Getting Cardiac Troponin Right: Appraisal of the 2020 European Society of Cardiology Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation by the International Federation of Clinical Chemistry and Laboratory Medicine Committee on Clinical Applications of Cardiac Bio-Markers

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The IFCC Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) represents international groups from laboratory medicine, cardiology, and emergency medicine that provide global educational guidance pertaining to the analytic and clinical applications of cardiac biomarkers. For that reason, most members are involved with national and international studies and trials pertaining to high-sensitivity cardiac troponins I and T (hs-cTnI and hs-cTnT, respectively) (1–3).

The recently published 2020 European Society of Cardiology (ESC) guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation present some topics well; however, the current special report was developed to delineate our specific concerns regarding the ESC guidance for the use of hs-cTn (4).

Guidelines should be based on a systematic review of the literature, an assessment of quality, and the bias of the evidence, and recommendations should be made with input from a multidisciplinary group with active participation from cardiology, laboratory medicine, and emergency medicine. Instead, the section on hs-cTn in the 2020 ESC guidelines document is overly focused on a single research consortium that comprises >50% of all references. Consequently, in our estimation, it fails to accommodate certain areas of practice that are important on a global scale, not just in Europe. The topics we address in this special report would have been identified if the ESC guidelines had been developed with more active participation from laboratory medicine and vetted more extensively. Many concerns expressed in the current document are relevant to the international laboratory medicine community. This gap in the review process is surprising, given the large number of analytic and clinical biomarker experts in Europe and the presence of a designated ESC Biomarker Committee that includes both laboratorians and clinicians (5).

Universal Definition of Myocardial Infarction (2018)

The Universal Definition of Myocardial Infarction (2018) document (6) endorses the use of sex-specific 99th-percentile upper reference limits (URLs) for hs-cTn assays while acknowledging differences among assays. In contrast, the 2020 ESC guidelines state, “The use of uniform cut off concentrations should remain the standard of care in the early diagnosis of MI [myocardial

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infarction).” This ignores the advocacy of the 2018 Universal Definition (6), which was endorsed by the ESC, and guidelines from the IFCC C-CB and the AACC Academy (3).

The ESC’s justification for using uniform hs-cTn cutoffs is based on the concept that other confounders like age, renal dysfunction, or time from onset of chest pain also might need to be considered to optimize cutoff values in patients presenting with symptoms suggestive of ischemia. The ESC guidelines acknowledge sex as a confounder (7) but state, “Until information technology tools that allow the incorporation of the effect of all four variables are available, the use of uniform cutoff concentrations should remain the standard of care in the early diagnosis of MI.” We disagree. This argument for use of uniform cutoff concentrations is predicated predominantly on findings using a uniform URL for hs-cTnT and fails to recognize the multiple other studies, including some that incorporate data from hs-cTnT, that provide data suggesting the benefit of such an approach (7–12). It is also in contrast to conventions in the field of laboratory medicine that advocate for appropriate and statistically based URLs by sex (8), for which all assays manifest an analytic difference (as in this situation). Indeed, multiple factors influence cTn values. For most factors, there is a continuum of effects depending on the magnitude of the influence, for example, as reflected in renal disease (13). Correcting for all of them would be extremely complex; however, that fact should not keep us from correcting the problems associated with the underdiagnosis and undertreatment of women with myocardial injury and infarction (14). Furthermore, the clinical studies and trials used to validate the shorter triage periods work in large part because they presage eventual adherence to the Universal Definition criteria, which are most often used as the gold standard. That fact is not as clear as it might be in the ESC guidelines.

The Universal Definition document identifies patients who are “late presenters” as a separate group and warns that they may not manifest significant serial cTn changes over a short time period because the downslope of the time–concentration cTn curve is slower than the upslope. It further notes that there is a high degree of variability in the kinetics of hs-cTn in those with ischemic heart disease so that many patients reach peak hs-cTn values early after the onset of symptoms and presentation. The ESC guidelines fail to describe this important group. In our opinion, clinicians need to be sensitive to this group of patients who have increased cTn concentrations that do not change substantially over 1–2 h because they are on the downslope of the curve. Such patients deserve additional sampling to ensure they are not simply presenting later after the onset of MI. This extremely important caveat was highlighted initially by the SWEDEHEART group, which reported that 26% of patients with MI might not manifest a changing pattern primarily for this reason (15).

**Early Presenters and Kinetics**

The ESC guidelines state, “In patients with MI, levels of cardiac troponin rise rapidly (i.e., usually within 1 h from symptom onset if using high-sensitivity assays) after symptom onset.” This statement could be prone to misinterpretation. The detection of a change in cTn within the reference interval is improved using hs-cTn assays but may be limited for time points close to the index event. There is concern about the use of these rapid diagnostic algorithms for patients presenting <3 h from symptom onset (16); that concern is acknowledged for the single sample but not for the 1-h rule-out. We would argue that this caveat deserves additional emphasis. Such occurrences can be easily missed because findings from studies using both hs-cTnI and hs-cTnT plotted against time from onset of non–ST-segment elevation MI index events demonstrate that the median time from symptom onset to obtaining the first draw is often >3 h. In addition, the time to first increase above sex-specific URLs is also >3 h, and women are less likely than men to cross those URLs in the baseline sample (16–18). Consequently, clinicians may not be sensitive to the fact that early presenters can pose a problem.

**Overdiagnosis of Myocardial Injury and Infarction**

The ESC also states, “Data from large multicenter studies have consistently shown that hs-cTn increases diagnostic accuracy for MI at presentation as compared with conventional assays.” This statement is true only when transitioning from the analytically insensitive fourth-generation cTnT assay to the hs-cTnT assay, for which a change in MI rates from 22% to 36% has been reported (19). This substantial increase is not observed with a transition from an analytically sensitive contemporary cTnI to an hs-cTnI assay. Such data have been reported for both Abbott (20) and Siemens (21) assays. However, this misconception has fueled clinicians’ concerns about an anticipated, large number of increased cTn concentrations above URLs that would overwhelm their practices. This outcome is not likely when transitioning from good, contemporary cTnI assays. It is even more unlikely in heterogeneous patient populations with poorer healthcare that are often found in urban US emergency departments and that also exist in some areas of Europe. The hs-cTn assays do not necessarily translate into higher clinical sensitivities at presentation compared with contemporary assays in emergency department populations of patients presenting with diverse
pathophysiology for myocardial injury and more type 2 MIs (20).

**Conventional vs High-Sensitivity Assays**

The most potentially confusing information is presented in figure 2 of the ESC document. The left panel depicts conventional assays and visualizes concepts from the 1990s. The numbers appear to come from the fourth-generation cTnT assay, an analytically insensitive assay that could not distinguish between the 99th-percentile URL and the assay’s limit of detection. In fact, many conventional cTn assays had good analytics, as outlined on the IFCC C-CB website (22). The right panel represents a schematic also predominantly predicated on the Roche hs-cTnT assay. It does not represent the 99th-percentile URLs for hs-cTn assays, as reported in tables on the IFCC C-CB website (23). The “red zone” for pathological disease begins at >20 ng/L, which is substantially lower than the overall and sex-specific URLs for many hs-cTn assays. The 99th-percentile URLs for the Siemens VISTA and Abbott ARCHITECT hs-cTnI assays (both CE marked) are as follows: VISTA shows 59 ng/L overall, 54 ng/L female, and 79 ng/L male; ARCHITECT shows 26 ng/L overall, 16 ng/L female, and 34 ng/L male. This misrepresentation will no doubt cause confusion for clinical laboratories and clinicians who attempt to implement these assays based on the ESC guidelines.

**Sample Types**

The ESC guideline fails to emphasize to practitioners that cTn URLs are assay and sample-type dependent. URLs demonstrate differences in hs-cTn concentrations among serum, lithium heparin plasma, and EDTA plasma (3, 23). To avoid potential misclassification, laboratories should utilize the same specimen type used in clinical studies to generate the data and algorithms for specific sample types.

**High-Sensitivity vs Point-of-Care cTn Testing**

The ESC guidelines acknowledge that point-of-care (POC) assays have not been evaluated as thoroughly as automated central laboratory assays. However, the guidelines advocate for the use of POC assays based on clinical performance criteria alone—a position that ignores several analytic issues. This problem is highlighted by the following statement: “The first hs-cTnI POCs [POC tests] have recently been shown to provide comparable performance characteristics to that of central laboratory hs-cTn I/T assays.” This statement applies only to clinical studies in which specimens were biobanked and plasma specimens, not whole blood samples, were analyzed by research technologists. For many POC assays, the jump from plasma to whole blood is a substantial challenge. In addition, the guideline does not address analytic performance aspects that can occur when nonlaboratory staff conduct POC testing (24). We concur with the recent National Institute for Health and Care Excellence guidelines that until a POC device is appropriately validated using whole blood, it should not be designated as hs-cTn POC assay (25). We suggest this should be the ESC position as well.

**Markers Other Than cTn**

The ESC guidelines state, “Myosin-binding protein C (cMyC) is more abundant than cTn and may therefore provide value as an alternative to, or in combination with, cardiac troponin.” This recommendation is concerning because the underlying study data are extremely limited; originate predominantly from one or two research laboratories using partially automated research assays, which take hours to report results; and are poorly biologically and analytically validated outside of patients with acute coronary syndrome. In the published literature, when myosin-binding protein C was measured with a so-called high-sensitivity immunoassay, the sensitivity and specificity for MI diagnosis were comparable to those of hs-cTnT or hs-cTnI (26). Not only is this analyte not ready for clinical use, it does not have any regulatory approval for clinical use at present. Furthermore, the guidelines state, “Routine use of copeptin as an additional biomarker for early rule-out of MI is recommended in increasingly uncommon settings where hs-cTn assays are not available. Copeptin does not have relevant added value for institutions using one of the well-validated hs-cTn-based rapid protocols in the early diagnosis of MI.” We find this recommendation confusing. Both the Universal Definition and the ESC guidelines advocate for hs-cTn assays. Why incur the regulatory burden, cost, and added logistics of implementation of an additional test that adds no real value in conjunction with hs-cTn and is not well validated for detection of patients with type 2 MI and myocardial injury? In addition, recent studies have concluded that, compared with several “rapid” rule-out diagnostic strategies, the combined use of copeptin and hs-cTn was not as safe (27) and that copeptin does not demonstrate early release kinetics, as do hs-cTnI and hs-cTnT, after experimental coronary balloon occlusion (28).

**Rule-in and Rule-out Algorithms**

ESC guidelines address rapid rule-in and rule-out algorithms, noting, “This seems to substantially reduce the delay to diagnosis, translating into shorter stays in...
the emergency department and lower costs.” One novel aspect of the guidelines is the focus on 0/2-h algorithms which are more robust regarding analytic variability than the 0/1-h algorithms. It is important to note that many of these algorithms have been developed from populations with chest pain only for Roche hs-cTnT and Abbott hs-cTn assays. The Ortho VITROS, LSI Pathfast, and Quidel Triage True assays have only one publication for algorithms (Singulex closed operations in 2019), and none have evaluated the “new” 0/1-h algorithm that was presented in the ESC document. Nevertheless, cutoff values that are assay specific are presented in table 5 of the guidelines. Except for hs-cTnT, this table needs to be updated for the majority of hs-cTn assays for which, in some instances, there is substantial literature. Peer-reviewed literature for the Abbott and Siemens hs-cTn assays, for example, suggests alternative values. Abbott hs-cTn algorithms have used <2 ng/L and <5 ng/L to rule out MI predicated on a single sample (29–31). This approach has also been reported for the Siemens assays (32, 33). However, the ESC has listed the rule-out cutoff for the Abbott assay as <4 ng/L. In previous publications, the rule-in cutoff was listed as ≥52 ng/L, but now it is ≥64 ng/L. Data that support significant analytic variability are present throughout the low range of hs-cTn assays but have not been adequately addressed regarding how such variability affects clinical decisions (34, 35). Numerical cutoffs are important because different controls should be used if one is using <2 ng/L vs <4 ng/L. We have checked values published in the guideline and note numerous discrepancies.

The High-Sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome (High-STEACS) group has published widely on hs-cTn algorithms with particular regard to a single-test rule-out using a 5-ng/L threshold (31, 36), along with the Use of Troponin in Acute Coronary Syndromes (UTROPIA) cohort studies (29). The High-STEACS algorithms have been validated in very large observational studies and in a large stepped-wedge randomized controlled trial (37). For those who currently follow those algorithms in practice, the omission appears notable. The same cutoff value seems appropriate for the Siemens assays (32).

Both accelerated (0/1-h and 0/2-h) and 0/3-h algorithms are recommended by the ESC for early rule-out of MI. It must be noted that these are different types of protocols. The accelerated algorithms are based on hs-cTn concentrations at presentation and absolute changes within the first 1 or 2 h. They are based on the ability to predict that the patient will be ruled in or out for MI according to the Universal Definition of MI on further testing. The guidelines state, “It is recommended to use the 0 h/1 h algorithm (best option, blood draw at 0 h and 1 h) or the 0 h/2 h algorithm (second-best option, blood draw at 0 h and 2 h)” (see figure 3 in the ESC guidelines). However, the 0/3-h High-STEACS pathway is also recommended and is an alternative to the multiple threshold pathways that are designated as “preferred.” Are there data that show this pathway is superior, and what criteria should be used in guidelines? Based on our own experiences in daily practice with cardiac biomarkers and MI diagnosis, the facts are that baseline specimens typically are taken a median of about 3 h from onset of symptoms, and the timing of a second draw worldwide is rarely at 1 h. Consequently, many patients are evaluated closer to 3–4 h than at 1–2 h. Is it clear that the change in criteria will work equivalently in very early presenters (e.g., at 1–2 h) or with the “late” presenters? Given these concerns, should the early 0/1-h protocols be preferred?

No consideration was given to the value of clinical decision aids and risk scores (38). Emergency physicians must take multiple factors into account when assessing their patients, including the electrocardiogram and patient history. Although the ESC guidelines recommend clinical evaluation, for some clinicians who are less experienced in cardiology, “troponin-only” algorithms are often used, and this approach is potentially dangerous. Decision aids force a clinical component on the process. Decision aids are widely used in clinical practice, and several have been studied in randomized controlled trials (Improved Assessment of Chest Pain Trial [IMPACT]; Emergency Department Assessment of Chest Pain Score [EDACS]; Thrombolysis in Myocardial Infarction [TIMI] score; Accelerated Diagnostic Protocol [ADAPT]; Manchester Acute Coronary Syndromes [MACS] trial). Their omission from the guideline will appear notable to practicing emergency physicians. This also extends to the situation with unstable angina. Some clinicians will likely rely on hs-cTn rather than clinical decision-making unless prompted by clinical risk aids and can make subjective judgements about how to manage patients with electrocardiogram changes (e.g., ST depression or T-wave inversion) despite normal cTn concentrations.

The Path Forward

An international randomized control trial should address both the 0/1-h and 0/2-h algorithms for the central laboratory and whole-blood POC hs-cTn assays, with events adjudicated by the Universal Definition of MI using a 0/3-h protocol. Special attention should be given to both early and late presenters. This approach would be evidence based. Such a trial could include novel tools such as the machine learning myocardial–ischemic injury index (MI³) (39). These tools could provide individualized risk that incorporates age, sex, and single and
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serially paired hs-cTn results. It could probe the data for the optimal magnitude and rate of change in cTn as a risk estimator for MI. It could also probe whether fixed concentration thresholds, fixed absolute or percentage changes in concentration, and the mandating of specific time points for serial testing are necessary.

Summary

Our IFCC C-CB evidence-based appraisal addresses numerous concerns about the use of hs-cTn testing in diagnostics for which the ESC guidelines have deficiencies. Some recommendations appear to contradict the ESC endorsed Fourth Universal Definition of Myocardial Infarction as well as laboratory medicine practice guidelines.

Nonstandard Abbreviations C-CB, Committee on the Clinical Application of Cardiac Biomarkers; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; ESC, European Society of Cardiology; URL, upper reference limit; MI, myocardial infarction; POC, point of care; High-STEACS, High-Sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome.

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