A cute chest pain presents a clinical challenge because of its prevalence, broad differential, and risk of serious morbidity and mortality. The diagnosis is complicated by its spectrum of presentations, including the most severe ST-elevation myocardial infarction (MI) and unstable angina (UA), where biomarker evidence of myocardial damage is lacking. Event prediction remains difficult even if coronary atherosclerotic disease (CAD) can be demonstrated, as the majority of plaque ruptures are—perhaps surprisingly—from a clinically silent, with acute coronary syndromes (ACS) occurring stochastically in proportion to CAD burden.

If patients can be determined to be CAD-negative, however, they have essentially zero risk, both in the short and long term.

This review discusses the state of coronary CT angiography (CCTA) for management of acute chest pain in the emergency department (ED). CCTA directly visualizes coronary plaque burden, thereby ruling out a greater proportion of negative patients than any other noninvasive test. Simultaneously, it delivers the best short-term diagnostic accuracy in comparison to existing accelerated diagnostic protocols (Table 1). CCTA also provides the best long-term prognosis at the earliest time point, as well as positive effects on downstream morbidity and mortality. Nevertheless, the present level of CCTA utilization does not reflect its superior ability. We will explore the effectiveness of CCTA and advocate for its intelligent use in this patient population.

Non-CCTA Accelerated Diagnostic Protocols

Chest pain places a significant burden on the ED and the health care system as a whole. Standards of care include clinical observation, serial electrocardiograms (ECGs), serial cardiac biomarkers, and provocative functional or imaging tests, with the overall goal of reducing short-term major adverse cardiovascular events (MACE). Several accelerated diagnostic protocols have been developed to reduce ED and total costs without compromising patient safety.

The TIMI (Thrombolysis In Myocardial Infarction) score was initially developed to assess ACS severity in diagnosed patients; it has been used with varying degrees of success to predict ACS itself. The ADAPT accelerated diagnostic pathway combines the lowest possible TIMI score of zero with negative conventional troponin-I at 2 hours to reduce the risk of ACS to 0.3%. The ADAPT pathway has a specificity of approximately 25%, meaning only approximately a quarter of disease negative patients actually test negative. The remaining three quarters test positive, are not “ruled out,” and are exposed to additional testing. A randomized clinical trial (RCT) employing ADAPT vs. standard of care found that ADAPT doubles the early discharge rate without compromising patient safety. The APACE pathway uses high-sensitivity troponin-I at 2 hours with a TIMI score as high as 1 to achieve essentially the same low-risk rate as ADAPT and a specificity proportion of close to 50%.

The HEART risk score was specifically constructed to predict the risk of ACS and was validated within the ED patient population. The HEART pathway successfully combines a low-risk HEART score with a 3-hour conventional troponin-I to reduce the risk of MACE rate to zero with a specificity proportion of approximately 50%. ADAPT and APACE recommend outpatient functional testing following early discharge due to a fatality within the study cohort in which a stress test was performed but incorrectly interpreted. Notably, the HEART pathway investigators suggest that based on their results, low-risk patients require no further outpatient testing. Additional protocols have been suggested (Table 1).

Acute setting accelerated diagnostic pathways must avoid provocative testing because of the real—albeit unlikely—possibility of provoking infarction. Functional accelerated protocols must therefore rely on the resting state as a pseudo-stress equivalent.
rest single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) demonstrates a 99% negative predictive value (NPV) for acute MI, but examinations must be read critically with a resultant loss of specificity.\textsuperscript{10,11} Moreover, these findings are for MI only. With respect to all short-term MACE, the miss rate appears closer to 7%.\textsuperscript{10} In practice, an RCT employing SPECT after negative biomarker testing demonstrated reduced admissions with no change in short-term outcome. However, widespread implementation of this protocol is unlikely due to the practical difficulties surrounding the unscheduled use of radionuclide pharmaceuticals.\textsuperscript{12}

### CCTA-based Acute Chest Pain Management

CTA for patients with acute chest pain is more effective at many levels. A systematic review and meta-analysis performed in 2008 yielded an NPV of 100% and specificity of 89% in predicting significant CAD.\textsuperscript{13} In 2012, a systematic review and meta-analysis concluded that CCTA has an NPV of 99.3% for ACS and a specificity of 87%, meaning only approximately 1 in 10 negative patients are exposed to further testing.\textsuperscript{14} Three ensuing large multicenter RCTs compared CCTA and functional protocols and demonstrated that CCTA accelerates diagnosis, with twice to quadruple as many direct discharges from the ED, a reduction in ED costs of 18% to 38%, and no increase in short-term MACE.\textsuperscript{15} An RCT comparing CCTA with the cheapest and most widely used functional test, treadmill exercise stress ECG, shows that costs with CCTA are still lower, primarily driven by decreased length of stay.\textsuperscript{16} In 2014, the American Heart Association-American College of Cardiology Non-ST Elevation Acute Coronary Syndrome (AHA/ACC NSTE-ACS) guidelines assigned CCTA the highest level of evidence. The 2015 AHA/ACC released appropriate use criteria jointly with the American College of Radiology (ACR) that endorse CCTA as a first-line exam.\textsuperscript{17}

#### Table 1. Test characteristics for ED chest pain management strategies in terms of short-term MACE, assuming population with 15% prevalence

<table>
<thead>
<tr>
<th>Management strategy</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
<th>Risk if Protocol Positive (%)</th>
<th>Risk if Protocol Negative (%)</th>
<th>Share of Negative Patients Ruled Out (%)</th>
<th>Overall Diagnostic Accuracy (%)</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical judgement</td>
<td>1.32</td>
<td>0.14</td>
<td>19</td>
<td>2.5</td>
<td>27.4</td>
<td>96.1</td>
<td>85.8</td>
</tr>
<tr>
<td>TIMI score = 0</td>
<td>1.30</td>
<td>0.11</td>
<td>19</td>
<td>1.9</td>
<td>25.0</td>
<td>97.2</td>
<td>86.4</td>
</tr>
<tr>
<td>TIMI score = 0 and 2-hour conventional troponin-I (ADAPT Pathway)</td>
<td>1.30</td>
<td>0.01</td>
<td>19</td>
<td>0.2</td>
<td>23.4</td>
<td>99.7</td>
<td>88.3</td>
</tr>
<tr>
<td>TIMI score ≤ 1 and 2-hour high-sensitivity troponin-I (APACE Pathway)</td>
<td>1.86</td>
<td>0.01</td>
<td>25</td>
<td>0.2</td>
<td>46.5</td>
<td>99.4</td>
<td>91.5</td>
</tr>
<tr>
<td>Low-risk HEART score and 3-hour conventional troponin-I (HEART Pathway)</td>
<td>1.98</td>
<td>0.00</td>
<td>26</td>
<td>0.0</td>
<td>49.6</td>
<td>100.0</td>
<td>92.4</td>
</tr>
<tr>
<td>Presentation high-sensitivity troponin-T and clinical gestalt</td>
<td>2.04</td>
<td>0.06</td>
<td>26</td>
<td>1.0</td>
<td>52.5</td>
<td>97.0</td>
<td>90.3</td>
</tr>
<tr>
<td>Presentation high-sensitivity troponin-I</td>
<td>2.29</td>
<td>0.02</td>
<td>29</td>
<td>0.3</td>
<td>56.8</td>
<td>98.9</td>
<td>92.6</td>
</tr>
<tr>
<td>Acute rest SPECT MPI alone</td>
<td>2.08</td>
<td>0.38</td>
<td>27</td>
<td>6.3</td>
<td>63.5</td>
<td>75.8</td>
<td>74.0</td>
</tr>
<tr>
<td>Acute CCTA alone</td>
<td>7.31</td>
<td>0.06</td>
<td>56</td>
<td>1.0</td>
<td>87</td>
<td>95</td>
<td>93.8</td>
</tr>
</tbody>
</table>
CCTA and High-Sensitivity Troponins

The benefit of CCTA continues in the high-sensitivity troponin era, although its advantages have recently been questioned. A 2016 RCT in the Netherlands comparing CCTA to usual care including high-sensitivity troponins showed a 6% increase in direct ED discharges with CCTA, 65% vs. 59%, although without attaining statistical significance. The authors suggest their study was underpowered to show the small CCTA ED discharge rate benefit. They also note that the integrated nature of the Netherlands health system and excellent access to primary care steered a greater proportion of low-risk, CAD-negative and, hence, CCTA-negative patients away from the ED. The diagnostic power of CCTA rests in its excellent ability to identify patients without CAD and, therefore, without risk; thus, as CAD burden increases within the test population, the diagnostic accuracy decreases. From RCTs in the United States, it has been calculated that cost savings will occur only in populations where CCTA will show <50% stenosis in at least 72% of patients, ie, populations with relatively lower risk of ACS. The Netherlands study just barely met this quota, with 74% of patients negative for obstructive CAD. These caveats suggest that in a U.S. population with lower risk, the ED discharge rate for a combined CCTA and higher-sensitivity troponin strategy might be higher.

Moreover, although the Netherlands study reports that both cohorts demonstrated similar median lengths of stay, 6.3 hours, outcomes within the next quartile of patients dramatically differed. Specifically, 75% of CCTA cohort stays were <11.1 hours, while 75% of patients within the usual care group were not discharged until >25.5 hours. CCTA also prevented additional downstream testing. It is not surprising that CCTA led to statistically significant lower short-term costs, a savings of approximately one-third, despite the higher prevalence of CAD. The different findings from the U.S. studies may reflect a practice pattern emphasizing earlier ED disposition decisions, but certainly do not reduce the central conclusion of shorter stays and lower costs using CCTA.

Technical Improvements in CCTA

The spatial resolution of CCTA is typically 0.35 mm as compared to 0.16 mm for invasive angiography. Whereas a 3-mm coronary lumen is delineated on 18 pixels in fluoroscopy, CCTA displays the same vessel over 9 voxels, limiting determination of the exact degree of CAD. CCTA stenosis severity is therefore reported in increments of 25%. While interventional coronary angiography (ICA) outpaces CCTA in differentiating patients with varying degrees of CAD severity, surpassing CCTA’s positive predictive value (PPV), the NPV of CCTA at least equals that of ICA.

CCTA continues to improve technically. Traditionally, CCTA struggled to match the temporal resolution of the invasive exam. Fluoroscopy yields 30 frames per second, corresponding to a resolution of 33 milliseconds, essentially eliminating motion artifact. Increased CCTA temporal resolution on an ECG-gated exam is now achieved using multicycle reconstructions, higher gantry rotation speeds, use of multiple x-ray sources, and wider detectors.

Radiation dose in CCTA initially matched the effective dose of SPECT.

**FIGURE 1.** Surface rendering of the heart performed from CCTA volumetric acquisition. RCA = right coronary artery; LMCA = left main coronary artery; LCx = left circumflex artery; LAD = left anterior descending artery.
MPI exams of approximately 12-14 mSv; however, prospective gating, faster scanning, and better reconstruction algorithms have halved the dose, with improvement continuing. By comparison, a noncomplicated diagnostic cardiac catheterization delivers 8-10 mSv. Controversy exists as to whether exposure < 50 mSv imparts any increased risk, with major societies at odds about appropriate recommendations. Assuming, for the sake of caution—as the ACR does—the absence of a threshold for radiation-induced damage, the lifetime attributable risk of fatal cancer for a 5 mSv study would be a single additional fatal cancer per 2,000 examinations, undoubtedly a small fraction of the likely study benefit. The latest CT scanners deliver diagnostic scans at approximately 1 mSv. At such doses, radiation is no longer a realistic concern.

A principal technical advantage of CCTA is that the data obtained is intrinsically 3-dimensional. Images from a single acquisition can be viewed from any angle or projection with no vessel overlap, unlike the 2-dimensional data produced by angiography. This benefit partially compensates for CCTA’s lesser spatial and temporal resolution. Commonly used projections and reformations include surface rendering (Figure 1), curved multiplanar reconstructions (Figure 2), and straightened multiplanar reconstructions along the course of the vasculature (Figure 3).

**High-risk Coronary Features Indicate Increased Risk**

CCTA demonstrates prognostically important pathology not seen on catheter angiography. High-risk CCTA coronary plaque features include positive remodeling (increase in the outside diameter of the vessel, Figure 4), spotty calcium (Figure 5A), low attenuation plaque (Figures 5A-B), and rim-enhancing plaque (the “napkin-ring” sign, Figure 6), the latter likely indicating the presence of a lipid-laden plaque core. The relative risk of these high-risk plaque features for short-term MACE within the ED population is comparable to that of obstructive CAD, approximately 30 times. This holds true even after controlling for the presence of obstructive disease, thus increasing exam utility. CCTA-positive patients with nonobstructive CAD and without high-risk features could be classified as lower risk, increasing the proportion of patients that CCTA could clear. In patients with obstructive CAD and high-risk features, the PPV of the exam increases. High-risk features also serve as a biomarker of functional disease, as both plaque volume and high-risk characteristics correlate with the functional significance of a lesion as determined by invasive measurement of the pressure differential across the lesion, ie, ICA with measurement of the fractional flow reserve (FFR).

**Long-term Prognosis: The 6-Year CCTA Guarantee**

In outpatients, a completely negative CCTA provides a virtual guarantee of approximately 6 years of MACE-free survival, while nonobstructive CAD indicates a stable small risk for at least 2 years. The risk of MACE is approximately 0.5% per year for limited nonobstructive CAD and between 2-3 times that number with obstructive disease or extensive non-obstructive disease. Risk increases with the number of vessels involved. Just as high-risk features affect short-term risk, they also increase risk over the long term.

No stress modality can rival CCTA in detecting nonobstructive disease, since stress testing is blind to disease that is not flow limiting. Thus, only CCTA can provide information about the early CAD stages noninvasively. For this same reason, CCTA provides a longer guarantee if negative, in addition to comparable prognostic information when positive. Comparison between CCTA and exercise ECG actually demonstrates increased long-term risk in CCTA-positive patients irrespective of functional testing results. CCTA and SPECT can work synergistically to risk-stratify patients at the cost of increased radiation dose.
Clinical Benefit to Anatomical over Functional Testing

Long-term studies reveal a clinical benefit to CCTA. Not surprisingly, CCTA outperforms functional tests when anatomical findings on ICA are used as the reference standard. Within a population of 6200 patients undergoing CCTA after a functional test, for example, the relative risk of a false-positive or false-negative stress test as compared to an inaccurate CCTA was 1.4 and 3.1, respectively. An analysis of the nationwide elective ICA registry confirms the higher PPV of CCTA vs. all the various stress tests at approximately 70% vs. 46%. Newer research, however, suggests that revascularization should be guided by the functional perfusion deficit as measured by FFR during ICA, and a systematic review and meta-analysis demonstrate that SPECT outperforms CCTA in identifying lesions when ICA with FFR is used as the new gold standard. One would expect, based on this research, to find clinical benefit for noninvasive functional testing; however, the opposite has been shown.

A meta-analysis of recent clinical trials in outpatients with CAD (PROMISE, SCOT-HEART, and two smaller RCTs) shows a statistically significant reduction of annual MI in patients who underwent CCTA, to approximately 0.7 times the rate of patients with functional exams. Three-year follow-up of SCOT-HEART similarly demonstrates a statistically significant cardiac fatality and MI risk ratio of 0.5. This benefit is attributed to statistically significant changes in medical and invasive management. CCTA is already a first-line test for outpatient CAD in Europe, and these results suggest it should be first-line in the United States as well.

Undoubtedly, CCTA could be improved if functional data could be derived from the exam. CT-FFR is a computational technique that noninvasively calculates the pressure gradient across lesions using the 3-dimensional coronary anatomy, without catheterization, without adenosine administration, and with no increase in contrast material injected or in radiation dose. A meta-analysis with invasive FFR as the reference standard validates its accuracy; CT-FFR improves both the sensitivity and specificity of the CCTA exam. However, the PLATFORM RCT showed no downstream clinical benefits of CT-FFR compared to CCTA. Although the rate of future clinical deterioration may depend on the functional deficit, it likely primarily flows from the background clinical and anatomical risk, especially if assessed earlier and/or in a lower-risk population.

Finally, the CATCH trial directly elucidates the long-term impact of CCTA use within the ED population, despite the difficulty in assembling enough patients and events to power a study of this kind. In CATCH, patients with potential ACS admitted for less than 24 hours underwent both functional testing and CCTA prior to discharge, but the CCTA data was reported to the referring physician in only half of the patients. After 18 months, the CCTA cohort demonstrated a 2% reduction in cardiac death or MI. This difference was just shy of statistical significance, with p-value of 0.06. The usual care cohort, in contrast, had a statistically significant increased risk of all MACE, 5% vs. 2%, and when including readmission, had a statistically significant higher risk of adverse outcomes, 16% to 11%. Complementing these findings, retrospective analysis of CCTA patients shows five-fold lower odds of recidivism. These results demonstrate a morbidity and mortality benefit to early
use of CCTA in the ED population, just as in outpatients.}

In the long term, CCTA leads to an increase in downstream procedures, which degrades the initial cost-savings. However, a meta-analysis of the ED RCTs, which suggests a relatively matched increase of 2% in the patients who undergo ICA and revascularization after CCTA, also suggest that these major procedures are performed appropriately. These increased revascularizations may drive the clinical benefits discussed above. Impressively, retrospective analysis found a seven-fold lower likelihood of undergoing ICA without revascularization in ED patients triaged by CCTA. ED providers and radiologists should be aware that patients who receive early testing with CCTA rather than downstream functional tests are well-served clinically.

CCTA includes a final ancillary benefit: The most common incidental finding on CCTA is a pulmonary nodule, occurring at approximately the same rate as the general population, one in five. One in 10 nodules may represent a neoplasm, with a potential morbidity and mortality benefit of 1% if just half can be detected. Further work is necessary, but recent studies suggest additional downstream costs are minimal.

**Suggestions for Management**

The CAD-RADS (Reporting and Data System) has been introduced to standardize CCTA reporting and guide further research and management. Highlights are as follows: Patients with left main coronary stenosis of > 50%, any vessel stenosis of 70%, or 3-vessel disease are described as CAD-RADS-4 and may be candidates for revascularization. In the acute setting, this score indicates that ACS is at least likely. CAD-RADS-3 includes any other stenosis > 50% where ACS is possible and where admission and at least a functional test for further risk stratification would be considered appropriate. CAD-RADS-2 includes stenoses between 25% and 49%, where ACS is unlikely despite the presence of CAD, although high-risk plaque features would lead to a CAD-RADS-2/V designation and should escalate level of concern and further care.

**Conclusion**

CCTA for acute chest pain provides powerful diagnostic and prognostic information, decreases ED length of stay, reduces ED costs, and provides tangible clinical benefits. The latest biomarkers do not alter these findings. Accelerated diagnostic pathways that encourage early discharge without objective anatomic testing deny patients the proven benefits of CCTA. Further trials will hopefully lead to varied high-sensitivity troponins or integrated risk score cutoffs that stratify patients even better. Until that time, the use of early CCTA to further guide care represents the evidence-based strategy of maximal benefit and least harm, as is strongly supported by data.

**References**
