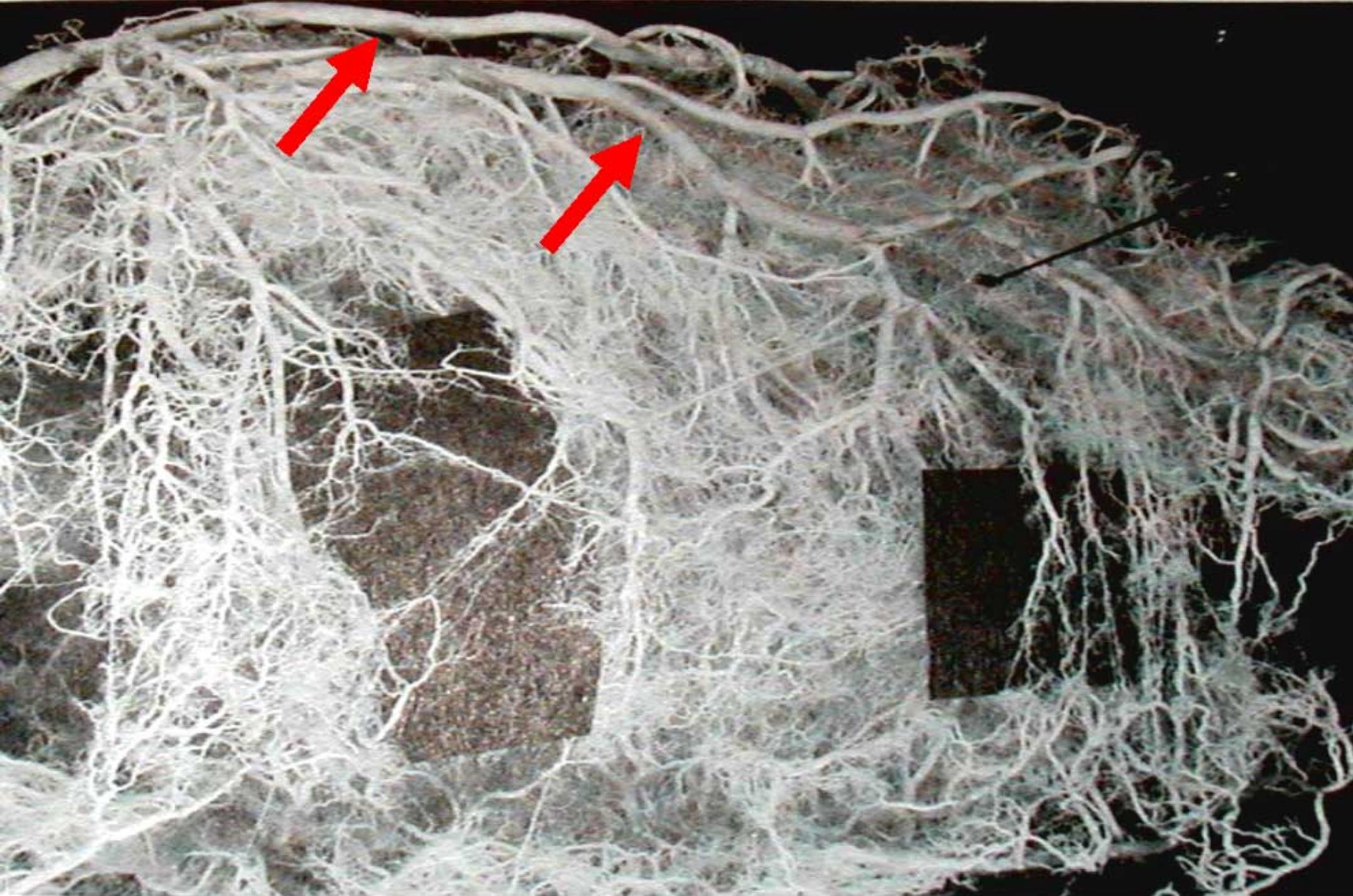


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## Coronary microvascular dysfunction

**Filippo Crea**  
Institute of Cardiology  
Catholic University of the Sacred Heart  
Rome, Italy





The NEW ENGLAND JOURNAL *of* MEDICINE

REVIEW ARTICLE

**MEDICAL PROGRESS**

# Coronary Microvascular Dysfunction

Paolo G. Camici, M.D., and Filippo Crea, M.D.

# Pathophysiology of CMD

Alterations	Conditions
<b>Structural</b>	
Luminal obstruction	STEMI, PCI
Vascular wall infiltration	Fabry's disease
Vascular remodeling and rarefaction	LVH (HCM, Hypertension, Aortic stenosis)
<b>Functional</b>	
Endothelial dysfunction	Risk factors, MVA, SA, NSTEMI-ACS
SMC dysfunction	Takotsubo syndrome
Autonomic dysfunction	STEMI, MVA
<b>Extravascular</b>	
Extramural compression	LVH (Aortic stenosis, Hypertension, HCM)
Diastolic perfusion time	LVH (Aortic stenosis, Hypertension, HCM)

**Table 1. Clinical Classification of Coronary Microvascular Dysfunction.**

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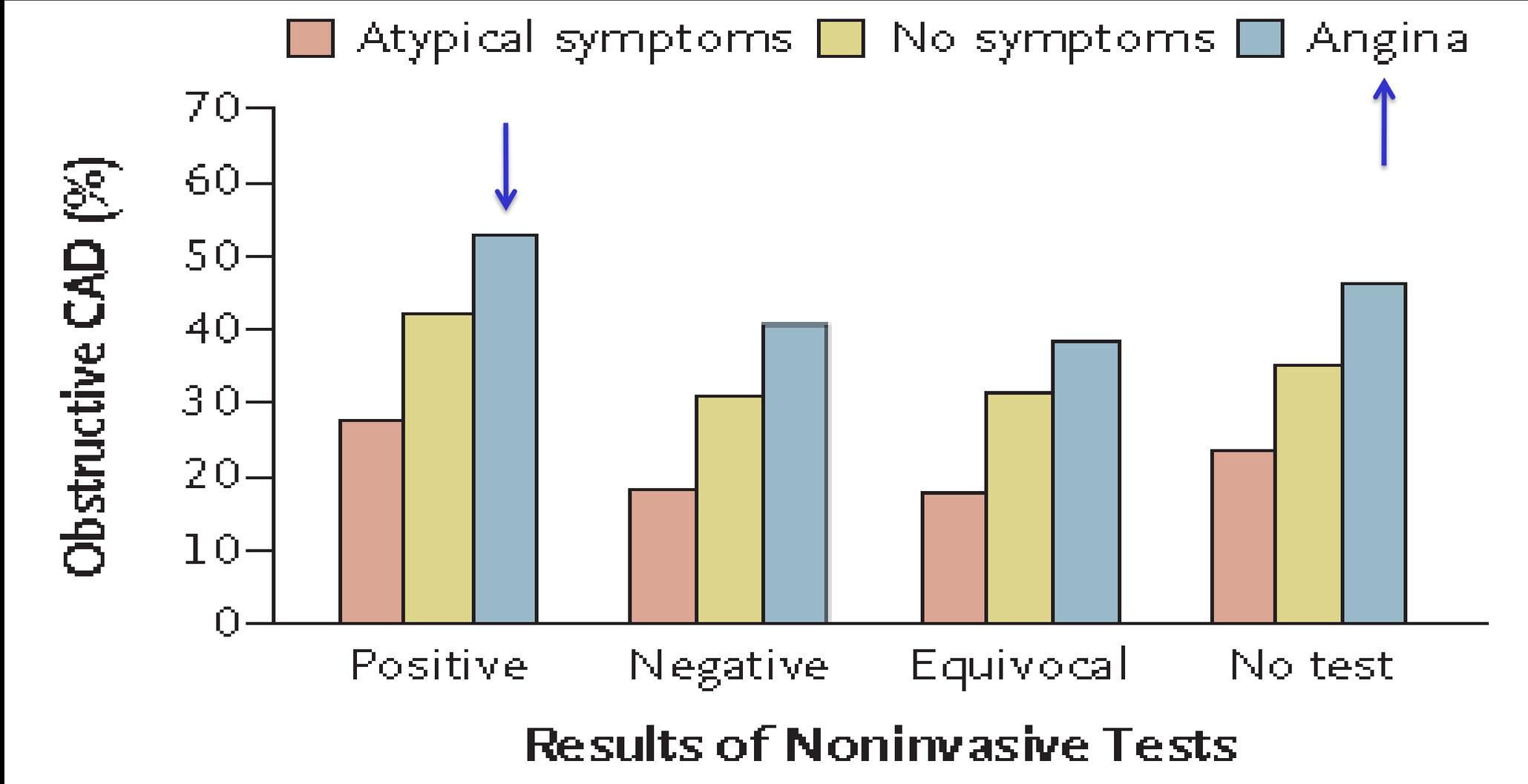
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This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization. It can be identified with the use of either invasive or noninvasive means on the basis of a reduced coronary flow reserve, which seems to revert spontaneously in the weeks after revascularization. Pharmacologic treatment has been shown to promptly restore coronary flow reserve, and it may also change the clinical outcome. The likelihood of distal embolization can be reduced by the use of appropriate devices during high-risk procedures.

# Stable MVA

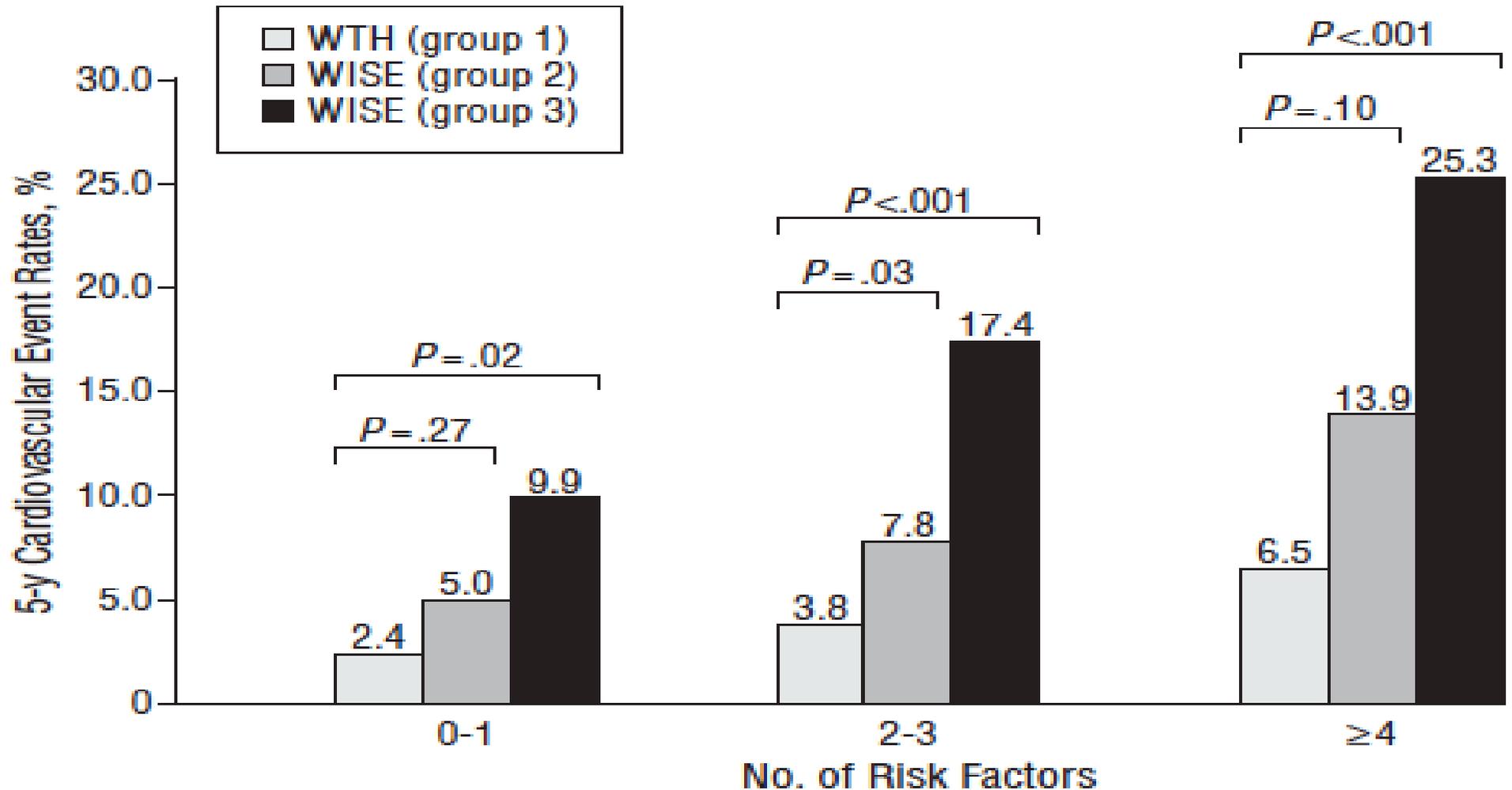
- Angina
- Evidence of stress-induced myocardial ischemia
- Normal coronary arteries
- No coronary spasm

# Prevalence of obstructive CAD in relation to symptoms and non invasive testing in patients undergoing selctive coronary angiography (n=398,978)

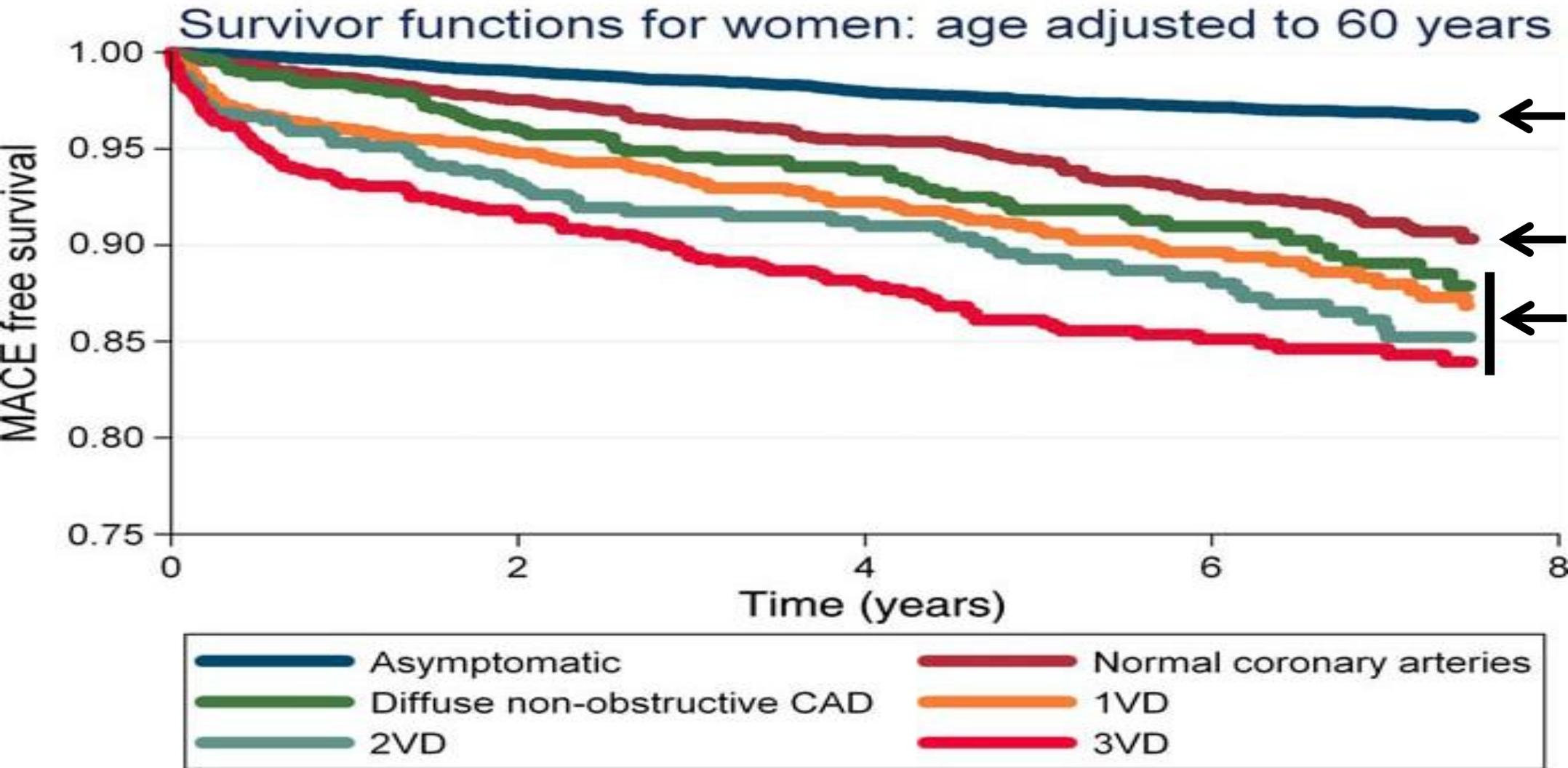


(Patel et al, NEJM 2010)

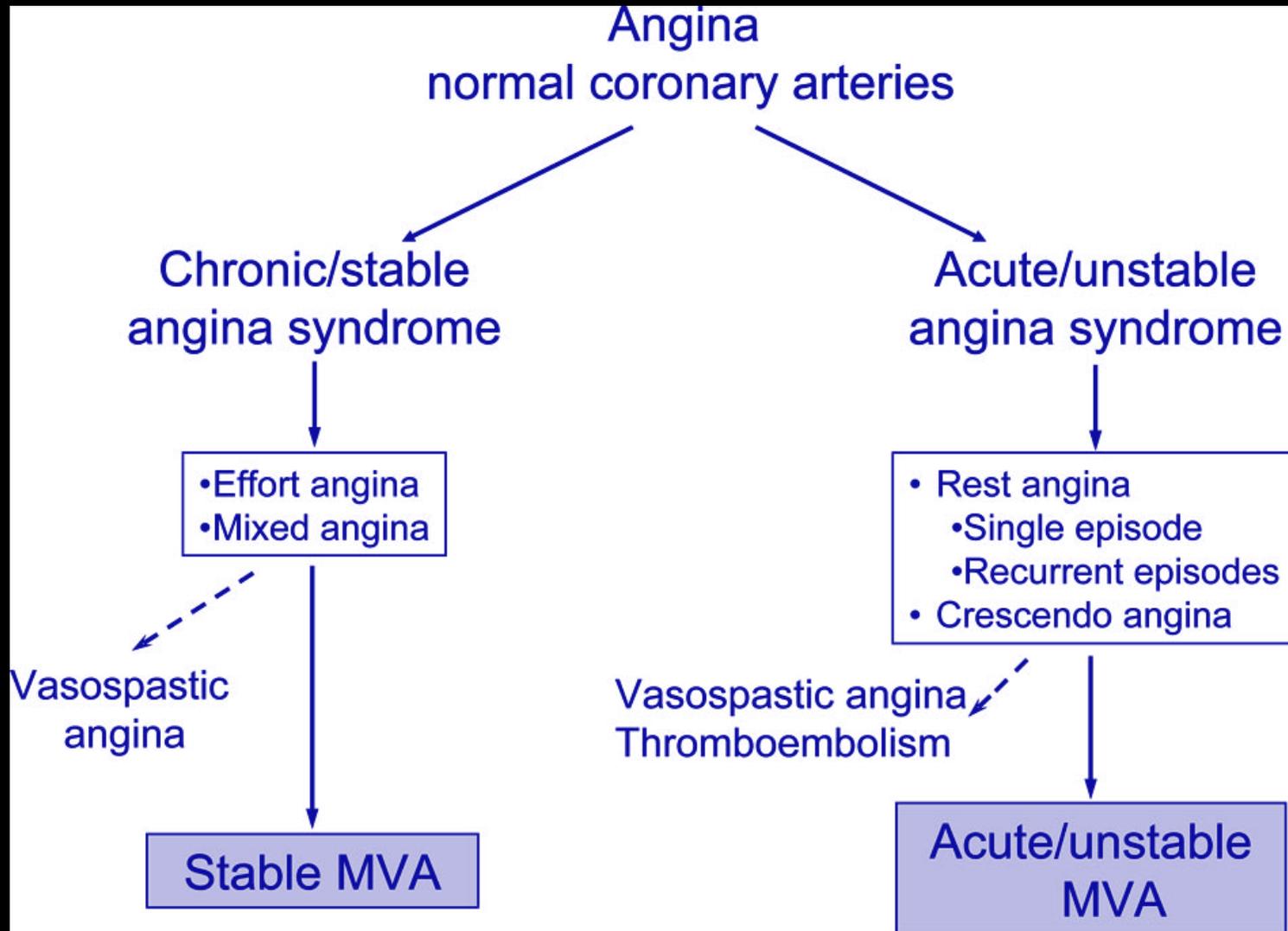
# Stable MVA in women is associated with higher risk of MACEs (n=1,540)



# SA in women with NCA is associated with higher risk of MACEs (n=4,711)

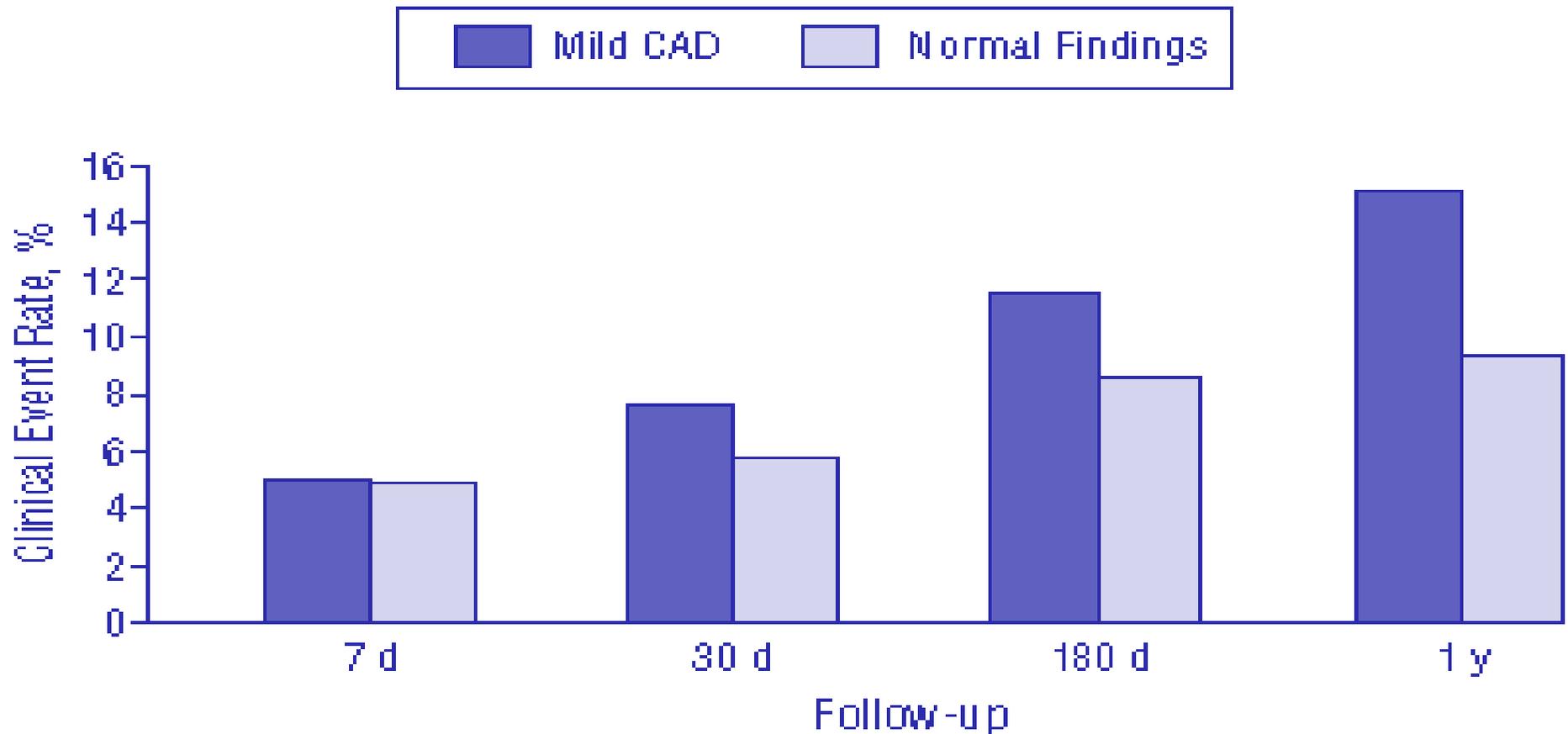


# Primary Coronary Microvascular Dysfunction



(Lanza and Crea, Circulation 2010)

# Outcome of patients with NSTEMI-ACS and normal coronary arteries or mild CAD enrolled in TIMI 11B, TIMI 16 and TIMI 22 (9.1% di 7656 pazienti)



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Coronary microvascular dysfunction in the presence of obstructive CAD

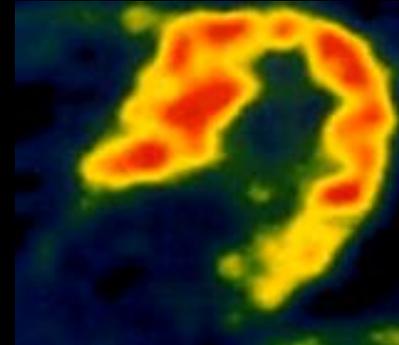
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Iatrogenic coronary microvascular dysfunction

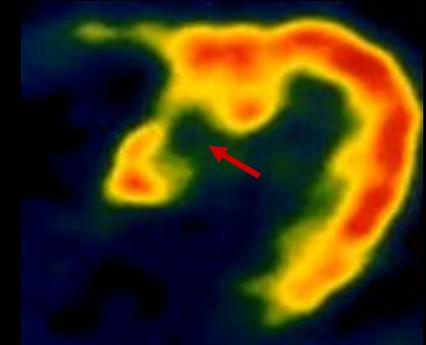
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# Microvascular dysfunction and prognosis in HCM

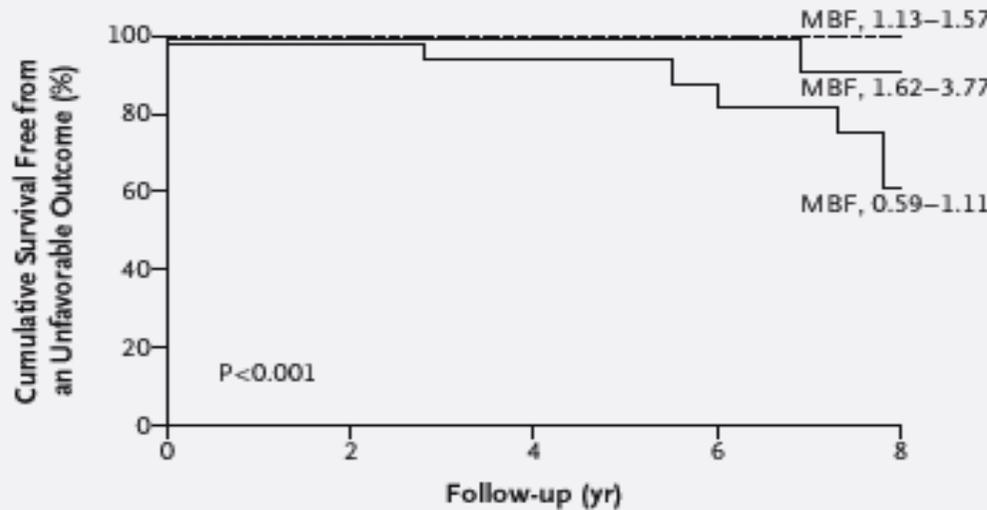
PET myocardial blood flow



Rest



Stress



No. at Risk	0	2	4	6	8
MBF, 0.59–1.11	18	16	14	9	
MBF, 1.13–1.57	16	14	13	11	
MBF, 1.62–3.77	17	16	14	13	

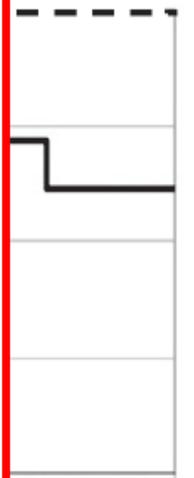
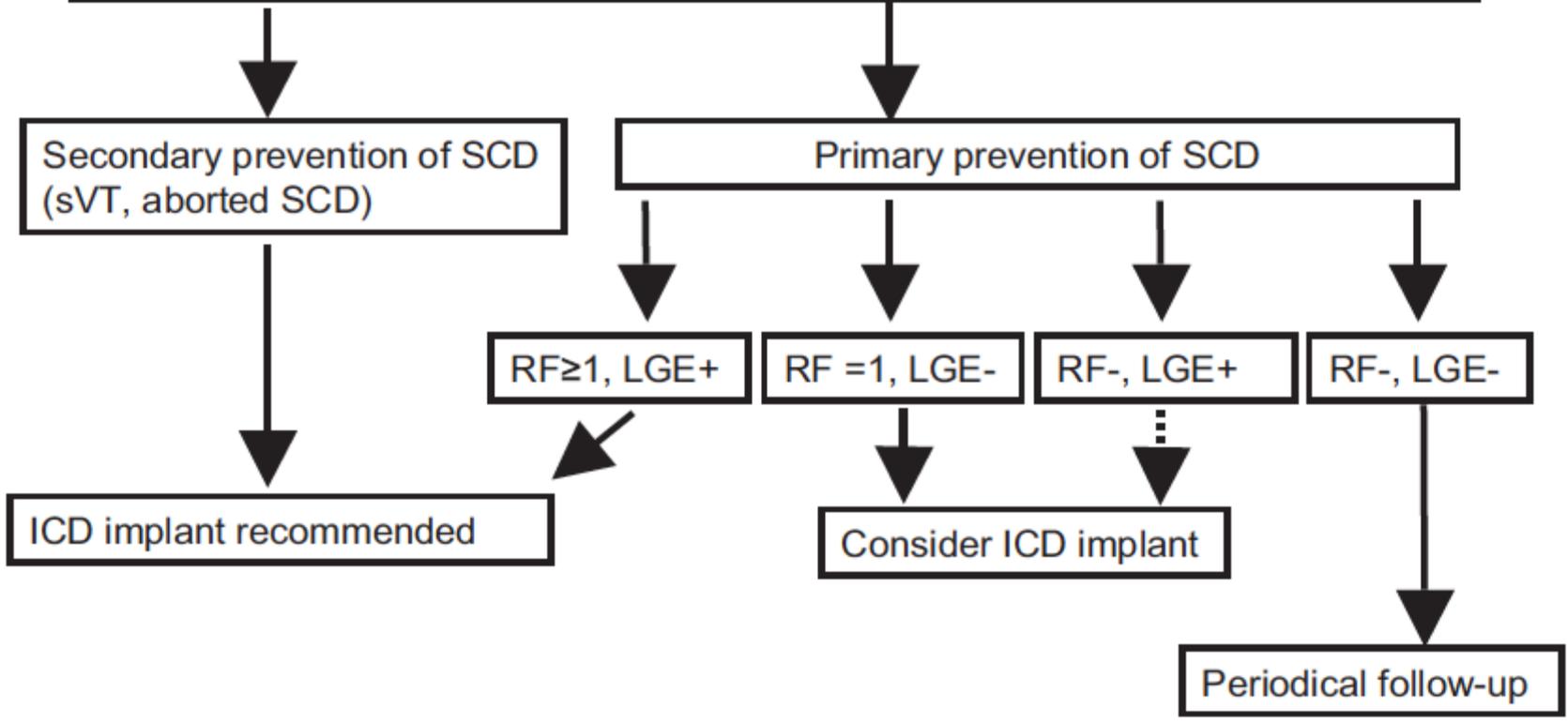


(Cecchi et al, NEJM 2003)

Overall HC population

Work-up:

- History, clinical examination, genetics if indicated
- (Holter-) ECG, exercise ECG
- Echocardiography (septal hypertrophy, LVOT obstruction, SAM)
- CMR (with LGE)



1825  
40  
19

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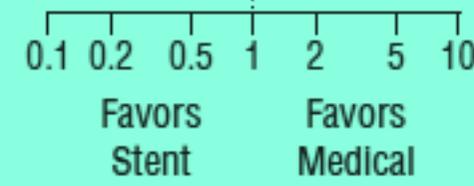
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# OMT vs OMT + stenting in patients with SA (n=7229)

Source	OR (95% CI)	P Value	OR (95% CI)
TOAT <sup>16</sup>	2.20 (0.19-25.52)	.53	
DECOP1 <sup>18</sup>	0.83 (0.31-2.23)	.71	
OAT <sup>5</sup>	1.04		
MASS II <sup>14</sup>	0.95		
COURAGE <sup>6</sup>	0.88		
JSAP <sup>26</sup>	0.85		
BARI 2D <sup>7</sup>	1.06		
	0.98		
Heterogeneity Q = 1.52 (P = .96)			

Source	OR (95% CI)	P Value	OR (95% CI)
TOAT <sup>16</sup>	3.41 (0.34-34.65)	.30	
Hambrect et al <sup>17</sup>	3.12 (0.12-78.45)	.49	
DECOP1 <sup>18</sup>	1.43		
OAT <sup>5</sup>	1.45		
MASS II <sup>14</sup>	0.70		
COURAGE <sup>6</sup>	1.12		
JSAP <sup>21</sup>	0.42		
BARI 2D <sup>7</sup>	1.12		
	1.12		
Heterogeneity Q = 7.36 (P = .007)			

Source	OR (95% CI)	P Value	OR (95% CI)
TOAT <sup>16</sup>	0.69 (0.11-4.42)	.69	
Hambrect et al <sup>17</sup>	8.14 (0.96-68.81)	.05	
DECOP1 <sup>18</sup>	0.66 (0.26-1.72)	.40	
OAT <sup>5</sup>	1.20 (0.68-2.13)	.53	
MASS II <sup>14</sup>	0.60 (0.40-0.89)	.01	
COURAGE <sup>6</sup>	0.91 (0.67-1.24)	.56	
JSAP <sup>21</sup>	0.46 (0.29-0.72)	<.001	
BARI 2D <sup>7</sup>	0.92 (0.75-1.12)	.39	
	0.79 (0.60-1.05)	.10	
Heterogeneity Q = 16.8 (P = .02); I <sup>2</sup> = 58.2			

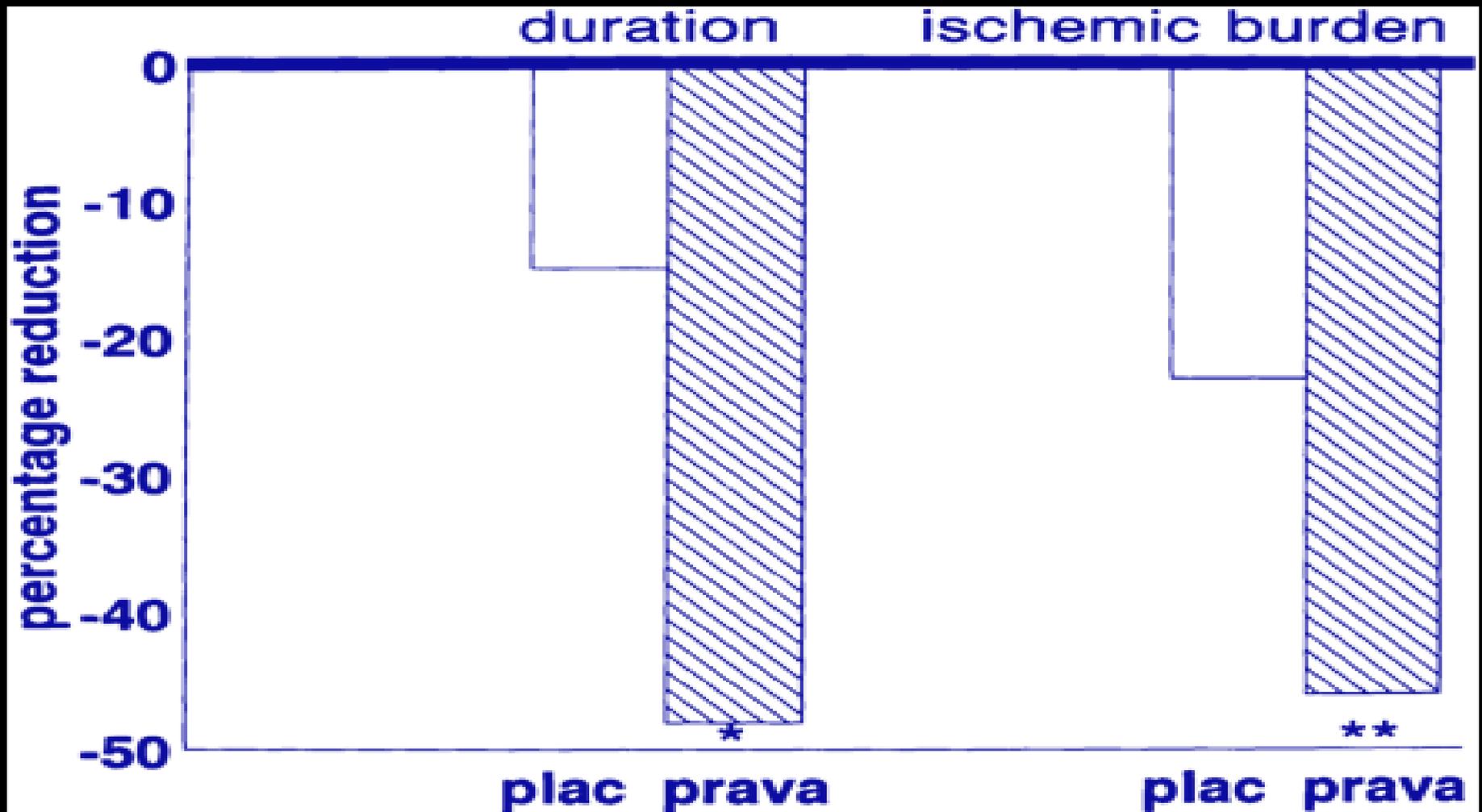


Death

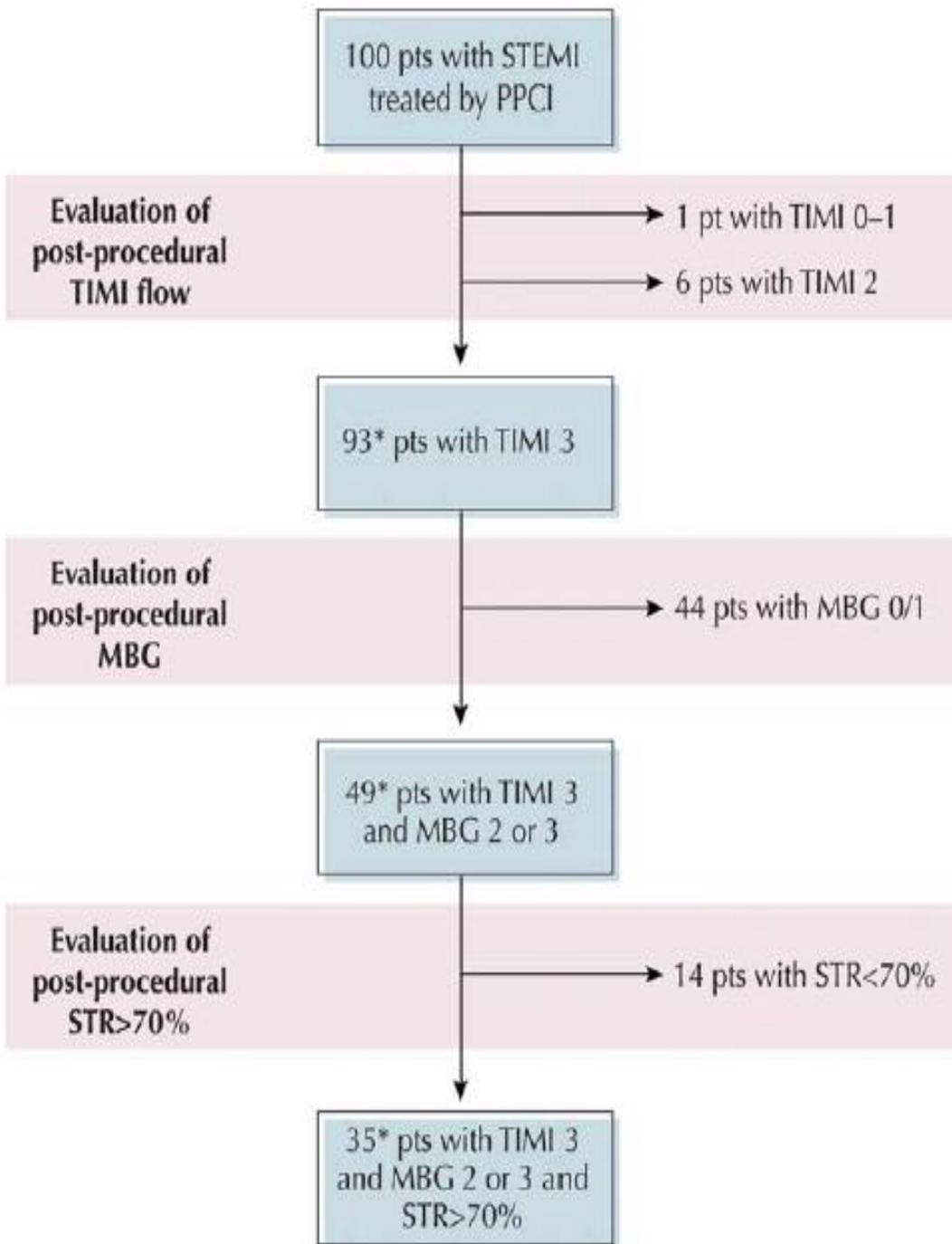
Non fatal MI

Persistent angina

# Reduction of transient myocardial ischemia with Pravastatin in stable angina (n=768)



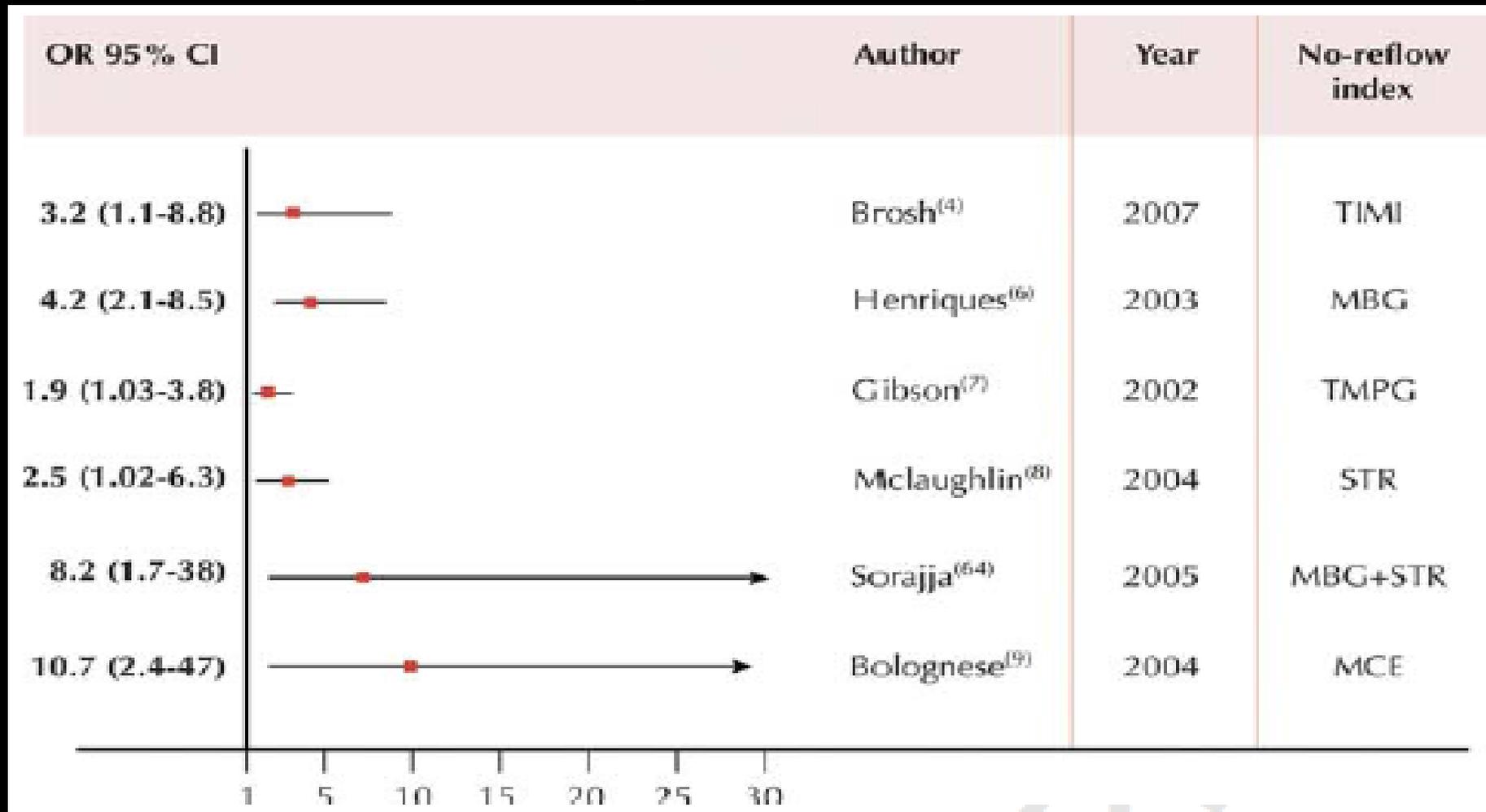
(REGRESS, Circulation 1996)



# The illusion of reperfusion after primary PCI

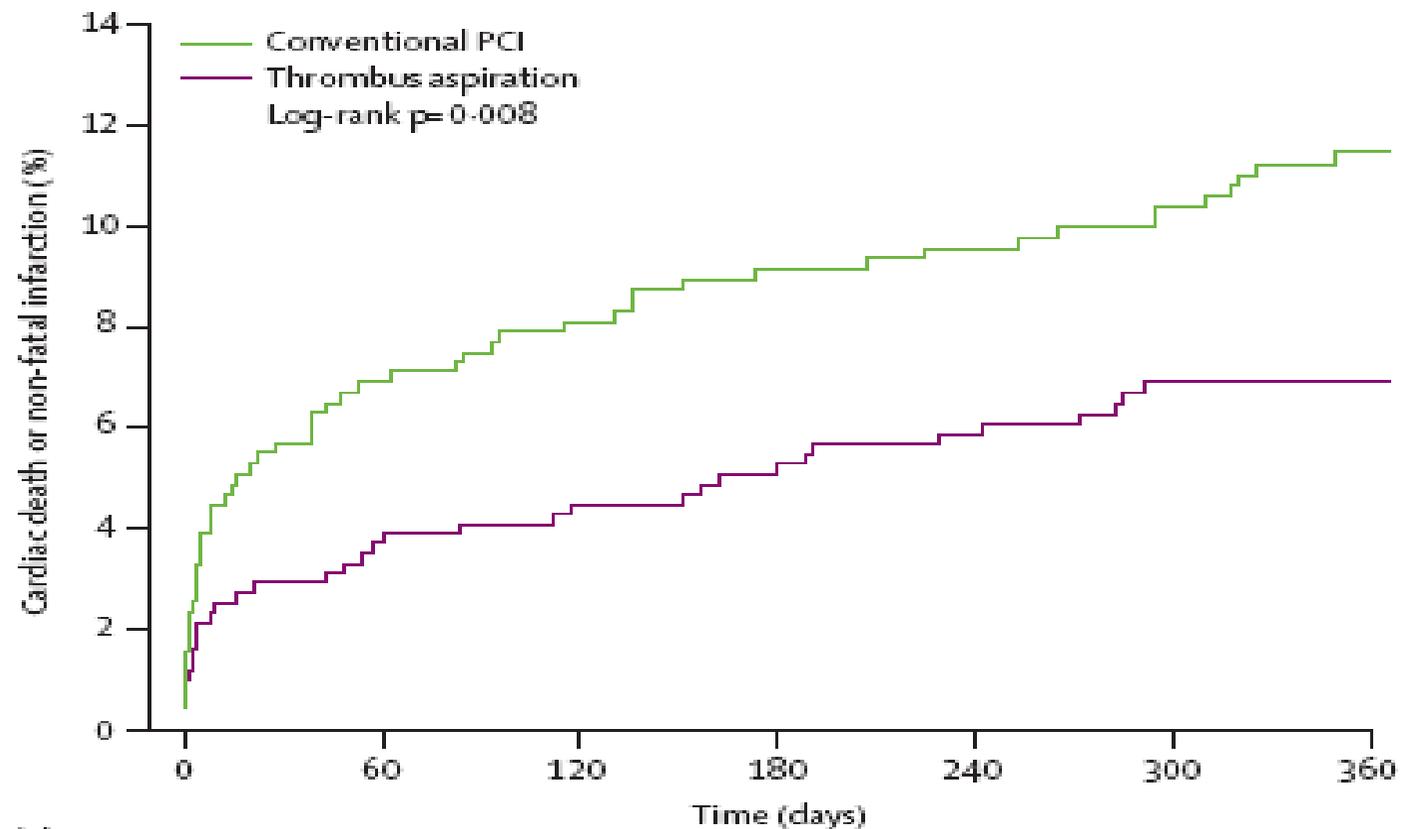
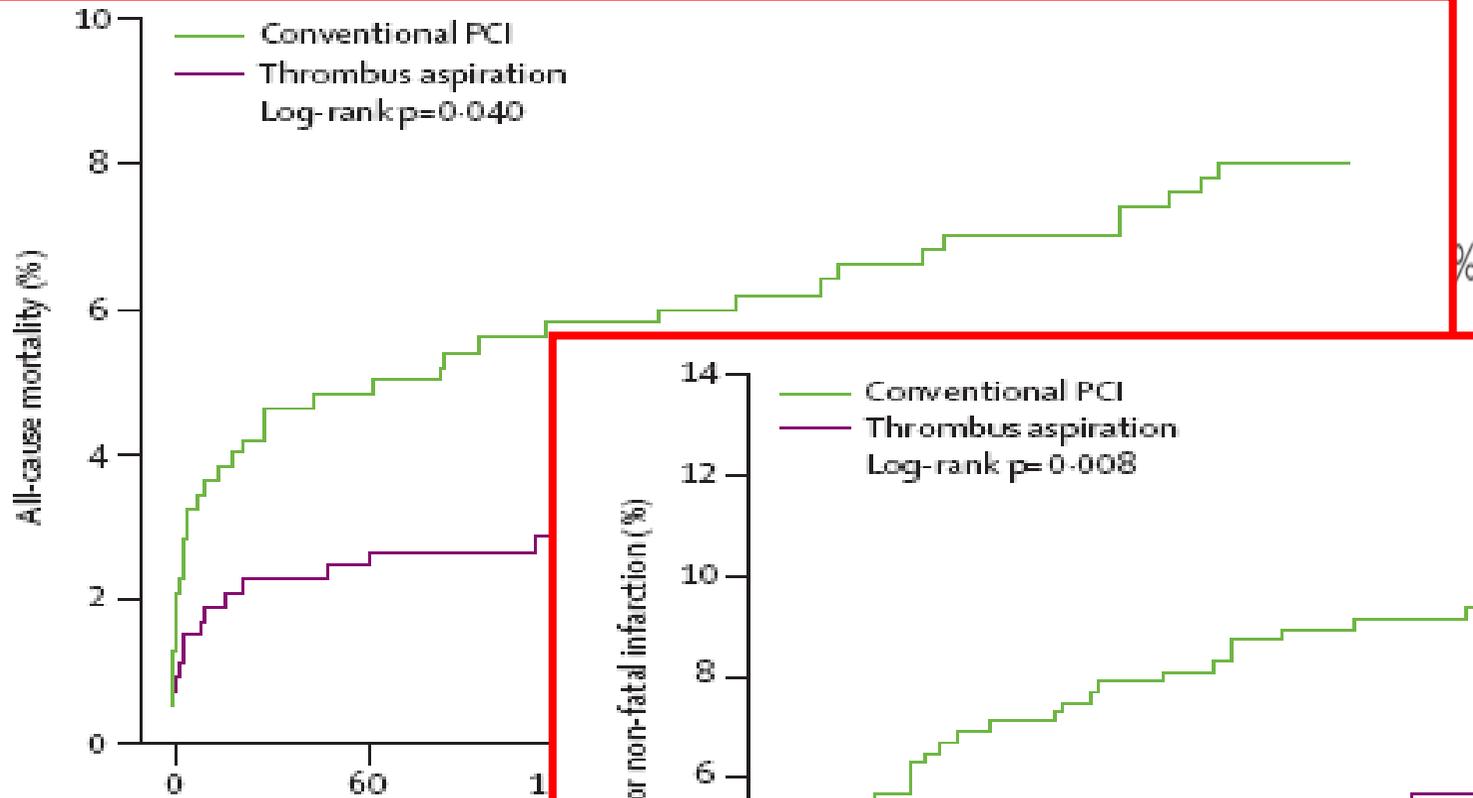
(Niccoli et al. JACC 2009)

# Prognostic Value of MO According to Angiographic, ECG, and Echo-contrastographic Indexes



(Niccoli et al. JACC 2009)

# TAPAS trial (n=1060)



(Vlaar et al,  
Lancet 2007)

# REOPEN-AMI

471 STEMI patients were assessed for eligibility

123 patients did not meet angiographic eligibility criteria

- 12 did not undergo PCI
- 97 had TIMI flow 2-3 did not provide written informed consent
- 4 had culprit lesion non-identified
- 5 had culprit lesion in a by-pass graft
- 6 had stent thrombosis
- 6 had left main disease
- 3 had acute CABG

108 patients did not meet clinical or ECG eligibility criteria

- 13 had a diagnosis other than STEMI
- 7 did not provide written informed consent
- 5 died before entry into the cath-lab
- 12 had a previous STEMI in the same territory
- 16 had cardiogenic shock
- 5 had contraindications to contrast agent
- 13 had contraindications to study medications
- 12 had severe renal failure
- 25 had left bundle block, frequent ventricular ectopy, paced rhythm, or pre-excitation

240 STEMI patients (TIMI flow 0-1) were randomly assigned to a treatment group

80 were assigned to TA+saline

(2 ml of heparinized saline as fast bolus followed by 33 ml of heparinized saline in 2 min as slow bolus)

drug through the guiding catheter due to TA failure

N=7

drug through the TA device

N=73

80 were assigned to TA+Adenosine

(120 mcg as fast bolus followed by 2 mg in 33 ml of saline in 2 min as slow bolus)

drug through the guiding catheter due to TA failure

N=8

drug through the TA device

N=72

80 were assigned to TA+Nitroprusside

(60 mcg as fast bolus followed by 100 mcg in 33 ml of 5% glucose in 2 min as slow bolus)

drug through the guiding catheter due to TA failure

N=9

drug through the TA device

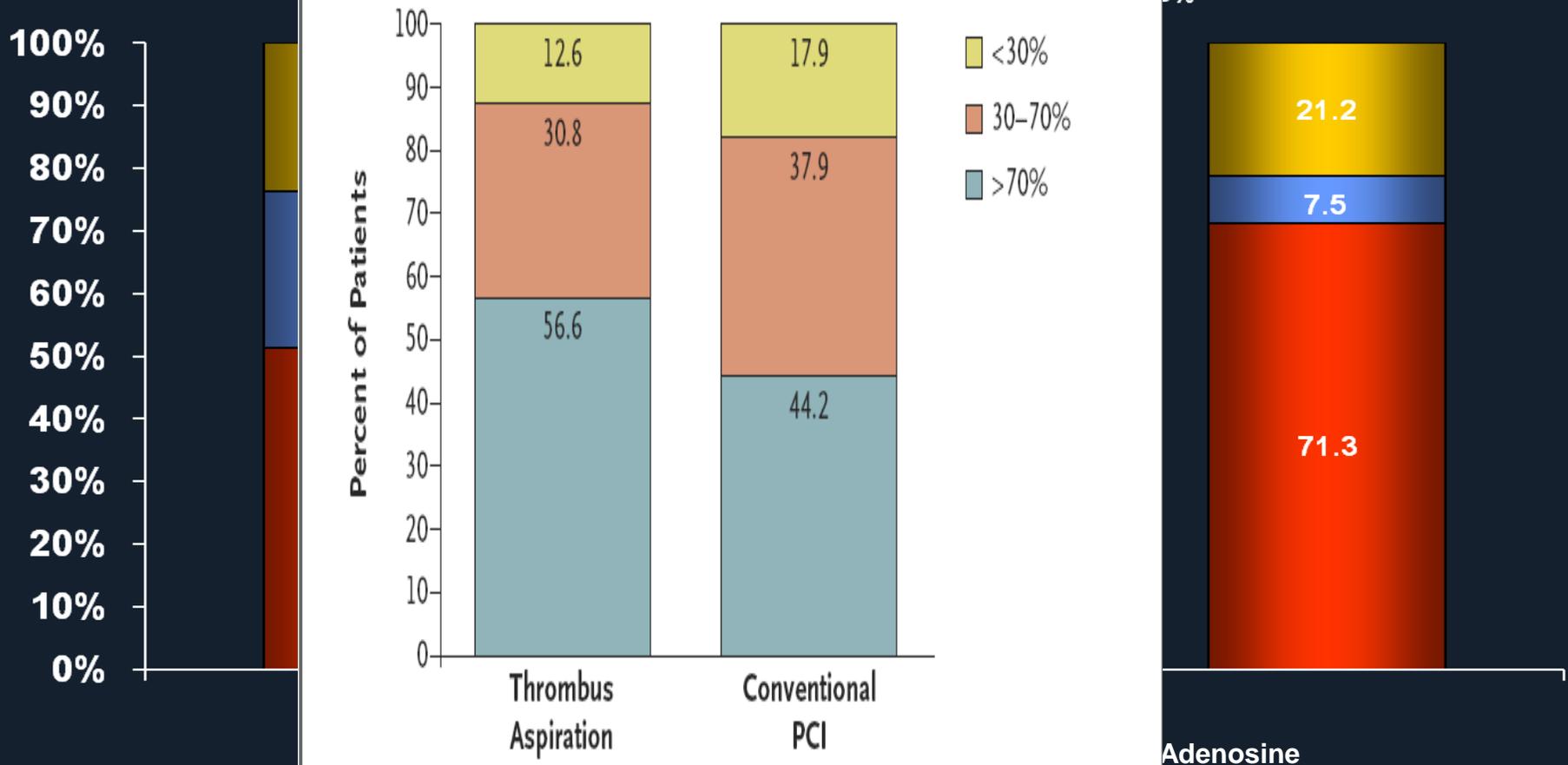
N=71

All patients received a weight adjusted bolus and infusion of abciximab for 12 h

(Niccoli et al, in press)

# ST-segment resolution

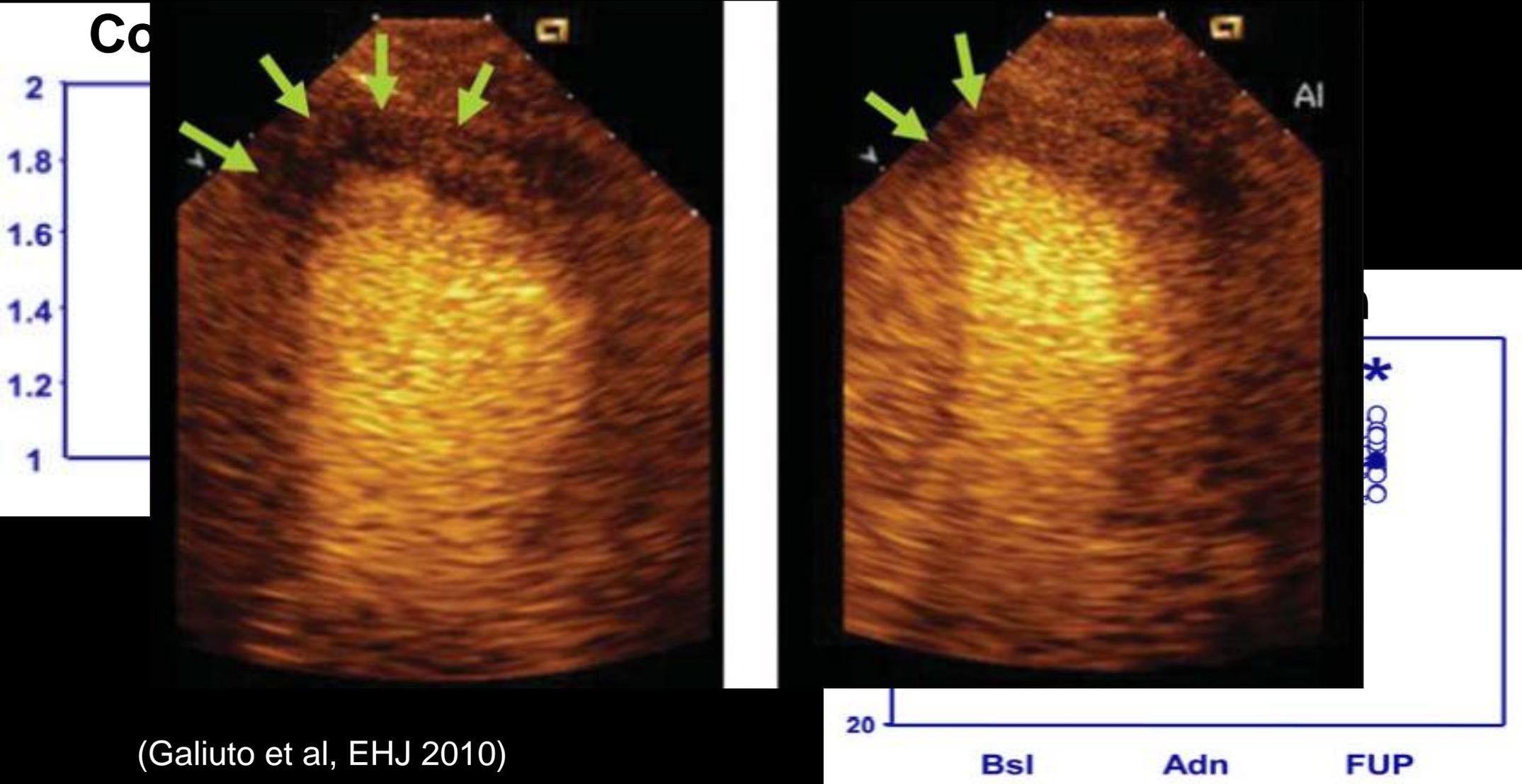
B Resolution of ST-Segment Elevation



**Adenosine vs Saline  $p = 0.009$**   
**Nitroprusside vs Saline  $p = 0.75$**

(Niccoli et al, in press)

# Coronary microvascular dysfunction in Tako-tsubo syndrome



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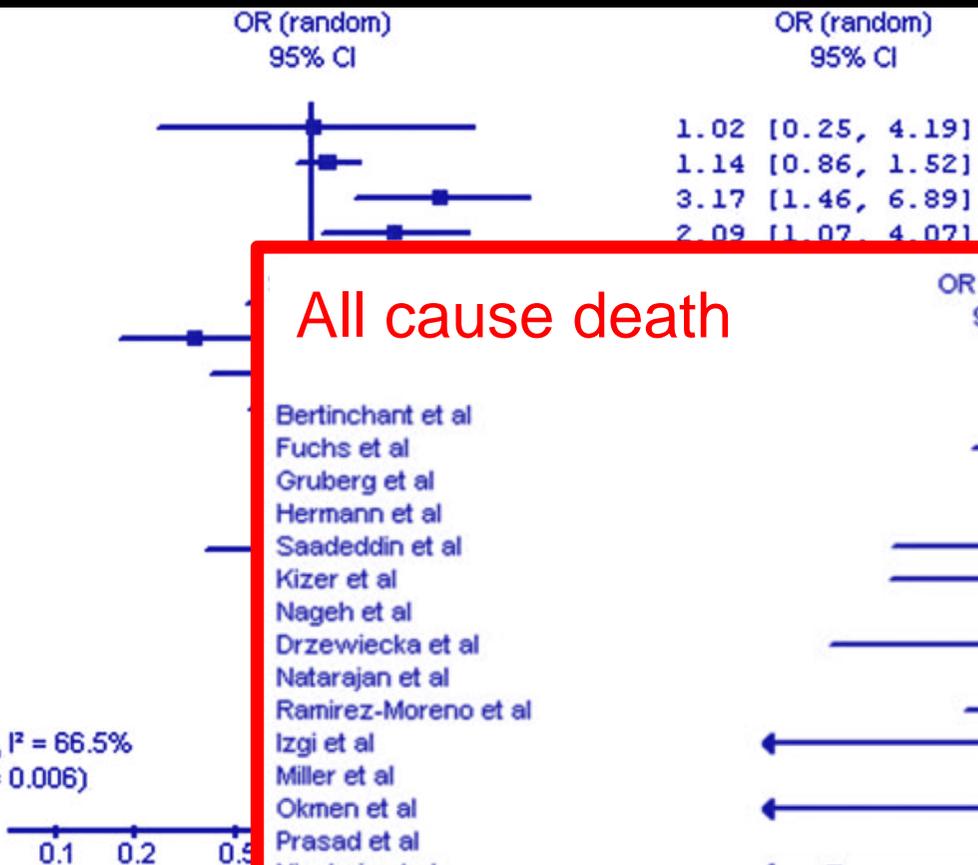
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# MI after PCI: a meta-analysis of troponin elevation (29%) (n=7578)

## MACEs

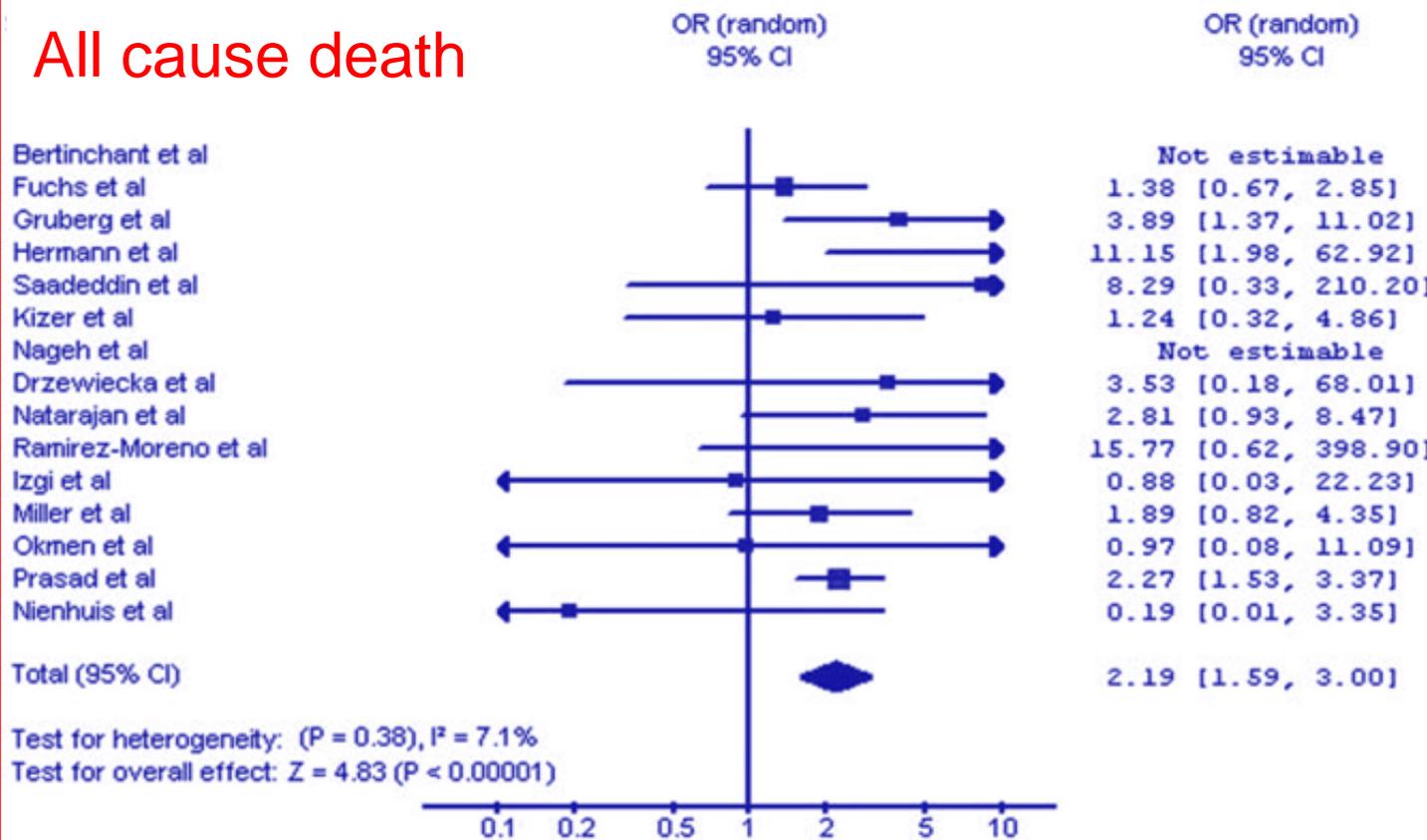
Bertinchant et al  
 Fuchs et al  
 Gruberg et al  
 Hermann et al  
 Saadeddin et al  
 Kizer et al  
 Nageh et al  
 Drzewiecka et al  
 Natarajan et al  
 Ramirez-Moreno et al  
 Izgi et al  
 Miller et al  
 Okmen et al  
 Prasad et al  
 Nienhuis et al



Test for heterogeneity: (P = 0.0001), I<sup>2</sup> = 66.5%  
 Test for overall effect: Z = 2.73 (P = 0.006)



## All cause death



Test for heterogeneity: (P = 0.38), I<sup>2</sup> = 7.1%  
 Test for overall effect: Z = 4.83 (P < 0.00001)



# Conclusions

- **CMD is frequent in a large number of cardiovascular diseases**
- **The pathophysiology is complex as CMD can be caused by structural, functional and extravascular alterations**
- **In some cases CMD is simply a marker of disease, in other cases is a useful prognostic marker, in other cases it is an important therapeutic target**