No reflow in ACS: Treatment strategies and Developments



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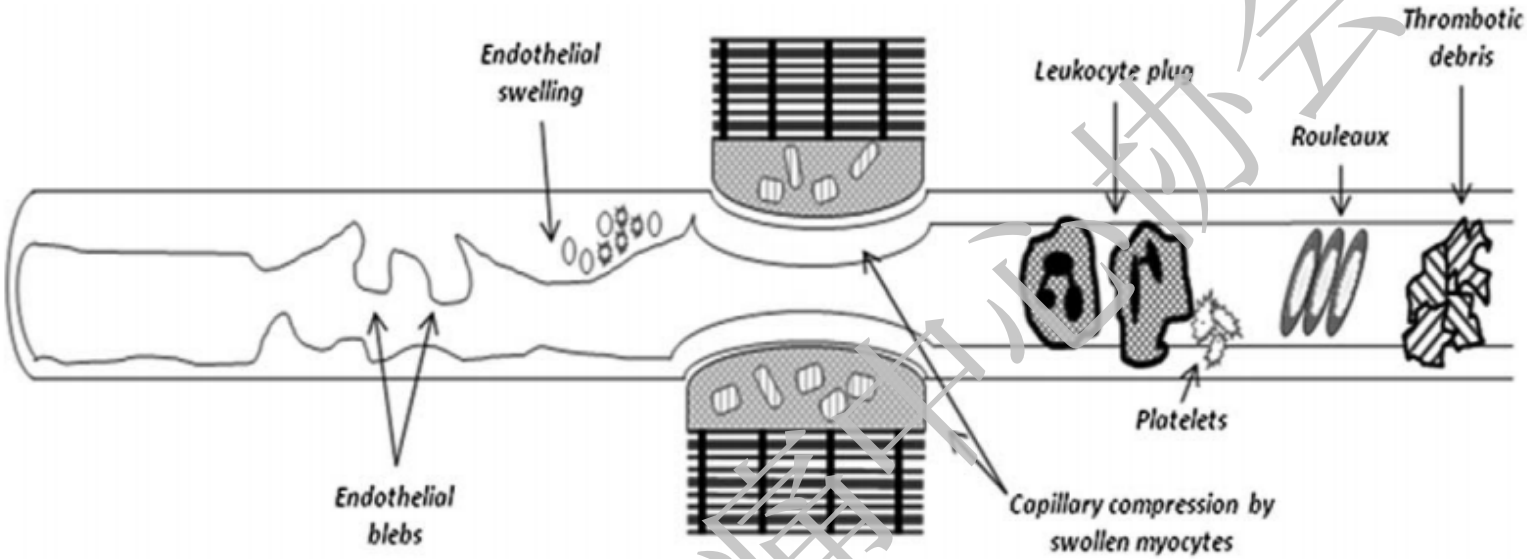
Epidemiology

- No-reflow is defined as a failure to restore antegrade normal coronary flow despite appropriate treatment of coronary obstruction.
- The prevalence of this complication occurs in 0.6% to 5% of PCIs.
- The incidence of no-reflow appears to be highest in patients undergoing PCI of SVGs, during acute myocardial infarction (AMI) or during rotational atherectomy .
- It can occur in as high as 50% of PCI cases involving the treatment of thrombus-containing lesions .
- A history of diabetes mellitus, or the absence of preinfarct angina, was found to increase the risk of no-reflow.

Mechanisms responsible for No-Reflow



✓Mechanical obstruction for distal embolization of thrombus and/or atherosclerotic debris.

✓Vascular auto-regulation. Severe micro-vascular dysfunction due to alpha-adrenergic macro- and micro-vascular constriction and vasospasm.

✓Extrinsic coagulation pathway. Endothelial cell dysfunction/vasoconstriction induces exposure of TF leading to thrombosis.

✓Leukocyte adherence, platelet thrombi and free radicals. Oxygen free radical-mediated endothelial injury. Capillary plugging by red cells and activated neutrophils.

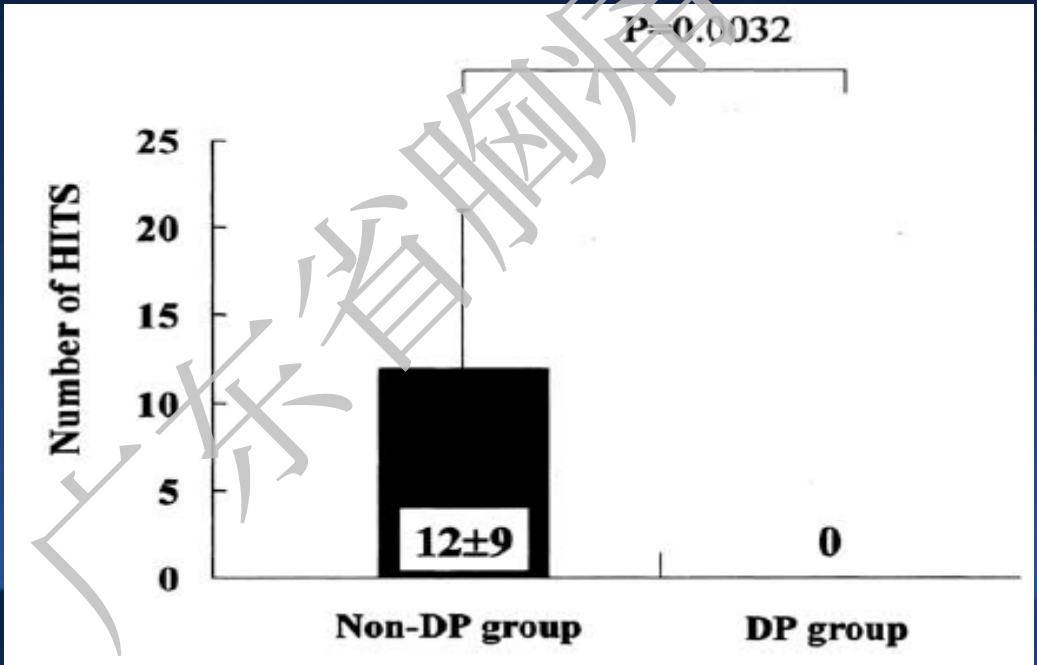
Pathophysiology

- Platelet aggregation
- Distal embolization
- Spasm of microcirculation
- Neutrophilic plugging
- Tissue edema
- increased oxidative stress
- *--a combination of these factors*

Piana RN, et al. Circulation 1994;89:2514–8.
Taniyama Y, et al. J Am Coll Cardiol 1997;30:1193–9.
Engler RL, et al. Am J Pathol 1983;111:98–111.

Distal embolization

- Emboli originate from thrombus and atherosclerotic plaques
- A small number of emboli is unlikely to affect coronary blood flow
- Emboli (>200 µm diameter) can obstruct pre-arterioles, causing infarctlets
- Doppler guidewire in patients undergoing PPCI allows detection of high-intensity transient signals and counting of embolic particles
- Average number of emboli throughout PPCI is 12
  - However, none detected in patients with distal protection device



J Am Coll Cardiol 2005;45:212–5

Independent predictors of distal embolization: thrombus

- Angiographic thrombus with greatest linear dimension >3 times reference lumen diameter
- Cutoff pattern –No taper before occlusion
- Accumulated thrombus proximal to lesion
- Floating thrombus
- Persistent contrast medium distal to the obstruction
- Reference lumen diameter >4 mm

CHEST 2002; 122:1322–1332

Risk Factors of No-Reflow

- Thrombus-containing lesions
- Degenerative SVG grafts
- PCI for AMI
- Rotablator atherectomy
- Lipid pool-like images on intravascular ultrasound
- High-risk clinical status

Klein LW, et al. Catheter Cardiovasc Interv 2003;60:194–201.

Clinical Risk Factors of No-Reflow

- AMI PPCI
- Angina after MI
- Unstable angina
- Cardiac shock
- Hyperglycemia
- Hyper- TC, TG,LDL
- Hyper - NT-pro BNP

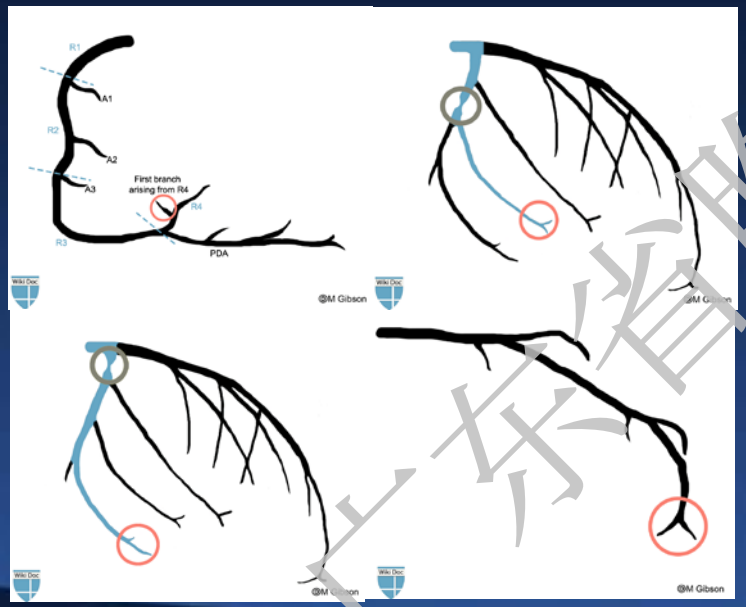
Predictors of no-reflow

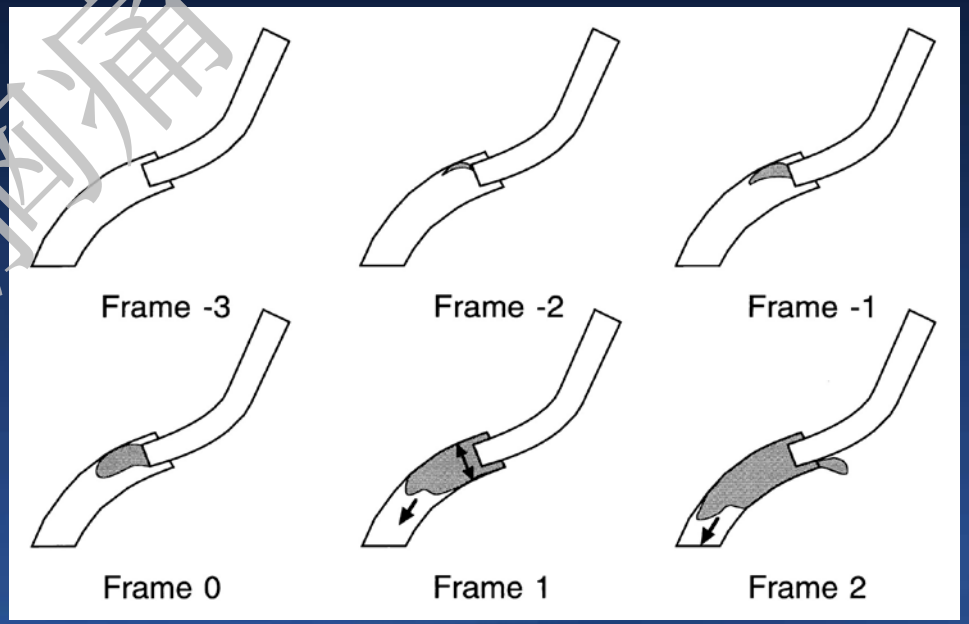
- Killip class
- Number of Q waves
- Wall motion score on UCG
- Initial CAG show TIMI 0 grade flow

- Preinfarction angina: attenuate no-reflow, due to inchemia preconditioning

TIMI frame count

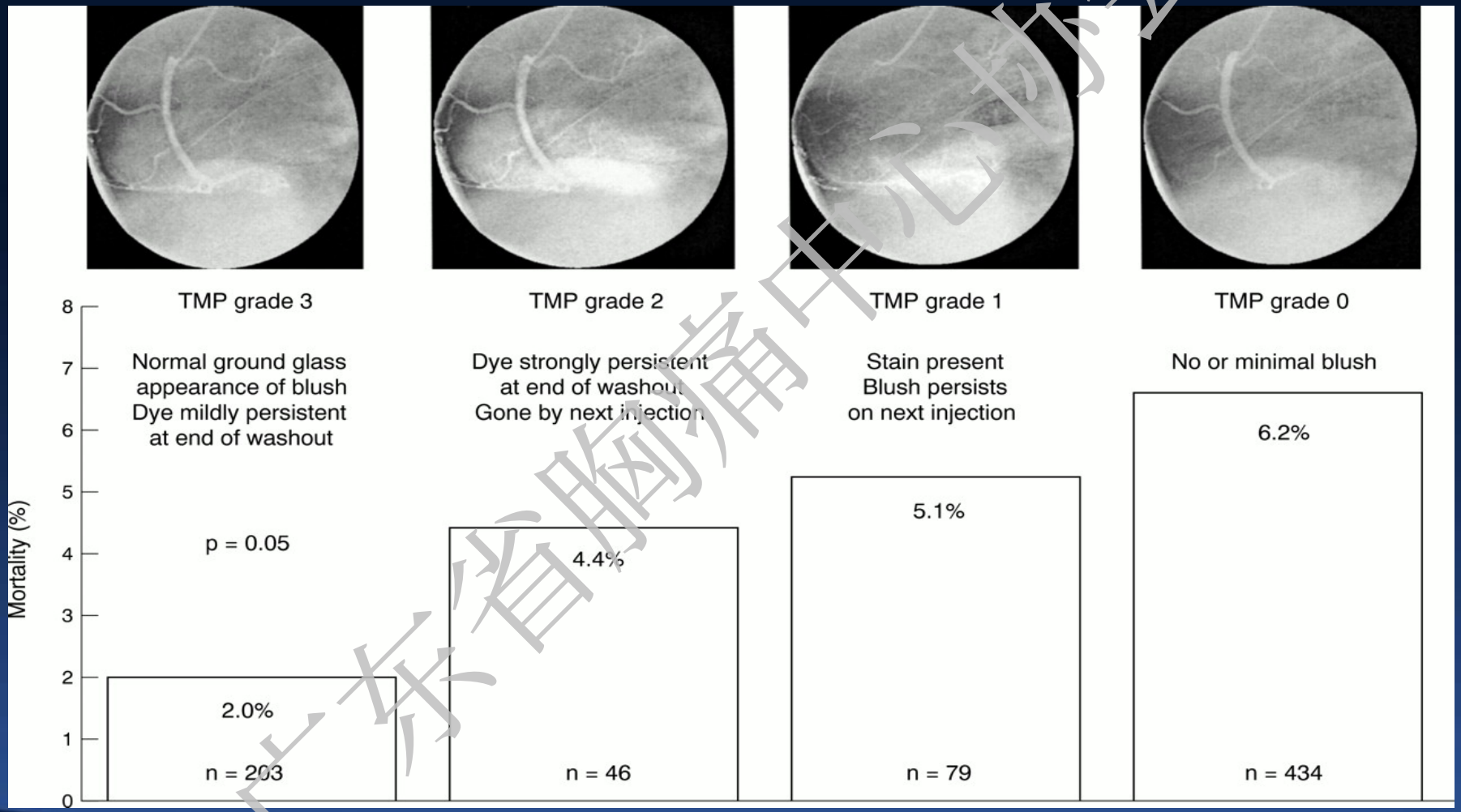
- TIMI frame count is defined as the number of cineframes required for contrast to reach a standardized distal coronary landmark in the culprit vessel.
- The number is expressed based upon a cinefilming rate of 30 frames/second.





C. Michael Gibson et al. Circulation. 1996;93:879-888
http://www.wikidoc.org/index.php/TIMI_frame_count_%28TFC%29

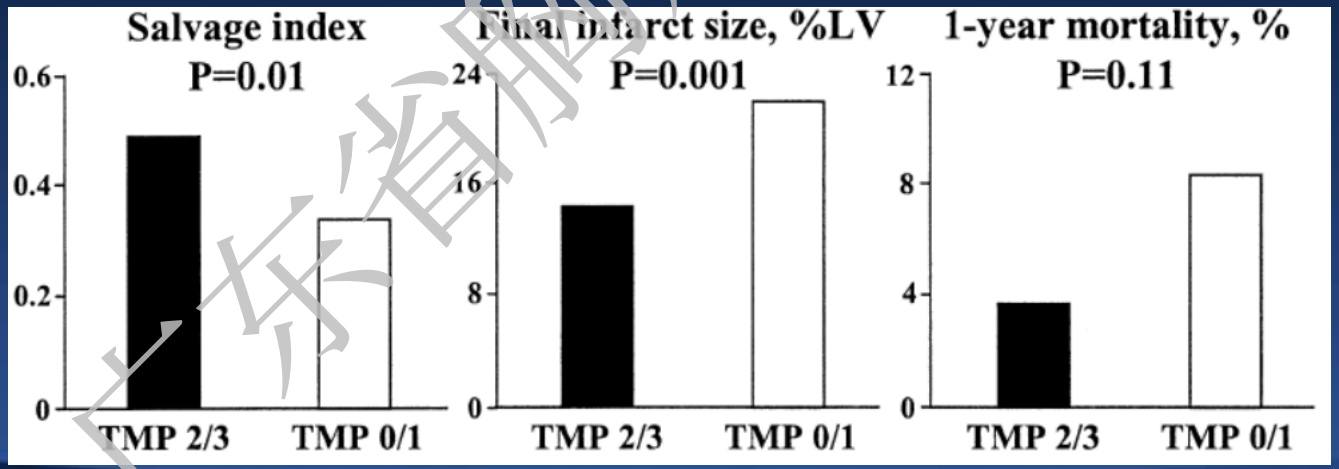
TIMI myocardial perfusion (TMP) grades



MARK A APPLEBY et al. Heart 2001;86:485-486

TIMI myocardial perfusion grade (TMPG) (or myocardial blush grade)

- A novel technique to assess myocardial perfusion or “blush” on a coronary angiogram.
- TMP grade correlates with the final infarct size in patients with AMI treated with thrombolysis.
- Also a reliable indicator of the degree of myocardial salvage achieved with reperfusion therapy.

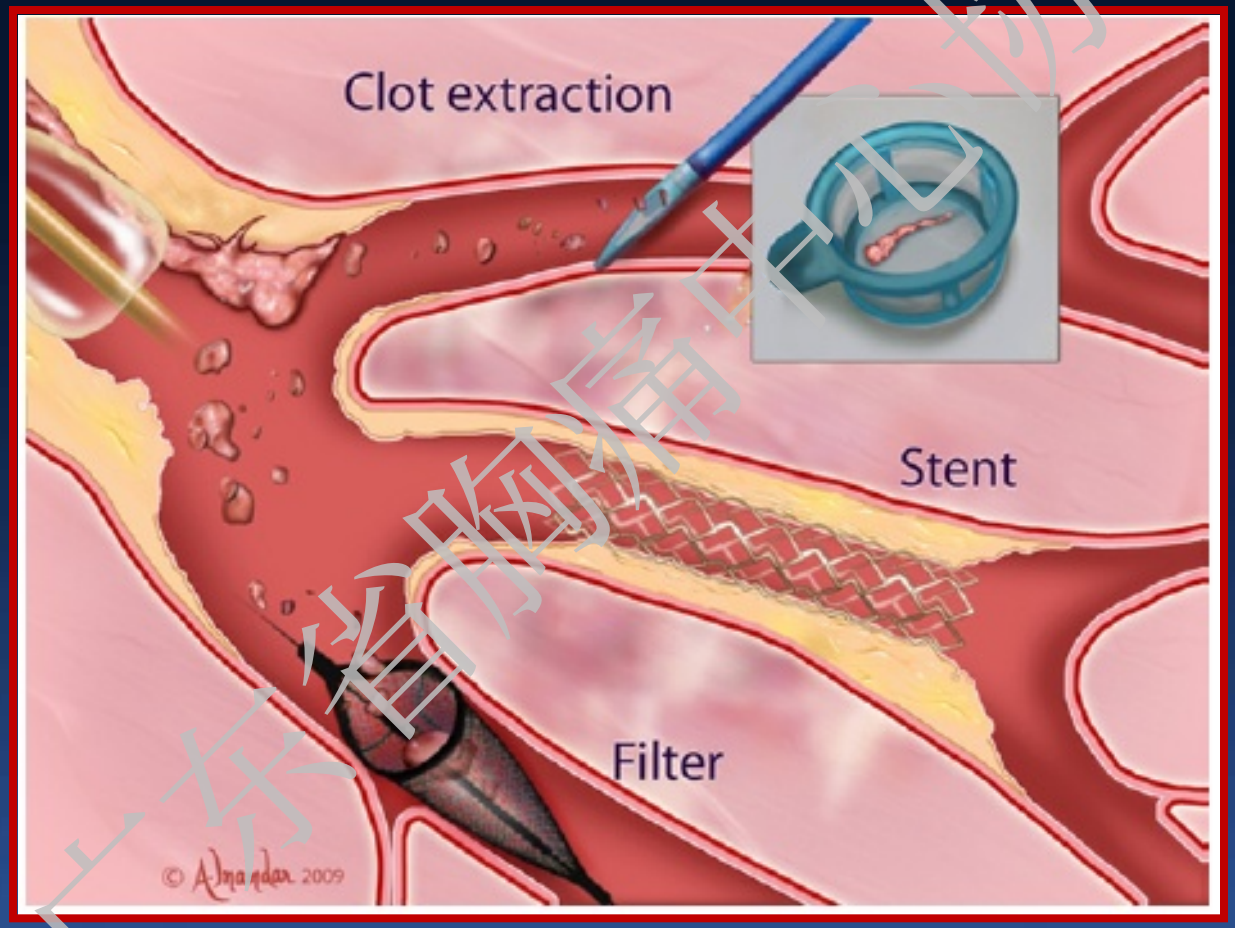


Dibraet al. JACC Vol. 41, No. 6, 2003:925–9

Prevention

- The use of thrombectomy
- Distal embolic protection
- Direct stenting
- Systemic infusion of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors
- Intracoronary infusion of vasodilating or antithrombotic/thrombolytic agents

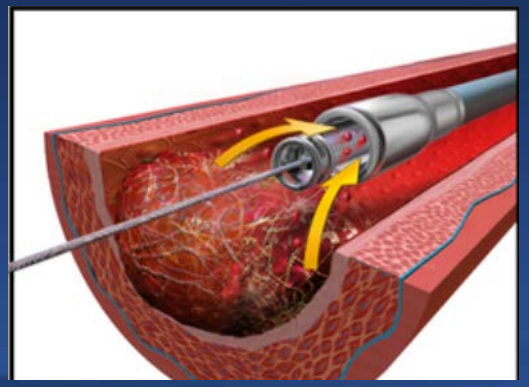
Mechanical Strategies to Prevent Reperfusion No-Reflow



Jeffe R. et al. J Am Coll Cardiol Intv 2010;3:695–704

Thrombectomy

- For patients undergoing primary PCI, we suggest not performing routine manual thrombectomy (thrombus aspiration; aspiration thrombectomy).
- While thrombus burden can be reduced by using manual thrombectomy, the evidence does not demonstrate a significant benefit from its routine use.
- With regard to mechanical (rheolytic) thrombectomy, the results of randomized trials do not show benefit in the aggregate.



2015 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions focused update on primary PCI for patients with STEMI

TOTAL, TASTE & TAPAS trials

	Pt. of manual thrombectomy followed by PCI or PCI alone	Primary outcome	results
TOTAL	**N=10732**	cardiovascular death, recurrent MI, cardiogenic shock, NYHA IV heart failure	**347 vs. 351 events,** hazard ratio 0.9, 95% CI 0.85-1.15
TASTE	**N=7244**	death from any cause at 30 days; mortality at 1year	**No difference between two groups**
TAPAS	**N=1071**	myocardial blush grade of 0 or1 (absent or minimal myocardial reperfusion)	**17.1%: 26.3%** (p<0.001)

- Key safety outcome of stroke occurred more often with thrombectomy
- Risks of all-cause mortality (the primary end point) and MACE, a composite of death, MI, and target vessel revascularization, were lower with aspiration thrombectomy

1. Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med 2015; 372:1389.
2. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008; 358:557.

TOTAL trial: no differences between groups in primary endpoint

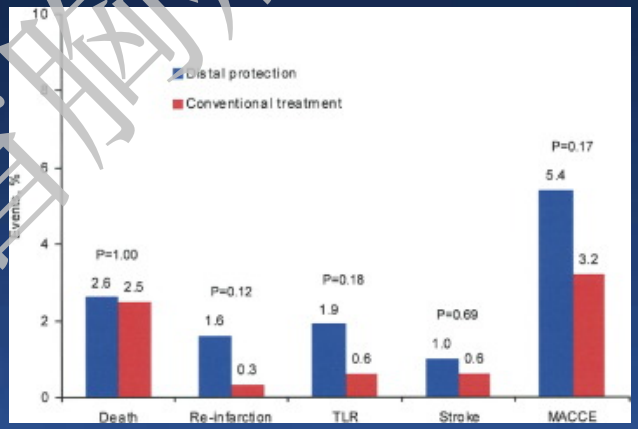
Table 1. Clinical Outcomes at 180 Days

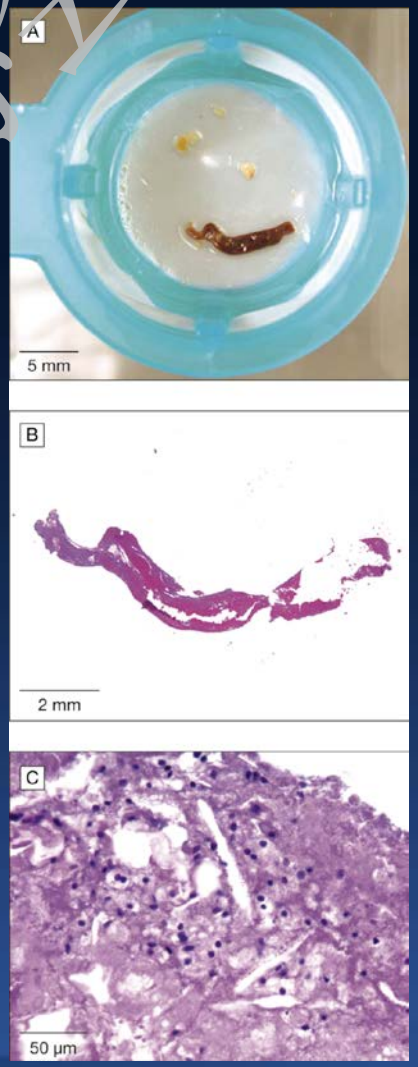
	Thrombectomy + PCI (n = 5,033)	PCI Alone (n = 5,030)	HR (95% CI)
Primary Outcome + Stent Thrombosis or TVR	9.9%	9.8%	1.00 (0.89-1.14)
Cardiovascular Death	3.1%	3.5%	0.90 (0.73-1.12)
Recurrent MI	2.0%	1.8%	1.07 (0.81-1.43)
Cardiogenic Shock	1.8%	2.0%	0.92 (0.69-1.22)
NYHA Class IV Heart Failure	1.9%	1.8%	1.09 (0.82-1.45)
Stent Thrombosis	1.5%	1.7%	0.88 (0.65-1.20)
TVR	4.5%	4.3%	1.03 (0.85-1.24)
Major Bleeding	1.6%	1.5%	1.02 (0.75-1.40)

Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med 2015; 372:1389.

Distal embolic protection devices

- Increasingly used with PCI in SVGs due to the substantial potential for embolization of both thrombus and atheromatous material
- A lack of benefit in trials; do not recommend as routine adjunctive therapy to primary PCI with STEMI patients
- EMERALD
  PROMISE
  DEDICATION trials



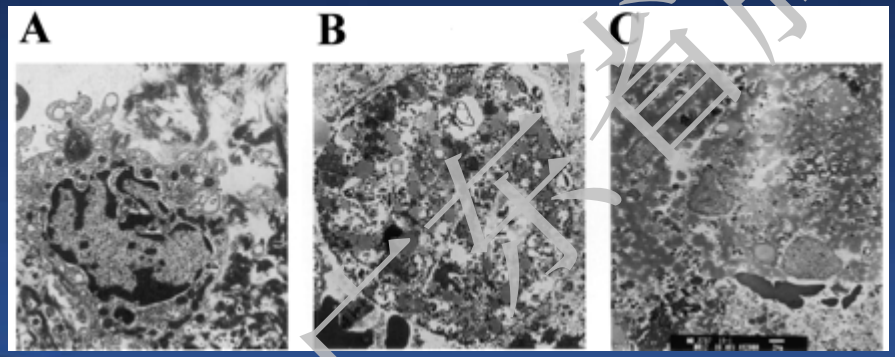


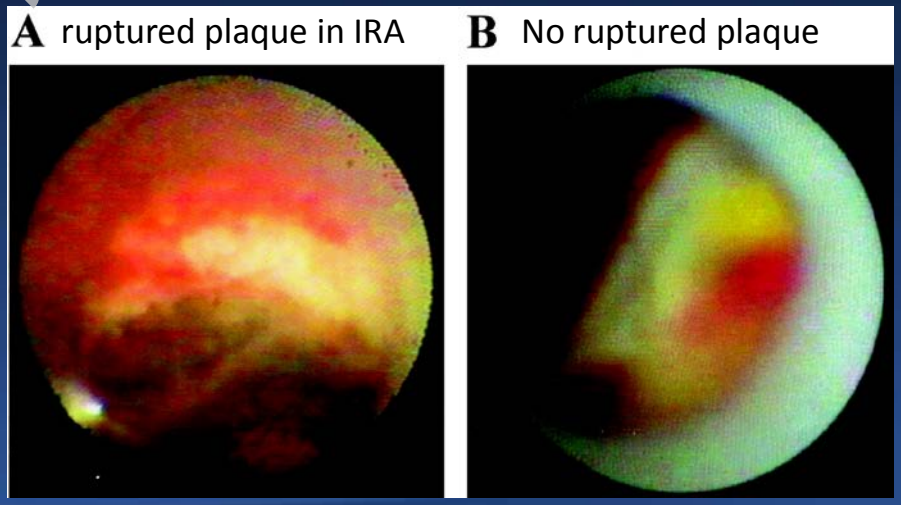
Stone GW, Webb J, Cox DA, et al. Distal microcirculatory protection during percutaneous coronaryintervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial.JAMA 2005; 293:1063.

Type of leison

- No-reflow was most common in patients with a ruptured plaque treated without distal protection.
- Clinical benefit from distal protection (as estimated from ST segment resolution, myocardial blush grade, and left ventricular ejection fraction) was only seen in patients with ruptured plaque.

- Macrophage with platelets and fibrin (A), lipid-containing macrophage (B), and lipid drops (C)





Mizote I, Ueda Y, Ohtani T, et al. Distal protection improved reperfusion and reduced leftventricular dysfunction in patients with acute myocardial infarction who had angioscopicallydefined ruptured plaque. Circulation 2005; 112:1001.

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Direct stenting and deferred stenting

- Direct stenting, without predilation, may lower the incidence of no-reflow.
- In high-risk STEMI patients, deferred stenting in primary PCI reduced no-reflow and increased myocardial salvage.

Table 2 Primary and Secondary Angiographic and Electrocardiographic Outcomes

Outcome	Randomly Assigned Groups: Immediate Stenting (n = 59)	Deferred Stenting (n = 51)*	Odds Ratio (95% CI)	p Value†	Registry (N = 310)
Primary outcome					
No- or slow-reflow (TIMI 0 to 2)‡					
Yes	14 (28.6)	3 (5.9)	0.16 (0.03–0.63)	0.005	45 (14.5)
Secondary angiographic outcomes					
No-reflow (TIMI grade 0 or 1)					
Yes	7 (14.3)	1 (2.0)	0.12 (0.03–1.02)	0.052	16 (5.2)
Final TIMI coronary flow grade post-PCI§					
3	39 (79.6)	50 (98.0)			273 (88.6)
2	6 (12.2)	0 (0.0)	0.08 (0.01–0.65)	0.018	25 (8.1)
0/1	4 (8.2)	1 (2.0)			10 (3.2)
Final TIMI myocardial blush grade post-PCI‖					
Missing	0	1			
3	26 (53.1)	40 (80.0)			
2	18 (36.7)	9 (18.0)	0.28 (0.11–0.65)	0.004	—
0/1	5 (10.2)	1 (2.0)			
No- or slow-reflow (TIMI grades 0–2), with MBG ≤1					
Missing	0	1			
Yes	5 (10.2)	1 (2.0)	0.18 (0.00–1.72)	0.195	
No- or slow-reflow (TIMI grades 0–2), with MBG ≤2					
Missing	0	1			
Yes	12 (24.5)	2 (4.0)	0.13 (0.01–0.64)	0.007	
All intraprocedural thrombotic events	28	9	—	—	68
Patients with at least 1 intraprocedural thrombotic event	16 (32.7)	5 (9.8)	0.23 (0.06–0.73)	0.010	63 (20.3)
Distal embolization	10 (20.4)	1 (2.0)	0.08 (0.02–0.60)	0.006	5 (1.3)
Other secondary outcome					
ECG: resolution of ST-segment elevation 60 min post-PCI					—
Complete, ≥70%	19 (38.8)	26 (50.0)			
Partial, 30% to <70%	21 (42.9)	15 (28.8)	0.77 (0.37–1.6)	0.484	
None, ≤30%	9 (18.4)	11 (21.2)			

David Carrick, et al. J Am Coll Cardiol 2014;63:2088–98

Systemic GP IIb/IIIa inhibitors

- It is unclear whether GP IIb/IIIa inhibitors when infused peripherally reduce the incidence of no-reflow
- Do not recommend the routine use of glycoprotein (GP) IIb/IIIa inhibitors
- Randomized trial/ CADILLAC trials

Costantini CO, Stone GW, Mehran R, et al. Frequency, correlates, and clinical implications ofmyocardial perfusion after primary angioplasty and stenting, with and without glycoprotein IIb/IIIaInhibition, in acute myocardial infarction. J Am Coll Cardiol 2004; 44:305.

Intracoronary administration of tirofiban for no-reflow phenomenon

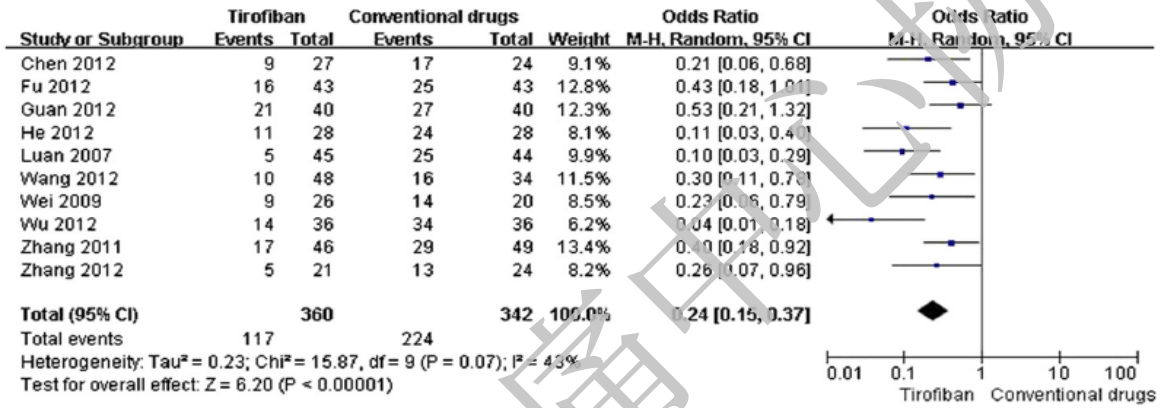

Figure 2 Forest plot of OR for TIMI flow transformation.

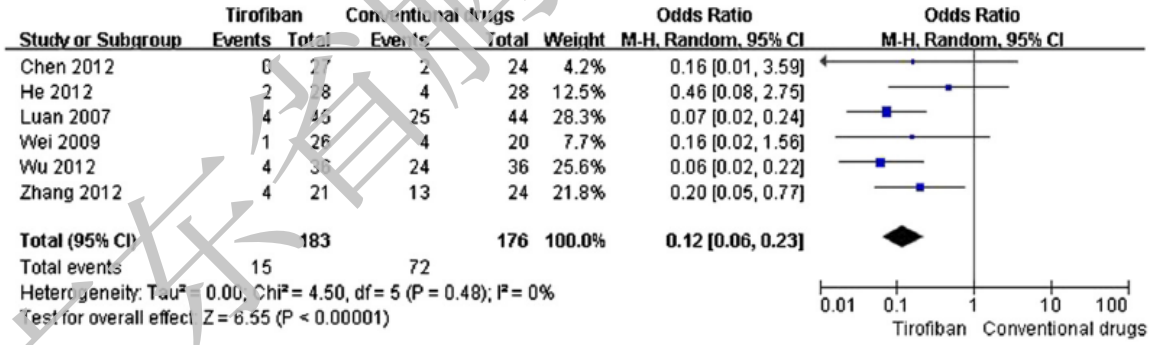

Figure 3 Forest plot of OR for MACE.

Qin et al. BMC Cardiovascular Disorders 2013, 13:68

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Effect of abciximab on clinical outcome

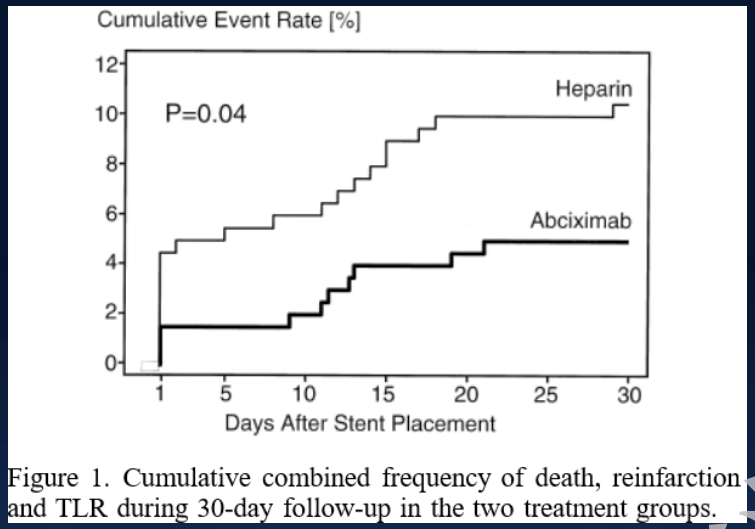


Figure 1. Cumulative combined frequency of death, reinfarction and TLR during 30-day follow-up in the two treatment groups.

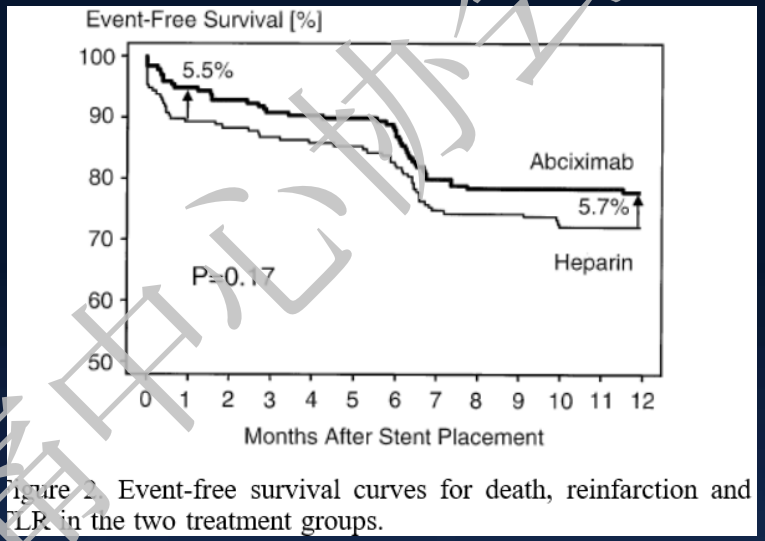


Figure 2. Event-free survival curves for death, reinfarction and TLR in the two treatment groups.

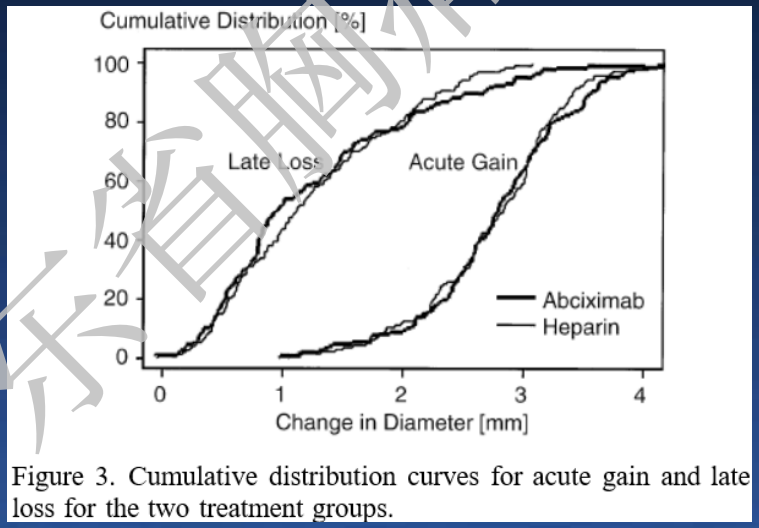


Figure 3. Cumulative distribution curves for acute gain and late loss for the two treatment groups.

Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade onrecovery of coronary flow and left ventricular function after the placement of coronary-artery stentsin acute myocardial infarction. Circulation 1998; 98:2695.

Intracoronary infusions:
Vasodilator therapies- adenosine & verapamil

- Adenosine and verapamil are of uncertain benefit when given for slow coronary flow in STEMI.
- However, we use these agents from time to time despite convincing evidence of benefit.
- Either agent reduced short-term, all-cause mortality or non-fatal myocardial infarction; In addition, there was an increase in the risk of adverse effects such as bradycardia or hypotension with adenosine.

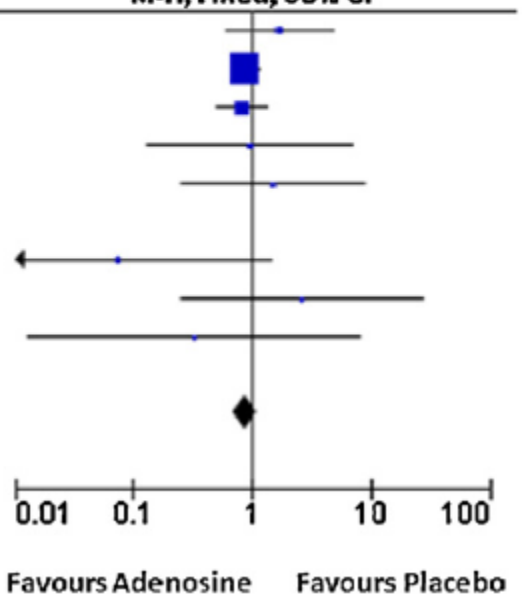
Adenosine improves post-procedural coronary flow

Mortality

Study or Subgroup	adenosine Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMISTAD I	10	119	6	117	3.7%	1.70 [0.60, 4.83]
AMISTAD II	146	1414	83	703	65.7%	0.86 [0.65, 1.14]
ATTACC	32	302	39	306	22.9%	0.81 [0.49, 1.33]
Desmet	2	56	2	54	1.3%	0.96 [0.13, 7.09]
Fokkema	3	226	2	222	1.3%	1.48 [0.24, 8.94]
Grygier	0	35	0	35		Not estimable
Marzilli	0	27	5	27	3.6%	0.07 [0.00, 1.42]
Stoel	3	27	1	22	0.6%	2.63 [0.25, 27.19]
Vijayalakshmi	0	51	1	50	1.0%	0.32 [0.01, 8.05]
Total (95% CI)		2257		1536	100.0%	0.87 [0.69, 1.09]
Total events	196		139			

Heterogeneity: Chi² = 5.90, df = 7 (P = 0.55); I² = 0%

Test for overall effect: Z = 1.20 (P = 0.23)



Eliano Pio Navaresea, et al. Atherosclerosis 2012; 222: 1– 7

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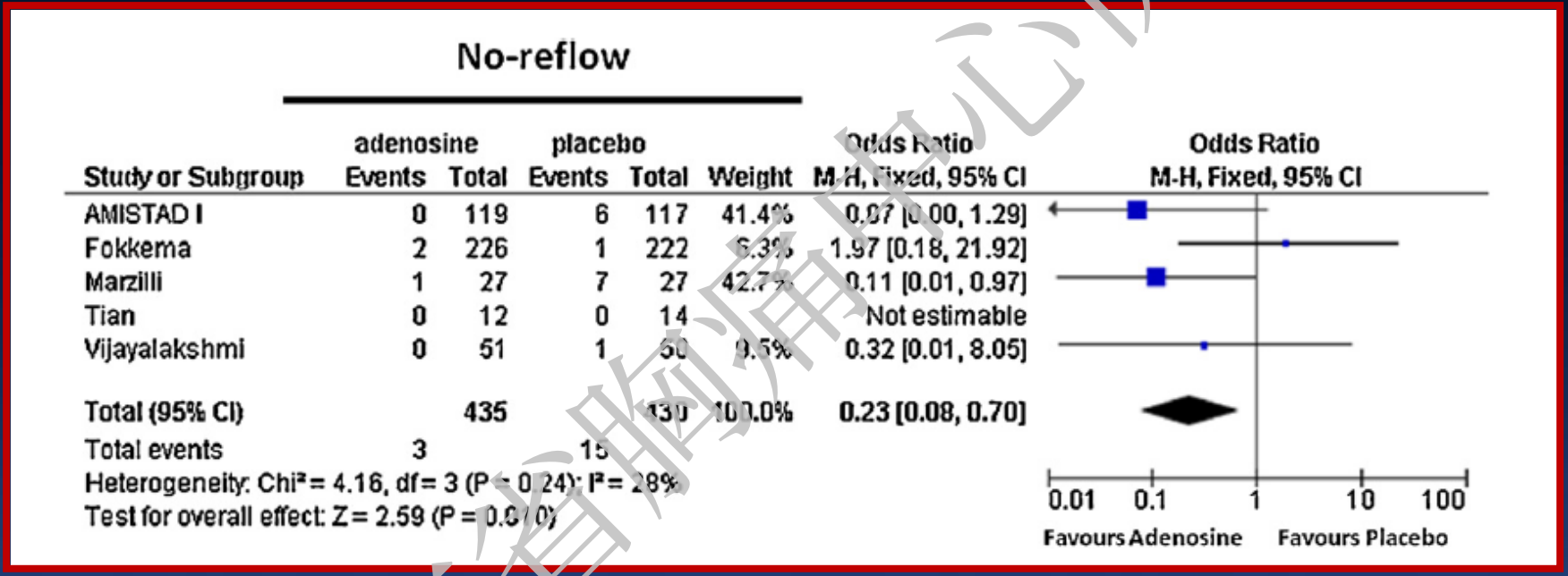
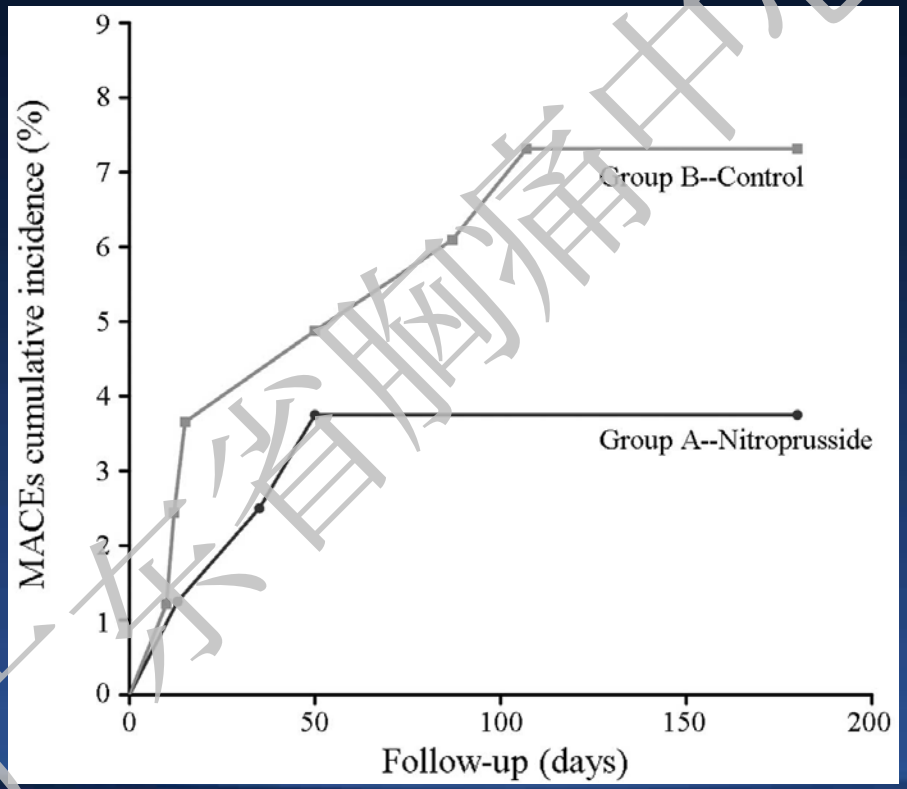
Adenosine improves post-procedural coronary flow



Eliano Pio Navaresea, et al. Atherosclerosis 2012; 222: 1– 7

Intracoronary nitroprusside

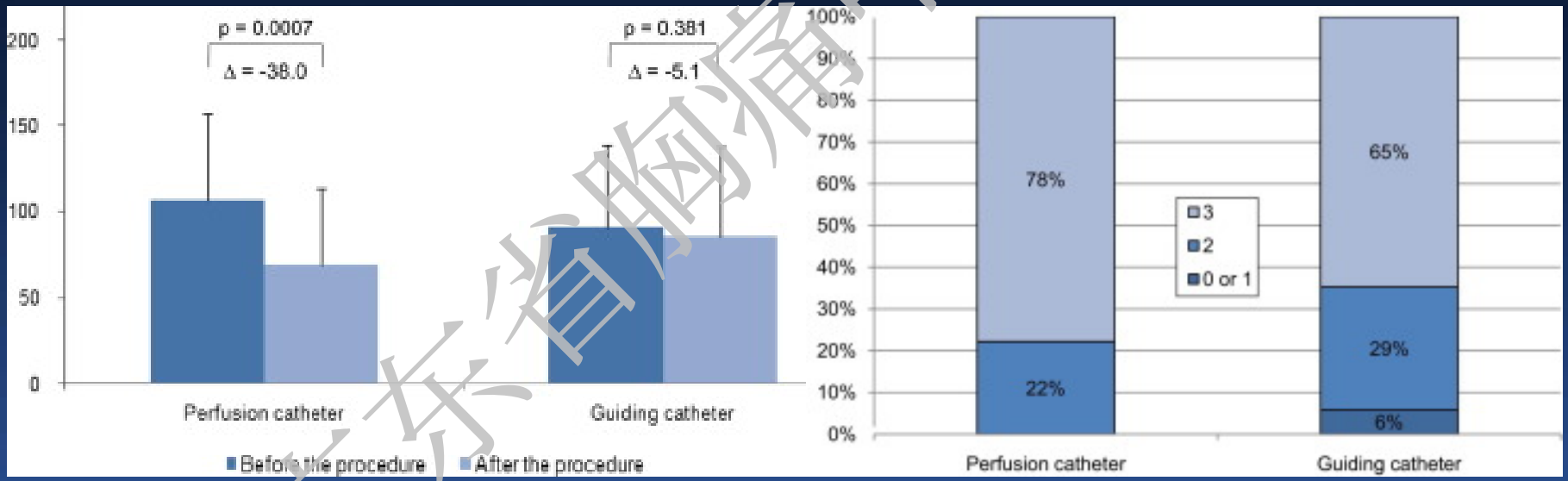
- Doses of 50 to200 μg, has shown promising results when given alone or with intracoronary adenosine



J Am Coll Cardiol 2001; 37:1335
Experimental and Therapeutic Medicine 6.2 (2013): 479-484.

Intracoronary infusions:
Antithrombotic/thrombolytic therapies

- Intracoronary abciximab and low dose intracoronary streptokinase (250,000 U) have the ability to improve microvascular perfusion.



N Engl J Med 2007; 356:1823
JACC Cardiovasc Interv 2010; 3:928

Chronic statin therapy

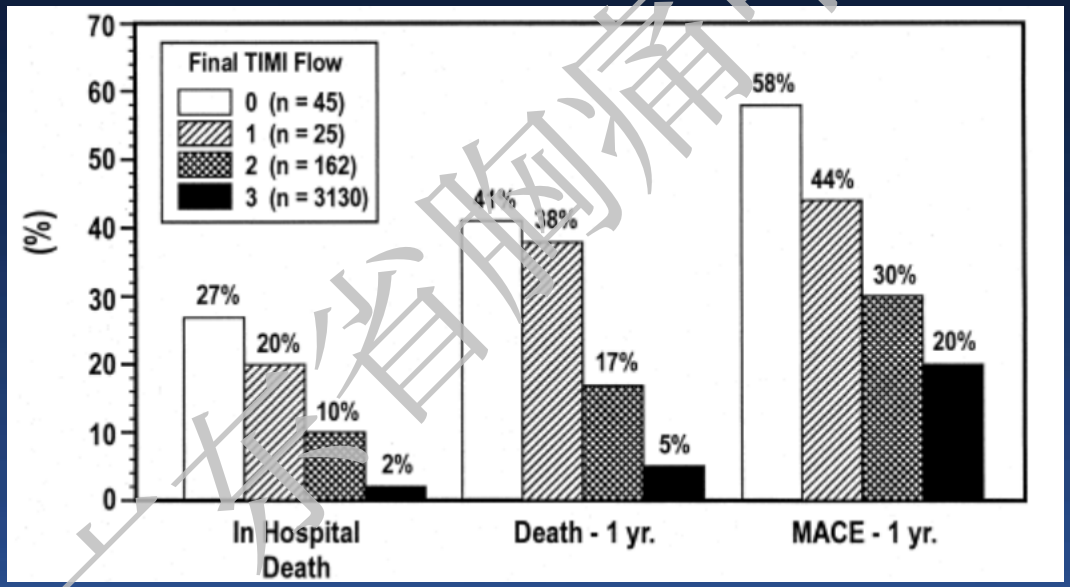
- An observational study from Japan of 293 consecutive patients.
- Statin-treated patients had a much lower rate of no-reflow (9 versus 35 percent), better wall motion, and a higher left ventricular ejection fraction.
- Statin therapy reduces myocardial injury, stabilizes plaque after PCI.

Support treatment

- For those patients with hypotension and/or hypoperfusion, intravenous vasopressors, inotropic agents, and IABP support may be of benefit.

Prognosis

- No-reflow usually presents with acute ischemia, EKG changes, chest pain, atrioventricular block, and hypotension.
- The occurrence of no-reflow has been associated with adverse short- and long-term outcomes.



p for trend <0.0001 for all three outcomes.

J Am Coll Cardiol. 2003 Nov 19;42(10):1739-46.

Prognosis

- No-reflow has been associated with an increase in acute MI of up to 32% and a 15% higher incidence of death.

- The long-term detrimental effect of no-reflow has been documented to include increased risk for cardiac death, congestive heart failure, malignant arrhythmias and decrease in ejection fraction.

Prognosis of No-reflow during PCI in 1 and 5 years

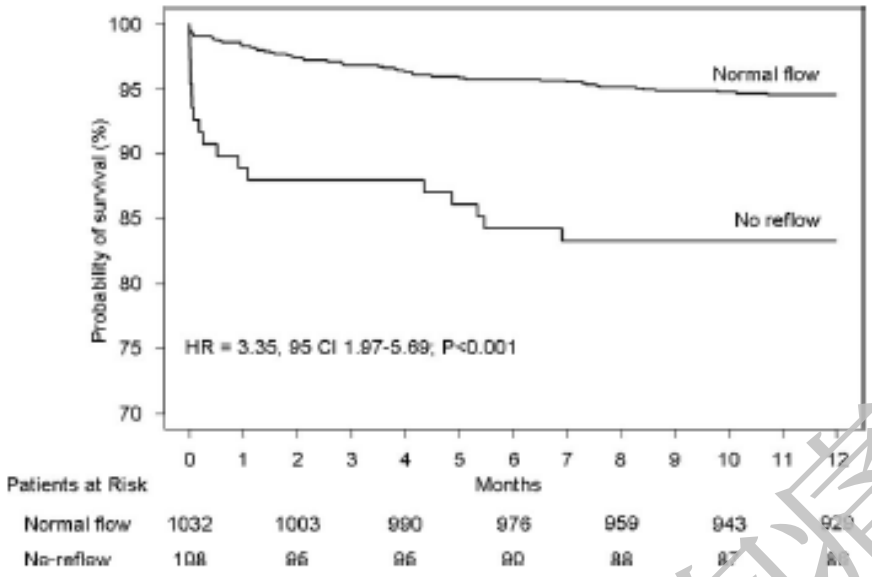


Figure 4. Probability of 1-year survival among patients with normal flow and no reflow after primary PCI. HR indicates hazard ratio.

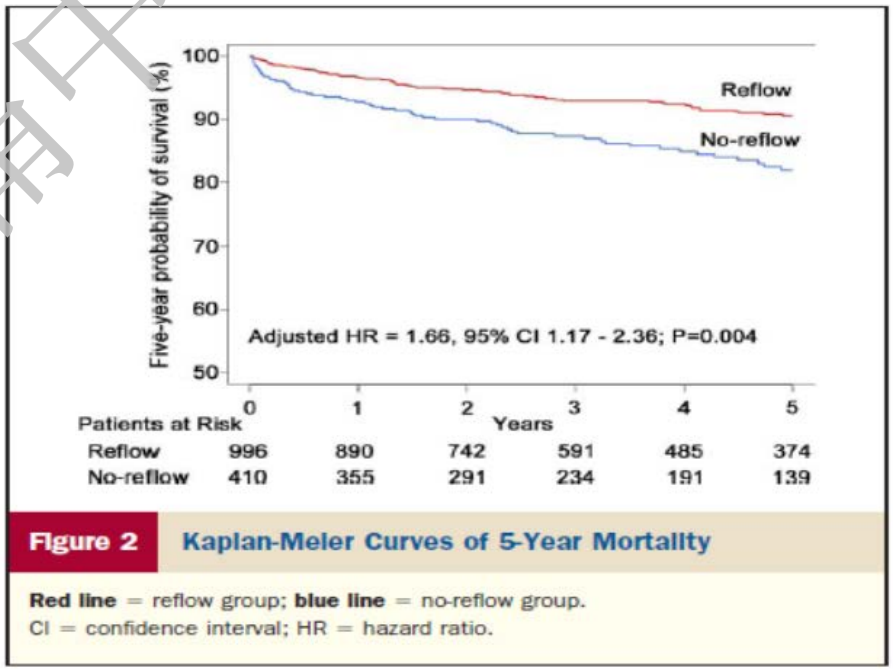


Figure 2 Kaplan-Meier Curves of 5-Year Mortality

Red line = reflow group; **blue line** = no-reflow group.
CI = confidence interval; HR = hazard ratio.

Gjin C, etal, Cir Cardiovasc Interv, 2010,3,27-33

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SUMMARY and RECOMMENDATIONS

- PCI in STEMI patients establishes normal or near normal antegrade blood flow, as assessed by the Thrombolysis in Myocardial Infarction (TIMI) flow grade 3, in over 90 percent of cases.
- The most common causes of TIMI flow grade ≤2 are persistent stenosis, thrombus, dissection, spasm, or distal macroembolism.
- Age ≥70 years, diabetes, longer time to reperfusion, initial TIMI flow grade ≤1, left ventricular ejection fraction <50 percent, heart failure on presentation, and incomplete ST segment elevation resolution are predictors of suboptimal reperfusion.

SUMMARY and RECOMMENDATIONS

- Direct stenting lessens the likelihood of no-reflow.
- The benefit ofglycoprotein (GP) IIb/IIIa inhibitors or the intracoronary infusion of adenosine remains speculative.
- We suggest not routinely performing thrombus aspiration in primary PCI. It is reasonable to use aspiration thrombectomy in patients with a large thrombus burden.
- Distal embolic protection does not appear to protect against no-reflow in the native coronary circulation but is effective in SVGs.
- Patients with hypotension and/or hypoperfusion should be treated with the same approach used in other patients with cardiogenic shock following acute myocardial infarction.

Thank you for your attention !