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Fast 0/1-h algorithm for detection of NSTEMI: are current high-sensitivity cardiac troponin assays fit for purpose? An EQA-based evaluation

Abstract

Background: High-sensitivity cardiac troponin T/I (hs-cTnT/I) assays have improved analytical sensitivity for the detection of myocardial infarction (MI). To gain clinical specificity and sensitivity, interpretation of changes in cTn concentrations over time is crucial. The 2015 ESC NSTEMI guideline defines absolute delta values as additional rule-in and rule-out criteria for MI. A critical assumption for application of this rule is that total analytical imprecision within the delta period, including inter-instrument bias, is comparable to analytical imprecision in the validation studies.
Methods: Data from the Dutch External Quality Assessment Scheme (EQAS) were used to calculate inter-instrument bias and estimate imprecision for the measuring range where the proposed delta values are relevant: for Roche Elecsys hs-cTnT, 5–52 and 5–12 ng/L; for Abbott Architect hs-cTnI, 2–52 and 2–5 ng/L for rule-in and rule-out, respectively.
Results: For Elecsys, the median inter-instrument bias is 0.3 ng/L (n = 33 laboratories), resulting in reference change values (RCVs) of 3.0 and 1.7 ng/L, respectively, for rule-in and rule-out with imprecision as claimed by the manufacturer. With RCVs smaller than the guideline's

delta thresholds, 100% of the laboratories have adequate specifications. RCVs for rule-in/rule-out increased to 4.6 ng/L/2.5 ng/L, respectively, with individual imprecisions as estimated from EQA data, resulting in 64% and 82% of laboratories with adequate specifications. For Architect, 40% of instruments (n = 10) might falsely qualify the result as clinically relevant; hence, inter-instrument bias could not be determined.
Conclusions: We advise laboratories that use the fast 0/1-h algorithm to introduce stringent internal quality procedures at the relevant/low concentration level, especially when multiple analyzers are randomly used.

Keywords: analytical specifications; cardiac troponin; diagnosis; EQAS; high-sensitivity methods; myocardial infarction.

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Introduction

Cardiac troponins (cTn) are the most specific markers today for cardiomyocyte necrosis and consequently for the diagnosis of acute myocardial infarction (MI). Accordingly, diagnosis of MI is defined as the detection of an increase and/or decrease of cTn concentrations with at least one value above the 99th percentile of the upper reference limit (myocardial injury) and at least one of five symptoms/observations of ischemia [1]. While for ST-segment elevation myocardial infarction (STEMI) diagnosis is based largely on ECG monitoring, for non-ST elevation myocardial infarction (NSTEMI) cTn is key to diagnosis [2, 3].

Introduction of high-sensitivity assays resulted in earlier detection of myocardial injury in patients presenting with chest pain [4, 5], being defined as able to measure cTn concentrations with a CV ≤10% at the 99th percentile URL and concentrations at/above the level of detection (LoD) for >50% of healthy individuals [6, 7]. However, the consequence of high-sensitivity measurements is that cTn is also detected in patients with other conditions such as stable angina or even healthy persons [8, 9]. Therefore, considering serial changes of cTn concentrations is essential to gain specificity for MI.

To interpret a rise/fall in biomarker concentrations, generally the reference change value (RCV) is used [10], meaning that the change in cTn concentrations must exceed the combined intra-individual biological variation (CV_i) and analytical variation (CV_a) to be clinically relevant. Biological variation for cTn is difficult to determine as the healthy population has undetectable or very low concentrations and thereby seemingly unpredictable analytical variation. An increase of 20% (based on >3 times CV_a 5–7%) on top of elevated baseline concentrations is generally considered to be clinically relevant [11, 12] but is not valid under the 99th percentile because of poorer analytical performance of the assay.

Currently, the 2015 ESC guideline proposes a fast 0/1-h algorithm with specific rule-out and rule-in criteria [2]. For three assays (Elecsys hs-cTnT, Architect hs-cTnI and Dimension Vista hs-cTnI), absolute values for clinically relevant changes were determined and clinically validated [13–17]. The algorithm proposes a delta value of ≥5 ng/L for Elecsys hs-cTnT and 6 ng/L for Architect hs-cTnI as an additional rule-in criterion [2]. An additional rule-out criterion is a delta value of <3 ng/L for Elecsys and <2 ng/L for Architect, but is only valid for a small patient group with initial cTn values of 5–12 and 2–5 ng/L, respectively. For Dimension Vista hs-cTnI, a precommercial research assay was used [16]; therefore, this assay is not further discussed. For application of these rules, it is critical that the total analytical imprecision within the 1-h period is not larger than the imprecision in the core laboratories measuring cTn in the derivation/validation studies that defined the delta values. When applying the RCV formula, these delta values define specific maximum allowable imprecisions. Moreover, many laboratories randomly present samples to more than one instrument, meaning that the inter-instrument bias must also be taken into account. Thus, laboratories implementing the 0/1-h algorithm need to comply with strict analytical performance specifications including inter-instrument bias. The Dutch External Quality Assessment Schemes (EQAS) coordinated by the SKML obtains analytical performance data from >95% of medical laboratories across the country at the instrument level and therefore allows the analysis of inter-instrument bias. The aim of this study was to investigate whether EQAS data can be used to evaluate adherence to this algorithm in terms of inter-instrument bias and imprecision, and secondly whether laboratories in the Netherlands in general and individually are able to comply with these demanding analytical specifications.

Materials and methods

Samples

Data from the Dutch EQAS organization (SKML) participants for hs-cTn were extracted from surveys performed in the period 2015–2017. Hs-cTn (T/I) was evaluated by four rounds of six samples of fresh frozen sera derived from pooled patient samples (obtained in agreement with the principles of the Declaration of Helsinki) and concluded by a yearly report (total n = 24 samples; 12 blinded duplicates used for post-hoc stability confirmation). Every participant can send in results for several instruments. For the Elecsys hs-cTnT assay (Roche, ref 05092744/190 [regular] and 05092728/190 [STAT]), 94 and 102 different instruments participated in 2015/2016, respectively, as measured on Cobas 6000/8000, Elecsys and Modular systems. For the Architect STAT hs-cTnI (Abbott Laboratories, ref 3P25), results were submitted for eight of 10 instruments in 2015/2016, measured on Architect I2000/Ci8200 systems. See Table 1 for an overview of the number of samples per relevant concentration range for cTnT/cTnI. Results from 2017 were excluded as not enough EQA samples were within the algorithm's relevant range. Only instruments that participated in all four rounds of the yearly scheme were included. Instruments with both duplicates missing for a given level in the relevant range were excluded.

Data analysis

Bias and imprecision were calculated analogous to the Multi Sample Evaluation (MUSE) scoring system as applied by the SKML for their standard respectively year reports [18]. Outliers were excluded based on curve fitting for all laboratories combined and against

Table 1: EQA samples.

Survey	Number of samples	cTnT		cTnI	
		~5–12 ng/L range samples	~5–52 ng/L range samples	~2–5 ng/L range samples	~2–52 ng/L range samples
2015	24 (12 duplicates)	6	8	4	6
2016	24 (12 duplicates)	6	8	4	6
2017	24 (12 duplicates)	2	8	2	2

The number of EQA samples per survey (2015–2017) and cTnT/cTnI concentration range are presented.

the individual regression line per laboratory, but only when also exceeding >3*SD. Values were evaluated against method consensus values derived by the mean of all participants minus outliers. Bias was calculated as the mean of all deviations vs. consensus for all levels within the respective relevant concentrations ranges. Imprecision (SD) was calculated from deviations as compared to the regression function vs. consensus so as to exclude bias. RCV was calculated according to the formula by Fraser and Harris, $RCV = Bias + \sqrt{2} * z\text{-value} * \sqrt{(CV_a^2 + CV_i^2)}$ [10], z-value of 2.33 for 99% confidence for the rule-in criterion and 1.65 for 95% confidence for the rule-out criterion, one-tailed. Ninety-nine percent confidence for rule-in ensures highest specificity, whereas 95% confidence for rule-out should ensure high enough sensitivity (the lower the confidence of the RCV, the higher the chance that the result is not clinically different from the initial result); this is also to make RCVs for rule-in and rule-out not to overlap, to justify the observational category, see Supplementary Figure 1. Significance of comparisons was determined by one-way non-parametric ANOVA (Kruskal-Wallis) and Dunn's corrected multiple comparisons ($p < 0.05$).

Results

Maximum allowable inter-instrument bias

The proposed 0/1-h delta values of ≥5 ng/L for rule-in and <3 ng/L for rule-out for Elecsys hs-cTnT correspond to maximum imprecisions of 1.5 ng/L and 1.3 ng/L, respectively, as calculated with the RCV formula (hourly CV_i is assumed to be 0; $CV_a = RCV/[\sqrt{2} * z\text{-value}]$). However, when multiple instruments are used within the laboratory, inter-instrument bias should also be taken into account when randomly presenting samples. Thirty and 33 laboratories sent in EQAS results for ≥2 instruments for 2015 and 2016, respectively. The median inter-instrument bias for all laboratories in 2016 was 0.3 ng/L for the relevant ranges for rule-in (5–52 ng/L) and rule-out
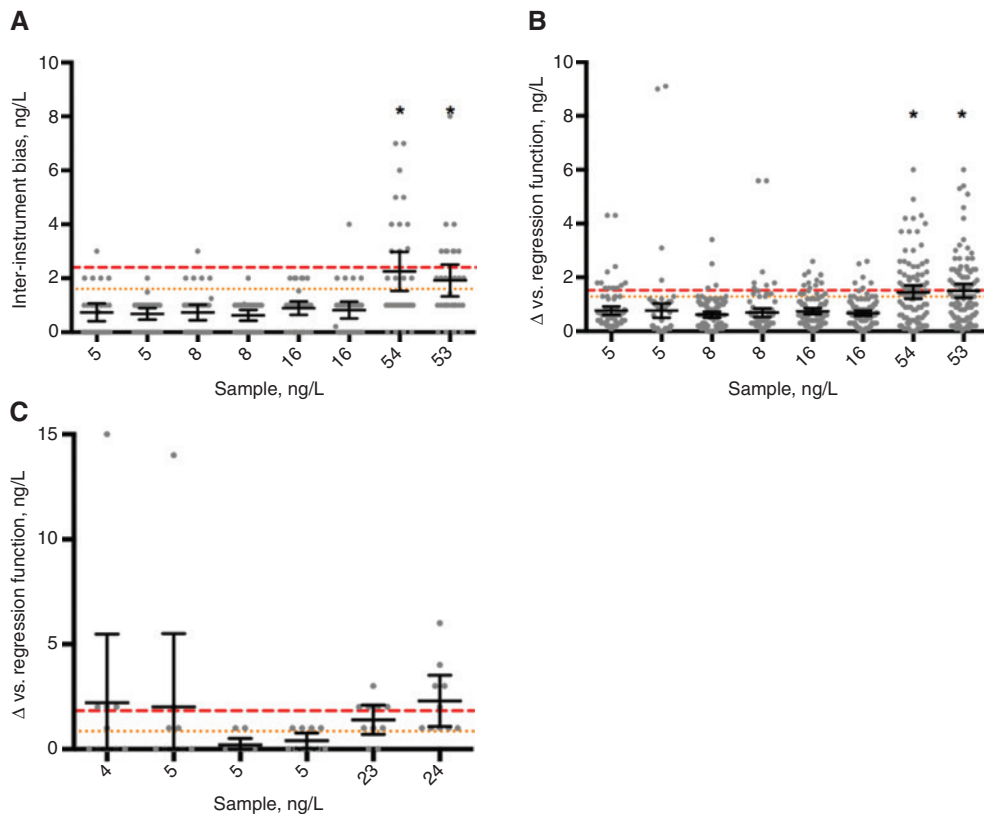

Figure 1: Inter-instrument bias and imprecision within the relevant measuring range. Depicted are absolute values (in gray) with means and 95% CI (black bars).
A. Inter-instrument bias as derived from absolute deviations vs. consensus values for Elecsys hs-cTnT EQAS 2016 (n = 33 laboratories). In red, the 2.4 ng/L (striped) and 1.6 ng/L (dotted) maximum allowable inter-instrument biases for rule-in and rule-out, respectively, are depicted (based on manufacturer within-run SD of 0.8 and 0.6 ng/L, respectively). B. Imprecision as demonstrated by absolute deviations vs. regression line for Elecsys hs-cTnT EQAS 2016 (n = 102 instruments). In red, the 1.5 ng/L (striped) and 1.3 ng/L (dotted) maximum allowable imprecision for rule-in and rule-out, respectively, are depicted. C. Imprecision as demonstrated by absolute deviations vs. regression line for Architect hs-cTnI EQAS 2016 (n = 10 instruments). In red, the 1.8 ng/L (striped) and 0.9 ng/L (dotted) maximum allowable imprecision for rule-in and rule-out, respectively, are depicted. EQAS, External Quality Assessment Scheme; CI, confidence intervals. *Significantly different, $p < 0.05$.

(5–12 ng/L) (Table 2). With the manufacturer reported maximal within-run imprecision of 0.8 ng/L, this results in a median RCV of 3.0 ng/L for rule-in, well below the delta value of ≥5 ng/L. For rule-out, the RCV is 1.7 ng/L with a manufacturer imprecision of 0.6 ng/L. Thereby 100% of the laboratories have adequate inter-instrument bias for application of the rule-in and rule-out criteria. For 2015, results are comparable. Two of the included laboratories reported results for more than two analyzers; for these laboratories, the maximal inter-instrument bias was used. For 2016, these were 1.0 and 0.9 ng/L for three and nine analyzers, respectively, for the 5–52 ng/L range, and 0.7 ng/L and 1.0 ng/L for the 5–12 ng/L range. Hence, both laboratories are allowed to measure on all analyzers interchangeably.

For Architect hs-cTnI, only one laboratory sent in results for more than one analyzer (four analyzers). For this laboratory, the maximal inter-instrument bias was 12.5 ng/L for 2016 for the 2–52 ng/L range and 1.3 ng/L for the 2–5 ng/L range. The maximal within-run imprecision as reported by the manufacturer is 0.8 ng/L, resulting in an RCV of 1.9 ng/L based on imprecision alone. This means that the error budget for using a delta value of <2 for rule-out is already spent on imprecision, thus allowing no inter-instrument bias. For rule-in, the delta value of ≥6 could result in false-positive diagnoses with an RCV of 15.1 ng/L.

Maximum allowable imprecision

The aforementioned calculations were based on the assumption that the within-instrument short-term imprecision meets the claimed performance. Ideally this should be validated and monitored using within-1-h precision studies at the concentration levels of interest. Laboratory's internal quality control data can validate such claim, although such data span multiple days and therefore may overestimate short-term imprecision relevant for compliance with the ESC guideline. The SKML calculates imprecision based on residuals of regression analysis of the external quality data. As for internal quality control, long-term EQA imprecision data might overestimate imprecision, but could give a good indication whether the claimed performance is met. As stated already, for Elecsys hs-cTnT, the maximum imprecisions for rule-in and rule-out are 1.5 ng/L and 1.3 ng/L, respectively. For Architect hs-cTnI, these are 1.8 ng/L and 0.9 ng/L. When calculated from EQAS data, for Elecsys in 2016, the median imprecision (SD) for all analyzers was 1.1 ng/L for the rule-in range (5–52 ng/L) and 0.7 ng/L for the rule-out range (5–12 ng/L) (Table 3). For all single analyzers (no inter-instrument bias), this results in a median RCV of 3.5 ng/L and 1.7 ng/L. Average imprecision for 2015 is comparable, but slightly higher. As a result, in 2016, 78% of the instruments had an estimated imprecision below the maximum allowable imprecision as based on RCV as defined earlier for the rule-in criterion and 89% for the rule-out criterion. When combining individual EQA estimated imprecisions with the individual inter-instrument biases as presented earlier, the median laboratory RCV is 4.6 ng/L for rule-in and 2.5 ng/L for rule-out. This results in 64% and 82% of laboratories that have adequate specifications for application of the rule-in and rule-out delta values, respectively. The Architect assay demonstrates a median imprecision of 1.5 ng/L in n = 10 instruments, also below the allowed maximum imprecision of 1.8 ng/L. However, here only 60% of the instruments have adequate imprecision for proper application of the rule-in criterion. Due to the lower delta value for rule-out, only 20% is suitable for application of the rule-out criterion, with a median imprecision of 1.3 ng/L. No data are available for inter-instrument bias.

Table 2: Laboratory adequacy based on EQA assessed inter-instrument bias and industry imprecision claim.

	Guideline		SD[a]	Bias (range)	Lab RCV (range)	% Adequate labs
	Delta	Range				
Rule-in, ng/L						
Elecsys	≥5	5–52	0.8			
2015				0.4 (0.0–1.4)	3.0 (2.6–4.1)	100
2016				0.3 (0.0–1.3)	3.0 (2.6–4.0)	100
Rule-out						
Elecsys	<3	5–12	0.6			
2015				0.4 (0.0–1.4)	1.8 (1.4–2.8)	100
2016				0.3 (0.0–1.0)	1.7 (1.4–2.4)	100

Inter-instrument bias (ng/L) was calculated for the relevant concentration ranges for rule-in (5–52 ng/L) and rule-out (5–12 ng/L) for Elecsys hs-cTnT assays, n = 8 and 6 samples, respectively. Presented are median bias and laboratory RCV for n = 30 and 33 laboratories for 2015 and 2016, respectively. RCV, reference change value. [a]Maximal SD as supplied by the manufacturer for the relevant concentration range.

Table 3: Laboratory adequacy based on EQA assessment of both inter-instrument bias and imprecision.

	Guideline		SD (range)	Analyzer RCV (range)	% Pass	Lab RCV (range)	% Pass
	Delta	Range					
Rule-in, ng/L							
Elecsys	≥5	5–52					
2015			1.2 (0.5–4.3)	3.8 (1.6–14.3)	79	4.6 (2.3–15.0)	57%
2016			1.1 (0.3–4.0)	3.5 (1.1–13.1)	78	4.6 (2.0–13.3)	64%
Architect	≥6	2–52					
2015			1.2 (0.7–4.6)	4.1 (2.3–15.0)	88	–	–
2016			1.5 (1.1–7.5)	4.8 (3.5–24.6)	60	–	–
Rule-out							
Elecsys	<3	5–12					
2015			0.9 (0.3–5.0)	2.0 (0.7–11.6)	80	2.8 (1.3–11.8)	57%
2016			0.7 (0.2–4.4)	1.7 (0.6–10.3)	89	2.5 (1.4–10.3)	82%
Architect	<2	2–5					
2015			1.2 (0.5–5.5)	2.7 (1.2–12.9)	38	–	–
2016			1.3 (0.3–10.4)	3.1 (0.7–24.3)	20	–	–

SD (ng/L) was calculated for the relevant concentration ranges for rule-in and rule-out for Elecsys hs-cTnT and Architect hs-cTnI assays. n = 8 and 6 samples, respectively, for Elecsys, and n = 6 and 4 samples, respectively, for Architect. Presented are median SD and analyzer RCV for Roche n = 94 and n = 102, Abbott n = 8 and n = 10 instruments for 2015 and 2016, respectively, also laboratories with one instrument were included. Presented are median laboratory RCV for n = 30 and 33 laboratories for 2015 and 2016, respectively, as calculated from analyzer RCV and inter-instrument bias. RCV, reference change value.

Variability of inter-instrument bias and imprecision within the measuring range

As can be observed from the data presented in Tables 2 and 3, inter-instrument bias has a smaller range and imprecision appears to be lower for the rule-out concentration range as compared to the range for rule-in. For Elecsys, inter-instrument bias for the different EQAS samples is significantly higher in the 53/54 ng/L concentration samples as compared to the 5, 8 and 16 ng/L levels (Figure 1A). Similarly, imprecision (depicted as the residuals of the regression function) is significantly larger for the 53/54 ng/L levels vs. the lower concentration samples. The mean deviation is 0.8 ng/L (95% CI 0.6–0.9/0.5–1.0) at the lower 5 ng/L concentrations and 1.4/1.5 ng/L (95% CI 1.2–1.7/1.2–1.8) at the higher 53/54 ng/L concentrations (Figure 1B). Although the number of participating instruments for Architect is smaller, a similar picture emerges (Figure 1C).

Imprecision and bias between instrument types

Results for Elecsys assays were derived from different Roche instruments: Cobas 6000, Cobas 8000, Elecsys and Modular (n = 57, 20, 7 and 14, respectively). No significant differences were observed in imprecision and bias for the 5–52 ng/L (Figure 2A, B) and 5–12 ng/L (data not shown) concentration ranges.
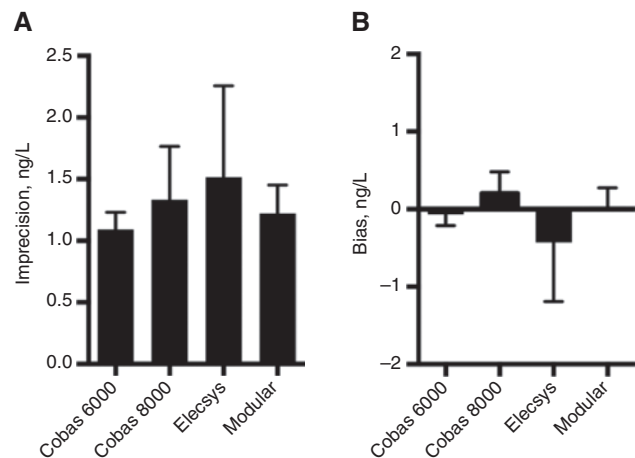

Figure 2: Inter-instrument bias and imprecision for Elecsys hs-cTnT assays.
Depicted are mean values and 95% CI (black bars). A. Mean imprecision for Cobas 6000, Cobas 8000, Elecsys and Modular (n = 57, 20, 7 and 14, respectively) for the 5–52 ng/L concentration range. B. Mean overall bias for Cobas 6000, Cobas 8000, Elecsys and Modular (n = 57, 20, 7 and 14, respectively) for the 5–52 ng/L concentration range. No significant differences were observed.

Discussion

The 0/1-h NSTEMI algorithm demands compliance with strict analytical specifications concerning short-term imprecision and if applicable inter-instrument bias. Although not perfect, imprecision deduced from EQAS

data is a reasonable estimate of short-term imprecision, as long-term components are filtered out as bias. For Elecsys hs-cTnT, Roche reports within-run SDs of 0.3–0.8 ng/L for the different controls, instruments and assays (normal/STAT), confirmed in recent reports demonstrating within-hour SDs of 0.26/0.18 ng/L at 5/12 ng/L concentration levels [19]. Consequently, the median SD of 1.1 ng/L probably is an overestimation of short-term imprecision, resulting in an even higher specificity in practice. EQAS data are especially suited to give information about bias and inter-instrument bias. For evaluation of adherence to the guideline, it is important that SD and inter-instrument bias are calculated using data from the relevant concentration ranges and cannot be deduced from the SD/bias for the complete measuring range. Hence, it is crucial that EQAS organizers provide enough samples within the relevant concentration range. SKML samples consist of unmanipulated human sera which makes commutability likely. Therefore, biases and imprecisions as calculated from these samples are likely representative for regular patient samples. Others have used EQA to assess analytical specifications around the 2 ng/L and 99th percentile cut-off values for Architect hs-cTnI. They reported SDs of 3.1 ng/L at the 35 ng/L level, 1.3 ng/L at 15 ng/L and 0.8 ng/L at 2 ng/L (n = 32), and concluded that this assay is not ready for the 0/1-h guideline, especially as the LoD is not adequately determined [20].

The RCV is used to determine whether the change in cTn concentrations is clinically relevant and thus exceeds the combined analytical variation (CV_a) and intra-individual biological variation (CV_i). As stated, biological variation for cTn is difficult to determine. The reported 90-min intra-individual variation is 1.2% for cTnT and 5.0% for cTnI (Architect assay) [21], but seems highly dependent on the exact study population and measurements [22–24]. Also, the reported 5.0% CV_i for cTnI means an RCV of 6.6 ng/L at a 40 ng/L concentration (when inter-instrument bias and CV_a are assumed to be 0), allowing no delta value of 6 ng/L to be clinically significant. As the 0/1-h algorithm has been clinically validated in multi-center studies [13–17], in practice biological variation must be lower than the reported values. Although based on small numbers of individuals, for cTnT the reported CV_i does appear realistic, and would result in minor increases in RCV. The median laboratory RCV would be 3.1 ng/L instead of the currently reported 3.0 ng/L, and the median analyzer RCV 3.6 ng/L instead of 3.5 ng/L (for 2016) for the rule-in criterion (at a level of 21 ng/L). For the rule-out criterion, both RCVs are increased by 0.1 ng/L. In all cases, there is no effect on the percentage of adequate laboratories/analyzers. More research is needed to establish reliable hourly

CV_i for cTn (T/I) in the relevant population. Another even more unpredictable factor in defining the clinical significance of a concentration change is pre-analytical variation, most importantly the degree of hemolysis [25] and should be regarded as well when implementing and evaluating the 0/1-h protocol. In addition, also outlier frequency is an important factor for correct rule-in or rule-out, with reported frequencies of 0.47% for Architect hs-cTnI [26] and 0.06% for Elecsys hs-cTnT [27].

Concerning inter-instrument bias, awareness is needed when laboratories would use the 0/1-h algorithm. EQAS results from 33 laboratories using Elecsys hs-cTnT demonstrate that inter-instruments bias is no problem when imprecision is within the limits as stated by the manufacturer. However, Haagensen et al. recently demonstrated for hs-cTnT that lot-to-lot differences are ranging from 3 to 6 ng/L [19]. Hence, in addition to a significant impact on patient rule-in/rule-out based on decision limits, for correct decisions based on delta values, it might be crucial to run the same lot on all analyzers within the laboratory. For Architect, only one laboratory submitted results for multiple analyzers. There, inter-instrument bias is not adequate and requires more attention. When imprecision is calculated from EQAS data, ~100 instruments demonstrate that on average Elecsys assays are technically capable to meet the desired specifications to use the guideline's delta values. Towards the higher end of the concentration range, absolute imprecision is significantly higher, but with a mean deviation of 1.5 ng/L and a 95% CI of 1.2–1.8 ng/L, it is still well below the 5 ng/L RCV. Nevertheless, in 2016, only 78% of the participating instruments had adequate imprecision and thus an RCV lower than the proposed delta value of 5 ng/L, lowered to 64% when also inter-instrument bias is taken into account for the 33 laboratories that sent in results for ≥2 instruments. As a result, these laboratories might falsely rule-in and (invasively) treat patients for MI. Not meeting analytical specifications for rule-out means a broader observational range and thus might result in less economical and patient-friendly benefits from the fast algorithm, but does not affect patient safety. For Architect, in 2016, median RCVs of 4.8 and 3.1 ng/L were observed for rule-in and rule-out, respectively, which do not allow adequate implementation of the guideline's delta values. Kavsak et al. reported misclassification of two out of 50 patients due to delta values ≥6 ng/L when remeasuring the exact same sample with Architect hs-cTnI (no CV was reported) [28]. Based on analytical feasibility, a lot-to-lot bias of 1.8 ng/L and an SD of 0.8 ng/L, they propose a TEA of <3.5 ng/L for concentrations under ≤10 ng/L to be acceptable [29]. The current study demonstrates that the best performing instruments

for Architect (imprecision 0.3 ng/L) are similar to the best performing Elecsys instrument (0.2 ng/L), suggesting that with optimal quality control adequate imprecision on Architect should be feasible.

In addition to interpreting increases/decreases, the algorithm uses LoD for rule-out (<5 ng/L for Elecsys hs-cTnT, <2 ng/L for Architect hs-cTnI), demanding very strict analytical specifications around this cut-off value. For hs-cTnT, negative predictive values of 99.8% were observed for the 5 ng/L cut-off for rule-out [30]. However, simulation studies for Architect hs-cTnI demonstrate ~10% misclassification when a bias of 1 ng/L exists [31]. As a result, the AACC/IFCC recommendations of 2018 propose a maximum allowable total error of 1 ng/L for use with the ESC guideline for early rule-out [7]. Thus, analytical performance is key to acquire high sensitivity and specificity as became clear from the validation studies of the 0/1-h algorithm by Pickering et al., demonstrating a lower positive predictive value and especially lower sensitivity essential for safe rule-out as compared to the original studies [32].

Concerning this study, the following limitations need to be considered. Firstly, imprecision deduced from EQAS data may be a helpful estimate of short-term imprecision, but is no valid substitute for 1-h precision experiments, especially as the calculated SD is an estimate based on only six of eight samples measured over a year. Secondly, although the presented data are useful for the evaluation of the individual participants, no general conclusions could be drawn for the performance of Architect assays due to a low number [8–12] of participating instruments and lower number of adequate sample levels (six levels measured vs. eight for Elecsys). Also, EQA levels were more neatly spread along the measuring range for Elecsys. Inter-instrument bias could only be assessed for one laboratory. Thirdly, also validity of the data for Elecsys would be higher with more samples in the relevant low concentration range. Fourthly, although commutability of the samples for cTn (T/I) is likely, it has not been studied. Fifthly, it must be kept in mind that participants can submit data for single instruments, averages of multiple instruments, or a member of a group of instruments. Therefore, if combined results for more instruments had been submitted, inter-instrument bias would be part of the imprecision.

The limited number of participants for some assays and limited information on the statistical origin of data applied by participants make the data less suitable to express the performance of particular IVD products. Notwithstanding these limitations, current data show that at least some IVD products can meet the required analytical performance requirements in the hands of at least some users, which should encourage IVD providers to keep developing their products to meet these specifications. In addition, laboratories using these products should be encouraged to design their processes to meet the specifications, requiring a strict IQA in the concentration range of interest. In future studies, it would be interesting to evaluate why some laboratories achieve better results than others and what is necessary for optimal results, e.g. more controls in the lower range. To EQAS organizers we recommend to utilize enough samples in the relevant concentration range and to report analytical specifications related to the 0/1-h algorithm, including explicit conclusions whether the performance of participants is adequate to comply. Also, SKML reports which have earned appreciation for their multi sample approach [18, 33–34], enabling participants to differentiate between bias and imprecision as source for their inaccuracy, could be improved by adding this specific information. In addition, SKML and other EQAS could contribute to the root cause analysis of between-laboratory variation in imprecision by grouping sub-method results such as hs-cTnT STAT vs. regular assays. Addressing the relationship with the intended use is in line with the EFLM recommendations on analytical specifications [35–36] and its evaluation by EQAS organizers [37].

Conclusions

By presenting both bias and imprecision for the relevant concentration ranges for Roche Elecsys hs-cTnT type assays and Abbott Architect hs-cTnI type assays, the yearly SKML EQAS reports are valuable tools for medical laboratories to estimate compliance with stringent analytical performance specifications essential for the 0/1-h NSTEMI algorithm. We advise laboratories that claim to be able to rule-in and rule-out patients based on small increments to introduce stringent internal quality procedures at the relevant (low) concentration level, especially when multiple analyzers are randomly used.

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