Title of Manuscript: Major adverse cardiac events after ED 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 month, 6 months and 12 months after a negative coronary CTA (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 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 I2 statistic.

Results: Twenty-one studies evaluated follow up at 1 month with cCTA having a 0.09% (95CI 0.03% - 0.26%) pooled MACE compared to 0.23% (95CI 0.01% - 5.8%) of the exercise stress testing(p=1). MPS and cCTA had an overall event rate of 0.15% (95CI 0.06%-0.41%) at 6 months (I2 = 0%). At 12 months, a subgroup analysis found a pooled cCTA MACE of 0.16% (95CI 0.04% – 0.65%) compared to 1.68% (95CI 0.01% - 2.6%) for stress echocardiography with low within-group heterogeneity (I2 = 0%). Subgroup analysis of cCTA with no disease vs non-obstructive disease (<50% stenosis) did not find statistical difference in the MACE at both 1-month (0.17% (95CI 0.04% - 0.67%) vs 0.06% (95CI 0.01% - 0.34%)) and 12 months (0.44% (95CI 0.09% - 2.2% vs 0.54% (95CI 0.19% - 1.5%)).

Conclusions: Patients presenting with chest pain that 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.

Introduction

Coronary artery disease is a leading cause of death in the United States (365,00 deaths in 2017).[1] Quick and reliable identification of patients at risk for acute coronary syndrome is important in the emergency department (ED). Approximately 95% of patients that 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 is one of the top 3 common final diagnosis among claims involving emergency medicine.[3] One study reported the rate of patients diagnosed with an acute coronary syndrome seven days after an ED presentation was 3%.[4] Additional factors associated with admissions for cardiac evaluation include knowledge of poor compliance with follow-up in under-resourced 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. This practice is consistent with guideline recommendations and represent anatomic and functional cardiac testing.[8] Anatomic testing encompasses cCTA while functional testing includes stress echocardiography and myocardial perfusion scintigraphy.[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 workups for low-risk patients with chest pain for each risk stratification were 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 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 upon exam findings and prior pre-test probabilities such as risk-stratification testing.[13] However, there is 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 above. Ideally, the evaluation of patients with recurrent chest pain would utilize this 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 evaluate 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 I. 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.) were 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 month, 6 months, or 12 months) to assess the occurrence of subsequent MACE as a primary or secondary outcome. MACE was defined as death, myocardial infarction (MI), hospitalization due to heart failure, percutaneous cardiac catheterization with intervention, or coronary artery bypass grafting.[21] We did not limit any articles on the basis of age, gender, race or location, and all article meeting the stated criteria were included. Articles were excluded if a full text version was unavailable. Patients that were lost to follow up were not included in the data, even if no MACE was present on chart review.

Data extraction and quality assessment

Baseline data was 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 2 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.

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

Statistical 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 3 pre-specified end points of 1 month, 6 months, 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 "Non-obstructive CAD" for both 1- and 12-month end points. 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, 7 were randomized controlled trials, [30,35,36,39,45,52,60] 17 were prospective cohort studies,[31,33,34,38,40-43,46-48,51,53-55,58,61] and the remaining 9 were retrospective cohort studies.[32,37,44,49,50,56,57,59,62] The type of testing utilized varied in each study, and some assessed multiple modalities. Specifically, 21 utilized cCTA for risk stratification (7,153 patients),[30-50] 5 utilized stress echocardiography (1892 patients),[54-58] 4 assessed myocardial perfusion scintigraphy (1,237 patients),[59-62] and 3 studies assessed exercise stress testing (521 patients).[51-53] 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 average age of 54 years (+/-11) with 47% female.

Twenty-one studies evaluated MACE events occurring at a 1-month follow-up end point.[30-35,38,39,41-53] None of the myocardial perfusion scintigraphy 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 amongst the two different modalities at 1 month with cCTA having a 0.09% (95CI 0.03% - 0.26%) pooled event rate compared to 0.23% (95CI 0.01% - 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 myocardial perfusion scintigraphy and the cCTA having an overall event rate of 0.15% (95CI 0.06%-0.41%) with no significant difference found between the two groups' rate of MACE and both having low within-group heterogeneity (Figure 2).[32,36,40,41,46-48,59,60,62,65]

There were eight studies evaluating MACE events at 12 months with overall considerable heterogeneity when pooling.[40,42,44,47,48,54,56,57] Subgroup analysis performed found a pooled cCTA rate of MACE 0.16% (95CI 0.04% – 0.65%) compared to 1.68% (95CI 0.01% - 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 non-obstructive CAD (<50% stenosis) compared to no identified stenosis. There were 17 studies included for the 1-month end point.[30-35,38,39,41-50] There were 5 studies included for the 12-month end point.[40,42,44,47,48] Pooled analysis showed a low heterogeneity overall at both

1-month and 12-month end points with an overall event rate of 0.09% (95CI 0.03% – 0.27%) and 0.5% (95CI 0.21% - 1.2%) respectively. Additionally, no significant effect difference was appreciated between the two groups with a MACE event rate of 0.06% (95CI 0.01% - 0.34%) for the non-obstructive cohort and 0.17% (95CI 0.04% - 0.67%) at 1 month (Figure 4) and 0.54% (95CI 0.19% - 1.5%) and 0.44% (95CI 0.09% - 2.2%) at 12 months (Figure 5) respectively.

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 month, 6 months, 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 EM physician survey showed an acceptable MACE rate is <1%.[63]

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.[64,65] 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 to a 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 non-obstructive 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 look at 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 over testing 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 post-evaluation 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 1 death or MI, and 200 to avoid 1 major adverse cardiovascular event 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 life-time 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 only 33 met our bias criteria as defined above. 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 end points. The studies were multi-modal (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 cCTA has comparable rates of MACE when compared stress electrocardiogram (ECG), stress echocardiography, and myocardial perfusion scintigraphy for risk stratification. There is an extremely low incidence of MACE at the 12-month mark following the above testing modalities. Future research should evaluate the MACE 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 two years. Coronary CTA 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 cCTA as their risk stratification of choice in patients that are low to intermediate risk for ACS. If the cCTA shows minimal disease, the literature supports safe discharge of these patients from the ED with a low risk of MACE at 1, 6, and 12 months.

References

1. Heron M. Deaths: Leading Causes for 2017. Natl Vital Stat Rep 2019;68:1-77.

2. Hsia RY, Hale Z, Tabas JA. A National Study of the Prevalence of Life-Threatening Diagnoses in Patients With Chest Pain. JAMA Intern Med 2016;176:1029-32.

3. Myers LC, Einbinder J, Camargo CA, Jr., Aaronson EL. Characteristics of medical malpractice claims involving emergency medicine physicians. J Healthc Risk Manag 2021;41:9-15.

4. Chang MP, Vigen R, Sharma S, Diercks DB. Possible Missed Acute Coronary Syndrome Rate in North Texas: Is There Room to Improve? Crit Pathw Cardiol 2019;18:121-4.

5. Sutton J, Gu L, Diercks DB. Impact of Social Determinants of Health, Health Literacy, Self-perceived Risk, and Trust in the Emergency Physician on Compliance with Follow-up. West J Emerg Med 2021;22:667-71.

6. Natsui S, Sun BC, Shen E, et al. Higher Emergency Physician Chest Pain Hospitalization Rates Do Not Lead to Improved Patient Outcomes. Circ Cardiovasc Qual Outcomes 2021;14:e006297.

7. Yau AA, Nguyendo LT, Lockett LL, Michaud E. The HEART Pathway and Hospital Cost Savings. Crit Pathw Cardiol 2017;16:126-8.

8. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44-e164.

9. Morris JR, Bellolio MF, Sangaralingham LR, et al. Comparative Trends and Downstream Outcomes of Coronary Computed Tomography Angiography and Cardiac Stress Testing in Emergency Department Patients With Chest Pain: An Administrative Claims Analysis. Acad Emerg Med 2016;23:1022-30.

10. Khare RK, Mark Courtney D, Powell ES, Venkatesh AK, Lee TA. Sixty- four–slice Computed Tomography of the Coronary Arteries: Cost–Effectiveness Analysis of Patients Presenting to the Emergency Department with Low- risk Chest Pain. Acad Emerg Med 2008;15:623-32.

11. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291-300.

12. Safdar B, Dziura J, Bathulapalli H, et al. Chest pain syndromes are associated with high rates of recidivism and costs in young United States Veterans. BMC Fam Pract 2015;16:88.

13. Sandhu H, Carpenter C, Freeman K, Nabors SG, Olson A. Clinical decision making: opening the black box of cognitive reasoning. Ann Emerg Med 2006;48:713-9.

14. Musey PI, Jr., Bellolio F, Upadhye S, et al. Guidelines for reasonable and appropriate care in the emergency department (GRACE): Recurrent, low-risk chest pain in the emergency department. Acad Emerg Med 2021;28:718-44.

15. Samad Z, Hakeem A, Mahmood SS, et al. A meta-analysis and systematic review of computed tomography angiography as a diagnostic triage tool for patients with chest pain presenting to the emergency department. J Nucl Cardiol 2012;19:364-76.

16. Iannaccone M, Gili S, De Filippo O, et al. Diagnostic accuracy of functional, imaging and biochemical tests for patients presenting with chest pain to the emergency department: A systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care 2019;8:412-20.

17. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Coronary computed tomographic angiography for detection of coronary artery disease in patients presenting to the emergency department with chest pain: a meta-analysis of randomized clinical trials. Eur Heart J Cardiovasc Imaging 2013;14:782-9.

18. Athappan G, Habib M, Ponniah T, Jeyaseelan L. Multi-detector computerized tomography angiography for evaluation of acute chest pain-a meta-analysis and systematic review of literature. Int J Cardiol 2010;141:132-40.

19. Chaikriangkrai K, Palamaner Subash Shantha G, Jhun HY, et al. Prognostic Value of Coronary Artery Calcium Score in Acute Chest Pain Patients Without Known Coronary Artery Disease: Systematic Review and Meta-analysis. Ann Emerg Med 2016;68:659-70.

20. Hulten E, Pickett C, Bittencourt MS, et al. Outcomes after coronary computed tomography angiography in the emergency department: a systematic review and meta-analysis of randomized, controlled trials. J Am Coll Cardiol 2013;61:880-92.

21. Tsai IT, Wang CP, Lu YC, et al. The burden of major adverse cardiac events in patients with coronary artery disease. BMC Cardiovasc Disord 2017;17:1.

22. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

23. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.

24. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

25. Harrer M, Cuikpers P, Furukawa TA, Ebert DD. Doing Meta-Analysis with R: A hands-on guide. Boca Raton:Chapman & Hall/CRC Press; 2021.

26. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2. Chichester:Cochrane;2021.

27. R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

28. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. Journal of Open Source Software [Internet]. 2019; Available from https://doi.org/10.21105/joss.01686.

29. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153-60.

30. Anaya P, Moliterno DJ. CT angiography for emergency decision making in acute coronary syndromes: applying future vision now. Curr Cardiol Rep 2012;14:537-9.

31. Chang AM, Le J, Matsuura AC, Litt HI, Hollander JE. Does coronary artery calcium scoring add to the predictive value of coronary computed tomography angiography for adverse cardiovascular events in low-risk chest pain patients? Acad Emerg Med 2011;18:1065-71.

32. Christiaens L, Duchat F, Boudiaf M, et al. Impact of 64-slice coronary CT on the management of patients presenting with acute chest pain: results of a prospective two-centre study. Eur Radiol 2012;22:1050-8.

33. Cury RC, Feuchtner GM, Batlle JC, et al. Triage of patients presenting with chest pain to the emergency department: implementation of coronary CT angiography in a large urban health care system. AJR Am J Roentgenol 2013;200:57-65.

34. Dedic A, Ten Kate GJ, Neefjes LA, et al. Coronary CT angiography outperforms calcium imaging in the triage of acute coronary syndrome. Int J Cardiol 2013;167:1597-602.

35. Dedic A, Lubbers MM, Schaap J, et al. Coronary CT Angiography for Suspected ACS in the Era of High-Sensitivity Troponins: Randomized Multicenter Study. J Am Coll Cardiol 2016;67:16-26.

36. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. J Am Coll Cardiol 2011;58:1414-22.

37. Grunau B, Leipsic J, Purssell E, et al. Comparison of Rates of Coronary Angiography and Combined Testing Procedures in Patients Seen in the Emergency Room With Chest Pain (But No Objective Acute Coronary Syndrome Findings) Having Coronary Computed Tomography Versus Exercise Stress Testing. Am J Cardiol 2016;118:155-61.

38. Halpern EJ, Deutsch JP, Hannaway MM, et al. Cardiac risk factors and risk scores vs cardiac computed tomography angiography: a prospective cohort study for triage of ED patients with acute chest pain. Am J Emerg Med 2013;31:1479-85.

39. Hamilton-Craig C, Fifoot A, Hansen M, et al. Diagnostic performance and cost of CT angiography versus stress ECG--a randomized prospective study of suspected acute coronary syndrome chest pain in the emergency department (CT-COMPARE). Int J Cardiol 2014;177:867-73.

40. Hansen M, Ginns J, Seneviratne S, et al. The value of dual-source 64-slice CT coronary angiography in the assessment of patients presenting to an acute chest pain service. Heart Lung Circ 2010;19:213-8.

41. Hascoet S, Bongard V, Chabbert V, et al. Early triage of emergency department patients with acute coronary syndrome: contribution of 64-slice computed tomography angiography. Arch Cardiovasc Dis 2012;105:338-46.

42. Schlett CL, Banerji D, Siegel E, et al. Prognostic value of CT angiography for major adverse cardiac events in patients with acute chest pain from the emergency department: 2-year outcomes of the ROMICAT trial. JACC Cardiovasc Imaging 2011;4:481-91.

43. Hollander JE, Chang AM, Shofer FS, et al. One-year outcomes following coronary computerized tomographic angiography for evaluation of emergency department patients with potential acute coronary syndrome. Acad Emerg Med 2009;16:693-8.

44. Kim J, Lee H, Song S, et al. Efficacy and safety of the computed tomography coronary angiography based approach for patients with acute chest pain at an emergency department: one month clinical follow-up study. J Korean Med Sci 2010;25:466-71.

45. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med 2012;366:1393-403.

46. Nagori M, Narain VS, Saran RK, Dwivedi SK, Sethi R. Efficacy of multi-detector coronary computed tomography angiography in comparison with exercise electrocardiogram in the triage of patients of low risk acute chest pain. Indian Heart J 2014;66:435-42

47. Nasis A, Meredith IT, Nerlekar N, et al. Acute chest pain investigation: utility of cardiac CT angiography in guiding troponin measurement. Radiology 2011;260:381-9.

48. Nasis A, Meredith IT, Sud PS, Cameron JD, Troupis JM, Seneviratne SK. Long-term outcome after CT angiography in patients with possible acute coronary syndrome. Radiology 2014;272:674-82.

49. Pena E, Rubens F, Stiell I, Peterson R, Inacio J, Dennie C. Efficiency and safety of coronary CT angiography compared to standard care in the evaluation of patients with acute chest pain: a Canadian study. Emerg Radiol 2016;23:345-52.

50. Poon M, Cortegiano M, Abramowicz AJ, et al. Associations between routine coronary computed tomographic angiography and reduced unnecessary hospital admissions, length of stay, recidivism rates, and invasive coronary angiography in the emergency department triage of chest pain. J Am Coll Cardiol 2013;62:543-52.

51. Schaer BA, Jenni D, Rickenbacher P, et al. Long-term performance of a simple algorithm for early discharge after ruling out acute coronary syndrome: a prospective multicenter trial. Chest 2005;127:1364-70.

52. Dadkhah S, Almuwaqqat Z, Sulaiman S, et al. Sensitive Troponin I and Stress Testing in the Emergency Department for the Early Management of Chest Pain Using 2-Hour Protocol. Crit Pathw Cardiol 2017;16:89-92.

53. Colon PJ, 3rd, Guarisco JS, Murgo J, Cheirif J. Utility of stress echocardiography in the triage of patients with atypical chest pain from the emergency department. Am J Cardiol 1998;82:1282-4, A10.

54. Bedetti G, Pasanisi EM, Tintori G, et al. Stress echo in chest pain unit: the SPEED trial. Int J Cardiol 2005;102:461-7.

55. Bholasingh R, Cornel JH, Kamp O, et al. Prognostic value of predischarge dobutamine stress echocardiography in chest pain patients with a negative cardiac troponin T. J Am Coll Cardiol 2003;41:596-602.

56. Innocenti F, Lazzeretti D, Conti A, Zanobetti M, Vicidomini S, Pini R. Stress echocardiography in the ED: diagnostic performance in high-risk subgroups. Am J Emerg Med 2013;31:1309-14.

57. Innocenti F, Cerabona P, Donnini C, Conti A, Zanobetti M, Pini R. Long-term prognostic value of stress echocardiography in patients presenting to the ED with spontaneous chest pain. Am J Emerg Med 2014;32:731-6.

58. Gaibazzi N, Squeri A, Reverberi C, et al. Contrast stress-echocardiography predicts cardiac events in patients with suspected acute coronary syndrome but nondiagnostic electrocardiogram and normal 12-hour troponin. J Am Soc Echocardiogr 2011;24:1333-41.

59. Peix A, Batista E, Cabrera LO, et al. Gated-SPECT myocardial perfusion imaging and coronary calcium score for evaluation of patients with acute chest pain and a normal or nondiagnostic electrocardiogram. Coron Artery Dis 2012;23:438-44.

60. Lim SH, Anantharaman V, Sundram F, et al. Stress myocardial perfusion imaging for the evaluation and triage of chest pain in the emergency department: a randomized controlled trial. J Nucl Cardiol 2013;20:1002-12.

61. Gallagher MJ, Ross MA, Raff GL, Goldstein JA, O'Neill WW, O'Neil B. The diagnostic accuracy of 64-slice computed tomography coronary angiography compared with stress nuclear imaging in emergency department low-risk chest pain patients. Ann Emerg Med 2007;49:125-136.

62. Lerakis S, McLean DS, Anadiotis AV, et al. Prognostic value of adenosine stress cardiovascular magnetic resonance in patients with low-risk chest pain. J Cardiovasc Magn Reson 2009;11:37.

63. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. Int J Cardiol 2013;166:752-4.

64. Villines TC, Hulten EA, Shaw LJ, et al. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry. J Am Coll Cardiol 2011;58:2533-40.

65. Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic Value of Noninvasive Cardiovascular Testing in Patients With Stable Chest Pain: Insights From the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017;135:2320-32.

66. Hoshino M, Yonetsu T, Usui E, et al. Clinical Significance of the Presence or Absence of Lipid-Rich Plaque Underneath Intact Fibrous Cap Plaque in Acute Coronary Syndrome. J Am Heart Assoc 2019;8:e011820.

67. Vafaie M, Slagman A, Mockel M, et al. Prognostic Value of Undetectable hs Troponin T in Suspected Acute Coronary Syndrome. Am J Med 2016;129:274-82 e2.

68. Carpenter CR, Raja AS, Brown MD. Overtesting and the Downstream Consequences of Overtreatment: Implications of "Preventing Overdiagnosis" for Emergency Medicine. Acad Emerg Med 2015;22:1484-92.

69. Brooker JA, Hastings JW. Major-Monfried H, The Association Between Medicolegal and Professional Concerns and Chest Pain Admission Rates, Acad Emerg Med 2015; 22:883-886.

70. Kawatkar AA, Sharp AL, Baecker AS, et al. Early Noninvasive Cardiac Testing After Emergency Department Evaluation for Suspected Acute Coronary Syndrome. JAMA Intern Med 2020;180:1621-9.

71. Cordiner D, Al-Ani M, Jia X, Marchick M, Allen B, Winchester DE. Estimates of radiation exposure and subsequent risk of malignancy due to cardiac imaging in the emergency department for evaluation of chest pain: a cohort study. Coron Artery Dis 2019;30:626-8.

72. Porath JD, Meka AP, Morrow C, et al. Patient Preferences for Diagnostic Testing in the Emergency Department: A Cross-sectional Study. Acad Emerg Med 2018;25:627-33.

Table and Figures

Table 1. Risk of bias assessment of included studies.

Table 2: List of studies reviewed.

Figure 1: Study screening and selection.

Figure 2: Forest Plot comparing subgroups at 1 month when moderated by modality of risk stratifying imaging utilized.

Figure 3: Forest Plot comparing subgroups at 6-months when moderated by modality of risk stratifying imaging utilized.

Figure 4: Forest Plot comparing subgroups at 12-months when moderated by modality of risk stratifying imaging utilized.

Figure 5: Forest Plot comparing subgroups of cCTA at 1 month when moderated by classification of obstruction.

Figure 6: Forest Plot comparing subgroups of cCTA at 12 months when moderated by classification of obstruction.

	Cochrane Risk of Bias						Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I)						
First author, year	Sequence Generation	Allocation concealment	Blinding of participants	blinding of outcome assessors	Incomplete outcome data	selective outcome reporting	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
Pena, 2016	low	low	low	low	low	low	low	low	high	low	high	high	low
Hamilton-Craig, 2014	Low	Unclear	High	Low	High	Low	Low	Low	Low	Low	Low	Low	Low
Peix, 2012	low	low	low	low	low	low	low	low	high	low	low	low	low
Schaer, 2005	low	low	low	low	low	low	low	high	high	low	low	low	low
Nasis, 2014	low	low	low	low	low	low	low	high	high	low	low	low	high
Poon, 2013	low	low	low	low	low	low	low	low	high	high	low	low	low
Nagori, 2014	low	low	high	high	low	low	low	low	high	high	low	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	low	low	high	low	low	high	high
Hansen, 2010	low	low	low	unclear	low	low	low	low	high	unclear	low	unclear	high
Hollander, 2009	low	low	high	high	high	low	low	low	low	high	low	low	high
Hollander 2007	low	low	low	low	low	low	low	low	low	low	low	low	low
Gaibazzi 2011	low	unclear	high	high	unclear	low	low	Low	low	low	low	low	low
Grunau, 2016	low	low	low	low	low	low	low	low	high	high	low	low	low
Cury, 2013	low	high	high	high	low	low	low	low	low	low	low	low	low
Dedic, 2017	low	low	low	low	low	low	high	low	low	high	low	low	low

Goldstein, 2011	low	low	low	low	high	low							
Bholasingh, 2002	low	low	low	low	low	low	low	low	low	low	low	low	low
Lerakis, 2009	low	low	high	high	low	low	low	low	unclear	low	low	unclear	low
Colon Ill, 1998	unclear	low	high	low	unclear	low	low	low	high	low	low	low	high
Christiaens, 2012	unclear	high	high	unclear	low	low	low	low	high	low	low	low	high
Hoffman, 2009	low	high	low	low	low	low	low	low	high	low	low	low	low
Schlett, 2011	low	high	low	low	low	low	low	low	high	low	low	low	low
Bedetti, 2005	high	high	high	high	low	low	low	low	low	low	low	low	high
Innocenti, 2014	low	unclear	high	high	low	low	low	low	high	low	low	unclear	high
Chang, 2011	high	low	high	low	low	high	low	low	high	low	low	low	low
Anaya, 2012	low	unclear	high	unclear	unclear	low							
Kimlitt, 2010	Unclear	High	High	High	High	Low	Low	Low	Low	Low	Low	Low	Low
Gallagher, 2007	low	unclear	high	high	low	low	low	low	high	low	low	low	high
Halpern, 2013	unclear	high	unclear	unclear	high	low	low	low	unclear	low	low	high	low
Hascoet, 2012	Unclear	high	high	high	low	low	low	low	high	low	low	low	high
Dedic, 2013	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dadkhah, 2017	low	high	high	unclear	low	high							
Innocenti, 2013	high	unclear	high	high	high	low	low	low	low	low	low	high	high

Author, Year	Type of Study	Population	Intervention	Characteristics	Test Results	Outcome	% MACE (95% CI)
Coronary CT							
Anaya, 2012[30]	Randomized control trial	1390 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)	Not provided	cCTA group 754 (83%) had <=50% stenosis	MACE at 30 days	cCTA <=50% 0% (95% CI 0-0.4)
Chang, 2011[31]	Prospective cohort study	1,049 patients with a chief complaint of chest pain for whom a coronary CTA was ordered for evaluation of potential ACS, a non-ischemic initial electrocardiogram (ECG), and a Thrombolysis in Myocardial Infarction (TIMI) score of 0-2	cCTA with CAS	male 453 (43%), median age 48.4 (IQR 42.4-53.5), 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% (95% 0-.7%) cCTA <50%, CACS>0 = 0.5% (95% CI .01-3%)
Christiaens, 2012[32]	Retrospective cohort study	175 patients with no ECG changes and low to intermediate risk with first troponin <0	64 slice cCTA, coronary calci um score	male 124 (71%), mean age 60 ± 8 , TIMI 0-2 148 (85%), TIMI >2-3 26 (15%), TIMI >4 0	cCTA <=50% sten osis, N-130	MACE at 6 months ± 2	0% (95% CI, 0-2.7%)
Cury, 2013[33]	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-hour time interval, and negative or non-diagnostic ECG findings	cCTA	male 44%, mean age 52.1, TIMI score <=2 100%	cCTA negative=21 7, cCTA mild (<50%) =151	MACE at 30 days	cCTA neg 0% (95% CI 0-1.6%) cCTA mild disease 0% (95% CI 0-2.4%)
Dedic, 2013[34]	Prospective cohort study	111 patients age over 40 with no STE, no history of coronary artery disease	cCTA, CAC	64% male, mean age 57 SD 11	cCTA neg=37, CAC: 40 neg	MACE at 3 months	Neg cCTA 0% (95% CI 0-9.5%) Neg CAC 0%(95% CI 0-8.8%)

Dedic, 2016[35]	Randomized control 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 standard of care(n=250)	cCTA: male 51%, mean age 55 ± 9, TIMI 0=29.6%, TIMI=1 33.6%, TIMI>= 36.8%; SOC: male 55%, mean age 53 ± 9, TIMI 0=33.2%, TIMI=1 36.4%, TIMI>= 30.4%	CT with no disease=106 (47%), did not specify negative SOC tests	MACE/undetected coronary artery disease at 30 days	*Entire cCTA cohort 0.4% (95% CI .01-2.2%)
Goldstein, 2011[36]	Randomized Controlled Trial	749 patients with acute chest pain, normal or non-diagnostic ECG for ischemia, TIMI score <=4	cCTA (n=361) vs. standard of care MPI (n=338)	cCTA: male 163 (45.2%, mean age 50 ± 10, TIMI risk score 0.99 ±0.84, MPI: male 159 (47.0%, mean age 50 ± 10, TIMI risk score 1.04 ±0.87	cCTA group 268 with <50% stenosis, MPI normal or probably normal in 266 with follow-up.	MACE at 6 months	cCTA <50% stenosis 0.7% (95%CI .1-2.6%) MPI 0.4% (95%CI 0-2.0%)
Grunau, 2016[37]	Retrospective cohort study	1700 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=1179)	cCTA: male 322 (61.8%), median age 51(44-59), TIMI=0 296 (56.8%), 1: 212 (40.7%, 2:12 (2.5%); EST: male 655 (55.6%), median age 51(44-58), TIMI=0 709(60.1%), 1:426 (436.1%,) 2:24 (2.0%)	cCTA normal N=298 (55.5%), EST normal 869 (73.7%)	MACE at 30 days	All cCTA 1.3% (95% CI .5-2.7%) ALL EST 0.4% (95% CI .1-.9%)
Halpern, 2013[38]	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	male 109(44%), mean age 50.9 ±11, 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% (95%CI 0-1.6%)

Hamilton-Craig, 2014[39]	Randomized controlled trial	662 differentiated chest pain, TIMI risk <4, negative troponin I.	cCTA (n=322)/ ExECG(n=240)	58% male, mean age 52 SD 10.3	cCTA neg=277, Ex ECG: 213 neg	MACE at 30 days, MACE at 12 months	30-day MACE Neg cCTA 0% (95% CI 0-1.3%) Neg ExECG 0% (95%CI 0-1.5%) 1-year MACE Neg cCTA 0.3% (95%CI 0-1.9% Neg ExECG 0% (95%CI 0-1.5%)
Hansen, 2010[40]	Prospective cohort study	89 patients admitted to a chest pain assessment service and had a normal first troponin	cCTA and treadmill exercise testing	male 56 (63%), mean age 56.3 ± 8.6	cCTA normal=35, CCTA <50% disease N=38	MACE at mean follow-up 355 ± 72 days	cCTA normal 0% (95%CI 0-10%), cCTA mild disease 0% (95%CI 0-9.3%)
Hascoet, 2012[41]	Prospective cohort study	123 Low to intermediate risk for ACS. Acute chest pain with normal ECG and no evidence of ischemia	64 slice MSCT	70.4% male, mean age 50.9 ± 13, TIMI 0=72 (58.5%, 1: 41(33%), TMI 2 10(8.1%)	MSCT neg CAD <=50% stenosis=93	MACE: median follow-up 15 months (I7-30 months)	negative CT MACE 0 (95% CI 0-5%)
Hoffman, 2009 Schlett, 2011[42]	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	male 223 (61%, mean age 52.7 ± 12, TIMI score Low/Medium/High = 94.3/5.4/0.3 percent	cCTA negative= 183 (50.3%) cCTA<50% stenosis =117	MACE at 6 months, MACE at 1 year	6 months cCTA neg 0% (95%CI 0-2%) 1 year cCTA neg 0 % (95% CI 0-2.3%) cCTA <50%: 4.3 % (95% CI 1.4-10%)
Hollander 2007 Hollander, 2009[43]	Prospective cohort study	568 low risk TIMI score patients	cCTA	male =252 (44%), mean age 47 ±8.9, TIMI=0 343 (60%), TMII=1 133 (29%), TMII=2 50(9%), TMII=3 59(2%)	cCTA <50% lesion n=508	MACE at 30 days, MACE at 1 year	30 day 0%, (95%CI 0-0.8%) 1 year 0 % (95% CI 0-0.76%)
Kim, 2010[44]	Retrospective cohort study	296 patients divided into 2 groups. Group 1 <50% lesion and low risk profile and Group 2: <50% lesion and intermediate risk profile	cCTA	Group 1: 53.8% male, mean age 49, 4.9% known CAD; Group 2 56.9% make, mean age 44.2, 11.5%	Group 1 neg: cCTA 103, Group 2: neg 104	MACE at 30 days	Group 1: 0% (95%CI 0-.5%) Group 2: 4.8% (95%CI 1.6-10.8%)

				known CAD			
Litt. 2012[45]	Randomized controlled trial	1370 patients with signs or symptoms that were consistent with a possible acute coronary syndrome were eligible if the treating physician determined that they would require admission or objective testing to rule out an acute coronary syndrome, if the electrocardiogram (ECG) at presentation did not reveal acute ischemia, and if the patient had an initial Thrombolysis in Myocardial Infarction risk score of 0 to 2	cCTA (n=908) vs. standard care (n=463)	male 443 (49%), mean age 49 ± 9, 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%, (95%CI 0-0.57%)
Nagori, 2014[46]	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)	cCTA: male 29 (70%), mean age 52.9±8.9: ExECG male 27 (67.5%), mean age 51.2 ± 0.35	ExECG neg =31; cCTA <50% stenosis=22	MACE at 6 months	ExECG9.6% (95%CI 2.0-25.7%); cCTA 0% (95%CI 0-15.4%)
Nasis, 2011[47]	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	male 123 (60%), mean age 58 ±11, TIMI =0 64(32%), TIMI=1 73(36%). TIMI=2 47 (23%)	cCTA <50% stenosis 172 (85%%)	MACE at follow-up mean 14.2 months (range 5.5-24.7)	cCTA<50% stenosis 0% (95%CI 0-2.1%)
Nasis, 2014[48]	Prospective cohort study	585 patients with ow to intermediate risk for ACS and negative findings at TnI measurement (ie, TnI level ,0.04 mg/L); and absence of ST segment deviation on an electrocardiogram.	cCTA	male 339 (58%), mean age 58 ± 10, TIMI 0 158 (27%), TIMI 1 225 (38%), TIMI 2 39 (24%)	cCTA no plaque n=196 (34%), non-obstructive plaque (<40%) N=288 (49%),	MACE median follow-up 47.4 months (range 24-57)	cCTA normal 0% (95%CI 0-1.9%); CCT <40% 0% (95%CI 0-1.3%)

Pena, 2016[49]	Retrospective cohort study	258 patients > 25 years of age presenting to the ED with a primary complaint of chest pain possibly secondary to acute coronary syndrome, with negative cardiac enzyme and normal or nondiagnostic ECG	cCTA (n=128) compared to standard of care	cCTA male =81 (63.3%), mean age 56.7± 11.7, TIMI IQR 1.5 (1,2): standard of care: 80 (61.5%), mean age 5701± 14.3 TIMI I QR 1 (1,3)	cCTA <50% N=86	MACE at 30 days	cCTA <50% 0% (95%CI 0-4.1%)
Poon, 2013[50]	Retrospective cohort study	1788 patients presenting with chest pain who had a 12-lead ECG and cardiac troponin I. Propensity matched before and after when cCTA became standard of care	cCTA (n=894) versus standard evaluation (n=894)	cCTA; male 430 (48%), mean age 49 ± 11, standard evaluation 430 (48%), mean age 49 ± 12	cCTA <50% stenosis N=835	MACE at 30 days	cCTA <50% stenosis 0% (95%CI 0-0.4%)
Exercise treadmill testing							
Schaer, 2005[51]	Prospective cohort study	161 Included were only patients with normal ECG findings or ECG tracings with nonsignificant ST-segment depression (0.5mm) or T-wave alterations already documented in previous ECGs and normal troponin results both at presentation and 6 hours later.	Exercise testing	male 76 (47.2%), mean age 58 ±10.6, known CAD 47	Exercise testing Neg=125	MACE at 30 days	1.6% (95%CI .2-5.7%)
Dadkhah, 2017[52]	Randomized control trial	60 patients with no ECG changes suggestive if ischemia, randomized prior to troponin testing. Randomized to a 2-hour protocol (n=29) and a 4-hour protocol (n=31)	Stress test: 36 exercise treadmill stress tests, 24 had either nuclear or echo stress test	2-hour protocol male 59%, mean age 49, hx CAD 17.2, 4-hour protocol, 41% male, mean age 51, 28.1% known CAD	2-hour protocol 23 negative stress test, 4-hour protocol 30 negative stress tests	MACE at 6 months	0% (95%CI 0-6.7%)

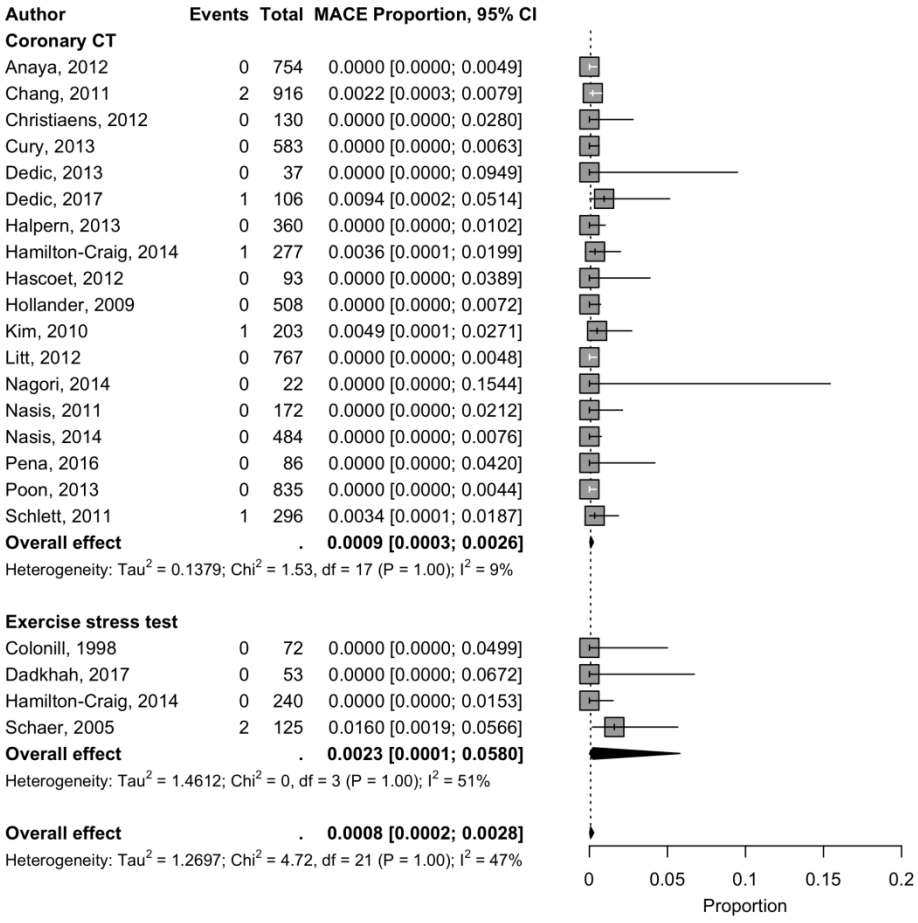
Colon III, 1998[53]	Prospective cohort study	108 patients with unexplained chest pain, normal cardiac markers, and ECG not diagnostic for ischemia or injury pattern	Exercise treadmill test (n=78) or dobutamine treadmill test (n=3090	male 54 (52%), mean age 54+/1 12	72 negative stress tests	MACE at follow-up, mean 12.8 ± 7.2 months	0% (95%CI 0-4.9%)
Stress Echocardiography							
Bedetti, 2005[54]	Prospective cohort study	552 acute chest pain without acute ECG ischemic changes or troponin elevations	Stress echocardiography	male 321 (58.2%), mean age 58 +/1 12.6, known CAD 103 (19%)	502 with negative stress echo	MACE with median follow-up 13 months	1.2% (95% CI .1-1.7%)
Bholasingh, 2002[55]	Prospective cohort study	377 presenting to the ED within 6 hours of pain with normal or non-diagnostic ECG and negative serial troponins	Dobutamine stress echo	male 237 (58%), age 56 ± 12, known CAD 77 (20%)	351 negative stress echo	MACE at 6 months	3.9% (95%CI 2.1-6.6%)
Innocenti, 2013[56]	Retrospective cohort study	474 consecutive patients presented to ED with spontaneous chest pain,non-diagnostic ECG and negative cardiac necrosis markers at the time of initial evaluation, after 6 and 12 hours	exercise stress echo N=270; dobutamine stress echo N=218* some already had ESE	male 276 (58%), mean age 67 ± 12, Known CAD 119 (25%)	Negative ESE =208; Negative DSE=112 Total neg=266	MACE at mean follow-up 679 ± 299 days	1.5% (95%CI .4-3.8%)
Innocenti, 2014[57]	Retrospective cohort study	626 consecutive unselected patients who were evaluated in the observation unit with SE and answered a follow-up call	ESE (n=365), DSE (N=261)	male 361(58%). mean age 67 ± 12, Known CAD 162 (26%)	292 negative ESE, 131 Negative DSE	MACE up to 4 years	ESE: 1.0% (95%CI .2-2.9%) DSE: 5.3% (95%CI 2.2-10.6%)
Gaibazzi, 2011[58]	Prospective cohort study	545 consecutive patients presenting to the emergency department with suspected ACS but non-diagnostic ECG findings and normal 12-hour troponin levels	Contrast Stress echocardiogram	male 317(58%), TIMI risk 0-1 240(44%), TIMI risk 2-4 305(56%)	350 patients with normal perfusion and wall motion	MACE at follow-up, mean time 361 days	MACE 0.9% (95%CI .2-2.5%)

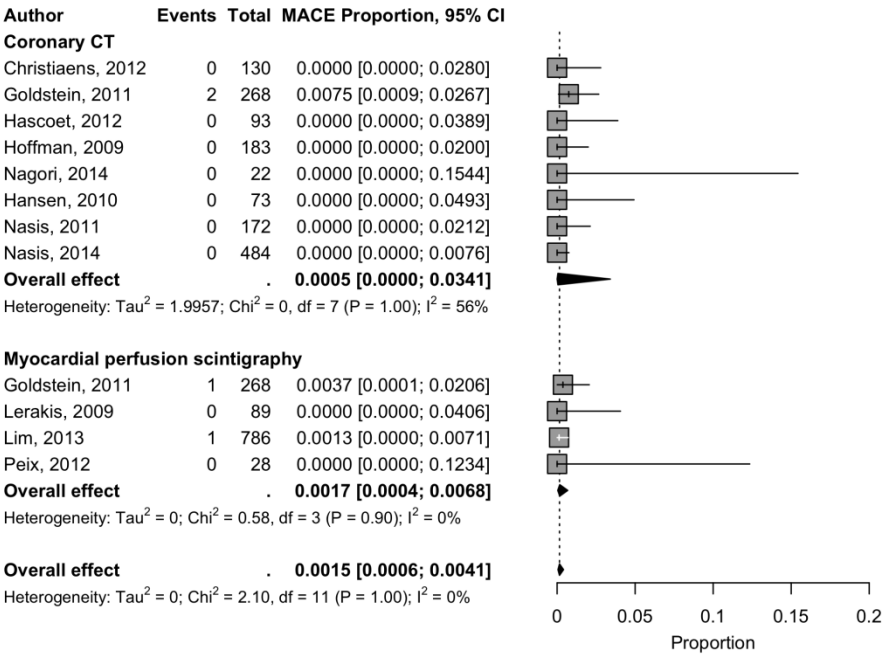
Nuclear perfusion Imaging							
Peix, 2012[59]	Retrospective cohort study	55 patients with chest pain and a normal or non-diagnostic ECG	GATED-SPECT myocardial perfusion imaging	male 68%, mean age 53 ±12	MPI negative = 28	MACE at 1 year	0% (95%CI 0-13.7%)
Lim, 2013[60]	Randomized controlled trial	1508 patients with acute chest pain and who's initial 12-lead ECG was non-diagnostic for myocardial ischemia or AMI	stress myocardial imaging (n=1004) vs. standard clinical assessment (n=504)	SMPI: male 59.6%, mean age 52.02 ±12.4, known CAD 4.1%: Clinical Assessment male 56.6%, mean age 51.8 ±12.8, known CAD 4.4%	SMPI normal=786; SMPI probably normal with attenuation N=115	MACE at 1 year	SMPI normal .1% (95%CI 0-0.7%) SMPI probably normal with attenuation0.8 % (.02%-4%)
Gallagher, 2007[61]	Prospective cohort study	92 patients with negative troponins and no new ischemic changes and no known coronary CAD	MDCT and stress nuclear imaging (SNI)	male =53%, mean age 49 ± 11, TIMI average 0.8 ± 0.8	MDCT negative, SNI negative=66	MACE at 30 days	0% (95%CI 0-5.4%)
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	male 38 (36.9%), mean age 56.7 ±12.3, 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% (95%CI 0-4.1%)

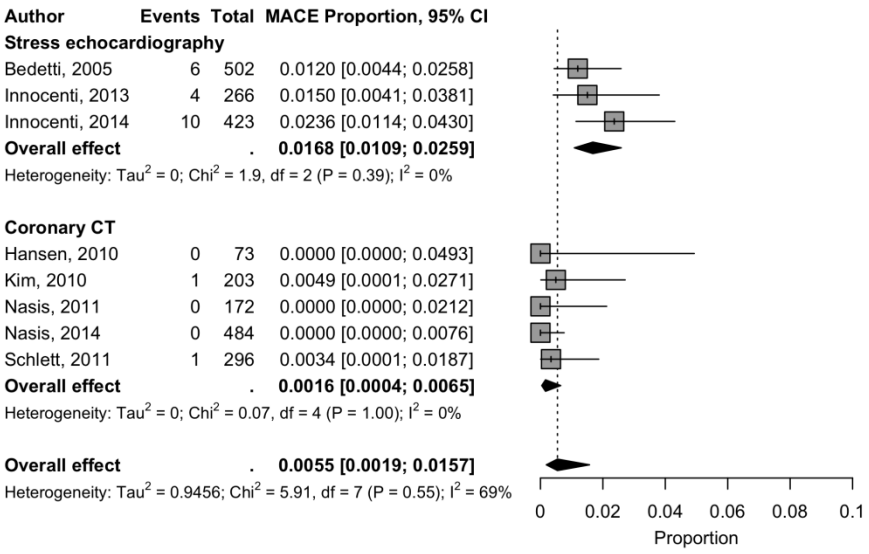
Table 2: List of studies reviewed

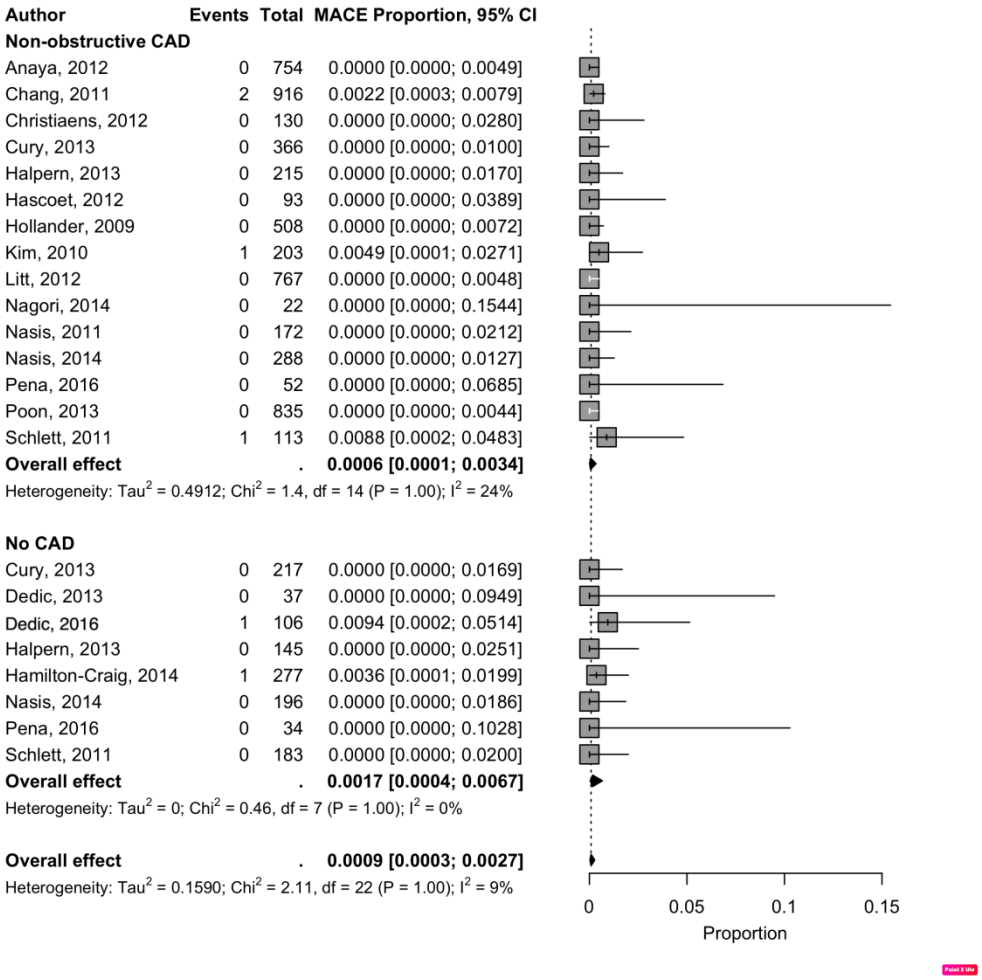
ACS: acute coronary syndrome; CABG: coronary artery bypass graft; CACS: coronary artery calcium score; CAD: coronary artery disease; CT: computed tomography; CAC: coronary artery calcium; DSE: dobutamine stress echocardiogram; ED: emergency department; ESE: exercise stress echocardiogram; EST: exercise 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; SD: standard deviation; SOC: standard of care; SMPI; SPECT myocardial perfusion imaging; STE: ST segment elevation; TIMI: Thrombolysis in myocardial infarction









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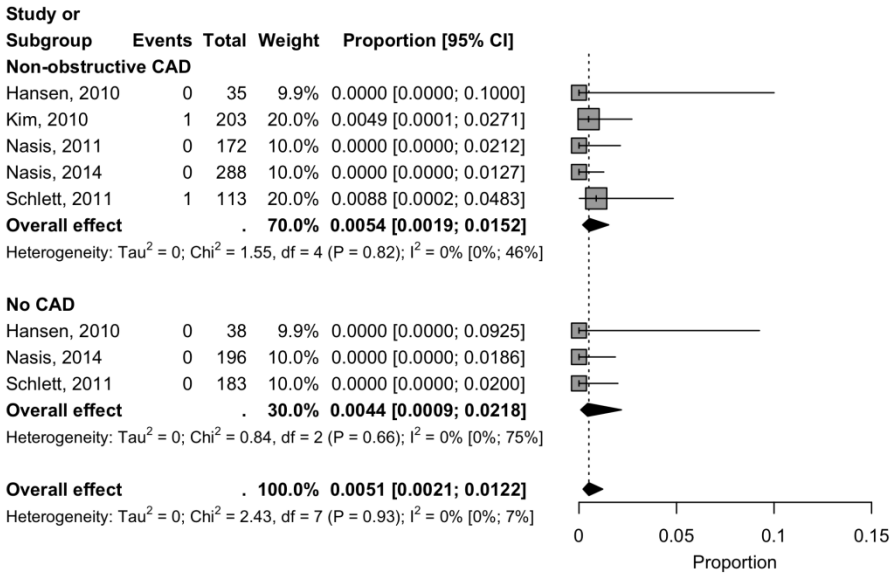

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APPENDIX I - Literature and search strategies

Total citations

MEDLINE 319

MEDLINE In-process, Other non-indexed citation, or Epub ahead of print 19

Embase 548

Cochrane 66

MEDLINE		
#	**Searches**	**Results**
1	chest pain/ or exp angina pectoris/	(54915)
2	(chest pain or angina or thorax pain or thoracic pain).twkf.	(74451)
3	1 or 2	(92880)
4	Emergency Service Hospital/	(66790)
5	(emergency adj (room* or department* or unit* or ward*)).twkf.	(89938)

6	(ER or ED).twkf.	(123509)
7	4 or 5 or 6	(209764)
8	3 and 7	(5229)
9	limit 8 to english language	(4839)
10	limit 9 to humans	(4817)
11	limit 9 to animals	(37)
12	9 not 11	(4802)
13	10 or 12	(4832)
14	Computed Tomography Angiography/	(9175)
15	Coronary Angiography/	(64287)
16	(coronary CT angiograph* or coronary computed tomograph* angiograph* or CT angiograph* or coronary CTA or cardiac CT angiograph* or cardiac computed tomographic angiograph* or cardiac CTA or heart CT angiograph* or heart computed tomograph* angiograph* or heart CTA).twkf.	(11231)

17	14 or 15 or 16	(78038)
18	13 and 17	(608)
19	Echocardiography Stress/	(2958)
20	stress echo*.twkf.	(4100)
21	nuclear stress test*.twkf.	(103)
22	stress imaging.twkf.	(446)
23	19 or 20 or 21 or 22	(5634)
24	13 and 23	(95)
25	18 or 24	(668)
26	myocardial ischemia/ or acute coronary syndrome/	(53101)
27	((myocardial or coronary or cardiac or heart) adj ischemia).twkf.	(27132)
28	(acute coronary syndrome* or ACS).twkf.	(34580)
29	26 or 27 or 28	(91843)
30	25 and 29	(319)

MEDLINE In-process, Other non-indexed citation, or Epub ahead of print		
#	**Searches**	**Results**
1	chest pain/ or exp angina pectoris/	(0)
2	(chest pain or angina or thorax pain or thoracic pain).twkf.	(7996)
3	1 or 2	(7996)
4	Emergency Service Hospital/	(0)
5	(emergency adj (room* or department* or unit* or ward*)).twkf.	(19505)
6	(ER or ED).twkf.	(23843)
7	4 or 5 or 6	(37630)
8	3 and 7	(888)
9	limit 8 to english language	(874)
10	limit 9 to humans	(0)
11	limit 9 to animals	(0)

12	9 not 11	(874)
13	10 or 12	(874)
14	Computed Tomography Angiography/	(0)
15	Coronary Angiography/	(0)
16	(coronary CT angiograph* or coronary computed tomograph* angiograph* or CT angiograph* or coronary CTA or cardiac CT angiograph* or cardiac computed tomographic angiograph* or cardiac CTA or heart CT angiograph* or heart computed tomograph* angiograph* or heart CTA).twkf.	(2076)
17	14 or 15 or 16	(2076)
18	13 and 17	(36)
19	Echocardiography Stress/	(0)
20	stress echo*.twkf.	(418)
21	nuclear stress test*.twkf.	(23)
22	stress imaging.twkf.	(67)

23	19 or 20 or 21 or 22	(498)
24	13 and 23	(8)
25	18 or 24	(42)
26	myocardial ischemia/ or acute coronary syndrome/	(0)
27	((myocardial or coronary or cardiac or heart) adj ischemia).twkf.	(2599)
28	(acute coronary syndrome* or ACS).twkf.	(6717)
29	26 or 27 or 28	(9178)
30	25 and 29	(19)

Embase		
#	**Searches**	**Results**
1	thorax pain/	(87238)

2	exp angina pectoris/	(95896)
3	(chest pain or angina or thorax pain or thoracic pain).twkw.	(124850)
4	1 or 2 or 3	(203200)
5	emergency ward/	(140955)
6	hospital emergency service/	(4356)
7	(emergency adj (room* or department* or unit* or ward*)).twkw.	(171390)
8	(ER or ED).twkw.	(236414)
9	5 or 6 or 7 or 8	(382306)
10	4 and 9	(15189)
11	limit 10 to (english language and embase)	(8198)
12	limit 11 to human	(8010)
13	limit 11 to animals	(9)
14	limit 11 to animal studies	(18)
15	13 or 14	(19)

16	11 not 15	(8179)
17	12 or 16	(8186)
18	computed tomographic angiography/	(55780)
19	coronary angiography/	(23524)
20	(coronary CT angiograph* or coronary computed tomograph* angiograph* or CT angiograph* or coronary CTA or cardiac CT angiograph* or cardiac computed tomographic angiograph* or cardiac CTA or heart CT angiograph* or heart computed tomograph* angiograph* or heart CTA).twkw.	(24042)
21	18 or 19 or 20	(81751)
22	17 and 21	(1128)
23	stress echocardiography/	(8306)
24	stress echo*.twkw.	(8012)
25	nuclear stress test*.twkw.	(327)
26	stress imaging.twkw.	(895)

27	23 or 24 or 25 or 26	(11627)
28	17 and 27	(182)
29	22 or 28	(1239)
30	heart muscle ischemia/	(92071)
31	acute coronary syndrome/	(55927)
32	((myocardial or coronary or cardiac or heart) adj ischemia).twkw.	(42625)
33	(acute coronary syndrome* or ACS).twkw.	(73430)
34	30 or 31 or 32 or 33	(187494)
35	29 and 34	(548)

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#1 MeSH descriptor: [Chest Pain] this term only

#2 MeSH descriptor: [Angina Pectoris] explode all trees

#3 ("chest pain" OR angina OR "thorax pain" OR"thoracic pain"):ti,ab,kw

#4 #1 OR #2 OR #3

#5 MeSH descriptor: [Emergency Service, Hospital] this term only

#6 (emergency NEXT (room or rooms or department or departments or unit or units or ward or wards)):ti,ab,kw

#7 (ER or ED):ti,ab,kw

#8 #5 OR #6 OR #6

#9 #4 AND #8

#10 MeSH descriptor: [Computed Tomography Angiography] this term only

#11 MeSH descriptor: [Coronary Angiography] this term only

#12 (“Coronary CT angiograph” or “coronary CT angiographies” or “coronary CT angiography” or “coronary computed tomographic angiograph” or “coronary computed tomographic angiographies” or “coronary computed tomographic angiography” or “CT angiograph” or “CT angiographies” or “CT angiography” or “coronary CTA” or “cardiac CT angiograph” or “cardiac CT angiographies” or “cardiac CT angiography” or “cardiac computed tomographic angiograph” or “cardiac computed tomographic angiographies” or “cardiac computed tomographic angiography” or “cardiac CTA” or “heart CT angiograph” or “heart CT angiographies” or “heart CT angiography” or “heart computed tomographic angiograph” or “heart computed tomographic angiographies” or “heart computed tomographic angiography” or “heart CTA”):ti,ab,kw

#13 #10 or #11 OR #12

#14 #9 and #13

#15 MeSH descriptor: [Echocardiography, Stress] this term only

#16 ("stress echo" or "stress echocardiograph" or "stress echocardiographies" or "stress echocardiography"):ti,ab,kw

#17 ("nuclear stress test" or "nuclear stress tests" or "nuclear stress testing"):ti,ab,kw

#18 ("stress imaging"):ti,ab,kw

#19 #15 OR #16 OR #17 OR #18

#20 #9 AND #19

#21 #14 or #20

#22 MeSH descriptor: [Myocardial Ischemia] this term only

#23 MeSH descriptor: [Acute Coronary Syndrome] this term only

#24 ("myocardial ischemia" or "coronary ischemia" or "cardiac ischemia" or "heart ischemia"):ti,ab,kw

#25 ("acute coronary syndrome" or "acute coronary syndromes" or ACS):ti,ab,kw

#26 #22 or #23 or #24 or #25

#27 #21 and #26 in Trials

PennState Health
Emergency Medicine
Residency Program Director

Penn State Health Milton S. Hershey Medical Center is seeking an Emergency Medicine Residency Program Director to join our exceptional academic team located in Hershey, PA. This is an excellent opportunity to join an outstanding academic program with a national reputation and inpact the lives of our future Emergency Medicine physicians.

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- Competitive salary and benefits
- Sign-On Bonus
- Relocation Assistance
- Leadership for Emergency Medicine Residency Program
- Comprehensive benefit and retirement options

What We're Seeking:

- MD, DO, or foreign equivalent
- BC/BE by ABEM or ABOEM
- Leadership experience
- Outstanding patient care qualities
- Ability to work collaboratively within a diverse academic and clinical environment

FOR MORE INFORMATION PLEASE CONTACT:

Heather Peffley, PHR CPRP
Physician Recruiter
Penn State Health

Email: hpeffley@pennstatehealth.psu.edu
Website: careers.pennstatehealth.org

What the Area Offers:

Located in a safe family-friendly setting, Hershey, PA, our local neighborhoods boast a reasonable cost of living whether you prefer a more suburban setting or thriving city rich in theater, arts, and culture. Known as the home of the Hershey chocolate bar, Hershey's community is rich in history and offers an abundant range of outdoor activities, arts, and diverse experiences. We're conveniently located within a short distance to major cities such as Philadelphia, Pittsburgh, NYC, Baltimore, and Washington DC.