Postoperative Troponin Monitoring

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UChicago Medicine

Outline

- Cardiac Troponin/ High-sensitivity Cardiac Troponin
- What is the Cause of Postop. Troponin Elevations?
- Should we measure cTn in all patients?
  - Before surgery?
  - After surgery?
- Management of Postop. Troponin Elevation

Conflicts of Interest

Dr. Nagele has received research support from **Roche Diagnostics and Abbott Diagnostics.**

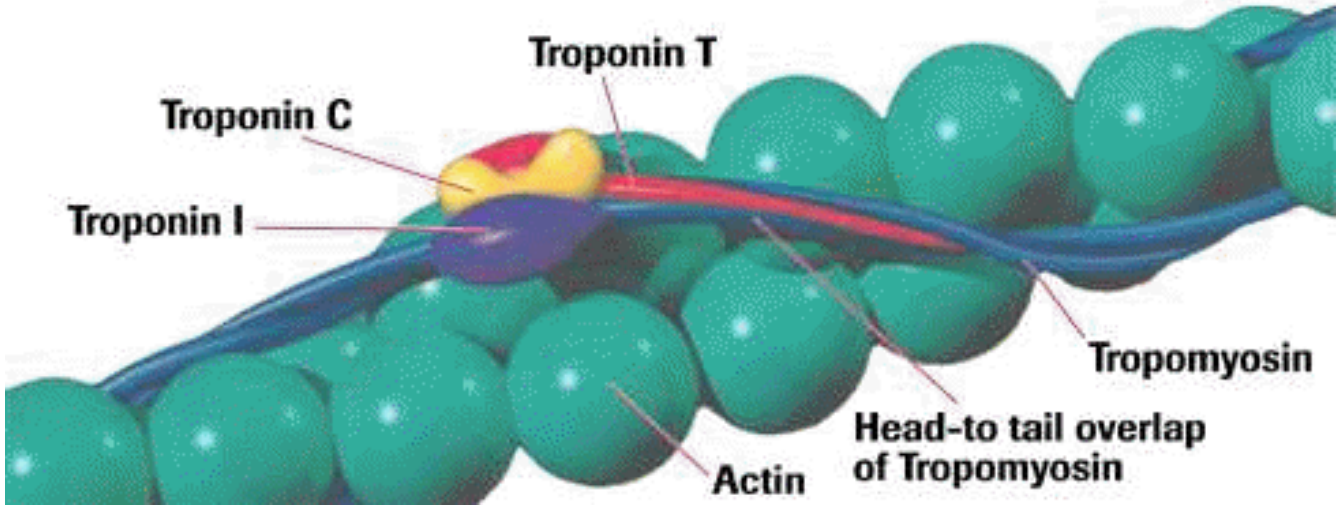
Roche's hscTnT assay has recently received FDA clearance

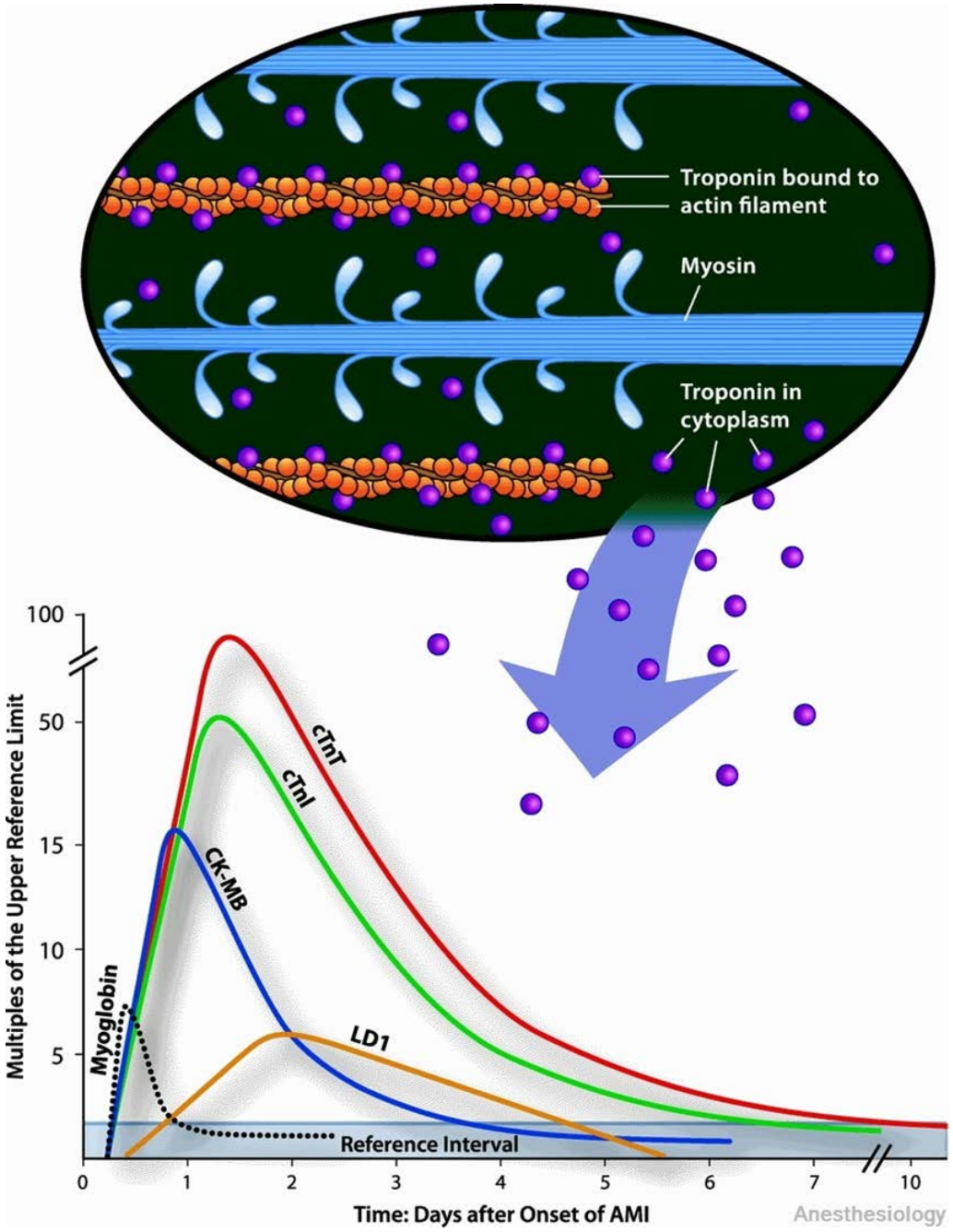
All other hscTn assays are not cleared by the FDA

Cardiac troponins

TROPONIN T

A regulatory protein released when cardiac cell necrosis occurs.





Anesthesiology 2010; 112:1005–12

Medicine

Cardiac Troponin

- Gold Standard for diagnosis of acute MI
- Absolute myocardial tissue specificity except for:
  - In the fetus, cTnT also expressed in skeletal muscle (cTnI not)
  - In rare muscle diseases, cTnT may be re-expressed in adult skeletal muscle
- High clinical sensitivity
- 2 forms: cTnI and cTnT
  - cTnT: one assay
  - cTnI: >10 assays – substantial variability
- <u>Assays are not standardized or harmonized</u>

High-Sensitivity Cardiac Troponin

“Or why troponin is no longer like a pregnancy test”

High-sensitivity cardiac troponin assays

- Measure the same cTn molecule!
- Much higher sensitivity - into ng/L range
- Can be detected at baseline

2 Potential Game-Changing Features

- Risk Prediction at baseline
- Rapid acute MI diagnosis

How is an abnormal troponin defined?

Any measurement above the 99th percentile of a normal reference population (URL) = "Elevation"

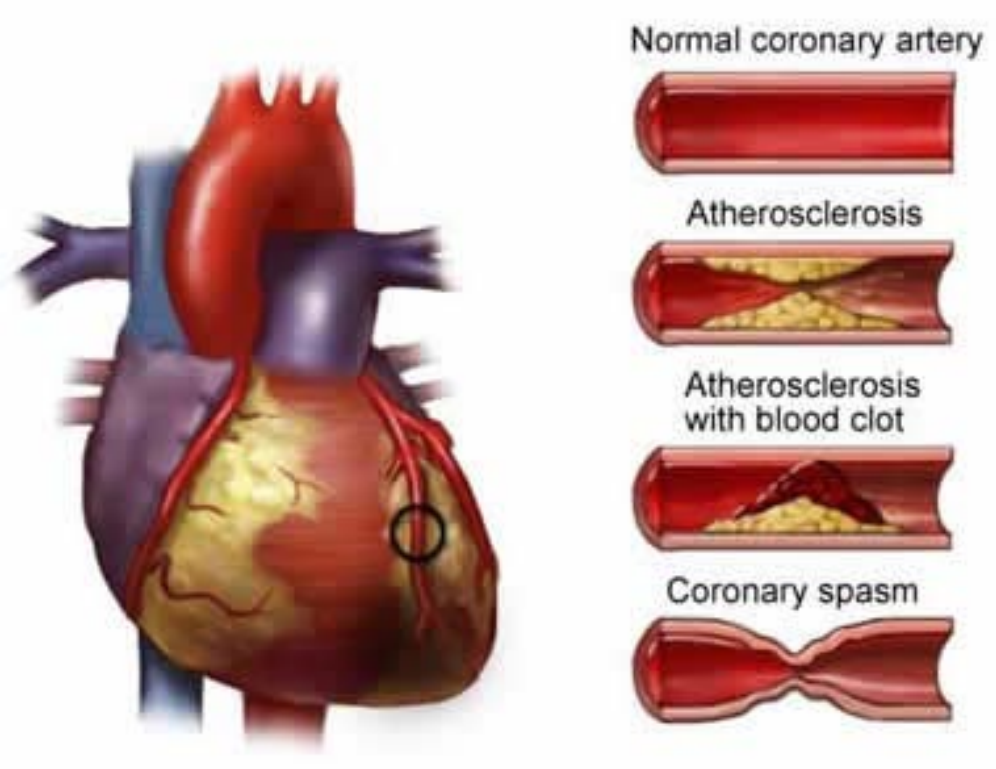
Method	Limit of Detection (LOD) (ng/L)	99th % (ng/ml)	% Healthy Subjects above LOD
Roche cTnT "4th Gen"	10	100	0.7
Roche hscTnT "5th Gen"	5	14	25
Abbott "Contemporary" cTnI	10	28	2
Abbott hscTnI	1.2	16	96
Siemens "Contemporary" cTnI	40	70	2

What is the cause of postop. cTn elevations?

Do all postop. cTn elevation indicate myocardial injury/necrosis/infarction?

What causes acute cTn elevations?

- Myocardial ischemia
  - Thrombotic event
  - Demand ischemia (stable CAD)

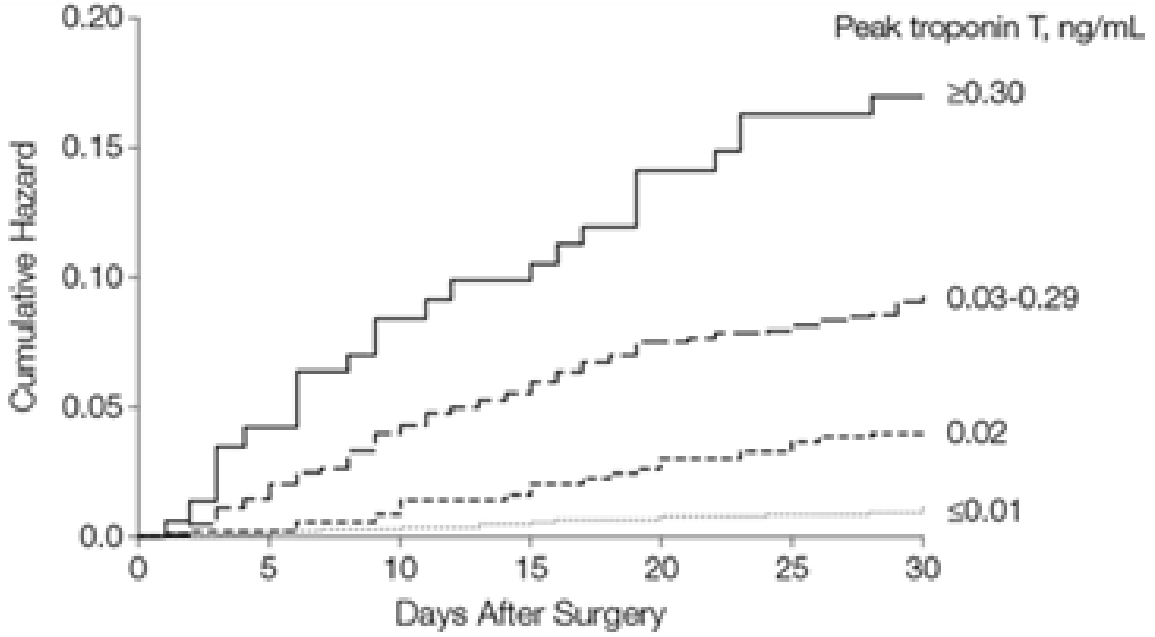


	Mechanism
Cardiac	
Thrombotic acute coronary syndrome	Hypoxic damage to myocytes
Spontaneous coronary artery dissection	Hypoxic damage to myocytes
Acute heart failure	Global wall stretch, systemic and coronary hypoperfusion
Myocarditis	Direct damage to myocytes
Pericarditis	Direct damage to myocytes
Aortic dissection (Stanford A)	Dissection of coronary artery with hypoxic damage to myocytes
Cardiac procedures	
• Coronary angioplasty	Side branch occlusions, coronary dissection, bulky devices causing transient ischemia and microembolism
• Electrophysiologic ablations	Direct damage to myocytes
• Electrical cardioversions	Direct damage to myocytes
• Open heart surgery	Direct surgical trauma, incomplete cardioprotection, reperfusion injury, myocardial infarction
Defibrillator shocks	Direct damage to myocytes
Heart transplantation	Inflammatory/immune mediated, direct surgical trauma
Cardiotoxic drugs	Direct toxic effects to myocytes
Cardiac contusion after blunt chest wall trauma	Direct damage to myocytes
Noncardiac	
Pulmonary embolism	Right ventricular strain
Septic shock/critically ill patients	Oxygen supply/demand mismatch, cytokine/ endotoxin-mediated toxicity, heterophile antibodies (false-positives)
Strenuous exercise	Ventricular stretch, right ventricular strain
Rhabdomyolysis	Direct damage to myocytes, cross-reactivity between skeletal and cardiac muscle isoforms with cTnT
Acute kidney failure	

Sara JD, Holmes DR, Jr., Jaffe AS. Fundamental concepts of effective troponin use: important principles for internists. *The American journal of medicine*. 2015;128(2):111-119.

Postoperative Troponin Release

Prognosis of myocardial injury



No. at risk

Peak troponin T, ng/mL							
≥0.30	142	136	129	127	121	118	117
0.03-0.29	1121	1103	1075	1058	1036	1030	1018
0.02	494	492	489	485	480	477	473
≤0.01	13376	13348	13300	13271	13250	13230	13209

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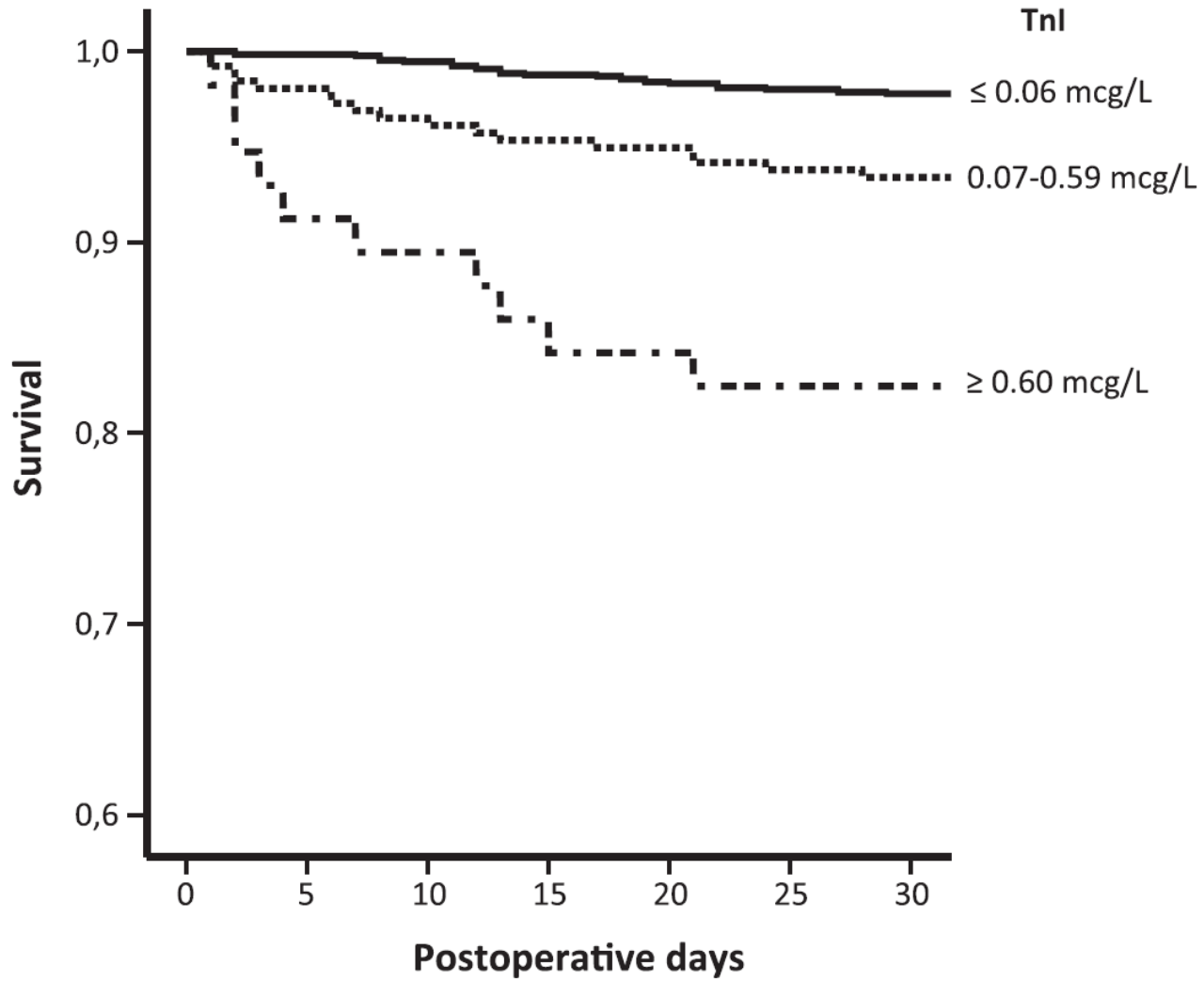
JAMA. 2012;307(21):2295-2304

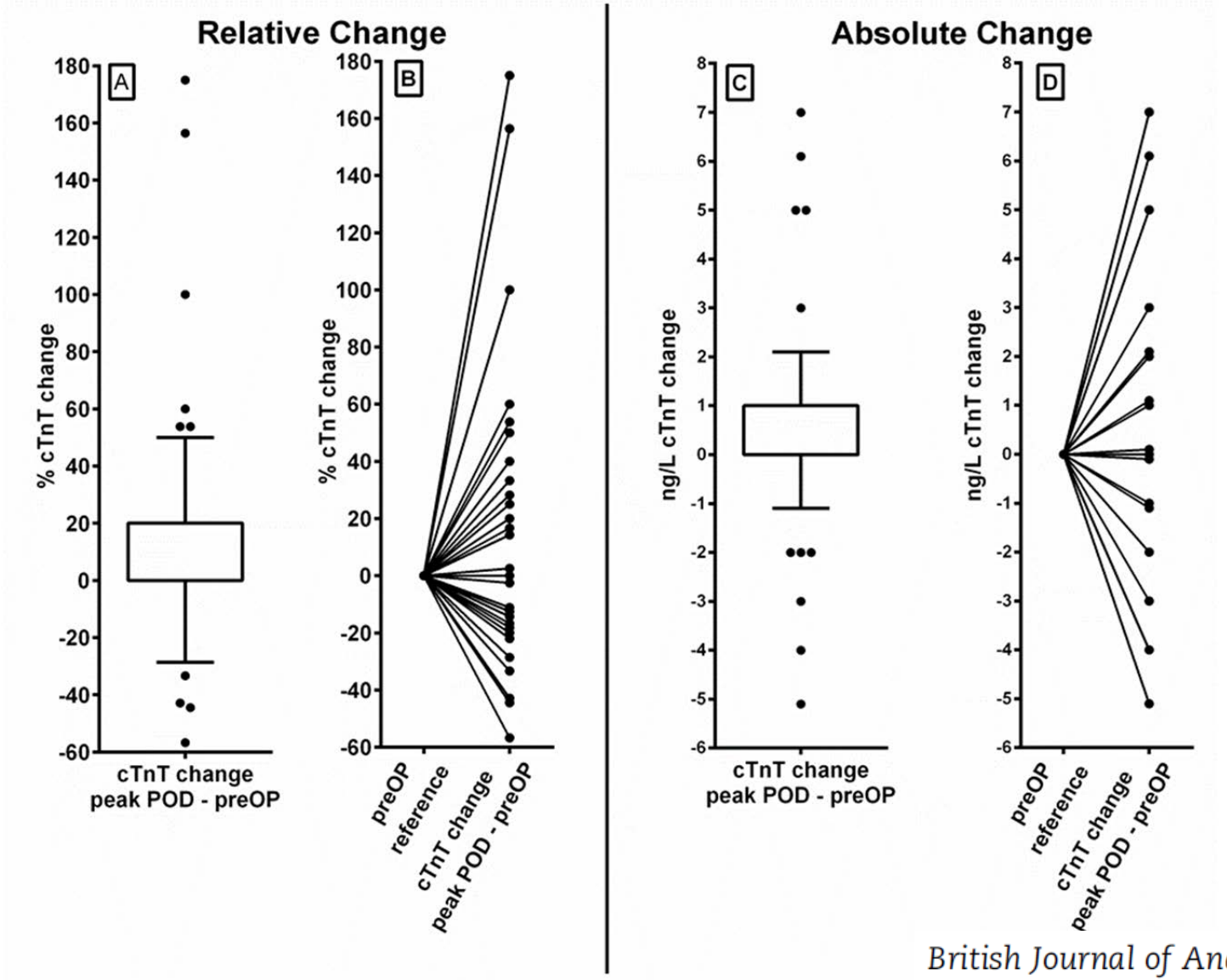


Judith A.R. van Waes, Hendrik M. Nathoe, Jurgen Č. de Graaff, Hans Kemperman, Gert Jan de Borst, Linda M. Peelen and Wilton A. van Klei

Circulation. 2013;127:2264-2271;

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

High-sensitivity cardiac troponin T in young, healthy adults undergoing non-cardiac surgery



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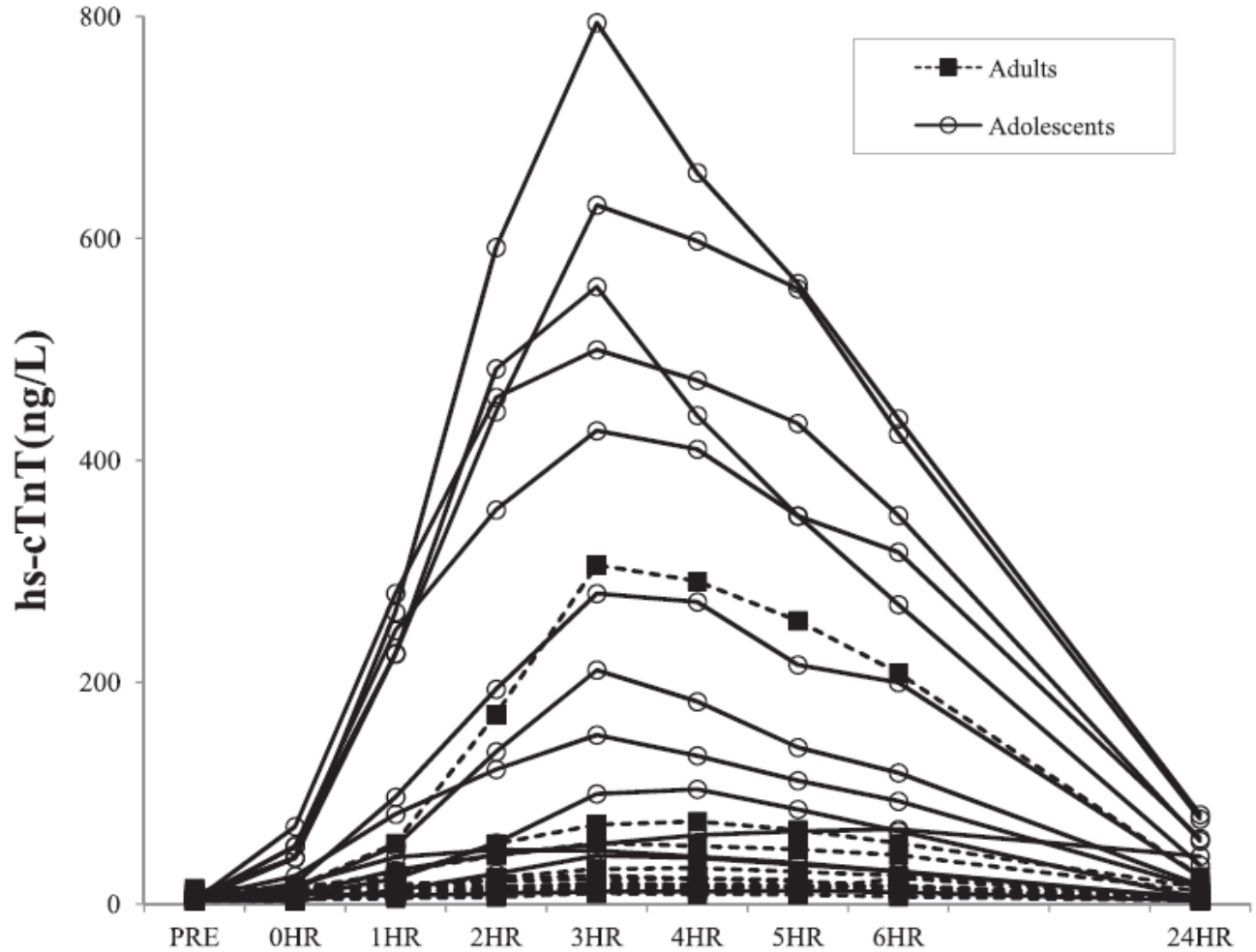
British Journal of Anaesthesia, 120 (2): 291—298 (2018)

The kinetics of highly sensitive cardiac troponin T release after prolonged treadmill exercise in adolescent and adult athletes



J Appl Physiol 113: 418–425, 2012.

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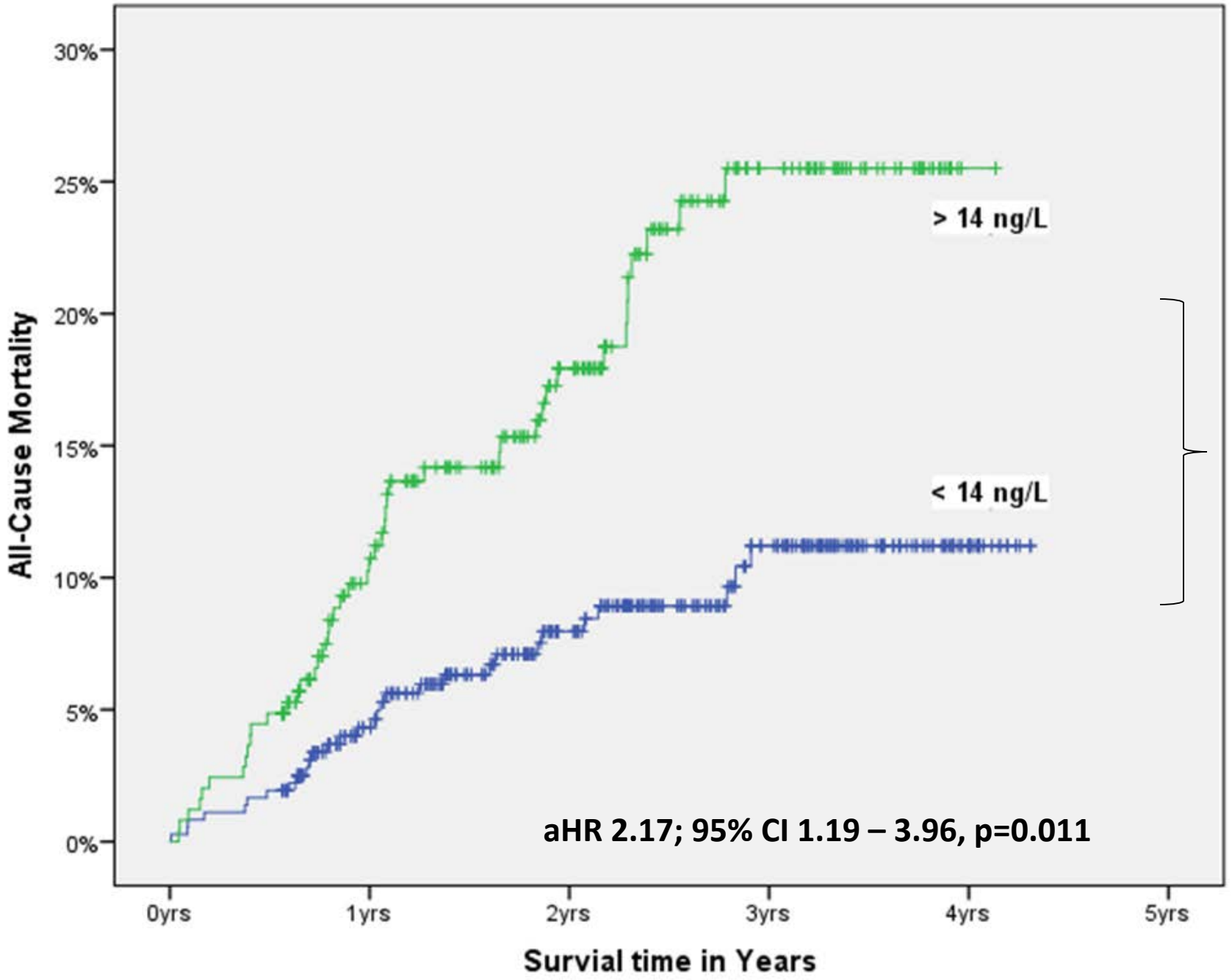
Should we measure cTn in all patients?

Before surgery?

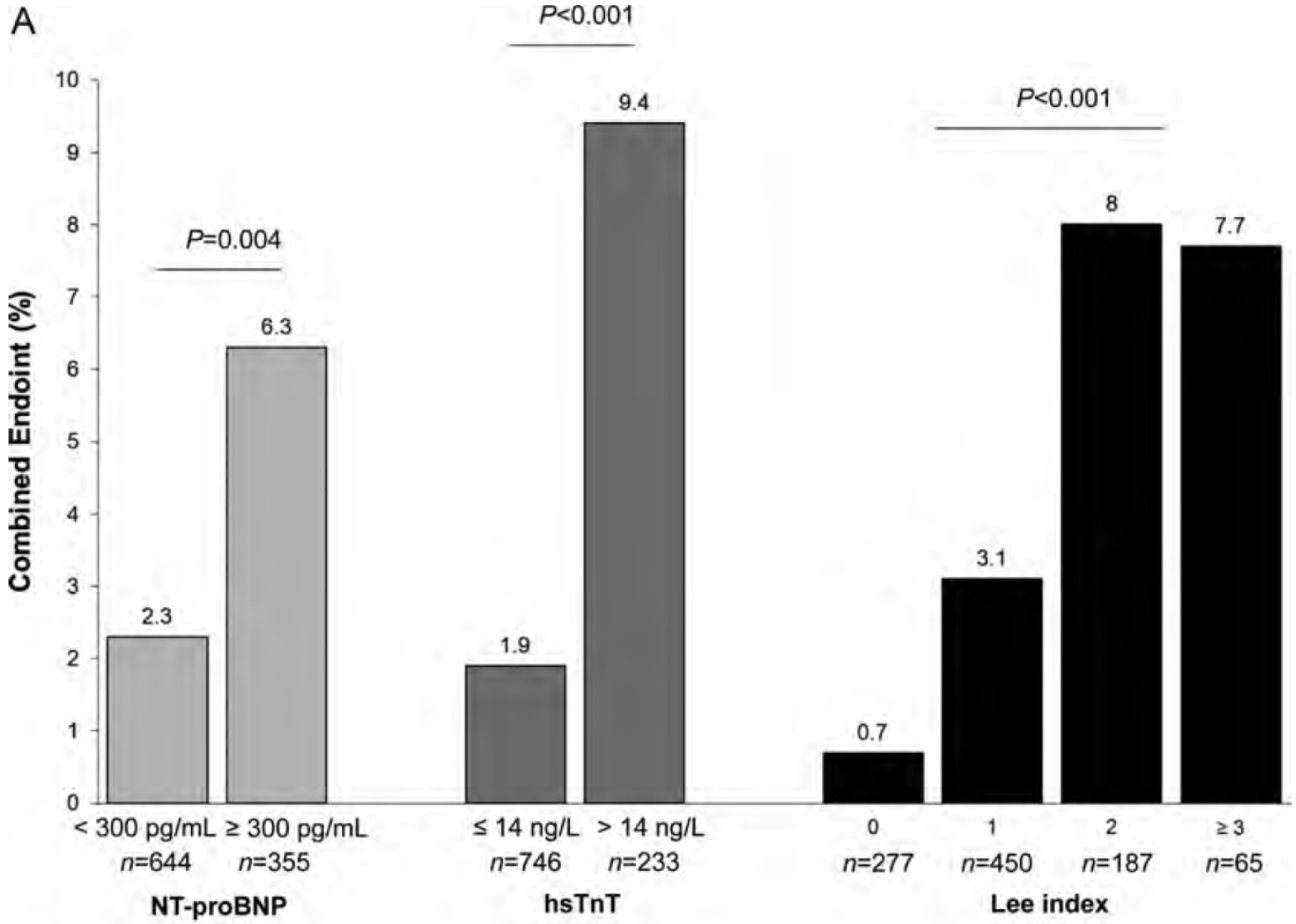
After surgery?

Preop. Risk Prediction



P=0.001

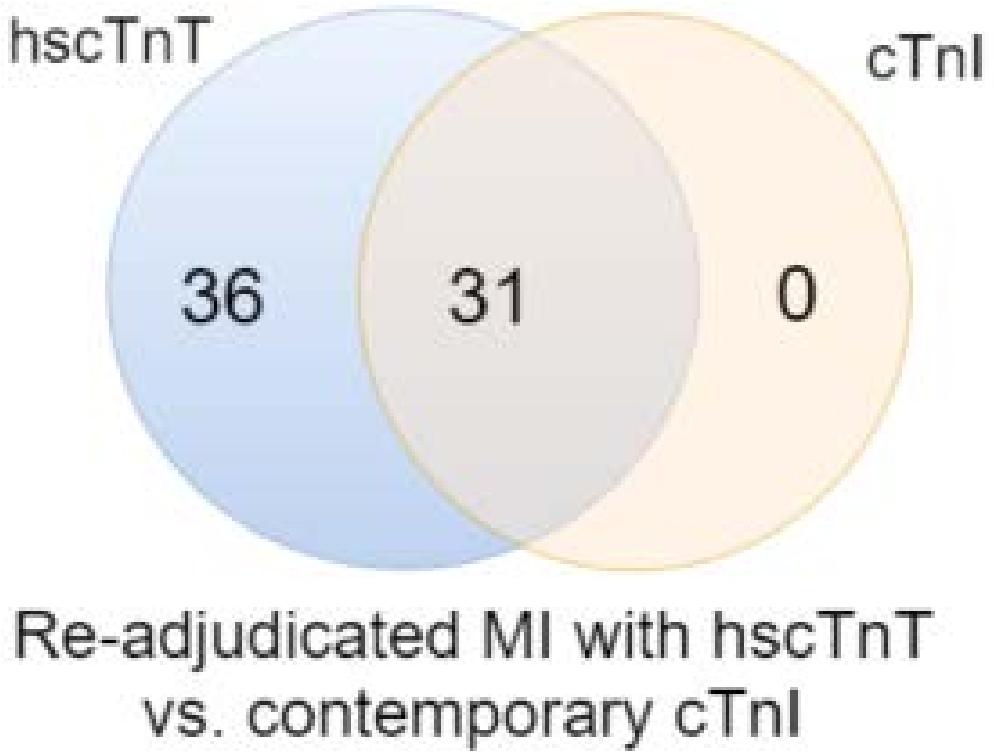
Am Heart J. 2013 Aug;166(2):325-332



European Heart Journal (2013) **34**, 853–862
doi:10.1093/eurheartj/ehs445

Improved Diagnosis of Postop. MI

HscTn increases detection rate of postop MI



Brown J, et al. Anesth Analg 2017

VIEWPOINT

The Case for a Revised Definition of Myocardial Infarction—Resolving the Ambiguity of Type 2 Myocardial Infarction

JAMA Cardiology June 2016 Volume 1, Number 3

Etiology of acute coronary syndrome after non-cardiac surgery

Anesthesiology, 2018 Jun;128(6):1084-1091

Study Design

- 215,077 BJH patients screened
- Acute coronary syndrome within 30d after non-cardiac surgery
- Had urgent coronary angiography
- Cath films were reviewed blinded by 2 cardiologists
- Main endpoints:
  - Type 1 (plaque rupture/thrombus)
  - Type 2 (demand ischemia, stable CAD)
  - Type 4B MI (stent thrombosis)

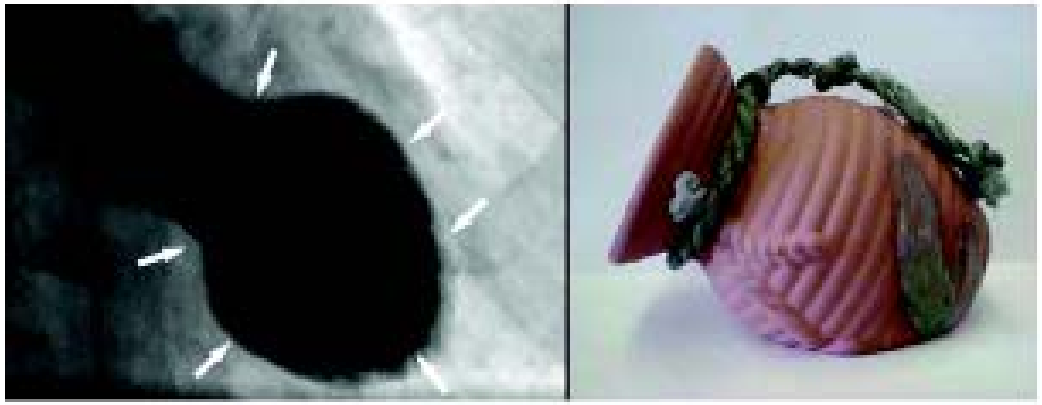
Characteristics of acute coronary syndrome events

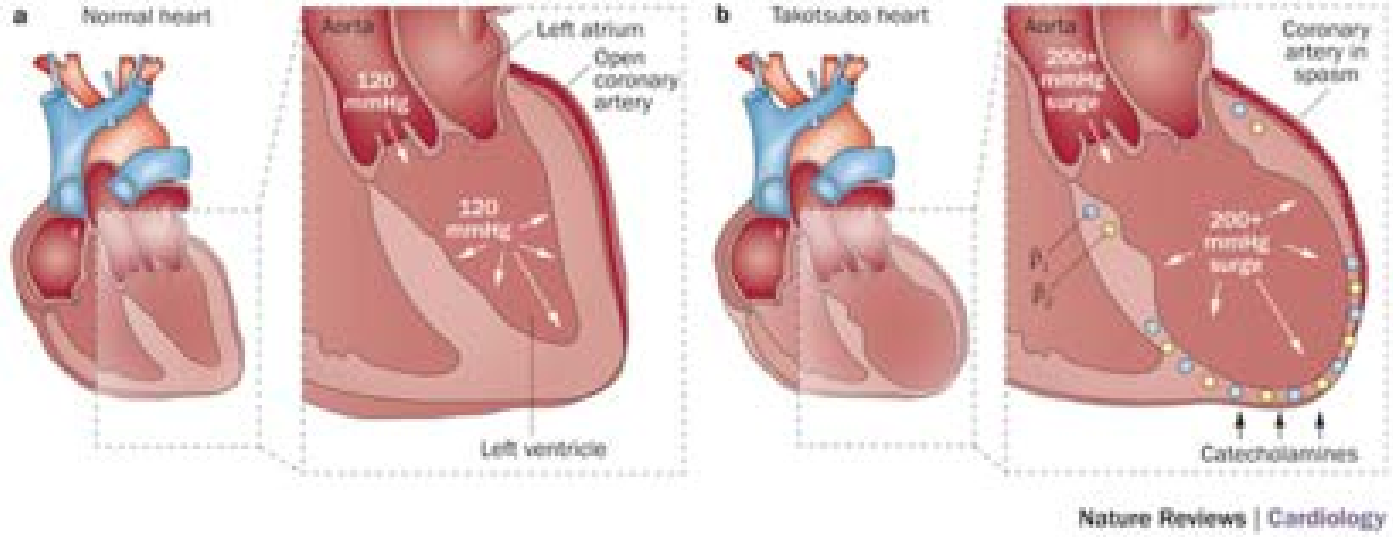
	All events n=146 (100%)	Type 1 MI n=37 (25.3%)	Type 2 MI n=106 (72.6%)	Type 4B MI n=3 (2.1%)*
Type of event, n (%)				
STEMI	21 (14.4)	5 (13.5)	14 (13.2)	2 (66.7)
NSTEMI	117 (80.1)	31 (83.8)	85 (80.2)	1 (33.3)
Unstable Angina	8 (5.5)	1 (2.7)	7 (6.6)	0

Table 3. Coronary Angiography Findings

	All Events n=146 (100%)	Type 1 MI n=37 (25.3%)	Type 2 MI n=106 (72.6%)	Type 4B MI n=3 (2.1%)
Normal or mild disease, n (%)	39 (26.7)	2 (5.4)	37 (34.9)	0
Calcification, n (%)	78 (53.4)	25 (67.6)	53 (50)	0
Haziness, n (%)	77 (52.7)	33 (89.2)	41 (38.7)	3 (100)
Ulceration, n (%)	28 (19.2)	25 (67.6)	1 (.9)	2 (66.7)
Thrombus, n (%)	5 (3.4)	2 (5.4)	0	3 (100)
Stress-induced Cardiomyopathy, n (%)	14 (9.6)	0	14 (13.2)	0

Takotsubo (Stress) Cardiomyopathy





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Controversies

- What is the cause of postop. cTn elevations?
- Do all postop. cTn elevation indicate myocardial injury/necrosis/infarction?
- Are all postop. cTn elevations bad?
- What is the role of hscTn?
- What to do with postop. cTn elevations?

How to manage postop. cTnI elevations

- Is it acute or chronic? (Do you have a preop. sample?)
- Rule in/out non-cardiac causes
  - Right heart (PE, pulm. hypertension, etc.)
  - Acute/chronic kidney injury/damage
- Are there clinical symptoms consistent with myocardial ischemia?
- ECG changes?
- Consider obtaining a separate biomarker (BNP, NT-proBNP)

The MANAGE Trial

Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial

*P J Devereaux, Emmanuelle Duceppe, Gordon Guyatt, Vikas Tandon, Reitze Rodseth, Bruce M Biccard, Denis Xavier, Wojciech Szczeklik, Christian S Meyhoff, Jessica Vincent, Maria Grazia Franzosi, Sadeesh K Srinathan, Jason Erb, Patrick Magloire, John Neary, Mangala Rao, Prashant V Rahate, Navneet K Chaudhry, Bongani Mayosi, Miriam de Nadal, Pilar Paniagua Iglesias, Otavio Berwanger, Juan Carlos Villar, Fernando Botto, John W Eikelboom, Daniel I Sessler, Clive Kearon, Shirley Pettit, Mukul Sharma, Stuart J Connolly, Shrikant I Bangdiwala, Purnima Rao-Melacini, Andreas Hoeft, Salim Yusuf, on behalf of the MANAGE Investigators**

Lancet 2018; 391: 2325–34

Study Design

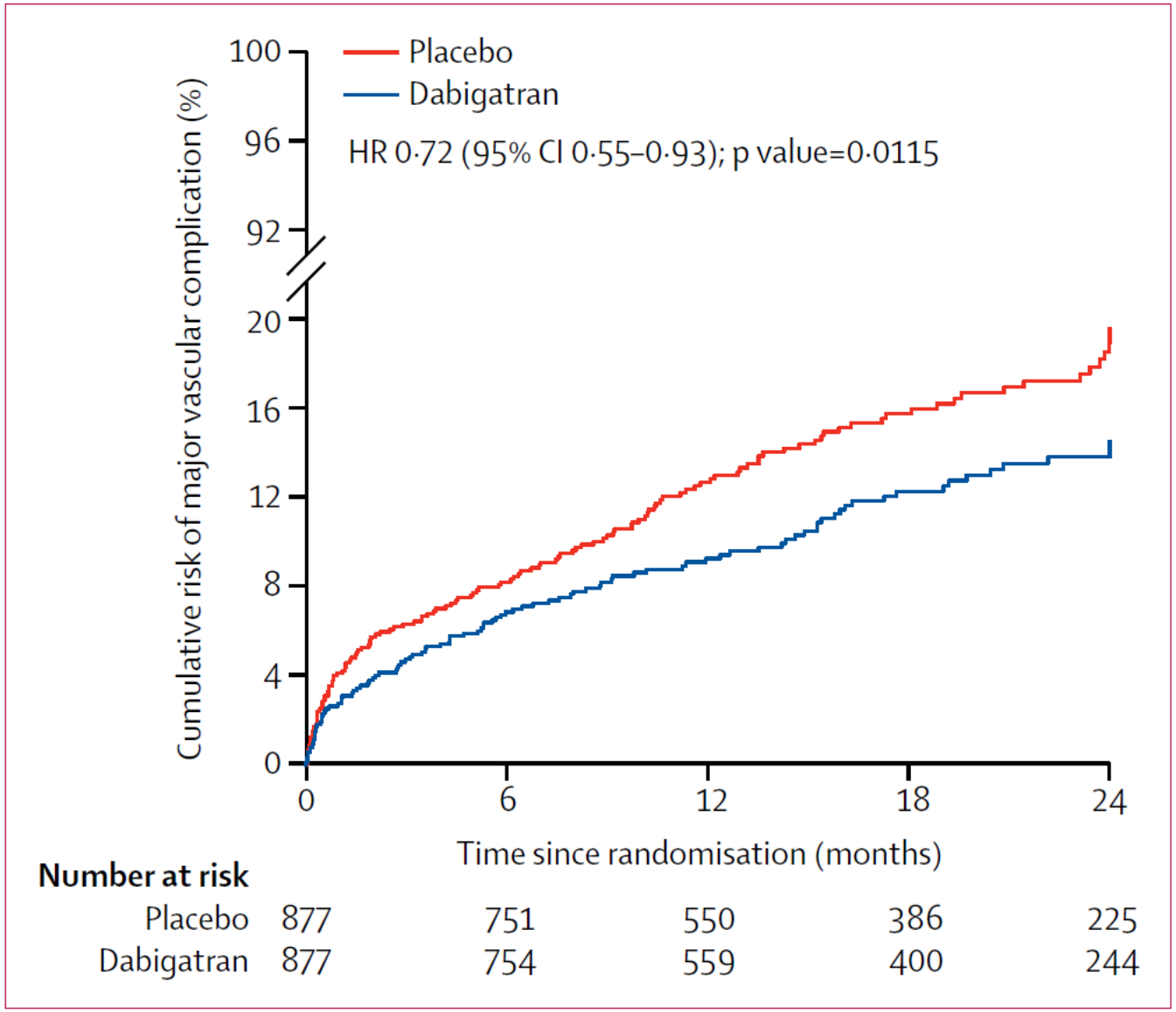
- Patient with MINS
- Randomized to either 110 mg dabigatran for 2 years or placebo
- Complex composite endpoint – changed during the trial
- N= 1,754
- Stopped early

	Dabigatran group (n=877)	Placebo group (n=877)
Age (years)	70 (11)	70 (11)
Sex		
Male	453 (52%)	443 (51%)
MINS diagnostic criteria		
Myocardial infarction	172 (20%)	173 (20%)
Isolated ischaemic troponin elevation	705 (80%)	704 (80%)
Troponin data associated with MINS		
Peak measured troponin value (ng/L)	82 (45–196)	82 (45–200)
Difference between the highest and lowest troponin values (ng/L)*	40 (16–160)	48 (18–154)
Difference between the highest and lowest troponin values ≥5 ng/L	592/625 (95%)	590/627 (94%)
Time from surgery to MINS diagnosis (days)	1 (1–2)	1 (1–2)
Time from MINS diagnosis to randomisation (days)	5 (2–14)	5 (2–14)
Medical history		
Previous myocardial infarction	116 (13%)	110 (13%)
Recent high-risk coronary artery disease†	17 (2%)	21 (2%)
Previous stroke	29 (3%)	42 (5%)
Previous peripheral arterial disease	124 (14%)	128 (15%)
Previous pulmonary embolism	6 (1%)	7 (1%)
Previous deep venous thrombosis	16 (2%)	15 (2%)
Diabetes	222 (25%)	234 (27%)
Hypertension	585 (67%)	587 (67%)

	Dabigatran (n=877)	Placebo (n=877)	Hazard ratio (95% CI)	p value
Primary efficacy outcome				
Composite of vascular mortality and non-fatal myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism	97 (11%)	133 (15%)	0·72 (0·55–0·93)	0·0115
Secondary efficacy outcomes				
Vascular mortality	52 (6%)	64 (7%)	0·80 (0·56–1·16)	..
All-cause mortality	100 (11%)	110 (13%)	0·90 (0·69–1·18)	..
Myocardial infarction	35 (4%)	43 (5%)	0·80 (0·51–1·26)	..
Cardiac revascularisation procedure	32 (4%)	21 (2%)	1·53 (0·88–2·65)	..
Non-haemorrhagic stroke	2 (<1%)	10 (1%)	0·20 (0·04–0·90)	..
Peripheral arterial thrombosis	0	4 (<1%)	..	..
Amputation	18 (2%)	26 (3%)	0·70 (0·38–1·27)	..
Symptomatic venous thromboembolism	8 (1%)	17 (2%)	0·47 (0·20–1·08)	..
Readmission to hospital for vascular reasons	113 (13%)	130 (15%)	0·86 (0·67–1·11)	..

Data are n (%) unless otherwise indicated.

Table 2: **Efficacy outcomes**



	Dabigatran (n=877)	Placebo (n=877)	Hazard ratio (95% CI)	p value
Primary safety outcome				
Composite of life-threatening, major, and critical organ bleeding	29 (3%)	31 (4%)	0·92 (0·55–1·53)	0·78
Secondary safety outcomes				
Life-threatening bleeding	9 (1%)	8 (1%)	1·11 (0·43–2·88)	..
Major bleeding	21 (2%)	25 (3%)	0·83 (0·46–1·48)	..
Critical organ bleeding	5 (1%)	10 (1%)	0·49 (0·17–1·43)	..
Intracranial bleeding	4 (<1%)	3 (<1%)	1·32 (0·30–5·90)	..
Haemorrhagic stroke	2 (<1%)	2 (<1%)	0·98 (0·14–6·96)	..
Clinically significant lower gastrointestinal bleeding	15 (2%)	6 (1%)	2·50 (0·97–6·44)	..
Clinically non-significant lower gastrointestinal bleeding	33 (4%)	7 (1%)	4·77 (2·11–10·80)	..
Minor bleeding	134 (15%)	84 (10%)	1·64 (1·25–2·15)	..
Fracture	39 (4%)	28 (3%)	1·38 (0·85–2·24)	..
Dyspepsia	129 (15%)	98 (11%)	1·33 (1·02–1·73)	..

Data are n (%) unless otherwise indicated.

Table 3: **Safety outcomes**

	Dabigatran	Placebo	Hazard ratio (95% CI)	$p_{interaction}$ value
	Events/patients	Events/patients		
Timing of randomisation				0·09
≤5 days of MINS while still in hospital	52/432 (12%)	85/436 (20%)	0·60 (0·42–0·84)	
>5 days after MINS or after hospital discharge	45/445 (10%)	48/441 (11%)	0·94 (0·63–1·42)	
MINS diagnostic criterion				0·22
Myocardial infarction	25/172 (15%)	44/173 (25%)	0·55 (0·33–0·89)	
Isolated ischaemic troponin elevation	72/705 (10%)	89/704 (13%)	0·80 (0·58–1·09)	
History of peripheral arterial disease				0·22
Yes	30/124 (24%)	51/128 (40%)	0·58 (0·37–0·91)	
No	67/753 (9%)	82/749 (11%)	0·80 (0·58–1·11)	
Receiving dual antiplatelet therapy at the time of randomisation				0·90
Yes	6/22 (27%)	11/29 (38%)	0·68 (0·25–1·87)	
No	91/855 (11%)	122/848 (14%)	0·72 (0·55–0·95)	
Overall	**97/877 (11%)**	**133/877 (15%)**	**0·73 (0·56–0·95)**	

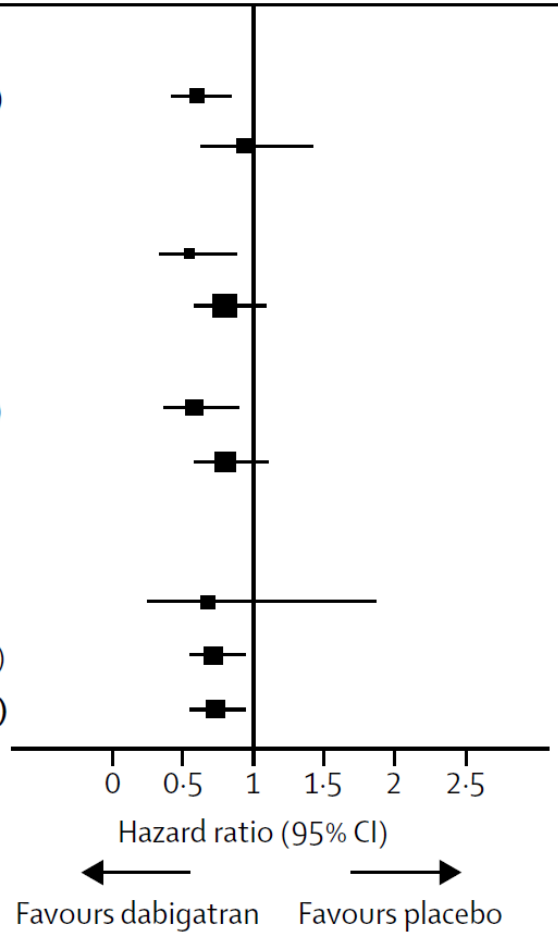


Figure 3: **Subgroup analyses of the primary efficacy outcome**
MINS=myocardial injury after non-cardiac surgery.

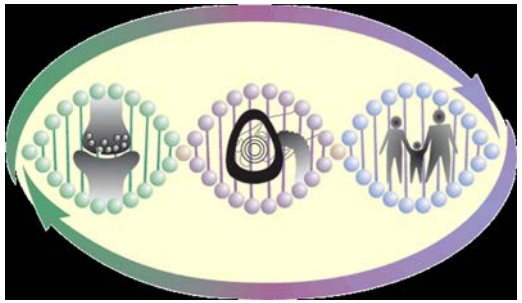
How should we interpret MANAGE?

- Interesting signal
- Not a treatment of MINS
- Cautious – results of a single trial should not be immediately put into clinical practice
- Higher bleeding
- Most patients stopped dabigatran
- Secondary prevention

Funding Sources

NIH
National Heart, Lung, and Blood Institute

American Heart Association®
Learn and Live℠



Roche

FAER

Abbott

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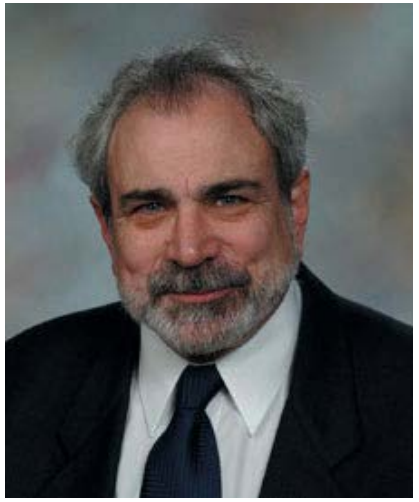
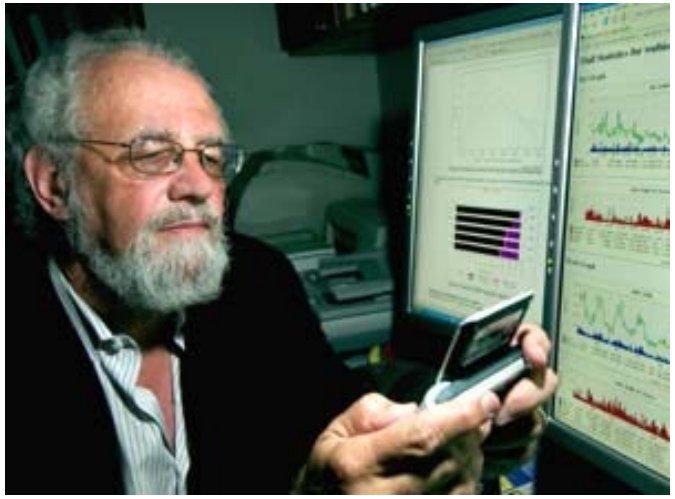
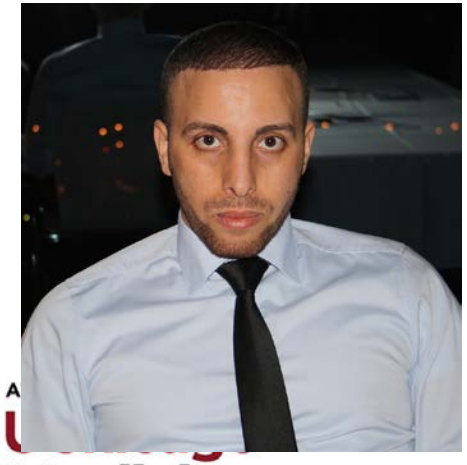
Thanks



Medicine

Rapid MI Diagnosis

Acute MI diagnosis

Standard scenario:

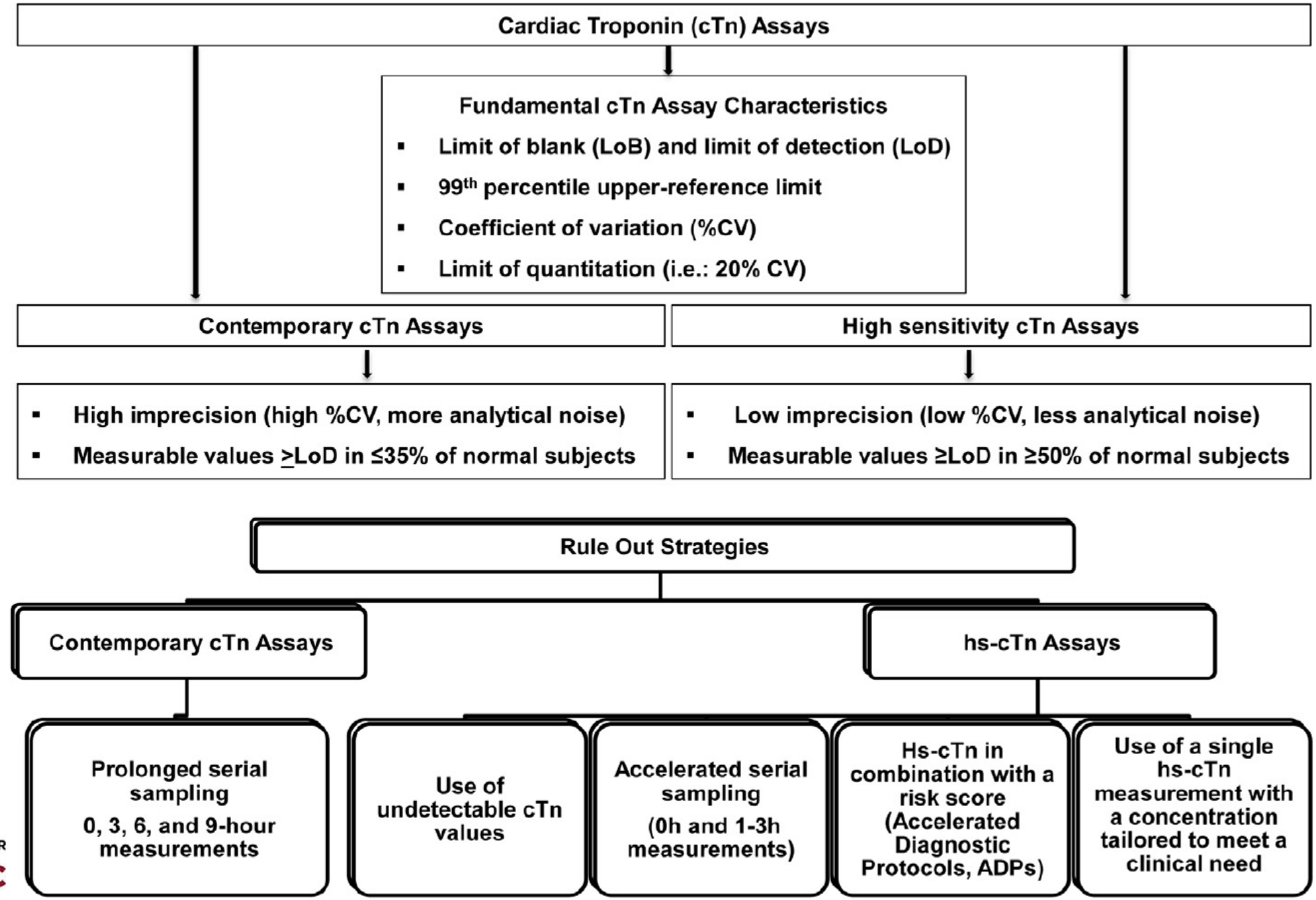
Patient with chest pain in ED

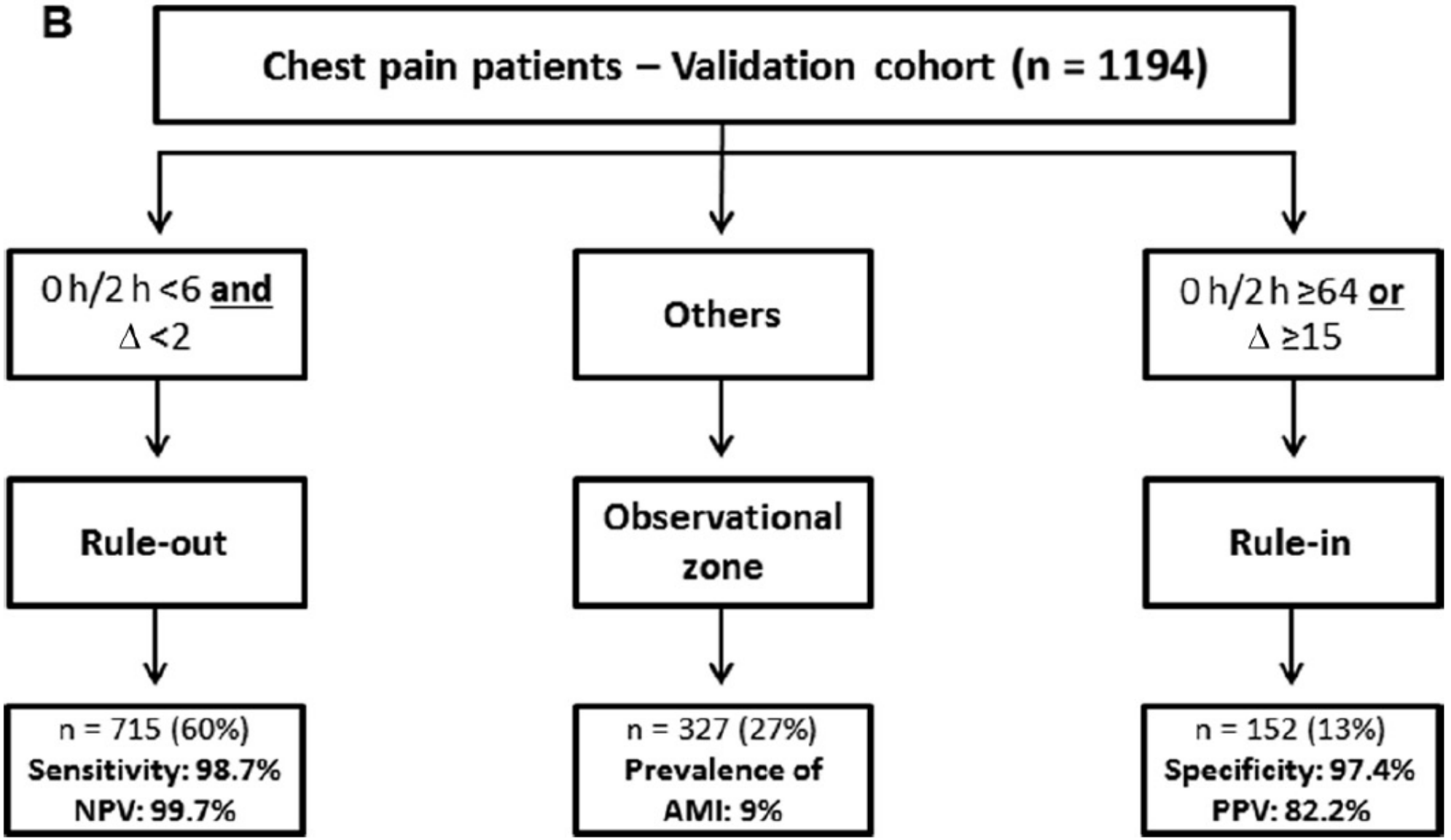
The Universal Definition of MI

Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia

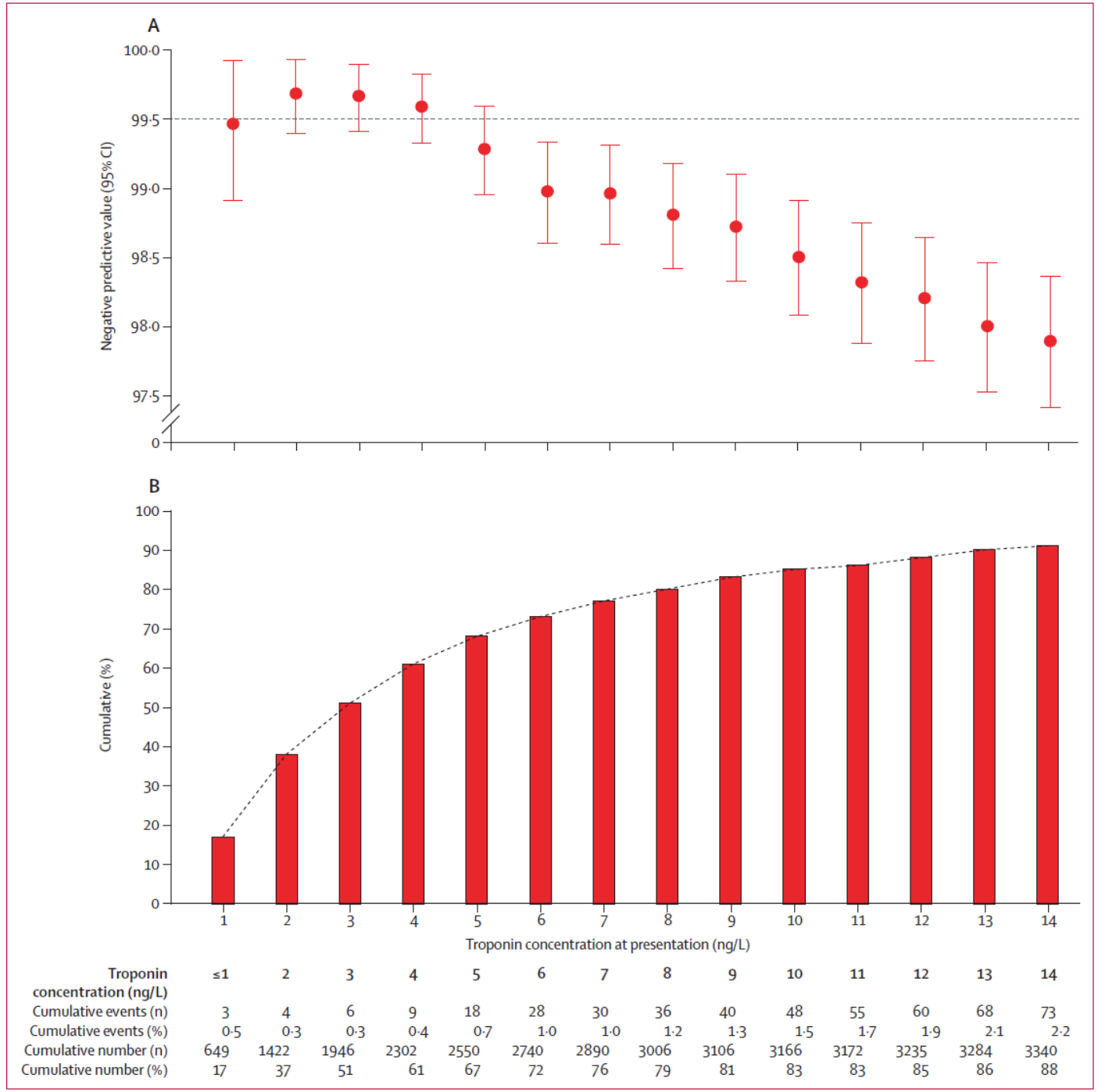
- Rise and/or fall in cTn (one value >99th percentile) PLUS either
  - Symptoms of Ischemia
  - New ST-segment-T-wave changes or LBBB
  - New pathological Q waves
  - Imaging evidence

Circulation. 2012;126:2020-2035





Clinical Chemistry 62:3
494–504 (2016)



Troponin concentration (ng/L)	≤1	2	3	4	5	6	7	8	9	10	11	12	13	14
Cumulative events (n)	3	4	6	9	18	28	30	36	40	48	55	60	68	73
Cumulative events (%)	0·5	0·3	0·3	0·4	0·7	1·0	1·0	1·2	1·3	1·5	1·7	1·9	2·1	2·2
Cumulative number (n)	649	1422	1946	2302	2550	2740	2890	3006	3106	3166	3172	3235	3284	3340
Cumulative number (%)	17	37	51	61	67	72	76	79	81	83	83	85	86	88

Figure 1: Cardiac troponin I concentration at presentation and risk of myocardial infarction

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Lancet 2015; 386: 2481–88

Hs-cTn change values

- **Analytical variability**: <5%
- **Short-term biological variability**:
  - Up to 20% for values at 99th percentile
  - Up to 50% in lower values (e.g. 4-8 ng/L)
- **Long-term biological variability**:
  - Up to 85%

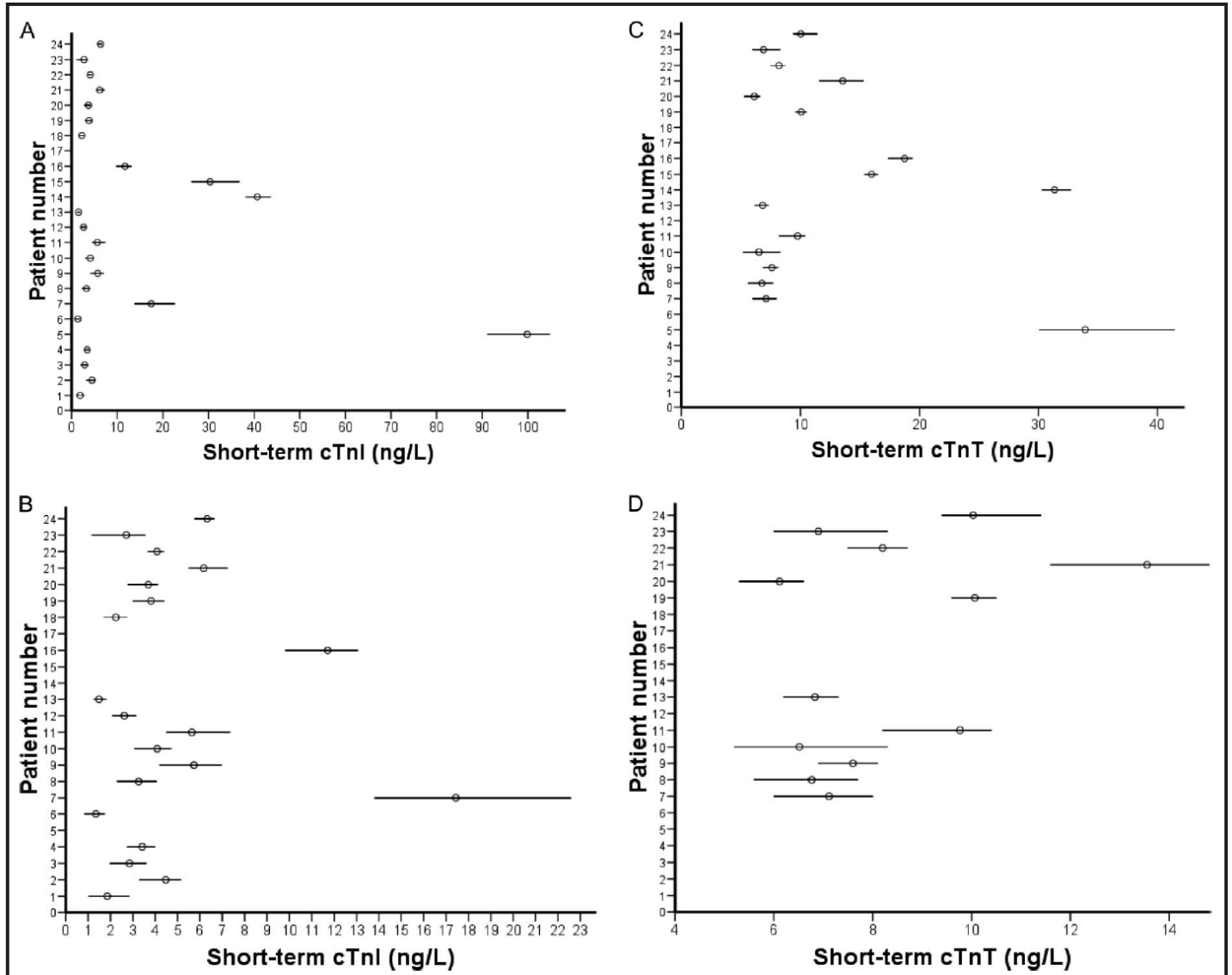
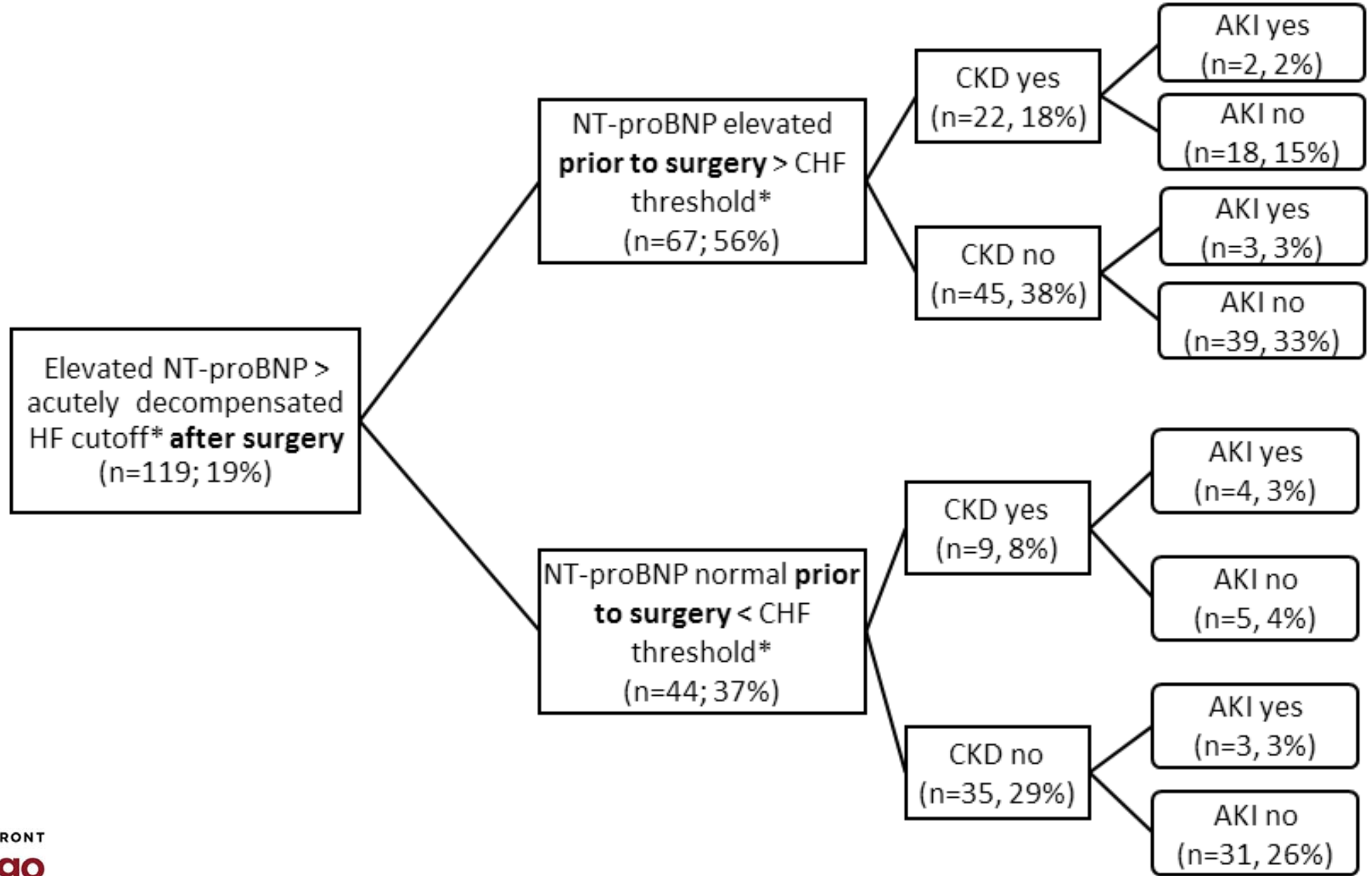


Fig. 2. Short-term distribution of cTnI and cTnT values showing the mean and range for all 23 patients with measurable values of cTnI (*A*), for the 19 patients with values below the 99th percentile (16 ng/L) for cTnI (*B*), for all 16 patients with measurable values for cTnT (*C*), and for the 11 patients with values below the 99th percentile (14 ng/L) for cTnT (*D*).

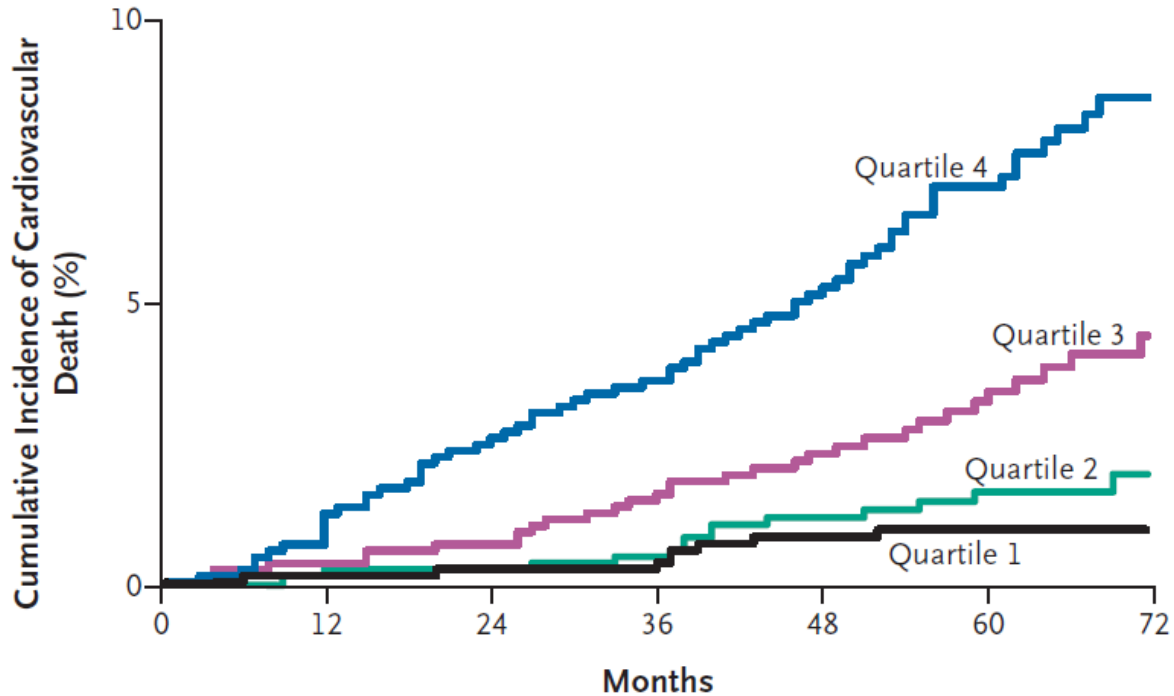
	NT-proBNP elevation	Clinical Symptoms	Imaging/ echo	Concomitant MI	Concomitant Myocardial Injury	Concomitant AKI	N (%)	Total n (%)
Probable	+	+	+	5 (45)	7 (64)	2 (18)	11 (1.8)	11 (1.8)
Possible	+	+	-	8 (35)	11 (48)	2 (9)	23 (3.7)	29 (4.7)
	+	-	+	3 (50)	3 (50)	1 (17)	6 (1.0)	
Uncertain	+	-	-	17 (22)	29 (38)	6 (8)	76 (12.3)	86 (13.9)
	-	+	+	3 (100)	2 (67)	0	3 (0.5)	
	-	+	-	1 (20)	3 (60)	0	5 (0.8)	
	-	-	+	0	1 (50)	0	2 (0.3)	
Unclear	-	-	-	6 (21)	12 (41)	1 (3)	28 (4.5)	29 (4.7)
Total	116	42	22	43	56 (36)	12 (8)	155 (25.1)	155 (25.1)



Risk Prediction

A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease

N Engl J Med 2009;361:2538-47.

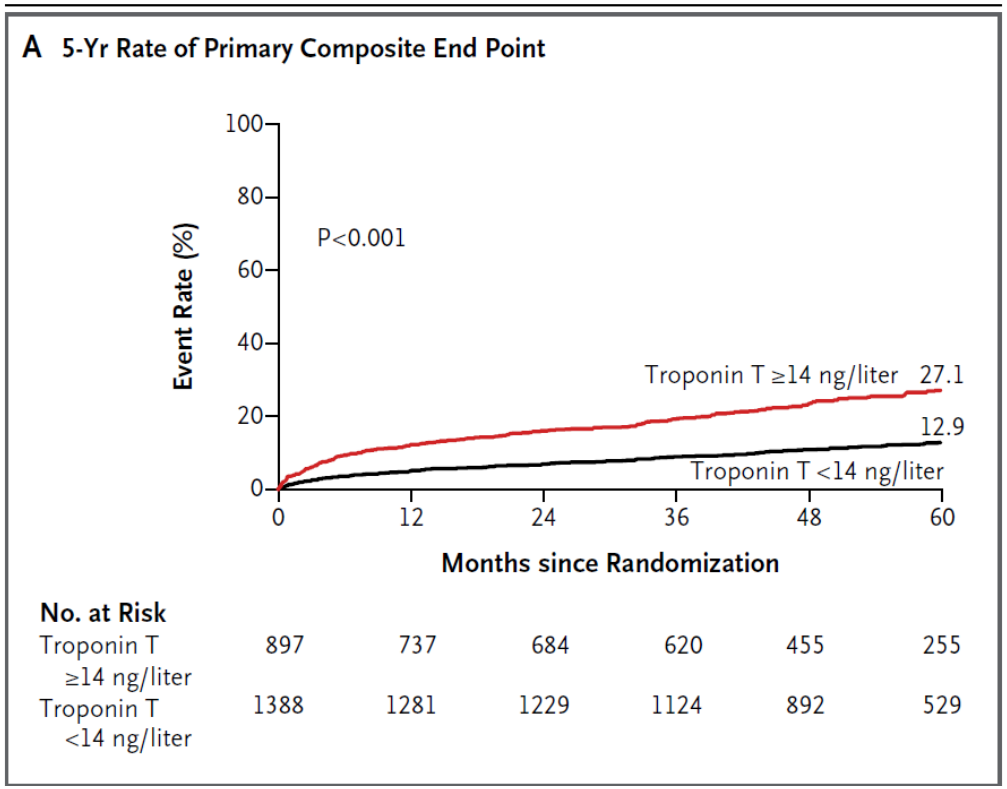


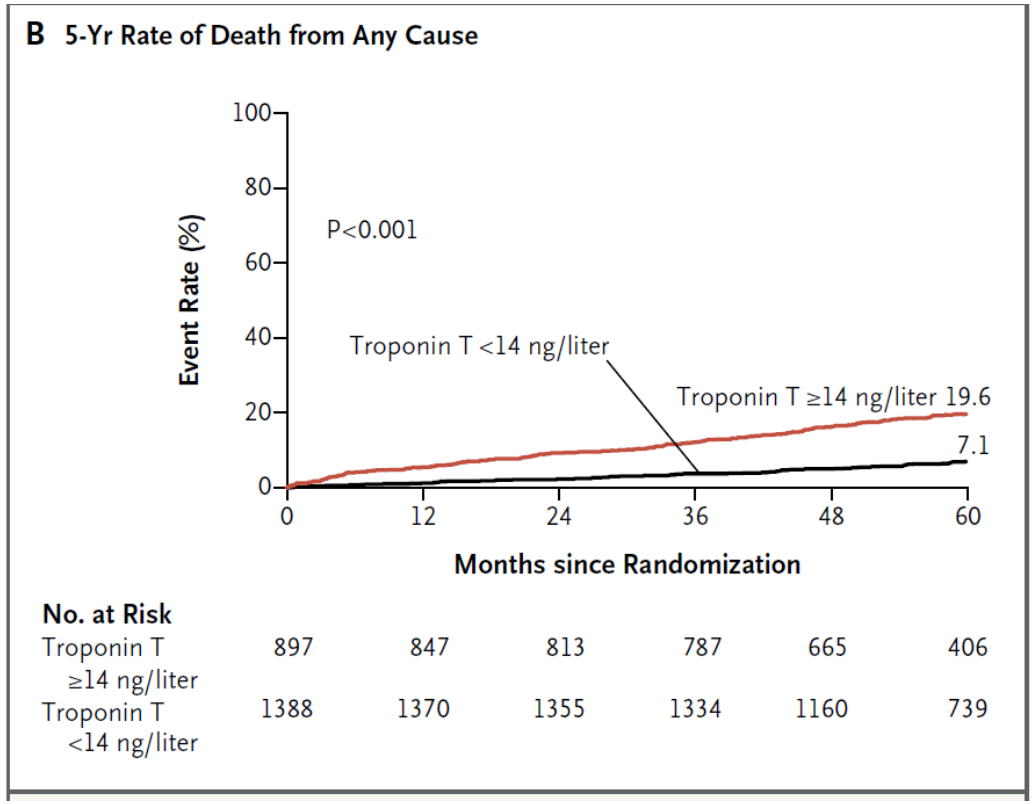
High-sensitivity cardiac troponin T levels (μg/liter)	Q1	Q2	Q3	Q4
Men	≤0.0042	0.0043–0.0062	0.0063–0.0095	≥0.0096
Women	≤0.0027	0.0028–0.0045	0.0046–0.0073	≥0.0074

Figure 2. Incidence of Cardiovascular Death According to Quartile of High-Sensitivity Cardiac Troponin T Level.

ORIGINAL ARTICLE

Troponin and Cardiac Events in Stable Ischemic Heart Disease and Diabetes





N Engl J Med 2015;373:610-20.

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