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Review

Evaluation of acute chest pain: Evolving paradigm of coronary risk scores and imaging

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There is a broad differential diagnosis for patients presenting with acute chest pain. History, physical examination, electrocardiogram, and serial troponin assays are pivotal in assessing patients with suspected acute coronary syndrome. However, if the initial workup is equivocal, physicians are faced with a challenge to find the optimal strategy for further triage. Risk stratification scores have been validated for patients with known acute coronary syndrome, such as the TIMI and GRACE scores, but there may be limitations in undifferentiated chest pain patients. Advancements in imaging modalities such as coronary computed tomography angiography and the addition CT derived fractional flow reserve, have demonstrated utility in evaluating patients presenting with acute chest pain. With this article, we aim to provide a comprehensive review of the non-invasive modalities that are available to evaluate acute chest pain patients suspected of cardiac etiology in the emergency room. We also added a focus on new imaging modalities that have shown to have prognostic implications in stable ischemic heart disease.

Keywords

1. Introduction

Annually, there are more than 8 million emergency department (ED) visits in the United States for acute undefined chest pain (Owens et al., 2010; Pitts et al., 2008; Rui and Kang, 2015). Approximately 30-80% of these patients are admitted, often to rule out acute coronary syndrome (ACS), due to the significant morbidity and mortality associated with coronary artery disease (Cotterill et al., 2015; Hoffmann et al., 2009; Hsia et al., 2016; Owens et al., 2010; Pitts et al., 2008; Pozen et al., 1984; Rui and Kang, 2015). This imparts an economic and clinical challenge as these patients undergo extensive testing that costs approximately $8 billion a year. More often, the presenting chest pain proves to be non-cardiac, however, 2-10% of these patients that are discharged prematurely from the ED have ACS (Hoffmann et al., 2009; Lee et al., 1987; Pope et al., 2000; Schor et al., 1976; Waxman et al., 2018).

In one of the largest studies, Schor et al. (1976) followed patients presenting to the ED with presumed coronary artery disease over a one-year period. Approximately 50% of the patients were admitted, and only 6% of the admitted patients had a final diagnosis of myocardial infarction (MI). Furthermore, approximately 10% of the patients discharged directly from the ED were later diagnosed as a missed MI. This is concerning for patient outcomes as well as potential litigation. The failed diagnoses led to 24-26% of the money paid in closed malpractice claims in emergency medicine from 1985 to 2007 (America, PIAo, 2004; Oetgen et al., 2010; PIAA, 2014). Karcz et al. (1993) found that missed MI was the largest monetary loss category in emergency medicine accounting for 21% of the total dollars paid in lawsuits.

The evaluation of chest pain starts in the emergency room to determine acuity. This includes assessment for life-threatening etiologies such as pulmonary embolism, aortic dissection, tension pneumothorax, and acute coronary syndromes. The basic ACS work-up includes history and physical examination, a 12 lead electrocardiogram (EKG) and a chest x-ray. Patients with acute findings on electrocardiogram, such as ST-segment elevation myocardial infarction, have a clear algorithm for management (Amsterdam et al., 2010). However, for patients without acute electrocardiographic findings or cardiac enzyme elevation who are categorized in the low to intermediate-risk group, the workup varies as our guidelines continue to change. The American Heart Association published a revised statement in Circulation 2010 emphasizing the importance of accurate risk stratification and exclusion of ACS or other serious conditions in the acute chest pain evaluation rather than detection of coronary artery disease (CAD) (Amsterdam et al., 2010).

In addition, coronary computed tomography angiography (CCTA) demonstrated high sensitivity and specificity initially for evaluation of stable ischemic heart disease (Budoff et al., 2008; Garcia et al., 2006; Marano et al., 2009; Meijboom et al., 2008; Miller et al., 2008). Subsequent studies have established its utility for ACS rule out in the emergency department (ED) (Hoffmann et al., 2012; Litt et al., 2012; Poon et al., 2013). The addition of non-invasive fractional flow reserve (FFR_{CT}) provides a functional component to a robust anatomical imaging modality. This technology was recently tested in the ED and was found to have feasibility without any difference in the overall costs and major

cardiac events when compared to CCTA alone (Chinnaiyan et al., 2019). The utilization of coronary CT angiography was found have a significant impact on prognosis with a reduction in myocardial infarction due to detection of non-obstructive coronary artery disease followed by initiation of preventive medications.

The purpose of this article is to review the different noninvasive strategies including advanced imaging modalities that are currently available to evaluate low to intermediate-risk chest pain in the emergency room. Also, we aim to discuss the advanced modalities not only in the ED but also their strong impact on prognosis in stable ischemic heart disease.

2. History and physical examination

Chest pain characteristics are valuable in determining which patients require acute attention. Important presenting features include the quality, duration, and radiation of the pain as well as other associated symptoms. Chest pain described as "heaviness, crushing, burning, aching, or tightness" and with radiation into the neck, arm or jaw has been associated with cardiac chest pain. Traditionally, cardiac chest pain is classified as typical angina, atypical angina and non-anginal chest pain. Typical angina has three components: (1) substernal chest pain or discomfort, (2) provoked by exertion or emotional stress, (3) relieved by rest and/or nitroglycerin. Atypical angina consists of two of the three components for typical angina. Nonanginal chest pain has one or none of the components for typical chest pain (Diamond and Forrester, 1979; Gibbons et al., 2002).

Classifying patients into typical and atypical chest pain have traditionally been used in the initial evaluation of patients with acute chest pain. Nakas et al. (2018) investigators in a single-center assessed 686 patients undergoing angiography for suspected CAD. They sought to determine the chest pain characteristics that strongly correlate with obstructive CAD. Typical anginal symptoms were associated with a higher prevalence of CAD (OR 3.47, $P < 0.001$). In multivariate analysis, the investigators found that typical anginal symptoms were an independent predictor for CAD (OR, 2.54, $P < 0.001$) and more predictive than other clinical risk factors (area under the curve [AUC], 0.715, $P < 0.001$) (Nakas et al., 2018). However, Hermann et al. (2010) reviewed 2,525 patients with no previous history of coronary artery disease seen in the ED for chest pain. Typical and atypical chest pain characteristics were compared with cardiac enzymes and stress testing. They concluded that there was no significant difference in those with typical versus nonanginal and atypical chest pain for inducible myocardial ischemia (Hermann et al., 2010).

In 1979, Diamond and Forrester (DF) published a model using age, gender, and typical chest pain features to predict the likelihood of obstructive CAD in an outpatient cohort (Diamond and Forrester, 1979), as outlined in Table 1. Hamburger et al. (2016) attempted to validate the DF classification in low to intermediate-risk patients in the ED with exercise treadmill test and CCTA to confirm CAD. The authors concluded that typical angina as defined by the DF classification in this low-risk population was not predictive of CAD (Hamburger et al., 2016). The modified DF clinical model includes other cardiovascular risk factors, such as hypertension, diabetes, hyperlipidemia and smoking in addition to age, gender and chest pain features. The model has been recommended for assessing pre-test probability for CAD (Gibbons et al., 2002, 1997).

Moreover, researchers have attempted to identify chest pain features that most strongly correlate with ACS (Amsterdam et al., 2010; Body et al., 2010; Hermann et al., 2010; Nakas et al., 2018). In the prospective study by Body et al. (2010), patients were evaluated in the ED with suspected cardiac chest pain. Of the 796 patients, 148 had confirmed a myocardial infarction. No single feature was identified in their presenting history that could alone predict acute MI or adverse events. Diaphoresis noted on the exam was the strongest predictor of acute myocardial infarction (AMI) (odds ratio (OR) 5.18, 95 CI 3.02-8.86). Reported vomiting was also strongly associated with AMI (OR 3.50, 95 CI 1.81-6.77). Contrary to common belief, chest pain described as the same quality pain as their previous MI was less likely to have AMI with an OR 0.42 (95 CI, 0.26-0.69). They demonstrated that "typical" symptoms may have no diagnostic value, and several atypical symptoms may make ACS more likely (Body et al., 2010).

In addition, a thorough history and physical exam help to differentiate between cardiac and non-cardiac pain. Hypotension and hemodynamic instability, evidence of systolic dysfunction and S3 gallop are more urgent features that prompt cardiac workup (Cayley, 2005; Roffi et al., 2016). Pain that is reproducible on exam suggests that cardiac etiology is less likely. A study by Grani et al. (2015) found that reproducible chest pain had a negative predictive value of 98% (CI 95%, 89.9-99.7%). Pulse differences of upper extremities are concerning for aortic dissection. Fevers, egophony, and dullness to percussion are indicative of a pneumonia diagnosis (Cayley, 2005; Roffi et al., 2016). The physical exam is often normal in ACS but it is important in the initial triage process of chest pain.

3. Traditional risk factors

The Framingham heart study has helped to identify the classic risk factors associated with coronary artery disease, such as hypertension, hyperlipidemia, smoking history, age, and family history of early events (Kannel et al., 1961). More recent updates on cardiac risk have recognized increased inflammation such as HIV as cardiac risk factors (Kaplan et al., 2007). Traditionally, risk factors have been an essential tool for assessing the likelihood of acute cardiac ischemia in patients with acute chest pain.

Many studies have looked at whether using these factors can be predictive for the diagnosis of ACS (Body et al., 2008; Han et al., 2007; Jayes et al., 1992; Kannel et al., 1961; Kaplan et al., 2007). In a prospective study by Jayes et al. (1992), 5,773 patients were evaluated to determine whether the presence of classic risk factors increased the likelihood of acute ischemia. In the male patients, Diabetes and family history was associated with increased risk of ACS with a RR 2.4 and 2.1, respectively (95% CI 1.2-4.8 and 1.4-3.3). Traditional risk factors in females were not associated with an increased risk of ACS and did not assist in risk stratification. Overall, the group concluded that conventional risk factors were not diagnostic of ACS.

In addition, Han et al. (2007) used an Internet Tracking Registry of Acute Coronary Syndrome (i*trACS) to address the utility of conventional cardiac risk factors for diagnosing ACS in patients with acute chest pain. Of the 10,806 patients with 17,713 ED visits

Table 1. Diamond and Forrester classification table likelihood of coronary artery disease (Diamond and Forrester, 1979).

Age	Typical Angina [A]		Atypical Angina [B]		Non-anginal Chest pain [C]	
	Male	Female	Male	Female	Male	Female
30-39	76%	26%	34%	12%	4%	2%
40-49	87%	55%	51%	22%	13%	3%
50-59	93%	73%	65%	33%	20%	7%
60-69	94%	86%	72%	51%	27%	14%

Chest pain (CP) criteria: 1. Substernal CP or discomfort, 2. Provoked by exertion or emotional stress, 3. Relieved by rest and/or nitroglycerin.

[A] Typical Angina: 3 out of 3 criteria
[B] Atypical Angina: 2 out of 3 criteria
[C] Non-anginal chest pain

for ACS rule out, 871 or 8.1% of these patients had an ACS. Age was determined to be the strongest predictor of ACS. The authors concluded that cardiac risk factors have limited diagnostic value for acute coronary syndrome, especially in patients older than 40 years of age (Han et al., 2007).

Overall, cardiac risk factors alone are nondiagnostic in the acute setting of chest (Body et al., 2008; Han et al., 2007; Jayes et al., 1992; Kannel et al., 1961; Kaplan et al., 2007). Cardiac risk factors are needed as part of the collective risk stratification to predict cardiac events in the emergency room setting.

4. Electrocardiogram

The electrocardiogram (EKG) is an essential, risk-stratifying tool in patients presenting with acute chest pain. The EKG demonstrates diagnostic and prognostic features that are key for triage. According to the ACC/AHA guidelines, a standard twelve lead EKG should be performed within 10 minutes of a patient presenting with acute chest pain. It is also recommended that the EKG should be repeated every 15-30 minutes for evaluation of evolving MI within the first hour of presentation (Amsterdam et al., 2014).

A normal EKG does not exclude ACS, and the estimated prevalence of ACS with a normal EKG is 1-6% (Amsterdam et al., 2014). In a study by Rouan et al. (1989) investigators sought to determine the prevalence and characteristics of AMI in 7,115 patients who initially presented with normal or nonspecific changes on EKG. They found that AMI patients with an initially normal or nonspecific EKG were less likely to have a history of CAD. The estimated probability for AMI in patients with chest pain and normal or nonspecific EKG was about 3%. Also of note, lateral wall MI related to the left circumflex artery has been associated with decreased or limited ST-segment elevation and can be often missed (Amsterdam et al., 2014; Oraii et al., 1999; Roffi et al., 2016; Rouan et al., 1989; Zalenski et al., 1993).

EKG remains the essential primary tool in the triage of patients with acute chest pain, where it is critical in diagnosing an acute MI (Amsterdam et al., 2014), but a normal EKG paves the path for further diagnostic work up which we further discuss.

5. High sensitivity troponins assays

The universal definition of AMI as determined by the American College of Cardiology (ACC), American Heart Association (AHA) and the World Heart Federation (WHF) Task Force includes an elevated cardiac biomarker, preferably a high sensitivity cardiac troponin assay (Thygesen et al., 2018). High-sensitivity cardiac troponin (hs-cTn) assays enable the detection of cardiac troponin concentrations in at least 50% of healthy individuals with improved precision at the 99th percentile of the normal reference population. Hs-cTn concentrations can be detected at an earlier time period of an evolving MI, which could improve the triage process of patients presenting with acute chest pain (Thygesen et al., 2018).

There are studies that have attempted to validate the utility of Hs-cTn assays for ruling out AMI. Studies have also sought to assess the utility of a single hs-cTn assay or the degree of change in hscTn concentration for predicting AMI (Bandstein et al., 2014; Korley and Jaffe, 2013; Mueller et al., 2016; Pickering et al., 2017). Pickering et al. (2017) assessed 2,825 low-risk patients, defined as new ischemia on ECG and Hs-cTn concentration less than 0.005 μg/L. Of the 2,825 low-risk patients, 14 were found to have an acute MI. The sensitivity of MI detection in the troponin level less than 0.005 μg/L was 98% and sensitivity for 30-day MACE ranged 87.9-100%. In 2014, a retrospective analysis of 14,636 patients that presented to a Swedish ED with chest pain sought to evaluate various presenting hscTn concentration cut-offs for the primary outcome of fatal and nonfatal MI within 30 days. Those with a hscTn concentration less than 5 ng/L had a 99.8% negative predictive value for MI and a value of 100% for the negative predictive value of death (Bandstein et al., 2014).

In addition, the hs-cTn assay for RAPID rule out of acute myocardial infarction (TRAPID-AMI) trial was a prospective analysis of 1,282 patients with acute chest pain for which hs-cTn assays were drawn at presentation and 1 hour. The sensitivity and negative predictive value with those with negative hs-cTn assay was 96.7% (95% CI 93.4- 98.7%) and 99.1% (95% CI, 98.2- 99.7%), respectively (Mueller et al., 2016). More recently, Neumann et al. (2019) investigated the use of serial hs-cTn assay in a cohort of 22,651 patients presenting to the ED with acute MI. The authors found that smaller absolute changes in troponin level was associated with reduced likelihood of acute MI and cardiac event at 30 days. Based on these findings in absolute change in hs-Tn levels, the investigators developed a risk assessment tool for utilizing hs-Tn assays in the acute ED setting (Neumann et al., 2019).

Rapid screening protocols with hs-cTn assays have been proposed for patients for whom ruling in or out an acute myocardial

infarction (AMI) is difficult. Various cut-offs for troponin concentrations have been proposed for aide in the diagnosis of acute MI. With the increase in sensitivity of the cardiac enzyme assay, there seems to be a corresponding increase in non-Type I MI causing elevation of hs-cTn levels. Type 2 MI, a supply and demand mismatch, causes a rise in the hscTn level, for which it may be difficult to differentiate from a type 1 MI. Type 2 MI can be induced by conditions such as hypotension or respiratory failure for which management involves treating the underlying cause. Type 1 MI is caused by plaque rupture, and the management includes more aggressive measures such as anticoagulation and revascularization (Korley and Jaffe, 2013; Thygesen et al., 2018). Differentiating the type of MI depends on clinical judgment. Of note, patients with chronic conditions such as end-stage renal disease can also cause elevations of hs-cTn concentration that may make a standard cut off for ACS difficult to define (Korley and Jaffe, 2013; Pickering et al., 2017; Thygesen et al., 2018).

Protocols in Europe have been adopted for obtaining hs-cTn assays as part of ACS workup. The European Society of Cardiology (ESC) guidelines for acute ACS assessment recommends that the time interval for obtaining hs-cTn levels depends on the assay used (National Institute for Health and Clinical Excellence, 2016). Assays were validated for two different time intervals including a 0 hour (h) and 3h from the presentation as well as a 0h and 1h from presentation (Roffi et al., 2016). In conjunction with ECG findings and risk assessment scoring tool, the patients that have negative troponins assay and low clinical risk are categorized in a rule-out group. This rule-out group had a negative predictive value of 98% and recommended for early discharge or outpatient work up (Roffi et al., 2016).

6. Risk assessment tools and stratification

A number of scoring systems have been developed over time to attempt to risk stratify ACS patients. The GRACE and TIMI risk scores are commonly used assessment tools for high risk ACS patients to determine therapy (Antman et al., 2000, 1999; Chase et al., 2006; Granger et al., 2003; Morrow et al., 2001). The FRISC score was also validated for high-risk ACS patients to determine the effect of early invasive strategies (Lagerqvist et al., 2005). Other scoring systems, such as the PURSUIT score did not take into account cardiac enzymes (Boersma et al., 2000). The HEART, HEART Pathway and EDACS-ADP are more recent methods that are useful for triaging patients with acute chest pain (Backus et al., 2013, 2010; Mahler et al., 2015; Six et al., 2008; Than et al., 2014).

The TIMI risk score was developed from the Thrombolysis in MI (TIMI)-11B trial, a randomized control trial of 1,957 ACS patients that compared treatment with unfractionated heparin to enoxaparin (Antman et al., 2000, 1999). There were seven features identified in a multivariate analysis, for which were statistically significant as outlined in Table 2. TIMI score predicted risk for all-cause mortality, MI and severe recurrent ischemia requiring revascularization within 14 days. The ESSENCE Trial along with subsequent trials further validated the scoring system (Antman et al., 2000).

In addition, a registry of 11,389 ACS patients was used to develop the GRACE score. A multivariate logistic regression analysis allowed for the identification of 8 independent risk factors asso-

Table 2. TIMI Risk Score (Antman et al., 2000)

Age greater than 65	+ 1
3 CAD Risk factors (hypertension, hypercholesterolemia, diabetes, family history of CAD or current smoker)	+ 1
Known CAD (stenosis of greater than 50%)	+ 1
Aspirin use in past 7 days	+ 1
Severe Angina (≥ 2 episode in 24 hours)	+ 1
EKG ST segment changes (≥ 0.5 mm)	+ 1
Positive Cardiac marker	+ 1

Score: 1 (5% risk), 2 (8% risk), 3 (13% risk), 4 (20% risk), 5 (% risk), 6 (% risk), 7 (40% risk)

Table 3. GRACE Score (Granger et al., 2003)

Variables
Age
Heart Rate
Systolic Blood pressure
Creatinine
Cardiac Arrest on admission
St segment deviation on EKG
Abnormal Cardiac enzymes
Killip class

ciated with morality both inpatient and at 6 months of discharge, as outlined in Table 3 (Granger et al., 2003). Both the GRACE and TIMI scores were validated in patients with known ACS rather than those with undifferentiated chest pain (Antman et al., 2000, 1999; Chase et al., 2006; Granger et al., 2003). The scores are useful in high-risk patients to help determine aggressive therapy. There is some data that suggests that the GRACE may be superior to the TIMI risk score in undifferentiated chest pain (Ramsay et al., 2007), however GRACE score cannot be easily performed at bedside.

In 2008, the HEART system was developed in the Netherlands as a rapid risk stratification tool for patients with acute chest pain in the ED (Six et al., 2008). The system classifies patients into low, moderate and high-risk groups based on history, ECG, age, risk factors, and troponin assay. This tool was validated with a single-center retrospective study of 122 patients as well as a multicenter retrospective study of 880 patients (Backus et al., 2010; Six et al., 2008). In these studies, the investigators used the HEART score to assess the likelihood of composite endpoints MI, percutaneous coronary intervention (PCI), Coronary Bypass Grafting (CABG) or death within 6 weeks of presentation. As outlined in Table 4, the low-risk group was at 2.5% risk for endpoints-for which patient disposition recommended for early discharge. Intermediate group patients were at a 20% risk and recommended for admission. The high-risk group was 73% risk for endpoints and should be managed aggressively (Backus et al., 2010; Six et al., 2008).

In 2013, investigators compared the HEART risk score to the GRACE and TIMI scores in a prospective study of 2,388 patients with chest pain across 10 hospitals in the Netherlands (Backus et al., 2013) with a primary endpoint of major adverse cardiac event

Table 4. HEART Score (Six et al., 2008)

History	Highly suspicious	2 points
	Moderately suspicious	1 point
	Slightly or Non-suspicious	0 points
ECG	Significant ST-Depression	2 points
	Nonspecific repolarization	1 point
	Normal	0 points
Age	> 65 years	2 points
	45-65 years	1 point
	< 45 years	0 points
Risk Factors	> 3 risk factors or History of CAD	2 points
	1 or 2 risk factors	1 point
	No risk factors	0 points
Troponin	> 3 x normal limit	2 points
	> 1- < 3 x normal limit	1 point
	< Normal limit	0 points

Table 5. EDACS Risk Score (Than et al., 2014)

Age	2-20
Gender	Male+6
Known CAD or ≥ 3 risk factors	4
Diaphoresis	3
Pain radiating to arm, shoulder, neck or jaw	5
Pain occurred or worsed with inspiration	-4
Pain is reproduced by palpation	-6

(MACE) within 6 weeks of initial presentation. Of note, MACE was defined as acute MI, PCI, CABG, angiographic evidence of procedurally correctable stenosis that is managed conservatively, and death. Of the patients classified as low risk based on each scoring system, the TIMI and GRACE scores demonstrated a 2.8 and 2.9% MACE rate, respectively, while the low risk HEART group had 1.7% MACE. The c-statistic for the HEART score was 0.83 and was statistically greater than the TIMI at 0.75 and GRACE at 0.70 ($P < 0.0001$). This suggests that the HEART score is a more favorable tool for predicting undifferentiated chest pain, especially in the emergency room setting.

In addition, Mahler et al. (2015) developed the HEART Pathway risk score for assessment and triage of acute undifferentiated chest pain in low-risk patients. Investigators used the HEART score for patients with the addition of troponin levels on presentation and at 3 hours. The 282 patients were randomized into the HEART Pathway group and standard care group to assess the primary endpoint of cardiac testing, such as stress tests or angiography. Secondary endpoints included MACE, length of stay and early discharge. The HEART Pathway group was associated with an absolute reduction of 12.1% ($P = 0.048$) in cardiac testing. Early discharge occurred in 56 of the 141 patients in the HEART Pathway group (39.7%) compared to the 26 of the 141 patients with standard care (18.4%): an absolute increase of 21.3% ($P = 0.001$). More importantly, no MACE events occurred at 30 days in patients who were discharged early.

Moreover, a group from New Zealand developed the Emergency Department Assessment of Chest pain Score (EDACS) with the aim to identify acute chest pain patients as low risk (Than et al., 2014). The addition of serial troponin assays further increased the proportion of low risk patients identified as an accelerated diagnostic protocol (EDACS-ADP). The score was derived from a logistic regression from 1974 patients presenting with acute chest pain for greater than 5 minutes to identify major adverse cardiac events (MACE) for predictive factors as outlined in Table 5. Approximately 42.2% of patients in this cohort were found to be low

risk for MACE with a 99% sensitivity and 49.9% specificity. A validating cohort of 608 patients demonstrated 100% sensitivity with 59.0% specificity for low risk of MACE events (Than et al., 2014). Investigators from Kaiser Permanente in California sought to compare the EDACS with the HEART score for identifying low risk patients (Mark et al., 2018). In a retrospective analysis of 118,822 potential acute ACS patients, the authors compared the EDACS with the HEART for endpoints of MACE at 60 days. Both risk scores were able to predict low risk patients with a NPV of 99.5% but the EDACS score identified more patients as low risk ($P = 0.0001$).

7. Functional testing in the emergency room

Several studies have investigated the implementation of noninvasive imaging to rule out ACS in the low-risk patient population. Functional tests including exercise, echocardiogram or myocardial perfusion imaging (MPI) are the standard for evaluation of patients with intermediate risk chest pain.

There was concern regarding the safety of performing stress testing in patients with acute chest pain. Amsterdam et al. (2002) demonstrated that immediate exercise treadmill testing (ETT) in low-risk patients with normal ECG and negative biomarker was safe. Prior to this study, the recommendation was to perform ETT after 48 hours of presentation.

The major stress imaging methods currently utilized are MPI and echocardiography. The literature demonstrates low event rates after normal MPI in this subset of patients with probable 1% rate of events. MPI can be performed at rest to detect ischemia and can be used to triage patients in the ED. MPI was found to decrease unnecessary admission for patients without acute ischemia, without reducing appropriate hospitalizations (Udelson et al., 2002). Data for stress MPI revealed sensitivity of 87% and specificity of 73% for predicting obstructive CAD. Sensitivity and specificity for stress echocardiography were 86% and 81%, respectively (Klock et al., 2003).

Testing can be performed in the ED or in a nuclear lab. Rest MPI may be performed in the ED with an injection of a nuclear tracer at the time of symptoms. One small study using technetium sestamibi for the evaluation of ischemia in patients with chest pain demonstrated 100% sensitivity in detecting acute ischemia (Varetto et al., 1993).

8. The diagnostic efficiency of CCTA compared to standard of care in the ED

There are many researchers who have sought to assess the diagnostic efficiency of CCTA in the evaluation of acute chest pain, including impact on the length of stay, discharge rates, and cost.

Table 6. Summary of the endpoints from the CT-STAT trial (Goldstein et al., 2011).

Outcomes	CCTA (n = 361)	MPI (n = 338)	P Value
Primary outcome: Diagnostic Efficiency			
Time to diagnosis, Hrs	2.9 (2.1-4.0)	6.2 (4.2-19.0)	< 0.0001
Secondary outcome: ED costs of care and safety			
Total ED costs, $	2,137 (1,660-3,077)	3,458 (2,900-4,297)	< 0.0001
MACE in patients with normal index test	2/268 (0.8%)	1/266 (0.4%)	0.29

The investigators of the ROMICAT II sought to study the efficiency of CCTA for 987 low risk patients for ACS rule out with a length of stay, discharge rate from the ED, MACE at 28 days (Hoffmann et al., 2012). The median length of stay for patients in the CCTA group was 8.6 hours compared to 26.7 hours in the standard-evaluation group ($P < 0.001$). More patients in the CCTA group were discharged directly from the ED than the standard care group without significant difference in MACE events. There was also no significant difference in cost between CCTA and standard group ($P = 0.65$). As outlined in Table 6, the investigators of the CT-STAT trial aimed to assess the efficiency, cost and safety of CCTA compared to MPI in low-risk patients with acute chest pain in the ED. The patients in the CCTA group were associated with a significant decrease in time to diagnosis and ED costs, and there was no difference in MACE events between these two arms (Goldstein et al., 2011).

In addition, Poon et al. (2013) revealed that the length of stay in the ED was 1.55 times higher with the standard evaluation (SE) compared to those who underwent CCTA (OR 1.55; 95% CI: 1.2-2.04; $P < 0.001$). Litt et al. (2012) randomized 1,370 low to-intermediate risk patients with suspected ACS to CCTA or SE groups. The CCTA cohort was associated with an increased rate of discharges from the ED (50% compared to 23%) and reduced the length of stay (18 hours versus 25 hours) compared with the SE group.

The investigators of the CATCH trial (Cardiac CT in the treatment of acute chest pain) assessed long term outcomes by comparing the use of CCTA to standard evaluation with functional testing (such as MPI) in patients presenting with acute chest pain concerning for ACS. The primary endpoints included MACE, unstable angina after discharge, late symptom driven revascularization and readmission for chest pain at median 18 month follow up. Of the 576 patients, primary endpoint occurred in 11% of the CCTA cohort versus 16% in the standard of care group (hazard ratio [HR]: 0.62 [95% CI: 0.40-0.98]; $P = 0.04$). Of note, the CCTA group demonstrated increased number of revascularizations compared to the standard group that could be potentially attributed to accurate diagnosis of obstructive coronary artery disease and changes to medical therapies when non-obstructive disease was discovered (Linde et al., 2015).

In the follow-up CATCH-2 trial, the authors sought to evaluate the clinical efficacy of combining CCTA with adenosine computed tomography perfusion (CTP) imaging compared to CCTA alone (Sorgaard et al., 2018). The primary endpoint included the rate of revascularization in patients referred for invasive coronary angiography (ICA). Of the 300 patients, the primary endpoint occurred in 41 patients or 14% of the CCTA with CTP cohort compared to 89 patients or 30% assigned to CCTA alone ($P < 0.0001$). The total number of revascularizations were significantly lower in the CCTA + CTP combined strategy (7% vs. 14%, respectively $P = 0.0045$). This was one of the first randomized controlled trials to assess the clinical safety and diagnostic efficacy of a combined anatomical and functional test. The authors concluded that the addition of CT perfusion imaging to an already robust anatomical modality substantially reduced the number of patients who underwent for ICA and the total number of revascularizations. After 17 months of median follow up, there was no significant difference in the cardiac deaths, post-index revascularizations, and hospital recidivism due to chest pain, unstable angina and acute myocardial infarction in the two diagnostic strategies. Although this study demonstrates that the addition of CTP may further safely reduce unnecessary ICAs, CTP requires expertise, specific equipment and greater exposure to radiation. Therefore, further investigation is necessary for assessing the safety and cost-effectiveness for the addition of other functional imaging modalities.

Overall these major studies demonstrate that CCTA can be efficient and safe and is associated with a reduction in hard events for this low to intermediate-risk population when employed in triaging acute cardiac chest pain patients. However, these benefits might have to be weighed against the risk of potential radiation exposure, contrast and the presence of a facility that harbors this technology with expert readers.

Of note, the above studies did not involve the use of hs-Tcn assays. Dedic et al. (2016) in the BEACON trial compared the use of hs-Tcn assays in a standard evaluation to utilization of CCTA in patients presenting to the ED for acute chest pain suspicious for ACS. The primary end point was to identify significant CAD requiring revascularization at 30 days. The investigators found CCTA was associated with less outpatient testing and lower costs, but there was no difference between the CCTA and standard care with hs-Tcn assays in identifying patients with significant CAD requiring revascularization within 30 days ($P = 0.40$).

In 2015, a multi-group committee including the American Heart Association (AHA), American College of Cardiology (ACC), and American College of Radiology (ACR) published appropriateness criteria for the utilization of cardiovascular imaging in the ED for patients presenting with acute chest pain (Rybicki et al., 2015). Several clinical scenarios were deemed appropriate for CCTA use. This included patients with equivocal or initial troponin concentration elevation without other findings significant

Table 7. Summary of published multicenter trials on the diagnostic accuracy of cardiac CT for the detection of significant coronary artery stenosis (> 50% luminal narrowing) in the low to intermediate risk population without known coronary artery disease.

Study	n	Sensitivity (%)	NPV (%)	Specificity (%)	PPV (%)
CATSCAN (Garcia et al., 2006). 7 countries, 11 sites	187	94 (89-100)	98 (94-100)	51 (43-59)	28 (19-36)
NIMISCAD (Marano et al., 2009). 20 sites in italy	327	94 (89-97)	91 (85-95)	88 (81-93)	91 (86-95)
ACCURACY (Budoff et al., 2008). 16 US sites	230	95 (85-99)	99 (96-100)	83 (76-88)	64(53-75)
CORE64 (Miller et al., 2008). 7 countries, 9 sites	291	85 (79-90)	83 (75-89)	90 (83-94)	91 (86-95)
Meijboom et al. (2008). 3 sites in Holland	360	99 (98-100)	97 (94-100)	64 (55-73)	86 (82-90)

for ACS as well as serial ECG and troponin concentrations negative or indeterminate for ACS.

Fig. 1 and Fig. 2 depicts the CCTAs and invasive angiogram for two different subsets of patients within the same risk group, but were found to have separate diseases which were accurately identified with CCTA.

9. Anatomical testing with Coronary CT angiography (CCTA): A focus on stable ischemic heart disease and prognosis

9.1 CCTA effectiveness and safety for assessing coronary artery disease in the outpatient setting

Over the past two decades, CCTA initially established its role in evaluation of CAD in the outpatient setting, for which Table 7 highlights major trials (Budoff et al., 2008; Garcia et al., 2006; Marano et al., 2009; Meijboom et al., 2008; Miller et al., 2008). Fig. 3 reveals CCTA that was performed in a patient experiencing atypical chest pain referred from his outpatient cardiologist. He was found to have non-obstructive CAD and the patient was started on appropriate preventive medication. CCTA has shown to be an effective tool for assessing CAD due to its high sensitivity and negative predictive value (NPV) (Budoff et al., 2008; Garcia et al., 2006; Marano et al., 2009; Meijboom et al., 2008; Miller et al., 2008). However, the limitation of CCTA is the low positive predictive value (PPV). Severe coronary calcification can impair the specificity of stenosis detection, but there is no established threshold on non-contrast studies to suggest limited use of contrast-enhanced studies. Other factors that alter the specificity of the modality include inadequate heart rate control, language barrier, following breathing instructions, small vessel size, body mass index (BMI) of the patient, image acquisition protocols, local expertise and inter-reader interpretation variability (Achenbach and Daniel, 2010). Despite these limitations, there is a growing volume of data for CCTA to suggest that this imaging modality has potential functionality in chest pain evaluation for stable ischemic heart disease.

9.2 CCTA and invasive coronary angiograms (ICA)

Moreover, investigators have sought to establish the role of CCTA as a preliminary step for determining the need for invasive angiography. The PROMISE trial assessed 10,000 patients across 193 sites and demonstrated that the rates of invasive angiograms were lower in the cohort where a CCTA strategy was employed (Douglas et al., 2005). The PROMISE trial revealed that there was no difference in cardiac events including all-cause mortality, non-fatal MI, unstable angina and procedural complications.

In addition, the investigators of the SCOTHEART trial demonstrated that though rates of invasive angiography were similar between CCTA and SE groups (409 vs. 401; $P = 0.451$), the CCTA route led to more appropriate use invasive coronary angiograms (ICA). In those assigned to the CCTA, ICA was less likely to demonstrate normal coronary arteries (20 vs. 56; HR: 0.39; $P < 0.001$) but more likely to show obstructive coronary artery disease (283 vs. 230; HR: 1.29; $P = 0.005$) (Williams et al., 2016). As previously discussed, Poon et al. (2013) also found similar results while comparing a CCTA to a SE cohort. The SE group was associated with a 7-fold greater likelihood of invasive coronary angiography without revascularization (OR 7.17; $P < 0.001$). Therefore, growing evidence has shown that the CCTA can be an appropriate modality to assess the need for ICA.

9.3 CCTA associated with decreased myocardial infarction (MI) and increase in secondary prevention

In low to intermediate-risk patients with chest pain undergoing CCTA, there have been several studies that have demonstrated an associated reduced incidence of MI as well as an increase in secondary preventive therapies such as aspirin and statins. As briefly mentioned, the SCOT-HEART trial was a multicenter study assessing 4,146 patients with stable chest pain in the outpatient setting (Newby et al., 2015). The investigators compared the use of CCTA to standard evaluation (SE) for changes in preventative therapy and clinical outcomes. At one year, the CCTA cohort was associated with a significantly increased initiation of preventive therapies (293 vs. 84; OR: 4.12 [95% CI: 3.19 to 5.33]; $P < 0.001$). Investigators also assessed outcomes based on the introduction of preventative therapy. At events greater than 50 days after initiation of therapy, the fatal and nonfatal MI was approximately half of the patients allocated to CCTA compared with those assigned to SE (17 vs. 34; HR: 0.50; $P = 0.020$). At 5 years, these results were resonated as investigators found a significant reduction in rates of myocardial infarctions in the CCTA cohort (Newby et al., 2018). Recently, Adamson et al. (2019) reported a post hoc analysis on the mechanism and consistency of the 5-year reduction of their primary endpoint. They demonstrated a consistent effect on events across all demographics in this trial, including presentation and risk factor profile. They further confirmed that due to greater diagnostic power of CCTA, there was improved risk stratification and increased use of pharmacological preventive therapies in the CCTA group. Therefore, it was made largely plausible that the observed reduction in death from coronary heart disease or nonfatal myocardial infarction was due to targeted initiation of preventive medical therapies.

In a recent meta-analysis by Foy et al. (2017), the investigators systematically reviewed 13 randomized control trials from 2001 to
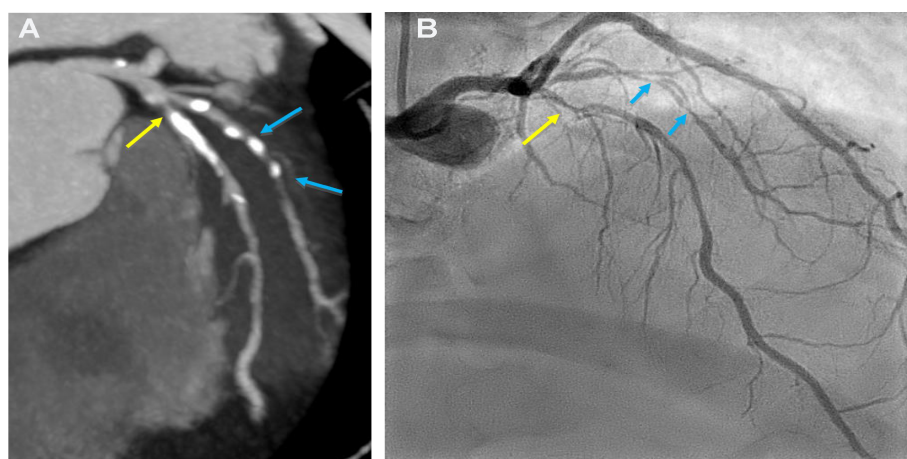
Figure 1. 60 year old female with history of hypertension without known coronary artery disease, presented to the ED for acute chest pain relieved by nitroglycerin. The initial ECG and troponin were normal and underwent a CCTA. Her calcium score 403. Panel A shows a heavily calcified left anterior descending artery (LAD) with a discrete area of stenosis due to high risk non-calcific plaque immediately proximal to the heavily calcified area (Yellow arrow). Two sequential lesions with severe stenosis were noted in the first diagonal branch (blue arrow) with similar plaque characteristics as noted in the LAD. Panel B demonstrates the invasive angiogram that confirmed severe stenosis in the proximal LAD (Yellow arrow) and D1 (blue arrow) requiring drug eluding stents.
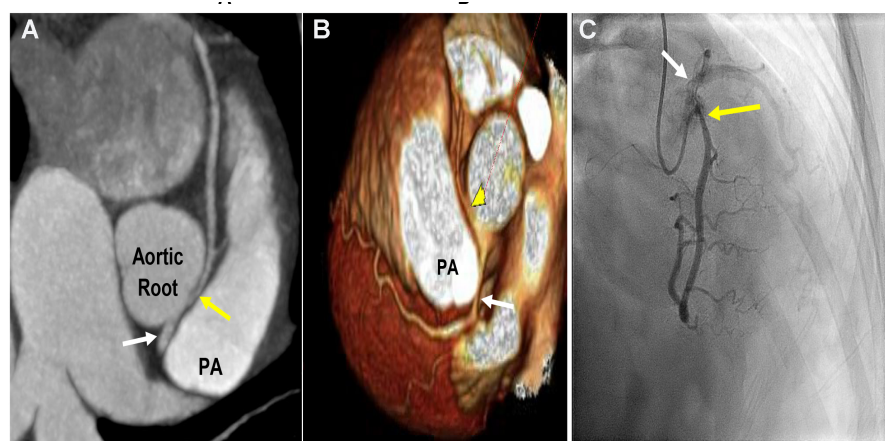

Figure 2. A 35-year-old female with a strong family history of coronary artery disease presented to the ED with exertional chest pain and shortness of breath. The patient's exercise nuclear perfusion stress imaging did not reveal hemodynamic compromise or perfusion imaging defects. (A) CCTA with maximal intensity projection and (B) 3D reconstruction at the level of the aortic root demonstrating an acute anomalous origin of the right coronary artery (RCA, yellow arrows and arrow head) from the left coronary cusp (LCC), with a supra-pulmonic origin traveling between the pulmonary artery (PA) and ascending aorta, indicating a malignant course. (C) Coronary angiogram revealing a narrowing at the ostium of the RCA (Yellow arrow) without obstructive plaque confirming the acute angle take off the anomalous RCA. White arrows demonstrate the appropriate origin of the left main coronary artery from the LCC (white arrows). The patient was discharged on a calcium channel blocker for symptomatic and heart rate control.

2016 for the comparison of the clinical efficacy of CCTA to functional testing in patients with suspected CAD. There was no significant difference between CCTA and functional stress testing in all-cause mortality (ratio [RR], 0.93; 95% CI, 0.71-1.21) or cardiac hospitalization (RR, 0.98; 95% CI, 0.79-1.21). However, CCTA was associated with a reduced incidence of MI (RR, 0.71; 95% CI, 0.53-0.96). The CCTA groups were also more likely to have a new diagnosis of CAD as well as increased initiation of preventative therapies such as aspirin or statins. Of note, the patients undergoing CCTA were significantly more likely to undergo ICA (RR, 1.33; 95% CI, 1.12-1.59) and revascularization (RR, 1.86; 95% CI, 1.43-2.43). The increased rates of ICA and revascularization in the CCTA groups are likely due to the ability of the modality to detect coronary calcification, both obstructive and non-obstructive plaque. With increased rates of detection, this also likely led to an increase in prescriptions for secondary preventative therapies like aspirin and statins. As shown by the SCOT-HEART trial, the CCTA group was found to have reduced incidence of fatal and non-fatal MI after initiation of preventative therapy at five years (Newby et al., 2015, 2018).

In November 2016, the National Institute for Health and Care Excellence (NICE) updated its clinical guideline on the evaluation
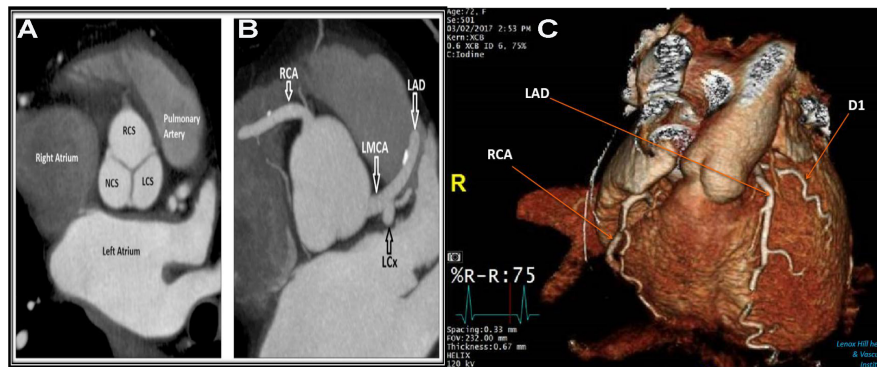
Figure 3. 58 year old male with atypical chest pain sent in from his outpatient cardiologist office that revealed a minimally elevated calcium score and non-obstructive disease on the coronary CCTA. (A) Maximal intensity projection of the aortic root at the level of the sinuses of valsalva. (B) The image illustrates the origins of the coronary arteries. RCS: Right coronary sinus; NCS: Non-coronary sinus; LCS: left coronary sinus; RCA: Right coronary artery; LMCA: Left main coronary artery; LAD: Left anterior descending artery; LCx: Left circumflex artery. (C) The image depicts 3D rendered volume reconstruction of the heart revealing the LAD, LAD and D1.
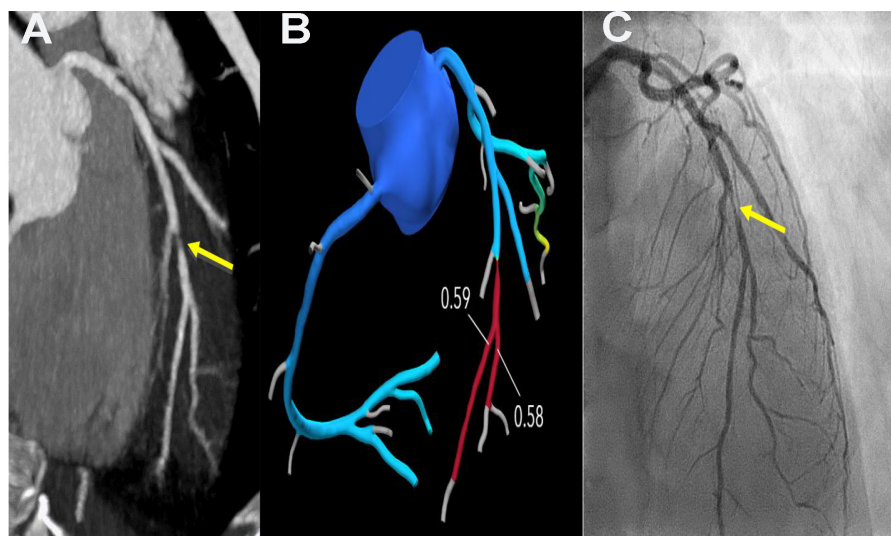

Figure 4. 61 year old male presenting with atypical chest pain for an outpatient CCTA. (A) Image reveals a discrete lesion of severe mid LAD stenosis due to high risk non-calcified plaque (Yellow arrow). (B) There was a concern that motion artifact was overestimating the degree of stenosis. FFR_{CT} served as an adjudicator and revealed a grossly positive result (0.59). (C) Severe stenosis was confirmed on invasive angiogram with a positive iFFR (< 0.80) requiring a drug eluding stent.

of patients with recent onset of chest pain (National Institute for Health and Clinical Excellence, 2016). These British guidelines recommend CCTA as the initial test of choice for all patients without known (CAD) who present with atypical and typical angina as well as patients with nonanginal chest pain who have an abnormal resting electrocardiogram.

10. Non-invasive fraction flow reserve derived from CT (FFR_{CT})

10.1 What is FFR_{CT} ?

Fractional flow reserve is the measurement of pressure differences to calculate maximal blood flow through a diseased coronary artery to provide physiologic information for ischemia and anatomic assessment that has traditionally been used in ICA. Non-invasive fractional flow reserve, or FFR_{CT}, is a novel method that serves as an adjutant for CCTA that adds a functional component

to the anatomical test. The standard data obtained by the CCTA is used for computation without need for changes in protocols, additional radiation exposure or use of medications. Computer programmed algorithms use the principles of fluid dynamics to calculate flow and pressure within the coronary vessel for quantifying lesion-specific FFR_{CT} values (Koo et al., 2011; Pijls et al., 1993).

In recent years, FFR_{CT} has shown to complement the anatomical power of CCTA with its functional component. Similar to CCTA, the initial evidence for FFR_{CT} was tested in the outpatient setting. The emerging data has shown that FFR_{CT} when compared to standard of care is an accurate, reliable safe method for enhanced detection of CAD and ischemia. The DISCOVER-FLOW trial evaluated an outpatient population undergoing CCTA and ICA in order to compare the FFR_{CT} to CCTA. The trial demonstrated high sensitivity (84.3%), specificity (87.9%) and negative predictive value (92.2%) that support its role for detecting and rul-

ing out cardiac ischemia (Koo et al., 2011). As demonstrated in Fig. 4, FFR$_{CT}$ can help confirm a severe stenosis with correlation on invasive angiogram and invasive FFR (iFFR).

In the PLATFORM trial, researchers assessed 581 patients with new, stable chest pain over a one-year period to compare the standard evaluation to CCTA with FFR$_{CT}$ (Douglas et al., 2016). The CCTA with FFR$_{CT}$ cohort was found to have no significant difference in MACE events. The FFR$_{CT}$ group was also found to have 33% lower costs than those in the SE group ($8,127 FFR$_{CT}$ vs $12,145 usual care, $P = 0.0001$).

Patel et al. (2019) recently published 1-year outcomes from the ADVANCE registry. The ADVANCE registry was a prospective, multicenter international registry of patients that were investigated suspected for CAD with CCTA and the addition of FFR$_{CT}$. Investigators found that patients with normal FFR$_{CT}$ had significantly lower rates of cardiovascular death or MI than those with an abnormal FFR$_{CT}$ ($P = 0.01$). These findings are consistent with the PLATFORM trial and the work of Norgaard et al. (2014) demonstrating lower rates of cardiac events in patients with a negative FFR$_{CT}$.

10.2 FFR$_{CT}$ in the ED

A sub study from the ROMICAT II trial assessed 68 of their patients suspected for ACS with stenosis > 50% on CCTA with the addition of FFR$_{CT}$ (Ferencik et al., 2016). Patients with a positive FFR$_{CT}$ score (< 0.80) were associated with higher grade stenosis and high risk plaque on CCTA (OR 3.91, 95% CI 1.55-9.85, $P = 0.004$). These patients were also associated with a higher risk of ACS (OR 4.03, CI 1.56-10.36) and need for revascularization (RR 3.5, 95% 1.12-10.96). These preliminary results were the first to report the correlation of FFR$_{CT}$ with high-risk plaque characterization, interventions and clinical outcomes in patients with acute chest pain (Ferencik et al., 2016).

Chinnaiyan et al. (2019) also sought to investigate the clinical utility of CT-derived fractional flow reserve FFR$_{CT}$ in the ED. The investigators sought to examine the safety, feasibility, costs and clinical outcomes associated with FFR$_{CT}$ in acute chest patients without known CAD using the CCTA based strategy. There was no statistical difference in MACE at 90 days (4.3% vs 2.7%; $P = 0.310$ and costs ($8,582 vs. $8,048; $P = 0.550$). when comparing the use of FFR$_{CT}$ to CCTA alone. Patients with negative FFR$_{CT}$ (< 0.8) had a statistically higher frequency of non-obstructive findings on ICA than positive FFR$_{CT}$ (> 0.8) and CCTA ($P = 0.001$). Therefore, the addition of FFR$_{CT}$ can potentially aid in determining need for revascularization in patients without known CAD presenting to the ED with acute chest pain.

Overall, the mounting evidence supports that functional component added by FFR$_{CT}$ to CCTA aspires to be the potential gatekeeper to the cardiac catheterization lab for stable ischemic heart disease and in the ER setting where patients are being triaged for ACS.

11. Summary

For patients presenting to the emergency room with acute chest pain, there are a number of non-invasive modalities for the initial triage and work up for ACS. As previously outlined, the quality of chest pain is less predictive of ACS than previously thought. Diaphoresis on exam was one of the significant features for pre-

dicting ACS, and chest pain similar to past MI was not predictive for ACS (Body et al., 2010). In addition, traditional cardiac risk factors have been used for assessing the likelihood of acute cardiac ischemia, but no single cardiac risk factor has been identified to make ACS more likely. High sensitivity cardiac troponin (hs-cTn) concentrations can be detected at an earlier time point of an evolving MI, which can improve the evaluation of patients with acute chest pain (Thygesen et al., 2018). However, the increased sensitivity results in an increase in non-Type I MI causing hs-cTn concentration elevation. Despite this challenge, European guidelines have started to incorporate hs-cTn assays in the ACS work up (Roffi et al., 2016).

Risk stratification scoring tools have been developed to attempt to assess the risk for ACS in patients with chest pain. The GRACE and TIMI risk scores are commonly used risk scores to determine aggressive therapy for high-risk ACS patients (Antman et al., 2000, 1999; Chase et al., 2006; Granger et al., 2003). Data suggests that the HEART and Heart pathway are superior predictive tools for evaluating undifferentiated chest pain in low to intermediate risk populations (Backus et al., 2013, 2010; Mahler et al., 2015; Six et al., 2008).

Anatomical testing such as CCTA has demonstrated high sensitivity in evaluating stable ischemic ischemic heart disease as well as acute chest pain patients in the ED (Budoff et al., 2008; Garcia et al., 2006; Marano et al., 2009; Meijboom et al., 2008; Miller et al., 2008). The use of CCTA has shown to reduce length of stay, costs, and increase the use of preventative therapies (Foy et al., 2017; Goldstein et al., 2011; Hoffmann et al., 2012; Newby et al., 2015), which have correlated a reduction in myocardial infarctions (MI) and death from non-fatal MIs. The addition of non-invasive fractional flow reserve, or FFR$_{CT}$, is a novel technological advancement that uses computational fluid dynamics to add functional data. This has improved diagnostic accuracy for the detection of flow limiting coronary artery stenosis and appropriate selection of patients to undergo invasive coronary angiograms (Chinnaiyan et al., 2019).

Authors' Contributions

EA contributed to the conception and drafting the manuscript. ES contributed to drafting and revision of manuscript. ZK contributed to drafting and revision of manuscript. MP and NC contributed to revision of manuscript.

Acknowledgement

Conflict of Interest

Abbreviations

ACS: acute coronary syndrome; ACC: American College of Cardiology; ACR: American College of Radiology; AHA: American Heart Association; AMI: acute myocardial infarction; AUC: area under the curve; BMI: Body Mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CCTA:

coronary computed tomography angiography; CI: confidence interval; CP: chest pain; CT: computed tomography; CTP: computed tomography perfusion; DF: Diamond and Forrester; ED: emergency department; EDACS: Emergency Department Assessment of Chest pain Score; EDACS-ADP: Emergency Department Assessment of Chest pain Score-Accelerated; Diagnostic Protocol; EKG: electrocardiogram; ESC: European Society of Cardiology; ETT: exercise treadmill testing; FFRCT: non-invasive fractional flow reserve with CCTA; HR: hazard ratio; Hs-cTn: high-sensitivity cardiac troponin; ICA: invasive coronary angiogram; MACE: major adverse cardiac events; MI: myocardial infarction; MPI: myocardial perfusion imaging; NICE: National Institute for Health and Excellence; OR: odds ratio; PCI: percutaneous coronary intervention; PPV: Positive predictive value; SE: standard evaluation; RR: relative risk; WHF: World Heart Federation.

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