Mini-Review

Update on global conversion to high sensitivity cardiac troponin assays

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Abstract: Progressive improvements in immunoassay performance for cardiac troponin (cTn) has resulted in the current generation of high sensitivity assays. These are characterised by the ability to measure troponin with high precision. The most important aspect is that they are able to measure levels below the 99th percentile with some able to measure values close to the population lower reference limit. Rapid predictive algorithms to support early classification of patients presenting with chest pain into those at high, intermediate or low risk of developing myocardial infarction (MI) utilising these high sensitivity assays have been developed. High sensitivity troponin assays have now been made available worldwide. Implementation into routine clinical practice has occurred at different rates globally. The major challenge to initial adoption has been largely due to regulatory acceptance. In some areas there have been financial constraints but this has largely influenced the transition from conventional "cardiac enzyme" measurement to troponin measurement rather than the conversion to a high sensitivity assay. Clinical utilisation has largely been with replacement of the previous generation troponin assay with a high sensitivity assay. There have been significant delays in implementing novel rapid diagnostic pathways that exploit the ability to discharge on single sample measurement on admission as well as rapid predictive algorithms. There also appears to be widespread use of high sensitive troponin measurements in a range of emergency department (ED) populations beyond those with chest pain. The challenge with implementing these assays is their use in the appropriate population and the feasibility of implementing the rapid diagnostic protocols that high sensitivity assays support.

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The evolution of cardiac troponin (cTn) measurement to high sensitivity assays

The introduction of cTn measurement into the routine clinical laboratory repertoire has led to a profound shift in the role of cardiac biomarker testing. Originally used for retrospective diagnosis, cardiac biomarkers in their current incarnation of high sensitivity cardiac troponin (hs cTn) for measurement of cardiac troponin T (hs cTnT) and cardiac troponin I (hs cTnI) are now recommended by national guideline agencies (1) and professional societies (2). Measurement of cTn is now the "gold standard" test for the diagnosis of myocardial infarction (MI) and has replaced all other cardiac biomarkers (3). The reasons for the transformation are twofold and interlinked. First, the measurement of cTn either as cardiac troponin T (cTnT) or cardiac troponin I (cTnI) was shown to detect prognostically significant myocardial damage, missed MI, in patients considered to have unstable angina by conventional "cardiac enzyme" measurement (4,5). Second, the evidence of the superiority of cTnT and cTnI measurement led to the redefinition of MI in terms of cTn measurement (6).

Uptake of high sensitivity troponin assays

hs cTn assays are defined by two criteria. First, the ability

to measure with an imprecision of less than 10% at the 99th percentile of a reference population. Second, they are able to produce numeric values in at least 50% or more of the reference population, both male and female (7,8). The evolution of cTn assays from the first versions, which were relatively insensitive, to the current versions has been iterative, they did not spring fully formed like Athena from Zeus. Two factors have driven the development of hs cTn assays. First, there is the natural tendency of manufacturers to develop and improve assays. This is nicely illustrated by the conversion of the first to second generation cTnT assay which showed a problem of cardio specificity due to choice of antibodies in the presence of extreme elevation of skeletal troponin T (9). Second, the redefinition of MI mandated an analytical performance that was not met by any of the assays on the market at the time the guideline was produced (6). The first hs cTn assay introduced was the Roche diagnostics cTnT assay (Roche Diagnostics, Switzerland). The performance uplift was quite significant with the limit of detection of the assay moving from (in nanograms) 30 to 3 ng/L. A similar trend for cTnI assays has occurred, although here the shift in performance has not been quite as dramatic. The majority of the existing cTnI assays provided acceptable analytical performance characteristics. There is now an hs cTn assay available from all of the major diagnostics companies. The major problem to date has been regulatory approval with assays available in Europe and Worldwide long before clearance by the US Food and Drug administration (FDA). Clearance of hs cTnT occurred only in January 2017 and the first hs cTnI assay (Abbott) only in 2020.

Uptake of cardiac troponin testing and the use of hs cTn has been monitored over time by a series of European surveys, the CARdiac MARker Guideline Uptake in Europe (CARMARGUE) project of the European Federation of Laboratory Medicine (formerly the European Society of Laboratory Medicine) (10-14). This project undertook a regular internet-based questionnaire survey performed after publication of guidelines and recommendations from clinical and laboratory societies worldwide. A consistent finding was the rapid adoption of cTn measurement and its use as the preferred biomarker. This has been accompanied by a decline in other biomarkers offered with aspartate transaminase (AST) and lactate dehydrogenase (LDH). In the most recent survey, no laboratories reported using AST and LDH as part of their routine cardiac profile. Creatine kinase especially measurement of the MB isoenzyme (CK-MB) remains in routine clinical use although there is little evidence to support this (15). The usual reason expressed for retaining CK-MB is clinician preference. An international telephone survey performed in 2016 found the same trend with cardiac troponin being used as the preferred marker (16). At this point, hs cTn assays were available worldwide but not in the US with on average approximately 50% conversion from conventional sensitive to high sensitivity assays. A comparative survey in the United Kingdom performed in 2014 (when high sensitivity assays were available although not from all manufacturers) found a 60% conversion to high sensitivity assays. Most recently, this has increased to 88% (17). Currently in Europe, there is almost complete transition to high sensitivity assays (14) with laboratories either currently using or intending to use hs cTn (14). Interestingly, where diagnostic facilities are using point of care testing (POCT), which is not high sensitivity, they are shifting to an hs laboratory assay. Internationally, there has been a change to hs cTn. Currently, manufacturer's offer both a conventional sensitive and hs cTn assay but with the universal intention of phasing out the conventional sensitive assay entirely (personal communication). The stage of completeness in phasing out the conventional sensitive assay depends on the regulatory status and the timing of introduction of the hs cTn assay from any given manufacturer. Early introduction and approval has produced almost 100% transition to hs cTn. In Europe, only hs cTnT is currently sold whereas in the US laboratories are still transitioning. A further complication may be that laboratories are in the process of changing instrumentation and may delay introduction of the high sensitivity assay until the instrument change has occurred. Use of non-high sensitivity assays is now largely confined to countries where there is a current lack of regulatory approval of a high sensitivity assay or where there has been a significant delay in introduction. Here, retention of a conventional sensitive is only prior to conversion to high sensitivity. It is expected that over the course of the next 5 years only high sensitivity assays will be in use internationally.

The significant advantage of hs cTn assays over conventional sensitive assays is the ability to measure cTn at very low levels, values in the lowest quartile of the reference population and typically in the lower centile with very high reproducibility on repeat measurement. This is referred to as the ability to measure with high sensitivity and low imprecision. These analytical characteristics have resulted in the development of a number of accelerated predictive and diagnostic pathways, described in detail later in this

issue, based on measurement of cTn using a high sensitivity method on admission and 1, 2 or 3 hours from admission. Utilisation of these strategies has however significantly lagged behind the uptake of hs-cTn measurement (14,16).

Utilization of high sensitivity troponin measurements in routine clinical practice—the reality challenges

Ever since troponin testing was introduced there has been a chronic problem of over requesting (18,19). The high degree of cardio specificity of cTn measurements means that there has been a tendency to use measurement as a general rule out test for any form of cardiac injury. This is a double-edged sword as non-specific requesting may in fact delay appropriate care (20). There is no doubt that troponin elevations outside the acute coronary syndrome (ACS) population carry prognostic significance (21). There is therefore some logic to the concept of using troponin measurement when diagnosis is uncertain to exclude myocardial injury. The advent of hs cTn measurement has increased the prevalence of troponin elevations outside the ACS population. Indeed, it is now the case that more troponin elevations are due to type 2/ischemic myocardial injury than to type 1 (classical) MI (22). The problem is that only a minority of patients presenting to the emergency department (ED) have a final diagnosis that includes ischemic heart disease. Typically, in a low-risk chest pain population presenting to the ED 9% have a final diagnosis of MI and 8% angina (23). The problems of a large number of patients who do not have the ischemic heart disease but have troponin elevations has been considered in the fourth redefinition of MI. The introduction of a classification recognizing myocardial injury distinct from MI acknowledges the problems of elevation in a wide spectrum of clinical conditions (3). One approach to this problem is closer liaison between clinical and laboratory staff to more closely define requesting protocols. This must be accompanied by regular audits cycles and reporting back of the results.

A significant problem is that clinicians do not adhere to current recommendations for diagnosis and show a high variability in choice of diagnostic cut-offs (13) and protocols (17,24,25). In the most recent audit of requesting practice at St. George's Hospital (26) over a 4-month period, 4,869/7,352 requests (66%) were for a single troponin of which 2,664 (36%) were in the range 3–50 ng/L (cTnT) which should, according to protocol, have undergone serial testing. The use of rapid diagnostic algorithms is predicated by appropriate sample timings. A 0–3-hour repeat testing protocol was in use at the time, but the timing of the second sample was variable with a median of 3 hours but an interquartile range of 2.2–3.9 hours. Similar problems with sample timings were seen on switching to a 0–2-hour repeat testing protocol where a repeat sample taken at 3 hours from hospital admission was used for the final diagnostic classification (27). Sample timings of the 2 hours sample showed a median time interval between first and second sample (anticipated 2 hours) of 2.2 hours (interquartile range 1.8–2.7 hours) and between the second and third samples (anticipated 1 hour) the median interval was 1.2 hours (interquartile range 0.9–1.9 hours). According to the protocol, the second sample should have been taken at 2 hours from hospital admission and the third at 3 hours from hospital admission. A recently reported audit of introduction of a 0–1-hour protocol provides almost identical data (28) and reflects the difference between reported academic studies and the reality of real world utilisation of such strategies.

The current situation may however be transitional as the relative novelty of rapid diagnostic algorithms recedes. Growing clinician confidence with hs cTn assays as well as a growing body of evidence of the validity of the rapid diagnostic algorithms and their endorsement by professional societies is likely to increase their rate of adoption. A further factor may be that hs cTn assays are now becoming available by POCT. POCT has a very rapid turnaround time, typically 15 minutes or less, which will greatly facilitate provision of results within the timing of a decision making framework. Timeliness of results makes rapid diagnostic protocols more attractive. There may also be another factor in that many troponin requests are entirely protocol driven before the physician assesses the patient. POCT with its potential for result availability within the time of the initial consultation might produce more directed testing (29).

Conclusions

At present there is some geographical variation in the utilization of hs cTn measurement. This has been largely driven by regulatory problems which has delayed implementation. However, it is expected that there will be global utilization of high sensitivity assays. The major problem at present is the widespread use of non-specific troponin testing. Currently, utilization of rapid assessment protocols remains low and problematic. It remains a

challenge for laboratory professionals and clinicians to formulate strategies that will facilitate the obvious promise of hs cTn assays in the real world and balance appropriate patient selection with the use of rapid diagnostic protocols to confirm or exclude ACS.

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Footnote

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