Trials of Imaging Use in the Emergency Department for Acute Chest Pain

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ABSTRACT

Over 8 million patients seek emergency department care for acute chest pain annually in the United States alone, and <5% have an acute coronary syndrome. In the absence of overt electrocardiographic or biomarker evidence, expensive and time-consuming diagnostic strategies are frequently required. Beginning in 2000, radionuclide myocardial perfusion, stress echocardiography, cardiac magnetic resonance imaging, and coronary computed tomographic angiography have become increasingly common in evaluating these patients. This review paper focuses on randomized clinical trials that provide the evidence base for these diagnostic strategies. Novel imaging modalities combining high-sensitivity troponin with imaging or combined anatomic-physiological evaluation using fractional flow reserve by computed tomography are also discussed. (J Am Coll Cardiol Img 2017;10:338–49) © 2017 by the American College of Cardiology Foundation.

Accurate and efficient triage of acute chest pain (ACP) is a major health care challenge. The 2011 National Hospital Medical Care Survey reported that 5.8% of over 136 million emergency department (ED) visits in the United States were for ACP (1). It has been estimated that 8 million ACP patients incurred diagnostic health care expenditures of $10 billion to $14 billion. Nearly 75% of these patients are diagnosed with noncardiac or nonischemic cardiac problems, and <20% of the remaining meet criteria for acute coronary syndromes (ACS) (2,3). However, the missed diagnosis of ACS carries significantly increased morbidity and mortality and is the largest single source of ED malpractice lawsuits. A generally acknowledged target is to achieve <1% missed ACS. However, the old paradigm of hospital admission for days to "rule-out" ACS is no longer tenable in an age of spiraling health care costs.

Patients at either end of the coronary risk spectrum are easily triaged: those with definite ACS and those with very low probability for coronary ischemia. However, those with low-to-intermediate cardiac risk and no clear evidence of diagnosis present an expensive diagnostic dilemma. It is frustrating to patients, health care providers, and insurers that these patients require many hours and costly tests to receive a negative diagnosis. Over the last 20 years, cardiac imaging has played an increasing role in the search for a more efficient approach.

Before the advent of thrombolytic and interventional therapy for the treatment of acute myocardial infarction in the early 1980s (4), diagnostic evaluation of patients with ACP was less time critical. However, despite the adoption of specialized chest pain units in many EDs, in the 1990s, 2% to 8% of ACS patients were reportedly misdiagnosed and discharged (5). The risk-adjusted mortality of patients incorrectly discharged compared with those who were hospitalized was 1.9 for acute myocardial infarction and 1.7 for those with unstable angina. The 2000 American College of Cardiology/American Heart Association Guidelines for Management of Unstable Angina and Non-ST-Elevation Myocardial Infarction (6) emphasized clinical evaluation, electrocardiograms (ECGs), and biomarkers repeated over 6 to 12 h as the cornerstone of diagnosis, along with adjunctive ECG stress testing. Noninvasive imaging was not mentioned. In 1989, Gianrossi et al. (7) published a meta-analysis of 147 studies of stress ECG compared with invasive coronary angiography (ICA) that

included over 24,000 patients. They reported a mean sensitivity of only 68%, and specificity of 77% (7). The low sensitivity of ECG-only stress testing may have contributed to the misdiagnosis of ACP seen in the 1990s. This hypothesis was tested in several of the comparative effectiveness trials included in this review.

Noninvasive cardiac imaging was introduced as an adjunct to the evaluation of ACP in the late 1990s. In succeeding decades, a host of technological advances in noninvasive imaging have been applied to ED diagnosis. The randomized clinical trials (RCTs) that evaluate these diagnostic strategies are the subject of this review.

METHODOLOGY

Information for this review was obtained through a search of PubMed, cross-referencing noninvasive imaging modalities, clinical trials, and ACP. Major societal guidelines and appropriate use criteria were also surveyed (8–11). Preference was given to larger multicenter RCTs and influential single-center trials. Within each imaging modality, studies are presented in chronological order to follow the logical development of evidence.

RANDOMIZED TRIALS OF RADIONUCLIDE MYOCARDIAL PERFUSION IMAGING

Reported in 2002, ERASE (Emergency Room Assessment of Sestamibi for the Evaluation of Chest Pain) was a clinical effectiveness trial that tested whether providing results of resting single-photon emission computed tomography myocardial perfusion imaging (MPI) to ED clinicians for patients with low-to-intermediate likelihood of ACS would improve clinical decision making, defined as the appropriateness of an admitting decision (12) (**Table 1**). Between July 1997 and May 1999, 2,475 patients at 7 centers were randomized to 1 of 2 evaluation strategies: 1) a rest MPI study, with the scan read right away and results provided to the ED clinician, who incorporated those results with other available information to make a decision to admit or discharge from the ED; or 2) a standard-of-care (SOC) diagnostic strategy that could include stress ECG. The hypothesis was that incorporation of the imaging results would reduce unnecessary admissions without compromising appropriate admissions.

The results supported the hypothesis. Among the patients randomized to the imaging strategy who ultimately were found to not have ACS, admissions were significantly reduced in the MPI compared with the SOC group (48% vs. 56%; p < 0.001), and unnecessary admissions on the basis of clinical outcomes were reduced (relative risk 0.84; 95% confidence interval: 0.77 to 0.92), whereas there was no change in appropriate admission for those with a final diagnosis of ACS. Results of resting MPI predicted the major adverse cardiac event (MACE) rate (normal 3%, equivocal 6%, and abnormal 20%; p < 0.001). This landmark clinical effectiveness RCT of rest MPI provided the first strong evidence that incorporating imaging for diagnosis of ED patients with ACP could improve triage decisions.

In 2013, Lim et al. (13) reported an RCT in which 1,508 ED patients with ACP (enrollment period August 2000 to May 2002) were randomized 2:1 to stress MPI within 24 h (n = 1,004) or SOC (n = 504). The SOC protocol consisted of standard clinical assessment for ACS as judged by the attending ED physician. Patients clinically considered to have likely ACS were hospitalized, whereas the remainder of SOC patients were discharged for outpatient cardiac clinic follow-up within 1 week. Stress MPI patients were eligible for discharge from the ED if the results were negative. Hospitalized SOC patients underwent stress ECG and/or ICA at the discretion of attending physicians. Patients were followed-up at 1 month and 1 year.

The primary outcome was adverse cardiac events within 1 year, defined as the occurrence of any 1 of the following after a 6-h observation period: cardiac death, ventricular fibrillation, myocardial infarction, cardiogenic shock, or acute pulmonary edema. Secondary endpoints included hospitalization rate during the index visit, and the rate of coronary stenosis ≥70% in patients going to ICA in each arm.

There was no difference in the primary outcome, with cardiac events being similar between stress MPI and SOC groups (0.7% vs. 1.0%), relative risk 0.70 (95% confidence interval: 0.22 to 2.20). Patients in the stress MPI group had a significantly lower hospital admission rate (10.2% vs. 18.5%; p < 0.005). Patients in the stress MPI arm had a lower ICA rate (7.3% vs. 11.1%; p = 0.02), and patients with positive stress MPI had fewer negative ICAs compared with SOC patients (21.9% vs. 39.3%; p = 0.03). Among patients undergoing stress MPI, the accuracy for predicting a combined outcome of adverse cardiac event or coronary stenosis ≥70% showed a sensitivity and specificity of 85% and 93%, respectively, whereas the corresponding accuracy of stress ECG was 56% and 98%, respectively.

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TABLE 1 Randomized Trials of Imaging for Acute Chest Pain

Trial Name, First Author (Ref. #)	Design Overview	Target Population	Total and by Arm	Major Inclusion/Exclusion Criteria	Intervention Details	Duration of Follow-Up	Primary Endpoint Results	Major Secondary Endpoint Results	Important Subanalyses
ERASE, Udelson et al. (12)	RCT	ED ACP	N = 2,475 n = 1,215 rest MPI n = 1,260 SOC	Incl: ACP neg ECG Excl: prior MI	Rest MPI	30 days	Admission rate MPI 48% SOC 56% p < 0.001	MPI MACE rate Neg 3% Equivocal 6% Abnormal 20% p < 0.001	
Lim et al. (13)	RCT	ED ACP	N = 1,508 n = 1,004 stress MPI n = 504 SOC	Incl: ACP Excl: ACS	Stress MPI	1 yr	1 yr MACE 0.7% MPI 1.0% SOC p = 0.7	ICA rate 7.3% MPI 11.1% SOC p = 0.02	Sensitivity/ specificity for ≥70% lesion on ICA: stress MPI 85%/ 93% stress ECG 56%/ 98%
ASSENCE, Nucifora et al. (14)	RCT	ED ACP	N = 199 n = 110 stress echo n = 89 stress ECG	Incl: ACP, able to do stress echo Excl: ACS	Stress echo	2 months	Direct costs $1,029 stress echo $1,684 stress ECG p < 0.001	In-hospital ACS 18% stress echo 12% stress ECG	Length of stay 23 h stress echo 31 h stress ECG p = 0.01
Jeetley et al. (15)	RCT	ACP	N = 433 n = 218 stress echo n = 215 stress ECG	Incl: ACP 2 or more risk factors Excl: ACS, known CAD	Stress echo	9 months	Combined high-risk endpoint 16% stress echo stress ECG 15% p = 0.78	Reclassification to low risk 77% stress echo 33% stress ECG p < 0.001	Cost to diagnosis €326 stress echo €495 stress ECG p = 0.01
Miller et al. 2010 (16)	RCT	ED ACP	N = 110 n = 53 CMR observation unit n = 57 admit SOC	Incl: ACP Intermediate- high risk for ACS by ED doctor Excl: ACS, inability to do CMR	Stress CMR in observation unit	30 days	Median hospital costs $2,062 CMR $2,680 SOC	ED discharge 77% stress CMR 0% Inpatient SOC	
Miller et al. 2012 (18)	RCT	ED ACP	N = 123 n = 62 CMR n = 61 provider-selected stress test	Incl: ACP Intermediate risk Excl: ACS, inability to do CMR	Stress CMR in observation unit	30 days	Median hospital costs $2,005 CMR $1,686 SOC p = 0.01	Similar outcomes Length of stay, ICA rate, admission rate	
Miller et al. 2013 (19)	RCT	ED ACP	N = 105 n = 52 stress CMR n = 53 triage by consulting physician	Incl: ACP Intermediate- high risk by ED doctor Excl: ACS prior PCI	Stress CMR in observation unit	3 months	Combined: revascularization, readmission, recurrent testing 38% SOC 13% CMR Hazard ratio 3.4	Index visit length of stay 21 h stress CMR 26 h SOC p <0.001	
Goldstein et al. (20)	RCT	ED ACP	N = 197 n = 99 Coronary CTA n = 98 MPI	Incl: ACP, low- intermediate risk Excl: ACS, prior known CAD	Coronary CTA	6 months	6 months MACE Coronary CTA 0 MPI 0 p = NS	Time to diagnosis Coronary CTA 3.4 h MPI 15.0 h p < 0.001	ED costs of care $1,586 Coronary CTA $1,872 MPI p < 0.001

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TABLE 1 Continued

Trial Name, First Author (Ref. #)	Design Overview	Target Population	Total and by Arm	Major Inclusion/Exclusion Criteria	Intervention Details	Duration of Follow-Up	Primary Endpoint Results	Major Secondary Endpoint Results	Important Subanalyses
CT-STAT, Goldstein et al. (21)	RCT	ED ACP	N = 699 n = 361 Coronary CTA n = 338 MPI	Incl: ACP, low-intermediate risk Excl: ACS, prior known CAD	Coronary CTA	6 months	Time to diagnosis 2.9 h Coronary CTA 6.2 h MPI p < 0.001	ED costs of care $2,137 Coronary CTA $3,458 MPI p < 0.001	MACE after normal test 0.8% Coronary CTA 0.4% MPI p = 0.29
ACRIN, Litt et al. (23)	RCT	ED ACP	N = 1,370 n = 908 Coronary CTA n = 462 SOC	Incl: ACP, low-intermediate risk Excl: ACS	Coronary CTA	30 days	Safety in Coronary CTA after normal test Coronary CTA <1% MACE	ED discharge 49.6% Coronary CTA 22.7% SOC	Length of stay 18.0 h Coronary CTA 24.8 h SOC p < 0.001
ROMICAT II, Hoffmann et al. (22)	RCT	ED ACP	N = 1,000 n = 501 Coronary CTA n = 499 SOC	Incl: ACP Excl: Known CAD, ACS	Coronary CTA	28 days	Length of stay, median 8.6 h Coronary CTA 26.7 h SOC P < 0.001	Time to diagnosis 5.8 h Coronary CTA 21.0 h SOC p < 0.001	ED discharge 47% Coronary CTA 12% SOC p < 0.001
PROSPECT, Levsky et al. (26)	RCT	ACP	N = 400 n = 200 Coronary CTA n = 200 MPI	Incl: ACP, intermediate risk Excl: ACS, prior known CAD	Coronary CTA	1 yr	ICA rate 1 yr 15% Coronary CTA 16% MPI p = NS	Length of stay, median 28.9 h Coronary CTA 30.4 h MPI p = 0.06	Radiation dose 9.6 mSv Coronary CTA 27.0 mSv MPI p < 0.001
BEACON, Dedic et al. (31)	RCT	ED ACP	N = 500 n = 250 Coronary CTA n = 250 SOC	Incl: ACP Excl: ACS, known CAD, urgent ICA	High-sensitivity troponin Coronary CTA	30 days	Revascularization rate with positive work-up 9% Coronary CTA 7% SOC p = 0.40	ED discharge rate 65% Coronary CTA 59% SOC p = 0.16	Direct medical costs €337 €511 p < 0.01

ACP = acute chest pain; ACRIN = American College of Radiology Imaging Network; ACS = acute coronary syndrome; ASSENCE = Assessment of Cost-Effectiveness of Several Strategies of Early diagnosis in patients with acute chest pain and Non-conclusive Electrocardiogram; BEACON = Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography; CTA = computed tomographic angiography; CT-STAT = Computed Tomography for Systematic Triage of Acute Chest Pain to Treatment; ECG = electrocardiogram; echo = echocardiogram; ED = emergency department; Excl = exclusion; ICA = invasive coronary angiography; Incl = inclusion; LOS = length of stay; MI = myocardial infarction; MPI = radionuclide myocardial perfusion imaging; PROSPECT = Prospective Randomized Outcome trial comparing radionuclide Stress myocardial Perfusion imaging and ECG-gated CCTA; RCT = randomized clinical trial; ROMICAT II = Rule-Out Myocardial Infarction with Computed Tomography II; SOC = standard of care.

Thus, this study showed equivalent safety with a lower admission rate for the stress MPI group. Compared with stress ECG, stress MPI more accurately predicted the occurrence of the combined outcome of adverse coronary events or severe coronary stenosis over a 1-year follow-up period. Overall, fewer stress MPI patients required ICA and they had fewer false positive evaluations.

RANDOMIZED TRIALS OF STRESS ECHOCARDIOGRAPHY

In 2007, Nucifora et al. (14) published the results of ASSENCE (Assessment of Cost-Effectiveness of Several Strategies of Early diagnosis in patients with acute chest pain and Non-conclusive Electrocardiogram), a 10-center RCT that compared the cost-effectiveness of early dobutamine-atropine stress echocardiography (echo) to stress ECG testing. A total of 199 patients were randomized: 110 to stress echo and 89 to SOC including stress ECG. Inclusion criteria included ECG that was not diagnostic of ACS, negative initial biomarkers for myocardial injury, and the ability to perform ECG stress testing. Imaging studies had to be completed within 18 h after randomization according to protocol. This was a clinical efficacy trial, in that all patients with negative studies were immediately discharged after the test by protocol. Patients randomized to stress echo who failed to have interpretable results were included on an intention-to-treat basis. Patients were followed for 2 months.

The main ASSENCE study endpoint was cost-effectiveness, taking into account length of hospitalization during the index admission and repeat hospitalizations, in-patient and outpatient diagnostic procedures, and treatments (rest and/or stress echocardiography, MPI, ICA, percutaneous coronary intervention [PCI], or coronary artery bypass surgery). Secondary outcomes included frequency of early and late MACE, rehospitalization, and coronary revascularization.

Among the 110 patients in the stress echo arm, 90 (82%) were directly discharged, as compared with 78 out of 89 (88%) in the stress ECG arm. For these patients, overall costs at 2 months were 39% lower in the stress echo arm compared with the stress ECG arm ($1,029 vs. $1,684; p = 0.005). In patients requiring admission, costs between the diagnostic strategies did not differ significantly. Thus, the ASSENCE trial confirmed the general trend that the addition of imaging to SOC nonimaging diagnostic strategies is cost-effective. The source of these cost savings was attributable to fewer late events (none in the echo arm vs. 11% in the ECG arm) including

rehospitalizations, ACS, and late PCI after negative stress ECG. These late events after normal stress ECG may reflect the low 68% sensitivity of stress ECG reported in the large Gianrossi et al. (7) meta-analysis.

In the same year, Jeetley et al. (15) reported on a single-center RCT in 433 patients who had negative initial evaluations for ACS (enrollment January 2003 to April 2004) and were randomized to either stress echo (n = 218) or stress ECG (n = 215). The primary outcome was correct identification of patients who were at high risk of a combined endpoint of cardiac death, nonfatal myocardial infarction, or coronary revascularization. Pre-test risk was classified by TIMI (Thrombolysis In Myocardial Infarction) risk score. Post-test risk was considered low if test results were negative and high if positive, regardless of pre-test risk. The secondary endpoint was cost to diagnosis. Cost analysis was carried out from the United Kingdom National Health Service perspective.

This was a clinical effectiveness trial, in that, after initial stress testing, all subsequent decisions were made by the attending physicians. In this study, all patients were admitted, and stress ECG or stress echo was performed within 24 h by protocol, although only 69% achieved testing within this time frame. Comparative demographics showed that pre-test risk was evenly matched between the 2 groups. Significantly more stress echo patients than stress ECG patients were classified as having low post-test risk and were therefore eligible for immediate discharge (77% vs. 33%; p < 0.001). The majority of patients in both groups with positive stress tests went on to ICA. Of these, there was no significant difference in the rate of correctly predicting >50% coronary stenosis (stress echo 77% vs. stress ECG 61%; p = 0.17). There also was no significant difference between the 2 groups in the rate of occurrence of the combined clinical endpoint (cardiac death, nonfatal myocardial infarction, or coronary revascularization), but a positive high-risk stress echo was more accurate than stress ECG in predicting this primary outcome (51% vs. 29%; p = 0.01). The rate of normal ICA in the positive stress ECG group was nearly twice as high as in the stress echo group (39% vs. 23%). Significantly more stress ECG patients than stress echo patients required further diagnostic testing over the follow-up period (47% vs. 20%; p < 0.001).

The mean cost to diagnosis was significantly lower in the stress echo group than the stress ECG group (£326 vs. £495; p = 0.01). Overall, the authors concluded from their study that stress echo had "significant clinical and cost-benefits over stress ECG in assessing patients for CAD" in suspected ACS patients.

RANDOMIZED TRIALS OF CARDIAC MAGNETIC RESONANCE IMAGING

Miller et al. (16-19) explored the use of stress cardiac magnetic resonance (CMR) in a series of randomized, single-center studies with stress CMR performed as part of an observation unit protocol. In their first publication published in 2010 (enrollment period January 2008 to March 2009), 110 patients with intermediate or high probability for ACS but negative ECG and biomarkers were randomized to a stress CMR/observations unit strategy versus standard care as an inpatient (16). The inclusion of prior known coronary artery disease (CAD) and high-risk patients is notable and different that in other modalities, due to the ability of CMR to distinguish between acute and chronic infarction (**Figure 1**). The primary outcome was direct ED and hospital costs, including professional costs. The CMR/observation unit strategy reduced median costs compared with control patients who were directly admitted ($2,062 vs. $2,680), and 79% of CMR cases were managed without hospital admission. Patients were followed-up to 1 year to assess cumulative costs (and to rule out that the initially lower costs could have been due to deferral of testing) (17), and the benefits were sustained.

In 2012, the authors also examined the stress CMR/observation unit strategy compared with a stress testing modality selected by the patients' clinicians, which was stress echocardiography in the majority of cases (18). This study randomized 123 patients to either directed stress CMR (n = 62) or SOC (n = 61). A difference from their prior study was that this trial randomized lower-likelihood patients. The results showed no differences between the randomization groups in length of stay, referral for catheterization, admitting decision, or 30-day incidence of ACS. However, compared with stress CMR, costs were lower in the clinician-directed group ($2,005 vs. $1,686; p = 0.01). The authors concluded that in intermediate-risk patients with suspected ACS, "...the ability of a physician to select a cardiac stress imaging modality (including echocardiography, CMR, or radionuclide testing) was more cost-effective than a pathway that mandates a CMR stress test."

In 2013, the same authors reported on 105 intermediate-risk patients with ACP randomized to a stress CMR/observation unit strategy or usual care as provided by the patients' cardiologists and internists, unlike the prior study in which inpatient care was the comparator (19). Patients in the SOC arm underwent evaluation in the ED observation unit and then consultation by the admitting service about whether to hospitalize or discharge for further evaluation. The CMR group underwent vasodilator stress CMR, and reports from stress CMR were provided to ED observation unit physicians who independently made the decision to discharge the patient or to obtain cardiology consultation.

The primary outcome was a composite of coronary revascularization, all-cause hospital admission, and recurrent cardiac testing within 90 days. The secondary outcome was index visit length of stay. The group randomized to the CMR strategy had reduced rates of revascularization, hospital readmissions, and recurrent cardiac testing over 90 days of follow-up (23% vs. 38%; hazard ratio: 3.4), as well as a shorter length of stay (21.1 h vs. 26.3 h; p < 0.001).

This interesting series of studies reveals the potential for CMR imaging to be incorporated into an evaluation strategy pathway for higher-risk ED patients, including patients with known disease and even prior myocardial infarction. Unlike almost all of the trials involving MPI or coronary computed tomographic angiography (CTA), the CMR studies examined patients at intermediate-to-higher likelihood of ACS, in part on the basis of the stronger capability of CMR to differentiate ischemia from prior infarct, which is particularly important in patients with prior known CAD. However, when lower-risk patients were studied, more "standard" tests appeared to be less costly and similarly effective.

RANDOMIZED TRIALS OF CORONARY CTA

Between 2007 and 2011, 4 randomized trials compared the effectiveness of anatomic imaging using coronary CTA to functional testing, or to an SOC chosen at the discretion of the attending physicians (20-23). A common hypothesis of these studies was that a diagnostic strategy using coronary CTA as the primary initial diagnostic test would be more efficient than SOC using either traditional ECG/biomarkers/stress testing, and would still achieve the safety target of <1% missed ACS.

Goldstein et al. (20) published the first RCT of coronary CTA in 2007. Between March 2005 and September 2005, this single-center trial randomized 197 patients 1:1 to either a diagnostic strategy with coronary CTA as the primary imaging modality or to rest-stress MPI, after negative initial serial biomarkers and ECGs for overt ischemia. After coronary CTA, interpreting physicians recommended a course of action on the basis of scan results, but patient care was ultimately guided by attending physicians. In the coronary CTA arm, patients were eligible for discharge if there was no stenosis >25% or calcium score >100 Agatston units, and MPI group patients were eligible

FIGURE 1 Cardiac Magnetic Resonance Imaging in Assessment of Acute Coronary Syndrome
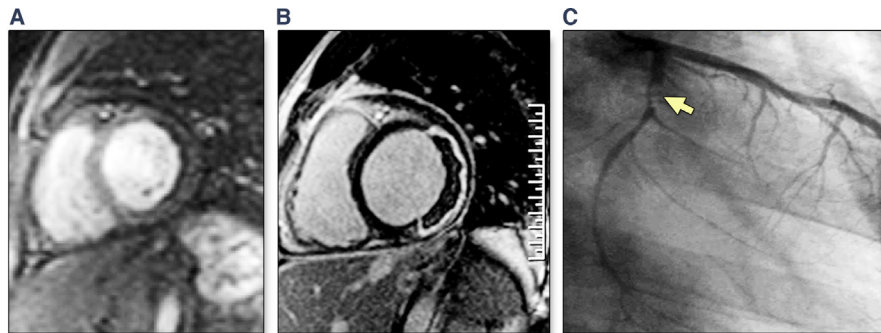
A 30-year-old individual with a history of cocaine abuse presented with recurrent chest pain, fever, T-wave inversion, and borderline troponin elevation. **(A)** Cardiac magnetic resonance was performed to exclude myocarditis revealed resting posterior defect on first pass perfusion. **(B)** Delayed enhancement imaging showed a bright area of enhancement surrounding endocardial microvascular obstruction, suggesting recent transmural infarction. **(C)** Invasive coronary angiography of the left coronary artery. The **arrow** indicates proximal left circumflex subtotal stenosis.

for discharge in the absence of definite ischemia. Patients with stenosis >70% were recommended for invasive angiography, and those with intermediate stenosis (26% to 70%) or nondiagnostic scans were recommended to cross over for MPI. The primary outcome was safety over 6 months of follow-up, defined as the absence of MACE in patients with no obstructive CAD results on coronary CTA or no ischemia on MPI. The primary outcome was confirmed; both groups had 100% safety. Coronary CTA shortened time to diagnosis as compared with MPI (3.4 h vs. 15.0 h; p < 0.001) and significantly lowered ED cost of care ($1,586 vs. $1,872). However, patients in the coronary CTA arm compared with the MPI arm underwent more additional testing by ICA (coronary CTA 11.1% vs. 3.1%) and noninvasive testing.

Three subsequent multicenter RCTs of coronary CTA enrolled a total of more than 3,000 patients. In 2011, Goldstein et al. (21) published CT-STAT (Computed Tomography for Systematic Triage of Acute Chest Pain to Treatment), the first multicenter RCT comparing coronary CTA triage to SOC. In this study, 699 patients were randomized at 16 sites to have a coronary CTA study or stress MPI (enrollment period June 2007 to November 2008) after serial ECGs and biomarker studies ruled out ACS. The primary endpoint was time to diagnosis, defined as the time from enrollment until the time test results were reported to the ED clinician. This outcome isolated the intrinsic time difference in the 2 tests, unaffected by other clinical events that might delay diagnosis; thus, this was primarily an efficacy trial. Safety (MACE rate over 6 months) and total direct costs of care in the ED

were the secondary outcomes. The use of coronary CTA was associated with a 54% reduction in time to diagnosis (median 2.9 h vs. 6.3 h; p < 0.001). Costs of ED care were lower in the coronary CTA group (coronary CTA median $2,137 vs. MPI median $3,458; p < 0.001), and there was no difference in the very low event rate observed in either group.

Two subsequent multicenter RCTs compared coronary CTA to an SOC that encompassed the full range of diagnostic strategies available in their site's ED, including direct discharge without testing (22,23). Patients were predominantly enrolled at centers that performed inpatient functional testing, as opposed to the ED observation units available in the CT-STAT trial.

In 2012, Litt et al. (23) published a large multicenter ED RCT (commonly referred to as the ACRIN trial, for the American College of Radiology Imaging Network, which was the study coordinating center). The study enrolled 1,370 low- to intermediate-risk patients at 5 sites and randomized them 2:1 (coronary CTA n = 908; SOC n = 462) to coronary CTA or to an SOC diagnostic strategy chosen by the ED physician, including a variety of clinical options (23). Enrollment was from July 2009 through November 2011. In this case, the primary endpoint was safety in the coronary CTA group, defined as the absence of myocardial infarction or cardiac death during the 30 days after enrollment among coronary CTA patients who had no stenosis ≥50% in a major branch or first-order branch. The primary safety endpoint of the trial did not compare results with the SOC group, as it would not have been feasible to power comparative effective for safety in such low-risk patients.

Secondary endpoints demonstrated a significantly reduced length of stay in the coronary CTA group (18.0 h vs. 24.8 h) and increased direct ED discharge (49.6% vs. 22.7%). Over the course of 30 days after presentation, unlike in the CT-STAT trial (and the ROMICAT II [Rule-Out Myocardial Infarction with Computed Tomography II] trial presented later in the text) there was no significant difference between the coronary CTA and SOC groups in use of ICA (5.1% vs. 4.2%) or in the rate of revascularization (2.7% vs. 1.3%). Patients in the coronary CTA arm were less likely to have negative ICA findings compared with SOC (29% vs. 53%). There was no difference between groups on late resource utilization including repeat ED, hospitalization, or cardiology office visits.

The authors concluded that, "a strategy in which coronary CTA is used as the first imaging test for low-to-intermediate-risk patients presenting to the ED with possible ACS appears to allow the safe discharge of patients after a negative test. Increased rates of discharge home and a reduced length of stay make this strategy more efficient than traditional care" (23).

Also in 2012, Hoffmann et al. (22) reported the multicenter ROMICAT II study. A total of 1,000 patients (coronary CTA n = 501; SOC n = 499) at 9 centers (enrollment period April 2010 to January 2012) with low-to-intermediate likelihood of ACS and an initial negative troponin were randomized to an evaluation strategy incorporating coronary CTA results or to SOC. Similar to the ACRIN trial, SOC included the full range of potential tests other than coronary CTA, including discharge without testing. The prevalence of ACS at final diagnosis was 8%, higher than in the other coronary CTA randomized trials. The length of stay was significantly shorter in the group randomized to the coronary CTA strategy (23.2 h vs. 30.8 h; p < 0.001) due to a higher rate of early discharge (**Figure 2**). Secondary endpoints demonstrated that there were far more direct discharges from the ED in the coronary CTA group (47% vs. 12%; p < 0.001), which is largely responsible for the reduced length of stay. It should be noted that functional testing was only available after admission, as compared with the CT-STAT study, where the presence of observation units with MPI yielded very high direct discharges in both arms (88.2% vs. 89.9%).

There was an increase in additional functional testing and ICA rate in the coronary CTA arm compared with SOC, but this did not reach statistical significance for ICA (12% vs. 8%; p = 0.06). In their meta-analysis, Hulten et al. (24) estimated the increase in invasive coronary angiography and percutaneous coronary interventions (PCIs) after coronary CTA to be 21 and 20 per 1,000 c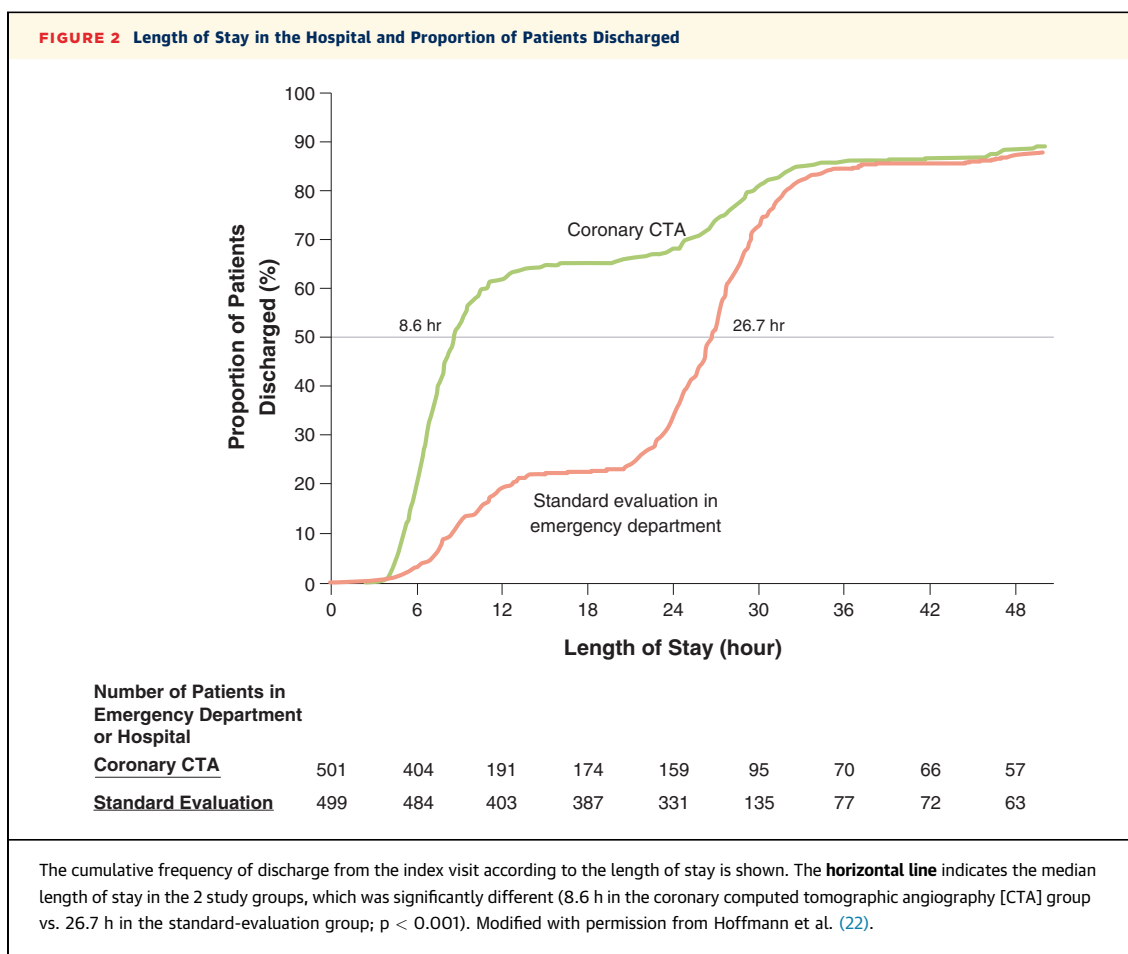oronary CTA scans, respectively. Similar findings were reported by Uretsky et al. (25). There are no reliable data at this point to indicate whether the improved detection of CAD and subsequent PCI in this acute setting will improve long-term health outcomes due to preventive care.

Despite the increase in subsequent testing after coronary CTA, the overall cost of the index hospitalization was not significantly higher in those randomized to coronary CTA in these studies, as the greater rate of direct discharges and the more rapid triage likely balances the excess testing that occurs in some patients. The estimated radiation exposure in the coronary CTA group was higher (13.9 mSv) as compared with SOC (4.7 mSv) in the ROMICAT II trial, which included patients undergoing only exercise treadmill stress test or stress echocardiography. Radiation dose was similar in a direct comparison of coronary CTA (11.2 mSv) to MPI (12.8 mSv) in the CT-STAT trial. The authors concluded that early coronary CTA, as compared with SOC, improved the efficiency of ED triage, shortened length of stay, and increased the rate of direct ED discharge, with equivalent safety. However, there was an increase in overall late testing and radiation dose.

In 2015, Levsky et al. (26) reported the results of PROSPECT (Prospective Randomized Outcome trial comparing radionuclide Stress myocardial Perfusion imaging and ECG-gated CCTA), which compared coronary CTA to stress MPI in the care of ED patients with ACP. The primary outcome of the PROSPECT trial was superior selection of patients for invasive management over a 1-year period. This was defined as a lower rate of ICA not leading to PCI or surgical revascularization within 1 year. This was a clinical effectiveness trial; attending physicians made all clinical decisions after the primary imaging test.

The population consisted of 400 patients with ACP admitted to a telemetry unit (enrollment period July 2008 to March 2012) and with at least 1 intermediate risk criterion for death or myocardial infarction, on the basis of the American College of Cardiology Foundation/American Heart Association 2011 Guideline for ACS (27); patients were randomized 1:1 to coronary CTA or stress MPI. Rest MPI was performed only if stress MPI was abnormal. Length of stay was calculated from randomization to discharge. Safety outcomes included complications from noninvasive testing and/or invasive procedures, renal dysfunction, radiation dose, all-cause mortality, and nonfatal MACE. Subsequent resource utilization over 1 year was also analyzed as a secondary outcome.

The primary outcome was similar between the 2 groups. The ICA rate for the CTA and MPI groups was 15% versus 16% (p = 0.89), and the

FIGURE 2 Length of Stay in the Hospital and Proportion of Patients Discharged

Number of Patients in Emergency Department or Hospital								
Coronary CTA	501	404	191	174	159	95	70	66	57
Standard Evaluation	499	484	403	387	331	135	77	72	63

The cumulative frequency of discharge from the index visit according to the length of stay is shown. The **horizontal line** indicates the median length of stay in the 2 study groups, which was significantly different (8.6 h in the coronary computed tomographic angiography [CTA] group vs. 26.7 h in the standard-evaluation group; p < 0.001). Modified with permission from Hoffmann et al. (22).

revascularization rate was 7.5% versus 10% (p = 0.41). Coronary CTA demonstrated a trend toward greater efficiency, with median length of stay of 28.9 h versus 30.4 h, but it did not reach statistical significance (p = 0.057). It is also notable that median radiation dose was significantly lower (9 mSv for CTA, 27 mSv for MPI; p < 0.001). Downstream resource utilization, including repeat hospitalizations, ED visits, office visits for cardiac symptoms, and noninvasive and invasive testing, did not differ between the groups.

The authors concluded that there was "no significant difference between initial coronary CTA and MPI in catheterization not leading to revascularization" and that "length of stay, downstream resource utilization and clinical events did not differ," whereas "coronary CTA was associated with lower radiation dose and a better patient experience." The fact that coronary CTA was not more efficient in the PROSPECT trial is divergent from the other RCTs, but it is notable that patients were enrolled after they had been admitted to an inpatient telemetry unit. The results from the ROMICAT II trial illustrated in **Figure 2** show

that the majority of length-of-stay reduction was attributable to direct ED discharge.

RANDOMIZED TRIAL OF HIGH-SENSITIVITY TROPONIN AND IMAGING

The introduction of high-sensitivity troponin (hsTn) suggests the possibility of rapid direct discharge of hsTn-negative patients with ACP, potentially without further stress ECG, functional, or anatomic testing in the ED (28–30). In Europe, where hsTn is widely available, it has become incorporated into ACP SOC. It is uncertain whether early coronary CTA or other noninvasive testing is still advantageous after incorporating hsTn. The first clinical effectiveness RCT addressing this issue was reported by Dedic et al. (31) in 2016. The BEACON (Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography) trial randomized 500 patients with ACP at 7 European sites between July 2011 and January 2014, to either coronary CTA-guided care or SOC that included alternative stress ECG, functional testing, or

FIGURE 3 Case Studies in Clinical Use of Fractional Flow Reserve by Computed Tomography
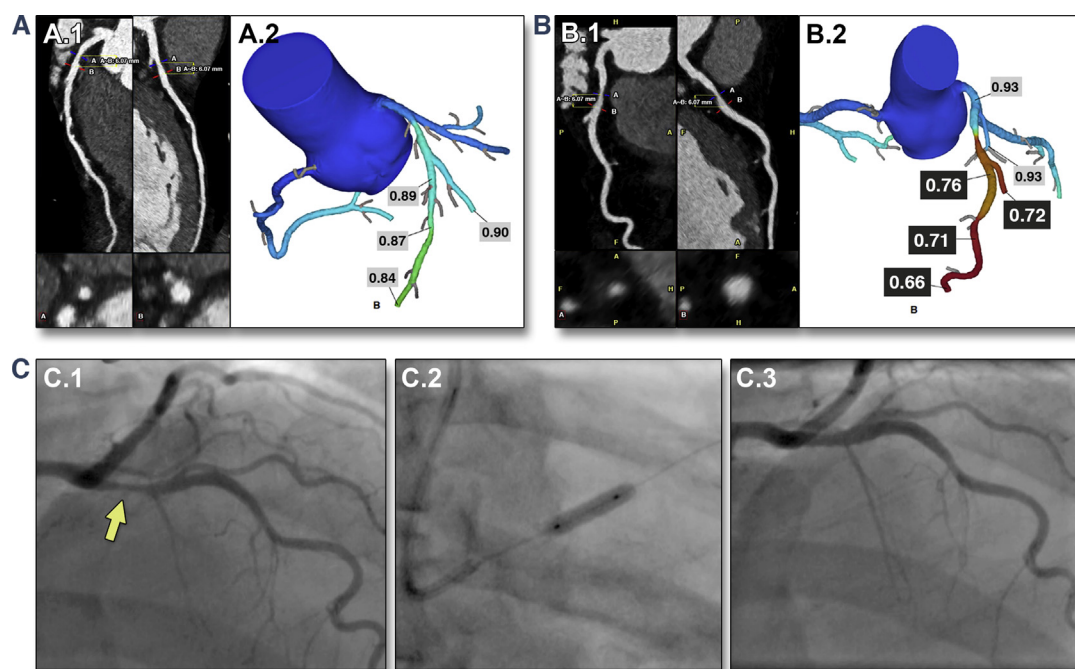
(A.1) A 65-year-old patient presented with acute chest pain after running with his dog. Coronary computed tomographic angiography (CTA) shows a smooth proximal 50% to 70% noncalcified stenosis. **(A.2)** Fractional flow reserve by computed tomography (FFRct) value distal to the lesion was 0.89, and the patient was treated medically. **(B.1)** A 41-year-old patient presents with a history of left upper back pain radiating to the arm with coughing. Coronary CTA shows 50% to 70% tubular proximal noncalcified stenosis. **(B.2)** FFRct value distal to the lesion is 0.76 and it falls to 0.66 at the apex. **(C.1, C.2, and C.3)** FFRct value was confirmed by invasive FFR, and the patient was treated with coronary intervention. Modified with permission from Chinnaiyan KM, Raff GL. Coronary CT angiography in the emergency department: current status. Curr Treat Options Cardiovasc Med 2016;18:62.

direct discharge without testing. Results from hsTn testing were available in both arms. Patients were followed up at 72 h and 30 days.

The primary endpoint of the study was the number of patients with positive coronary CTA or SOC testing requiring revascularization, on the basis of the hypothesis that a coronary CTA-driven strategy would identify more clinically important CAD. Secondary endpoints included expedited discharge from the ED, length of hospital stay, undetected ACS, cumulative radiation dose, direct medical costs, and repeat ED or hospital admission for recurrent chest pain.

The primary outcome was similar for the coronary CTA and SOC groups: coronary revascularization was required in 9% versus 7%, respectively (p = 0.40). Safety endpoints in terms of repeat ED and hospitalization were also similar, as were MACE events. A similar number of patients were discharged immediately from the ED after coronary CTA (65% vs. 59%; p = 0.16), and the median length of stay was similar. Outpatient testing was less frequent with coronary

CTA than SOC (4% vs. 11%; p < 0.01), and overall, direct medical costs after 30 days were lower (€337 vs. €511; p < 0.01).

The authors concluded that when hsTn is available for ED evaluation of patients with ACP, coronary CTA is associated with lower costs and less outpatient testing than SOC that includes functional testing. However, coronary CTA does not identify more patients with CAD requiring revascularization, nor does it shorten hospital length of stay or allow more immediate ED discharge. The generalizability of the BEACON trial to U.S. patients with ACP must be further tested, as patients were at a higher risk category for ACS compared with patients included in U.S. coronary CTA trials to date.

FUTURE DIRECTIONS: COMBINED ANATOMIC-FUNCTIONAL IMAGING

Although rapid and sensitive visualization of coronary plaque by coronary CTA is useful in expediting

the care of low- to intermediate-risk patients, anatomic stenosis per se (by coronary CTA or ICA) cannot predict flow. Thus, invasive fractional flow reserve is required for optimal decision making about revascularization. It is evident that combining functional and anatomic imaging in a single noninvasive imaging modality or session would be advantageous, particularly in higher-risk patients with ACP who are more likely to have multiple plaques. Three such tests are currently available: positron emission tomography or MPI combined with computed tomography angiography in a single scanner (32), computed tomography perfusion (33-35), and fractional flow reserve by computed tomography (36-38) (**Figure 3**). The use of single-scanner positron emission tomography or MPI combined with coronary CTA is limited by scanner availability. By contrast, computed tomography perfusion and fractional flow reserve by computed tomography are performed on widely available conventional scanners. Comparing the 2 techniques, computed tomography perfusion has the advantage of immediate results, but the disadvantage of requiring vasodilator stress and repeat coronary CTA. Fractional flow reserve by computed tomography requires no additional stress testing or imaging, but at this point there is a delay of several hours before the results are available. As of yet, neither of these tests has been validated by RCTs for use in ACP.

SUMMARY

RCTs are vital precedents before widespread adoption of new medical procedures. With over 8 million patients/year seeking care for acute chest pain in the United States alone, more rapid, cost-effective diagnostic strategies are essential. This paper has reviewed multiple randomized trials that suggest that adjunctive noninvasive imaging is safe and effective in expediting care and reducing hospital admissions for low- to intermediate-risk patients with ACP. These trials also compared the effectiveness of radionuclide MPI, stress echo, CMR, and coronary artery computed tomography. The 1 randomized trial of hsTn suggests that coronary computed tomography continues to reduce cost. The advantages of noninvasive imaging in low- to intermediate-risk patients with ACP are not available to higher-risk patients, due to the frequency of multiple plaques that may not be flow-limiting. Future trials of combined anatomic-functional imaging and other novel technologies are needed to assess whether this challenge can be met. The exact role of adjunctive imaging once hsTn is widely available is an important area for continued research.

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