Troponin I and Myocardial Injury vs. Infarction: The 4th Universal Definition of Myocardial Infarction

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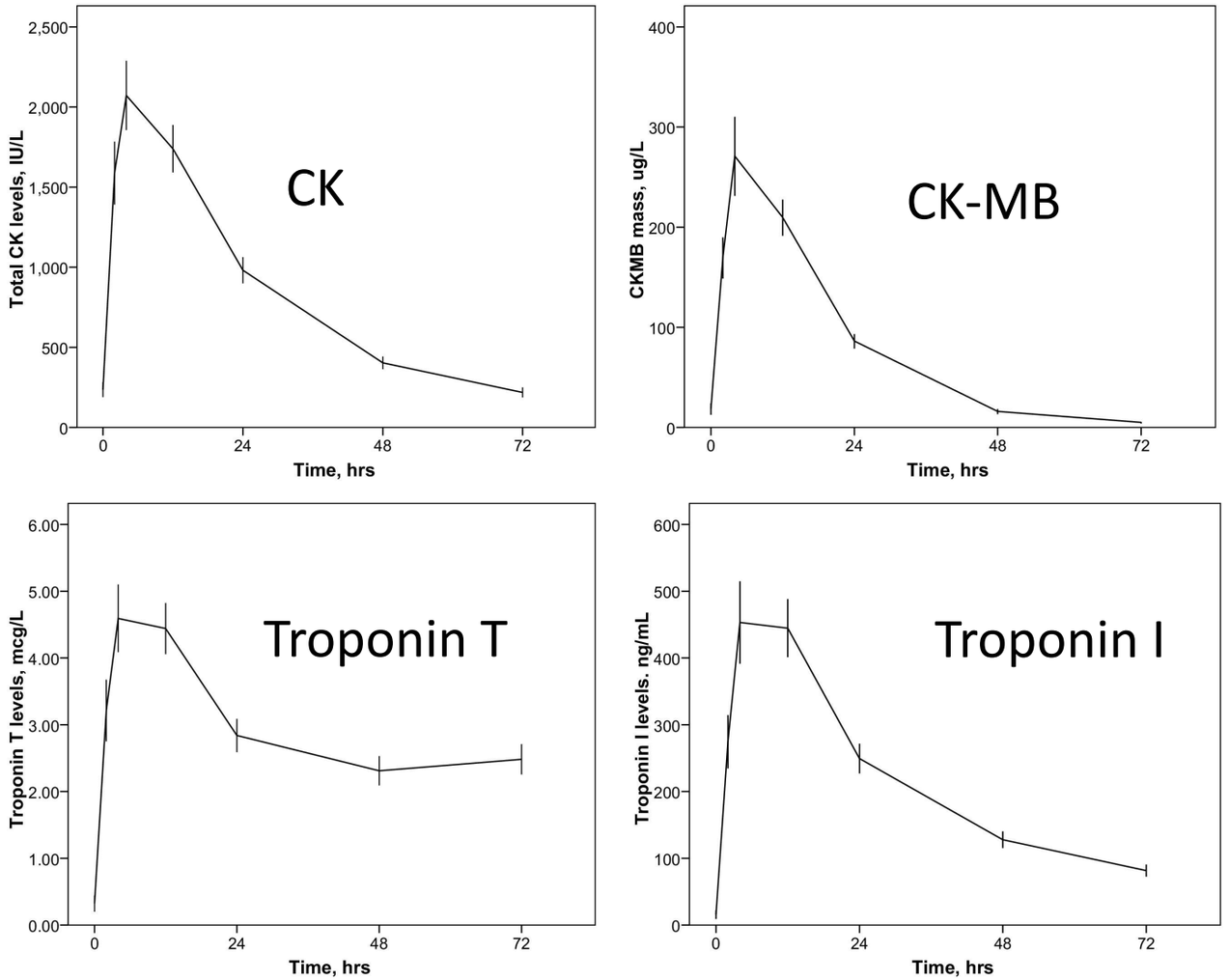
Overview

- Review the major mechanisms of myocardial infarction as updated in the 4th Universal Definition of Myocardial Infarction guidelines.
- Understand the concept of “myocardial injury” and how to differentiate this from myocardial infarction.
- Review preclinical research showing that Troponin I release reflecting programmed myocyte death (apoptosis) can arise from brief ischemia (similar to coronary spasm) and elevations in LV filling pressure.

Time-Concentration Curves for Cardiac Biomarkers After Primary PCI for STEMI



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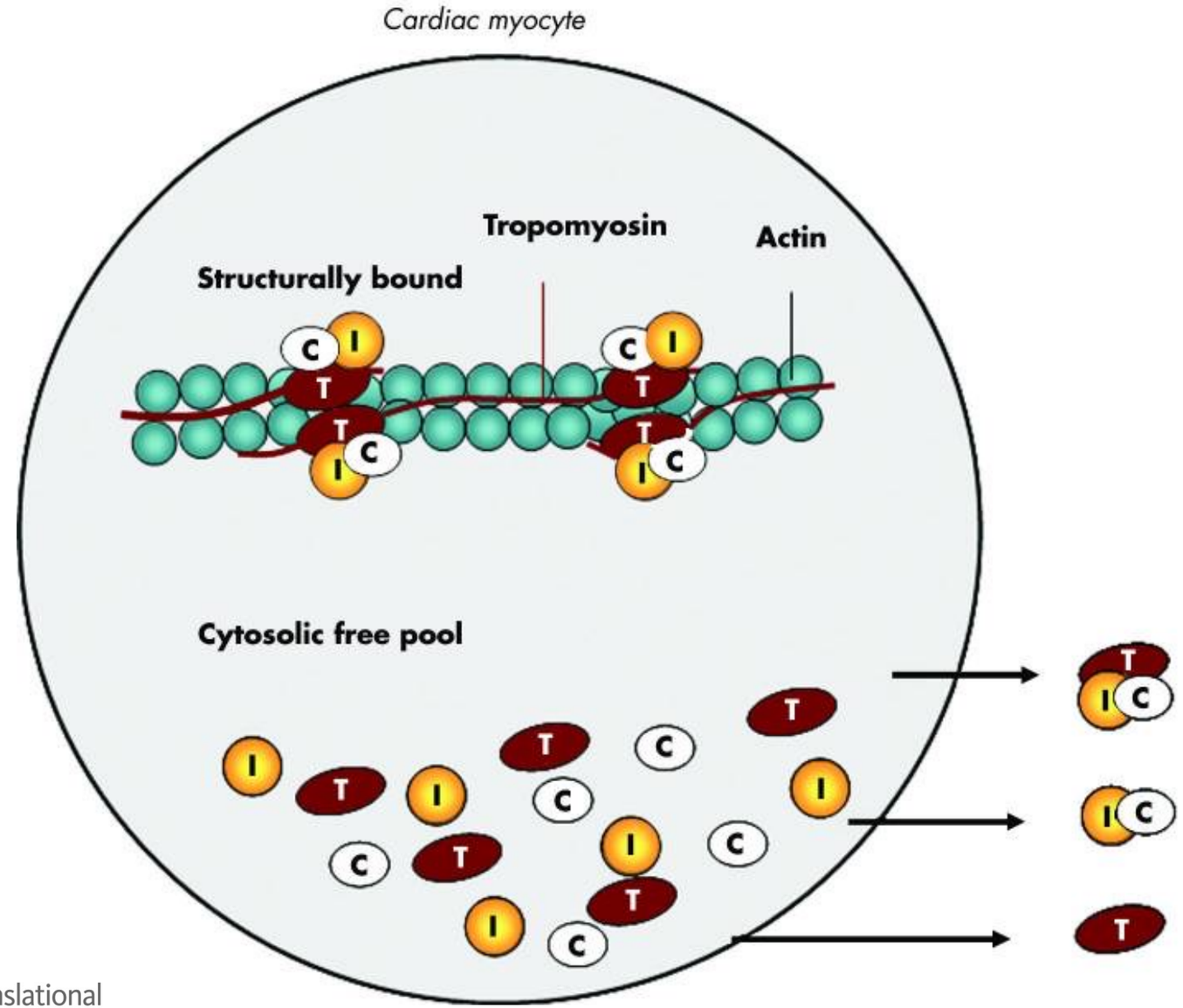
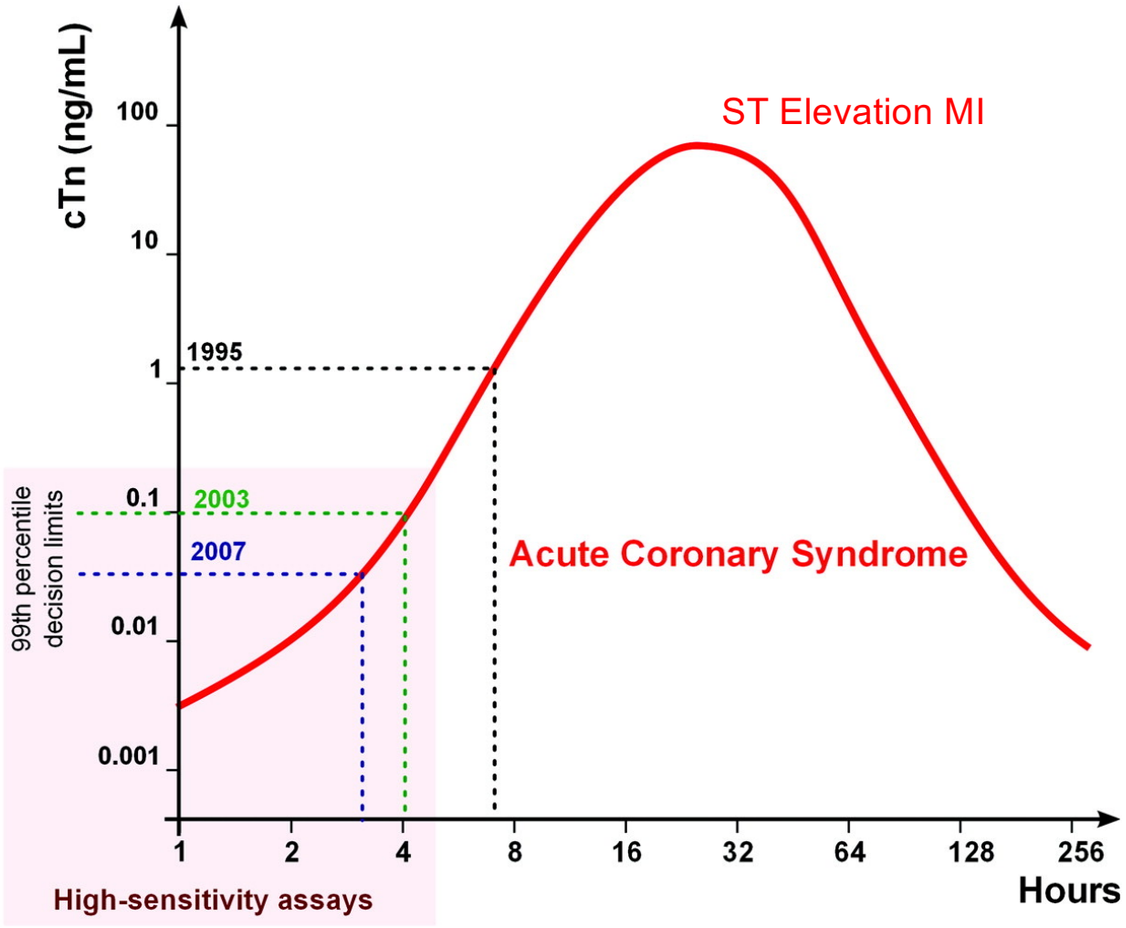
Chia et al. JACC, Cardiovasc. Interventions. 1:415–423, 2008

Troponin Tropomyosin Complex in Cardiac Myocytes



Cardiac troponin (cTn) assays are very sensitive assays of myocyte death

Log serum Troponin ng/mL



cTn Assay	Diagnostic cutoff	Implementation
TnI	≥ 1.5 ng/mL	1995
cTnI	> 0.10 ng/mL	2003
TnI-Ultra	> 0.04 ng/mL	2007

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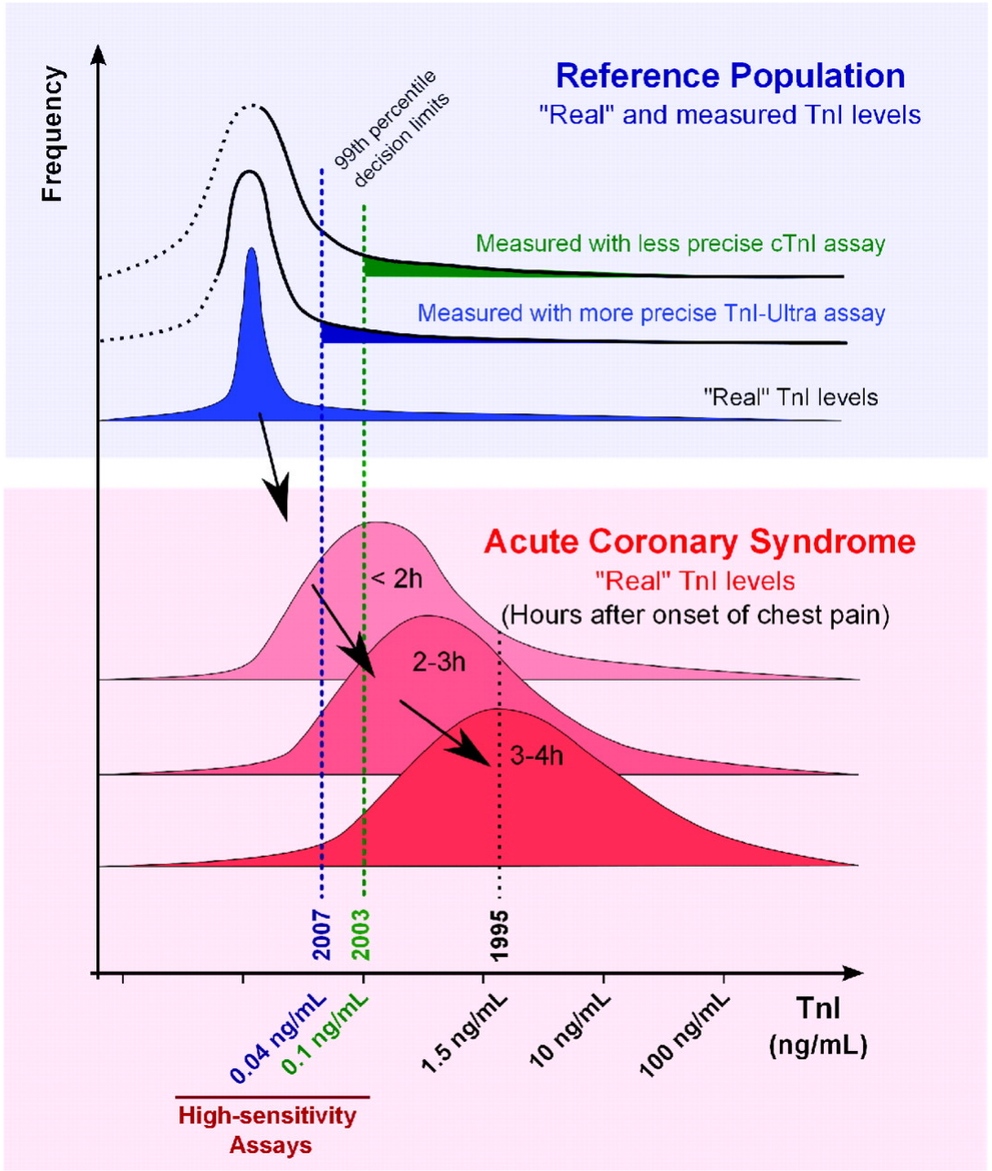
Mahajan et al, Circulation. 2011;124:2350-2354

Impact of Increasing TnI Assay Sensitivity on Early Diagnosis of MI



Distribution of TnI in Normals

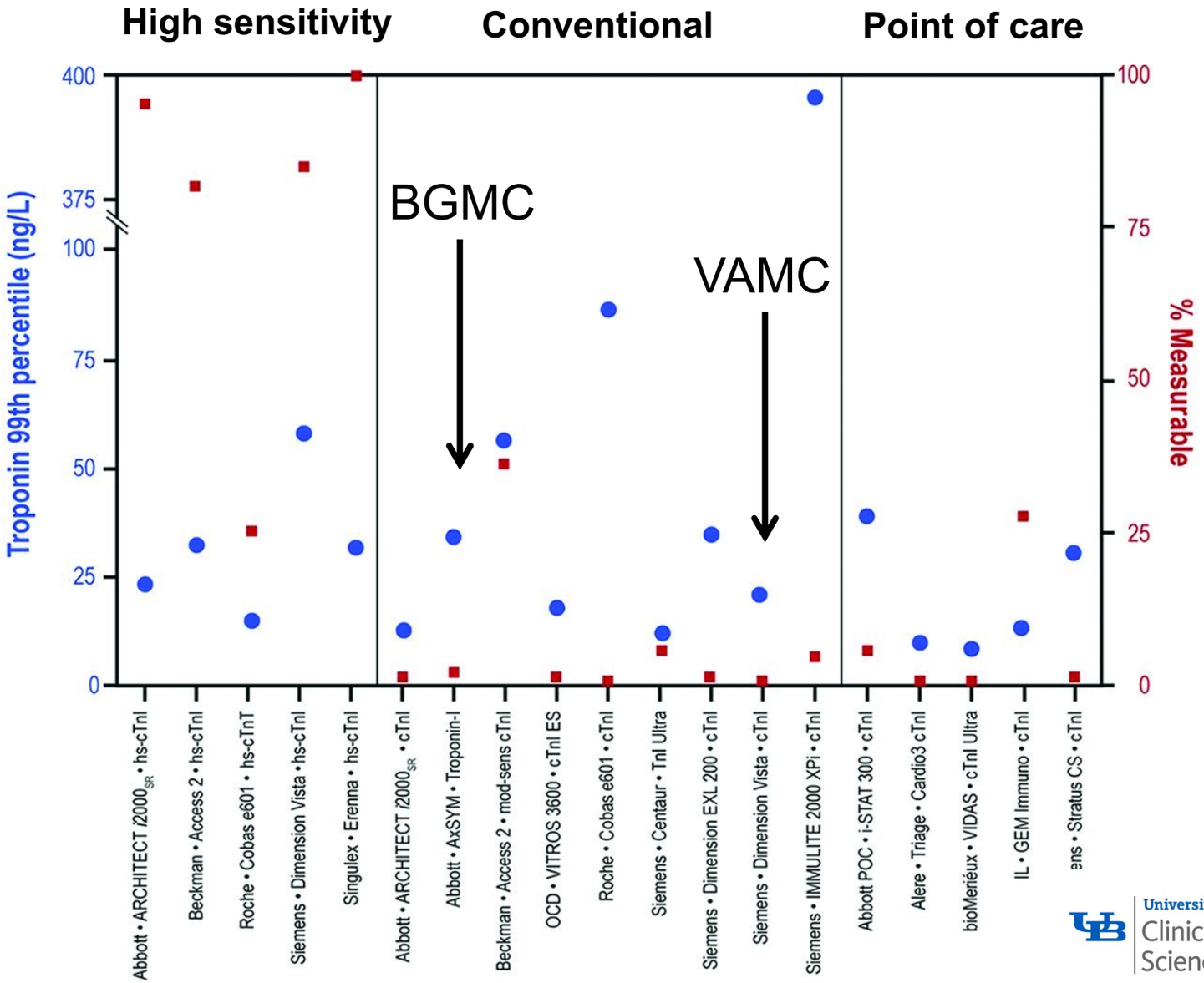
Frequency of ACS Diagnosis vs Time from Presentation

Mahajan et al, Circulation. 2011;124:2350-2354

What's the Difference Between High Sensitivity vs Conventional Troponin Assays?

High sensitivity troponin assays (hs-cTn) are differentiated from contemporary or point of care assays by their ability to detect measurable cTn above the assays' lower limit of detection in more than 50% of normal subjects that are asymptomatic

Assay variability in the 99th percentile cutoff for Troponin in Normals vs. the % of normal patients with a measurable TnI



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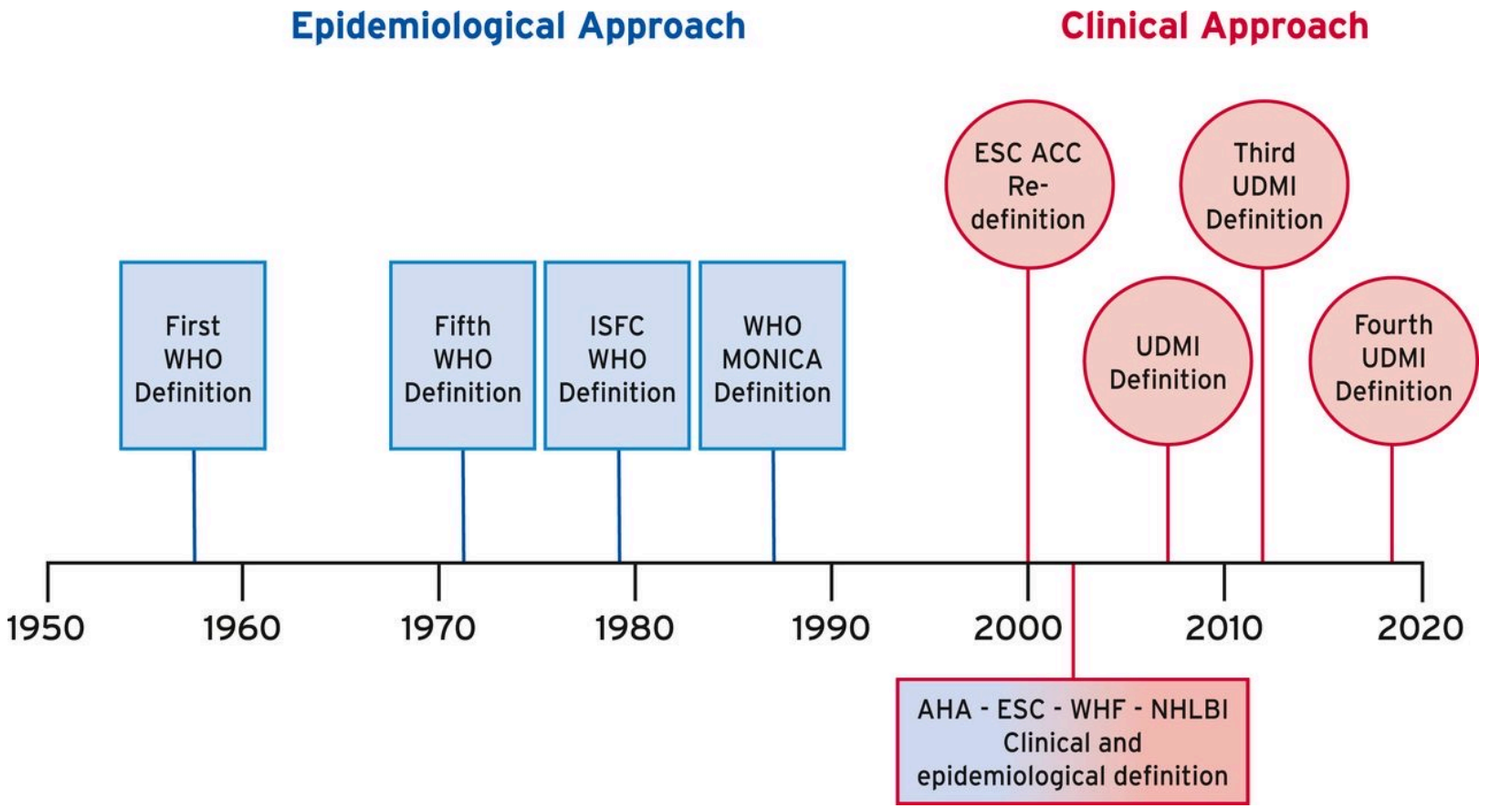
Historical Transition to a Troponin Standard Integrated with a Clinical Approach for Diagnosing MI



LDH, SGOT CPK MB Troponin I and T

Modified from Thygesen et. al., Fourth Universal Definition of Myocardial Infarction (2018)

J Am Coll Cardiol. 2018;72:2231-2264

PUBLISHED BY ELSEVIER

EXPERT CONSENSUS DOCUMENT

Fourth Universal Definition of Myocardial Infarction (2018)

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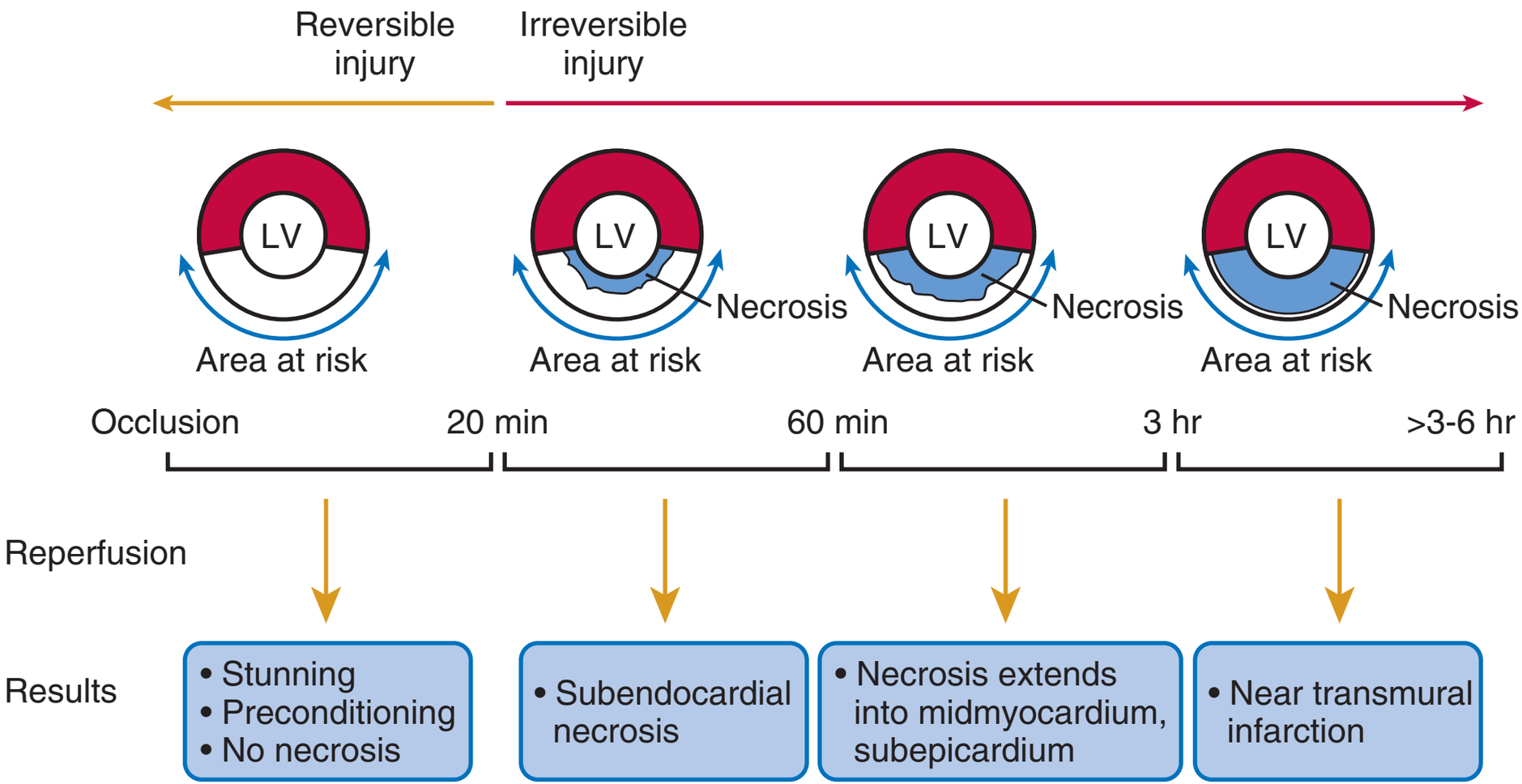
Why Do We Keep Needing to Refine the Definition of Myocardial Infarction?

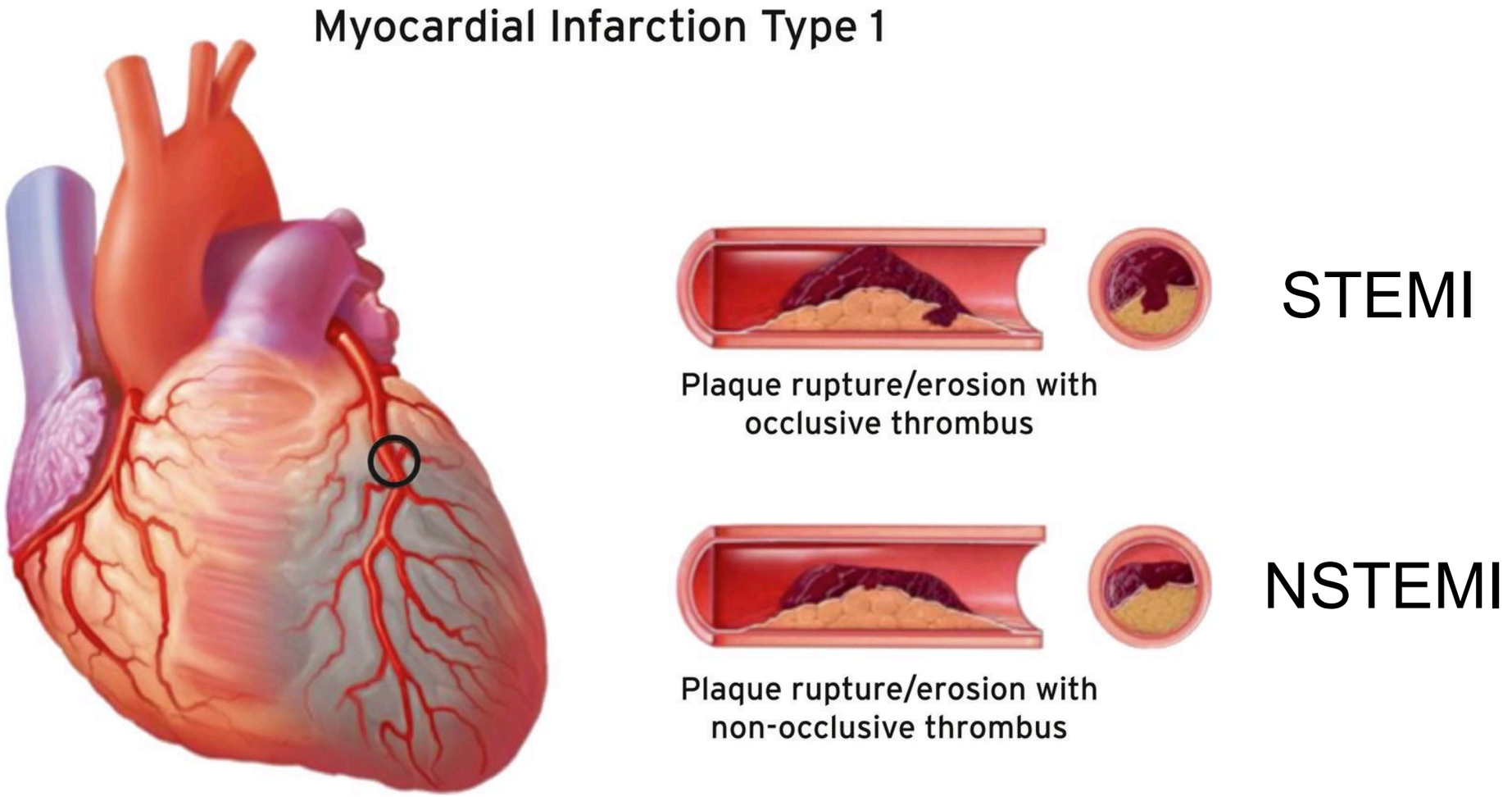
- Increased utilization of TnI testing in low pretest probability settings
  - High sensitivity but declining specificity test for MI when used in isolation
- Increasing frequency of TnI elevations without ACS
  - Nonischemic myocyte injury now accounts for over half of TnI elevations
- New research demonstrating TnI release after stresses not producing pathological evidence of MI
  - Heart failure, exercise testing, marathon runners etc.
  - Brief ischemia compatible with angina and stretch induced myocyte injury
- Evolving understanding of nonischemic myocyte cell death
  - Apoptosis and autophagy can lead to myocyte death and TnI release without pathological infarction
  - ? Normal myocyte turnover

Reversible vs Irreversible Myocardial Ischemia



From Canty and Duncker, Chapter 49 in Braunwald's Heart Disease, 2015

Plaque Rupture with Thrombus Distinguishes Type 1 Myocardial Infarction



Thygesen et. al., Fourth Universal Definition of Myocardial Infarction (2018)

J Am Coll Cardiol. 2018;72:2231-2264

Type 1 Myocardial Infarction

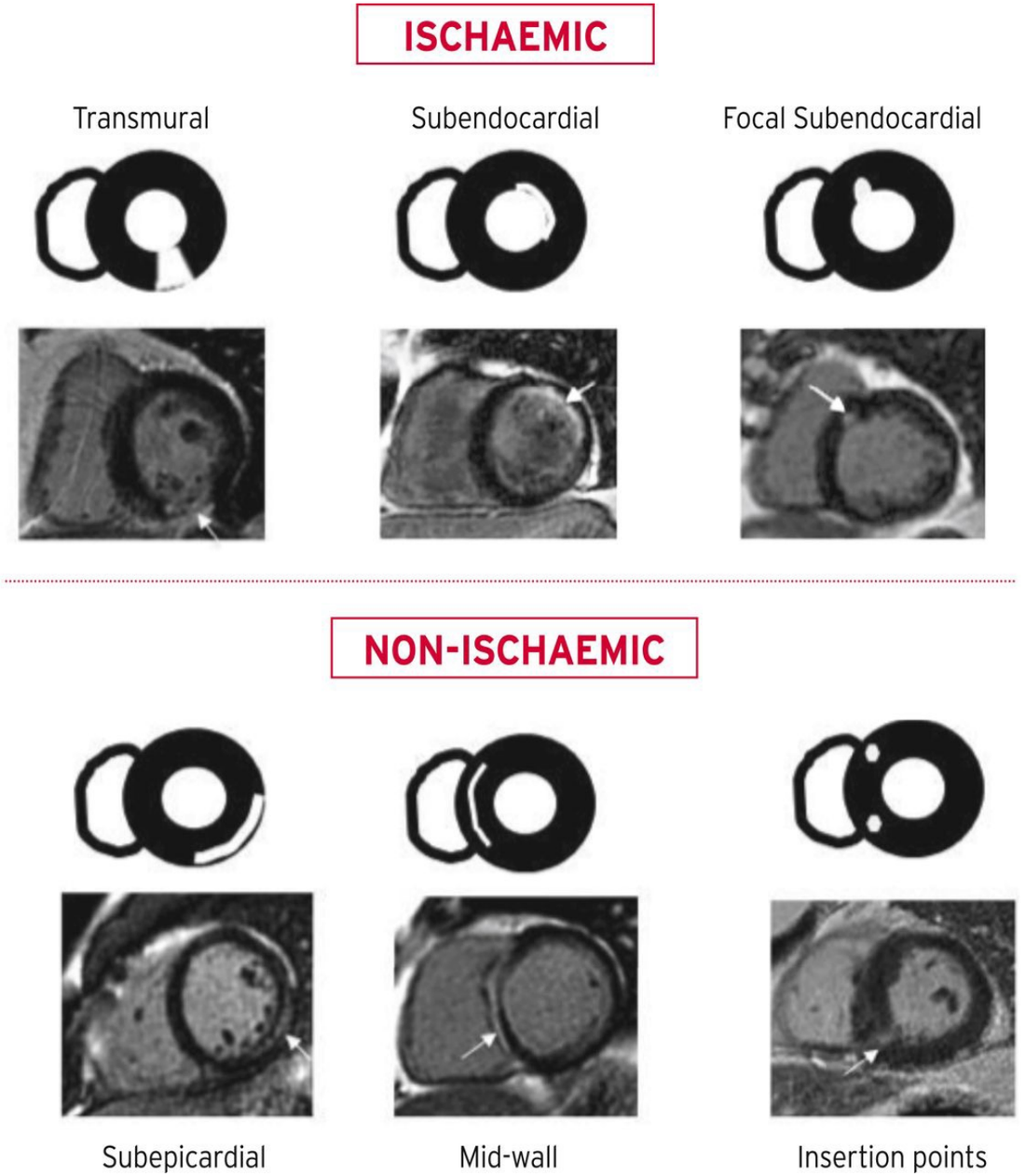
- Usually spontaneous in onset with associated ECG changes such as ST-segment depression or elevation.
- Patients often describe ischemic chest discomfort or an angina equivalent.
- Associated troponin levels tend to be higher than in Type 2 MI, but this is not invariably the case.
- Absence of conditions leading to elevated myocardial oxygen consumption or decreased oxygen carrying capacity
- Plaque rupture, ulceration, fissuring, erosion, or dissection with complex plaque and coronary arterial thrombus often seen during coronary angiography.

Criteria for Type 1 Myocardial Infarction

Detection of a rise and/or fall of cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit (URL) along ***with at least one of the following***:

- ✓ Symptoms of acute myocardial ischemia
- ✓ New ischemic ECG changes
- ✓ Development of pathological Q waves
- ✓ Imaging evidence of new infarction or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- ✓ Identification of a coronary thrombus by angiography or autopsy.

Cardiac MRI Patterns Of Fibrosis



Thygesen et al., J Am Coll Cardiol. 2018;72:2231-2264

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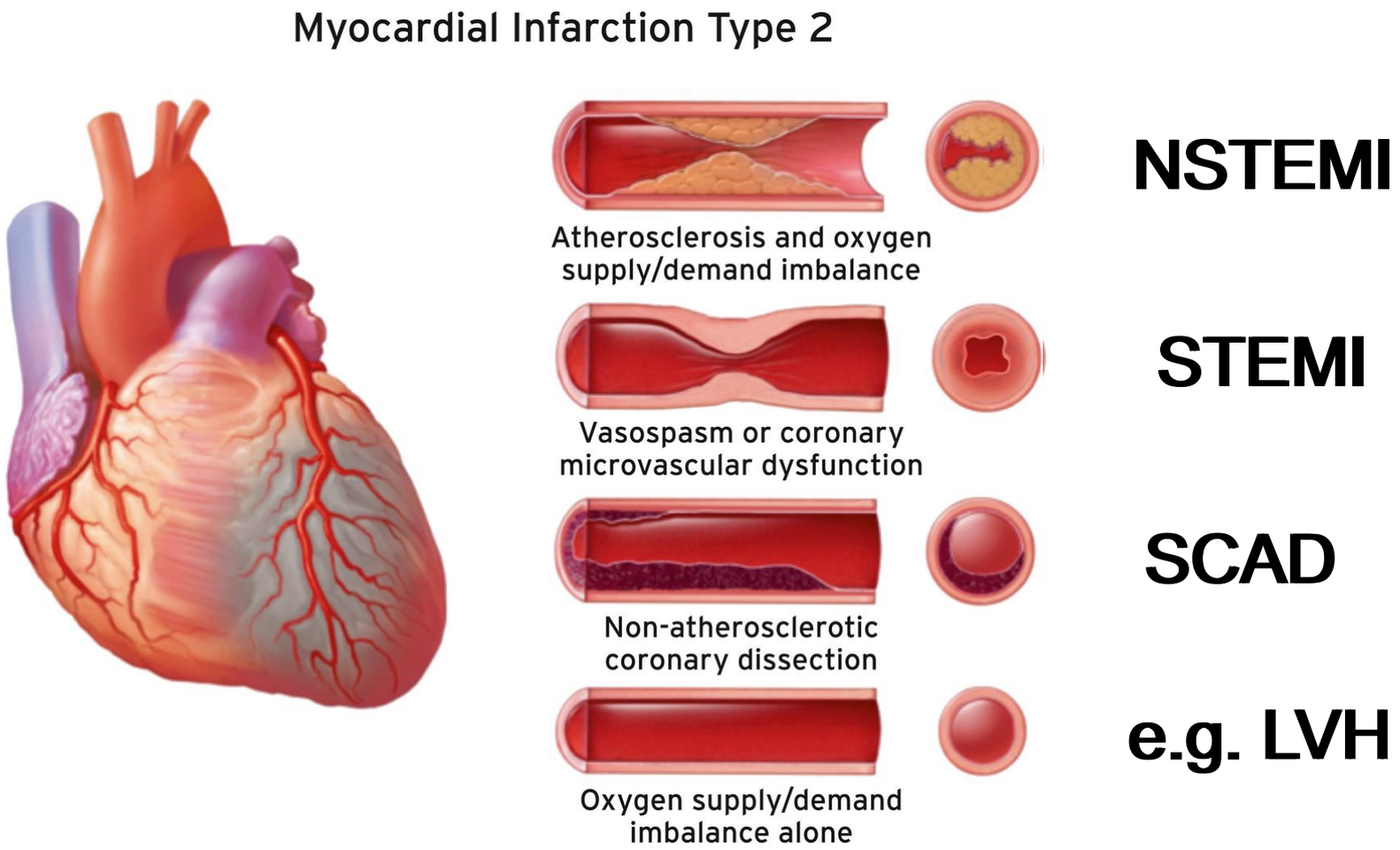
Type 1 Myocardial Infarction – Diagnosis and Treatment Evidence Based and Directed at Reducing Plaque Instability

- Usually an invasive diagnostic strategy employing PCI when anatomy amenable to percutaneous revascularization

  ✓ STEMI – Acute PCI
  ✓ NSTEMI – Semi urgent PCI unless recurrent ischemia or hemodynamic instability

- Low molecular weight (preferred in NSTEMI) or standard unfractionated heparin
- Antiplatelet therapy with aspirin and platelet $P2Y_{12}$ inhibitors
- Anti-ischemic therapy with beta blockers/nitrates
- Hyperlipidemic (and anti-inflammatory) therapy with high intensity statins

Type 2 Myocardial Infarction - Ischemia Developing from an Oxygen Supply-Demand Imbalance in the Absence of an Unstable Coronary Artery Plaque



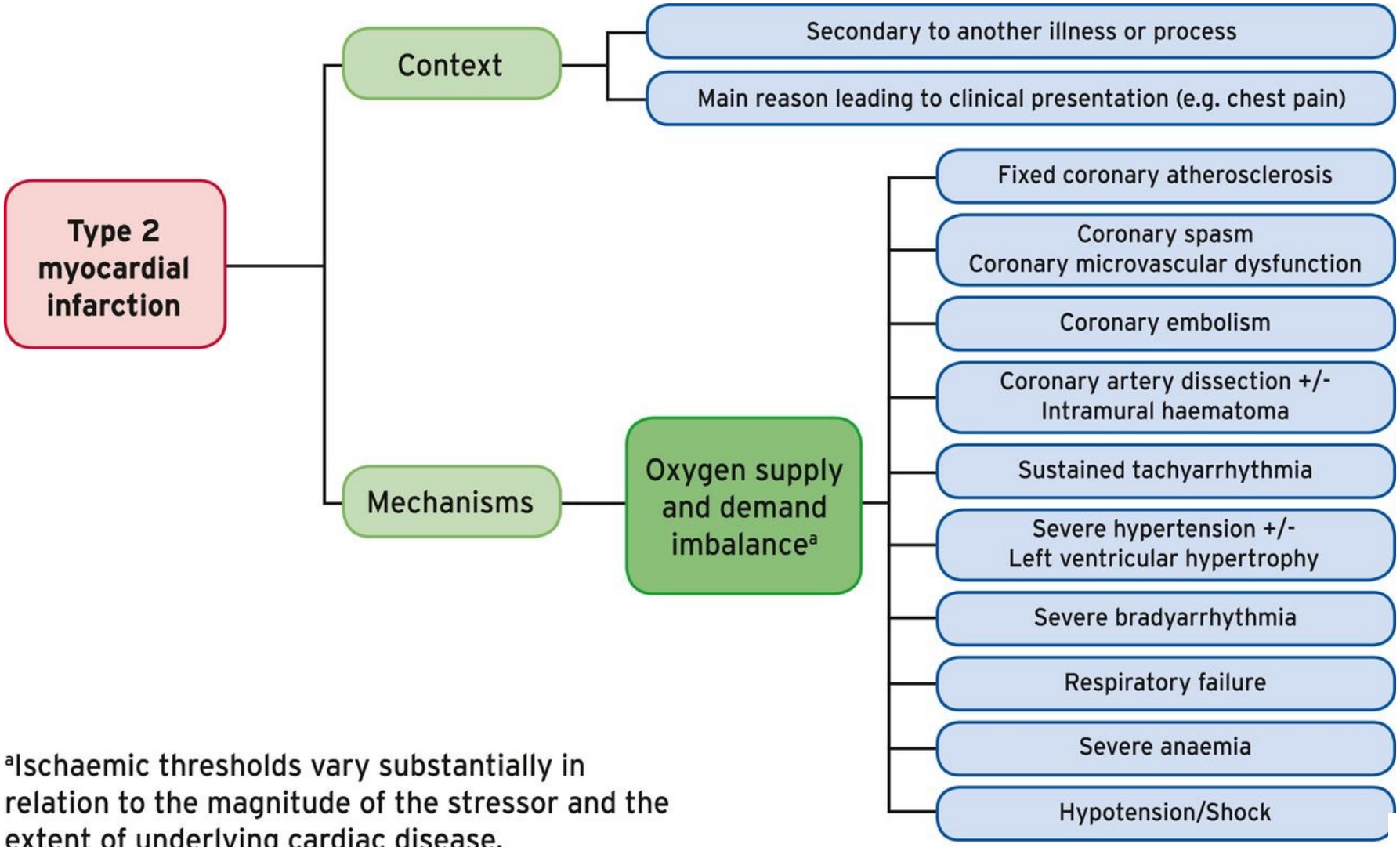
Thygesen et al., J Am Coll Cardiol. 2018;72:2231-2264

Criteria for Type 2 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, **and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis**, ***requiring at least one of the following:***

- ✓Symptoms of acute myocardial ischaemia
- ✓New ischemic ECG changes
- ✓Development of pathological Q waves
- ✓Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

Physiological Factors Underlying Type 2 Myocardial Infarction



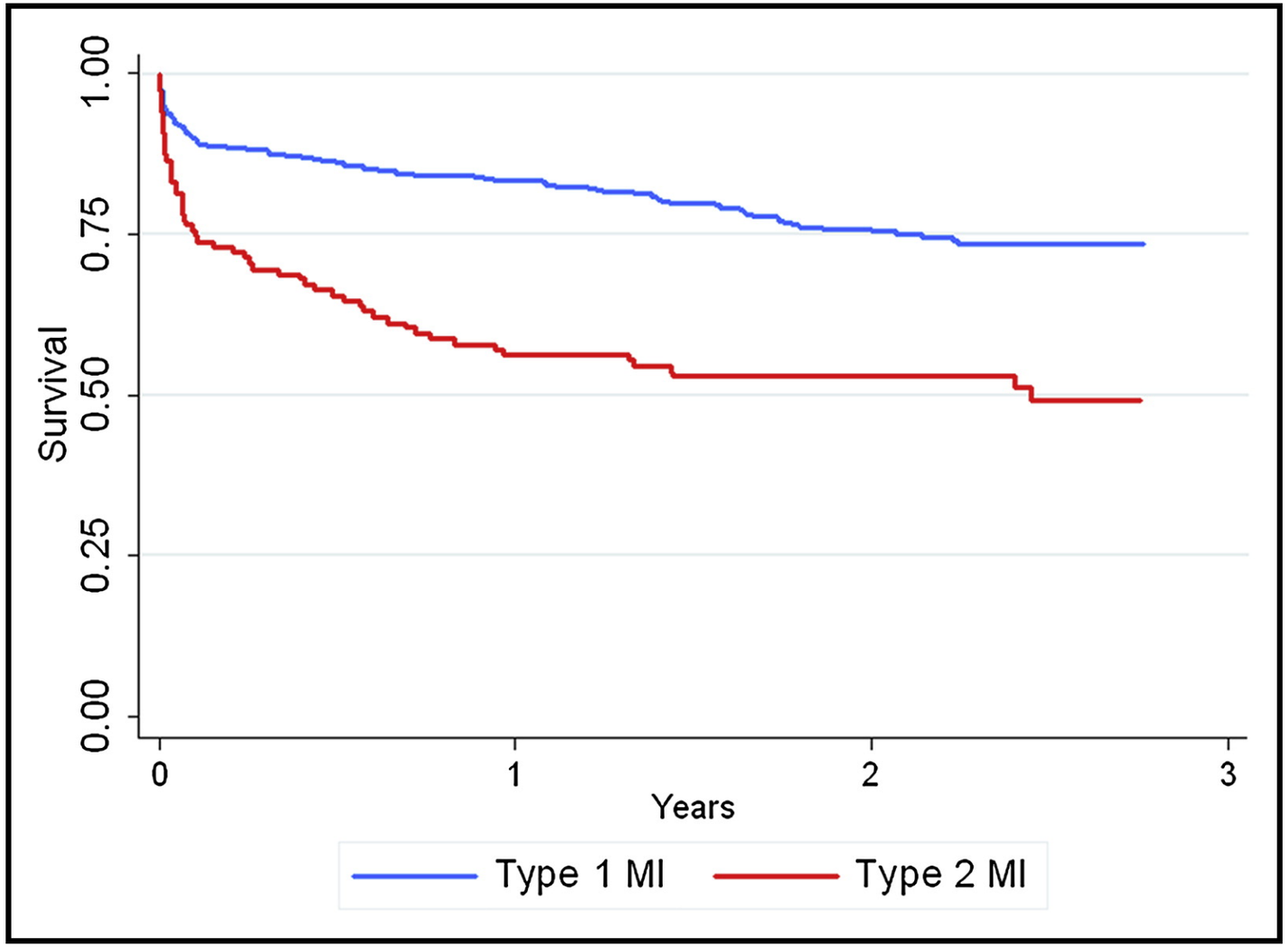
[a]Ischaemic thresholds vary substantially in relation to the magnitude of the stressor and the extent of underlying cardiac disease.

Thygesen et al., J Am Coll Cardiol. 2018;72:2231-2264

Type 2 Myocardial Infarction

- Usually associated with conditions that lead to elevated myocardial oxygen demand (e.g. tachycardia, hypertension) or decreased subendocardial oxygen delivery (e.g. anemia, hypotension, tachycardia, elevated preload)
- Transient ST depression is diagnostic, but ECG changes may be absent or non-specific.
- Associated blood troponin levels are usually elevated to values less than seen in ST elevation infarction.
- Ischemic chest discomfort or equivalent may be absent due to multiple underlying comorbid conditions.
- Angiography does not commonly demonstrate plaque rupture or associated thrombus.

Mortality of Type 2 vs Type 1 Myocardial Infarction in Denmark



Saaby et al. Am J Medicine, 127: 2014,p 295–302

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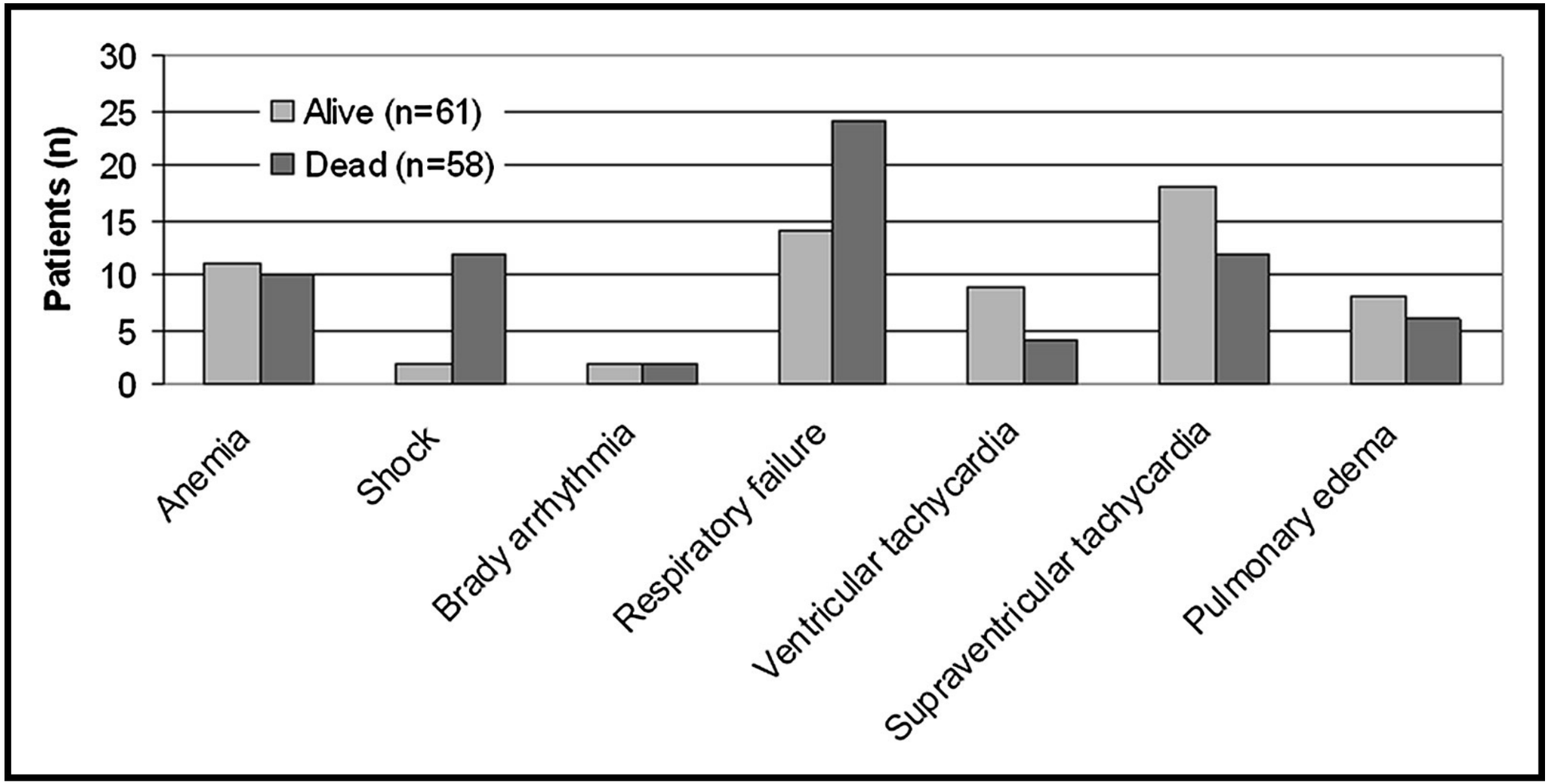
Survival Following Type 2 MI is Largely Related to the Underlying Triggering Condition



Saaby et al. Am J Medicine, 127: 2014,p 295–302

Type 2 Myocardial Infarction – Diagnosis and Treatment is Not Currently Evidence Based - *This is what I do*

- Therapy primarily directed at reversing the underlying condition precipitating the Type 2 MI
- No clear indication for acute antithrombotic therapy
- Control hypertension and tachycardia (particularly using beta blockers)
- Optimize O_2 carrying capacity when a significant reduction in Hgb precipitated the event or hypoxemia is present
- Lower preload while optimizing arterial pressure (CHF, shock)
- Elective evaluation for CAD when underlying medical problems are not life limiting. (Frequently using a physiologically based noninvasive strategy).

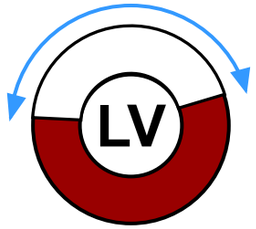
Remaining Questions

- Does troponin release always reflect myocyte necrosis with the subsequent development of a fibrotic scar?
- Is Troponin released after brief ischemia compatible with angina?

Is Brief “Reversible” Ischemia and Stunned Myocardium Accompanied by Myocyte Injury?

Reversible Ischemia – “Angina”

Area at risk



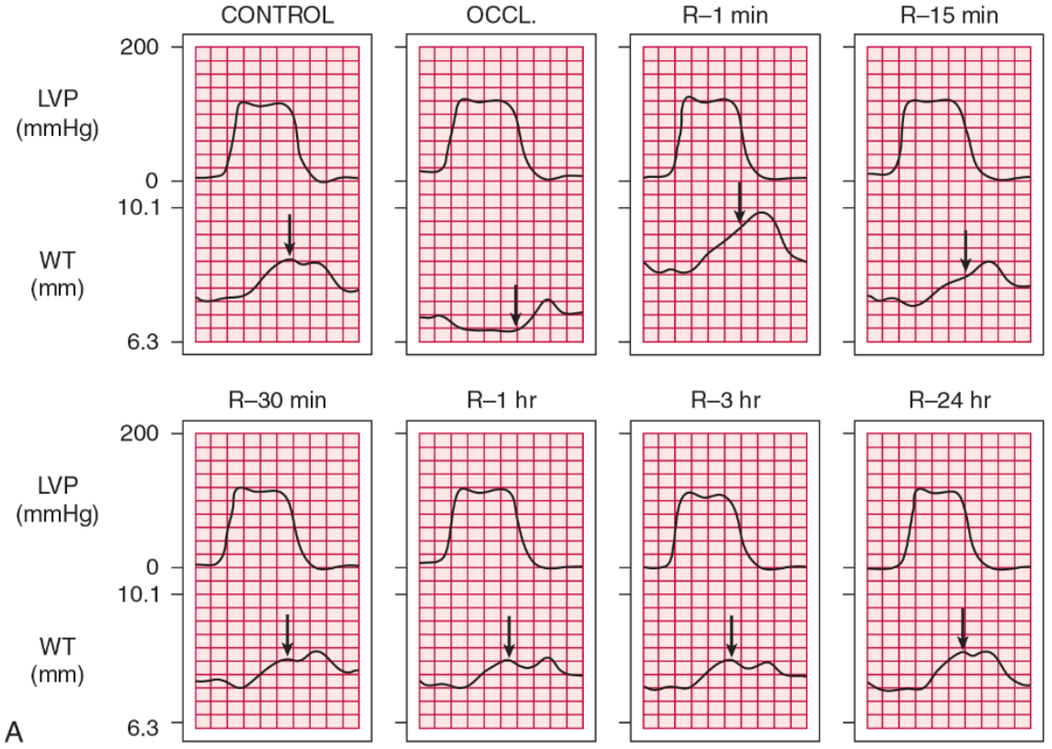
Occlusion **10 minutes**

Reperfusion

Results

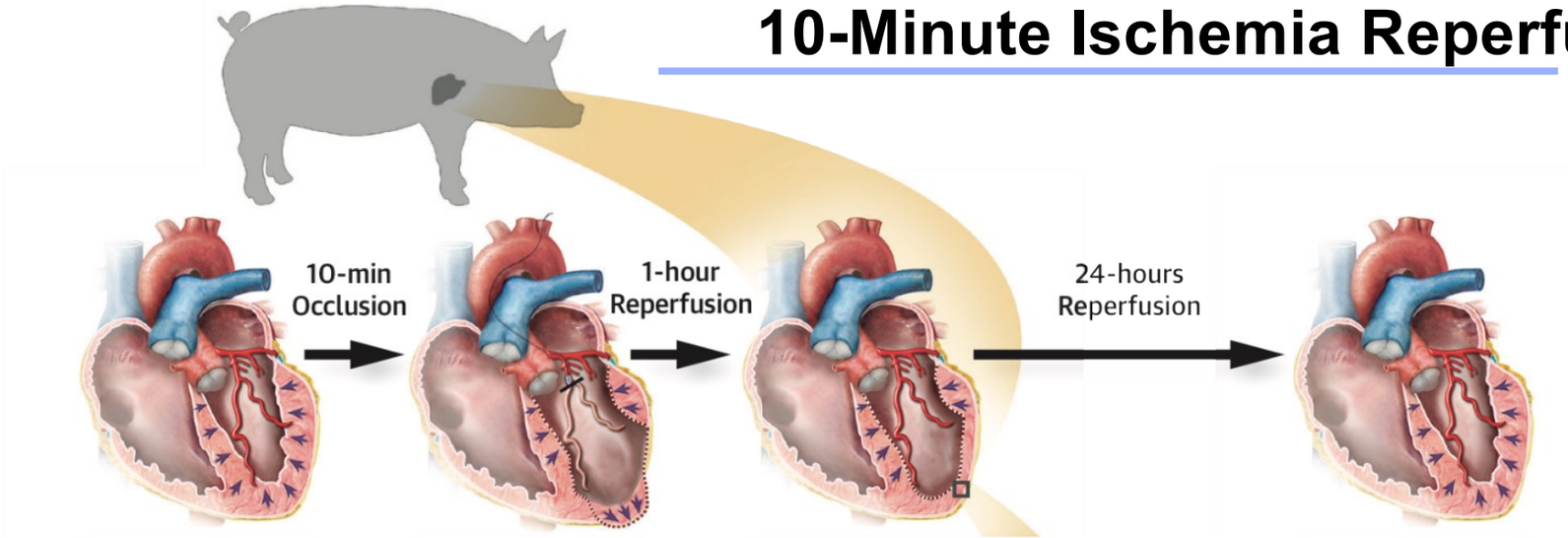
- **Reversible Stunning**
- **No necrosis**
- **No fibrosis**

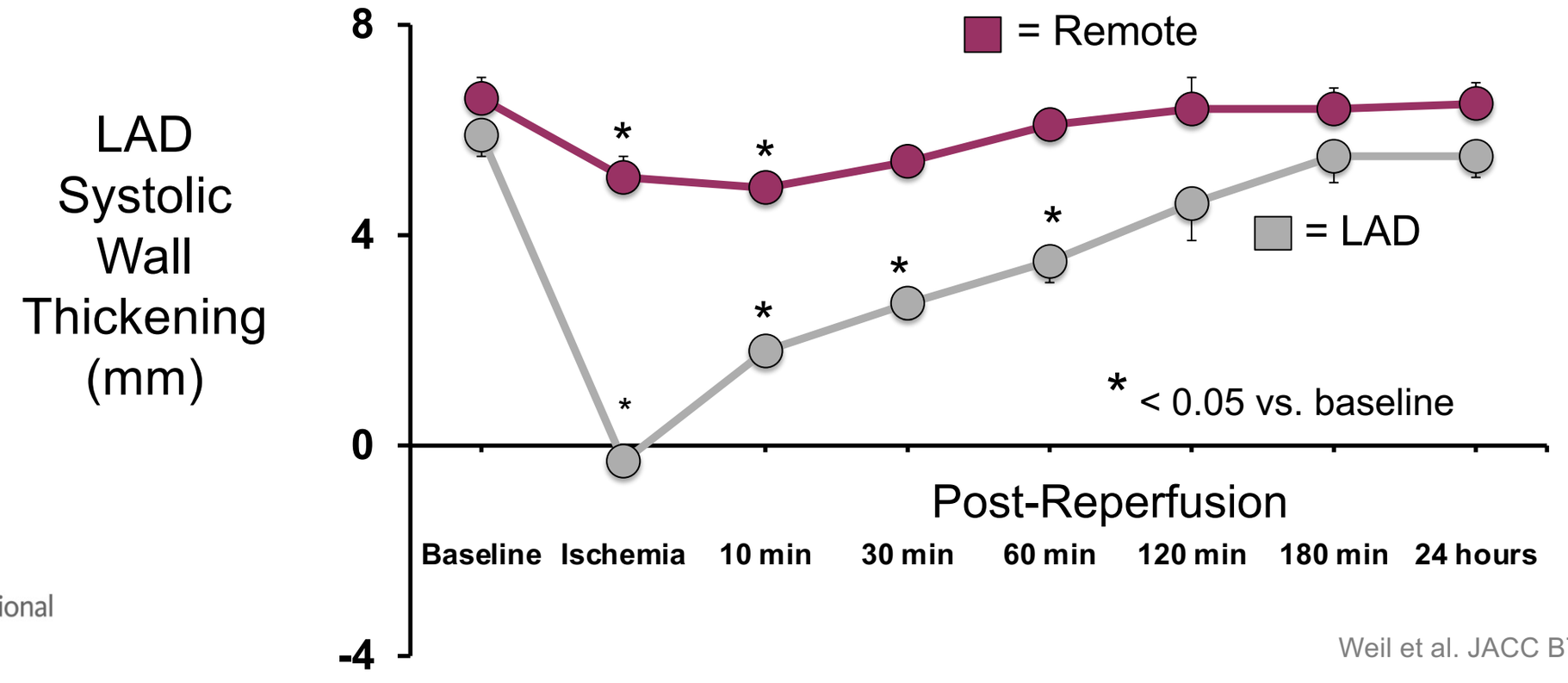
Dyskinesis



Adapted From Heyndricks et al. Am J Physiology 1978, 234 H653

10-Minute Ischemia Reperfusion





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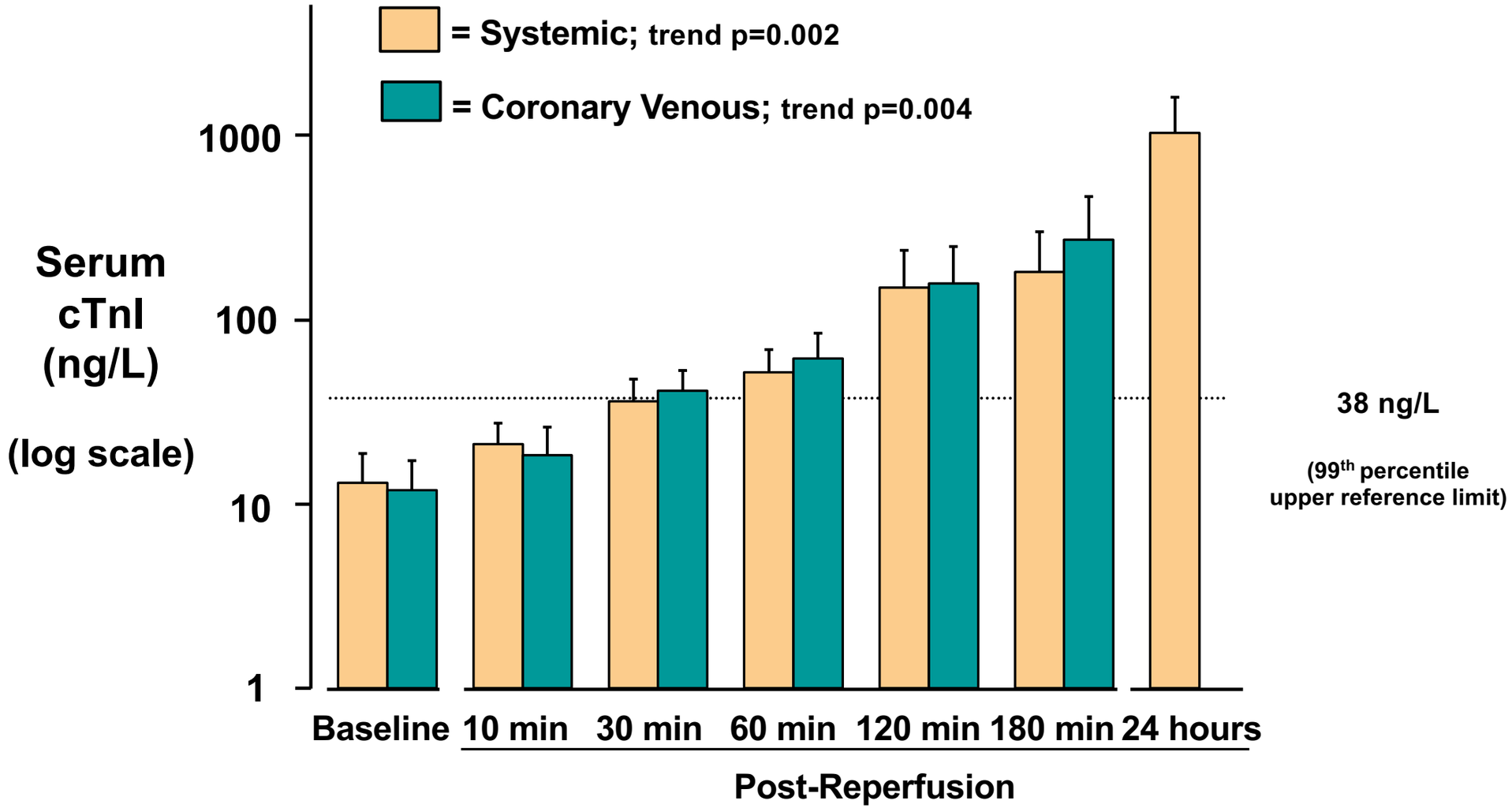
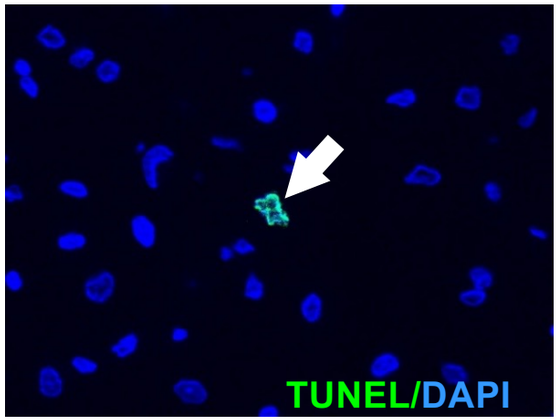
Weil et al. JACC BTS, 2017; 2: 105-114

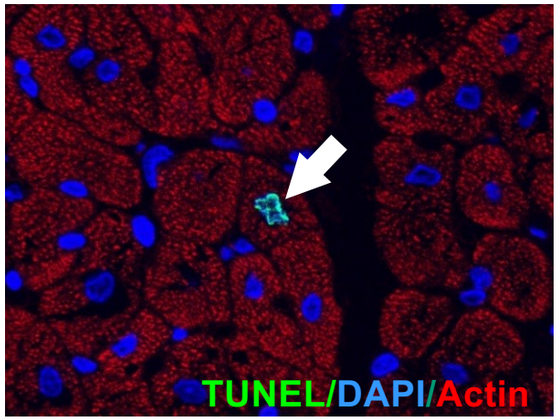
Troponin I is Released After “Reversible” Ischemic Injury

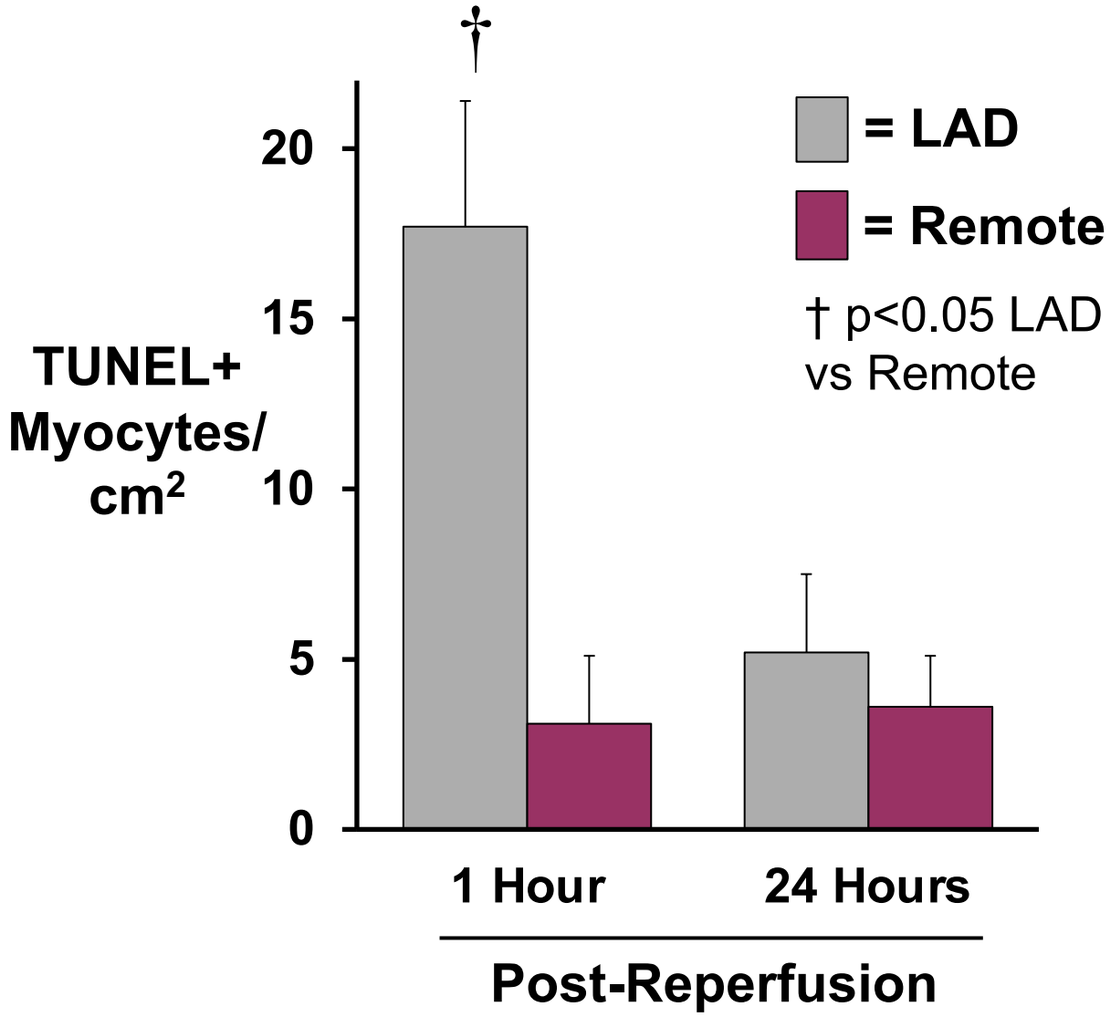


Weil et al. JACC BTS, 2017; 2: 105-114

“Reversible” Myocardial Ischemia is Associated with a Transient Increase in Cardiomyocyte Apoptosis







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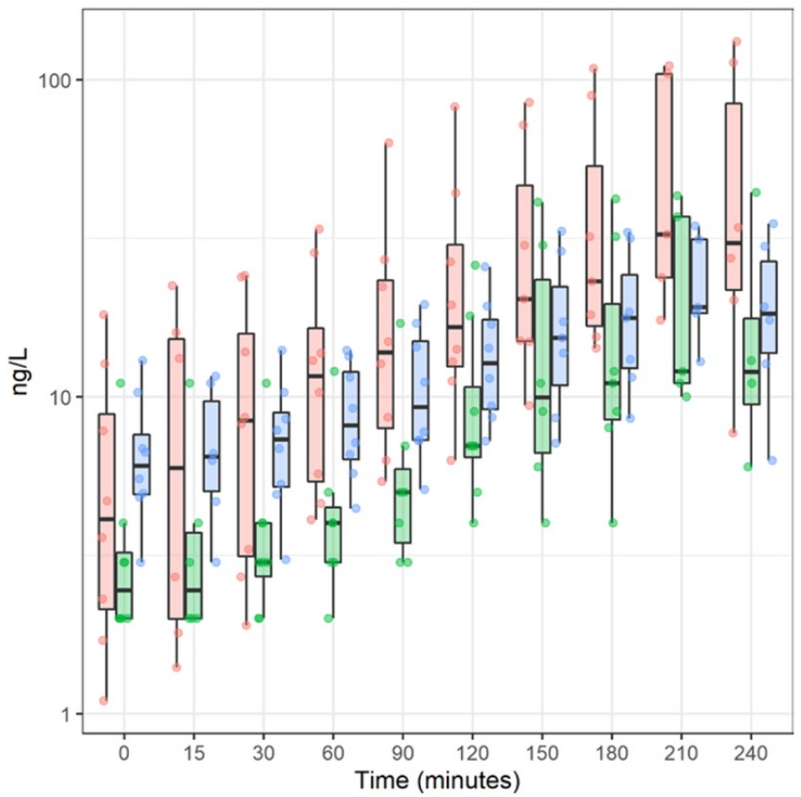
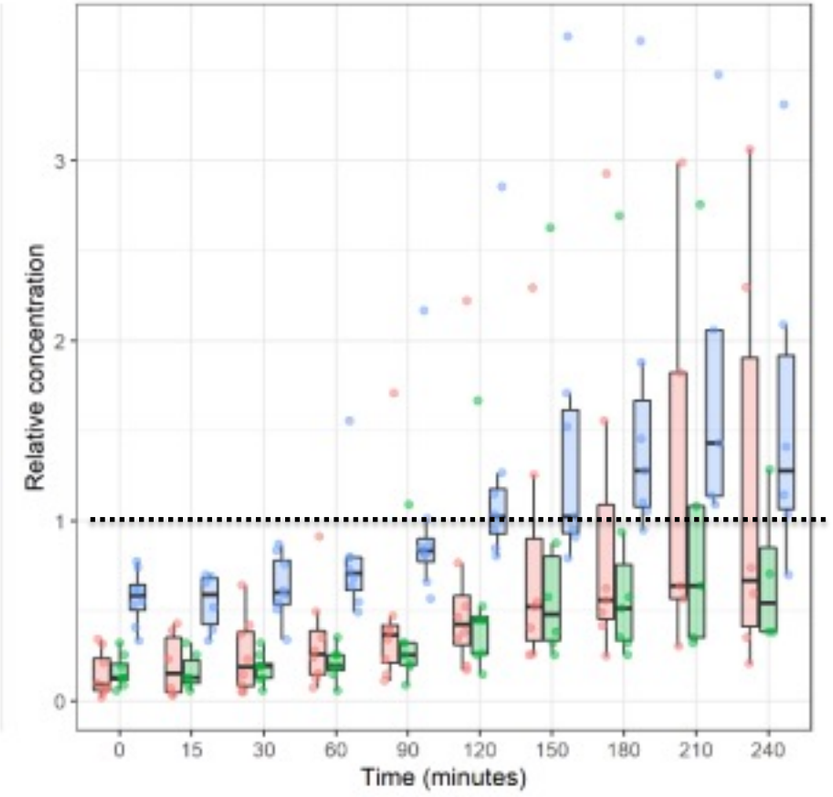
Weil et al. JACC BTS, 2017; 2: 105-114

Troponin Release Occurs after a 90 Second LAD Occlusion in Patients Without CAD

Absolute Troponin



Troponin relative to 99th percentile URL



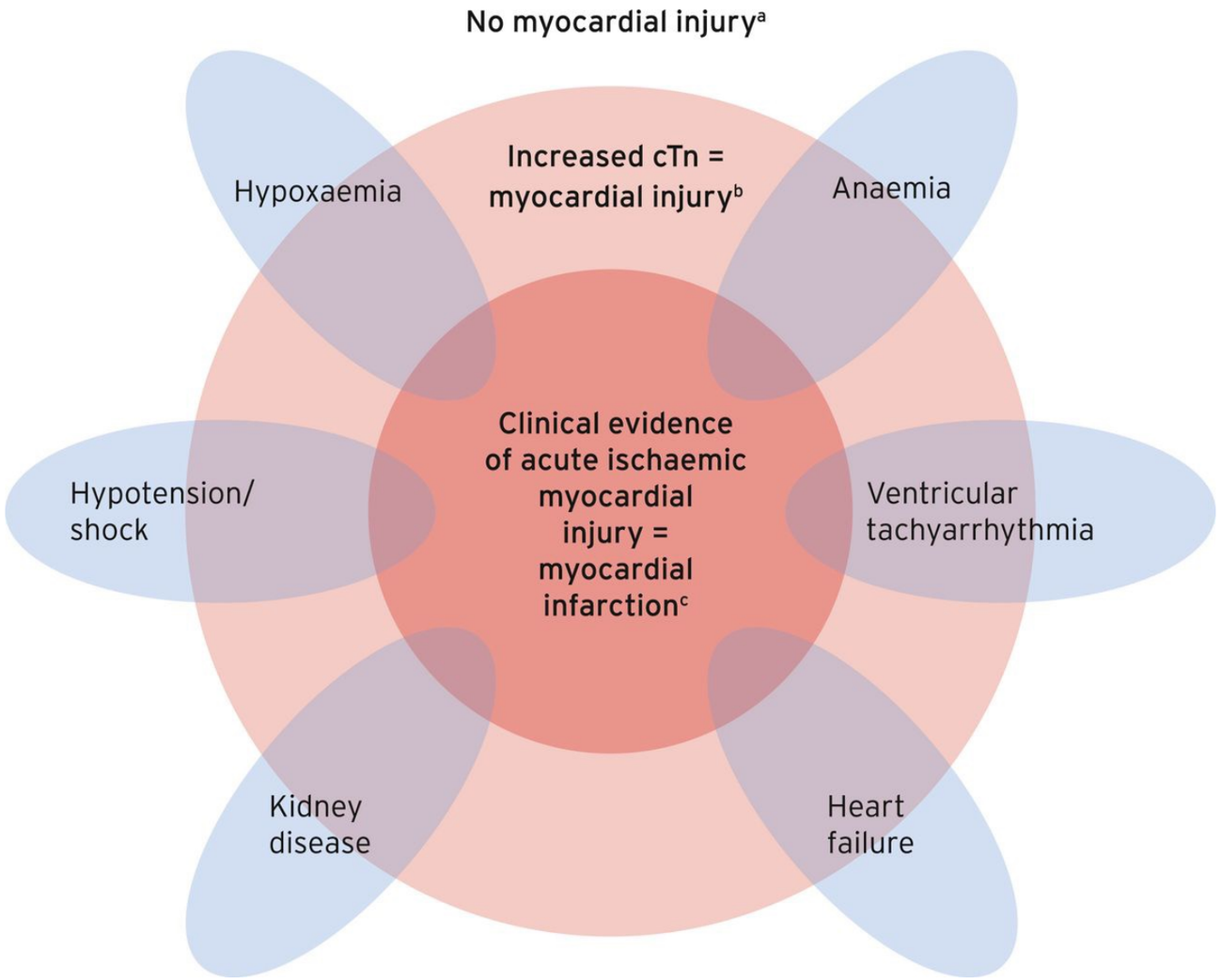
Blue – hs cTnT
Red – hs cTnI (Siemens)
Green – hs cTnI (Abbott)

99th percentile upper reference limit

Time after occlusion

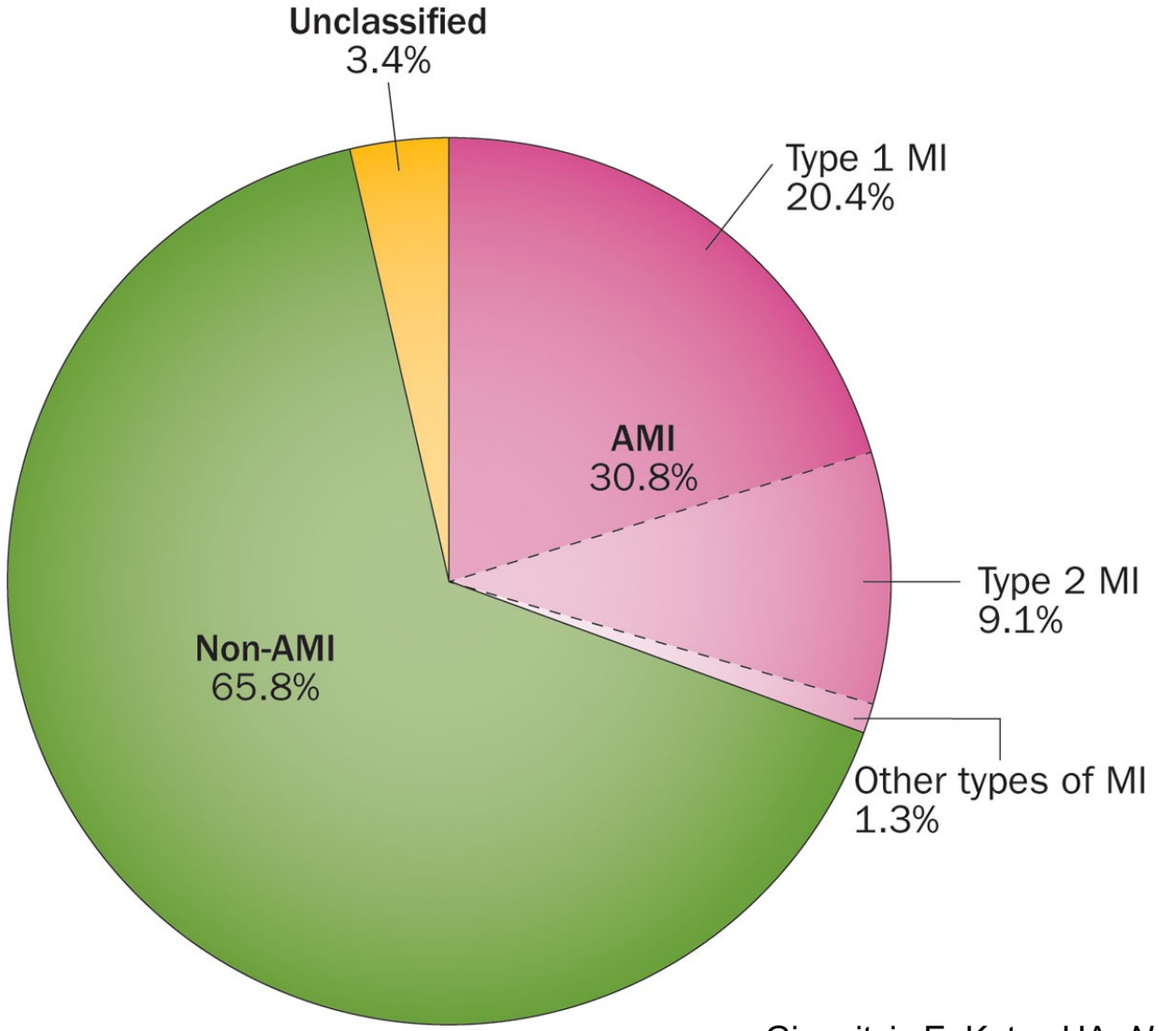
Adapted from Arnadottir et al. Circulation. 2021;143:1095–1104

Troponin I Release From Myocardial Injury



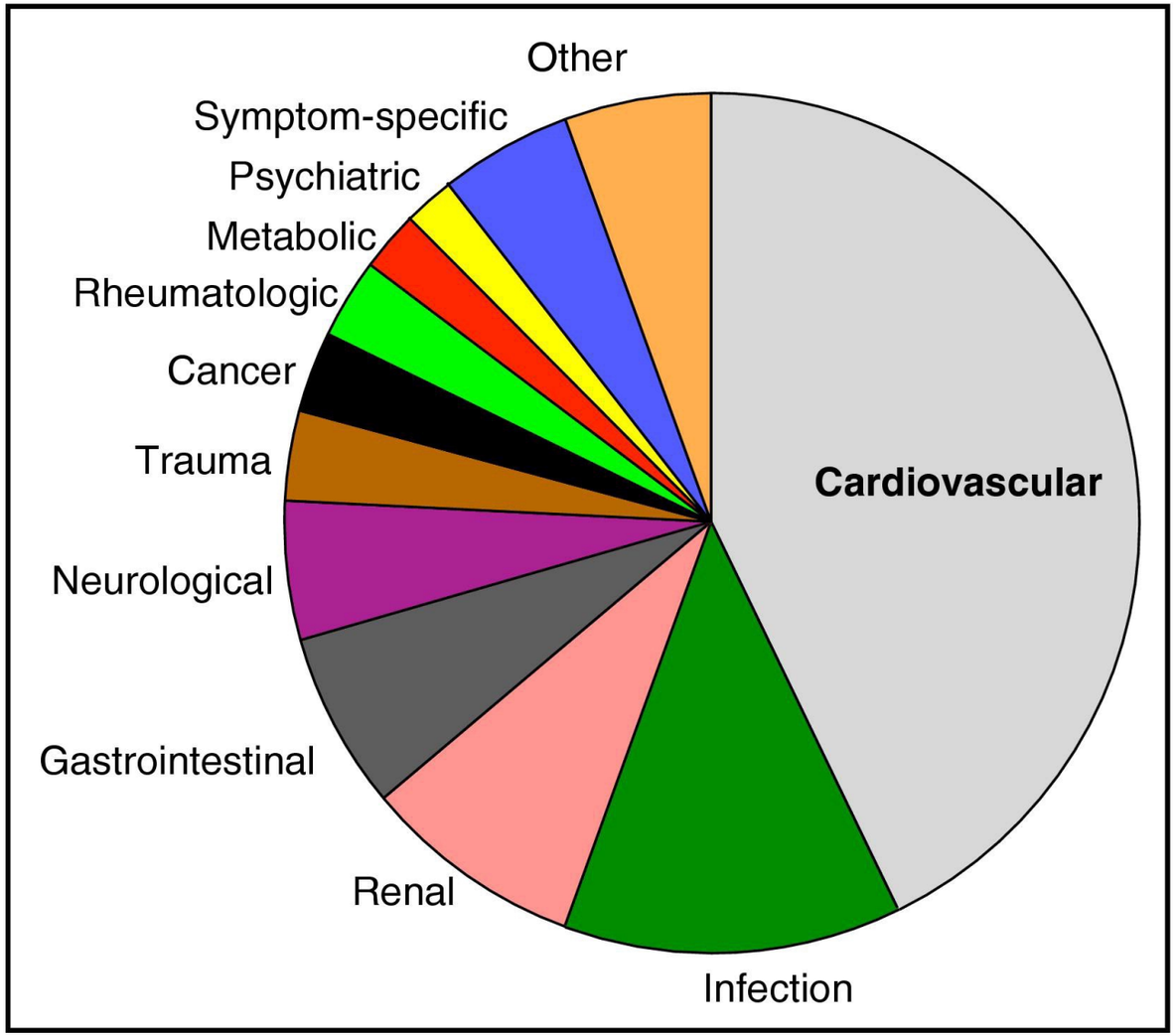
Thygesen et al., J Am Coll Cardiol. 2018;72:2231-2264

Most cTnI elevations among patients admitted to an emergency department over a 3-month period are not due to an acute myocardial infarction



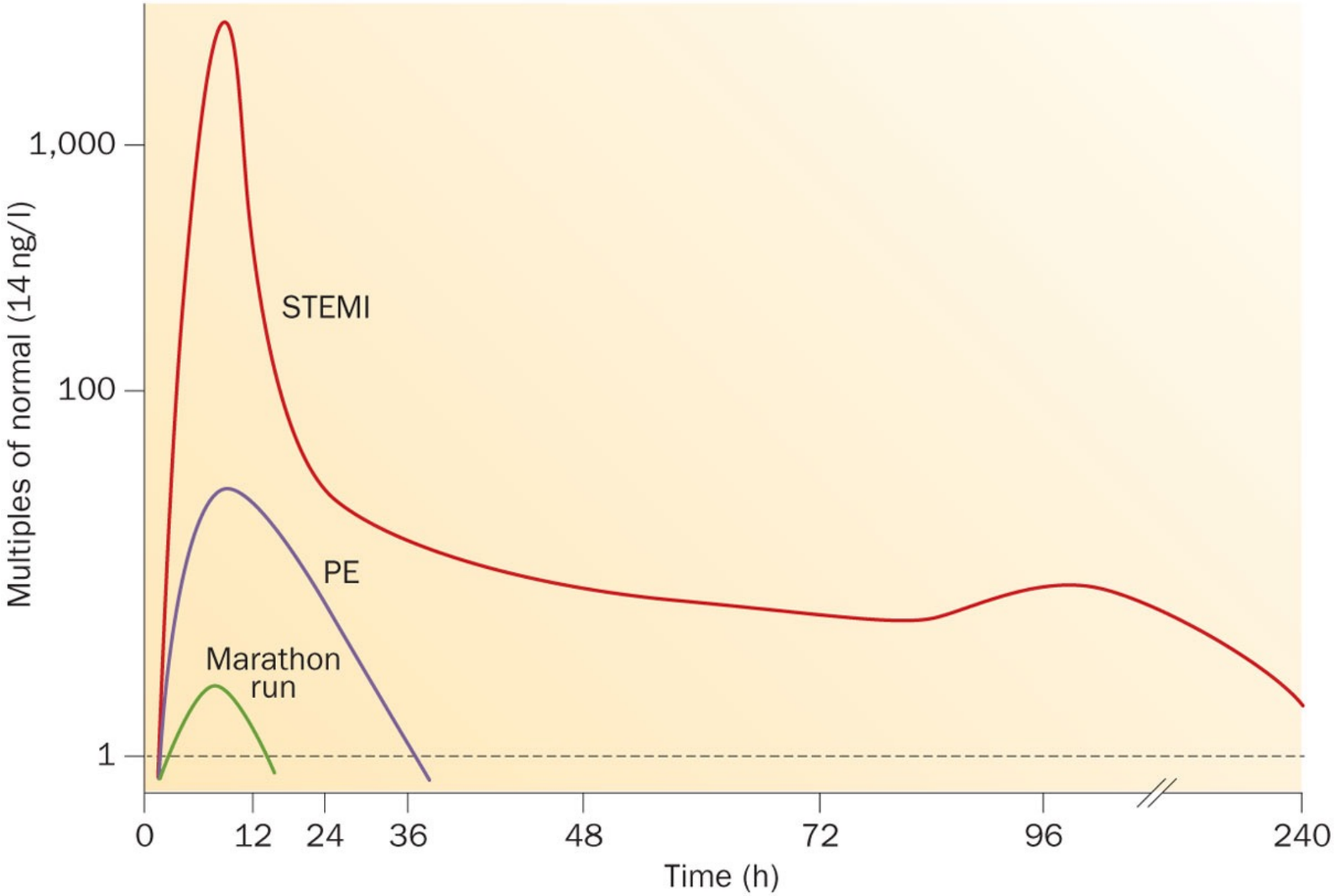
Giannitsis E, Katus HA. *Nat. Rev. Cardiol.* 10:623, 2013

Underlying Diseases and Conditions in Patients with Myocardial Injury and a non ACS TnI Elevation



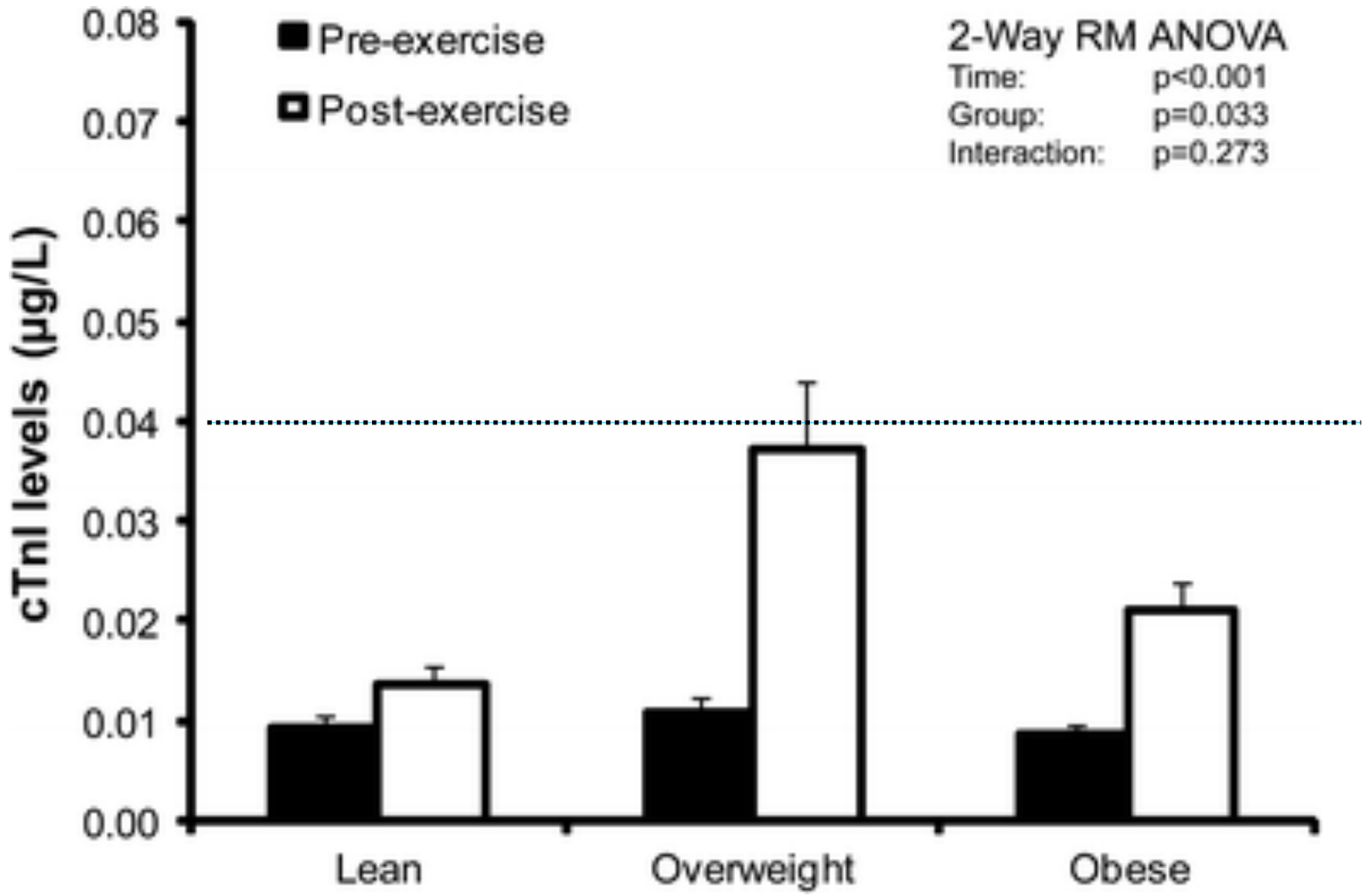
McFalls et al. Am J Med, 2011, p 630–635

Release of cTnT after reperfused STEMI, after acute pulmonary embolism, and after a marathon run – All have a rise and fall !



Giannitsis E, Katus HA. *Nat. Rev. Cardiol.* 10:623, 2013

Transient hs-TnI Release after a 30 to 50 km Walk



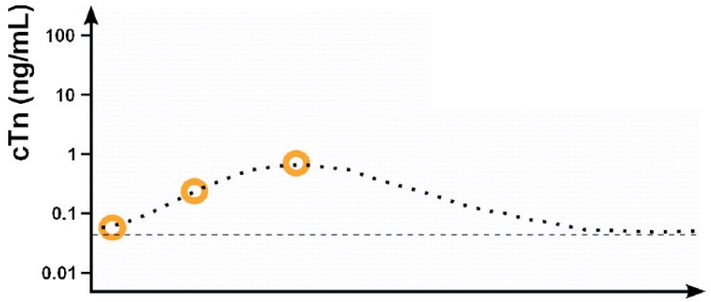
Eijsvogels et al. Eur J Appl Physiol, 2012;112:1725-32

Criteria for Myocardial Injury

Detection of an increase of cTn values with at least one value above the 99th percentile upper reference limit (URL) of normal (for the specific assay used) indicates myocardial injury.

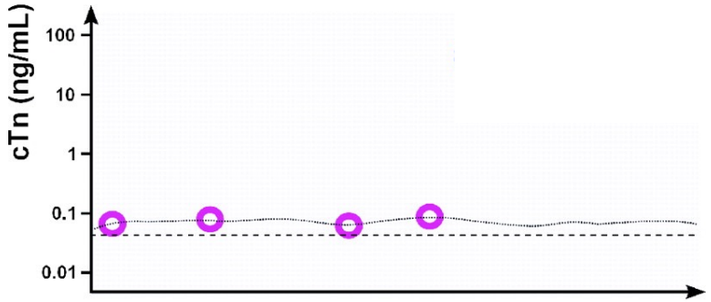
Patterns of Troponin I Release Do Not Always Distinguish Myocardial Injury from Infarction

Myocarditis



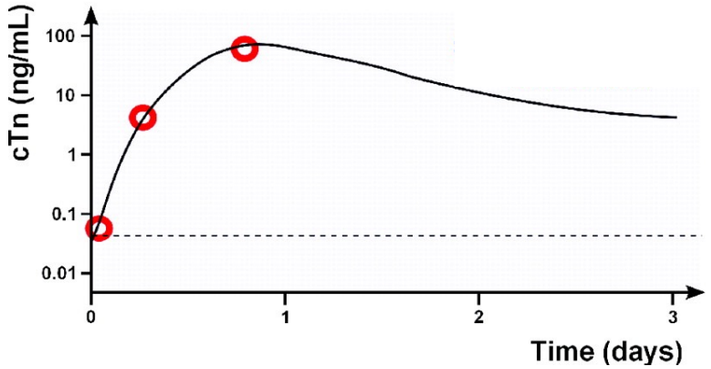
Acute Myocardial Injury

Heart Failure



Chronic Myocardial Injury

Myocardial Infarction



Infarction

Adapted from Mahajan et al, Circulation. 2011;124:2350-2354

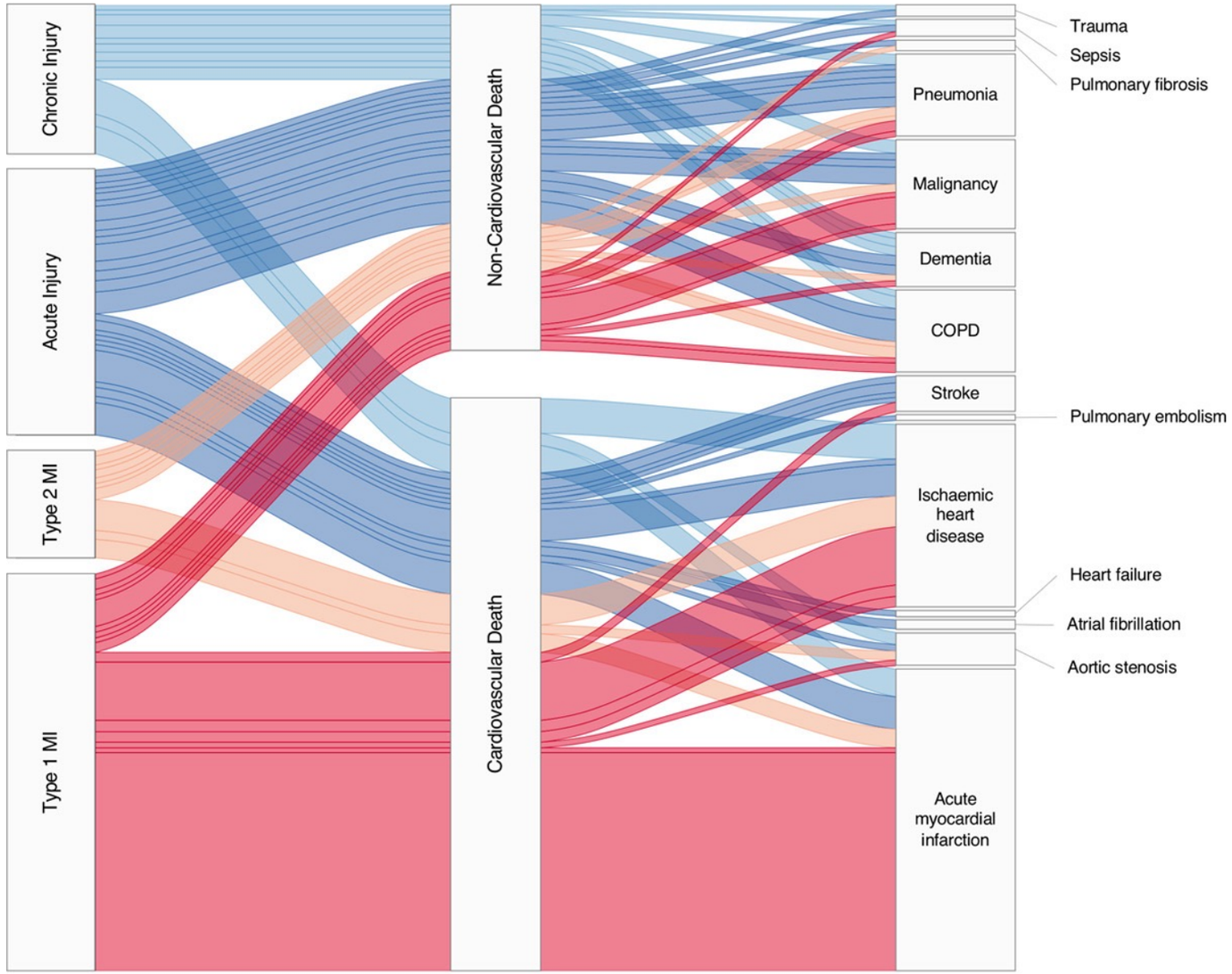
Nonischemic myocardial injury indicates myocyte cell death

- Usually occurs in patients with critical illness (e.g. sepsis, respiratory failure) or in patients with chronic conditions associated with low grade on-going myocardial injury (e.g. severe heart failure, renal failure, chemotherapy)
- ECG changes are often minimal, absent or non-specific
- Blood troponin levels often minimally elevated and frequently do not demonstrate a prominent rise and fall pattern
- Ischemic chest discomfort or equivalent is absent
- Angiography if performed may not demonstrate significant underlying coronary artery disease

Alluvial Plot of Cause Specific Mortality from Myocardial Injury vs. Type 1 and Type 2 MI

4th UDMI in 48,282 Consecutive Patients

High-STEACS Investigators



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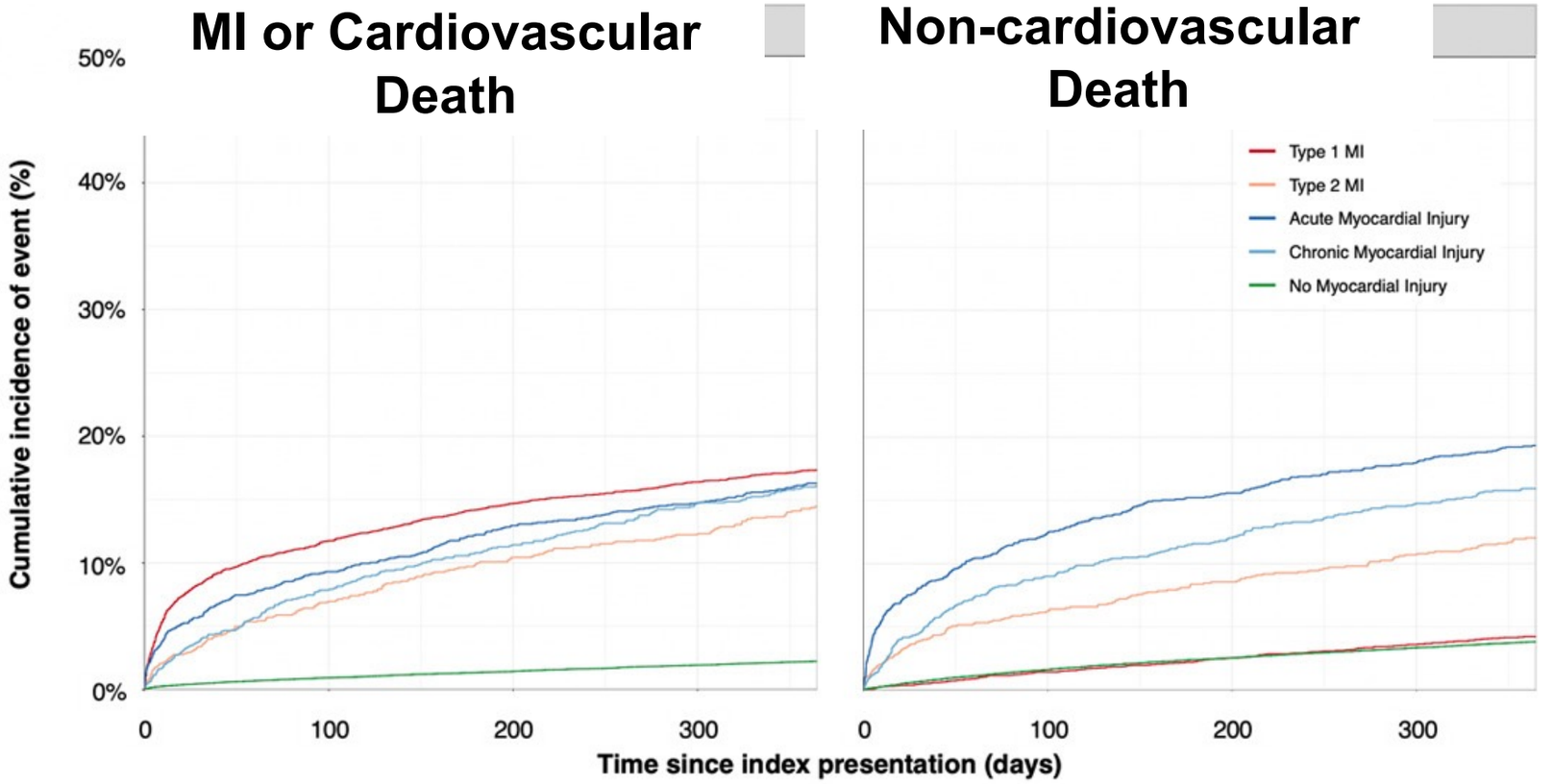
Chapman et al. Circulation. 2020;141:161–171

Troponin I Elevation (>99th URL) from Myocardial Injury and Type 2 MI Are Associated with Increased Cardiovascular and Non-cardiovascular Death

4th UDMI in 48,282 consecutive patients with suspected ACS (9115 with TnI elevation)

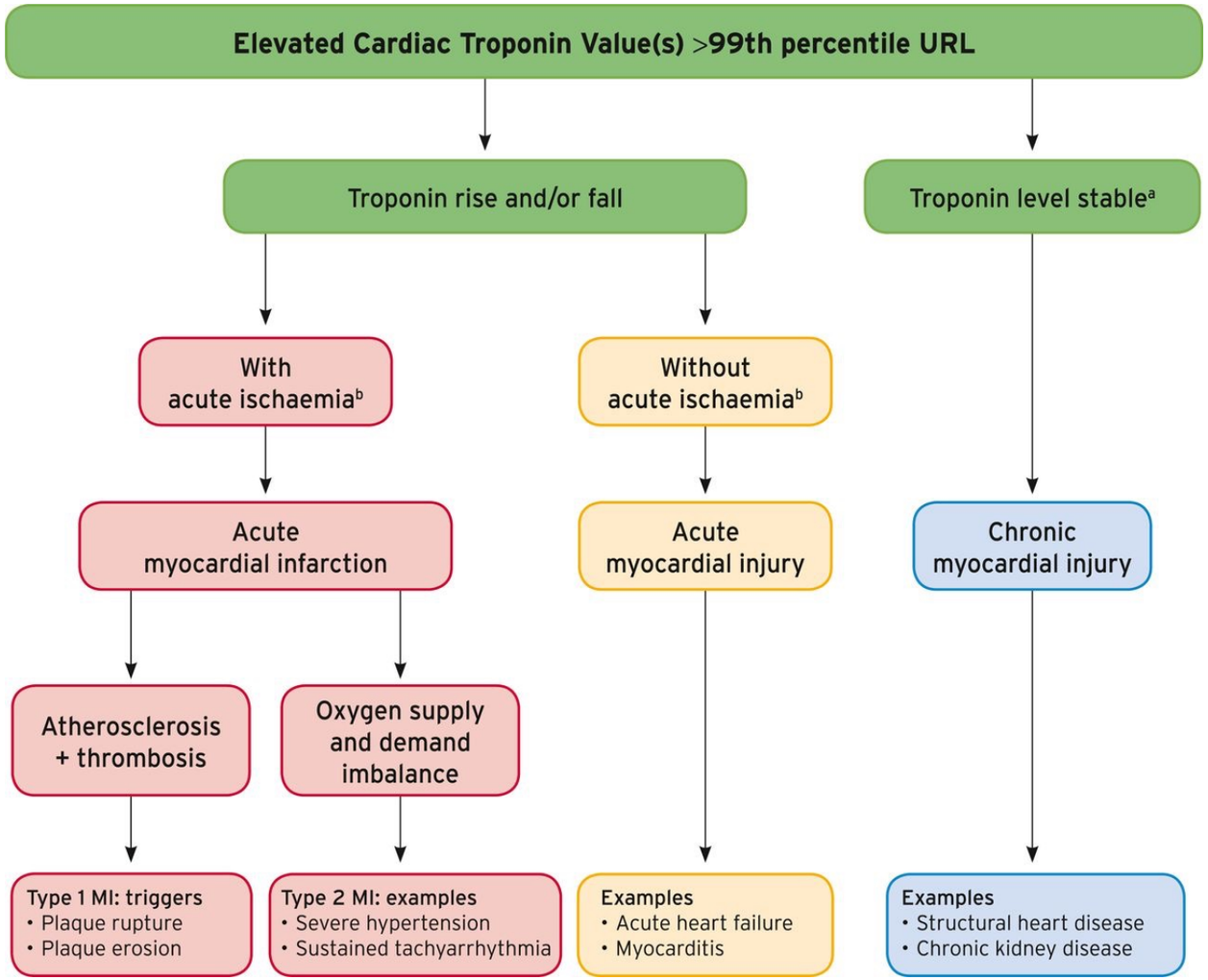
High-STEACS trial



Type 1 MI	4981	4397	4250	4165	4981	4576	4432	4322
Type 2 MI	1121	1044	1004	984	1121	993	938	897
Acute Myocardial Injury	1676	1520	1459	1429	1676	1328	1224	1158
Chronic Myocardial Injury	1287	1186	1141	1098	1287	1087	1011	944
No Myocardial Injury	37922	37569	37381	37190	37922	37084	36613	36186

Chapman et al. Circulation. 2020;141:161–171

How Do We Differentiate Acute and Chronic Myocardial Injury from Type 1 and Type 2 Myocardial Infarction?



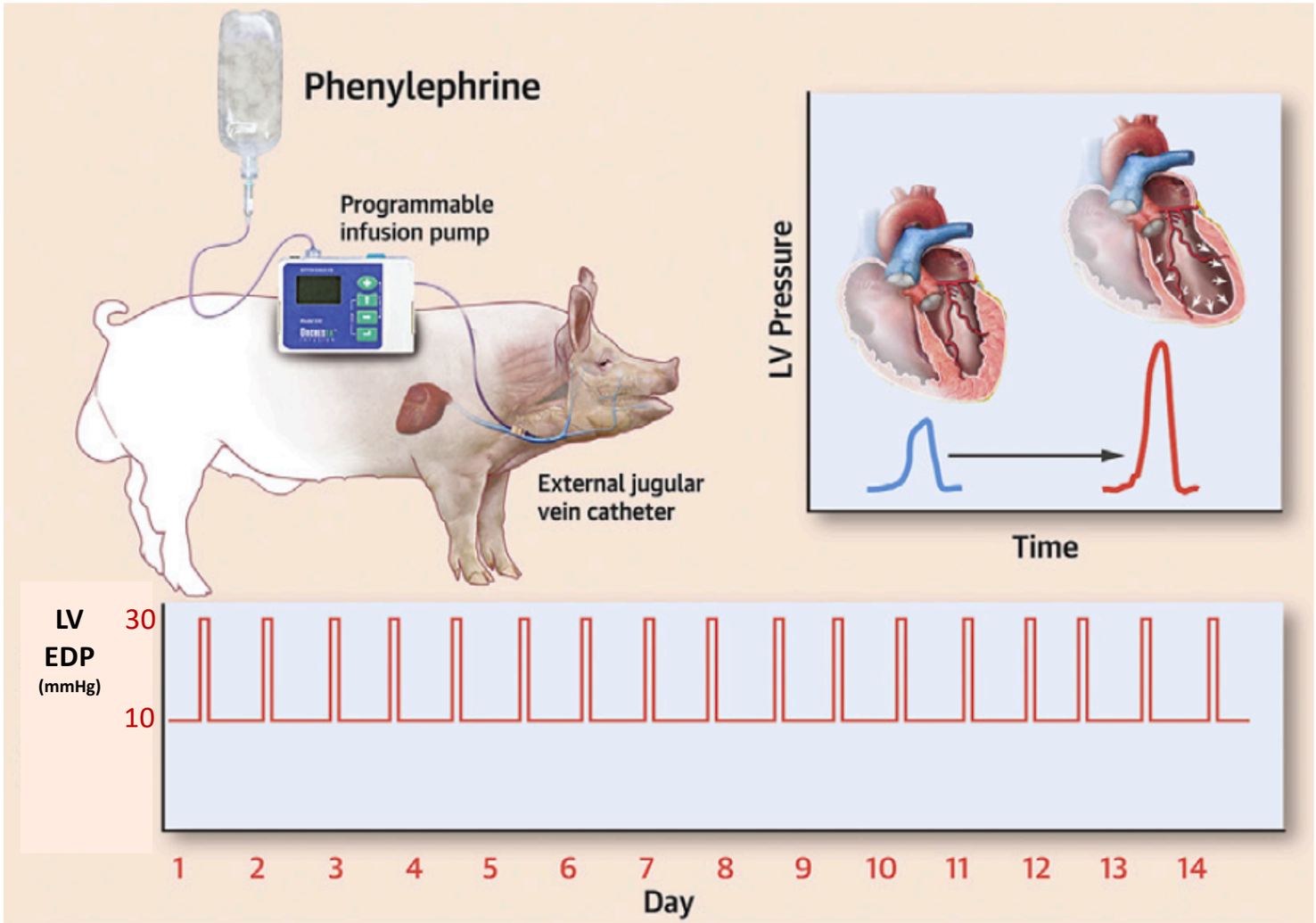
Thygesen et al. J Am Coll Cardiol. 2018;72:2231-2264

Myocardial Injury and TnI Elevations Often Occur in States Associated with Elevated Preload

- Congestive heart failure – ischemic and nonischemic
- Renal failure – acute as well as on chronic dialysis
- ICU – after fluid resuscitation for sepsis, trauma, burns

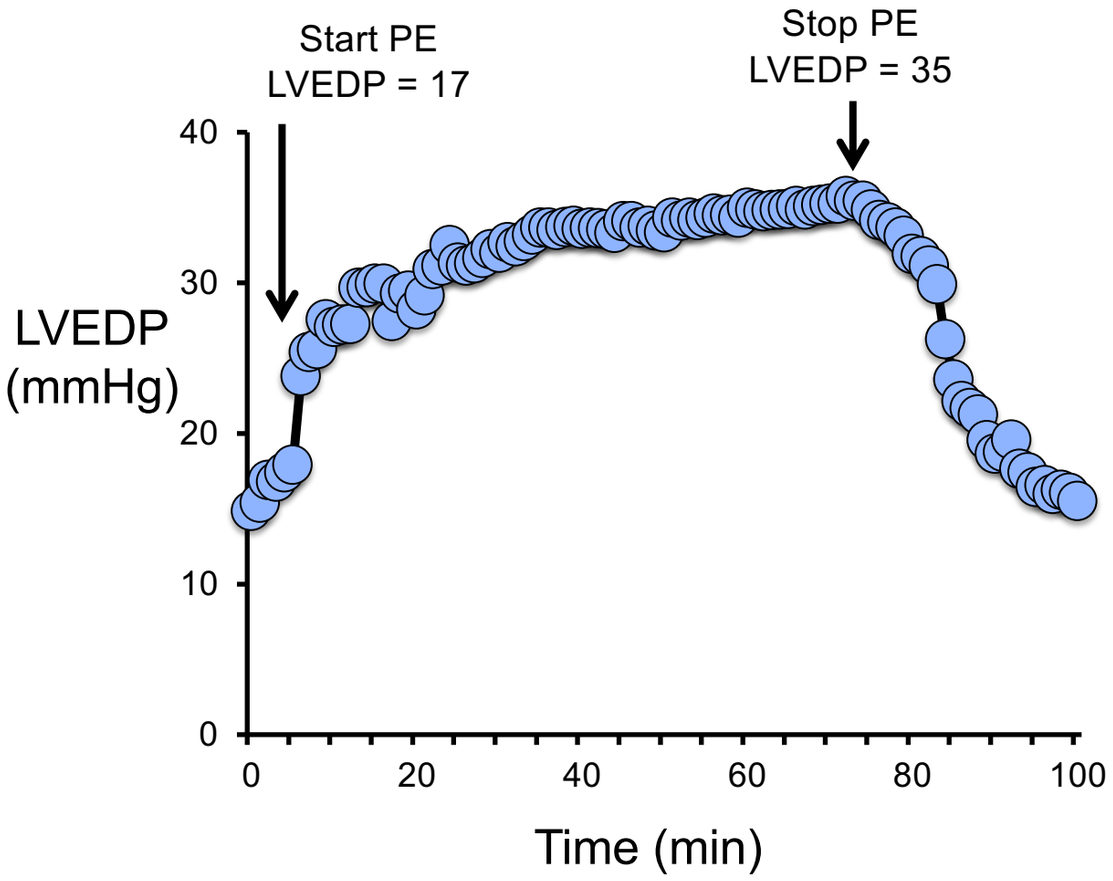
Can myocyte stretch from transiently elevated LV diastolic filling pressure in vivo cause apoptosis, TnI release and myocyte loss in the absence of ischemia?

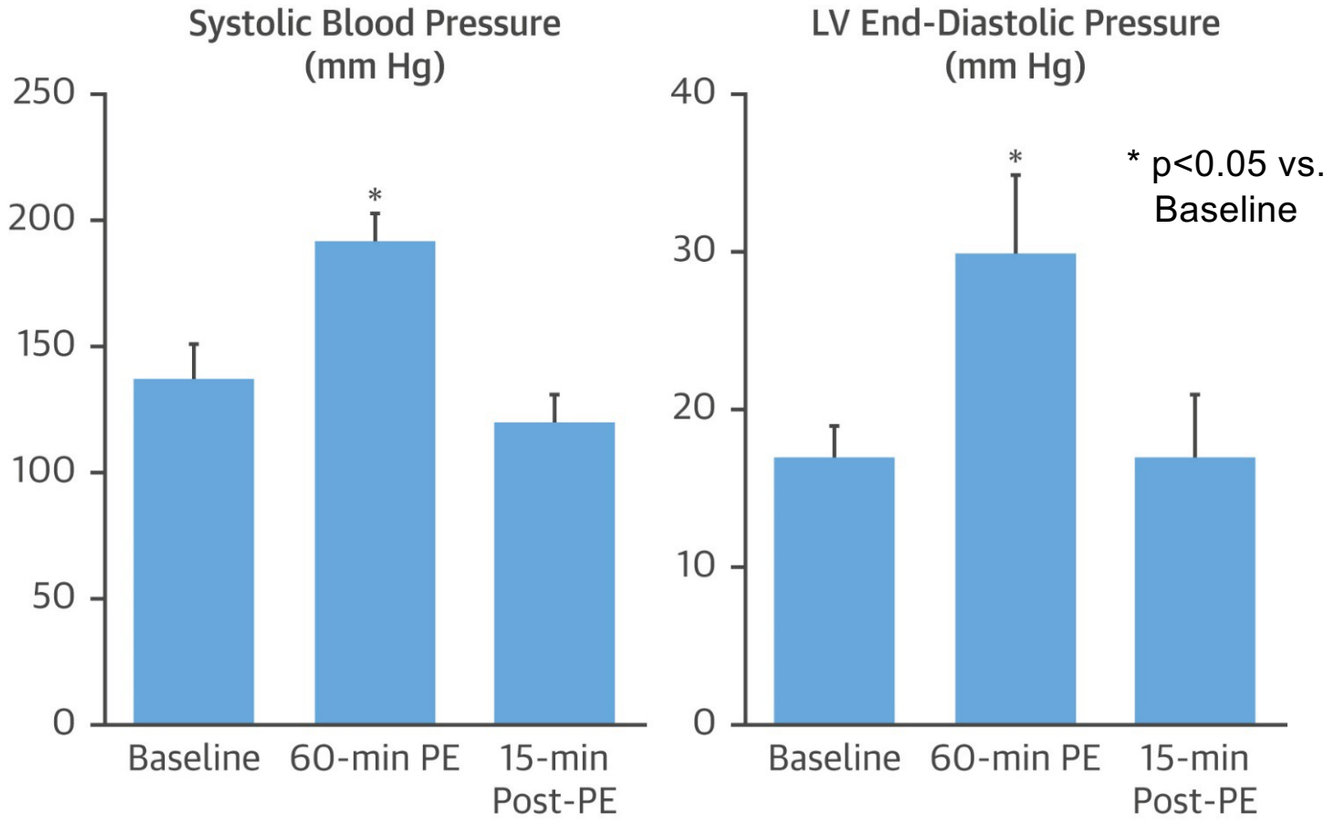
Elevations in LV End-diastolic Pressure Lead to Troponin I Release in the Absence of Ischemia?



Weil et al. *JACC Basic Transl Sci.* 2019; 4(4): 527-541.

Phenylephrine Increases Afterload and Transiently Raises LV End-diastolic Pressure (LVEDP) in Swine



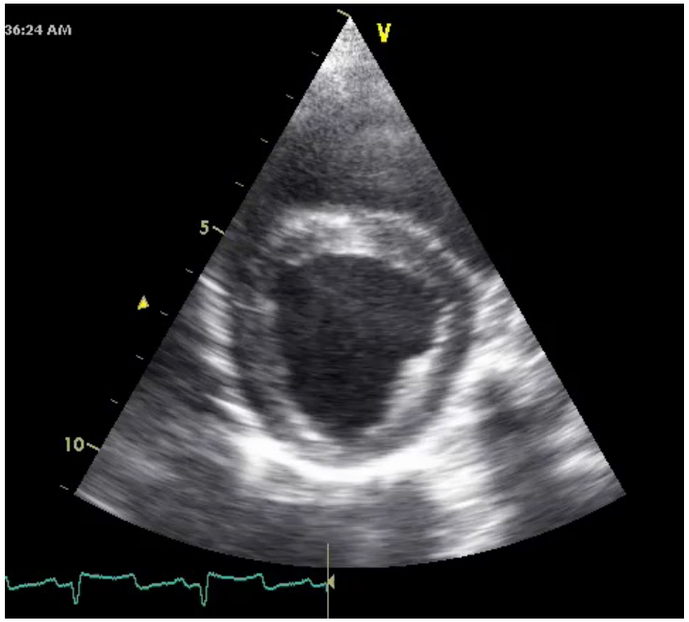


Weil et al. JACC 2018: 71, 2906-2916

Transient Pressure Overload Produces Stretch-induced Stunning

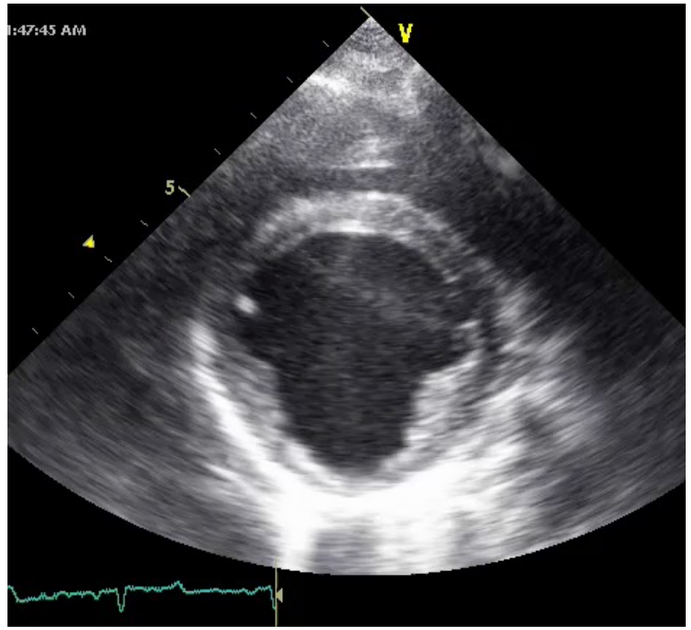
Rest

BP: 124/78
LVEDP: 9



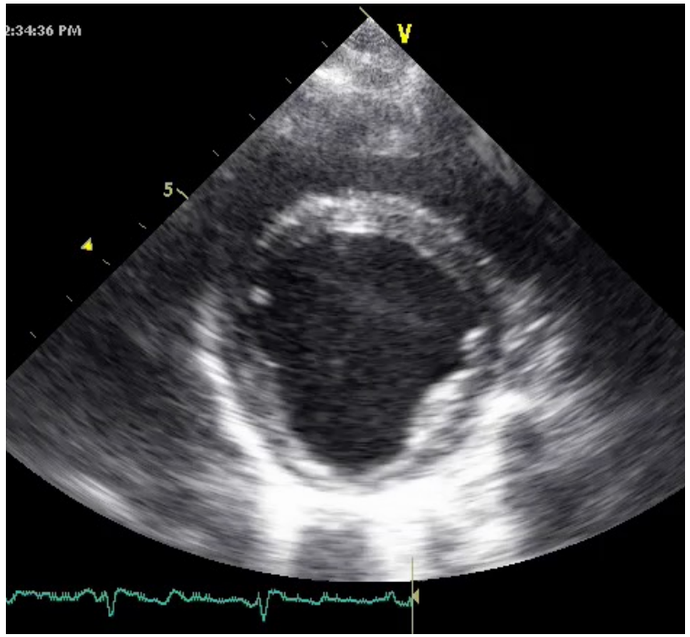
i.v Phenylephrine

BP: 216/155
LVEDP: 37

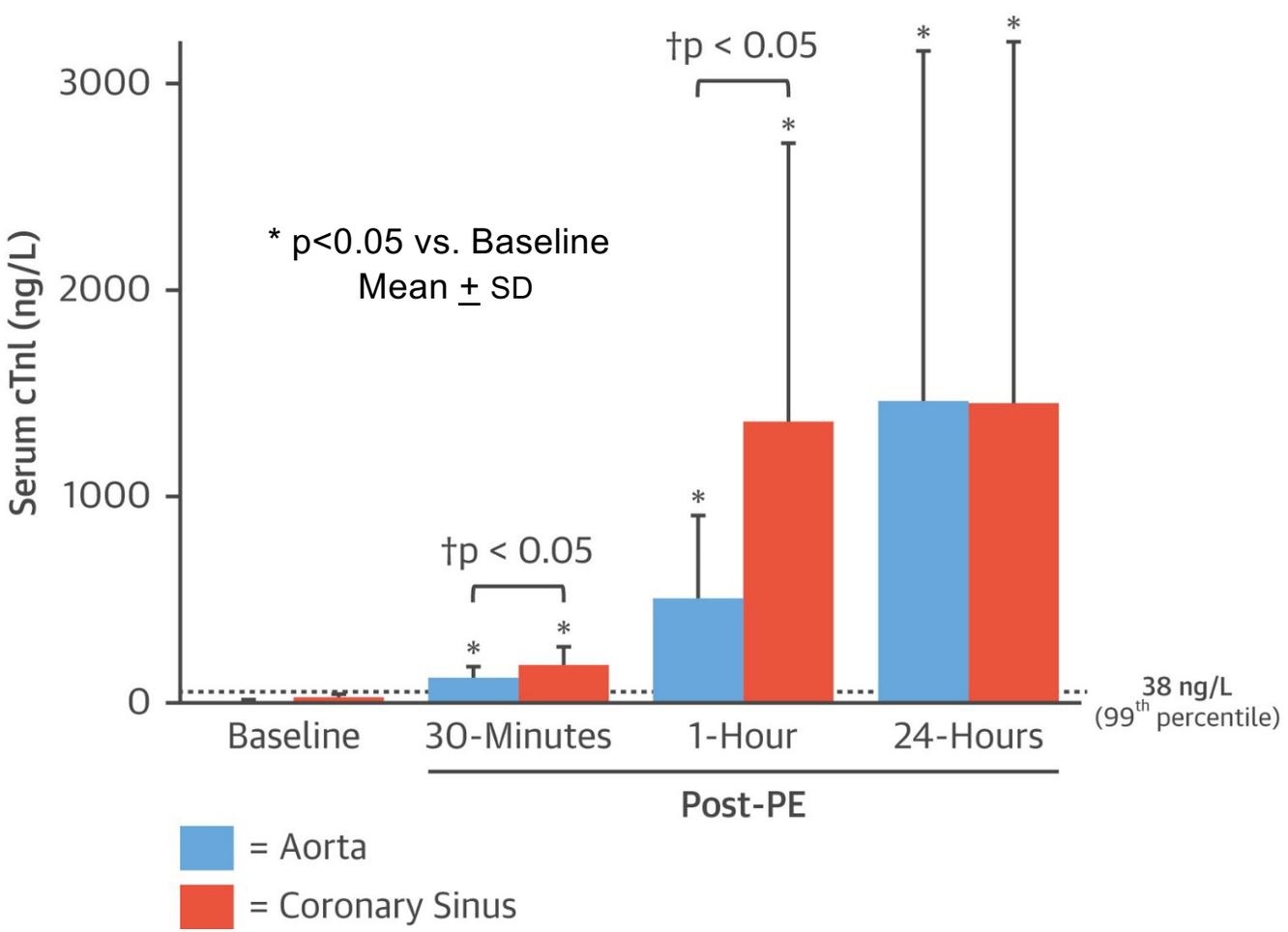


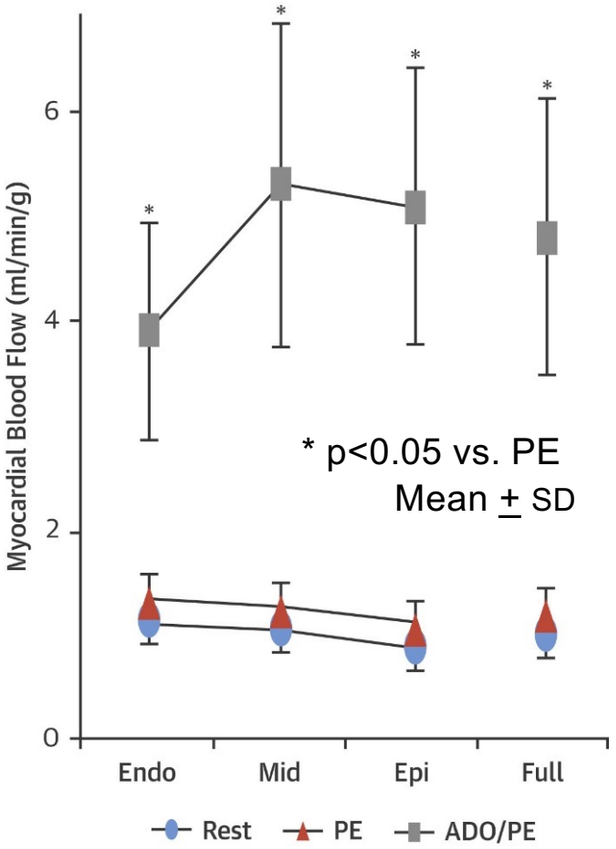
1 Hr Post-Phenylephrine

BP: 125/86
LVEDP: 14



Transient Stretch From Preload Elevation Leads to TnI Release In the Absence of Myocardial Ischemia





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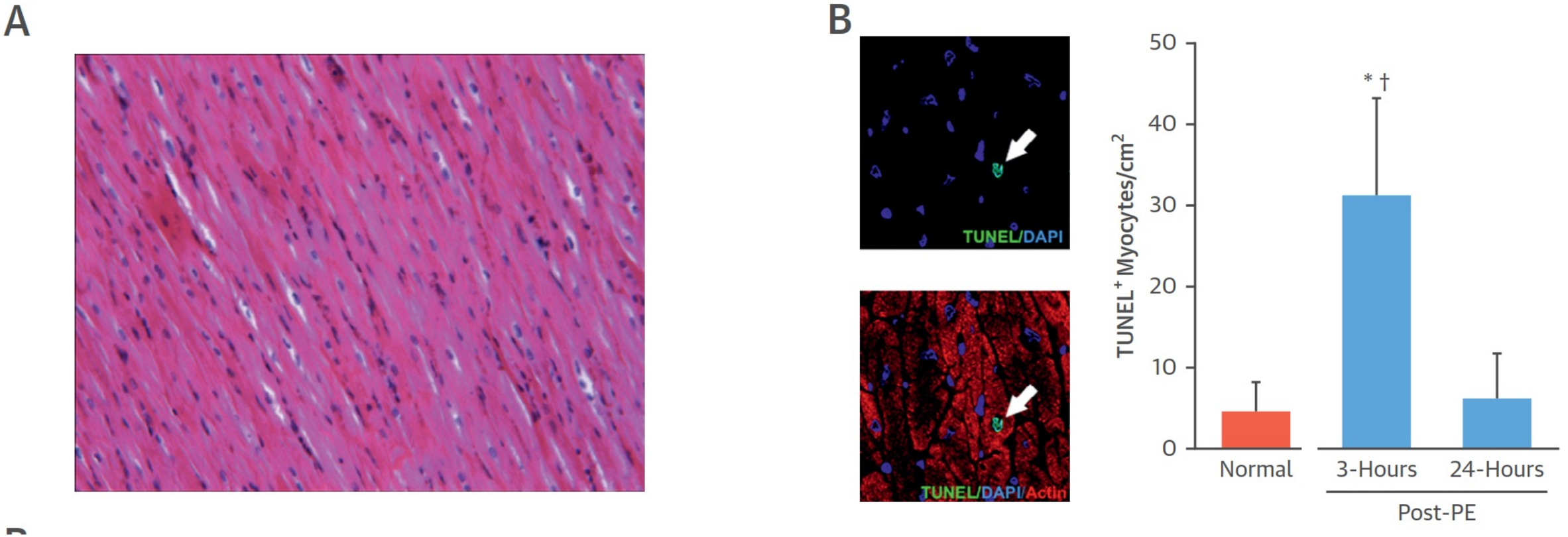
Weil et al. JACC 2018: 71, 2906-2916

Transient Preload Elevation Leads to Myocyte Apoptosis in Swine

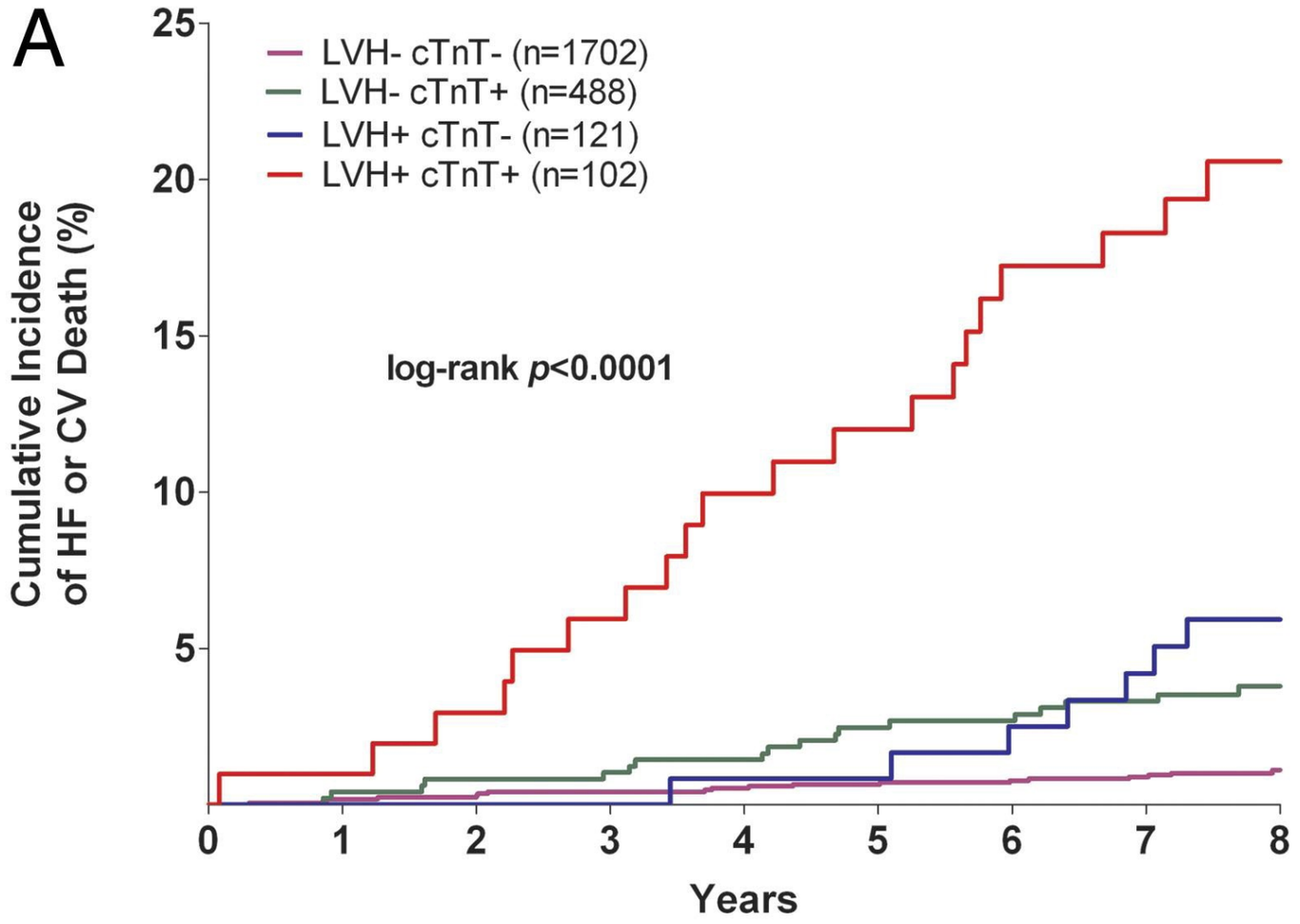


Weil et al. JACC 2018: 71, 2906-2916

High sensitivity troponin assays (hs-cTn) are differentiated by their ability to detect measurable cTn above the assays' lower limit of detection in more than 50% of normal subjects that are asymptomatic

What is the Significance of High Sensitivity Troponin Values Within the Normal Range in Asymptomatic Subjects?

Prognostic impact of cTnT and LVH on survival and the development of heart failure – Dallas Heart Study

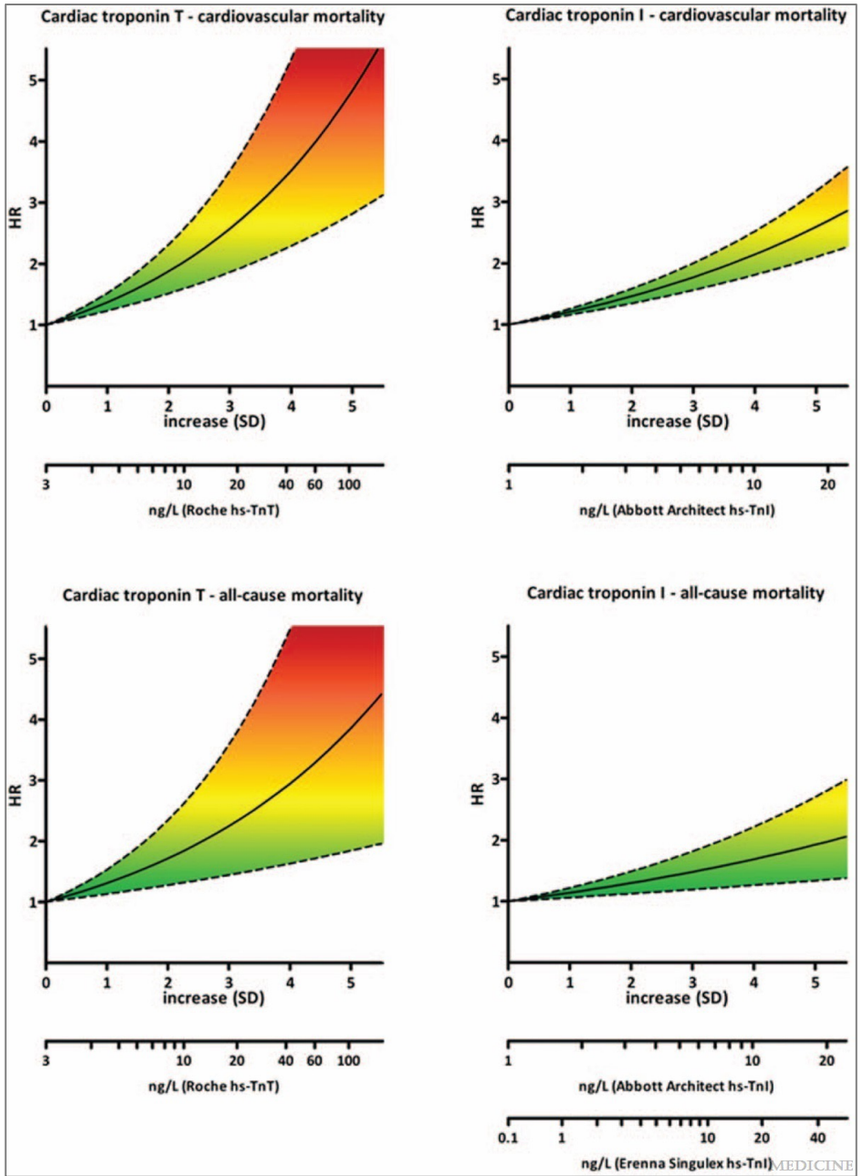


Neeland et al. JACC 61; 2013, p187–195

Circulating hs-cTnT and hs-cTnI Within the Normal Range in Asymptomatic Populations Impacts Cardiovascular and Total Mortality

Cardiovascular Mortality

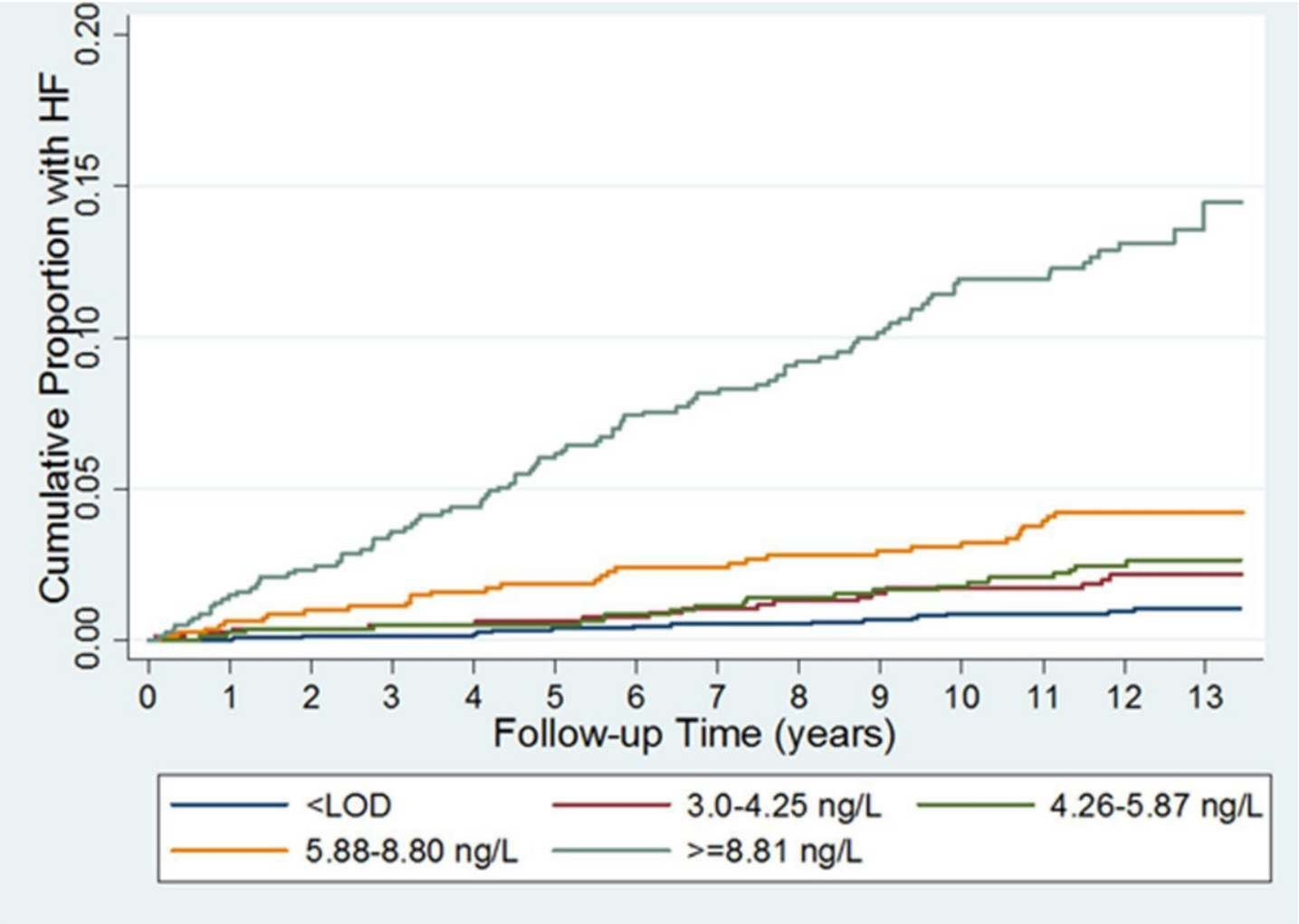
All-cause Mortality



Meta analysis 11 studies, 65,000 participants

van der Linden et al.
Medicine 95:e5703, 2016

Cumulative Incidence of Heart Failure by hs-cTnT Category - MESA Study



Seliger et al. Circulation. 2017;135:1494–1505

Summary - Arriving at a Diagnosis of Myocardial Infarction Requires More Than an Elevated Troponin I Level

Distinguishing Troponin elevation from MI vs injury using the criteria set forth in the 4th Universal Definition of MI requires integration of:

- Clinical findings
  - symptoms compatible with ischemia
  - comorbid conditions predisposing to myocardial ischemia and injury
- Patterns on the ECG
  - dynamic ST changes or new Q waves
- Laboratory data
  - rise and fall of TnI, TnT
- On occasion, evidence of lost myocardial tissue
  - imaging procedures (e.g. Gd MRI)
  - postmortem pathological findings (Type III MI)

All of these should be viewed in the context of the time horizon over which a suspected event unfolds.

Summary- Myocardial Injury and TnI
Clinical Take Home Message

- As the sensitivity of TnI assays has increased, the specificity of the test for detecting myocardial infarction has predictably decreased

  - With contemporary TnI assays, the majority of TnI elevations in hospitalized patients reflect myocardial injury as opposed to ischemia from a Type I or Type II myocardial infarction

  - Despite this, TnI elevations from myocardial injury remain prognostic for all cause mortality (and also cardiac mortality)

- Measurable TnI I in normal individuals probably reflects normal cardiomyocyte turnover from apoptosis

  - Even within the normal range, the magnitude appears to be related to the long-term risk of heart failure.

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