State of the Art—High-Sensitivity Troponins in Acute Coronary Syndromes

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KEYWORDS

• High-sensitivity troponin • Acute coronary syndrome • Myocardial injury • Myocardial infarction • Biomarker

KEY POINTS

- Because of limited sensitivity and accuracy of symptoms and electrocardiogram for the diagnosis of acute coronary syndrome, biomarkers have become an indispensable tool for diagnosis.
- Over the last years, high-sensitivity troponin (hsTN) assays have become ubiquitously available.
- The implementation of hsTN assays allows for the implementation of rapid rule-in and rule-out algorithms with a high negative predictive value.
- Because of their high sensitivity, a relevant number of positive troponin tests outside the setting of myocardial infarction is a frequent challenge to the clinician.
- The use of high-sensitivity troponins led to the redefinition of the term "myocardial injury," with clinical and prognostic implication for patient care.

INTRODUCTION

History: Biomarkers for the Diagnosis of Acute Myocardial Infarction—from Liver Enzymes to High-Sensitivity Troponin

Biomarkers indicating acute myocardial damage have become an indispensable cornerstone in diagnosis and risk stratification in emergency medicine in patients with suspected acute coronary syndrome (ACS), particularly for cases in which the accuracy of clinical parameters and electrocardiogram (ECG) changes is thought to be limited.[1,2] Only 60 years ago, biomarkers were established as a tool for the diagnosis of acute myocardial infarction (MI) for the first time in 1956[3] (**Fig. 1**). At that time, measurement of serum levels of aspartate transaminase was widely used, and the proof of elevated levels entered the first World Health Organization (WHO) definition of MI.[4] In the 1970s, lactate dehydrogenase (LDH), creatine kinase (CK), and myoglobin were introduced and further enhanced the available spectrum of blood markers in the context of the early differential diagnosis of MI.[5] Yet, a relevant lack of specificity of these markers limited their use. Later advances in electrophoresis allowed detection of cardiac-specific isoenzymes of CK and LDH (ie, CK-MB and LDH-1 and -2), which led to a modification of WHO criteria to rule out acute MI in 1979.[6] Although the high rate of false-positive results due to equally high positivity in

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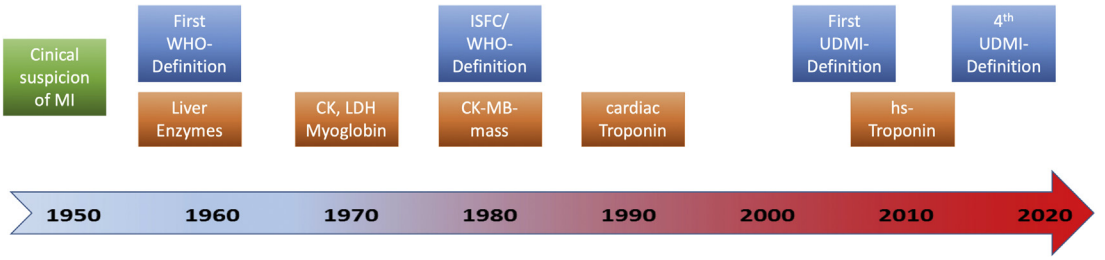

Fig. 1. Timeline of clinical definitions of myocardial infarction and development of cardiac biomarkers. For details, see text. CK, creatine kinase; hs, high-sensitivity; ISFC, International Society and Federation of Cardiology; LDH, lactate dehydrogenase; MI, myocardial infarction; UDMI, universal definition of myocardial infarction; WHO, World Health Organization. (*Data from* Garg P, Morris P, Fazlanie AL, et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. Intern Emerg Med 2017;12:147-155. And Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. Eur Heart J 2018;40:237-269.)

the setting of skeletal muscular injury relevantly impaired their diagnostic accuracy, CK and LDH played a crucial role in the diagnosis of MI up to the 1990s. Troponin—a protein component of myofibrils—had already been discovered in 1965.[7] In 1989, a reliable immunoassay to detect serum levels of cardiac troponin (cTN) levels as cardiospecific protein was developed.[8] In contrast to the contemporary approach, cTN measurements were initially only used in cases of ST-segment elevation MI (STEMI) to monitor infarct size.[9] In the context of acute MI, elevated cTN levels can be detected after 4 to 10 hours after onset of symptoms with a peak at 12 up to 48 hours and return to normal concentrations after 4 to 10 days. Test sensitivity of cTN measurements for MI was found to be as high as nearly 100% after 6 to 12 hours after symptom onset with these early assays.[10,11] Thus, guidelines of the early 2000s established a rule-out strategy for patients with ACS presenting without ST-segment elevation (NSTE-ACS) based on the sequential measurements of cTN levels, repeated after 6 to 12 hours (eg,[12]).

The Protein Troponin as Component of the Cardiomyocyte

The contractile apparatus of skeletal and cardiac myocytes is constructed as a sliding filament mechanism centered on the interaction between actin and myosin filaments. Their calcium-dependent activation is regulated by the troponin complex. The cardiac troponin complex is formed by 3 subunits: troponin C, T, and I. While troponin C harbors the calcium-binding site, troponin T attaches to the actin filament and troponin I works as inhibitor of interaction with myosin heads in the absence of calcium. Of these 3 subunits, cTNI and cTNT isoforms are specific to cardiac myocytes, and thus, their level in serum can be used as surrogate for myocardial damage.[5,13]

Evolution of High-Sensitivity Cardiac Troponin Assays

High-sensitivity (hs) TN assays are capable to detect cTNI or cTNT concentrations 10- to 100-fold lower than conventional tests. Their superior sensitivity entails exact quantification of cTN levels in up to 95% of the healthy individuals.[14] With this development, an even more rapid rule-out strategy for patients with acute chest pain became generally available. Two ground-breaking trials were published in 2009 demonstrating an excellent diagnostic performance of hsTN assays to improve early diagnosis and risk stratification of patients with ACS.[15,16] In 2011, European Society of Cardiology (ESC) guidelines—in contrast to US guidelines—endorsed a 3-hour instead of 6-hour algorithm of repeated cTN measurements, if a hs-assay is available.[17,18]

DEFINITIONS

Over the last years, hsTN-essays have become ubiquitously available and found their way into everyday clinical practice. From a theoretic point of view, they might not only be capable to increase patients' safety by an expedited clinical diagnosis or rule-out of acute MI, but they are also fulfilling caregivers' demands of an economic management of stationary wards, allowing shorter delays to establish or exclude a diagnosis. Nevertheless, the wide-spread use of even more sensitive troponin testing over the last years also poses a challenge to the clinician—whether cardiologist or not—as in more and more cases questions arise about potential consequences and clinical

implications of positive cTN tests, especially those derived outside the setting of suspected MI.

Accounting for this clinical dilemma, the ESC and the American College of Cardiology (ACC) updated their consensus statement on the "Fourth Universal Definition on Myocardial Infarction" in August 2018.[19] This position paper aims to solve the question how to discriminate between different entities, which were formerly all submersed under the prevailing definition of "myocardial infarction" based on elevated biomarkers in a setting of now commonly available hsTN tests. Although a classification into 5 different types of "MI" introduced before was adopted, a term of "myocardial injury" was newly redefined. It accounts for the circumstance that elevated levels of cardiac biomarkers—in particular hsTN—are highly sensitive to detect damage of cardiomyocytes but are not specific for the detection of a "classical" ischemic MI. Per definition, all conditions characterized by an elevation of serum troponin levels—that is, defined by exceeding the 99th percentile upper reference level (URL) of serum levels of the healthy population—are now summarized as "myocardial injury," independent of their underlying pathology. Although different biomarkers indicating myocardial damage have been frequently used in the past, the position paper restricts the diagnosis of "myocardial injury" solely to abnormal serum cTN values because of their superior specificity for myocardial tissue.

A chronic form of myocardial injury is to be discriminated from its acute variant based on repetitive serum cTN tests, as stated by the position paper's authors. A myocardial injury is considered as "acute" if cTN levels show a relevant kinetic in serial blood tests—regardless of increase or decrease—with at least one value higher than the 99th percentile URL (**Fig. 2**). Stable cTN values indicate for a chronic myocardial injury. Thresholds for determining a significant difference between two serial cTN values are assay dependent. Elevated cTN levels cannot identify their cause—including ischemic as well as nonischemic conditions. Thus, the diagnosis of acute or chronic myocardial injury per se does not primarily justify a specific treatment, for example, direct referral to heart catheterization, but should lead to a further thorough clinical investigation.

Acute Myocardial Injury, Myocardial Ischemia, and Acute Myocardial Infarction

Various causes can induce a liberation of intracellular proteins (cTN and other markers) from the cardiomyocytes by pathophysiological mechanisms including preload-induced mechanical stretch and physiologic stress even in healthy hearts. On a histologic base, this release might be mediated by increased cellular turnover as well as apoptosis, liberation of cTN-degradation products, increased cellular wall permeability, release of membranous blebs, and myocyte necrosis.[20] Because of its broad and heterogenous cause, myocardial injury has a relatively high clinical incidence, which poses a challenge to the clinician and—per se—has negative influence on patients' prognosis independent of its pathophysiology.[21,22] Clinicians will have to rule out between a variety of nonischemic causes of myocardial injury, including primary cardiac diseases, for example, myocarditis, or noncardiac pathologies, for example, renal failure, and ischemic forms in kind of 1 of the 5 subtypes of MI (for an overview, see **Fig. 2**, **Table 1**). A proof of myocardial ischemia in combination with elevated hsTN levels justifies the clinical diagnosis of an MI (see **Fig. 2**). Typical clinical presentation, electrocardiographic signs, as well as characteristic findings in cardiac imaging—for example, echocardiography or cardiac magnetic resonance tomography—are accepted clinical surrogates for myocardial ischemia qualifying for the diagnosis of MI (eg, type 1 or type 2). Notably, this definition does not distinguish among the different mechanisms of MI, which may be based on a primary coronary problem as plaque rupture, coronary spasm, embolism, or dissection, but may also follow systemic processes resulting in decreased coronary perfusion of the cardiomyocytes, for example, due to hemodynamic deterioration by relevant bradycardia, hypotension, or any form of shock, as well as also compromised systemic oxygenation by acute diseases of the respiratory system or anemia. Furthermore, any cause of increased aerobic metabolism, for example, tachycardia or hypertension, might result in myocardial ischemia.

Clinical Concept of Acute Coronary Syndrome as Working Diagnosis and Different Types of Acute Myocardial Infarction

The concept of ACS as working diagnosis in emergency medicine comprises a clinical pathway for optimal risk stratification in patients presenting with acute chest discomfort or other ischemic symptoms. To optimize the timing of treatment strategies such as reperfusion therapy, patients must receive a 12-lead electrocardiography performed within 10 minutes after first medical contact, which will allow allocation into a category with a working diagnosis of STEMI, based on typical electrocardiographic findings in kind of ischemic repolarization patterns demanding for

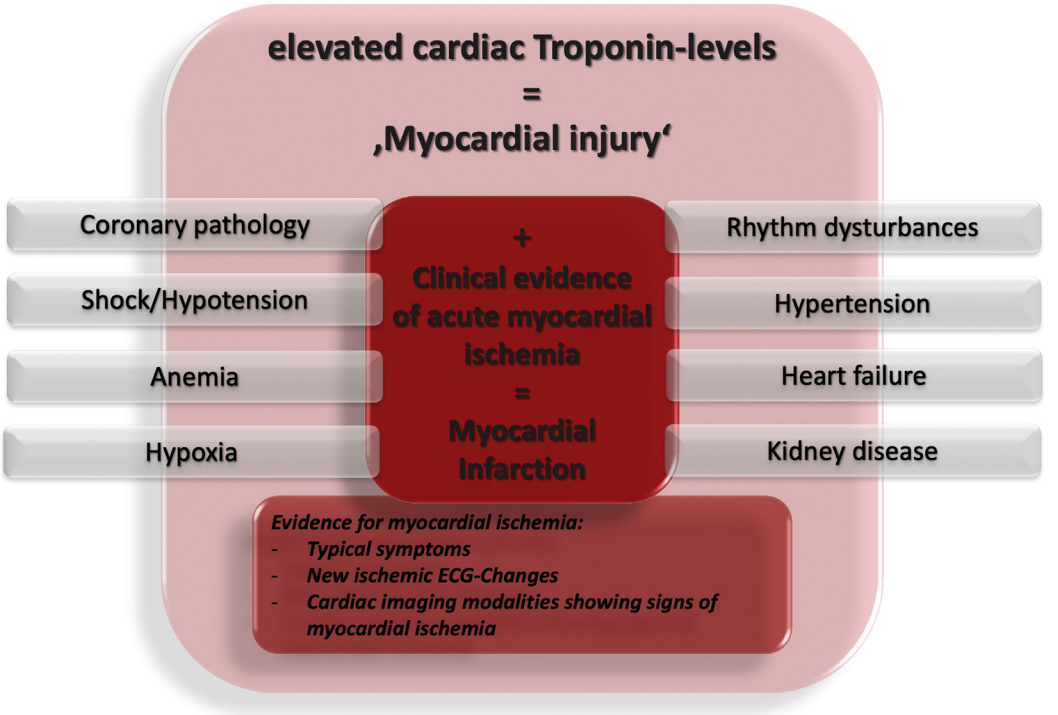

Fig. 2. Discrimination between the entities of myocardial injury and myocardial infarction. For details, see text. (*From* Wild J, Wenzel P: Myocardial Injury and myocardial infarction – consequences for clinical care in the light of current guidelines. Aktuel Kardiol 2019;8:193-198.)

urgent referral to heart catheterization or the group of patients without those typical ischemic ECG changes (working diagnosis of NSTE-ACS). For these, sequential cTN testing is essential for rule-in (or rule-out) of acute MI. In this context, it must be emphasized that a small subgroup of patients with NSTE-ACS also qualifies for an immediate invasive management in case of high-risk criteria as hemodynamic instability or refractory angina pectoris. Clinical pathways and timing of further diagnostic strategies in patients presenting with STEMI or NSTE-ACS are described in the specific guidelines.[17,18]

According to the "Universal Definition of MI" position paper, all of these clinical settings defining acute MI may be classified into 5 types, based on pathologic, clinical, and prognostic differences. This allocation to different types of MI grounded on their distinct pathophysiology might also justify different and individual treatment strategies.[1] MI type 1 is defined as the presence of atherothrombotic coronary artery disease resulting in an acute occlusion or relevant stenosis of a coronary vessel precipitated by atherosclerotic plaque disruption (rupture or erosion). Confirmation of the diagnosis is based on identification of a coronary thrombus by angiography including intracoronary imaging or post mortem by autopsy.

Type 2 MI is also defined by the confirmation of acute myocardial ischemia, which—in contrast to type 1 MI—is not caused by an acute coronary plaque disruption but rather by an imbalance of myocardial oxygen supply and demand. Patients with type 2 MI might also suffer from known or presumed coronary artery disease and might thus be prone to ischemia in cases of additional acute stress such as hemorrhagic conditions with a relevant drop of hemoglobin or sustained heart rhythm disorders. Although coronary atherosclerosis is a common finding in type 2 MI, it has to be emphasized that the presence of coronary artery disease is not a mandatory precondition for every type 2 MI. Other potential causes comprise various pathologies including severe hypoxemia, shock, coronary artery dissection, or spasm and microvascular dysfunction, for instance. Interestingly, type 2 MI has worse short- and long-term outcomes as compared with type 1 MI. A large meta-analysis found a significantly higher intrahospital (15% vs 4.7%), 30 days (17.6% vs 5.3%) and 1-year mortality (27% vs 13%) and a higher rate of major adverse cardiovascular events

Table 1
Overview of variable causes resulting in elevations of cardiac troponins/myocardial injury

Cardiac Pathology	Noncardiac Pathology
Myocardial infarction/ischemia	SIRS or sepsis, infectious diseases
Heart failure	Renal failure or chronic kidney disease
(Peri-) myocarditis	Stroke or cerebral hemorrhage
Cardiomyopathies (of any type)	Pulmonary embolism, pulmonary hypertension
Valvular heart disease	Amyloidosis, sarcoidosis
Takotsubo syndrome	Cardiotoxicity, for example, chemotherapy
Cardiac procedures of any kind (PCI, intervention for structural or valvular heart disease, heart surgery, catheter ablation)	Shock, critically ill patients
	Extensive exercise training
Cardioversion/defibrillator shocks	
Cardiac contusion	

Abbreviations: PCI, percutaneous coronary intervention; SIRS, systemic inflammatory response syndrome.
Data from Wild J, Wenzel P: Myocardial Injury and myocardial infarction – consequences for clinical care in the light of current guidelines. Aktuel Kardiol 2019;8:193-198. And Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. Eur Heart J 2018;40:237-269.

(MACE; 20% vs 9%) in patients with type 2 versus type 1 MI. Moreover, a higher incidence of relevant cardiac and noncardiac comorbidities (diabetes mellitus, hypertension, renal failure, preexisting heart failure, chronic obstructive pulmonary disease) and a higher mean age of these patients seem to account for these findings, at least partially. As to be expected, only a minority of patients with type 2 MI (13.7%) who underwent invasive diagnostics were treated by percutaneous coronary intervention (PCI). Noncardiac surgery (20%), sepsis (19%), cardiac rhythm disturbances (19%), heart failure (15%), and anemia (12%) were identified as most probable causes for concomitant myocardial damage.[23] For definitions of MI types 3, 4a-c, and 5, see **Fig. 3**.

DISCUSSION

Type 2 Myocardial Infarction, Myocardial Injury, and Implications for Prognosis

Type 2 MI shares many of the prerequisites and diagnostic features of the rather broad definition of acute myocardial injury, and thus a clear-cut distinction between type 1 and type 2 MIs according to the contemporary definition will not always be possible. As outlined earlier, the diagnosis of type 2 MI based on the current classification additionally requires the clinical proof of myocardial ischemia—for example, by symptoms, dynamic changes in ECG, or cardiac imaging modalities besides elevated cTN levels. Thus, it might not be surprising that—with regard to prognosis—diagnoses of acute myocardial injury and type 2 MI are both correlated to a higher rate of adverse outcome in comparison to patients with type 1 MI: After a 1-year follow-up, mortality rates of 31% in type 2 MI and 37% in myocardial injury were reported, compared with 16% in type 1 MI.[24,25] A Scottish monocentric registry including more than 2000 patients analogously reported on a doubled mortality in long-term follow-up of patients with noncardiac or multifactorial cause of myocardial injury and a similar rate of MACE compared with patients with type 1 MI.[26] A Danish cohort study with analogous design (approximately 1000 patients included) concluded that acute myocardial injury relevantly impaired prognosis when the cause was not primarily associated to cardiac diseases such as, for example, valvular heart disease or other causes of heart failure.[22] Based on these studies, the relatively high mortality after type 2 MI and myocardial injury might be mainly influenced by noncardiac comorbidities.[22,26,27]

Definition of a Proper Threshold for "Normal" cTN Values in the Context of High-Sensitivity Assays

As in all cases of all tests allowing hs-diagnostics, a proper interpretation of elevated serum hsTN indicating for AMI becomes more and more challenging—especially in cases with mild aberrance from normal values. As shown earlier, elevated cTN levels can be found in patients with a variety of cardiac coronary and noncoronary, as well as noncardiac disorders. Although the cut-off value (99th percentile URL) has been adopted by the guidelines as soon as 2007,[12] the definition of this threshold for determination in "normal" and "pathologic" findings is still under debate. The high negative predictive value of hsTN assays allows for a safe and time-efficient rule-out of most of the patients presenting with chest discomfort.

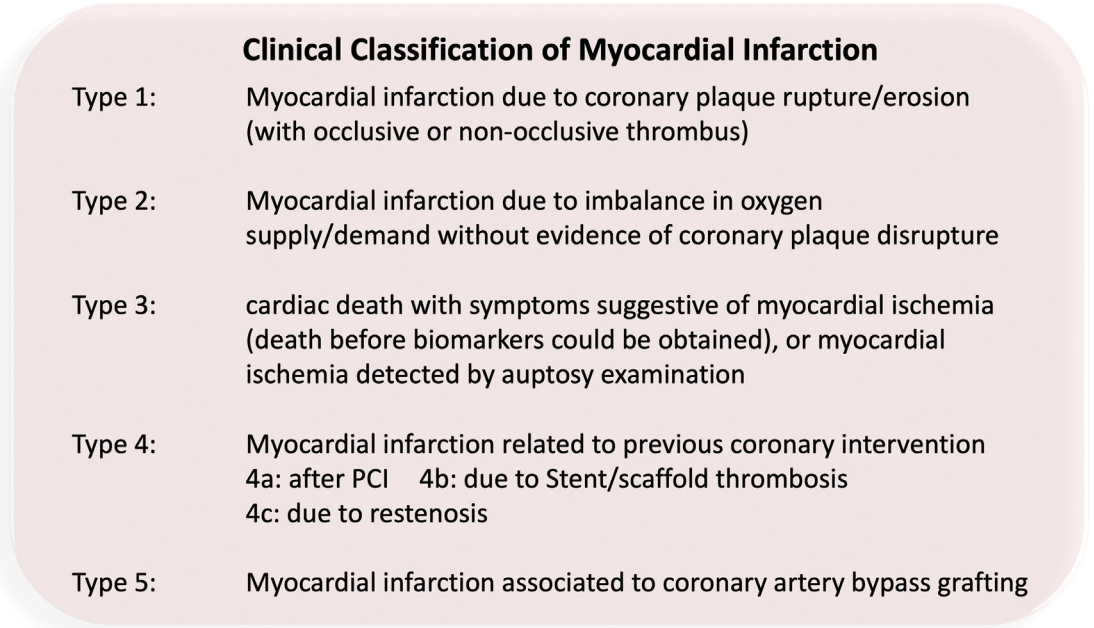

Fig. 3. Clinical classification of different subtypes of acute myocardial infarction. PCI, percutaneous coronary intervention. For details, see text. (*Data from* Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. Eur Heart J 2018;40:237-269.)

On the other hand, more patients will be found at putatively pathologic cTN levels using hsTN over conventional assays. A study on 3327 consecutive patients admitted to the Chest Pain Unit of the University of Heidelberg reported that in up to 69% of the patients the finding of an elevated hsTNT level could finally not be correlated to an ACS.[28] Recently, a large Scottish multicenter trial on more than 48,000 patients found that implementation of an hsTN assay in patients presenting as ACS in emergency departments led to a reclassification in kind of an additional increase of patients meeting criteria of myocardial injury or acute MI by 17% in comparison to conventional cTN testing; yet, the incidence of MI or cardiovascular death after 1 year could not be reduced by using hsTN over the conventional assay.[29] The controversy about a proper cut-off level for normal findings of hsTN has been heated up further by the fact that physiologic cTN levels are influenced by a variety of causes, for example, renal failure, gender, stroke, obesity, age,[30] and even circadian rhythm.[31] Up to now, the implementation of adapted thresholds, for example, sex-specific or dependent on renal function,[32] are not recommended by current guidelines. Nevertheless, as discussed earlier, there is solid evidence that any clinical situation with a documented increase of cTN levels higher than the defined threshold levels conveys important prognostic implications for the patients, regardless of the cause of this finding—MI or any other clinical setting of myocardial injury—and demands further evaluation [for example, [28,33]].

Future Developments in Clinical Risk Stratification Based on Cardiac Biomarkers

The implementation of hs-assays has expedited clinical algorithm for the management of ACS. More sensitive troponin tests allow for the detection of smaller myocardial injury and thus, swifter and safer diagnostics in confirmation or rule-out of acute MI. In the future, further progress and evidence in biomarker testing might unleash further potential for acceleration without a loss of diagnostic accuracy. At the moment, European Guidelines endorse a fast 0/3 hours strategy as standard algorithm if hsTN testing is available or an even swifter 0/1 hours rule-out strategy if validated hsTN assays are used. Contemporarily this is applicable to the kits of many vendors; nevertheless, even lower hsTN thresholds (in comparison to the "regular" cut-off level of 99th percentile URL) have to be applied for this expedited diagnostic workup. Even more, a "direct" rule-out pathway has been introduced, allowing for a negative predictive value of more than 99% if initial hsTN levels are less than the limit of detection at admission.[17] It is important to emphasize that these rapid rule-out strategies are not recommended in "very early presenters" (onset of

symptoms < 3 hours) due to a potential time-shift in cTN release. A "dual marker strategy," including the measurement of Copeptin (a fragment of vasopressin) might enable an even higher diagnostic accuracy in rapid algorithms. Furthermore, the implementation of clinical scores (eg, GRACE-Score) is strongly recommended before discharge.[34] Future developments might lead to superior biomarker tests, facilitating ambulatory "point of care" diagnostics at highest safety. This might be a further aid to the clinician in the emergency department having to distinguish between the high-risk patient requiring for urgent treatment and low-risk patients, of which some will have to be discharged rapidly. In this context, dedicated emergency units specialized for the evaluation of patients presenting with chest pain, so called chest pain units (CPU), have been established in many countries. There is evidence that a concept of CPUs undergoing standardized certification process entail a better adherence to guidelines[35] and might influence survival positively.[36] In this regard, the Acute Cardiovascular Care Association of the ESC has published a position paper endorsing standardized implementations of CPUs in emergency departments.[37]

SUMMARY

Because of a rather limited specificity and predictive value of symptoms and other clinical findings including ECG in the context of MI, biomarkers have become an indispensable tool for daily diagnostic and risk stratification. Among a variety of blood tests available, cTN levels may serve as best surrogates for myocardial damage up to now. The implementation of hsTN assays in clinical practice has expedited rule-out pathways for MI due to a higher negative predictive value in comparison to conventional cTN tests. Yet, higher sensitivity of markers for myocardial damage may result in a higher number of patients "ruled-in." In 2018, the updated "Fourth Universal Definition on Myocardial Infarction" was published as ESC/ACC consensus statement, defining the term of "myocardial injury" comprising all nonischemic and ischemic causes of myocardial damage, including MI. Whereas the diagnosis of myocardial injury is based on cTN testing, the confirmation of MI requires the clinical proof of cardiac ischemia. Myocardial injury is a heterogenous entity that can be caused by a large variety of cardiac as well as extracardiac disorders; furthermore, it exceeds "classical" type 1 MI in mortality. As a matter of fact, abnormal biomarker values are always to be interpreted within their clinical context; serial samplings can be helpful in ruling-in and -out strategies. Of many biomarkers used, hsTN assays are one of those that have truly proved the potential diagnostic power of blood tests in emergency medicine. They have not only changed our diagnostic strategy in ACS but also allow superior risk stratification in the context of noncardiac disorders. In the future, potentially superior and tailored biomarkers might allow quickest optimal diagnostic and therapeutic guidance to identify patients at risk for future cardiovascular events.

CLINICS CARE POINTS

- Clinical symptoms as typical angina pectoris and ECG compatible with cardiac ischemia are a frequent cause for admission to emergency units, but only have limited predictive value for the prevalence of significant coronary stenoses
- Biomarkers for myocardial damage have become an indispensable tool for diagnostics in settings of acute coronary syndromes
- Over the last years, hs-cardiac troponin (hsTN) assays have become ubiquitously available
- Because of high sensitivity, hsTN testing has expedited rule-in and -out algorithms
- In 2018, the fourth universal definition on MI was published, which redefined the condition of myocardial injury
- Myocardial injury is diagnosed by elevated troponin serum levels even in the absence of myocardial ischemia and is characterized by impaired prognosis that may even exceed that of type 1 MI
- Clinical implications based on elevations of serum troponin must always be validated in their clinical context
- The diagnosis of MI requires clinical proof of myocardial ischemia in the addition of elevated cardiac troponin levels
- hsTN assays allow safe and economic therapeutic guidance for the clinician in the emergency unit

DISCLOSURE

The authors have nothing to disclose.

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