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The quality of laboratory aspects of troponin testing in clinical practice guidelines and consensus documents needs to be improved

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ABSTRACT

Objective: The European Federation of Laboratory Medicine (EFLM) and the Union of European Medical Specialists (UEMS) joint Working Group on guidelines recently proposed a checklist to help standardize the description of laboratory investigations in clinical practice guidelines (CPG).
Methods: Nine CPGs or consensus documents published from 2011 to 2013 describing the investigation of chest pain, diagnosis of acute coronary syndrome, or myocardial infarction were evaluated against the published checklist.
Results: Clinical use of troponin analysis are commonly dealt with but the publications present variable, vague and sometimes conflicting information regarding this laboratory test being very much relied on upon making a diagnosis of acute coronary syndrome. Most of the laboratory related checklist items are not considered or need to be updated e.g. suggested analytical quality goals are not applicable for the high sensitive assays and important interferences that may lead to false positive or negative diagnoses are commonly not mentioned.
Conclusion: The current paper sums up important analytical and biological issues related to troponin assays and gives suggestions for analytical quality goals that could be included in CPG's.

1. Introduction

The description of laboratory tests in clinical guidelines is variable with often inadequate information provided. It is important that clinicians referring to these guidelines are fully aware of all aspects of the tests being considered for use, not just in relation to the clinical scenario but also in a wider context.

Recently the European Federation of Laboratory Medicine (EFLM) and the Union of European Medical Specialists (UEMS) joint Working Group on guidelines proposed a checklist to help standardize the description of laboratory investigations in clinical practice guidelines (CPG) [1]. The definition of myocardial infarction has been regularly updated and relates heavily to troponin measurements, therefore adequate information about troponin test must be provided [2]. However, uniform and correct interpretation of troponin results is still questionable; earlier studies have shown that the interpretation of myocardial markers in clinical practice is only partly in line with the universal definition of myocardial infarction [3]. One way of improving the situation would be to present consistent and updated information through clinical practice guidelines. Our aim was to investigate if the guidelines were up to date with respect to troponins and whether they ensured best practice use of troponin test results.

2. Methods

CPGs or consensus documents published from 2011 to 2013 describing the investigation of chest pain, diagnosis of acute coronary syndrome (ACS), or myocardial infarction (MI) were considered for inclusion in the study, by searching PubMed and a guideline database (National Guideline Clearinghouse). In addition the websites of various cardiovascular societies were examined to search for publications

Abbreviations: CPG, clinical practice guidelines; ACS, acute coronary syndrome; MI, myocardial infarction; CVa, analytical variation; STEMI, ST-elevation MI; ESC, European Society of Cardiology; RCV, reference change values; CVi, biological variation.

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relating to guidelines on diagnosis of acute chest pain or ACS (National Academy of Clinical Biochemistry, Pan African Society of Cardiology, Asian Pacific Society of Cardiology, and the Canadian Cardiovascular Society). The short time frame for the search was chosen since earlier guidelines are likely to be updated in the near future due to third universal definition of MI being published in 2012. Guidelines exclusively dealing with treatment (e.g. revascularization or follow-up of already diagnosed ACS/MI) were excluded.

The included papers were evaluated against the published checklist for the optimum description of tests in guidelines including the pre-analytical phase (test request and sampling), analytical phase (troponin measurement), and post-analytical phase (test reporting and interpretation) [1].

3. Results

Nine international guidelines or consensus documents were identified [2,4–11] and the description of troponin testing was reviewed according to the checklist. Results are shown in Table 1.

3.1. Pre-analytical issues

Virtually all guidelines included information related to the use of troponin; for which specific condition the test should be used; frequency of testing; the time frame between clinical event and testing; how to define the diagnosis; and the diagnostic cut off applicable (seven documents suggested the 99th percentile to be used and one suggested both the 99th percentile (to define ACS) and 100 ng/L (to define clinical MI) [10]). The guideline about ST-elevation MI (STEMI) did not suggest any diagnostic cut off value for troponins [11].

Variable advice was given regarding the number of tests required to diagnose ACS; two documents suggested that the diagnosis could be made after performing only one test [6,10], while the others recommended serial testing including at least two results. Comparison between similar diagnostic tests were quite frequently done: several documents compared conventional and high sensitivity troponin assays [4,6,8], one guideline did conclude that creatine kinase (CK)-MB should not be used any longer [7] and also stated that a high sensitive troponin I assay (ARCHITECT STAT hs-cTnI, Abbott Diagnostics) had better clinical performance compared to other troponin assays. Other guidelines however specified that both troponin T and I assays were clinically equal in performance [9,10]. The guideline dealing with STEMI compared troponin testing with electrocardiography, which is the first line diagnostic tool for this type of MIs.

3.2. Analytical issues

Information about well-known analytical interferences (e.g. hemolysis and heterophilic antibodies [12,13]) was scarcely reported [2,4]. Five guidelines gave some information about desirable analytical variation (CVa), i.e. 10% at the diagnostic cut-off for MI defined as the 99th percentile of a normal reference population. Comprehensive analytical performance goals including bias and total error are missing. Standardization and traceability recommendations are insufficient. The use of internal or external quality assurance was not mentioned in any document. The European Society of Cardiology (ESC) guideline recommends the use of point-of-care tests for troponin when a laboratory cannot consistently provide test results within 60 min (maximum turnaround-time) [9].

3.3. Post-analytical issues

Even though 6/9 documents suggested that the diagnosis of ACS was based upon sequential changes in troponin results, only the ESC consensus document quantified these changes [4]. They considered that the changing assay scene renders definitions transient but propose that at the moment if the baseline sample is <Upper reference limit (URL), then a clinical significant change should be defined as >50% whereas if the initial value is >URL, then a lower increase of >20% is appropriate (high sensitive assays). These recommendations were given after a discussion of analytical variation of troponins, reference change values (i.e. random variation caused by analytical and biological variation) and the magnitude of absolute high sensitive troponin T changes seen in patients with MI. However, specific analytical quality demands in relation to this were not discussed. Troponin elevations due to non-ACS causes such as acute illness [2,4–6,8,9], acute phase reaction [2,4,6,8,9] and some medications [2,5,6,9] were frequently mentioned. Age and gender differences commonly seen for high sensitive assays [14] were rarely addressed [7], and similarly elevations related to physical activity or acute illness [15,16] were seldom mentioned [2,6].

With regard to non-ACS causes of troponin elevation acute illness [2,4–6,8,9], acute phase reaction and some medications were frequently mentioned. Age and gender differences were rarely addressed, and similarly elevations related to physical activity were seldom included.

4. Discussion

The main findings in this study are that clinical information related to the use of troponins is frequent in CPGs. However, even though a universal definition of myocardial infarction has been available for several years the recommendations differ between the guidelines investigated. Important information related to the interpretation of test results (e.g. analytical quality specifications, possible sources of analytical interference or non-ACS influence of troponin results and quantification of significant changes) are frequently missing or outdated.

Good analytical performance is absolutely crucial in facilitating the correct interpretation of laboratory results and the analytical quality of commercially available assays (e.g. HbA1c or troponins) can improve very substantially if better performance is endorsed through cooperation between clinicians and laboratory professionals. Analytical performance specifications commonly include imprecision (CVa) and bias (i.e. systematic errors) goals and are preferably based on clinical need or biological variation [17]. The recommendation from the ESC articulates a clinical need that, at the 99th percentile, the assay should have an analytical variation low enough to detect a 20% change in consecutive troponin results. The expected random variation (i.e. the reference change values; RCV) for consecutive troponin results may be calculated (95% CI) as described by Fraser and Harris [18]:

$$RCV = bias + z\ \ value \times \sqrt{2} \times \left(\sqrt{CVa^2 + CVi^2}\right).$$

If the goal is to detect a 20% concentration change (i.e. the RCV should be below 20%) with a high level of confidence (e.g. 95% CI), will the desirable CVa for the assay be dependent on the biological variation (CVi) for the particular constituent measured? Short term (i.e. 1–4 h) CVi for some of the high sensitive troponins has recently been published and ranges from 1–7% (hs-cTnT Roche) to 5–14% (hs-cTnI Abbott) [19–21]. If the lowest of these numbers are used in the above stated equation with a bias of zero the CVa needs to be from less than 5% (hs-cTnI Abbott) to 7% (hs-cTnT Roche) to give a RCV value of less than 20%. This shows that the "10%-rule" (i.e. an assay should have 10% CVa at the 99th percentile) does not apply anymore. New goals should address the clinical need for applying a certain delta value at a certain level of confidence and take the analytical and biological variation for the different high sensitive troponin assays into account ensuring applicability.

The reviewed recommendations regarding analytical performance for troponins up to now include no information about allowable bias. The need for comprehensive analytical performance goals for troponins was highlighted in 2012 when a significant shift between lots (i.e. 6 ng/L) was detected by in-house low internal quality control samples [22]. This