Clinical update

Highly sensitive troponin and coronary computed tomography angiography in the evaluation of suspected acute coronary syndrome in the emergency department

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The evaluation of patients presenting to the emergency department with suspected acute coronary syndrome (ACS) remains a clinical challenge. The traditional assessment includes clinical risk assessment based on cardiovascular risk factors with serial electrocardiograms and cardiac troponin measurements, often followed by advanced cardiac testing as inpatient or outpatient (i.e. stress testing, imaging). Despite this costly and lengthy work-up, there is a non-negligible rate of missed ACS with an increased risk of death. There is a clinical need for diagnostic strategies that will lead to rapid and reliable triage of patients with suspected ACS. We provide an overview of the evidence for the role of highly sensitive troponin (hsTn) in the rapid and efficient evaluation of suspected ACS. Results of recent research studies have led to the introduction of hsTn with rapid rule-in and rule-out protocols into the guidelines. Highly sensitive troponin increases the sensitivity for the detection of myocardial infarction and decreases time to diagnosis; however, it may decrease the specificity, especially when used as a dichotomous variable, rather than continuous variable as recommended by guidelines; this may increase clinician uncertainty. We summarize the evidence for the use of coronary computed tomography angiography (CTA) as the rapid diagnostic tool in this population when used with conventional troponin assays. Coronary CTA significantly decreases time to diagnosis and discharge in patients with suspected ACS, while being safe. However, it may lead to increase in invasive procedures and includes radiation exposure. Finally, we outline the opportunities for the combined use of hsTn and coronary CTA that may result in increased efficiency, decreased need for imaging, lower cost, and decreased radiation dose.

Keywords   Acute coronary syndrome   •   Acute chest pain   •   Highly sensitive troponin   •   Coronary computed tomography angiography

Current standards in the evaluation of patients with suspected acute coronary syndrome in the emergency department

The evaluation of patients presenting to the emergency department (ED) with suspected acute coronary syndrome (ACS) remains a clinical challenge. Acute chest pain is one of the most common chief complaints in the ED in Europe and the USA: among 100 million ED visits every year, ~6 million patients present with acute chest pain.[1,2] Ultimately, a cardiac cause is suspected in ~4 million patients. However, only approximately one-third of patients are eventually diagnosed with an ACS. On the other hand, among patients who are diagnosed with non-cardiac chest pain, 1–4% suffer ACS, and these missed diagnoses are associated with substantially higher risk for death.[3,4]

Practice guidelines of the European Society of Cardiology and American Heart Association/American College of Cardiology provide algorithms for the evaluation of suspected ACS.[5,6] The

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algorithms acknowledge the limitations of chest pain history and clinical risk factors. While these factors are important in the evaluation, they do not allow for a definitive exclusion of ACS.[4–6] The standard of care for subjects with suspected ACS includes electrocardiograms and cardiac troponin (Tn) measurements (*Figures 1* and *2*). Differences exist between guidelines and practice in the USA and Europe due to the lack of US Food and Drug Administration approval for highly sensitive Tn (hsTn) assays in the USA. In Europe, clinicians have had now >5 years of experience with hsTn and the most recent guidelines include hsTn with baseline and 3-h assessment in the recommended algorithm (*Figure 1*).[5] Furthermore, a possibility of rapid 1-h protocols is suggested for centres with appropriate expertise and availability of assays provided in the guidelines.[5] In contrast, longer work-up with serial measurements of conventional Tn at least 6 h is currently recommended in the USA (*Figure 2*).[5,6]

While the hsTn methods have improved sensitivity for the detection of myocardial necrosis compared with conventional assays, the specificity of hsTn assays for the clinical diagnosis of myocardial infarction (MI) is lower when evaluated as a dichotomous value. Such approach may lead to the need for repeat Tn testing, evaluation with advanced diagnostic testing with or without imaging, in-hospital observation, and high healthcare cost. European guidelines emphasize that hsTn should be interpreted as a quantitative marker with higher levels being associated with higher likelihood of MI.[5] Whether using conventional Tn or hsTn, there will be a group of patients requiring further work-up and objective tests are needed to support clinical judgement. Given these challenges, there is a clinical need for diagnostic strategies that will lead to rapid and reliable triage of patients with suspected ACS. In this review, we discuss the potential roles of hsTn and coronary computed tomography angiography (CTA) as individual tests and also in combination for the evaluation of patients with suspected ACS in the ED.

Highly sensitive troponin assays

Conventional cardiac Tn assays have been used to detect acute MI for over two decades. For diagnosis, the third Universal Definition of MI Global Task Force recommended the use of a cardiac Tn cutoff that is the 99th percentile of a healthy patient population.[7] The challenges of conventional Tn assays include higher limit of detection (typically 10–60 ng/L) and inaccuracy at very low concentrations of the biomarker (coefficient of variation at the 99th percentile value typically ≥10%) along with a time dependency to their detectability, given the need for substantial efflux of the cytosolic Tn pool into the blood stream.[8,9] Conventional Tn methods require at least several hours from the onset of myocardial injury before becoming abnormal, therefore, leading to the 'Tn blind interval'. In contrast, hsTn assays provide increased precision at or <99th percentile. Two criteria have to be met to define an assay as hsTn: (i) total imprecision (coefficient of variation) at the 99th percentile value ≤10% and (ii) measurable concentrations <99th percentile attainable at a concentration value above the assay's limit of detection for at least 50% (and ideally 95%) of healthy individuals.[8,9] This increased sensitivity results in measurable values of hsTn in the majority of normal subjects and in subjects with prevalent cardiovascular disease. Therefore, the Study Group on Biomarkers in Cardiology of ESC emphasized that the elevation of hsTn alone is not sufficient to make a diagnosis of MI.[9]
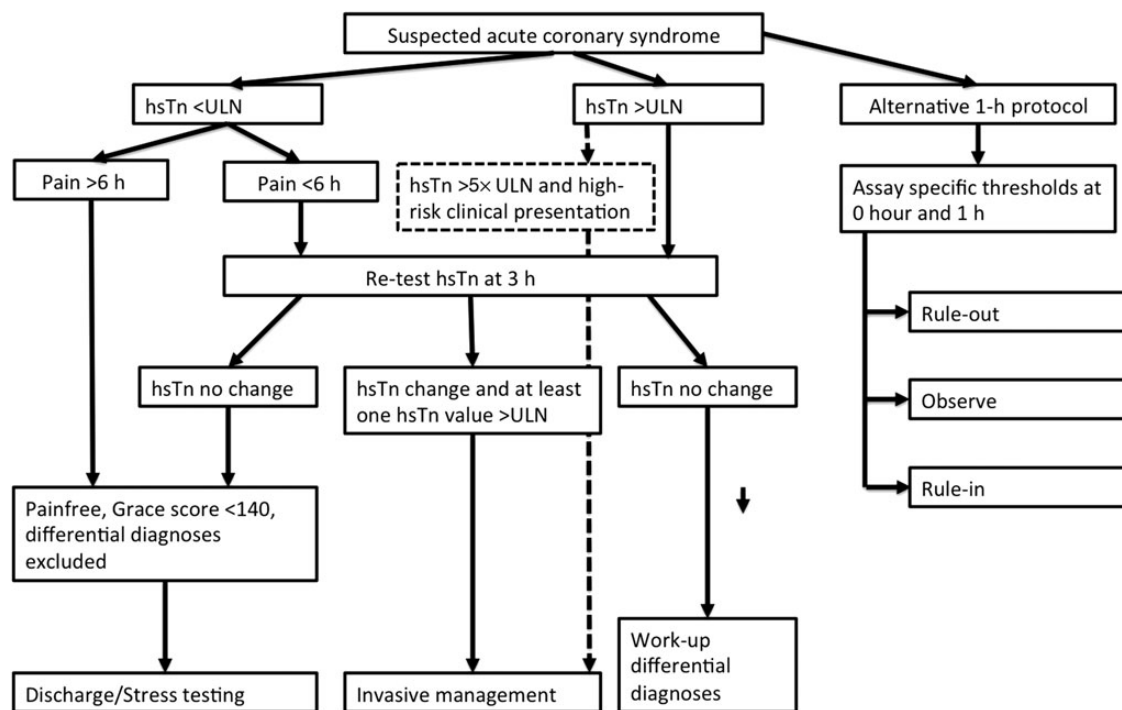
Figure 1 Simplified algorithm for the management of patients with suspected acute coronary syndrome based on European Society of Cardiology guidelines.[5]
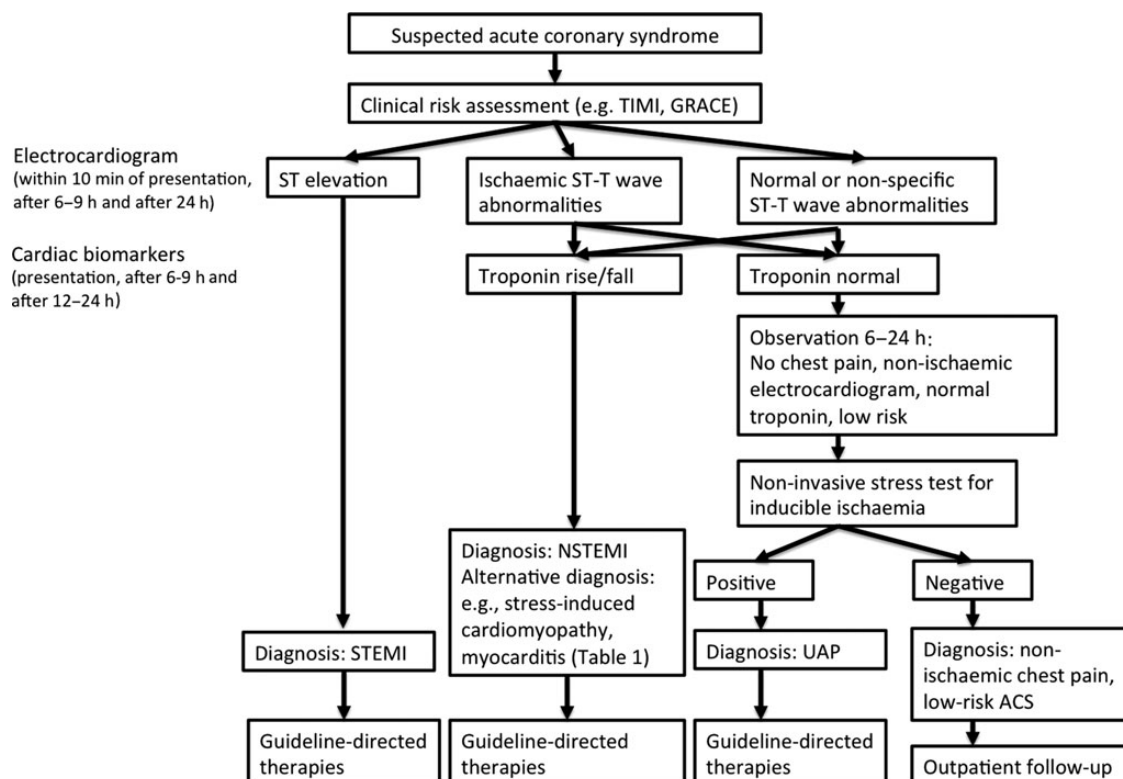
Figure 2 Simplified algorithm for the management of patients with suspected acute coronary syndrome based on American Heart Association/American College of Cardiology guidelines.[6]

Prognostic value of highly sensitive troponin in normal populations

Values >99th percentile provide prognostic information for future major cardiovascular events (MACE) in subjects free of clinical cardiovascular disease.[10−12] In the population from Dallas Heart Study, hsTn >99th percentile when compared with below the limit of detection were associated with increased cardiac structural abnormalities [left ventricular (LV) hypertrophy and dysfunction] and with 2.8 times increased risk of all-cause mortality after adjustment.[10] Similarly in Atherosclerosis Risk in Communities Study study, hsTn >99th percentile was associated with an increased risk of incidental coronary heart disease (hazard ratio 2.3), mortality (hazard ratio 4.0), and heart failure (hazard ratio 6.0).[11] Finally, in the Framingham Heart Study, higher hsTn was associated with an increased risk of all-cause mortality, MACE, and heart failure (hazard ratio per standard deviation increase: 1.16, 1.28, and 1.18, respectively).[12]
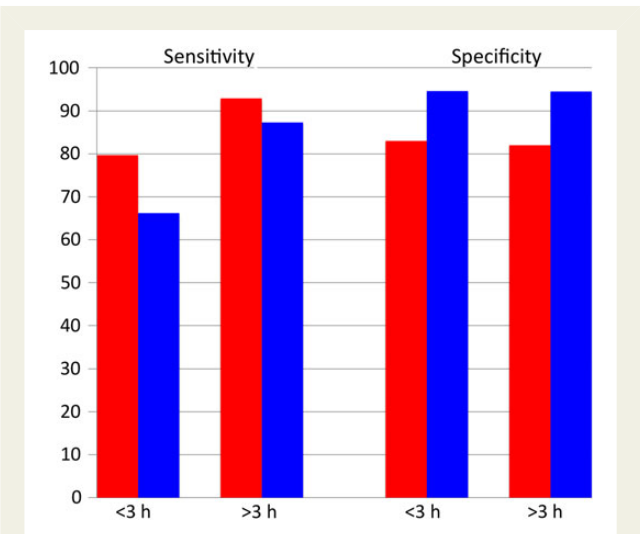
Diagnostic performance of highly sensitive troponin for myocardial infarction

In the evaluation of patients with suspected MI, use of hsTn assays provides superior diagnostic accuracy with very high sensitivity and negative predictive value compared with conventional assays.[13−18]

The diagnostic accuracy is significantly improved particularly in patients who present within 3 h of symptom onset, thus resulting in excellent ability to exclude acute MI at an earlier time frame through rapid serial assessment (Figure 3).[14,15,17,18] In addition to early identification of patients with MI, hsTn can re-classify up to one-third of patients with unstable angina pectoris to a new diagnosis of MI.[19,20]

Importantly, however, increased sensitivity of the hsTn assays for the detection of small amounts of myocardial necrosis comes with the cost of modestly decreased specificity and misdiagnosis of MI, especially in patients with multiple complex comorbid conditions, or other diagnoses leading to myocardial necrosis (Table 2). While increasing prognostic value for adverse outcomes across a broad range of cardiovascular disease, loss of positive predictive value of an elevated hsTn for the clinical diagnosis of acute MI may therefore result in increase in downstream testing and costly interventions.[20−23]

Several keys exist to assist in improving the accuracy of hsTn testing for acute MI, helping to separate 'coronary' from 'non-coronary' causes of hsTn elevation.[24] These include an understanding of the usual expected hsTn values associated with disorders that may lead to myonecrosis (Table 1), use of serial testing, and combining hsTn testing with clinical risk scoring. One specific area is hsTn in the setting of renal dysfunction and associated cardiac disease. While the levels elevated of hsTn can be observed in the population of patients with renal dysfunction, hsTn assays maintain high diagnostic accuracy for MI, particularly when significant rise and/or fall

Figure 3 The diagnostic performance of highly sensitive troponin (red bars) when compared with conventional troponin (blue bars) for acute myocardial infarction in patients presenting <3 and >3 h of chest pain onset (adapted from Body *et al.*[15]). Highly sensitive troponin assay provides significantly improved sensitivity for the detection of myocardial infarction in patients presenting within 3 h of chest pain onset. There is no difference in the specificity in those who present <3 or >3 h of chest pain onset.

Table I   Possible non-acute coronary syndrome causes of troponin elevation

Renal dysfunction and associated cardiac disease
Severe congestive heart failure—acute or chronic
Hypertensive crisis
Tachy- and brady-arrhythmia
Pulmonary embolism, severe pulmonary hypertension
Myocarditis
Acute neurological disease (stroke, subarachnoid haemorrhage)
Aortic dissection, aortic valve disease, or hypertrophic cardiomyopathy
Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
Hypothyroidism
Stress-induced cardiomyopathy
Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, and scleroderma
Drug toxicity, e.g. anthracyclines, Her-2 blockers, 5-fluorouracil, and snake venoms
Burns, if affecting >30% of body surface area
Rhabdomyolysis
Critically ill patients, especially with respiratory failure, or sepsis

Modified from European Society of Cardiology guidelines.[5]

is observed. To ensure the best possible clinical use, higher assay-specific optimal cut-off levels might be considered.[25]

Assessment of highly sensitive troponin in patients with suspected acute coronary syndrome

While the great majority of patients tested in an ED setting have measureable hsTn concentrations, a certain percentage are below the limit of detection for the assay. Depending on the lower end sensitivity, being below the limit of detection may be associated with a high likelihood for an absence of ACS and/or acute MI.[13,16,19,26] For example, in a large registry study of almost 15 000 patients, between 10 and 15% of patients had hsTn below the limit of detection and such patients were very low risk with a 0.44% MACE rate at 30 days.[27] In another study, Body *et al.* showed that hsTn T below the limit of detection at arrival had a 100% negative predictive value for acute MI, allowing for exclusion of the diagnosis at first draw in this cohort in up to nearly 28%.[15] Subsequently, other studies have confirmed and extended these results; in the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) II trial, Januzzi *et al.* recently showed concentrations of hsTn I below the limit of detection not only excluded ACS (including unstable angina pectoris) with 100% negative predictive value, but also excluded significant coronary stenoses in those undergoing subsequent coronary CTA.[19] Thus, when using hsTn methods, very low biomarker concentrations may be useful.

When employing serial testing, clinicians should understand that the demonstration of a significant increase (or decrease) in hsTn is

usually indicative of an acute disease process, as opposed to an unchanging Tn result that is seen in chronic disease states.[18,28] In this regard, a very low and stable value helps to exclude MI, while the detection of a substantial rise and/or fall of hsTn in a very short period of time may correctly identify acute MI in a large percentage of cases.

For example, in the Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) study, Reichlin *et al.* studied patients with undifferentiated chest pain in the ED with hsTn measurements at the time of presentation and after 1 h.[14] They derived the low hsTn T threshold (<12 ng/L) at the time of presentation and a small absolute change of hsTn T (<3 ng/L) at 1 h as criteria for rule out of ACS. They validated their results in an independent cohort and achieved 100% sensitivity and negative predictive value for the diagnosis of acute MI. In a subsequent analysis from the same cohort, Druey *et al.* showed that an accelerated protocol of hsTn I testing over a 1-h period correctly excluded acute MI in 65% of subjects with no change in hsTn I (with negative predictive value of 98.6%) and correctly identified acute MI in 12% when hsTn I was elevated or rising (with positive predictive value of 76.3%).[29] In both analyses, however, a significant number of subjects were between the 'rule-out' and 'rule-in' categories, and would require observation and/or further testing.

Beyond accuracy for diagnosis, rapid ED protocols with two hsTn measurements at the time of presentation and after 1 or 2 h also allow for sensitivity and negative predictive value of >99% for 30-day MACE.[14,18,30] Up to 40% of patients presenting to the ED with suspected ACS were classified as low risk in these studies and are potential candidates for early discharge from the ED and outpatient work-up.

Table 2 Summary of randomized, controlled, and multicentre trials comparing coronary computed tomography angiography with standard of care in patients with suspected acute coronary syndrome in the emergency department

Study	CT-STAT[40]		ACRIN[46]		ROMICAT II[51]	
Population (n)	699		1370		1000	
Mean age (years)	50		49		54	
Women (%)	54		53		47	
TIMI risk score	0−4		0−2		N/A	
MI during index hospitalization (%)	0.9		0.9		2.3	
Control group	Stress myocardial perfusion imaging		Standard of care		Standard of care	
Randomization	1:1		2:1		1:1	
Number of centres	16		5		9	
Conventional Tn assays and thresholds used in the study	Tn I, Bayer, thresholds not reported		Not reported		Tn T, Roche: 0.03 ng/mL Tn I, Alere: 0.40 ng/mL Tn I, Beckman: 0.07/0.04 ng/mL	
	Coronary CTA	**Controls**	**Coronary CTA**	**Controls**	**Coronary CTA**	**Controls**
ACS during index hospitalization (%)	1.2	2.7	4	2	9	6
MACE during follow-up (%)	0.8	0.4	3	1	0.4	1.2
Time to diagnosis (h)	2.9[a]	6.2[a]	–	–	–	–
Length of stay (h)	–	–	18.0[a]	24.8[a]	23.2[a]	30.8[a]
Direct ED discharges (%)	–	–	50[a]	23[a]	47[a]	12[a]
Invasive coronary angiography (%)	7	6	5	4	11	7
Coronary revascularization (%)	4	2	3	1	7	4
ED cost ($)	2137	3458	–	–	2101	2566
Radiation dose (mSv)	12	13	–	–	14[a]	5[a]

[a]Significant difference between coronary CTA and control groups ($P < 0.05$).

As biomarker testing should never be used in isolation without clinical corroboration, studies have focussed on the development of accelerated diagnostic protocols (ADP) for ED triage. These protocols not only include information from serial hsTn testing but also add clinical information, namely electrocardiogram and clinical risk assessment such as the Thrombolysis in Myocardial Infarction (TIMI) risk score. For example, in the 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker (ADAPT) study, Than et al. showed that among 1975 patients, incorporation of a TIMI risk score of 0 together with hsTn values below the 99th percentile value allowed for sensitivity of 99.7% and negative predictive value 99.7% for excluding risk for MACE.[31] In a subsequent analysis, pooling the ADAPT and APACE trials, the investigators explored the negative predictive value of an ADP incorporating an electrocardiogram without ischaemic changes, TIMI score of 0 or ≤1 and serial hsTn <99th percentile at the time of presentation and after 2 h.[18] The negative predictive value of the ADP triage with the threshold of TIMI score of 0- for 30-day MACE was 100%. When patients with TIMI score of 1 were included, the negative predictive value decreased to 99.7%. However, the proportion of patients who could be potentially discharged from the ED increased from 25 to 39%. The results for rapid ED protocols were confirmed with various hsTn assays.[18,30]

While the use of low concentrations of hsTn at presentation, reassuring serial measurements, and/or ADP-supported evaluation allow for prediction of very low 30-day MACE event rates and assist in more rapid discharge, risk may be still present in this patient group indicating the need for close outpatient follow-up. For patients with measurable (i.e. above the limit of detection) hsTn values, particularly those with a TIMI risk score >1, and/or those in the 'observation' categories in rapid serial testing protocols, further testing such as stress testing or coronary CTA will likely be needed.

Coronary computed tomography angiography in patients with suspected acute coronary syndrome

Coronary CTA has evolved in an alternative diagnostic testing strategy for patients with suspected ACS in the ED. The major strength of coronary CTA is its high negative predictive value for obstructive coronary artery disease (CAD). In the clinical practice, the majority of patients with ACS have obstructive CAD and the absence of significant stenosis significantly decreases the likelihood of ACS.[32,33] The diagnostic performance of coronary CTA for the assessment of coronary stenosis has been demonstrated in many studies, among them several multicentre trials that compared coronary CTA with invasive coronary angiography in patients with stable chest pain (sensitivity between 85 and 99%, specificity between 64 and 97%,

negative predictive value >95%).[34–37] The performance of coronary CTA can be limited in patients with high heart rates and the presence of extensive coronary calcium.

Earlier single-centre studies of patients with suspected ACS demonstrated that the exclusion of a significant coronary stenosis by coronary CTA has high negative predictive value (>99%) for ACS and thus may potentially allow for earlier discharge than functional testing.[38–50]

Subsequently, three multicentre randomized trials were performed that compared coronary CTA with the standard evaluation of acute chest pain patients in the ED.[40,46,51] The results from those studies that enrolled >3000 patients with low-to-intermediate likelihood of ACS are summarized in *Table 2*. The inclusion criteria included the ED presentation with low-to-intermediate likelihood of ACS, negative initial conventional Tn, and non-ischaemic electrocardiograms. Patients with previous history of CAD were excluded. In all three trials, the primary outcome of interest—the length of stay or time to diagnosis—was significantly shorter in the coronary CTA arm when compared with standard of care, which included stress testing in the majority of patients (*Figure 4*). The proportion of direct discharges increased approximately four times (50 vs. 12%).[46,51] The increased efficiency of the ED triage was accomplished safely, without an increase in MACE during a 28-day follow-up.

The downside of the coronary CTA use in the ED patients is a trend towards increased additional testing and invasive procedures.[40,46,51] This trend is probably due to the increased sensitivity of coronary CTA for the detection of CAD and the overestimation of stenosis degree in routine clinical practice. The increase in invasive coronary angiography and percutaneous coronary interventions (PCI) after coronary CTA was estimated at 21 and

20 per 1000 scans, respectively.[52] At this point, there are no reliable data to indicate whether the improved detection of CAD and subsequent PCI in this acute setting will improve long-term health outcomes. Despite the increase in subsequent testing and interventions, the overall cost of the index hospitalization was not significantly higher in those randomized to coronary CTA.[51] Furthermore, lifelong Markov modelling from the ROMICAT II trial demonstrated cost-effective improvement of health outcomes when compared with functional testing with incremental cost-effectiveness ratio of $37 000 per quality-adjusted life-year.[53]

The estimated radiation exposure for those evaluated using coronary CTA may be a concern. In clinical trials, those randomized to coronary CTA had higher (13.9 mSv) radiation dose when compared with the standard of care (4.7 mSv), including patients undergoing only exercise treadmill stress test or stress echocardiography,[51] but was similar in a direct comparison of coronary CTA (11.2 mSv) and stress myocardial perfusion imaging (12.8 mSv) in the Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) trial.[40] Some authors propose that these radiation doses are associated with increased lifelong risk of cancer, although there is an ongoing discussion about the carcinogenic effect of ionizing radiation used in medical imaging and direct epidemiological data confirming this effect are missing. The estimated life-time-associated risk of cancer was estimated to be between 1 in 100 and 1 in 3000 CT scans with estimated radiation dose of 9–21 mSv.[54] The risk increases with younger age and is higher in women. With coronary CTA protocols now allowing for less radiation exposure (average dose of 3 mSv and low-dose scans performed with doses <1 mSv) without loss of diagnostic accuracy, this concern may be allayed.[55]

Novel approaches for the assessment of coronary computed tomography angiography

There is growing evidence that additional information obtained during coronary CTA such as the assessment of global and regional LV function, evaluation of myocardial perfusion, non-invasive fractional flow reserve (FFR), and coronary plaque analysis have the potential to improve the accuracy and efficiency of coronary CTA.

Evaluation of global and regional LV function is feasible with coronary CTA acquisition, which covers all phases of cardiac cycle, and the results compare favourably with echocardiography and cardiac magnetic resonance imaging.[56,57] The analyses of ED patients showed that the presence of regional LV dysfunction incrementally and independently improved the diagnostic accuracy for ACS beyond stenosis detection in patients with the presence of CAD (sensitivity of coronary stenosis vs. coronary stenosis and LV dysfunction: 77 vs. 87%).[58–60] This is specifically valuable in patients with non-diagnostic assessment for significant stenosis or borderline stenosis.

The evaluation of first-pass myocardial perfusion at rest is feasible with a standard coronary CTA acquisition.[57] First-pass perfusion defects were observed in the majority of patients with MI, but less commonly in patients with unstable angina pectoris.[61,62] Several small studies demonstrated that resting first-pass myocardial
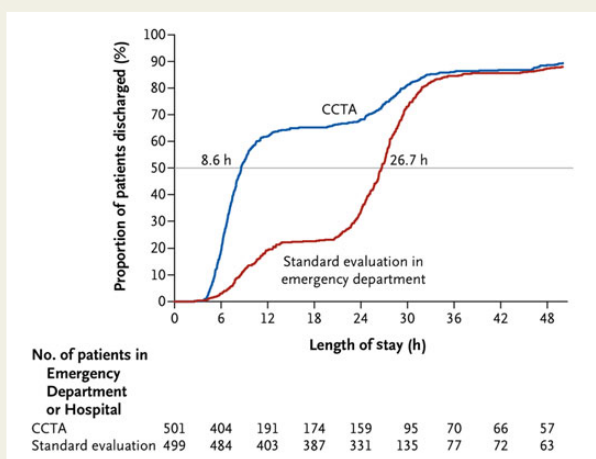
Figure 4 Length of stay and proportion of patients discharged in the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography II trial. The cumulative frequency of discharges from the index visit according to the length of stay is shown. The horizontal line indicates the median length of stay in the two study groups, which was significantly different (8.6 h in the coronary computed tomography angiography vs. 26.7 h in the standard-evaluation group, *P* < 0.001). Reprinted with permission from Hoffmann *et al.*[51]

perfusion defects detected on coronary CTA increased specificity and positive predictive value for ACS (from 67 to 90%).[59,63–65]

The recent developments in computational fluid dynamics and image-based modelling now permit the determination of non-invasive FFR without the need for additional imaging, modification of coronary CTA acquisition protocols, or administration of medication (adenosine).[66] Non-invasive FFR measurements have been shown to correlate with invasive FFR.[67,68]

In the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography study, non-invasive FFR demonstrated sensitivity of 73% and specificity of 90% for the detection of per-patient ischaemia as determined by invasive FFR.[68] The overall diagnostic accuracy of non-invasive FFR for per-patient detection of ischaemia was significantly better when compared with the detection of obstructive CAD by coronary CTA [area under the curve (AUC) 0.81 vs. 0.68, $P < 0.001$]. Similar results were reported in the Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) study.[69] Non-invasive FFR when compared with anatomic coronary CTA detection of significant stenosis improved the diagnostic accuracy for the detection of lesion-specific ischaemia with the improvement of specificity from 34 to 79% and overall accuracy (AUC 0.90 vs. 0.81, $P < 0.001$). Furthermore, the addition of FFR to the traditional assessment for obstructive CAD improved specificity for the detection of ischaemia and diagnostic accuracy in patients with intermediate stenoses (40–69%).[70] The addition of FFR to the assessment of coronary CTA may improve the sensitivity and specificity of the test and correctly identify patients with haemodynamically significant CAD with lesion-specific ischaemia in the ED. However, no studies have been performed in a population of patients with acute chest pain presentations up to date.

Feasibility of coronary plaque analysis using coronary CTA data has been well established.[71–73] Coronary CTA permits assessment of plaque composition based on CT attenuation and detection of high-risk plaque features such as positive remodelling, percentage of plaque burden, low CT attenuation plaque, napkin-ring sign, and spotty calcium.[72,74–81] High-risk plaque features were more often seen in culprit coronary lesions of ACS than in stenotic lesions in stable angina pectoris patients.[82–87] Furthermore, the presence of high-risk plaque was independent of significant stenosis for the detection of ischaemia as measured by invasive FFR.[88] In the ROMICAT I trial, patients with acute chest pain presentation and with the presence of ≥50% stenosis could be differentiated into those with and without ACS using a coronary plaque score, which included spotty calcium, low CT attenuation, positive remodelling, and length of stenosis.[89] More recently, the analysis of almost 500 patients randomized to the coronary CTA arm of the ROMICAT II trial showed that the presence of high-risk plaque features (positive remodelling, low CT attenuation plaque with <30 Hounsfield units, napkin-ring sign, and spotty calcium) was independent and incremental to ≥50% stenosis for the diagnosis of ACS (Figure 5).[90] Overall, there is an increasing evidence that advanced plaque characterization may provide incremental value for the management of acute chest pain patients, specifically identifying those whose symptoms may not be associated with significant CAD found 'incidentally' on coronary CTA and those without significant CAD who may be at increased risk for ACS.

Combined use of highly sensitive troponin and coronary computed tomography angiography

Based on the presented data for hsTn and coronary CTA, the combined approach of these two diagnostic tests may permit rapid evaluation and triage of the majority of ED patients with suspected ACS (Figure 6). In Europe, recently updated guidelines include rapid hsTn rule-out and rule-in protocols and significantly decrease the proportion of patients who require further work-up.[5] Nevertheless, there is a subgroup of patients that even with hsTn will require observation status and rapid coronary CTA will permit early discharge. Furthermore, there are patients with mildly elevated or 'intermediate' hsTn without typical rise and fall, who may also benefit from coronary CTA.

We performed a retrospective analysis in a subset of 160 patients from the ROMICAT II trial who had blood samples available and underwent coronary CTA. Highly sensitive Tn I (hsVista, Siemens) below the limit of detection at the time of presentation had negative predictive value of 100% for ACS during the index hospitalization and would permit rapid discharge of 6% patients without further testing.[91] Patients with hsTn I >99th percentile represented a high-risk group with ACS event rate of 58%. Patients with intermediate hsTn I levels at the time of presentation (above the limit of detection, but <99th percentile) had an intermediate risk of ACS with an event rate of 9%. Coronary CTA could reclassify the risk of ACS in this group. Among those patients with measurable but not elevated hsTn I and with no evidence of significant stenosis or high-risk plaque (54%), none had ACS (negative predictive value of 100%), whereas those with measurable but not elevated hsTn I with significant stenosis and high-risk plaque had high risk of ACS (event rate 69%). In summary, 60% of patients (hsTn below the limit of detection or negative coronary CTA) could be possibly discharged after initial hsTn and coronary CTA, usually within 2 h of their presentation to the ED. On the other hand, additional 16% of patients (hsTn >99% percentile or positive coronary CTA) could be categorized as highest risk and receive appropriate therapies early in the course of their hospitalization. The combined use of hsTn and coronary CTA may result in cost-saving and decreased radiation exposure by decreasing the need for additional advanced cardiac testing in patients with hsTn below the limit of detection. Additionally, among those safely discharged from the ED but with anatomic definition of their coronary arteries, knowledge of the presence of previously unsuspected sub-critical CAD should allow for aggressive application of secondary prevention measures, such as more directed use of statins or anti-platelet agents.

There is an increased interest in the rapid rule-out protocols with clinical assessment followed by hsTn and discharge to outpatient follow-up if the risk of ACS is low. The advantages of rapid protocols are decreased time to discharge and cost-efficiency. However, there is still a need for outpatient testing, which may be challenging, and follow-up varies significantly among various medical systems and countries. In addition, coronary CTA provides prolonged warranty period beyond the initial ED presentation with the evidence of virtually no MACE in patients with no evidence of coronary atherosclerosis for ~2 years; thus, possibly decreasing the need for testing during subsequent ED presentations.[92] Furthermore,
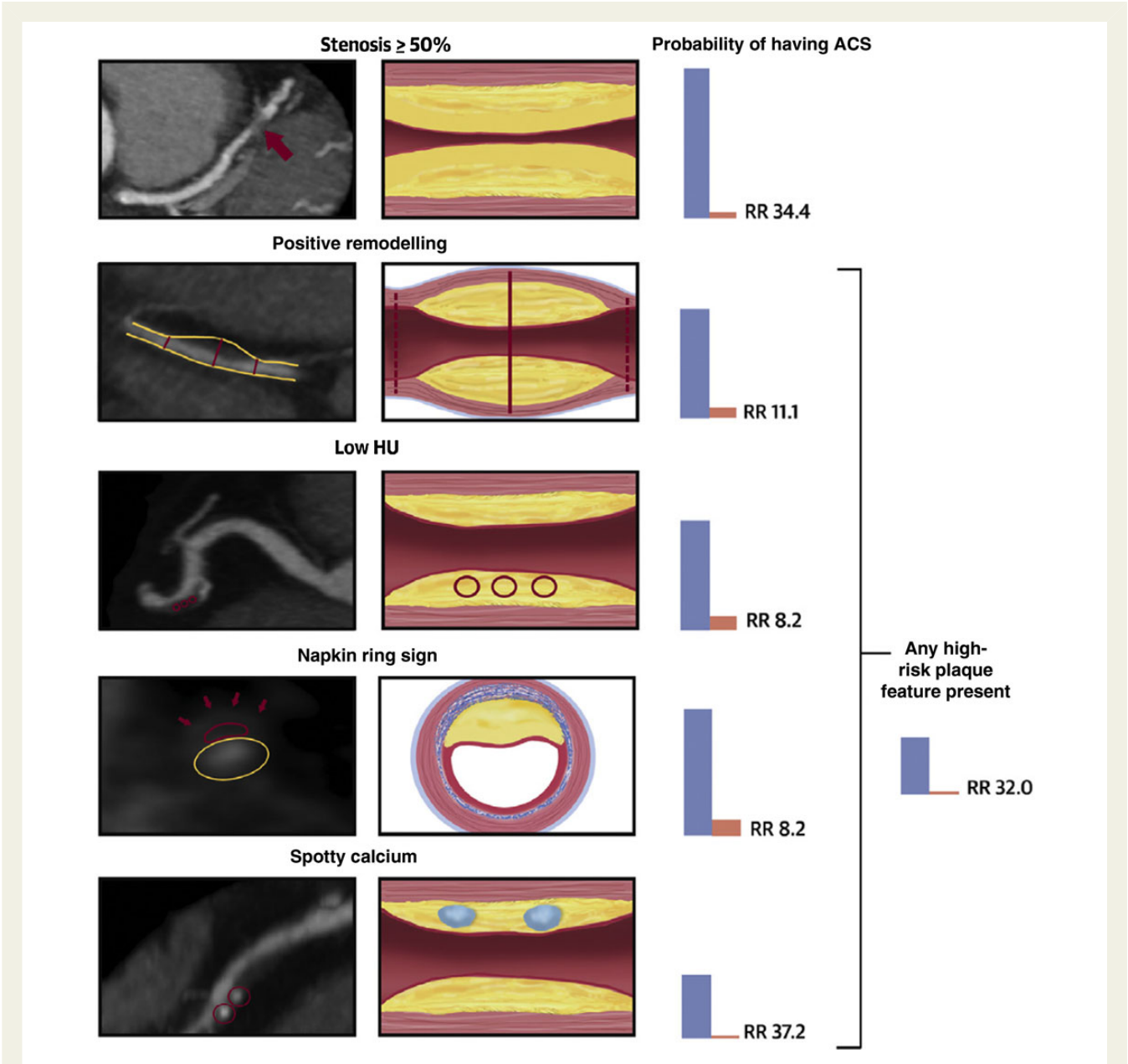
Figure 5 The association of significant stenosis and high-risk plaque features with the probability of acute coronary syndrome in the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography II trial. Stenosis ≥50%: severe stenosis of the mid-left anterior descending coronary artery (red arrow). Positive remodelling: non-calcified plaque with positive remodelling in the distal right coronary artery. The two-dotted red lines demonstrate the vessel diameters at the proximal and distal references (both 1.8 mm), and the solid red line demonstrates the maximal vessel diameter in the mid-portion of the plaque (2.7 mm). The remodelling index is 1.5. Low Hounsfield units plaque: partially calcified plaque in the mid-right coronary artery with low <30 Hounsfield unit plaque. The red circles demonstrate the three regions of interest, with mean computed tomography numbers of 22, 19, and 20 Hounsfield units. Napkin-ring sign: napkin-ring sign plaque in the mid-left anterior descending coronary artery. Schematic cross-sectional view of the napkin-ring sign. The red line demonstrates the central low Hounsfield unit area of the plaque adjacent to the lumen (yellow ellipse) surrounded by a peripheral rim of the higher computed tomography attenuation (red arrows). Spotty calcium: partially calcified plaque in the mid-right coronary artery with spotty calcification (diameter <3 mm in all directions; red circles). Reprinted with permission from Puchner et al.[90]

coronary atherosclerosis is detected in approximately half of patients with suspected ACS in the ED by coronary CTA and would not be detected with rapid rule-out protocols.[40,46,51] This may have significant consequences for the outpatient management and preventative therapies. Whether the appropriate preventative strategies, guided by coronary CTA finding, will lead to improved outcomes will need to be studied. In summary, we believe that combination of hsTn and coronary CTA in the ED patients with suspected ACS is a valuable concept that should be tested in a well-designed randomized trial.
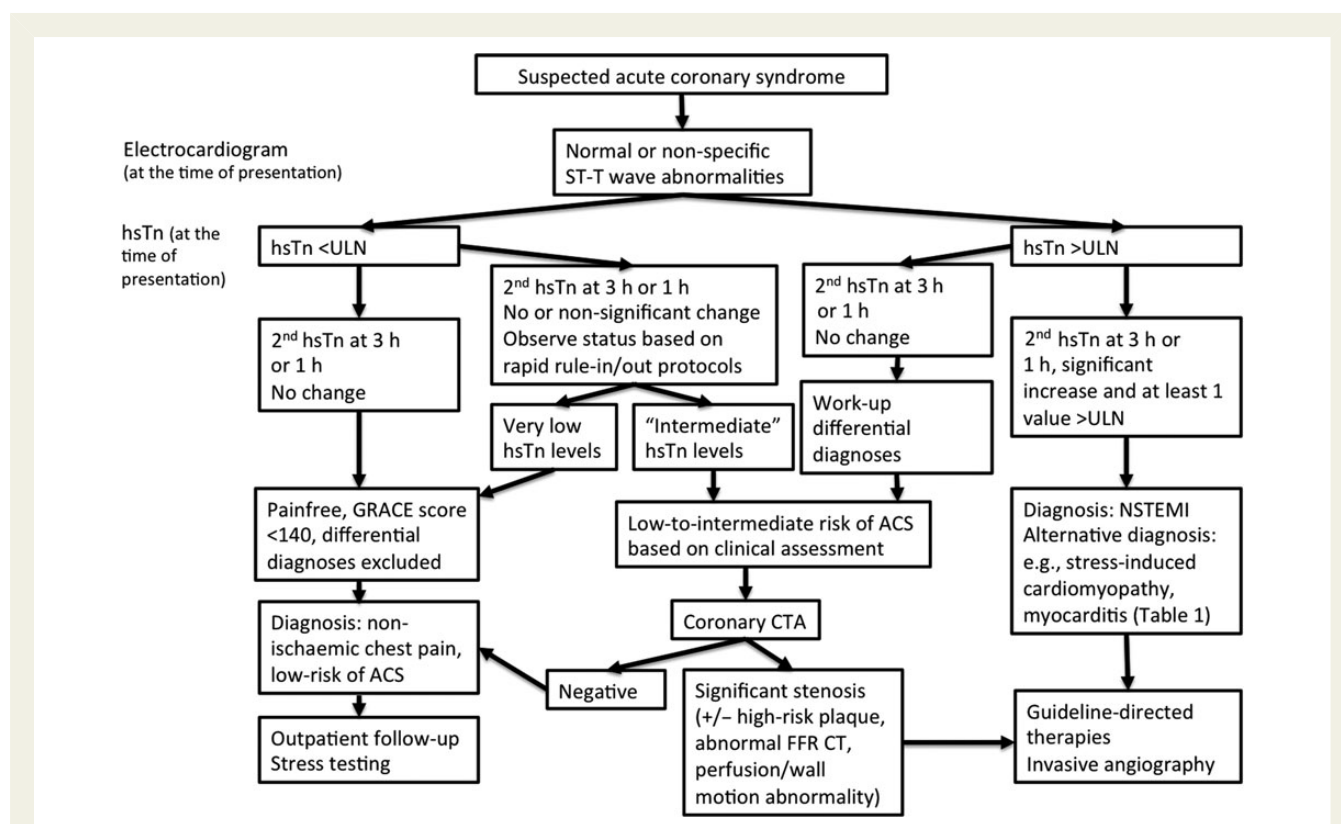
Figure 6 Possible implementation of highly sensitive troponin and coronary computed tomography angiography in the evaluation of patients with suspected acute coronary syndrome in the emergency department.

Conclusions

Highly sensitive Tn assays are an established tool for the rapid and efficient triage of ED patients with suspected ACS. Coronary CTA is a promising diagnostic tool, which in a subset of patients may facilitate early discharge. It will be critical to educate clinicians about the advantages of both techniques with a specific emphasis on the interpretation of the results on probabilistic basis rather than as dichotomous values (i.e. positive vs. negative test). The results of both tests (especially in those with intermediate results) have implications for outpatient management and preventative strategies and need to be effectively communicated to primary care providers.

Authors' contributions

M.F., U.H., F.B., and J.L.J. handled funding and supervision, acquired the data, conceived and designed the research, drafted the manuscript, and made critical revision of the manuscript for key intellectual content.

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