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# Exploring the Universal Definition of MI: The Role of High-Sensitivity Troponin CME

Allan S. Jaffe, MD; David A. Morrow, MD, MPH; Kristian Thygesen, MD; Harvey D. White, MB, ChB, MSc

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Cardiac biomarkers have become an integral part of the assessment for patients with suspected acute coronary syndrome (ACS). While physicians are generally familiar with the use of biomarkers in this context, the application of testing is often subject to uncertainty, particularly with regard to more sensitive assays as is the case with the new generation of high-sensitivity cardiac troponin assays. These assays have both the sensitivity and specificity for detecting myocyte injury and have emerged as the preferred biomarkers for the detection of acute MI, thereby greatly improving the diagnosis, risk stratification, and care of patients with ACS to such an extent that they constitute an important component of the "universally accepted definition" of MI. Drs Jaffe, Morrow, Thygesen, and White review the progress made , the current applications, and the challenges ahead for using these diagnostic tools to better manage patients with ACS.

## Exploring the Universal Definition of MI: The Role of High-Sensitivity Troponin

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**Slide 1.**

**Allan S. Jaffe, MD:** Hello. I'm Dr Allan Jaffe, professor of medicine from the Mayo Clinic, and I'd like to welcome you to this program, "Exploring the Universal Definition of Myocardial Infarction: The Role of High-Sensitivity Troponin." Joining me today are Dr David Morrow, who is an associate professor of medicine and cardiology at Harvard Medical School at the Brigham and Women's Hospital; Dr Harvey White, who is a professor of medicine from Auckland City Hospital in Auckland, New Zealand; and Dr Kristian Thygesen, who is a professor of medicine from Aarhus Hospital in Aarhus, Denmark. Welcome.

Today we are going to discuss the current universal definition of myocardial infarction (MI) and describe biomarkers and serial biomarker strategies. Then, we will explain the significance of troponin levels detected by high-sensitivity assays in acute coronary syndrome (ACS) and non-ACS and the implications of these assays on current treatment guidelines.

Let us start with a little background on the universal definition. Dr Thygesen, would you start, as you and Joe Alpert were the initiators of this global initiative, and update us not only on the process and the thinking, but where we are now in 2012?
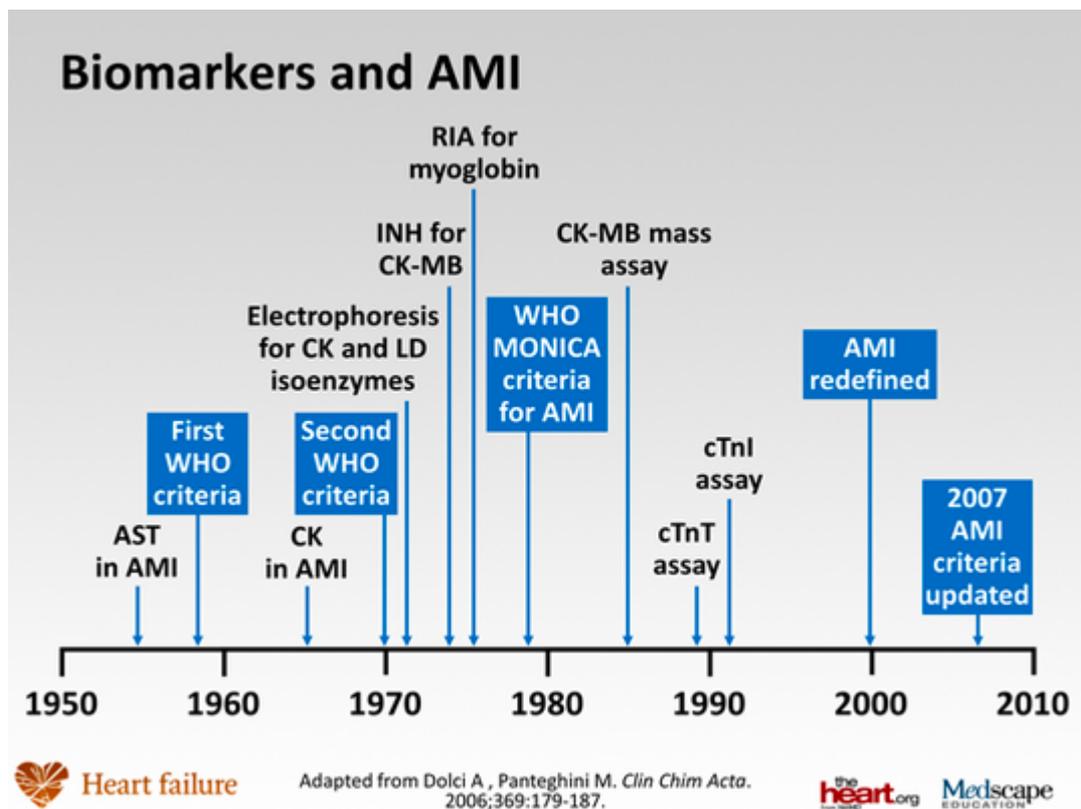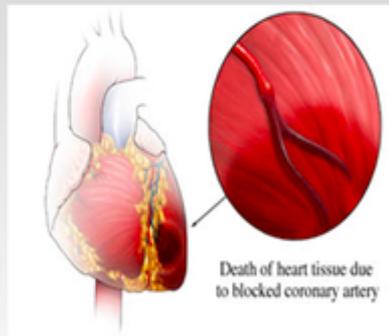
**Slide 2.**

**Kristian Thygesen, MD:** Thank you, Allan. I'll be happy to give a background on that. It goes back to the 1990s when there was a discussion in the European Heart House on the current definition. At that time, the definition was based on the World Health Organization's definition going back to the 1950s and 1960s, which was based on physiology. In the 1990s, we could see that did not match the criteria we used in the clinics and, also at that time, new biomarkers were coming into the market, namely troponin. So, at a meeting at the European Heart House in 1999, members from the United States and Europe discussed how we should proceed.

**Slide 3.**

At that time, we were sure that we should keep the pathological definition of myocardial infarction based on necrosis due to prolonged ischemia.



**Slide 4.**

We came up with the first paper in 2000, putting a lot of emphasis on troponins being the preferred marker for myocardial infarcts. After that, we could see that there was still something that needed to be discussed, and after many letters to the presidents of the societies in the United States and in Europe, we succeeded in setting up the Global Task Force on Myocardial Infarction with 50 members and came up with the universal definition of myocardial infarct in 2007, which was published in *Circulation*, *Journal of the American College of Cardiology (JACC),* and *European Heart Journal*. The updated definition kept the troponins as the preferred marker for myocardial necrosis but, in addition, we added criteria for procedures and the classification of myocardial infarcts. From that time, we could see that clinicians were more receptive to the use of troponins and since then they have been used worldwide. However, we still see that there are some details that need to be discussed and, therefore, we have reassembled the Global Task Force. Again, we have about 50 members and now, in 2012, we are ready to come up with a third universal definition of myocardial infarct.

**Dr Jaffe:** Harvey joined the task force in 2007 as one of the leaders of that initiative and one of his innovations was to add the concept of different types of MI and, in particular, distinguishing spontaneous MI between types 1 and 2. Dr White, would you expound on this? It's going to become important as we talk about the high-sensitivity assays.



## Classification of Myocardial Infarction

| | |
|---|---|
| Type 1 | Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection |
| Type 2 | Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply  (eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension) |
| Type 3 | Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-elevation, or new LBBB, or presumably new major obstruction in a coronary artery by angiography and/or pathology, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood |
| Type 4a | Myocardial infarction associated with PCI |
| Type 4b | Myocardial infarction associated with stent thrombosis as documented by angiography or autopsy |
| Type 5 | Myocardial infarction associated with CABG |

Thygesen K, et al. *Eur Heart J.* 2007;28:2525-2538.

**Slide 5.**

**Harvey D. White, MB, ChB, MSc:** Yes, I think that it is important as well that we do distinguish the different types of MI. We actually have 5 different types of MI. Type 1 is spontaneous, which we think is related to plaque rupture or fissuring and the treatment is angiography, stenting, and intensive antithrombotic therapy. Type 2 is based on oxygen supply and demand, often occurs after surgery, and is related to hypertension or anemia, for example, and treatment is quite different. Type 3 is sudden death and it is very important to have those data on percutaneous coronary intervention (PCI) and define periprocedural infarcts. Type 4 is with PCI. We have a type 4a, which is ischemic-related complications that occur with the PCI procedure, and a type 4b, which is stent thrombosis. The capturing of metrics is very important for clinical trials and in the interpretation of data. Then, type 5 is with coronary artery bypass graft surgery (CABG).

They all occur in the setting of ischemia and if biomarkers are available, then troponin is the preferred

biomarker.

**Dr Jaffe:** Before we talk about high sensitivity, we ought to talk about how we use the assays that do not have high sensitivity. High-sensitivity assays are available in much of the world, but not in the United States. Dr Morrow, would you tell us the key biomarker characteristics that ought to be emphasized when implementing this Global Task Force definition?



## Criteria for Acute Myocardial Infarction Types 1 and 2

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit together with evidence of ischemia with at least 1 of the following:

- Symptoms of ischemia
- ECG changes of new ischemia (new ST-T changes or new LBBB)
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

**Slide 6.**

**David A. Morrow, MD, MPH:** If I have any advice for the clinician, it is to know your assays: the 99th percentile reference cut point and the analytical performance of the assay, especially down at the low end. The crux of the current guideline is to use the 99th percentile single cut point for the diagnosis of MI in conjunction with a good clinical story. As Harvey said, you are superimposing your clinical evaluation of the patient to help stratify the MI into a group type, so you need to work with your laboratory to understand where the 99th percentile is. In addition to that, I think that using the deltas, or dynamic changes, which we are going to talk about a lot more, are important. There is a rising/ falling pattern of troponin that helps you with the diagnostic specificity for an acute injury, as opposed to a chronic reason for an elevation of troponin.
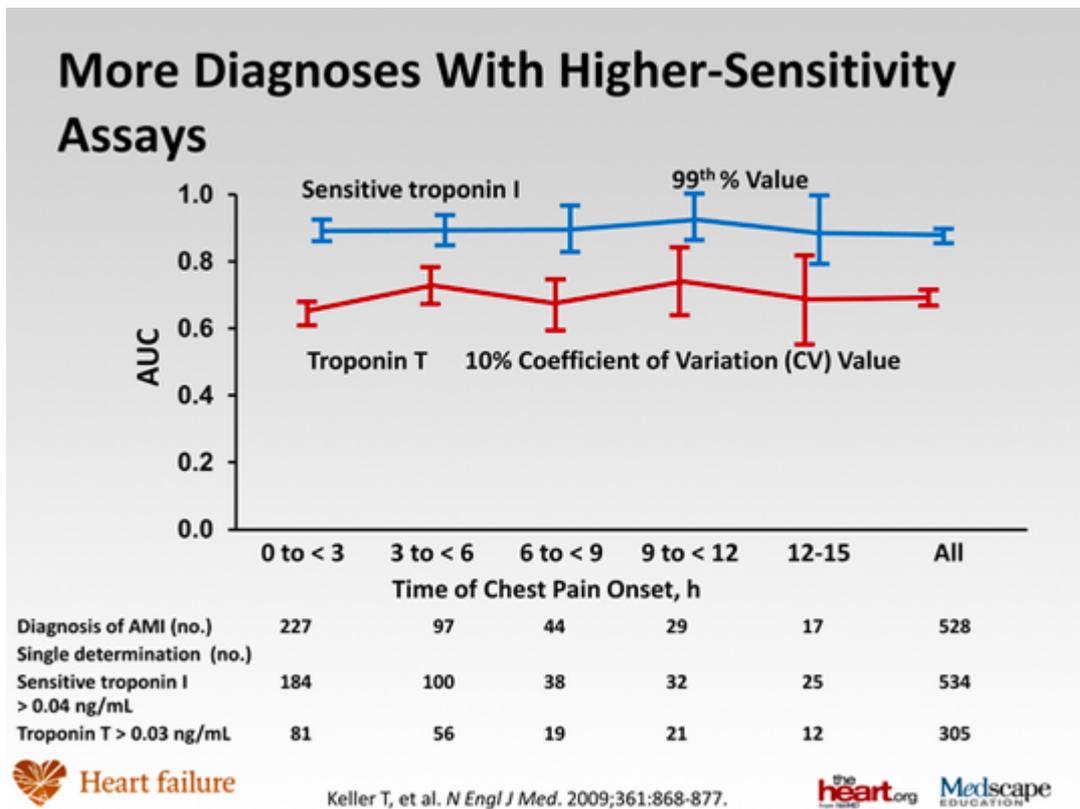
**Slide 7.**

**Dr Jaffe:** With that, I think we ought to move to the high-sensitivity assays and some degree of explanation about what a high-sensitivity assay is, because the literature has been confusing about this point. There have been multiple papers suggesting that there are more sensitive ways to detect patients who are at risk, but many of them have simply begun to implement the 99th percentile cut-off values as part of that definition. The consequence is that there are 2 trends.

## Accuracy by Time of Admission
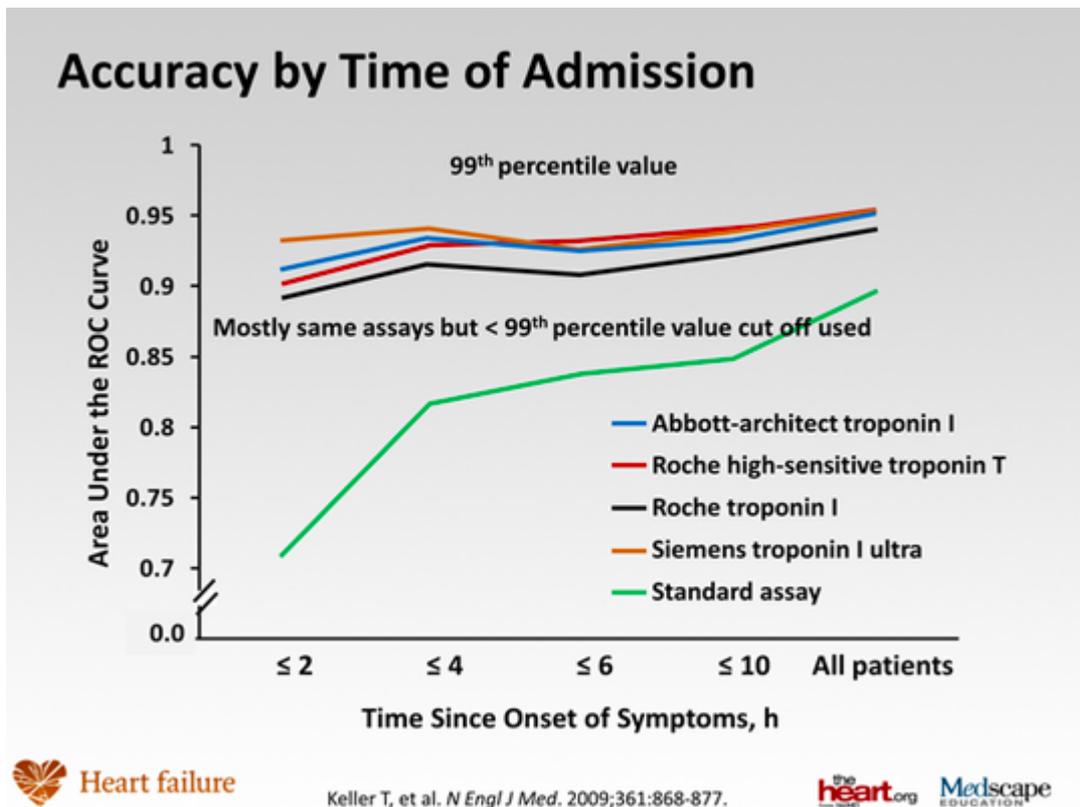


**Slide 8.**

One trend is starting to use the appropriate cut-off values, which increases the sensitivity of the assays and identifies more patients at risk.

## Event-Free Survival During the Validation and Implementation Phases of the Study
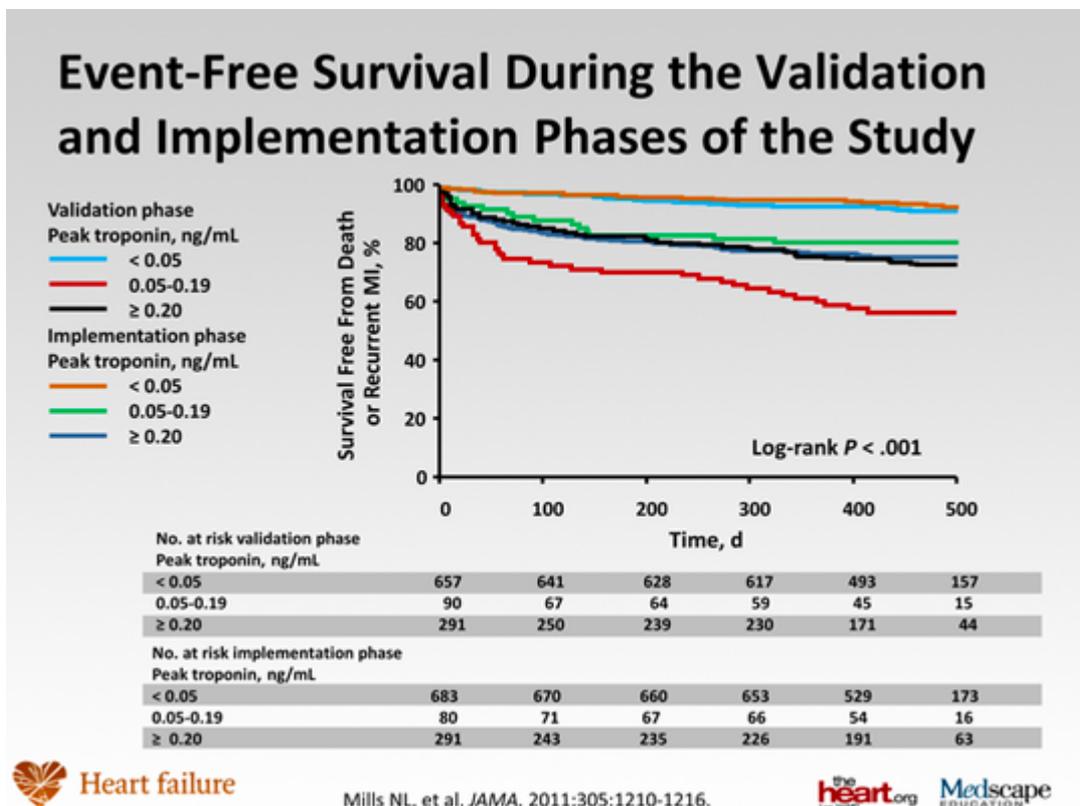


**Slide 9.**

A second initiative is development of higher-sensitivity assays. Perhaps the best way to distinguish them, and the only way that has been suggested so far, has been to look at the number of normal individuals who have MI detected with these assays.
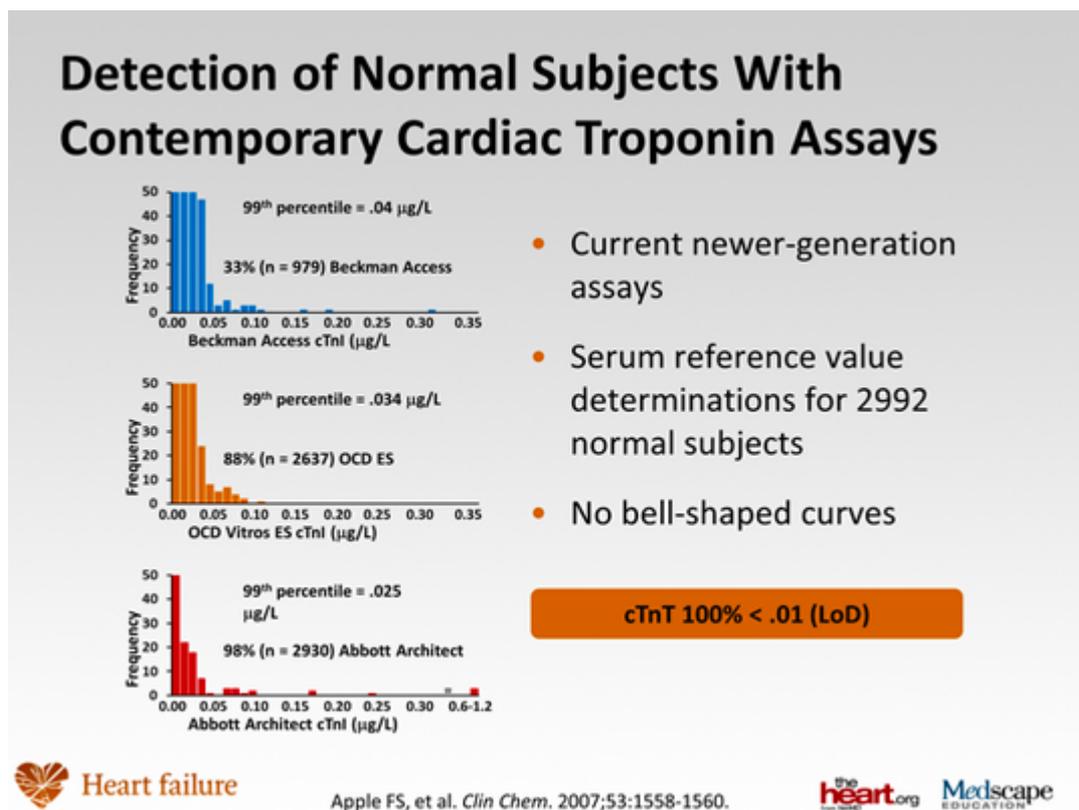


**Slide 10.**

With the assays that are presently available that we would call non-high-sensitivity assays, very few patients, usually less than a third of normal patients, have values that are detectable.

## Cardiac Troponin Assay Score Card

| Acceptance Designation | Total Precision at 99th Percentile |
|---|---|
| Guideline Acceptable | ≤ 10% |
| Clinically Usable | > 10 to ≤ 20% |
| Not Acceptable | > 20% |

| Assay Designation | Measurable Normal Values Below 99th percentile |
|---|---|
| Level 4 3rd Generation, High Sensitivity | ≥ 95% |
| Level 3 2nd Generation, High Sensitivity | 75 to < 95% |
| Level 2 1st Generation, High Sensitivity | 50 to < 75% |
| Level 1 Contemporary | < 50% |

Heart failure      Apple FS, et al. *Clin Chem.* 2009;55:930-937.

**Slide 11.**

Whereas with the high-sensitivity assays, detection is usually greater than 50%, and in some circumstances as high as 90%, suggesting increased sensitivity. That is not necessarily clinical sensitivity and we have to be careful about that, but that is what has been proposed. It is important for clinicians to understand that some increased sensitivity comes from using the right cut-offs at another level from these new assays.

## Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays

| Company/Platform/ Assay | Cardiac Troponin Concentration | | | Amino Acid Residues of Epitopes Recognized by Capture (C) and Detection (D) Mabs |
|---|---|---|---|---|
| | LoD (µg/L) | 99th Percentile (µg/L [CV]) * | 10% CV Concentration (µg/L) | |
| **hs-cTnI** | | | | |
| Abbott ARCHITECT* | 1.2 | 16 (5.6%) | 3.0 | C: 24-40; D: 41-49 |
| Beckman Access* | 2-3 | 8.6 (10%) | 8.6 | C: 41-49; D: 24-40 |
| Nanosphere MTP* | 0.2 | 2.8 (9.5%) | 0.5 | C: 136-147 D: Mab PA1010 |
| Singulex Erenna* | 0.09 | 10.1 (9.0%) | 0.88 | C: 41-49; D: 27-41 |
| Siemens Vista* | 0.5 | 9 (5.0%) | 3 | C: 30-35 D: 41-56, 171-190 |
| **hs-cTnT** | | | | |
| Roche Elecsys† | 5.0 | 14 (8%) | 13 | C: 136-147 D: 125-131 |

*Under development and not available for commercial use; †available for use worldwide but not cleared by US Food and Drug Administration for use in United States.

Heart failure      Apple FS, et al. *Clin Chem* 2012 58(1):54-61.

**Slide 12.**

With that said, when you start using high-sensitivity assays, Dr Morrow, you have written about and participated in other studies on the frequency of elevations in non-ACS patients. How does one begin to think of how we ought to use these assays that have really high sensitivity, as just defined?

## Prevalence of Detectable cTnT and Levels ≥ 99th Percentile URL

| Group | Sample Size | cTnT Level, ng/mL | | | |
|---|---|---|---|---|---|
| | | ≥ 0.003 | | ≥ 0.014 | |
| | | N (%) | Sample Weight-Adjusted Prevalence, % (95% CI) | N (%) | Sample Weight-Adjusted Prevalence, % (95% CI) |
| Overall population | 3546 | 957 (27.0) | 25.0 (22.7-27.4) | 122 (3.4) | 2.0 (1.5-2.6) |
| Restricted population Without CHD | 3428 | 891 (26.0) | 24.2 (21.8-26.5) | 103 (3.0) | 1.8 (1.2-2.4) |
| Without cardiovascular disease | 3277 | 813 (24.8) | 23.7 (21.3-26.1) | 82 (2.5) | 1.9 (1.0-2.0) |
| Without cardiovascular disease or CKD | 3222 | 773 (24.0) | 23.1 (20.7-25.5) | 65 (2.3) | 1.2 (0.8-1.7) |
| Without cardiovascular disease, CKD, subclinical heart disease, diabetes, or hypertension | 2554 | 510 (20.0) | 19.3 (16.8-21.8) | 43 (1.7) | 1.1 (0.6-1.7) |

Heart failure    DeLemos JA, et al. *JAMA*. 2010;304:2503-2512.    heart.org    Medscape EDUCATION

**Slide 13.**

**Dr Morrow:** We will probably come back to the delta again, but we have to recognize that we will have detectable troponin using the more sensitive assays in a greater proportion of patients. So, for example, one study that I was involved in was a population-based study using the standard assay, for lack of a better term. Less than 1% of the population had a detectable value with that assay. When you introduce the high-sensitivity assays, that percentage rose to 25% having a detectable level. It is very age sensitive. For patients older than 60, these troponin levels are detectable in as much as two-thirds of that population. If you have an average patient coming in to your emergency department (ED), say a 75-year-old individual, you have to recognize that you might have a detectable troponin with a high-sensitive assay in that case. That's why both thinking about the clinical scenario and looking for dynamic changes becomes so important.

**Dr Jaffe:** What percentage of individuals have values around the 99th percentile of the upper reference limit (URL)?

**Dr Morrow:** That's a good point. Even though values may be detectable in 25%, it is only on the order of 3% to 5% in the whole population. In elderly patients, it can be as high as 10% in some of the population-based studies. So we have to recognize that it's not a trivial number of patients who may have elevations, usually in association with structural heart disease. That point is important: elevated values in a normal state of health.

**Dr Jaffe:** Patients who have structural heart disease are the ones who are coming to the ED. With 3% of these patients in the whole population, it may be as many as 10% in the ED or even 30% in the hospital.

Let's talk about the use of a high-sensitivity assay. One of the key metrics is to look at change as a way to distinguish these chronic elevations that you've described from acute elevations. Dr Thygesen, can you tell us

how you do this? You're using a high-sensitivity troponin-T assay in Denmark. When you see these patients, what sort of metrics do you use? How do you think about them and how well has the assay worked for you?

**Dr Thygesen:** We started to use high-sensitivity troponins about one year ago, and in the beginning it was puzzling as to how to use them. Not only us as cardiologists but also our colleagues -- surgeons and other colleagues -- were wondering how we should deal with these new values. Should we be transporting these patients to the cardiac units? There were a lot of things to discuss. I must admit that we started with a fixed value, so to not increase the number of infarcts. We transferred the values from the old troponin assays and tried to have a higher limit or cut-off point for the high-sensitivity troponins. After a while, we could see that it was not the right way to go. So, we struggled to find a way to use the assay. We discussed in the study group that we should use the 99th percentiles and add something showing the delta waves.

## Elevations of Troponin in the Absence of Overt Ischemic Heart Disease

- Cardiac contusion or other trauma including surgery, ablation, pacing, etc.
- Congestive heart failure (acute and chronic)
- Aortic dissection, aortic valve disease
- Hypertrophic cardiomyopathy
- Tachyarrhythmias, bradyarrhythmias, or heart block
- Apical ballooning syndrome
- Rhabdomyolysis with cardiac injury
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Acute neurological disease, including stroke, or subarachnoid hemorrhage
- Infiltrative diseases (eg, amyloidosis, hemochromatosis, sarcoidosis, or scleroderma)
- Inflammatory diseases (eg, myopericarditis/pericarditis or myocardial extension of endocarditis)
- Drug toxicity or toxins
- Critically ill patients, especially with respiratory failure or sepsis
- Burns, especially if affecting > 30% of body surface area
- Extreme exertion

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**Slide 14.**

We still think it is very important to keep this rise and fall to detect necrosis in contrast to, and we heard David say, a chronic disease. I'm not sure we have the right answer yet, but at least we have tried to come up with these values saying that if you have this 99th percentile upper reference limit and then you add something, that could be 50% of the upper reference limit for people coming in with values below the upper reference levels. In contrast, if patients are admitted with values above the upper reference level, we stick to these 20% increases as we have before with the older troponin assays.

**Dr Jaffe:** Has that worked well for you when you see patients?

**Dr Thygesen:** I'm not saying that it has worked well, but we are in the learning phase. It is taking time because there are a lot of physicians in my department and other departments to convince how to use the assays. So, it's a long educational process. We have had new physicians come in and our laboratory has changed almost overnight, and we are just now teaching the cardiologists how to use them.

**Dr Morrow:** It is worth commenting that the data show that even though we can get smarter about the way we use high-sensitivity assays, when you compare their overall diagnostic accuracy in a population with a

reasonable pretest probability, meaning that the clinician thinks there is a reasonable chance of acute coronary syndrome, even without using the delta, the assays are superior for their overall accuracy. When I talk to my colleagues about it, I do it with that same frustration about the uncertainty when the assay is applied in the lower-probability patients. They lose track of the fact that overall, the improvements in the analytical performance have improved our diagnostic accuracy in patients in whom, clinically, we think they have an acute coronary syndrome.

**Dr Jaffe:** I couldn't agree more. Harvey, you've stimulated the development of guidelines in Australia and New Zealand, and you have a smaller group to deal with so I think that you have a little more homogeneity. Can you tell us what your experience has been?
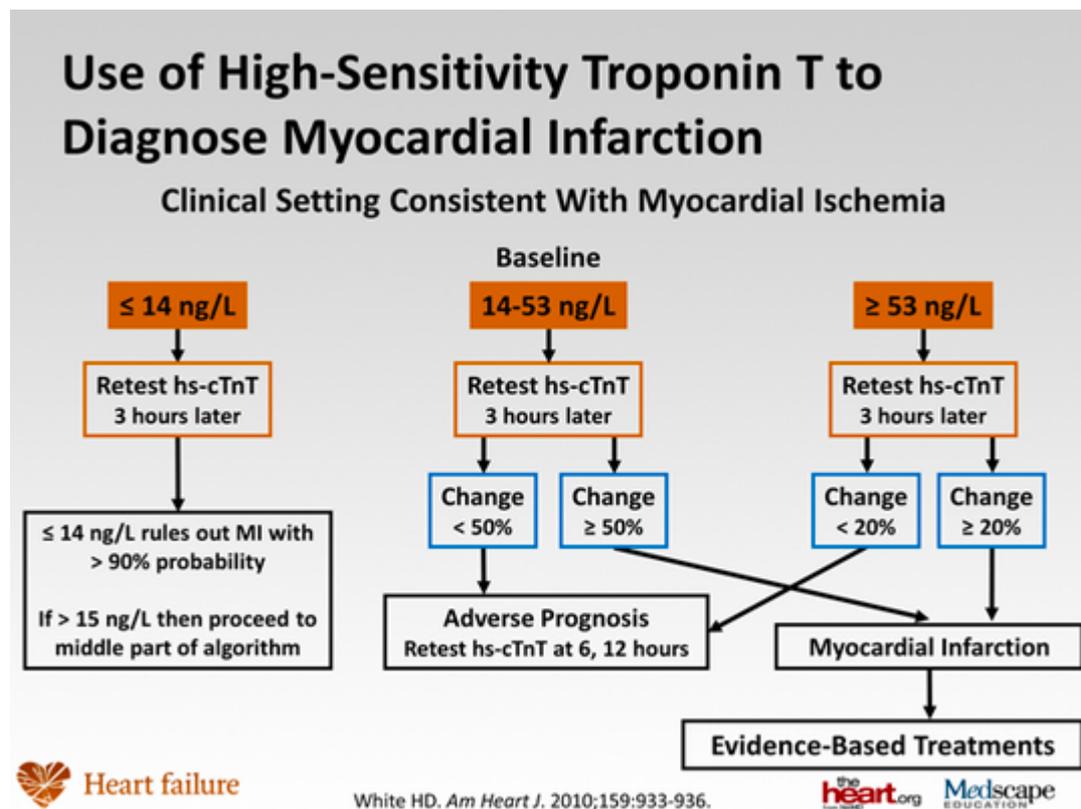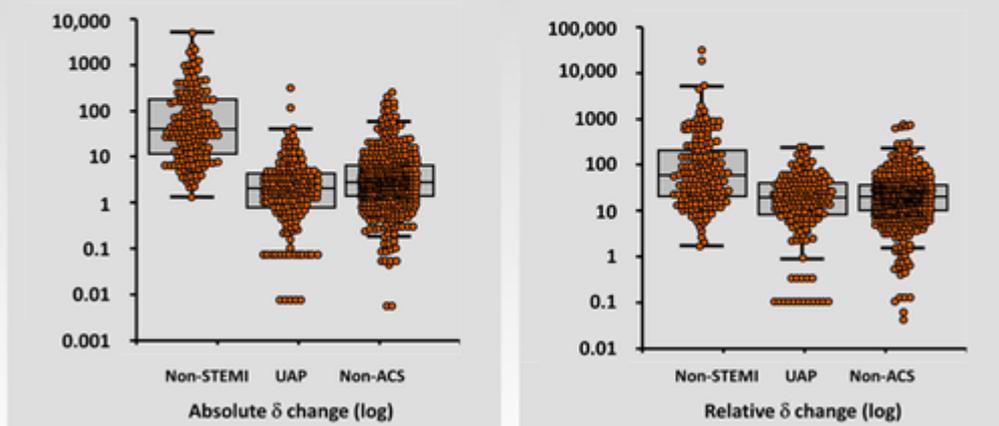


Slide 15.

**Dr White:** I may have a smaller group, but it is used extensively throughout India and China, and so the algorithm that we set up is used in most of the world. Two years ago, we decided that it's very important to have education: discussions with a biochemist and multiple meetings with cardiologists. The first thing to get across is that these are better tests. They rule in. You can get patients out of the ED faster. They rule out. Down at lower levels, we have some information that you may use in an invasive strategy, for example. We decided that we would use a 50% change, a delta based on the literature at that time, and the biological variability can measure this in all patients. The data are between 32% and 85%. There were issues with the population from which those data were chosen, issues about the platform used, and we had a 32% delta. So, I think you need to use a delta. It's like with renal disease. You have to look at it from the point of view that almost everybody has an elevated troponin level and you have to look at the delta in the setting of ischemia. We have a 50% delta below the previous cut point for contemporary troponin-T. Above that, we have 3 standard deviations, which were recommended by the National Academy of Clinical Biochemistry (NACB) for renal disease, so 3 standard deviations, 20% change. We instituted that 2 years ago. We'll need to make our data available soon, but the increase in infarcts is 5%. It's not 40%, because we are now looking at a rise and/or fall. When you take those patients to the catheterization lab, you see thrombus, you see plaque rupture. You don't see lots of normal coronaries. For surgeons, this is very important. With general medical patients, we use the old cut points of the previous contemporary troponin-T and it's working very well. I think it's fabulous for patient care. They get

evidence-based treatment.

**Dr Jaffe:** Both Dr Thygesen and Dr White have emphasized the use of percentage changes, but there is literature to suggest that maybe absolute changes could be even better. David, you've written about this in an editorial in *Clinical Chemistry* .[1] Do you want to take the other side of that argument for the sake of our clinical colleagues and tell them what those other studies suggest?



**Slide 16.**

**Dr Morrow:** I must admit, I started in the same place. In fact, the recommendations that I was a part of from the National Association of Clinical Biochemistry used a 20% relative increase, but there have been several recent studies, 2 in particular, that compared absolute percentage increases and found that absolute increases significantly improved the diagnostic accuracy compared to using relative deltas. So, for example, with the 2 assays that they studied, 1 was a contemporary sensitive assay, the absolute delta that worked best was .02 ng/mL and it ended up being about roughly half of the 99th percentile. Similarly with the high-sensitivity assay that they were studying, the absolute delta was down to .007 ng/mL, roughly about half the 99th percentile with that assay and it outperformed the relative change, where the optimal cut point was 117% change. It has to do with the extent to which there is variability across the range of troponin elevation. When you are operating down at the very low range, very small incremental changes are big percentage changes, but they may not be clinically meaningful, and the absolute delta trims that off and, overall, the data show it does better. So I think, progressively, moving from using a relative change to an absolute change may make the most sense.

**Dr Jaffe:** It should be clear to all of us that implementing any of these changes seems to improve specificity, but it may reduce sensitivity modestly, and that depends upon the gold standard criteria that one uses. If the percent changes are less than biologic variation, by definition, you are going to include some patients who are normal.

**Dr White:** It does not make sense to me to use an absolute change that is below biological variability. Absolute change at high levels? That's reasonable. You want a certain amount of myocyte necrosis to indicate an infarct, but at no level should it go below the biological variability. So when you use the terms "advancing" or "progressive," I think you are still waiting for a lot of data on that point.

**Dr Morrow:** I agree that the jury is still out, meaning first of all that the delta has to be established for each assay if you're going to use a cut point like that. So we need to have evidence from more than 1 or 2 assays. But there are at least 3 different studies that have shown in a head-to-head comparison that the absolute delta performed better.

**Dr White:** You're comparing a relative operating characteristic (ROC) curve which is balancing sensitivity and specificity and we as physicians might want different components of that. We as cardiologists want to rule in, while ED physicians want to rule out. So, looking at an ROC curve, using the American College of Cardiology (ACC) definition of MI, may not be an appropriate comparator. There are a lot of issues here.

**Dr Jaffe:** This is going to be a continuing debate and there are other issues we should get to. Dr Thygesen, how soon can rule outs and rule ins be done with these higher-sensitivity assays? One of the claims is that given they're more sensitive, we can do everything much more rapidly.

**Dr Thygesen:** It seems from the literature that we can evaluate 3 hours after the onset of symptoms and that is very good because then the triage will be much faster than before. It also seems that we don't need to have the isoenzymes and myoglobins anymore for that. So for patients who are coming in to the hospital, even the ED or in ambulances, we can evaluate after 3 hours. We still have to be suspicious of MIs. If they have ongoing ischemia and the first value is normal, you should take another blood drawing after 6 hours and in some patients, perhaps even later on. But in most cases, we have the answer in 3 hours and that is great progress with the new highly sensitive troponins.

**Dr Jaffe:** I agree, but I would call attention to the fact that most of those studies were done utilizing the less-sensitive assays as the gold standard, and if one uses the high-sensitivity assays, which is what clinicians are using as the gold standard, then there is at least a subset of patients who take longer. Your concern is about making sure that if there is suspicion, later samples that are obtained are good ones.

Dr White, we have both type 1 and type 2 MIs and there is some concern that the mixture between type 1 and type 2 MIs may change with the use of high-sensitivity assays, leading to an excess number of patients who get aggressive anticoagulation and invasive strategy. How do you deal with that in your practice?

## Confounding Factors in the Postoperative Setting

- Chest discomfort
- ECG changes
- Echocardiogram changes
- Changes in wall motion
- Variability of troponin levels
- Plaque rupture
- Catecholamine outpouring
- Thrombogenic potential
- Hypotension

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**Slide 17.**

**Dr White:** Well I'm challenged, but that is a good thing, and the biggest challenge is the postoperative elevation of troponins. We have to do what we do with the other types. It's got to be in the setting of ischemia. It's challenging because they may be anesthetized, but in the setting of ischemia, which means chest discomfort, ECG changes, there might be echo changes or wall motion, and a rise and a fall of troponins. When we have hypotension, is it plaque rupture, which may occur in 50% of the patients? We know that catecholamine outpouring occurs. There is also the thrombogenic situation when, of course, the patient becomes hypotensive. Here's a situation: a lady comes in and has a history of hysterectomy, loses blood, hypotension, biomarkers go up, ECG goes through ischemic changes -- that's a type 2 infarct. The management of this is the old way we used to manage infarcts, which is β-blockers, do a test for inducible ischemia, treadmill, echo -- manage the patient that way. It doesn't mean you go off to the catheterization lab. The treatment of this patient is not treatment of plaque rupture. It's not hypotensive antithrombotic therapy. It's not putting in a drug-eluting stent, the electrogenic issues further down the line, the clopidogrel, etc. But it's very hard in the individual patient. Clinical judgment is critical.

## Association of Longest Ischemia Duration With Biochemical Markers of MI

| | Total | | Ischemia > 15 min | | Ischemia > 30 min | | Ischemia > 60 min | | Symptoms attributable to MI | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % |
| CK > 170 IU and MB > 5% | 34 | 6.7 | 17 | 50.0 | 14 | 41.2 | 12 | 35.3 | 7 | 20.5 |
| CK > 170 IU and MB > 10% | 14 | 2.9 | 8 | 57.1 | 7 | 50.0 | 7 | 50.0 | 5 | 35.7 |
| cTn-I > 0.6 ng/mL and or cTn-T > 0.03 ng/mL | 107 | 23.9 | 34 | 31.8 | 29 | 27.1 | 21 | 19.6 | 19 | 17.7 |
| cTn-I > 1.5 ng/mL and or cTn-T > 0.1 ng/mL | 41 | 8.7 | 38 | 87.8 | 24 | 58.3 | 19 | 46.3 | 18 | 43.9 |
| cTn-I > 3.1 ng/mL and or cTn-T > 0.2 ng/mL | 21 | 4.2 | 19 | 90.5 | 17 | 81.0 | 17 | 81.0 | 13 | 61.9 |

Heart failure          Landesberg G, et al. *J Am Coll Cardiol.* 2003;42:1547-1554.          theheart.org   Medscape EDUCATION

**Slide 18.**

**Dr Jaffe:** It is an important consideration because Giora Landesberg has suggested that a vast majority of these postoperative events can be attributed to some supply-demand abnormality, but if one looks at the pathologic information, the patients who die tend to have plaque rupture. So they probably represent a small percentage of patients who have something really bad. How we can tease that out is not totally clear. One final question for you, Dr Morrow: How do you think the high-sensitivity assays are going to affect the type 4 and the type 5 MIs, post-PCI and post-CABG?

**Dr Morrow:** Well, thanks for asking a very straightforward question. I wish we had a clear answer. "I think we have a lot more to learn" is the shortest version of the answer. Nevertheless, I guess there are 2 basic areas that I'll comment on. The first is that your work has shown us that recognizing a preceding myocardial injury is much more important overall prognostically for the patient who comes in and has elective PCI and then has subsequent elevation of biomarkers. Detecting at baseline and understanding what that means is much more

important than what happens afterwards in terms of how the patient is going to do clinically. Having said that, I still think that we can identify <mark>periprocedural</mark> injury that may matter.

The data for that almost come entirely from literature using CK-MB. There are limitations to those studies that I'm sure we could talk about for about an hour, but still acknowledging that, I believe we can identify infarcts that matter in that setting. At least in my view right now, we have a lot to learn about the high sensitivity assays -- what relative changes and what absolute changes are meaningful. Because of that shared interest, we are going to see over the next 1 to 3 years a substantial amount of research that will help us untangle that, I hope.

**Dr Jaffe:** Well it should be clear, hopefully to all of you who are listening, that there is a great deal more to learn and research to be done, but there is a great deal of enthusiasm and opportunity to benefit our patients. I'd like to thank Dr Morrow, Dr White, and Dr Thygesen for participating this afternoon.

How will you improve your practice? Assess your performance in comparison with your peers by completing this brief survey.

**Case #1:** A 64-year-old man with a history of hypertension and mild hyperlipidemia presents to the emergency department (ED) with a 1-hour history of nonexertional substernal chest pressure that radiates to his left arm. The patient denies any prior history of heart disease and exercises occasionally and without angina. His electrocardiogram (ECG) demonstrates a 1-mm ST-segment depression and T-wave flattening in the inferior leads.

What minimal criteria would you need in order to diagnose this patient with an acute myocardial infarction (MI)?

- ○ One troponin value above the upper reference limit (URL) used by the laboratory in your hospital
- ○ Two troponin values above the URL used by the laboratory in your hospital
- ○ One troponin value above the 99th percentile of a healthy reference population with a rising pattern of values
- ○ Two troponin values above the 99th percentile of a healthy reference population

If this patient has 2 negative high-sensitivity troponin values within 3 hours of the onset of chest pain, which of the following best describes your diagnosis?

- ○ Noncardiovascular cause of chest pain
- ○ Unstable angina
- ○ Pulmonary embolism
- ○ Possible MI; acute MI cannot be ruled out at this time

**Case #1 (cont):** The patient is given sublingual nitroglycerin, which resolves his chest pain and normalizes his ECG. High-sensitivity troponin testing reveals a positive result at 0.05 µg/L. You determine that the patient has experienced an acute MI and you admit him to the hospital.

Which of the following will best increase the specificity of your diagnosis of MI in this patient?

- ○ Elevated creatine kinase-myocardial band (CK-MB) isoenzyme
- ○ Repeat positive result using the high-sensitivity troponin assay
- ○ An increase in the subsequent troponin level using the high-sensitivity troponin assay
- ○ Repeat troponin greater than 3 times the upper limit of normal

**Case #1 (cont):** The next day, the patient's troponin level peaks at 1.5 μg/L.

Which of the following best describes this patient's MI?

○ Type 1
○ Type 2
○ Type 3
○ Type 4
○ Type 5

**Case #1 (cont):** Two days after his admission to the hospital, the patient is sent for percutaneous coronary intervention (PCI) and a stent is placed in the right coronary artery. One day later, his troponin level -- which was elevated but not rising prior to the procedure -- has now increased modestly.

Which of the following describes how you would determine long-term prognosis for this patient?

○ Long-term prognosis should be based on his pre-PCI troponin value
○ Long-term prognosis should be based on his post-PCI troponin value
○ Long-term prognosis should based on both pre- and post-PCI troponin values

**Case #2:** A 60-year-old woman with type 2 diabetes presents for evaluation of atypical chest pain, which has been intermittent for the past 24 hours, though she currently denies chest pain. She has no prior history of angina or coronary artery disease. She has mild renal insufficiency with a serum creatinine level of 1.5 mg/dL. A 12-lead ECG shows no acute changes. High-sensitivity troponin is increased at 0.05 μg/L (99th percentile URL is 0.01 μg/L).

What is your approach to the patient at this time?

○ Diagnose with acute MI; no additional information is needed to make this diagnosis
○ Check CK-MB level; a positive high-sensitivity troponin on initial presentation invalidates its diagnostic value in this patient
○ Recheck troponin in 4 to 6 hours; diagnose with acute MI if it has increased by what has been determined to be a significant increment
○ Recheck troponin in 4 to 6 hours; diagnose with acute MI if it has increased by greater than or equal to3 times the URL

**Case #2 (cont.):** Three hours later, the patient's troponin is unchanged.

Would you diagnose this patient with MI at this time?

○ Yes; 2 values are above the 99th percentile of a healthy reference population
○ No; the diagnosis of MI cannot be made until at least 4 hours after initial presentation
○ No; a CK-MB test must be ordered because the initial troponin value was positive using the high-sensitivity troponin assay
○ No; MI is unlikely because there is no change in troponin level

Which of the following measures would you use to follow serial troponin values in this patient?

○ Absolute change
○ Percentage change
○ Progressive change

○ Standard change

The use of high-sensitivity cardiac troponin assays has which of the following advantages?

○ Higher specificity than conventional troponin assays
○ Earlier detection of MI
○ Improved differentiation between type 1 and type 2 MI
○ Increased incidence of the diagnosis of unstable angina

**Case #3:** A 45-year-old man presents to the ED with a 3-hour history of acute-onset shortness of breath, accompanied by chest and mild back pain. His chest pain is intermittent, unrelieved by rest, and exacerbated by deep inspiration. Physical examination reveals pulse 90 beats per minute, heart regular S1 S2 with no murmur, and lungs clear. ECG demonstrates non-specific ST-T wave changes and initial troponin using a high-sensitivity assay is 0.10 µg/L (URL less than 0.02 µg/L). Three hours later, repeat troponin level is 0.50 µg/L.

Which of the following is this patient's most likely diagnosis?

○ MI
○ Unstable angina
○ Pulmonary embolism
○ Heart failure

In patients presenting early after the onset of chest pain and with ST-segment elevation on ECG, is a positive troponin level required to make the diagnosis of MI?

○ Yes
○ No

Diagnosis of which type of MI is expected to increase with the use of high-sensitivity troponin assays?

○ Type 1
○ Type 2
○ Type 3
○ Type 4
○ Type 5

Upon approval by the US Food and Drug Administration, which of the following do you anticipate will be the most significant barrier to the optimal use of high-sensitivity troponin assays for the diagnosis of MI?

○ The increased sensitivity of these assays will limit their utility due to the increased number of false positives; reduced specificity
○ Lack of physician understanding of how to interpret troponin values
○ The incremental increase in the sensitivity of these assays is fairly modest compared to standard assays when the proper cut-off values are utilized
○ Physician resistance to use the new assay due to comfort with conventional troponin and CK-MB assays; physician inertia
○ Lack of evidence supporting their utility

Please indicate how relevant this continuing medical education (CME) activity is to your practice: Approximately how many patients per week do you see who are at risk for an MI?

○ 0
○ 1 to 25
○ 26 to 50
○ 51 to 75
○ Greater than 75

Submit



**Slide 19.**

For those of you who are participating in this activity, you can take the CME posttest by clicking on the "Earn CME credit" link. Please also take a moment to complete the program evaluation.

*This transcript has been edited for style and clarity*.

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IU = international units

LBBB = left bundle branch block

LD = lactate dehydrogenase

LoD = limit of detection

MB = MB fraction

MI = myocardial infarction

MLC = myosin light chains

MONICA = Monitoring of Trends and Determinants in Cardiovascular Disease

MTP = microtiter plate

NACB = National Academy of Clinical Biochemistry

NT-proANP = amino-terminal fragment of proANP

NT-proBNP = amino-terminal fragment of proBNP

PCI = percutaneous coronary intervention

RIA = radioimmunoassay

STEMI = ST-segment elevation myocardial infarction

UAP = unstable angina pectoris

URL = upper reference limit

WHO = World Health Organization

1. Apple FS, Morrow DA. Delta cardiac troponin values in practice: are we ready to move absolutely forward to clinical routine?*Clin Chem*. 2012;58:8-10.

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**http://www.medscape.org/viewarticle/763254**

# Exploring the Universal Definition of MI: The Role of High-Sensitivity Troponin

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Professor of Medicine

Aarhus University

Aarhus, Denmark

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Brigham & Women's Hospital

Senior Investigator, TIMI Study Group

Associate Professor of Medicine

Harvard Medical School

Boston, Massachusetts

**Harvey D. White, MB, ChB, MSc**

Director, Coronary Care and Green Lane Cardiovascular Research Unit

Green Lane Cardiovascular Service

Auckland City Hospital

Auckland, New Zealand

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# Definition of Myocardial Infarction

## Pathology

Acute myocardial infarction is defined as myocardial cell death due to prolonged myocardial ischemia



Death of heart tissue due to blocked coronary artery

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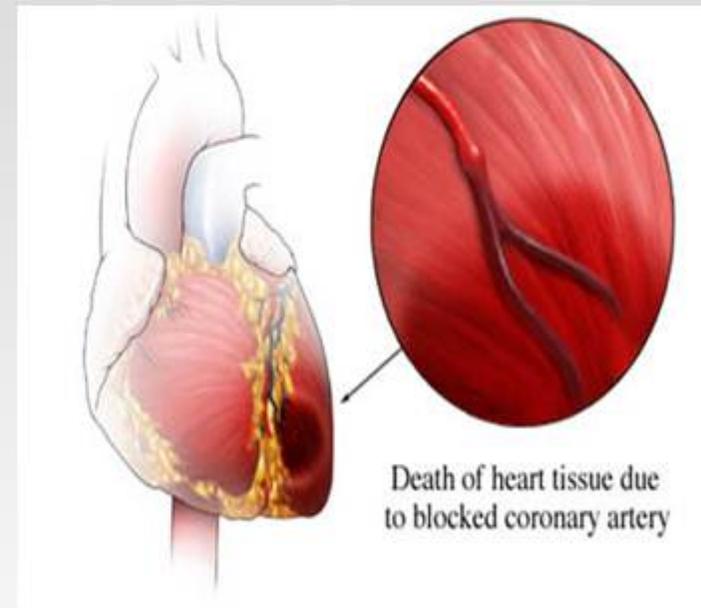
# Biomarkers for Detection of Myocardial Infarction
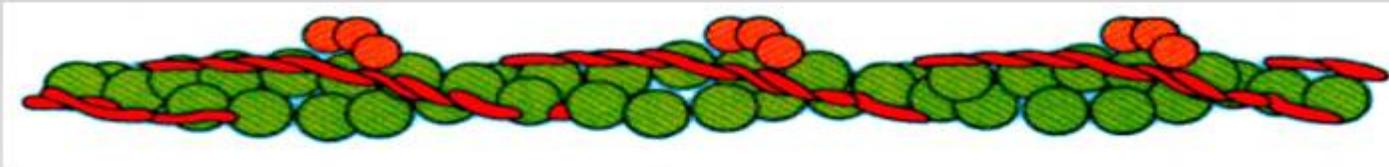


## Preferably

- Detection of the rise and/or fall of troponin (I or T) with at least 1 value above the 99th percentile of the upper reference limit measured with a coefficient of variation ≤ 10%

## When troponin is not available

- Detection of the rise and/or fall of CK-MB mass with at least 1 value above the 99th percentile of the upper reference limit measured with a coefficient of variation ≤ 10%

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# Classification of Myocardial Infarction

| | |
|---|---|
| **Type 1** | Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection |
| **Type 2** | Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply (eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension) |
| **Type 3** | Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-elevation, or new LBBB, or presumably new major obstruction in a coronary artery by angiography and/or pathology, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood |
| **Type 4a** | Myocardial infarction associated with PCI |
| **Type 4b** | Myocardial infarction associated with stent thrombosis as documented by angiography or autopsy |
| **Type 5** | Myocardial infarction associated with CABG |

Thygesen K, et al. *Eur Heart J.* 2007;28:2525-2538.

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# Criteria for Acute Myocardial Infarction Types 1 and 2

**Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99$^{th}$ percentile of the upper reference limit together with evidence of ischemia with at least 1 of the following:**

- Symptoms of ischemia
- ECG changes of new ischemia (new ST-T changes or new LBBB)
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

# More Diagnoses With Higher-Sensitivity Assays

Sensitive troponin I

99th % Value

AUC

1.0

0.8

0.6

Troponin T    10% Coefficient of Variation (CV) Value

0.4

0.2

0.0
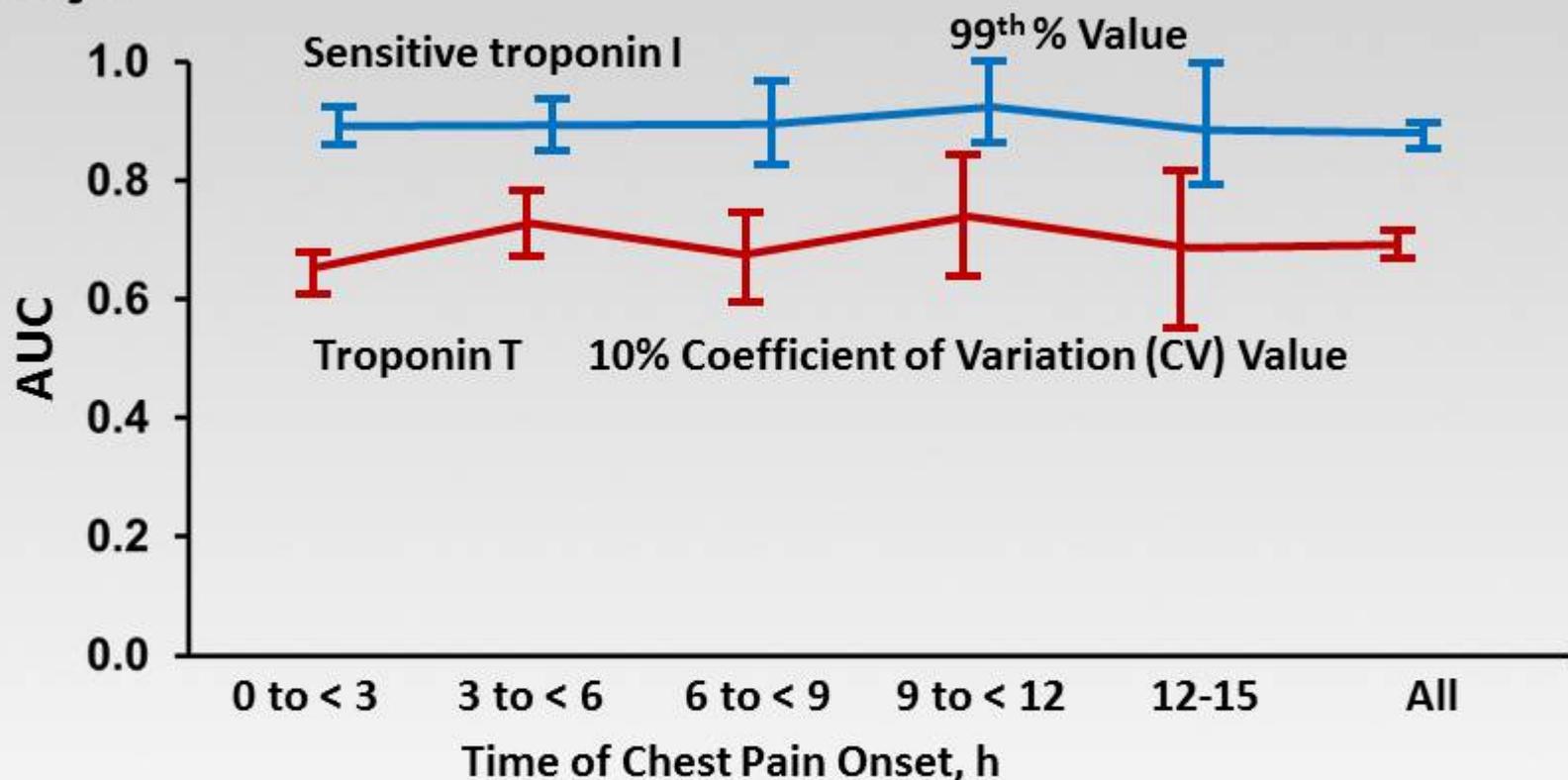
| | 0 to < 3 | 3 to < 6 | 6 to < 9 | 9 to < 12 | 12-15 | All |
|---|---|---|---|---|---|---|
| **Diagnosis of AMI (no.)** | 227 | 97 | 44 | 29 | 17 | 528 |
| **Single determination (no.)** | | | | | | |
| **Sensitive troponin I > 0.04 ng/mL** | 184 | 100 | 38 | 32 | 25 | 534 |
| **Troponin T > 0.03 ng/mL** | 81 | 56 | 19 | 21 | 12 | 305 |

Time of Chest Pain Onset, h

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Keller T, et al. *N Engl J Med*. 2009;361:868-877.

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Accuracy by Time of Admission

Keller T, et al. *N Engl J Med*. 2009;361:868-877.
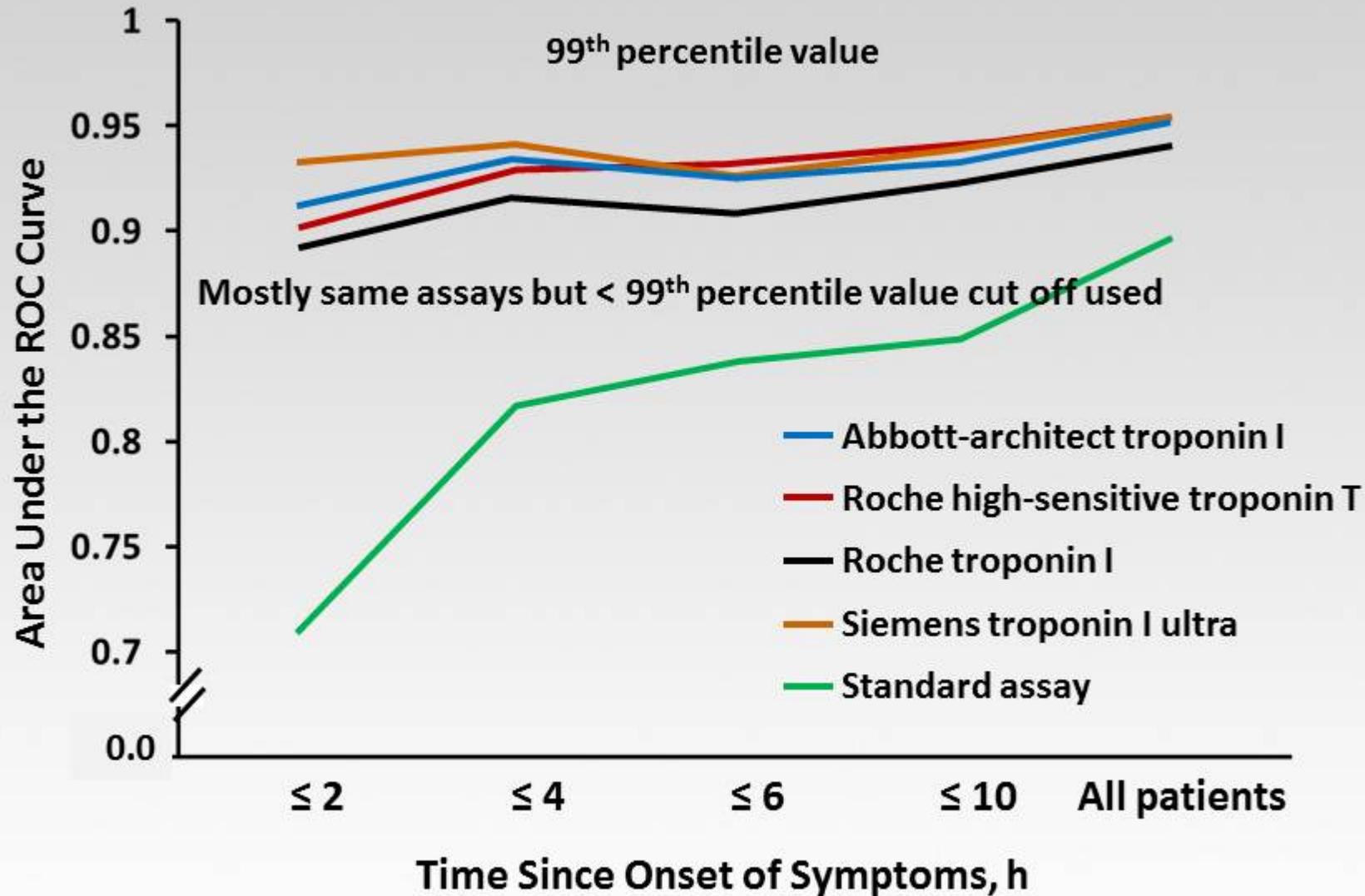
# Event-Free Survival During the Validation and Implementation Phases of the Study

**Validation phase**
**Peak troponin, ng/mL**
— < 0.05
— 0.05-0.19
— ≥ 0.20
**Implementation phase**
**Peak troponin, ng/mL**
— < 0.05
— 0.05-0.19
— ≥ 0.20

Survival Free From Death or Recurrent MI, %

Time, d

Log-rank *P* < .001
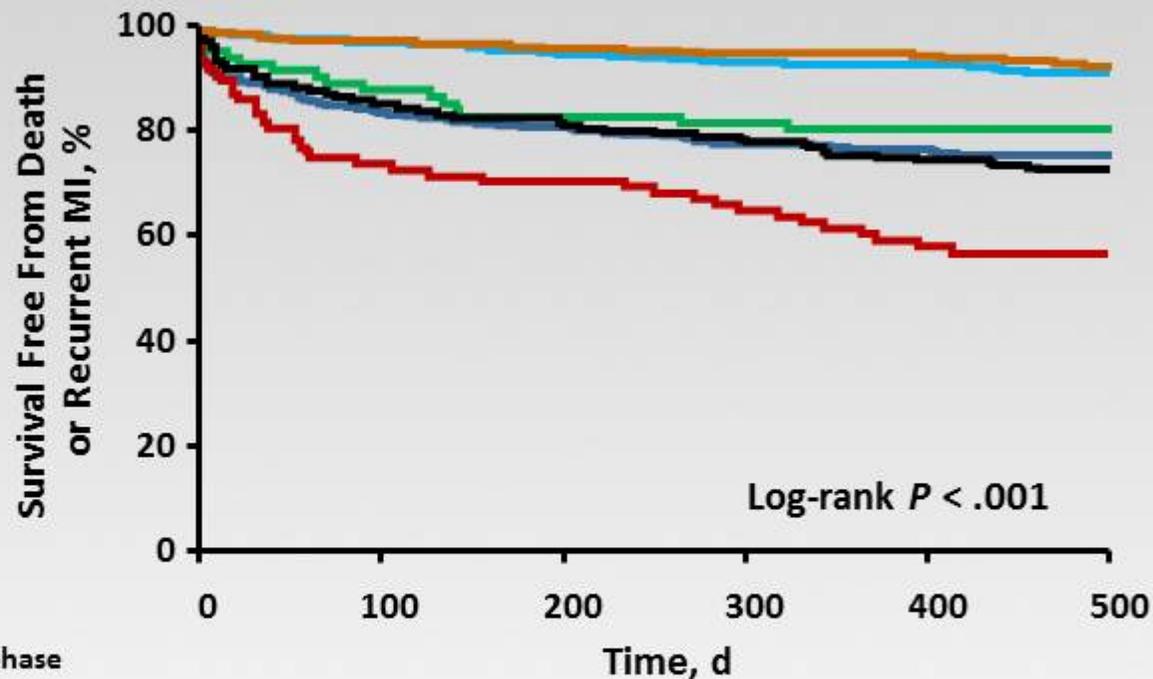
| No. at risk validation phase Peak troponin, ng/mL | | | | | | |
|---|---|---|---|---|---|---|
| < 0.05 | 657 | 641 | 628 | 617 | 493 | 157 |
| 0.05-0.19 | 90 | 67 | 64 | 59 | 45 | 15 |
| ≥ 0.20 | 291 | 250 | 239 | 230 | 171 | 44 |

| No. at risk implementation phase Peak troponin, ng/mL | | | | | | |
|---|---|---|---|---|---|---|
| < 0.05 | 683 | 670 | 660 | 653 | 529 | 173 |
| 0.05-0.19 | 80 | 71 | 67 | 66 | 54 | 16 |
| ≥ 0.20 | 291 | 243 | 235 | 226 | 191 | 63 |

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Mills NL, et al. *JAMA*. 2011;305:1210-1216.

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# Detection of Normal Subjects With Contemporary Cardiac Troponin Assays

99th percentile = .04 µg/L

33% (n = 979) Beckman Access

Beckman Access cTnI (µg/L)

99th percentile = .034 µg/L

88% (n = 2637) OCD ES

OCD Vitros ES cTnI (µg/L)

99th percentile = .025 µg/L

98% (n = 2930) Abbott Architect

Abbott Architect cTnI (µg/L)
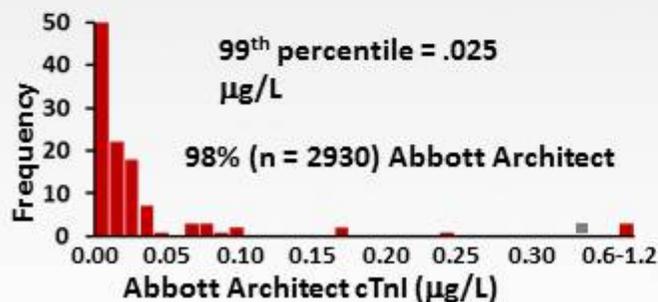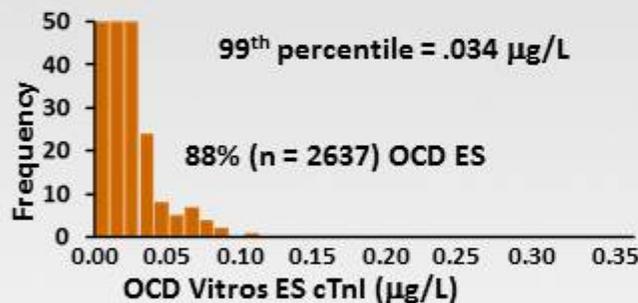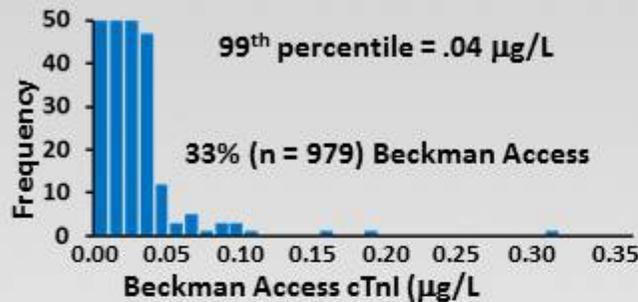
- Current newer-generation assays

- Serum reference value determinations for 2992 normal subjects

- No bell-shaped curves

cTnT 100% < .01 (LoD)

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Apple FS, et al. *Clin Chem*. 2007;53:1558-1560.

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# Cardiac Troponin Assay Score Card

| Acceptance Designation | Total Precision at 99th Percentile |
|---|---|
| Guideline Acceptable | $\leq 10\%$ |
| Clinically Usable | $> 10$ to $\leq 20\%$ |
| Not Acceptable | $> 20\%$ |

| Assay Designation | Measurable Normal Values Below 99th percentile |
|---|---|
| Level 4<br>3rd Generation, High Sensitivity | $\geq 95\%$ |
| Level 3<br>2nd Generation, High Sensitivity | 75 to $< 95\%$ |
| Level 2<br>1st Generation, High Sensitivity | 50 to $< 75\%$ |
| Level 1<br>Contemporary | $< 50\%$ |

Apple FS, et al. *Clin Chem*. 2009;55:930-937.

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# Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays

| Company/Platform/ Assay | Cardiac Troponin Concentration | | | Amino Acid Residues of Epitopes Recognized by Capture (C) and Detection (D) Mabs |
|---|---|---|---|---|
| | LoD (µg/L) | 99th Percentile (µg/L [CV]) * | 10% CV Concentration (µg/L) | |
| hs-cTnI | | | | |
| Abbott ARCHITECT* | 1.2 | 16 (5.6%) | 3.0 | C: 24-40; D: 41-49 |
| Beckman Access* | 2-3 | 8.6 (10%) | 8.6 | C: 41-49; D: 24-40 |
| Nanosphere MTP* | 0.2 | 2.8 (9.5%) | 0.5 | C: 136-147 D: Mab PA1010 |
| Singulex Erenna* | 0.09 | 10.1 (9.0%) | 0.88 | C: 41-49; D: 27-41 |
| Siemens Vista* | 0.5 | 9 (5.0%) | 3 | C: 30-35 D: 41-56, 171-190 |
| hs-cTnT | | | | |
| Roche Elecsys[†] | 5.0 | 14 (8%) | 13 | C: 136-147 D: 125-131 |

*Under development and not available for commercial use; †available for use worldwide but not cleared by US Food and Drug Administration for use in United States.

**Heart failure**

Apple FS, et al. Clin Chem 2012 58(1):54-61.

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# Prevalence of Detectable cTnT and Levels ≥ 99<sup>th</sup> Percentile URL

| Group | Sample Size | cTnT Level, ng/mL | | | |
|---|---|---|---|---|---|
| | | ≥ 0.003 | | ≥ 0.014 | |
| | | N (%) | Sample Weight-Adjusted Prevalence, % (95% CI) | N (%) | Sample Weight-Adjusted Prevalence, % (95% CI) |
| Overall population | 3546 | 957 (27.0) | 25.0 (22.7-27.4) | 122 (3.4) | 2.0 (1.5-2.6) |
| Restricted population Without CHD | 3428 | 891 (26.0) | 24.2 (21.8-26.5) | 103 (3.0) | 1.8 (1.2-2.4) |
| Without cardiovascular disease | 3277 | 813 (24.8) | 23.7 (21.3-26.1) | 82 (2.5) | 1.9 (1.0-2.0) |
| Without cardiovascular disease or CKD | 3222 | 773 (24.0) | 23.1 (20.7-25.5) | 65 (2.3) | 1.2 (0.8-1.7) |
| Without cardiovascular disease, CKD, subclinical heart disease, diabetes, or hypertension | 2554 | 510 (20.0) | 19.3 (16.8-21.8) | 43 (1.7) | 1.1 (0.6-1.7) |

DeLemos JA, et al. *JAMA*. 2010;304:2503-2512.

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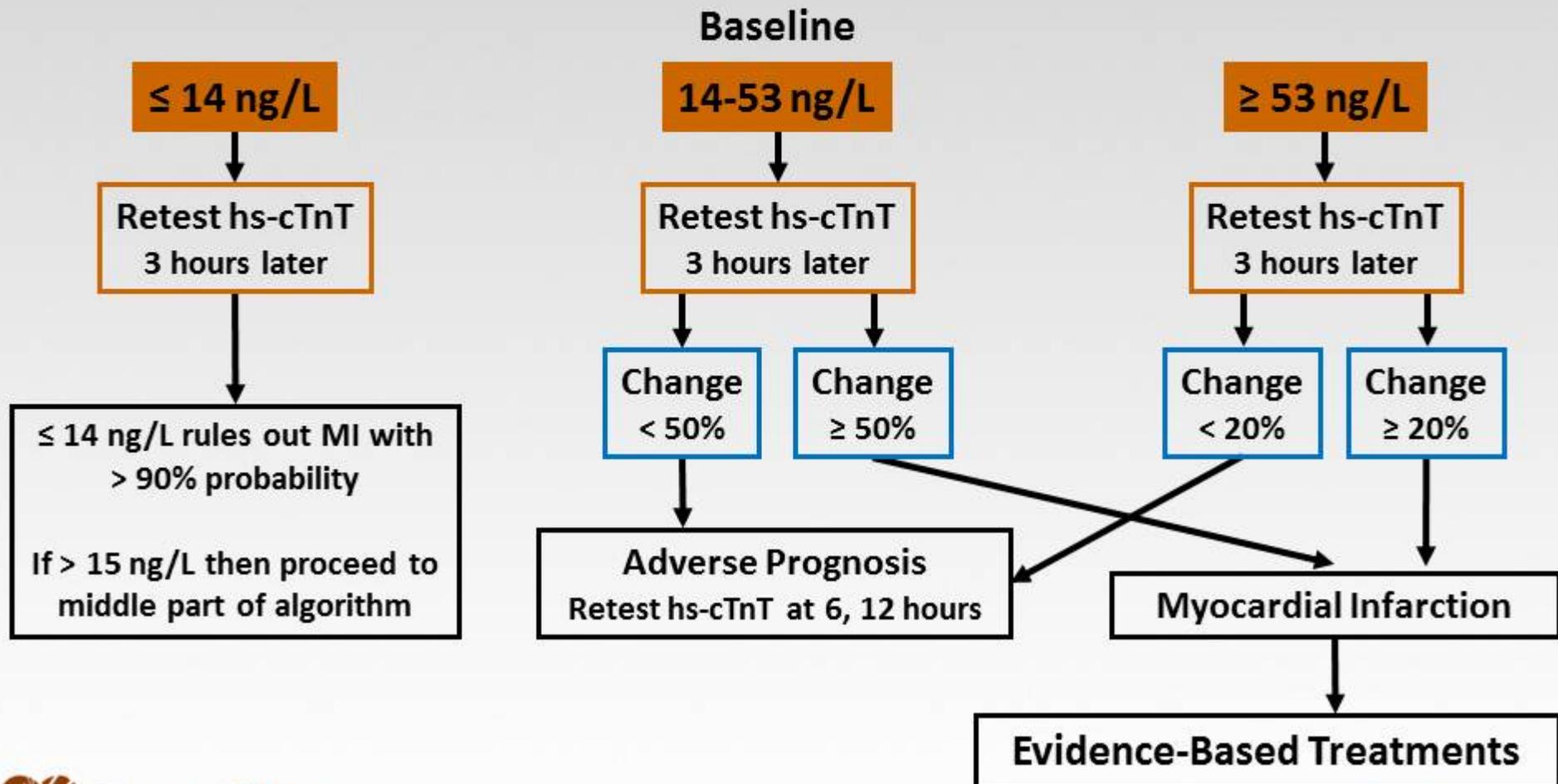the heart.org from WebMD    Medscape EDUCATION

# Elevations of Troponin in the Absence of Overt Ischemic Heart Disease

- Cardiac contusion or other trauma including surgery, ablation, pacing, etc.
- Congestive heart failure (acute and chronic)
- Aortic dissection, aortic valve disease
- Hypertrophic cardiomyopathy
- Tachyarrhythmias, bradyarrhythmias, or heart block
- Apical ballooning syndrome
- Rhabdomyolysis with cardiac injury
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Acute neurological disease, including stroke, or subarachnoid hemorrhage
- Infiltrative diseases (eg, amyloidosis, hemochromatosis, sarcoidosis, or scleroderma)
- Inflammatory diseases (eg, myopericarditis/pericarditis or myocardial extension of endocarditis)
- Drug toxicity or toxins
- Critically ill patients, especially with respiratory failure or sepsis
- Burns, especially if affecting > 30% of body surface area
- Extreme exertion

# Use of High-Sensitivity Troponin T to Diagnose Myocardial Infarction

## Clinical Setting Consistent With Myocardial Ischemia

**Baseline**

| ≤ 14 ng/L | 14-53 ng/L | ≥ 53 ng/L |
|---|---|---|

**Retest hs-cTnT 3 hours later**

**Retest hs-cTnT 3 hours later**

**Retest hs-cTnT 3 hours later**

≤ 14 ng/L rules out MI with > 90% probability

If > 15 ng/L then proceed to middle part of algorithm

Change < 50%

Change ≥ 50%

Change < 20%

Change ≥ 20%

**Adverse Prognosis**
Retest hs-cTnT at 6, 12 hours

**Myocardial Infarction**

**Evidence-Based Treatments**

White HD. *Am Heart J.* 2010;159:933-936.

Absolute and Relative Changes in Patients With AMI, Unstable Angina, and Noncardiac Chest Pain
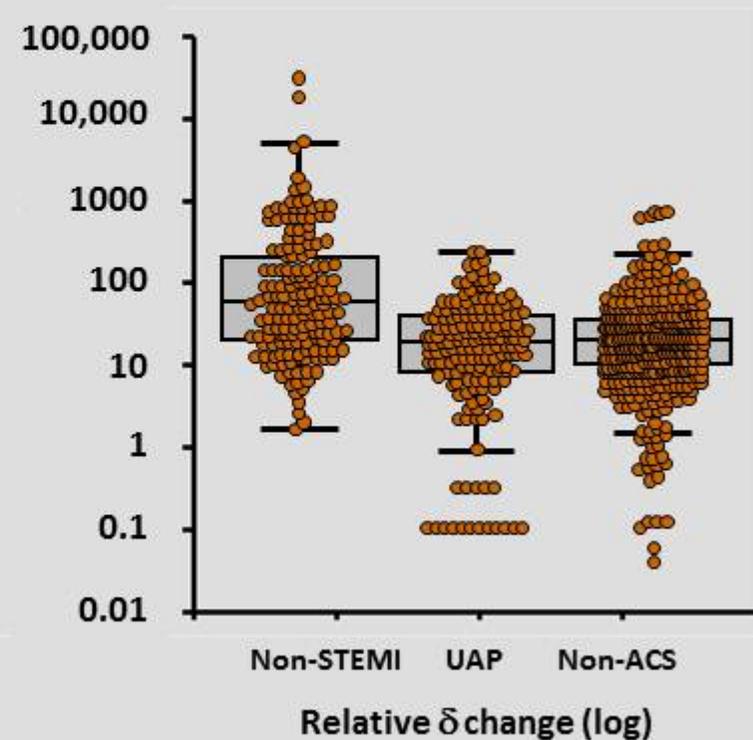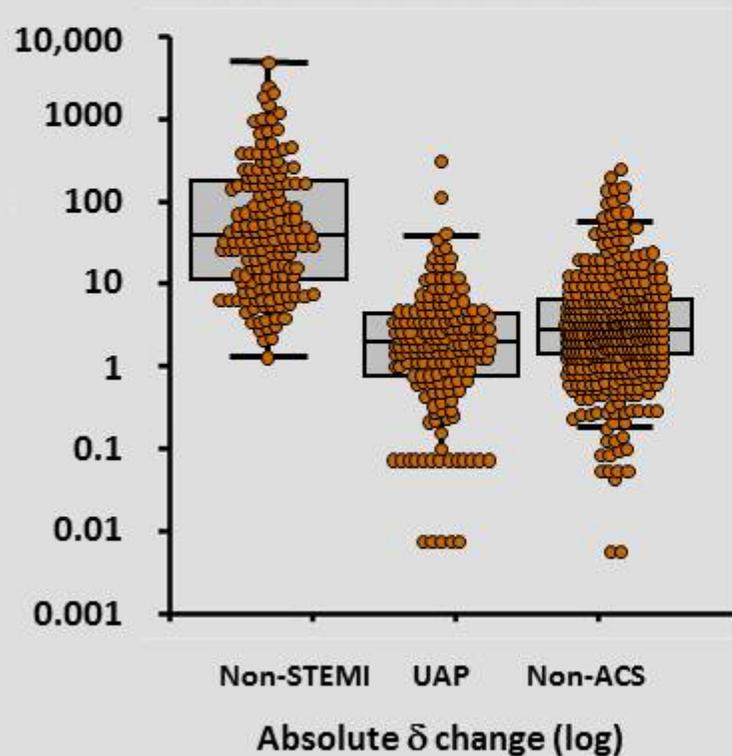
Mueller M, et al. *Clin Chem*. 2012;58:209-218.

# Confounding Factors in the Postoperative Setting

- Chest discomfort
- ECG changes
- Echocardiogram changes
- Changes in wall motion
- Variability of troponin levels
- Plaque rupture
- Catecholamine outpouring
- Thrombogenic potential
- Hypotension

# Association of Longest Ischemia Duration With Biochemical Markers of MI

| | Total | | Ischemia > 15 min | | Ischemia > 30 min | | Ischemia > 60 min | | Symptoms attributable to MI | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % |
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Heart failure

Landesberg G, et al. *J Am Coll Cardiol*. 2003;42:1547-1554.

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Heart failure

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MI = myocardial infarction

MLC = myosin light chains

MONICA = Monitoring of Trends and Determinants in Cardiovascular Disease

MTP = microtiter plate

NACB = National Academy of Clinical Biochemistry

NT-proANP = amino-terminal fragment of proANP

NT-proBNP = amino-terminal fragment of proBNP

PCI = percutaneous coronary intervention

RIA = radioimmunoassay

STEMI = ST-segment elevation myocardial infarction

UAP = unstable angina pectoris

URL = upper reference limit

WHO = World Health Organization

Heart failure

the heart.org from WebMD   Medscape EDUCATION