Turkish Society of Cardiology consensus report on the rational use of cardiac troponins in daily practice

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Background and aim of the document

Cardiac troponins (cTn T and I) are protein molecules that are part of the contractile apparatus of the cardiac muscle. Increase in these biomarkers represents injury of myocardial cells without giving any evidence for the underlying mechanism (1, 2). In the latest (fourth) Expert Consensus Document of Universal Definition of Myocardial Infarction (2), it has been emphasized that the clinical definition of myocardial infarction (MI, types 1, 2, and 3) refers to the presence of acute myocardial injury detected by typical rise and/or fall of cTn in the setting of acute myocardial ischemia evidenced by at least one of the following findings:

- Ischemic symptoms
- New alterations in electrocardiography (ECG) related with ischemia
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Demonstration of coronary thrombus

Cardiac troponins are also the mainstay for diagnostic algorithms of acute chest pain as explained in the latest European Society of Cardiology (ESC) Guideline to manage acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation (3).

Troponins have typically been used for the diagnosis and prognosis of ACS, but they may be elevated in many stable and unstable cardiac and non-cardiac conditions. The clinicians, mainly the cardiologists, emergency and intensive care physicians, and family physicians, should be aware of all these entities. The use of new-generation high-sensitivity cTn assays have lowered the diagnostic threshold (specificity) leading to overdiagnoses of patients with ACS, a vast number of cardiac consultations and inappropriate coronary angiograms or unnecessary hospitalizations causing increased complications and cost. The underlying mechanisms and clinical significance of troponin elevations in some cardiac and non-cardiac conditions have not been completely elucidated. Additionally, many clinicians are not aware of the biochemical assay problems and pre-analytical and analytical factors that may result false-positive troponin measurements (4, 5).

Consequently, there is a need for an up-to-date consensus paper systematically explaining the causes of cTn elevations to make an accurate differential diagnosis. This document does not

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aim to evaluate cTn only in acute chest pain. It will first address the identification of pre-analytical and analytical factors affecting cTn measurement; then it will discuss cardiac and non-cardiac causes of acute and chronic cTn elevations. The potential underlying mechanisms and clinical and prognostic significance of troponin elevations will be emphasized. We sought to represent messages and recommendations for daily practice with a multidisciplinary approach.

Definition of myocyte injury using cardiac troponins

The diagnosis of MI requires assessment of ischemic symptoms, ECG changes, patient characteristics, and biochemical evidence of myocardial injury. Any molecule should be highly specific and sensitive for myocardial injury to be used as a cardiac biomarker. Since their identification, cTn has become the mainstay for definition of myocardial injury. While both skeletal and cardiac myocytes possess troponin, troponin I (TnI) and troponin T (TnT) have distinct cardiac and skeletal isoforms, whereas troponin C (TnC) is shared in both tissues (6). Therefore, assays for cTnI and cTnT that target the most stable regions were developed (7). With the advent of high-sensitive cTn assays, there has been a shift in evaluation of troponin test from binary (negative-positive) results to highly quantitative assays (8). However, improved sensitivity has identified several non-ischemic cardiac and non-cardiac conditions that have cTn concentrations above the 99th percentile, although not as high as expected with a major coronary occlusion (9). The definition of MI has been modified over the years because of these advances, and the fourth Universal Definition of MI has been recently published (2). Detection of an elevated cTn value above the 99th percentile upper reference limit is acknowledged as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values, and chronic in the event of persistent cTn elevations.

Kinetics of cardiac troponins

In patients with an acute MI, myocyte necrosis ensues after 15 min of ischemia, and troponins become elevated 2–4 h after symptom onset and peak at 24–48 h (10). Early observations revealed an initial peak of troponins followed by sustained elevation lasting up to 14 days. This initial peak was evident only in patients with successful reperfusion suggesting a biphasic release (11). The explanation for biphasic profile depends on subcellular localization of cTn. Cardiac troponins are attached to cardiac myofibrils via tropomyosin. Approximately 6%–8% of cTnT and 2%–4% of cTnI is loosely bound that form the cytosolic pool (or the early-release pool), and the remaining cTn is bound as a ternary complex (12). Following myocardial necrosis, cytosolic pool including free Tn is released first that forms the initial peak; continuous degradation of structurally bound Tn (structural pool) contributes to sustained release of binary and ternary complexes, which is also related to infarct size. Since the cytosolic pool of cTnI is

smaller, biphasic profile of cTnI is not as prominent as cTnT (13). In addition, both binary and ternary forms may undergo post-translational modifications in the cytosol, and are susceptible to proteolysis and oxidation in the circulation. Current assays detect all these different forms, so these changes do not affect sensitivity (7).

Pre-analytical and analytical factors affecting troponin measurement
Alterations of the assays

Because of their myocardial tissue specificity, cTnI and cTnT are accepted as gold standard biomarkers to detect myocardial injury (2). For cTn measurement, numerous contemporary and bedside [point of care (POC)] tests have been approved. In clinical practice, standardizing of cTnI assays is not feasible leading to non-identical values, since different antibodies recognize different epitopes of cTnI. In contrast to cTnI, in cTnT assays, same antibodies are used. However, because of use of different calibrations, the reported values are not the same between fourth and fifth generation (high-sensitive, hs) assays (14, 15). To overcome the equivocacy of assay-to-assay differences, direct comparisons of approved cTn assays are needed (14).

There are some terms used in determination of the analytical view of cTn assays:
- Coefficient of variation (CV) is an estimation of reproducibility of the test (day-to-day imprecision), and it is calculated as the ratio of the standard deviation over the mean value for repeated testing of the same sample over multiple days (14, 16).
- Limit of detection (LOD) is the lowest value measured by progressively dilutions, and used for ruling out MI (14, 17).
- The upper reference limit (URL) is the upper limit of the population of interest, and is defined as the 99th percentile of the normal distribution. Hence, 1% of otherwise healthy subjects may still have a cTn value higher than the 99th percentile URL (16).

High-sensitivity assays should have a CV of <10% at the 99th percentile value. Additionally, with hs assays, concentrations above the LOD, but below the 99th percentile should be detectable for at least >50% of healthy individuals (2, 14).

The use of non-hs-cTn assays without <10% CV at the 99th percentile URL makes the monitoring of significant changes more difficult, but it does not result in false-positive results. Assays with CVs between 10% and 20% are acceptable for clinical use. However, assays with CVs >20% should not be used. If a cTn assay is not available, the best option is measurement of CK-MB mass activity. As with hs-cTn assays, an increased CK-MB denotes a value above the 99th percentile URL (sex-specific URLs are recommended for both) (2).

Immunoassay interferences

Interferences in immunoassay may cause in confounding results, and they lead the physician to give inappropriate treatments

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even to perform unnecessary interventions. Interfering substances may result in falsely elevated or falsely low measurements in different assay systems. Laboratories should detect, test, and report suspected interferences. It is of great importance to communicate with the laboratory for any discordance between the clinical characteristics and the laboratory data (18).

Pre-analytical interferences

Serum, plasma, and anticoagulated whole blood are available specimens for the analyses (14). When hs-cTnI assays are utilized, important differences can be obtained using different samples (serum vs. heparin plasma vs. EDTA plasma) (19).

Several cTn assays are influenced by hemolysis dependent of the amount of cTn and free hemoglobin concentrations. Some assays reported decreased results, and the others are either unaffected by hemolysis or reported falsely elevated results (19). In this point, clinicians should view the properties of the commercial kits in coordination with central laboratory.

Fibrin may be present in the blood collection tubes as visible clot or invisible strands. These fibrin substances may affect cTn assays by interfering with antigen-antibody binding. Fibrin strands can be eliminated if the recommended times subsequent centrifugations are appointed (18).

Antibody interferences

Both heterophile and anti-animal antibodies may result in immunoassay interferences. Heterophile antibodies are emerged against many antigens that are not clearly determined. The differentiation of these antibodies is not always possible (20). Autoimmune antibodies can cause immunoassay interferences. In many cases, a specific antigen is not well defined. However, in some cases, antibody production occurs because of exposure to intestinal and pulmonary bacteria. Even dietary proteins, vaccines, and multiparity may be responsible for this reaction. Interfering antibodies are detected more in males, and they have been shown to rise in response to blood transfusions and exposure to foreign proteins. The presence of RF in blood samples of the patients either with rheumatic or with non-rheumatic diseases is responsible for false-positive troponin assays (20). Human anti-animal antibodies are specific polyclonal antibodies against to specific animal immunogens, most commonly to mouse, but also rat, rabbit, goat, sheep, pig, cattle, and horse antigens (18, 20). These antibodies are also found in subjects having contact with domestic animals such as cat and dog.

Initially, the prevalence of interfering antibodies was reported between 10% and 40% depending on the assay and population of interest. However, the newer assays containing blocking agents added to reagents have lowered the ratio of interference to less than 2% (20). In addition, increased activity of endogenous alkaline phosphatase (ALP), or treatment with exogenous ALP (asfotase) in patients with phosphatasia may cause interference with some cTnI assays (21, 22).

There are some techniques to deal with antibody interferences. A simple method is the analysis of the sample using an alternate assay. Another procedure is measurement before and after applying of a blocking reagent or using heterophile-blocking tubes. Repeated measurement with manufacturer's diluents is another option. An anti-animal interference can also be eliminated by precipitation with polyethylene glycol precipitation (PEG 6000) (18).

The conditions related with elevation in cardiac troponins

There is a wide range of conditions related with elevated cTn. In Figure 1, we have summarized reasons for acute and chronic elevations. From our point of view, classifying of these conditions as cardiac and non-cardiac and as stable and unstable can be instructive for understanding the underlying
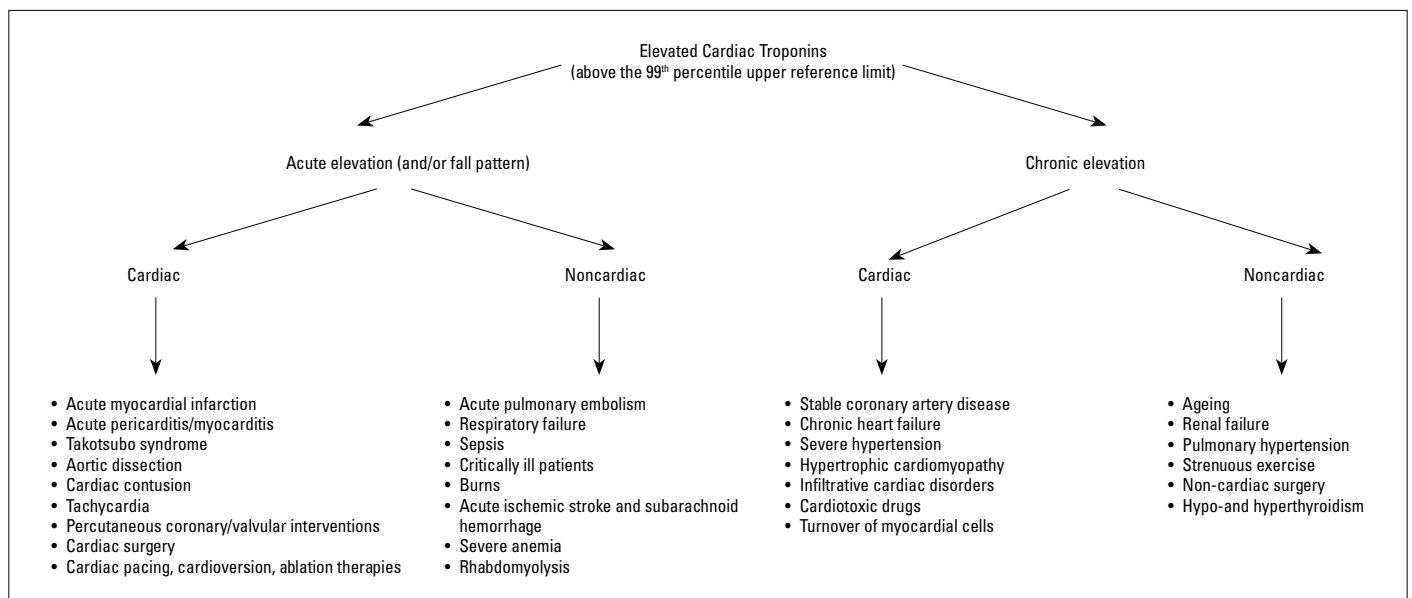

Figure 1. Schematic presentation of the conditions related with elevated cardiac troponins

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mechanisms and helpful in decision making. In this sense, first, we explain the stable and unstable cardiac and non-cardiac conditions. Later, we propose an algorithm for management of elevated cTn (Fig. 2). We strongly recommend against using the term of "troponinemia". Any increase in the troponins needs to be taken into account and should be monitored. When persistently elevated cTn levels (that means ≤20% variation) are detected, conditions related with chronic cardiac injury should be regarded. When these conditions are excluded, biochemical factors could be the culprit. A typical rise and/or fall of troponin levels (with at least one value above the 99th percentile upper reference limit) after repeated measure (preferably 3 h later) is called as acute myocardial injury, which is further defined as acute MI when accompanied by myocardial ischemia; otherwise, unstable cardiac and non-cardiac conditions should be considered.

Stable cardiac conditions
Chronic heart failure

In patients with advanced heart failure (HF), elevated troponin levels are commonly observed and are indicative of adverse prognosis (23). Increased volume and pressure load results in myocardial wall strain and myocyte death that are accepted to be the underlying mechanisms (23, 24). The relationship between wall strain and myocyte death could be explained by impaired subendocardial perfusion leading to cell death (25). Increased brain natriuretic peptide (BNP) level, which is an indicator for myocardial strain, correlates with increased troponin levels (26). Moreover, in rat myocardium, increased strain resulted in

troponin elevation regardless of ischemia (27). Myocardial cell loss is considered the main underlying mechanism in progression of advanced HF. Sympathetic system and RAS activation, inflammatory mediators, and increased integrin levels as well as oxidative stress may enhance myocardial loss in patients with HF (28, 29). Increased troponin levels were also associated with acute decompensation, progressive disease, and poor prognosis in acute and chronic HF (30, 31).

Hypertrophic cardiomyopathy

In hypertrophic cardiomyopathy (HCMP), troponin rise may be seen because of several factors such as increased myocardial volume, increased oxygen need, and decreased flow volume because of remodeling (32). Increased serum troponin level observed in a significant ratio of the patients with HCMP and is an independent predictor of adverse outcome (33). Elevated troponin levels have also been detected in other structural heart diseases associated with left ventricular wall thickening.

Infiltrative cardiac disorders

According to the accumulating substance, some of the infiltrative cardiac diseases increase ventricular wall thickness, while others cause chamber enlargement with secondary wall thinning. Cardiac amyloidosis is a primary restrictive cardiomyopathy. Although pathophysiology of troponin elevation remains unclear, myocyte compression injury due to extracellular deposition of the amyloid plaque is held to be responsible (34). Dispenzieri et al. (35) showed that in cardiac amyloidosis, troponin levels are more valuable as survival predictors than ECG and symptoms. Likewise,
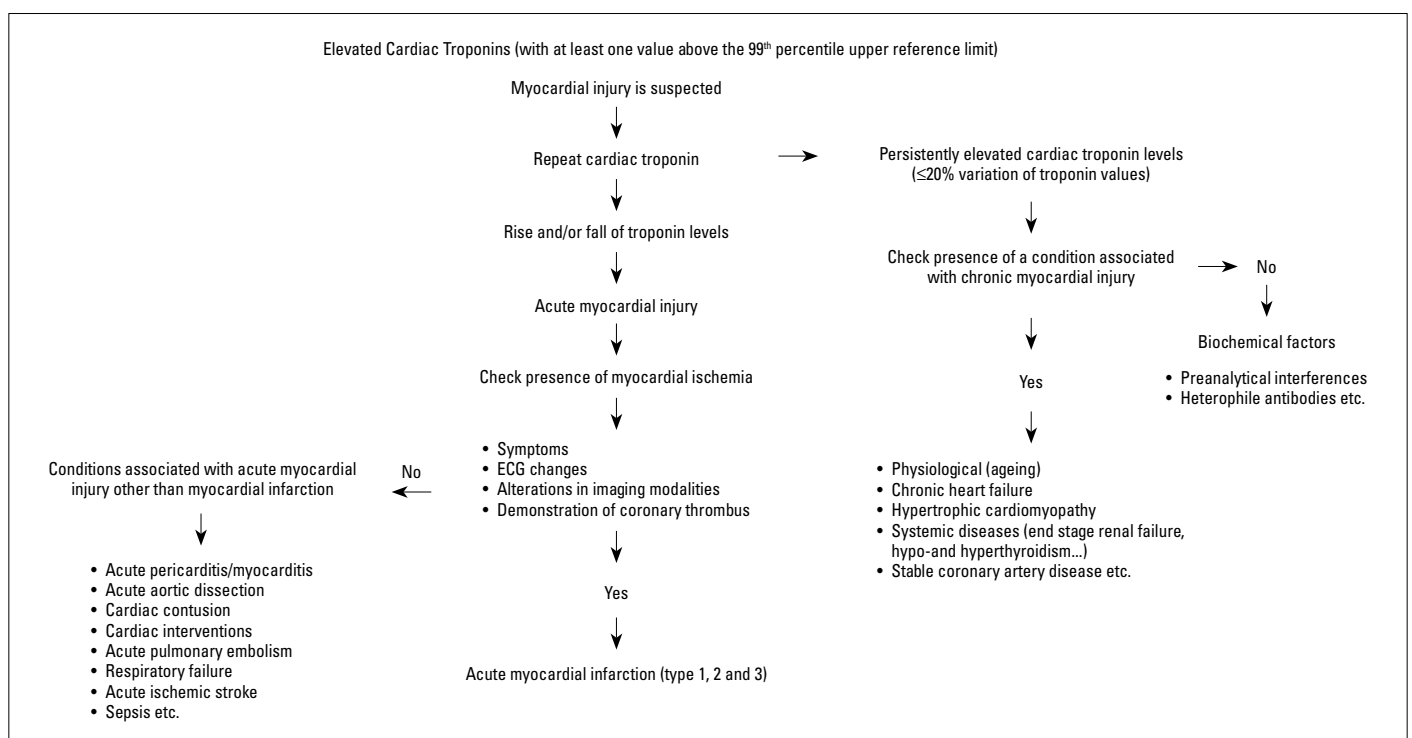

Figure 2. Algorithm for the management of the cardiac troponin elevation

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Consensus Statements for Elevation of Cardiac Troponins		References
Cardiac troponins (cTn) are the mainstay for definition of myocardial injury.	💚	1-3
Cardiac troponins should be used for the diagnosis and prognosis of acute coronary syndromes.	💚	2, 3
An elevated troponin level should always be interpreted in the context of the clinical presentation • Typical rise and fall, with at least one value above the 99th percentile URL, in the setting of acute myocardial ischemia (evidenced by ischemic symptoms, and alterations in ECG or imaging modalities) are needed for an accurate diagnosis of myocardial infarction. • Troponin follow-up along with symptoms and ECG changes are required in case of suspicion	💚	2, 3
A "sole" troponin elevation should not be defined as myocardial infarction.	❤️	2, 3
Troponin elevation is not recommended for the purpose of identification of the etiology of myocardial injury.	❤️	2, 3
Stable coronary artery disease, chronic heart failure, acute pericarditis, myocarditis, Takatsubo syndrome, tachycardia, cardiac interventions should be considered among the stable and non-stable cardiac conditions of increased troponins (generally with different enzyme kinetics).	💚	2, 30, 44, 45, 51, 61, 73, 82, 88
Aging, renal failure, sepsis, pulmonary hypertension, acute pulmonary embolism, critically ill patients, acute cerebrovascular events should be considered among the stable and non-stable non-cardiac conditions of increased troponins (generally with different enzyme kinetics).	💚	92, 96, 100, 113, 117, 123
Troponin elevation is prognostic even when ACS is excluded. • Troponin levels are recommended to predict prognosis in patients with heart failure, stable chest pain, chronic renal disease, pulmonary diseases, stroke or after cardiac interventions and cardiac surgery. • Troponins may be used as surrogate markers of coronary artery disease mortality for screening and monitoring of healthy subjects.	💚 💛	30, 49-51, 96, 111, 116, 125
Numerous assays are approved for troponin measurement. • 99th percentile for high-sensitive (hs) cTn assays should be measured with an analytical imprecision (coefficient of variation -CV-) of 10% or less.	💚	
• Non-hs-cTn assays with CV between 10% and 20% may also be used.	💛	
• Assays with CVs >20% should not be used.	❤️	14-16, 18-20
• Measurement of CK-MB mass activity may be used if a cTn assay is not available.	💛	
• Analysis of the sample using an alternate cTn assay, measurement before and after using of heterophile-blocking tubes, and measurement of a series of dilutions may be used to deal with laboratory interferences related with false- positive results.	💛	
• Physicians should communicate with the laboratory when a persistent cTn elevation (that means ≤20% variation by repeated measures) cannot be explained by any clinical condition.	💚	

hs-TnT value in sarcoidosis is considered an important marker of disease activity and is decreased following steroid therapy (36).

Turnover of myocardial cells, apoptosis

Troponin values increase generally because of myocyte necrosis caused by ischemia and MI. In some cases, an increase in troponin levels may be seen without myocyte necrosis. All cells, including cardiomyocytes, have death protocols that are activated when appropriate conditions are met. These protocols can be activated because of temporary conditions such as apoptosis, preload increase, ischemia, or pulmonary hypertension (37). Our present knowledge is not sufficient to determine by which potential effects apoptosis increases troponin levels (38).

Drug toxicity

Many agents can have cardiotoxic effects. Cardiotoxicity is often observed with use of anthracyclines, which are effective drugs for the treatment of solid and hematologic malignancies,

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and trastuzumab-like drugs, which is an HER-2/neu (Human Epidermal Growth Factor Receptor 2) receptor antagonist. While cardiotoxic effects of anthracycline derivatives are dose-dependent and irreversible, trastuzumab-like drugs have reversible effects. Cell membrane damage, caused by oxidative stress, reactive oxygen species, and lipid peroxidation, is held responsible for anthracycline group cardiotoxicity. Anti-HER2 drug group toxicity has reversible, functional, and structural effects on contractive proteins, and mitochondria, therefore rarely causes cell death (39, 40). Chemotherapy-induced troponin rise can predict the forthcoming left ventricular (LV) dysfunction (41, 42).

Cardiac surgery

As in all patient groups, post-operative troponin elevation is associated with poor prognosis. Troponin level increases >10 times of the 99th percentile URL in patients with normal baseline values on the first 48 h after "on pump" valve or coronary by-pass surgery is an important predictor for the first year survival rate (2, 43).

Percutaneous coronary/valvular interventions

Troponin level increase can be observed in percutaneous coronary interventions in stable settings due to flow discontinuation during balloon dilatation or ischemia due to distal embolization, and it is indicative of myocyte necrosis. At least five-fold increase in troponins predicts cardiovascular events at 30 days and one-year follow-up (2). Troponin level increase can also be observed after percutaneous valvular interventions such as transcutaneous aortic valve implantation (TAVI). Pre-interventional increased troponin values are observed in most of the patients undergoing TAVI due to critical aortic stenosis. Pre- and post-interventional levels are considered important prognostic factors of one-year survival rate independently from the success of intervention (44).

Cardiac pacing, cardioversion, and ablation therapies

Troponin increase can occur following permanent pacemaker insertion due to minimal myocardial damage caused during endocardial lead implantation (45). A mild but still significant increase in troponin levels has been observed following electrical cardioversion (CV) in non-valvular atrial fibrillation (AF). This increase is even more significant in patients with increased LV volume and low ejection fraction (EF) (46). Even though troponin increase may show progression of the present HF status, we must also keep in mind that this increase can be due to implantable cardioverter defibrillator shocks in patients with HF (47).

Radiofrequency ablation, which is performed in various arrhythmias such as supraventricular tachycardia (SVT), AF, and ventricular tachycardia, causes cardiac damage via thermal energy, therefore causing troponin increase (48).

Stable coronary artery disease

Several clinical studies have demonstrated that troponin value in otherwise healthy subjects could be a predictor of sub-sequent adverse cardiac events including mortality (49, 50). The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) study has provided that in patients with stable chest pain and suspected coronary artery disease (CAD), the upper hsTnI quartiles were independently related with death, acute MI, or hospitalization for unstable chest pain during one-year follow-up period (51). Despite promising results, further data are required using troponins as surrogate markers of CAD mortality to screen and monitor the healthy subjects.

Unstable cardiac conditions
Acute coronary syndrome

ACS is a term that includes patients with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). Cardiac biomarker elevations are required to distinguish NSTEMI from UA and helpful in patients with chest pain. Many diagnostic algorithms incorporated with serial cTn measurement are proposed to rule-in/out in patients with acute chest pain (3, 52, 53). It should be remembered that some diseases like myocarditis, takotsubo cardiomyopathy might produce dynamic changes in cTn levels (53); and late presentation of ACS might not show meaningful changes in cTn.

Rapid rule-in and rule-out strategies for patients admitted with chest pain to the emergency department use different time points and cut-off values. The latest ESC Guideline for the management of ACS in patients presenting without persistent ST-segment elevation (3) depicted a comprehensive algorithm. Briefly, in acute chest pain, either 1-h or 3-h strategy should be used. The 1-h strategy is applicable if chest pain onset is >3 h, and there is a high pre-test probability for NSTEMI. Additionally, it can be applied when only high-sensitivity cTn assays are available [hs-cTnT (Elecsys), hs-cTnI (Architect), and hs-cTnI (Dimension Vista) are the validated hs-cTn assays]; and the cut-off levels are assay specific. The guideline recommended using the 3-h strategy, in which one delta value is greater than URL during follow-up prompts invasive strategy. We believe that the 3-h strategy is more user friendly and has a high validity, and it should be preferred. These strategies have a negative predictive value (for rule-out) exceeding 98%. On the other hand, the positive predictive value (for rule-in) is between 75% and 80% (3).

Apart from its diagnostic usefulness, cTn elevation conveys prognostic value. The patients with elevated cTn have increased mortality rate; and they are likely to have coronary thrombosis, more complex coronary lesions, and diminished ventricular function (54, 55).

Severe hypertension

Increased troponin levels can be seen in hypertensive crisis because of supply-demand mismatch or obstructive CAD. In the study reported by Pattanshetty et al. (56), increased troponin levels in patients referring to the hospital because of hypertensive crisis were related with increased adverse cardiac events ratio.

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Interestingly, in one-fourth of these patients, obstructive CAD was not seen.

Aortic dissection

Almost 90% of the patients with aortic dissection (AD) have abnormal ECG with 25%–35% having ACS-like ECG features resembling NSTEMI and 4%–16% have ECG findings of STEMI (57-60). Troponin positivity was reported from 16% to 33% with standard assays and 54% to 61% with hs assay with no difference between type A and type B dissection. Troponin elevation in the setting of AD may be due to intimal flap obstructing the coronary ostia, coronary ostia dissection, decreased blood pressure, aortic regurgitation, LV pressure and volume overload, increased sympathetic drive leading to microvascular dysfunction, and pre-existing CAD (57-60).

Takotsubo syndrome

Takotsubo syndrome (TTS) is characterized by temporary LV wall motion abnormality that is usually preceded by emotional or physical triggers. The clinical presentation of patients with TTS is very similar to those of ACS subjects. The International Takotsubo Registry (61) found that troponin levels were elevated in 87% of 1750 patients on admission. Recorded troponin values are disproportionally low considering the extensive LV involvement (62). The mean troponin levels at admission were found to be similar to those in patients with ACS. Yet, peak values of cTn are lower in TTS than patients with ACS, though comparable values with NSTEMI could be observed (61). Troponin peaks occur earlier, usually at presentation or within 24 h following the onset of symptoms and normalizes faster than STEMI (63). Higher TnI values were observed in patients with TTS presenting with cardiogenic shock (64).

Cardiac contusion

Cardiac contusion or currently preferred term blunt cardiac injury (BCI) is usually suspected in blunt thoracic trauma (BTT). There are no definitive diagnostic criteria, but various combinations of clinical picture, ECG, troponin, or cardiac imaging were used to define BCI. Therefore, the incidence of BCI in patients with BTT varies from 3% to 56% (65-67). The release of troponin reflecting myocardial cell injury is believed to be because of mechanical transmission of force through the chest wall (68). But, troponin elevation was also observed in 25%–35% of trauma subjects who had no BTT (67, 69). Among patients with severe traumatic brain injury, around 30% at admission and 41% overall had elevated cTnI (70). Thus, other mechanisms like hypotension due to blood loss, pro-inflammatory cytokines, free radical and oxidative injury, and adrenergic activation with catecholamine spillover might have a role in troponin elevation (71). Trauma patients with elevated troponins have increased mortality rate even in the absence of BCI (67, 72).

Tachycardias

In a pooled analysis of seven observational studies including 1155 patients with SVT, 66% of patients were investigated with troponin (73). Of these, 32% had positive troponin test result. Troponin elevation in the setting of SVT was not predictive of coronary or structural heart disease (74, 75). Myocardial oxygen demand is increased due to increased heart rate, and oxygen delivery is attenuated because of short-diastole in SVT. This may cause ischemia that probably alters the myocyte membrane permeability and might result in the release of cTn from the free cytosolic pool or its loosely attached cytoskeleton. Myocardial stretch was also postulated as another possible mechanism of tachycardia-related troponin elevation (76, 77). The reported predictors of troponin elevation were maximal heart rate, older age, duration of tachycardia, chest pain, and lower diastolic blood pressure (78). The data about the prognostic role of troponin elevation in SVT is not satisfactory because of limited number of patients. On the other hand, in a recent study performed in 1754 patients with AF admitted with 2754 symptomatic AF episodes to emergency department, elevated hs-TnT levels were independently related with midterm (median: two years) mortality (79).

Acute pericarditis

Detectable levels of troponin were reported in 32%–71% of patients with acute pericarditis (80, 81). Troponin was beyond the acute MI threshold in 7%–22% of cases (80, 82). Younger age, ST-segment elevation, recent onset of infection, male gender, and pericardial effusion were the properties associated with elevated troponin levels in patients with pericarditis (80, 83). In one study, troponin elevation was found to be related with mortality in acute pericarditis (84). However, two large studies did not find such a negative prognostic value (80, 85).

Myocarditis

The patients presenting early in the course of the disease were shown to have increased concentrations of cTnT in a small sized biopsy-proven myocarditis study (86). Smith et al. (87) demonstrated that cTnI values were elevated in one of three patients with myocarditis. Lauer et al. (88) showed that among clinically suspected myocarditis subjects with elevated troponin, myocarditis was evident on 93% of biopsy specimens. However, 44% of subjects without troponin elevation had also biopsy-proven myocarditis. Thus, negative troponin does not rule out myocarditis (88). Patients with shorter history of symptoms are more likely to have higher concentrations of troponins (89). Subjects with fulminant myocarditis have higher troponin elevation than patients with acute myocarditis (90). Peak troponin levels of acute myocarditis are usually lower than that of ACS (91), but release kinetics might mimic ACS (92).

Stable non-cardiac conditions
Aging

Elderly people may have elevated hs-cTnT and hs-cTnI, mostly due to increased cardiovascular comorbidities, anemia, decreased renal function with aging, and structural/functional cardiac abnormalities. Gore et al. (93) showed that 10% of men, aged 65–74 years, with no cardiovascular disease had elevated

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cTnT above the MI threshold. Reiter et al. (94) reported that mild troponin elevations are common in elderly non-AMI patients. Therefore, they argued that the optimal cut-off levels to separate acute MI from non-cardiac troponin elevations should be higher in elderly as compared with younger patients. Wu et al. (95) found that 44% of the elderly inpatients without ACS had an hs-cTnT level >99th percentile URL, and baseline hs-cTnT level in those patients was associated with all-cause death after discharge, and the mortality rate increased with increased hs-cTnT level.

Renal failure/end-stage renal disease

Cardiac troponins are frequently elevated in patients with renal failure. The prevalence of increased serum cTnT and cTnI increases with severity of renal failure, and cTnT is more frequently increased compared with cTnI in asymptomatic patients with end-stage renal disease (ESRD) (96, 97). The mechanisms causing increases in TnT concentrations in patients with renal failure are not clear. Troponin elevations are not solely caused by decreased renal clearance, but also possibly due to direct toxic effects of the uremic state on the myocardium, anemia, hypotension, and accompanying CAD (98).

cTnT is associated with mortality in patients with ESRD (99). The NACB Laboratory Medicine Practice Guidelines (100) recommend the use of troponin for diagnosis of MI in all patients with renal failure (regardless of the severity of renal impairment) who have symptoms or electrocardiographic evidence of myocardial ischemia. The guidelines also advise relying on dynamic changes in troponin values of ≥20% in the 6 h after presentation to define acute MI, even in chronically elevated troponin levels.

Pulmonary hypertension

Torbicki et al. (101) reported that cTnT was detected in serum of 14% of patients with chronic precapillary pulmonary hypertension (PH) and was a strong independent marker of mortality. Severe PH results in disturbance in the physiological pattern of right ventricular (RV) myocardial perfusion and lower systemic blood pressure, both at rest and during exercise, decreasing coronary perfusion gradient (102). Troponin elevations in these patients may be due to both myocyte death and intracellular degradation of troponin caused by excessive intracellular Ca^{2+} concentration in the failing myocardium.

Physical Exercise (Strenuous)

The reviews and meta-analysis have shown that cTnT levels are frequently elevated after extreme exercise (marathons, triathlons, mountain bicycle races, ultraendurance events) (103, 104). Postulated mechanisms include cellular shifts in cytoplasmic troponin due to exercise-induced inflammatory cytokines, dehydration, hemoconcentration, and oxidative stressors rather than typical myocardial necrosis. Cardiac magnetic resonance imaging has not shown any functional changes or any detectable myocardial inflammation or fibrosis after exercise (105). In addition, during strenuous exercise, cTnT can be detected in

less than 2 h and generally return to normal within 24 h, which is different than the course of ACS. One-year clinical follow-up showed no cardiac events or symptoms in the troponin-positive group (106). A recent meta-analysis evaluating elevation in hs-cTn after exercise and pharmacological stress tests revealed that the rising patterns were inconsistent and were not related with inducible myocardial ischemia. So, adding hs-cTn to cardiac stress tests may not improve diagnostic utility (107).

Non-cardiac surgery

In the non-cardiac perioperative surgical setting, troponin elevations may be seen in nearly 8%–11% of the patients without apparent ACS in the early post-operative timeframe, and they are associated with increased mortality and longer length of stay. Bleeding, pain, and increased catecholamines may result in tachycardia causing mismatch in oxygen demand or supply, while vasoconstriction or pain may increase blood pressure that in turn increases wall stress; all of which may be responsible from cTnT elevation (108-110).

Hypo-and hyperthyroidism

Thyroid hormones are related with cardiac functions. Creatine kinase and troponins may increase in patients with hypothyroid without apparent myocardial damage (111, 112). However, despite these rare case reports, studies in consecutive patients with significant hypothyroidism have not reported elevated TnI levels (113) or TnT levels even in patients with increased CK-MB levels (114). Hence, the importance of these findings related to hypothyroidism needs to be determined. Hyperthyroidism may induce tachyarrhythmias and increase oxygen demand resulting in myocyte damage and cTnT release.

Unstable non-cardiac conditions
Acute pulmonary embolism

Pulmonary embolism (PE) is one of the most common non-ACS causes of increased troponins (115). Serum troponins are elevated in up to 50% of patients with PE (116). This cTnT release is attributed to the combination of acute pressure overload within the RV, impaired coronary artery flow, and the hypoxic state caused by PE (117). Endothelial damage in the pulmonary vasculature, which has an abundance of angiotensin-converting enzyme, may cause derangements in the renin/angiotensin/aldosterone system affecting cTnT blood concentrations (118). In contrast to patients with ACS, cTnT peaked after a median of 10 h and remained detectable for a median of only 40 h after admission in patients with PE (119). Troponin elevation is associated with prolonged hypotension and cardiogenic shock, need for inotropic support and mechanical ventilation, and increased mortality in patients with PE (95).

Respiratory failure

cTnT may be elevated in advanced/decompensated chronic lung disease. Hypercapnia, hypoxemia and/or respiratory acido-

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sis, the worsening of PH resulting in RV hypertrophy, dilation, and subendocardial demand-induced ischemia, the increased work and oxygen cost of breathing, and the increase in LV afterload related to the more negative intrathoracic pressure may all contribute to myocardial injury and cTnT released during episodes of exacerbation. Elevated cTnI is a strong and independent predictor of in-hospital death also in patients admitted for acutely exacerbated chronic obstructive pulmonary disease (120).

Sepsis/systemic inflammatory response syndrome

There are modest elevations of troponins in patients with sepsis, septic shock, and the Systemic inflammatory response syndrome (SIRS), mostly in the absence of CAD. Causes of troponin elevation in sepsis are multifactorial. It has been suggested that inflammatory cytokines released from neutrophils, particularly tumor necrosis factor-α and interleukin-6, are responsible for direct myocardial depression and increased cell membrane permeability to troponin molecules in sepsis. Decreased myocardial perfusion because of hypotension, increased oxygen consumption due to tachycardia, release of noradrenaline and adrenaline with subsequent vasoconstriction, and increased coagulation of capillary bed also may play significant part in myocyte damage and subsequent troponin release (95). Although troponin elevation in sepsis is associated with mortality and impaired LV function, routine troponin testing in septic patients is not recommended (1).

Critically ill patients

Elevations of cTn are common among critically ill patients in the intensive care unit (ICU), and they are associated with increased mortality and ICU length of stay regardless of the underlying disease state (121). Similar to sepsis, inflammatory cytokines are responsible for direct myocardial depression and increased cell membrane permeability to troponin molecules in critically ill patients.

Burns

Cardiac dysfunction associated with severe burns has been suggested by several reports (122, 123). Wang and He (124) reported increased cTn levels in patients with severe burns. There was a significant correlation with a positive troponin test and burns greater than 15% total body surface area. The myocardial damage is attributed to adverse effects of inflammatory mediators on myocardium and severe hypovolemia.

Acute ischemic stroke and subarachnoid hemorrhage

An increase in cTn in patients with stroke has been documented in a systematic review of 15 studies using old-generation cTn assays (125). Elevations that are more significant have been shown in the studies using hs-troponin assays in association with both ischemic and hemorrhagic cerebrovascular events (CVE) (126-128). The underlying pathophysiology may be the cardiac damage caused by stunned myocardium with

acute neurological insult resulting in "neurogenic stress cardiomyopathy" that is a relatively new terminology. Neurogenic stress cardiomyopathy indicates acute cardiac damage due to catecholamine excess and unopposed inflammation caused by alterations in autonomic nervous system related to acute CVE (129). On the other hand, similar risk factors such as age, hypertension, diabetes, precipitate stroke, hemorrhagic CVE, and cardiovascular diseases. Thus, the exacerbation of occult cardiac disease in response to stress caused by neurological insult may lead to cTn elevation in these patients (130). Data regarding elevated pro-BNP levels in patients with stroke are compatible with this theory. Moreover, an adverse prognosis in association with elevated cTn values has been suggested in patients with acute CVE (131).

Severe anemia

Although there is no study investigating the rise in cTn levels in different hemoglobin levels in large patient populations, severe anemia was shown to be related with increased troponin levels in children with malaria (132, 133). Severe anemia has also been found to relate with mortality in patients with MI and HF (134, 135). Barbarova et al. (136) showed that patients with severe anemia and elevated troponin levels presenting to internal medicine departments due to non-cardiac problems had worse long-term survival if they did not get blood transfusion. The main reason of the increase in cTn in case of severe anemia may be resultant tissue hypoxia leading to myocardial injury.

Rhabdomyolysis

Several studies have found increased cTn levels in patients with rhabdomyolysis or neuromuscular diseases (137, 138). Although TnI and TnT are accepted to be expressed by only cardiomyocytes, their messenger RNA can be reexpressed in skeletal muscle disease and may result in misinterpretation of cardiac injury (139, 140). Moreover, TnT is also expressed in fetal skeletal muscle. In case of skeletal muscle injury, it may be reexpressed because of regeneration process included in repair (141). Rhabdomyolysis may cause a rise in cTn level with this mechanism or may include direct cardiac muscle degradation (142, 143).

Conclusion

Increase in cTn has typically been used for the diagnosis and prognosis of ACS. Nevertheless, these biomarkers are also elevated in a variety of stable and unstable cardiac and non-cardiac conditions. The introduction of new-generation hs-cTn assays has allowed detection of these markers even in majority of the healthy individuals, also has lowered the specificity of the tests in acute chest pain syndromes leading to unnecessary interventions. Consequently, consideration of pre-analytical and

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analytical factors affecting troponin measurement and systematic evaluation of conditions related with troponin elevations are of great importance to obtain accurate diagnosis.

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