Guidelines and Recommendations

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High-sensitivity cardiac troponin I and T methods for the early detection of myocardial injury in patients on chemotherapy

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Abstract: Important advances achieved in pharmacological cancer treatment have led progressively to a reduction in mortality from many forms of cancer, and increasing numbers of previously incurable patients can now hope to become cancer-free. Yet, to achieve these improved outcomes a high price has been paid in terms of untoward side effects associated with treatment, cardio-toxicity in particular. Several recent studies have reported that cardiac troponin assay using high-sensitivity methods (hs-cTn) can enable the early detection of myocardial injury related to chemotherapy or abuse of drugs that are potentially cardiotoxic. Several authors have recently suggested that changes in hs-cTn values enable the early diagnosis of cardiac injury from chemotherapy, thus potentially benefitting cancer patients with increased troponin values by initiating early cardioprotective therapy. However, large randomised clinical trials are needed in order to evaluate the cost/benefit ratio of standardised protocols for the early detection of cardiotoxicity using the hs-cTn assay in patients treated with chemotherapy.

Keywords: cardiac troponin; cardio-toxicity; chemotherapy; high-sensitivity methods; myocardial injury.

Aim of the consensus document

Since the year 2000, international guidelines have recommended cardiac troponin I (cTnI) and T (cTnT) measurement as the first line laboratory test for the diagnosis of acute coronary syndromes (ACS) [1–3]. In recent years, thanks to the progressive improvement achieved in the analytical performance of immunometric assays, cTnI and cTnT circulating levels can be measured in the majority of apparently healthy adults [4–17]. The use of the last generation immunoassay techniques, defined as high-sensitivity methods for cardiac troponin assay (hs-cTn), has improved not only our knowledge of pathophysiological mechanisms underlying myocardial injury and acute myocardial infarction (AMI), but also of the diagnostic algorithm, and the management of patients admitted to emergency departments for ACS [1–3, 5, 18, 19].

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The aim of the present consensus document was to examine available experimental and clinical data on the utility of hs-Tn methods for the early detection of myocardial injury due to chemotherapy in cancer patients. Furthermore, this consensus document may provide rational and practical indications for targeted preventive strategies against cancer therapy-induced cardiac dysfunction and its associated clinical complications.

Analytical characteristic and performance of hs-cTn methods

The fourth universal definition of myocardial infarction, published in September 2018, states that "the term myocardial injury should be used when there is evidence of elevated cardiac troponin values with at least one value above the 99th percentile upper reference limit (URL)" [3]. Myocardial injury is considered acute if there is a rise and/or fall of cTn values [3], and all recent international guidelines recommend that hs-cTn methods should be considered the approach of choice for the detection of myocardial injury, and the diagnosis of AMI [1–3].

In 2018, the expert opinion document from the American Association for Clinical Chemistry (AACC) and the International Federation of Clinical Chemistry (IFCC) [2] stated that two fundamental analytical criteria must be met to establish that a method should be defined as hs-cTn. First, the error measurement (expressed as %CV) of the cTn concentration corresponding to the 99th percentile URL value should be ≤10%. [2] Second, measurable cTn concentrations should be obtainable at a value at, or above, the assay's limit of detection (LoD) in more than 50% of healthy individuals [2]. Furthermore, these guidelines call for measurable concentrations to be demonstrated in two population groups of healthy men and women, with at least 50% of measurable concentrations above the assay's LoD. Importantly, at least 300 men and 300 women are needed for the appropriate 99th percentile upper reference limit (URL) definition for each gender. Considering that, on average, women of fertile age present significantly lower cTn levels than age-matched men, an immunoassay method should enable the reliable measurement of cTn concentrations in a population of at least 300 apparently healthy women in order to satisfy the second criterion. Thanks to their better analytical performance, the most recent international guidelines strongly recommend the use of hs-cTn methods instead of other less sensitive immunoassays in order to more accurately detect the presence of a myocardial injury and the diagnosis of myocardial infarction [1–3].

Pathophysiological and clinical relevance of circulating levels of hs-cTn in individuals with biomarker values around the 99th percentile URL value

From the pathophysiological viewpoint, it is important to underline that current hs-cTnI methods have an analytical sensitivity (expressed as LoD value) ranging from about 1 to 2 ng/L (Table 1). In recent studies it has been reported that these LoD values correspond to the biomarker amount in about 5–8 mg of myocardial tissue, while the 99th percentile URL values correspond to the biomarker amount in about 20–40 mg of myocardial tissue [17–19]. The amount of myocardial tissue related to the cut-off value of myocardial injury (i.e. 99th percentile URL) corresponds to a myocardial volume that is too low to be detected by non-invasive cardiac imaging [5, 17–19]. In line with the body of experimental evidence available [5, 17–19], the fourth universal definition of myocardial infarction recommends the hs-cTn assay as the gold standard for the detection of myocardial injury [3].

Table 1: Analytical characteristics and distribution parameters for some hs-cTnI methods commercially available in Italy since 2016.

hs-cTnI methods	LoD, ng/L	LoQ 10%, ng/L	Median, ng/L (25th–75th percentiles)	99th percentile URL, ng/L	Number of subjects
ARCHITECT	1.3	4.7	1.8 (1.2–2.8)	18.9	1463
ACCESS DxI	1.3	5.3	2.7 (1.9–4.0)	16.8	1460
ADVIA CENTAUR XPT	2.2	8.4	3.3 (1.8–4.9)	46.9	1411

LoD, limit of detection; LoQ, limit of quantitation. 99th percentile URL: the 99th percentile values were evaluated in an Italian reference population of apparently healthy individuals of both sexes (women/men ratio 0.95, age range 18–86 years, mean age 51.5 years, SD: 14.1 years) [16]. Analytical parameters and median (interquartile range) values were evaluated according to previous studies [10–13, 16, 20, 21].

Although elevated hs-cTn values reflect myocardial injury, they do not indicate pathophysiological mechanisms underlying the clinical condition [3]. The different pathophysiological mechanisms suggested to explain the release of cTn from the myocardium include normal myocardial cell turnover apoptosis, cellular release of biomarker degradation products, increased cellular wall permeability, the formation and release of membranous blebs and myocyte necrosis [5, 17–19]. However, from the clinical viewpoint, it appears impossible to distinguish between the mechanisms responsible for increased cTn values [3, 17–19].

An interesting question concerns the physiological interpretation of the biomarker circulating levels, measured with hs-cTn methods, in healthy subjects. Several authors suggest that the hs-cTn concentration is a reliable index of cardiomyocyte renewal [5, 17–19]. According to the results reported in experimental studies on animals and humans [5, 17–19, 22] the 99th percentile URL values of hs-cTnI methods (about 17–47 ng/L) (Table 1) correspond to about 30–40 mg of cardiomyocyte renewal.

Recent studies (including three meta-analyses) demonstrate that individuals in the general population presenting hs-cTn values in the upper tertile of the total distribution (i.e. ≥66.7th percentile) have a significantly increased cardiovascular risk (on average about 30%) with respect to individuals with hs-cTnI values in the lower tertile (i.e. ≤33.3th percentile) [23–31]. This relevant pathophysiological evidence can be obtained only by using hs-cTn methods with the analytical performance required for the measurement of extremely low circulating biomarker levels in healthy subjects [14–17], as well as low intra-individual biological variation (from 4% to 12%) [32–37]. Indeed, thanks to the optimal analytical performance of hs-cTn methods, the critical difference between two measurements with a confidence limit of 95% is about 30%, also when considering biomarker values around the 99th percentile URL [16, 20, 21, 38, 39]. These data are in agreement with recent results reporting that even small, but progressively increasing hs-cTnI values (e.g. about 5 ng/L) can significantly increase cardiovascular risk in asymptomatic individuals in the general population [25]. These results can be explained by the distinctly asymmetrical distribution of hs-cTn values in healthy adults. Accordingly, the 99th percentile URL value, suggested by the manufacturers (Table 2), for hs-cTnI methods is about 6- to 14-fold greater than the median value (i.e. from 1.8 to 3.3 ng/L) (Table 1). Therefore, cardiomyocyte renewal should also increase by 6- to 14-fold before the hs-cTnI concentration value can exceed the threshold of myocardial injury [5, 16, 31].

Table 2: Reference interval suggested by the manufacturers for some hs-cTnI methods commercially available in Italy since 2016.

	Architect, ng/L	Access, ng/L	ADVIA Centaur, ng/L
General population	26.2	17.5 (14.0–42.9)	47.3 (34.4–64.3)
Women	15.6	11.6 (8.4–18.3)	37.0 (30.2–72.6)
Men	34.2	19.8 (14.0–42.9)	57.3 (38.6–90.2)
Number of subjects	1531	1089	2010

The 95% CIs of the 99th percentile URL values are reported in brackets. ARCHITECT, Architect method (Abbott Diagnostics) [10, 16]; ACCESS, Access method on DXI platform (Beckman Coulter Diagnostics) [11, 16]; ADVIA Centaur, ADVIA method on Centaur XPT platform (Siemens Diagnostics) [13, 16].

Early evaluation of myocardial injury in patients administered chemotherapy for malignant disease

It is well known that chemotherapy has serious cardiotoxic effects in patients treated for malignant disease [40–42]. Different definitions have been used to define cardiotoxicity induced by chemotherapy agents [43–48]. In 2015, the expert consensus document by the American Society of Echocardiography and the European Association of Cardiovascular Imaging defined cardiotoxicity in patients with malignant disease treated with chemotherapy drugs as a decrease in the left ventricular ejection fraction (LVEF) of >10% points with respect to a normal reference value of 53% [46]. The LVEF decrease should be confirmed by repeat imaging examinations, as the low reproducibility of echocardiography is well known [49–52]. The repeat study should be performed 2–3 weeks after the baseline diagnostic evaluation showing the initial decrease in LVEF [46]. In the year 2019, these practical clinical recommendations were also supported by an expert consensus document endorsed by several Italian Scientific Societies including areas of Oncology, CardioOncology and Laboratory Medicine [53]. However, this definition of myocardial injury, concerning cancer patients treated with chemotherapy agents, should be revised according to the document fourth universal definition of myocardial infarction [3]. This important consensus document, endorsed by the European Society of Cardiology (ESC), the American College of Cardiology (ACC), the American Heart Association (AHA) and the World Heart Federation (WHF), states

that the presence of myocardial injury should be evidenced by elevated cardiac troponin values [3]. Non-invasive and invasive cardiac examinations (such as echocardiography, stress test, computed axial tomography, coronary angiography, radionuclide techniques and nuclear magnetic resonance) are recommended for the evaluation of myocyte viability, myocardial thickness, thickening and motion, and the effects of myocyte loss on the kinetics of paramagnetic or radio-opaque contrast agents, indicating myocardial fibrosis or scar [3]. These techniques should be adopted for the differential diagnosis between the huge numbers of pathophysiological conditions that can cause myocardial injury [1, 3, 18, 19, 54, 55].

Several analytical, biological and pathophysiological characteristics should be taken into consideration in order to understand why hs-cTn methods have a greater diagnostic accuracy than cardiac imaging techniques in the detection of myocardial injury [5, 18, 56]. First, the analytical sensitivity of hs-cTn methods is greater than that of the spatial resolution of cardiac imaging techniques, including high-spatial resolution magnetic resonance [5, 18, 56]. Second, the reproducibility (about 4%–6% CV at the 99th percentile URL level) of the hs-cTn assay is better than that of cardiac imaging techniques [54], and, in addition, cardiac imaging techniques (echocardiography in particular), are also instrumentation- and/or operator-dependent [49–51, 57]. On the contrary, all hs-cTn immunoassays are standardised, and commercially available on fully automated platforms. The quality performance of these laboratory tests is regularly verified and monitored by internal and external quality control programs [58]. Third, the cost of some cardiac imaging techniques is about 10- to 20-fold higher than that of hs-Tn assay (about 10–20 Euro, compared to 50–150 Euro for echocardiography, and about 500 Euro for cardiac magnetic resonance). Fourth, cardiac imaging techniques have numerous limitations. The disadvantage for patients is significantly lower for a laboratory test than for a cardiac imaging examination: cardiac imaging techniques are time consuming (taking more than 30 min); some of them use ionising particles radiation or contrast agents, which can have (some serious) collateral effects [49–51, 57, 59, 60]. Finally, cardiac imaging techniques are contraindicated in some patients [49–51, 57, 59, 60]. Of course, the evaluation of high-sensitivity troponin (or other biomarkers, such as cardiac natriuretic peptides) cannot replace imaging techniques – such as echocardiography or cardiac magnetic resonance – that allow the evaluation of anatomy and size of cardiac chamber size, systolic and diastolic function, morphology and function of valves, pericardium, cardiac tissue characteristics and fibrosis [45–48].

Several studies have recently demonstrated that hs-cTn assays enable the early detection of myocardial injury in patients treated with chemotherapy agents [61–72]. In particular, two recent studies using hs-TnI [67] and cTnT [68] methods demonstrate that biomarker elevation during chemotherapy allows the identification of patients more prone to developing myocardial dysfunction and cardiac events. Furthermore, these studies demonstrate that the progressive increase of biomarker throughout a chemotherapy regimen is more sensitive and accurate than the measurement of a single sample collected after only one cycle of treatment [61, 62, 73]. Consequently, hs-cTn measurement should always be undertaken before the first cycle of chemotherapy, in order to obtain a baseline value allowing progressive increase to be calculated throughout all cycles of chemotherapy [61, 62, 73]. In patients presenting a progressive increment in biomarker values during the treatment, the use of some cardioprotective drugs (e.g. ACE inhibitors, angiotensin receptor blockers or beta-blockers) has proven effective in improving clinical outcomes, prompting cardioprotective strategies in a selected population [62, 73].

From a clinical viewpoint, the extraordinary advances made in pharmacological cancer treatments have progressively led to a reduction in mortality from numerous forms of cancer [65, 73]. Accordingly, many patients can now hope to become cancer-free. However, to achieve these better outcomes a considerable price has been paid in terms of untoward side effects associated with treatment, cardiotoxicity in particular [65, 73]. The spectrum of cardiovascular complications of cancer therapy can include acute coronary syndromes, thromboembolic events, hypertension and arrhythmias. The most clinically relevant manifestation of cardiotoxicity, left ventricular dysfunction, can progress to congestive heart failure, which may become fatal [65, 73, 74]. Moreover, the mortality rate of patients at the last stage of heart failure is significantly higher than that of patients with the more aggressive forms of cancer [74].

In 2020, a meta-analysis aimed to evaluate whether cardiac troponins and cardiac natriuretic peptides predict cancer therapy-related LVEF [75]. This meta-analysis included data on measurement of cTn concentrations reported in 51 studies (32 for cTnI, and 33 for cTnT) for a total of 5204 adult patients undergoing cancer therapy. Conventional or point-of-care cTn tests were used in 12 studies (1654 subjects), while hs-Tn methods were used in five studies (509 subjects). Post-treatment cTn values were elevated in 22.4% of patients, and cardiotoxicity, as indicated by decreased LVEF values, was observed in 17.0% (367/2163) patients [75]. Patients with elevated

troponins receiving chemotherapy were at higher risk for left ventricular dysfunction (OR 11.9, 95% confidence interval [CI] 4.4–32.1; n = 2163). Furthermore, overall sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) for the diagnostic value of the cTn assay were 69%, 87%, 52% and 93%, respectively, with any statistical differences between the results observed with conventional or high-sensitivity methods [75]. These data on diagnostic sensitivity on average indicate that, considering 100 patients undergoing cancer therapy with increased over the 99th percentile URL values of the hs-cTn assay, only 69 have left ventricular dysfunction, while the others 31 have a myocardial injury [3], but LVEF values in the normal range (i.e. these patients should be considered false positive for left ventricular dysfunction). On the other hand, patients undergoing cancer therapy with hs-cTn concentrations in the low-normal range have very little chance to present left ventricular dysfunction due to the very high NPV of the hs-cTn assay [75].

Notably, the results of this meta-analysis are in good agreement with a lot of studies, recently performed in the general population [23–31], in the elderly community [32, 33, 76], as well as in well-trained athletes after strenuous endurance physical exercise [77–80], demonstrating that individuals with hs-cTn values over the 99th percentile URL value are at high risk to early progression to left ventricular dysfunction and symptomatic heart failure.

Therefore, the use of the hs-cTn assay for the early identification of patients at a high risk of cardiotoxicity from chemotherapy can provide a rationale for targeted preventive strategies against myocardial injury and left ventricular dysfunction [43, 44, 61–63, 73]. In particular, early cardiotoxicity detection and its prompt treatment appear crucial to marked improvement in cardiac function [61–63, 73]. In addition, the early identification of cancer patients with myocardial injury makes it possible to limit prophylactic therapy to a restricted number of patients at a high risk of progression to heart failure [43, 44, 61–63, 73].

Monitoring myocardial injury in cancer patients treated with chemotherapy agents

In order to reliably evaluate any increase in biomarker values throughout all chemotherapy cycles, the hs-cTn assay must be performed before the first cycle of chemotherapy (i.e. basal sample value) in all cancer patients, including those without symptoms of cardiac disorders and/or with a clinical history negative for cardiovascular alterations, [61–63, 73]. As the 99th percentile URL values (i.e. the clinical cut-off values recommended in all guidelines) vary greatly between hs-cTnI methods (Tables 1 and 2), cTnI should always be measured using the same method (preferably in the same laboratory). For both hs-cTnI (Table 2) and cTnT [81] methods, sex-related cut-offs are recommended by international guidelines [2].

From the pathophysiological viewpoint, patients with hs-Tn values ≥75th percentile but <99th (Table 1) are actually at higher cardiovascular risk [23–31, 76]. These patients should be considered more susceptible to a progressive derangement of ventricular function after one or more chemotherapy cycles [61–63, 73]. According to the international guidelines, patients with hs-cTn concentrations >99th percentile URL value in the basal sample should be considered as having myocardial injury [3]. In these cases, clinicians should use both laboratory tests (in particular, BNP or NT-proBNP) and functional and cardiac imaging examinations in order to assess the pathophysiological mechanisms and clinical conditions responsible for myocardial damage. Furthermore, prompt cardioprotective treatment seems to be crucial for improvement in cardiac function [61–63, 73].

In order to evaluate chemotherapy-induced myocardial damage, the hs-cTn assay should be performed some days (usually <2 weeks) after the treatment cycle after every chemotherapy session [61, 62, 65, 73]. Indeed, an increment in the circulating levels of both cardiospecific biomarkers (i.e. cardiac natriuretic peptides and cTn) is frequently found in treated patients 2–7 days after the administration of chemotherapy, especially if high-sensitivity methods are used for biomarker assay [61–64, 67–69]. However, only patients at high risk of progressive cardiac dysfunction tend to present hs-cTn values significantly higher than basal value after the first treatment cycle [61, 62, 65, 73]. Recent studies have demonstrated that only an increase in hs-cTn values ≥30% compared to baseline value should be considered significant with a CI of 95% [20, 21, 38, 39]. Of course, myocardial injury is present only in patients undergoing cancer chemotherapy who have hs-Tn values over the 99th percentile URL, according to the international guidelines [3]. Patients presenting a progressive and significant increase in hs-cTn values (compared to baseline value) throughout all chemotherapy cycles should be considered at a high risk of developing myocardial dysfunction, even if their biomarker levels remain under the 99th percentile URL value [61, 62, 65, 73].

Comparison of pathophysiological characteristics and clinical interpretations of cardio-specific biomarkers

More than 100 biomarkers have been suggested to be useful in the diagnosis, prognosis and/or risk stratification in patients with cardiac disease [31, 74, 82, 83]. However, only cardiac natriuretic peptides and cTn are actually considered cardio-specific biomarkers [82–88]. It is important to note that cardiac natriuretic peptides and cTn actually show different, but complementary, pathophysiological characteristics [31, 74, 82–85]. Accordingly, circulating levels of cardiac natriuretic peptides and cTn may be affected differently by pathophysiological mechanisms responsible of cardiac dysfunction and/or damage [31, 74, 82–85].

From a pathophysiological point of view, an increment in circulating levels of both biomarkers suggests that some powerful stressor mechanisms have already caused relevant alterations on cardiac function (i.e. increased cardiac natriuretic peptides levels) [31, 82, 83, 85], as well as a significant damage on cellular structure (i.e. increased hs-cTn levels) [3, 5, 18, 19, 31, 82, 83]. These finding are in good accordance with the results of a number of experimental and clinical studies reporting that individuals with both increased cardio-specific biomarkers have a more severe outcome than those with only one altered biomarker [31, 74, 82–88].

Cardiac troponins actually show a more favourable analytical and biological profile for a cardio-specific biomarker than BNP/NT-proBNP [31, 82]. Indeed, cardiac troponins are more stable *in vivo* and *in vitro* than BNP, and both plasma and serum matrices can be used for the cTn assay; while only EDTA plasma samples are recommended for BNP assay [31, 82]. Moreover, cardiac troponins show considerably lower intra-individual (from 4% to 12%) than inter-individual variations (about 50%) [32–37], while the intra- and inter-biological variations of BNP are both about 40%–60% [31, 82].

The very recent meta-analysis by Michel et al. [75] reported that mean BNP/NT-proBNP levels were significantly increased post-treatment in patients undergoing cancer therapy, but biomarker circulating values did not consistently indicate prediction of left ventricular dysfunction (OR 1.7, 95% CI 0.7–4.2; n = 197), while patients with elevated cTn were at higher risk for left ventricular dysfunction. Recent studies have confirmed that the hs-cTn assay should be considered the best biomarker for evaluating chemotherapy-induced cardiac injury [65, 73], being the only cardiac-specific biochemical marker recommend by international guidelines for the detection of myocardial injury [3] and also for diagnosis of acute myocardial infarction [1–3].

Conclusions and future perspectives

The biomarkers cTnI and cTnT, measured with high-sensitivity methods, are recommended in international guidelines for detecting myocardial injury [3]. Although hs-cTn methods are used for the diagnostic workup of patients with suspected AMI in particular, their measurement also facilitates risk-stratification in patients with suspected ACS [1, 3]. Thanks to hs-cTn methods, low-risk patients can be promptly identified, thus enabling the safe and early discharge of selected patients, and of those at a high risk of myocardial injury who require admission and warrant further evaluation [1, 3, 72].

Recently, further clinical applications have been suggested for the hs-cTn assay, including the detection of myocardial injury in individuals on cardiotoxic drugs [31, 43, 44, 63, 65, 68, 72, 73]. In particular, numerous studies have demonstrated that the hs-cTn assay enables the detection of myocardial injury in patients treated with chemotherapy for malignant diseases [43, 44, 61–73]. Marked hs-cTn changes over time allow for the early diagnosis of cardiac injury caused by chemotherapy administration in cancer patients who can benefit from early cardioprotective therapy [63, 65, 68, 73]. However, large randomised clinical trials are needed in order to evaluate the cost/benefit ratio of standardised protocols for the early detection of cardiotoxicity using the hs-cTn assay in patients administered chemotherapy for malignant disease.

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