Clinical Chemistry

Manuscript Title:	The IFCC Clinical Application of Cardiac Biomarkers Committee's Appraisal of the 2020 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-segment Elevation: Getting Cardiac Troponin Right
Manuscript No:	CLINCHEM/2020/332908 [R1]
Manuscript Type:	Special Report
Date Submitted by the Author:	14 Dec 2020
Complete List of Authors:	Fred S Apple, Paul Collinson, Peter Kavsak, Richard Body, Jordi Ordóñez-Llanos, Amy Saenger, Torbjorn Omland, Ola Hammarsten, and Allan Jaffe
Keywords:	99th percentile; biomarkers; cardiac troponin; myocardial infarction; risk outcomes ; sex-specific reference limits

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The IFCC Clinical Application of Cardiac Biomarkers Committee's Appraisal of the 2020 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-segment Elevation: Getting Cardiac Troponin Right

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Dr. Kavsak: grants/reagents/consultant/advisor/ honoraria, Abbott Laboratories, Abbott Point of Care, Beckman Coulter, Ortho

Clinical Diagnostics, Quidel, Randox Laboratories, Roche Diagnostics, Siemens Healthcare Diagnostics; McMaster University has filed patents with Dr. Kavsak listed as an inventor in acute cardiovascular biomarker field;

Dr. Jaffe: consultant, Beckman, Abbott, Siemens, Roche, Radiometer, ET Healthcare, Sphingotec, Amgen, Novartis

Dr. Ordonez-Llanos – none.

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Dr.Body: Consultant, LumiraDx, Beckman, Siemens; Donation of reagents for research and or grant, Roche, Abbott POC, Beckman;

Dr. Hammarsten: None;

Dr. Omland: Consultant or Advisory Role, Abbott Diagnostics, Roche Diagnostics, CardiNor; Honoraria, Abbott Diagnostics, Roche Diagnostics; Research Funding, Abbott Diagnostics, Roche Diagnostics, SomaLogic, Novartis, all to institution.

The Committee on the Clinical Application of Cardiac Biomarkers (C-CB) of the International Federation of Clinical Chemistry (IFCC) represents international groups from laboratory medicine, cardiology and emergency medicine involved with providing global educational guidance pertaining to the analytical and clinical applications of cardiac biomarkers. For that reason, most of the members are involved with national and international studies and trials pertaining to high sensitivity (hs)-cTnI and hs-cTnT (1-3). Although 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' do somethings very well, this special report was developed to delineate our specific concerns regarding the guidance for the use of hs-cTn (4). Guidelines should be based on a systematic review of the literature, assessment of quality and bias of the evidence, and recommendations should be made with input from a multi-disciplinary group with active participation from cardiology, laboratory medicine and emergency medicine. Instead, the section on hs-cTn is overly focused on a single research consortium which subsumes >50% of all references. Thus, it fails in our estimation to accommodate certain areas of practice that are important on a global scale, not just in Europe. The topics we address in this article would have been identified if the guidelines had been developed with more active participation from Laboratory Medicine and vetted more extensively. Many of the concerns being 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 analytical and clinical biomarker experts in Europe and the presence of a designated

ESC Biomarker Committee which contains both laboratorians and clinicians (5).

Universal Definition of Myocardial Infarction (2018)

The Universal Definition of Myocardial Infarction (2018) (6) endorses the use of sex-specific 99th percentile upper reference limits (URLs) for hs-cTn assays while acknowledging differences between 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." This ignores the advocacy of the 2018 Universal Definition (6) which was endorsed by the ESC, as well as guidelines from the IFCC-CB and the Academy of the American Association for Clinical Chemistry (AACC) (3).

The ESC justification for using uniform hs-cTn cut-offs is based on the concept that other confounders like age, renal dysfunction or time from chest pain onset also might also need to be considered to optimize cut-off values in patients presenting with symptoms suggestive of ischemia. The ESC guidelines do 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 cut-off concentrations should remain the standard of care in the early diagnosis of MI". We disagree. It is predicated predominantly on findings using a uniform URL for hs-cTnT and fails to recognize the multiple other studies, including hs-cTnT, that provide data suggesting the benefit of such an approach (7-12). It also is in contrast to conventions in the field of laboratory medicine that advocates for appropriate and statistically based URLS by sex (8), when as in this situation all assays manifest an analytical difference. Indeed multiple issues influence cTn values. Most provide a continuum of effects depending on the magnitude of the influence, as reflected in renal disease for example (13).

Correcting for all of them would be extremely complex. That fact however should not keep us from correcting the problems associated with the underdiagnosis and under treatment 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 is most often used as the gold standard. That fact is not as clear as it might be in the ESC guidelines.

The Universal Definition 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 because the downslope of the time-concentration cTn curve is slower than the upslope. It further notes the high degree of variability in the kinetics of hs-cTn in those with ischemic heart disease with many patients reaching 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 these patients who have increased cTn concentrations that do not change substantially over an hour or two because they are on the downslope of curve. They deserve additional sampling to ensure they are not simply presenting later after the onset of MI. This terribly important caveat was highlighted initially by the SWEDEHEART Group who reported that 26% of patients with MI might not manifest a changing pattern mostly 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. To detect a change in cTn

within the reference interval is certainly 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 hours (16) that is acknowledged for the single sample, but not for the one-hour rule out. We would argue that this caveat deserves additional emphasis. The issue can be easily missed, because findings from studies using both hs-cTnI and hs-cTnT plotted against time from onset of NSTEMI index events demonstrates that the median time from symptom onset to obtaining the first draw is often > 3 hours. In addition, the time to first increase above sex-specific URLs is also > 3 hours, and women are less likely than men to cross those URLs in the baseline sample (16-18). Thus, clinicians may not be sensitive to the fact that early presenters can be 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 only true when transitioning from the very analytically, insensitive 4th gen cTnT assay to the hs-cTnT assay where a change in MI rates from 22% to 36% has been reported (19). This substantial increase is not observed with a transition from an analytical sensitive contemporary cTnI to a hs-cTnI assay. This has been reported for both Abbott (20) and Siemens (21) assays. This misconception has fueled clinicians concerns about an anticipated, large numbers of increased cTn concentrations above URLs which would overwhelm their practice. This outcome is not likely when transitioning from good contemporary cTnI assays. This is even more the case in more heterogeneous patient populations with poorer healthcare,

as often found in inner city USA emergency departments, which also exist in some areas of Europe. hs-cTn assays do not necessarily translate into higher clinical sensitivities at presentation compared to contemporary assays in ED populations of patients presenting with diverse pathophysiologies for myocardial injury and more type 2 MIs (20).

Conventional vs. high-sensitivity assays

The most glaring, 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 4th generation cTnT assay, an analytically insensitive assay that could not distinguish between the 99th percentile URL and the assay's limit of detection (LoD). In fact, many conventional cTnI assays had good analytics as outlined on the IFCC C-CB website (22). The right panel represents a schematic predominately also predicated on the Roche hs-cTnT assay. It does not represent the 99th percentile URLs for hs-cTnI assays, as reported in tables on the IFCC C-CB website (23). The 'red zone' for pathological disease begins at > 20ng/L, which is substantially less than the overall and sex-specific URLs for many hs-cTnI assays. For example, 99th percentile URLs for the Siemens VISTA and Abbott ARCHITECT hs-cTnI assays (both CE Marked) are: VISTA: overall 59ng/L, female 54 ng/L and male 79 ng/L; ARCHITECT: overall 26 ng/L, female 16 ng/L and male 34 ng/L. 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 sensitize practitioners to the fact that indicates that cTn URLs are assay and sample type dependent. URLs demonstrate differences in hs-cTn concentrations between serum, lithium heparin plasma, and EDTA plasma (3,23). Laboratories should utilize the same specimen type used in clinical studies to generate the data and algorithms for specific sample types to avoid potential misclassification.

High sensitivity vs. point of care cardiac troponin testing

The ESC guidelines acknowledge that point-of-care (POC) assays have not been as thoroughly evaluated as automated central laboratory assays. They then proceed to advocate for their use based on clinical performance criteria alone which ignores several analytical issues. This is highlighted by the following statement, "The first hs-cTnI POCTs have recently been shown to provide comparable performance characteristics to that of central laboratory hs-cTn I/T assays". This statement only applies to clinical studies where specimens were bio-banked and plasma specimens, not whole blood was analyzed by research technologists. For many POC assays, the jump from plasma to whole blood is a substantial challenge. In addition, it does not address analytical performance aspects that might be influenced when non-laboratory staff conduct POC testing (24). We concur with the recent NICE guidelines that until a POC device is appropriately validated using whole blood it should not be designated as hs-cTn POC assay (25). We would suggest the ESC position should as well.

Other markers than cardiac troponin

The 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 as study data are extremely limited, originate predominately 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 acute coronary syndrome patients. In the published literature, cMyC measured with a so-called high-sensitivity immunoassay, the sensitivity and specificity for MI diagnosis was comparable to that of hs-cTnT or hs-cTnI (26). Not only is it not ready for clinical use, it also does not have any regulatory approval for clinical use at present. Further, guidelines state, "Routine use of copeptin as 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. Further, recent studies have concluded that compared to 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-hour algorithms which are more robust in regard to analytical variability than the 0/1-hour algorithms. It is important to note that many of these algorithms have been developed from chest pain only populations for Roche hs-cTnT and Abbott hs-cTnI assays. The Ortho VITROS, LSI Pathfast and Quidel Triage True assays have only one publication for algorithms (Singulex closed operations in 2019), and none that have evaluated the 'new' 0/1h algorithm that was presented in the ESC document. Despite that, cut-off values which are assay-specific are presented in the guidelines table 5. Except for hs-cTnT, this table needs to be updated for the majority of hs-cTnI assays where in some instances there is a substantial literature. For example, there is peer reviewed literature for the Abbott and Siemens hs-cTnI assays that suggest alternative values. Abbott hs-cTnI algorithms have used <2 ng/L and < 5 ng/L to rule-out MI predicated on a single sample (29-31). This 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 supports significant analytical variability is present throughout the low range of hs-cTn assays but has not been adequately addressed regarding how that affects clinical decisions (34,35). Numerical cutoffs matter as different controls should be used if one is using < 2 ng/L versus < 4 ng/L. We have checked values that the guideline has published, and note numerous discrepancies.

The High-STEACS group has published widely on hs-cTn algorithms with particular regard to a single test rule-out using a 5ng/L threshold (31.36) along with the USA UTOPIA 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 cut off value seems appropriate for the Siemens assays (32).

Both accelerated (01/hour and 0/2 hour) and 0/3hour algorithms are recommended by the ESC for early rule out of MI. It needs to 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 hours. They are based on the ability to predict that the patient will rule 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) (ESC Figure 3)." However, the 0/3-hour HighSTEACS pathway is also recommended and is an alternative to the multiple threshold pathways that are designated as 'preferred'. Are there data that it is superior, which should be the criteria employed in guidelines? Based on our own experiences in daily practice with cardiac biomarkers and MI diagnosis, the facts are that baseline specimens typically are a median of about 3h from onset of symptoms and the timing of a second draw worldwide is rarely at 1h. Thus, many of these patients are evaluated closer to 3-4 hours than at 1 or 2 hours. Thus, is it clear that the change criteria will work equivalently in very early presenters (say at 1 or 2 hours) or with the "late presenters." Given these concerns, should the early 0/1-hour protocols be preferred?

No consideration was given to the value of clinical decision aids and risk scores (338). Emergency physicians must take many multiple factors into account when assessing their patients, including the ECG and patient history. Although the ESC guidelines do recommend clinical evaluation, for some who are less experienced in

cardiology, 'troponin-only' algorithms are used and this is potentially dangerous. Decision aids force a clinical component on the process. Decision aids are widely used in clinical practice and several have been subjected to randomized controlled trials (HEART impact study; EDACS v TIMI; ADAPT; MACS trial). Their omission from the guideline will appear notable to practicing emergency physicians. This extents to the situation with unstable angina as well. Some clinicians will likely rely on hs-cTn rather than clinical decision making, unless prompted by clinical risk aids so they can make subjective judgements about how to manage patients with ECG changes (e.g. ST depression or T wave inversion) despite normal cTn concentrations.

The path forward

An international randomized control trial should be carried out addressing both the 0/1 hour and 0/2 hour 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 hour protocol. Special attention would be given to both "early" and "late" presenters. This would provide an evidence based option. Such a trial could include novel tools such as the machine learning myocardial-ischemic-injury-index (MI^3) (39,40). These tools could provide individualized risk that incorporates age, sex, and single and 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, or the mandating specific time-points for serial testing are necessary.

Summary

Our IFCC C-CB evidence-based appraisal address numerous concerns about the use of hs-cTn testing in diagnostics that the ESC guidelines are deficient in. Some appear to contradict the ESC endorsed Fourth Universal Definition of Myocardial Infarction as well as Laboratory Medicine practice guidelines.

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