Review Article

High-sensitivity cardiac troponin testing in routine practice: economic and organizational advantages

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: C Galli; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Very seldom, if ever, a single laboratory test has provided such a paradigm shift in the managed care as cardiac troponin (cTn) testing. More than twenty years of improvements in test design and analytical features have contributed to revolutionize the clinical recommendations and guidelines, and the diagnosis of myocardial infarction (MI) is now highly dependent upon the kinetics of cTn within a suggestive clinical setting. Despite the advent of high-sensitivity cTn (HS-cTn) immunoassays has allowed a more accurate and timely diagnosis as well as a higher prognostic accuracy, the focus is now shifting on the most suitable algorithms and on a comprehensive approach to the clinical management of acute coronary syndrome (ACS). In this article we aim to discuss the implications of HS-cTn testing for ruling out and ruling in ACS. In the latter instance, main improvements are related to ACS diagnosis in women, in whom this pathology is still often underdiagnosed or misdiagnosed. A quick and accurate rule out will also regarded as a great advantage from both an organizational and economic standpoint. The advantages that will stem from this new approach have been recently assessed, and shortening of repeated testing 1 or 2 h from conventional algorithms entailing blood sampling at 3 and 6 h seems attainable. The larger benefits will definitely occur in clinical settings where the actual diagnosis rate of MI among patients with suspect ACS is lower and, consequently, the negative predictive value (NPV) of HS-cTn is the highest.

Keywords: Cardiac troponin I (cTnI); myocardial infarction (MI); major adverse events; emergency room; health technology assessment

Submitted Jun 17, 2016. Accepted for publication Jun 23, 2016.
doi: 10.21037/atm.2016.07.04
View this article at: http://dx.doi.org/10.21037/atm.2016.07.04

Cardiac troponins (cTn) and myocardial infarction (MI)

The troponin C (TnC), I (TnI) and T (TnT) are structural components of the myofilaments that regulate muscle contraction by interacting with calcium and tropomyosin, and inhibiting the ATPase activity of actomyosin. In the late 1980's a first assay (radioimmunoassay, RIA) for specific detection of cTn was made available, and shortly afterwards several more practical assays based on immunoenzymatic techniques were developed (1,2). The clinical adoption of cTn immunoassays was based on the assumption that the specific antibodies used in the assays were able to distinguish cTnI or cTnT from their skeletal muscle isoforms (2), thus enabling to reliably identify a cardiac myocyte injury. The nearly absolute cardiac specificity of both cTnI and cTnT immunoassays has then allowed to widespread their use as a valuable support for diagnosing MI. Despite their specificity, the genuine qualitative approach to cTn testing based on the rough equivalency "positive cTn equals MI" is erroneous, though still difficult to be erased from many physicians' attitude. Increased values of cTn are often consequence of myocardiocytes damage, but not necessarily secondary to an ischemic event nor to a specific cardiac disease (3). The obvious consequence of the purely

qualitative approach would be a dramatic increase in the number of tentative diagnosis of MI. Indeed, a dynamic view of cTn testing has been suggested before the turn of the century. In 1997 Hamm *et al*. (4) described the results of an interventional study on 773 consecutive patients with onset of chest pain for less than 12 h and without ST segment elevation. The cTn concentration (both cTnI and cTnT) was assayed by repeated testing, at patient arrival and after 4 h or more. By this approach, cTn values were found to be positive in 16% (cTnT) to 22% (cTnI) of all patients. During a follow-up of 30 days, 20 deaths and 14 nonfatal MIs were recorded, and both cTnI and cTnT were proven to be strong and independent predictors of cardiac outcome, wherein the event rates in patients with negative tests were only 1.1% for cTnT and 0.3% for cTnI.

The greater diagnostic value of cTn compared to other biomarkers (e.g., myoglobin and creatine kinase MB; CK-MB), along with the need of evaluating the biomarker kinetics, were reaffirmed by both the European and American cardiology societies in the 2000 (5,6), concluding that testing on admission and 6–12 h thereafter would provide a better risk stratification than using previous algorithms based only on single testing. Another cornerstone, besides repeat testing, is that test results should be made available within 30–60 minutes (7), because increased cTn values would be helpful for identifying those patients who benefit most from early invasive strategies (5,6).

A further refinement of cTn testing, impacting both the interpretation of results and testing algorithms, was the establishment of reference values to be used as thresholds. Historically, the "cutoff" for cTn assays had been established by receiver-operating characteristics (ROC) curves, as usual in laboratory medicine when evaluating "quantitative" assays. At the eve of the new century, the joint guidelines of the National Academy of Clinical Biochemistry (NACB) and the International Federation of Clinical Chemistry (IFCC) (7) recommend the use of the 99th percentile derived from a healthy population as the decision limit. Notably, it was also affirmed that such value would require a total imprecision (coefficient of variation; CV) ≤10% to make cTn testing suitable for clinical use. The guidelines also enforced the need of collecting additional blood specimens after those drawn on admission, and to guide the diagnosis on the basis of results obtained by sequential sampling. This aspect introduced a paradigm shift in laboratory organization, since most laboratories did not have a mechanism for automatic "reflex testing" i.e., testing entailing the ordering or cancellation of follow-up tests on a given sample based on results of preliminary tests (7).

Unfortunately, none of the cTn commercial assays available at that time complied with the "10% at 99th" requirement, so that all manufacturers were forced to retool their products and market them as "high" or even "ultra" sensitivity (8). Indeed, that was an odd and quite arbitrary definition, wherein a universally agreed criterion for classifying the methods according to their analytical sensitivity was lacking at that time (8). Moreover, the use of new thresholds without a clear understanding and agreement about the clinical interpretation of cTn data led to a substantial increase in the rate of MI diagnosis in the emergency department (ED), especially attributable to the presence of increased cTn values in elderly patients as well as in those with extra-cardiac diseases (e.g., impaired renal function) (8,9). As a consequence, the number of patients referred to cardiac intensive care units or directly to the catheterization lab skyrocketed, thus placing additional workload on those units and generating the uneasy feeling that the so-called "troponinoses" were causing more harm than good in clinical practice. The feelings from many clinicians are well reflected by the celebrated sentence "when troponin was a lousy assay it was a great test, but now that it's becoming a great assay, it's getting to be a lousy test" (10). As most of us would agree, the sensitivity of cTn immunoassays should not be considered as important as its global diagnostic performance, which shall ultimately respond to the need of the emergency physicians.

Additional refinements for the appropriate use of cTn in diagnosing ACS have been warranted. In the 2012 two papers of utmost relevance were almost simultaneously published. A joint committee of the major international scientific societies for cardiology released the 3rd universal definition of MI (11), which definitely affirmed the central role of the increase/decrease of cTn values over time for establishing a definitive diagnosis of myocardial ischemic injury. Shortly afterward, a "ad hoc" committee of the IFCC eventually established the criteria to define a "high sensitivity (HS)" assay for cTn (12), as follows:

(I) Total imprecision (i.e., CV) not exceeding 10% at the decisional value represented by the 99th percentile of a reference healthy population;
(II) Capability of detecting cTn values in at least 50% of the above mentioned population.

In the same year Apple *et al*. (13) emphasized that virtually none of the on-market immunoassays was able to fulfill both criteria. The rate of detection of cTn in a "normal" population of 524 presumably healthy North

American individuals ranged from 0–35% with the available assays for both cTnI and cTnT, and only one of those was able to detect cTnI in as many as 96% individuals in that cohort. Despite the frequency of detectable cTn in the general population largely depends on selection criteria (14-16), a very high rate of positivity has been observed in ensuing studies carried out in representative samples of the general population (17-20), as well as in the pediatric age (21,22) (*Figure 1*).

A comprehensive review of the history of cTn has been recently published by Conrad and Jarolim (23), and the characteristics of the different generations of immunoassays are summarized in *Table 1*. In summary, current evidence suggests considering cTn as a truly quantitative parameter, thus overcoming the former concept of "negative or positive" (i.e., the "black or white" paradigm) results (24). Therefore, the current section can be summarized and concluded with the statement contained in the most recent guidelines of the European Society of Cardiology (ESC) (25): "Cardiac troponin should be interpreted as a quantitative marker: the higher the level, the higher the likelihood for the presence of myocardial infarction".

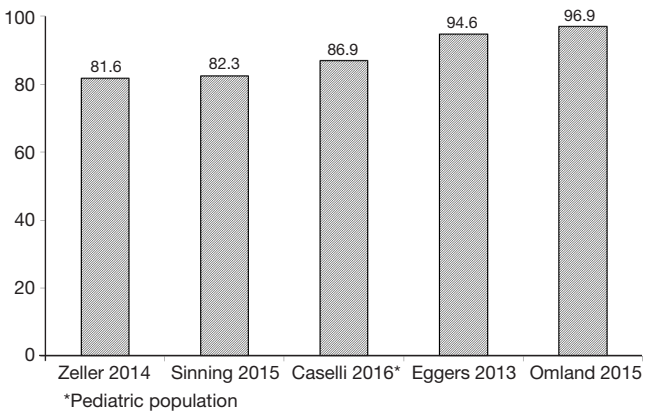

Figure 1 Rate of detection of cardiac troponin I using a high sensitivity cardiac troponin I (HS-cTnI) immunoassay in open population studies carried out in Australia (21) and in Europe (17-20,22). Studies are reported in increasing order of detection of cTnI.

MI in the ED

Now that most of the semantic controversies that plagued the field of cTn testing in ACS should have come to an end, it is time to focus on the real-life impact of HS-cTn immunoassays as a first-line test in one of the most crucial health care settings that is represented by short stay units, especially the ED.

The current workload of EDs has remarkably increased in many countries over the last decade, due to several factors such as lower resources for extra-hospital treatment of acute patients, increase of resident population and enhancement of life expectancy, which then leads to a higher number of elderly people presenting to the ED with acute exacerbations of chronic diseases. It has been estimated that 10–15% of ED patients present with chest pain or other signs suggestive of myocardial ischemia, but a final diagnosis of ACS can only be made in 15–25% of them, which overall represents the 2–5% of all incomers (26-31). The overcrowding of the ED is directly associated with clinical endpoints (e.g., mortality), and also with care processes that bear a high clinical relevance, such as time to initiate treatment for patients in critical conditions or diseases with a potentially severe outcome (32). Specifically, the negative effect of overcrowding has been demonstrated, and was found to be especially relevant for the higher risk of adverse cardiovascular outcomes in patients with both ACS-related and non-ACS-related chest pain syndrome (26). Despite remarkable advances in this field, the misdiagnosis of MI remains a tangible risk. The relevance of using

Table 1 Timetable and main features of the diagnostic assays for cardiac troponin I from the origins to the present; modified from Gamble *et al.* (24)

Generation	Availability	Limit of detection (ng/L)	Detection in a "normal" population (%)	Recommended time to testing after T0 (hours)
First	Late 80s'	500	0	12–24
Second	Late 90s'	100	0	12
Third ("contemporary" sensitive)	2000–2007	20–50	0–35	3–6
Fourth (high sensitive)	2012	1–3	>50	1–3
Fifth (ultra-high sensitive)	Research	0.2	>95	NA

appropriate decision values has been pinpointed by Wildi *et al*. (33), who demonstrated that a significantly harm, in terms of morbidity and mortality, may occur in patients that are withheld from evidence-based therapies (e.g., rhythm monitoring for 24–48 h, antiplatelet therapy, high-dose statins and early revascularization).

Another peculiar setting is represented by the (mis) diagnosis of MI and the higher mortality for cardiovascular diseases in the female gender. Major inequalities still exist between men and women in treatment and outcome of ACS, since both early and late deaths are considerably higher in women (34,35). Accordingly, cardiovascular disease in the female gender is now regarded as one of the primary targets for activity of the EU-funded project EUGenMed (36). Very recently, the American Heart Association (AHA) has issued a document (37) reaffirming the existence of sex-specific differences in presentation, pathophysiological mechanisms, and outcomes in patients with MI. This evidence was been then confirmed in subsequent analyses, reviewed elsewhere (38,39). Traditionally, the notion that a diagnosis of MI is less likely in women with suspected ACS has been attributed to the less frequency of typical symptoms and the lower frequency of suggestive electrocardiography findings. Women are also less likely to be referred to a cardiologist or undergo coronary revascularization (40). It has been recently demonstrated that cTn may play a substantial role in the female gender. Women have a lower concentration of circulating cTn, and this strongly impacts on the expected "normal" values and the calculation of the 99th percentile. Although this aspect has been known for a long time, even before the development of HS assays, the difference of normal values between genders does not translate - in clinical practice-into different diagnostic criteria because the former, along with the "contemporary" assays (*Table 1*), were not accurate enough for measuring the low values of cTn commonly found in women. Conversely, the use of a recently developed HS-cTnI test, which displays a functional sensitivity (10% total CV at 5 ng/L) at a much lower level than the 99th percentile in women (i.e., 16 ng/L) (13), would allow a more accurate diagnosis in both genders. The clinical relevance of this approach has been brilliantly demonstrated by a recent study published by Shah *et al*. (40), including 1,126 consecutive patients with suspected ACS. The novel HS-cTnI immunoassay was employed with the adoption of gender specific thresholds of 34 ng/L for men and 16 ng/L for women and compared with the previous, "contemporary" assay on the same platform and using a common diagnostic threshold of 50 ng/L in both genders. The adoption of gender-specific cutoffs using the HS-cTnI technique was hence effective to generate a considerable improvement in the diagnostic rate of MI in women (i.e., from 11% to 22%), though it produces a more marginal improvement in men (from 19% to 21%).

Besides the diagnosis of an actual ACS, prognostication is also a crucial issue in patients with heart disease. Short-term clinical outcomes, usually at 30-day after admission, are of major relevance in the ED, in order to exploit a safe rule out. A survey carried out in the US indicated that 0.4% of patients discharged directly by the ED died or had a documented MI within 30 days (41). Some recent papers have tried to address this issue in direct relationship to the use of HS-cTn, by evaluating the association between biomarker values at admission and occurrence of major cardiovascular adverse events (MACE) at 30 days. Bohula May *et al*. (42) investigated the prognostic performance of a HS-cTnI immunoassay for predicting cardiovascular death or new MI at 30 days in 4,695 patients with non-ST elevation MI (NSTEMI) enrolled in two prospective clinical trials (EARLY-ACS and SEPIA-ACS1-TIMI (43). Values of cTnI were detectable at baseline in all patients and, after adjusting for the TIMI (Thrombolysis In Myocardial Infarction) risk score, patients with cTnI values above the non-gender specific 99th percentile (i.e., 26 ng/L) had a 3.7-fold higher adjusted risk of cardiovascular death or MI at 30 days compared to patients with cTnI values lower than the 99th percentile. Notably, a significant difference was found between cTnI and cTnT in this cohort, inasmuch as patients with a negative cTnT value (i.e., <10 ng/L) but with cTnI >26 ng/L were at increased risk of death or MI compared to patients with cTnI values <26 ng/L. Therefore, a very low cTnI level at presentation, that is reliably measurable with HS immunoassays, can identify patients with NSTEMI who have a higher risk of recurrent events of clinical relevance at 30 days.

HS-cTn in the ED: organizational and economic aspects

The introduction of the universal definition of MI has led to a major degree of worldwide harmonization in diagnosing ACS (25,43,44), thus contributing to reduce diagnostic inconsistencies. The diagnosis of MI is not only made by measuring cTn, since the risk scores based on anamnesis and clinical presentation along with the information provided by electrocardiography and (possibly) imaging techniques are still crucial to the process. However,

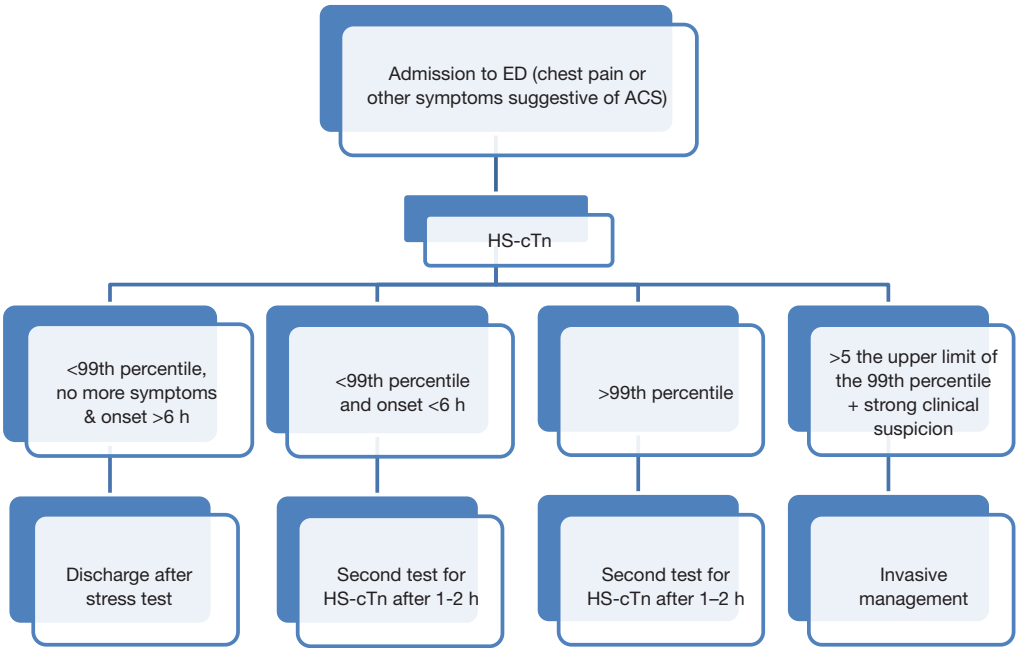

Figure 2 General algorithm for initial troponin testing using high sensitive cardiac troponin (HS-cTn) immunoassays in emergency department patients with suspected non-ST elevation myocardial infarction (NSTEMI) according to the guidelines of European Society of Cardiology (ESC) [modified from Roffi *et al*. (25)]. ED, emergency department.

clinicians should be aware of the central relevance of cTn testing and shall consider the application of diagnostic protocols that are both up to date and feasible within their work environment (43-46) (*Figure 2*). It is hence worthwhile mentioning here the recommendations issued in 1999 by the NACB (7):

(I) Members of EDs, divisions of cardiology, hospital administrations, and clinical laboratories should work collectively to develop an accelerated protocol for the use of biochemical markers in the evaluation of patients with possible acute coronary syndromes (ACS) (Class I);

(II) For simplicity, this protocol should apply to either the facilitated diagnosis or the rule-out of AMI in the ED or to routine diagnosis from other areas of the hospital, should a patient develop symptoms consistent with ACSs while hospitalized (Class II).

According to the many aspects discussed in the previous section of this article, the organizational advantages of introducing HS-cTn testing in the ED are mostly related to early rule out. This is because the vast majority (80–85%) of patients admitted with suspected ACS and for whom cTn testing is required, end up with a diagnosis different from ischemic heart disease (27). The suitability of ruling out an ACS according to the initial values of cTn has been envisioned in the ESC guidelines already in 2011 (47), subsequently reaffirmed by an Italian "ad hoc" interdisciplinary working group (45), and finally reiterated in the most recent ESC guidelines (25). In all documents it is clearly affirmed that an initial cTn value below the 99th percentile is necessary to possibly rule out an ACS. The exclusion of myocardial ischemia may be confirmed when the cTn value measured with a HS immunoassay remains fairly stable also on repeated testing. Therefore, considering the turnaround time of the currently available techniques, an ACS may be ruled out and eventually patients may be discharged after 3–4 h from admission, at the latest. While this algorithm represents a definite advantage compared to the use of contemporary sensitive cTn assays, the most of which requires a 6-h algorithm for safe rule out of ACS, additional refinements have been suggested. The most recent ESC guidelines (25) indicate that, whenever a HS-cTn immunoassay "with a validated protocol" is available, an accelerated algorithm encompassing shortened testing (i.e., baseline and after 1–2 h) may be seen as a valuable perspective. Recent evidences also suggest that the cTn value at presentation combined with a delta of absolute cTn values should be preferable over the use of the percentage

Table 2 General characteristics of five algorithms aimed at ruling out acute myocardial infarction in the ED, based on current guidelines or on published evidences (25,27,31,45-48)

Algorithm	ESC 2016 guidelines 3 h	ESC 2016 guidelines 1 h	99th percentile	5–6 ng/L	LoD (1.2–1.9 ng/L)
Ease of adoption in ED	High	Moderate	High	High	High
Sequential samples needed	Yes/no*	Yes/no*	No	No	No
Gender-specific thresholds	Yes	Yes	No	No	No
Estimated sensitivity (%)	93.2–100	97.6–98.8	77.5–82.3	92.2	99.0
Time to discharge from admission (hours)	2–4	2	2	2	2
Ruled out at T0 (%)	None	50.5	84.6	56–61	12.3–18.8
Impact on ED crowding	Moderate	High	Very high	High	High

*, according to the need of testing after 1–3 h from admission; ESC, European Society of Cardiology; ED, emergency department.

variation that was originally proposed (25,27). This approach would enable faster rule, being characterized by a very high negative predictive value (NPV), ranging from 99.6% (31) to 99.8% (48). Interestingly, shorter sampling with HS-cTn immunoassays were found to have almost equal diagnostic accuracy compared to the "standard" 3 h algorithm (48). The absolute delta increase of cTn values should however be tailored according to the analytical characteristics of the method, thus always higher than the value characterized by 10% imprecision (8). Therefore, standard algorithms need to be developed and validated for each of the potential HS immunoassays that are (or will be) available in the market.

An even faster approach would encompass the use of a single, lower cutoff value for ruling out MI, that will also resolve the debate regarding the appropriateness of using multiple age-adjusted and sex-adjusted thresholds (49). One key point of the 1 h algorithm is that the cutoff is much lower than the 99th percentile, so increasing both sensitivity and NPV. This has been the matter of other studies aimed at identifying better thresholds than the 99th percentile to rule out MI at presentation, prompted by insufficient sensitivity for clinical use of the 99th percentile (50). A lower threshold, set around 5–6 ng/L, has hence been proposed (48,49), as both values are within the 10% total CV of the novel HS-cTnI immunoassay. Shah *et al.* (51) analyzed a cohort of more than 6,300 consecutive patients and found that 56–61% of patients without MI showed cTnI concentrations <5 ng/L, and the NPV for ruling out MI was as high as 99.4–99.6%, remaining consistent across groups stratified by age, sex, risk factors and previous cardiovascular disease. Carlton *et al.* (52) studied 3,155 patients presenting with suspect ACS and non-ischemic ECG, showing that the value corresponding to the limit of detection (LoD) as diagnostic threshold yielded a sensitivity as high as 99.0% (95% CI, 96.8–99.7%) and a NPV of 99.5% (95% CI, 98.4–99.9%), allowing early discharge of a considerable number of patients (approximately 20%). The key aspect here may be of interest for the emergency physicians when adopting the different diagnostic options for ruling out ACS by HS-cTn (*Table 2*).

The organizational advantages that will emerge from these approaches (i.e., accelerating the discharge of patients from the ED), are basically the same. The adoption of specific algorithms and timing for serial sampling should then be planned considering the sensitivity for MI and its diagnostic accuracy for predicting short-term outcomes, but should also consider some environmental factors (i.e., distance between the ED and the laboratory, means of sample transportation, type of health care facility, etc.) and analytic criteria (8).

From an economic perspective, we should first remember that the incremental cost of these protocols is substantially meaningless. The diagnosis of NSTEMI is now almost entirely based on cTn, the total cost of which rarely exceeds $2–4 US (53), i.e., approximately 2-time higher than that of a contemporary sensitive method. On the other side, in a western country like Italy the average cost for each patient admitted to the ED for MI or arrhythmia (a typical yellow/red code) is around $700 US and a single hour of stay costs about approximates $100 US (54,55). The cost emerging from replacing contemporary sensitive with HS techniques

would hence be completely overwhelmed by a most efficient diagnosis and a much earlier discharge.

A systematic review and meta-analysis of diagnostic strategies for suspect ACS (56) has revealed that in most scenarios, HS-cTn measurement was the most effective strategy, with an incremental cost-effectiveness ratio (ICER) of less than the £20,000–30,000/QALY (quality-adjusted life years) (ICER £7,487–17,191/QALY). This aspect was further investigated by the UK National Institute for Clinical Excellence (57), reaching rather similar conclusions. Notably, the transferability of these results is limited, since these figures were based on the evidence available at the time of the studies, which were mostly based in the use of the 99th percentile as the decision value. Additional studies are ongoing to establish whether or not the use of short sampling algorithms entailing the use cutoffs lower than the 99th percentile value may be really effective to reducing the overall healthcare cost and enabling a more efficient use of resources in the ED.

Conclusions

Recent evidence suggests that the use of HS-cTn may guarantee better analytical performances and will enable a shift to more rapid rule out strategies (58,59). This is especially true when the decision cutoff is lower than the 99th percentile value. A single, very low value of HS-cTn at presentation may be sufficient to rule out MI with a NPV that is really close to 100%, especially in low-risk patients and in ED settings where a lower prevalence of MI diagnosis is observed in patients presenting with suspect ACS. To achieve a high NPV, the low LoD (i.e., a cTnI value of around 5–6 ng/L) appears to be the safer criterion and will allow to discharge rapidly 20% or more of patients with negative ECG findings with a high accuracy, whereas higher cutoff values will increase this percentage compounded by with a higher risk of false negative results (i.e., non-ischemic injury). Indeed, the time of presentation after symptoms onset is critical and it seems advisable to obtain a second sample after 1–2 h in patients who present earlier or with uncertain timing, as well as in patients with a high risk score (25). The economic benefits that will stem from an accelerated rule-out depend upon the demographics of people admitted to the ED and the health care policies of the different countries and regions. However, considering the relatively low cost of HS-cTn immunoassays, the cost/benefit analysis will predictably generate a favorable scenario. Throughout the history of ACS diagnostics many advancements have make it possible to substantially ameliorate the clinical decision making (60,61) and, indeed, the routine use of HS-cTn immunoassay will represent the next paradigm in this constantly evolving scenario.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Galli is currently employed by Abbott Diagnostics as the Associate Director, Medical Scientific Liaison Europe. Dr. Lippi has no conflicts of interest to declare.

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Cite this article as: Galli C, Lippi G. High-sensitivity cardiac troponin testing in routine practice: economic and organizational advantages. Ann Transl Med 2016;4(13):257. doi: 10.21037/atm.2016.07.04