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Biomarkers in cardiovascular medicine: towards precision medicine

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Summary

Biomarkers are noninvasive, inexpensive, highly reproducible tools that allow clinicians to quantify pathophysiological processes relevant to a specific disease. Although the concept of biomarker-guided precision medicine is still in its infancy once a specific cardiovascular diagnosis is established, biomarker guidance has become the standard of care in the early diagnosis of acute cardiovascular disease in patients presenting to the emergency department with common symptoms such as acute chest pain or acute dyspnoea. This review highlights recent advances and remaining uncertainties regarding the use of the most relevant cardiovascular biomarkers, namely high-sensitivity cardiac troponin and natriuretic peptides in established indications such as the early diagnosis of acute myocardial infarction and heart failure. In addition, we address emerging indications such as the screening for perioperative myocardial infarction.

Keywords: *high-sensitivity cardiac troponin, B-type natriuretic peptide, acute myocardial infarction, perioperative myocardial infarction/injury, diagnosis*

High-sensitivity cardiac troponin

High-sensitivity cardiac troponin plays a major role in the diagnostic work-up of patients presenting to the emergency department with symptoms suggestive of acute myocardial infarction (AMI) [1]. Clinical assessment and the 12-lead electrocardiogram (ECG) are important, but unfortunately do not have high enough accuracy to reliably diagnose or exclude non-ST-segment-elevation myocardial infarction (NSTEMI). Therefore, the addition of blood tests to quantify the extent of myocardial injury, a pathophysiological hallmark of AMI, using cardiac troponin (cTn) T or I, form one cornerstone for the early diagnosis of AMI.

Recent advances in the analytical sensitivity and precision of cTn-assays have led to the development of high-sensitivity cardiac troponin assays and thereby the clinical ability to detect and precisely quantify even small amounts of cardiomyocyte injury [2–35]. In comparison with the conventional cTn assay, these new assays increased the diagnostic accuracy for AMI at presentation, reducing the "troponin-blind" interval and allowing the development of novel strategies for the rapid rule-out or early rule-in of NSTEMI [2–34]. These improved assays are classified as "sensitive" when able to detect cTn in ~20–50% of healthy individuals and as "high-sensitivity" if they detect a cTn level in >50% of apparently healthy subjects, and if they have a coefficient of variation of <10% at the 99th percentile upper reference limit of the assay [8]. High-sensitivity assays have the ability to accurately detect cTn at lower levels than older generation assays, giving them higher sensitivity for the detection of AMI at presentation, which means that the time interval to the second measurement of high-sensitivity cTn (hs-cTn) can be significantly shortened to 3 hours or even 1 hour using the algorithms described in detail below [2–36]. Additionally, these strategies reduce the time to discharge from the emergency department, with substantial cost savings as hs-cTn assays are inexpensive tests. The cost of hs-cTn assays is identical to that of conventional cTn assays. It varies substantially from country to country worldwide ranging from about EUR 2–15.

Both cTnT and cTnI are structural proteins specific to the heart. However, they are not disease-specific markers. Hs-cTnT and hs-cTnI assays exactly quantify the amount of myocardial injury [3, 35, 36]. They must be interpreted as quantitative variables and not in a binary fashion (negative/positive) like a pregnancy test. From a diagnostic perspective, it is highly inappropriate to label a patient as "cTn-positive", as this would put together patients with only mildly elevated cTn levels barely above the 99th percentile

ABBREVIATIONS:

AMI	acute myocardial infarction
BNP	B-type natriuretic peptide
cTn	cardiac troponin
ECG	electrocardiogram
ESC	European Society of Cardiology
hs-cTn	high-sensitivity cardiac troponin
NSTEMI	non-ST-segment-elevation myocardial infarction
NT-proBNP	N-terminal-pro-B-type natriuretic peptide
PMI	perioperative myocardial infarction/injury
sST2	soluble suppression of tumourigenicity 2

Author contributions
Danielle Menosi Gualandro and Raphael Twerenbold contributed equally to this manuscript.

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and an associated positive predictive value for NSTEMI of only about 40–50% with patients with markedly elevated cTn levels (e.g., about five times above the 99th percentile) and an associated positive predictive value of 90%. The higher the cTnT/I concentration, the higher the likelihood for the presence of AMI. To differentiate AMI from other causes of chest pain, absolute rather than relative hs-cTn changes are preferable [12, 19–21]. The larger the absolute cTnT/I change within 1, 2, or 3 hours, the higher the likelihood for the presence of AMI [12, 19–21]. Continuing medical education and training of physicians in these concepts is essential to avoid inappropriate interpretation as AMI of chronic mild elevations of cTnT/I associated with, for example, heart failure or other structural cardiac disorders.

"False-positive" cardiac troponin measurements, "troponinaemia" and "troponinitis"

In the absence of overt myocardial ischaemia, elevated cTnT/I concentrations are sometimes labelled as "false positive" cTnT/I results, "troponinaemia" or "troponinitis". These terms should definitely be avoided, as the vast majority of these unexpected cTnT/I elevations, are "true positive" for myocardial injury (rather than AMI) and reflect previously undetected or underestimated myocardial disease including valvular heart disease, heart failure and chronic coronary artery disease, or even AMI with atypical symptoms. The clinical use of hs-cTn assays has taught us that multiple cardiac as well as primarily noncardiac disorders (such as septic shock) may lead to substantial amounts of myocardial injury and thereby hs-cTnT/I elevations (table 1) [3, 8]. It is important to note that patients with stable cTnT/I elevations (chronic myocardial injury) have a worse prognosis than similar patients without a cTnT/I elevation, irrespective of the underlying disease. This is true regardless of whether the patient has heart failure, renal dysfunction-associated cardiac disease, gastrointestinal bleeding, sepsis, respiratory disease, pulmonary embolism, subarachnoid haemorrhage or stroke, or whether the patient is asymptomatic without known cardiovascular disease [37]. Obviously, the medical consequences of myocardial injury as quantified by cTnT/I elevations will be highly individualised and different from that in patients with AMI.

There are two uncommon, but well-described exceptions to this rule. First, particularly hs-cTnI assays may have "true false-positive" values due to heterophilic antibodies. These heterophilic antibodies are endogenous human antibodies that bind to immunoglobulins of other species and can occasionally exist in blood samples. In high titres, they can bind to the antibody of the hs-cTnI immunoassay, giving a positive result in the absence of the antigen to be detected (cardiac troponin I) [38]. Second, particularly the hs-cTnT assay may have "true false-positive" values as a result of rare chronic skeletal muscle diseases such as Duchenne [39]. If such an analytical problem is expected, measurement of the other hs-cTn (hs-cTnT and I, respectively) and cardiac imaging including magnetic resonance imaging usually rapidly clarifies the case [38]. In case of "true elevations", hs-cTnI and hs-cTnT are concordant and both elevated. In case of "false elevations", hs-cTnI and hs-cTnT are discordant.

Hs-cTn in patients with suspected acute myocardial infarction

Rapid triage algorithms using high-sensitivity cardiac troponins

The most important clinical and economic advantage of hs-cTnT/I assays is their ability to substantially reduce the "troponin-blind" interval in the first hours of an AMI. This allowed the development of several troponin-based strategies aimed at early rule-out or rule-in of NSTEMI. Two of them, the 0/1h-algorithm and the 0/3h-algorithm, are currently recommended by the European Society of Cardiology (ESC) as a class I recommendation [3].

It is important to consider the following aspects when applying troponin-based strategies in clinical practice (fig. 1). First, these early hs-cTn-based algorithms should be used only in conjunction with full clinical assessment. Second, they should be considered as triage strategies rather than definite diagnostic strategies, and additional imaging tests such as invasive coronary angiography, stress testing, echocardiography or coronary computed tomography angiography may be necessary for a definite diagnosis. Third, the percentage of patients eligible for rule-out or rule-in varies widely from about 10 to 80% depending on the underlying algorithm, the hs-cTnT/I assay used and the clinical setting, including the prevalence of NSTEMI [20, 23]. Fourth, these strategies should only be applied after the initial ECG has excluded ST-segment-elevation myocardial infarction, since these high-risk patients need prompt identification based on the ECG and immediate reperfusion therapy without the need for hs-cTnT/I testing [2]. Fifth, like any other triage strategy, these novel hs-cTnT/I based strategies should be implemented only after extensive training of all involved clinicians and nurses, and em-

Table 1: Conditions other than myocardial infarction associated with cardiac troponin elevations.

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g., shock, sepsis, burns)
Myocarditis
Tako-tsubo cardiomyopathy
Structural heart disease (e.g., aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease
Coronary spasm
Acute neurological event (e.g., stroke or subarachnoid haemorrhage)
Cardiac contusion or cardiac procedures (e.g., CABG, PCI, ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypo- and hyperthyroidism
Infiltrative diseases (e.g., amyloidosis, haemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g., doxorubicin, 5-fluorouracil, trastuzumab, snake venoms)
Extreme endurance efforts
Rhabdomyolysis
CABG = coronary artery bypass surgery; PCI = percutaneous coronary intervention Adapted from Twerenbold et al. [4] with permission from the publisher. Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, et al. Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. J Am Coll Cardiol. 2017;70(8):996–1012.

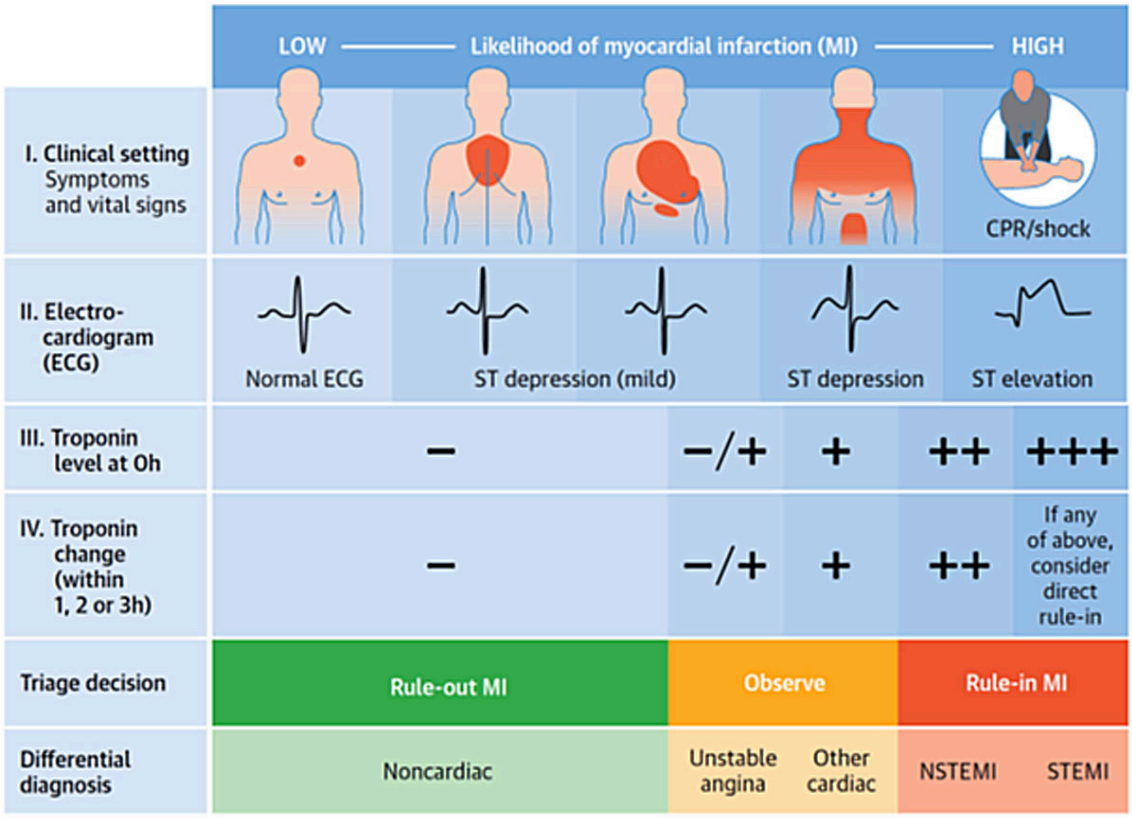
bedded in the local standard operating procedures of the emergency department.

Recent studies have shown that the ESC 0/1h-algorithm provides even better performance characteristics than the ESC 0/3h-algorithm and should be the preferred triage algorithm (fig. 2), as it provides the most favourable balance between patient safety and triage efficacy [40–43].

The concept of the ESC 0/1h-algorithm is exclusively based on hs-cTn concentrations at the emergency department presentation and their absolute change after 1 hour, using assay-specific cutoffs. This concept is depicted in figure 2B; an example with assay-specific cutoffs for the hs-cTnT assay is in figure 2C. [3, 20, 29, 30, 44, 45]. In addition to serial sampling, the ESC 0/1h-algorithm allows direct rule-out of NSTEMI based on a single hs-cTnT/I measurement if hs-cTnT/I concentration at presentation is extremely low, but only in patients with a chest pain onset >3 hours prior to the emergency department presentation, as safety of this single measurement strategy was reduced in the very early presenters. [46] The ESC-0/1h-algorithm results in safe rule-out of NSTEMI (negative predicted value of 99–100%) and allows an accurate early triage in about 75% of patients: 60% towards rule-out and in 15% towards rule-in of NSTEMI [45]. The application of the ESC 0/1h-algorithm is also possible in institutions with a median assay turn-around time of more than 1 hour since the 1 hour only refers to the timing of the serial sample. In these institutions, the second blood draw simply needs to be performed while the results from the first blood draw are still awaited, because these values have anyway to be evaluated together in order to determine the hs-cTn delta value.

The ESC 0/1h-algorithm may also be applied in patients with renal dysfunction and the elderly without the need to adjust cut-off values, as excellent safety was confirmed in these high-risk patients also [47–49]. However, fewer patients will be triaged to the rule-out group given the higher pre-test probability for NSTEMI in these subgroups.

Figure 1: Clinical assessment of patients presenting with suspected acute coronary syndrome. The initial assessment is based on the integration of low likelihood and/or high likelihood features derived from clinical setting (symptoms, vital signs), 12-lead ECG, and cardiac troponin determined at presentation to the emergency department and serially thereafter. "Other cardiac" includes, among others, myocarditis, Tako-tsubo cardiomyopathy and congestive heart failure. "Noncardiac" refers to thoracic diseases such as pneumonia or pneumothorax. Cardiac troponin and its change during serial sampling should be interpreted as a quantitative marker: the higher the 0h-level or the absolute change during serial sampling, the higher the likelihood for the presence of myocardial infarction. In patients presenting with cardiac arrest or haemodynamic instability of presumed cardiovascular origin, echocardiography should be performed/interpreted by trained physicians immediately following a 12-lead ECG. If the initial evaluation suggests aortic dissection or pulmonary embolism, D-dimers and multi-detector computed tomography angiography are recommended according to dedicated algorithms.CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; MI = myocardial infarction; NSTEMI = non-ST-segment-elevation myocardial infarction; STEMI=ST-segment-elevation myocardial infarctionAdapted from Twerenbold et al. [4] with permission from the publisher. Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, et al. Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. J Am Coll Cardiol. 2017;70(8):996–1012.

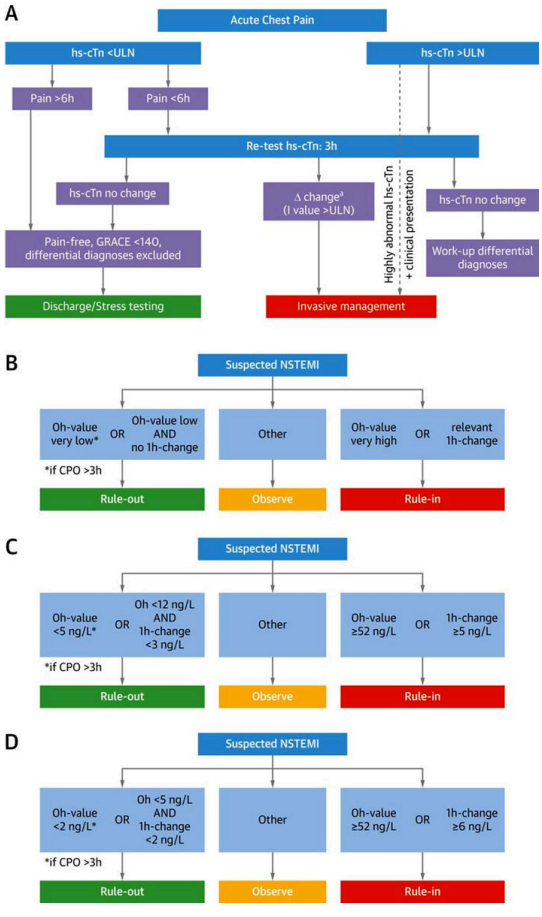


Additional helpful steps in the observe zone

The ESC 0/1h-algorithms [3, 20, 29, 30, 44, 45] are very helpful for either rapid rule-in or rule-out of NSTEMI in about 75% of patients, leaving about 25% in the observe zone [3, 18, 20, 29, 30, 44, 45, 50, 51]. These patients are typically older men with known coronary artery disease. Patients in the observe zone require detailed clinical assessment, additional an hs-cTn measurement at 3 hours and, usually, cardiac imaging including echocardiography to make an accurate diagnosis [52] The clinical interpretation of mildly abnormal hs-cTn levels is crucial for physicians in the emergency department since up to one third of patients triaged to the observe zone are finally diagnosed with NSTEMI or unstable angina. Therefore, further serial hs-cTn re-testing at 3 hours should be performed to better differentiate an acute cardiac disease (such as NSTEMI) associated with a dynamic hs-cTn course from a chronic cardiac disease reflected by stable hs-cTn course (chronic myocardial injury). Coronary angiography (in those with high likelihood for NSTEMI), echocardiography and functional stress imaging (in those with low likelihood for NSTEMI) seem to be the preferred tests in observe zone patients [52].

Coronary computed tomography angiography seems a suitable imaging modality in only a minority [53]. A randomised controlled trial recently showed no benefit of routine coronary computed tomography angiography over standard optimal care encompassing hs-cTnT in patients with suspected acute coronary syndrome, with regard to identification of significant coronary artery disease requiring revascularisation within 30 days, duration of hospital stay or direct discharge from the emergency department [54]. Functional instead of anatomical testing is mandatory to differentiate coronary lesions resulting in myocardial ischaemia and acute chest pain at rest from lesions that are innocent bystanders in relation to the acute chest pain episode leading to emergency department presentation [52].

Figure 2: European Society of Cardiology (ESC) rapid triage algorithms. (A) The ESC 0/3h rule-out and rule-in algorithm of non–ST-segment–elevation myocardial infarction (NSTEMI) using high-sensitivity cardiac troponin (hs-cTn) assays. (B) The ESC 0/1h rule-out and rule-in algorithm using hs-cTn assays in patients presenting with suspected (NSTEMI) to the emergency department. (C) The ESC 0/1h rule-out and rule-in algorithm with assay-specific cutoff values for the Elecsys® hs-cTnT assay by Roche.CPO = chest pain onsetAdapted from Twerenbold et al. [4] with permission from the publisher. Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, et al. Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. J Am Coll Cardiol. 2017;70 [8]:996-1012.



Overruling a triage recommendation

Hs-cTn-based triage algorithms must always be used in conjunction with detailed clinical assessment and interpretation of the ECG. This analysis may result in overruling a "rule-out" recommendation provided by the hs-cTn-based algorithms in some patients perceived to be at high-risk of NSTEMI. Overruling should then lead to the identical process described for patients assigned the observe zone and should always include an additional hs-cTn measurement at 3 hours. For example, if a patient was classified as "rule-out" of AMI, but has chest pain characteristics typical for unstable angina, he/she would still possibly benefit from hospitalisation and intensification of medical therapy, and probably from coronary angiography or noninvasive imaging for coronary artery disease.

Rule-out of non-ST-segment-elevation myocardial infarction does not always equal outpatient management

The novel strategies were developed to safely rule-out NSTEMI, but not other disorders that still may require hospital admission such as unstable angina, pulmonary embolism, aortic dissection or severe sepsis from pneumonia. Accordingly, the percentage of patients who can possibly be managed in an out-patient clinic is smaller than the percentage of patients ruled-out for NSTEMI. Besides, standard operating procedures should be in place to ensure appropriate follow-up of patients rapidly discharged from the emergency department, which often will include outpatient functional cardiac stress testing in patients with intermediate to high-risk probability for coronary artery disease.

Emerging indication: patients undergoing noncardiac surgery

More than 300 million surgical procedures are performed annually worldwide [55]. In spite of improvements in surgical and anaesthetic techniques, the morbidity and mortality related to these procedures remain higher than expected [56]. Cardiac complications, including perioperative myocardial infarction/injury (PMI), are important contributors to mortality after non-cardiac surgery [57–59]. Therefore, it is paramount to identify which patients are at greater risk for postoperative complications, not only to provide the best medical care, but also to assess the risk-benefit ratio

of surgical procedures. The currently available risk stratification tools to identify these patients, such as the Revised Cardiac Risk Index, have only moderate accuracy [60–62]. Biomarkers could improve the prediction of cardiac complications and mortality after noncardiac surgery. Additionally, biomarkers are essential for prompt diagnosis of postoperative complications, including PMI. Currently, the most solid scientific evidence available indicates that cardiac troponins and natriuretic peptides are the most useful biomarkers in the perioperative setting [58, 63].

Perioperative evaluation: perioperative myocardial Infarction/injury, the silent and neglected killer

Elevated preoperative hs-cTnT/I concentrations are independent predictors of mortality and major cardiac events after noncardiac surgery [64–67]. Current guidelines differ in their recommendation regarding the preoperative measurement of hs-cTnT/I concentrations, indicating ongoing controversy whether the improvement in risk stratification documented in recent studies is of clinical value [2, 68, 69]. Similarly, current guidelines also differ in their recommendation regarding perioperative screening for PMI in high-risk patients by measurement of hs-cTn after surgery [2, 68–70]. As a considerable number of patients undergoing surgery have chronic myocardial injury, it seems reasonable to obtain a preoperative sample from these patients in order to differentiate acute from chronic myocardial injury after surgery [68–70].

Observational studies have also addressed the prognostic role of postoperative hs-cTnT/I elevations [57, 58, 65, 67, 71, 72]. In the VISION study (the vascular events in noncardiac surgery patients cohort evaluation), the authors measured hs-cTnT on the first three days after noncardiac surgery, in a prospective cohort of 21,842 patients aged above 45 years. The peak postoperative hs-cTnT concentration was significantly associated with 30-day mortality and the higher the hs-cTnT concentration, the higher the mortality (even for patients with concentrations within the normal range, when compared with patients with undetectable values) [57]. These results corroborate the findings of previous studies that reported the adverse impact of hs-cTn values on prognosis of patients with several clinical conditions (diabetes, coronary artery disease, heart failure, renal failure) and also in the primary prevention setting [73–76]. In order to determine the extent and the true impact of surgery itself on prognosis, it is paramount to differentiate the acute myocardial injury precipitated by surgery from chronic myocardial injury.

In the Basel-PMI study, hs-cTnT concentrations were measured before and for 2 days after 2546 noncardiac surgeries in consecutive patients either older than 65 years or older than 45 years with documented coronary, cerebral or peripheral artery disease. In order to distinguish acute from chronic injury, PMI was defined as an absolute increase in hs-cTnT of 14 ng/l (the 99th percentile upper reference limit for the assay studied) above preoperative concentrations or between two postoperative concentrations. PMI occurred after 16% of the procedures, and only 6% of the patients had chest pain. This documents the major clinical problem that more than 90% of cases of PMI are asymptomatic and can therefore only be detected by routine hs-cTnT/I screening. After 30 days, nearly 10% of patients with PMI had died versus 2% of patients without PMI. Mortality was identical in patients with PMI in whom other criteria required for the definition of spontaneous AMI such as ECG changes and/or chest discomfort were also present versus those in whom no additional criteria were present. The occurrence of PMI was independently related to mortality [58].

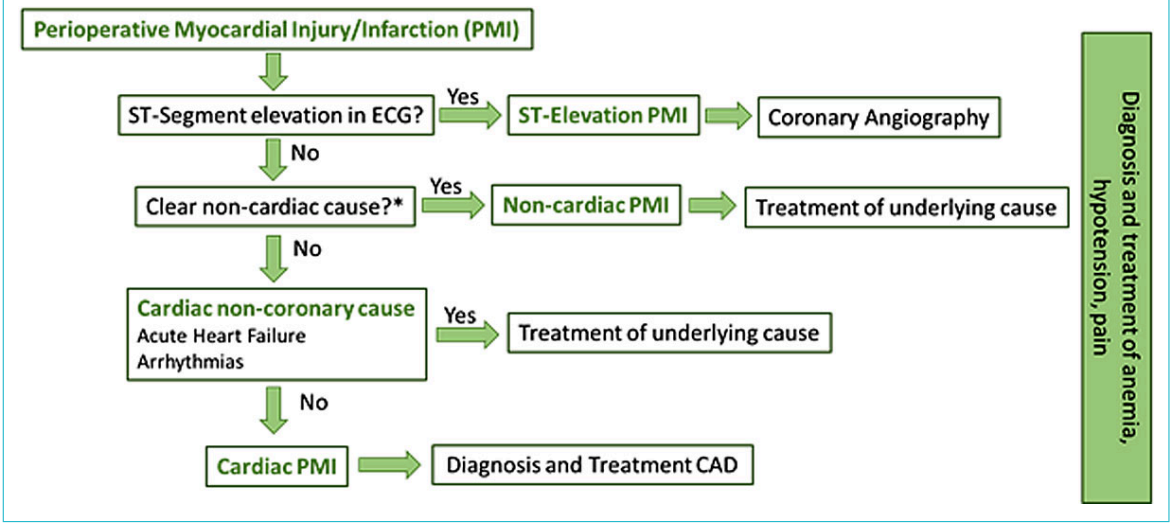
As with spontaneous myocardial infarction, different pathophysiological processes may underlie the development of PMI [59, 77]. Type 1 myocardial infarction (atherosclerotic plaque rupture and/or erosion) and type 2 myocardial infarction (supply-demand mismatch of oxygen) seem to be the most common, but several other cardiac and even primarily noncardiac conditions may contribute to myocardial injury and therefore to the differential diagnosis of PMI (table 1). Therefore, the approach to patients with PMI should be personalised, with a careful clinical evaluation, including an ECG, with the aim to identify and treat the most likely mechanism (fig. 3). In the presence of ST-segment-elevation myocardial infarction (a rare event in the perioperative period), this should be treated as usual with primary percutaneous coronary intervention. As these patients are at increased bleeding risk, dual antiplatelet therapy with clopidogrel rather than more potent antiplatelet agents should be preferred. The next step is to exclude a primarily noncardiac cause, such as severe sepsis, stroke, cardiac trauma or pulmonary embolism [78]. In the presence of a primarily noncardiac cause, the specific condition should be treated. Then a cardiac but non-coronary cause, such as acute heart failure or arrhythmias, should be identified and treated according to current guidelines [79]. Potential causes for type 2 myocardial infarction, such as anaemia, tachycardia due to pain and hypotension should always be assessed and treated accordingly. For the remaining patients, diagnosis and treatment of coronary artery disease should be performed. The recommendation and timing for invasive or noninvasive diagnosis depends on patient characteristics, clinical presentation and ECG findings, and should be individualised [68, 80]. The Basel-PMI study revealed that the vast majority of cases of PMI (86%) are cardiac and about 14% have a primarily noncardiac trigger [58].

Insights gained in VISION, Basel-PMI and other recent studies fully support the description of PMI as a silent (>90% are asymptomatic!) and neglected (these events are missed in most institutions worldwide!) killer with a 30-day mortality exceeding 10%. These findings fully support the recommendation within the universal definition of myocardial infarction for systematic screening using hs-cTnT/I measurements once before surgery and once daily in the first two postoperative days in high-risk patients such as those older than 65 years or older than 45 years with documented coronary, cerebral or peripheral artery disease if undergoing major noncardiac surgery [2, 68–70].

Natriuretic peptides

Natriuretic peptides – B-type natriuretic peptide (BNP) or N-terminal-pro-B-type natriuretic peptide (NT-proBNP) – are quantitative markers of haemodynamic cardiac stress and heart failure [81–83]. As the extent of heart failure, often unknown to patients and their physicians, is a powerful predictor of mortality and cardiac complications [84–86],

Figure 3: Flowchart for classification of perioperative myocardial infarction/injury.* Sepsis, cardiac trauma, stroke, pulmonary embolismECG = electrocardiogram; PMI = perioperative myocardial infarction/injury; CAD = coronary artery disease



preoperative concentrations of BNP and NT-proBNP have consistently been shown to be accurate and independent predictors of mortality and cardiac events after noncardiac surgery [63, 66, 87–90]. The higher the natriuretic peptide values, the higher the risk for cardiac complications or death. In an individual patient data meta-analysis, preoperative BNP concentrations above 100 pg/ml or NT-proBNP concentrations above 300 pg/ml worked well as cut-off values [63]. Preoperative measurements of BNP/NT-proBNP increased the accuracy of the Revised Cardiac Risk Index score for prediction of postoperative events [66, 89, 91]. Guidelines suggest measurement of BNP or NT-ProBNP in high-risk patients undergoing noncardiac surgery, such as patients older than 65 years, or patients older than 55 years with at least one cardiovascular risk factor [68–70]. Future studies need to define in more detail which cardiac work-up and/or therapy would allow mitigation of the increased risk identified by the elevated BNP/NT-proBNP concentrations. The postoperative measurement of BNP/NT-proBNP should be restricted to symptomatic patients with unclear dyspnoea for the diagnosis of acute heart failure [92].

Other cardiovascular biomarkers

Several pilot studies have evaluated the potential clinical utility of several other cardiovascular biomarkers in the perioperative setting. ST2 is an interleukin-1 family receptor, and its soluble isoform (sST2) is related to cardiac hypertrophy and fibrosis following cardiac overload. In patients with acute and chronic heart failure, high sST2 levels have been related to worse prognosis and might be used for risk stratification [93]. With regard to noncardiac surgery, in a small study including 175 patients sST2 concentrations were measured in the first 3 days after surgery. Peak sST2 concentration was independently related to 30-day major adverse cardiac events (death, nonfatal cardiac arrest, myocardial infarction and acute heart failure) [94]. Copeptin, the C-terminal fragment of the provasopressin peptide, was related to postoperative events, but did not provide added value on top of NT-proBNP and cTn [95]. Similarly, concentrations of midregional proadrenomedullin, leptin, heart-type fatty acid-binding protein and survivin have been shown to associated with adverse events after noncardiac surgery in small studies [96–99]. Further research is needed to determine the potential clinical utility of these biomarkers in patients undergoing noncardiac surgery.

Conclusion

Routine clinical use of cardiovascular biomarkers, specifically hs-cTnT/I represents a critical step towards precision medicine in the early diagnosis of acute myocardial infarction, and in the early detection of perioperative myocardial infarction/injury. In order to optimise its use, physicians need to be aware of three essential concepts:

1. Hs-cTnT/I concentrations should always be interpreted as a quantitative variable, and not binary like a pregnancy test.
2. In the case of unexpected hs-cTnT/I elevations, “true elevations” due to myocardial injury from unknown or underestimated cardiac disease such as heart failure are much more likely than “false elevations” due to analytical problems.
3. Hs-cTnT/I concentrations should always be interpreted within the context of the clinical presentation of the patient using all other clinical information available and not in isolation.

Potential competing interests

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