

CRITICAL ILLNESS INSURANCE

Highly Sensitive Troponin and Critical Illness Insurance: Have the Goalposts Moved Again?

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An elevated cardiac troponin is *a sine qua non* for the clinical diagnosis of myocardial infarction. The sensitivity of troponin assays has improved repeatedly since troponin entered clinical use in the late 1990s. Its most recent iteration, “highly sensitive” troponin will shortly enter clinical use in North America. It is able to detect amounts of troponin 10 times smaller than the current assay. As a result, more myocardial infarctions will be diagnosed. This may have an impact on the number of critical illness claims for heart attack.

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Over the past 50 years, various blood tests have been used to corroborate a diagnosis of myocardial infarction (MI). At the outset, these were used in a supportive manner for a diagnosis that was primarily clinical and electrocardiographic. In the last 3 decades, as the blood tests (now called “cardiac biomarkers”) became more refined, they assumed greater diagnostic importance. This is reflected in the

3 European-North American “consensus” definitions of MI that have been published in the past 15 years. In the first definition, published in 2000¹ by the Joint European Society of Cardiology/American College of Cardiology, elevated cardiac biomarkers became the cornerstone of the clinical diagnosis: a typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers

of cardiac necrosis," was required to satisfy the diagnosis. In the 2007 Universal Definition of Myocardial Infarction of the joint ESC/ACCF/AHA/WHF, the wording was modified: "typical rise and gradual fall" was replaced by "a detection of the rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile upper reference limit (URL)."² This definition thus anointed troponin (cTn) as the preferred biomarker.

In 2012, the ESC/ACCF/AHA/WHF published the Third Universal Definition of Myocardial Infarction.³ While the wording of the 2007 definition was largely unchanged, the cTn levels required to satisfy the diagnosis of MI following percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) were changed. This modification reflected both the increasing experience with troponin measurements and the arrival of highly sensitive troponins (hs-cTn).

Cardiac troponins were introduced to clinical care in the early 1990s. They are structural proteins that attach to the thin actin filaments of cardiac muscle and regulate calcium-actin-myosin binding and thus muscle contraction. A smaller amount of cTn, perhaps 5%, is present in the cytosol; it is hypothesized that leakage from this cytosolic pool explains cTn elevations following pulmonary embolism and marathon running.^{4,5}

Three isomers of cTn are expressed in cardiac muscle, cTn-T, cTn-I and cTn-C. As cTn-C is also detected in skeletal muscle current cTn assays target either cTn-T or cTn-I. There does not appear to be any inherent diagnostic advantage of one over the other. The presence of cTn in peripheral blood indicates cardiac myocyte damage, usually myonecrosis. However, the hs-cTn assay can detect tiny amounts of troponin in healthy individuals; these are likely a reflection of physiologic cardiac cell turnover. Their presence fuels an ongoing debate whether all cTn elevation is pathologic. For the present and until this debate is resolved, all cTn elevations are presently considered a reflection of myocardial damage.

Over the past 10 years, the assays for detecting cTn have become progressively more sensitive. Their nomenclature, unfortunately, is confusing, with monikers such as – contemporary, conventional, 4th generation, medium-sensitivity, sensitive, highly sensitive, super-sensitive, and ultrasensitive – tending to confuse rather than enlighten. By convention, a "highly sensitive" assay is one that can detect cTn in >50% of a normal (ie, reference) population.⁶ In contrast, a "conventional" assay, ie, the assay that is in widespread use in North America detects cTn in only 1%-20% of normal individuals. Highly sensitive cardiac troponin (hs-cTn) assays, which are in widespread use in Europe, will soon become the standard assay in North America.

Highly Sensitive Troponin Testing Brings 3 Advantages

1. As the hs-cTn assays can detect cTn levels about 10 times lower than conventional assays many individuals who would previously have been labeled 'unstable angina' will now be diagnosed with MI. This ability to detect new MIs has been demonstrated in most but not all studies.⁷⁻¹⁶ A representative Swiss study evaluated 1124 consecutive patients presenting with suspected MI.¹⁵ The use of hs-cTn resulted in 242 diagnosed MIs rather than 198 with the conventional assay, a relative increase of 22%. Other studies have shown increases ranging from 7% to 82%.¹⁰⁻¹²

Different study populations may partially explain the lack of consistency across all studies. It should also be pointed out that many of these studies were performed in settings with high prevalence of cardiovascular disease; results in a general emergency department may be different. However, on balance, it seems likely that more MIs will be detected following the introduction of hs-cTn to North America. These new infarctions will be small, non-ST segment elevation infarcts (NSTEMIs)

as ST-elevation infarcts, being as a rule more extensive than NSTEMIs, are readily detected by current troponin assays. It is anticipated that this increase in NSTEMIs will be reflected by a proportional reduction in the number of diagnoses of unstable angina.

2. The arrival of hs-cTn will identify individuals with a worse prognosis. Recent data have demonstrated that patients diagnosed with MI following a positive hs-cTn test have poorer clinical outcomes than those who remain in the unstable angina cohort.¹¹⁻¹³ In the Swiss study, the 30-month mortality rate was 23.9% in patients diagnosed with the conventional assay, 16.4% in those diagnosed with the hs-cTn assay ($p < .001$) and 4.8% in those without MI.

As this new cohort will now be eligible for early antithrombotic therapy and/or invasive assessment, their prognosis may be improved. While this seems plausible, supportive data are not yet available. Parenthetically, the ability of hs-cTn to predict hospital admission and all-cause mortality has been illustrated in a variety of cardiac and non-cardiac conditions. Furthermore, hs-cTn is currently being evaluated as a prognostic marker in a variety of asymptomatic populations both with and without cardiovascular risk factors.^{17,18}

3. High-sensitivity cTn will allow more rapid 'rule out' and 'rule-in' of MI. A negative hs-cTn at time of admission rules out MI with a sensitivity of around 90%-95%. After 3 hours, the sensitivity rises to 99%-100%.¹⁹ This will allow earlier patient discharge than is presently the case. Conversely, hs-cTn will also permit a more rapid MI "rule-in" if values are elevated at time of arrival and even more elevated with a second estimation 3-6 hours later; conventional hs-cTn requires repeat blood draws at 6 and 12 hours. A more rapid "rule-in" will allow definitive treatment to be started earlier. As experience with hs-cTn accumulates, it is possible that

this time schedule will be shortened further. A 2-hour "rule-in", "rule-out" protocol for acute MI has been studied in patients with suspected ACS; only 20% of patients required prolonged surveillance.²⁰

Highly Sensitive Troponin Testing Major Shortcoming

While the heightened sensitivity of hs-cTn brings significant advantages, the price is poorer specificity. In comparison to the conventional assay, many more conditions, both cardiac and non-cardiac, will enter the differential diagnosis (see Table). This will cause substantial challenges in the emergency room and a substantial challenge for the critical illness claims adjudicator. So, while the negative predictive value of a normal hs-cTn at 3 hours is close to 100%, the positive predictive value (PPV) of an elevated hs-cTn may be as low as 50%, depending on the clinical setting (disease prevalence or pre-test likelihood of disease). In the emergency department, it is suggested that only 50% of elevated hs-cTn can be explained by ischemic myonecrosis. So, while the ability to quickly "rule out" MI and to detect smaller MIs are clear advantages, they are offset by an ever-lengthening list of differential diagnoses.

The dilemma arises when the hs-cTn is elevated at time of arrival in the Emergency Room. The 2012 criteria for the diagnosis of MI require, "a detection of the rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile upper reference limit (URL)." Thus, a second and higher hs-cTn value is required to confirm the diagnosis. When the clinical presentation is typical (eg, classical retrosternal chest pain in a 55-year-old, hypertensive smoker), a subsequent minor hs-cTn rise might satisfy the treating physician. When the clinical presentation is not typical (eg, non-anginal chest pain, few or no vascular risk factors in a 40-year-old woman) the treating physician may deem a similar rise inadequate. The 2012 consensus definition recognizes this conundrum and specifically

Table 1. Cardiac and Non-Cardiac Causes of HS-cTn Elevation

Cardiac Causes	Non-Cardiac Causes
Heart Failure	Renal failure
Myocarditis	Pulmonary embolism
Pericarditis	Stroke
Left ventricular hypertrophy	Subarachnoid hemorrhage
Tachyarrhythmias and bradyarrhythmias	Pulmonary hypertension
Heart block	Sepsis
Aortic valve disease	Hypothermia/hyperthermia
Cardiac surgery	Amyloidosis
Cardiac contusion	Extreme exertion
Rhabdomyolysis with myocyte necrosis	Major burns

mentions: "The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia."

However, it can be fairly anticipated that physicians will differ in their evaluation of both the clinical setting and the relevance of different degrees of hs-cTn elevations. Inappropriate labels of MI will be assigned raising the specter of inappropriate CI claims.

Ideally, a quantification of hs-cTn change, in either absolute or relative terms, could avoid an insignificant increase being incorrectly assigned to cardiac myonecrosis. However, there is presently no agreement about appropriate change values or how to recognize values that represent simple analytical variation. As hs-cTn values differ by race, ethnicity, age and sex,²¹ one can anticipate that it will be some time before agreement on change values is reached.

Highly Sensitive Troponin Assays Drawbacks

When compared to cTn, all analytical problems are accentuated with hs-cTn assays. As it is an immunoassay, it is subject to interference by heterophile antibodies that competitively bind to the cTn epitope, falsely increasing the hs-cTn result.²² Autoantibodies

to cTn are found in 5% to 20% of individuals and will reduce detection of hs-cTn.²³ Values will also differ depending on specimen type, ie, blood vs plasma vs serum. Finally, hemolysis can also affect test accuracy, underscoring that pre-analytic issues will require special consideration. Clinicians who are not familiar with these analytical drawbacks may make decisions based on flawed information.

Impact on Number of Diagnosed MIs and Critical Illness Claims

At first flush, it would appear that the introduction of hs-cTn will produce an increase in the incidence of MI and hence CI claims for MI. However, the real answer will probably be more nuanced. The following factors may mitigate this anticipated increase:

1. The incidence of MI in most countries has been decreasing over the past decades, largely due to more effective primary prevention.²⁴ Should this trend continue, the impact of hs-cTn might be blunted.
2. This reduction in MI incidence occurred despite the replacement of CK-MB in the late 1990s by cTn, followed by year-on-year improvements in cTn assay sensitivity (today's assays are 1000 more sensitive than the prototype cTn). One might have anticipated an increase in MI incidence over this period, rather than the opposite.
3. If the hs-cTn assay is detecting MIs that are occurring in individuals who are at higher risk than average, underwriting may have a salutary effect. Several studies suggest that, in fact, hs-cTn predominantly detects MI in older individuals who have a higher prevalence of established CAD and a higher prevalence of hypertension, hyperlipidemia and diabetes.^{7,8,10,15} In the Swiss study, almost half of the "only diagnosed with hs cTn group" had a previous MI, compared to 30% of those diagnosed with conventional cTn.¹⁵ Extrapolating from these studies, it seems likely that underwriting would mitigate some fraction of future claims in a similar group of insured lives.

4. The evidence that hs-cTn will detect more MIs is not entirely concordant. In one study, which compared the diagnostic performance of hs cTn compared to standard cTn testing in an emergency department setting, no significant difference in MI diagnosis was found.¹⁴
5. While the global insurance experience with critical illness claims for MI is not available, a major reinsurer in Canada has not experienced an unexpected increase in claims over the past decade, a time during which the diagnostic criteria for MI changed and troponin testing became more sensitive (Munich Re internal data). While sufficient time has not elapsed to be fully confident about this observation, it is nonetheless pertinent.

CHALLENGES FOR CRITICAL ILLNESS INSURERS

The introduction of more sensitive tests and repeated changes in the definition of MI pose a challenge if they result in an unexpected number of claims or if pricing has to be repeatedly adjusted. CI definitions, for both MI and other covered conditions, have evolved in different directions in different jurisdictions in an effort to future-proof against such challenges. In some countries, “measures of severity” (eg, imaging evidence of myocardial damage) have been added, whose purpose is to prevent claims for minor or “non-critical” variants of a covered condition. While this sounds logical, it creates problems of its own: the more an insurance definition deviates from the accepted clinical definition, the more difficult to defend it, should litigation ensue. Other jurisdictions have taken the opposite tack: the CI definition approximates as much as possible the clinical definition, and the price is adjusted accordingly.

The arrival of hs-cTn may well restart discussions. Its ability to diagnose ever-smaller infarctions might push some insurers in the “severity measure” direction, arguing that such a move would be ‘in the spirit’ of CI insurance. However, the counterarguments

are substantive: (i) hs-cTn is not identifying innocuous infarcts, (ii) the more an insurance definition deviates from a clinical one the more contentious the claim and more likely the litigation, (iii) brokers and clients may perceive that a “watered-down” version of heart attack is not an attractive purchase.

CONCLUSION

The arrival of hs-cTn will result in a shift from the diagnosis of “unstable angina” toward the diagnosis of MI. It is unclear if there will be an increase in the number of MIs, given the overall context of decreasing MI incidence and the risk profile of individuals in whom hs-cTn appears to be most effective. However, as hs-cTn is substantially less specific than conventional cTn, there is a high likelihood that other medical conditions causing elevated hs-cTn will be mislabeled as MI.

Until such time as algorithms are developed to appropriately guide the treating physician faced with an elevated hs-cTn, this situation is likely to continue. The adjudication of critical illness claims for MI will become more challenging. When faced with an MI claim and an elevated hs-cTn, the assessor will have to contextualize all the relevant information and decide if the evidence for MI is compelling. Insurers may have to revisit their definitions and decide whether a measure of severity should be added. The arrival of hs-cTn illustrates that CI definitions will always be a work in progress. Let’s get used to shifting goalposts; they’re not settling down anytime soon.

REFERENCES

1. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J.* 2000;21:1502-1513.
2. Thygesen K, Alpert JS, White HD, Joint ESCAA-HAWHFTFftRoMI. Universal definition of myocardial infarction. *J Am Coll Cardiol.* 2007;50:2173-2195.

3. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Nature reviews. Cardiology*. 2012;9:620-633.
4. Lippi G, Schena F, Salvagno GL, Tarperi C, Aloe R, Guidi GC. Comparison of conventional and highly-sensitive troponin I measurement in ultramarathon runners. *J Thrombosis and Thrombolysis*. 2012;33:338-342.
5. Traiperm N, Gatterer H, Wille M, Burtscher M. Cardiac troponins in young marathon runners. *Am J Cardiol*. 2012;110:594-598.
6. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clin Chem*. 2012;58:1574-1581.
7. Mills NL, Churchhouse AM, Lee KK, et al. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA*. 2011;305:1210-1216.
8. Mills NL, Lee KK, McAllister DA, et al. Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. *BMJ*. 2012;344:e1533.
9. Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Eng J Med*. 2009;361:868-877.
10. Bonaca M, Scirica B, Sabatine M, et al. Prospective evaluation of the prognostic implications of improved assay performance with a sensitive assay for cardiac troponin I. *J Am Coll Cardiol*. 2010;55:2118-2124.
11. Wilson SR, Sabatine MS, Braunwald E, Sloan S, Murphy SA, Morrow DA. Detection of myocardial injury in patients with unstable angina using a novel nanoparticle cardiac troponin I assay: observations from the PROTECT-TIMI 30 Trial. *Am Heart J*. 2009;158:386-391.
12. Meune C, Balmelli C, Twerenbold R, et al. Patients with acute coronary syndrome and normal high-sensitivity troponin. *Am J Med*. 2011;124:1151-1157.
13. Mueller M, Celik S, Biener M, et al. Diagnostic and prognostic performance of a novel high-sensitivity cardiac troponin T assay compared to a contemporary sensitive cardiac troponin I assay in patients with acute coronary syndrome. *Clin Res Cardiol*. 2012;101:837-845.
14. Hammerer-Lercher A, Ploner T, Neururer S, et al. High-sensitivity cardiac troponin T compared with standard troponin T testing on emergency department admission: how much does it add in everyday clinical practice? *J Am Heart Assoc*. 2013;2:e000204.
15. Reichlin T, Twerenbold R, Reiter M, et al. Introduction of high-sensitivity troponin assays: impact on myocardial infarction incidence and prognosis. *Am J Med*. 2012;125:1205-1213e1.
16. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA*. 2011;306:2684-2693.
17. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA*. 2010;304:2494-2502.
18. de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304:2503-2512.
19. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Euro Heart J*. 2012;33:2252-2257.
20. Reichlin T, Cullen L, Parsonage WA, et al. Two-hour Algorithm for Triage Toward Rule-out and Rule-in of Acute Myocardial Infarction Using High-sensitivity Cardiac Troponin T. *Am J Med*. 2015;128:269-379.
21. Gore MO, Seliger SL, Defilippi CR, et al. Age and Sex Dependent Upper Reference Limits for the High Sensitivity Cardiac Troponin T Assay. *J Am Coll Cardiol*. 2014;63:1441-1448.
22. Tate J, Ward G. Interferences in immunoassay. *Clin Biochem Rev*. 2004;25:105-120.
23. Eriksson S, Hellman J, Pettersson K. Autoantibodies against cardiac troponins. *N Engl J Med*. 2005;352:98-100.
24. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155-2165.