Ischemic Postconditioning During Primary Percutaneous Coronary Intervention

Mechanisms and Clinical Application



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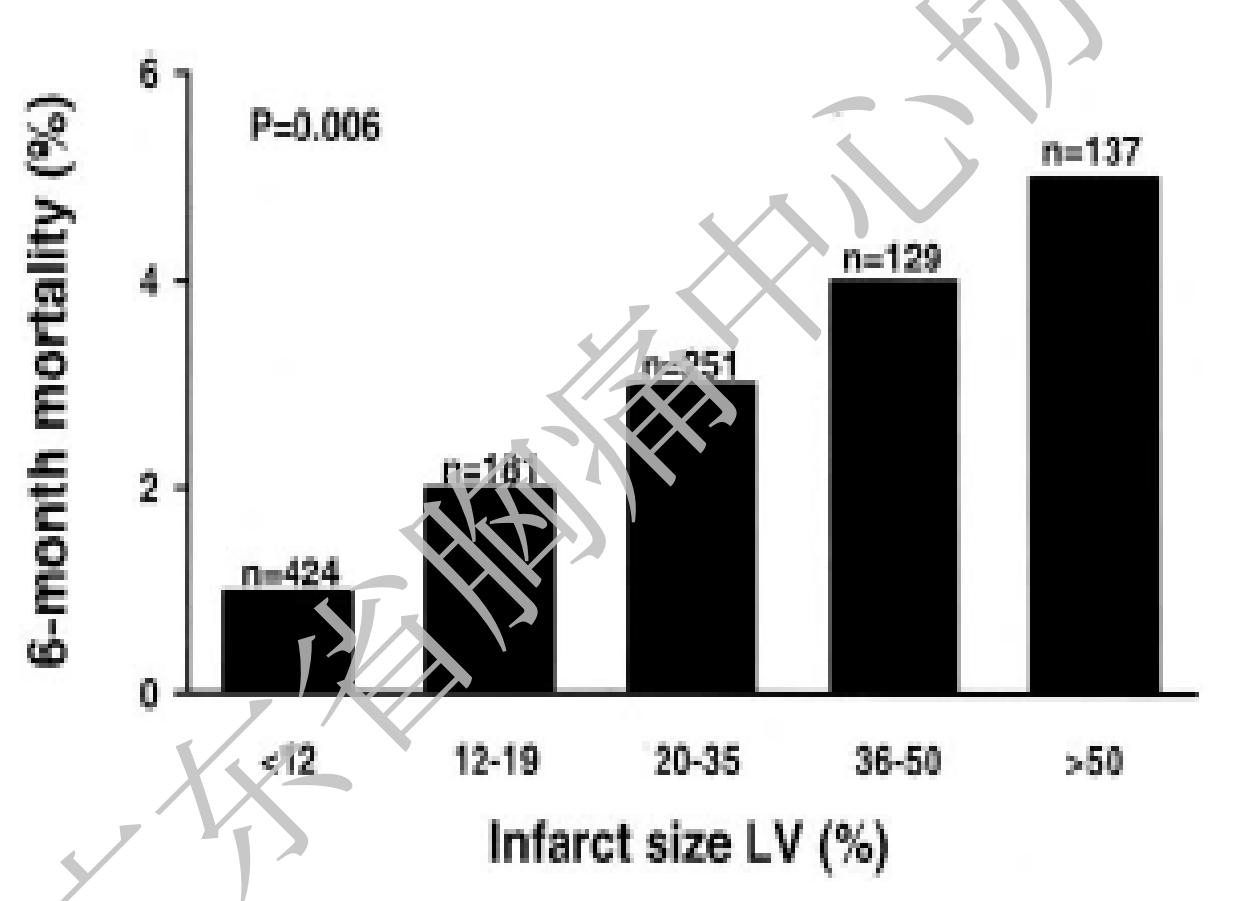
Infarct size is a determinant of mortality in Acute Myocardial Infarction



Gibbons et al. JACC 2004;44:1533-1542

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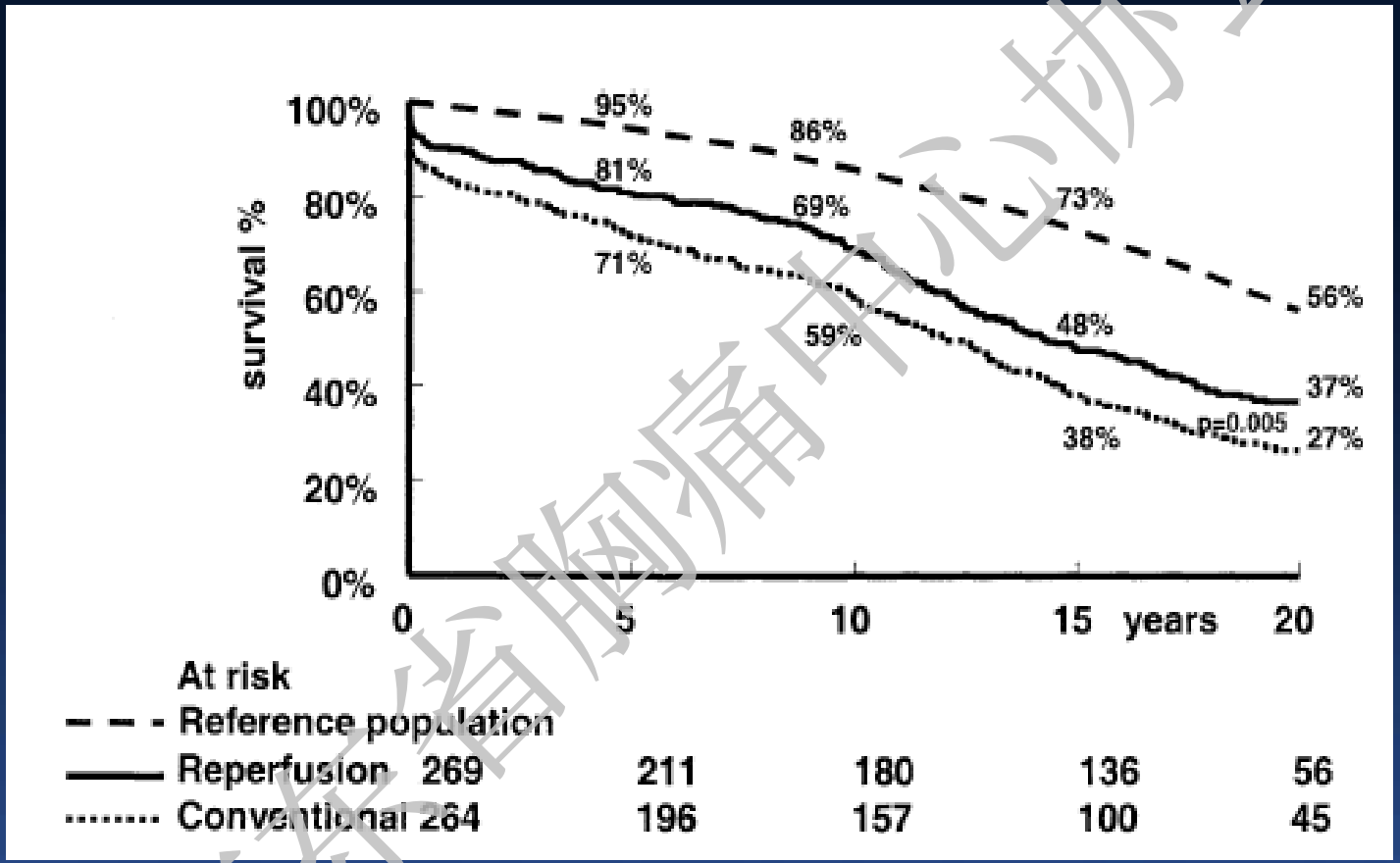
Reperfusion improves outcome



van Domburg et al. JACC 2005:15–20

Current treatment of AMI

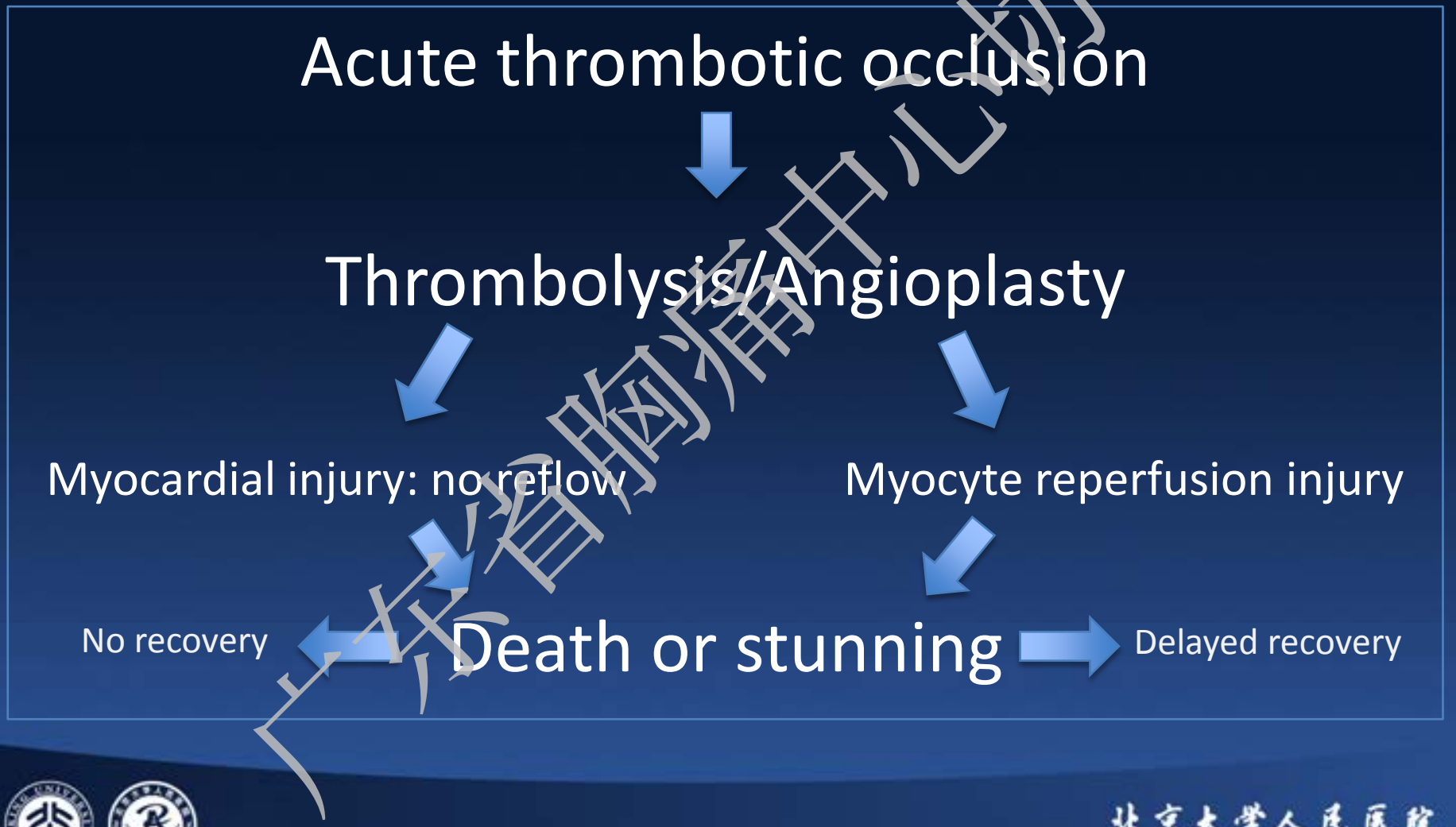
- β-blockers
- ACE inhibitors
- statins
- ….

improve post-MI outcome,
but ***not via a reduction in infarct size***

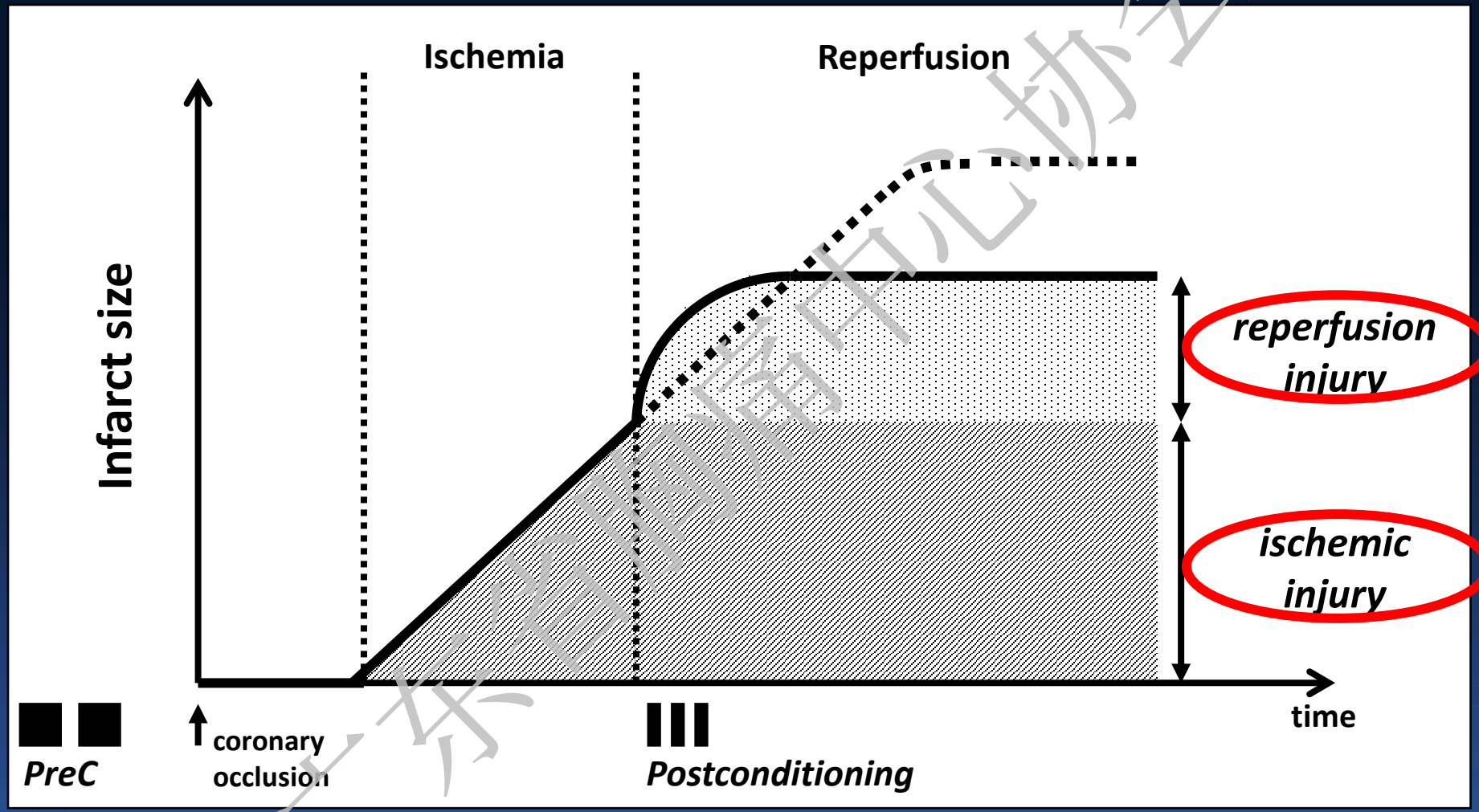
Action on infarct size

- **Ischemic damage** : YES
  - thrombolysis / PCI — ischemia time
  - antiplatelet agents — ischemia time
- **Reperfusion damage** : NO

Reperfusion Injury: the two facets



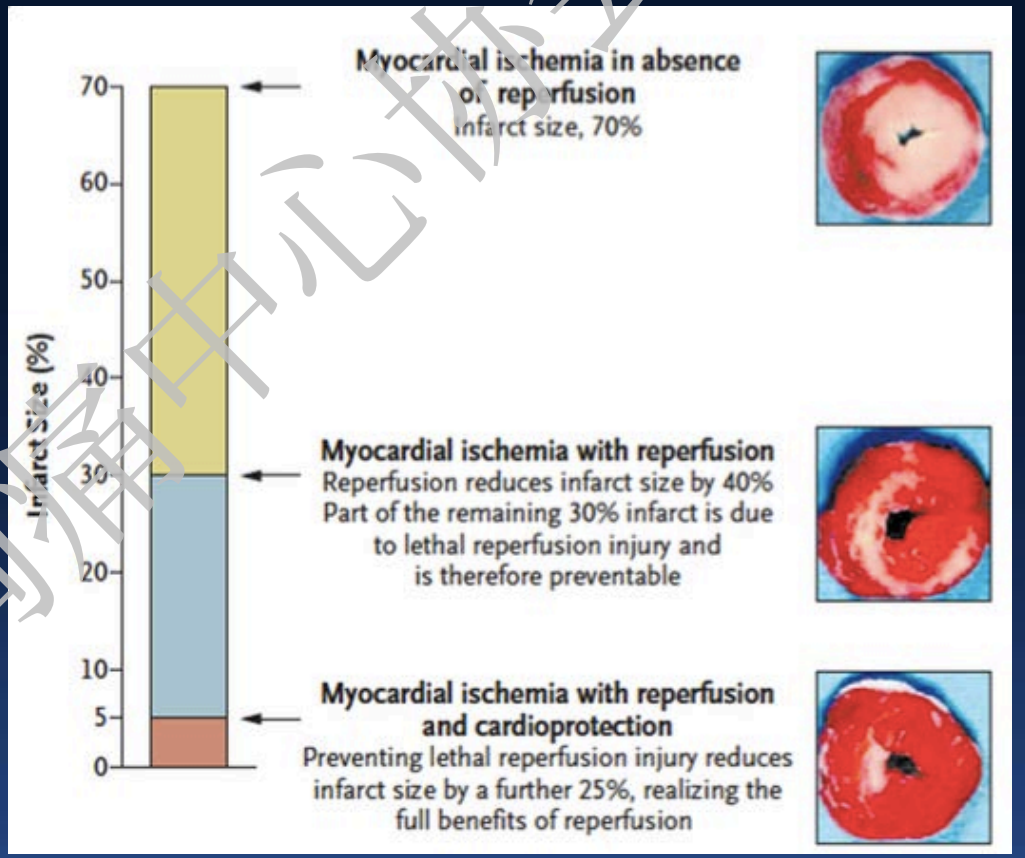
Infarction: a two-component damage



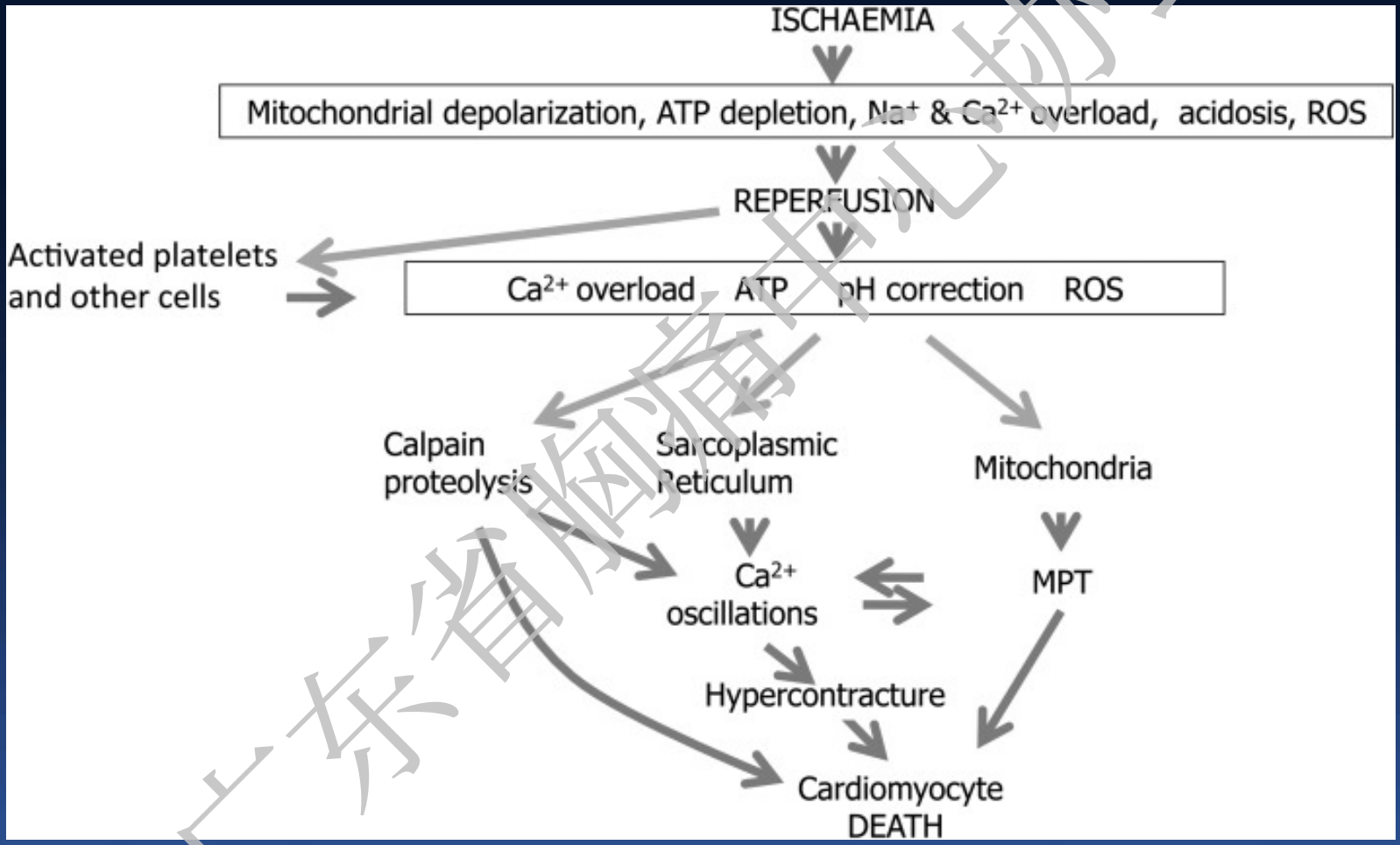
Reperfusion Injury

- Reperfusion injury increase infarct size

- Increasing myocyte cell death, activation of apoptosis and promotion of endothelial dysfunction



Main mechanisms of cardiomyocyte cell death during myocardial reperfusion



Hausenloy D.J et al Eur H J 2017

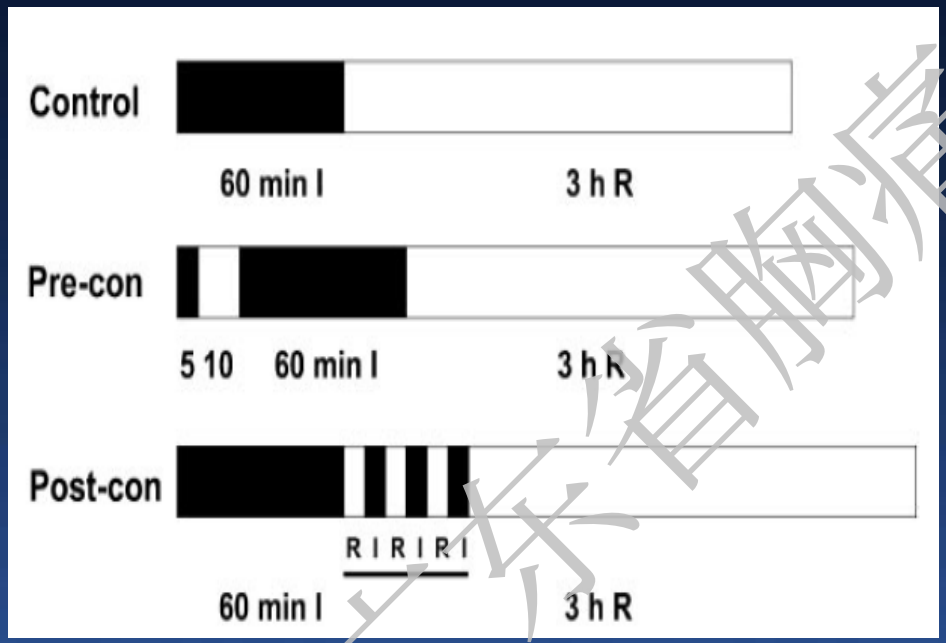
Ischemic Postconditioning

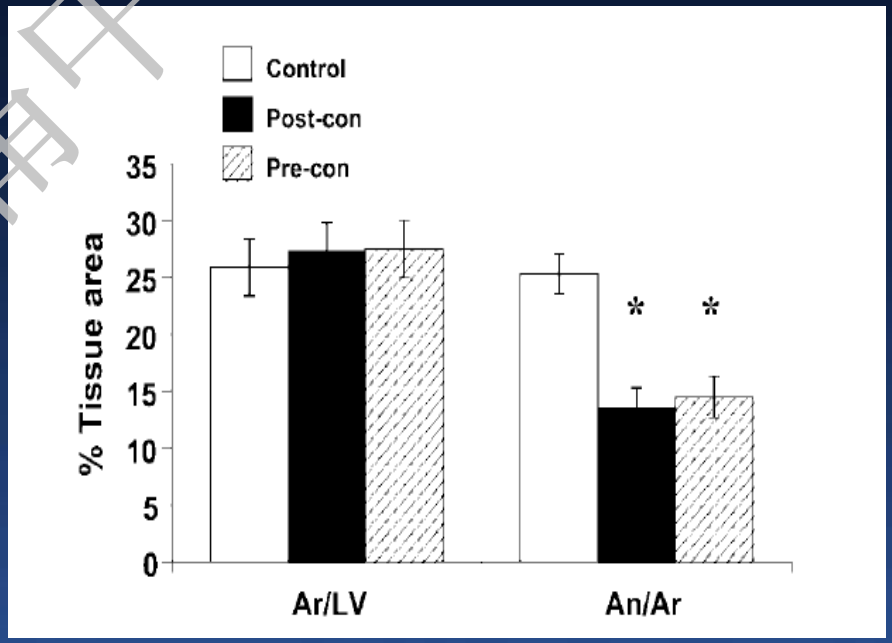
- Zhao et al. were the first to describe a phenomenon known as “post-conditioning” in which a sequence of repetitive interruption of coronary blood flow was applied immediately after reopening of the occluded vessel can reduced infarct size.

Zhao, ZQ et al. AM J Physiol Heart Circ 2003

Ischemic Postconditioning

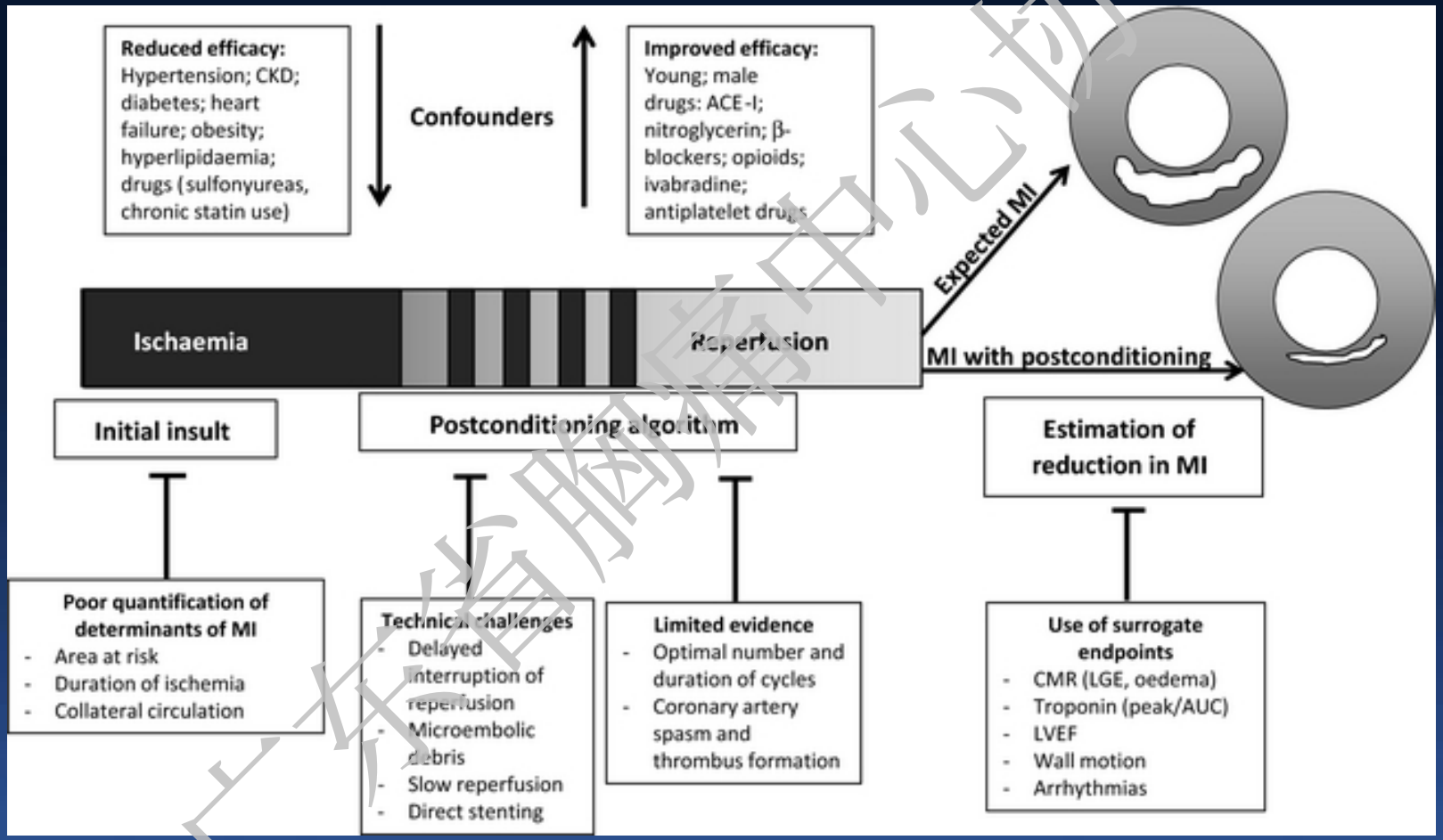
- Repetitive reversible ischemia during early reperfusion after the prolonged ischemic insult.
- Comparable protective effects to preconditioning in animal studies.





Zhao ZQ et al. Am J Physiol 2003

Ischaemic postconditioning: cardiac protection after the event



Anaesthesia volume 70 issue 5, pages 598-612, 16 FEB 2015 DOI: 10.1111/anae.12974

Does Postconditioning protect the human heart ?

A « proof of concept » study

Postconditioning the Human Heart

Patrick Staat, MD; Gilles Rioufol, MD, PhD; Christophe Piot, MD, PhD; Yves Cottin, MD, PhD; Thien Tri Cung, MD; Isabelle L'Huillier, MD; Jean-François Aupetit, MD, PhD; Eric Bonnefoy, MD, PhD; Gérard Finet, MD, PhD; Xavier André-Fouët, MD; Michel Ovize, MD, PhD

(*Circulation*. 2005;112:2143-2148.)

Study population
A First « Human Model » of Postconditioning

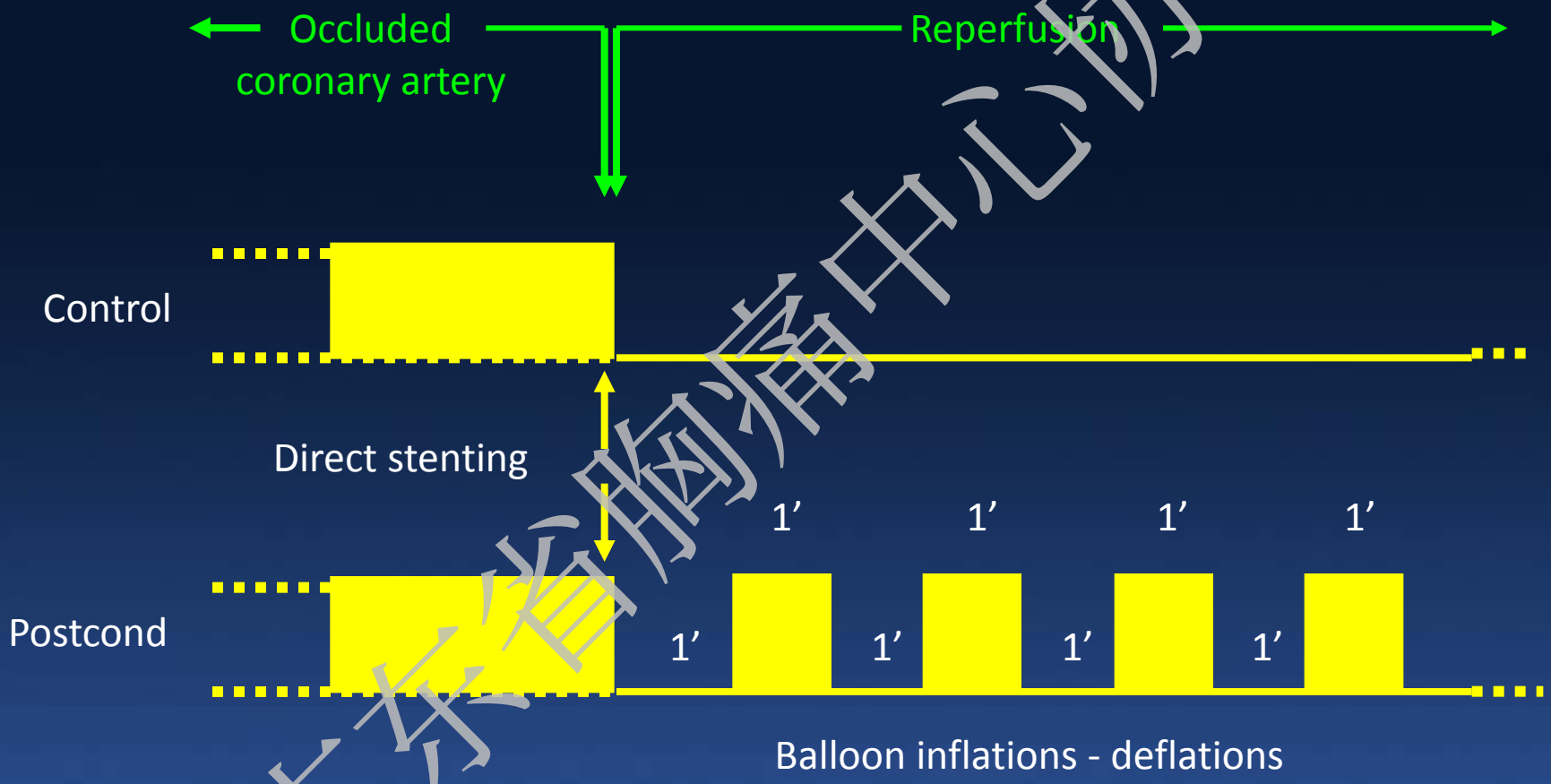
Inclusion criteria

1. Age ≥ 18
2. First acute (STE)MI / chest pain onset < 6 hrs
3. Need for emergency PTCA

Exclusion criteria

1. Cardiac arrest
2. Cardiogenic shock
3. Circumflex coronary artery as culprit for AMI

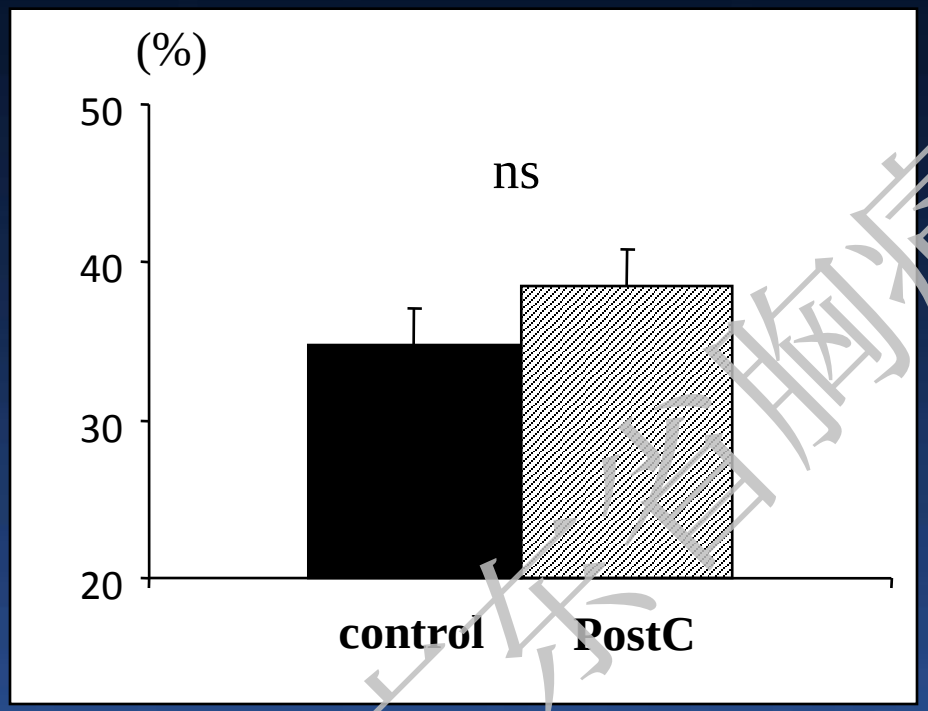
Post-Conditioning algorythm



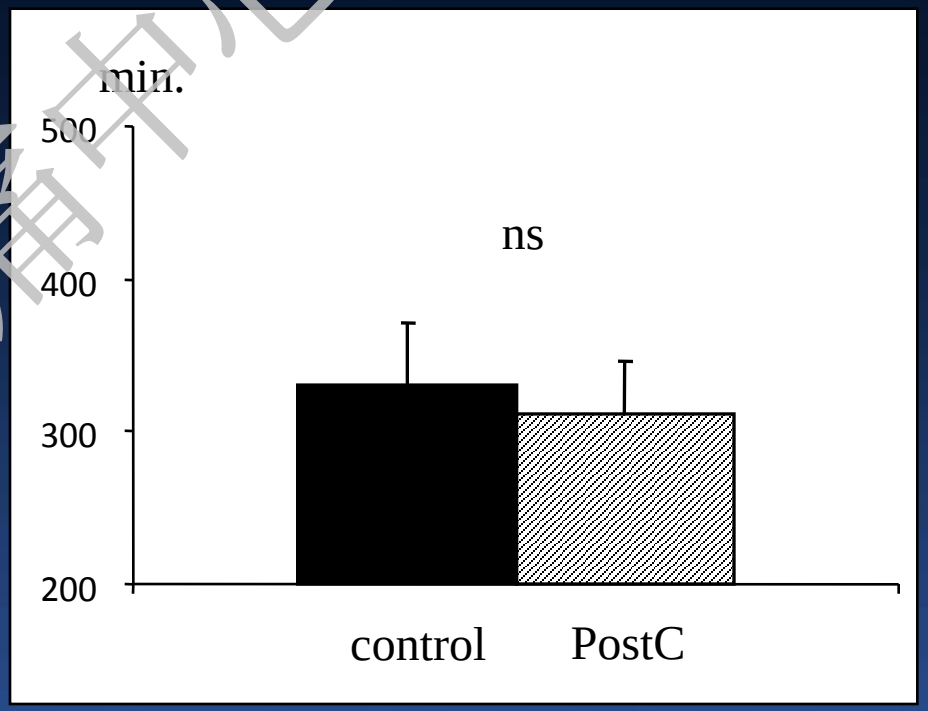
Staat et al. Circulation. 2005;112:2143-2148

Determinants of infarct size

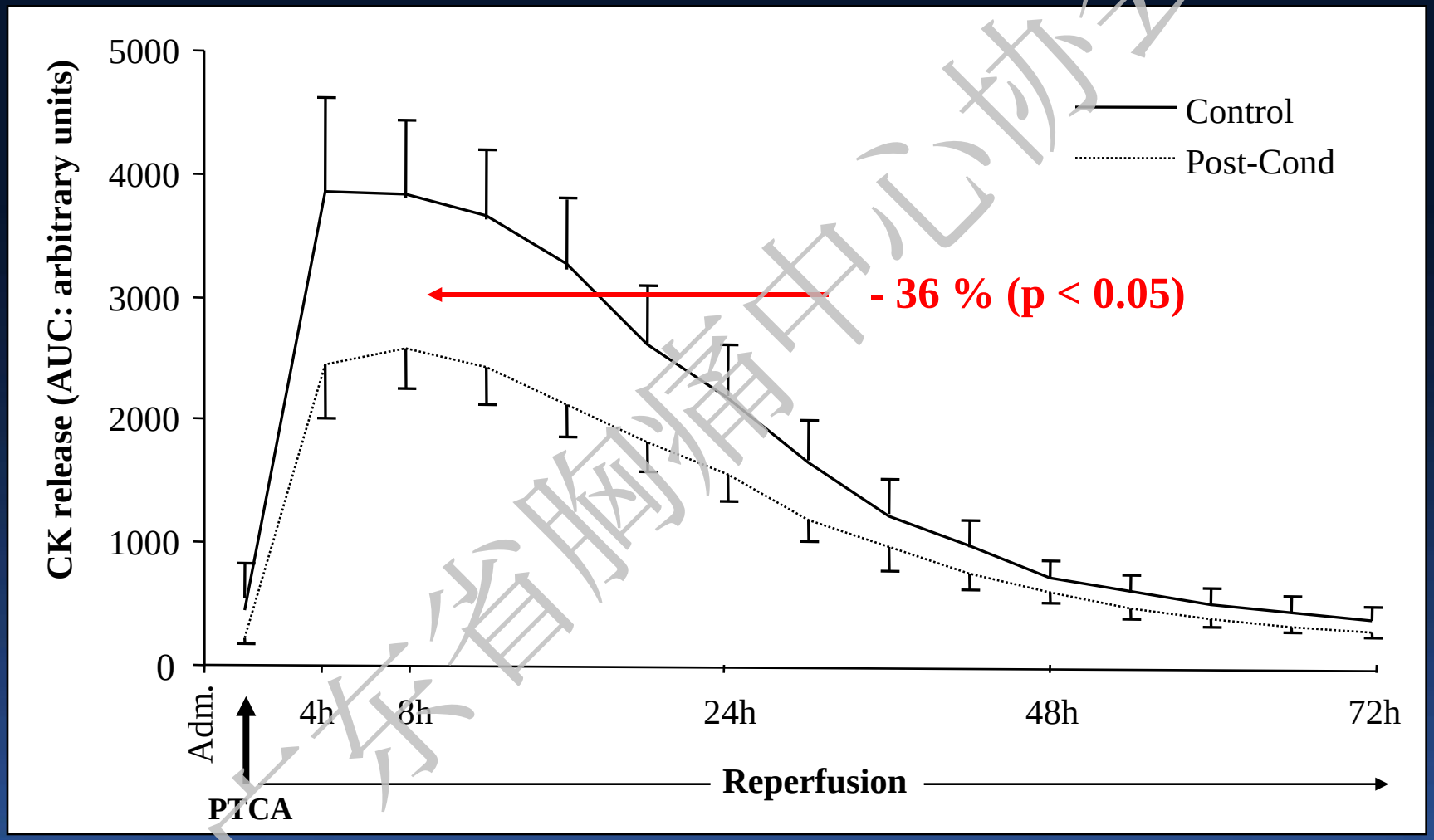
Area at Risk size (ACS)



Duration of Ischemia

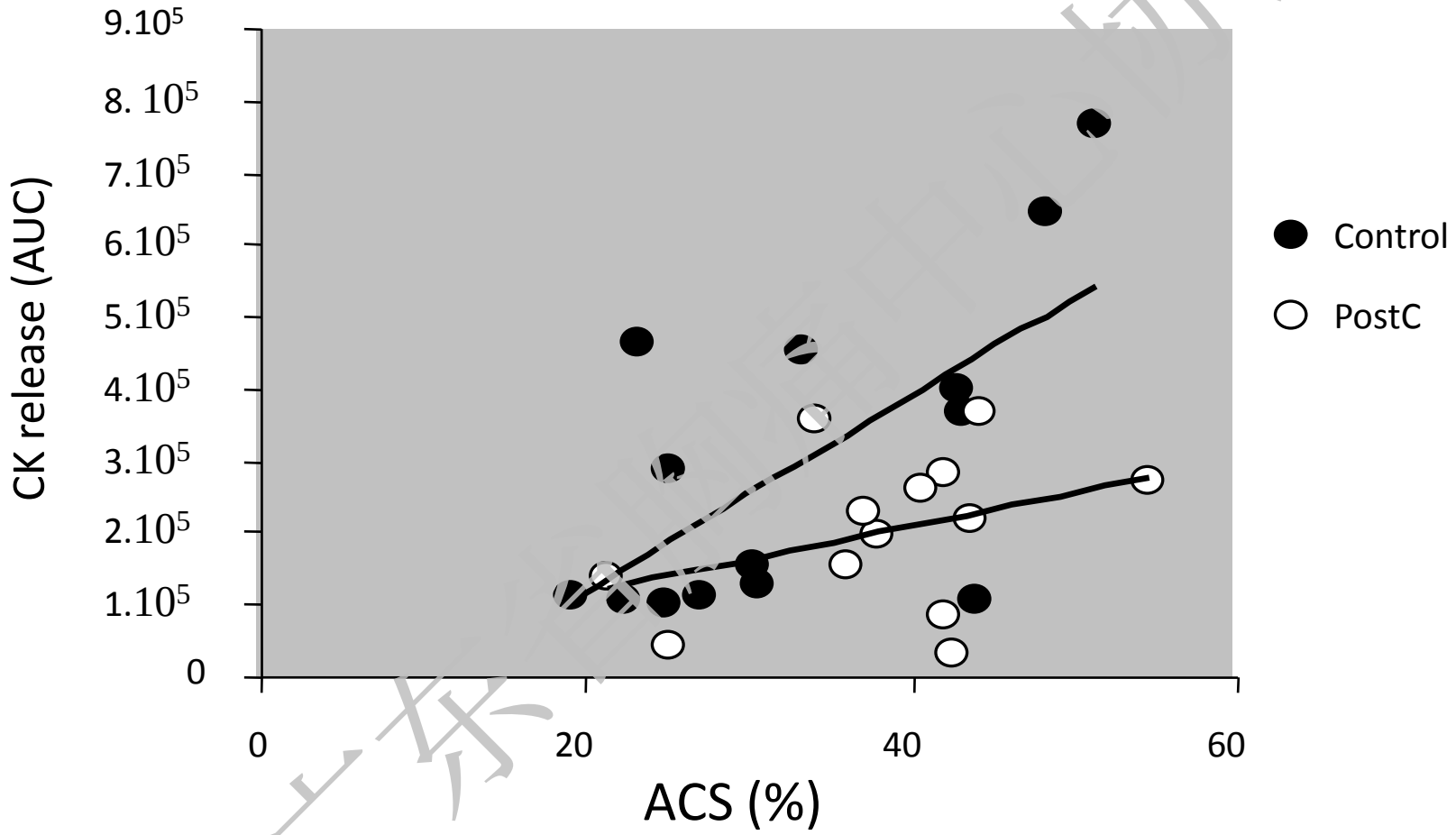


CK release during reperfusion

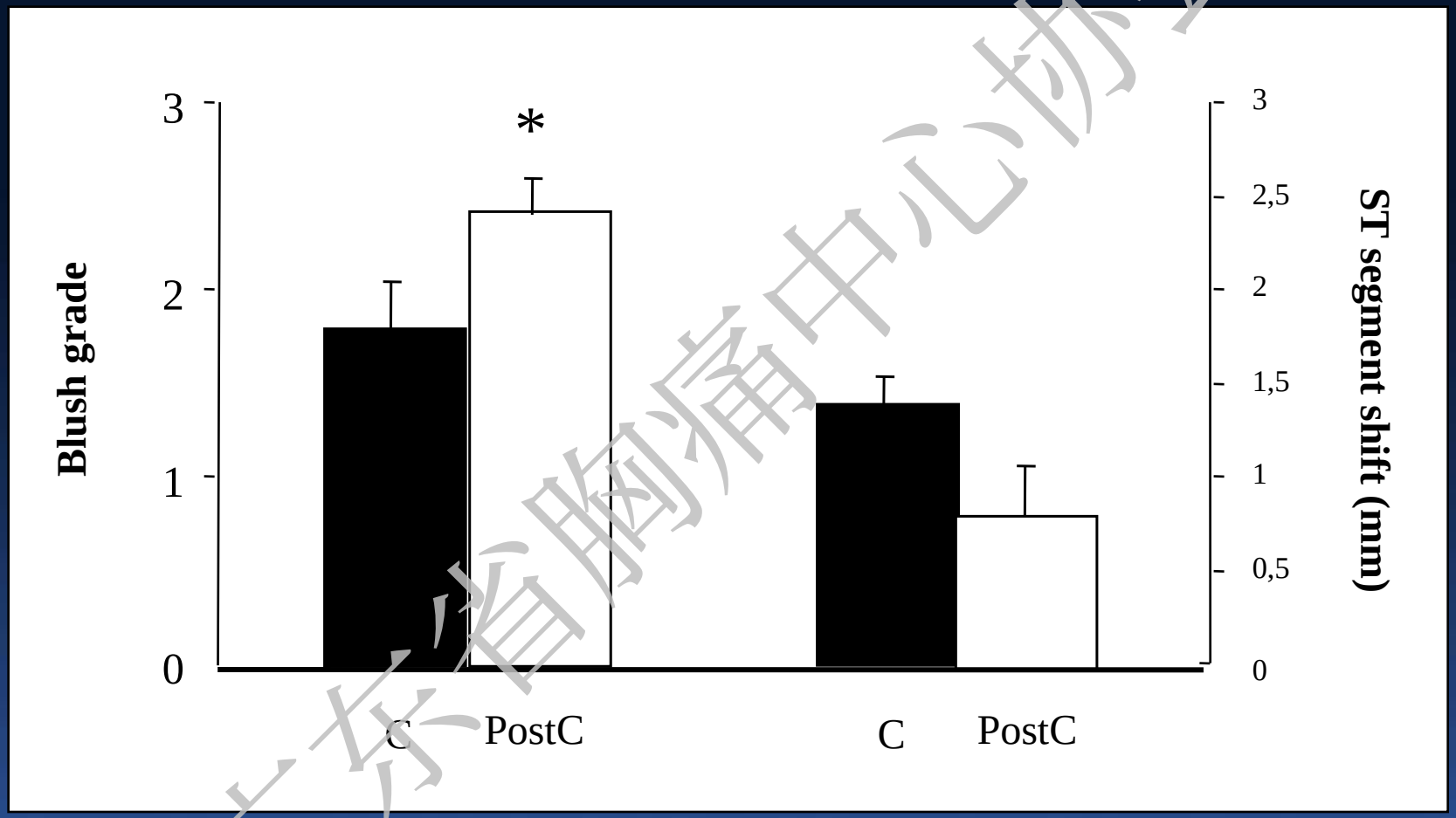


Staat et al. Circulation. 2005;112:2143-2148

CK release versus ACS (infarct size versus area at risk)



Estimation of « no reflow »



Staat et al. Circulation. 2005;112:2143-2148

Ischemic Postconditioning

- Postconditioning reduced enzymatic infarct size in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).
  - Staat P et al. Circulation 2005, the first report in human
- Inconsistent results of studies using CE-MRI for infarct size.
  - Lonborg J et al. Circ Cardiovasc Interv 2010
  - Thuny F et al. J Am Coll Cardiol 2012
  - Sorensson P et al. Heart 2010
  - Freixa X et al. Eur Heart J 2012
  - Tarantini G et al. Int J Cardiol 2012

  } PostC is Protective!

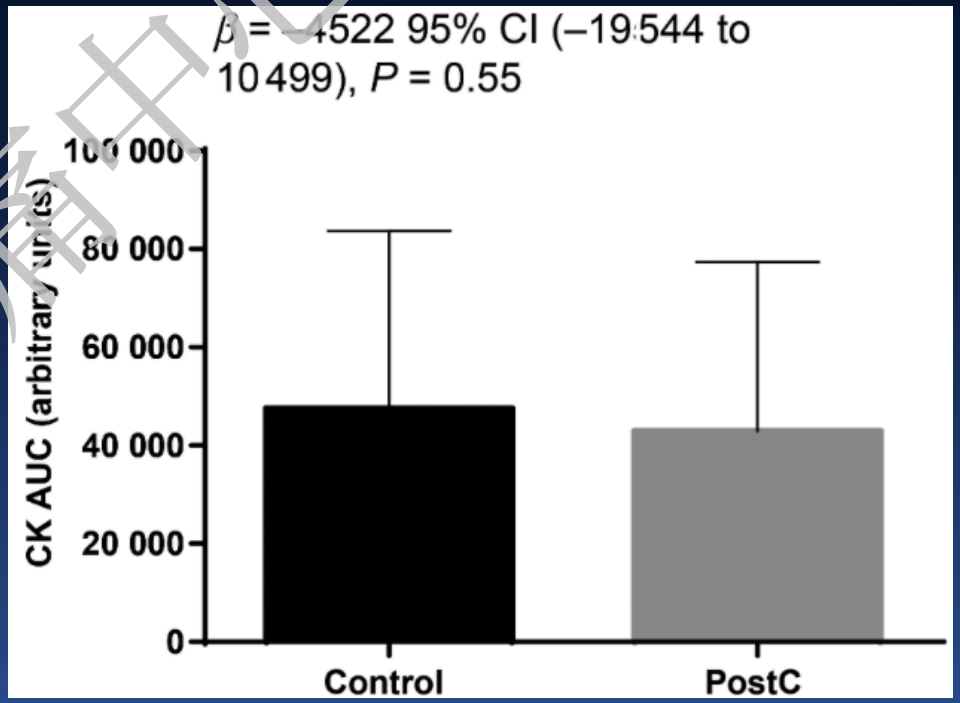
- No large scale trials

  } PostC is harmful!

Post-conditioning effects

Post-conditioning and injury biomarkers

- In a multi-center randomized controlled study, Roubille et al. failed to show any significant decrease in CK and TnI release, even after adjustment for the size of the area at risk.



Roubille, F et al, *European Heart Journal 2014*

Post-conditioning effects

Post-conditioning and no-reflow

Postconditioning attenuates no-reflow in STEMI patients.

Mewton N[1], Thibault H, Roubille F, Lairez O, Rioufol G, Sportouch C, Sanchez I, Bergerot C, Cung TT, Finet G, Angoulvant D, Revel D, Bonnefoy-Cudraz E, Elbaz M, Piot C, Sahraoui I, Croisille P, Ovize M.

⊕ **Author information**

Abstract

After acute myocardial infarction, the presence of no-reflow (or microvascular obstruction: MVO) has been associated with adverse left ventricular (LV) remodeling and worse clinical outcome. This study examined the effects of mechanical ischemic postconditioning on early and late MVO size in acute ST-elevation myocardial infarction (STEMI) patients. Fifty patients undergoing primary coronary angioplas = 25) or control (n followed by a 1-mi ssed by contrast-e 8 in PC versus 7. O; P = 0.01). Thi on infarct siz postcondi

Using contrast-enhanced cardiac-MRI within 3 days after reperfusion, Mewton et al. showed that post-conditioning was associated with smaller, early and late microvascular obstruction size (p = 0.01).

Mewton N, et al Basic Res Cardiol 2013

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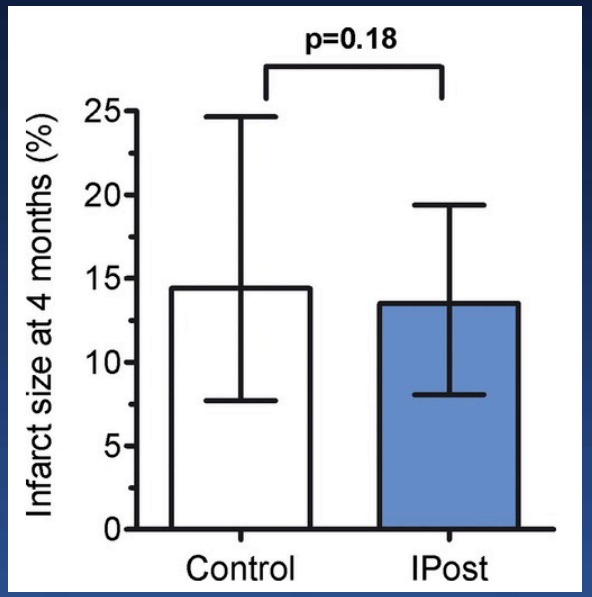
Post-conditioning effects

Post-conditioning and left ventricular function

- In the POSTEMI trial, 272 patients were randomized to post-conditioning group (*n* = 136) and control group (*n* = 136)
- Primary endpoint was infarct size measured by cardiac MRI.
- After 4 months, no difference was observed between control group and post-conditioning group.



Limalanathan S ,et.al. J AM Heart Assoc. 2014

Post-conditioning effects

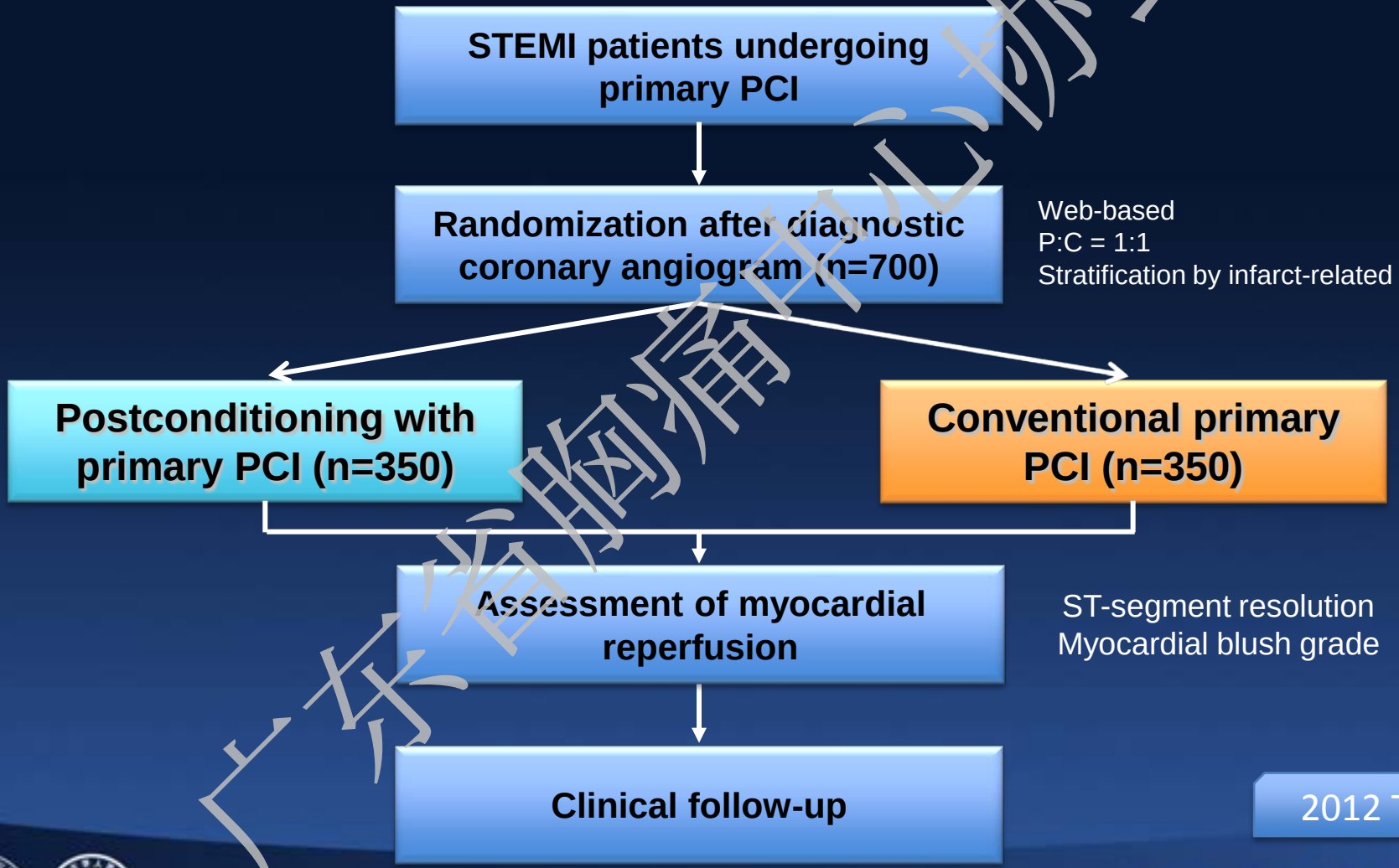
Post-conditioning and clinical outcome

- In a meta-analysis of 15 randomized trials including 1545 patients with a mean follow-up of 4.7 months, Khalili et al. did not note any impact of mechanical post-conditioning on mortality (OR = 1.52; 95% CI 0.77–2.99; p = 0.23), recurrent myocardial infarction (OR = 3.04; 95% CI 0.74–12.54; p = 0.12), stent thrombosis (OR = 1.24, 95% CI 0.51–3.04; p = 0.83), or the composite MACE outcome (OR = 1.53; 95% CI 0.89–2.63; p = 0.13).

Khalili, H *Catheter Cardiovasc Interv*. 2014

Effect of Postconditioning on Myocardial Reperfusion during Primary Percutaneous Coronary Intervention： POST Trial Design

A Korean multicenter, prospective, randomized, open-label, blinded endpoint trial



2012 TCT

ClinicalTrials.gov identifier: NCT00942500

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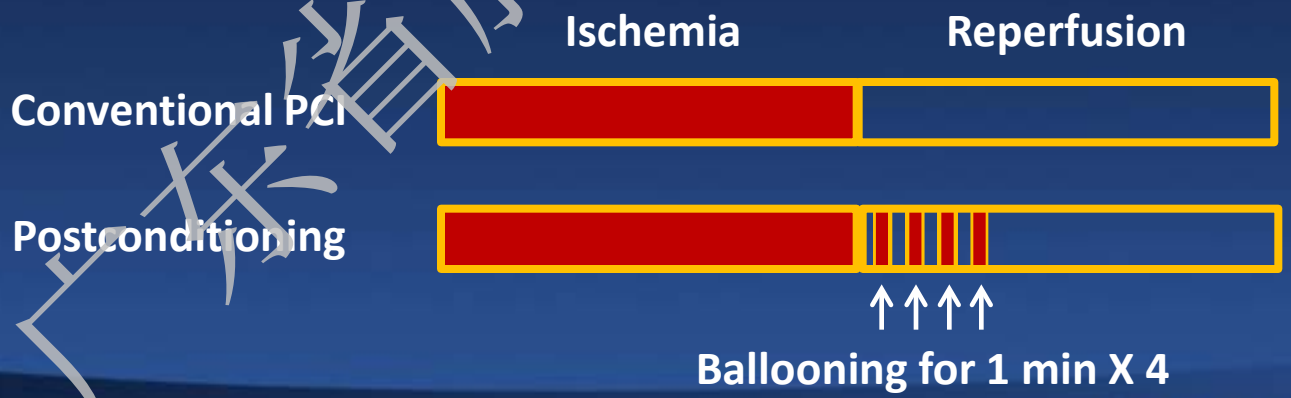
Study Protocol

- Postconditioning
  - Four episodes of 1-minute balloon occlusion and 1-minute deflation*
  - Immediately (within 1 minute) after restoration (TIMI grade ≥2) of coronary flow (without regard to method of achieving reflow)
- Aspirin 300 mg and clopidogrel 600 mg
- Thrombus aspiration, predilation before stenting, or use of glycoprotein IIb/IIIa inhibitors were left to the operators' discretion.



*Staat P et al. Circulation 2005;112:2143-2148

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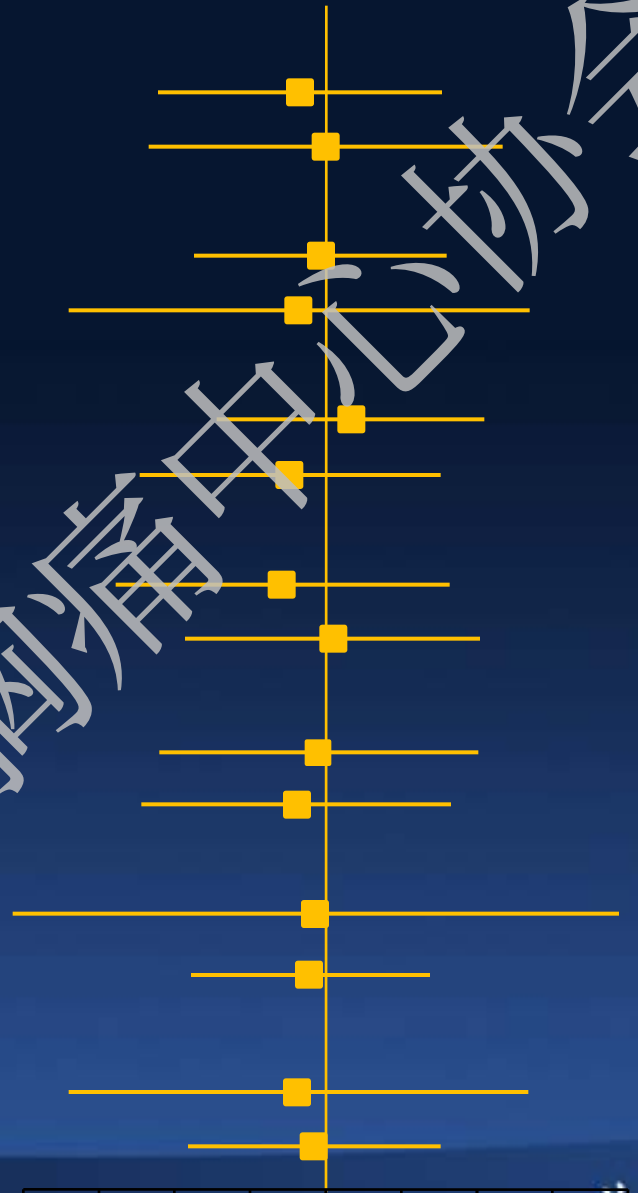
Endpoints

- Primary End point
  - Complete ST-segment resolution (STR >70%) at 30 minutes after the procedure
- Secondary End Points
  - TIMI flow grade after PCI
  - Myocardial blush grade
  - Major adverse cardiac events (MACE: a composite of death, reinfarction, severe heart failure*, or stent thrombosis†) at 30 days
  - Each component of MACE at 30 days
  - Target vessel revascularization at 30 days

* Heart failure with documented arterial partial pressure of oxygen less than 60 mmHg or with pulmonary edema documented radiographically or requiring intubation, 100% oxygen, or insertion of a mechanical support device.

†Definite or probable stent thrombosis by the ARC definition

	Postconditioning	Conventional PCI	Difference (95% Confidence Interval)	P value
	n / total n (%)			
Age				
<65	87/211 (41.2%)	88/205 (42.9%)	-1.7 (-11.1 to 7.7)	0.73
≥65	51/130 (39.2%)	51/130 (39.2%)	0.0 (-11.7 to 11.7)	0.99
Sex				
Male	105/269 (39.0%)	98/249 (39.4%)	-0.3 (-8.7 to 8.0)	0.94
Female	33/72 (45.8%)	41/86 (47.7%)	-1.8 (-17.0 to 13.5)	0.82
Infarct-related artery				
LAD	32/158 (20.3%)	28/151 (18.5%)	1.7 (-7.2 to 10.5)	0.70
Non-LAD	106/183 (57.9%)	111/184 (60.3%)	-2.4 (-12.3 to 7.6)	0.64
Symptom onset-to-reperfusion time				
<3 hours	71/154 (46.1%)	75/153 (49.0%)	-2.9 (-13.9 to 8.2)	0.61
≥3 hours	67/187 (35.8%)	64/181 (35.4%)	0.5 (-9.3 to 10.2)	0.93
Thrombus aspiration				
Yes	60/154 (39.0%)	67/170 (39.4%)	-0.5 (-11.0 to 10.1)	0.93
No	78/187 (41.7%)	72/165 (43.6%)	-1.9 (-12.2 to 8.3)	0.72
Direct stenting				
Yes	17/41 (41.5%)	19/45 (42.2%)	-0.7 (-20.7 to 19.4)	0.97
No	121/300 (40.3%)	120/290 (41.4%)	-1.1 (-8.9 to 6.9)	0.80
Glycoprotein IIb/IIIa inhibitors				
Yes	35/79 (44.3%)	36/78 (46.2%)	-1.9 (-17.0 to 13.4)	0.82
No	103/262 (39.3%)	103/257 (40.1%)	-0.8 (-9.1 to 7.6)	0.86



Angiographic Outcomes

	Postconditioning (n=350)	Conventional PCI (n=350)	P Value
TIMI flow after PCI			0.08
0/1	8/349 (2.3%)	19/348 (5.5%)	
2	20/349 (5.7%)	23/348 (6.6%)	
3	321/349 (92.0%)	306/348 (87.9%)	
Myocardial blush grade after PCI			0.20
0/1	60/349 (17.2%)	78/348 (22.4%)	
2	108/349 (30.9%)	106/348 (30.5%)	
3	181/349 (51.9)	164348 (47.1)	

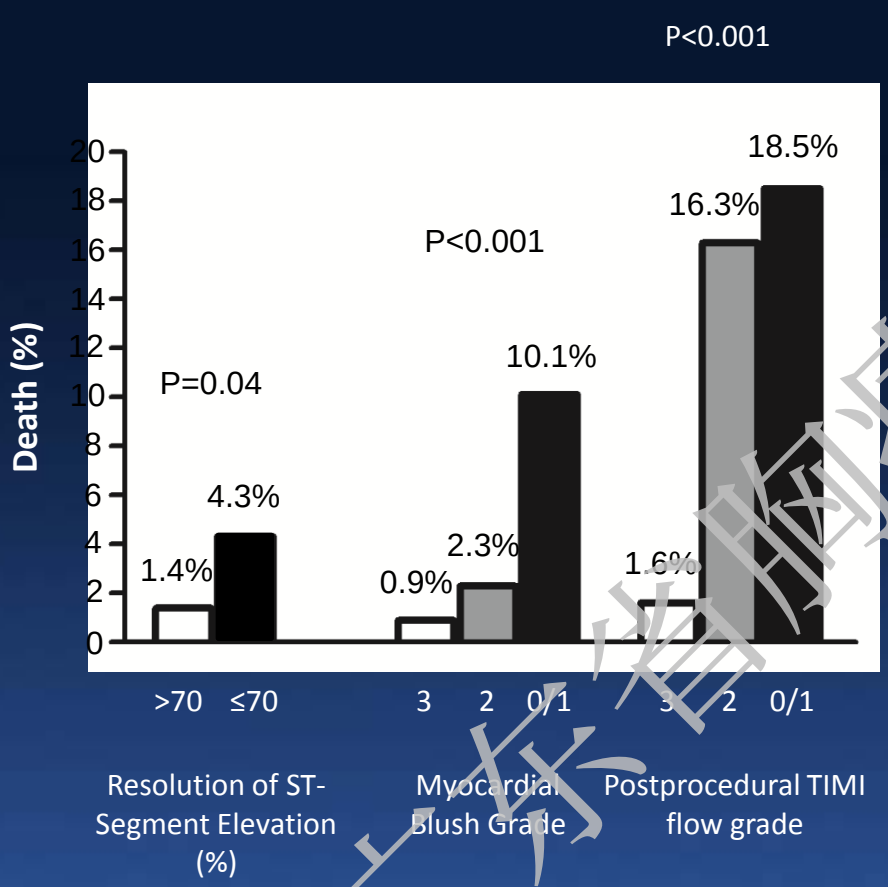
TIMI = thrombolysis in myocardial infarction.

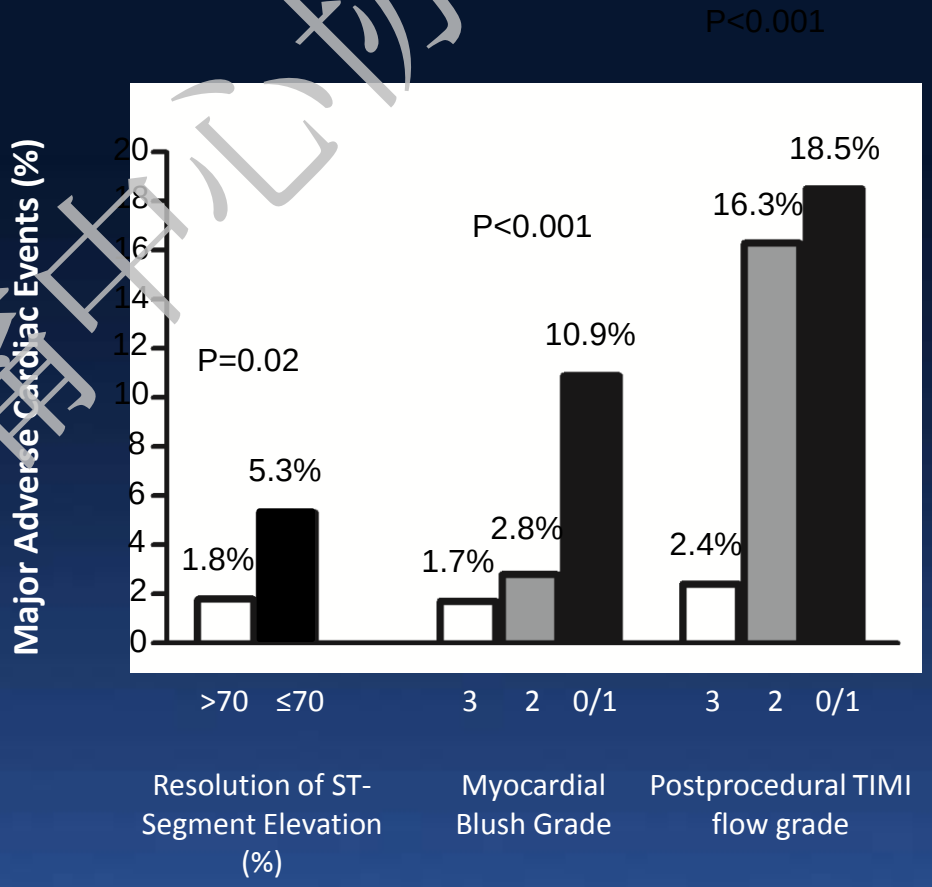
Clinical Outcomes at 1-month

	Postconditioning (n=350)	Conventional PCI (n=350)	Relative risk (95% CI)*	P Value
Death	13 (3.7%)	10 (2.9%)	1.30 (0.58-2.92)	0.53
Cardiac death	10 (2.9%)	9 (2.6%)	1.11 (0.46-2.70)	0.82
Reinfarction	2 (0.6%)	1 (0.3%)	2.00 (0.18-21.74)	0.99†
Severe heart failure	2 (0.6%)	5 (1.4%)	0.40 (0.08-2.05)	0.29†
Stent thrombosis	7 (2.0%)	6 (1.7%)	1.17 (0.40-3.44)	0.78
Target-vessel revascularization	3 (0.9%)	3 (0.9%)	1.00 (0.20-4.92)	0.99†
MACE‡	15 (4.3%)	13 (3.7%)	1.15 (0.56-2.39)	0.70

* Relative risk is for the postconditioning group as compared with the conventional PCI group.
† The P value was calculated with the use of Fisher's exact test.
‡ Major adverse cardiac event was a composite of death, reinfarction, severe heart failure, or stent thrombosis.

Outcomes according to STR, postprocedural MBG and TIMI flow grade





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Long-term Effects of Ischemic Postconditioning on Clinical Outcomes

POST trial: 700 STEMI patients randomized to standard primary PCI or PCI plus ischemic postconditioning, July 2009-June 2012.

1-Year Outcomes	Postconditioning (n = 350)	Control (n = 350)	HR (95% CI)
Major Adverse Events	6.1%	4.6%	1.32 (0.69-2.53)
Death	4.9%	3.7%	1.32 (0.64-2.71)
Severe Heart Failure	2.6%	2.3%	1.13 (0.44-2.94)

In addition to failing to improve myocardial reperfusion after primary PCI, ischemic postconditioning does not reduce major adverse events through 1 year.

Hahn J-Y, et al. *Am Heart J*. 2015;

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POST Trial: Conclusions

In this multicenter, prospective, randomized, open-label, blinded endpoint trial,

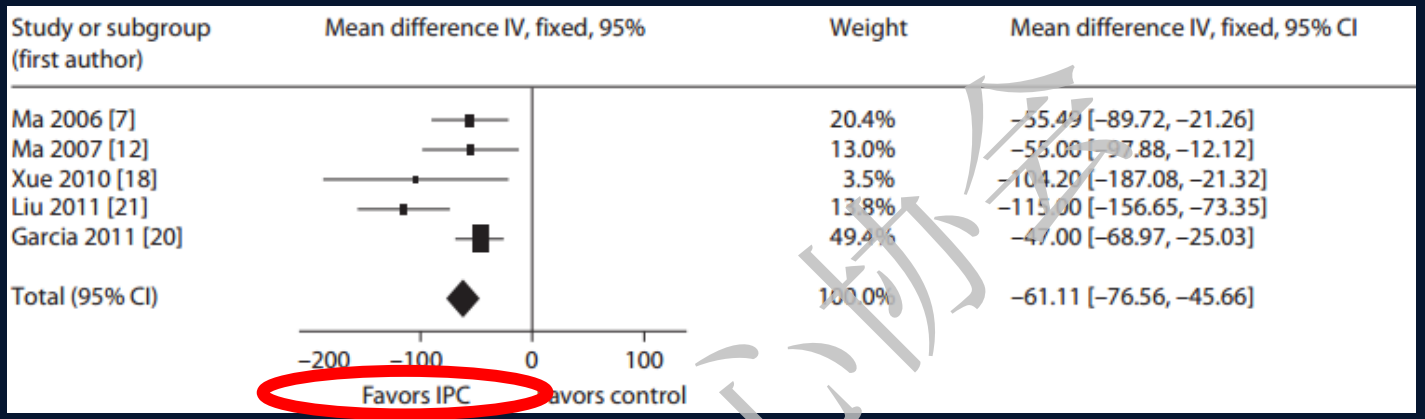
- Ischemic postconditioning with primary PCI did not improve myocardial reperfusion compared with conventional primary PCI.
- Clinical outcomes at 1-month and 1-year were not significantly different between the randomized groups.
- Cardioprotective effect of ischemic postconditioning was not found in any of prespecified subgroups.

Meta-analysis: Inconsistent Results

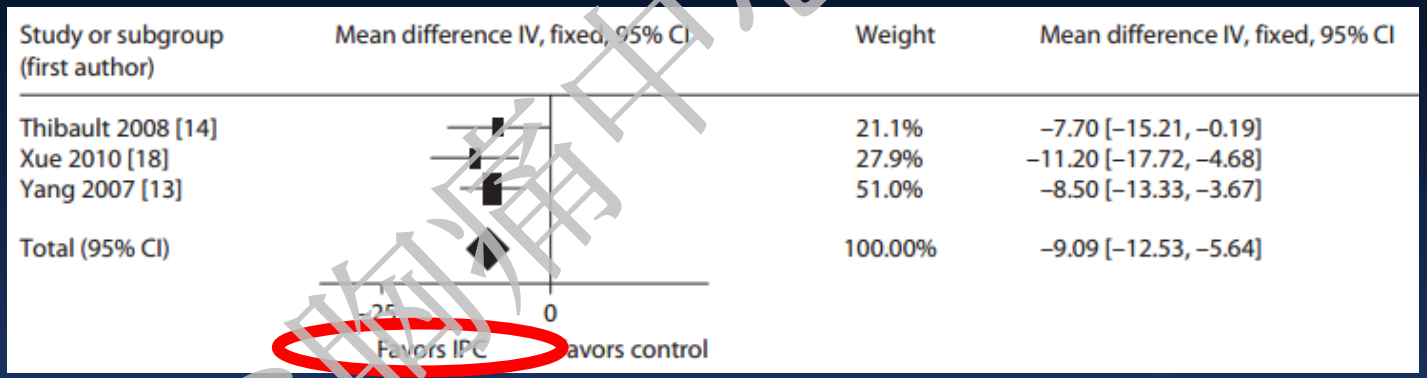
More high-quality multicenter RCTs focusing on MACE are warranted.

- **A meta-analysis of 5 eligible studies on peak CK-MB.**

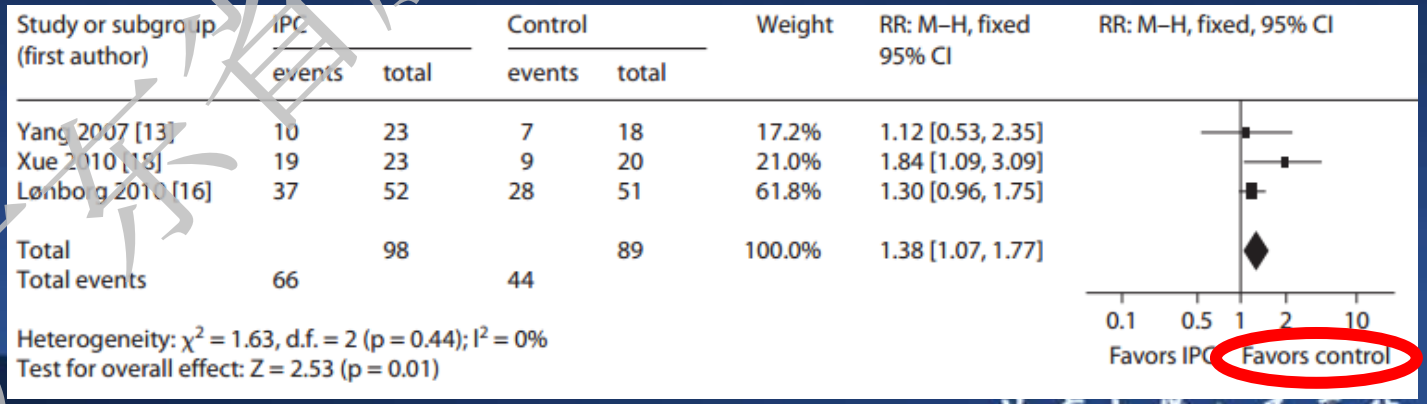
Test for overall effect: Z = 7.75 (p < 0.00001)



- **A meta-analysis of 3 eligible studies on SPECT determining infarct size.**



- **A meta-analysis of 3 eligible studies on complete ST-segment resolution.**



Cardiology 2012;123:225–233 DOI: 10.1159/000342660

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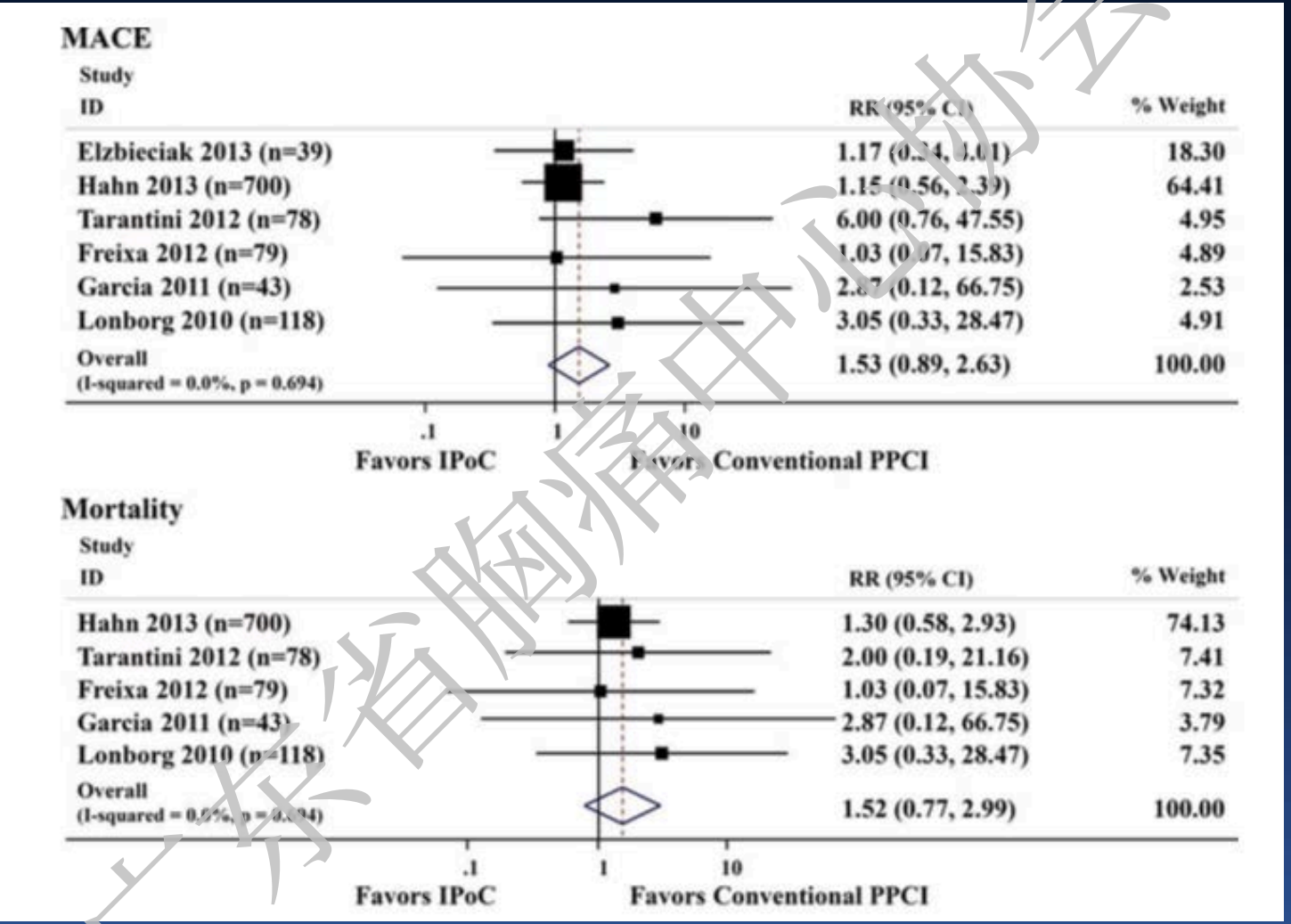
Forest plot for clinical outcomes for IPoC vs. conventional PPCI



Khalili, H *Catheter Cardiovasc Interv*. 2014

The cardioprotection of ischemic postconditioning in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

- IPoC might improve cardiac function and reduce the incidence of heart failure and serious arrhythmia in patients with STEMI undergoing PPCI.

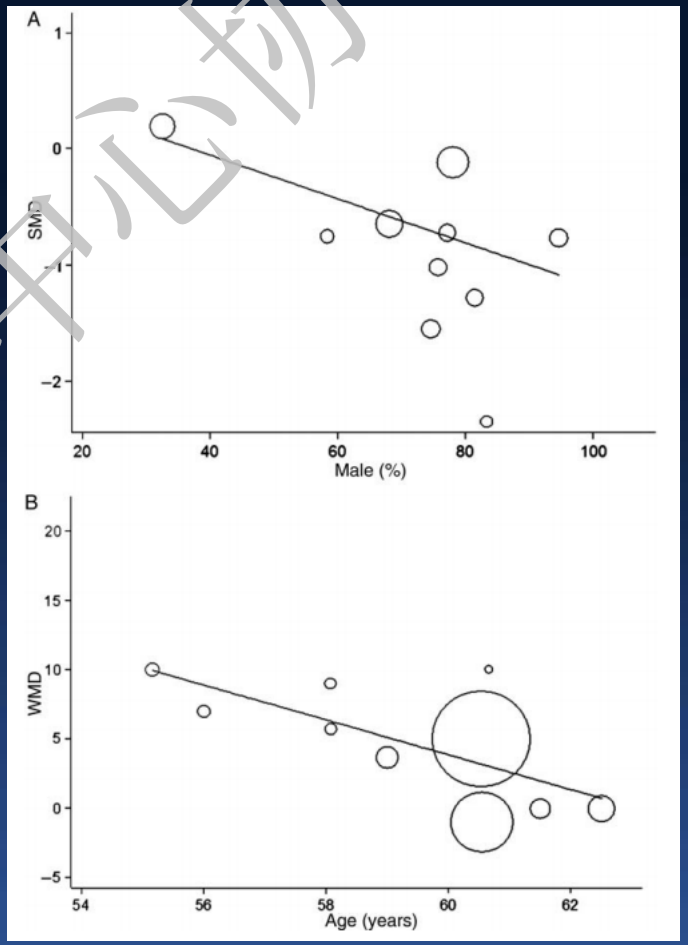
The effect of IPoC on clinical outcomes in patients with STEMI undergoing PPCI.

Outcomes after PPCI	sample size (IPoC/control)	Heterogeneity	WMD or OR	95% CI	P value
Heart failure	753/752	0	0.47	0.29 to 0.78	0.003
Serious arrhythmia	112/113	0	0.34	0.13 to 0.90	0.03
LVEF(> = 3 months)	307/316	70%	0.03	0.01 to 0.05	0.004
WMSI	206/219	14%	−0.12	−0.16 to −0.08	<0.00001
Death	818/815	0	1.36	0.79 to 2.36	0.27
Stent thrombosis	444/446	0	1.01	0.40 to 2.56	0.99
Reinfarction	405/406	0	3.11	0.62 to 15.63	0.17
ACS	486/486	58%	0.53	0.06 to 4.72	0.57
MACE	605/612	26%	0.96	0.64 to 1.44	0.85
LVEF in acute phase	670/713	77%	0.02	−0.01 to 0.04	0.19
CTFC	164/216	58%	−3.96	−6.85 to −1.06	0.007
CK peak	293/341	93%	−255.66	−745.22 to 231.89	0.30
CK-MB peak	566/619	95%	−21.29	−65.55 to 22.98	0.35
TnI peak	96/100	99%	56.81	−48.24 to 161.85	0.29
Infarct size	172/171	84%	−0.70	−6.23 to 4.83	0.80
Area at risk	01/100	0	0.38	−2.54 to 3.30	0.80
Complete ST segment resolution	654/7[illegible]	76%	1.58	0.78 to 3.17	0.20
MBG	725/725	25%	1.18	0.92 to 1.52	0.20
MSI	107/113	81%	−3.83	−20.12 to 12.48	0.65

LVEF, left ventricular ejection fraction; WMSI, wall motion score index; MACE, major adverse cardiovascular events; CTFC, corrected TIMI frame count; CK, creatine kinase; CK-MB, creatine kinase-MB; TnI, Troponin I; MBG, myocardial blush grades; MSI, myocardial savage index. WMD, weighted mean difference; OR, odd ratio.

Stenting technique, gender, and age are associated with cardioprotection by ischaemic postconditioning in primary coronary intervention: a systematic review of 10 randomized trials

- Available evidence from the present systematic review and meta-analysis suggests that IPoC may confer cardioprotection for STEMI during primary PCI.
- Cardioprotective effects of IPoC are more pronounced among young and male patients, and those in whom direct-stenting techniques were used.



European Heart Journal (2012) 33, 3070–3077
Am Heart J. 2014 Oct;168(4):512-521.e4.

Strategy

Mechanical post-conditioning

- In the majority of studies, post-conditioning was performed by four 30–60-s cycles of low pressure balloon inflations (4–6 atm) at the site of previous occlusion, each separated by 30–60 s of reflow.

Protocols employed in different trials on post-conditioning in PCI

Study	Year	Protocol of POC	N POC/controls
Staat et al. [6]	2005	60 s × 4	14/16
Ma et al. [34]	2006	30 s × 3	47/47
Yang et al. [26]	2007	30 s × 3	23/18
Thibault et al. [25]	2008	60 s × 4	17/21
Sorensson et al. [27]	2010	60 s × 4	38/38
Freixa et al. [28]	2012	60 s × 4	39/40
Tarantini et al. [29]	2012	60 s × 4	39/39
Zhao et al. [38]	2012	60 s × 4	32/30
Hahn et al. [20]	2013	60 s × 4	350/350
Dwyer et al. [41]	2013	30 s × 4	50/52
Limalanathan et al. [23]	2014	60 s × 4	136/136

Strategy

Pharmacological post-conditioning alternative

- Adenosine

Nicolli et al. showed that the use of adenosine results not only in significant improvement of microvascular obstruction assessed by ST-segment resolution but also in MACE occurrence at 30 days.

- Natriuretic peptide

Kitakaze et al. showed patients with AMI who were given atrial natriuretic peptide had lower infarct size of 14.7% (95% CI 3.0–24.9%), and better LVEF at 6–12 months (ratio 1.05, 95% CI 1.01–1.10, p = 0.024).

Strategy

Remote ischemic conditioning alternative

- Remote ischemic conditioning（RIC）is transient non-injurious ischemia of one organ or tissue can protect a distant organ or tissue from ischemic injury.
- Several clinical studies have found that RIC using transient arm or leg ischaemia/reperfusion reduced MI size by 20–30% (assessed by cardiac enzymes, SPECT or cardiac MRI) in STEMI patients reperfused by either PPCI or thrombolysis.

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- RIC using transient limb ischaemia/reperfusion holds promise as an adjunct to PPCI in STEMI patients for reducing MI size. Whether it can improve long-term clinical outcomes is not known.

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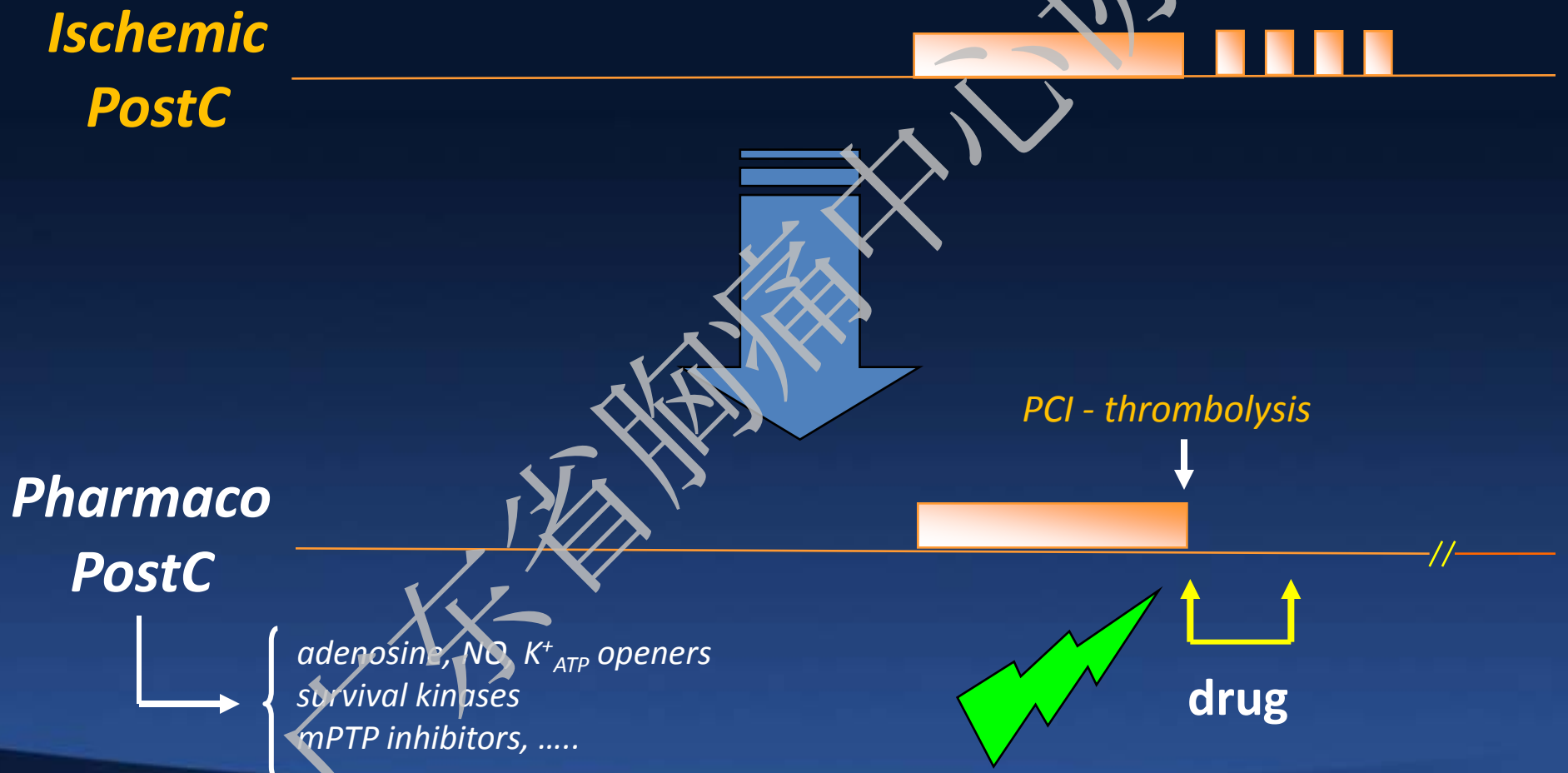
Toward New Clinical Strategies



Conclusion

- Trials confined to 2003~2015, no large RCTs these two years.
- According to what we have:
  - Ischemic postconditioning during PCI in ST-segment elevation myocardial infarction appears to be superior to PCI alone in reduction of both myocardial injury or damage and improvement in left ventricular function.
  - The effect seems to be more pronounced when a greater myocardial area is at risk, among young and male patients, and those in whom direct-stenting techniques.
  - No detailed operation methods to achieve Ischemic Postonditioning.

Thank you for your attention!