

# **Chaos in PMI in trials comparing PCI vs CABG How do we reconcile?**

**Patrick W. Serruys**

**Established professor of interventional medicine and innovation  
National University of Ireland Galway**

Hironori Hara  
Masafumi Ono  
Kawashima Hideyuki  
Yoshinobu Onuma



**NUI Galway**  
**OÉ Gaillimh**

# JACC Oct 2020: PMI in the SYNTAX and EXCEL trials

## Impact of Peri-Procedural Myocardial Infarction on Outcomes After Revascularization



Hironori Hara, MD,<sup>a,b,\*</sup> Patrick W. Serruys, MD, PhD,<sup>b,c,\*</sup> Kuniaki Takahashi, MD,<sup>a</sup> Hideyuki Kawashima, MD,<sup>a,b</sup> Masafumi Ono, MD,<sup>a,b</sup> Chao Gao, MD,<sup>b,d</sup> Rutao Wang, MD,<sup>b,d</sup> Friedrich W. Mohr, MD, PhD,<sup>e</sup> David R. Holmes, MD,<sup>f</sup> Piroze M. Davierwala, MD,<sup>e</sup> Stuart J. Head, MD, PhD,<sup>g</sup> Daniel J.F.M. Thuijs, MD,<sup>g</sup> Milan Milojevic, MD, PhD,<sup>g</sup> Arie Pieter Kappetein, MD, PhD,<sup>g</sup> Scot Garg, MD, PhD,<sup>h</sup> Yoshinobu Onuma, MD, PhD,<sup>b</sup> Michael J. Mack, MD,<sup>i</sup> for the SYNTAX Extended Survival Investigators

## Implications of Alternative Definitions of Peri-Procedural Myocardial Infarction After Coronary Revascularization



John Gregson, PhD,<sup>a</sup> Gregg W. Stone, MD,<sup>b,c</sup> Ori Ben-Yehuda, MD,<sup>c,d</sup> Björn Redfors, MD, PhD,<sup>c,d,e</sup> David E. Kandzari, MD,<sup>f</sup> Marie-Claude Morice, MD,<sup>g</sup> Martin B. Leon, MD,<sup>c,d</sup> Ioanna Kosmidou, MD, PhD,<sup>c,d</sup> Nicholas J. Lembo, MD,<sup>c,d</sup> W. Morris Brown III, MD,<sup>f</sup> Dimitri Karmpaliotis, MD,<sup>c,d</sup> Adrian P. Banning, MD,<sup>h</sup> Jose Pomar, MD,<sup>i</sup> Manel Sabaté, MD,<sup>i</sup> Charles A. Simonton, MD,<sup>j</sup> Ovidiu Dressler, MD,<sup>c</sup> Arie Pieter Kappetein, MD, PhD,<sup>k</sup> Joseph F. Sabik III, MD,<sup>l</sup> Patrick W. Serruys, MD, PhD,<sup>m,n</sup> Stuart J. Pocock, PhD<sup>a</sup>

## Procedural Myocardial Infarction



Definitions Everywhere, But Not Any That May Fit\*

Donald E. Cutlip, MD

# What is the advice of Editorial



## Procedural Myocardial Infarction

Definitions Everywhere, But Not Any That May Fit\*

Donald E. Cutlip, MD

- “We may be forced to accept that the **same procedural MI definition cannot be fit** to both procedures.
- Determining that **threshold** remains a topic of debate.
- If we cannot find definitions that fit these purposes, then perhaps it is time to **remove procedural MI from primary composite endpoints.**”

# Rationales for using PMI as events in trials

- **PMI as a “dated event”** has been integrated as a critical item in composite endpoints.
- Its definitions encompass a **variety of combined or isolated** phenomena, such as enzyme elevation, permanent ECG change, anatomic occlusion of vessels, and loss of viable myocardium.
- Conversely, the **clinical relevance** of a PMI should be defined as a PMI leading to death, re-intervention, or hospitalization for heart failure.
- **Isolated enzymatic “PMI events”** are frequently incorporated into time to event composite endpoints to satisfy trial designers **in search of a powered sample size**, but they may artificially influence the interpretation of the real benefit of a novel treatment.

# Which definition should we use?

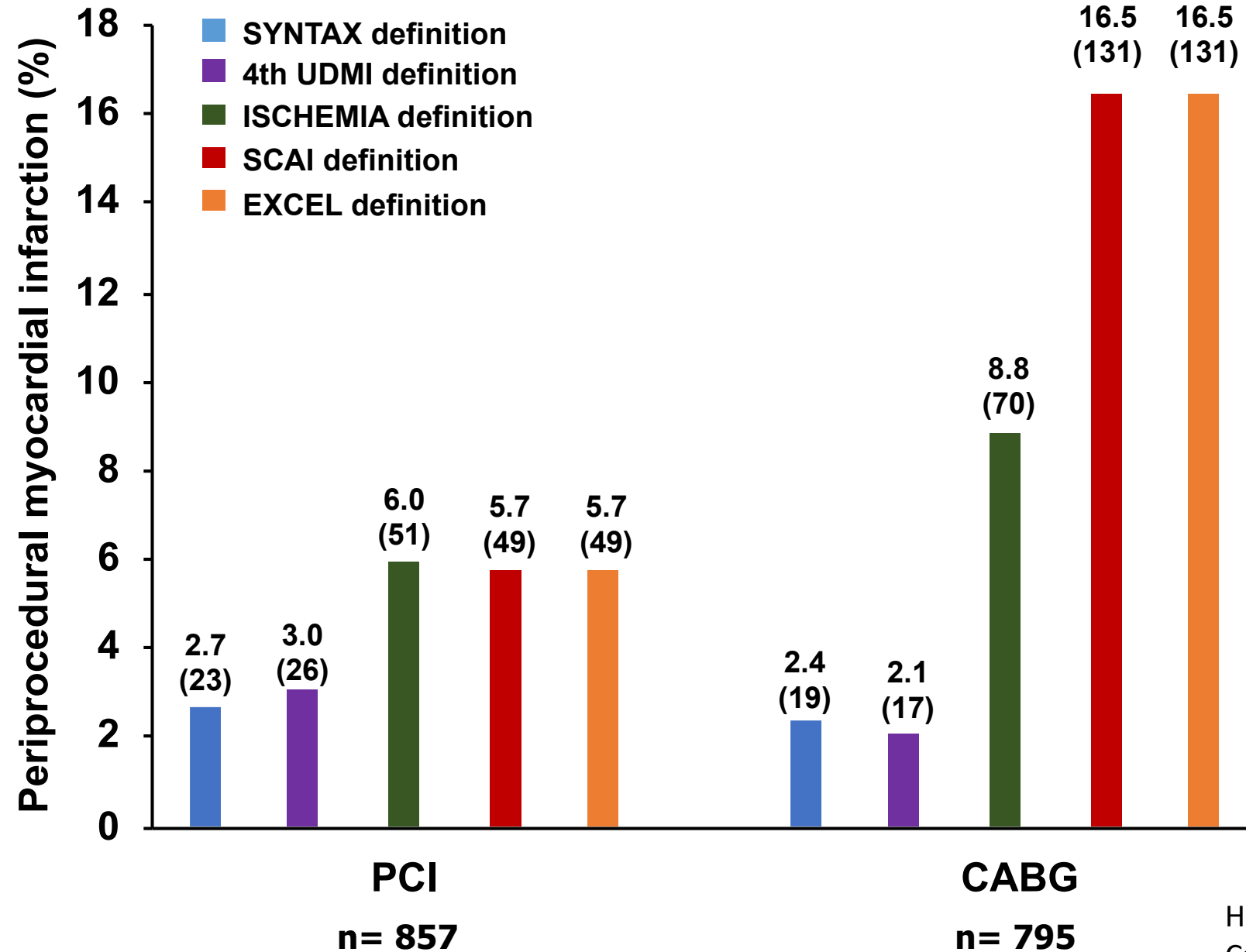
## Five PMI definitions applied to the SYNTAX trial (Only CK-MB was available)

Definitions	Time after procedure	PCI arm	CABG arm
SYNTAX	in the first 48 hours	("CK-MB $\geq$ 5x ULN" and "ECG criteria: new Q waves in $\geq$ 2 leads")	

**Different thresholds for  
PCI and CABG**

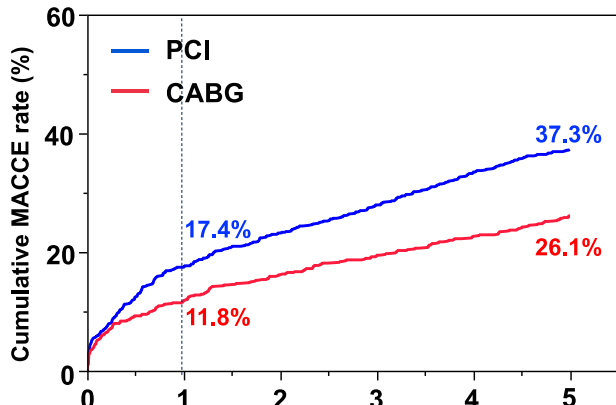
**No additional evidence  
of infarction**

# PMI rates according to definitions in the SYNTAX trial



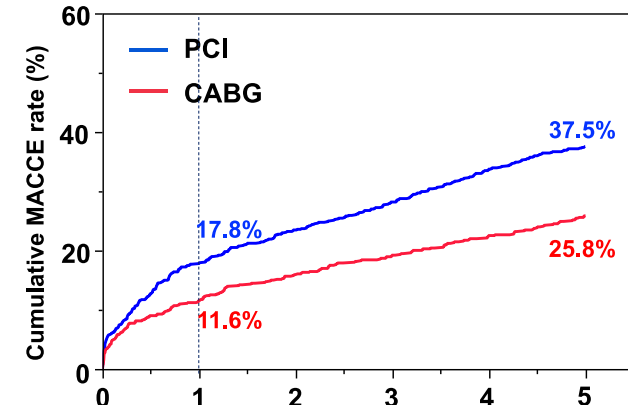
# MACCE rates according to PMI definitions in the SYNTAX trial

## SYNTAX definition



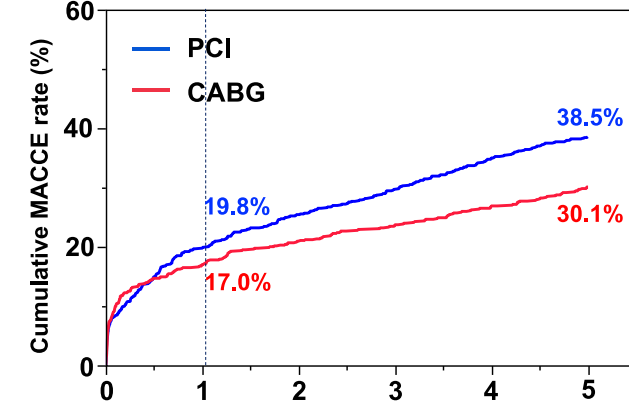
Patient number at risk	0	1	2	3	4	5
PCI	857	703	653	611	563	518
CABG	795	679	637	609	584	548

## 4th UDMI definition



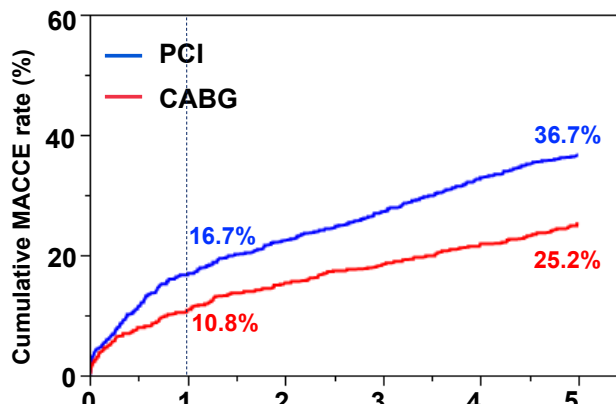
Patient number at risk	0	1	2	3	4	5
PCI	857	700	651	609	561	516
CABG	795	681	639	611	586	550

## ISCHEMIA definition



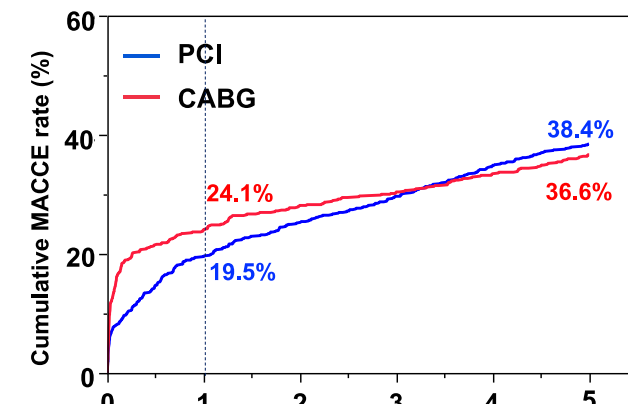
Patient number at risk	0	1	2	3	4	5
PCI	857	683	634	595	550	508
CABG	795	638	600	576	552	518

## Excluding PMI



Patient number at risk	0	1	2	3	4	5
PCI	857	709	659	616	568	522
CABG	795	687	644	616	591	553

## SCAI or EXCEL definition



Patient number at risk	0	1	2	3	4	5
PCI	857	685	635	596	551	509
CABG	795	583	545	524	500	469

# Impact of PMI on all-cause mortality in SYNTAX : Which definition is clinically relevant ?

## SYNTAX definition

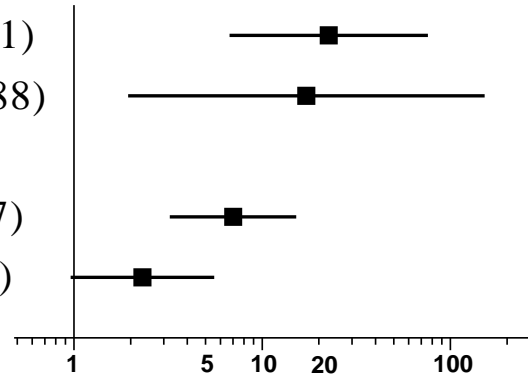
Adjusted HR (95% CI)

### At 1 year

PCI arm	22.57 (6.71-75.91)
CABG arm	17.15 (1.94-151.88)

### At 10 years

PCI arm	7.01 (3.23-15.17)
CABG arm	2.31 (0.96-5.56)



## 4th UDMI definition

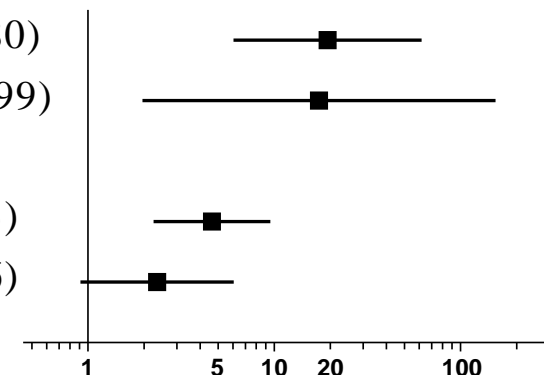
Adjusted HR (95% CI)

### At 1 year

PCI arm	19.33 (6.04-61.80)
CABG arm	17.38 (1.96-153.99)

### At 10 years

PCI arm	4.63 (2.25-9.53)
CABG arm	2.35 (0.91-6.06)



## ISCHEMIA definition

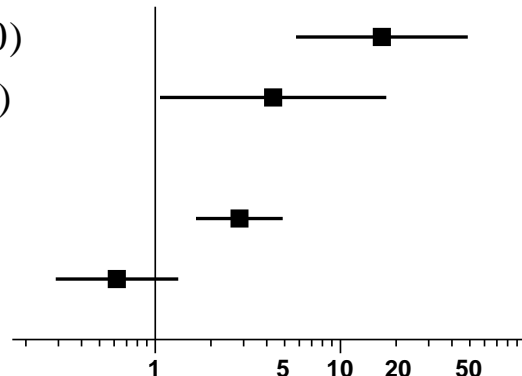
Adjusted HR (95% CI)

### At 1 year

PCI arm	16.74 (5.76-48.70)
CABG arm	4.33 (1.06-17.70)

### At 10 years

PCI arm	2.85 (1.66-4.88)
CABG arm	0.62 (0.29-1.33)



## SCAI or EXCEL definition

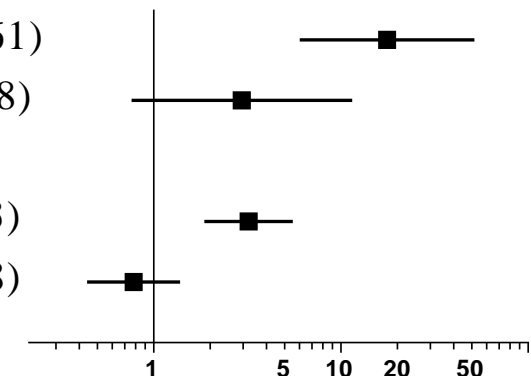
Adjusted HR (95% CI)

### At 1 year

PCI arm	17.63 (6.02-51.61)
CABG arm	2.95 (0.76-11.48)

### At 10 years

PCI arm	3.21 (1.86-5.53)
CABG arm	0.78 (0.44-1.38)

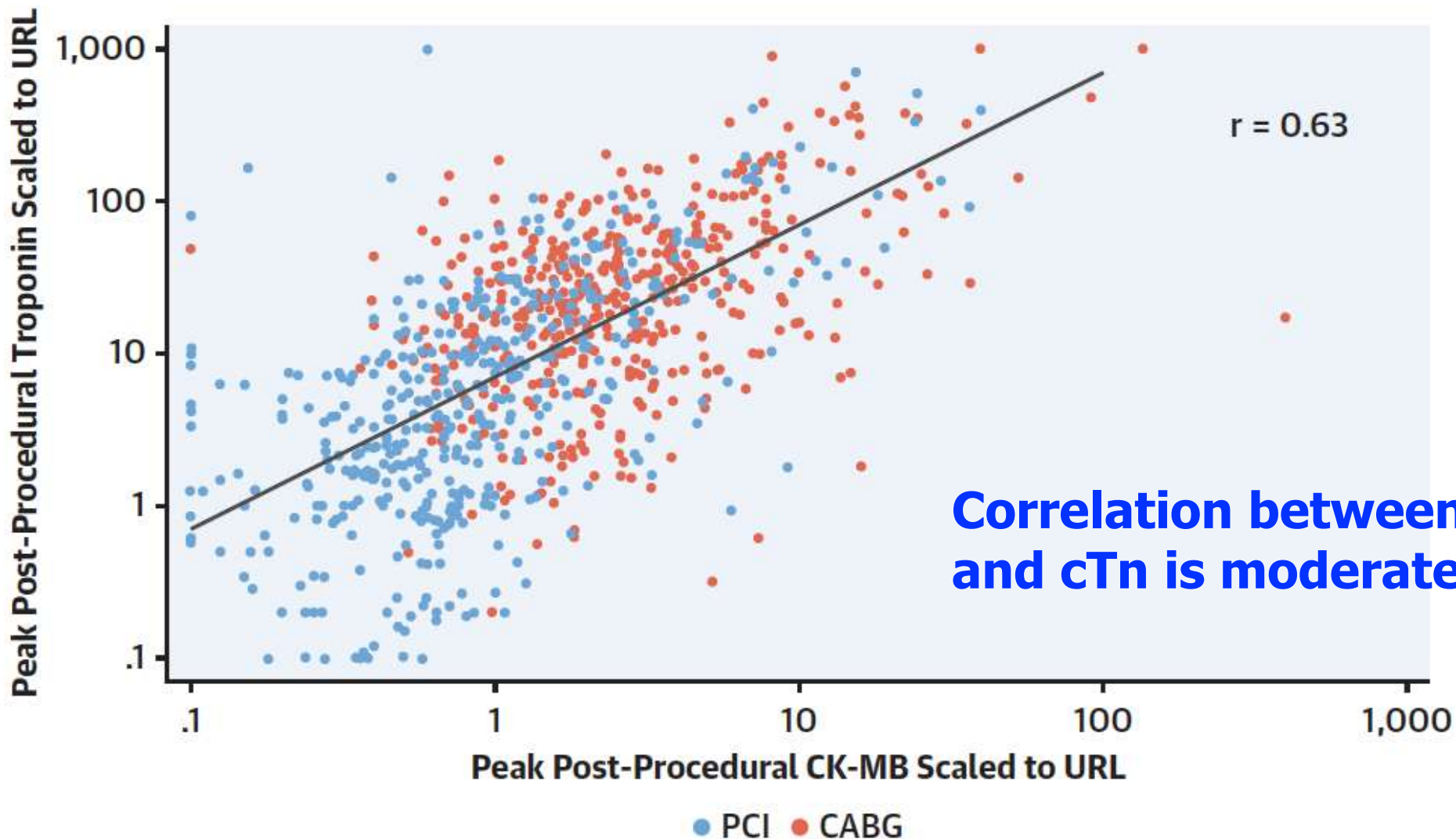




# PMI definitions applied to the **EXCEL trial**

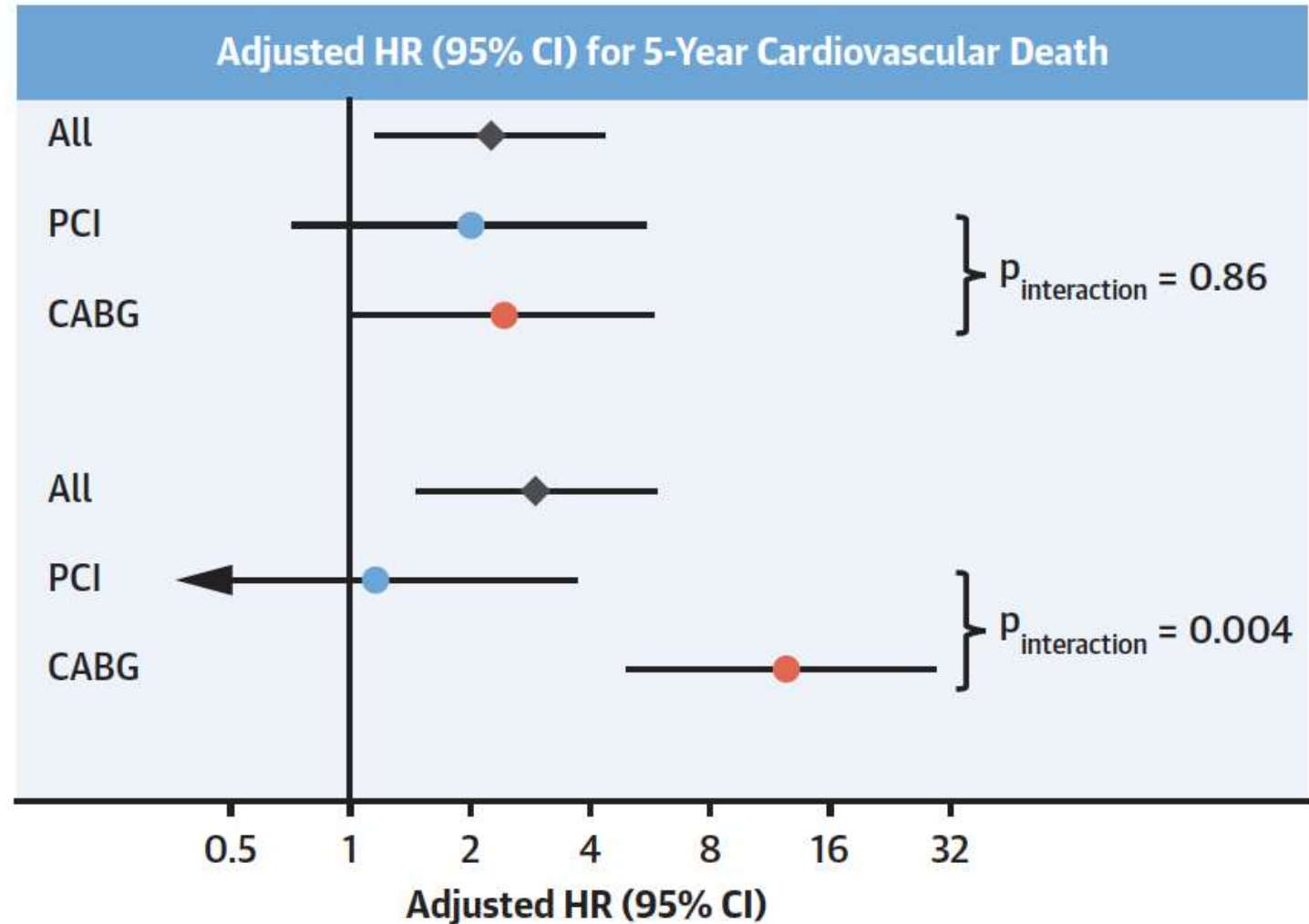
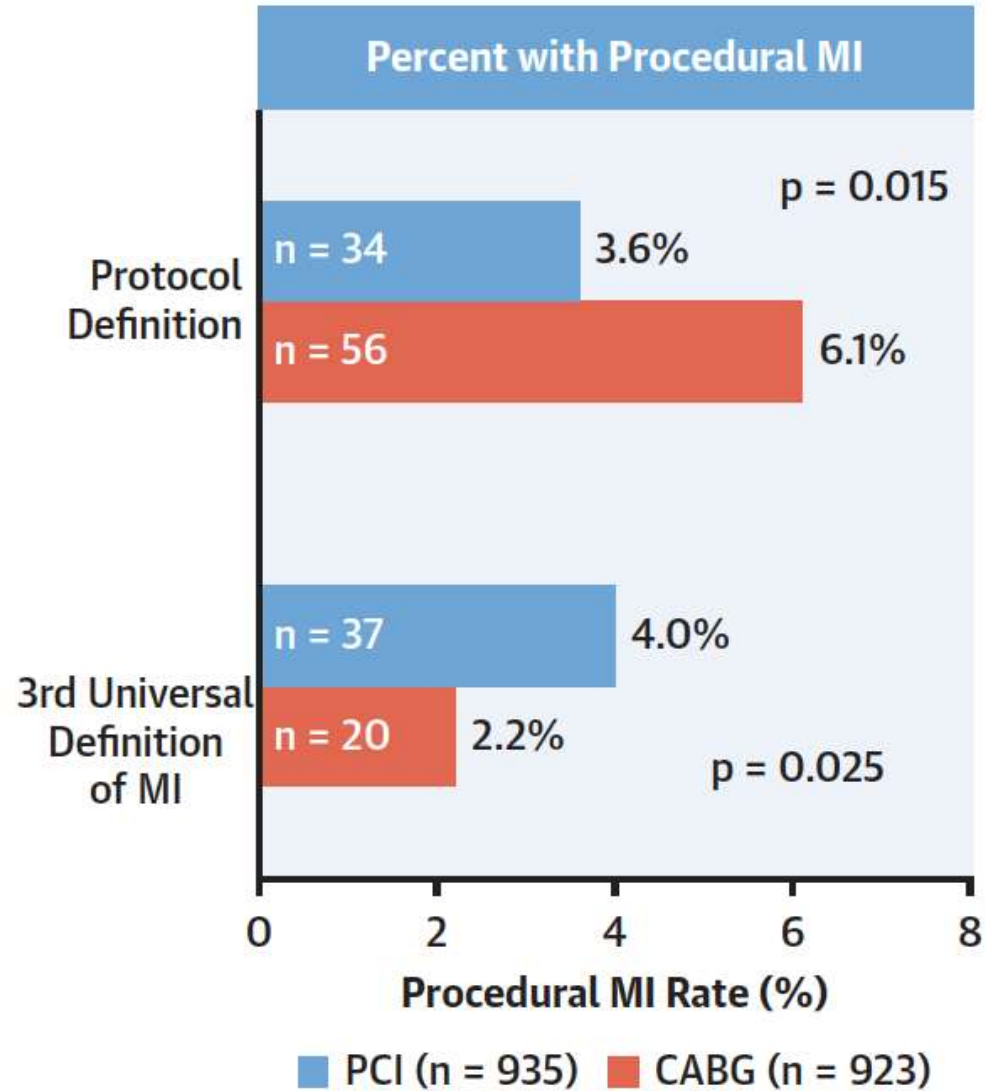
Definition	Modality	Time after procedure	Peak biomarker threshold	Supporting evidence required
<b>Protocol Definition</b>		Within 72 hrs		
	PCI		CKMB >10x URL* or CKMB >5x URL*	None <b>No additional evidence</b>
<b>CK-MB is preferred</b>				<p><i>One or more of the following:</i></p> <p><u>ECG</u>: new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB</p> <p><u>Angiographic</u>: graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow</p> <p><u>Imaging</u>: new loss of viable myocardium or new regional wall motion abnormality</p>
	CABG		Exact same as PCI	Exact same as PCI
<b>3<sup>rd</sup> Universal Definition</b>		Within 48 hrs		<b>Additional evidence is mandatory</b>
<b>cTn is preferred</b>				<p><i>One or more of the following:</i></p> <p><u>Clinical</u>: symptoms suggestive of myocardial ischemia (such as ischemic chest pain lasting ≥20 minutes)</p> <p><u>ECG</u>: new ischemic changes (ST segments or new pathologic Q waves) or new LBBB</p> <p><u>Angiographic</u>: consistent with a procedural complication (loss of patency of a major coronary artery or side branch or persistent slow- or no-reflow or embolization)</p> <p><u>Imaging</u>: evidence of new loss of viable myocardium or new regional wall motion abnormality</p>
	PCI (type 4a)		cTn >5x 99 <sup>th</sup> percentile URL† (or CKMB >5x 99 <sup>th</sup> percentile URL† if cTn unavailable)	<p><i>One or more of the following:</i></p> <p><u>Clinical</u>: no criteria</p> <p><u>ECG</u>: new pathologic Q waves or new LBBB</p> <p><u>Angiographic</u>: new graft or new native coronary artery occlusion</p> <p><u>Imaging</u>: new loss of viable myocardium or new regional wall motion abnormality</p>
	CABG (type 5)		cTn >10x 99 <sup>th</sup> percentile URL† (or CKMB >10x 99 <sup>th</sup> percentile URL† if cTn unavailable)	<p><i>One or more of the following:</i></p> <p><u>Clinical</u>: no criteria</p> <p><u>ECG</u>: new pathologic Q waves or new LBBB</p> <p><u>Angiographic</u>: new graft or new native coronary artery occlusion</p> <p><u>Imaging</u>: new loss of viable myocardium or new regional wall motion abnormality</p>

# Peak Post-Procedural CK-MB and Troponin Levels in the EXCEL trial



**Correlation between CK-MB and cTn is moderate.**

# PMI rates according to definitions (UDMI vs Excel) and impact of PMI on CV death in the EXCEL trial



# Association of Myocardial Enzyme Elevation and Survival Following Coronary Artery Bypass Graft Surgery

Which enzyme should we use?

Michael J. Domanski, MD  
Kenneth Mahaffey, MD  
Vic Hasselblad, PhD  
Sorin J. Brener, MD  
Peter K. Smith, MD  
Graham Hillis, MBChB, PhD  
Milo Engoren, MD

John H. Alexander, MD, MHS  
Jerrold H. Levy, MD  
Bernard R. Chaitman, MD  
Samuel Broderick, MS  
Michael J. Mack, MD  
Karen S. Pieper, MS  
Michael E. Farkouh, MD, MSc

**CK-MB**  
**cTn**

**30 Days mortality in CABG patients**  
**18908 patients from 7 studies**

**CK-MB could be recommended as a cardiac enzyme for PMI in CABG, compared to cTn.**

Creatine kinase MB ratio category <sup>b</sup>		
1 to <5		
5 to <10	4525	2.98 (1.55-5.60)
10 to <20	2094	4.47 (2.27-8.81)
20 to <40	880	8.73 (4.37-17.43)
≥40	369	27.01 (13.15-55.45)
Troponin I ratio category <sup>c</sup>		
5 to <10	1153	1.00 (0.26-3.92)
10 to <20	1694	1.89 (0.55-6.48)
20 to <40	1374	2.22 (0.64-7.65)
40 to <100	1237	3.61 (1.08-12.04)
≥100	934	10.91 (3.35-35.53)

**CK-MB >5x**

**cTn >40x**

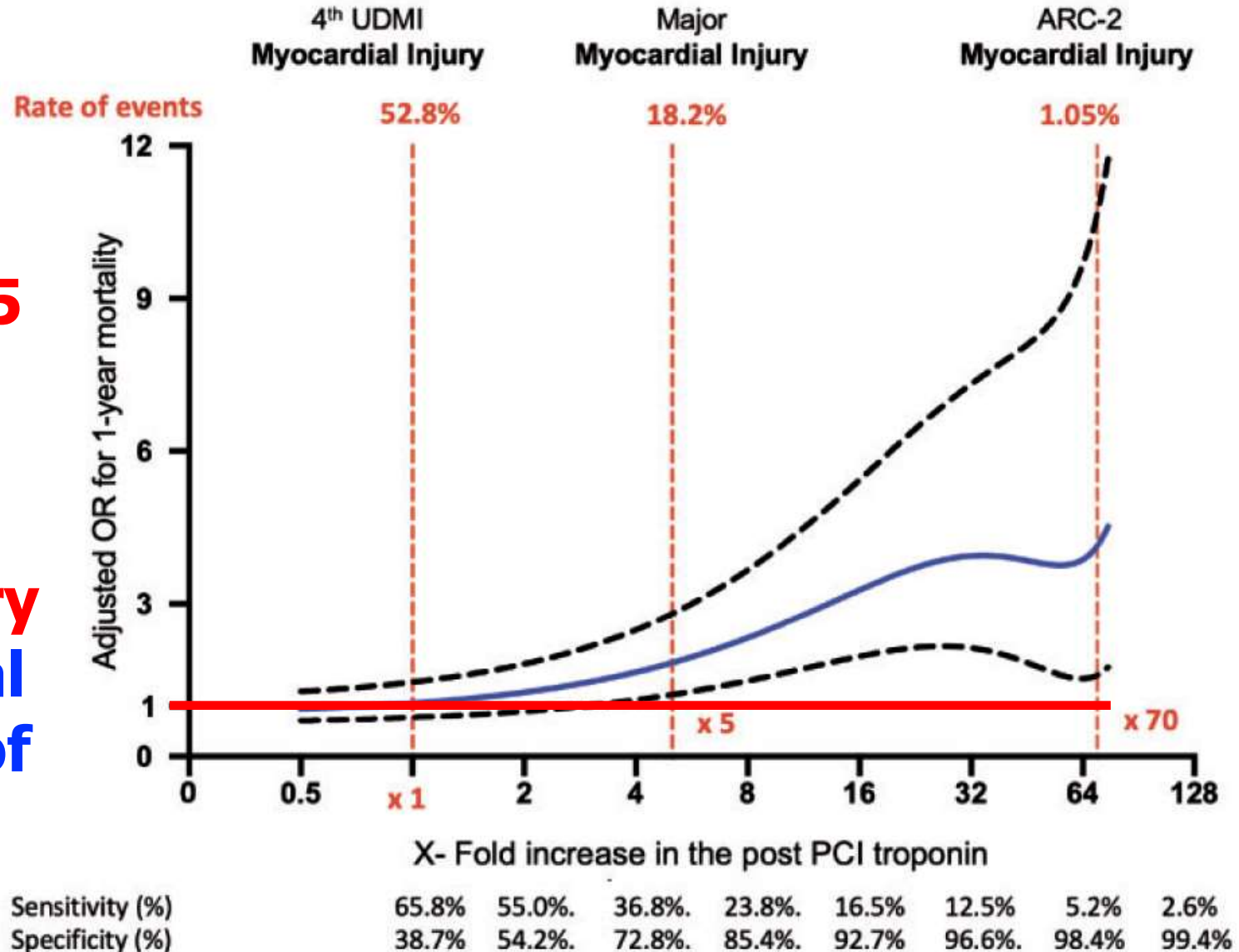


**Cardiac procedural myocardial injury, infarction, and mortality in patients undergoing elective percutaneous coronary intervention: a pooled analysis of patient-level data**

Johanne Silvain<sup>1\*</sup>, Michel Zeitouni<sup>1</sup>, Valeria Paradies<sup>2</sup>, Huili L. Zheng<sup>3</sup>, Gjin Ndrepepa<sup>4</sup>, Claudio Cavallini<sup>5</sup>, Dimitri N. Feldman<sup>6</sup>, Samin K. Sharma<sup>7</sup>, Julinda Neme<sup>8</sup>, Stefania Di Sibio<sup>9</sup>, Emanuele Barbato<sup>10</sup>, Giuseppe Tarantini<sup>11</sup>, Sze Y. Ooi<sup>12</sup>, Clemens von Birgelen<sup>13</sup>, Allan S. Jaffe<sup>14,17</sup>, Kristian Thygesen<sup>18</sup>, Gilles Montalescot<sup>1</sup>, Heerajnarain Bulluck<sup>19†</sup>, and Derek J. Hausenloy<sup>20,21,22,23†</sup>

**9801 patients treated with PCI** **cTn**

**Isolated cTn elevation of  $\geq 5$  x URL is associated with 1-year mortality and could be used to detect 'major' procedural myocardial injury in the absence of procedural complications or evidence of new myocardial ischaemia.**



# Conclusion (1/2):

1. **Current chaos exists;**
2. **Based on survey, CKMB is progressively leaving the scene ( use in hospitals) replaced by troponin - cTn (including high-sensitive cTn);**
3. **One school : MI is not an" isolated release of enzymes" but has to be accompanied by a permanent irreversible "sign" (e.g. new Q-wave, wall motion abnormality, loss of viable myocardium,vessel occlusion) and myocardial injury is not synonymous of myocardial infarction that has a different physiopathological mechanism after CABG and PCI and different clinical reference.**
4. **The other school : Isolated cTn elevation of  $\geq 5$  x URL is associated with 1-year mortality and could be used to detect 'major' procedural myocardial injury**

# Conclusion (2/2):

5. The TIMI group will review the PMI of the SYNTAX, PreCOMBAT, EXCEL and Noble studies under the leadership of Eugene Brauwald
6. The Academic Research Consortium will try to redefine the definition of PMI;
7. Ultimately, we could **eliminate** the item PMI from the equation (composite endpoint), since a clinically relevant MI is ultimately translated in early or late death or heart failure;
8. For our patients a long enjoyable life is their personal prospect. For us, trialists, it has a name : **Quality-Adjusted Life-Year (QALY)**