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# Implementation of High-Sensitivity and Point of Care Cardiac Troponin Assays Into Practice: Some Different Thoughts

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## Abstract

Background: The primary role of the International Federation of Clinical Chemistry (IFCC) Committee on Clinical Application of Cardiac Bio-Markers (C-CB) is to provide educational materials about cardiac biomarker use, emphasizing high-sensitivity cardiac troponin assays.

Content: This mini-review, regarding high-sensitivity cardiac and point of care troponin assays, addresses: a) new IFCC C-CB/ AACC Academy laboratory practice recommendations; b) new and updated concepts from the Fourth Universal Definition of Myocardial Infarction; c) the role of point of care assays in practice and research; d) regulatory challenges concerning point of care assays; e) testing in the COVID-19 world.

Summary: Implementation of high-sensitivity cardiac troponin assays makes a difference now and into the future in clinical practice and research. Providing point of care high-sensitivity cardiac troponin assays and optimizing studies to allow clearance of these assays by regulatory agencies, in a timely fashion, may provide improved patient management and outcomes.



How to implement high-sensitivity cardiac troponin (hs-cTn) assays in practice is not a harmonized process (1). The International Federation of Clinical Chemistry (IFCC)

Committee on Clinical Application of Cardiac Bio-Markers (C-CB) provides educational materials about cardiac biomarkers, emphasizing hs-cTn assays (2,3). Growth of regulatory clearances, shown in Fig. 1 for hs-cTnI and hs-cTnT assays, is found on IFCC C-CB website (4). This mini-review, regarding hs-cTn assays: a) highlights new IFCC C-CB/ AACC Academy laboratory practice recommendations; b) addresses new/updated concepts from the Fourth Universal Definition of Myocardial Infarction (UDMI) recommendations; c) discusses role of point of care (POC) assays in practice; d) identifies regulatory challenges concerning POC assays.

**IFCC C-CB/AACC Academy Laboratory Practice Recommendations for hs-cTn**

Consensus recommendations by the AACC Academy in collaboration with the IFCC TF-CB, addresses conversion of contemporary assays to hs-cTn. Expert opinion clinical laboratory practice recommendations for hs-cTn assays focused on 10 topics: a) quality control (QC) utilization; b) validation of lower reportable analytical limits; c) units used in reporting measurable concentrations for patients and QC materials; d) $99^{th}$ percentile sex-specific upper reference limits (URLs); e) criteria required to define hs-cTn assays; f) communicating with and educating clinicians regarding preanalytical and analytical problems that confound results; g) how authors need to document analytical assay details in hs-cTn studies; h) harmonizing assay results and commutable materials; i) time to reporting of results from sample collection to receipt; j) changes in serial hs-cTn concentrations over time and role of biological variation in interpreting results. New practices, shown in Table 1, include: using QC at sex-specific URLs, emphasizing not to perform an underpowered study to establish an URL, role of appropriate statistics to define $99^{th}$ percentiles, importance of limit of detection (LoD) in defining hs-assays measuring $\geq$50% of normal males and females individually (not combined), and reporting hs-cTn results with whole numbers, designated ng/L, to distinguish from contemporary assays.

A recent study determined overall and sex-specific 99$^{th}$ percentiles in 9 hs-cTnI and 3 hs-cTnT assays using a universal sample bank screened by health questionnaire and surrogate biomarkers (5). Subjects were age, ethnic, and racially diverse. Overall and sex-specific 99$^{th}$ percentiles showed substantial differences between and within both hs-cTnI and hs-cTnT assays. Men had higher 99$^{th}$ percentiles than women, shown in Fig 2. Both overall and sex-specific 99$^{th}$ percentiles varied according to statistical method and assay used. Not all assays provided a high enough percentage of measurable concentrations in women to qualify as hs-assay, and the surrogate exclusion criteria used to define normality tended to lower the 99$^{th}$ percentiles.

Following a meeting between US laboratory medicine, emergency medicine, and cardiology biomarker experts and FDA, guidelines for uniform analytical and clinical standards for studies performed by manufacturers seeking cTn 510k assay clearance was published (6). Recommendations addressed: 1) number of reference individuals for determination of 99th percentiles, 2) limit of quantification, 3) total imprecision requirements, 4) enrollment of subjects for diagnostic studies, 5) patient adjudication processes, and 6) clinical end points and outcomes. The focus was to ensure common protocols applied to hs-cTn assays. Unfortunately, published recommendations were not endorsed by the FDA.

**Recommendations of Fourth Universal Definition of Myocardial Infarction** (7)

For global harmonization of care in patients presenting with symptoms suggestive of myocardial injury, the UDMI assists clinicians in a common focus on how to utilize biomarkers in alignment with IFCC C-CB and AACC Academy guidelines. First, it recommends myocardial injury be used when there is evidence of increased cTn with at least one value above the 99th percentile sex-specific URL (3). Myocardial injury is considered acute with a rise and/or fall of cTn between serial samplings. Fig. 3. shows representative myocardial injury. Complexity of clinical circumstances may make it difficult to discriminate specific individual mechanism(s) of injury. Second, greater attention was placed on recognition of type 2 MI; defined in settings with oxygen demand and supply imbalance unrelated to acute coronary thrombosis (8). If myocardial injury is not acute and related to chronic structural heart disease, serial cTn values may be stable and unchanging. Third, cTnI and cTnT remain standard biomarkers for ruling in/out MI and myocardial injury. cTn release into the circulation is dependent of blood flow around injured myocardium and kinetics of increasing, peaking, and falling values are assay dependent (9); as cTn assays are not standardized. Utilizing hs-cTn assays, most rule in/rule out decisions are made within 3 hours of initial sampling, based on assay dependent algorithms (10). Fourth, analytical sensitivity provided by hs-cTn assays is critical for early rule out and assists in defining assay dependent deltas. Recommendations emphasize clinicians to become educated about details of the specific assay they use in practice. Fifth, the UDMI supports IFCC guidelines of defining hs-cTn assays based on imprecision (10%CV at sex-specific URL) and ability to measure normal subjects above the LoD in ≥50% of measurements (2,3); differentiating hs assays from contemporary and POC assays that are a) generally analytically and clinically inferior for diagnostic use and b) unable to define biological variation (1).

## Clinical role of POC testing in era of laboratory hs-cTn

*Rationale for POC testing*

The basic assumption for use of POC testing is that rapid provision of results will have a direct impact on clinical decision-making. Evidence is limited. Randomized controlled trials comparing POC with central laboratory testing are summarized in Table 2 (11-15); with inconsistent results. Some studies demonstrated a clear improvement in outcome as judged by treatment impact or length of stay, while some had no impact. One consistent finding is that to have impact on clinical decision-making, biomarker measurements had to be integrated within a defined clinical pathway. A detailed analysis of the patient flow within the Randomized Assessment of Treatment using Panel Assay of Cardiac markers (RATPAC) trial revealed clear differences between length of stay directly due to the clinical pathways being used in different hospitals (16). A systematic evidence based review of POC testing identified the need for integration of POC within the decision-making pathway as a key requirement to demonstrate benefit (17). Studies utilized cTn POC methods with comparable analytical sensitivity to those in the central laboratory at the time trials were performed; using diagnosis based on exceeding a diagnostic cutoff in use or the $99^{th}$ percentile. Although these studies support a role for POC testing, they are not compatible with current clinical diagnostic strategies. Two key requirements for any study are that POC testing has, a) comparable analytical performance with the central laboratory cTn assay, which is now hs-cTn, and b) provision of test results is demonstrably the rate-limiting step in the diagnostic pathway.

**Clinical decision-making in era of hs-cTn and rapid diagnostic algorithms**

Introduction of hs-cTn assays into routine clinical practice has led to a transformation in the way cTn measurements are used in decision making. No longer are diagnostic pathways based solely upon serial sampling over a six (or more) hour period post admission until the value exceeds the $99^{th}$ percentile with a significant change between consecutive measurements (delta value). Diagnostic pathways now exploit two key features of hs assays, the ability to measure a) low values such as the LoD, and b) low cTn values above the LoD, both with acceptable %CVs. Users need to be cautious regarding the recently published assay specific hs-cTn cut-off concentrations by the ESC for 0 h/1 h and 0 h/2 h algorithms, as the values posted in their Table 5 are not consistent with the larger evidence based literature not referenced in the 2020 guideline (18).Measurement of hs-cTn values above the LoD have been shown to be assay specific, that also reliably identify patients at low risk of subsequent adverse events (MI, injury, mortality) within 30 days (18-21). A recent Patients can often be safely and immediately discharged from the emergency department (ED) based on a single cTn measurement on admission when combined with clinical assessment, electrocardiogram. This strategy is attractive to ED physicians as it permits immediate discharge of ≥20% of patients presenting with ischemic symptoms. The ability to measurement low cTn values with hs- assays with low %CVs has also been exploited with the use of short sampling intervals. cTn measurements are made on admission and repeated 1, 2, or 3 hours later (10,18-21); allowing rapid categorization of patients for discharge (rule out), immediate admission (rule in) or in need of further investigation (observational). This approach is followed when the initial cTn is still <99th percentile sex-specific URL but not low enough to drive a 'one and done' protocol. The European Society of Cardiology has endorsed such rapid diagnostic algorithms (22). Support for rapid diagnosis based on hs-cTn algorithms underwent systematic review by the UK National Institute for Health and Care Excellence (NICE) (23). When admission measurement exceeds the 99$^{th}$ percentile, serial testing needs to be carried out to determine whether myocardial injury is acute (rising pattern) or chronic (static, flat pattern) to allow appropriate triage, and may require a further 6 hour sample.

Rapid diagnostic algorithms seem to be ideally suited for POC testing. The absolute caveat is cTn POC testing must demonstrate high-sensitivity analytical performance. Currently, the majority of POC cTn assays have, at best, performed as contemporary assays. Such systems are perfectly adequate for ruling in myocardial injury but require repeat sampling, typically at 3 to 6 hours post admission to achieve adequate sensitivity for rule out. Admission measurement of cTn by POC may in fact be diagnostically inferior to an admission risk score alone (24). When sampling over 6 hours is compared with the possibility of immediate discharge based on a single measurement or the possibility of complete diagnostic categorization within 1-3 hours from admission, the advantages of central lab-based hs-cTn assays are obvious, even with 60 minute turnaround time. Diagnosis within 1 to 3 hours of admission outweighs having to wait 3-6 hours by POC testing, even where a whole blood sample can be used with results available in 10-15 minutes.

**POC testing - analytical versus clinical evidence**

Independent analytical validation of performance claims of a putative hs-cTn POC assay is important, but is only the background to clinical implementation and use. POC testing must have the ability to permit immediate safe discharge by single sample rule out or support a rapid diagnostic, serial testing algorithm. The majority of studies claiming comparable clinical utility to high sensitivity assay (25) or safe diagnosis (26) for POC testing have not been performed on this basis. POC assays studies that evaluated rapid rule out algorithms utilized stored, plasma samples, not fresh 'whole blood, which will be required for a universally, acceptable validation' (27-29). To date, there have been no whole blood or prospective studies, either observational or randomized controlled trials, that have demonstrated that POC testing with high sensitivity analytical performance is clinically reliable, safe and confers patient benefit. This is in contrast with central laboratory hs-cTn methods, demonstrated by meta-analysis of trials (30,31). While one assay (Pathfast) has an FDA clearance for POC with preliminary data that meets hs-criteria along IFCC guidelines (32), in practice users of this large instrument are often laboratorians and not designated POC operators. Several novel, in development POC technologies, will hopefully provide diagnostic data to be utilized in practice soon.

**Role of cTn POC Testing**

cTn POC testing does have a clinical role, but it's complimentary to hs-cTn laboratory measurements. When timely access to laboratory facilities for decision-making is not possible, POC testing may be a solution. This is particularly the case in rural healthcare were sample transportation time may impact turnaround time and where the decision to move a patient to a more centralized facility, which performs intervention, may require a long land journey or air evacuation. POC cTn measurement has been shown to significantly improve management of patients with suspected acute coronary syndromes in the rural Australian environment (33). In the RATPAC trial, with a contemporary POC assay and diagnosis based on the 99$^{th}$ percentile, measurements on admission and 90 minutes were diagnostically accurate and safe in low risk patients. This study did not evaluate single sample rule out but did demonstrate serial testing performed well by POC. However, there can be downsides with diagnoses missed by overreliance on test measurement which is insufficiently sensitive (34). POC cTn limitations must be appreciated (potential for false negative results on admission because lack of analytical sensitivity) and the need for repeat testing (up to 6 hours) are built into the diagnostic protocol for rule out. However, a positive test by POC testing would allow immediate patient characterization and expedite management (35). There are risks if POC and central laboratory testing are mixed within a single health system. Degradation of diagnostic sensitivity may occur as a result of attempting to harmonize different assays by arbitrarily matching diagnostic cut offs (36); as cTn assays are neither standardized or harmonized.

**POC regulatory innovation & regulation**

Innovation and investments in research and development have led to disruptive technologies that fundamentally change patient management and or yield incremental improvements in assay performance (37). Innovations have to prove their value before there is widespread acceptance with stakeholders ( physicians, regulators, payers). Potential harm when introducing new products to market is real and regulatory bodies are tasked with ensuring safety and efficacy of devices.

It took nearly a decade after regulatory clearance outside the USA, supported by numerous publications, for manufacturers to convince the FDA that hs-cTn tests were not only more analytical sensitive than contemporary and POC assays but also safe and effective for patient care. To remedy this, the 21st Century Cures Act, signed into US law in 2016, is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently (38). It provides new authority to the FDA to a) improve recruitment and retention of scientific, technical, and professional experts, b) receive alternative sources of data for regulatory approvals such as real-world evidence, provided adequate quality of the data are maintained and c) establishes new expedited product development programs, including the *Breakthrough Devices program*. This allows opportunities for manufacturers to expand claims for on-market devices if technologies exist to capture quality real-world data. Introduction of *In Vitro* Diagnostic

Medical Device Regulation (IVDR) is strengthening the oversight and review process in the European Union (39). Manufacturers of currently approved *in vitro* diagnostic medical devices will have a transition time of five years to meet the requirements of the IVDR. Some of the key changes are more stringent documentation, rigorous clinical evidence and reclassification of devices according to risk.

As technology advances, the ability to offer POC hs-cTn assays have been developed. New guidance from regulatory bodies demand manufacturers conduct their clinical studies for registration in the intended care environment or as similar to the intended care environment as possible (40). In the US, if a manufacturer desires to achieve a CLIA waiver for a POC device, that device must be challenged in the environment where it will be used and operated by typical end-users found in that environment. FDA studies are extremely difficult to execute and are expensive, as most applied research sites prefer to provide dedicated research personnel, who qualify under CLIA as operators, to separate research from clinical staff. It is a misconception by the FDA that research staff may not be under the same stressors as a typical end-user managing patient care aspects while performing testing. Yet, the FDA mandates these POC studies be performed by typical end-users (such as nurses) who are responsible for routine clinical duties rather than allow research personnel focused only on testing. This adds burden to nurses, in an already financially stressed, FTE-short workplace, in the pandemic COVID-19 world hospitals are living through, is not realistic.

Currently, there are no CLIA-waived POC hs-cTn assays on the market. The challenge for cTn in obtaining CLIA waiver lies with the interpretation and judgement aspects of testing. CLIA waiver requires the operators to be able to run the test without formal training. The test must be designed so a lay person could run it with only the instructions packed in the kit and be able to easily interpret the result. With the exception of providers (nurses, clinicians, residents, technologists), rarely would a CLIA-waived operator with another job class know what to do with these results unless driven by protocol within the institution. Technology has advanced such that simplicity of testing is seldom a concern for these devices. Performing the testing in whole blood with limited knowledge on the part of the end user and little to no interaction with calibration and quality control is a baseline expectation for POC devices. Manufacturers are tasked with demonstrating that typical end users can perform testing and results are comparable to a predicate device. For POC hs-cTn, the expectation is that manufacturers compare their POC device to a 510K cleared laboratory cTn instrument. Analytical precision, linearity, accuracy and reportable range need to be demonstrated; as only quantitative assays are recommended for hs-cTn (3). POC devices will need to establish their own 99th percentile URL studies. Diagnostic accuracy needs to be performed, meaning analytical accuracy is not enough to demonstrate safety and effectiveness for FDA clearance. POC hs-cTn testing is expected to be validated no different than a central laboratory method. However, in the US, the FDA requirements for POC assay clearance are more difficult than a central laboratory method.

**Strategies for regulation going forward**

Globally, two important questions need to be considered: a) are clinical studies still necessary if analytical validity can be demonstrated from one platform to the next; b) do matrix studies that demonstrate similar performance with plasma and whole blood need to be repeated in fresh whole blood collections for POC studies? What will more regulation bring in terms of cost, timelines, and innovation in relation to balance improvements in safety and efficacy of *in vitro* diagnostic products.

A regulatory system that allows well characterized tests to be evaluated for modifications to occur without having to submit new evidence of performance, waiting years to bring the next generation test to market, is needed. Trust in the system to allow for regulation without stifling innovation could bring devices to market more efficiently and safely. The 'risk' of bringing new hs-cTn devices to market is substantially lower today, based on evidence-based analytical and clinical literature amassed for known intended uses. Post market analysis can help serve to mitigate risks for new intended uses or incremental improvements over previous generations, without having to refile for new regulatory clearances. Being able to mitigate these risks with innovative regulatory processes will balance the need for improved products without compromising patient safety. Adverse patient outcomes will be better predicted, with improved patient management providing considerable cost savings to hospitals and patients.

We propose the FDA consider the following process for patient enrollments into manufacturers' 510K submissions.

1. Regulatory agencies, including the FDA, should write a guidance document describing the minimal requirements needed to submit for clearance as they have done for glucose POC testing. With guidance, manufacturers would have more consistent study protocols, populations, and potential use of predicate devices. Presently, there is too much variation between study protocols and the feedback manufacturers receive is inconsistent.
2. Revise the inconsistent and biased enrollment of subjects identified in the ED using the IRB informed consent process based on new blood draws. This practice is time consuming, expensive, and misses over 70% of eligible

patients who would qualify for enrollment; making the study population biased compared to the real practice.

3. Obtain IRB approved waste specimen use from patients' orders from their clinical indications by the provider that are already in the laboratory for testing for plasma and serum, and likely EDTA whole blood remnant samples; except for capillary samples that would need to be fresh.
4. As patients present for treatment and are registered before entering the hospital system, provide the patient with an authorization and consent form that includes a section that clearly defines that the institution conducts research. The patient, can at their choice, agree or not to agree to participate in medical research to allow for better understanding of diseases and how care is provided, and by signing the document agrees that investigators may use health information and waste specimens already collected.

   This will allow for:

   a. consecutive enrollment of patients, 24/7, without the bias of time delays of blood draws by informed consent;
   b. testing whole blood in real time, with a matched plasma or serum specimens allowing rapid sample processing;
   c. use of fresh specimens that match real practice testing, instead of freezing and thawing for analysis, often in batches.
5. This novel practice will allow manufacturers to:
   a. enroll of over 2500 patients in >3 selected institutions in 3 to 4 months;

b. more rapidly acquire and compile data;

c. draft documents more quickly for submission to FDA for review;

d. provide substantial financial savings by cutting a 2 to 3 year process to < 1 year.

Finally, the FDA should consider Emergency Use Authorization (EUA) for novel hs-cTnI and hs-cTnT POC devices and assays, without sacrificing quality. While it is understood that when the EUA period is over the test will require a 510k clearance to remain on the market, this period would allow manufacturers the ability to collect data for 510k submissions. This would assist inner-city and rural providers to rapidly measure of hs-cTn, the cardiac biomarker that makes a difference now and into the future; “for the times they are a-changin”.



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Table 1. New and updated IFCC C-CB and AACC Academy recommendation for practice utilizing high sensitivity cardiac troponin assays.

1. Quality control materials need to be implemented at concentrations consistent with both the male and female sex-specific upper reference limits.
2. Quality control materials should be considered at concentrations consistent with the limit of detection (LoD) of each hs-cTnI and hs-cTnT assay to provide ongoing confidence when used for rule out protocols.
3. Avoid implementing upper reference limits that use underpowered subject numbers to establish $99^{th}$ percentiles.
4. Appropriate statistical analyses to define $99^{th}$ percentiles include the non-parametric and Harrell Davis methods, with the Robust method not acceptable.
5. High sensitivity assays are now defined base on measuring $\geq$50% of normal males and $\geq$50% normal females individually, not combined.
6. Beware of contemporary assays that report results using whole numbers, designated ng/L, that are only designated for high sensitivity assays.

Table 2. Clinical trials of point of care testing predicated on cardiac troponin monitoring.

| Type | Methodology | Diagnosis | Outcome measure | Result | Author |
|---|---|---|---|---|---|
| Single centre RCT – CCU admissions | Roche cTnT CLT vs POCT | Troponin testing at 12 hours from admission. Diagnostic cut off 0.2 µg/L | Duration of length of stay (LOS). | Positive – Reduced LOS for non-CCU and total hospital stay in pre-specified rule out group. | Collinson et al (11) |
| Multicentre RCT in the ED Disposition Impacted by Serial Point of Care Markers in Acute Coronary Syndromes (DISPO-ACS) | iSTAT cTnI vs central laboratory cTnI | Serial testing over 6 hours or serial testing at 8-12 hours (1 site) | Time to discharge home or transfer to inpatient care | Inconclusive – the bedside troponin group had varying and inconstant changes in ED length of stay compared with the central laboratory group. Reduction in one site and increase in another | Ryan et al (12) |
| Single centre RCT in the ED | Stratus CS vs Dimension RxL | Testing post randomization. Protocol not stated. Diagnostic cut off 0.1 µg/L | Time to treatment Length of stay in the ED | Positive - Reduced time to commencing anti-ischemic treatment No reduction in ED stay | Renaud et al (13) |
| 2 Centre Cluster randomized controlled trial in the ED. One centre did not have 24 h on site laboratory access. | iStat vs Beckman Coulter Accu I | Protocol not stated | Length of ED stay | Inconclusive – Reduced LOS but not significant. Increased proportion of patients discharged <8 hours. From admission | Loten et al (14) |
| Randomized Assessment of Treatment using Panel Assay of Cardiac markers (RATPAC) | Stratus CS vs Central Lab | Testing on admission and 90 minutes post admission. Discharge for Troponin <0.7 µg/L and no delta. | Discharges <4 hour Length of hospital stay MACE | Positive - Increased discharge <4 hours with less admissions MACE was equivalent in POCT and CLT groups | Goodacre et al (15) |

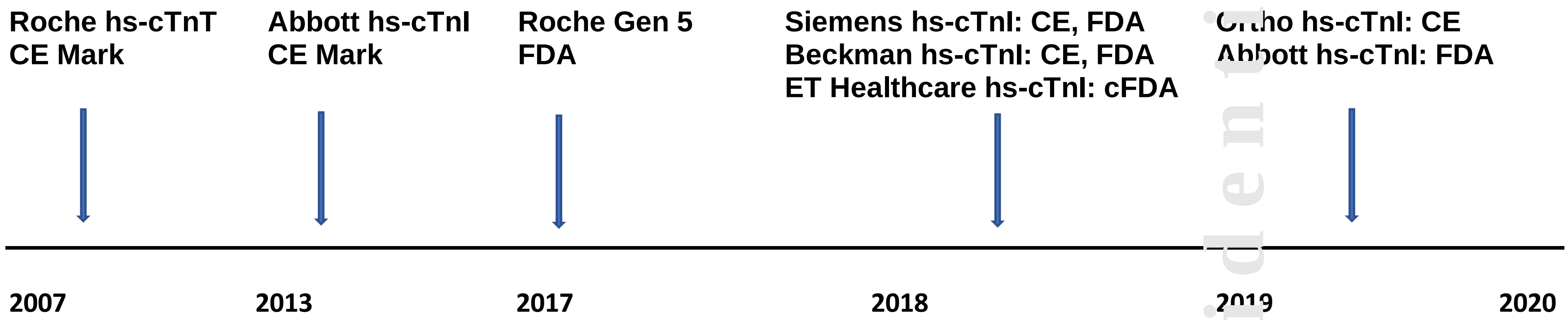
| | | | | | |
|---|---|---|---|---|---|
| 6 centre RCT in the ED | | | | | |

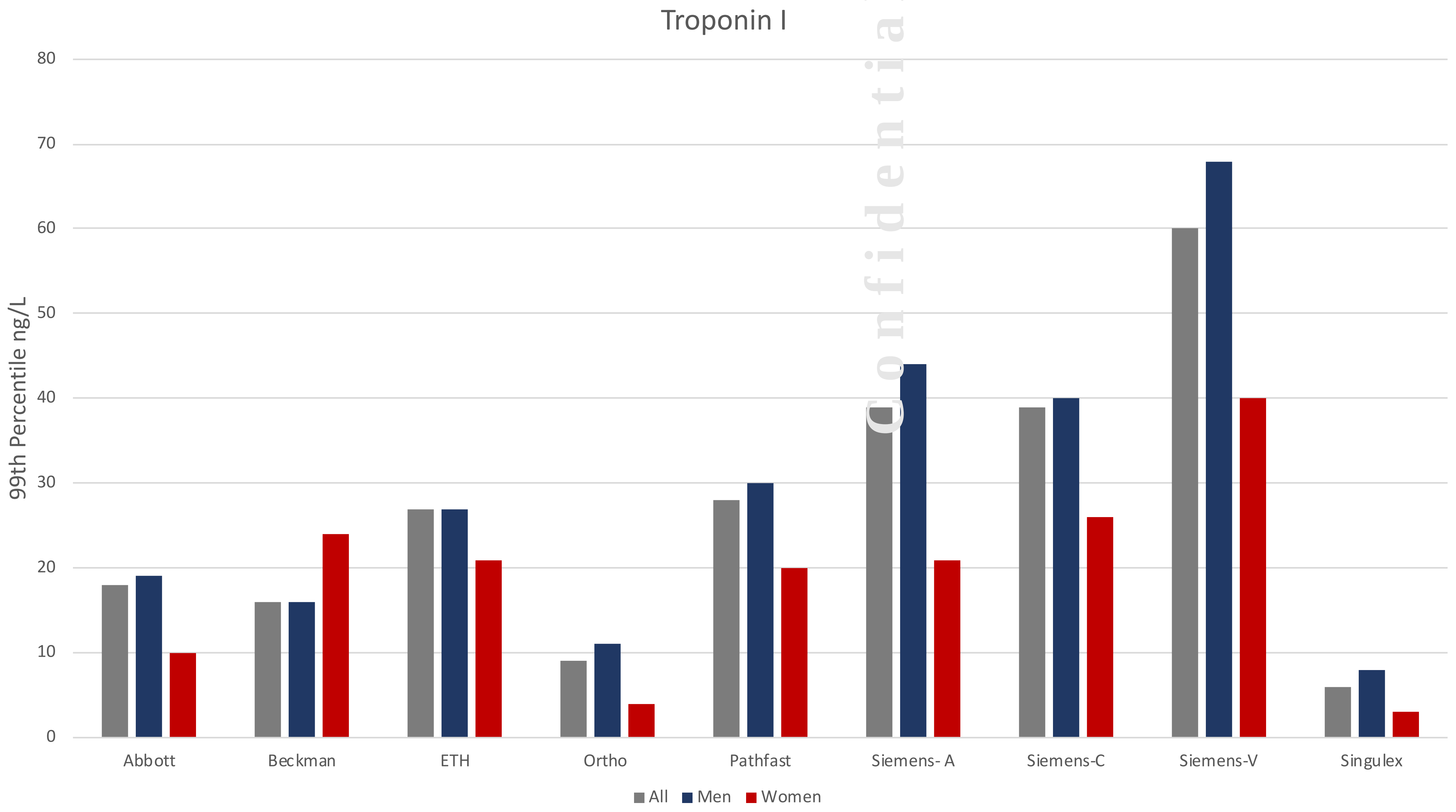
Abbreviations: RCT, randomised controlled trial; cTnT, cardiac troponin T; cTnI, cardiac troponin I; ED, emergency department; CCU, Coronary Care Unit; MACE, major adverse cardiac events

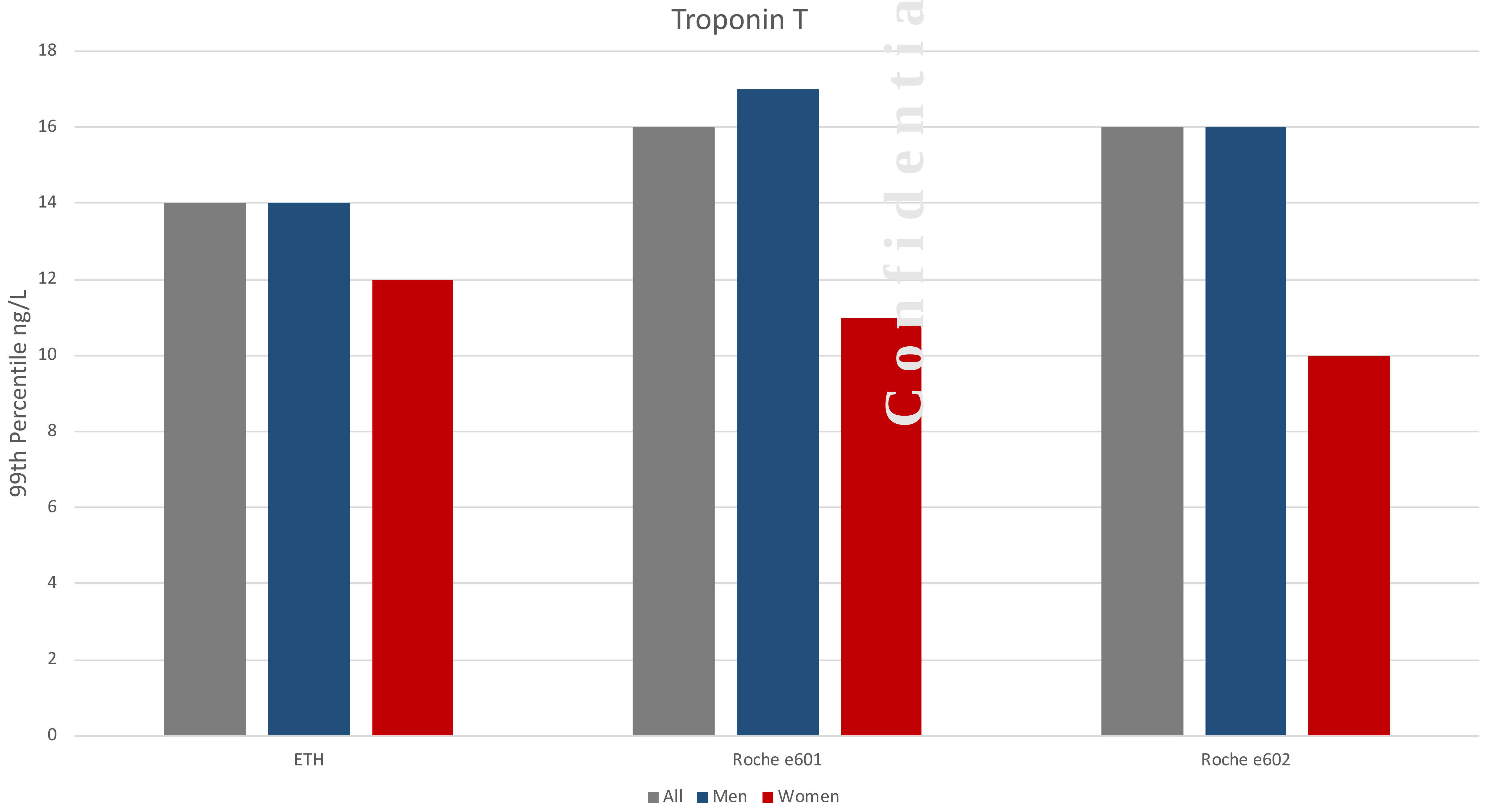
Figure 1. Representative timeline for regulatory clearance for clinical use of hs-cTn assays.

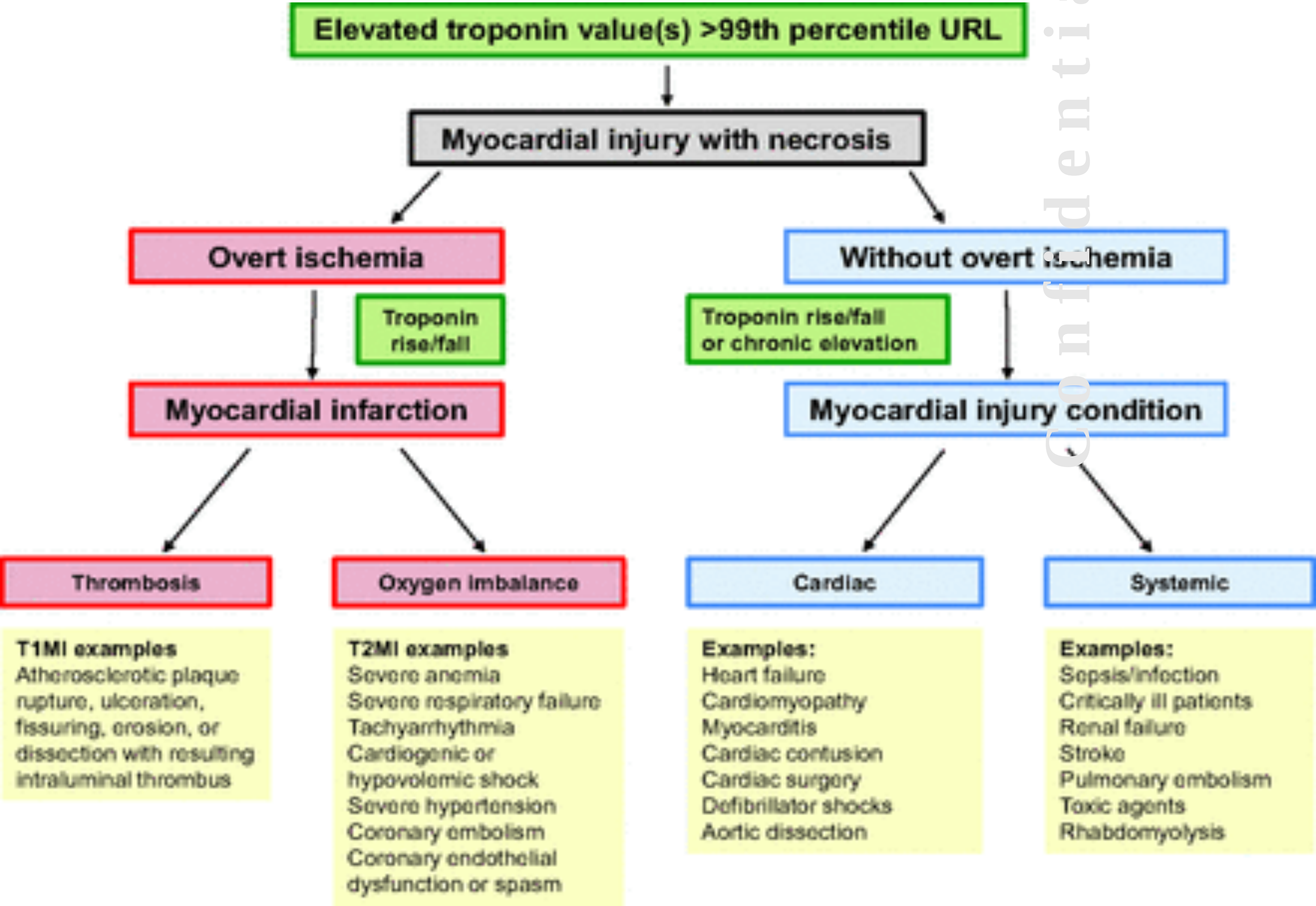
Figure 2. Men had higher 99$^{th}$ percentile URLs for multiple hs-cTnI (A) and cTnT (B) assays compared to most women (from reference 5).

Figure 3. Conceptual model for myocardial injury and myocardial infarction (from reference 8).


Roche hs-cTnT
CE Mark
Abbott hs-cTnI
CE Mark
Roche Gen 5
FDA
Siemens hs-cTnI: CE, FDA
Beckman hs-cTnI: CE, FDA
ET Healthcare hs-cTnI: cFDA
Ortho hs-cTnI: CE
Abbott hs-cTnI: FDA
2007
2013
2017
2018
2019
2020


Troponin I
99th Percentile ng/L
80
70
60
50
40
30
20
10
0
Abbott
Beckman
ETH
Ortho
Pathfast
Siemens- A
Siemens-C
Siemens-V
Singulex
All
Men
Women
Confidential


Troponin T
99th Percentile ng/L
0
2
4
6
8
10
12
14
16
18
ETH
Roche e601
Roche e602
All
Men
Women
Confidential


Elevated troponin value(s) >99th percentile URL
Myocardial injury with necrosis
Overt ischemia
Without overt ischemia
Troponin rise/fall
Troponin rise/fall or chronic elevation
Myocardial infarction
Myocardial injury condition
Thrombosis
Oxygen imbalance
Cardiac
Systemic
T1MI examples
Atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus
T2MI examples
Severe anemia
Severe respiratory failure
Tachyarrhythmia
Cardiogenic or hypovolemic shock
Severe hypertension
Coronary embolism
Coronary endothelial dysfunction or spasm
Examples:
Heart failure
Cardiomyopathy
Myocarditis
Cardiac contusion
Cardiac surgery
Defibrillator shocks
Aortic dissection
Examples:
Sepsis/infection
Critically ill patients
Renal failure
Stroke
Pulmonary embolism
Toxic agents
Rhabdomyolysis