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Review

The place of cardiac troponin assessment in perioperative management: a narrative review

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Abstract

The recent 2022 European Society of Cardiology Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery emphasize the role of cardiac troponin assessment in the evaluation and management of potential perioperative myocardial injury. This central role is however challenged. The current contribution assesses the current knowledge on the place of cardiac troponin in the assessment of perioperative myocardial injury in non-cardiac surgery patients. Additionally, it explores the implications of routine cardiac troponin surveillance for healthcare systems, focusing on costs, resource allocation, and organisational challenges.

Keywords: **Cardiac troponins, myocardial injury, non-cardiac surgery, perioperative diagnosis, perioperative management, cost-effectiveness.**

Introduction

The recent 2022 European Society of Cardiology (ESC) Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery emphasize the role of cardiac troponin (cTn) assessment in the evaluation of potential perioperative myocardial injury. A strong class I B (recommended / indicated based on evidence from data derived from a single randomized clinical trial or large non-randomized studies) recommendation was issued to measure high sensitivity cTn (hs-cTn) T or I in patients with known cardiovascular disease, cardiovascular risk factors (including age ≥65 years), or symptoms suggestive of cardiovascular disease, before intermediate- and high-risk non-cardiac surgery and at 24 h and 48 h afterwards[1]. However, this recommendation is contested due to limited evidence supporting routine implementation[2,3]. The recent 2023 European Society of Anaesthesiology and Intensive Care (ESAIC) focused guideline on cardiac biomarkers in perioperative risk evaluation could not recommend combined pre- and postoperative cTn-enhanced management on a routine basis due to the limited evidence with low certainty. Therefore the task force considered it prudent to have such strategy embedded in a clinical research framework[4].

This review evaluates the current knowledge on the place of cTn in the assessment of perioperative myocardial injury in non-cardiac surgery patients. Additionally, it explores the implications of routine cTn surveillance for healthcare systems, focusing on costs, resource allocation, and organisational challenges.

Definition of myocardial infarction

The Fourth Universal Definition of Myocardial Infarction (MI) from 2018 (not yet updated) defines five different types of acute myocardial infarction (Table I). For four of these (except for type 3) the detection of cTn in the blood is fundamental for establishing the diagnosis. Types 1 and 2 refer to an acute myocardial injury with detection of an increase in cTn concentrations with at least one value exceeding the 99th percentile upper reference limit (URL) and at least one of the following: symptoms of myocardial ischemia, new ischemic

Table I. — Classification of the different types of acute myocardial infarction as defined by the fourth universal definition of myocardial infarction (2018)[5].

Type	Cause	Diagnosis
1	coronary plaque rupture with thrombosis	cTn elevation with at least 1 value above the 99th percentile URL and at least 1 additional sign of myocardial ischemia
2	myocardial oxygen supply/demand mismatch	cTn change with at least 1 value above the 99th percentile URL and at least 1 additional sign of myocardial ischemia
3	sudden cardiac death with typical signs and symptoms of myocardial infarctionbefore cTn elevation is detected	identification of coronary occlusion on autopsy or coronarography
4	~ to coronary procedures: PTCA (4A), stent thrombosis (4B), or restenosis (4C)	elevation of cTn values >5 times of the 99th percentile URL in patients with normal baseline values and at least 1 additional sign of myocardial ischemia
5	myocardial infarction that occurs during CABG	elevation of cTn values >10 times of the 99th percentile URL in patients with normal baseline values and at least 1 additional sign of myocardial ischemia

cTn = cardiac troponin; URL = upper reference limit; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary arterial bypass grafting.

electrocardiographic (ECG) changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology and-for type 1-potential identification of a coronary thrombus. Types 4 and 5 must meet the criteria for a >5 (type 4) or >10-fold (type 5) increase of cTn (in patients with normal baseline concentrations) and manifest a change from baseline value >20% (in patients with an elevated baseline)[5]. Notably, this Fourth Universal Definition of Myocardial Infarction report does not mention the potential occurrence of myocardial injury in the context of non-cardiac surgery.

While in the non-surgical setting, coronary thrombosis is involved in about two thirds of the acute MIs (type I), this is only in less than 15% of cases, the causal mechanism for a perioperative acute MI[6]. Perioperative MIs after non-cardiac surgery are indeed largely caused by a myocardial oxygen supply-demand mismatch (type II)[6,7]. Of note, perioperative MIs are usually clinically silent. Indeed, in about 80% of cases no chest pain or any other typical clinical myocardial ischemic symptom is reported and also ECG changes are only present in about 35% of these patients[8]. In fact, most perioperative MI's present as an isolated cTn elevation after non-cardiac surgery, without any accompanying symptoms or signs[8-10].

Myocardial injury after noncardiac surgery

The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study (VISION) studies have demonstrated that clinically silent cTn elevations after non-cardiac surgery are associated with major postoperative morbidity and mortality[9,10]. To define this clinical entity of isolated postoperative cTn elevations after non-cardiac surgery without the classical associated clinical symptoms or signs of MI, the VISION investigators have introduced the concept of myocardial injury after non-cardiac surgery (MINS). The association between postoperative isolated cTn elevations and postoperative outcome has been confirmed in later studies (reviewed in refs. 11-16)[11-16].

MINS can thus be defined by elevated postoperative cTn concentrations that exceed the 99th percentile of the upper reference limit of the assay and are attributable to a presumed ischemic mechanism, with or without concomitant symptoms or signs of myocardial ischemia. It is important to underscore that this clinical entity does not include perioperative Tn elevations due to non-ischemic causes such as sepsis, rapid atrial fibrillation, pulmonary embolism, renal failure or chronically elevated Tn concentrations[12,14].

The incidence of MINS has been reported at 20% (95% CI: 16% to 23%), which implies that one in five patients will develop myocardial injury after non-cardiac surgery[17]. As the diagnosis of MINS is essentially based on an assessment of cTn values, it is crucial to understand the clinical relevance of an elevated postoperative cTn. In other words: does an elevated postoperative cTn value automatically imply postoperative myocardial ischemic injury?

cTn assays: what are we measuring?

Both cTnI and cTnT are intracellular proteins that regulate cardiomyocyte contraction and relaxation. They share only 40 to 60% homology with their

skeletal muscle counterparts and can therefore be considered as sensitive biomarkers for myocardial injury[18]. They can be detected in circulating blood about 3 to 4 hours after myocardial damage and concentrations remain elevated for 10 to14 days[19].

Circulating cTn is usually detected by immunoassay methods. Currently, high sensitivity assays are in use, which exhibit much improved analytic performance, resulting in low 99th percentile URLs and high precision[20]. It has been shown that the 99th URL of hs cTn assays can be reached by necrosis of just 40 mg of myocardium[21]. This amount is too small to be detected by any noninvasive imaging technique[22]. However, the 99th percentile URLs may vary substantially between assays and are influenced by race, age, sex, and comorbidities[23,24]. This variability impairs differentiation between normal and high circulating cTn concentrations among various studies[25]. In contrast to cTnT, commercially available cTnI assays are heterogeneous because their antibodies target different epitopes with varying specificity. Hence, analytical characteristics vary. and it is of prime importance for clinicians to be aware of the characteristics of the assay used in their practice[26]. The Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) of the International Federation of Clinical Chemistry and Laboratory medicine provides regularly updated tables reporting the analytical characteristics of commercially available cardiac Tn assays (https://www.ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/).

It is important to understand that circulating cTn may appear in various molecular forms going from large covalent complexes of cTn released early after ischemia/reperfusion over free intact proteins and large cTn fragments to small cTn fragments (chronic real failure, marathon runners (Figure 1)). The reader is referred to some excellent reviews to learn more about this topic[22,26-28]. Commercially available assays detect all forms of cTn, provided they contain the epitope detected by the antibodies of the test[29]. However, these commercially available assays are not able to discriminate amongst the different molecular forms, to detect the sizes of fragments or to determine the relation between fragmentation and infarct size[23]. As a consequence the current assays are not specific for myocardial ischemia or infarction and are limited in detecting the source of the cTn.

Moreover, there is no universally accepted definition for the cTn cutoff value to define

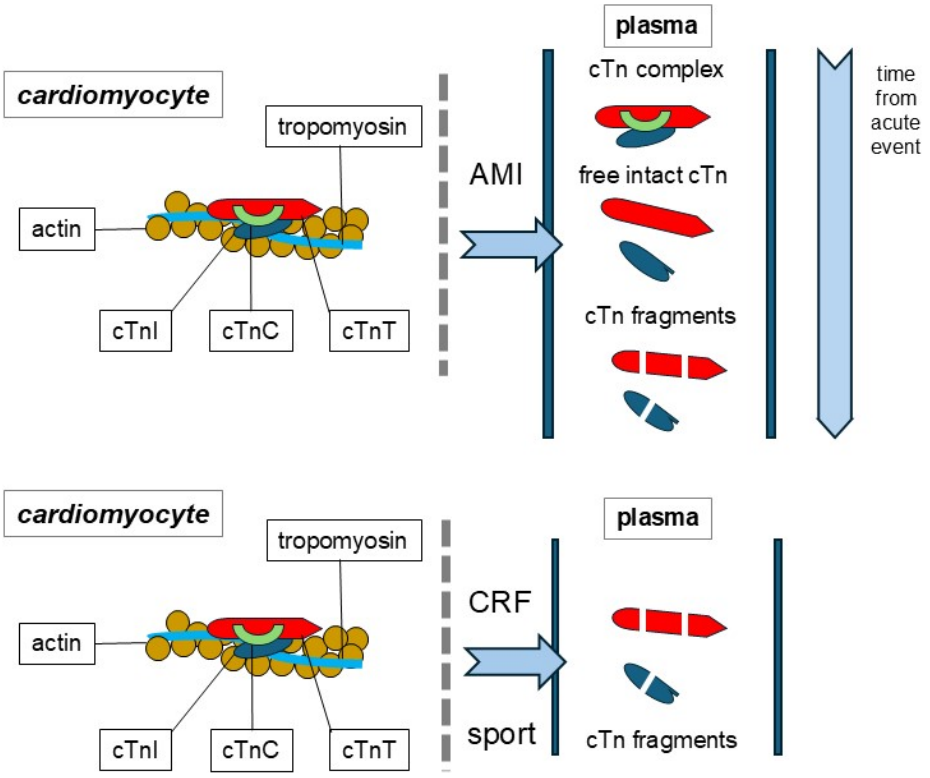

Fig. 1 — Molecular forms of cardiac troponins (cTn) released into plasma in different contexts. In Acute Myocardial Infarction (AMI), cTn is initially released as large complexes, followed by free intact proteins and smaller fragments over time. In Chronic Renal Failure (CRF) or after strenuous exercise, smaller cTn fragments predominate in plasma. The dashed line represents the cardiomyocyte membrane, and the time axis indicates progression from the acute event." (adapted from ref. 22).

a significant perioperative change and there is considerable heterogeneity of cut-offs in literature. Also the minimal clinically important difference for perioperative cTn changes remains undefined[4]. The pragmatic approach suggested by the European Society of Cardiology is to consider an absolute increase of at least the 99th percentile URL postoperatively, compared to the preoperative level[1].

Proposed role of cTn measurement in the perioperative setting of non-cardiac surgery

The 2022 ESC Guidelines have recommended a cTn based strategy for the assessment and management of perioperative myocardial injury after non-cardiac surgery (Figure 2). In patients with known cardiovascular disease, cardiovascular risk factors (including age ≥65 years), and symptoms suggestive of cardiovascular disease, undergoing intermediate or high risk surgery, hs-cTn should be measured before and 24 and 48 hours after surgery. An absolute increase in hs-cTn concentration of more than the URL on days 1 or 2 after surgery compared to the preoperative level is defined as MINS. In the absence of a pre-operative hs-cTnT/I concentration, a very high hs-cTnT/I concentration on day 1 (e.g. more than five-times the URL) or a relevant change from day 1 to day 2 (absolute increase or decrease more than the URL vs. day 1) would also be indicative of MINS. Detection of MINS is then the trigger for an extended evaluation of the patient in order to identify the cause of the perioperative cTn increase and consider an adapted treatment[1].

At this stage, it is crucial to recognize that a perioperative cTn increase may suggest, but does not definitively indicate, myocardial injury. Indeed, cTn rises may occur because of various extracardiac perioperative events, such as pulmonary embolism and stroke or may be chronically elevated, for instance in the presence of chronic renal failure. In addition, studies have observed important cTn rises (up to the level requested for diagnosis of AMI), in young healthy patients undergoing elective minor orthopedic surgery[30]. Moreover, increased cTn levels have been reported in marathon runners[31] and in healthy and active children and adults after a football game, (all participants showed an increase in cTn levels and 69 % had a cTn value exceeding the threshold for acute myocardial injury 3 h after the match)[32]. Figure 3 illustrates the potential causes of elevated perioperative cTn values, highlighting the need to differentiate physiological responses from pathological processes. A first question to be addressed is whether the cTn increase is just a mere physiological response or whether it is, on the contrary, a sign of an underlying pathological process that is responsible for increased morbidity and mortality. In the latter case, it needs to be identified whether the cause is extracardiac (for instance, sepsis, pulmonary embolism and stroke) or cardiac. A cardiac cause can be either related to a myocardial ischemic problem or to another

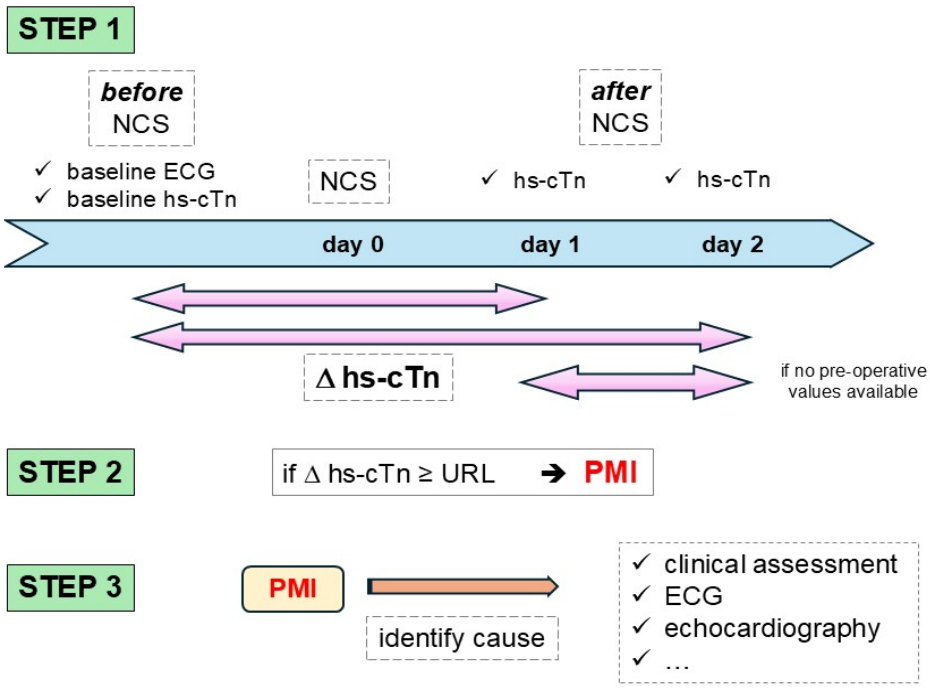

Fig. 2 — Recommended cTn measurements to assess and detect the risk of post-operative cardiac complications (adapted from ref. 1).
NCS = non-cardiac surgery; ECG = electrocardiogram; hs-cTn = high sensitivity cardiac troponin; PMI = peri-operative myocardial infarction/injury; URL = upper reference limit of normal.

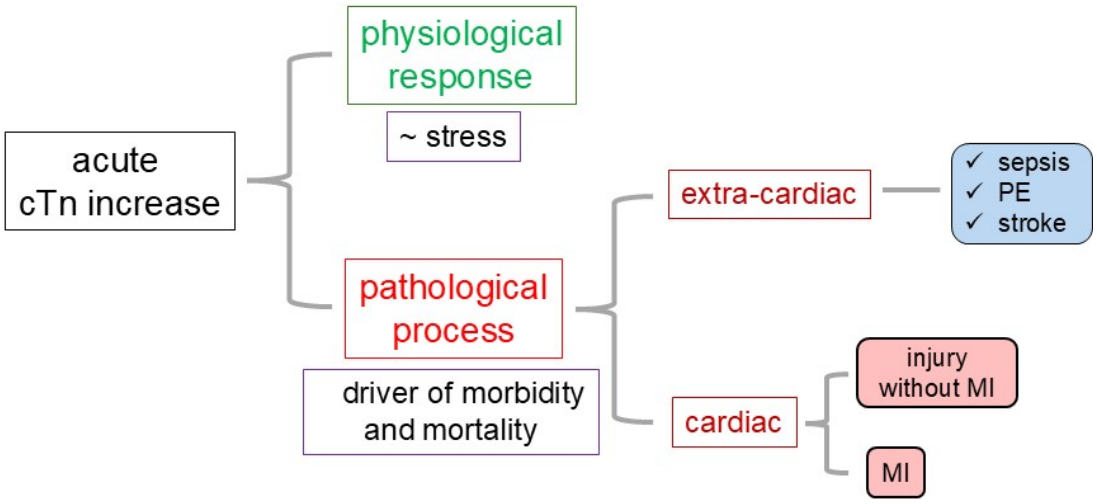

Fig. 3 — Differential diagnosis in the presence of an acute cardiac troponin (cTn) increase. MI = myocardial infarction.

cardiac cause such as tachyarrhythmias, acute heart failure or aortic valve stenosis.

What are the implications for clinical practice?

The updated 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac significantly expanded the indications for preoperative testing, including the use of cardiac biomarkers[1]. These guidelines underscore the prognostic value of hs-cTn in perioperative assessment, although the strength of evidence supporting these recommendations remains variable. It is therefore also important to analyze the implications for both daily clinical practice and healthcare costs.

Schweizer et al. have addressed this question for their practice in a tertiary university hospital in France, looking at the ratio of actually performed tests in their practice versus those recommended regarding both preoperative transthoracic echo and NT-proBNP/BNP (brain natriuretic peptide) assays. The results showed an important gap between the guidelines and routine practice in their hospital. The ratio performed to recommended preoperative echocardiographies was 0.21 (9/43) and for preoperative NT-pro-BNP/BNP assays the ratio was zero (0/61)[33]. Implementing these recommendations will clearly have substantial organizational and financial implications for hospital administrations.

The financial implication of implementing a perioperative cTn systematic screening strategy has first been addressed by Lurati Buse et al.[34]. They conducted a model-based cost–consequence analysis to compare the impact of routine cTnT monitoring versus standard care (cTnT measurement triggered by ischemic symptoms) on the incidence of MINS detection using data from the Canadian patients enrolled in the VISION study. The analysis revealed that the incremental cost to avoid missing a MINS event was 1,632 $ (2015 Canadian dollars).

A recent study in 1,473 Spanish patients compared standard care to a cTn surveillance programme based on 1 pre- and 2 postoperative hs-cTn measurements and calculated the incremental cost-effectiveness ratio of the systematic hs-cTnT strategy, defined as the expected cost per any additional perioperative myocardial ischemic injury detected. Direct costs from cTn measurements, diagnostic work-up in presence of elevated cTn and derived treatment (e.g. statin, aspirin and/or coronary interventions) were considered[35]. The incremental cost-effectiveness ratio in this study cohort was 425 € per additionally detected case.

Both studies thus report a moderate incremental cost to detect additional cases of myocardial injury in the perioperative period among patients with increased cardiovascular risk. However, the estimates of cost-effectiveness in these studies is based only on the detection of myocardial injury as the outcome of interest. As long as effects of management strategies for MINS are not established, it is impossible to provide an accurate estimate of the cost-effectiveness of a cTn-based strategy with respect to postoperative morbidity and mortality[36,37]. The implementation of routine perioperative cTn surveillance presents significant challenges, including the need for enhanced laboratory resources, staff training, and the development of standardised management protocols. Additionally, such surveillance may widen healthcare inequalities, particularly in resource-limited settings where access to advanced diagnostic tools is constrained. These logistical and financial hurdles must be carefully balanced

against the potential benefits of improved patient outcomes.

What is the evidence for a routine cTn based strategy to detect MINS?

The proposed pivotal place for cTn measurements remains challenged for various reasons already discussed earlier[2,3]. The recent 2023 ESAIC focused guideline for the use of cardiac biomarkers in perioperative risk evaluation aimed to critically analyze the current available evidence on the proposed central role of cardiac biomarkers in the risk assessment management of patients undergoing non-cardiac surgery[4]. These guidelines were prepared using Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology including the definition of critical outcomes, a systematic literature search, appraisal of certainty of evidence, evaluation of biomarker measurement in terms of the balance of desirable and undesirable effects including clinical outcomes, resource use, health inequality, stakeholder acceptance, and implementation. A panel of key opinion leaders differentiated between three different scopes of applications: cardiac biomarkers as prognostic factors, as tools for risk prediction, and for biomarker-enhanced management strategies. A modified Delphi process was applied to define; 12 critical outcomes. The systematic literature search resulted in over 25,000 hits, of which 115 full-text articles were the basis for assessment of evidence for the various recommendations[4].

The recommendations and their grade of evidence are summarized in Figure 4. Overall, it appears that the evidence for most outcome variables is moderate to very low. Evidence for improved risk prediction by preoperative cTn measurement was rated very low for 30-day all-cause mortality, 1-year MACE, and 30-day cardiac complications[4]. Of note, it has been shown that preoperatively increased cTn levels provide additional predictive value over validated risk scores[38,39].

The evidence supporting a place for postoperative cTn assessment in risk prediction is considered weak. In addition, it should be noted that serial postoperative cTn measurements will allow to identify acute changes but in the absence of a comparative pre-operative value, the relevance of an increased value cannot be assessed. This may represent an issue in cases of chronic cTn elevations. For this reason, pre- vs. postoperative cTn measurements are required to allow differentiation between chronic cTn elevation, acute cTn changes and acute on chronic cTn elevations. Finally, there is high evidence supporting the measurement of cTn before and after surgery for prognosis of 30-day mortality and moderate evidence for prognosis of 1-year mortality. High evidence also supports serial measurement of cTn before and after surgery to facilitate the prognosis of major adverse cardiac events within 30 days of surgery[4].

Taking these elements together with the uncertainties regarding the benefit for health outcomes and the financial and organizational impact of routine serial cTn measurements in these patients, led the ESAIC task force to conclude that systematic perioperative measurement of cTn to improve risk prediction or to trigger biomarker-enhanced management should be limited to a research context[4]. In addition, it remains currently undetermined whether intensification of therapy, in case of perioperative cTn elevation, actually improves clinical outcome. To date, the only prospective randomized controlled trial on the topic is the MANAGE trial. The results of this study, conducted in patients with myocardial injury of presumed ischemic injury after non-cardiac surgery with presumed ischemic origin, suggest that treatment with dabigatran 110 mg twice daily reduced major vascular complications beyond 12

	PROGNOSIS		PREDICTION		MANAGEMENT	
	R	E	R	E	R	E
pre-op	suggestion	very low	–	very low	–	no data
post-op	suggestion	moderate	suggestion	low	–	very low
combined	suggestion	moderate	suggestion	very low	–	very low

Fig. 4 — Summary of recommendations (R) and evidence (E) for the use of pre-operative (pre-op), post-operative (post-op) and combined pre- and post cardiac troponin (cTn) assessment in the prognosis, prediction, and management of perioperative adverse cardiac events. For prognosis, the question is: how does an elevated cTn concentration influence the risk of specific outcomes? This relates to a potential difference in incidence of an outcome over time in a population of interest. For prediction, the question is: how does cTn assessment contribute to the differentiation of patients at risk? This relates to the ability to discriminate between patients with and without adverse cardiac events. For management, the question is: does adaptation of a perioperative management strategy triggered by cTn assessment improve outcome, compared to routine management?

months of surgery (11% in the dabigatran group vs 15% in the placebo group)[40]. The results of this trial should however be interpreted with caution as several pitfalls have been identified that make generalization of the conclusions hazardous. Among these, there was the high drop-out rate (45% of patients discontinued the dabigatran treatment), the fact that the control group was treated with placebo instead of the current recommended treatment strategy in the presence of suspected MINS (aspirin and statins) and the fact that venous and arterial thrombotic events were pooled into the same group and managed all with dabigatran, which goes against established management strategies, such as low molecular weight heparins for venous events and dual antiplatelet therapy for arterial events[41-43].

Early diagnosis of elevated cTn levels should prompt a thorough evaluation of possible causes. Acute myocardial infarction, heart failure, and sepsis can be treated with evidence-based methods if detected early. Unfortunately, there is no evidence to establish the discriminatory value of cTn in perioperative settings[44]. Prospective studies of management strategies based on perioperative cardiac troponin surveillance are also currently under way (IMPLEMENT-PMI, NCT05859620). These approaches may revolutionize perioperative care for high-risk patients by providing more precise, evidence-based care.

Of note, the 2024 AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM guideline for perioperative cardiovascular management for non-cardiac surgery, while acknowledging that preoperative cTn levels can be used to evaluate perioperative risk for specific patients underscore the fact that there have been no studies evaluating whether this information is useful for clinicians to improve patient outcomes and impact health care costs. They conclude that the use of preoperative cTn testing for patients undergoing elevated-risk non-cardiac surgey has uncertain value because the relationship between medical cost and health benefit cannot be determined[45].

Conclusion

Serial hs-cTnT/I assessment is essential for the diagnosis of AMI and its potential value for diagnosis and risk assessment of myocardial injury after non-cardiac surgery is increasingly suggested and underscored. However, unlike the AMI setting, where the ischemic origin of the biomarker increase is readily confirmed by clinical signs, electrocardiographic changes and/or imaging findings, perioperative myocardial ischemic injury often lacks these corroborative indicators. In addition, multiple events may trigger cTn release in the perioperative period and therefore detection of circulating cTn does not unequivocally indicate cardiomyocyte cell death. Consequently, it is important to identify the underlying cause of the perioperative cTn increase in order to apply the most appropriate treatment.

While perioperative serial cTn measurements may indeed help in perioperative risk assessment, current evidence is still considered too limited to advocate for a routine cTn assessment-based strategy for prediction and/or management of MINS. Taking the uncertainties regarding the balance in desirable and undesirable health outcomes and the balance in terms of health gains versus resource use into account, the ESAIC task force of the focused guidelines for the use of cardiac biomarkers in perioperative risk evaluation reached the conclusion that systematic measurement of cTn to improve risk prediction or to trigger biomarker-enhanced management should be limited to a research context.

Therefore, the ESAIC task force recommends that, when centres decide to implement pre- and postoperative cTn surveillance and corresponding management algorithms to improve outcomes, such strategies be embedded in a clinical research framework with a multidisciplinary approach that uses standard definitions and well-defined shorter and longer term outcome variables. Importantly, the etiology of perioperative myocardial injury must be clearly identified before applying biomarker-enhanced management strategies, and their impact on the previously defined outcomes should be rigorously assessed alongside their cost effectiveness[4].

In conclusion, while perioperative cTn monitoring has the potential to improve patient outcomes, general implementation outside of research settings is premature. Future research should focus on improving diagnostic thresholds, understanding the mechanisms that cause perioperative cTn rises, and assessing the therapeutic value and cost-effectiveness of biomarker-driven therapies. Until strong evidence is available, perioperative cTn surveillance should be prioritised in research, with evidence-based procedures and a commitment to improving patient care guiding its implementation.

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