I “dieci comandamenti” della troponina ad alta sensibilità

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Congresso Regionale SIBioC, Bologna 30 novembre 2018

Reference:

ESC European Society of Cardiology
European Heart Journal (2018) **00**, 1–33
doi:10.1093/eurheartj/ehy462

EXPERT CONSENSUS DOCUMENT

Fourth universal definition of myocardial infarction (2018)

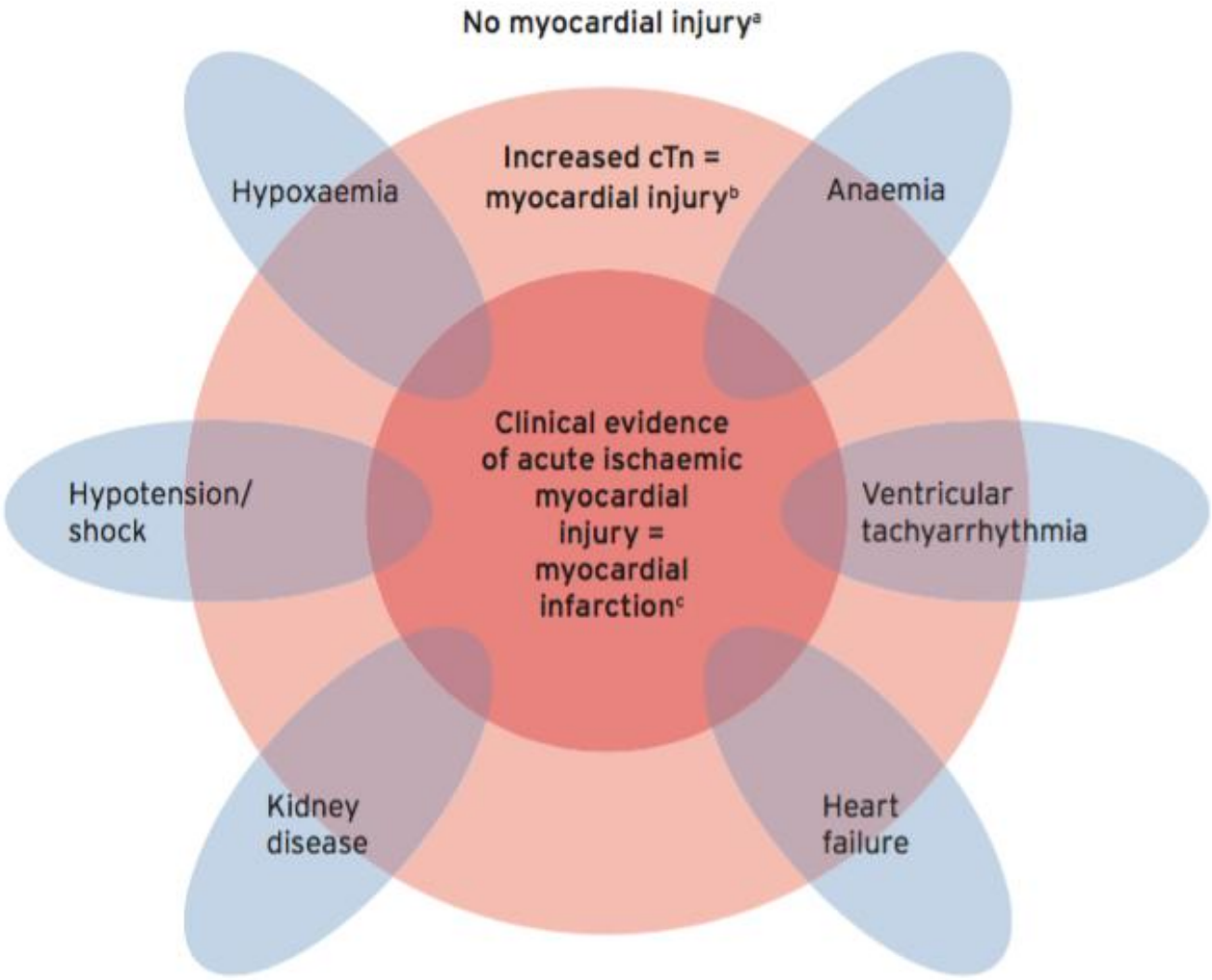
Kristian Thygesen* (Denmark), Joseph S. Alpert* (USA), Allan S. Jaffe (USA), Bernard R. Chaitman (USA), Jeroen J. Bax (The Netherlands), David A. Morrow (USA), Harvey D. White* (New Zealand): the Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/ American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction

What's new in the universal definition of myocardial infarction?

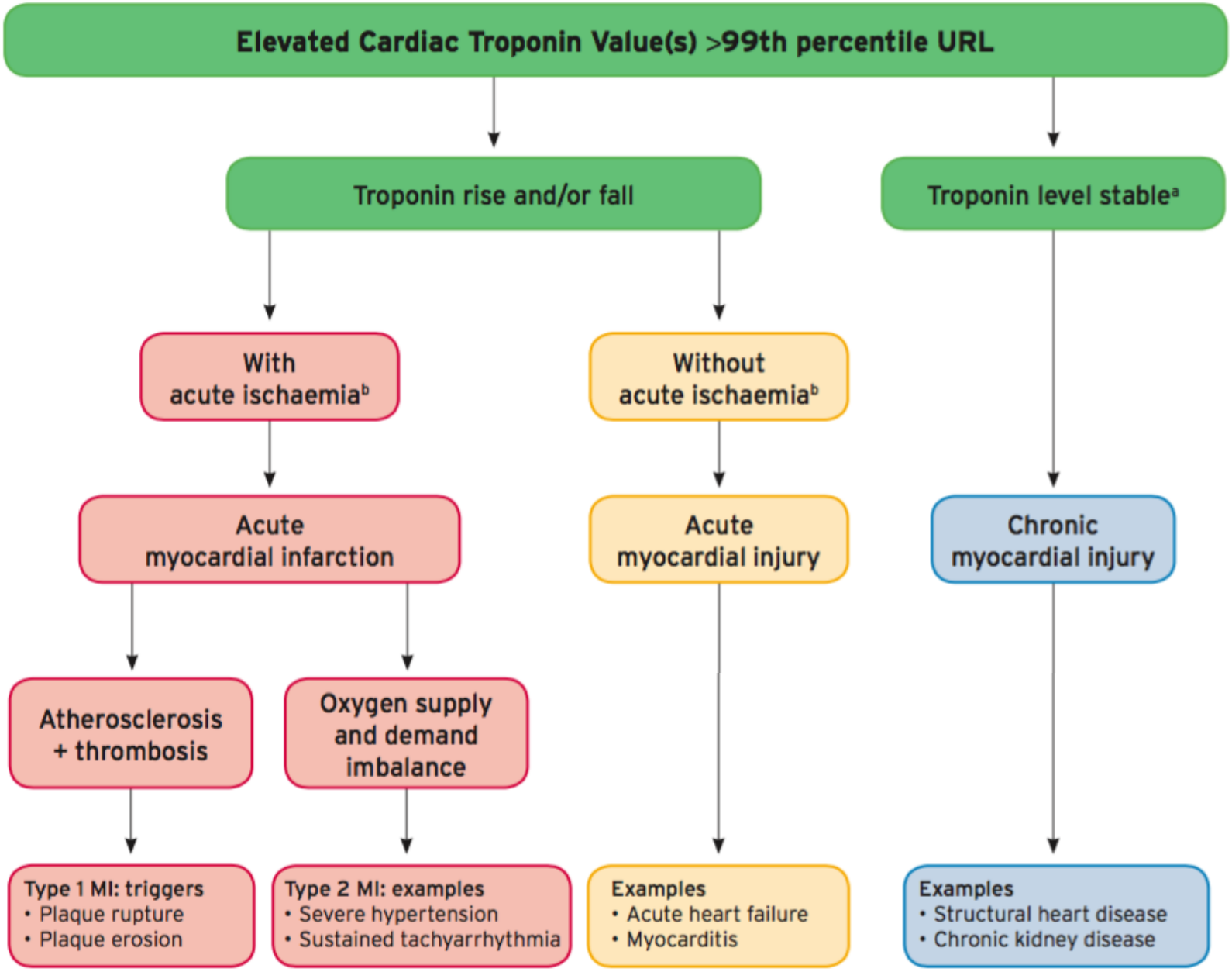
Updated concepts

- Type 1 myocardial infarction: Emphasis on the causal relationship of plaque disruption with coronary athero-thrombosis; *new Figure 3*.
- Type 2 myocardial infarction: Settings with oxygen demand and supply imbalance unrelated to acute coronary athero-thrombosis; *new Figures 4 and 5*.
- Type 2 myocardial infarction: Relevance of presence or absence of coronary artery disease to prognosis and therapy.
- Differentiation of myocardial injury from type 2 myocardial infarction; *new Figure 6*.
- Type 3 myocardial infarction: Clarify why type 3 myocardial infarction is a useful category to differentiate from sudden cardiac death.
- Types 4-5 myocardial infarction: Emphasis on distinction between procedure-related myocardial injury and procedure-related myocardial infarction.
- Cardiac troponin: Analytical issues for cardiac troponins; *new Figure 7*.
- Emphasis on the benefits of high-sensitivity cardiac troponin assays.
- Considerations relevant to the use of rapid rule-out and rule-in protocols for myocardial injury and myocardial infarction.
- Issues related to specific diagnostic change ('delta') criteria for the use of cardiac troponins to detect or exclude acute myocardial injury.
- Consideration of new non-rate-related right bundle branch block with specific repolarization patterns.
- ST-segment elevation in lead aVR with specific repolarization patterns, as a STEMI equivalent.
- ECG detection of myocardial ischaemia in patients with an implantable cardiac defibrillator or a pacemaker.
- Enhanced role of imaging including cardiac magnetic resonance imaging for the diagnosis of myocardial infarction; *new Figure 8*.

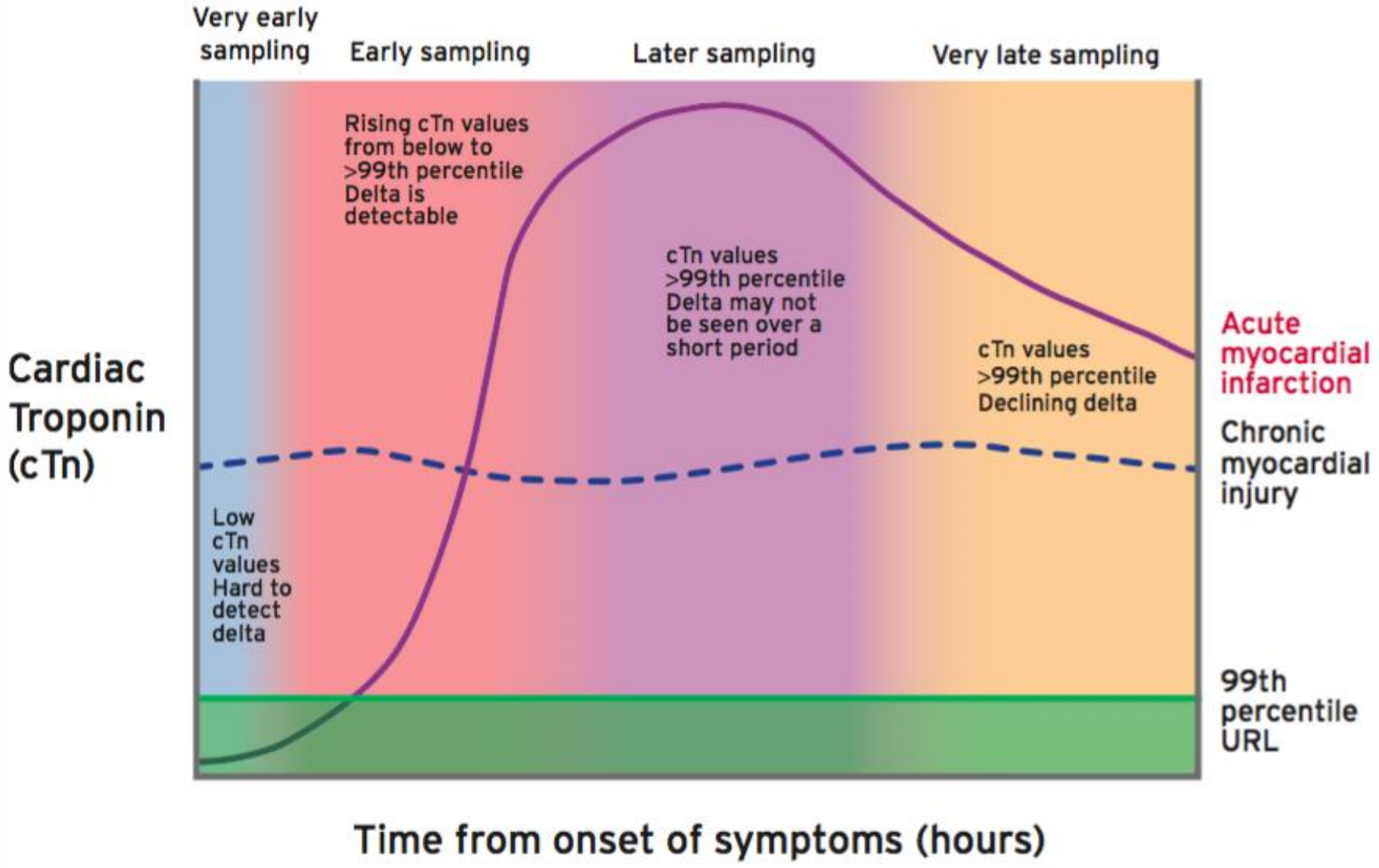
Spectrum of Myocardial Injury, Ranging from No Injury to Myocardial Infarction.



A Model for Interpreting Myocardial Injury



Early Cardiac Troponin Kinetics in Patients after Acute Myocardial Injury Including Acute Myocardial Infarction

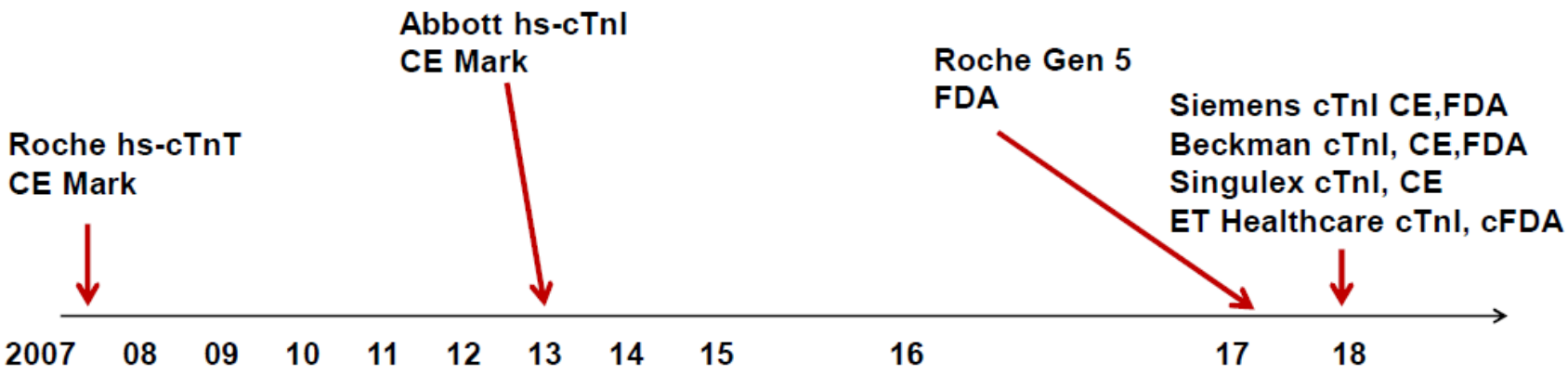


New Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome

Fred Apple, PhD
Amy Saenger, PhD
Torbjorn Omland, MD PhD MPH
Rick Body, MB ChB PhD

Joint Industry Sponsored Workshop
IFCC Committee on Clinical Applications of Cardiac Biomarkers
Developed in Partnership with AACC
August 1, 2018 Chicago, IL

hs-cTnT/I Assay Implementation



Clinicians and Laboratories in Europe/ Rest of World OUS have used hs-cTnT (Roche) for 11 years and hs-cTnI (Abbott) for 5 years

References:

Clinical Chemistry 64:4
645–655 (2018)

Special Report

Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine

Alan H.B. Wu,[1*] Robert H. Christenson,[2] Dina N. Greene,[3] Allan S. Jaffe,[4] Peter A. Kavsak,[5] Jordi Ordonez-Llanos,[6] and Fred S. Apple[7]

Clinical Chemistry 63:1
73-81 (2017)

Mini-Reviews

Cardiac Troponin Assays: Guide to Understanding Analytical Characteristics and Their Impact on Clinical Care

Fred S. Apple,[1*] Yader Sandoval,[2] Allan S. Jaffe,[3] and Jordi Ordonez-Llanos,[4] for the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers

Clinical Laboratory Practice Recommendations for Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from Academy of the AACC and the Task Force on Clinical Applications of Cardiac Bio-Markers of the IFCC

1. Quality control (QC) utilization
2. Assay limits validating the lower reportable analytical limits (LoD)
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4. 99th percentile sex-specific upper reference limits defining the reference interval
5. Criteria required to define hs-cTn assays
6. Communication with clinicians and laboratory role in educating clinicians on the influence of pre-analytic and analytic issues that confound assay results
7. Authors/manuscripts need to document pre-analytical/analytical variables on hs-cTn assays
8. Harmonizing and standardizing assay results and role of commutable materials
9. Time to reporting of results from sample receipt and sample collection
10. Changes in hs-cTn concentrations over time and role of both analytical and biological variabilities in interpreting results of serial blood collections

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Wu, Christenson, Greene ,Jaffe, Kavsak, Ordonez-Llanos, Apple *Clin Chem*, 64(4): 645-655 (2018)

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Limit of Blank (LoB), Limit of Detection (LoD), Limit of Quantification (LoQ)

- The **Limit of Blank (LoB)** is the highest cardiac troponin concentration expected to be found when replicates of a sample containing the zero calibrator for a cardiac troponin assay are tested.

- The **Limit of Detection (LoD)**, a concentration greater than the LoB, is the lowest detectable cardiac troponin concentration reliably distinguished from the LoB in a sample containing a low cardiac troponin concentration that can confidently be reported for clinical use.

- The **Limit of Quantification (LoQ)** is the lowest cardiac troponin concentration that demonstrates a 20% CV.

Recommendation #1: For hs-cTn Assays, Laboratories Should Measure at Least 3 Different Concentrations of QC Materials at Least Once Per Day.

Before patient testing can be initiated, the values for acceptable imprecision must be at a minimum, consistent with those specified by the manufacturer.

Quality gap: users are unaware of performance of contemporary cTn assays at 99th percentile

Three QC concentrations for hs-cTn assays:

1. Concentration between LoD and the lowest sex-specific 99th percentile
2. Concentration higher than, but close (within 20%) to the highest sex-specific 99th percentile
3. Concentration that challenges upper analytical range of hs-cTn results

Recommendation: Total analytical error <3.5 ng/L be used for hs-cTnI and hs-cTnT for QC concentrations ≤10 ng/L; labs whose physicians use ESC guidelines may opt for error of <1 ng/L to avoid patient misclassification (<10%)

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Clin Chem, 64(4): 645-655 (2018)

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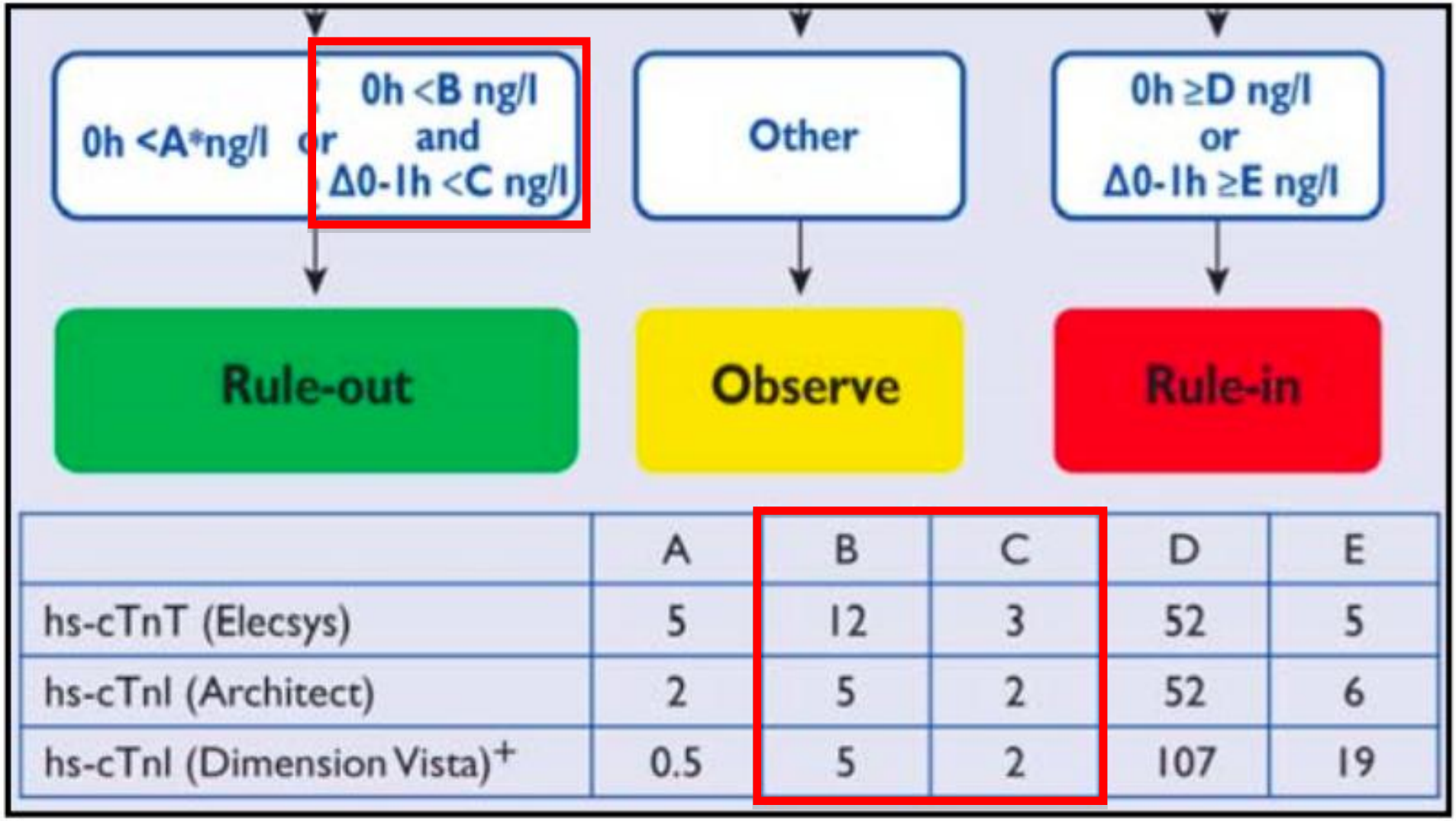
European Society of Cardiology 0-Hour/1-Hour Algorithm to Rule-Out and Rule-In Acute Myocardial Infarction



	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)+	0.5	5	2	107	19

Recommendation #2: During Initiation of hs-cTn Testing, Clinical Laboratories Should Validate the LoD and LoB.

These analytical parameters should be verified minimally on an annual basis or more frequently as deemed necessary.

- **IFCC TF-CB recommends the LoD (limit of detection) as lowest analytical reportable limit for determining hs-cTn assay designation-concentration detected with acceptable probability**
  - FDA appears to only allow reporting to LoQ in the US (limit of quantitation; 20% CV concentration)

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Recommendation #2: During initiation of hs-cTn testing, clinical laboratories should validate the LoD and LoB.

These analytical parameters should be verified minimally on an annual basis or more frequently as deemed necessary.

1. Annual validation of LoB, LoD (outside the US) and LoQ (US)
   - If using LoD due to improved clinical utility, validate and consider as LDT (lab developed test)
2. Drift over time at the 99th percentile can (and has) happened
   - Reagent and calibrator lot changes
   - Instrument maintenance
   - Instrument to instrument variability
3. Analytical deviations difficult to detect because QC and most proficiency testing materials are non-commutable (i.e. different from plasma/serum) and do not report low enough values

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Recommendation #3: Report hs-cTn in Whole Numbers (ng/L, SI Units) Without Decimal Points.

For reporting QC values, we recommend 1 decimal point.

- A contemporary cTn assay result of 0.014 µg/L will be **14 ng/L** for an hs-cTn assay
- This designation, as an expert opinion, has been supported by many Journals and is globally recognized as a way to distinguish hs-cTn assays from contemporary cTn assays
- QC reporting will be, for example, **18.5 ng/L**
- Note: this recommendation is not relevant for contemporary assays

Countries which do NOT use SI units

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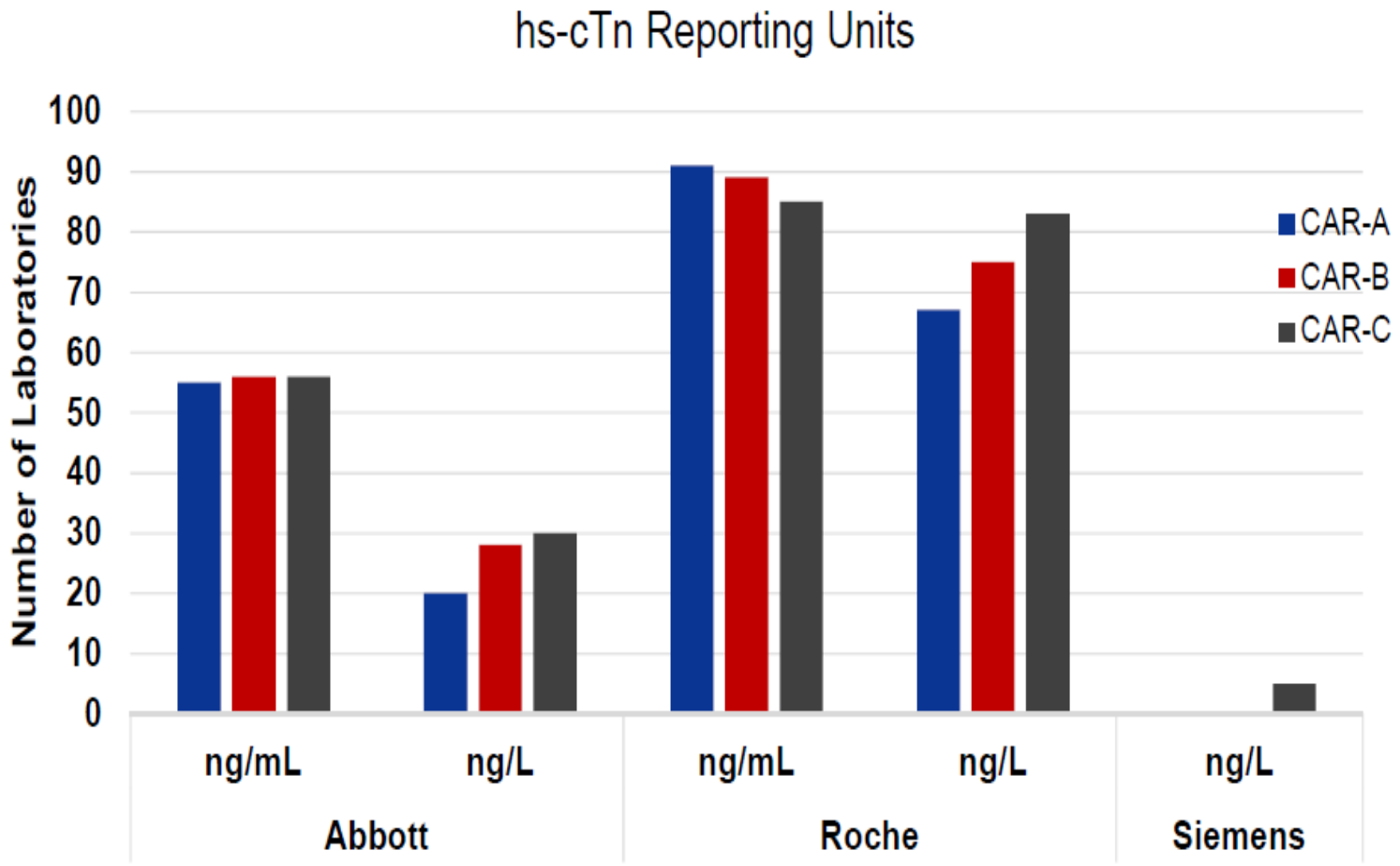
How Are Laboratories Reporting hs-cTn Results/Units Today?
*Data aggregated from 2017 CAP Cardiac PT Surveys



Recommendation #4: Use a Defined Reference Population to Report 99th Percentile Concentrations According to Sex-Specific Cutoffs for hs-cTn Assays*

Note: use of the 99th percentile but not sex-specific cutoffs is relevant for contemporary assays

- Fourth Universal Definition of MI (to be released at ESC) endorses sex-specific 99th percentiles recognizing URLs are lower for women than men
- Minimum 300 men and 300 women needed to defined URL for each sex
  - Use patients representative of your geographic area
  - Ages distributed over 20y and greater
  - Ethnic and racial mix with population
- More rigorous criteria for defining and excluding normal subjects lowers the 99th percentile: a) comorbidities, b) medication use, c) surrogate biomarkers (eGFR, HbA1C, NP)
- Statistical approach can influence 99th percentile (*nonparametric, Harrel-Davis, robust)

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* **New Recommendation** - *Clin Chem*, 64(4): 645-655 (2018)

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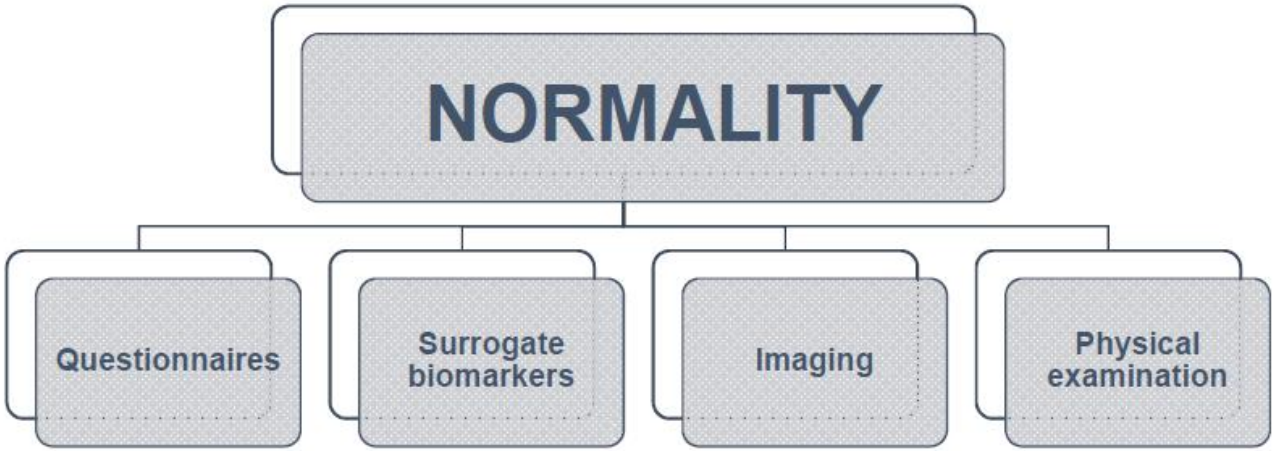
The Global Need to Define Normality: The 99th Percentile Value of Cardiac Troponin



Statins

- eGFR (>60 mL/min/1.73 m^2)
  - CKD-EPI equation
- NT-proBNP (125 ng/L)
- A1C ≥ 6.5% (5.7-6.4% pre)

Cost prohibitive

Sandoval Clin Chem 2014, Apple Clin Biochem 2015, Wu Clin Chem 2018

Recommendation #5: Assays Unable to Detect cTn at Concentrations At or Above the LoD in at Least 50% of Healthy Men and Women Should Be Labeled as Contemporary cTn Assays

- Analytical criteria need to be met to be a high-sensitivity (hs)
  - First, the %CV at the 99th percentile URL should be ≤10%
  - Second, measurable concentrations should be attainable at a concentration at or above the assay's LoD for ≥50% of healthy individuals for both men and women*
- New guidelines expand on this second point by requiring both men and women individually attain measurable concentrations, with at least 50% measurable concentrations above the assay's LoD
- Data to support claims need to be published in peer-review literature
- Need to understand the term 'high-sensitivity' addresses the assay not a different form of cTn

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* **New Recommendation** *Clin Chem*, 64(4): 645-655 (2018)

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Cardiac Troponin Assays Marketed as High-Sensitivity (hs)

Percent Measurable with USB	Men	Women
@* Abbott cTnI	91%	81%
@# Beckman Coulter cTnI	82%	48%
@ bioMerieux cTnI	data not available	
$ ET Healthcare	94%	86%
@#* LSI Medience cTnI	78%	52%
@# Roche cTnT	65%	21%
@#* Siemens cTnI	97%	88%
@* Singulex cTnI	99%	99%

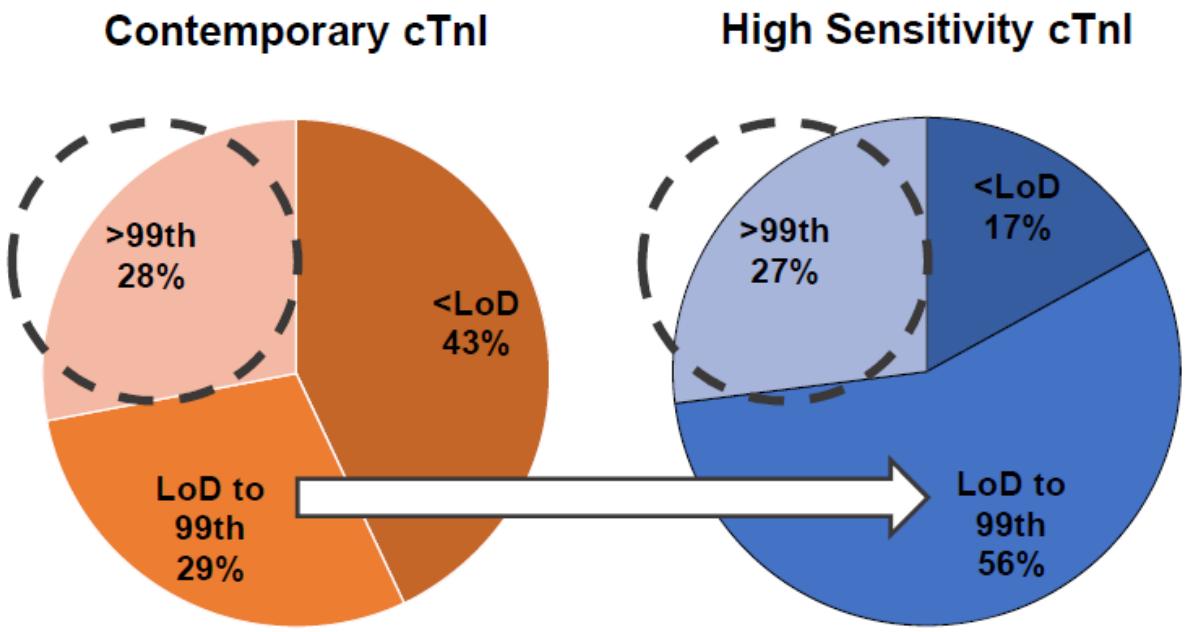
- No regulatory agency has established an approval of an assay to be labeled as 'high sensitivity'
- IFCC/AACC Academy document [*Clin Chem*, 64(4): 645-655 (2018)] has provided guidance in establishing 'hs' criteria

http://www.ifcc.org/media/463453/HighSensitivityCardiacTroponinI_T_AssayAnalyticalCharacteristics_v060617.pdf

@Conformite Europeane , CE Mark; #FDA 510k; *Meets IFCC/AACC Academy Guideline; $cFDA

Apple 2018

Expected Measurement Impacts Are Upon Transition to High-Sensitivity Assays: cTnI Experience



Across serial measurements
Over 7000 samples.

- No increase in values above 99th URL
- Marked increase in measurable values (>LoD)

Clin Chem 2016

Recommendation #6: Laboratories Should Communicate with Clinicians on the Influence of Pre-analytic and Analytic Problems that Confound hs-cTn Assays.

For institutions or health systems using 2 or more cTn assays, differences in the sensitivity of the various cTn assays should be communicated to assist clinicians in understanding discrepancies when patients are transferred from other facilities

- Would be ideal (not realistic) to report the manufacturer/instrument used for testing
- Need to make sure clinicians/providers know what assay (cTnI or cTnT) is being used as well as the version: contemporary, POC, high-sensitivity
- Routine discussions with clinicians about known issues/interferences should occur:
  - Biotin / Hemoglobin / Skeletal muscle cross-reactivity
- http://www.ifcc.org/media/463453/HighSensitivityCardiacTroponinI_T_AssayAnalyticalCharacteristics_v060617.pdf
- http://www.ifcc.org/ifcc-education-division/emd-committees/task-force-on-clinical-applications-of-cardiac-bio-markers-tf-cb/
- http://www.ifcc.org/media/477243/040218_ifcc-c-cb-troponin-interference-table-040218.pdf

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Recommendation #7: Authors of Studies Using hs-cTn Assays Should Document Pre-Analytical and Analytical Variables Important to the Study and Be Explicit Concerning Their Post-Analytical Interpretative Approaches

- Ability to directly compare data across studies is critical to effectively utilize any biomarker, including cTn, as there is heterogeneity across cTn assays
- Publications that exclude critical analytic parameters (i.e. assay manufacturer, instrument model, 99th percentile URL, LoB, LoD, LoQ, overall assay imprecision, specimen type, reagent lot numbers) are difficult to interpret because there is no ability to know whether or not the appropriate metrics were used
- Need for consistency in the literature for reporting all these parameters used within any given study

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Recommendation #8: Commutable Materials Should Be Developed for Use in Harmonizing and Standardizing cTn Measurements

- To achieve harmonization or standardization, a system is required that provides reliable transfer of the measurement values from the highest available hierarchical concentration to field methods that are routinely used in clinical laboratories
- Key elements of the system are the reference measurement procedure and appropriate reference material, which are assigned certified values with known uncertainty
- Extremely difficult to achieve standardization because of lack of uniformity of capture/detection antibodies used; harmonization a possibility but there are still a large number of patient/specimen specific differences

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Recommendation #9: Cardiac Troponin Results Should Be Reported Within 60 Minutes or Less of When a Sample is Received.

There should be continued efforts to improve this to a time of 60 minutes from when the sample was collected.

- Previous NACB (AACC Academy) recommendations: <60 min from time of blood collection to reporting results
- Many varied options as to when the 'clock' should start
  - Patient registration
  - When patient first observed by a provider
  - Time of blood draw
- Only control the laboratory has is when the sample arrives in the lab
  - Instruments analysis times vary by assay

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Recommendation #10: The Laboratory Should Help Educate Clinicians on the Importance of Specific Metrics By Which True Clinical Changes in cTn Concentrations Can be Distinguished From Analytical & Biological Variabilities.

- Cutoff concentrations for denoting a statistically significant change in serial cTn results must be established with biological variability studies by calculating the reference change value (RCV)
  - Contemporary assays typically measure < 10% of "normal" patients
- Absolute changes, rather than relative (percent) changes, appear preferable for hs-cTn assays at low concentrations
- Serial testing may provide a better means for diagnosis than use of a population-based 99th percentile
  - 4th UDMI supports serial 0 and 1/2/3h
    - later times will not miss potential very early presenters
- Serial monitoring helps in distinguishing acute from chronic injury

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Wu, Christenson, Greene ,Jaffe, Kavsak, Ordonez-Llanos, Apple *Clin Chem*, 64(4): 645-655 (2018)

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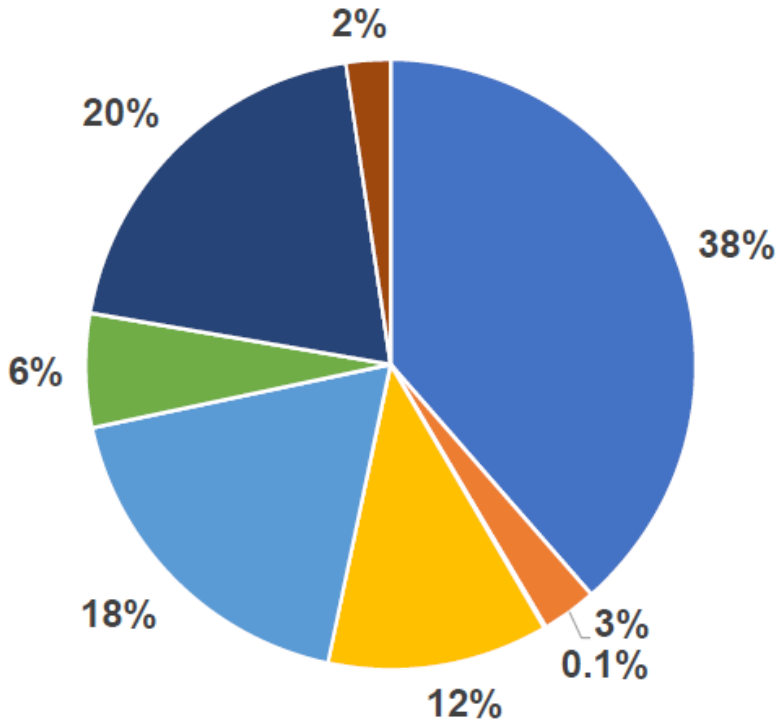
GRAZIE PER L'ATTENZIONE!

What Cutoff Are Laboratories Using Today for Reporting cTn Results? Reporting hs-cTn Results/Units Today?

*Data obtained from CAP PT user survey



US Participants, n = 2680

- 99th Percentile
- 10% CV
- 20% CV
- Institution Derived
- Literature Based Cutoff
- WHO Cutoff
- Don't Know
- Other

Saenger CAP Survey Data, Oct. 2017

High-Sensitivity Troponin Assays Refined

International Group of Experts comprised of Clinical Chemists, and Cardiologists & Emergency Medicine Clinicians
Endorsed by Universal Definition of MI Task Force

Acceptance Designation	Total Precision at 99th Percentile
Guideline Acceptable	10%
Clinically Usable	>10 to ≤ 20%
Not Acceptable	> 20%
Assay Designation	**Measurable Normal Values of Males and Females Below the 99th Percentile**
Level 4 - 3rd gen hs	≥ 95%
Level 3 - 2nd gen hs	75 to < 95%
Level 2 - 1st gen hs	50 to < 75%
Level 1 - Contemporary	< 50%

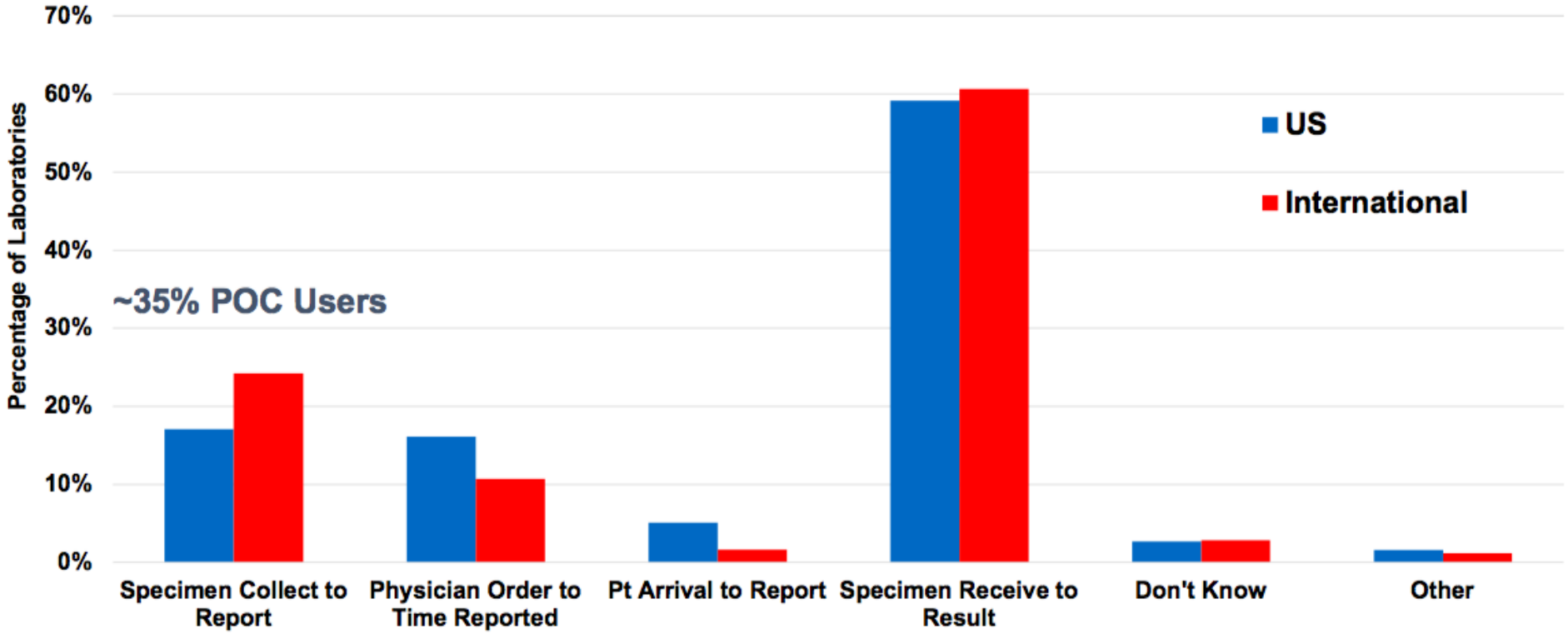
Apple FS, Jaffe AS et al. *Clin Biochem* (2015); 48(4): 201-3
Apple, FS *Clin Chem* (2009); 55(7):1303-6

Why Sex-Specific Cardiac Troponin URL Cutoffs?

- Women with acute coronary syndromes are
  - Less frequently diagnosed with AMI
  - More likely to be managed conservatively
  - Often have worse outcomes than men

- Sex-specific reference limits may:
  - Improve ability to detect women with coronary disease
  - Reduce underdiagnosis of AMI in women with little impact in men
  - However, so far superiority of sex-specific cutoffs concerning hard clinical end-points have not yet been clearly demonstrated

Turnaround Time Metrics Defined (Lab Perspective)



99% had a TAT GOAL of <60 min once the sample was received in the lab; unclear how often they meet this goal

CAP Survey Data, Oct. 2017