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Biological Variation of Cardiac Troponins in Health and Disease: A Systematic Review and Meta-analysis

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BACKGROUND: Many studies have assessed the biological variation (BV) of cardiac-specific troponins (cTn), reporting widely varying within-subject BV (CV_I) estimates. The aim of this study was to provide meta-analysis-derived BV estimates for troponin I (cTnI) and troponin T (cTnT) for different sampling intervals and states of health.

METHODS: Relevant studies were identified by a systematic literature search. Studies were classified according to their methodological quality by the Biological Variation Data Critical Appraisal Checklist (BIVAC). Meta-analyses of BIVAC-compliant studies were performed after stratification by cTn isoform, exclusion of results below the limit of detection, states of health, and sampling interval to deliver reference change values (RCV), index of individuality (II) and analytical performance specifications (APS) for these settings.

RESULTS: Sixteen and 15 studies were identified for cTnI and cTnT, respectively, out of which 6 received a BIVAC grade A. Five studies had applied contemporary cTnI assays, but none contemporary cTnT. High-sensitivity (hs-) cTnI and cTnT delivered similar estimates in all settings. Long-term CV_I estimates (15.1; 11.3%) derived from healthy individuals were higher than short-term (4.3%; 5.3%) for hs-cTnI and hs-cTnT, respectively, although confidence intervals overlapped. Estimates derived from diseased subjects were similar to estimates in healthy individuals for all settings.

CONCLUSIONS: This study provides robust estimates for hs-cTnI and hs-cTnT applicable for different clinical settings and states of health, allowing for the use of RCV both to aid in the diagnosis of myocardial injury and for prognosis. BV-based APS appear too strict for some currently available technologies.

Introduction

Cardiac-specific troponins (cTn) are the preferred biomarkers for the detection of myocardial injury. In the Fourth Universal Definition of Myocardial Infarction (MI) (1), published in 2018, a MI diagnosis is defined, in the appropriate clinical context, as the demonstration of increased cTn values with at least one value above the 99th percentile of the reference population. Thus, analytical performance, especially for imprecision, is critical. Well-defined analytical performance specifications (APS) are a prerequisite for effective application of cTn, especially in the rapid decision-making setting where a patient presents with chest pain and suspected acute coronary syndromes. In principle there are three ways to set APS (2): 1) outcome studies, b) biological variation (BV), and c) state of the art. Considering the central and well-defined role of cTN in the diagnosis of a specific disease, the optimal approach, in particular for use in rule-in and rule-out algorithms, would be the adoption of clinical outcome-based studies (2). Unfortunately as of yet, appropriate outcome studies are still lacking. In the absence of such studies, the BV

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model has been proposed as an acceptable secondary approach (3), but requires high-quality BV data. The availability of such BV data can also be used to deliver "delta values" that may be included in diagnostic algorithms for MI (4).

Over the last decade, many cTn BV studies have been published, reporting results from individuals in different states of health and where different sampling intervals have been applied. The within-subject BV (CV_I) estimates presented in these studies vary greatly, ranging from 2.6%–117.0%, to a large degree dependent on the concentration of cTn (5–8). One of the challenges inherent in some of these studies is methodological, such as the use of cTn results below the assay's limit of detection (LoD) to deliver BV estimates, a circumstance in which they should not be applied (4). Improvements in analytical performance characteristics of next generation assay systems, delivering high-sensitivity measurements with improved LoD and limit of quantification, mean that cTn has become measurable in healthy populations and this has enabled derivation of more robust BV estimates, albeit still at low concentrations. However, the quality of available BV data may also be compromised by the study design, as has been shown for many other measurands (9, 10). The Biological Variation Data Critical Appraisal Checklist (BIVAC) is a tool to assess the quality of BV publications by verifying whether all essential elements that may impact on veracity and utility of the data are present and, furthermore, allows for a meta-analysis approach to deliver global BV estimates based on BIVAC compliant studies (9).

The study reported here has been undertaken with the aim to identify published BV studies of cTn that are BIVAC compliant to enable collation of data sets of sufficient quality to deliver meta-analysis derived BV estimates for cTn I (cTnI) and cTn T (cTnT) in different states of health and sampling intervals.

Materials and Methods

A literature search for BV studies on cTnI and cTnT published until April 15, 2020 was conducted as previously described (9, 10). Briefly, searches were carried out in PubMed, using as key terms [the measurand] in question with each of the following combinations: "within-subject*," "between-subject*," "within-person*," "between-person*," "interindividual*," and "intraindividual*," where the asterisk denotes "biological variation," "variation," "coefficient of variation," and "CV."

We considered 4 different measurands, those being defined by the generation of the assay used (contemporary and high-sensitivity) and the troponin isoforms cTnI and cTnT. The applied definition of a high-sensitivity (hs) cTn method was that proposed by Jarolim et al. (11) (i.e, an analytical method that delivers measurable results in at least 50% of healthy subjects and with an analytical imprecision (CV_A) of <10% at the 99th percentile).

When applying the BIVAC, each study is appraised with regard to 14 quality items (QI), which focus on the preanalytical procedures, the measurand/measurement procedure, applied statistical methods, and the presentation of data (Supplemental Table 1). Each QI may be assigned either an A, B, C, or D score, indicating increasing noncompliance, and the lowest score of any QI decides the overall BIVAC grade. BV estimates derived from studies that receive one or more D scores are considered unsuitable for use. Two appraisers assessed all the studies independently, and consulted the full group if they disagreed on the scores. The overall BIVAC grade was used as weight in a meta-analysis together with the inverse width of the confidence interval (CI), in a weighted median approach to deliver the global CV_I and CV_G estimates (9). Meta-analysis was performed for short- and long-term studies with BIVAC grades A, B, and C studies fulfilling the following inclusion criteria: age 18–75 years, > 2 subjects and >2 samples per subject, BV estimates given as CV, and a numerical estimate of CV_A included. For studies reporting more than one BV estimate derived by different analytical methods from the same set of samples, the estimate based on the highest number of measurable samples, or a randomly selected estimate, was included. Meta-analyses were performed for 1) short-term BV, defined as within-day samplings and 2) long-term BV (all sampling intervals longer than within-day, up until quarterly) separately in the groups of healthy and non-healthy study subjects.

cTn values in healthy people are not normally distributed, but lie close to the LoD (12). Meta-analyses were therefore undertaken both for all studies and after excluding studies in which results below the declared LoD of the cTn assay had been included as the basis for the BV estimates (when this was stated in the article or it was deducible from graphical illustrations provided in the publication).

For each published study, detailed information on study design, study population, health status of the participants, analytical method including estimates of CV_A and the reagent IVD provider were recorded.

The CV_I and CV_G estimates were used to determine APS for CV_A and bias/systematic error (13), reference change values (RCV) (14) that with a stated probability assess what changes between 2 measurements can be explained by analytical and biological variation, and the index of individuality (II) that refers in the case of cTn to the balance in an individual between its release and elimination (15).

– $CV_A = 0,5 \cdot (CV_I)$
– Bias $= 0.5 \cdot (CV_I^2 + CV_G^2)^{0,5}$
– RCV $= 100\% \cdot (\exp(\pm Z \cdot 2^{1/2} \cdot (CV_{LnA}^2 + CV_{LnI}^2)^{1/2}) - 1)$;

where CV_{Ln} refers to ln-transformed data $= (\text{Ln}(1 + CV^2))^{1/2}$ and "Z" refers to the Z-score equal to the number of standard deviations appropriate for the selected probability. To calculate the RCV, we applied the mean CV_A estimate derived from all the studies included in the meta-analysis for the 2 cTn isoforms.

$$-\text{II} = CV_I/CV_G$$

Results

In total, 31 studies were identified, reporting BV estimates for different states of health and/or sampling intervals, delivering in total 69 BV estimates, hereafter referred to as subgroup estimates. An overview of all appraised studies including the BIVAC grade and information on the study population, the health status of participants, sampling intervals (short-term vs. long-term) and the reagent suppliers is provided for hs-cTn in Supplemental Table 2 and for contemporary cTn in Supplemental Table 3.

Sixteen studies with results for 31 subgroups were identified for hs-cTnI, and 17 studies with results for 32 subgroups for hs-cTnT. Six studies received a BIVAC grade A delivering 11 subgroup estimates for hs-cTnI and 7 for hs-cTnT (Table 1). None received a BIVAC grade D. Thirteen studies reported BV estimates from healthy individuals and 16 for unhealthy individuals, including the following disease states; cardiac (n = 7), kidney (n = 7), diabetes and obesity (n = 1), random patients (n = 1).

Fourteen short-term and 15 long-term BV estimates were identified from studies in healthy subjects and 7 and 17 in non-healthy subjects, respectively (Table 1). The majority of long-term estimates were derived by weekly or bimonthly sampling intervals (n = 9 cTnI; n = 15 cTnT), with less studies applying monthly (n = 1 cTnI; n = 3 cTnT), and from quarterly to biannual (n = 1 cTnI and n = 3 cTnT) samplings. No studies reported results based on daily samplings.

Large variations in reported CV_I (Figs. 1 and 2) and CV_G estimates (Supplemental Figs. 1 and 2) were observed both for healthy and nonhealthy individuals. As expected, concentration ranges in nonhealthy subjects were higher than in healthy subjects (Supplemental Table 4). Twenty-nine studies fulfilled the meta-analysis criteria and were included to provide global BV estimates (Table 2). Twenty-two of these studies had excluded results below the LoD, however, including

Table 1. Number of subgroup BV estimates identified for short-term and long-term settings for healthy and nonhealthy individuals with the associated BIVAC grade, with results for a) all subgroup BV estimates, b) all subgroup BV estimates included in the meta-analysis and 3) subgroup estimates included in the meta-analysis and where results below LoD had been excluded.

	Healthy		Non-healthy	
	Short-term	Long-term	Short-term	Long-term
A	**All subgroup BV estimates (Derived from hs-cTnI = 16, hs-cTnT = 17 studies)**			
hs-cTnI	2 A, 1B, and 6 C (n = 9)	3 A, 3B, and 4 C (n = 10)	1 A and 1 C (n = 2)	5A, 3B, and 2 C (n = 10)
hs-cTnT	1A and 4 C (n = 5)	1 A and 4 C (n = 5)	1 A, 2B, and 2 C (n = 5)	4A, 5B, and 8 C (n = 17)
B	**Subgroup BV estimates included in the meta-analysis *(Derived from hs-cTnI = 14, hs-cTnT = 15 studies)***			
hs-cTnI	2 A, 1B, and 3 C (n = 6)	2 A, 3B, and 3 C (n = 8)	1A and 1 C (n = 2)	5A, 3B, and 1 C (n = 9)
hs-cTnT	1A and 4 C (n = 5)	1A and 4 C (n = 5)	1A, 2B, and 2 C (n = 5)	4 A, 5B, and 4 C (n = 13)
C	**Subgroup BV estimates included in the meta-analysis and where results LoD have been excluded *(Derived from hs-cTnI n = 10, hs-cTnT = 12 studies)***			
hs-cTnI	1 A, 1B, and 3 C (n = 5)	2A, 1B, and 1 C (n = 4)	1 A and 1 C (n = 2)	5A and 1B (n = 6)
hs-cTnT	1A and 3 C (n = 4)	1A and 2B (n = 3)	1A, 2B, and 2 C (n = 5)	4A, 5B, and 1 C (n = 10)

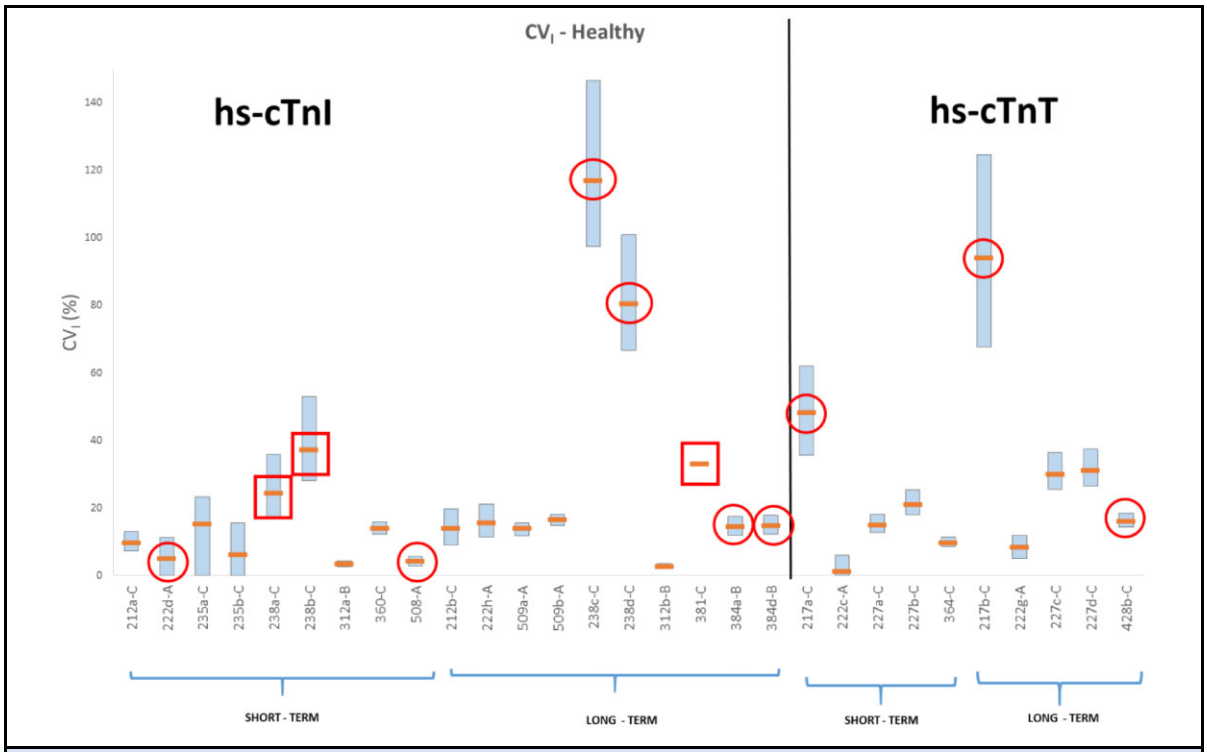

Fig. 1. Estimates of CVI (95%CI) in healthy subjects (short- and long-term) for both hs-cTn. X-axis: the reference number, as provided in the EFLM-BVD and Supplemental Table 3, subscripts indicate different subgroups from the same study, followed by the BIVAC grade. Squares: estimates did not fulfill meta-analysis criteria; circles: excluded from the second meta-analysis (results below the LoD used to derive BV).

estimates only from these studies did not give significantly different results compared to the original meta-analysis (Table 2).

The relationship between the CV_I estimate and the concentration reported for each study (Fig. 3) and the associated CV_A estimate (Supplemental Fig. 3) are also illustrated for hs-cTnI and hs-cTnT separately.

Table 3 provides results for the II, RCVs, and APS for imprecision (CV) and bias, based on meta-analysis derived BV estimates for hs-cTnI and hs-cTnT in all settings.

Discussion

cTn measurements are the cornerstone of the non-ST-elevation MI diagnosis (1). Consequently, the applications of well-defined APS for cTn are crucial to patient care, in particular in the emergency setting. With the lack of relevant outcome studies, the BV model is the best alternative for setting APS, but it depends on the availability of robust BV data. In our review, 6 studies were identified as fully BIVAC compliant. Many of these were quite recent, and 6 studies reported following the BIVAC recommendations. Approximately the same number of studies were identified in which cTnI and cTnT methods were applied, with 5 reporting results for contemporary cTnI assays. In many studies, authors distinguished between short- and long-term BV (about half of the studies) and stratified for different disease entities (mainly kidney and heart disease) (16–18). Although it is recommended that the 99th percentile should be established by gender, only one study had assessed BV estimates in men and women separately: the European Biological Variation Study (EuBIVAS) (6). Here no notable differences were found for 2 hs-cTnI methods, based on weekly samplings of the 91 study participants. Further BV studies are needed to explore potential significant differences in BV estimates between men and women in the short-term setting.

Due to the fact that the healthy population follows a left-skewed distribution for cTn, a high number of results could potentially be under the LoD if the sensitivity of the method is not adequate. Several studies had not excluded results below the LoD when deriving the BV estimates. Such results should be reported as "below LoD" and the numerical result delivered by the

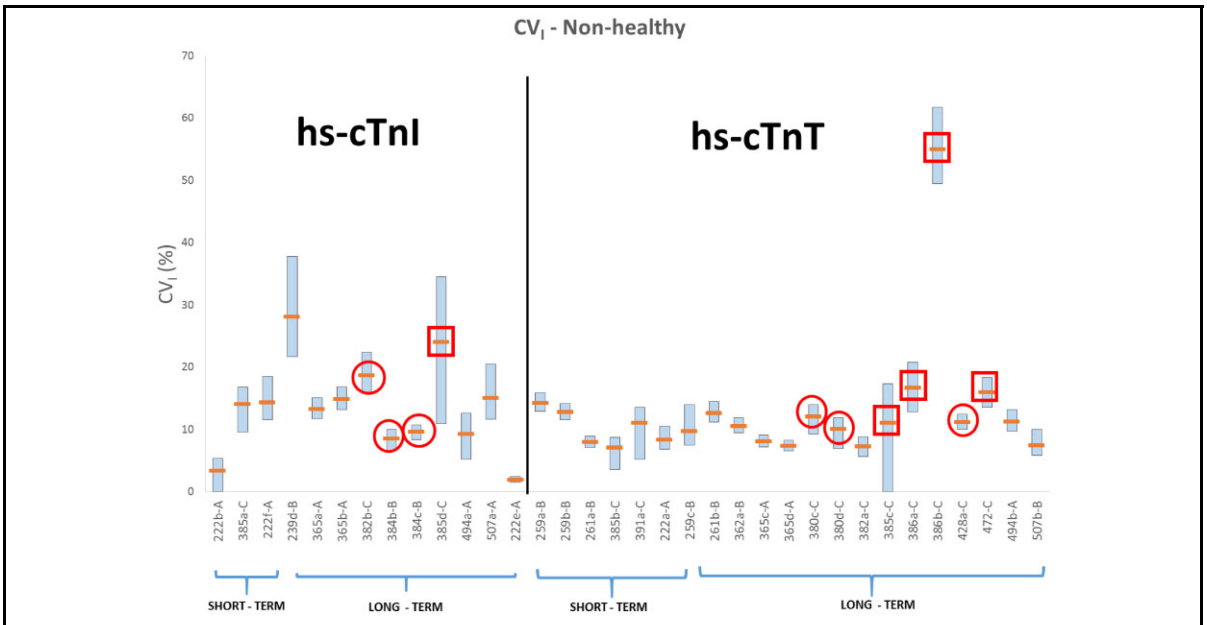

Fig. 2. Estimates of CVI (95%CI) in nonhealthy subjects (short- and long-term) for both hs-cTn. X-axis: the reference number, as provided in the EFLM-BVD and Supplemental Table 3, subscripts indicate different subgroups from the same study, followed by the BIVAC grade. Squares: estimates did not fulfill meta-analysis criteria; circles: excluded from the second meta-analysis (results below the LoD used to derive BV).

Table 2. Global BV estimates with 95% confidence intervals for hs-cTn derived from (A) all studies that met the meta-analysis inclusion criteria and (B) studies that met the meta-analysis inclusion criteria and had excluded results below LoD.

	Healthy				Nonhealthy			
	Short-term		Long-term		Short-term		Long-term	
	CV_I	CV_G	CV_I	CV_G	CV_I	CV_G	CV_I	CV_G
A hs-cTnI	4.1 (3.4-4.9)	25.0 (23.4-37.7)	15.0 (2.6-16.6)	35.9 (25.9-39.4)	5.0 (3.3-14.0)	156.0 (148.1-187.0)	14.0 (9.2-15.2)	75.4 (35.0-110.0)
hs-cTnT	5.6 (1.2-13.4)	36.2 (32.6-47.3)	11.5 (8.3-21.7)	32.2 (26.9-51.2)	3.1 (1.9-12.4)	60.7 (39.4-110.0)	8.8 (7.6-10.9)	69.0 (57.2 - 97.5)
B hs-cTnI	4.3 (3.4-9.0)	36.7 (25.3-81.8)	15.1 (2.6-16.6)	34.6 (25.9-37.9)	5.0 (3.3-14.0)	156.0 (148.1-187.0)	14.1 (9.2-15.0)	63.8 (35.0-126.7)
hs-cTnT	5.3 (1.2-14.7)	34.9 (32.6-47.2)	11.3 (8.3-30.5)	26.8 (19.3-47.8)	3.1 (1.9-12.4)	60.7 (39.4-110.0)	8.4 (7.6-10.5)	68.3 (51.8-98.0)

A: All studies fulfilling meta-analysis criteria.
B: Studies fulfilling meta-analysis criteria and having excluded results below LoD.

instrument should not be included as a basis for BV estimates (4). We, therefore, performed a separate meta-analysis after excluding studies which had included results below the LoD. However, the impact on the BV data was minimal, as demonstrated by the 95% CI overlap of estimates pre- and post-exclusion (Table 2). An explanation for this may lie in the fact that the majority of the excluded studies had been graded as BIVAC C (6 out of 9) and carried less weight in the meta-analysis.

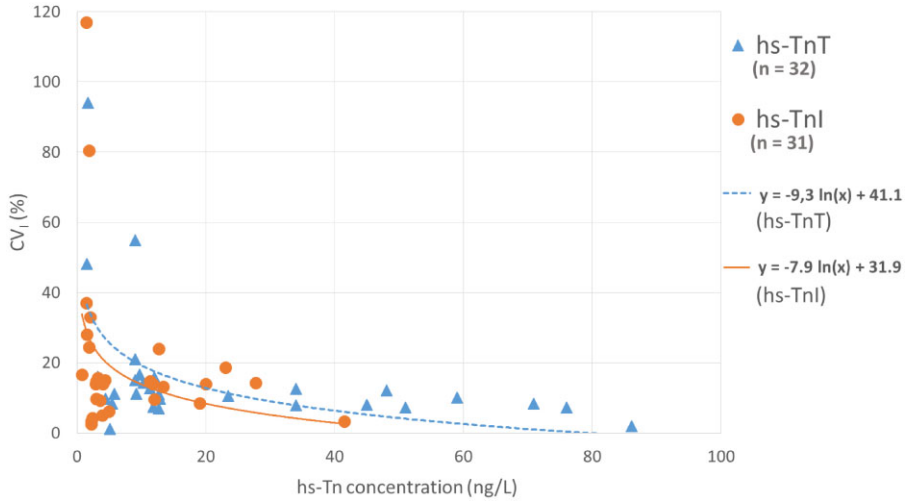

Fig. 3. CVI estimates from all the subgroups, plotted against the corresponding hs-Tn concentration.

Table 3. Index of individuality (II), two-sided ($z = 1.96$) reference change values (RCV) and desirable analytical performance specifications (APS): imprecision (CV) and bias/systematic error, based on short-term and long-term meta-analysis derived BV estimates in healthy and non-healthy study populations.

	Healthy				Non-healthy			
	Short-term		Long-term		Short-term		Long-term	
	II[a,b] (RCV%)	APS% (CV/Bias)	II[a,b] (RCV%)	APS% (CV/Bias)	II[a,b] (RCV%)	APS% (CV/Bias)	II[a,b] (RCV%)	APS% (CV/Bias)
hs-cTnI	0.12 (-25.6 to 34.4)	2.1/9.2	0.44 (-38.0 to 61.4)	7.6/9.4	0.03 (-25.5 to 34.1)	2.5/39.0	0.22 (-33.2 to 49.6)	7.1/16.3
hs-cTnT	0.15 (-26.2 to 35.6)	2.7/8.8	0.42 (-37.8 to 60.6)	5.7/7.3	0.05 (-23.6 to 30.8)	1.6/15.2	0.12 (-29.1 to 41.1)	4.2/17.2

[a]The CV_A estimate used is the mean CV_A of all the studies included in the meta-analysis for each subgroup (9.8% for hs-TnI and 9.2% for hs-TnT.).
[b]RCV is calculated as two-sided RCV with a probability of 95% ($z = 1.96$).

Two studies reported CV_I estimates for the same cTnI isoform measured on different analytical platforms in the same set of subjects. Apple et al. (19) reported different CV_I hs-cTnI estimates, though with overlapping 95% CI, for Abbott (CV_I: 15.2% (CI: 0–23.1%)) and Beckman CV_I: 6.1% (CI: 0–15.5%) systems. This might be explained by differences in measurement specificities because the capture antibodies are not targeted to the same epitopes, as well as delivery of different analytical performance near the LoD. However, as indicated by the CI there are large uncertainties around these point estimates, and this study received a BIVAC grade C. The second study (6), the EuBIVAS, classified as a BIVAC grade A study, assessed BV of hs-cTnI in samples collected weekly, reporting similar estimates for Singulex (CV_I : 15.8% (CI : 14.7–17.0%)) and Siemens Atellica (CV_I : 13.9% (CI : 12.7–15.0%)) platforms when the same measurable samples were used as basis, despite the use of measurement procedures targeting different epitopes. Thus, it still remains unclear as to the mechanism and extent that BV estimates may be influenced by the choice of the target epitope or the assay design and configuration of analytical platforms.

Given the clinical uses of cTn, we categorized the BV experimental designs into short- and long-term BV estimates. This reflects the application of cTn in the clinical settings of MI diagnosis and of prognosis of cardiac-related outcomes (20, 21), in line with recent studies indicating the utility of cTn as a risk marker (22). The categorized data sets were subjected to

separate meta-analyses to derive BV estimates that reflect the time frame defined by the clinical context. Our results show that short-term estimates were similar between different states of health. Long-term BV estimates were twice the magnitude of the short-term estimates, regardless of cTn isoform and health status, but large and overlapping 95% CI were observed, as detailed below.

SHORT-TERM BV ESTIMATES

Only 2 studies (each with 2 subgroups) for hs-TnI and 4 (5 subgroups) for hs-TnT were identified in the short-term setting (Supplemental Table 3), and estimates were similar for both isoforms in all settings (Table 2). As expected, cTn concentrations in healthy individuals were lower than in non-healthy individuals (Supplemental Table 4). When plotting CV_I estimates against their corresponding concentration (Fig. 3) and CV_A (Supplemental Fig. 3), we observed an inverse correlation that fits a Ln function. This indicates, as expected, that the BV estimates given as CV% are influenced by the concentration level.

LONG-TERM BV ESTIMATES

The higher BV estimates derived from the long-term setting could have impact on the strategy for interpreting serial patient results and defining laboratory APS. For hs-cTnI, the long-term estimate established for non-healthy appear higher than that from healthy individuals, but also here the 95% CI overlap (Table 2). Clinical conditions included in the different studies were related to renal impairment, with reported CV_I estimates ranging from 14.3%–18.3% for hs-cTnI and 7.2%–12.6% for hs-cTnT, and stable coronary artery disease and chronic heart failure, where CV_I estimates ranged from 8.%5–24.0% for hs-cTnI and 11.0%–11.2% for hs-cTnT (Supplemental Tables 4 and 5).

INDEX OF INDIVIDUALITY AND REFERENCE CHANGE VALUE

II for hs-cTnI and hs-cTnT were <0.6 in all settings, reflecting a high degree of individuality, consistent with the idea that the concentration in each individual reflects a balance between release from the myocardium and cTn elimination. It was of a lower magnitude than the II for measurands recognized as subject to strict homeostatic regulation, such as electrolytes (23). The low II indicates that monitoring serial cTn results by the use of RCVs could be included in diagnostic algorithms. Different approaches are presently in use for hs-cTn in rule-in and rule-out strategies for MI. Current diagnostic algorithms include both relative and absolute delta changes, with the discussion moving towards the use of absolute delta. The European Society of Cardiology algorithms are based on absolute delta changes provided for each analytical method (24, 25). The use of absolute delta, however, has some limitations (26). Cut-off concentrations and absolute changes defined for rule-in and rule-out algorithms are not established for all analytical methods and a high number of patients with unspecific high hs-cTn concentrations are ruled-in, leading to costly follow-up examinations. The American Heart Association/American College of Cardiology (AHA/ACC) uses as a criterion a 20% increase if the previous cTn result was above the 99th percentile, or 3SD if the cTn concentration was below (27). This concept is derived from the traditional practice of establishing the LoD based on >3SD of standard analytical performance. When this target was set, methods typically had an analytical performance of around 5%–7%, which thus resulted in the estimate of 20% (28). It is, however, important to keep in mind that the analytical imprecision depends on the method and the concentration of the measurand and that new hs-cTn methods have improved their analytical performance. Furthermore, this concept does not include the contribution of BV nor clinical rationale.

The AACC and the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers, on the other hand, recommend the detection of statistically significant changes in serial cTn results over time, where these expected changes in concentrations should be established by RCVs derived from BV studies (4). The application of the BV based estimates as basis for delta values has not been widely accepted, mostly due to the discrepancies found in the individual BV studies as described in this review. Furthermore, if the MI onset has occurred a long time before sampling for hs-cTn, the diagnosis could be missed if such RCVs are used as basis. It is also important to consider that RCVs can be one-sided or two-sided. Following the Fourth Definition of MI, both the decrease and increase of cTn concentration around the 99th percentile should be considered, so in this setting, a two-sided RCV concept should be applied. An increment can be interpreted as a potential liberation of troponin in the MI situation, whereas a decrement would mean a clearance mechanism after a prior release. It must also be considered with what probability (z-value) a change is to be detected. In this study, we have calculated a two-sided RCV using the mean CV_A from all the studies included in our meta-analysis for the short-term setting (9.8% for hs-cTnI and 9.2% for hs-cTnT). This gives two-sided RCVs ranging from 20% to 35% for the two cTn isoforms. These RCVs, which are estimated with 95% probability ($z = 1.96$) are in line with the changes (20%) proposed for a MI diagnosis in the Fourth Universal Definition (1). If one-sided RCVs were calculated, these would range from 20%–30%, with an 80% probability ($z = 1.64$). A one-

sided RCV could be applied when the baseline hs-cTn value was below the 99th percentile and only an increase was of interest.

The low II found in different states of health makes cTn suitable also when interpreting serial results in populations with renal and cardiac conditions (29), where RCVs based on relevant long-term estimates may be used to assess cardiac or kidney disease prognosis. Furthemore, RCVs may also be useful in the diagnosis of MI in the presence of renal disease, where increased baseline cTn concentration could be related to the renal impairment (30, 31).

Our RCVs are based on BV estimates derived from meta-analysis of several differently designed studies. These BV estimates are associated with some uncertainty and the associated RCVs should be considered with caution. In clinical practice, every laboratory should calculate its own RCV using a CV_A estimate from their own laboratory, at every concentration level if their analytical performance is different along the measuring interval. It is also important to be aware that RCV only implies that a change in serial test results can be explained by biological and analytical variation, with a given probability. Thus, this does not mean that clinically important changes cannot occur with a change less than the RCV (32).

ANALYTICAL PERFORMANCE SPECIFICATIONS

The application of our meta-analysis based BV estimates, derived for the short- and long-term settings, will impact laboratories' preferred APS, and decisions as to acceptable performance may be subject to considerations of intended clinical use. In an emergency laboratory, mainly focused on MI diagnosis, with rule in and rule out strategies, it would be recommended to apply stricter APS when applying hs-cTn assays because short-term BV estimates are smaller, whereas a general laboratory dedicated to monitoring the clinical course of a patient and including multiple pathological conditions not specifically addressed to MI diagnosis, but prognosis, could have wider APS goals, as indicated in Table 4.

The current recommendations for diagnosis of MI (rule-in and rule-out strategies) by high-sensitivity methods, state that the analytical performance should deliver a CV_A less than 10% at the 99th percentile (11). However, this criterion could be considered too permissive in light of our BV estimates. If BV estimates derived from the meta-analysis for short-term sampling of healthy individuals were used to set (desirable) APS, methods would be required to have analytical imprecision of 2.2% and 2.7% for hs-cTnI and hs-cTnT, respectively, for use in the rapid and early decision-making setting (Supplemental Table 4).

In conclusion, this study provides an overview and critical appraisal of BV studies for cTn and delivers meta-analysis derived estimates for hs-cTnI and hs-cTnT for short-term and long-term settings and for different states of health. Our study shows that CV_I estimates for cTnI and cTnT were similar in all settings. There appears to be a difference in CV_I estimates for the short- and long-term setting, but there is a large uncertainty around these point estimates. Estimates were similar in healthy subjects and patients suffering from various chronic diseases. The low individuality index of cTn highlights the usefulness of monitoring serial patient results by RCV both for MI diagnosis and in the follow-up of chronic diseases complementing the classical cut-off limits. Our BV estimates can be used to deliver APS for different clinical scenarios. These goals are stricter than those presently recommended for the diagnosis of MI and may be too strict for most of the current analytical methods.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: BV, biological variation; cTn, cardiac-specific troponin; cTnI, cardiac-specific troponin I; cTnT, cardiac-specific troponin T; hs-cTnI, high-sensitivity cardiac-specific troponin I; hs-cTnT, high-sensitivity cardiac-specific troponin T; CI, confidence interval; CV, coefficient of variation; CV_A, analytical CV; CV_I, CV, within-subject BV estimate; CV_G, CV, between-subject BV estimate; EFLM, European Federation of Clinical Chemistry and Laboratory Medicine; II, index of individuality; LoD, limit of detection; RCV, reference change value; SE, systematic error; TG-BVD, EFLM Task Group on Biological Variation Database.

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