Acute chest pain in the high-sensitivity cardiac troponin era: A changing role for noninvasive imaging?

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Management of patients with acute chest pain remains challenging. Cardiac biomarker testing reduces the likelihood of erroneously discharging patients with acute myocardial infarction (AMI). Despite normal contemporary troponins, physicians have still been reluctant to discharge patients without additional testing. Nowadays, the extremely high negative predictive value of current high-sensitivity cardiac troponin (hs-cTn) assays challenges this need. However, the decreased specificity of hs-cTn assays to diagnose AMI poses a new problem as noncoronary diseases (eg, pulmonary embolism, myocarditis, cardiomyopathies, hypertension, renal failure, etc) may also cause elevated hs-cTn levels. Subjecting patients with noncoronary diseases to unnecessary pharmacological therapy or invasive procedures must be prevented. Attempts to improve the positive predictive value to diagnose AMI by defining higher initial cutoff values or dynamic changes over time inherently lower the sensitivity of troponin assays. In this review, we anticipate a potential changing role of noninvasive imaging from ruling out myocardial disease when troponin values are normal toward characterizing myocardial disease when hs-cTn values are (mildly) abnormal. (Am Heart J 2016;177:102-11.)

Acute chest pain is one of the most common reasons for emergency department (ED) presentation, accounting for 10% of all visits.[1] Diagnostic evaluation of patients with acute chest pain remains challenging due to the heterogeneous spectrum of underlying etiologies that can be of cardiovascular or noncardiovascular origin, and pernicious or benign.[2,3] Although most patients have a non–life-threatening disorder, approximately 15% are diagnosed as having acute myocardial infarction (AMI) and in rare cases with acute aortic dissection (AAD) or pulmonary embolism (PE).[2,4] Even after thorough evaluation, a firm diagnosis remains uncertain in a subset of patients that can unsettle patients and physicians. Particularly in those with atypical chest pain, the pain can be musculoskeletal, gastrointestinal, or respiratory in origin and the yield of additional investigations is generally low.[3,5] Nevertheless, informing patients about their very low probability of future adverse cardiac events when additional noninvasive test results in the ED are negative is often sufficient for reassurance.

For decades, biomarker testing has been playing a central role in the evaluation of patients with acute chest pain and cardiac troponin (cTn) testing has substantially reduced the likelihood of erroneously discharging patients with AMI. An elevated cTn concentration is defined as a measurement exceeding the 99th percentile upper reference limit (URL) of an apparently healthy reference population.[6] Contemporary cTn assays (ie, non–high-sensitive) do not have optimal precision at the recommended 99th percentile. Although serial sampling improves sensitivity, ED physicians are often still reluctant to discharge patients without ordering additional noninvasive (imaging) tests.

Current high-sensitivity (hs) cTn assays measure cTn concentrations above the limit of detection in ≥50% of normal individuals with ≤10% coefficient of variation at the recommended 99th percentile, thereby increasing the ability to determine small changes in cTn.[7-9] Because of the

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extremely high negative predictive value (NPV) of hs-cTn assays for the diagnosis of AMI, the need for additional testing to rule out AMI is challenged.[10–12]

Instead, because of a substantially lower specificity to diagnose AMI, ED physicians are increasingly confronted with abnormal hs-cTn values that may be related to various acute or chronic conditions other than AMI (ie, myocarditis, stress [takotsubo] cardiomyopathy, severe hypertension, tachycardia, renal failure, nonacute structural myocardial disease, AAD, PE, or even stable coronary artery disease [CAD]).[13,14]

Thus, abnormal hs-cTn levels (ie, above the 99th percentile) in patients presenting with acute chest pain and nondiagnostic electrocardiograms (ECGs) do not automatically equate AMI and warrant a more sophisticated approach. Thorough history taking, determination of risk factors, physical examination, and (serial) ECGs remain important tools but lack specificity for a certain diagnosis. Additional noninvasive imaging techniques may be useful to further characterize myocardial disease and prevent unnecessary invasive procedures or aggressive treatments. This review is intended to create a different mind set how noninvasive cardiac imaging in patients presenting with acute chest pain can be useful in the hs-cTn era. It does not come down on the side of any particular imaging strategy as evidence is still building up on this topic.

Initial evaluation

Patients with acute chest pain may have a life-threatening condition, necessitating a rapid evaluation by an experienced physician.[15,16] The ED evaluation primarily focuses on the early exclusion of acute life-threatening conditions and risk stratification to identify patients who can be discharged early or might benefit from tailored treatment, rather than anatomically detecting CAD.[17] For instance, CAD may just be coincidental and an unrelated finding in patients with musculoskeletal chest pain. Hospital admission is usually indicated in case of an acute coronary syndrome, perimyocarditis, stress cardiomyopathy, or certain "malignant" arrhythmias, and may also be appropriate for certain patients with pneumonia or pneumothorax. The acceptable miss rate regarding major adverse cardiac events (mostly AMI, death, or life-threatening arrhythmia) within 30 days of ED presentation for acute chest pain must be <1%.[18]

Although medical history taking is subjective, the absence of typical angina pectoris characteristics and cardiovascular risk factors decreases the probability of AMI substantially, but conversely increases with an increasing number of risk factors.[19,20] Physical examination is often unremarkable, but may be supportive of both coronary and noncoronary causes (eg, PE, acute aortic syndromes, perimyocarditis, valvular disease), as well as extracardiac causes of acute chest pain (eg, pneumothorax, pneumonia). Moreover, reproducible chest wall tenderness on palpation of the thorax substantially reduces the likelihood of AMI or unstable angina pectoris (UA).[20,21]

The ECG remains an essential, first noninvasive test in suspected AMI patients and should be assessed within 10 minutes after ED arrival.[15,16] The likelihood of AMI is lower when the ECG is normal or nondiagnostic but substantially increases in the presence of marked ST-segment deviations.[20,22] Because a single normal ECG does not rule out AMI, it is recommended to obtain serial ECGs or perform continuous ECG monitoring.[23]

Although the prevalence of acute life-threatening noncardiac causes of acute chest pain requiring admission (eg, AAD, PE, and certain patients with pneumothorax or pneumonia) is low, additional testing (ie, D-dimers, chest x-ray, or computed tomographic angiography [CTA]) is useful when clinical suspicion is high.

The initial evaluation remains the cornerstone of risk stratification, but lacks sufficient NPV to exclude all patients with AMI and positive predictive value (PPV) to diagnose AMI or other (myocardial) diseases.[20] Although decision making is usually straightforward in patients presenting with typical cardiac symptoms and pronounced ST-segment deviation, this can be troublesome in patients with atypical symptoms and nondiagnostic ECGs. In these patients, biomarker testing is decisive but elevated biomarkers must always be considered in the clinical context.

Cardiac biomarkers

Cardiac biomarkers are proteins that are released after cardiomyocyte injury. Until 2000, creatine kinase-MB was the most frequently used cardiac biomarker and the frequency of mistakenly discharging patients with AMI was approximately 2%.[24,25] After the year 2000, cTns (cTnI and cTnT [ie, contemporary troponin assays]) became the preferred biomarkers to diagnose myocardial injury because of their cardiac specificity and superior sensitivity to detect myocardial damage.[26] However, the risk for adverse cardiac events is still considered non-negligible in patients with acute chest pain and normal contemporary troponins. Therefore, ED physicians still seek for a higher level of confidence to exclude AMI and often order additional noninvasive and sometimes even invasive tests before discharging a patient. The NPV of distinct noninvasive modalities for adverse cardiac events ranges from 95% to 100% and is shown in online Supplementary Table S1.

High-sensitivity cTn assays

The improved analytical performance of the current hs-cTn assays has enabled the detection of troponins at almost 10-fold lower concentrations and with higher precision. Hs-cTn levels below the 99th percentile URL rule out AMI with extremely high confidence (NPV 99%).[6,10–12] Undetectable hs-cTn levels rule out AMI with

even higher confidence and indicate an excellent prognosis (NPV >99.5%).[12,27] Together with a considerable shorter period after symptom onset to detect increased serum troponin levels, hs-cTn assays have shown superior ability to exclude AMI in comparison with the contemporary cTn assays.[10,11] Of note, serial testing should still be considered in patients with normal initial hs-cTn levels presenting very early after symptom onset.

Inversely, the incidence of AMI increases with increasingly higher hs-cTn values at presentation.[28,29] It follows that rather sharply defined lower range hs-cTn cutoff values can be used to achieve an extremely high NPV but that defining the upper hs-cTn cutoff values to diagnose AMI is more gradual and less absolute. Studies to define the optimal upper hs-cTn cutoff to rule-in AMI are unique for each hs-cTn assay. For the purpose of this review, mildly elevated hs-cTn levels refer to hs-cTn levels > URL and cTn levels that were previously not captured by contemporary cTn-assays without providing specific values.

Low specificity and PPV of hs-cTn assays

The increased diagnostic sensitivity of hs-cTn assays comes at the expense of a lower specificity and PPV to diagnose AMI.[10,11,13,30] This applies to both type 1 MI (ie, related to plaque rupture or thrombotic occlusion) and type 2 MI (ie, secondary to supply-demand mismatch with or without CAD).[31] Type 2 MI is becoming increasingly recognized but is poorly defined, making differentiation from type 1 MI often clinically difficult.[32,33] Differentiation is based on clinical judgment that takes into account various coexisting factors (tachycardia's, anemia, hypertension, sepsis, renal failure, etc).

Using the currently set diagnostic cutoff value for AMI, the PPV to diagnose AMI is only 50% to 70%.[6,10,11] The PPV for AMI is even lower (approximately 20%) when hs-cTn levels are mildly abnormal.[28] Abnormal hs-cTn levels may indicate myocardial injury, but are not specific for type 1 MI and can be due to type 2 MI (tachycardia, hypertension, sepsis, anemia, etc), nonischemic (perimyocarditis, stress cardiomyopathy) or extracardiac diseases (AAD or PE). Moreover, hs-cTn assays allow for the detection of very low troponin values as seen also in patients with (asymptomatic) "stable" CAD and patients with structural heart disease (ie, congestive heart failure, cardiomyopathies, or hypertensive heart disease).[14,34] Regardless, even in asymptomatic patients, mildly elevated hs-cTn levels provide incremental prognostic information.[14,34]

Finally, higher baseline hs-cTn levels are observed in male and elderly patients that may exceed the URL of normal. It has therefore been suggested that age- and gender-specific cutoffs should be applied.[8,35,36] Currently, uniform hs-cTn cutoff levels are used for all patients irrespective of age and sex, resulting in more positive test results in male and elderly patients and potentially missed myocardial disease in female patients.[37]

Attempts to improve the specificity of hs-cTn assays

It is becoming increasingly clear that hs-cTn levels should be interpreted as quantitative rather than qualitative values, and that the terms positive and negative troponin should be avoided. Several algorithms have been suggested and validated to improve the diagnostic specificity of hs-cTn assays to diagnose AMI. A common method is using predefined relative or absolute dynamic changes in hs-cTn levels quantified as the delta troponin over a specified period rather than a single baseline value. This is in accordance with the Third Universal Definition of MI that requires a rise and/or fall pattern of hs-cTn levels.[6] Although the hs-cTn change must be at least above the reference change value that is based on the analytical variation of the respective assay and the biological variation, the magnitude and the time frame of this change are still debated.

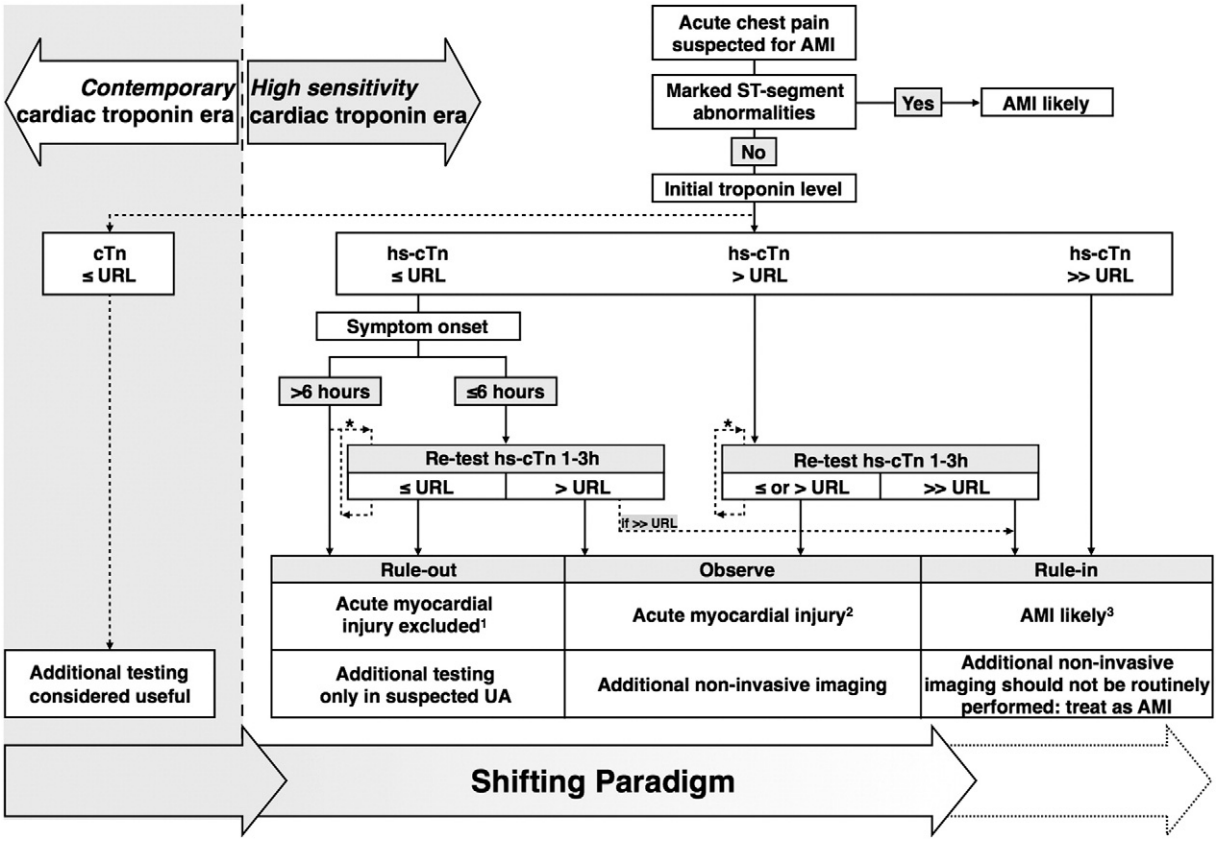
Several relative and absolute changes (eg, 20%-50% and for hs-cTnT 7-9 ng/L) have been suggested but are dependent on the patient population and the immunoassay used.[38,39] Moreover, many of these suggested dynamic changes have been determined retrospectively with an adjudicated AMI diagnosis that was based often on contemporary cTn assays. A recent study demonstrated that relative hs-cTnT changes <20% and absolute changes <9 ng/L are not uncommon (26% and 12%, respectively) in non–ST-elevation myocardial infarction.[40] An editorial comment to that study suggested that for using different delta values, 5% to 67% of AMI may be missed.[41] This raises caution against the strict use of delta values to exclude AMI in patients with an otherwise high clinical probability of AMI. Moreover, dynamic changes are also not exclusive to AMI but rather indicative of acute myocardial injury.

Nevertheless, the European Society of Cardiology has recommended an algorithm for clinical use that incorporates hs-cTn baseline values and 1-hour absolute changes (hs-cTn 0-h/1-h algorithm).[16] This algorithm assigns patients into 3 groups: (1) a rule-out group (60% of patients), (2) a rule-in group (17% of patients), and (3) an observe group with substantial diagnostic uncertainty (23% of remaining patients).[29] Although this algorithm improves clinical decision making, still 22% in the rule-in group and 81% in the observe group eventually do not have AMI. Most patients in the observe group are diagnosed as having noncoronary myocardial or noncardiac disease, although preexisting CAD may be frequently present.[29,42,43]

Increased biomarker levels should always be evaluated in light of the clinical scenario, patient characteristics, and pretest probabilities because isolated (mildly) abnormal hs-cTn levels are insufficient to diagnose AMI.[6] On the other hand, higher baseline hs-cTn and delta values may be indicative of acute (ongoing) myocardial injury and increase the probability of AMI.[29,38]

In summary, current clinical interpretation of abnormal hs-cTn levels in acute chest pain is useful but lacks sufficient

Figure



Risk stratification algorithm in patients with acute chest pain suspected for myocardial ischemia. ">>" means markedly elevated and/or substantially rising hs-cTn level. [1]Acute myocardial injury can be ruled out confidently and prognosis is excellent. Of note: UA may still be present in a small subset of these patients. [2]Acute myocardial injury: both coronary and noncoronary causes (myocarditis, cardiomyopathies [stress, hypertrophic, dilated], PE) may be responsible. [3]AMI highly likely. *Reassess hs-cTn if clinical suspicion for AMI is high and/or symptom-onset uncertain. cTn, contemporary cTn assay (ie, non–high-sensitive); STEMI, ST-elevation myocardial infarction.

specificity for a certain myocardial disease and methods to improve the diagnostic specificity inherently lower sensitivity.

Usefulness of additional noninvasive cardiovascular testing

Based on the initial hs-cTn values and repeated measures, the European Society of Cardiology guidelines support the classification of patients into 3 groups.[16] Figure shows a modification of this algorithm and provides suggestions for the usefulness of additional testing or noninvasive imaging: (1) rule-out group: in patients with hs-cTn levels ≤ URL or undetectable levels, AMI can be ruled out confidently (ie, prognosis is excellent and the rate of missing AMI is extremely low) and additional testing is generally discouraged to prevent false-positive test results; (2) observe group: in patients with (mildly) abnormal (>URL) hs-cTn levels but without a substantial rise and/or fall, additional testing and characterization of myocardial injury is often necessary (to differentiate between coronary and noncoronary myocardial disease or even extracardiac disease); and (3) rule-in group: patients with markedly elevated and/or substantially rising hs-cTn levels and the appropriate clinical setting have a high likelihood for AMI and should undergo invasive testing when indicated. With the exception of indicated echocardiography, additional noninvasive tests should not unnecessarily delay invasive management in the rule-in group.

In cohort studies comparing 2 sequential periods, introducing the hs-cTn assay significantly increased the prevalence of AMI, use of ACS medications, invasive coronary angiograms, revascularization procedures, and length of hospital stay as compared with the contemporary assay period. Whether this more aggressive approach

improves outcome is still unknown because studies have been conflicting.[44–46] Although abnormal hs-cTn values should always be interpreted in the light of symptoms and pretest probability, a certain diagnosis cannot be reliably ruled in or out at this time. Therefore, careful clinical evaluation and diagnostic workup should precede routine invasive management and may be particularly useful in the "observe" group with most considerable diagnostic uncertainty.[42]

Furthermore, studies are needed that optimally define "markedly elevated and/or substantially rising hs-cTn levels." These studies should ideally include imaging end points to more accurately define AMI (to identify new loss of viable myocardium or new regional wall motion abnormalities), rather than an adjudicated diagnosis based on clinical parameters only.

In patients with normal and undetectable hs-cTn levels

In the contemporary cTn era (ie, non–high-sensitive) and supported by guidelines, additional noninvasive testing was often performed before discharging patients with normal troponin levels with increased certainty. High-sensitivity cTn assays now rule out AMI with an NPV of 99%, and even >99.5% when hs-cTn levels are undetectable.[10–12,27] In combination with a much shorter time to rule out AMI after presentation, this may obviate the need for additional noninvasive testing at all or at least in the ED in these patients. Additional testing in extremely low-risk patients may even cause harm because of an increased number of false positive test results (according to Bayes' theorem). Regardless, clinical judgment by an experienced ED physician remains crucial. Typical angina symptoms, acceleration of previously stable angina, presence of cardiovascular risk factors, signs of atherosclerosis on physical examination, preexisting coronary artery stenosis ≥70%, or positive cardiac exercise test result may still require admission for suspected UA or discharge with additional testing in the outpatient clinic. It should be noted that the prevalence of UA declines when using hs-cTn assays because many patients diagnosed as having UA using contemporary cTn assays can be reclassified as AMI.[44,47]

Although AMI can be ruled out reliably, normal hs-cTn levels (<URL) or stable hs-cTn elevations not fulfilling the criteria for AMI obviously do not rule out the presence of CAD or UA. Unstable angina pectoris is suspected on the basis of clinical judgment (pretest probability, risk factors, typical angina) and warrants in-hospital management. On the other hand, systematically searching for CAD (using CTA) and initiating preventive medication in a low-risk population has not yet shown to improve outcome or to be cost-effective thus far.[48] A systematic search for CAD in the ED is not recommended and the detection of CAD might rather be a finding unrelated to current symptoms.[17]

In summary, the high NPV of current hs-cTn assays questions the need for urgent additional noninvasive testing before patients can be safely discharged from the ED.[9,49,50] Conversely, additional noninvasive testing remains necessary in suspected UA.

In patients with mildly abnormal hs-cTn levels

The challenge now lies in the clinical interpretation of mildly abnormal hs-cTn levels (patients in the observe group) because this may reflect AMI or acute noncoronary (structural) myocardial disease, or may be associated with chronic stable CAD, renal dysfunction, or even be a variation of normal (in the elderly and men). Clearly, patients not having AMI should not be subjected to unnecessary aggressive antithrombotic, antiplatelet therapy, or invasive coronary angiography. Although symptoms, physical examination, serial ECGs, and height of initial hs-cTn levels contain pivotal information, the initial evaluation is often not specific for a certain diagnosis. This is even more difficult when hs-cTn levels are only mildly abnormal. Noninvasive cardiovascular imaging early in the diagnostic process could therefore be particularly useful to further characterize myocardial disease and hence serve as a gatekeeper to prevent unnecessary invasive procedures or aggressive therapy.

Exercise testing is generally considered contraindicated in patients with suspected AMI.[51] Apart from this, it does not provide structural information and does not allow for differentiating between myocardial diseases. *Two-dimensional (2D) echocardiography* by a trained physician can be very helpful for the initial assessment of certain patients with acute chest pain, especially when patients are hemodynamically compromised. Current guidelines recommend 2D echocardiography to detect AMI or other acute pathologies, such as AAD or PE.[16] However, recent studies challenge the generally believed high accuracy of 2D echocardiography to detect AMI based on the visual assessment of segmental wall motion abnormalities (SWMAs).[52] Importantly, SWMAs are not specific for AMI and can be found in myocarditis as well.[53] Myocardial contrast echocardiography accurately reflects decreased myocardial perfusion and has been shown to increase the diagnostic accuracy to detect AMI over visual assessment of SWMA.[54] Strain analysis using speckle-tracking echocardiography appears promising to detect AMI but still needs additional validation.[55] Moreover, suboptimal acoustic windows in a substantial number of patients hinder all echocardiographic techniques. Therefore, its usefulness in patients with mildly abnormal hs-cTn levels is limited.

Alternative noninvasive imaging tests include nuclear cardiovascular imaging, cardiovascular magnetic resonance imaging (CMR), and cardiac CTA. Although they visualize different aspects of disease, each modality can be used uniquely to differentiate between coronary and noncoronary myocardial disease.

Resting myocardial perfusion can be assessed with *single-photon emission computed tomographic* (SPECT) using ^{99m}Technetium-Sestamibi or, less frequently nowadays,

^{201}Thallium. The sensitivity to detect AMI ranges from 90% to 100% (NPV 99%-100%).[56,57] Patients with acute chest pain and normal rest myocardial perfusion have an excellent prognosis.[56,57] In addition to detecting myocardial perfusion, gated SPECT allows for determining global and regional ventricular function.[58] However, SPECT has not gained widespread clinical acceptance for use in patients with acute chest pain, because smaller defects remain undetected and there are logistic restraints in the ED setting.[59] Although *positron emission tomography* (PET) myocardial perfusion more accurately detects CAD in comparison to SPECT in an outpatient setting, its usefulness is less well studied in the ED.[60] Increased uptake of ^{18}F-fluorodeoxyglucose can be observed in active myocardial inflammation, whereas uptake is decreased in AMI and ischemic myocardium.[61] ^{18}F-fluorodeoxyglucose PET has also been used to image plaque instability and inflammation, but accurate interpretation of the coronary arteries is often hindered by interference with background myocardial uptake as well as the rather low spatial and temporal resolution.[62] ^{18}F-sodium fluoride PET imaging is promising and abnormal coronary artery uptake strongly suggests acute coronary pathology.[62] However, ^{18}F-sodium fluoride PET imaging is at this time not feasible in the ED. Other PET tracers, such as rubidium-82 and the novel tracer flurpiridaz F-18, provide information on myocardial perfusion. However, for both tracers but mainly for flurpiridaz, data on their performance in detecting perfusion defects on rest images are rare and require further evaluation in larger clinical trials.[63] Furthermore, flurpiridaz is not yet available for clinical use. A major drawback of nuclear imaging (both SPECT and PET) is the inability to exclude or diagnose more than one disease, whereas the differential diagnosis in patients with mildly abnormal hs-cTn levels is broad. Hence, "one-stop-shop" imaging to identify the underlying cause cannot be expected because nuclear medicine tracers are more or less specifically usable for one clinical indication, and therefore, different radiotracers are required to exclude different potential causes. A hybrid approach of PET with CT or CMR may increase the clinical potential of nuclear imaging in the cardiac ED, but availability of these hybrid scanners is very limited. Currently, it seems unlikely that PET or SPECT will play an important role in the emergency setting as a tool to differentiate between myocardial diseases when hs-cTn levels are abnormal. Finally, nuclear imaging exposes patients to ionizing radiation and imaging protocols can be time-consuming.

Several *CMR* techniques can be used to comprehensively assess patients with acute chest pain and abnormal hs-cTn levels. A CMR protocol, including cine, T2-weighted, rest perfusion and delayed enhancement (DE) CMR, has been shown to be highly accurate to diagnose AMI.[64,65] Delayed enhancement CMR is a well-validated technique to assess the presence, location, etiology, size, and transmural extent of myocardial scarring.[66] Delayed enhancement CMR can detect a very small amount of injury (<1 g myocardial tissue).[67] The pattern of hyperenhancement on DE-CMR provides important information regarding the underlying etiology.[68] In particular, a subendocardial or transmural hyperenhancement pattern is most frequently observed in ischemic injury, based on the wave front phenomenon of ischemic myocardial injury, whereas a mid- to epicardial hyperenhancement pattern suggests nonischemic pathology (eg, myocarditis).[68] A comprehensive CMR investigation been shown to provide a final diagnosis in 70% of patients with acute chest pain, with normal or insignificant coronary artery stenosis (<50%) on invasive coronary angiography.[69,70] Absence of significant obstructive CAD or angiographic evidence of acute plaque rupture is part of the proposed criteria for diagnosing takotsubo cardiomyopathy. Cardiovascular magnetic resonance imaging typically shows left ventricular wall motion abnormalities extending beyond a single coronary perfusion bed, high signal on T2-weighted sequences, and absence of scar on DE-CMR.[71,72] In the presence of an appropriate clinical setting, these typical CMR findings may be diagnostic and eliminate the need for invasive coronary angiography. Cardiovascular magnetic resonance imaging is highly accurate to detect structural heart disease that may be responsible for stable and mildly abnormal hs-cTn levels (eg, dilated, hypertrophic, or infiltrative cardiomyopathy). Although generally considered less accurate than CTA, CMR may also be useful to exclude AAD or PE.[73,74] Although a normal CMR study including stress-rest perfusion imaging does not provide a final diagnosis in patients with acute chest pain, it does indicate an excellent prognosis.[70,75] Disadvantages of CMR are limited availability, need for specialized equipment and personnel, time-consuming scanning protocols that can be strenuous for patients, and restricted applicability in patients with ferromagnetic implants.

Computed tomographic angiography is a relatively straightforward technique and available in many centers on a 24/7 basis, but inevitably requires exposure to ionizing radiation and iodine contrast agents. This noninvasive imaging modality provides insight in coronary and noncoronary causes of acute chest pain. Administration of iodinated contrast agents is required because a native CT scan (without angiography) is insufficient to exclude AMI and other disease (ie, AAD or PE).[76] Although a "triple rule-out" protocol may be useful to rule out AAD, PE, and CAD, the overall diagnostic yield of this strategy has not yet shown to be superior to coronary CTA alone.[4,77,78] Besides assessing the severity of coronary stenosis, several plaque characteristics associated with AMI can be assessed including outward remodeling, spotty calcifications, and a low-density lipid core.[79] Although a ≥50% coronary stenosis on CTA is suspicious for a coronary etiology of chest pain and elevated hs-cTn levels, it may merely be a coincidental and unrelated finding.[80] Computed tomographic angiography may erroneously exclude AMI or UA in up to 20% of patients with no or mild CAD, whereas they remain at high risk for long-term recurrent ischemic events

and may benefit from antiplatelet therapy.[81,82] Rest myocardial perfusion CT and fractional flow reserve CT appear promising to further improve the diagnostic yield by evaluating the functional consequence of a stenosis.[83,84] A fractional flow reserve CT–guided strategy has been associated with fewer unnecessary invasive coronary angiograms in patients with new-onset chest pain.[85] Delayed enhancement CT may be used to visualize scar similar to DE-CMR.[86,87] Whether these CT technologies also allow for characterizing myocardial disease in patients with mildly elevated hs-cTn levels is unknown. Some studies suggest that CTA may be useful to detect extracardiac disease in highly selected patients with acute chest pain and mildly abnormal cTn levels, but whether these findings are related to symptoms is disputable.[88]

Although patients should be diagnosed as early as possible to prevent erroneous or delayed therapy, the relatively low-risk profile allows for deferral of additional noninvasive imaging for at least 24 hours.[16] Which noninvasive imaging modality is most useful in these patients is currently unknown but dependent on several factors. Nevertheless, the current hs-cTn era will change the deployment of noninvasive imaging, from ruling out acute myocardial disease toward characterizing myocardial disease. The ongoing CARMENTA trial (NCT01559467) investigates whether implementing CTA or CMR early in the diagnostic process in patients presenting with acute chest pain, nondiagnostic ECGs, and abnormal hs-cTnT levels can prevent invasive procedures in comparison to routine clinical management without adversely affecting outcome.[89] Computed tomographic angiography and CMR have their own and unique ways to prevent invasive coronary angiography by excluding (significant) CAD and to detect other diseases such as AAD and PE (CTA and CMR) or myocarditis and stress cardiomyopathy (CMR). Furthermore, this trial may help to determine the preferential imaging modality in this setting, to better define hs-cTn cutoff levels that rule in AMI and to improve the differentiation between types 1 and 2 MI. Especially patients who have undergone both (non-) invasive coronary angiography and CMR will be suitable to investigate the latter.

Patients with markedly abnormal hs-cTn levels

An (early, within <24 hours) invasive approach is usually recommended in patients with high-risk clinical features and markedly elevated or rising and/or falling troponin levels.[15,16] Although the extent of these values has not been properly defined yet, the probability of AMI increases substantially when initial hs-cTn values and "delta" values changes are higher.[28,29,38] Patients with persistent ST-elevation or ST-depression and other high-risk features (cardiogenic shock, ventricular tachycardias) should undergo immediate invasive coronary angiography that should not be delayed by routine preprocedural advanced noninvasive imaging. Despite this, echocardiography can occasionally be extremely valuable to assess ventricular function, complications (myocardial rupture, pericardial effusion), valvular disease, or other life-threatening diagnoses (AAD, PE).

Nonetheless, in up to 20% of patients suspected for AMI no or nonobstructed (<50%) CAD is found after invasive coronary angiography.[90,91] The differential diagnosis includes AMI caused by a temporary coronary artery occlusion (spontaneous recanalization, embolism with spontaneous thrombolysis, or spasm), myocarditis, stress cardiomyopathy, PE, or AAD. Evidence for certain diagnoses can already be obtained during invasive coronary angiography and include testing for vasospasm or searching for vulnerable plaques with intravascular ultrasound or optical coherence tomography. Cardiovascular magnetic resonance imaging is a very useful secondary diagnostic step in patients with "normal" coronary arteries, to differentiate between coronary and noncoronary myocardial disease.[68–70] In the presence of a typical MI pattern (ie, subendocardial or transmural scar), the coronary angiogram should be reassessed to search for small-occluded side branches that initially may have been overlooked. Additional CTA may detect outward remodeled vulnerable plaques that were initially not apparent, or detect AAD or PE. In the presence of a typical CMR pattern of MI but normal coronary arteries on CTA, patients can be tested for a hypercoagulable state (spontaneous coronary thrombosis) or paradoxical embolism (patent foramen ovale or atrial septal defect).

Conclusion

Despite normal contemporary cTn levels in patients with acute chest pain, ED physicians often needed additional noninvasive tests to achieve a higher level of confidence before safely discharging patients. Current hs-cTn assays now rule out AMI with high confidence and challenge this need for additional testing. This does not apply for UA, because hs-cTn assays do not rule out UA. However, the reduced specificity of the hs-cTn assays for AMI confronts ED physicians with a new problem because (mildly) abnormal hs-cTn values are increasingly being encountered and may reflect an underlying coronary, noncoronary myocardial disease, or even noncardiac disease. Consequently, a shifting paradigm of the deployment of noninvasive imaging is anticipated from ruling out toward characterizing myocardial disease and prevent that patients are subjected to unnecessary aggressive antithrombotic treatment and invasive procedures. As evidence is still building up, the most appropriate imaging modality or even multicomponent strategy is currently unknown, but an individualized approach of "tailored diagnostics" seems plausible. Prospective studies are required that not only investigate the diagnostic accuracy of imaging modalities, but also the therapeutic consequences related to the diagnostic findings.

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Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.03.025.

References

1. Mockel M, Searle J, Muller R, et al. Chief complaints in medical emergencies: do they relate to underlying disease and outcome? The Charite Emergency Medicine Study (CHARITEM). Eur J Emerg Med 2013;20(2):103-8.
2. Lee TH, Goldman L. Evaluation of the patient with acute chest pain. N Engl J Med 2000;342(16):1187-95.
3. Fruergaard P, Launbjerg J, Hesse B, et al. The diagnoses of patients admitted with acute chest pain but without myocardial infarction. Eur Heart J 1996;17(7):1028-34.
4. Burris II AC, Boura JA, Raff GL, et al. Triple rule out versus coronary CT angiography in patients with acute chest pain: results from the ACIC consortium. JACC Cardiovasc Imaging 2015;8(7):817-25.
5. Spalding L, Reay E, Kelly C. Cause and outcome of atypical chest pain in patients admitted to hospital. J R Soc Med 2003;96(3):122-5.
6. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60(16):1581-98.
7. Apple FS, Collinson PO, Biomarkers ITFoCAoC. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem 2012;58(1):54-61.
8. Apple FS, Jaffe AS, Collinson P, et al. IFCC educational materials on selected analytical and clinical applications of high sensitivity cardiac troponin assays. Clin Biochem 2015;48(4–5):201-3.
9. Sandoval Y, Smith SW, Apple FS. Present and future of cardiac troponin in clinical practice: a paradigm shift to high-sensitivity assays. Am J Med 2016;129(4):354-65.
10. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361(9):858-67.
11. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol 2011;58(13):1332-9.
12. Shah ASV, Anand A, Sandoval Y, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015;386(10012):2481-8.
13. Mueller C. Biomarkers and acute coronary syndromes: an update. Eur Heart J 2014;35(9):552-6.
14. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304(22):2503-12.
15. Amsterdam EA, Wenger NK, Brindis RG, et al. AHA/ACC guideline for the management of patients with non-st-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64(24):e139-228.
16. Roffi M, Patrono C, Collet JP, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.
17. Amsterdam EA, Kirk JD, Bluemke DA, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. Circulation 2010;122(17):1756-76.
18. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the emergency department? A clinical survey. Int J Cardiol 2013;166(3):752-4.
19. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. JAMA 2005;294(20):2623-9.
20. Fanaroff AC, Rymer JA, Goldstein SA, et al. Does this patient with chest pain have acute coronary syndrome? The rational clinical examination systematic review. JAMA 2015;314(18):1955-65.
21. Grani C, Senn O, Bischof M, et al. Diagnostic performance of reproducible chest wall tenderness to rule out acute coronary syndrome in acute chest pain: a prospective diagnostic study. BMJ Open 2015;5(1):e007442.
22. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78-140.
23. Fesmire FM, Percy RF, Bardoner JB, et al. Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. Ann Emerg Med 1998;31(1):3-11.
24. McCarthy BD, Beshansky JR, D'Agostino RB, et al. Missed diagnoses of acute myocardial infarction in the emergency department: results from a multicenter study. Ann Emerg Med 1993;22(3):579-82.
25. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000;342(16):1163-70.
26. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36(3):959-69.
27. Bandstein N, Ljung R, Johansson M, et al. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. J Am Coll Cardiol 2014;63(23):2569-78.
28. Melki D, Lugnegård J, Alfredsson J, et al. Implications of introducing high-sensitivity cardiac troponin T into clinical practice. J Am Coll Cardiol 2015;65(16):1655-64.
29. Reichlin T, Schindler C, Drexler B, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med 2012;172(16):1211-8.

30. Lipinski MJ, Baker NC, Escarcega RO, et al. Comparison of conventional and high-sensitivity troponin in patients with chest pain: a collaborative meta-analysis. Am Heart J 2015;169(1):6-16.e6.
31. Sandoval Y, Smith SW, Thordsen SE, et al. Supply/demand type 2 myocardial infarction: should we be paying more attention? J Am Coll Cardiol 2014;63(20):2079-87.
32. Korley FK, Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. J Am Coll Cardiol 2013;61(17):1753-8.
33. Sandoval Y, Smith SW, Schulz KM, et al. Diagnosis of type 1 and type 2 myocardial infarction using a high-sensitivity cardiac troponin I assay with sex-specific 99th percentiles based on the third universal definition of myocardial infarction classification system. Clin Chem 2015;61(4): 657-63.
34. Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361(26):2538-47.
35. Cardinaels EP, Mingels AM, Jacobs LH, et al. A comprehensive review of upper reference limits reported for (high-)sensitivity cardiac troponin assays: the challenges that lie ahead. Clin Chem Lab Med 2012;50(5):791-806.
36. Gore MO, Seliger SL, Defilippi CR, et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. J Am Coll Cardiol 2014;63(14):1441-8.
37. Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ 2015;350:g7873.
38. Mueller M, Biener M, Vafaie M, et al. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. Clin Chem 2012;58(1): 209-18.
39. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124(2):136-45.
40. Bjurman C, Larsson M, Johanson P, et al. Small changes in troponin T levels are common in patients with non–ST-segment elevation myocardial infarction and are linked to higher mortality. J Am Coll Cardiol 2013;62(14):1231-8.
41. Morrow DA, Bonaca MP. Real-world application of "delta" troponin: diagnostic and prognostic implications. J Am Coll Cardiol 2013;62(14):1239-41.
42. Nestelberger T, Wildi K, Boeddinghaus J, et al. Characterization of the observe zone of the ESC 2015 high-sensitivity cardiac troponin 0 h/1h-algorithm for the early diagnosis of acute myocardial infarction. Int J Cardiol 2016;207:238-45.
43. Reichlin T, Twerenbold R, Wildi K, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. CMAJ 2015;187(8):E243-52.
44. Eggers KM, Lindahl B, Melki D, et al. Consequences of implementing a cardiac troponin assay with improved sensitivity at Swedish coronary care units: an analysis from the SWEDEHEART registry. Eur Heart J 2016, http://dx.doi.org/10.1093/eurheartj/ehw029.
45. Mills NL, Churchhouse AM, Lee KK, et al. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. JAMA 2011;305(12):1210-6.
46. Sanchis J, Garcia-Blas S, Mainar L, et al. High-sensitivity versus conventional troponin for management and prognosis assessment of patients with acute chest pain. Heart 2014;100(20):1591-6.
47. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? Circulation 2013;127(24):2452-7.
48. Litt HI, Gatsonis C, Snyder B, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med 2012;366(15):1393-403.
49. Redberg RF. Coronary CT, angiography for acute chest pain. N Engl J Med 2012;367(4):375-6.
50. Prasad V, Cheung M, Cifu A. Chest pain in the emergency department: the case against our current practice of routine noninvasive testing. Arch Intern Med 2012;172(19):1506-9.
51. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997;30(1):260-311.
52. Jaarsma C, Schalla S, Cheriex EC, et al. Incremental value of cardiovascular magnetic resonance over echocardiography in the detection of acute and chronic myocardial infarction. J Cardiovasc Magn Reson 2013;15:1-10.
53. Pinamonti B, Alberti E, Cigalotto A, et al. Echocardiographic findings in myocarditis. Am J Cardiol 1988;62(4):285-91.
54. Rinkevich D, Kaul S, Wang XQ, et al. Regional left ventricular perfusion and function in patients presenting to the emergency department with chest pain and no ST-segment elevation. Eur Heart J 2005;26(16):1606-11.
55. Sjoli B, Orn S, Grenne B, et al. Diagnostic capability and reproducibility of strain by Doppler and by speckle tracking in patients with acute myocardial infarction. JACC Cardiovasc Imaging 2009;2(1):24-33.
56. Heller GV, Stowers SA, Hendel RC, et al. Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. J Am Coll Cardiol 1998;31(5):1011-7.
57. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99 m sestamibi imaging. J Am Coll Cardiol 1998;32(1):57-62.
58. Anagnostopoulos C, Gunning MG, Pennell DJ, et al. Regional myocardial motion and thickening assessed at rest by ECG-gated 99mTc-MIBI emission tomography and by magnetic resonance imaging. Eur J Nucl Med 1996;23(8):909-16.
59. Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. Lancet 2003;361(9355):374-9.
60. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol 2012;59(19):1719-28.
61. Rischpler C, Nekolla SG, Kunze KP, et al. PET/MRI of the heart. Semin Nucl Med 2015;45(3):234-47.
62. Joshi NV, Vesey AT, Williams MC, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. Lancet 2014;383(9918):705-13.
63. Maddahi J, Packard RR. Cardiac PET perfusion tracers: current status and future directions. Semin Nucl Med 2014;44(5):333-43.
64. Kwong RY, Schussheim AE, Rekhraj S, et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. Circulation 2003;107(4):531-7.
65. Cury RC, Shash K, Nagurney JT, et al. Cardiac magnetic resonance with T2-weighted imaging improves detection of patients with acute coronary syndrome in the emergency department. Circulation 2008;118(8):837-44.

66. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100(19):1992-2002.
67. Ricciardi MJ, Wu E, Davidson CJ, et al. Visualization of discrete microinfarction after percutaneous coronary intervention associated with mild creatine kinase-MB elevation. Circulation 2001;103(23):2780-3.
68. Mahrholdt H, Wagner A, Judd RM, et al. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J 2005;26(15):1461-74.
69. Assomull RG, Lyne JC, Keenan N, et al. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. Eur Heart J 2007;28(10):1242-9.
70. Gerbaud E, Harcaut E, Coste P, et al. Cardiac magnetic resonance imaging for the diagnosis of patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. Int J Cardiovasc Imaging 2012;28(4):783-94.
71. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. JAMA 2011;306(3):277-86.
72. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008;155(3):408-17.
73. Stein PD, Chenevert TL, Fowler SE, et al. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). Ann Intern Med 2010;152(7):434-43. [W142–3].
74. Moore AG, Eagle KA, Bruckman D, et al. Choice of computed tomography, transesophageal echocardiography, magnetic resonance imaging, and aortography in acute aortic dissection: International Registry of Acute Aortic Dissection (IRAD). Am J Cardiol 2002;89(10):1235-8.
75. Chopard R, Jehl J, Dutheil J, et al. Evolution of acute coronary syndrome with normal coronary arteries and normal cardiac magnetic resonance imaging. Arch Cardiovasc Dis 2011;104(10):509-17.
76. Dedic A, Ten Kate GJ, Neefjes LA, et al. Coronary CT angiography outperforms calcium imaging in the triage of acute coronary syndrome. Int J Cardiol 2013;167(4):1597-602.
77. Takakuwa KM, Halpern EJ. Evaluation of a "triple rule-out" coronary CT angiography protocol: use of 64-section CT in low-to-moderate risk emergency department patients suspected of having acute coronary syndrome. Radiology 2008;248(2):438-46.
78. Ayaram D, Bellolio MF, Murad MH, et al. Triple rule-out computed tomographic angiography for chest pain: a diagnostic systematic review and meta-analysis. Acad Emerg Med 2013;20(9):861-71.
79. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. J Am Coll Cardiol 2014;64(7):684-92.
80. Ferencik M, Liu T, Mayrhofer T, et al. hs-Troponin I followed by CT angiography improves acute coronary syndrome risk stratification accuracy and work-up in acute chest pain patients: results from ROMICAT II trial. JACC Cardiovasc Imaging 2015;8(11):1272-81.
81. Lindholm D, Varenhorst C, Cannon CP, et al. Ticagrelor vs. clopidogrel in patients with non–ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J 2014;35(31):2083-93.
82. Rossini R, Capodanno D, Lettieri C, et al. Long-term outcomes of patients with acute coronary syndrome and nonobstructive coronary artery disease. Am J Cardiol 2013;112(2):150-5.
83. Pursnani A, Lee AM, Mayrhofer T, et al. Early resting myocardial computed tomography perfusion for the detection of acute coronary syndrome in patients with coronary artery disease. Circ Cardiovasc Imaging 2015;8:e002404.
84. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 2014;63(12):1145-55.
85. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRCT: outcome and resource impacts study. Eur Heart J 2015;36(47):3359-67.
86. Lardo AC, Cordeiro MA, Silva C, et al. Contrast-enhanced multidetector computed tomography viability imaging after myocardial infarction: characterization of myocyte death, microvascular obstruction, and chronic scar. Circulation 2006;113(3):394-404.
87. Gerber BL, Belge B, Legros GJ, et al. Characterization of acute and chronic myocardial infarcts by multidetector computed tomography: comparison with contrast-enhanced magnetic resonance. Circulation 2006;113(6):823-33.
88. Gruettner J, Fink C, Walter T, et al. Coronary computed tomography and triple rule out CT in patients with acute chest pain and an intermediate cardiac risk profile. Part 1: impact on patient management. Eur J Radiol 2013;82(1):100-5.
89. Smulders MW, Kietselaer BL, Das M, et al. The role of cardiovascular magnetic resonance imaging and computed tomography angiography in suspected non–ST-elevation myocardial infarction patients: design and rationale of the CARdiovascular Magnetic rEsoNance imaging and computed Tomography Angiography (CARMENTA) trial. Am Heart J 2013;166(6):968-75.
90. Collste O, Sorensson P, Frick M, et al. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. J Intern Med 2013;273(2):189-96.
91. Patel MR, Chen AY, Peterson ED, et al. Prevalence, predictors, and outcomes of patients with non–ST-segment elevation myocardial infarction and insignificant coronary artery disease: results from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE) initiative. Am Heart J 2006;152(4):641-7.