Troponin for the Estimation of Infarct Size: What Have We Learned?

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Key Words

Troponin · Acute myocardial infarction · Prognosis · Risk stratification

Abstract

In acute myocardial infarction (AMI), the extent of myocardial damage is closely linked to prognosis. Early determination of infarct size is therefore key to assessing the future risk of patients and instructive for optimization of therapeutic strategies. The cardiac troponins, by allowing the physician to track the extent of injury suffered by the myocardium, provide a window into the heart. This article addresses the relationship between the cardiac troponins and the infarct size in AMI. Taken together, the data suggest that the cardiac troponins provide very useful information in this respect and especially in patients with ST elevation myocardial infarction. More studies are needed to understand how cardiac troponin-estimated infarct size may be integrated with other prognostic assessments and employed systematically in risk stratification. Early data are promising and indicate that cardiac troponins could provide useful information for early risk assessment that is complementary to the determination of cardiac function and volumes.

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Introduction

In acute myocardial infarction (AMI), the extent of myocardial damage is closely linked to prognosis [1]. Infarct size is the strongest determinant of post-myocardial infarction (MI) chronic left ventricular function and of the compensatory and in the long-term adverse volumetric changes that occur in response to a depressed ejection fraction [2]. Early determination of infarct size following AMI is therefore key to assessing the future risk of patients and instructive for optimization of therapeutic strategies. Historically, the first attempts at estimating infarct size were performed by measurement of biochemical markers. In modern cardiology, imaging technologies allow for direct visualization of the injured myocardium and thus accurate measurement of infarct size. However, the routine use of imaging modalities to assess infarct size in daily clinical practice is constrained by costs and logistics. Thus, biochemical markers remain the most realistic and simple method in contemporary practice for infarct size estimation. The advent of the use of cardiac troponins for diagnostic and subsequently prognostic purposes in AMI during the last 15 years also stimulated investigations aimed at determining the usefulness of troponin measurements to quantify infarct size. Since then, many studies in this field have been published. The present article aims to review the use of troponins for infarct size estimation, suggest practical approaches for integration of this test into daily clinical

practice, identify areas where data are scarce and outline future directions in this research field. The case will be made that quantification of infarct size by use of cardiac troponins is an important and useful risk stratification tool in many AMI patients and may complement other metrics for risk assessment.

Historical Perspective: The Estimation of Infarct Size by Biochemical Markers

As the establishment of coronary care units in the 1960s reduced mortality from ventricular arrhythmias, most deaths following AMI were related to cardiogenic shock and progressive heart failure due to extensive myocardial damage. At the same time, emerging experimental evidence suggested that the evolution of AMI was a dynamic process susceptible to mitigation by therapeutic interventions. Alas, the initial attempts at estimating infarct size by the use of biochemical markers arose from the need to define surrogate parameters to evaluate experimental and clinical trials aimed at cardioprotection and infarct size reduction.

Elevation of transaminases in peripheral blood in patients with a very recent MI was described for the first time by Karmen et al. [3] in 1955, and the diagnostic utility of determination of serum enzyme levels in patients suspected of an acute coronary event was established in several studies published in the early 1960s. Historically, the three enzymatic markers mainly used for infarct size estimation have been creatine kinase (CK), its more cardiospecific isoenzyme CK-MB and lactate dehydrogenase (also known as α -hydroxybutyrate dehydrogenase). CK and CK-MB are present in the cytoplasm of myocardial muscle cells, and their release kinetics are characterized by an early peak (<24 h) and a rapid return to normal levels (<72 h) [4]. Lactate dehydrogenase peaks later (approx. 36 h) and remains elevated for a much longer time (>100 h) [4].

Quantitative models for the estimation of infarct size derived from measuring biochemical markers in the systemic circulation were introduced by two different research groups in the early 1970s (Witteveen et al. [5] and Sobel et al. [6]). In short, these models aimed to account for the cumulative release of the biomarker in question and then relate this directly to the amount of necrotic myocardium¹. In the absence of confirmation from infarct size determined in explanted hearts, surrogate measures related to cardiac function, electrocardiographic findings or clinical outcomes were used to validate the

enzyme measurements. Later, a multicenter, randomized study in which enzyme release was correlated directly to quantitative histologic measurements of infarct size in patients who died seemed to confirm the accuracy of the enzymatic models in humans [7].

The emergence of reperfusion therapy introduced a new source of uncertainty for enzyme-based infarct size estimation as it was found that early recanalization of an infarct-related artery accelerated enzyme release. This was initially documented in experimental animal studies and then confirmed in clinical trials [8]. The differences in the kinetics of enzyme liberation were not a problem per se, but it was uncertain whether the more rapid rise in enzyme levels also signaled a larger total release of enzymes caused by an increased release ratio. If this was the case, then possibly the cardioprotective potential of reperfusion therapy would not be apparent in comparison with conventional treatment modalities. Although no definite consensus has been established, several studies found that myocardial lactate dehydrogenase release was consistent regardless of whether thrombolytic therapy was administered or not [9, 10]. Results of much later investigations have since supported the validity also of measuring CK area under the curve (AUC) or CK-MB AUC for comparison of different reperfusion regimens [11].

The Cardiac Troponins in Acute Coronary Syndromes: Basic Pathophysiological Concepts

Troponin is a protein complex of three subunits (I, C and T) that modulate the calcium-mediated interaction between actin and myosin in skeletal and cardiac muscle tissue (fig. 1) [12]. Subunits I and T exist in 3 different isoforms, namely in fast and slow skeletal muscle and in myocardial cells. Each isoform is the product of a separate gene [13]. The unique myocardial isoforms cardiac troponin I (cTnI) and cardiac troponin T (cTnT) can be detected by assays of monoclonal antibodies directed against cardiac-specific epitopes. In the myocardial cells,

¹ The following parameters were needed: (1) the release ratio, which is the fraction of the marker depleted from the myocardium that is released into the circulation; (2) the clearance rate and distribution volume, which were needed to calculate the total amount of enzyme released into the blood; (3) the amount (activity or concentration) of the marker that represented a given weight of infarcted tissue, so that the size of the infarct could be calculated (this has conventionally been expressed as gram equivalents), and (4) lastly, the sampling interval necessary to determine a time activity (or concentration) curve so that the total amount released could be calculated accurately.

Fig. 1. The cardiac troponin subunits and their role in muscle contraction. Adapted from Collinson et al. [51].

the majority of the cardiac troponins are bound to the contractile apparatus, while a small fraction (3–8 and 6–7% of cTnI and cTnT, respectively) is free in the cytoplasm [14–16]. In the event of myonecrosis, troponins are released and can be detected in the bloodstream only a few hours afterwards, as the cytosolic form is released, and then for a prolonged period of up to 2 weeks, as the structural pool is slowly liberated [15, 17]. The cardio-specificity coupled with the fact that cTnT and cTnI do not circulate at measureable levels in healthy individuals (with conventional assays) has given rise to their use in clinical cardiology, thus by and large replacing older

markers of myocardial injury. Whether cardiac troponin may also be released in response to pure myocyte ischemia without necrosis remains controversial.

Cardiac Troponin for Infarct Size Estimation

The release kinetics of the cardiac troponins in the context of myocardial necrosis is characterized by an initial cytosolic liberation with a peak in the case of reperfusion and then a slowly abating plateau phase reflecting degradation of the structural pool [18, 19]. In the absence

of reperfusion, the release pattern is characterized by a slow increase in the plasma concentration which peaks at day 3 or 4 [15, 20]. Reperfusion therapy induces an early peak of both markers as the cytosolic pool is rapidly washed out, but there is no evidence that cumulative troponin release is impacted by reperfusion therapy [15, 20]. The data also suggest that plasma levels are independent of reperfusion status from the first day onwards, largely reflecting the slow degradation and liberation of the structural pool [15, 20]. In reperfused patients, it has been shown that while both cTnT and cTnI peak early (<12 h), the disappearance of cTnI is somewhat accelerated compared to cTnT, although both are still significantly elevated at 72 h [21, 22].

The properties outlined above make cardiac troponin uniquely suited to both early diagnosis of infarction and also, at a later time point, assessing the extent of the myocardial necrosis [15]. However, two shortcomings of cardiac troponin for infarct size estimation, one biological and one methodological, should also be acknowledged.

Firstly, the cardiac troponin concentration in cardiac tissue varies. The distribution of cardiac troponin content (per gram wet weight tissue and per gram of protein) in the myocardium has been shown to be lower in the atria compared to the ventricles [23]. The troponin content in the left ventricle is uniform but does exhibit some person-to-person variability. This interpatient variability suggests that cardiac troponin measurements based on plasma or serum measurements may never attain optimal precision with regards to estimation of infarct size [23].

Secondly, recent studies of cardiac troponin for infarct size estimation do not account for the complexity involved in the degradation and release of cardiac troponin. The earlier studies on other biochemical markers, as described in the previous section, were very detailed and meticulous in that they constructed mathematical models to account for the cumulative release of the marker of interest within the infarcted region of the heart. Studies on cardiac troponin have all adopted a much simpler approach by focusing solely on the concentrations of cardiac troponin in peripheral blood at one or several time points. The upside of this simplification is increased utility in daily clinical practice, but at the cost of a lack of precision.

In spite of these theoretical limitations, the empirical evidence suggests that the correlation between cardiac troponin and infarct size is strong enough to be of clinical utility. The next section summarizes the data.

The Empirical Evidence and the Key Learnings So Far

The first report describing the correlation between cTnT and infarct size was presented by Hugo Katus and colleagues at a congress in 1991 [24], and the first articles detailing the relationship between cTnT and infarct size were published in 1993 [25, 26]. Table 1 summarizes the published articles reporting correlations between infarct size and cardiac troponin.

As is apparent from the table, the various studies differ widely with regard to design, population investigated and endpoints used. In reviewing these studies, the most important variables to consider are: (1) the population studied, i.e. ST elevation MI (STEMI) versus non-STEMI, whether reperfusion was given and the reperfusion modality; (2) which standard was used for comparison, i.e. infarct size determined by single-photon emission computed tomography (SPECT), cardiac magnetic resonance (CMR) or other biomarkers, and at what time this examination was performed; (3) the cardiac troponin assay employed; (4) the time points used for sampling, and (5) which variables were used in the correlation analyses, i.e. peak troponin, AUC troponin or a specified time point.

Without exception, all studies have found a consistent and positive correlation between cardiac troponin and infarct size determined by both CMR and SPECT. Also, a similar, albeit somewhat weaker correlation with cardiac function and cardiac troponin has been reproduced in several datasets. The correlations reported between cardiac troponins and different imaging technologies of infarct size are generally between 0.6 and 0.75, although some have found coefficients above 0.8. One caveat is that most studies have looked exclusively or predominantly at STEMI populations. Cardiac troponins seem less useful in non-STEMI. The different studies may be best summarized by extracting some key messages based on an integrated interpretation of the findings, as summarized below.

STEMI Differs from Non-STEMI

Most studies have only looked at STEMI patients. Findings by Giannitsis et al. [27] suggest that correlations between cardiac troponin and infarct size are significantly weaker in non-STEMI patients. There are several plausible explanations for this observation. Firstly, non-STEMIs are on average substantially smaller than STEMIs. Thus, the imaging quantification of the extent of the infarcted tissue may be somewhat less precise, which would adversely impact the correlations with biomarker measurements. Secondly, of equal or even more importance is the fact that the timing of the ischemic onset is less well

Table 1. Overview of published studies on the association between cardiac troponin and infarct size

Report	Population studied	Design	Assay used	Sampling intervals	Variables used	Comparator (infarct size)	Other outcome measures	Correlation coefficients
Omura et al. (1993) [25]	AMI, Q wave (n = 34) thrombolysis	prospective	cTnT 1st generation [51]	every 3 h (0–24 h), every 6 h (24–72 h)	peak	SPECT 4 weeks	–	0.77
Wagner et al. (1993) [26]	AMI, Q wave (n = 21) thrombolysis	randomized trial	cTnT 1st generation [51]	every 4 h (0–24 h), every 8 h (24–48 h), daily until discharge	peak AUC	SPECT 5 weeks	–	0.73 (peak) 0.54 (AUC)
Mair et al. (1995) [33]	AMI, Q wave (n = 21) thrombolysis	randomized trial	cTnI (ERIA Diagnostics, F)	every 4 h (0–24 h), every 8 h (24–48 h), daily until discharge	AUC	SPECT 5 weeks	–	0.53
Tanaka et al. (1997) [34]	STEMI (n = 42) thrombolysis (n = 10) and pPCI (n = 32)	prospective	cTnI (Stratus, Dade Behring, USA) cTnT 1st generation [51]	every 3 h (0–24 h)	peak	–	regional hypokinesia (ventriculogram)	0.84 (cTnI) 0.85 (cTnT)
Apple et al. (1998) [35]	AMI (n = 39), thrombolysis (n = 12) and pPCI (n = 1)	prospective	cTnI (Stratus, Dade Int., USA)	6, 12, 24 and 36 h	peak	–	LVEF (echocardiogram)	0.46
Rao et al. (1998) [36]	STEMI (n = 50) thrombolysis (n = 32) no thrombolysis (n = 18)	retrospective	cTnT 1st generation [51]	1 sample between 12 and 48 h	single-point (12–48 h)	–	LVEF (ventriculogram) 2 days–32 weeks	0.72
Kanna et al. (2001) [37]	AMI (n = 121) thrombolysis (n = 71) pPCI (n = 3)	prospective	cTnT 1st generation [51]	1 sample on day 3 or 4	single-point (day 3–4)	–	LVEF (ventriculogram in 95; echo in 7; SPECT in 5)	0.48 (first AMI, n = 88)
Licka et al. (2002) [38]	AMI (n = 37) thrombolysis/pPCI (n = 23) and no/failed reperfusion (n = 14)	prospective	cTnT 2nd generation	every 4 h (0–24 h), every 8 h (24–72 h), once daily until day 10	single-point (72-hour value)	SPECT 10–18 days	–	0.72 (no reperfusion) 0.78 (reperused)
Panteghini et al. (2002) [39]	AMI (n = 65) thrombolysis/pPCI (n = 55); no revascularization (n = 10)	prospective	cTnT 3rd generation	every 6 h (0–48 h) and at discharge (40–160 h)	discharge and value	SPECT at discharge and at 3 months (n = 58)	LVEF (SPECT)	0.62 (at discharge) 0.56 and 0.70 (LVEF at discharge and 3 months)
Rao et al. (2003) [40]	STEMI (n = 201)	prospective	cTnT 2nd generation	1 sample 12–24 h	single-point (12–24h)	–	LVEF (echo)	no correlation ROC: 0.91 for LVEF <40%
Ohlmann et al. (2003) [22]	STEMI (n = 87) pPCI (n = 73)	prospective	cTnI (Stratus II, Dade Behring, USA)	3, 6, 9, 12, 24, 48, 72 h	single-point, peak, AUC	QLDH	LVEF (SPECT)	>0.8 (all time points from 6 h, AUC, peak) approx. 0.5 (LVEF)
Ingkanisorn et al. (2004) [41]	AMI (n = 33) thrombolysis (n = 23)	prospective	cTnI (assay not reported)	4 and 8 h	peak	CMR (1–2 days)	–	0.83 (for revascularized patients, n = 23)
Panteghini et al. (2005) [42]	STEMI (n = 63) pPCI (n = 29 + 11) thrombolysis (n = 25) no revascularization (n = 9)	prospective	cTnI (Accu-cTnI, Beckman Coulter, USA)	12 and 48 h	single-point	SPECT (first week)	LVEF (SPECT, first week, 3 months)	0.55/0.61 (12/48 h) LVEF, 1 week: 0.45/0.57 (12/48 h) LVEF, 3 months: 0.51/0.69 (12/48 h)

Table 1 (continued)

Report	Population studied	Design	Assay used	Sampling intervals	Variables used	Comparator (infarct size)	Other outcome measures	Correlation coefficients
Steen et al. (2006) [43]	AMI (STEMI: n = 23; non-STEMI: n = 21)	prospective	cTnT 3rd generation	96 h	single-point	CMR (4 days)	-	0.91 (STEMI) 0.58 (non-STEMI)
Younger et al. (2007) [44]	AMI (n = 93) thrombolysis (n = 71)	prospective	cTnI (Accu-cTnI, Beckman Coulter, USA)	12 and 72 h	single-point	CMR (2–5 days)	MVO	0.56/0.62 (12/72 h)
Giannitsis et al. (2008) [27]	AMI (n = 61) STEMI (n = 30)	prospective	cTnT 3rd generation	day 1, 2, 3, 4	single-point, peak, AUC	CMR (4 days)	-	0.64/0.66/0.65/0.66/0.65/0.7 (day 1/2/3/4/ peak/AUC)
Tzivoni et al. (2008) [28]	STEMI (n = 378) pPCI	randomized trial (CASTEMI)	cTnT (assay not reported)	2, 4, 12, 24, 48, 72 h	peak, AUC	SPECT (7 and 30 days)	LVEF	day 7: 0.71/0.72 (peak/AUC) day 30: 0.66/0.67 (peak/AUC)
Vasile et al. (2008) [45]	STEMI (n = 28)	retrospective	cTnI (Accu-cTnI, Beckman Coulter, USA)	day 1, 2, 3, 4	single-point	CMR (4 days)	-	0.75/0.78/0.71/0.71/0.76 (day 1/2/3/4/ peak/AUC)
Chia et al. (2008) [21]	STEMI (n = 378) pPCI	randomized trial (EVOLVE)	cTnI (AxSym Troponin I ADV, Abbot Labs, USA) cTnT 3rd generation	2, 4, 12, 24, 48, 72 h	single-point, AUC	SPECT (5 days, 30 days)	LVEF	cTnT at 72 h: 0.65/0.63 (5/30 days) cTnI at 72h: 0.73/0.71 (5/30 days)
Bohmer et al. (2009) [46]	STEMI (n = 103) pPCI	randomized trial (NORDISTEMI)	cTnT 3rd generation	67 h	single-point	CMR (3 months)	LVEF	0.84 0.63 (LVEF)
Hassan et al. (2009) [47]	STEMI (n = 168) pPCI	randomized trial (mission)	cTnT 3rd generation	every 6 h (0–48 h)	peak	CK (cumulative)	LVEF (SPECT, 3 months)	0.73 (CK and cTnT) 0.5 (LVEF)
Hallén et al. (2010, 2009) [29, 30]	STEMI (n = 227/132) pPCI	randomized trial (FIRE)	cTnI (AxSym Troponin I ADV, Abbot Labs, USA)	24 and 48 h	single-point	CMR (5 days and 120 days)	LVEF, EDV, ESV	cTnI at 24 h: 0.66/0.63 (5/120 days) cTnI at 48 h: 0.67/0.65 (5/120 days)
Byrne et al. (2010) [48]	STEMI (n = 1,237) pPCI	prospective	cTnT 2nd generation	8, 16, 24 h, then daily	peak	SPECT		0.45
Klug et al. (2011) [49]	STEMI (n = 103) pPCI	prospective	cTnT 4th generation	admission, 8, 16 h, day 1, 2, 3, 4	peak, AUC, single-point	CMR (<8 days)	LVEF, EDV, ESV	0.56/0.60/0.58/0.62/0.64/0.68 (day 1/2/3/4/ peak/AUC)
Mayr et al. (2011) [50]	STEMI (n = 80) pPCI	prospective	cTnT (assay not reported)	admission, 8, 16 h, day 1, 2, 3, 4	peak, single-point	CMR (2–4 days and 4 months)	LVEF, EDV, ESV	day 2: 0.58/0.65/0.62 4 months: 0.65/0.75/0.67 (day 1/2/3)

LVEF = Left-ventricular ejection fraction; pPCI = primary percutaneous coronary intervention; LDH = lactate dehydrogenase; MVO = microvascular obstruction; EDV = end-diastolic volume; ESV = end-systolic volume.

defined in non-STEMI. Thus, measurements at a fixed time point(s) following admission would represent different time points in the underlying pathophysiologic process from patient to patient.

Values on Admission Differ from Values Obtained following Reperfusion

While admission troponin values are also predictive of future risk, the correlation with infarct size is poor [21]. Estimates of infarct size are best performed at least 24 h after onset of ischemia, although peak values are also indicative [21, 28].

Single-Point Measurements Are as Effective as Derived Measures of AUC or Peak Values

Initially, it was considered more robust to use derived measures of cardiac troponin release such as the peak or AUC. However, several investigations have firmly established that single-point measures are just as effective from 24 h onwards [21, 27]. This has been shown for both cTnT and cTnI. Chia et al. [21] found that a 72-hour sample displayed the best correlation with infarct size for both cTnT and cTnI (Abbot AxSym ADV assay), but differences were minor at the other time points.

cTnT and cTnI Perform Equally Well

There is no evidence to suggest that cTnT or cTnI differ in their abilities to reflect the amount of infarcted tissue. Some studies have reported correlations for both cTnT and cTnI assays in the same population, and the results indicate no meaningful differences [21]. However, as there are multiple cTnI assays commercially available and in use, one should be careful to extrapolate results from specific cTnI assays to the class of cTnI assays as a whole. At this point, Abbot's AxSYM ADV assay is the most thoroughly investigated cTnI assay [21, 29, 30].

In STEMI, Cardiac Troponin Measurements Are Complementary to Early Assessment of Function and Volumes

The clinical utility of infarct size estimation with cardiac troponins depends on the additional prognostic value they confer in the context of other routinely obtained markers of future risk. Although data addressing this question are scarce, one study has found that cardiac troponin provides information in addition to early assessment of cardiac function and volumes with regard to the risk of chronic left-ventricular dysfunction and adverse remodeling [29]. This study replicated for cTnI what had been shown for both SPECT and CMR as measures of in-

farct size [2, 31]. Thus, while more research is needed, early indications are that infarct size estimation by cardiac troponins is useful also when integrated with other markers of risk.

Moving Forward: Future Research Directions

As shown above, most of the published research so far has investigated correlations between infarct size or cardiac function and levels of cardiac troponin. It is now time to broaden the scope and move the field forward. Several important questions remain to be addressed.

Firstly, there is a need to better understand how cardiac troponin estimation of infarct size fits in with the other prognostic information routinely obtained in post-AMI patients. Although one such study has been published with encouraging results, more investigations are needed in order to define the proper role that cardiac troponin sampling for infarct size estimation may or may not play in risk stratification in the context of AMI.

Secondly, more data are needed on the association between cardiac troponin and clinical endpoints in STEMI. There is an abundance of data on cardiac troponin on admission and outcomes in STEMI, but very little has been published on cardiac troponin measurements obtained following the index event at time points where cardiac troponin reflects infarct size.

Thirdly, a better understanding of cardiac troponin for infarct size estimation in non-STEMI would be useful, although this indication is probably inherently less suitable for infarct size estimation by cardiac troponin, as discussed above.

Clinical Utility of Cardiac Troponin for Infarct Size Estimation

The data gathered so far suggest that for AMI patients, and STEMI patients in particular, cardiac troponin may be employed systematically for crude infarct size estimation at an early time point following the acute event. The association between cardiac troponin and the amount of myocardial necrosis is robust, but it should be acknowledged that cardiac troponin measurements may not be precise enough to provide an accurate estimate of the extent of the myocardial injury in individual patients. Therefore, it may be more realistic to create cutoff values and employ cardiac troponin to stratify patients in categories based on the extent of myocardial injury. Success-

ful implementation of such a risk stratification strategy would entail establishing a fixed time point after admission, or preferably after onset of symptoms, at which cardiac troponin is sampled in all targeted patients. Appropriate cutoffs would need to be defined either based on the literature or by prospective validation in designated studies. The cardiac troponin values should be interpreted in light of other risk stratification metrics performed on most patients before discharge, most importantly early assessment of cardiac function and volume, as shown in a recent paper [29].

Cardiac troponin-guided estimation of infarct size may also be useful for clinical trials in at least two respects. Firstly, cardiac troponin can be employed as a surrogate endpoint for infarct size in trials aimed at cardioprotection and infarct size reduction. Cardiac troponin may be more precise than CK/CK-MB, and one single-point sample may be enough, although variability may be decreased and statistical power increased with a derived measure such as AUC. Secondly, cardiac troponin may be an attractive candidate for simple and objective identification of high-risk post-MI patients who will benefit the most from novel interventions aimed at improving long-term outcome.

Conclusion

The cardiac troponins, by allowing the physician to track the extent of injury suffered by the myocardium, provide a window into the heart [32]. This article has addressed the relationship between the cardiac troponins and infarct size in AMI. Taken together, the data suggest that the cardiac troponins provide very useful information in this respect and especially in STEMI patients. More studies are needed to understand how cardiac troponin-estimated infarct size may be integrated with other prognostic assessments and employed systematically in risk stratification. Early data are promising and indicate that cardiac troponins could provide useful information for early risk assessment that is complementary to the determination of cardiac function and volumes [29].

Conflict of Interest

Dr. Hallén has received research support from Roche Diagnostics and travel support from Siemens Diagnostics. He is currently an employee of Boehringer Ingelheim.

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