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High sensitivity cardiac troponin assays – how to implement them successfully

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ABSTRACT

High sensitivity troponin (hsTn) assays provide an unprecedented opportunity to improve the detection and treatment of cardiac injury from coronary and non-coronary causes. They may also play a role in guiding the primary and secondary prevention of cardiovascular disease. However, to derive maximal benefit from their use, careful planning for the implementation of these new assays is required. In this manuscript, we will discuss actions that can be taken during hsTn pre-implementation, implementation and post-implementation phases. Key concepts for consideration in the pre-implementation phase include: the establishment of a multi-disciplinary implementation team; development of quality control procedures; education of clinical staff; modification of existing clinical workflow and provision of computerized decision support. Strategies for ensuring successful implementation and post-implementation phases will also be discussed.

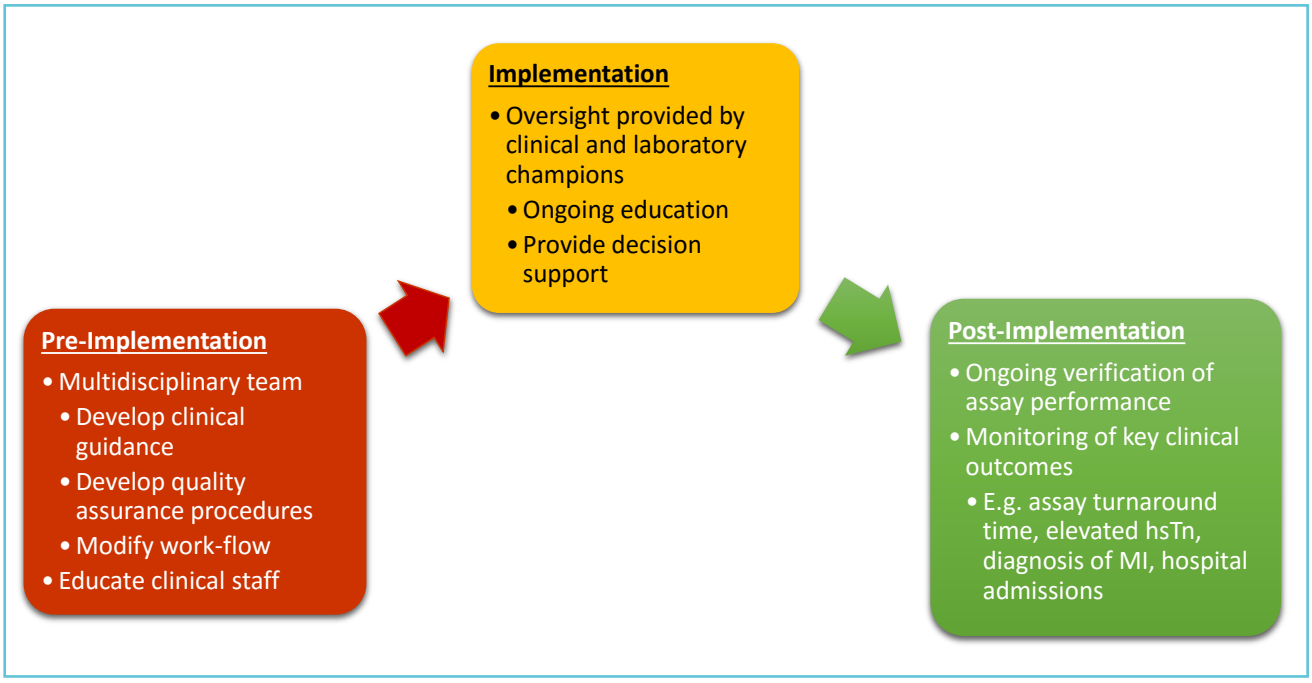
INTRODUCTION

The introduction of high sensitivity cardiac troponin (hsTn) assays provide an unprecedented opportunity for earlier and more accurate diagnosis of myocardial infarction; improved diagnosis of myocardial injury from non-coronary etiologies and guidance for primary and secondary prevention of cardiovascular disease.[1, 2] hsTn assays are able to accurately measure 10-fold lower concentrations of cardiac troponin than contemporary assays and therefore can measure troponin values in healthy persons. By definition, a hsTn assay measures troponin values in at least 50% of healthy individuals.[3] Additionally, hsTn assays measure troponin precisely with little variation between repeat measurements (co-efficient of variation (CV) ≤ 10% at the 99th% of a reference population).[4] hsTn assays have been approved for clinical use in most parts of the world, with the exception of the United States (it is anticipated that approval in the United States will occur within the coming 1-2 years).

Clinical use of hsTn has been associated with an increase in the diagnosis of myocardial infarction (especially in women[5]) and a reduction in morbidity and mortality of patients evaluated for acute coronary syndrome (ACS).[6] It also results in a reduction in the emergency department length of stay for patients evaluated for suspected ACS.[7] However, a number of questions remain unanswered regarding the potential negative consequences of using hsTn clinically. First, there is a concern that hsTn will lead to an increase in the number of patients with elevated troponin values and consequently, an increase in hospital admissions and downstream testing. Although some studies have reported increases in the frequency of troponin values >99th percentile with the use of hsTn,[8, 9] others have not.[10] The change in frequency of troponin elevations with implementation of hsTn is related to analytic sensitivity of the contemporary assay used and whether or not the 99th percentile of the contemporary assay was used for decision making. Additionally, an increase in the frequency of elevated troponin values may not necessarily result in an increase in the diagnosis of myocardial infarction (MI).[11] Second, there is no consensus on the appropriate thresholds for clinical decision making.[12] The threshold for ruling out MI, diagnosing MI, performing additional diagnostic evaluation for MI,[13, 14] and for risk-stratification of different cardiovascular diseases may be different.[15] Furthermore, gender-specific cut-offs may provide improved diagnostic value over gender-neutral cut-offs.[5] Third, optimal timing of serial troponin measurements and the ideal change values (relative versus absolute) for distinguishing between acute and chronic troponin elevations remain under investigation.[16, 17] Fourth, pre-analytical and analytical factors remain important in ensuring the accuracy of hsTn measures.[18]

Successful implementation of a novel test occurs in three phases: the pre-implementation phase, implementation phase and post-implementation phase (Figure 1). During the pre-implementation phase, a multi-disciplinary team tasked with developing clinical guidance and quality assurance procedures and educating clinical staff should be established. The implementation phase should be guided by clinical and laboratory medicine champions. Each discipline will need one or two champions who will provide ongoing education and decision support and be available to troubleshoot problems as they arise. During the post-implementation phase, ongoing assay performance verification should be performed. Additionally, key clinical outcomes such as: assay turnaround time, prevalence of elevated hsTn, and the number of hospital admissions for evaluation of ACS should be monitored. The following paragraphs discuss these concepts further.

Figure 1 Overview of strategies for successful implementation of hsTn



This figure depicts the strategies necessary for successful implementation of hsTn. It highlights important steps that ought to be taken in the pre-implementation, implementation and post-implementation phases.

ESTABLISHING A MULTI-DISCIPLINARY IMPLEMENTATION TEAM

Clinical implementation of hsTn requires a multi-disciplinary approach with the viewpoints of all stakeholders represented. At minimum, the implementation team should consist of representatives from cardiology, emergency medicine, internal medicine/hospitalists and laboratory medicine. This team will oversee the entire implementation process and will be responsible for making recommendations regarding protocols for interpreting hsTn values, threshold values for clinical decision making, education programs for clinical staff, and monitoring on-going quality improvement measures. This team will also be responsible for creating or endorsing a new diagnostic algorithm for ruling-out MI. The unique perspectives of each team member are important. For example, from the perspective of cardiologists who have the benefit of being able to observe the clinical course of hospitalized patients, a test that facilitates diagnosing MI with high specificity (i.e. low-likelihood of false positives) is desirable to avoid subjecting patients unnecessarily to procedures and treatments that can have adverse consequences. However, from the perspective of the ED physician challenged with determining the disposition of patients with symptoms suspicious of MI, a test that facilitates diagnosing MI with high sensitivity (i.e. low-likelihood of false negatives) is desirable to avoid missing the diagnosis of MI and inadvertently discharging MI patients to their homes. Despite having these conflicting perspectives, clinicians of different specialties trust clinical laboratory values implicitly[19] and don't always appreciate potential analytical confounds that often influence laboratory values. Therefore a multi-disciplinary approach will ensure that the viewpoint of all key stakeholders are represented, with the primary objective of doing what's best for patients. A number of key questions worth considering by the multi-disciplinary implementation team are presented in Table 1.

Table 1	Key questions for multi-disciplinary implementation team
1	What is the appropriate threshold for the 99th percentile (gender-specific versus gender-neutral versus a combination of the two)?
2	How much change in hsTn constitutes sufficient change for an acute process? Should absolute changes, relative changes or a combination of the two be used?
3	What is the recommended practice for managing patients with acute or chronic myocardial injury but no evidence of myocardial infarction?
4	What quality control checks are need to ensure the accuracy of troponin values?
5	How should results be reported? (preferably with whole numbers)
6	What decision support should be provided to clinicians?
7	How should clinicians be educated about hsTn?

DEVELOPING QUALITY CONTROL PROCEDURES

As part of the pre-implementation phase, quality control procedures should be developed. These should include assay verification procedures such as validating the limit of blank (LoB), evaluating precision at the reported limit of detection (LoD), and assessing the linearity range of the assay. Monitoring the accuracy of assay values below the 99th percentile will be of critical importance since rapid rule-out MI protocols rely on the accuracy of low hsTn values for risk-stratification. For example, a rule-out ACS strategy based on the 2015 European Society of Cardiology (ESC) guidelines will recommend discharging patients with an initial hsTn<99th percentile whose symptoms started more than 6 hours prior to blood draw, are pain free, have a Global Registry of Acute Coronary Event (GRACE) score <140 and in whom other life-threatening conditions have been excluded.[20] Therefore if the 99th percentile of an assay is 26 ng/L and the clinical chemistry laboratory reports an erroneous value of 25 ng/L instead of an actual value of 27 ng/L (7.4% difference), an MI patient may be inadvertently discharged home. The likelihood of inadvertently discharging MI patients will be even more significant if the rule-out ACS strategy is based on studies that deem it safe to rule-out MI in patients with initial hsTn<LoD.[21-23] Processes must be established to allow clinicians report cases in which hsTn values do not match the clinical scenario. Consequently, clinical chemistry laboratories should also have established protocols for addressing these inconsistencies.

Although hsTn assays produce more robust results and fewer outlier values than contemporary troponin (cTn) assays,[24] analytical confounds that currently affect cTn assays will continue to influence hsTn values. For example, hemolysis may result in decreases in hsTnT values and increases in hsTnI values.[25, 26] Additionally, the imprecision of hsTnI values is influenced by the extent of centrifugation performed.[27] Therefore quality control procedures should include actions that reinforce careful sample acquisition and preparation.

EDUCATING CLINICAL STAFF

In preparation for the implementation phase, physicians, nurse practitioners (NPs), physician assistants (PAs), nurses and ancillary support staff who perform blood draws should receive

education tailored to their role. Nurses and support staff who perform blood draws should be reminded of the importance using appropriate sample acquisition techniques. Nurses should receive additional education that highlights the differences between hsTn and cTn, and explains the new diagnostic algorithm formulated by the multidisciplinary team for ruling out MI. Physicians, NPs and PAs who will be utilizing hsTn tests need comprehensive education on hsTn. For many of them, learning to use hsTn will represent a paradigm shift in how they interpret troponin values. More than ever before, they will have to remember that troponin elevation is not synonymous with myocardial infarction. Understanding the differences between acute myocardial injury, chronic myocardial injury and myocardial infarction will continue to be critically important. Additionally, with the increase in the detection of type 2 MIs in the hsTn era, clinicians will have to learn to distinguish between type 1 and type 2 MIs,[28] and avoid treating type 2 MI patients the same way they treat type 1 MI patients. Improved understanding of the prognostic value of minor troponin elevations will be important in the hsTn era. On one hand, the often causal dismissal of minor troponin elevations as "troponemia" needs to be moderated by the realization that patients with any elevated troponin values have higher risk of adverse cardiovascular events than those without troponin elevations.[9, 29] On the other hand, the conservative approach to admit any patient with any troponin elevation also needs to be avoided. The success or failure of hsTn implementation will largely depend on the success or failure of clinician education.

MODIFY EXISTING CLINICAL WORKFLOW

Implementation of hsTn can result in a decrease in the length of stay of ED patients evaluated for ACS.[7] However, indiscriminate use of hsTn may also lead to an increase in the number of patients with elevated troponin values, and a potential increase in hospital admissions and downstream testing. Therefore, to derive maximal benefit from hsTn implementation, modification of the existing clinical workflow during the pre-implementation phase will be necessary. In United States EDs, nursing triage orders are often placed to facilitate patient evaluations and decrease time-to-treatment.[30] Troponin is often included in the list laboratory tests that triage nurses are allowed to order. In the era of hsTn, it will be important to provide clear guidance regarding the criteria for ordering hsTn by triage nurses. Lack of such guidance may lead to hsTn testing in patients with a very low pre-test probability of having ACS.

Decreasing the time it takes to rule-out MI using new protocols that incorporate hsTn testing also requires modifications to existing clinical workflow. For example, a number of studies have reported that 1-hour algorithms perform well in ruling-out MI.[31-33] The turnaround time for hsTn assays may be approximately 60 minutes,[34] thus to derive benefit from the 1-hour protocol, modifications to the work-flow, including obtaining the second troponin sample prior to receiving the results of the first troponin sample deserves consideration.

CONSIDER PROVIDING COMPUTERIZED DECISION SUPPORT

Interpreting hsTn values is not always simple. It often involves remembering complex decision making algorithms. The introduction of electronic medical records (EMR) provides a unique opportunity to provide computerized decision support that can guide clinical decision making. Diagnostic algorithms can be easily embedded into existing EMR to provide recommendations regarding the next steps of a patient's work-up. Absolute and relative changes in hsTn can also be calculated automatically and integrated in

decision support algorithms, fostering a systematic approach to patient evaluation and treatment using hsTn.

IMPLEMENTATION PHASE AND POST-IMPLEMENTATION PHASE

The implementation of hsTn should be led by champions from clinical chemistry, cardiology, emergency medicine and internal medicine. These champions should be available to provide ongoing education and decision support especially during the first month of implementation. They will also help troubleshoot problems as they arise. By modeling behaviors that exemplify best practices, clinical champions can be powerful agents of change during the implementation of hsTn.

The post-implementation phase is critical to ensuring a successful hsTn. During this period, ongoing verification of the accuracy of assay performance should be continued as is done for most clinical assays. To keep track of the effect of hsTn on clinical care, key clinical outcomes such as laboratory turnaround time, the prevalence of elevated hsTn, hospital admissions for suspected ACS should be monitored.

CONCLUSIONS

HsTn holds promise for transforming the diagnostic evaluations for cardiovascular disease. Careful planning for the implementation of these assays will allow patients to derive maximal benefit from their promise.

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