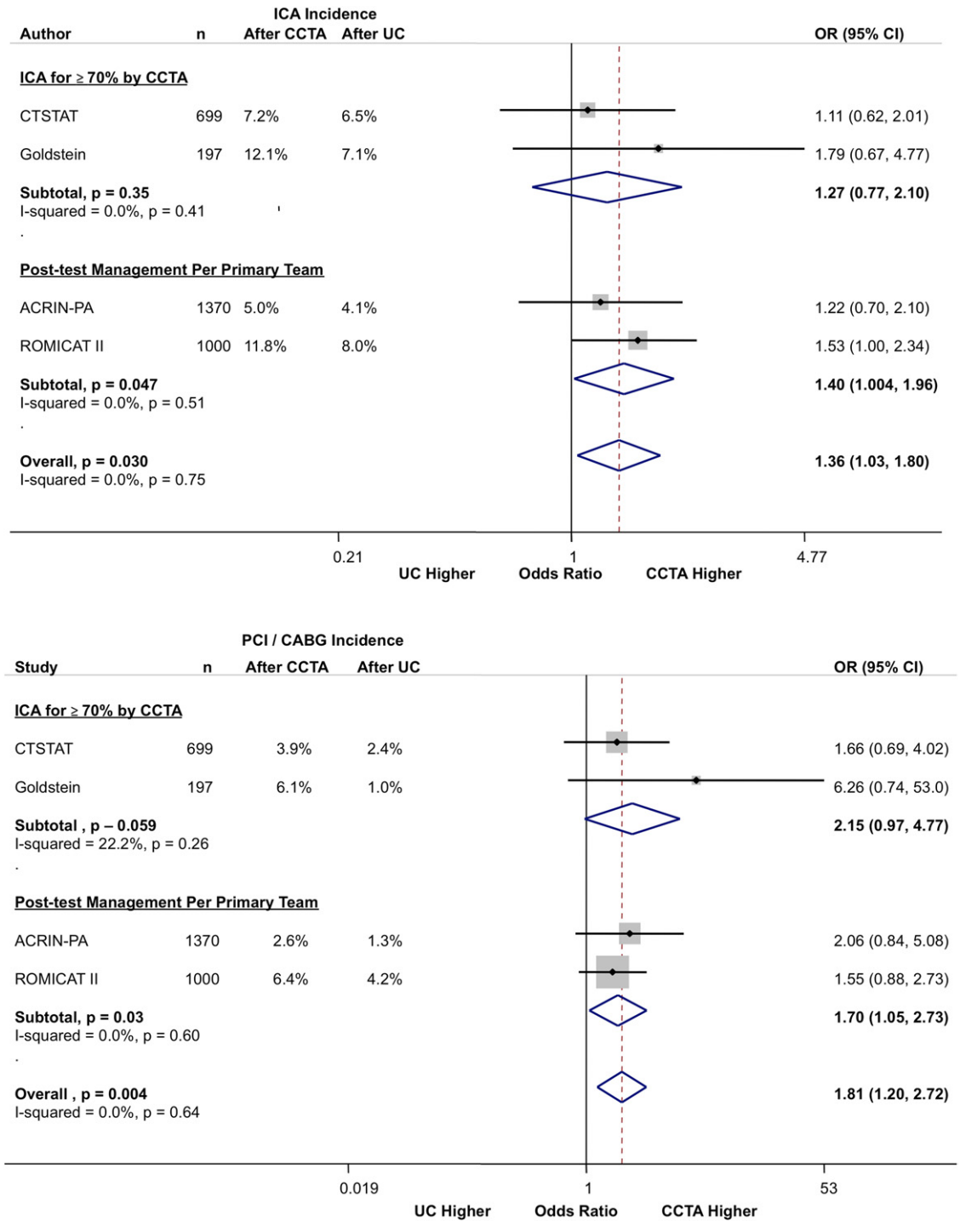


Figure 5 **Stratified Analysis of ICA and PCI/CABG According to Management Strategy After CCTA**

Although a strategy of encouraging ICA for any CCTA lesion ≥70% may increase ICA and consequently PCI/CABG, the increase in ICA and PCI/CABG is consistent also in studies that allow for primary team management discretion after CCTA. Pooled weighted incidences are reported and differ slightly from the absolute incidences shown in Table 3. Abbreviations as in Figures 1, 3, and 4.

UC in the ED. First, the use of CCTA in low- to intermediate-risk patients presenting to the ED with chest pain is safe. Indeed, the rate of death, MI, return ED visits, and recurrent hospitalization for cardiovascular causes was similar between patients evaluated with CCTA versus UC. Second, although the definitions used

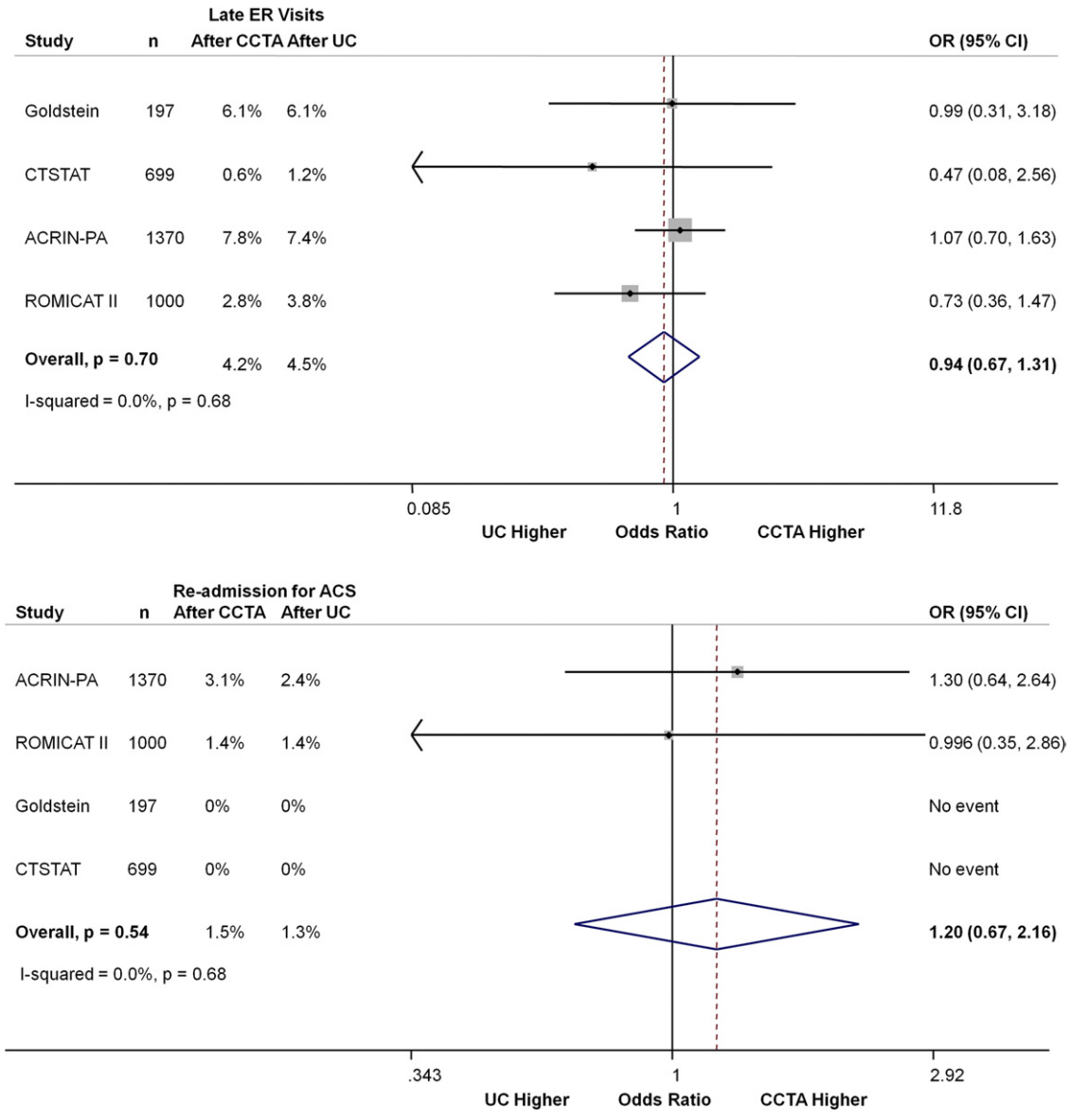


Figure 6 **OR for the Incidence of Post-discharge Visits to the Emergency Department for Recurrent Chest Pain and Re-Admission for ACS After Discharge**

Pooled weighted incidences are reported and differ slightly from the absolute incidences on Table 3. Abbreviations as in Figures 1 and 4.

for calculating LOS in each study differed and a pooled analysis was not possible, the average LOS reported in each study was consistently reduced in patients undergoing CCTA compared with those in the UC arm. Third, the use of CCTA in the ED significantly increased the downstream ICA and revascularization (PCI/CABG) incidence by 2% compared with the UC group. We found that there was 1 additional ICA for every 48 patients and 1 additional revascularization for every 50 patients evaluated with CCTA. However, the present analysis is not suitable for determining whether these results are due to overuse of ICA and PCI/CABG in the CCTA group or underuse in the UC group. In addition, a variety of factors influence the decision to pursue ICA after CCTA, including clinical judgment; technical quality of the CCTA; anatomic details regarding the presence, location, and severity of CAD; and experience and expertise of the readers (and end users) of the CCTA examination, none of which could be adequately evaluated by our analysis.

Due to many recent technical advances, CCTA has evolved into a powerful test that offers the ability to rapidly and accurately evaluate patients presenting to the ED with suspected ACS. A major attribute of this test is that the

Table 4 LOS and Cost Outcomes by Study

	Goldstein et al. (18)	CT-STAT (19)	ACRIN-PA (21)	ROMICAT II (20)	
Primary outcome	Safety, diagnostic efficiency	Time to diagnosis	Safety	Hospital LOS	
LOS definition	Time to diagnosis	Time to diagnosis	Hospital duration	Time to diagnosis	Hospital duration
UC LOS, h	15.0 (7.3–20.2)	6.2 (4.2–19.0)	24.8	18.7 (11.8)	30.8 (28.0)
CCTA LOS, h	3.4 (2.3–14.8)	2.9 (2.1–4.0)	18	10.4 (12.6)	23.2 (37.0)
UC-CCTA LOS, h	11.6*	3.4*	6.8*	8.3*	7.6*
Reduction, %	77.3*	54.8*	27.4*	44.3*	24.7*
Cost Definition	**ED Cost**	**ED Cost**	**N/A**	**ED Cost**	**Total Hospital**
UC cost, US$	1,872 (1,727–2,069)	3,458 (2,900–4,297)	N/A	2,566 (1,323)	3,874 (5,298)
CCTA cost, US$	1,586 (1,413–2,059)	2,137 (1,660–3,077)	N/A	2,101 (1,070)	4,026 (6,792)
UC-CCTA cost, US$	286*	1,321*	N/A	465*	−152
Reduction, %	15.3*	38.2*	N/A	18.1*	−3.9

Values are mean (SD) or median (interquartile range). Three studies evaluated time to diagnosis, which a CCTA triage strategy reduced by 44% to 77%. Two studies evaluated total hospital LOS, which a CCTA strategy reduced by 25% to 27%. Three studies reported ED cost, which a CCTA strategy reduced by 15% to 38%. One study reported total hospital cost, which was not significantly different. The reduction in ED cost due to faster time to diagnosis was offset by the downstream index hospital cost of higher ICA and PCI/CABG in the ROMICAT II study. ROMICAT II analyzed a subgroup of 649/1,000 patients with available cost data from 5 of 9 sites in the study. *$p < 0.05$.

LOS = length of stay; other abbreviations as in Tables 1 to 3.

absence of CAD on CCTA not only rules out the presence of ACS but also conveys an excellent prognosis, at least in patients with known or suspected stable CAD (30). Indeed, the use of CCTA among patients with negative initial biomarkers and electrocardiography is already included in the algorithm of acute chest pain evaluation in numerous EDs, a strategy that is supported by the current appropriate use criteria (31) and American College of Cardiology guidelines for unstable angina (32). Further supporting these documents, 3 of the 4 RCTs included in our study reported ED cost savings in the CCTA group compared with UC, although more data on the impact on downstream testing are needed because other studies in different patient populations suggest that CCTA may result in increased downstream testing and procedures (33).

Because ICA, PCI, and CABG are procedures that profoundly affect the cost of CAD care and in light of data that coronary revascularization procedures are not always beneficial (34,35), the pivotal question is whether their increase after CCTA represents an overuse of ICA and PCI/CABG after CCTA or an underuse in patients undergoing UC. Clinical outcomes such as death and MI were no different, but these studies were not designed to test for such a difference. Much larger studies would need to be performed to detect differences in clinical outcomes, given the (by design) low-risk nature of this population. In addition, longer term follow-up may identify other differences in downstream testing between CCTA and UC. For instance, it is not clear how physicians who evaluate patients with previously normal findings on CCTA or myocardial perfusion imaging will react when such a patient returns to the ED with chest pain. Will the higher negative predictive value of CCTA result in less downstream testing? On the other hand, previously abnormal findings on CCTA might lower the threshold for further testing and could increase the use of stress tests or ICA in this group.

There are several principles related to effective use of cardiac testing in the ED that are important to acknowledge. First, not all patients presenting with acute chest pain require any testing and among those who do need further testing, CCTA is not an appropriate study for "all comers": in very low risk populations, the use of CCTA will unnecessarily increase testing, radiation exposure, and downstream procedures because many of these patients could be safely triaged with no testing (36% of UC in ACRIN-PA, 22% in ROMICAT II) or exercise treadmill testing alone (20,36,37). On the other hand, in high-risk populations, use of CCTA may be associated with increased downstream testing due to the presence of lesions with uncertain hemodynamic significance (33). Second, even among low- to intermediate-risk individuals, all patients should not by default undergo CCTA, but rather should be triaged via a system that incorporates clinical and patient data together with an understanding of all available testing options in a given center to select the optimal testing strategy for a given patient. Third, not all patients with ≥50% stenosis on CCTA ought to undergo ICA, despite this recently being considered to represent appropriate use. Physiological assessment remains useful in many cases before ICA, whether by nuclear perfusion imaging (38), stress echocardiography, or potentially in the future stress computed tomography perfusion (39). Other measures that may reduce ICA and PCI/CABG include techniques to improve the specificity of CCTA to identify hemodynamically significant lesions such as evaluation of rest myocardial perfusion (40), incorporation of flow hemodynamic modeling such as shear stress (41) or computed tomography fractional flow reserve (42), and evaluation of transarterial gradients (43,44).

There are several important considerations regarding the studies included in our analysis. First, the majority of patients included in the analysis were at low to moderate risk of ACS with normal biomarkers and nondiagnostic or

normal findings on electrocardiography. For instance, in 2 studies that reported the Thrombolysis In Myocardial Infarction risk score, a mean of 1.29 and 1.01 was observed (Table 1). Accordingly, the overall prevalence of ACS was low across all studies, with ROMICAT II having the highest at 8%. Therefore, the current results cannot be extrapolated to higher risk patients. Nevertheless, low-risk chest pain remains a far more common presentation in the ED and is associated with substantial costs.

Second, the evaluation according to UC was not similar in all studies. In the CT-STAT (19) and in Goldstein et al. (18), the UC arm included routine myocardial perfusion imaging, whereas in the ROMICAT II (20) and ACRIN-PA (21), the use and type of testing were performed at the physicians' discretion. Accordingly, the last 2 studies had a lower rate of stress testing because some patients were discharged without any testing.

Third, the protocol after CCTA was not similar in all studies. Both studies by Goldstein et al. (18) had a predefined protocol that required further testing (myocardial perfusion imaging in most cases) following all intermediate lesions and also required that all severe lesions (≥70% stenosis) underwent direct ICA and revascularization if appropriate. The ACRIN-PA and ROMICAT II did not include a recommendation for myocardial perfusion imaging, ICA, or other downstream testing in the CCTA arm. Although excess ICA could have resulted from studies using a protocol that recommended the use of ICA for ≥70% CCTA stenosis, a stratified analysis by protocol recommended ICA for severe lesions (Goldstein et al. [18], CT-STAT [19]) did not have a higher incidence of ICA post-CCTA compared with studies (ACRIN-PA, ROMICAT II) without such a requirement (Fig. 5).

Study limitations. First, the studies have slightly differential follow-up (2 papers limited to 1 month post-discharge and 2 papers at 6 months). However, as shown, the overwhelming majority of events (89%, Table 3) occurred during the index hospitalization. Nevertheless, despite the low event rate in these overall low-risk patients at follow-up, it is possible that with additional time a divergence in repeat ED visits and re-admissions for ACS will occur. Although our study included the largest sample size of any study to date evaluating the use of CCTA in the ED (1,869 patients in the CCTA group and 1,397 in the UC group), it nevertheless remains underpowered to detect clinical differences in the safety endpoint of MI and death, which are rare in these patient groups. Second, although the ROMICAT II trial included centers without specific experience in CCTA use in the ED, the pooled analysis is likely affected by an expert center bias because most hospitals included have imaging expertise. The use of CCTA in centers with less expertise could potentially lead to increased false-positive and false-negative CCTA findings, although this hypothesis has not been adequately studied and the public health consequences of widespread use of CCTA in community EDs are not known. Finally, although each study design is randomized, it is important to note that allocation to UC or CCTA cannot be concealed and that CCTA findings were not blinded to patients and treating clinicians. Thus, CCTA findings may influence the likelihood of downstream ICA and revascularization (verification bias). However, test findings in the UC group may also influence downstream ICA and revascularization; thus, this verification bias should be considered separately from our finding that ICA rates were higher among those randomized to CCTA. Thus, for a randomized comparison of 2 diagnostic triage strategies, differences in these downstream rates are likely due to differences inherent to each strategy that should be considered when deciding how to triage such patients.

Conclusions

CCTA in the ED has safety comparable to that of UC evaluation and reduces ED cost and LOS, which may offer relief for the problem of ED overcrowding, but is associated with a 2% increased incidence of ICA and a similar 2% increased incidence of revascularization. Whether this increased rate of invasive procedures leads to improved patient outcomes or decreases the need for future testing is unknown. Finally, our findings highlight the importance of measuring in-hospital and downstream ICA and revascularization rates and including such endpoints when designing comparative effectiveness and cost-effectiveness studies.

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Key Words: coronary angiography ■ coronary artery bypass graft surgery ■ coronary computed tomography angiography ■ emergency department ■ percutaneous coronary intervention.

APPENDIX

For the MEDLINE search terms, and a supplemental table and figure, please see the online version of this article.