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SYSTEMATIC REVIEW

Major adverse cardiac events after emergency department evaluation of chest pain patients with advanced testing: Systematic review and meta-analysis

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Abstract

Objectives: Our primary objective was to describe the risk of major adverse cardiac events (MACE) at 1, 6, and 12 months after a negative coronary computed tomography angiogram (cCTA), electrocardiogram (ECG) stress test, stress echocardiography, and myocardial perfusion scintigraphy (MPS) in low- to intermediate-risk patients.

Methods: Initially, 952 articles were identified for screening, 81 met criteria for full-text review, and once risk of bias was assessed, 33 articles were included in this meta-analysis. We utilized a random-effects model to assess pooled MACE event proportion for patients undergoing evaluation of acute coronary syndrome (ACS) when risk stratified to a low- to intermediate-risk category after undergoing standard testing. Heterogeneity analysis was performed using Cochrane's Q-test and I^2 statistic.

Results: Twenty-one studies evaluated follow-up at 1 month with cCTA having a 0.09% (95% confidence interval [CI] = 0.03% to 0.26%) pooled MACE compared to 0.23% (95% CI = 0.01% to 5.8%) of the exercise stress testing (p = 1). MPS and cCTA had an overall event rate of 0.15% (95% CI = 0.06% to 0.41%) at 6 months (I^2 = 0%). At 12 months, a subgroup analysis found a pooled cCTA MACE of 0.16% (95% CI = 0.04% to 0.65%) compared to 1.68% (95% CI = 0.01% to 2.6%) for stress echocardiography with low within-group heterogeneity (I^2 = 0%). Subgroup analysis of cCTA with no disease versus nonobstructive disease (<50% stenosis) did not find statistical difference in the MACE at both 1 month (0.17% [95% CI = 0.04% to 0.67%] vs. 0.06% [95% CI = 0.01% to 0.34%]) and 12 months (0.44% [95% CI = 0.09% to 2.2% vs. 0.54% [95% CI = 0.19% to 1.5%]).

Conclusions: Patients presenting with chest pain who have a coronary CTA showing < 50% stenosis, negative ECG stress test, stress echocardiography, or stress myocardial perfusion scan in the past 12 months can be discharged without any further risk stratification if their ECG and troponin are reassuring given low MACE.

KEYWORDS
coronary CTA, ECG, emergency department, low-risk chest pain, MACE, major adverse cardiac events, meta-analysis, myocardial perfusion scintigraphy, stress ECHO, stress EKG, stress testing, systematic review, TIMI

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death in the United States (365,000 deaths in 2017).[1] Quick and reliable identification of patients at risk for acute coronary syndrome (ACS) is important in the emergency department (ED). Approximately 95% of patients who present to the ED with acute chest pain do not have active cardiac ischemia.[2] However, this does not mean they are not at risk for future major adverse cardiac events (MACE). One of the current challenges in emergency medicine is the disposition of patients who present with chest pain and do not have evidence of acute cardiac ischemia. Missed acute myocardial infarction (MI) is one of the top three common final diagnoses among claims involving emergency medicine.[3] One study reported the rate of patients diagnosed with an ACS 7 days after an ED presentation was 3%.[4] Additional factors associated with admissions for cardiac

TABLE 1 Risk of bias assessment of included studies

	Cochrane risk of bias					
First author, year	Sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting
Pena, 2016	Low	Low	Low	Low	Low	Low
Hamilton-Craig, 2014	Low	Unclear	High	Low	High	Low
Peix, 2012	Low	Low	Low	Low	Low	Low
Schaer, 2005	Low	Low	Low	Low	Low	Low
Nasis, 2014	Low	Low	Low	Low	Low	Low
Poon, 2013	Low	Low	Low	Low	Low	Low
Nagori, 2014	Low	Low	High	High	Low	Low
Litt. 2012	Low	Low	Low	High	Low	Low
Lim, 2013	Low	Low	Low	Low	Low	Low
Nasis, 2011	Low	Low	Low	Low	Low	Low
Hansen, 2010	Low	Low	Low	Unclear	Low	Low
Hollander, 2009	Low	Low	High	High	High	Low
	Low	Low	Low	Low	Low	Low
Gaibazzi 2011	Low	Unclear	High	High	Unclear	Low
Grunau, 2016	Low	Low	Low	Low	Low	Low
Cury, 2013	Low	High	High	High	Low	Low
Dedic, 2017	Low	Low	Low	Low	Low	Low
Goldstein, 2011	Low	Low	Low	Low	High	Low
Bholasingh, 2002	Low	Low	Low	Low	Low	Low
Lerakis, 2009	Low	Low	High	High	Low	Low
Colon III, 1998	Unclear	Low	High	Low	Unclear	Low
Christiaens, 2012	Unclear	High	High	Unclear	Low	Low
	Low	High	Low	Low	Low	Low
Schlett, 2011	Low	High	Low	Low	Low	Low
Bedetti, 2005	High	High	High	High	Low	Low
Innocenti, 2014	Low	Unclear	High	High	Low	Low
Chang, 2011	High	Low	High	Low	Low	High
Anaya, 2012	Low	Unclear	High	Unclear	Unclear	Low
	Unclear	High	High	High	High	Low
Gallagher, 2007	Low	Unclear	High	High	Low	Low
Halpern, 2013	Unclear	High	Unclear	Unclear	High	Low
Hascoet, 2012	Unclear	High	High	High	Low	Low
Dedic, 2013	Unclear	Low	Low	Low	Low	Low
Dadkhah, 2017	Low	High	High	Unclear	Low	High
Innocenti, 2013	High	Unclear	High	High	High	Low

evaluation include knowledge of poor compliance with follow-up in underresourced patients and patient underestimation of cardiovascular risk.[5] Approximately 14% of patients presenting to the ED with chest pain are admitted to the hospital for further stratification of their chest pain, resulting in an estimated cost of $10 billion annually.[6,7]

Current standard of care testing includes stress electrocardiogram (ECG)/echocardiography, coronary computed tomography angiogram (cCTA) imaging, and myocardial perfusion scintigraphy (MPS). This practice is consistent with guideline recommendations and represents anatomic and functional cardiac testing.[8] Anatomic testing encompasses cCTA while functional testing includes stress echocardiography and MPS.[9] ED-based studies have reported that cCTA is more cost-efficient when compared to other modalities. For example, one study estimated the total cost of care after ED work-ups for low-risk patients with chest pain for each risk stratification

Risk Of Bias In Non-Randomized Studies–of Interventions (ROBINS-I)						
Bias due to selection of reported measures	**Bias of confounding**	**Bias of selection**	**Bias of class intervention**	**Bias due to deviations from intended intervention**	**Bias due to missing data**	**Bias due to measurement of outcomes**
Low	Low	High	Low	High	High	Low
Low	Low	Low	Low	Low	Low	Low
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Low	Low	High	Low	Low	Unclear	High
Low	Low	High	Low	Low	Low	Low
Low	Low	Low	Low	Low	Low	Low
Low	Low	High	Low	Low	Low	High
Low	Low	Unclear	Low	Low	High	Low
Low	Low	High	Low	Low	Low	High
Low	Low	Low	Low	Low	Low	Low
Low	Low	Low	Low	Low	High	High

TABLE 2 List of studies reviewed

Author, year	Type of study	Population	Intervention
Coronary CT			
Anaya, 2012[30]	Randomized controlled trial	1,390 patients at intermediate risk for ACS with normal ECG, excluded if prior coronary angiogram within 1 year	cCTA (n = 908) vs. usual care (n = 462)
Chang, 2011[37]	Prospective cohort study	1,049 patients with a chief complaint of chest pain for whom a cCTA was ordered for evaluation of potential ACS, a nonischemic initial ECG, and a TIMI score of 0–2	cCTA with CAS
Christiaens, 2012[54]	Retrospective cohort study	175 patients with no ECG changes and low to intermediate risk with first troponin <0	64-slice cCTA, coronary calcium score
Cury, 2013[38]	Prospective cohort study	529 patients presenting with chest pain to the ED with a low to intermediate probability of ACS, a TIMI risk score of 2 or less, two initial negative cardiac enzyme results within a 2-h time interval, and negative or nondiagnostic ECG findings	cCTA
Dedic, 2013[39]	Prospective cohort study	111 patients age over 40 with no STE, no history of CAD	cCTA, CAC
Dedic, 2016[31]	Randomized controlled trial	500 patients with acute chest pain or symptoms suggestive of ACS warranting further diagnostic evaluation, as determined by the treating physician, were eligible for inclusion	cCTA (n = 250) compared to SOC (n = 250)
Goldstein, 2011[32]	Randomized controlled trial	749 patients with acute chest pain, normal or nondiagnostic ECG for ischemia, TIMI score ≤ 4	cCTA (n = 361) vs. SOC MPI (n = 338)
Grunau, 2016[55]	Retrospective cohort study	1,700 patients aged from 18 to 65 years with a primary complaint of nontraumatic chest pain were eligible and no objective findings of ACS	cCTA (n = 512) vs. exercise stress testing (n = 1,179)
Halpern, 2013[40]	Prospective cohort study	250 consecutive patients who presented to the ED with chest pain or similar symptoms that might represent an anginal equivalent and who were admitted to the observation unit and evaluated with cCTA	cCTA 256-MDCT scanner
Hamilton-Craig, 2014[33]	Randomized controlled trial	662 differentiated chest pain, TIMI risk < 4, negative troponin I	cCTA (n = 322) vs. ExECG (n = 240)
Hansen, 2010[41]	Prospective cohort study	89 patients admitted to a chest pain assessment service and had a normal first troponin	cCTA and treadmill exercise testing
Hascoët, 2012[42]	Prospective cohort study	123 low to intermediate risk for ACS, acute chest pain with normal ECG and no evidence of ischemia	64-slice MSCT

Characteristics	Test results	Outcome	% MACE (95% CI)
Not provided	cCTA group ≤50% stenosis *n* = 754	MACE at 30 days	cCTA ≤ 50% 0% (0%–0.4%)
Male 453 (43%); median age 48.4 years (IQR 42.4–53.5 years); TIMI 0, 613; TIMI 1–2, 416	cCTA < 50%, CACS = 0, *n* = 733, cCTA < 50%, CACS > 0, *n* = 183	MACE at 30 days	cCTA < 50%, CACS 0 0.1% (0%–0.7%) cCTA < 50%, CACS > 0 = 0.5% (0.01%–3%)
Male 124 (71%); mean ± SD age 60 ± 8 years; TIMI 0–2, 148 (85%); TIMI > 2–3, 26 (15%); TIMI > 4, 0	cCTA ≤ 50% stenosis, *n* = 130	MACE at 6 ± 2 months	0% (0%–2.7%)
Male 44%, mean age 52.1 years, TIMI score ≤ 2, 100%	cCTA negative *n* = 217, cCTA mild (<50%) *n* = 151	MACE at 30 days	cCTA negative 0% (0%–1.6%) cCTA mild disease 0% (0%–2.4%)
64% male, mean ± SD age 57 ± 11 years	cCTA negative *n* = 37, CAC *n* = 40 negative	MACE at 3 months	Negative cCTA 0% (0–9.5%) Negative CAC 0% (0–8.8%)
cCTA: male 51%; mean ± SD age 55 ± 9 years; TIMI 0, 29.6%; TIMI 1, 33.6%; TIMI ≥ 36.8%SOC: male 55%; mean ± SD age 53 ± 9 years; TIMI 0, 33.2%; TIMI 1, 36.4%; TIMI ≥ 30.4%	CT with no disease *n* = 106 (47%), did not specify negative SOC tests	MACE/undetected CAD at 30 days	Entire cCTA cohort 0.4% (0.01%–2.2%)
cCTA: male 163 (45.2%, mean ± SD age 50 ± 10 years, TIMI risk score 0.99 ± 0.84) MPI: male 159 (47.0%, mean ±SD age 50 ± 10 years, TIMI risk score 1.04 ± 0.87)	cCTA group *n* = 268 with < 50% stenosis, MPI normal or probably normal *n* = 266	MACE at 6 months	cCTA < 50% stenosis 0.7% (0.1%–2.6%) MPI 0.4% (0%–2.0%)
cCTA: male 322 (61.8%); median (IQR) age 51 (44–59) years; TIMI 0, 296 (56.8%); TIMI 1, 212 (40.7%, 2:12 [2.5%]) EST: male 655 (55.6%), median (IQR) age 51 (44–58) years; TIMI 0, 709 (60.1%); 1:426 (436.1%); 2:24 (2.0%)	cCTA normal *n* = 298 (55.5%), EST normal *n* = 869 (73.7%)	MACE at 30 days	All cCTA 1.3% (0.5%–2.7%) All EST 0.4% (0.1–0.9%)
male 109 (44%), mean ±SD age 50.9 ± 11 years; TIMI score 0, 37; TIMI 1, 110; TIMI 2, 70; TIMI 2, 22; TIMI 4, 7; TIMI 5, 1	cCTA no plaque *n* = 145 (57%), minimal plaque (<30%) *n* = 64 (26%), mild plaque (<50%) *n* = 26 (10%)	MACE at 30 days	cCTA < 50% stenosis 0% (0%–1.6%)
58% male, mean ± SD age 52 ± 10.3 years	cCTA negative *n* = 277, ExECG negative *n* = 213	MACE at 30 days, MACE at 12 months	30-day MACE negative cCTA 0% (0%–1.3%) Negative ExECG 0% (0%–1.5%) 1-year MACE Negative cCTA 0.3% (0%–1.9%) Negative ExECG 0% (0%–1.5%)
Male 56 (63%), mean ± SD age 56.3 ± 8.6 years	cCTA normal *n* = 35, CCTA < 50% disease *n* = 38	MACE at mean follow-up 355 ± 72 days	cCTA normal 0% (0%–10%), cCTA mild disease 0% (0%–9.3%)
70.4% male; mean ± SD age 50.9 ± 13 years; TIMI 0, 72 (58.5%); TIMI 1, 41 (33%); TIMI 2, 10 (8.1%)	MSCT negative CAD ≤ 50% stenosis = 93	MACE: median follow-up 15 months (17–30 months)	Negative CT MACE 0 (0%–5%)

(Continues)

TABLE 2 (Continued)

Author, year	Type of study	Population	Intervention
Schlett, 2011[43]	Prospective cohort study	368 patients with chief complaint of acute chest pain lasting 5 min during the past 24 h, normal initial troponin, and an initial ECG without evidence of myocardial ischemia	64-slice cCTA, coronary
Hollander, 2009[44]	Prospective cohort study	568 low-risk TIMI score patients	cCTA
Kim, 2010[56]	Retrospective cohort study	296 patients divided into two groups: group 1 < 50% lesion and low-risk profile and group 2 < 50% lesion and intermediate-risk profile	cCTA
Litt, 2012[34]	Randomized controlled trial	1,370 patients with signs or symptoms that were consistent with a possible ACS were eligible if the treating physician determined that they would require admission or objective testing to rule out an acute coronary syndrome, if the ECG at presentation did not reveal acute ischemia, and if the patient had an initial TIMI risk score of 0 to 2	cCTA ($n = 908$) vs. standard care ($n = 463$)
Nagori, 2014[45]	Prospective cohort study	81 patients with recent chest discomfort at rest not entirely typical of ischemia and free of pain when initially evaluated and without new ECG changes or elevated biomarkers	cCTA ($n = 41$) and ExECG ($n = 40$)
Nasis, 2011[46]	Prospective cohort study	203 consecutive patients with ischemic-type chest pain and negative initial troponin and no ST deviation presenting business hours	320-detector row cCTA
Nasis, 2014[47]	Prospective cohort study	585 patients with ow to intermediate risk for ACS and negative findings at troponin I measurement (i.e., troponin I level, 0.04 mg/L) and absence of ST-segment deviation on an electrocardiogram.	cCTA
Pena, 2016[57]	Retrospective cohort study	258 patients > 25 years of age presenting to the ED with a primary complaint of chest pain possibly secondary to ACS, with negative cardiac enzyme and normal or nondiagnostic ECG	cCTA ($n = 128$) compared to SOC
Poon, 2013[58]	Retrospective cohort study	1,788 patients presenting with chest pain who had a 12-lead ECG and cardiac troponin I. Propensity matched before and after when cCTA became SOC	cCTA ($n = 894$) vs. standard evaluation ($n = 894$)
Exercise treadmill testing			
Schaer, 2005[48]	Prospective cohort study	161 Included were only patients with normal ECG findings or ECG tracings with nonsignificant ST-segment depression (0.5 mm) or T-wave alterations already documented in previous ECGs and normal troponin results both at presentation and 6 hours later	Exercise testing
Dadkhah, 2017[35]	Randomized controlled trial	60 patients with no ECG changes suggestive if ischemia, randomized prior to troponin testing. Randomized to a 2-h protocol ($n = 29$) and a 4-h protocol ($n = 31$)	Stress test: 36 exercise treadmill stress tests, 24 had either nuclear or echo stress test

Characteristics	Test results	Outcome	% MACE (95% CI)
Male 223 (61%); mean ± SD age 52.7 ± 12 years; TIMI score low/medium/high, 94.3/5.4/0 (3%)	cCTA negative *n* = 183 cCTA < 50% stenosis *n* = 117	MACE at 6 months, MACE at 1 year	6 months cCTA negative 0% (0%–2%) 1 year cCTA negative 0% (0%–2.3%) cCTA < 50% 4.3% (1.4%–10%)
Male 252 (44%); mean ± SD age 47 ± 8.9 years; TIMI 0, 343 (60%); TIMI 1, 133 (29%); TIMI 2, 50 (9%); TIMI 3, 59 (2%)	cCTA < 50% lesion *n* = 508	MACE at 30 days, MACE at 1 year	30 days 0% (0%–0.8%) 1 year 0% (0%–0.76%)
Group 1: 53.8% male, mean age 49 years, 4.9% known CAD Group 2 56.9% male, mean age 44.2 years, 11.5% known CAD	Group 1 negative: cCTA *n* = 103, Group 2: negative cCTA *n* = 104	MACE at 30 days	Group 1: 0% (0%–0.5%) Group 2: 4.8% (1.6%–10.8%)
Male 443 (49%); mean ± SD age 49 ± 9 years; TIMI 0, 461 (51%); TIMI 1, 325 (36%); TIMI 2, 122 (13%)	cCTA < 50% stenosis *n* = 767	MACE at 30 days	cCTA < 50% stenosis 0% (0%–0.57%)
cCTA: male 29 (70%); mean ± SD age 52.9 ± 8.9 years ExECG: male 27 (67.5%); mean ± SD age 51.2 ± 0.35 years	ExECG negative *n* = 31, cCTA < 50% stenosis *n* = 22	MACE at 6 months	ExECG 9.6% (2.0%–25.7%); cCTA 0% (0%–15.4%)
Male 123 (60%); mean ± SD age 58 ±11 years; TIMI 0, 64 (32%); TIMI 1, 73(36%); TIMI 2, 47 (23%)	cCTA < 50% stenosis *n* = 172 (85%)	MACE at follow-up mean 14.2 months (range 5.5–24.7 months)	cCTA < 50% stenosis 0% (0%–2.1%)
Male 339 (58%); mean ± SD age 58 ± 10 years; TIMI 0, 158 (27%); TIMI 1, 225 (38%); TIMI 2, 39 (24%)	cCTA no plaque *n* = 196 (34%), nonobstructive plaque (<40%) *n* = 288 (49%)	MACE median follow-up 47.4 months (range 24–57 months)	cCTA normal 0% (0%–1.9%); CCT < 40% 0% (0%–1.3%)
cCTA male 81 (63.3%); mean ± SD age 56.7± 11.7 years; TIMI IQR, 1.5 (1–2) SOC: 80 (61.5%); mean ± SD age 5,701± 14.3 years; TIMI IQR, 1 (1–3)	cCTA < 50% *n* = 86	MACE at 30 days	cCTA < 50% 0% (0%–4.1%)
cCTA: male 430 (48%), mean ± SD age 49 ± 11 years; standard evaluation 430 (48%); mean ± SD age = 49 ± 12 years	cCTA < 50% stenosis *n* = 835	MACE at 30 days	cCTA < 50% stenosis 0% (0%–0.4%)
Male 76 (47.2%), mean ± SD age 58 ± 10.6 years, known CAD 47	Exercise testing negative *n* = 125	MACE at 30 days	1.6% (0.2%–5.7%)
2-h protocol male 59%, mean age 49 years, history of CAD 17.2, 4-h protocol, 41% male, mean age 51 years, 28.1% known CAD	2-h protocol *n* = 23 negative stress test, 4-h protocol *n* = 30 negative stress tests	MACE at 6 months	0% (95% CI 0–6.7%)

(Continues)

TABLE 2 (Continued)

Author, year	Type of study	Population	Intervention
Colon, 1998[49]	Prospective cohort study	108 patients with unexplained chest pain, normal cardiac markers, and ECG not diagnostic for ischemia or injury pattern	Exercise treadmill test ($n = 78$) or dobutamine treadmill test ($n = 3,090$)
Stress Echocardiography			
Bedetti, 2005[50]	Prospective cohort study	552 acute chest pain without acute ECG ischemic changes or troponin elevations	Stress echocardiography
Bholasingh, 2003[51]	Prospective cohort study	377 presenting to the ED within 6 h of pain with normal or nondiagnostic ECG and negative serial troponins	Dobutamine stress echo
Innocenti, 2013[59]	Retrospective cohort study	474 consecutive patients presented to ED with spontaneous chest pain, nondiagnostic ECG, and negative cardiac necrosis markers at the time of initial evaluation, after 6 and 12 h	Exercise stress echo $n = 270$; dobutamine stress echo $n = 218$
Innocenti, 2014[60]	Retrospective cohort study	626 consecutive unselected patients who were evaluated in the observation unit with Stress Echocardiogram and answered a follow-up call	ESE ($n = 365$), DSE ($n = 261$)
Gaibazzi, 2011[52]	Prospective cohort study	545 consecutive patients presenting to the ED with suspected ACS but nondiagnostic ECG findings and normal 12-h troponin levels	Contrast stress echocardiogram
Nuclear perfusion Imaging			
Peix, 2012[61]	Retrospective cohort study	55 patients with chest pain and a normal or nondiagnostic ECG	GATED-SPECT myocardial perfusion imaging
Lim, 2013[36]	Randomized controlled trial	1,508 patients with acute chest pain and whose initial 12-lead ECG was nondiagnostic for myocardial ischemia or AMI	Stress myocardial imaging ($n = 1,004$) vs. standard clinical assessment ($n = 504$)
Gallagher, 2007[53]	Prospective cohort study	92 patients with negative troponins and no new ischemic changes and no known coronary CAD	MDCT and SNI
Lerakis, 2009[62]	Retrospective cohort study	103 patients with no evidence of myocardial ischemia by cardiac markers (troponin I, MB fraction of creatinine kinase) as well as normal or inconclusive electrocardiograms	Adenosine stress cardiovascular magnetic resonance

Abbreviations: ACS, acute coronary syndrome; CACS, coronary artery calcium score; CAD, coronary artery disease; CT, computed tomography; CAC, coronary artery calcium; DSE, dobutamine stress echocardiogram; ESE, exercise stress echocardiogram; EST, exercise stress test; ExECG, exercise electrocardiogram; MACE, major adverse cardiac events; MDCT, multidetector computed tomography; MPI, myocardial perfusion imaging; MPS, myocardial perfusion scintigraphy; PTCA, percutaneous transluminal coronary angioplasty; SOC, standard of care; SMPI, SPECT myocardial perfusion imaging; SNI, stress nuclear imaging; STE, ST-segment elevation; TIMI, Thrombolysis in Myocardial Infarction.

was as follows: cCTA, $2,684 (95% CI = $1,773 to $4,418); stress echocardiography, $3,265 (95% CI = $2,383 to $4,836); and stress ECG, $3,461 (95% CI = $2,533 to $4,996).[10] It is important to note that none of these studies evaluated long-term costs that may be associated with repeat testing or radiation exposure. Also, there are downstream implications associated with these tests. For example, in a large cohort of stable chest pain patients, it was reported that patients who underwent cCTA had more coronary angiograms and less radiation exposure than patients who underwent functional testing.[11] For these reasons, careful consideration of patient history and risk factors should be factored into the decision to select a specific testing modality.

It is common for patients to present to the ED with recurrent chest pain. A 2015 retrospective cohort study reported that 25.3% of patients with unexplained chest pain returned to the ED with recurrent explained chest pain within a 1-year time period.[12] Anecdotally, patients presenting with recurrent chest pain are evaluated in a similar manner with every presentation. This typically represents an algorithmic approach to clinical decision making that tends to remove an aspect of independent thinking, as opposed to a hypotheticodeductive approach, which tends to allow the provider to adjust their diagnostic approach based on examination findings and prior pretest probabilities such as risk-stratification testing.[13] However, there are little data about when additional risk stratification should be done in this population with recurrent chest pain and reassuring EKG and troponin in the ED when they have previously undergone evaluation with the modalities mentioned

Characteristics	Test results	Outcome	% MACE (95% CI)
Male 54 (52%), mean ± SD age 54 ± 12 years	*n* = 72 negative stress tests	MACE at follow-up, mean ± SD 12.8 ± 7.2 months	0% (0%–4.9%)
Male 321 (58.2%), mean ± SD age 58 ± 12.6 years, known CAD 103 (19%)	*n* = 502 with negative stress echo	MACE with median follow-up 13 months	1.2% (0.1%–1.7%)
Male 237 (58%), mean ± SD age 56 ± 12 years, known CAD 77 (20%)	*n* = 351 negative stress echo	MACE at 6 months	3.9% (2.1%–6.6%)
Male 276 (58%), mean ± SD age 67 ± 12 years, known CAD 119 (25%)	Negative ESE *n* = 208, Negative DSE *n* = 112,	MACE at mean follow-up 679 ± 299 days	1.5% (0.4%–3.8%)
Male 361 (58%), mean ± SD age 67 ± 12 years, known CAD 162 (26%)	Negative ESE *n* = 292, Negative DSE *n* = 131	MACE up to 4 years	ESE: 1.0% (0.2%–2.9%) DSE: 5.3% (2.2%–10.6%)
Male 317 (58%); TIMI risk 0–1, 240 (44%); TIMI risk 2–4, 305 (56%)	normal perfusion and wall motion *n* = 350	MACE at follow-up, mean time 361 days	MACE 0.9% (0.2%–2.5%)
Male 68%, mean ± SD age 53 ± 12 years	MPI negative *n* = 28	MACE at 1 year	0% (0%–13.7%)
SMPI: male 59.6%, mean ± SD age 52.02 ± 12.4 years, known CAD 4.1% Clinical assessment: male 56.6%, mean ± SD age 51.8 ± 12.8 years, known CAD 4.4%	SMPI normal *n* = 786, SMPI probably normal with attenuation *n* = 115	MACE at 1 year	SMPI normal 0.1% (0%–0.7%) SMPI probably normal with attenuation 0.8% (0.02%–4%)
Male 53%, mean ± SD age 49 ± 11 years, TIMI average 0.8 ± 0.8	MDCT negative, SNI negative *n* = 66	MACE at 30 days	0% (0%–5.4%)
Male 38 (36.9%), mean ± SD age 56.7 ± 12.3 years, known CAD 12 (12.6%)	Adenosine stress cardiovascular magnetic resonance negative test *n* = 89	MACE mean followed mean 277 days (range 161–462 days)	0% (0%–4.1%)

above. Ideally, the evaluation of patients with recurrent chest pain would utilize these data to determine the need for subsequent testing. However, a literature search on this topic performed as a part of the Society for Academic Emergency Medicine's Guidelines for Reasonable and Appropriate Care in the Emergency Department (GRACE) yielded no direct evidence to provide guidance.[14]

There have been several meta-analyses to date that have evaluated the performance of diagnostic testing to risk stratify ED chest pain patients.[15–20] To our knowledge, this is the first meta-analysis to include low- and intermediate-risk ED chest pain patients with negative evaluations with the modalities cCTA, stress echocardiography, exercise stress testing, myocardial perfusion scan, and evaluation for subsequent MACE. Using this study design, we attempted to answer the question as to the warranty period of each of these risk stratification tools.

METHODS

Search strategy

We searched English language articles in the following four databases: Ovid MEDLINE, Ovid MEDLINE In-process & other non-indexed citations & Epub ahead of print, Embase, and The Cochrane Library. The search strategies used subject headings and free words and are listed in Appendix S1. The search strategy was developed in consultation with a research librarian.

Study selection

Two independent reviewers screened article titles and abstracts for eligibility. The eligible full-text articles were then evaluated for final inclusion. Disagreements were resolved by a third reviewer. Covidence (www.covidence.org) was the software platform used for the article selection process.

Articles were included if the study population (1) was low- to intermediate-risk patients as defined by a Thrombolysis In Myocardial Infarction (TIMI) score ≤ 5 or History-EKG-Age-Risk factors-Troponin (HEART) score ≤ 6, and/or in situations when none was provided having negative troponin and no acute ischemic findings on EKG; (2) were risk stratified for coronary artery disease (CAD) using any of the following tests—cCTA, exercise stress test, stress echocardiography, or stress myocardial perfusion scan; (3) then followed for a defined period (1, 6, or 12 months) to assess the occurrence of subsequent MACE as a primary or secondary outcome. MACE was defined as death, MI, hospitalization due to heart failure, percutaneous cardiac catheterization with intervention, or coronary artery bypass grafting.[21] We did not limit any articles on

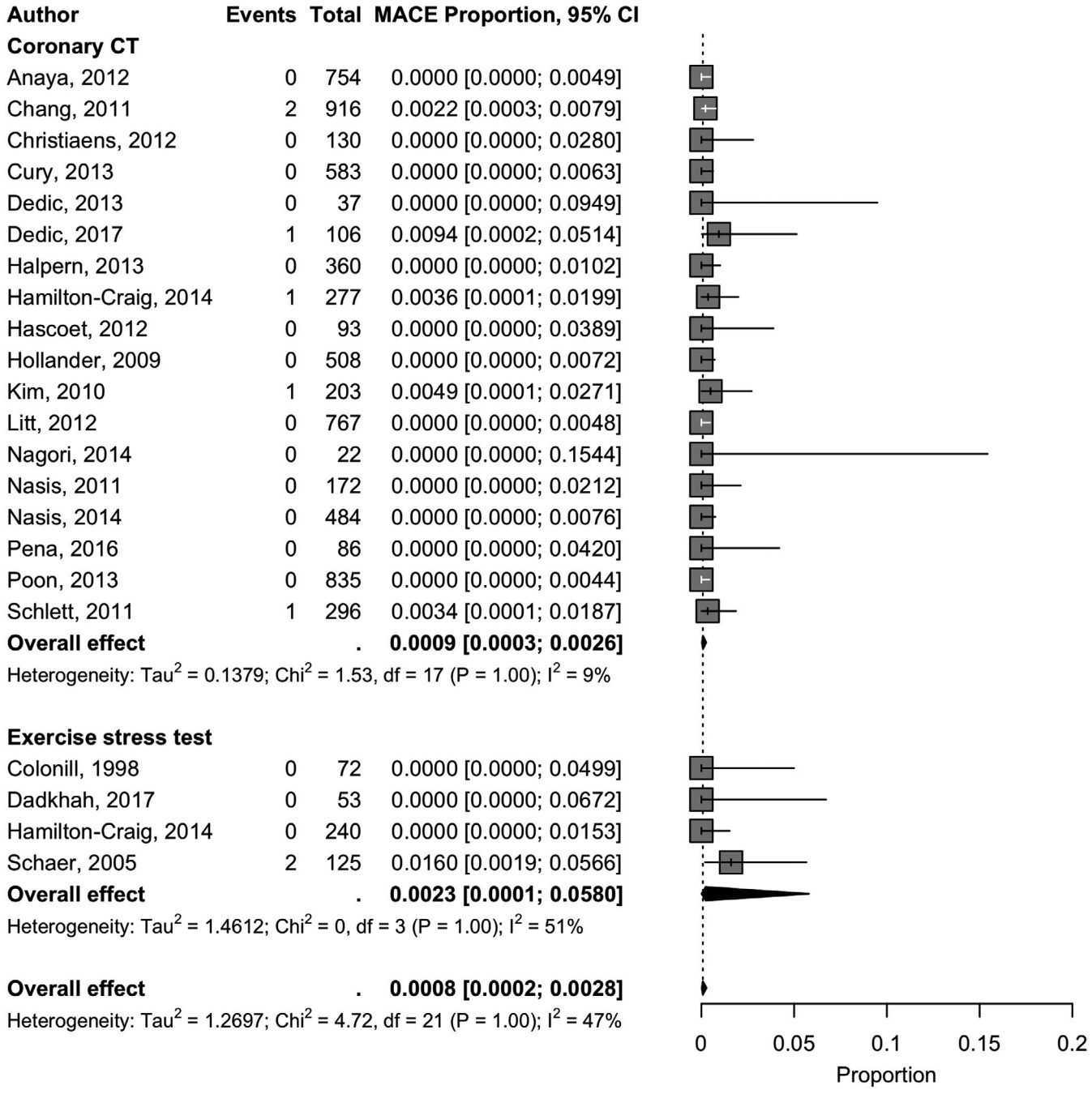

FIGURE 1 Forest plot comparing subgroups at 1 month when moderated by modality of risk stratifying imaging utilized. MACE, major adverse cardiac events

the basis of age, gender, race, or location, and all articles meeting the stated criteria were included. Articles were excluded if a full-text version was unavailable. Patients who were lost to follow-up were not included in the data, even if no MACE was present on chart review.

The Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 (PRISMA 2020) checklist was used for this review and meta-analysis.[24] A PROSPERO search was performed and identified no systematic reviews on this topic, so we preregistered this systematic review with meta-analysis with PROSPERO ID 266107.

Data extraction and quality assessment

Baseline data were extracted from included article, which consisted of the sponsorship source, country of origin, study setting, first author's name, study institution, study design, inclusion and exclusion criteria, gender distribution, HEART or TIMI scores (if included), risk stratification imaging modality performed, duration of follow-up, and rate of MACE. Risk of bias within completed clinical trials was assessed for each study by two independent reviewers using two bias assessments tools—revised tool for Risk of Bias in randomized trials (RoB 2.0) and Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I).[22,23] The Web-based platform Covidence was used to provide consensus for any disagreements between the two reviewers. Risk of bias assessment is included in Table 1.

Data analysis

We utilized a random-effects model to assess the pooled MACE event proportion for patients undergoing evaluation of ACS when risk stratified to a low- to intermediate-risk category after standardized ED testing (troponin and ECG) with three prespecified endpoints of 1, 6, and 12 months.[25] Heterogeneity analysis was performed using Cochrane's Q-test and I^2 statistic. Heterogeneity was classified with respect to the recommendations by the Cochrane handbook.[26] Subgroup analyses were performed to assess impact of modality on the event rate and heterogeneity. Given the focus on use of cCTA, we performed additional subgroup analysis on this cohort to evaluate differences in MACE events when stratified by CAD presence, categorized as "no CAD" or "nonobstructive CAD"

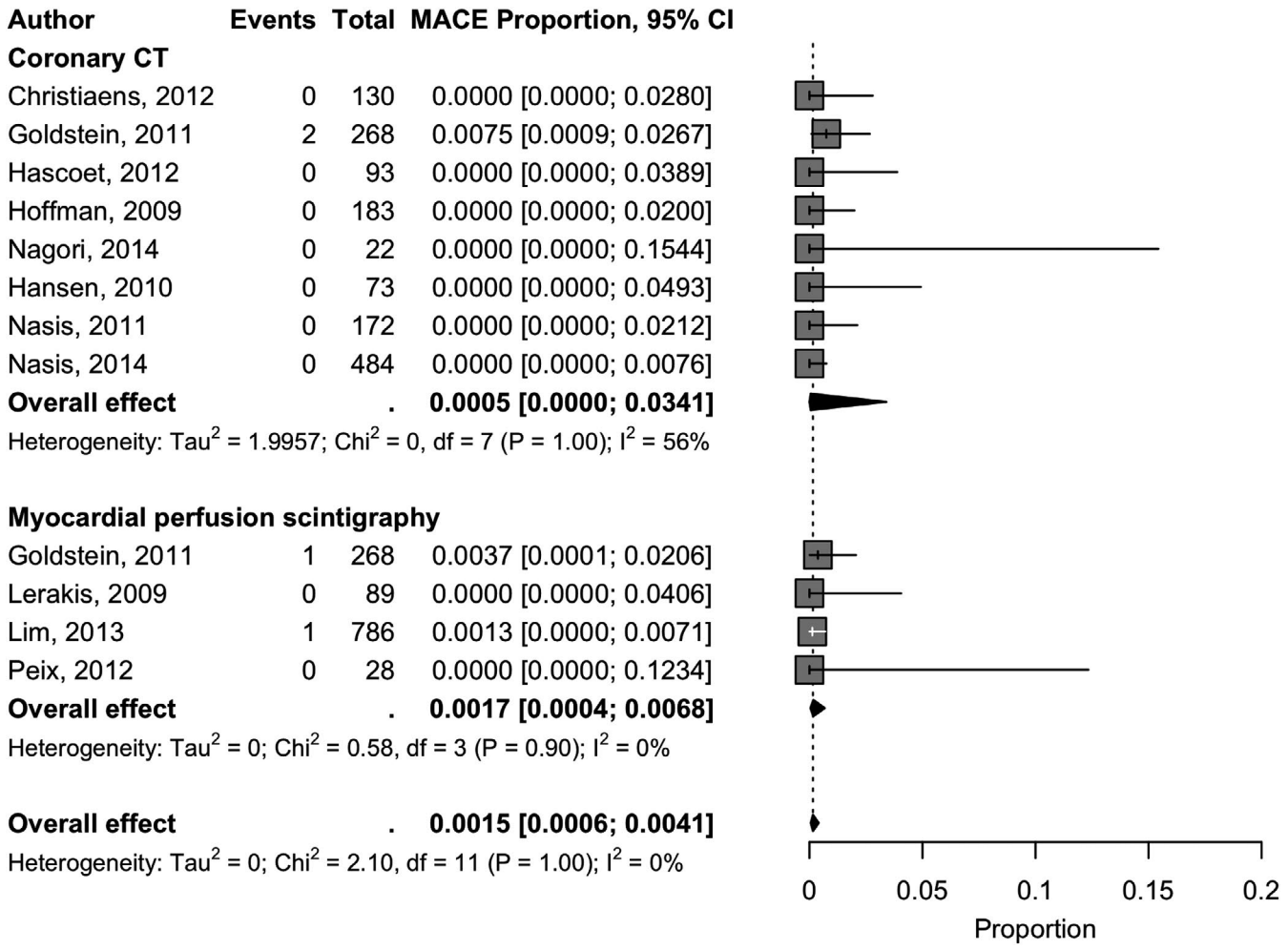

FIGURE 2 Forest plot comparing subgroups at 6 months when moderated by modality of risk stratifying imaging utilized. MACE, major adverse cardiac events

for both 1- and 12-month endpoints. All statistical and data analyses performed using R version 3.6.1 utilizing meta package for analysis.[27–29]

RESULTS

Search results

Initially, 952 articles were identified for screening, 81 met criteria for full-text review, and 33 articles were included in this meta-analysis. Of the 33 studies, seven were randomized controlled trials,[30–36] 17 were prospective cohort studies,[37–53] and the remaining nine were retrospective cohort studies.[54–62] The type of testing utilized varied in each study, and some assessed multiple modalities. Specifically, 21 utilized cCTA for risk stratification (7,153 patients),[30–34,37–47,54–58] five utilized stress echocardiography (1,892 patients),[50–52,59,60] four assessed MPS (1,237 patients),[36,53,61,62] and three studies assessed exercise stress testing (521 patients).[35,48,49] Study details are listed in Table 2.

Data analysis

Of the 33 studies, 30 provided age and gender estimates capable of pooling with an overall mean (±SD) age of 54 (±11) years with 47% female. Twenty-one studies evaluated MACE events occurring at a 1-month follow-up endpoint.[30,31,33–35,37–40,42–49,54,56–58] None of the MPS observations were pooled due to low numbers and zero event rates. There was moderate to substantial heterogeneity observed overall in this cohort (I^2 = 47%). Subgroup analysis of the modalities did not find a significant difference in the effect size among the two different modalities at 1 month with cCTA having a 0.09% (95% CI = 0.03% to 0.26%) pooled event rate compared to 0.23% (95% CI = 0.01% to 5.8%) of the exercise stress testing (p = 1). There was considerable heterogeneity seen in the exercise stress testing studies though (I^2 = 51%), compared to a low heterogeneity in cCTA studies (I^2 = 9%; Figure 1).

Seventeen studies evaluated MACE events at 6 months, which included studies from all modality groups. The studies within the exercise stress testing and stress echocardiography cohorts were removed from pooling due to considerable within-group heterogeneity. Eleven studies remained between both the MPS and the cCTA having an overall event rate of 0.15% (95% CI = 0.06% to 0.41%) with no significant difference found between the two groups' rate of MACE and both having low within-group heterogeneity (Figure 2).[32,36,41,42,45–47,54,61–63]

There were eight studies evaluating MACE events at 12 months with overall considerable heterogeneity when pooling.[41,43,46,47,50,56,59,60] Subgroup analysis performed found a pooled cCTA rate of MACE 0.16% (95% CI = 0.04% to 0.65%) compared to

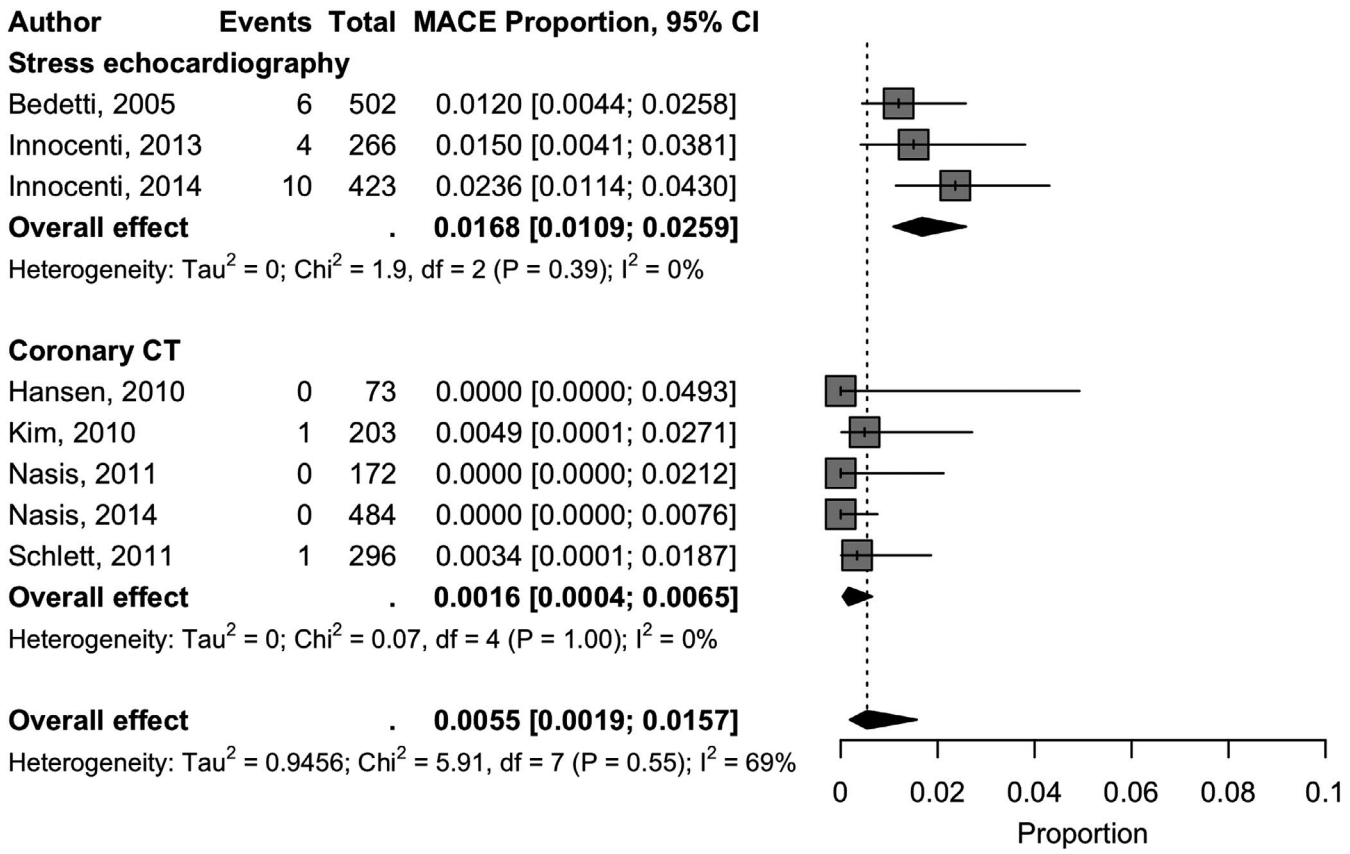

FIGURE 3 Forest plot comparing subgroups at 12 months when moderated by modality of risk stratifying imaging utilized. MACE, major adverse cardiac events

1.68% (95% CI = 0.01% to 2.6%) for stress echocardiography both with low within-group heterogeneity (Figure 3).

A subgroup analysis within the cCTA cohort was performed to assess the effect of being classified as nonobstructive CAD (<50% stenosis) compared to no identified stenosis. There were 17 studies included for the 1-month endpoint.[30,31,33,34,37–40,42–47,54,56–58] There were five studies included for the 12-month endpoint.[41,43,46,47,56] Pooled analysis showed a low heterogeneity overall at both 1-month and 12-month endpoints with an overall event rate of 0.09% (95% CI = 0.03% to 0.27%) and 0.5% (95% CI = 0.21% to 1.2%), respectively. Additionally, no significant effect difference was appreciated between the two groups with a MACE event rate of 0.06% (95% CI = 0.01% to 0.34%) for the nonobstructive cohort and 0.17% (95% CI = 0.04% to 0.67%) at 1 month (Figure 4) and 0.54% (95% CI = 0.19% to 1.5%) and 0.44% (95% CI = 0.09% to 2.2%) at 12 months (Figure 5), respectively.

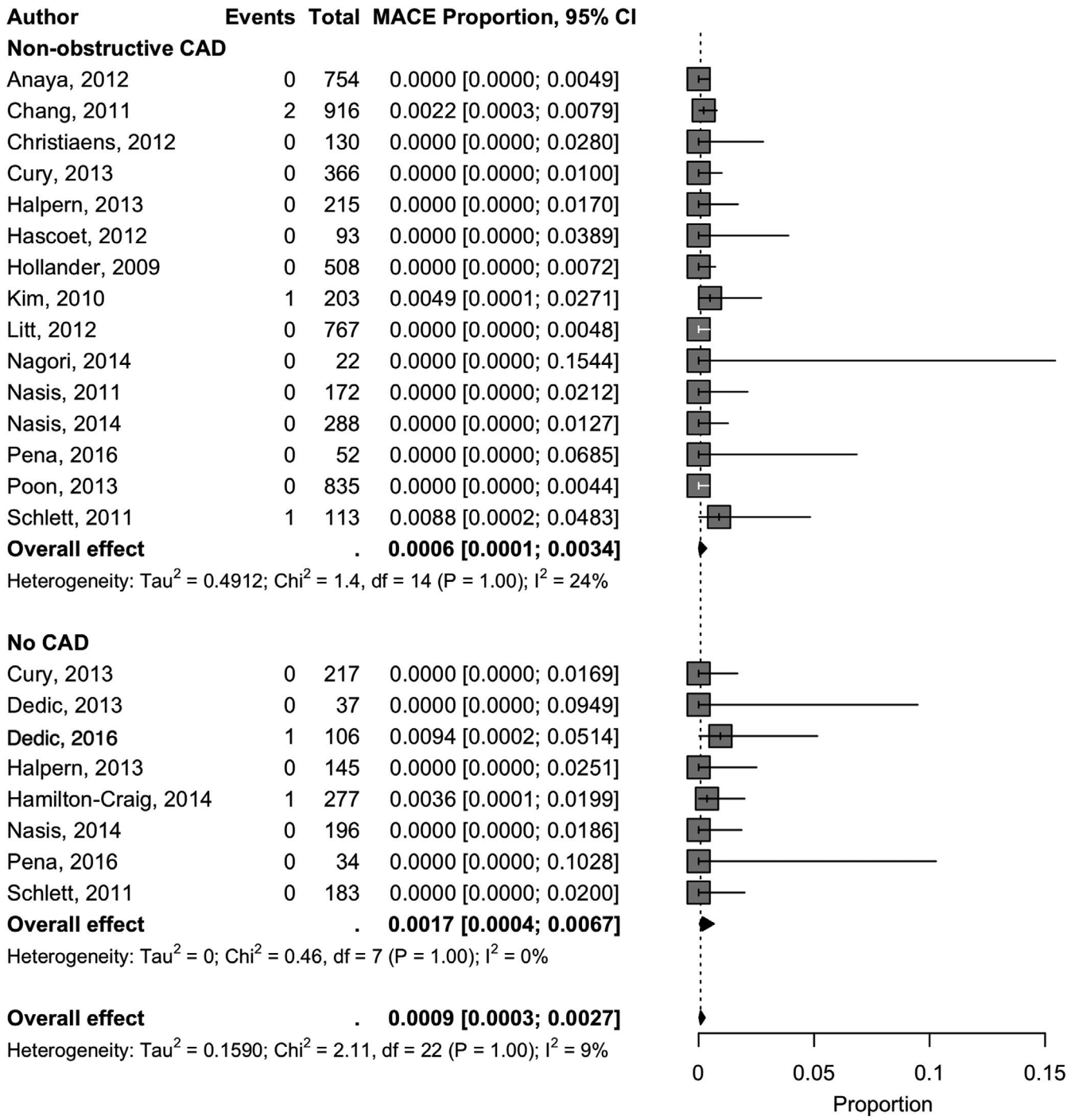

FIGURE 4 Forest plot comparing subgroups of cCTA at 1 month when moderated by classification of obstruction. CAD, coronary artery disease; cCTA, coronary computed tomography angiogram; MACE, major adverse cardiac events

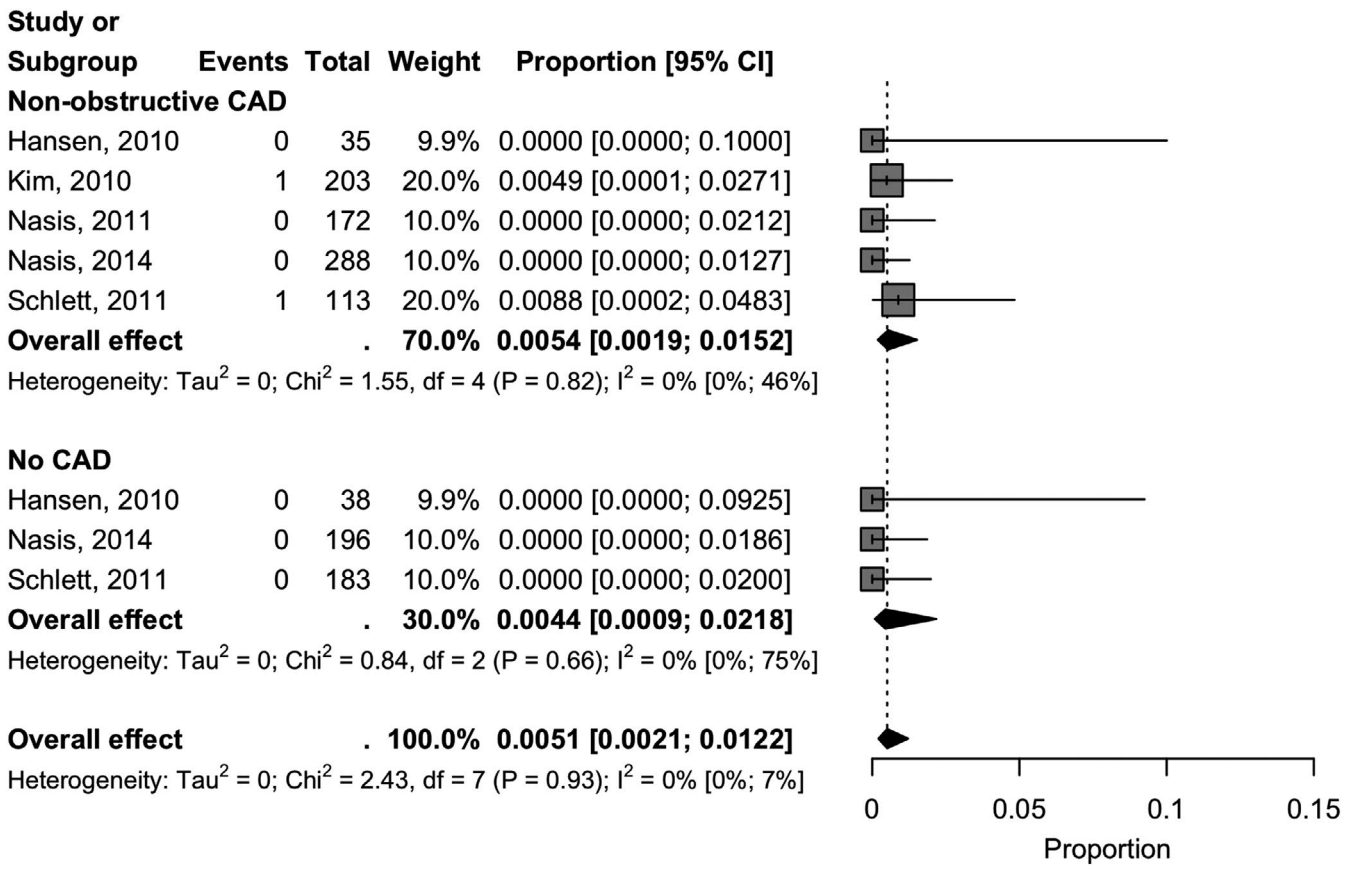

FIGURE 5 Forest plot comparing subgroups of cCTA at 12 months when moderated by classification of obstruction. CAD, coronary artery disease; cCTA, coronary computed tomography angiogram

DISCUSSION

In this meta-analysis we found that patients with a normal ED evaluation of chest pain (reassuring ECG and normal troponin) who subsequently had normal ECG stress testing, stress echocardiography, or stress myocardial perfusion scans had an extremely low overall risk of MACE at 1, 6, and 12 months. It is therefore possible to infer that repeating these tests within 12 months of a prior evaluation may not significantly provide more information regarding the risk of MACE as a 2013 emergency physician survey showed an acceptable MACE rate is <1%.[64]

ED-based studies that evaluated the risk of MACE after cCTA have utilized longer periods of follow-up. The results we note of extremely low risk of MACE after cCTA up to 12 months are consistent with results from these large registries. The CONFIRM Registry reported a risk of MACE of 0.6% with 2.1 years of follow-up in patients with a normal cCTA. The PROMISE Trial reported a risk of MACE in patients with a median follow-up of 26 months to be 0.3%. Since these registries were not limited to ED patient populations they were not included in our meta-analysis but still provide valuable information.[63,65] Given this information it may be reasonable to avoid additional testing in patients who had a prior cCTA within 2 years and have a no evidence of myocardial injury during their ED evaluation. The majority of the studies that met criteria for our systematic review and meta-analysis had durations of follow-up between 6 months and 1 year with a very low risk of pooled MACE.

We also noted an insignificant difference in the rate of MACE in patients who had a nonobstructive lesion (<50%) compared to those patients with no obstruction. In the CONFIRM Registry and PROMISE Trial, the risk of MACE with 2 years of follow-up was noted to be 2.4% and 1.6%, respectively. This needs to be considered when making decisions about repeat testing, and emergency physicians need to carefully read the prior cCTA results. Advancements in cCTA have led to an understanding that the risk of MACE may not only be related to the degree of stenosis but type of lesion. Using optical coherence tomography, investigators have shown that the lack of a lipid-rich plaque underneath an intact fibrinous cap in patients with an ACS is associated with reduced risk of MACE.[66] In the future, we may be able to further stratify patients with lesions < 50% into those with a low risk of MACE.

Given the differences in diagnostic accuracy between testing modalities and patient-specific features that may lead to a false-negative result, it may be reasonable to perform a test such as a cCTA after a negative stress test or MPS in higher-risk patients. However, it is important to examine the additional value such testing would add in a patient with negative ED evaluation for chest pain with already low rates of MACE at follow-up as described in this analysis (stress testing 0.39% compared to MPS 0.16%). In the era of

high-sensitivity troponin, low-risk patients as defined by the HEART score or other risk stratification tools have a very low risk of MACE when coupled with a high-sensitivity troponin below the limit of detection.[67] Additional risk stratification in these patients may not significantly alter the prior risk classification if the patient had a recent negative stress test and can further contribute to the issues of overtesting and increasing cost of ED visits.[68] A 2015 survey showed that when presented with hypothetical zero medicolegal risk, emergency physicians answered that they would not have admitted the patients in 30% of cases.[69] The data provided in this meta-analysis may help ease malpractice angst that exists regarding patients who return to the ED with recurrent chest pain but have recent negative testing.

It is also important to address what postevaluation level of risk is viewed as acceptable to patients and physicians. It has been reported that in patients who undergo cardiac testing after an ED visit, the number needed to treat was 250 to avoid one death or MI and 200 to avoid one MACE within 30 days. However, sensitivity analysis revealed higher numbers needed to treat for these outcomes when adjusting for weighted for probability.[70] This should be balanced with the risk of harm. For example, the increased lifetime risk of cancer associated with a single CT and MPS scan is 0.07% and 0.12%, respectively.[71] Interestingly, a structured survey study reported that increasing the risk of a diagnostic test did not seem to decrease a patient's desire for a test.[72]

LIMITATIONS

There are several limitations of this review. First, only a small number of studies were included. By using our specific search criteria, we narrowed 952 articles down to 81 eligible studies and found that only 33 met our bias criteria as defined. Each study had variable time ranges for the evaluation of MACE, so several studies were limited if they did not provide specific details of MACE for us to determine if it met our 1-month and 12-month endpoints. The studies were multimodal (retrospective, prospective, and randomized controlled trials) and thus carry variable strength of evidence. In addition, all studies evaluated the occurrence of MACE over a specified time period and did not directly answer our question of does repeat testing need to be obtained. MACE was defined differently in various studies, but given the low overall occurrence, we did not specify the single outcomes of MACE that occurred in each study. The demographics provided were for the total study population including patients who were excluded or lost to follow-up.

CONCLUSION

This meta-analysis evaluates the efficacy of different modalities of risk stratification for patients that are low to intermediate risk for acute coronary syndrome and found that coronary computed tomography angiogram has comparable rates of major adverse cardiac events when compared stress electrocardiogram, stress echocardiography, and myocardial perfusion scintigraphy for risk stratification. There is an extremely low incidence of major adverse cardiac events at the 12-month mark following the above testing modalities. Future research should evaluate the major adverse cardiac event rate with longer periods of follow-up than has been typical of the work presented here, especially given the low event rate found in a small subset of studies that extended follow-up out to 2 years. Coronary computed tomography angiogram has its diagnostic benefits as well as advantages such as time, safety, cost, availability, and tolerability. Given its feasibility to obtain in the ED, clinicians can use coronary computed tomography angiogram as their risk stratification of choice in patients that are low to intermediate risk for acute coronary syndrome. If the coronary computed tomography angiogram shows minimal disease, the literature supports safe discharge of these patients from the ED with a low risk of major adverse cardiac events at 1, 6, and 12 months.

CONFLICT OF INTEREST

The authors have no potential conflicts to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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