Non–ST-Segment Elevation Acute Coronary Syndromes
Targeted Imaging to Refine Upstream Risk Stratification

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Non–ST-segment elevation (NSTE) acute coronary syndromes (ACS), encompassing NSTE myocardial infarction (NSTEMI) and unstable angina, lack the declarative electrocardiographic findings that readily identify patients with STEMI, yet comprise >70% of all ACS.1–3 Unlike STEMI patients who receive uniform treatment to restore flow in an occluded artery, NSTE-ACS patients (who often present first to an emergency department [ED]) have varying degrees of coronary obstruction, undergo more heterogeneous management, and have worse long-term outcomes.2, 4 Despite guidelines, there remains inconsistent use of routinely advocated medical therapies and invasive evaluation5 that reflect uncertainty in initial evaluation. Greater age and comorbidities plus varied coronary artery disease (CAD) severity further complicate decision making. In addition, although cardiogenic shock, heart failure, and arrhythmias may be less than in STEMI, NSTE-ACS patients suffer more recurrent events and worse long-term outcomes.1

As our understanding of NSTE-ACS pathophysiology has grown, several noninvasive imaging techniques have emerged that offer high-resolution characterization of relevant markers of pathophysiology such as coronary atherosclerotic plaque and salvageable myocardium. Incorporating such techniques into evaluating the ED patient with suspected or established NSTE-ACS promises improved outcomes by demonstrating patient-specific, mechanistically based targets for therapy. This review summarizes NSTE-ACS, current imaging approaches, and emerging imaging advances to improve diagnosis, treatment, and outcomes.

Pathophysiology
NSTE-ACS is most commonly caused by disruption of a coronary artery atherosclerotic plaque, with myocardial ischemia and injury often resulting from partial or intermittent occlusion along the ischemic cascade.6 Other causes beyond the focus of this work include embolism and revascularization.7 Events in the coronary and downstream myocyte together offer targets for imaging in NSTE-ACS.

Events in the Coronary Artery
Coronary plaque formation has been well underway before NSTE-ACS presentation.8 The plaque prone to cause ACS has a thin fibrous cap, large lipid pool, and is susceptible to disruption via inflammation, metalloproteinases, and collagenases (Figure 1). Intraplaque hemorrhage, plaque neovascularization, and outward (positive) vessel wall remodeling further identify the vulnerable plaque. After a triggering event, a superimposed thrombus forms upon contact between luminal blood and the plaque’s highly thrombogenic lipid core; in 20% to 40% of ACS, coronary thrombosis occurs with only superficial plaque erosion (Figure 2; online-only Data Supplement Movies I–IV) rather than plaque rupture. Myocyte necrosis ensues via either subtotal occlusion or transient episodes of flow reduction (Figure 1). In unstable angina, subtotal occlusion and transient ischemia stop short of myocardial necrosis. Embolization of plaque and thrombotic materials may occlude the downstream microvasculature.9 External compression by edematous tissue, in situ thrombosis, vasospasm, leukostasis, and reperfusion injury exacerbate microvascular obstruction and myocyte necrosis, particularly after mechanical reperfusion.

Events in the Myocardium
Myocyte death may occur via oncotic or, to a lesser extent, apoptotic pathways.10, 11 An intact membrane infers potential for myocyte recovery; because water balance dictates many processes that impact membrane integrity, attention to edema is particularly relevant in recognizing at-risk but salvageable myocardium (Figure 1). Impaired oxygen delivery arrests oxidative phosphorylation and blunts energy production required to prevent intracellular sodium and chloride (and, therefore, water) accumulation. Lactate-induced acidosis releases water molecules from proteins, increasing the intracellular fraction of unbound versus bound water. Increased membrane permeability ultimately leads to physical disruption of the sarcolemma and cell death.

Timely reperfusion can salvage myocardium, yet reperfusion itself may contribute to cardiomyocyte death.10 As post-ischemic blood flow is restored, hyperosmotic extracellular...
fluid is replaced by normo-osmotic blood, creating an osmotic gradient favoring the movement of water into myocytes. Fragile sarcolemma resulting from energy-starved processes suffers mechanical stress-induced damage, and cells undergo necrosis. Reperfusion may also produce myocyte death via inflammation, oxidation, apoptosis, and autophagy.

Current Diagnosis and Risk Stratification in NSTE-ACS

Diagnosis

Historical descriptors such as substernal chest pain or recurrent angina equivalents in patients with known CAD facilitate diagnosis, and high-risk physical examination markers are well established. ACS mimics such as pericarditis, myocarditis, or noncardiac causes warrant consideration. The ECG in NSTE-ACS may show ST-segment depression, T-wave flattening or inversion, or even transient ST-segment elevation; variation with symptoms favors an ACS diagnosis. Biomarkers such as cardiac troponins are crucial in recognizing myocardial injury and differentiating NSTEMI from unstable angina. Emerging biomarkers may better rule-in or rule-out ACS; circulating biomarkers alone, however, cannot localize salvageable, at-risk myocardium or distinguish ACS mimics.

Risk Stratification

Initial risk stratification is important in NSTE-ACS because the benefit of intensive therapies varies with risk. Currently available risk stratification schemes (Table 1) offer good predictive value for adverse cardiac events at 30 days and 1 year. However, risk scores do not identify targets to lower risk, underscoring the difference between risk markers and risk factors. Imaging may not only improve risk stratification but also treatment selection by directly visualizing treatable targets in higher-risk individuals.

Current Imaging Approaches in NSTE-ACS

Myocardial Imaging: Contractile Function and Perfusion

Left ventricular ejection fraction is a critical parameter in conservative management pathways; echocardiography, nuclear...
scintigraphy, or invasive ventriculography most commonly provides ejection fraction in NSTE-ACS. More refined detection of regional dysfunction is afforded by strain measurement; Eck et al reported that strain echocardiography was able to predict acute coronary occlusion with a sensitivity and specificity of 85% and 75%, respectively, in NSTE-ACS patients without prior MI. In patients presenting to the ED with chest pain and no ST-segment elevation, visually assessed regional wall motion abnormality using contrast echocardiography better predicted adverse effects versus traditional clinical markers, more so than contrast echocardiography–derived myocardial perfusion. In such patients, normal contrast echocardiography–based wall motion may have incremental negative predictive value over low Thrombolysis in Myocardial Infarction (TIMI) risk score.

Myocardial perfusion imaging (MPI) is more commonly performed with nuclear techniques such as single-photon emission computed tomography (SPECT) MPI. The presence versus absence of perfusion defects may be useful to distinguish high-risk from low-risk ED chest pain patients. SPECT may be constrained by poor spatial resolution, particularly for the NSTE-ACS patient with subendocardial ischemia. Prior CAD may make it difficult to know whether a resting perfusion SPECT defect is because of prior infarction or represents a new region of at-risk myocardium. Use of positron emission tomography and emerging SPECT tracers may further refine recognition of myocardium at risk in ACS patients, and newer SPECT techniques have considerably shortened acquisition times.

One such tracer is β-methyl-p-[123I]-iodophenyl-penta-decanoic acid, a fatty acid analog that demonstrates reduced uptake in ischemic myocytes and indicates a cellular shift from fatty acid metabolism to glucose metabolism. In 448 ED chest pain patients without ST-segment elevation, Kontos et al showed that β-methyl-p-[123I]-iodophenyl-pentadecanoic acid imaging was more sensitive (42.9% versus 73.0%) and more specific (60.9% versus 63.2%) in diagnosing ACS. Ischemic memory helped to maintain sensitivity if imaging was performed 12 to 30 hours after symptom resolution versus within 12 hours of such (68.6% versus 77.1%).

MPI can also be performed with cardiac magnetic resonance (CMR), detecting patients with coronary artery stenoses of ≥70% with similar specificity and better sensitivity versus SPECT in the recently published landmark Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) trial. Another recently published multicenter, multivendor study showed superior sensitivity and inferior specificity of perfusion CMR to detect CAD versus SPECT.

Kwong et al demonstrated 84% sensitivity and 85% specificity for ACS using CMR without stress in 161 patients presenting to the ED with chest pain and no ST-segment elevation. CMR was more sensitive than ECG, troponin-I, and Thrombolysis in MI scores in detecting ACS. Using adenosine stress perfusion CMR, Plein et al showed even more accurate identification of NSTE-ACS patients requiring revascularization (sensitivity and specificity of 97% and 83%, respectively).

Late gadolinium-enhancement (LGE) CMR is an extensively validated technique to visualize in vivo irreversibly injured myocardium. Tissue characterization also assists in distinguishing true NSTE-ACS from ACS mimics: ACS-related hyperenhancement is subendocardial, LGE-positivity in myocarditis shows an epicardial or midwall distribution, and LGE-positivity in takotsubo cardiomyopathy is typically minimal.

### Coronary Imaging

Noncontrast CT-based coronary artery calcium scoring reflects coronary artery plaque burden, demonstrating a positive predictive value of ≥100% for atheromatous coronary plaque. Laudon et al found that coronary artery calcium ≤36 among patients who presented to the ED with chest pain strongly predicted noncardiogenic chest pain, whereas coronary artery calcium >36 predicted cardiogenic chest pain as defined by exercise treadmill testing. SPECT MPI, stress echocardiography, or invasive angiography. It should be noted that the negative predictive value of coronary artery calcium varies by the population in which it is used: 38% of Asian chest pain patients presenting to an ED who subsequently developed ACS had a calcium score of 0.

Coronary CT angiography (CCTA) has recently emerged as a reliable noninvasive modality for assessing epicardial luminal stenosis, with multiple studies demonstrating high diagnostic performance compared with invasive angiographic measures (Figure 3; online-only Data Supplement Movies V–VII). In ED patients with acute chest pain, negative initial troponin, and ECG without diagnostic changes of ischemia, Hoffmann et al reported that CCTA that showed no evident coronary plaque had 100% negative predictive value for ACS. Positive predictive value for ACS of coronary stenosis by CCTA was considerably lower (35%), particularly in patients aged >65 years.

In a smaller ED study of biomarker-negative chest pain patients with not only nonischemic presenting ECG but also normal or nondiagnostic treadmill stress ECG, CCTA fared better: positive and negative predictive values for ACS were 87% and 100%, respectively. And in a landmark multicenter trial, Litt et al showed that low-to-intermediate-risk ACS patients randomized to undergo CCTA had...
a higher rate of discharge from the ED, shorter length of stay, and higher rate of coronary disease detection versus those assigned to traditional care. Similar results of the Rule Out Myocardial Infarction Using Computer Assisted Tomography II (ROMICAT II) trial are anticipated.

### Emerging Imaging Approaches to NSTE-ACS

#### CT Perfusion

Early data suggest feasibility of CT perfusion at both rest and stress versus SPECT or CMR (Table 2). Rest findings alone can be derived at the time of CCTA. Ongoing multicenter studies (clinicaltrials.gov NCT00934037 and NCT01334918) will assess the robustness of early single-center data.

#### Plaque Characterization

In addition to stenosis assessment, CCTA provides noninvasive visualization of coronary artery plaque and wall characteristics, in a manner similar to invasive atherosclerosis imaging methods. Limited studies have investigated the clinical use of CCTA to detail these atherosclerotic plaque characteristics (APCs; Figure 4) as predictive metrics to identify individuals at heightened risk for unheralded or recurrent NSTE-ACS. APCs examined by CCTA may include plaque burden, plaque composition including low-attenuation plaques (consistent with lipid-rich necrotic cores) and spotty calcifications, positive remodeling, and other features including ulcer-like enhancement spaces within plaque (ie, napkin-ring sign). In the largest of these studies, Motoyama et al demonstrated predictive value of APCs for future ACS, focusing on low-attenuation plaques with Hounsfield unit densities <30 and positive remodeling with remodeling indices >1.10. Importantly, all events observed in the present study were for patients with <75% stenosis. Similarly, Kristensen et al who performed CCTA at the time of NSTEMI showed that baseline volume of nonobstructive plaque, especially noncalcified plaque, predicted recurrent adverse events. Although constrained by a small number of events, both studies suggest a potential prognostic role for CCTA-based APC assessment that may identify plaques that subsequently cause ACS.

Recently, Ozaki et al called into question the ability of CCTA to distinguish intact fibrous cap plaques from culprit lesions in a mixed group of ACS and stable angina patients who additionally underwent optical coherence tomography, angioscopy, and intravascular ultrasound. Although low-attenuation plaques and positive remodeling by CCTA occurred more commonly in ACS with ruptured versus intact fibrous cap, neither distinguished between intact fibrous cap ACS and stable lesions. Noting that a significant proportion of NSTE-ACS may result from erosion of thrombogenic plaques with intact fibrous cap, further work is needed for noninvasive techniques to be able to demonstrate such micron-scale characteristics.

The limits of agreement for APCs by CCTA versus intravascular ultrasound, including plaque volume by composition, are wide and can range up to 26% in our own laboratory’s experience. Similarly, although plaques with

| Table 2. Studies Comparing Stress CTP to Other Modalities |
|----------------------------------|-----------------|-----------------|-----------------|
| Author                          | N   | Comparison                | Major Findings            |
| George et al56                  | 40  | CTP vs SPECT               | Sensitivity/specificity: 70%/51% |
| Blankstein et al55              | 34  | (1) CTP vs ICA; (2) CTP vs SPECT | Sensitivity/specificity: (1) 92%/67%; (2) 84/80% |
| Okada et al54                   | 47  | CTP vs SPECT summed stress score | Agreement in 107/141; correlation r=0.56 |
| Tamarappoo et al53              | 30  | Agreement for perfusion deficit | Good agreement; κ=0.71 |
| Ho et al52                      | 35  | Dynamic CTP vs SPECT       | Sensitivity/specificity: 83%/78% |
| Ko et al51                      | 41  | CTP vs CMR                 | Sensitivity/specificity: 89%/78% |

CTP indicates computed tomography perfusion; SPECT, single-photon emission computed tomography; ICA, invasive coronary angiography; and CMR, cardiac magnetic resonance.
large (>10%) intraplaque necrotic cores demonstrate lower Hounsfield unit values, a wide range of Hounsfield unit values in necrotic core overlaps with those of nonnecrotic core fibrous plaque components. Thus, APCs by CCTA may represent a novel approach for enhanced risk stratification, but still required are (1) confirmation of the prognostic relevance of APCs in larger prospective studies, (2) determination of the independent and incremental value of APCs beyond stenosis severity alone, and (3) therapeutic outcome studies that stratify treatment approaches based on CCTA-based APCs.

One other exciting CCTA development that offers a physiological assessment of anatomic stenosis is the noninvasive estimation of fractional flow reserve (FFR) via computational fluid dynamics. FFR, commonly regarded as the reference standard for diagnosis of lesion-specific ischemia, has been demonstrated to improve event-free survival for stable patients with multivessel disease. FFR derived from CT is a noninvasive method that does not require any additional imaging, medication administration, or radiation exposure. Encouraging results from a recent prospective, multicenter study of FFR derived from CT versus invasive FFR behoove its evaluation in the broader ED chest pain population.

Myocardial Imaging: Necrosis and Edema

Ideally, noninvasive myocardial imaging in NSTE-ACS patients would identify not only necrotic myocardium (eg, using standard LGE-CMR) but also at-risk, not yet irreversibly injured muscle. Imaging myocardial water may provide this information based on classic preclinical studies that identified the edematous myocyte as potentially salvageable. Given its sensitivity to not only total change in myocardial water content but also changes in protein binding of water, T2-CMR holds significant appeal (Figure 5; online-only Data Supplement Movies VIII and IX).
Combining LGE and T2 may enhance our understanding of the time course of myocardial changes in ACS. Dall’Armellina et al67 performed 4 serial CMR examinations that included T2-weighted imaging in MI patients, showing that edema persists for at least 1 week post-MI and allows for retrospective identification of this signature. Abdel-Aty et al68 showed in a landmark study that this combination could distinguish old from acute infarction. Cury et al69 showed the use of T2-CMR in accurate detection of ACS in ED chest pain patients; a CMR protocol that included T2-weighted imaging, perfusion, cine, and LGE acquisitions improved the c-statistic over traditional risk assessment from 0.695 to 0.958 (P<0.0001). Berry et al70 performed bright-blood T2-weighted CMR in acute MI patients and showed excellent delineation of myocardial salvage in comparison with traditional measures of area at risk. Our group has evaluated the potential use of T2-weighted imaging, perfusion, cine, and LGE acquisitions improved the c-statistic over traditional risk assessment from 0.695 to 0.958 (P<0.0001). Berry et al70 performed bright-blood T2-weighted CMR in acute MI patients and showed excellent delineation of myocardial salvage in comparison with traditional measures of area at risk. Our group has evaluated the potential use of T2-CMR in upstream risk stratification, showing that the presence of edema had incremental value over clinical predictors such as Thrombolysis in MI risk score and troponin-I level to identify NSTE-ACS patients who subsequently require coronary revascularization.71 T2 mapping offers a further advance in quantifying myocardial edema and overcoming limitations of traditional T2-weighted imaging72, 71 (Figure 6).

Conclusions and Future Directions

Cost Considerations

The cost-effectiveness of imaging remains an important factor in determining its use in the ED for NSTE-ACS patients. Udelson et al71 in a randomized trial showed lower hospitalization rates and increased discharge home using SPECT MPI to rule out cardiac ischemia in patients presenting to the ED with chest pain and nondiagnostic ECG. Similarly, Stowers et al72 showed lower treatment costs and length of stay in ED patients with chest pain and nondiagnostic ECG by incorporating SPECT.

Goldstein et al73 randomized ED chest pain patients to CCTA or standard evaluation and further prescribed to the CCTA group (1) discharge of patients with minimal disease, (2) catheterization for those with stenosis >70%, and (3) stress testing for individuals with intermediate lesions or nondiagnostic scans. Although the diagnostic accuracy was similar in both groups, the CCTA cohort had shorter median time to definitive diagnosis (3.4 hours versus 15.0 hours) and reduced costs of care ($1586 versus $1872).

Miller et al77 recently demonstrated in a randomized trial of intermediate-risk ED patients that stress CMR delivered in an observation unit offers cost savings during the index visit and incurred lower total costs over the ensuing year ($3101 versus $4742) without an increase in adverse cardiac events. The same group subsequently showed that CMR does not afford such savings in low-risk ED patients,78 underscoring the need for careful clinical evaluation before implementing a testing strategy.

Cost data from retrospective studies caution against overuse of advanced imaging.79, 80 Implementation logistics also require consideration: access to the most appropriate technology and expertise is required at the right time for the right patient. Eliminating barriers as was done with deployment of coronary angiography in STEMI may be needed for noninvasive imaging to deliver on the promise of reducing uncertainty in NSTE-ACS diagnosis and management.

Molecular Imaging

Although clinical trials of molecular imaging in NSTE-ACS ED patients have not yet been performed, the appeal of targeting relevant cellular and molecular pathophysiological processes may be realized with increased availability of such imaging approaches. With imaging agents that target specific molecules, cellular structures and processes can be probed at a level not possible with current imaging techniques.

Selectins, integrins, and adhesion molecules may be suitable vascular imaging targets, coupling modalities like CMR with positron emission tomography or SPECT with CTA. Similarly, plaque imaging may target species of destabilization81 or metabolism.82 Proton-based CMR, with direct
visualization of hydrogen in various forms may be used to track water molecules in the pathophysiological changes of ischemia-reperfusion injury. Hofstra et al84 used Tc-99m-labeled annexin to detect apoptotic myocytes in patients post-MI. Annexin can also be tagged with CMR to detect apoptotic myocytes in patients.85 Finally, magnetic resonance spectroscopy techniques to visualize subcellular energetics85 and even acidosis86 are exciting advances to refine preclinical understanding and to develop novel therapeutic strategies.

However, even with useful affinity ligands as imaging agents, molecular imaging still faces many challenges before it can be considered a useful tool in the ED. Pharmacokinetic concerns include target molecule abundance, in vivo specificity, binding stability, and target-to-background ratios. Limited spatial and temporal resolution, even with state-of-the-art technologies, may not be able to consistently image small-caliber, rapidly moving coronary arteries.

Closing Remarks
Patients presenting with chest pain may currently be assigned to intensive medical therapy alone despite having, for instance, obstructive single vessel disease.87 Practitioners are all too familiar with instances of ACS after institution of medical management for stable CAD; these challenge the notions that current diagnostic modalities are sufficiently predictive and that current therapies are sufficiently preventive (Figure 7). And despite widespread use of high-sensitivity serum biomarkers, risk scores, and early invasive cardiac catheterization, only 55% of patients with NSTE-ACS have disease requiring percutaneous coronary intervention or bypass surgery, whereas the remainder receive medical therapy alone because of either extensive CAD or nonobstructive CAD, despite laboratory evidence of myocardial necrosis.88, 89 Patterns of care for patients with NSTE-ACS have been described as paradoxical: only ≈30% of high-risk patients are managed with an early invasive strategy compared with 75% of low-risk patients.90, 91 Increasing recognition of bleeding risk with aggressive use of antiplatelet and anticoagulant therapies underscores the need for better selection of patients likely to benefit from early invasive management.92

Noninvasive imaging targeting the underlying coronary and myocardial events that lead to adverse clinical sequelae can help reduce uncertainties in initial diagnosis and treatment. Recent advances in noninvasive plaque and flow assessment with CT and myocardium at-risk assessment with CMR warrant further prospective evaluation of their ability to (1) improve selection of patients for more costly, higher-risk invasive, and adjuvant medical therapies; (2) reduce morbidity and mortality via timely rescue of salvageable myocardium; and (3) improve distinction of NSTE-ACS from ACS mimics that require distinct treatments.

Although techniques for noninvasive detection of high-risk features have developed rapidly, trials addressing management of such high-risk features are now needed to deliver on the promise of predicting, preventing, and reducing the economic and societal burden of NSTE-ACS. Delivery on this promise will also require improved therapeutic options, for example, the noncritical coronary stenosis due to plaque with adverse features supplying at-risk but viable myocardium. Heterogeneous care that delivers inconsistent outcomes should sufficiently motivate the imaging community, clinicians, and scientists to develop better solutions for these patients.

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References


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