Opinion Paper

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Strategies to overcome misdiagnosis of type 1 myocardial infarction using high sensitive cardiac troponin assays

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Abstract: High sensitive cardiac troponin assays have become the gold standard in the diagnosis of an acute type 1 myocardial infarction (MI) in the absence of ST-segment elevation. Several acute or chronic conditions that impact cardiac troponin levels in the absence of a MI might lead to a misdiagnosis of MI. For example, patients with impaired renal function as well as elderly patients often present with chronically increased cardiac troponin levels. Therefore, the diagnosis of MI type 1 based on the 99th percentile upper limit of normal threshold is more difficult in these patients. Different diagnostic approaches might help to overcome this limitation of reduced MI specificity of sensitive troponin assays. First, serial troponin measurement helps to differentiate chronic from acute troponin elevations. Second, specific diagnostic cut-offs, optimized for a particular patient group, like elderly patients, are able to regain specificity. Such an individualized use and interpretation of sensitive cardiac troponin measurements improves diagnostic accuracy and reduces the amount of misdiagnosed MI type 1.

Keywords: acute myocardial infarction (AMI); diagnosis; misdiagnosis; NSTEMI; troponin; type 1 myocardial infarction.

High sensitive cardiac troponin assays: the gold standard in definition and diagnosis of myocardial infarction

Definition of myocardial infarction

According to the third universal definition of myocardial infarction (MI) published in 2012 [1] an MI is classified into five categories in patients with symptoms consistent with MI: type 1 MI – rise and/or fall of cardiac biomarkers and clinical evidence of an acute MI; type 2 MI has been defined if myocardial necrosis (with rise or/and fall of cardiac biomarkers) occurs not due to coronary artery disease (CAD) and plaque rupture but due to a secondary ischemic imbalance e.g. tachy- or bradyarrhythmia, arterial hypertension or coronary spasm; type 3 MI reflects suspected cardiac death before biomarkers could be obtained; type 4a MI is defined as elevation of cardiac biomarkers in the context of percutaneous coronary intervention (PCI), type 4b as stent thrombosis associated MI proven by coronary angiography or autopsy with related rise or fall in cardiac biomarkers. Coronary bypass grafting (CABG) associated MI is classified as type 5 (see also Table 1).

Cardiac troponins as biomarker of choice in diagnosis MI

Ebashi firstly described a “tropomyosin” complex in 1963 which is necessary for relaxing and contracting the muscle [3]. Three components constitute this complex named troponin I (TnI), troponin T (TnT) and troponin C (TnC) [4] and it was shown that there are cardiac specific isoforms [5]. By developing an enzyme linked immunoassays in the late eighties both for cTnI and cTnT the detection of cTn in the setting of MI was possible [6, 7]. In 2000,
Table 1: Different types of myocardial infarction.

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Rise and/or fall of cardiac biomarkers and clinical evidence of acute myocardial infarction</td>
</tr>
<tr>
<td>Type 2</td>
<td>Myocardial necrosis with rise or fall of cardiac biomarkers due to a secondary ischemic imbalance (not due to coronary artery disease)</td>
</tr>
<tr>
<td>Type 3</td>
<td>Suspected cardiac death before biomarkers could be obtained</td>
</tr>
<tr>
<td>Type 4a</td>
<td>Elevation of cardiac biomarkers in the context of percutaneous coronary intervention</td>
</tr>
<tr>
<td>Type 4b</td>
<td>Stent thrombosis associated myocardial infarction with related rise or fall in cardiac biomarkers</td>
</tr>
<tr>
<td>Type 5</td>
<td>Elevation of cardiac biomarkers in the context of coronary bypass grafting</td>
</tr>
</tbody>
</table>

Definition of different types of myocardial infarction based on the Third Universal Definition of Myocardial Infarction [2].

the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC) proposed a redefinition of MI which included cTn as the biomarkers of choice to diagnose MI paving the way for cTn into the diagnostic guidelines and the clinical routine [8].

As diagnostic threshold the assay specific upper limit of normal (ULN) was defined representing the 99th percentile concentration of the troponin assay in a healthy reference population. Furthermore, criteria of test sensitivity were defined as a coefficient of variation (CV) of 10% or less at this threshold concentration. Former cTn assays often showed a lack of sensitivity to detect cTn levels e.g. in healthy individuals. This led to an evolution of commercially available assays with improved sensitivity. These high sensitive assays are frequently able to detect low cTn levels even in apparently healthy individuals [9]. Their clinical application using the 99th percentile diagnostic threshold consistently showed an improvement in early diagnosis of MI type 1 [10, 11].

Gain of sensitivity – loss in specificity

The improved troponin assay sensitivity, facilitating a rapid diagnosis of MI type 1, could be confirmed in many clinical studies underlining the clinical benefit of sensitive troponin assays. Use of more sensitive assays allows detecting cardiac troponin levels even in healthy individuals; even a biological variation in healthy individuals is detectable without presence of an MI [12–14]. Elevated troponin levels can be found in the absence of an MI in patients with several other conditions such as in critically ill patients (e.g. acute neurological event, severe respiratory failure, severe pulmonary embolism) and troponin levels can be chronically increased in certain patient populations: this includes patients with impaired renal function or elderly patients (Figure 1). These elevations of troponin levels due to chronic or acute conditions other

Figure 1: Influences on troponin levels.
Different known confounding factors and diagnoses on cardiac troponin levels. AMI, acute myocardial infarction; SAH, subarachnoid hemorrhage.
than MI are associated with a loss of specificity of sensitive troponin assay in the diagnosis of MI type 1.

**Current recommendations for diagnosing MI**

While the diagnosis of an acute ST-segment-elevation myocardial infarction (STEMI) can be made primarily based on certain changes in the electrocardiogram (ECG), the diagnosis of an acute non ST-segment-elevation myocardial infarction (NSTEMI), according to the current ESC guidelines, relies on cardiac biomarkers, first and foremost on cardiac troponin measurement using a sensitive assay [15].

Besides from elevated cTn levels on admission above the ULN of the respective assay, a rise or fall in cTn levels (Delta cTn) is essential for the diagnosis of an NSTEMI in patients with suspected MI. In recent years, different approaches to evaluate Delta cTn levels have been proposed including the use of relative vs. absolute changes and the amount of change which could be considered significant [16–19]. The current ESC guidelines propose different algorithms to rule-in and to rule-out NSTEMI based on baseline hs-cTn as well as the change over time including the established 0 h/3 h algorithm and recent 0 h/1 h algorithm.

**Using serial troponin measurements for diagnosing MI**

To account for troponin elevations especially caused by non-acute conditions the diagnostic use of change in troponin concentration within a few hours is able to improve specificity for the diagnosis of MI type I. The following two algorithms are currently recommended by the ESC guidelines.

**First, the 0 h/3 h algorithm**

If the baseline hs-cTn level is lower than the ULN and the patient suffered from chest pain for more than 6 h prior to admission, the patients can be discharged without a second hs-cTn measurement. The reliability of this approach has recently been confirmed in two studies that investigated patients with suspected MI and first cTn level below ULN (even without respect to chest pain onset). Patients with baseline cTn below the ULN could be ruled-out with high confidence (sensitivity of 99.0%, negative predictive value of 99.5%) [20, 21]. If onset of pain was within 6 h before presentation and the baseline hs-cTn level is below ULN, a second hs-cTn testing after 3 h is recommended. If a relevant dynamic rise or fall in hs-cTn is observed, a rule-in is possible. In patients already presenting with highly abnormal (five-fold the ULN) hs-cTn levels and a high clinical likelihood for MI an invasive management should be targeted without further delay by waiting for a second hs-cTn measurement.

**Second, the 0 h/1 h algorithm**

This algorithm is based on observations [15], that very low (below the 99th percentile concentration) and very high hs-cTn levels on admission and small absolute changes in hs-cTn concentration after 1 h can already rule-in or rule-out patients who present with suspected MI. The proposed baseline and absolute 1 h delta cTn cut-offs are assay specific. Currently, thresholds for two hs-cTnI and one hs-cTnT have been published [22]. Use of this algorithm leads to a rule-in, a rule-out and an observation group that needs further diagnostic work-up. Recently, the safety of this approach was validated. Mueller et al. could verify the diagnostic utility and safety of this algorithm in a large cohort [23]. Furthermore, Neumann et al. investigated a comparable 0 h/1 h algorithm with different thresholds with respect to rule-out and rule-in of MI. This algorithm was validated in two independent cohorts, showing that their 1-h algorithm can rule-in and rule out MI with a comparable confidence as the established 0 h/3 h algorithm [24].

**Improving specificity by adding information of clinical risk scores**

Beyond using change in troponin concentration to improve the diagnostic specificity for MI type I the use of clinical parameters has been discussed. Indeed, it could be shown that serial cTn measurements combined with risk scores such as the HEART score that include history, ECG, age, risk factors, and troponin as parameters can improve diagnosis of MI [25, 26]. Furthermore, the combination of troponin determination and the Thrombolysis In Myocardial Infarction (TIMI) score improves diagnosis of MI [27].
Troponin cut-offs – one fits all?

Improving specificity in patients with impaired renal function

Over the last 20 years, several authors described increased cTnT and cTnI levels in patients suffering from chronic kidney disease (CKD). In 1994 Hafner et al. found increased cTnI and cTnT levels in 18 patients undergoing dialysis [28]. Li et al. not only described increased cTnT levels in patients undergoing hemodialysis but also in patients with CKD [29]. Over the next years these findings were reproduced by several other authors [30, 31]. This elevation might be due to poor renal elimination, micronecrosis or even an origin other than the heart. Evidence that increased cTnT levels are seen caused by poor renal elimination were found by Keddis et al. [32]. Tsuatomoto et al. compared the transcardiac gradient in patients with and without CKD. While CKD patients showed overall higher cTnT levels, there was no difference in the transcardiac gradient, which led to the assumption that the origin of cTnT in CKD patients is the heart, and that the increased levels are based on a poor renal elimination [33]. There is data that increased cTn levels reflect underlying cardiovascular diseases such as left ventricular hypertrophy, coronary artery disease or heart failure in CKD patients [34–36] and that both, cTnT and cTnI, are markers of mortality, cardiovascular mortality or major cardiovascular events in patients with CKD [37–41]. This on one hand underlines the high-risk status of these patients. On the other hand, adequate diagnosis of MI type 1 with subsequent treatment initiation that is based largely on cTn is more difficult in CKD patients.

Chenevier-Gobeaux et al. analyzed the diagnostic performance of hs-cTnT in CKD patients and suspected MI upon admission. The ULN of the respective hs-cTnT assay had a high specificity in detection of MI type 1 in patients with a preserved renal function (86%); whereas in CKD patients specificity for MI decreases to 54% (Table 2) [42]. This observation is supported by data by Pfortmueller et al. showing a comparable loss in specificity of hs-TnT levels upon admission and by Twerenbold et al. who compared the diagnostic utility of baseline cTn levels of four hs-cTn assays and one hs-cTnT assay in the evaluation of MI type 1 in CKD patients [43, 44] (Table 3). This loss in specificity poses the relevant risk for misdiagnosis in these specific patients based on the first cTn measurement. This is aggravated by the fact that CKD patients are at high risk for developing an MI [46].

The studies by Chenevier-Gobeaux et al. and Twerenbold et al. both could show that the area under the receiver operator characteristics curve (AUROC) for cTn to detect MI in CKD patients is comparable to the AUROC of patients with a preserved renal function. They state, that higher, AUROC-optimized cut-offs are in need to regain the diagnostic specificity of cTn in CKD. Chenevier-Gobeaux derived a higher optimized hs-cTnT cut-off for CKD patients that is able to detect MI with a specificity of 86% using the baseline cTn measurement, this is the same specificity provided by the ULN threshold in patients with a preserved renal function. This increase in specificity is not accompanied by a relevant loss of sensitivity (Table 2). The efficacy of higher optimized cut-offs in CKD patients to identify MI type 1 was also verified by Twerenbold et al. [44] (Table 3).

Improving specificity in elderly patients

Similar problems in the accurate diagnosis of MI type 1 as in CKD patients are seen in elderly patients. Several authors could show increased cTn levels in older patients irrespective of an acute MI. A recent study evaluated hs-cTnT levels in geriatric patients and found in over 50% of 679 hospitalized geriatric patients without MI (mean age 82.5±5.8 years) hs-cTnT levels above the ULN. Even in patients without known coronary artery disease, 46.6% had hs-cTnT levels above the ULN [47]. Saneger et al. described an association of hs-cTnT levels

Table 2: Performance of high sensitive cardiac troponin T in patients with and without chronic kidney disease.

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Cut-off</th>
<th>Sens. % (95% CI)</th>
<th>Spec. % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche hs-cTnT</td>
<td>&gt; 60 mL/min</td>
<td>ULN = 14 ng/L</td>
<td>90 (76–97)</td>
<td>86 (81–90)</td>
<td>51 (39–63)</td>
</tr>
<tr>
<td>≤ 60 mL/min</td>
<td>ULN = 14 ng/L</td>
<td>100 (76–100)</td>
<td>54 (40–67)</td>
<td>37 (23–53)</td>
<td>100 (86–100)</td>
</tr>
<tr>
<td>≤ 60 mL/min</td>
<td>ROC = 35.8 ng/L</td>
<td>94 (68–100)</td>
<td>86 (74–94)</td>
<td>65 (43–83)</td>
<td>98 (89–100)</td>
</tr>
</tbody>
</table>

Sensitivity (Sens.), specificity (Spec.), negative predictive value (NPV) and positive predictive value (PPV) of high sensitive troponin T (hs-cTnT) in patients with a preserved renal function (estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m²) or impaired renal function (eGFR ≤ 60 mL/min/1.73 m²) applying the upper limit of normal (ULN) as well as ROC optimized cut offs (ROC). Modified according to Chenevier-Gobeaux et al. [42].
with age [48] and Gore et al. evaluated hs-cTnT levels in elderly patients: here hs-cTnT was analyzed in apparently cardiac healthy elderly patients from three different population based studies. In patients without structural heart disease, without impaired left ventricular function or without elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) an impact on the ULN of hs-cTnT was seen [49]. Similar findings exist for hs-cTnI. Keller et al. showed a rise in hs-cTnI levels with patients’ age [50]. This data is supported by a study of McKie et al. [51]. The authors could show that hs-cTnI levels are significantly higher in elderly patients, apparently free of cardiovascular diseases. On the basis of these findings, elevated cTn levels in elderly patients cannot only be explained by an impaired renal function that is often seen in the elderly population, as these patients were excluded. Increased cTn levels indicate a higher risk for developing chronic heart disease as they might indicate subclinical myocardial damage [52, 53].

These data suggest that elevated cTn levels in elderly patients are caused by various reasons including silent cardiovascular disease but might also be increased in patients without cardiovascular disease [49, 53]. All these studies have in common, that elevated cTnT and cTnI levels were observed in patients in the absence of MI. This increase in cTn levels therefore leads to an increase of uncertainty in evaluation of suspected MI type 1 in elderly patients.

Reiter et al. analyzed the performance of three different sensitive cTn assays to diagnose MI type 1 in patients older than 70 years based on baseline cTn. Use of the respective ULN as diagnostic cut-off showed a decrease in specificity in elderly patients compared to patients younger than 70 years. To regain this loss in specificity age optimized cut-off were derived based on AUROC analyses [54] (Table 4). A similar approach was carried out in the analysis of Chenevier-Gobeaux et al. [42]. The authors evaluated hs-cTnT levels in patients older than 70 years and with suspected MI measured upon admission showing a specificity with 51% if using the ULN compared to a specificity of 88% in detection of MI in patients < 70 years. By applying higher, AUROC-optimized cTn cut-off levels, this loss in specificity could be regained (Table 5).

Based on the idea of increased cTn levels in elderly patients in the absence of an acute MI, a study carried out by Olivieri et al. derived age-specific cut off levels in a healthy reference population in patients older 75 years and tested their diagnostic performance in geriatric patients with suspected MI. The established 99th percentile ULN of the respective hs-cTnT assays is 14 ng/L whereas in individuals older than 75 years an ULN of 70.6 ng/L was derived. Using this higher ULN in geriatric patients with suspected MI gained a sensitivity of 94% and a specificity of 77% [55].

Also, Gore et al. defined ULN of hs-cTnT in their cohort of elderly patients apparently free of cardiovascular diseases [49]. Several ULNs for different ages, genders and races based on different population based studies were reported [49]. Mueller-Hennesen et al. recently tested the application of the reported higher ULN for individuals aged 65 years or older in a population of patients

<table>
<thead>
<tr>
<th>Assay</th>
<th>eGFR Cut-off</th>
<th>Sens. % (95% CI)</th>
<th>Spec. % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siemens Ultra s-cTnI</td>
<td>≥ 60 mL/min</td>
<td>ULN = 40 ng/L</td>
<td>75 (70–79)</td>
<td>94 (92–95)</td>
<td>71 (67–76)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ULN = 40 ng/L</td>
<td>79 (72–85)</td>
<td>81 (75–85)</td>
<td>69 (63–76)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ROC = 46 ng/L</td>
<td>77 (70–84)</td>
<td>84 (79–88)</td>
<td>73 (66–80)</td>
</tr>
<tr>
<td>Roche hs-cTnT</td>
<td>≥ 60 mL/min</td>
<td>ULN = 14 ng/L</td>
<td>88 (84–91)</td>
<td>86 (84–87)</td>
<td>56 (52–60)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ULN = 14 ng/L</td>
<td>98 (94–99)</td>
<td>32 (27–38)</td>
<td>45 (39–50)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ROC = 29.5 ng/L</td>
<td>84 (77–89)</td>
<td>79 (74–83)</td>
<td>69 (92–75)</td>
</tr>
<tr>
<td>Abbott Architect hs-cTn</td>
<td>≥ 60 mL/min</td>
<td>ULN = 26.2 ng/L</td>
<td>71 (66–76)</td>
<td>94 (93–95)</td>
<td>71 (66–76)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ULN = 26.2 ng/L</td>
<td>77 (69–84)</td>
<td>83 (78–88)</td>
<td>74 (66–81)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ROC = 29.4 ng/L</td>
<td>76 (68–82)</td>
<td>85 (80–89)</td>
<td>76 (68–83)</td>
</tr>
<tr>
<td>Siemens hs-cTnI</td>
<td>≥ 60 mL/min</td>
<td>ULN = 9.0 ng/L</td>
<td>93 (89–96)</td>
<td>78 (75–90)</td>
<td>45 (41–19)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ULN = 9.0 ng/L</td>
<td>94 (86–98)</td>
<td>56 (49–63)</td>
<td>51 (43–59)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ROC = 32.0 ng/L</td>
<td>82 (71–89)</td>
<td>83 (77–88)</td>
<td>90 (85–94)</td>
</tr>
<tr>
<td>Beckman-Coulter hs-cTn</td>
<td>≥ 60 mL/min</td>
<td>ULN = 9.2 ng/L</td>
<td>90 (85–94)</td>
<td>80 (77–82)</td>
<td>48 (43–54)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ULN = 9.2 ng/L</td>
<td>95 (87–99)</td>
<td>48 (39–57)</td>
<td>48 (39–57)</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 mL/min</td>
<td>ROC = 25.9 ng/L</td>
<td>81 (69–90)</td>
<td>83 (76–89)</td>
<td>71 (59–81)</td>
</tr>
</tbody>
</table>

Table 3: Performance of different troponin assays in patients with and without chronic kidney disease.
presenting with suspected MI. The authors analyzed reclassification of elderly patients with regard to the final diagnosis of acute coronary syndrome (ACS) or non-ACS. The influence on both diagnostic and prognostic reclassification was significant using an age-specific hs-cTnT ULN based cut-off level approximately two-fold of the established ULN of the assay [56].

**Gender differences in troponin levels – risk of underdiagnoses in females**

While chronically elevated cTn levels in patients free of an acute cardiovascular disease might make the use of optimized cTn cut-off levels beneficial, there is an ongoing debate about the need for gender specific cut-offs. It has been described, that male patients show higher cTn levels than females [49, 50]. Knowing that diagnosis of MI in female patients is often more difficult due to e.g. atypical symptoms or a lack of ECG changes [57, 58] underlines the importance of cardiac biomarkers. Given the higher troponin values observed in healthy men, use of a single ULN cut-off for both genders might lead to an underdiagnosis of MI in female patients. Several authors published gender specific ULN for several cTn assays derived in healthy reference populations stating lower ULN for females than for men:

In two different studies Apple et al. derived ULN for several hs-cTn assays in large populations of apparently healthy individuals with respect to possible gender differences with higher ULN in males compared to females [59, 60]. Giannitsis et al. described gender specific ULN in an apparently healthy population for hs-cTnT with 14.5 ng/L in males compared to 10.0 ng/L in females [61]. This gender difference in hs-cTnT ULN was also seen by others. Here, the ULN was derived in three population based cohorts and subcohorts with regard to the presence of cardiovascular diseases. In all of the three cohorts as well as in the respective subcohorts, the derived ULN for hs-cTnT were higher in men compared to women [2].

These cited publications investigated potential gender specific ULN for several cTn assays in healthy subjects, but did not investigate the impact on diagnostic performance of such gender specific ULN in patients with suspected MI and therefore their clinical relevance.

Mueller-Hennesen et al. applied the gender specific ULN cut-offs for hs-cTnT derived by Saenger et al. [48, 56] to a cohort of patients with suspected MI to evaluate a possible impact on diagnostic or prognostic reclassification. As expected, an increase of the final diagnosis of MI was seen in female patients while a decrease was observed in men. Unfortunately, this increase in MI diagnoses was accompanied by an increase of false positive diagnoses of MI in female patients. Furthermore, use of

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**Table 4: Performance of different troponin assays in patients older and younger than 70 years.**

<table>
<thead>
<tr>
<th>Assay</th>
<th>Age</th>
<th>Cut-off</th>
<th>Sens. % (95% CI)</th>
<th>Spec. % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche hs-cTnT</td>
<td>≤70 years</td>
<td>ULN = 14 ng/L</td>
<td>88 (78–94)</td>
<td>86 (83–89)</td>
<td>44 (36–52)</td>
<td>98 (97–99)</td>
</tr>
<tr>
<td></td>
<td>&gt;70 years</td>
<td>ULN = 14 ng/L</td>
<td>98 (92–100)</td>
<td>49 (44–55)</td>
<td>38 (32–44)</td>
<td>99 (95–100)</td>
</tr>
<tr>
<td></td>
<td>&gt;70 years</td>
<td>ROC = 54 ng/L</td>
<td>79 (69–86)</td>
<td>96 (93–98)</td>
<td>86 (77–92)</td>
<td>93 (90–96)</td>
</tr>
<tr>
<td>Siemens Ultra s-cTni</td>
<td>≤70 years</td>
<td>ULN = 40 ng/L</td>
<td>87 (77–93)</td>
<td>92 (89–94)</td>
<td>56 (47–65)</td>
<td>98 (97–95)</td>
</tr>
<tr>
<td></td>
<td>&gt;70 years</td>
<td>ULN = 40 ng/L</td>
<td>92 (85–96)</td>
<td>83 (79–87)</td>
<td>71 (62–79)</td>
<td>97 (94–99)</td>
</tr>
<tr>
<td></td>
<td>&gt;70 years</td>
<td>ROC = 45 ng/L</td>
<td>92 (85–96)</td>
<td>88 (84–91)</td>
<td>70 (62–78)</td>
<td>96 (93–98)</td>
</tr>
</tbody>
</table>

Sensitivity (Sens.), specificity (Spec.), negative predictive value (NPV) and positive predictive value (PPV) of two different troponin assays in patients older or younger than 70 years, applying the upper limit of normal (ULN) as well as ROC optimized cut-offs (ROC). Modified according to Reiter et al. [54].

**Table 5: Performance of high sensitive cardiac troponin T in elderly patients.**

<table>
<thead>
<tr>
<th>Assay</th>
<th>Age</th>
<th>Cut-off</th>
<th>Sens. % (95% CI)</th>
<th>Spec. % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche hs-cTnT</td>
<td>&lt;70 years</td>
<td>ULN = 14 ng/L</td>
<td>91 (75–98)</td>
<td>88 (83–91)</td>
<td>50 (37–63)</td>
<td>99 (96–100)</td>
</tr>
<tr>
<td></td>
<td>≥70 years</td>
<td>ULN = 14 ng/L</td>
<td>96 (76–100)</td>
<td>51 (38–64)</td>
<td>42 (29–57)</td>
<td>97 (82–100)</td>
</tr>
<tr>
<td></td>
<td>≥70 years</td>
<td>ROC = 32.4 ng/L</td>
<td>96 (76–100)</td>
<td>77 (64–86)</td>
<td>61 (44–76)</td>
<td>98 (88–100)</td>
</tr>
</tbody>
</table>

Sensitivity (Sens.), specificity (Spec.), negative predictive value (NPV) and positive predictive value (PPV) of high sensitive troponin T (hs-TnT) in elderly patients compared to patients younger 70 years applying the upper limit of normal (ULN) as well as ROC optimized cut-offs (ROC). Modified according to Chenevier-Gobeaux et al. [42].
female specific cut-offs was associated with a negative impact on outcome based on the hs-cTnT level. Similar results for cTnI have been proposed by Keller et al. Gender specific cTnI ULN cut-offs were calculated in a population based cohort of apparently healthy individuals and subsequently applied to a cohort of patients with suspected MI. As anticipated more female patients would have been categorized as patients suffering from MI, but similar to the findings of Mueller-Hennesen et al. this increase of the diagnosis MI also led to an increase in the rate of false positive results [50]. In contrast Shah et al. could show an improvement in risk prediction (recurrent AMI or death) using a gender specific ULN. Women presenting with hs-cTnI levels between 16 ng/L, the gender-specific ULN for women, and 26 ng/L, the ULN without gender-specificity, showed an increased event rate compared to women presenting with a baseline hs-cTnI levels below the female specific ULN (23% vs. 4%, p < 0.001) [62].

**Benefit of using individual troponin cut-off levels**

In several patient populations such as patients with impaired renal function or elderly patients cTn levels are chronically increased in the absence of acute cardiac diseases or MI. This complicates the diagnosis of MI type I based on cTn levels upon admission. Three strategies are recommended to improve specificity of cardiac troponins and to improve the diagnostic accuracy. First, use of serial troponin measurements to differentiate chronic elevations from increased levels due to an acute event with respective rise and later fall in marker concentration. Second, incorporation of clinical parameters such as risk scores like the HEART score.

Third, use of individually optimized cut-offs. Here, optimized cTn cut-offs need to be derived for every single cTn assay. Therefore, prospective studies are in need for different cTn assays to derive and evaluate cTn cut-offs in specific patient groups such as for elderly patients.

While for patients with CKD and for elderly patients individual cTn cut-offs seem beneficial, there is an ongoing discussion on the use of gender-specific ULN. There is ample data showing that women have lower cTn values than men leading to the risk of underdiagnosis of MI type 1 if using a unified diagnostic ULN. Otherwise, a lower female ULN might increase false positive results. So, the use of gender specific ULN has to be the aim of future prospective studies.

**Non MI type 1 caused acute troponin elevations**

In addition to chronically elevated cTn levels in the absence of MI in some patient populations, an acute increase of cTn levels can occur in settings other than a MI type 1 (Figure 1). Such an acute increase in cTn can occur in conditions without myocardial necrosis e.g. in rhabdomyolysis or acute subarachnoid bleeding, but mainly an acute increase in cTn levels reflects a secondary ischemic imbalance resulting in myocardial necrosis and a release of cTn.

Due to the increased cTn levels, it can be quite difficult to correctly diagnose a MI type I in these patients. One of the conditions in which cTn levels can be increased in the absence of MI Type 1 that is often seen in the emergency room constituting a common differential diagnosis is a cTn increase due to prevalent atrial fibrillation (afib). Two studies recently investigated cTn levels in patients with suspected MI and afib [45, 63]. Both publications described that cTn levels in patients suffering from afib are more likely to be elevated in the absence of MI type 1. One study could show that a baseline hs-cTnI level below the ULN and a low change in Delta hs-cTnI level can rule-out patients with afib and suspected MI [63]. The other study proposed the use of a higher optimized cTn cut-off in patients with afib and suspected MI to improve specificity [45]. This further underlines the concept of using serial troponin measurements and individualized diagnostic thresholds to improve the specificity of cardiac troponin to identify MI type I.

**Addition of other biomarkers – amending cardiac troponins?**

Cardiac troponins are the gold standard in diagnosis of MI. Given the reduced specificity in specific conditions that accompanies the improvement in sensitivity, combination with of other biomarkers might further improve diagnostic accuracy. Within the current ESC guidelines, besides cTn two biomarkers are discussed to add diagnostic information in certain clinical settings [22].

Copeptin, released into circulation in the same amount as vasopressin upon processing of their precursor, has been described to be a good risk predictor in MI patients [64]. It has been further investigated, if Copeptin might also serve as diagnostic biomarker for MI. Several studies tested the diagnostic performance of Copeptin in
patients with suspected MI in addition to cardiac troponin and observed, that Copeptin provided good sensitivity with only moderate MI specificity. The combination of troponin and Copeptin is able to improve early rule-out of MI type 1 [65–67]. The current ESC guidelines recommend the use of Copeptin to improve rule-out especially if no hs-cTn assays are available [22].

One important aspect of the kinetics of cardiac troponins is that the decline in concentration after an MI is much slower than the initial rise after myocardial necrosis. This makes it difficult e.g. to identify a re-infarction using cTn within days or even the first weeks after the initial event.

In the era before hs-cTn became the biomarkers of choice in the diagnosis of MI, creatinine kinase (CK) and creatinine kinase myocardial band (CK-MB) were major cornerstones in identification of MI. As CK-MB is sufficiently cardio-specific and declines more rapidly after MI compared to cTn, the current ESC guidelines recommend CK-MB as a diagnostic instrument in the detection of myocardial re-infarction [22].

Conclusions

At least since hs-cTn assays made their way into the clinical routine they have become the gold standard to diagnose MI without ST-segment elevations (NSTEMI). The standard use of hs-cTn assays in patients with suspected MI is recommended in the current ESC guidelines [22]. Different algorithms to rapidly rule-in and rule-out MI have been derived and recently proven to be safe and effective. The downside of more sensitive cardiac troponin assays with their unquestionable improvement of early diagnosis of MI type 1 is the increase of patients with cTn elevations due to non-MI conditions. To avoid misdiagnosis of MI, increased hs-cTn levels need to be interpreted cautiously in every patient within his clinical context.

As an increase of cTn levels in conditions other than MI type 1 is seen quite regularly, the diagnosis of MI type 1 in patients presenting with symptoms suggestive of an MI and additional conditions which could explain an increase in cTn diagnosis can be challenging. Here, serial troponin measurement can help to dissect chronic from acute increase in troponin concentration. Additionally, use of individual diagnostic thresholds adds diagnostic information that should be taken into account by the treating physician. Therefore, use of cTn ULN cut-offs, optimized for several comorbidities and conditions might add important further diagnostic power to hs-cTn assays in the diagnosis of MI type 1 reducing the number of mis-diagnosed patients.

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