Erasmus MC
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# *REVISED MI DEFINITIONS*
## IMPLICATIONS FOR CLINICAL TRIALS

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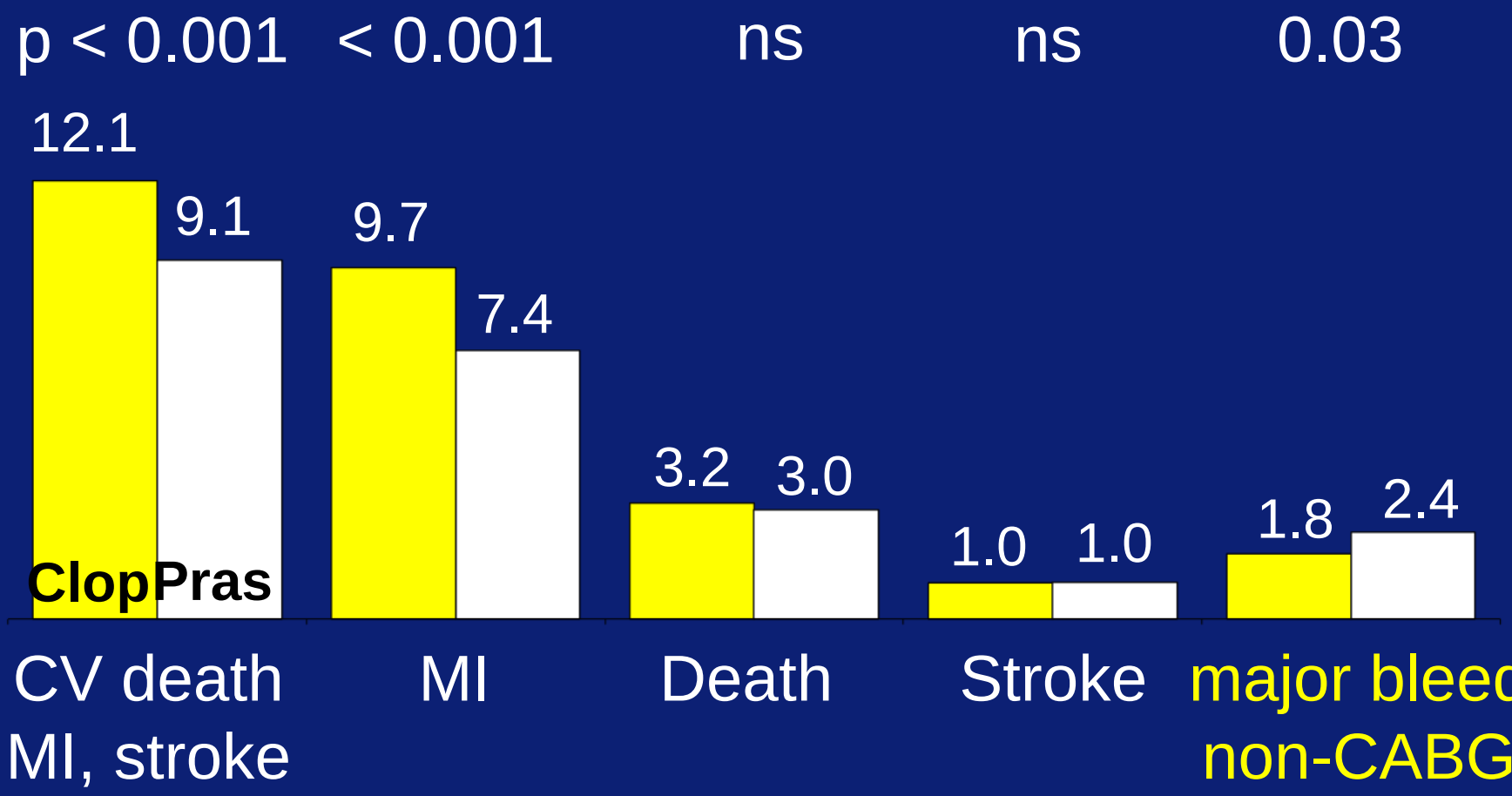
# TRITON Prasugrel ACS + PCI

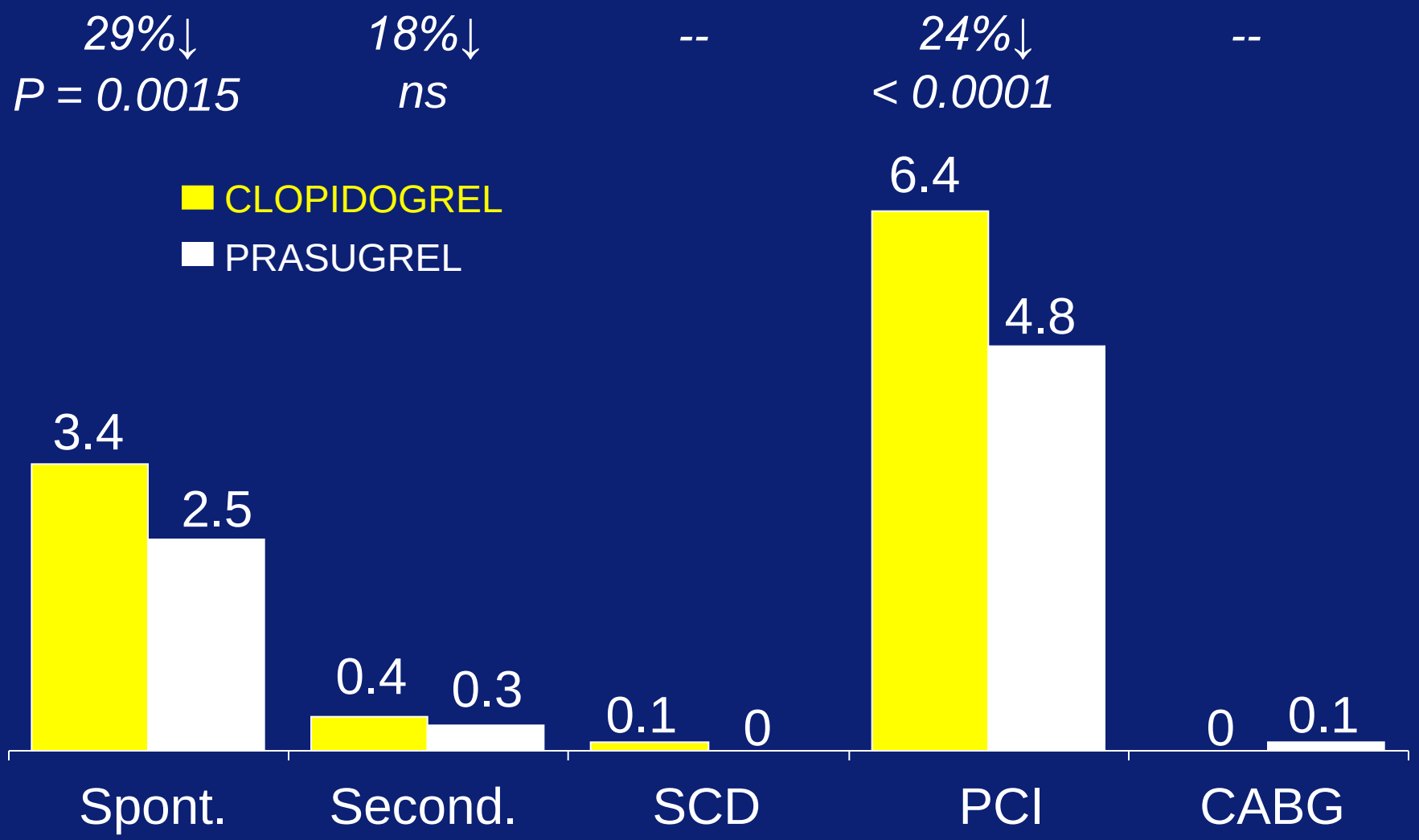
n = 13,608 moderate / high risk ACS, all PCI



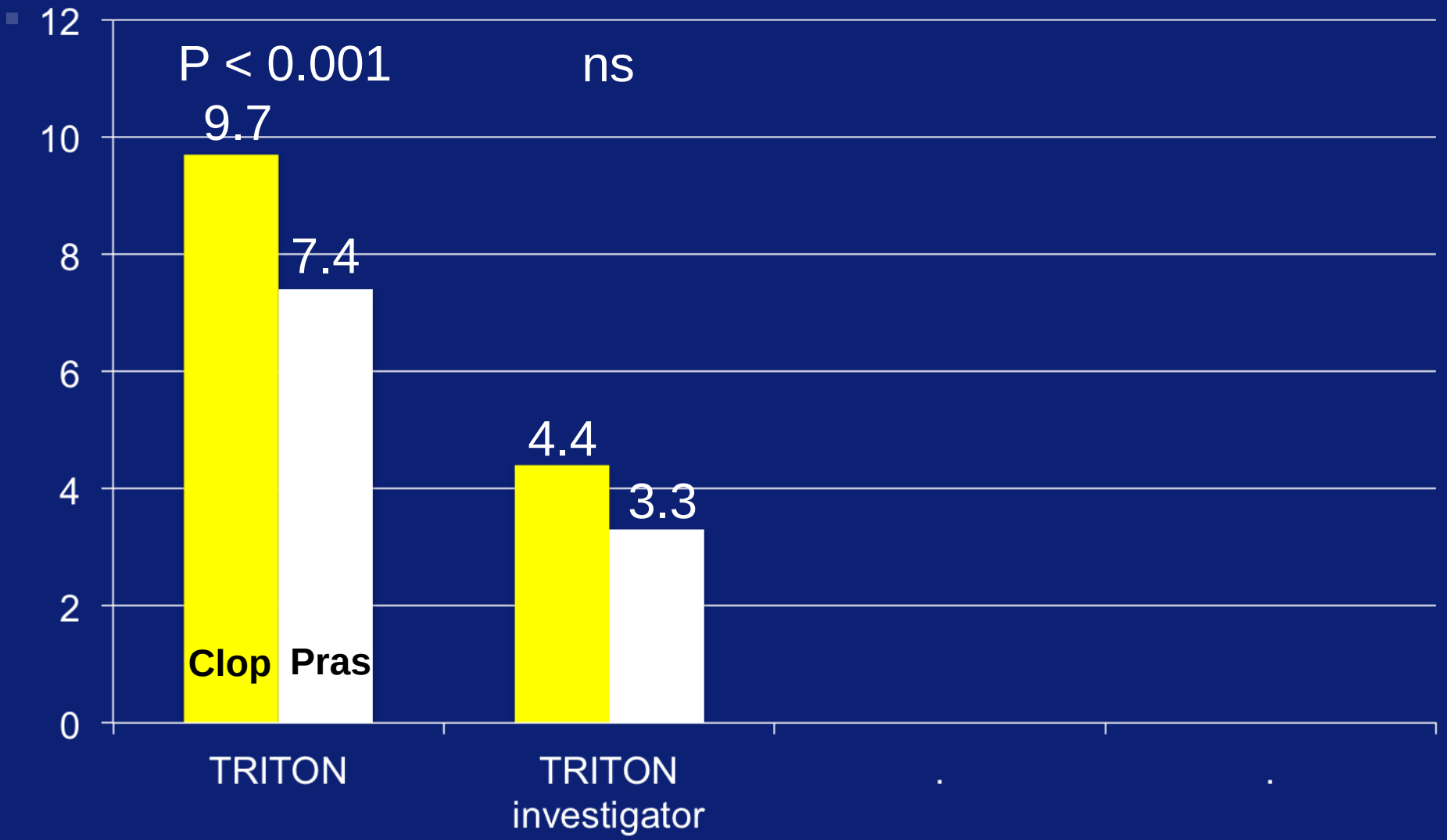

Wiviott NEJM 2007

# TRITON Prasugrel ACS + PCI

*Universal MI Classification*



# MI IN TRIALS: CEC - INVESTIGATOR




Serebruany Thromb Haemost 2012

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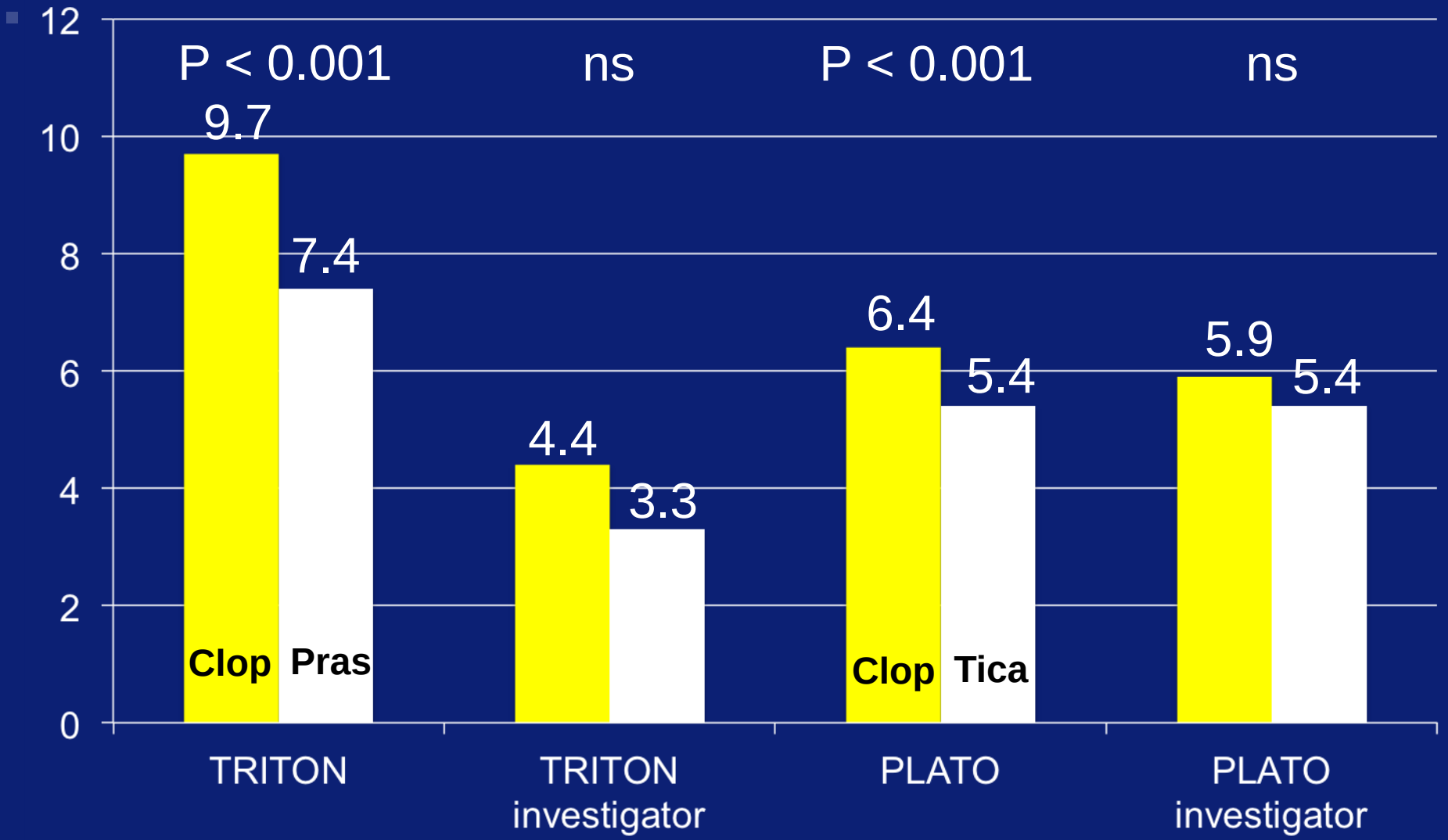


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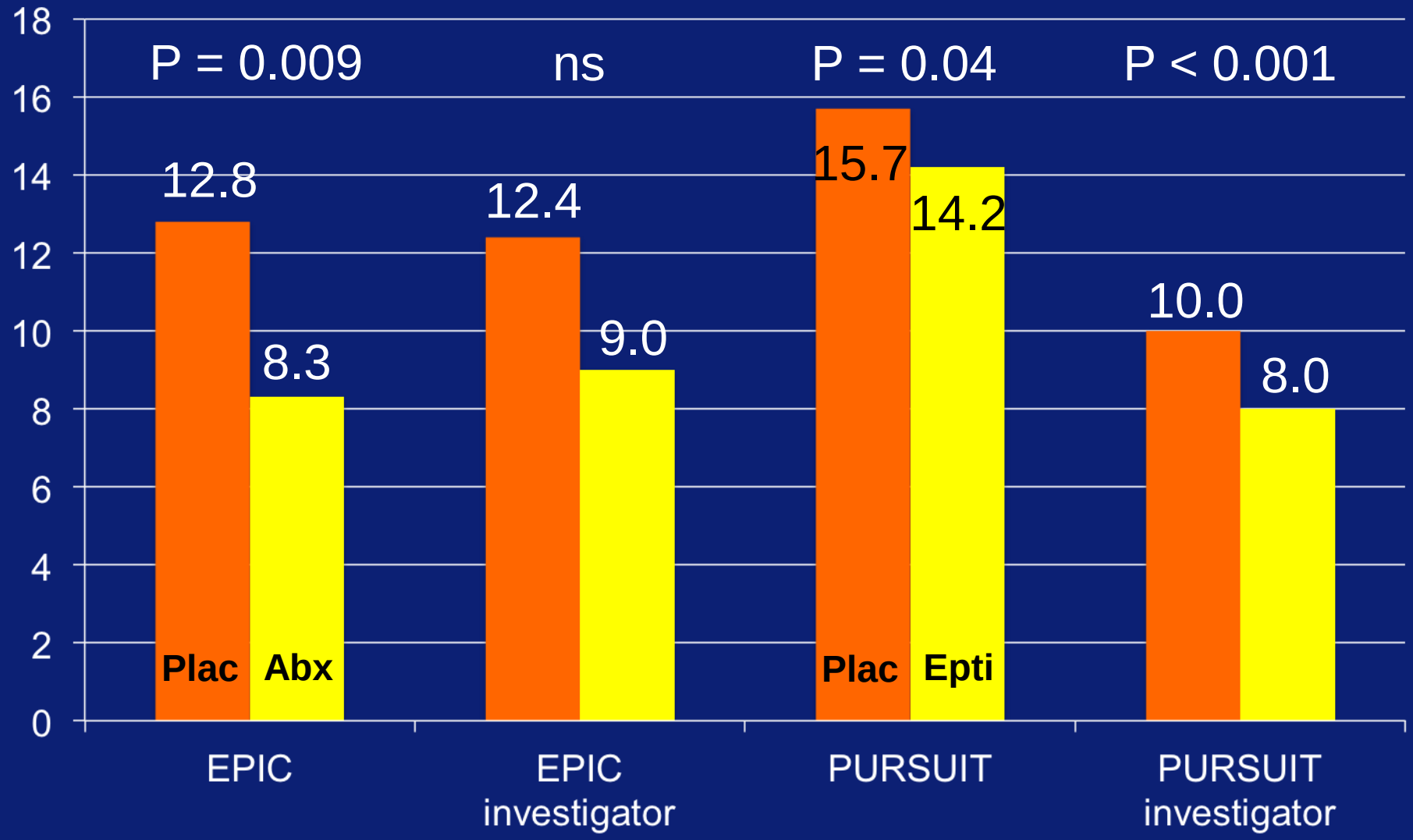
# MI IN TRIALS: CEC - INVESTIGATOR



# MI IN TRIALS: CEC - INVESTIGATOR

Outcome of trial may vary, depending on definitions of primary endpoints, particularly MI

The definition should be pre-specified,
according to ESC, ACC, AHA, WHF guidelines

Similarly pre-specify definitions of bleeding, stroke etc.

Both CEC and investigator reported endoints should be reviewed by regulatory agencies: EMA, FDA

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# *UNIVERSAL DEFINITION OF MI*

ESC, ACC, AHA Eur Heart J 2000

- MI = necrosis caused by ischaemia

ESC, ACC, AHA, WHF Eur Heart J 2007

- distinguish different causes (types) of MI

ESC, ACC, AHA, WHF Eur Heart J 2012

- more sensitive markers of myocardial necrosis
- myocardial necrosis in critically ill (MI or injury)
- myocardial necrosis with PCI or CABG

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# UNIVERSAL DEFINITION OF MI

*Evidence of myocardial necrosis*

- Rise and/or fall of markers of necrosis (troponin) with at least one value > 99% URL

*In clinical setting of myocardial ischaemia*

- Symptoms
- New (presumed new) ST-T changes or LBBB
- Development of (new) Q waves
- Imaging evidence of loss of viable myocardium or new wall motion abnormality
- Intracoronary thrombus by angio / autopsy

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# *MYOCARDIAL NECROSIS*

*Primary myocardial ischaemia (MI type 1)*

- Plaque rupture / fissure
- Intracoronary thrombus

*Ischaemia by supply / demand imbalance*

- Tachy-brady-arrhythmia
- Aortic dissection, severe Aortic valve disease
- Hypertrophic cardiomyopathy
- Cardiogenic, hypovolemic, septic shock
- Severe anaemia
- Hypertension (+/- LVH)
- Coronary spasm, embolism, vasculitis
- Endothelial dysfunction without significant CAD

# *MYOCARDIAL NECROSIS*

*Injury not related to myocardial ischaemia*

- Cardiac contusion, surgery, ablation, pacing, defibrillator shock
- Rhabdomyolysis (cardiac involvement)
- Myocarditis
- Cardiotoxic agents (antracyclines, herceptin)

*Multifactorial / undetermined myocardial injury*

- Heart failure, Stress (Takotsubo) cardiomyopathy
- Pulmonary embolism, pulmonary hypertension
- Sepsis and critical ill patients
- Renal failure, stroke, intracranial bleeding
- Amyloidosis, sarcoidosis, strenuous exercise

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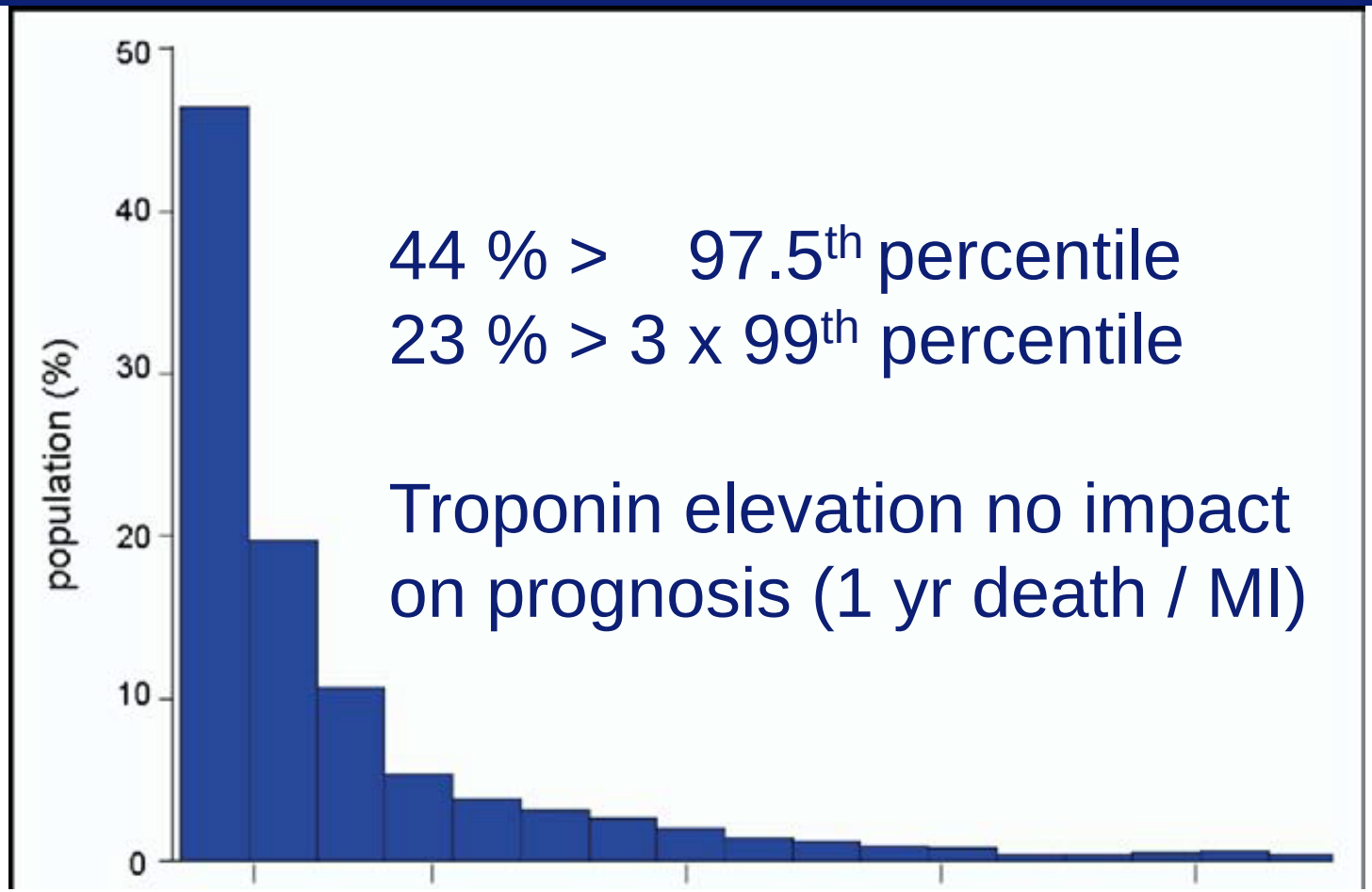
# PCI RELATED MI

Continuing discussion about relevance of PCI related myocardial injury:

- It is often unavoidable,
  however it is better if such injury could be limited
- It can be limited by careful catheter / wire handling and by anti-thrombotic therapy
- Even in patients with successful, elective PCI and a normal troponin level before the procedure, troponin elevation (myocardial injury) is frequent
- The long-term consequences are uncertain

Similarly, in cardiac surgery some injury is often unavoidable

# PCI RELATED MI




44 % > 97.5$^{th}$ percentile

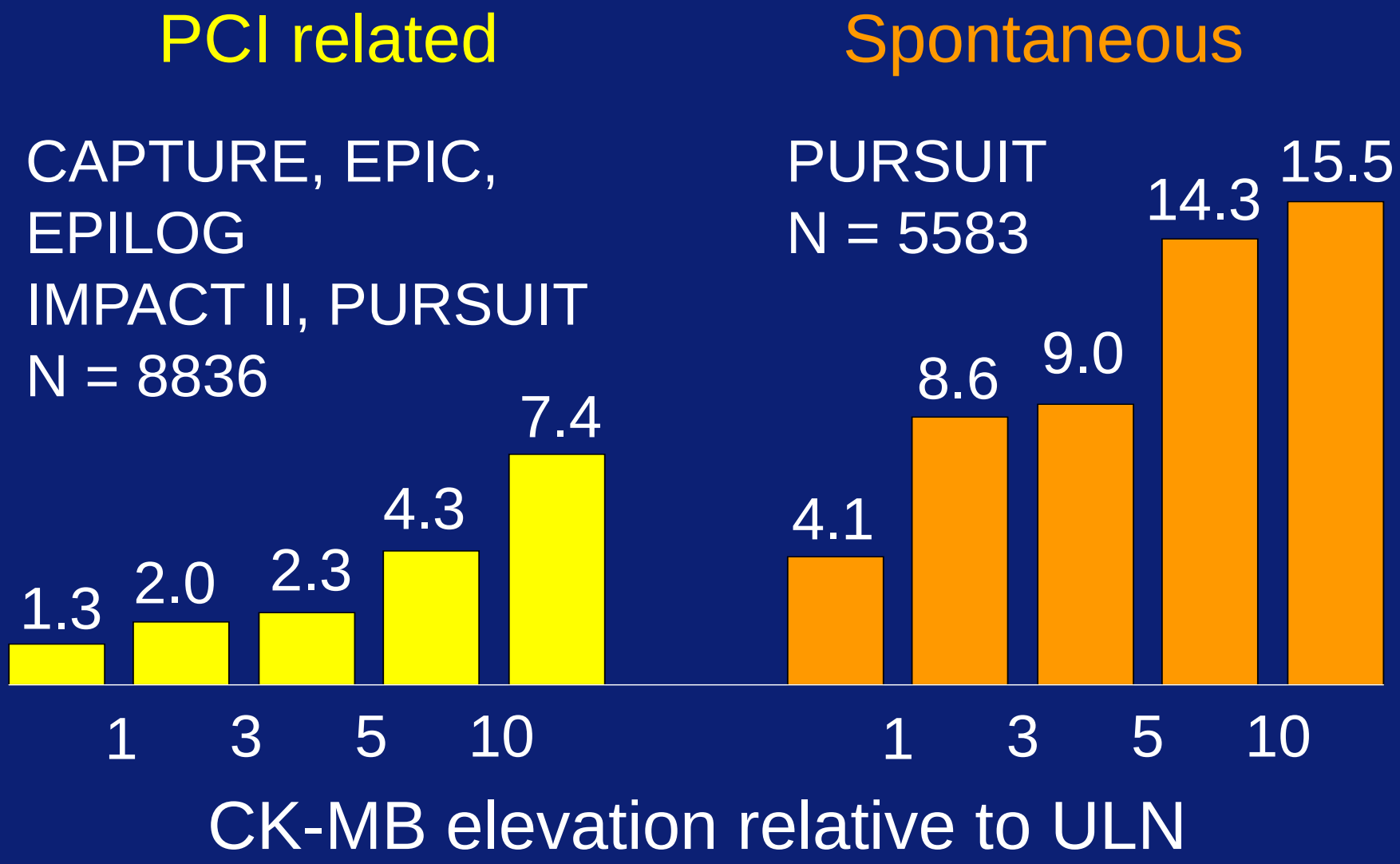
23 % > 3 x 99$^{th}$ percentile

Troponin elevation no impact on prognosis (1 yr death / MI)

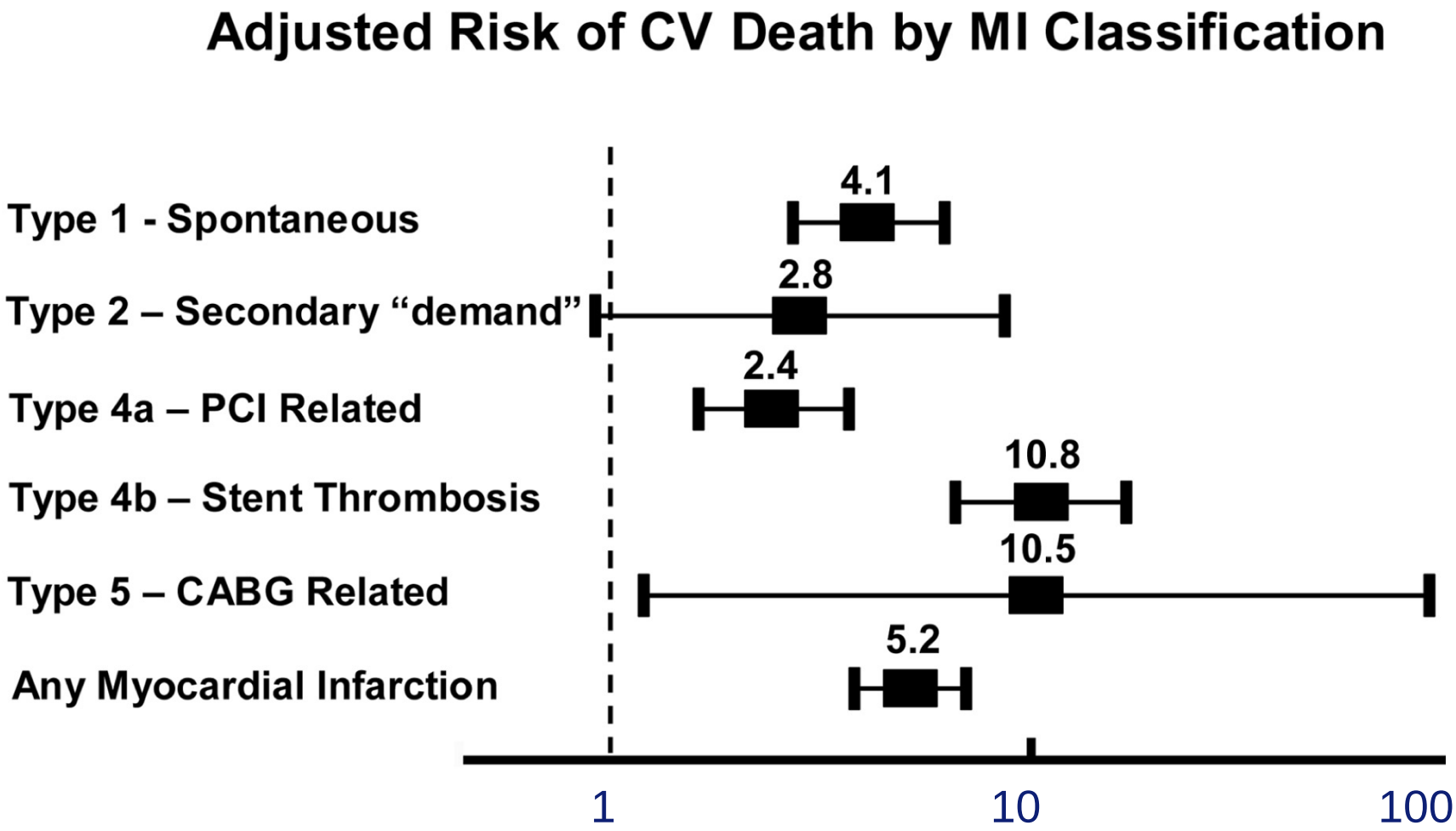
3200 patients, successful elective PCI De Labriolle Am J Card 2009

# Mortality at 6 months follow-up (%)

## Akkerhuis, Simoons Circulation 2002



# SPONTANEOUS / PCI RELATED MI

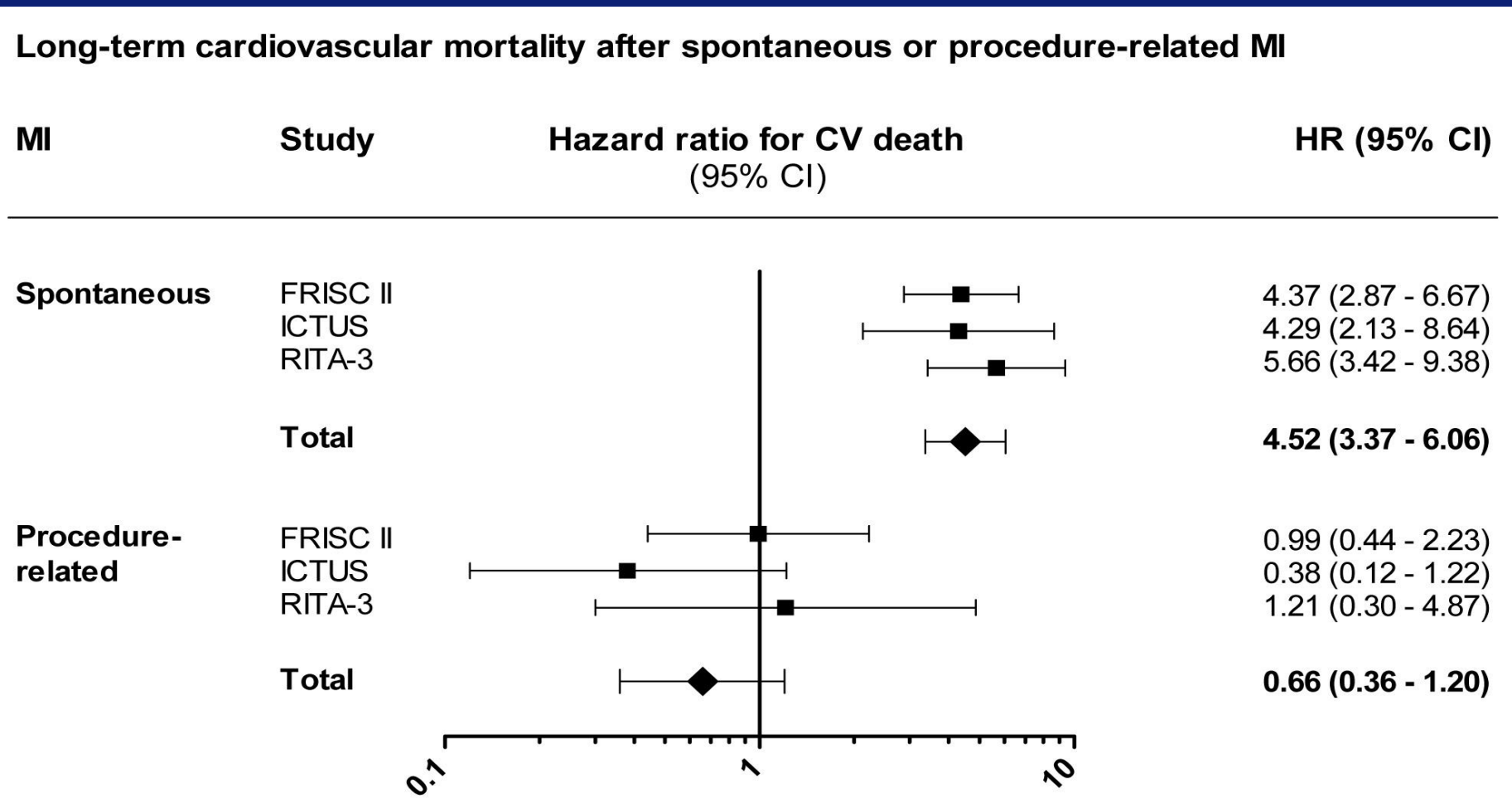



13,602 patients, 1118 new or recurrent MI after enrollment, 6 m follow-up

TRITON-TIMI 38 Bonaca et al Circulation 2012

# SPONTANEOUS / PCI RELATED MI

**Long-term cardiovascular mortality after spontaneous or procedure-related MI**




5467 patients, 212 PCI related MI, 236 spontaneous MI after enrollment, 5 year follow-up. FRISC II, ICTUS, RITA-3 Damman et al Circulation 2012

# *SPONTANEOUS / PCI RELATED MI*

Discussion about relevance of PCI related injury:

- Elective PCI / ACS; varying follow-up
- Inclusion or exclusion of patients with elevated markers of necrosis before PCI
- Even if CK or CK-MB was normal before PCI, troponin might have been elevated
- Results may depend on method of analysis, some studies were underpowered

*Consequences of PCI related myocardial injury are less severe than spontaneous MI, which is important for interpretation of trial results and for information to patients.*

Damman, Wallentin, Fox, Circ 2012

# PCI RELATED MI

In patients with normal baseline (< 99th %) troponin elevation > 5 x 99th % within 48 hours after the procedure (arbitrary) are indicative of MI, if

- Evidence of prolonged ischemia (pain > 20 min)
- Ischemic ST changes (>20 min) or new Q waves
- Angiographic evidence of flow limiting complications: side branch occlusion, no-reflow, persistent low flow, embolization
- Imaging evidence of new loss of viable myocardium or new wall motion abnormality

ESC, ACC, AHA, WHF 2012

# CABG RELATED MI

In patients with normal baseline (< 99th %) troponin elevation > 10 x 99th % within 48 hours after the procedure (arbitrary) are indicative of MI, if

- New Q waves or LBBB
- Angiographic evidence of graft- or coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new wall motion abnormality

ESC, ACC, AHA, WHF 2012

# REPORTING MI IN CLINICAL TRIALS

| Troponin > 99th % | | 1 - 3 | 3 - 5 | 5 - 10 | > 10 | Total |
|---|---|---|---|---|---|---|
| Spontaneous | 1 | | | | | |
| Secondary | 2 | | | | | |
| Death | 3 | | | | | |
| PCI related | 4 | | | | | |
| Stent occl. Restenosis | | | | | | |
| CABG | 5 | | | | | |

# *REPORTING MI IN CLINICAL TRIALS*

Collect blood samples at *baseline and 3 – 6 hours* later in patients with possible / suspected MI (ACS).
Collect samples before and 3 – 6 hrs after PCI / CABG

Assess cardiac *Troponin I / T*
(If Troponin cannot be measured use *CK-MB mass)*
Interpret using 99$^{th}$ percentile URL for each laboratory

Present the definition of MI to be used in the trial analysis plan and define role of Clinical Event Cie

Report MI, and other endpoints. (trial definitions).
Also report the full data table (Guidelines) such that alternative definitions can be applied in meta-analyses

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