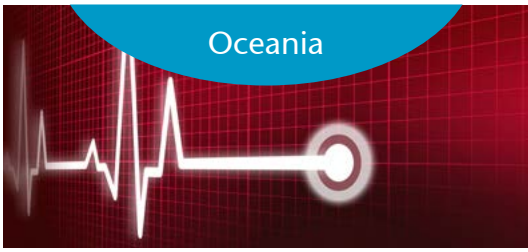


Insurers in Quest of the Perfect Heart Attack Definition

by Andres Webersinke, Gen Re, Sydney

Earlier this year Australian life insurers were in the spotlight, allegedly using "out-dated" medical definitions in their Trauma (Critical Illness) policies. As a consequence, many insurers reviewed their medical definitions and claims management practices, with particular focus on the definition for "heart attack".

The idea of Trauma insurance is simple. Insurers promise financial relief when the insured suffers a medical condition that is relatively common, generally recognised and dreaded (hence the earlier name of Dread Disease insurance), such as cancer or heart attack.

In the 1980s when Trauma insurance was first introduced, these conditions were easy to define. Cancer was either malignant and covered, or benign and excluded; cardiac biomarkers reliably assisted in the diagnosis of a heart attack. Grey areas were minimal.

This has changed dramatically in just a couple of decades. The goal of treating patients as early as possible resulted in ever-improving diagnostics, changing definitions and classifications of medical conditions. In some instances clinicians themselves discuss "over-diagnosis" – for example, the need to consider using the term "cancer" more sparingly.[1]

It is not surprising that insurers struggle to define conditions covered under a Trauma policy. These conditions need to be robust enough to offer sustainable premium rates and objective for claims assessment, but still offer transparency to customers and advisers concerning the level of cover.

Although medical definitions are part of an insurance contract, suggesting an absolute meaning, the insurer's claims philosophy must address questions such as, "What is intended to be covered?" or "Is the condition covered even if not all claims criteria are fully met?"

In the case of heart attacks, it is tempting to follow the clinical definition. But this still requires interpretation, not only by insurers but also clinicians.

When is a heart attack a heart attack? Gen Re addressed this question in a 2011 issue of *Risk Matters Oceania*. Since then, the universal definition of the heart attack has been updated once and the latest generation of troponin tests is in use. This article highlights concerns insurers need to address when considering the clinical definition of a heart attack for insurance purposes, as well as possible solutions to navigate the conflict zone between clinical medicine and an insurance contract wording.

About This Newsletter

A series of articles for life assurance professionals. The purpose of these publications is to share knowledge gleaned by Gen Re as we carry out research into the risks that affect the profitability of life protection business.

Clinical diagnosis and definition of myocardial infarction

Clinicians are challenged when a patient arrives at an emergency department with symptoms of an acute coronary syndrome (ACS – a range of disorders caused by the same underlying problem, including heart attacks) but may well turn out to be indigestion only. A quick diagnosis with the aim of providing the best treatment, and minimising waste of resources and waiting time for patients, is critical. This is often based on symptoms and more or less abnormal Electrocardiography (ECG) results.

To achieve this, clinicians need a reliable test that helps them to quickly rule out a possibly life-threatening condition, and cardiac troponin (cTn) has been recommended as the preferred biomarker for this purpose. Tests to detect the level of cTn in blood have evolved over the last 20 years. They have become increasingly sensitive, i.e. being able to detect smaller amounts of cTn. But this comes with a somewhat reduced specificity, i.e. where cTn is also detected in patients with other cardiac and non-cardiac conditions.

Globally, clinical experts agreed on a universal definition for the diagnosis of a myocardial infarction (MI), also known as heart attack. The third universal definition was published in 2012 and consists of 420 words. Life insurers covering heart attack under a Trauma policy primarily cover an acute (sudden onset versus prior or silent) MI but not all types of MI (e.g. MIs associated with a surgical procedure, such as an artery bypass grafting).

The key criterion of the clinical definition is the "detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL)".[2]

This requirement looks objective on the face of it. However, this seemingly simple requirement has limitations and the level of interpretation that is required before an MI can be finally diagnosed is not insignificant.

The most recent (fifth) generation of cTn assays (tests), also known as high sensitive cardiac troponin (hs-cTn) assays,[3] have been in use since 2010 in a number of hospitals in Australia and New Zealand. Interestingly, the U.S. Food and Drug Administration has not yet cleared them for clinical use.

In patients with MI, levels of cTn rise rapidly. With an hs-cTn assay, troponin elevation can be detected earlier, usually within one hour after symptom onset instead of three to four hours with an earlier generation assay. An hs-cTn assay is classified "high sensitive" if it detects troponin in more than half of healthy individuals.

Key issues with troponin and the universal definition of heart attack

Changing levels of troponin is a critical criterion of the universal definition of heart attack. Several key issues that insurers need to keep in mind when relying on this biomarker for the assessment of a lump sum claim are listed below, and are further discussed in separate text boxes.

Guidelines

The universal definition of heart attack does not exist in isolation. Clinicians use guidelines to diagnose and utilise the right treatment option. Guidelines differ from region to region and include specific algorithms to assist clinicians in predicting with some certainty whether a patient suffers a heart attack or not. These algorithms change with new cTn assays and research findings. [See Box 1]

Upper reference limit

The 99th percentile of an upper reference limit (URL) depends on the chosen assay and depends on how the manufacturer of the assay defined the healthy reference population. Differences by gender and race may exist. Also, different studies recommend different URLs for the same assay. In other words, clinicians and insurers depend – to some degree – on the choice of the assay used and which study the laboratory applies at any one time. Simple cut-off levels may thus be difficult to justify in all cases. [See Box 2]

(In)significance of a troponin value

In some emergency scenarios (e.g. when a so-called ST-elevation MI (STEMI) is suspected) troponin values are less relevant or even required for a diagnosis. Some algorithms also suggest a

Box 1 – Guidelines for determining heart attack

The consensus document with the third universal definition of heart attack outlines that blood samples for the measurement of cTn should be drawn on first assessment and repeated three to six hours later. To establish the diagnosis of an acute MI, a rise and/or fall in values is required, coupled with a strong pre-test likelihood.

The current guidelines of the Cardiac Society of Australia and New Zealand suggest that the rise or fall (also called delta (∂) change) must be at least 20%, if the initial cTn test was positive (i.e. ≥ 99th percentile), or the increase must be at least 50% if the cTn test was negative on admission.[6]

In contrast, the Pathology Service of the St Vincent's Hospital in Sydney suggests that a cTnT[7] higher than 100 ng/L (more than six times the 99th URL), together with a clinical history commensurate with an acute MI, can be diagnosed with a single troponin value.[8] In other cases, serial test results are needed; however, the laboratory differs from the guidelines of the Cardiac Society by suggesting a ∂ of more than 30% within 3-12 hours with at least one test result being elevated.

Suggested levels of rise and fall are not universal. Given the differences in assays and the nature of how troponin is released into the blood, ∂ changes should actually depend on the cTn assay used, the exact time period between tests and the onset of symptoms prior to hospital admission. In addition, while most guidelines suggest relative ∂ changes, the research literature supports absolute ∂ changes for the latest generation of cTn assays.[9]

In the quest to diagnose a NSTEMI (non-ST-elevation MI) earlier, the 2015 European guidelines suggest an alternative algorithm with a repeat test after only one hour.[10] The rule-in/rule-out algorithm requiring a one-hour repeat test reduces the delay in making a diagnosis. Furthermore, absolute (versus relative) ∂ changes are used. Table 1 summarises the algorithm for different hs-cTn assays.

Table 1 – Rule-in and rule-out algorithms for suspected NSTEMI

		Rule OUT*	Rule OUT (2 criteria)		Rule IN (1 criterion)	
	99th centile	1st test	1st test AND delta		1st test OR delta	
hs-cTnT Elecsys (Roche)	14	<5	<12	∂<3	≥52	∂≥5
hs-cTnI Architect (Abbott)	26 (♀:16 ♂:34)	<2	<5	∂<2	≥52	∂≥6
hs-cTnI Vista (Siemens)**	9†	<0.5	<5	∂<2	≥107	∂≥19

* *Only to be applied if chest pain onset was more than three hours ago.*

1st test *Troponin value from first blood test taken.*

Delta (∂) *Difference in troponin values between first test and second test taken one hour after first test.*

** *Not yet commercially available.*

† *Love et al. Incorporating high-sensitivity cardiac troponin assays into clinical practice: these assays are your friend. Heart Metab. 2015;67:9-14.*

Source: European Heart Journal, 2016;37:267-315

The guideline leaves a considerable grey zone. An initial hs-cTnI (Abbott) value of at least 5 but less than 52 requires a second test with a minimum change of 6 units to rule in a NSTEMI. Both test values may be below the 99th percentile. Besides the obvious grey area, this algorithm has a positive predictive value of only 75%-80% for MI amongst patients meeting the rule-in criterion. Of course, the advantage is that some patients can be sent home earlier. Besides an algorithm with single or multiple troponin values, the guidelines always suggest that a detailed clinical assessment, ongoing ACS symptoms (or the lack thereof) as well as ECG findings are integrated into any final assessment.

single high troponin reading (instead of a rise and/or fall). In these cases where a clinician does not require a rise and/or fall of cTn in order to initiate treatment to prevent an acute MI from further damage, insurers have to consider the overall clinical presentation and treatment provided. [See Boxes 1, 3 and 4]

Pattern of rise and fall

Following a cardiac injury, cardiac troponin is released into the blood. Troponin levels increase within a few hours after the onset of damage, peak after 24-48 hours and return to normal over a period of several days. Consequently, the clinician and the insurance claims assessor should bear in mind such factors as time interval from symptom onset to hospital admission and first cTn test, time interval of further cTn tests and assay used. Even if an algorithm suggests a high predictive value, predictability can be influenced by late admission to hospital, old cTn assays or the use of point-at-care devices (versus laboratory analysis). Insurers using definitions requiring a minimum cTn elevation should include an alternative requirement or otherwise address the fact that cTn rises and falls in a particular pattern.

Test accuracy

Every test has a particular sensitivity (identifying a condition amongst diseased people) and a particular specificity (producing a negative test result in a healthy person). The fifth generation cTn assay is particularly sensitive and thus useful in an uncertain emergency situation where the focus is in ruling out a heart attack as soon as possible – i.e. achieving a high negative predictability. Insurers, however, want to rely on a test result that has a high positive predictability. [See Box 3]

No troponin information

Besides the universal definition, the WHO has also weighed in with a definition of heart attack. It suggests that whenever there is incomplete information on cardiac biomarkers and other diagnostic criteria needed, the term MI should be used if both of the following criteria are present: a) symptoms of ischaemia and b) development of unequivocal pathological Q-waves (on the ECG).[4]

This part of the WHO definition could be considered alongside the third universal definition if biomarker results are not available or valid.

How to solve this conundrum?

In an earlier issue of *Risk Matters Oceania*, Gen Re addressed the question of when is a heart attack a heart attack, and the fact that most insurance policies are likely to be out of step with the clinical heart attack definition.[5] However, this article highlighted that the clinical definition is not the silver bullet answer in terms of objectivity and transparency. The purpose of the universal definition is to make the right decision in an emergency situation.

A Trauma product, on the other hand, intends to offer a single lump sum benefit when the customer's health has been compromised and permanently impaired, reducing the insured's life expectancy or the ability to work or demanding significant lifestyle changes. Consequently, the heart attack definition for insurance purposes should not be based solely on a diagnosis made during an emergency situation. In both Australia and New Zealand, the maximum sum assured under a Trauma policy can be in excess of AUD 2 million (respectively NZD 2 million) or an equivalent USD 1.5 million. Large benefit amounts should be based on the underlying medical condition and damage this has produced. This would be more consistent with other Trauma conditions.

Furthermore, the advances in diagnostics have resulted in more minor heart attacks being diagnosed. This trend can be expected to continue.

To offer affordable Trauma policies, insurers should consider paying significantly less than the full sum assured for heart attacks based on diagnosis alone.

Additional benefits can be considered when the insured is required to undergo further medical treatment, such as angioplasty or bypass grafting surgery as it approximates the extent of the underlying disease. This can be further differentiated by the number of coronary vessels treated and, in the case of an angioplasty, whether a stent is placed or not.

Alternatively or additionally, the benefit level could be tiered depending on the impact the heart attack has had on the heart's capacity to pump blood through the circulatory system (using the ejection fraction).

While the idea of Trauma insurance is simple, the underlying benefit trigger is complex. Insurers cannot make simple what is complex in nature. There are individual situations for which a definition may not be perfect. Insurers require a claims team that can understand the clinical presentation of a heart attack, knows local guidelines, communicates well with the Chief Medical Officer and the treating clinician, is prepared to go beyond the absolute meaning of a definition and uses all information presented in a holistic approach.

Product actuaries, too, need to appreciate weaknesses of a clinical definition when pricing and designing an insurance product.

Finally, just as the patient must have trust in the treating doctor, the insurance customer should have trust in the insurer assessing claims fairly. Building trust goes beyond the wording of a medical definition.

Box 2 – Who determines the URL anyway?

Defining a healthy population to determine the 99th percentile is challenging. Different studies have published very different numbers even for the same cTn assay. For example, for the hs-cTnT assay, 99th percentiles have ranged from 12 to 20 ng/L. For the Abbott hs-cTnI assay, the 99th percentile has ranged from 13 ng/L to 32 ng/L. These studies vary in the number of subjects enrolled as well as the makeup by age and gender. No definitive number of individuals to be included in a reference population has been defined nor have the criteria on what constitutes "healthy".[11]

Acute MIs in women are believed to have been under-diagnosed, and this has led to increasing requests for manufactures to develop gender-specific URLs for the latest generation of cTn assays, or, where they have been evidenced, to use them. With the introduction of gender-specific URLs, insurers can expect a significant increase in MI rates. For example, in one small study almost 40% more type 1 MIs (an acute MI due to a primary coronary event) were identified amongst women; the overall increase was 9% due to a corresponding reduction amongst males.[12]

About the Author

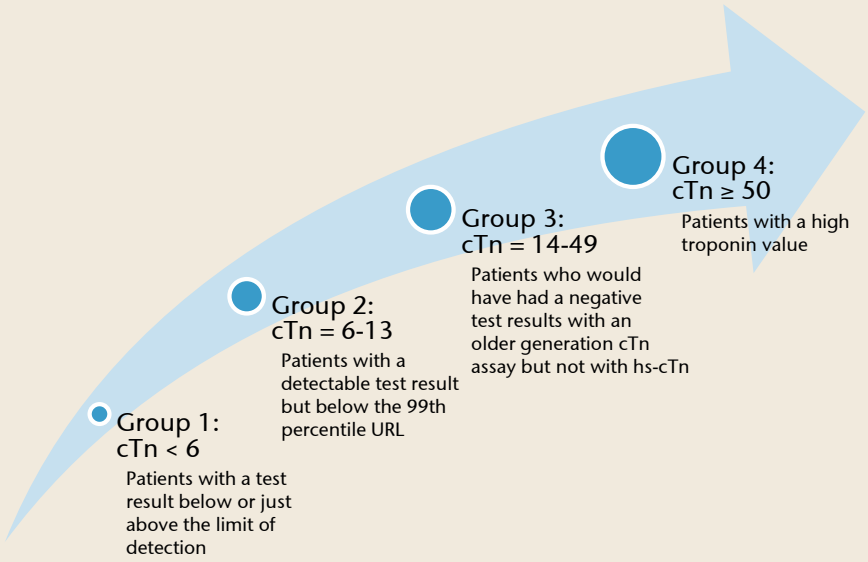
Andres Webersinke, *Managing Director of General Reinsurance Life Australia Ltd, is responsible for Gen Re's Life and Health business in Australasia. During the course of his more than 20 years with Gen Re he has held various technical, marketing and management positions in Germany, South Africa and AsiaPacific. He may be reached at +61 2 8236 6200 or webersin@genre.com.*

Box 3 – Ruling-in/ruling-out: how predictive is the test?

A large Swedish study categorised almost 50,000 patients who were admitted to a hospital because of symptoms suggesting ACS.[13] Patients were divided into four groups according to their maximum hs-cTnT value. The 99th percentile URL for this assay is 14 ng/L (all values shown here are in ng/L).

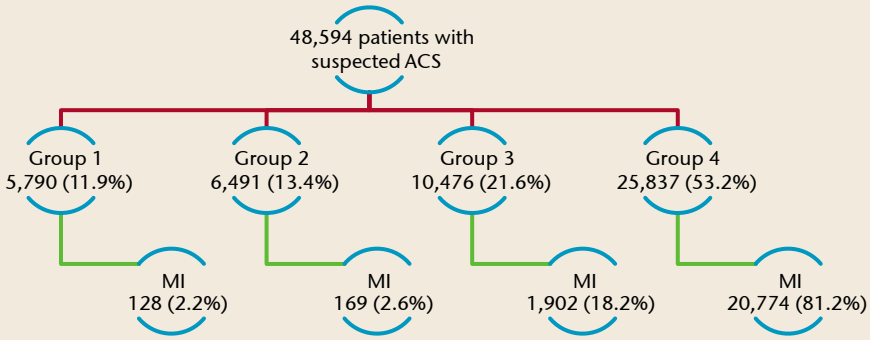
A quarter of the patients did not have an elevated cTn test result (Figure 2). They were assigned to Group 1 or 2. One in forty of these patients received the diagnosis of MI. Interestingly, the authors of the study suspect erroneous registration of cTn values due to the change in how values from hs-cTn assays are stated versus the prior generation troponin assays (different unit).

Figure 1 – Patient categorisation by maximum hs-cTnT value



Source: SwedeHeart Registry, JACC, 2015;65(16):1655-64

Figure 2 – Number and proportion of patients with different levels of high-sensitive cardiac troponin and diagnosis of MI



Source: SwedeHeart Registry, JACC, 2015;65(16):1655-64

It can be concluded that almost 10% more heart attacks were diagnosed due to the use of a more sensitive cTn assay (Group 3). Important to note is the fact that not all cTn increases are due to acute MI. About 80% of patients in Group 3 did not have a heart attack!

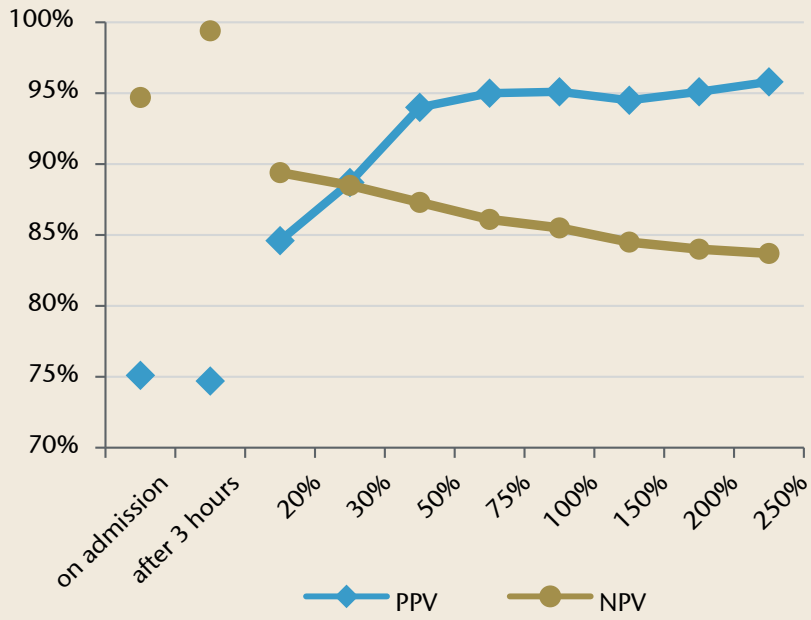
Even in Group 4, the diagnosis was not that of an acute MI for one in five patients.

Upon admission to an emergency department in a hospital, the negative predictive value (NPV) of a single hs-cTn test, which rules out an MI, is a satisfactory 95%. In contrast, the positive predictive value (PPV) is an unsatisfactory 75%. Clearly, the insurance industry does not want to pay a lump sum on the basis of only a 75% chance the claimable event occurred.

Clinical guidelines suggest a repeat cTn test after three to six hours if the initial test resulted in a value that is considered negative, or positive, but low. The positive predictability does not increase with a repeat test at three hours post admission but the negative predictive value is almost 100% in these cases.

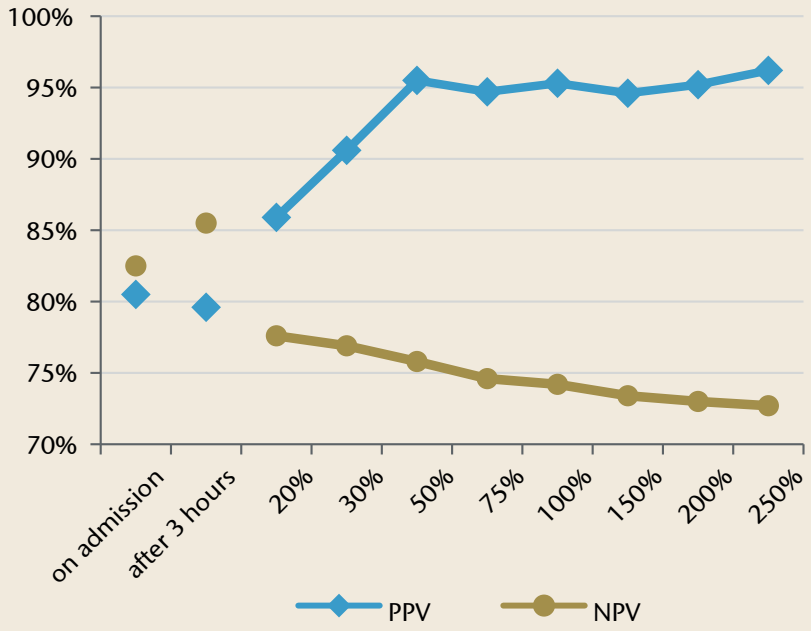
To rule in an MI, where other clinical features have not confirmed an MI, cTn must rise and fall – i.e. change. This increases the positive predictive value. It increases to 85% if a 20% change is considered. This can be further increased to 94% with a minimum change of 50% (Figure 3).[14] A higher change increases the PPV further but only marginally. Figure 4 shows similar PPV results when ECG readings do not suggest a STEMI, albeit with a much lower NPV.

Figure 3– Diagnostic performance for identification of acute MIs by use of serial hs-cTnI assay test results > 99th percentile on admission, after three hours and minimum delta change



Source: JAMA, 2011;306(24):2684-93

Figure 4 – Diagnostic performance for identification of acute NSTEMIs and unstable angina by use of serial hs-cTnI assay test results > 99th percentile on admission, after three hours and minimum delta change



Source: JAMA, 2011;306(24):2684-93 (Supplementary Online Content)

Box 4 – (In)significance of a troponin value

A troponin value is not immediately available but an ECG provides immediate information. ECG changes are used to differentiate MIs. Most patients with acute chest pain and persistent ST-segment elevation lasting for more than 20 minutes will develop a so-called ST-elevation MI (STEMI). These patients are most likely to be treated by an emergency diagnostic angiogram with either an angioplasty (often with removal of a clot and insertion of a stent) or a medication that dissolves any blood clot in the coronary artery and restores flow, thus minimising any damage to the heart muscle.[15] In other words, treatment may begin before any troponin value is made available.

The intention of a Trauma policy is to cover an evidenced STEMI requiring revasculisation, even if no troponin value or a series of troponin values is available to verify a rise and/or fall. Where troponin values are available, they may have limited value in particular after a treatment with a stent or bypass grafting as these procedures influence the level of released cTn.

Endnotes

1 Esserman et al. Overdiagnosis and Overtreatment in Cancer. JAMA. 2013;310(8):797-798.

2 Thygesen et al. Third universal Definition of Myocardial Infarction. Circulation. 2012:126:2020-2035.

3 An assay can be considered "highly sensitive" if the following two criteria are fulfilled: a) the ability to measure cTn in at least 50% of healthy reference subjects above an assay's limit of detection and b) has a coefficient of variation (standard deviation) of not more than 10% at the 99th percentile upper reference limit.

4 Mendis et al. World Health Organization definition of myocardial infarction: 2008-09 revision. Int J Epi. 2011;40:139-146.

5 Gen Re. When Is a Heart Attack a Heart Attack? *Risk Matters Oceania.* November 2011.

6 Based on the "2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of ACS 2006", published in Heart, Lung and Circulation. 2011;20:487-502.

7 Two subtypes of troponin (cardiac troponin I (cTnI) and T (cTnT)) are indicators of damage to the heart muscle (myocardium).

8 A highly abnormal hs-cTn typically defines a value beyond five times the upper limit of normal. Deltas will need to be individualised by hs-cTn assay because of their unique analytical and biological characteristics due to the lack of assay standardisation. Love et al. Incorporating high-sensitivity cardiac troponin assays into clinical practice: these assays are your friend. Heart Metab. 2015;67:9-14.

9 Apple et al. Implementing high sensitivity cardiac troponin assays. Clinical Laboratory News. 2015;41(12):8-12.

10 Roffi et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2016;37:267-315.

11 Koerbin G L. High sensitivity troponin – its use in diagnosis of cardiac dysfunction. University of Canberra. PhD Thesis.

12 Shah et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ. 2015;350:g7873.

13 Based on Melki et al. Implications of introducing high-sensitivity cardiac troponin T into clinical practice. Data from the SwedeHeart Registry. JACC. 2015;65(16):1655-64.

14 Keller et al. Serial changes in highly sensitive troponin I assay and early diagnosis of MI. JAMA. 2011;306(24):2684-93. Note: the 99th percentile used in this survey was 30 ng/L.

15 Steg et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal. 2012;33:2569-2619.

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The Sydney Oxfam Trailwalk starts on 19 August. This walk is a total of 100 km through dense Australian bush land and rugged unforgiving terrain. To successfully enter a team, it requires four individuals who must complete the walk within 48 hours. Three Gen Re Life Australia colleagues, Lindsay Cross, Rob Frank and Daniel Podmore, teamed up with Tania Du Plessis from TAL (Australia's largest life insurance group) to raise funds for Oxfam Australia. Known as the Dexys Midnight Walkers the team aim to reach the finish line within 36 hours. The team is proudly positioned amongst the top fund raisers within the Financial Services category and overall. They have a fantastic support crew in place, comprising of Gen Re colleagues and family members who will provide them with all the fluids and food to help them cross the finish line in one piece. Please feel free to view their progress via the website: https://trailwalker.oxfam.org.au/my/team/23479

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