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Novelties in the clinical use of high-sensitivity cardiac troponin – new assays, prediction of myocardial infarction by single measurements, and its use in the elderly

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Summary

In the evaluation of patients with symptoms suggestive of acute coronary syndrome (ACS), biomarker testing is best established for cardiac troponins (cTn). As a heart-specific marker of myocardial injury, cTn complements the clinical assessment and the 12-lead electrocardiogram in the diagnosis of ACS.

With the introduction of high-sensitivity cardiac troponin (hs-cTn) assays, reliable measurement of cTn concentrations in the normal range became possible, which increased diagnostic accuracy for myocardial infarction at presentation. Recent studies showed that single measurements of hs-cTn concentrations allow prediction of myocardial infarction with high probability and identification of high-risk patients who may benefit from early rhythm monitoring and/or invasive management. Novel hs-cTn assays are continuously being developed and clinically validated. Their clinical use embedded in diagnostic strategies facilitates the early triage of patients presenting with chest pain to the emergency department. Accordingly, the European Society of Cardiology recommends such strategies with a class I recommendation. Newer evidence suggest that the clinical use of these strategies is also safe in the elderly, a patient population with high prevalence of ACS.

Keywords: *high-sensitivity cardiac troponin, novel assay, ESC guidelines, acute coronary syndrome, myocardial infarction, prediction of myocardial infarction, myocardial infarction in the elderly*

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Clinical use of high-sensitivity cardiac troponin

Annually, millions of patients present with symptoms suggestive of acute coronary syndrome (ACS) to emergency departments worldwide [1, 2]. These patients present with a wide variety of symptoms, such as chest pain, shortness of breath, general weakness, nausea and vomiting or even fatigue. The inconsistent clinical picture of patients with ACS challenges physicians in making an appropriate diagnosis [3–5]. Although information on demographics, cardiovascular risk factors, chest pain characteristics and physical examination can assist disposition decisions, they are known to be insufficient by themselves to identify who does have an ACS [6–13]. Only a minority of patients may have objective evidence of a clear-cut diagnosis, and most present with nonspecific symptoms [14]. The majority will ultimately be found not to have ACS, but rather symptoms caused by noncardiac and often benign disorders such as musculoskeletal pain or gastroesophageal reflux [1].

In patients presenting with possible ACS, high-sensitivity cardiac troponin (hs-cTn) measurement complements clinical assessment and the 12-lead electrocardiogram (ECG) in diagnosis and risk stratification. Measurement of hs-cTn as a marker of myocardial injury is mandatory in all patients with suspected ACS [1, 2, 15–24]. However, it should not delay early coronary angiography in patients with clear ST-elevations in the ECG.

If the clinical presentation is compatible with myocardial ischaemia [25], then a significant rise and/or fall of cTn above the 99th percentile indicates myocardial infarction (MI). In patients with MI, levels of cardiac troponin rise rapidly after symptom onset (usually within 1 hour if hs-cTn assays are used) and remain elevated for a variable period of time (usually several days) [2, 26–30]. Advances in technology have led to a refinement in cTn assays and have improved the ability to detect and quantify cardiomyocyte injury [2, 26–36]. Novel hs-cTn assays are continuously being developed and clinically validated, and show comparable diagnostic performance to the established hs-cTn assays [37–40]. Data from large multicentre studies have

consistently shown that hs-cTn assays increase diagnostic accuracy for MI at the time of presentation as compared with conventional assays, especially in patients presenting early after chest pain onset, and allow a more rapid "rule-in" and "rule-out" of MI [1, 2, 18, 34, 41, 42].

The 2015 European Society of Cardiology (ESC) guidelines [2] recommend the implementation of hs-cTn assays and their use in combination with a diagnostic strategy: a 0/3h-algorithm with a second sample after 3 hours or a 0/1h-algorithm with a second sample after 1 hour. If the diagnosis is still uncertain or clinical suspicion for the presence of ACS remains high, cTn testing at later time-points is recommended. Furthermore, cTn concentrations should always be used in conjunction with the clinical presentation and history as well as with the 12-lead ECG [2].

Novel high-sensitivity cardiac troponin assays

Definition of "high-sensitivity"

The term "high-sensitivity" implies that an assay detects lower cTn concentrations than conventional, less-sensitive cTn assays. Novel hs-cTn assays have to fulfil predefined requirements that are defined by the International Federation of Clinical Chemistry (IFCC). According to their definition, novel cTn assays can be labelled "high-sensitive", if: (i) the % coefficient of variation at the 99th percentile value is ≤10% and (ii) if measurable concentrations are attainable with at a concentration above the assay's limit of detection for at least 50% of healthy individuals [43].

Clinical validation of novel assays

During the last decade, two hs-cTn assays (hs-cTnT-Elecsys and hs-cTnI-Architect) have been extensively investigated in large diagnostic studies, including the successful derivation and validation of rapid 0/1h-algorithms [1, 2, 17, 21, 29, 42, 44]. Within the last two years, several novel hs-cTn assays have been developed and most of them are already cleared by the Food and Drug Administration (FDA) for clinical use in the United States [37–40]. A recent study investigating patients with suspected MI who were enrolled in an international multicentre study at 12 centres in 5 European countries (APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation, ClinicalTrials.gov number NCT00470587) aimed to clinically validate one of the novel hs-cTnI assays, the hs-cTnI-Access assay [38]. Its diagnostic accuracy was directly compared with the established hs-cTn assays: hs-cTnT-Elecsys and hs-cTnI-Architect. In addition, an assay-specific 0/1h-algorithm following the recommendation by the ESC (fig. 1) that used hs-cTnI-Access concentrations at ED presentation and absolute 1h-changes for the very early triage of patients towards rule-out or rule-in of MI was derived and validated [38].

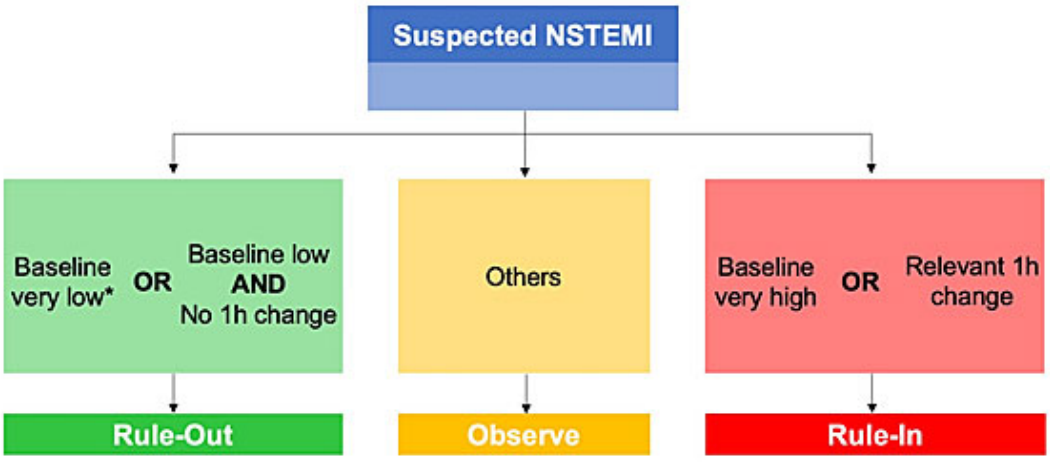
Diagnostic accuracy for myocardial infarction

An established approach to assess the discriminative power of hs-cTn assays to distinguish between the presence or absence of non-ST-segment elevation myocardial infarction (NSTEMI) is the calculation of the area under the curve (AUC) provided by receiver operating characteristic curves (ROC). In a recent validation study of the hs-cTnI-Access assay [38], the diagnostic accuracy of measurements obtained at presentation was 0.95 (95% confidence interval [CI] 0.94–0.96) for the hs-cTnI-Access assay, which was comparable to the accuracy of the hs-cTnT-Elecsys (0.94, 95% CI 0.93–0.95; p = 0.12) and even higher than that of hs-cTnI-Architect (0.92, 95% CI 0.91–0.94; p <0.001; fig. 2A). Similar findings emerged in early presenters (patients presenting within 3 hours after chest pain onset; fig. 2B). For hs-cTnI-Access, the AUCs for concentrations at 1, 2, and 3 hours were 0.97 (95% CI 0.96–0.99), 0.98 (95% CI 0.97–0.99) and 0.98 (95% CI 0.97–0.99), respectively (table 1). The use of sex-specific cut-off concentrations, whose clinical value is still a matter of debate, increased sensitivity and negative predictive value (NPV) in women at the cost of specificity and positive predictive value (PPV). For men, specificity and PPV increased at the cost of sensitivity and NPV.

Derivation and validation of an hs-cTnI-Access-specific 0/1h-algorithm

Following the concept of the current hs-cTn 0/1h-algorithms suggested by the ESC [2] (fig. 1), the authors de-

Figure 1: Concept of the European Society of Cardiology 0/1h-algorithm using high-sensitivity cardiac troponin for rule-out and rule-in of non-ST-segment myocardial infarction (NSTEMI) in patients presenting to the emergency department. * If chest pain onset >3 hours before presentation to the emergency department. From: Boeddinghaus J, et al. Clin Chem. 2019;65:893–904 [38], reprinted with permission.



veloped a novel hs-cTnI-Access-specific 0/1h-algorithm in a derivation validation design by randomly (1:1) assigning patients to either a derivation or a validation cohort. It was predefined that selected cut-off criteria should at least achieve an NPV of 99.0% for rule-out and a PPV of 70% for rule-in of MI.

After the derived optimal cut-off criteria (fig. 3A) were applied to the internal validation cohort, 409/680 patients (60%) could be classified as rule-out with a corresponding NPV of 99.8% (95% CI 98.6–100) and a sensitivity of 98.9% (95% CI 94.3–99.8; fig. 3B). The 0/1h-algorithm classified 92/680 patients (14%) as rule-in with a corresponding PPV of 73.9% (95% CI 64.1–81.8) and a specificity of 95.9% (95% CI 94.0–97.2). Overall, the hs-cTnI-Access 0/1h-algorithm allowed a definite diagnosis after 1 hour in 501/680 patients (74%; either rule-out or rule-in). The remaining 179/626 patients (26%) were classified "to observe" with an MI prevalence of 15%. The diagnostic performance was found to be comparable to that provided by the current ESC 0/1h-algorithms using hs-cTnT-Elecsys and hs-cTnI-Architect [38].

Predicting myocardial infarction with high-sensitivity cardiac troponin

With the introduction of hs-cTn assays, the interpretation of cTn concentrations changed. In contrast to conventional cTn assays, hs-cTn assays exactly quantify the amount of cardiomyocyte injury [1, 2, 36, 41]. Concentrations of cTn measured with an hs-cTn assay should be interpreted as a quantitative variable and not in a binary fashion using the terms "negative" and "positive" as for a pregnancy test [1,

Figure 2: Receiver operating characteristic curves describing the diagnostic performance of the three high-sensitivity cardiac troponin (hs-cTN) assays at presentation for the diagnosis of non-ST-segment elevation myocardial infarction in (A) all patients and (B) patients presenting early with a chest pain onset within the last 3 hours. AUC = area under the receiver operating characteristic curve; CI = confidence interval. From: Boeddinghaus J, et al. Clin Chem. 2019;65:893–904 [38], reprinted with permission.

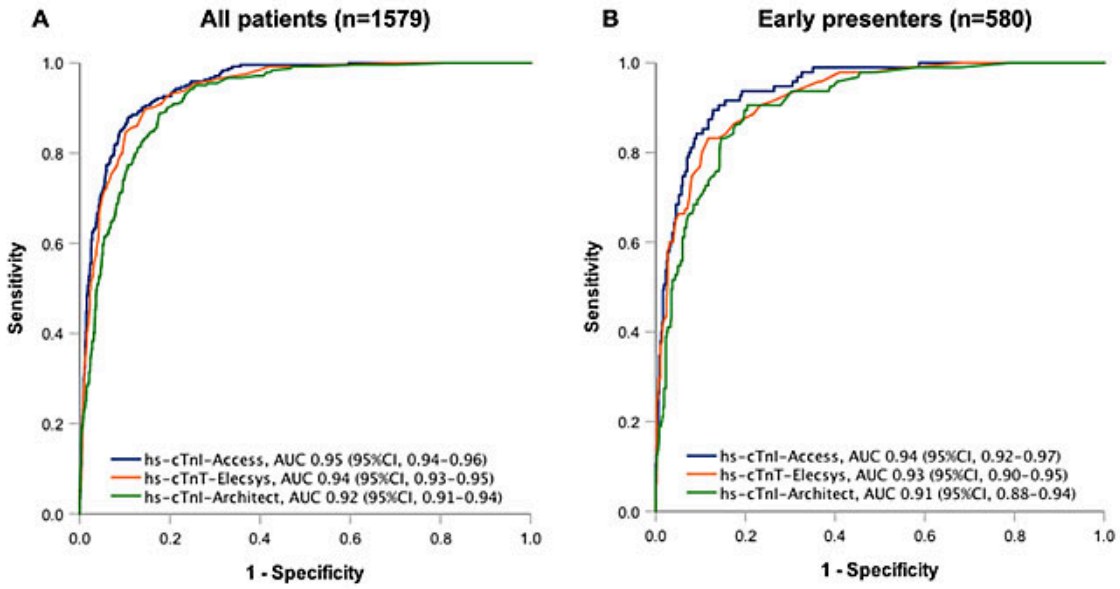


Table 1: Diagnostic accuracy expressed as areas under the receiver operating characteristic curves (with 95% confidence intervals) for single concentrations, absolute changes and their combination during serial sampling. From: Boeddinghaus J, et al. Clin Chem. 2019;65:893–904 [38], reprinted with permission.

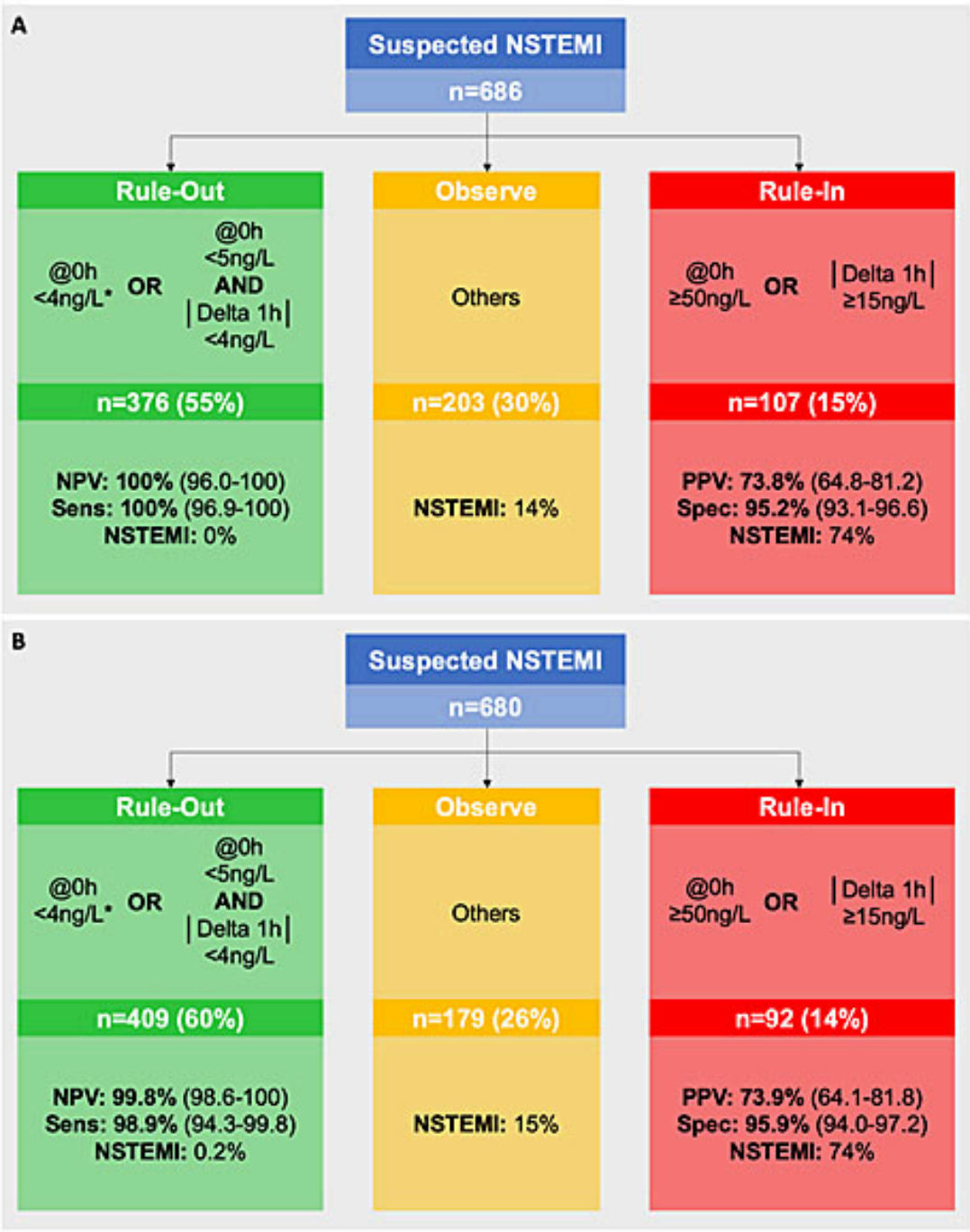
	Diagnostic accuracy of hs-cTnI-Access for single concentrations, absolute changes and their combination during serial sampling ROC AUC (95% CI)	Diagnostic accuracy of hs-cTnT-Elecsys for single concentrations, absolute changes and their combination during serial sampling ROC AUC (95% CI)	Diagnostic accuracy of hs-cTnI-Architect for single concentrations, absolute changes and their combination during serial sampling ROC AUC (95% CI)	Diagnostic accuracy of combination of hs-cTnI-Access and hs-cTnT-Elecsys for single concentrations, absolute changes and their combination during serial sampling - ROC AUC (95% CI)
hs-cTn at presentation	0.95 (0.94–0.96)	0.94 (0.93–0.95)	0.92 (0.91–0.94)	0.94 (0.92–0.95)
hs-cTn after 1 hour	0.97 (0.96–0.99)	0.96 (0.95–0.97)	0.95 (0.93–0.96)	0.95 (0.94–0.97)
hs-cTn after 2 hours	0.98 (0.97–0.99)	0.96 (0.95–0.97)	0.95 (0.94–0.96)	0.96 (0.95–0.97)
hs-cTn after 3 hours	0.98 (0.97–0.99)	0.96 (0.94–0.98)	0.96 (0.95–0.98)	0.97 (0.95–0.99)
hs-cTn 1h-delta	0.96 (0.93–0.99)	0.91 (0.88–0.93)	0.92 (0.90–0.94)	0.93 (0.91–0.95)
hs-cTn 2h-delta	0.96 (0.93–0.99)	0.94 (0.92–0.96)	0.91 (0.89–0.93)	0.95 (0.93–0.97)
hs-cTn 3h-delta	0.97 (0.95–0.99)	0.95 (0.92–0.98)	0.95 (0.91–0.98)	0.94 (0.89–0.99)
hs-cTn at presentation and 1h-delta	0.96 (0.95–0.97)	0.96 (0.95–0.97)	0.94 (0.93–0.96)	0.96 (0.95–0.97)
hs-cTn at presentation and 2h-delta	0.96 (0.95–0.97)	0.97 (0.96–0.98)	0.93 (0.92–0.95)	0.97 (0.96–0.98)
hs-cTn at presentation and 3h-delta	0.98 (0.96–0.99)	0.97 (0.95–0.99)	0.96 (0.94–0.98)	0.97 (0.95–0.99)

AUC = area under the curve; CI = confidence interval; Hs-cTn = high-sensitivity cardiac troponin; ROC = receiver operating characteristic curve

36]. From a diagnostic perspective, it is highly inappropriate to label a patient as "cTn-positive", as this would lump together patients with only mildly elevated cTn levels barely above the 99th percentile and an associated PPV for NSTEMI of only about 40–50%, and patients with markedly elevated cTn levels (e.g., about five times above the 99th percentile) and an associated PPV of 90%. A general rule to remember: the higher the cTn level, the higher the likelihood of the presence of MI.

The ESC 0/1h-algorithms using hs-cTn assays triage patients towards rule-in of MI if they present with either very high baseline cTn concentrations (direct rule-in) or a relevant 1-hour change in cTn concentrations [2]. The assay-specific cut-off criteria for rule-in were defined to give a high PPV of >70%. Although guidelines recommend the use of two measurements of cTn in the early diagnosis of MI to quantify early hs-cTn changes, a recent pilot study questioned the general need for serial sampling for rule-in of MI in some patients [45]. Since the concept of rapid rule-in of MI based on a single measurement of cTn has enormous medical and economic appeal, a recently published large multicentre diagnostic study aimed to determine the cTn concentrations necessary to achieve a PPV of

Figure 3: Performance of the high-sensitivity cardiac troponin I Access 0/1h-algorithm in (A) the derivation cohort and (B) validation cohort. |Delta 1h| denotes absolute (unsigned) change of high-sensitivity cardiac troponin I within 1 hour. NSTEMI = non-ST-elevation myocardial infarction; NPV = negative predictive value; Sens. = sensitivity; PPV = positive predictive value; Spec. = specificity. * If chest pain onset >3h before presentation to the emergency department. From: Boeddinghaus J, et al. Clin Chem. 2019;65:893–904 [38], reprinted with permission.



75% or more for MI using five different s-cTn and hs-cTn assays [46].

Final diagnoses according to high-sensitivity cardiac troponin concentrations at presentation

Final diagnoses of patients presenting with chest pain to the ED changes with increasing hs-cTn at baseline. The higher the hs-cTnT concentration at presentation, the higher the likelihood of MI. The number of patients with non-coronary cardiac disease remains mainly unchanged, whereas non-cardiac conditions and unstable angina decrease with increasing hs-cTnT concentrations (fig. 4) [46].

Positive predictive values for myocardial infarction of different high-sensitivity cardiac troponin T concentrations at presentation

The resulting PPVs for prediction of MI increased from 46.5% (95% CI 43.6–49.4) for hs-cTnT >14ng/l to 78.9% (95% CI 74.7–82.5) at >52ng/l (p <0.001), whereas PPVs in higher hs-cTnT strata remained largely unchanged. Similar findings emerged using the four (h)s-cTnI assays. Assay-specific cut-offs to achieve predefined PPVs of 70% and 75% or greater were highly variable among four different cTnI assays, and in general at least twice as high as the necessary cTnT concentration (table 2) [46].

The ability to achieve a high enough PPV with a single blood draw might reduce the time needed for the management decisions associated with the triage towards rule-in of MI, including admission to a monitored unit and, in general, early coronary angiography [1, 2, 47]. The vast majority of patients triaged towards rule-in with diagnoses other than MI, such as myocarditis, tako-tsubo cardiomyopathy and acute heart failure, will still require treatment in a monitored unit. Similarly, the vast majority of patients triaged towards rule-in with diagnoses other than MI still may require coronary angiography for a reliable diagnosis. The acceleration and simplification of patient pathways by decision making based on a highly increased cTn concentration obtained from a single blood draw may be associated with improved medical and economic outcomes [1, 2, 47].

The authors clearly state that serial sampling for cTn until the peak cTn concentration has been reached still should

Figure 4: Final diagnoses according to high-sensitivity cardiac troponin T concentrations at presentation. UA = unstable angina; AMI = acute myocardial infarction. From: Boeddinghaus J, et al. Clin Chem. Clin Chem. 2019;65:437–50 [46], reprinted with permission.

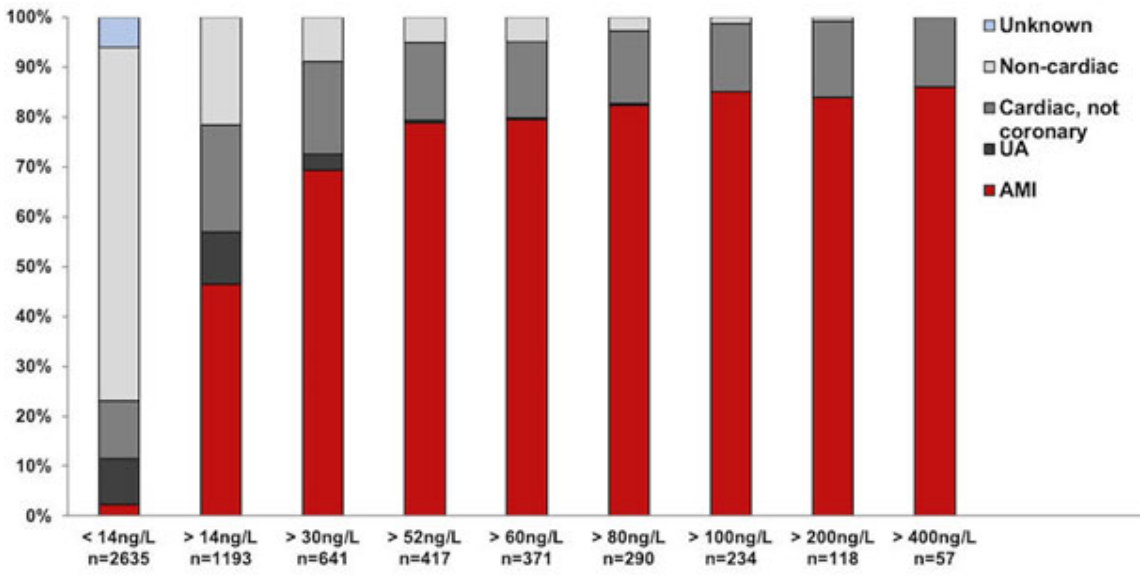


Table 2: Assay-specific cut-off concentrations to achieve predefined positive predictive values for myocardial infarction. From: Boeddinghaus J, et al. Clin Chem. Clin Chem. 2019;65:437–50 [46], reprinted with permission.

		Number of patients (%)
hs-cTnT Elecsys	Cut-off >30ng/l for PPV of about 70% or greater	641 (17%)
	Cut-off >52ng/l for PPV of about 75% or greater	417 (11%)
hs-cTnI Architect	Cut-off >100ng/l for PPV of about 70% or greater	411 (12%)
	Cut-off >300ng/l for PPV of about 75% or greater	246 (7%)
hs-cTnI Vista	Cut-off >100ng/l for PPV of about 70% or greater	245 (13%)
	Cut-off >200ng/l for PPV of about 75% or greater	177 (9%)
hs-cTnI Beckman Coulter	Cut-off >40ng/l for PPV of about 70% or greater	178 (16%)
	Cut-off >80ng/l for PPV of about 75% or greater	138 (13%)
s-cTnI Ultra	Cut-off >60ng/l for PPV of about 70% or greater	415 (15%)
	Cut-off >80ng/l for PPV of about 75% or greater	364 (14%)

PPV = positive predictive value

remain the standard of care, as it is an accepted method of estimating infarct size, is still required to differentiate acute from chronic cTn elevations and is essential for the diagnosis of MI [1, 2, 47]. However, waiting for the results of serial sampling in case of a highly elevated cTn concentration at presentation should not cause a delay in the management decision necessary early in the ED.

According to the findings of the study, serial sampling does not seem necessary for rule-in of MI and concurrent decision making in about 10% of patients with suspected MI at presentation, as it only marginally increases the PPV for MI and not in a statistically or clinically significant way. The hs-cTnT/I concentration achieving a high enough PPV for immediate triage towards rule-in is assay-dependent and highly variable. Physicians need to familiarise themselves in detail with the hs-cTnT/I assay(s) used in their institution to best be able to use these assays.

Clinical use of high-sensitivity cardiac troponin in the elderly

Irrespective of the presence or absence of MI, age is known to substantially impact on hs-cTnT and hs-cTnI blood concentrations [48–57]. As a result of a higher prevalence of cardiac and noncardiac comorbidities such as chronic heart failure, tachyarrhythmias and renal failure, mildly elevated cTn blood concentrations are commonly seen in the elderly without apparent ischaemic symptoms [2, 47–57]. To date, the impact of age on the diagnostic performance of the ESC 0/1h-algorithms is not well understood.

A recent study addressed this gap in knowledge by investigating the impact of age on the performance of the ESC 0/1h-algorithms in a large multicentre diagnostic study (APACE) using central adjudication [34]. Age-specific findings and aged-optimised alternative cut-off concentrations for the elderly were derived and validated in two large and well-characterised external diagnostic studies (Biomarkers in Acute Cardiac Care (BACC, first validation cohort) [58] and High-sensitivity cardiac Troponin T assay for RAPID rule-out of AMI (TRAPID-AMI, second validation cohort). Patients were stratified by age twice, once into three equally large cohorts (55 years [young], ≥55 to <70 years [middle-aged], ≥70 years [old]) and once into decades of age.

High-sensitivity cardiac troponin concentrations at presentation according to age and final diagnoses

Hs-cTnT/I concentrations at presentation showed a moderate correlation with age ($\rho = 0.6$ for hs-cTnT and $\rho = 0.49$ for hs-cTnI, both $p < 0.001$). Patients with NSTEMI had comparable hs-cTnT/I concentrations in the three age strata, but in those with other causes of acute chest discomfort, hs-cTnT and hs-cTnI concentrations were significantly higher in older patients [34]. The authors explain this finding by the higher prevalence of pre-existing cardiovascular disorders and their association with chronic myocardial injury in older patients.

Diagnostic accuracy of high-sensitivity cardiac troponin T and I for myocardial infarction

Diagnostic accuracy for MI of hs-cTnT/I concentrations at presentation decreased with increasing age because of a larger overlap in hs-cTnT and hs-cTnI concentrations between NSTEMI and other causes of acute chest discomfort. In the three age strata (young/middle-aged/old), AUCs of hs-cTnT at presentation were 0.96 (95% CI, 0.94–0.98), 0.93 (95% CI, 0.91–0.95) and 0.89 (95% CI 0.87–0.91), respectively, and AUCs of hs-cTnI were 0.95 (95% CI 0.93–0.97), 0.92 (95% CI 0.90–0.94) and 0.87 (95% CI 0.85–0.90), respectively [34].

Diagnostic performance of the ESC high-sensitivity cardiac troponin 0/1h-algorithms according to age

Age was found to substantially impact on the diagnostic performance of the ESC 0/1h-algorithm: safety remained very high in older patients, but the percentage of patients classified as rule-out, the specificity among patients classified as rule-in and, particularly, overall efficacy decreased with higher age. Consequently, older patients more often remained in the observe zone (two times more than middle-aged and four times more than young patients) requiring additional diagnostic testing including a 3-hour cTn measurement and cardiac imaging. Owing to an increase in MI prevalence with age, PPV remained high in older patients (fig. 5A) [34].

Derivation of alternative cut-off criteria for the ESC high-sensitivity cardiac troponin 0/1h-algorithms for use in the elderly

Use of individualised slightly higher cut-offs in older patients maintained very high safety of rule-out, increased specificity of rule-in, reduced overall efficacy for hs-cTnT, while maintaining efficacy for hs-cTnI (fig. 5B) [34]. Accordingly, the use of slightly higher cut-off concentrations may be considered, particularly if hs-cTnI is used. However, although age-specific cut-offs increased the specificity and PPV for rule-in of MI, applying them in busy

Figure 5A: Diagnostic performance of the ESC high-sensitivity cardiac troponin T 0/1h-algorithm in patients stratified according to age into decades.

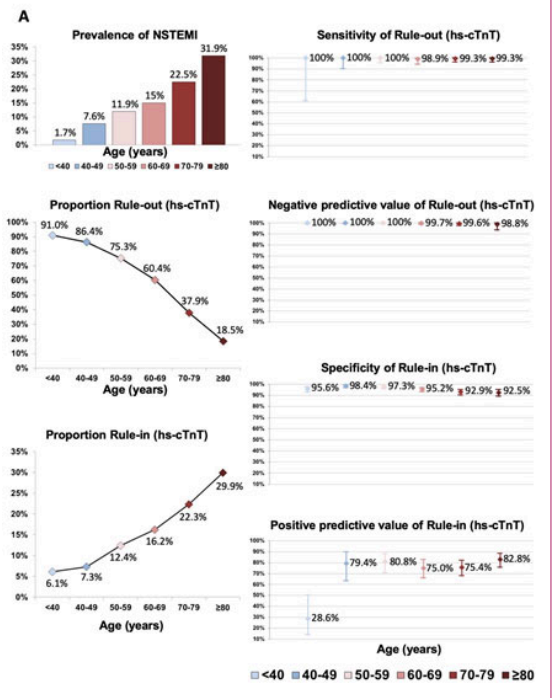
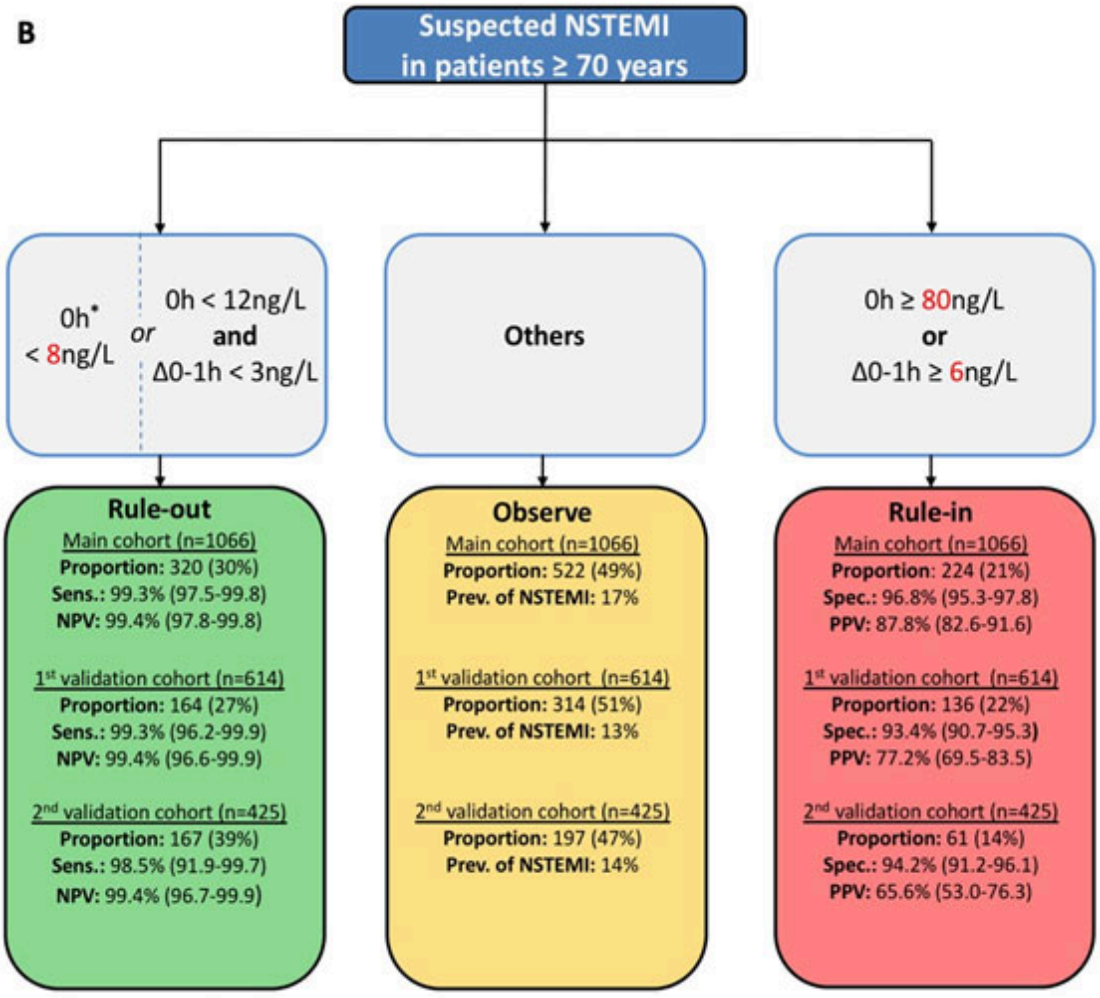


Figure 5B: Diagnostic performance of the ESC high-sensitivity cardiac troponin T 0/1h-algorithm using modified cut-off criteria for use in older patients (≥70 years). Red numbers indicate modified cut-off values that differ from the official cut-off criteria. * If chest pain onset >3 hours; delta = unsigned change within the first hour; NSTEMI = non-ST-segment elevation myocardial infarction. Sens. = sensitivity; NPV = negative predictive value; Prev. = prevalence; Spec. = specificity; PPV = positive predictive value. hs-cTnT = high sensitivity cardiac troponin T. From: Eur Heart J. 2018;39(42):3780–94 [34], reprinted with permission.



EDs could lead to confusion among physicians because of greater complexity without finally improving patients' management. Furthermore, it is most important to safely rule-out an MI in the ED. As suggested by the data, the rule-out performance of the ESC 0/1h-algorithms could not further be increased by using age-specific cut-off combinations, emphasising the use of the recommended cut-offs irrespective of age. Use of sex-specific cut-off criteria versus modified cut-off criteria in older patients did not further increase the overall diagnostic performance of both ESC 0/1h-algorithms. As well as age, the time from chest pain onset, sex, and renal function have also been shown to affect hs-cTnT and hs-cTnI concentrations. Although preliminary evidence suggests that the effect of these additional confounders overall is smaller than that of age [1, 2, 48, 51, 59], computerised integration of all confounders might be the most accurate approach once convenient physician / information technology interfaces become available.

Overall, the safety of the ESC 0/1h-algorithms remains very high in the elderly, but increasing age significantly reduces the overall efficacy and the accuracy of rule-in. Alternative slightly higher cut-off concentrations may therefore be considered for older patients, particularly if using hs-cTnI.

Conclusions

Biomarker research and especially the field of hs-cTn is progressing fast. The introduction of new hs-cTn assays may have important clinical implications for clinical laboratories that choose to use hs-cTn assays in practice, providing the benefits of hs-cTn and the 0/1h-algorithms to their patients presenting with suspected MI. Adoption of current clinical practice guideline recommendations without the logistical challenges and costs of introducing an additional analyser exclusively for the measurement of hs-cTn will be of economic value to those institutions. Use of hs-cTn assays improves the very early rule-in of MI. In patients presenting with highly elevated cTn concentrations, serial sampling does not seem necessary for predicting MI and concurrent decision making, as it only marginally increases the PPV. The clinical application of the ESC 0/1h-algorithms in all-comers with chest pain is safe and

effective. As a result of a higher prevalence of co-morbidities such as chronic heart failure, tachyarrhythmias, and renal failure, mildly elevated cTn concentrations are common in the elderly. Therefore, age has a major impact on the overall diagnostic performance of the ESC 0/1h-algorithms. Safety for rule-out remains high, whereas the percentage of patients assigned towards rule-out, the specificity among patients triaged towards rule-in and particularly overall efficacy decreased. Use of slightly higher cut-off concentrations for rule-in of MI may be considered, particularly if using hs-cTnI, but needs to be balanced against a greater complexity.

Swiss Amgen Research Award 2019
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