

## Evaluation of the cardiovascular risk in patients undergoing major non-cardiac surgery: role of cardiac-specific biomarkers

Consensus document by the Inter-Society Study Group on Cardiac Biomarkers of the Italian Societies of Clinical Biochemistry: European Ligand Assay Society (ELAS), Italian section; Società Italiana di Biochimica Clinica e Biologia Molecolare Clinica (SIBioC); Società Italiana di Patologia Clinica e Medicina di Laboratorio (SIPMeL)

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### ABSTRACT

#### Cardiovascular risk evaluation in patients undergoing major non-cardiac surgery: role of cardiac-specific biomarkers.

Joint document of the Italian Societies of Clinical Biochemistry: European Ligand Assay Society, Sezione Italiana (ELAS), Società Italiana di Biochimica Clinica e Biologia Molecolare Clinica (SIBioC), Società Italiana di Patologia Clinica e Medicina di Laboratorio (SIPMeL)

Patients undergoing major surgery have a substantial risk of cardiovascular events during the perioperative period. Despite the introduction of several risk scores based on medical history, classical risk factors and non-invasive cardiac tests, the possibility to predict cardiovascular events in patients undergoing non-cardiac surgery remains limited. The cardiac-specific biomarkers natriuretic peptides (NPs) and cardiac troponins (cTn) have been proposed as additional tools for risk prediction in the peri-operative period. This Consensus Document aims to discuss the value of preoperative levels and perioperative changes in cardiac-specific biomarkers to predict adverse outcomes in patients undergoing major non-cardiac surgery. Based on several prospective observational studies and 6 meta-analyses, some guidelines recommended the measurement of NPs to refine perioperative cardiac risk estimation in patients undergoing non-cardiac surgery. More recently, several studies reported a higher mortality in surgical patients presenting an elevation in high-sensitivity cTnT and cTnI, especially in elderly patients or those with comorbidities. This evidence should be considered in future international guidelines on the evaluation of perioperative risk in patients undergoing major non-cardiac surgery.

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## INTRODUCTION

Patients undergoing major non-cardiac surgery have a substantial risk of major adverse cardiovascular events during the peri-operative period (1-7). These events still represent a significant concern in patients undergoing non-cardiac surgery, despite a decreasing incidence over the last 30 years (8-11). Every year about 16 700 cardiac complications of non-cardiac surgery are reported, and 19000 of them are life-threatening events (8). The 2014 European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA) Guidelines recommended to perform a careful risk assessment of cardiac events also in patients undergoing non-cardiac surgery (8). Unfortunately, the possibility to predict cardiovascular events remains limited, despite the introduction of several algorithms to calculate the risk of adverse events, mainly death and major adverse cardiovascular events (MACE) based on the clinical history, risk factors (sex, age, lipid profile, serum creatinine) and non-invasive cardiac exams (electrocardiogram, echocardiogram, stress tests) (4,5,8,9). For this reason, cardiac-specific biomarkers have been proposed as additive tools to predict the risk of cardiovascular events (3,10-12).

The Canadian Cardiovascular Society (CCS) Guidelines published in 2017 recommended the measurement of cardiac natriuretic peptides [NPs; B-type NP (BNP)] or the N-terminal fragment of pro-BNP (NT-proBNP) before surgery to refine the prediction of cardiac events during the peri-operative period (13). These recommendations relied on prospective observational studies and 6 meta-analyses that evaluated the accuracy of NPs to predict major adverse cardiovascular events after non-cardiac surgery (14-21).

Over the last 10 years, increased concentrations of cardiac troponin (cTn) have been associated with a higher risk of cardiac events in the short- and long-term in patients undergoing non-cardiac surgery (10-13, 22-45). Nonetheless, at present there are no specific recommendations on the measurement of cTn during the peri-operative period.

This inter-society expert document aims to analyse in detail the clinical value of biomarkers measured before surgery and changes in biomarker levels during the peri-operative period, as well as their role, which is essential to predict the adverse events in patients undergoing major non-cardiac surgery. Building on published evidence we have formulated recommendations for the evaluation of patients at highest risk of MACE during non-cardiac surgery. This Consensus Document has been written by the Inter-Society Study Group on Cardiac Biomarkers of the Italian Societies of Clinical Biochemistry, and has been endorsed by the boards of the following Societies: European Ligand Assay Society (ELAS), Italian section; Società Italiana di Biochimica Clinica e Biologia Molecolare Clinica (SIBioC); Società Italiana di Patologia Clinica e Medicina di Laboratorio (SIPMeL).

## EVALUATION OF THE CARDIOVASCULAR RISK THROUGH THE USE OF CARDIAC BIOMARKERS IN PATIENTS UNDERGOING NON-CARDIAC SURGERY

Around half of cardiac deaths during the peri-operative period occurs in patients without a history of cardiac disease (7,10). This suggests that our current protocols for the assessment of subclinical cardiac disease are still suboptimal (10). The risk prediction models based only on clinical criteria, including the classical risk factors and cardiac stress tests, do not seem to improve the accuracy of pre-operative risk stratification and reduce 30-day mortality after non-cardiac surgery (9,11,12). Most notably, a 2019 meta-analysis included 6 studies on the accuracy of cardiac stress test to predict 30-day mortality, and concluded that there is insufficient evidence that stress testing leads to a reduction in peri-operative mortality (11).

Measurement of BNP and NT-proBNP has been widely accepted as a tool to refine risk stratification and improve prognostic accuracy in patients undergoing non-cardiac surgery, particularly as these biomarkers allow to identify a subclinical cardiac dysfunction (46,47). Furthermore, the measurement of cTnT and I with high-sensitivity (hs) assays has been recommended for identification of myocardial damage (43-45,48-50).

Cardiac NPs are hormones produced and secreted to a greater extent by the heart compared to other organs (43,46,51). International Guidelines recommend the measurement of BNP/NT-proBNP for diagnosis, risk stratification and monitoring of patients with acute and chronic heart failure (47,54). 2014 ESC/ESA Guidelines stated that NP measurement before surgery should not be performed in all patients who must undergo major non-cardiac surgery, but can be considered in all high-risk patients (8). Recently, prospective observational studies and 6 meta-analyses have reassessed the prognostic accuracy of BNP and NT-proBNP for the prediction of cardiovascular events after non-cardiac surgery (14-21). Based on these results, 2017 CCS Guidelines provided recommendations for peri-operative risk assessment before non-cardiac surgery (13). This document strongly recommends the measurement of BNP or NT-proBNP before surgery (including non-cardiac surgery) to improve the prediction of peri-operative MACE in patients with the following characteristics: age >65 years, age 45-64 years but known cardiovascular disease, a Revised Cardiac Risk Index (RCRI) score >1 (13). The RCRI algorithm includes: ischemic cardiac disease, heart failure, cerebrovascular disease, diabetes mellitus, serum creatinine >177  $\mu\text{mol/L}$  or 2.0 mg/dL, and high-risk major surgery (intra-peritoneal, vascular endo-thoracic or suprainguinal) (13).

2014 ESC/ESA Guidelines stated that cTnI or cTnT measurement can be considered in patients at high risk, before and 48-72 hours after major cardiac surgery, to detect a cardiac damage (8). This recommendation is based on the evidence that peri-operative increases in cTn are associated with a greater risk of cardiac events

in the short- and long-term in patients undergoing non-cardiac surgery, particularly when hs-cTnI and hs-cTnT methods are used (10-13,22-42).

In 2019, Humble et al. performed a systematic review and meta-analysis on the prognostic value of the increase of cTn above a decisional value (usually the 99<sup>th</sup> percentile upper reference limit) in adult patients undergoing non-cardiac surgery (35). The endpoints were MACE during the hospital stay or within 30 days from discharge or all-cause death. This meta-analysis included 19 studies that evaluated the pre-operative concentration of cTn and 3 studies assessing the peri-operative changes in cTn (35). cTn was measured in a total of 13 386 samples (from 33 to 4 575 across the different studies). The studies were mostly prospective and single-center, and patients underwent different types of non-cardiac interventions, but with an intermediate-to-high risk. Six studies employed hs-cTn methods (35). Pre-operative cTn measurement was able to predict adverse events on the short- [adjusted odds ratio (OR) 5.87, 95% confidence interval (CI) 3.24-10.65,  $p < 0.001$ ] and the long-term (adjusted hazard ratio 2.0, 95% CI 1.4-3.0,  $p < 0.001$ ) (35).

Recently, Lowe et al. evaluated the utility of the peri-operative increase in cTn as a predictor of cardiac morbidity and mortality in patients operated on femoral neck fractures (52,53). These fractures are rare in subjects aged  $< 50$  years in the absence of major traumas, while in elderly patients they may occur following minor traumas because of reduced bone density and bone frailty (39,52,53). This meta-analysis included 11 studies with a total of 1 363 patients (mean age 83 years, 351 men and 904 women) (39). In detail, 7 studies assessed cTnI, 3 hs-cTnT and one study assessed hs-cTnI. Overall, 497 patients (36.5%) have displayed an increase in cTn concentration after surgery. The peri-operative increase in troponin was significantly associated with all-cause mortality (OR 2.6, 95% CI 1.4-4.6,  $p < 0.001$ ) and cardiac complications (OR 7.4, 95% CI 3.5-15.8,  $p < 0.001$ ) (39). Higher cTn levels have been associated with pre-existing coronary artery disease, heart failure, hypertension, stroke and prior myocardial infarction (39). These results demonstrate that the peri-operative increase in cTn is significantly associated with an increase in mortality and post-operative cardiac complications in patients operated for femoral neck fractures (39).

#### TAKE-HOME MESSAGES

- *About one half of deaths for cardiac cause during the peri-operative phase occurs in patients without a history of cardiac disease. Therefore, there is a crucial need to assess more accurately the cardiovascular risk before major non-cardiac surgery.*
- *In 2014, ESC/ESA Guidelines stated that pre-operative measurement of NPs (BNP or NT-proBNP) should not be systematically performed for risk stratification in all patients who must undergo major non-cardiac surgery, but can be considered in patients with a high-risk (8.)*
- *The same Guidelines state that cTnI and cTnT*

*measurement may be considered in patients with a high risk, before or 48-72 hours after major surgery, to detect a myocardial damage (8).*

- *In 2017 the CCS recommended the measurement of BNP or NT-proBNP before surgery to better estimate the risk of peri-operative MACE in patients with a higher risk because of their clinical history, age ( $> 65$  years), or comorbidities.*

#### ANALYTICAL AND PATHOPHYSIOLOGICAL CONSIDERATIONS ON CARDIAC-SPECIFIC BIOMARKERS

Both NPs and cTn are useful prognostic indicators in patients undergoing major non-cardiac surgery (10-42). Nonetheless, clinicians should interpret measured values based on the analytical performance of the assay methods and the mechanisms of production and release by the heart. In healthy subjects, NPs and cTn are found in the circulation in a range of concentration (from about 3 to 50 ng/L) (43-45) that are 100 to 1 000 times lower than other biomarkers, including C-reactive protein, creatinine, cholesterol, D-dimer, neutrophil gelatinase-associated lipocalin (43,55-57). Some proteins and circulating peptides can influence directly the binding of NPs and cTn to specific antibodies used by immunometric methods, thus affecting results. As discussed in details elsewhere (43-45,58-60), this interference becomes more relevant when molar concentrations of different substances able to bind the monoclonal antibodies used by the immunometric systems increase compared to cardiac biomarkers. Furthermore, the measurement of cTnI and cTnT with immunometric methods can be influenced by the binding of these two cardiac troponins with troponin C, with some tissue or plasma proteins and also with some heterophile antibodies or autoantibodies, especially when macromolecular complexes are formed (58,59). Therefore, both the accuracy and the clinical interpretation of the measurement of cardiac biomarkers strongly depend on the analytical characteristics and the performance of the methods of determination (43,58-61).

#### Methods of determination of cardiac natriuretic peptides (BNP and NT-proBNP)

The determination of cardiac NPs is an essential diagnostic and prognostic tool in patients with cardiac disorders because these biomarkers are released following a stress able to activate the neuro-endocrine-immune system. It is important to specify that the increase in BNP/NT-proBNP by itself does not allow to define the stress mechanisms acting on an individual patient (51,60-62). In particular, variations in circulating levels of NPs are useful to detect cardiac stress in patients with risk factors or asymptomatic cardiovascular disease (51,60-63).

Cardiac NPs are rapidly degraded *in vivo*. The active hormone BNP has a shorter plasma half-life (20-40 minutes) than the inactive peptide NT-proBNP ( $> 60$  minutes) (51,60,64). Because of their rapid turnover, BNP

has a greater intra- and inter-individual variability (40-50% and 50-60%, respectively) compared with NT-proBNP (30-40% and 40-50%, respectively) (60,64). A wide variability is associated with large confidence intervals and large differences between serial measurements in a single individual, regardless of changes in the disease state (65).

Clinicians should be informed by biochemical chemistry experts and then consider some critical issues for a correct interpretation of changes in plasma concentrations of BNP/NT-proBNP (43,44,46,51). In particular, values should be interpreted based on sex, age, body mass index, comorbidities and current therapies (43,47,60-62). Furthermore, kidney disease can influence significantly peptide clearance increasing their circulating levels (60,61). Nevertheless, a meta-analysis has demonstrated that NT-proBNP retains a diagnostic utility for acute heart failure even in patients with chronic kidney disease (although with higher cut-offs) and holds prognostic value regardless of renal function (63).

The methods that measure BNP show greater systematic differences between them than methods that measure NT-proBNP (60,66). Because of its greater stability *in vivo* and *in vitro* and a lower difference between assay methods, NT-proBNP is a better indicator of disease and outcome than BNP (60).

From a clinical perspective, it is important to notice that international guidelines recommend decisional values for the diagnosis and risk prediction in patients with heart failure, but not for the risk stratification of patients undergoing major non-cardiac surgery (46,47). The lack of a general consensus on specific threshold values undoubtedly limits the use of BNP/NT-proBNP in clinical practice for the evaluation of the peri-operative risk. Optimal cut-offs have been calculated for MACE prediction, with a large variability in the proposed cut-offs. In 2009, a meta-analysis on 15 studies and 4856 patients reported that NT-proBNP cut-offs were higher than BNP cut-offs (range 201-791 ng/L vs. 35-255 ng/L, respectively) (16). More recently, Rodseth et al. have evaluated the prognostic value of pre-operative BNP for cardiovascular events (defined as cardiovascular deaths and non-fatal myocardial infarction) and all-cause mortality during the first 30 days after vascular surgery in an individual patient data meta-analysis assessing a total of 632 patients. From the receiving operating characteristics curve, the Authors calculated a BNP cut-off of 116 ng/L (sensitivity 66%, specificity 82%) as the value with the better combination of sensitivity and specificity, and then with the greater accuracy for outcome prediction (20). The Authors also proposed a value of 30 ng/L as a rule-out cut-off (sensitivity 95%, specificity 44%) and a value of 372 ng/L as a rule-in cut-off (sensitivity 32%, specificity 95%) (20).

### Assay methods for cTnI and cTnT

The assay methods for hs-cTnI and hs-cTnT have been recommended by the latest international guidelines as the golden standard methods to detect a myocardial damage and diagnose myocardial infarction (49,67-70).

The document published in 2018 from the American Association for Clinical Chemistry and the International Federation of Clinical Chemistry (67) establishes the two essential criteria that define the high-sensitivity methods for cTnI and cTnT. The first criterion is that the 99<sup>th</sup> percentile upper reference value (URL; the 99<sup>th</sup> percentile of the distribution of values of hs-cTnI or hs-cTnT in a reference population) must be measured with an error (expressed as coefficient of variation) lower than or equal to 10%. The second, more restrictive, criterion involves that hs-cTnI and hs-cTnT methods measure biomarker concentrations with values higher than the limit of detection of the method in at least 50% of individuals in a reference population including at least 300 apparently healthy women and men (67).

The mechanism underlying the presence of detectable levels of hs-cTnI and hs-cTnT in healthy subjects is not well understood (48,71-73). Theoretical considerations and some experiments in animals and in humans suggest that the 99<sup>th</sup> URL corresponds to the amount of hs-cTn within around 40 mg of myocardial tissue (48,71-73). Cardiac troponins are localized mostly in the sarcomere of cardiomyocytes and bound to myofibrils; while only around 4-9% of cTnI and cTnT are found in the cytosol of cardiomyocytes as unbound proteins (48,71,72). According to these studies, hs-cTn levels in adult subjects who are apparently healthy should be considered as a specific indicator of the physiological turnover of cardiomyocytes (48,71,72). The estimate of URL of hs-cTnI and hs-cTnT assay methods is influenced by the demographical characteristics of the reference population, in particular sex and age distribution, and likely also the ethnic group (58,59,67,74-76). A very important point is that the intra-individual biological variability of these two biomarkers is very low (on average about 9%) (77). Furthermore, the hs-cTnI and hs-cTnT methods have an excellent analytical imprecision (coefficient of variability 5-7%) at the 99<sup>th</sup> percentile URL (58,77). Because of these favorable characteristics, the critical differences (reference change value, RCV) between two values of hs-cTnI or hs-cTnT measured in the same subject in different times are inferior than other cardiac biomarkers. According to some recent studies, a RCV >30% can be considered as statistically significant for all hs-cTnI and hs-cTnT methods (77-83). Therefore, hs-cTnI and hs-cTnT are better suited to act as prognostic biomarkers than BNP and NT-proBNP because of the higher analytical and biological variability of NPs (58,77,84). The hs-cTnI and hs-cTnT methods indeed display ideal analytical and pathophysiological characteristics for prognostic biomarkers (44,48,58,60,84) (Table 1).

### Combined measurement of BNP/NT-proBNP and hs-cTn

According to the Fourth Universal Determination of Myocardial Infarction (49), published in 2018, the term myocardial injury should be employed when there are elevated concentrations of hs-cTnI or hs-cTnT with at least one value above the 99<sup>th</sup> percentile URL. There are many cardiac and extracardiac conditions that

**Table 1***Biological and analytical characteristics of cardiac troponins as cardiac-specific biomarkers*

Cardiac troponins are optimal cardiac-specific biomarkers because:

- Cardiac troponins are tissue-specific biomarkers, expressed just by cardiomyocytes in healthy subjects.
- Cardiac troponins are more stable in vivo and in vitro than cardiac natriuretic peptides.
- Cardiac troponins can be measured on both plasma (with EDTA or heparin) and serum.
- Reliable laboratory tests for both cardiac troponins are commercially available.
- High-sensitivity methods are available (limit of detection about 1-3 ng/L).
- The concentration value can be measured within 30 minutes with the most diffuse automated platforms.
- Both cardiac troponins have an intra-individual biological variability <10%, while the inter-individual variability is higher (40-50%) because it is correlated to age, sex and body mass (and then cardiac mass).
- Considering that both cardiac troponins have a similar intra-individual variability and also the analytical variability of all the hs-cTnI and T methods at the clinical cut-off is ≤10%, the reference change values are basically equal (<30%) for all assays.

**Table 2***Pathophysiological conditions associated to elevation of circulating levels measured using hs-cTnI and hs-cTnT methods due to the presence of myocardial injury, according to the Fourth Universal Definition of Myocardial Infarction (49)***Myocardial injury related to acute myocardial ischaemia (related to Type 1 AMI)**

- Atherosclerotic plaque disruption with thrombosis.

**Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance (related to Type 2 AMI)**

Reduced myocardial perfusion, e.g.

- Coronary artery spasm, microvascular dysfunction.
- Coronary embolism.
- Coronary artery dissection.
- Sustained bradyarrhythmia.
- Hypotension or shock.
- Respiratory failure.
- Severe anaemia.

Increased myocardial oxygen demand, e.g.

- Sustained tachyarrhythmia.
- Severe hypertension with or without left ventricular hypertrophy

**Other causes of myocardial injury**

Cardiac conditions, e.g.

- Heart failure.
- Myocarditis.
- Cardiomyopathy (any type).
- Takotsubo syndrome.
- Coronary revascularization procedure.
- Cardiac procedure other than revascularization.
- Catheter ablation.
- Defibrillator shocks.
- Cardiac contusion.

Systemic conditions, e.g.

- Sepsis, infectious disease.
- Chronic kidney disease.
- Stroke, subarachnoid haemorrhage.
- Pulmonary embolism, pulmonary hypertension.
- Infiltrative diseases, e.g. amyloidosis, sarcoidosis.
- Chemotherapeutic agents.
- Critically ill patients.
- Strenuous exercise.

can produce a myocardial damage in the absence of acute myocardial ischemia (Table 2). Acute myocardial infarction is defined as a myocardial damage with clinical evidence of myocardial ischemia and an increase and/or decrease of hs-cTnI or hs-cTnT with at least one value higher than the 99<sup>th</sup> percentile URL (49).

Many clinical studies and some meta-analyses have confirmed that there are some individuals with no evidence of cardiac disease who have concentrations of hs-cTnI or hs-cTnT in the third tertile of biomarker values (then still below the 99<sup>th</sup> percentile URL), who have nonetheless a higher risk of cardiac mortality even in the intermediate term (around 6-12 months) and/or rapid progression toward heart failure (84,85). The combined measurement of NPs and hs-cTn should allow to identify more easily these individuals who have a higher risk (44,77). Indeed, cardiac-specific biomarkers have different but complementary characteristics. Concentrations of NPs and hs-cTn are differently affected by the mechanisms causing cardiac dysfunction and/or damage (43,44,56,57,60). An increase in circulating levels of both biomarkers suggest that the stress mechanisms have already caused relevant alterations of cardiac function (increase in BNP/NT-proBNP) and also a significant damage to cellular structure (increase in hs-cTn) (43,44). Furthermore, experimental and clinical studies report that individuals from the general population or patients with cardiac disease and elevated values of both cardiac biomarkers have worse outcomes than individuals with just one abnormal biomarker (84-86). The same occurs in individuals undergoing non-cardiac surgery. In particular, Moon et al. have performed a retrospective evaluation of 2 490 adult patients undergoing liver transplantation between 2010 and 2018 to define the prognostic value of the measurement of BNP and hs-cTnI before organ transplantation to predict post-transplant mortality (87). The most important results are that the combined measure of cardiac-specific biomarkers predict mortality at 90 days after the transplant (2.9% of subjects). Indeed, patients with both biomarkers elevated above a threshold (400 ng/L for BNP, 60 ng/L for hs-cTnI) displayed an adjusted HR value of 21.19 (95%CI 11.9-37.48,  $p < 0.001$ ) compared with an adjusted HR of 4.23 (95%CI 1.98-9.03,  $p < 0.001$ ) in patients with both biomarkers below threshold, then a HR value about 5-fold higher. Therefore, the measurement of BNP and hs-cTnI before transplantation would help define the priority of liver transplantation in single individuals.

### TAKE-HOME MESSAGES

- Both NPs and hs-cTn are useful prognostic indicators in patients undergoing major non-cardiac surgery.
- Although the measurement of NPs is useful to detect cardiac stress, it is not able to discriminate the specific mechanisms causing cardiac dysfunction.
- Myocardial damage is defined as elevated concentrations of hs-cTnI or hs-cTnT with at least one value above the 99th percentile URL (i.e., the 99th percentile of the distribution of biomarker values in the reference population).

- There are many cardiac and extracardiac conditions that can cause a myocardial damage, and clinicians must always search for these conditions.
- The combined measurement of NPs and hs-cTn provides more accurate pathophysiological and clinical information than the measurement of single biomarkers. Therefore, both cardiac-specific biomarkers should be measured when there is a suspicion of cardiovascular disease.
- An increase in both biomarkers suggest that the stress mechanisms have already caused relevant alterations of cardiac function (increase in BNP/NT-proBNP) as well as a significant impairment of cellular structure (increase in hs-cTn).

### ASSESSMENT OF MYOCARDIAL DAMAGE IN PATIENTS UNDERGOING MAJOR NON-CARDIAC SURGERY

Several studies have evaluated the changes in circulating hs-cTnI and hs-cTnT in patients undergoing major non-cardiac surgery (6-9,22-42,88-92). The VISION study was a prospective cohort study enrolling 40 004 patients (aged  $\geq 45$  years, half of them men) undergoing non-cardiac surgery during hospital admission from 2007 to 2013 in 28 centers in 14 countries in North and South America, Asia, Europe, Africa and Australia (91). This study demonstrated a prevalence of MI after non-cardiac surgery (MINS) of 13% (95%CI 12.7-13.3). The prevalence was more common in vascular surgery (633 patients, 24.0%) and less common in urologic or gynecologic surgery (503 patients, 10.4%). Furthermore, the occurrence of MINS was significantly associated to 30-day mortality (314 deaths; adjusted HR 2.2, 95%CI 1.9-2.6) and was one of the main causes of death (91). cTnT levels were measured 6-12 hours after the surgery and on day 1, 2 and 3 after surgery using a not hs method, thus possibly underestimating the prevalence of MINS. Only the most recent studies have used hs-cTnI and hs-cTnT methods to detect the presence of MINS in patients undergoing extra-cardiac surgery (34,37,40,41,88,89). The most important elements of experimental design and results of studies using hs-cTnI (one study) and hs-cTnT (five studies) are summarized in Table 3. In two retrospective studies, the prevalence of MINS was 9% in a Spanish study where hs-cTnI was measured (41) and 3.5% in an US study where hs-cTnT was measured (91). The other 4 studies (34,37,40,88) wished to evaluate the association between hs-cTnT and peri-operative cardiovascular risk. Despite the large differences in term of experimental design, number of enrolled patients, type of surgery and results of surgery, the rate of mortality was clearly higher in patients with MINS than those without (34,37,40,88). Additionally, patients with MINS had more often other important complications such as sepsis or bleeding (37,40).

A study published in 2012 evaluated 46 539 adult patients undergoing non-cardiac surgery in 498 hospitals in 28 European countries (93). In this study, 1 855 patients (4%) died before discharge, 3,599 (8%) were admitted

**Table 3**

*Studies using hs-cTnI and hs-cTnT methods for cardiovascular risk evaluation in patients undergoing major non cardiac surgery*

Authors (year)	Method	Type of Study	Enrolled Population	Statistical results	Ref.
Górka et al. (2018)	hs-cTnT	Prospective observational cohort study	164 adult patients ( $\geq 45$ years, men 79.9%, mean age $66.1 \pm 9.1$ years) undergoing surgery for PAD (88.4%) or AAA (23.8%).	1-year mortality was higher in patients with MINS (23.1%), evaluated by increased hs-cTnT, than non-MINS patients (7.2%; $p = 0.006$ )	34
Ackland et al. (2020)	hs-cTnT	Prospective multicentre observational cohort study	4335 patients aged $\geq 45$ years undergoing elective noncardiac surgery (mean age, $65 \pm 11$ years, men 54.9%).	Patients with elevated troponin (49.8%) have more frequently noncardiac morbidity (OR: 1.95; 95%CI: 1.69-2.25), and are also at higher risk of infectious morbidity (OR: 1.54; 95%CI: 1.24-1.91) and critical care utilisation (OR: 2.05; 95%CI: 1.73-2.43).	37
Costa et al. (2021)	hs-cTnT	Prospective multicentre observational cohort study	2504 adult ( $\geq 45$ years) patients (mean age $61.9 \pm 11.0$ years; men 49%) undergoing noncardiac surgery at 2 tertiary hospitals.	MINS, evaluated by increased hs-cTnT within 30 days after noncardiac surgery, was related to higher mortality (HR: 3.17, 95%CI: 1.56-6.41), major bleeding (HR 5.76; 95%CI 2.75-12.05), sepsis (HR: 5.08; 95%CI: 2.25-11.46), and active cancer (HR 4.22, 95%CI 1.98-8.98).	40
Serrano et al. (2021)	hs-cTnI	Prospective cohort with retrospective analysis. Multivariable logistic regression analysis was used to study risk factors associated with MINS, evaluated by increased hs-cTnI.	3363 adult ( $\geq 45$ years) patients (mean age $72.9 \pm 11.7$ years; men 47.1%) undergoing major non-cardiac surgery.	The incidence of MINS was 9%. Preoperative risk factors that increased the risk of MINS were age, ASA classification and vascular surgery.	41
Kler et al. (2021)	hs-cTnT	Retrospective single centre study	109 consecutive patients (men 48.6%) who underwent open pancreaticoduodenectomy (median age 66 years, range 20-85 years)	ROC curves demonstrated a strong correlation between elevated mean hsTnT and 30-day (AUC=0.937), 90-day (AUC=0.852) mortality and MACE (AUC=0.779). In multivariate analysis hs-TnT was significantly associated with 90-day mortality (OR: 43.928, $p = 0.004$ ) and MACE (OR: 8.177, $p = 0.048$ ).	88
Turan et al. (2021)	hs-cTnT	Single centre retrospective analysis	4480 of adults ( $\geq 45$ years) with routine postoperative TnT monitoring after noncardiac surgery (mean age 62.9 years, men 51.1%)	The incidence of MINS was 155/4480 (3.5%). Lower postoperative haemoglobin values associated with MINS.	91

PAD: vascular surgery for peripheral artery disease; AAA: abdominal aortic aneurysm; MINS: myocardial injury after non-cardiac surgery; ASA: American Status Anaesthesiology; MACE: major adverse cardiovascular events.

in intensive care unit after surgery for a median of 1.2 days (0.9-3.6); 1,358 of the deceased patients (73%) were not admitted to intensive care unit after surgery (93). Nevertheless, the raw rates of mortality were highly different across countries (from 1.2%, 95%CI 0.0-3.0 in Islanda to 21.5%, 95%CI 16.9-26.29 in Lettonia), likely because of cultural, demographic, socio-economic and political differences between nations, all factors that affect the outcomes of surgery (93).

Overall, the data in Table 3 confirm that myocardial damage, evaluated with the hs-cTnI and hs-cTnT methods, is frequently observed in patients undergoing major non-cardiac surgery, particularly in more elderly patients or those with cardiac or extra-cardiac morbidity (34,37,40,41,88,91). These studies also confirm that increased hs-cTnI and hs-cTnT above the 99<sup>th</sup> percentile URL are significantly associated with an increased risk of mortality or MACE (34,37,40,88).

### **CLINICAL CONSIDERATIONS ON THE MEASURE OF CARDIAC-SPECIFIC BIOMARKERS IN PATIENTS UNDERGOING MAJOR NON-CARDIAC SURGERY**

Several technical aspects, surgical factors and clinical conditions may influence the evaluation and/or clinical interpretation of cardiac-specific biomarkers in patients undergoing major non-cardiac surgery. Some of these factors deserve a more detailed discussion.

#### **Clinical relevance of the measurement of biomarkers before surgery**

The stress induced by surgery and the anesthesia may cause myocardial ischemia by increasing oxygen requirements, reducing oxygen availability or by the combination of these mechanisms (8). According to the 2014 ESC/ESA Guidelines, the main goal of pre-operative evaluation is to search for and manage the cardiovascular risk factors in patients undergoing surgery (8). These Guidelines recommend to consider BNP and NT-proBNP measurement to predict the risk of peri-operative and late cardiac events in patients at high risk (class IIb, level B). cTn should be measured in patients at high risk, both before and 48-72 hours after major surgery (class IIb, level B). On the other hand, a systematic screening of cardiac biomarkers before surgery is not recommended (class III, level C) (8).

The Authors of the present document deem that NPs and hs-cTnI or T should always be measured before surgery (8,23), particularly in patients with a higher risk, for example because of their age (>65 years) and/or comorbidities (84,85). This proposal is based on pathophysiological considerations and the results of the most recent clinical studies (Table 3).

The prognostic information from the measurement of BNP/NT-proBNP and hs-cTn is independent and complementary to other important indicators of risk, such as those deriving from ECG and imaging techniques (6,8,23). Elevated levels of cardiac-specific biomarkers before surgery are associated with a markedly

higher risk of MACE during the peri-operative period (34,35,37,40,87,88). Importantly, if a preoperative measurement is not performed, it is impossible to assess the specific contribution of surgery to the increase in cardiac biomarkers observed during or just after the surgery.

The measurement of hs-cTnI or T can identify subjects free from symptomatic cardiac disease but having a higher cardiovascular risk. These subjects have hs-cTn values in the third tertile or even above the 99<sup>th</sup> percentile URL (84,85,94). Importantly, many cardiac and non-cardiac conditions may cause a myocardial damage, particularly in elderly patients with comorbidities (Table 2). Furthermore, the detection of high cardiac-specific biomarkers during the preoperative evaluation can prompt clinicians to perform further non-invasive or invasive cardiac tests to identify the underlying cardiac disease and then obtain further information on the clinical condition of the patient (2,8).

#### **Effects of cardiac-protective drugs**

Patients undergoing major non-cardiac surgery with increased concentrations of cardiac biomarkers, and then with a higher risk of peri-operative MACE, should be protected through cardiac-protective medications (8). According to ESC/ESA Guidelines, beta-blocker therapy may be considered before high-risk surgery if patients have at least 2 classic clinical risk factors or score at least 3 on the American Society of Anesthesiologists scale (class IIb, level B). Furthermore, beta-blockers before surgery might be considered also in patients with a history of ischemic cardiac disease or myocardial ischemia (class IIb, level B) (8).

The primary objective of a cardiac-protective therapy is to reduce the stress to the heart by counteract neurohormonal and immune activation (51,57,62,95). As a result, a continuous therapy with cardiac protective drugs such as beta-blockers, angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) tends to reduce circulating levels of biomarkers in patients with cardiac disease (51,57,62,95). Even diuretics, often prescribed to patients with hypertension or heart failure, should be maintained in patients undergoing major non-cardiac surgery (8). A continued therapy with diuretics tends to reduce NP levels (51,57,62).

#### **Chronic heart failure**

Heart failure is a well-established predictor of peri- and post-operative cardiac events and is included in several algorithms for risk prediction (8,96-98). In a study on a registry of 160 000 Medicare procedures including patients aged  $\geq 65$  years, heart failure was found in 18% of cases and was associated with a 63% higher risk of surgical mortality and a 51% higher risk of 30-day readmission for all causes compared to patients with coronary artery disease but no heart failure (96). In particular, a study reported that a left ventricular ejection fraction (LVEF)  $\leq 35\%$  is a strong predictor of cardiac events after vascular surgery (98). Circulating NP levels

are increased in patients with acute or chronic HF, with reduced or preserved EF (8,47).

Preoperative NP levels are strongly correlated with the outcome of patients with heart failure and with the peri- and post-operative morbidity and mortality (6,8,18,99). Furthermore, compared to a single pre-operative measurement of BNP/NT-proBNP, their post-operative measurement improves risk stratification for the composite outcome of death or non-fatal MI at 30 days and  $\geq 180$  days after non-cardiac surgery (20). Based on this evidence (6,18,20,99), Guidelines recommend that NPs are routinely measured before non-cardiac surgery when a cardiac dysfunction is known or suspected (8).

hs-cTnI and T are often elevated in patients with chronic HF, particularly those aged  $>65$  years or with comorbidities (43-47,50), suggesting the presence of heart failure associated with myocardial damage (usually not acute). Furthermore, the start of a specific therapy should be considered at least one week before surgery in stable patients with systolic HF (class IIa, level C) (8).

Importantly, some drugs such as ACEi or ARB tend to reduce circulating levels of both cardiac-specific biomarkers (43,44,50,60,95). In particular, sacubitril/valsartan has complex effects on the metabolism of NPs (100, 101). Therefore, clinicians should consider both the clinical conditions and the analytical characteristics of methods for BNP/NT-proBNP measurement to correctly interpret changes in biomarker levels, especially in patients undergoing major non-cardiac surgery and receiving sacubitril/valsartan, during the first month of treatment with this drug (100,101).

### Cardiac arrhythmias

Cardiac arrhythmias are common causes of morbidity and mortality during the peri-operative period (8). A systematic revision including 14 studies found that increased levels of BNP or NT-proBNP can identify patients at risk for post-operative atrial fibrillation (AF) after surgery, particularly after lung or esophageal resection (102). AF is the most common cardiac arrhythmia. Its prevalence increases with age, with a prevalence  $<0.2\%$  in adults  $<55$  years and around  $10\%$  in those aged  $\geq 85$  years, and is higher in men (103). Arrhythmias such as AF and ventricular tachycardia often denote an underlying structural cardiac disease (104). AF is an important risk factor for ischemic stroke (103). 2022 US Preventive Services Task Force (USPSTF) Guidelines state that the current evidence does not allow to assess the cost-effectiveness of a screening for AF in asymptomatic adults by intermittent or continuous screening strategies, with ECG or photoplethysmography (103). Nonetheless, the finding of these arrhythmias before surgery should lead to a cardiac evaluation including echocardiography (8).

Patients with AF usually have elevated values of BNP/NT-proBNP (usually, during acute episodes, over 5-fold higher than reference limits) (44). Due to their higher turnover *in vivo*, concentrations of NPs tend to decrease rapidly after an acute arrhythmic episode (BNP more rapidly than NT-proBNP), and reach values

within the reference limits if no cardiac dysfunction is present (44,97). Increased values of hs-cTn are found in 10-15% of patients with AF and suggest a structural cardiac disease, pointing to a high cardiac risk.

### Myocardial infarction

Values of BNP/NT-proBNP and hs-cTn above the threshold values before surgery denote a myocardial damage (44,49,50,60,72,73). To confirm an acute myocardial damage in a patient with evidence of acute myocardial ischemia, the measurement of hs-cTnI or T on at least two blood samples during the peri-operative period is needed (49) (Table 2). Recent studies confirm that the increase in hs-cTnI and T above the 99<sup>th</sup> percentile URL is significantly associated with a higher risk of death or MACE (34,37,40,41,88,91) (Table 3). 2014 ESC/ESA Guidelines recommend to consider myocardial revascularization before a high-risk surgery when there is evidence of inducible ischemia (class IIb, level B). Revascularization is not routinely recommended before low- or intermediate-risk surgery in patients with myocardial ischemia (class III, level B).

Even in patients undergoing major non-cardiac surgery, the diagnosis of MI during or after surgery should be performed through the measurement of changes in hs-cTnI or T (49,67-70,105). In particular, in patients with suspected MI without ST-segment elevation (NSTEMI), the preference for more rapid algorithms (with a repeated measurement within 3 hours) is justified by considering that an earlier diagnosis allow an earlier treatment and then the salvage of myocardium not irreversibly damaged (68,70,105).

### TAKE-HOME MESSAGES

- *The systematic assessment of results from recent studies confirms that myocardial damage, evaluated through hs-cTnI and T methods, can be frequently observed in patients undergoing major non-cardiac surgery, particularly in elderly patients or those with cardiac or non-cardiac morbidity.*
- *These studies confirm that hs-cTnI and T above the 99<sup>th</sup> percentile URL are associated with an increased risk of death or MACE.*
- *2014 ESC/ESA Guidelines recommend that BNP/NT-proBNP measurement be considered for the prognostic evaluation of peri-operative and late cardiac events in high-risk patients (class IIb, level B). Furthermore, cTn should be evaluated in patients at high risk, both before and 48-72 hours after major surgery (class IIb, level B). However, the routine measurement before surgery is not recommended for risk stratification and to prevent cardiac events (class III, level C).*
- *2014 ESC/ESA Guidelines recommend that pre-operative administration of beta-blockers be considered in patients before a high-risk surgery if they have at least two classical risk factors or a score 3 based on the ASA classification (class IIb, level B). Furthermore, pre-operative treatment with beta-*

- blockers might be considered also in patients with history of ischemic cardiac disease (class IIb, level B).*
- *2014 ESC/ESA Guidelines recommend that specific therapy for heart failure is continued during the surgery in stable patients with systolic heart failure (class IIa, level C).*
  - *A continuous therapy with the most used cardiac protective drugs (such as beta-blockers, ACEi or ARB) tends to reduce circulating levels of cardiac biomarkers in patients with heart disease.*
  - *Patients with AF usually present high levels of BNP/NT-proBNP, which usually fall within the reference limits after the acute arrhythmic episode and with the restoration of sinus rhythm, unless cardiac disease is present. Increased hs-cTn values are found in about 10-15% of patients with AF and suggest a structural heart disease, then the presence of a myocardial damage, pointing to a high cardiac risk. Even in patients undergoing major non-cardiac surgery, the diagnosis of MI during or after the intervention must be done through the evaluation of changes in hs-cTn or T changes, according to recent Guidelines.*

## FUTURE PERSPECTIVES

Further clinical studies are needed to define if a strategy based on the measure of cardiac-specific biomarkers before surgery significantly improves both patient outcomes and cost/benefit ratio. Another important question is if the combined measure of both cardiac-specific biomarkers adds significant information to the measurement of a single biomarker (BNP/NT-proBNP or hs-cTn). Importantly, hs-cTn can be considered an ideal cardiac biomarker because of its specificity, relatively low-cost and the possibility to obtain results through an automated platform within 20-30 minutes (45,48,50,58-60) (Table 1). Some point-of-care (POCT) methods recently introduced on the market can measure hs-cTnI using just a blood drop with similar analytical performance than assays for hs-cTnI using completely automated platforms (106,107). Therefore, these new POCT hs-cTnI methods can allow a more rapid diagnosis of myocardial damage at the bedside of the patient, in the outpatient clinic, in intensive care units or in the surgery room (106,107).

## CONCLUSIONS

Several recent studies have demonstrated the clinical relevance of the measure of cardiac-specific biomarkers to evaluate the cardiovascular risk before major non-cardiac surgery, particularly for the identification of MINS through hs-cTn assays. The Authors believe that BNP/NT-proBNP and hs-cTn should be measured in all patients during the clinical evaluation before surgery, particularly during intermediate- or high-risk surgery, in patients aged >65 years and/or with comorbidities. Several questions remain to be assessed in dedicated clinical studies, such as how to optimize the management of patients with raised cardiac specific biomarkers before

surgery, and whether a strategy based on biomarker measurement improves patient outcomes and is cost-effective.

## FINAL RECOMMENDATIONS

- *The prognostic information from the measurement of cardiac-specific biomarkers is independent and complementary to other important indicators of cardiac risk, such as ECG and imaging findings, in patients undergoing non-cardiac surgery.*
- *Elevated values of both cardiac-specific biomarkers (BNP/NT-proBNP and hs-cTn) before surgery are associated with a markedly higher risk of MACE in the peri-operative period.*
- *Elevated values of cardiac-specific biomarkers before surgery should suggest the need for a pathophysiological and clinical evaluation of the condition responsible for cardiac dysfunction and myocardial damage.*
- *Changes in hs-cTn values during the peri-operative period should be evaluated according to recommendations of international Guidelines for the diagnosis of MI.*
- *The Authors of this document deem that NPs and hs-cTn should always be measured before major non-cardiac surgery, particularly in patients with a higher cardiovascular risk before of their age (>65 years) and/or comorbidities.*

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