急诊PCI如何预防再灌注损伤？

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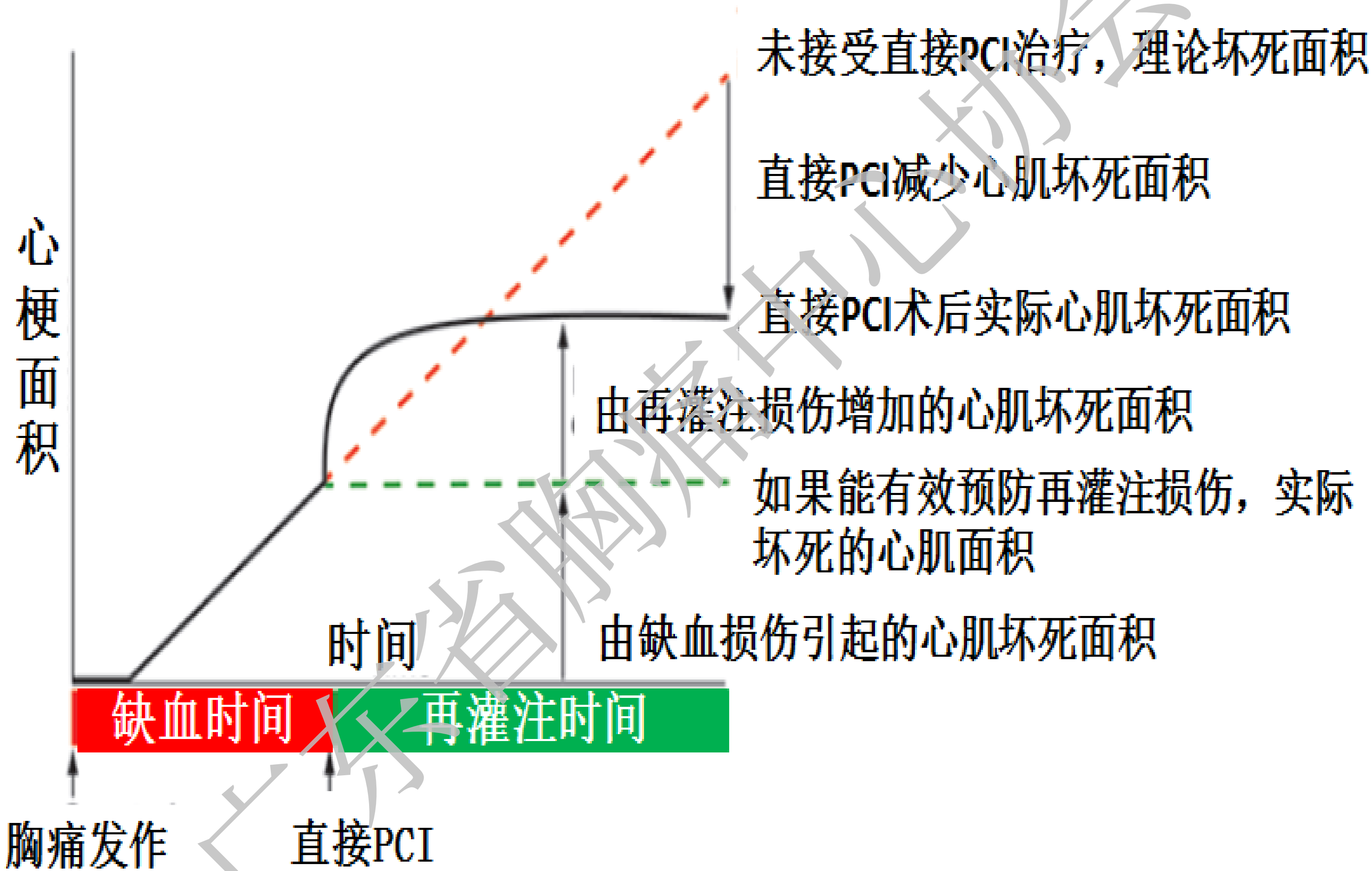
缺血再灌注损伤



急性心肌缺血损伤和PPCI再灌注损伤对STEMI发病后24h内最终心肌梗死面积的影响

缺血再灌注损伤发病机制

- 钙超载
- 活性氧/氧自由基的作用
- 微血管损伤/栓塞与白细胞的作用
- 线粒体损伤与高能磷酸化合物生成障碍

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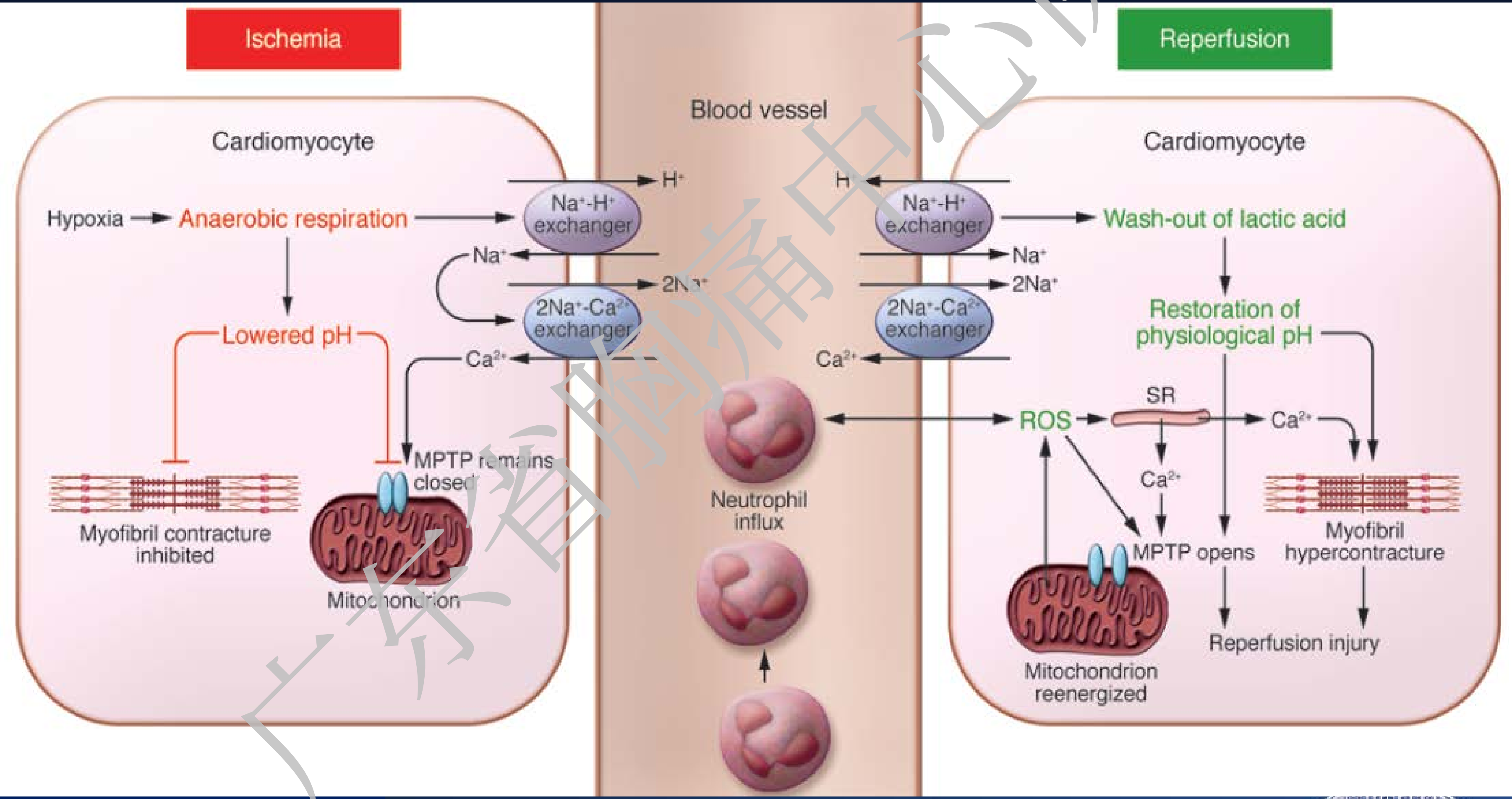
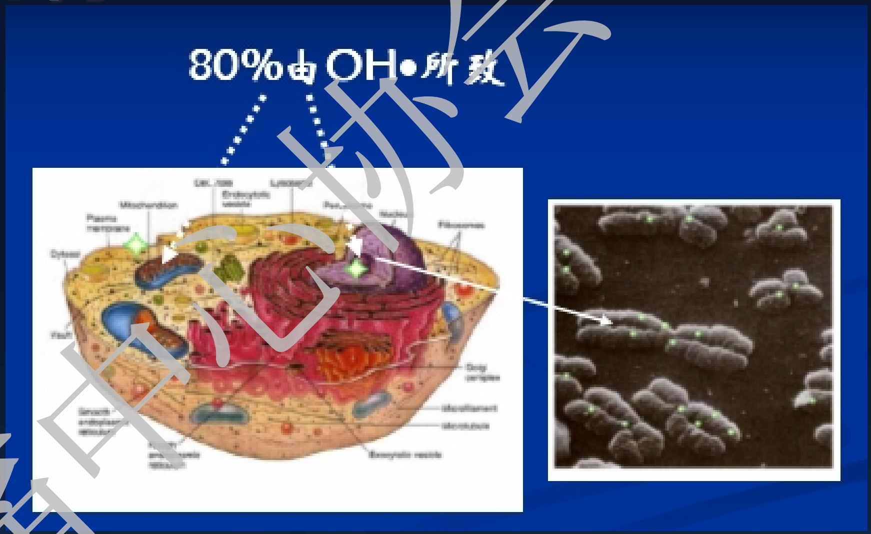
缺血再灌注损伤发病机制

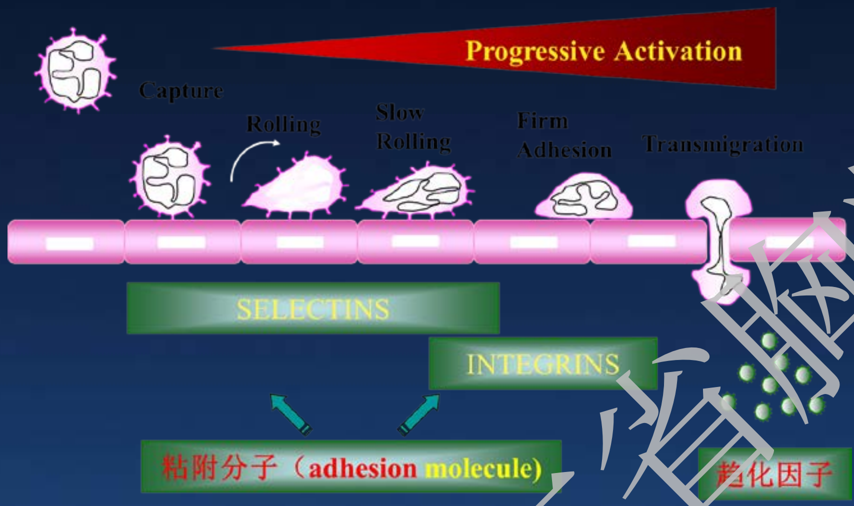
心肌细胞内生化和代谢的骤然变化：钙超载



缺血再灌注损伤发病机制

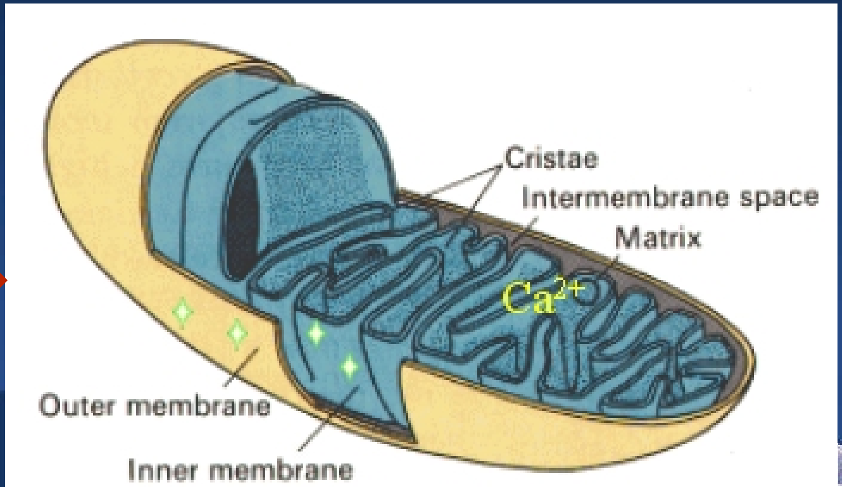
活性氧/氧自由基的损伤作用





微血管损伤/白细胞的作用

高能磷酸化合物生成障碍



缺血再灌注损伤的分类

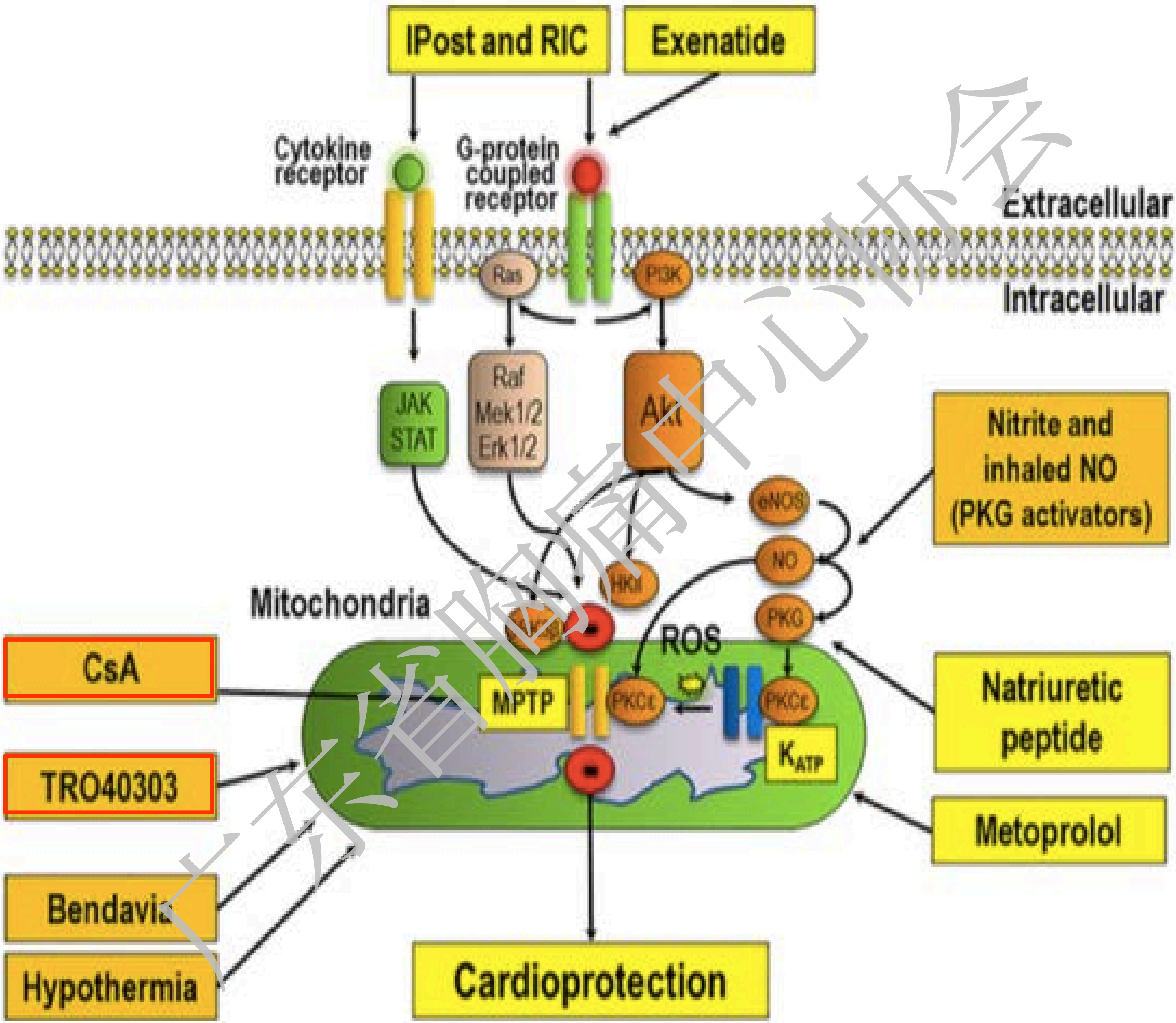
心肌再灌注损伤有四种类型，其中前两种具有可逆性，后两者为不可逆损伤。

1.再灌注心律失常（Reperfusion arrhythmia，RA）

2.心肌顿抑（Myocardial stunning）

3.微血管阻塞（microvascular obstruction，MVO)

4. 致死性心肌再灌注损伤（lethal myocardial reperfusion injury）


IPost and RIC
Exenatide
Cytokine receptor
G-protein coupled receptor
Extracellular
Intracellular
Ras
PI3K
JAK
STAT
Raf
Mek1/2
Erk1/2
Akt
eNOS
NO
PKG
Nitrite and inhaled NO (PKG activators)
HKII
Mitochondria
ROS
MPTP
PKCε
PKCε
K_{ATP}
CsA
TRO40303
Bendavia
Hypothermia
Natriuretic peptide
Metoprolol
Cardioprotection

Approach for Prevention of ischemia-reperfusion injury

Pharmacological

- GLP-1
- Cycloporine
- Bendavia
- Metoprolol

Nonpharmacological

- Ischemic post conditioning
- Remote ischemic preconditioning
- Aspiration and Thrombectomy

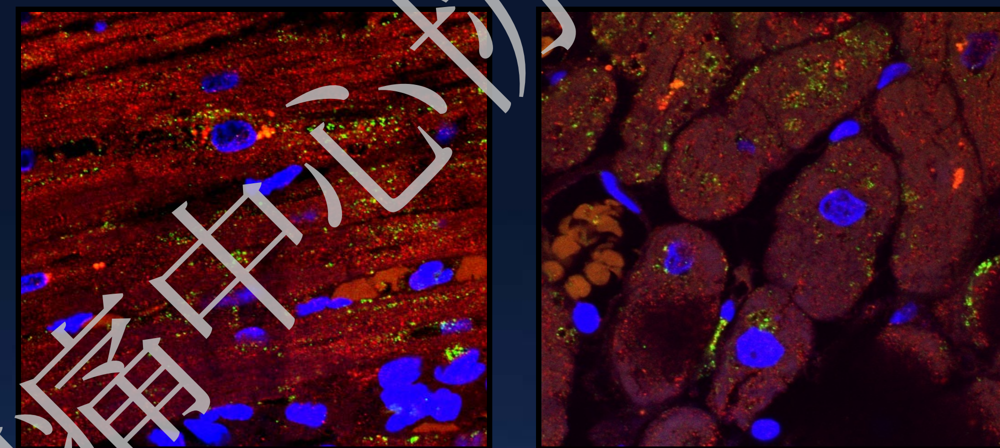
Therapeutic hypothermia /hyperoxemia

Pharmacological intervention – GLP-1

Pig model exenatide

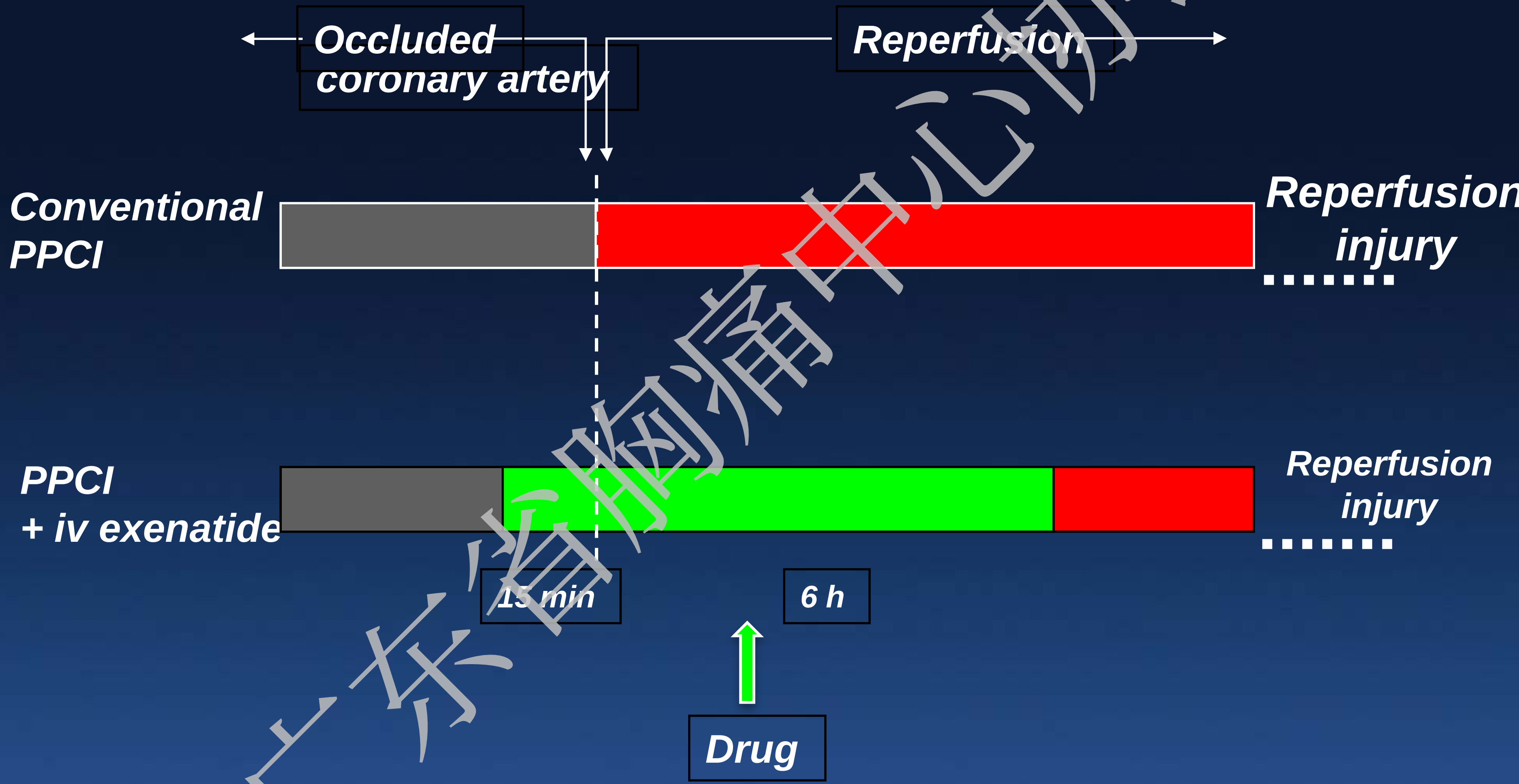
*p<0.05 vs. placebo

GLP-1 receptor expression in the human heart



Timmers et al. J Am Coll Cardiol 2009;53:501–10

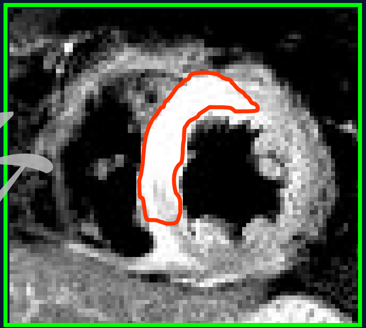
Pharmacological intervention
POSTCON II (exenatide)



Lønborg et al. Eur Heart Journal, 2011

Pharmacological intervention

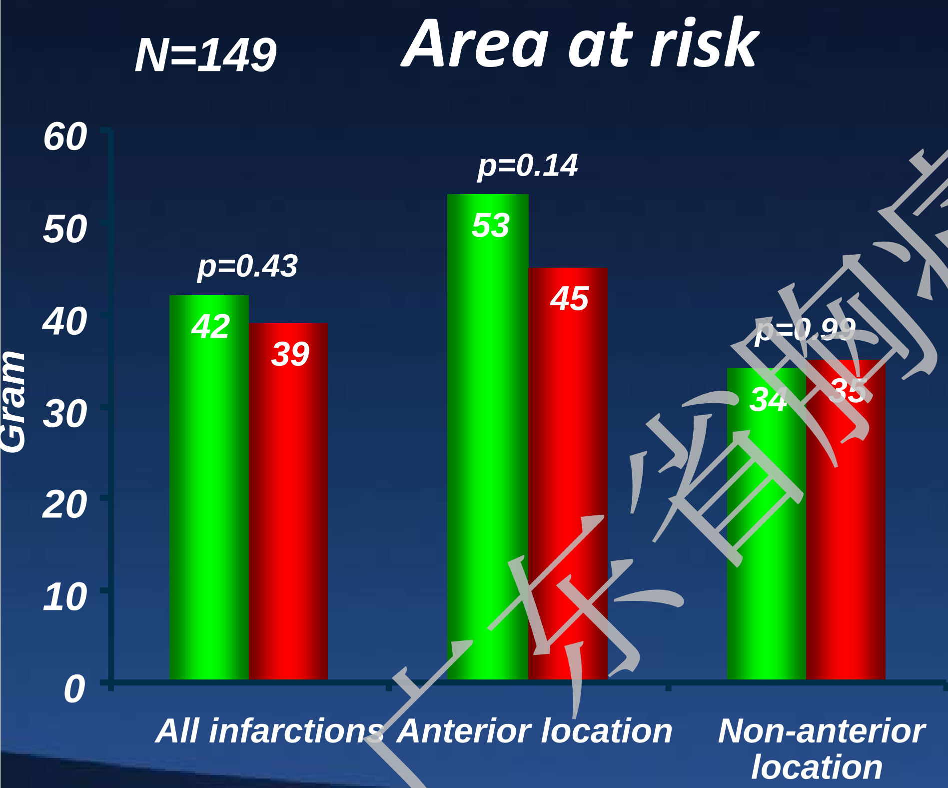
POSTCON II (exenatide)

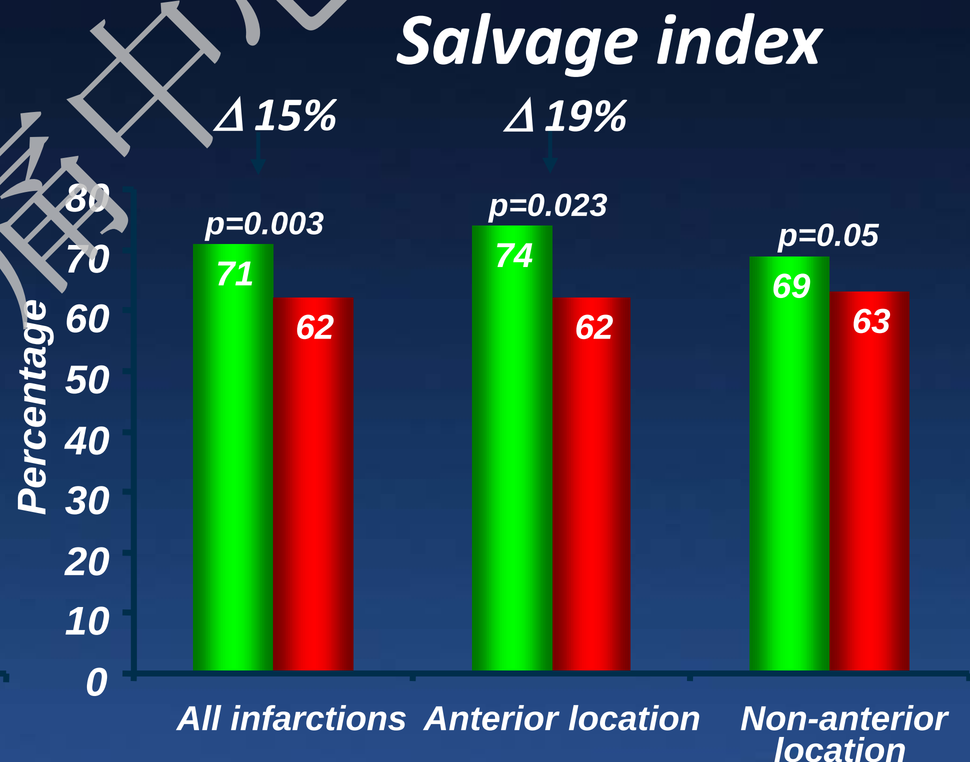


Exenatide

Placebo

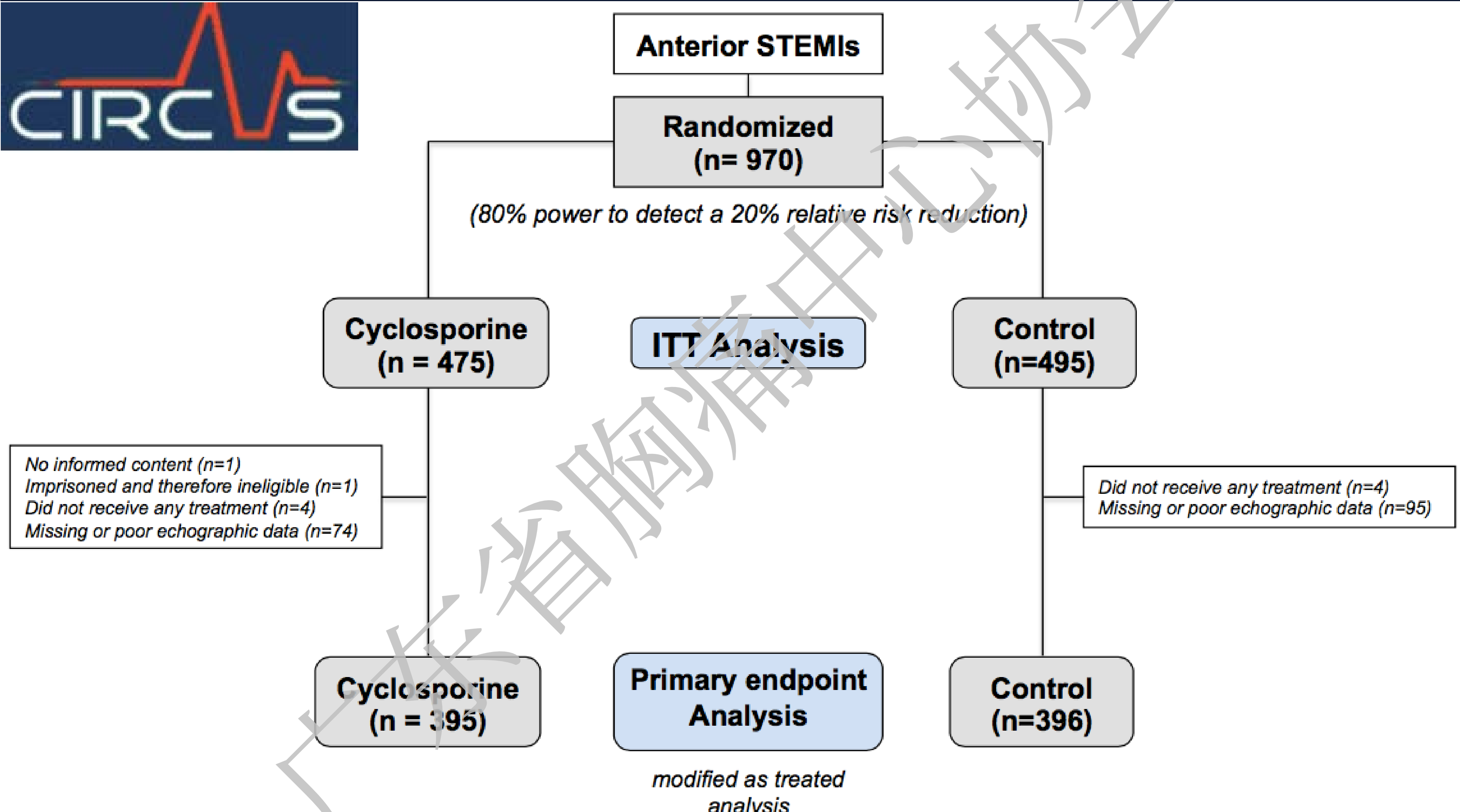
N=149





Lønborg et al. Eur Heart Journal, 2011

Pharmacological intervention – CyA



Primary endpoint

Combined incidence of **[all-cause mortality; worsening of heart failure during initial hospitalization or re-hospitalisation for heart failure ; LV remodeling]** within 1 year after acute MI

(LV remodeling (echo): increase > 15% of LVEDV at 1 year versus initial discharge)

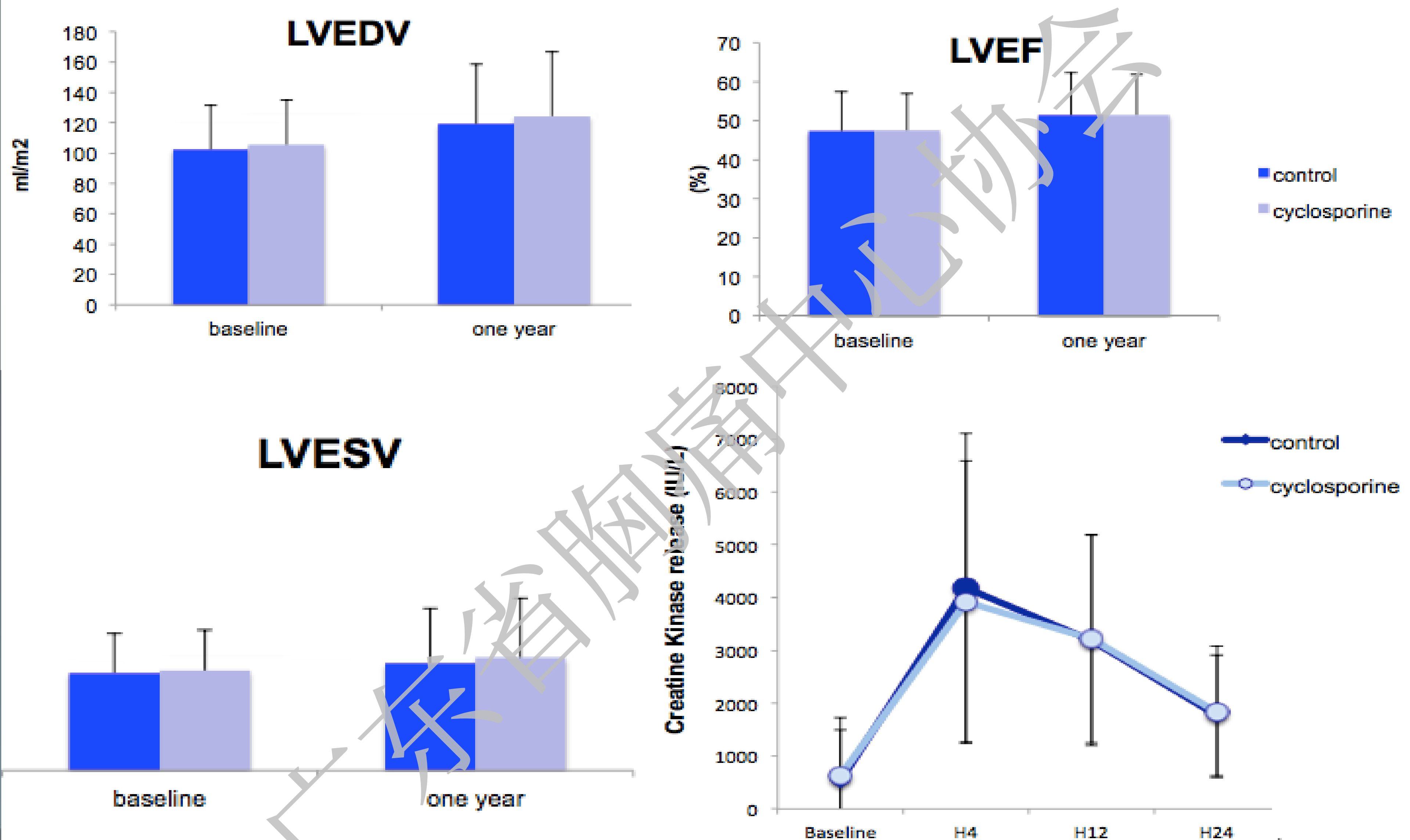
	Cyclosporine (n=395)	Control (n=396)	Odds Ratio (95% CI)	P value
(Death / HF / LV remodeling)	233 (**59.0 %**)	230 (**58.1%**)	1.04 [0.78; 1.39]	0.77

CIRCUS

Secondary endpoint

	Cyclosporine (n=395)	Control (n=396)	Odds Ratio (95% CI)	P value
Death: all-cause	7.1 %	6.6 %	1.09 [0.63 ; 1.90]	0.76
Death: cardiovascular	6.1 %	6.1 %	1.01 [0.56 ; 1.81]	0.98
HF worsening or re-hospitalization for HF	22.8 %	22.7 %	1.01 [0.72 ; 1.41]	0.97
HF worsening	15.7 %	16.9 %	0.92 [0.63 ; 1.34]	0.65
Re-hospitalization for HF	10.6 %	10.4 %	1.03 [0.65 ; 1.63]	0.89
Cardiogenic shock	6.6 %	6.1 %	1.09 [0.61 ; 1.94]	0.77
Recurrent Myocardial infarction	2.3 %	3.8 %	0.59 [0.26 ; 1.37]	0.22
Stroke	1.8 %	3.0 %	0.58 [0.22 ; 1.48]	0.25
Major bleeding	1.8 %	2.3 %	0.73 [0.27 ; 2.00]	0.54

HF: heart failure



JACC 2012；356:132

Pharmacological intervention
EMBRACE(Bendavia)

Patients with First Anterior STEMI

TIMI 0/1 flow in prox or mid LAD, anticipated Sx to PCI <4 hrs, shock

R 1:1 — *Blinded*

Volume-matched IV Placebo (N=147)	Bendavia IV at 0.05 mg/kg/hr (N=150)

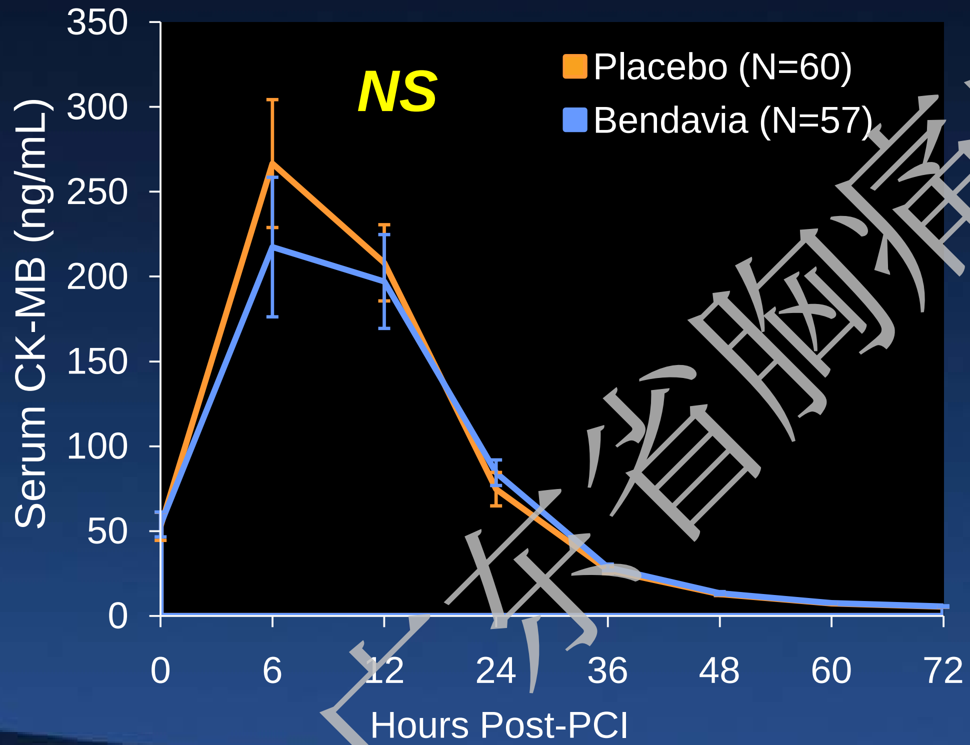
Administered > 15 min pre PCI & 60 min post

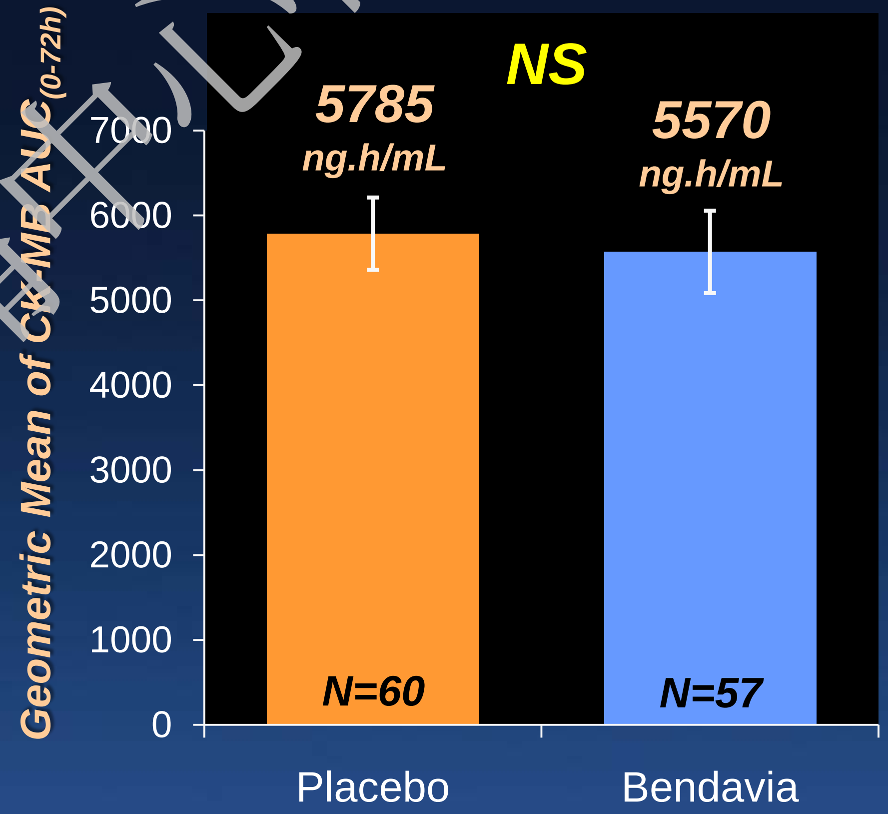
Primary Endpoint: *AUC for CK-MB over initial 72h post PCI*

Clinical Endpoint: *Composite of all cause death, new onset CHF >24h post-PCI within index hospitalization, and CHF rehospitalization*

Results: Primary Endpoint AUC CK-MB

CK-MB at 6 hours
Placebo: 266.6 ± 37.7 ng/mL
Bendavia: 217.4 ± 41.1 ng/mL





Results: Clinical Composite Endpoint

	Placebo (N=60)	Bendavia (N=58)	p-value
30 ± 7 days			
Death, new-onset CHF >24h post PCI, CHF rehospitalization, % (n)	5.0% (3)	8.6% (5)	NS
Death, new-onset CHF, CHF rehospitalization, % (n)	28.3% (17)	22.4% (13)	NS
6 ± 1.5 months			
Death, new-onset CHF >24h post PCI, CHF rehospitalization, % (n)	8.3% (5)	12.1% (7)	NS
Death, new-onset CHF, CHF rehospitalization, % (n)	28.3% (17)	25.9% (15)	NS

Pharmacological intervention

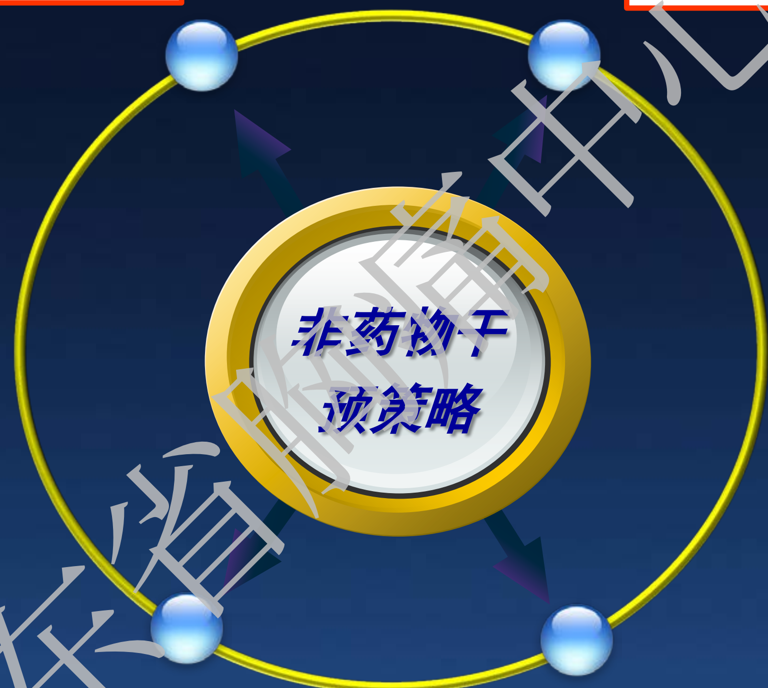
METOCARD-CNIC（iv metoprolol）

	Metoprolol (n = 106)	Control (n = 114)	Adjusted Treatment Effect	*P* Value
Infarct Size, g				
Overall	25.6±15.3	32.0±22.2	-6.52	0.012
TIMI 0/1 Subgroup	26.7±15.0	34.4±20.0	-8.13	0.002
LVEF	46.1±9.3%	43.4±10.4%	2.67	0.045

缺血再灌注损伤的非药物干预策略

缺血预处理

缺血后处理



远隔缺血处理

亚低温治疗

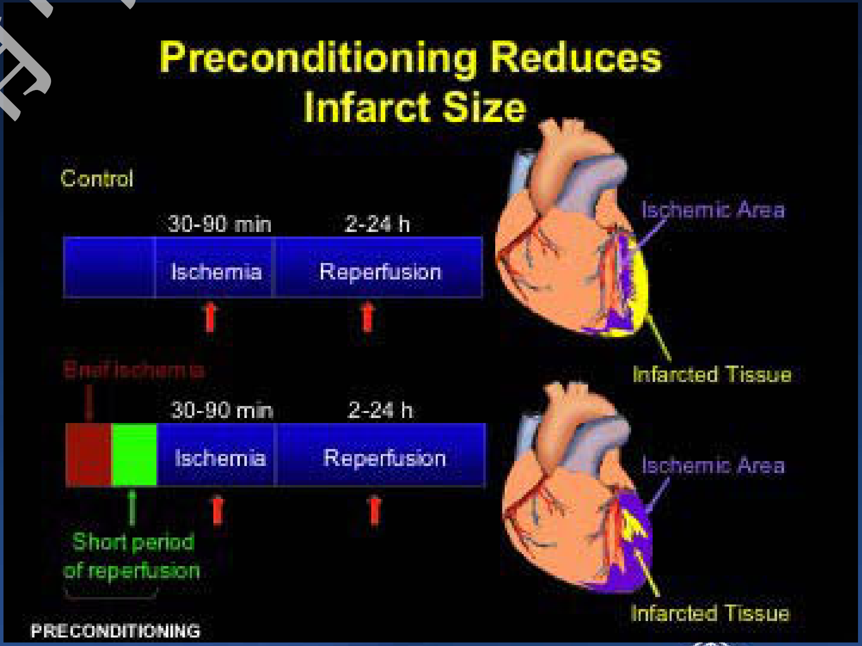
缺血再灌注损伤的干预策略

- *缺血预处理（ischemic preconditioning，IPC）*

  即冠状动脉多次短暂的缺血可以增强心肌对随后长时间缺血的耐受性,减轻缺血再灌注损伤.

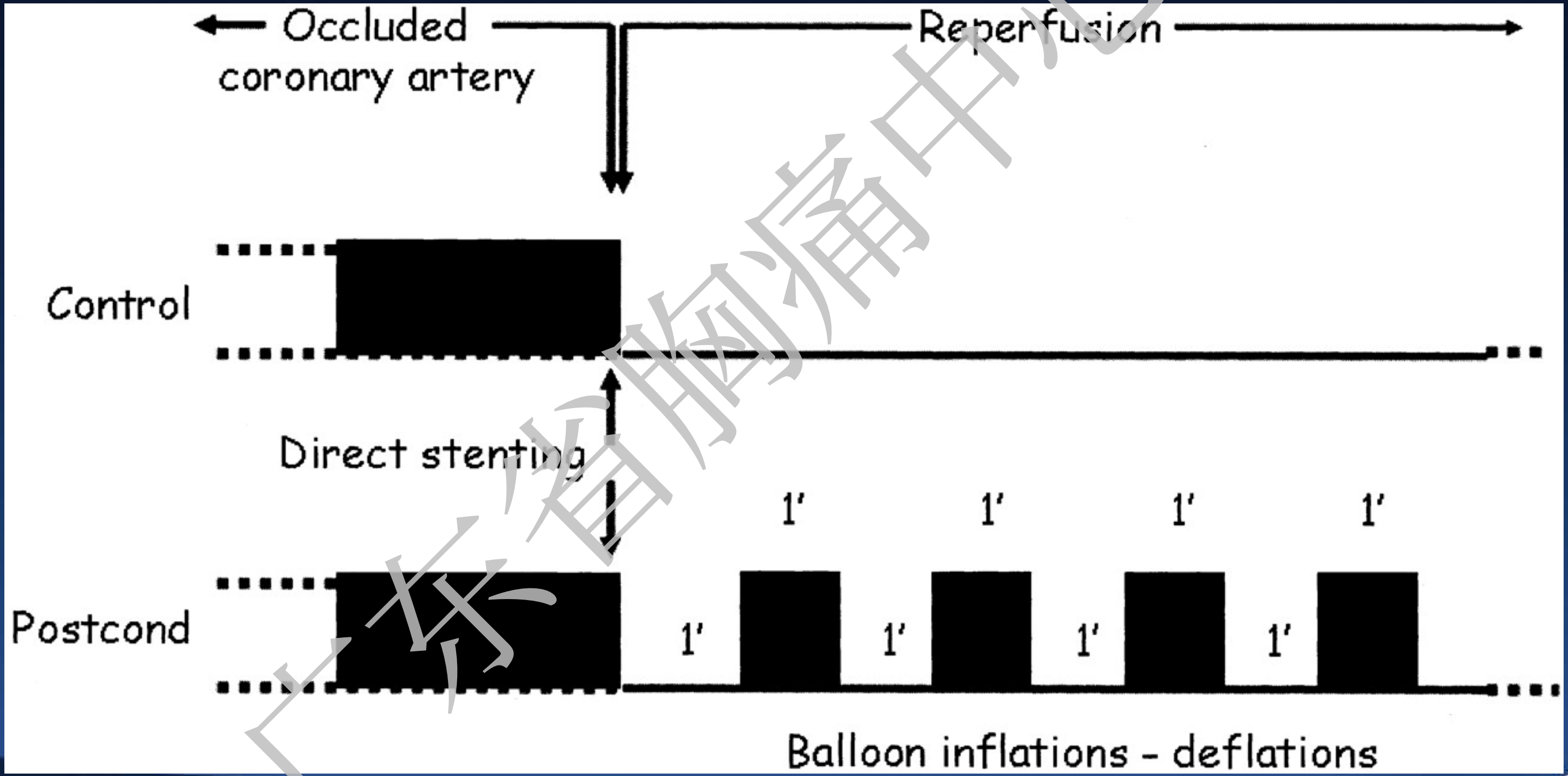
存在两个“时间窗”形式：

第一时间窗（即传统IPC，也称早期相），在预处理刺激后立即出现，并持续1～3h；第二时间窗（又称IPC迟后效应），出现在预处理刺激后的12～24h



缺血后适应（Ischemic post-conditioning）

Postconditioning is the phenomenon whereby several brief coronary artery reperfusion reocclusion cycles at the end of a long coronary artery occlusion (stuttering reperfusion) reduces infarct size.

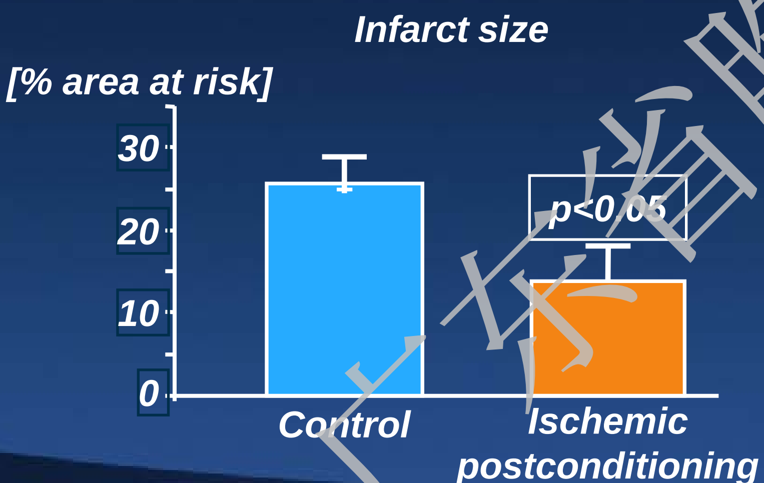


Zhao, Z-Q et al. Am J Physiol 2003;285:1574
Staat et al., Circulation 112:2143-2148 (2005)

Ischemic post-conditioning

Experimental

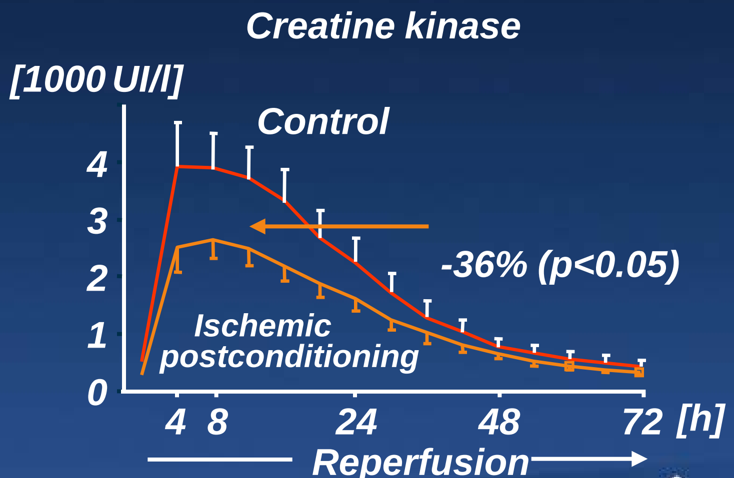
Ischemic postconditioning



Zhao et al., Am J Physiol 285:H579-H588 (2003)

Clinical

Ischemic postconditioning



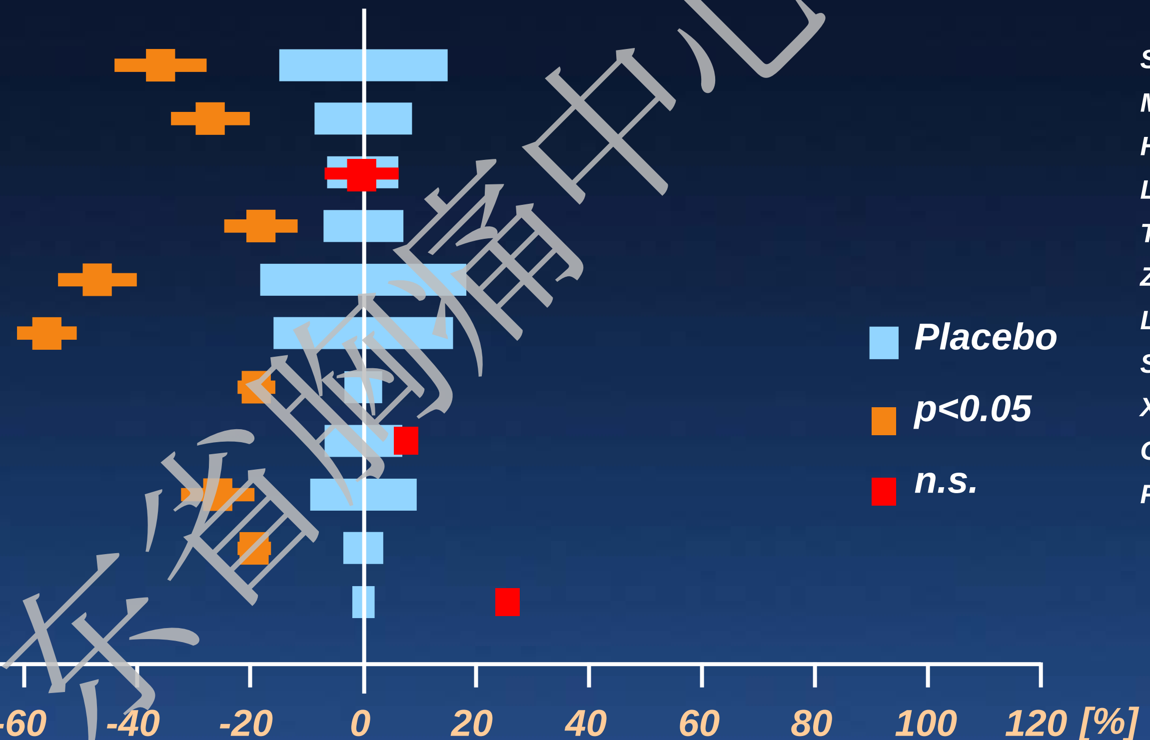
Staat et al., Circulation 112:2143-2148 (2005)

Ischemic post conditioning

Study	N	Therapeutic intervention	Result
IPost			
Staat et al. 2005 (66)	30	Four 60-s cycles of low-pressure inflation/deflation of angioplasty balloon	Reduction of MI size by 36% (72-hr AUC CK); improved myocardial blush grade
Thibault et al. 2008 (94)	38	Four 60-s cycles of low-pressure inflation/deflation of angioplasty balloon	Reduction of MI size by 40% (72-hr AUC CK); reduction of MI size by 39% at 6 mo, as assessed with SPECT; 7% increase in EF, as assessed with ECG, at one year
Lonborg et al. 2010 (95)	118	Four 60-s cycles of low-pressure inflation/deflation of angioplasty balloon	Reduction of MI size by 19% at 3 mo, as assessed with CMR; 31% increase in myocardial salvage index
Sorensson et al. 2010 (96)	76	Four 60-s cycles of low-pressure inflation/deflation of angioplasty balloon	No difference in 48-hr AUC CK-MB or Trop-T; no difference in myocardial salvage, as assessed with CMR, on days 7–9; significant increase in myocardial salvage in patients with large AAR (>30% of LV)
Tarantini et al. 2012 (97)	78	Four 60-s cycles of low-pressure inflation/deflation of angioplasty balloon; IPost protocol delivered in stent	Trend toward increased MI size; increased adverse events
Freixa et al. 2012 (98)	79	Four 60-s cycles of low-pressure inflation/deflation of angioplasty balloon; IPost protocol delivered in stent	Worse myocardial salvage; no difference in MI size
Engstrom et al. 2012 (99); DANAMI-3	2,000	Four 30-s cycles of low-pressure inflation/deflation of angioplasty balloon	Ongoing phase 3 study investigating the effect of IPost on death and HHF

Ischemic post-conditioning

End-point	PLA/PoCo	Authors
CK	27 / 28	Staat et al.
CK	47 / 47	Ma et al.
ST res	350 / 350	Hahn et al.
CK	12 / 13	Laskey et al.
TnI	21 / 17	Thibault et al.
TnI	26 / 25	Zhao et al.
MRI	59 / 59	Lønborg et al.
CK	38 / 28	Sørensson et al.
CK-MB	20 / 23	Xue et al.
C-MB	21 / 22	Garcia et al.
CK	39 / 40	Freixa et al.

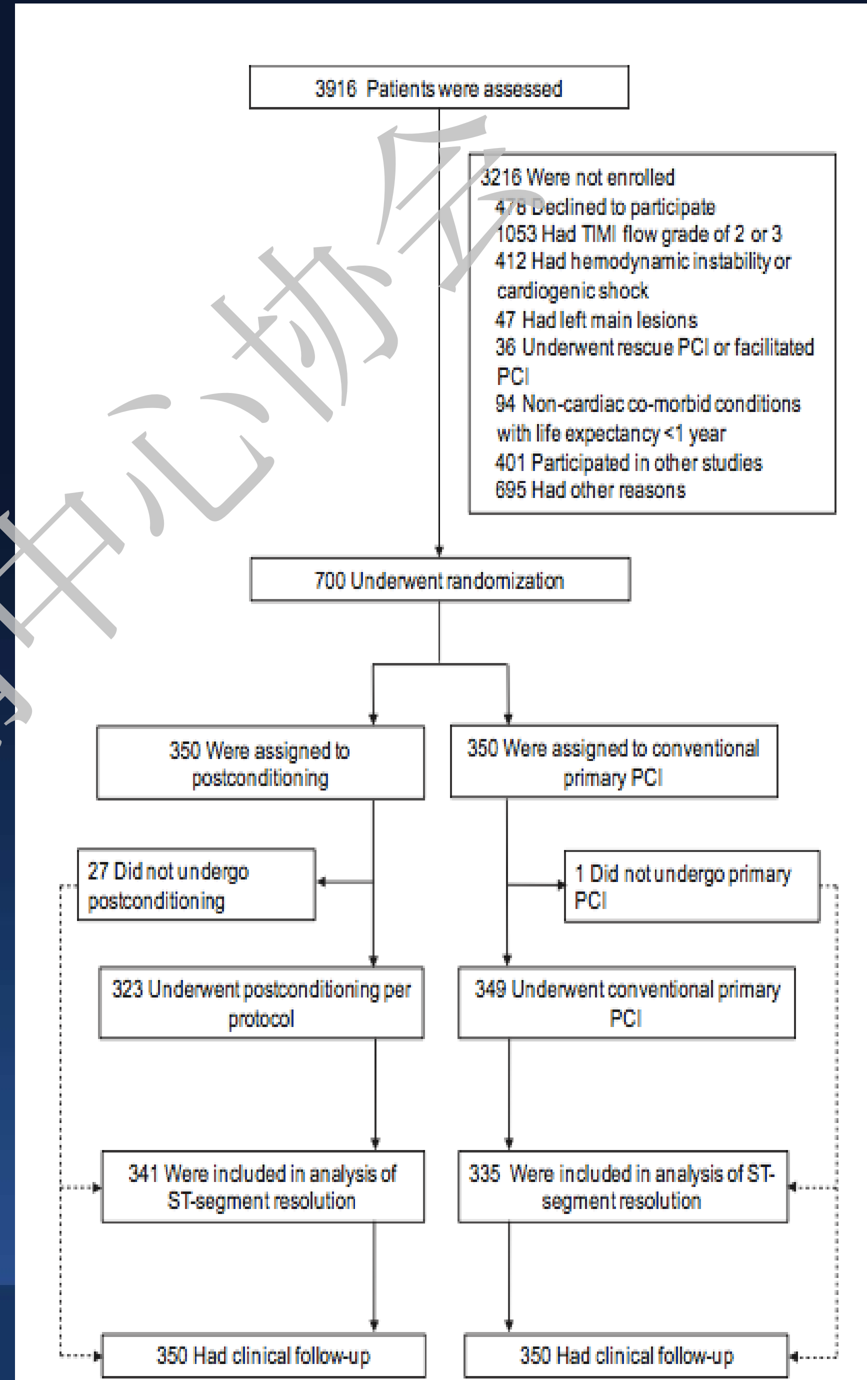


The Effects of Postconditioning on Myocardial Reperfusion in Patients With ST-Segment Elevation Myocardial Infarction (POST)

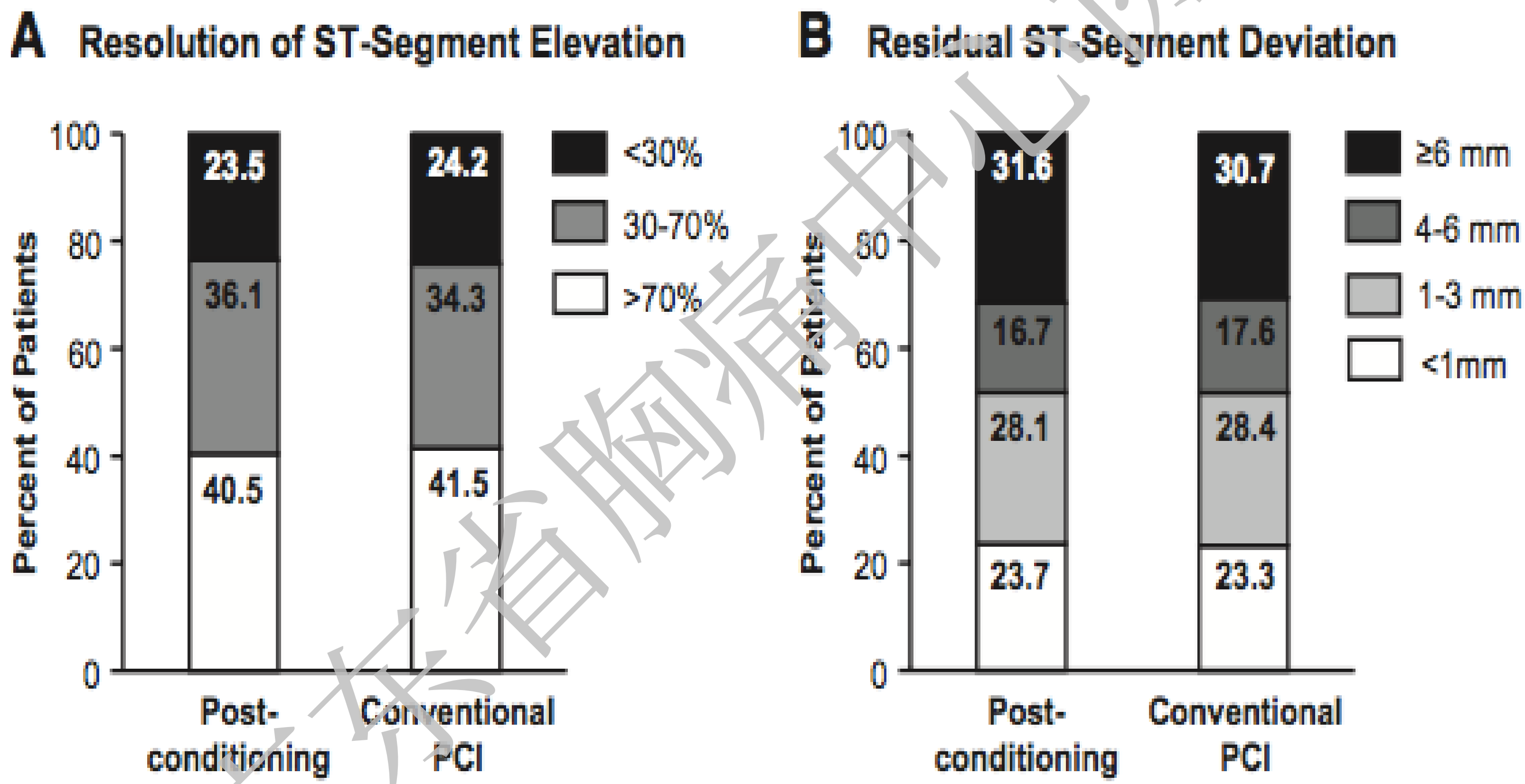
Randomized Trial

Primary endpoint
The rate of complete ST-segment resolution on ECG obtained 30 minutes after the procedure.

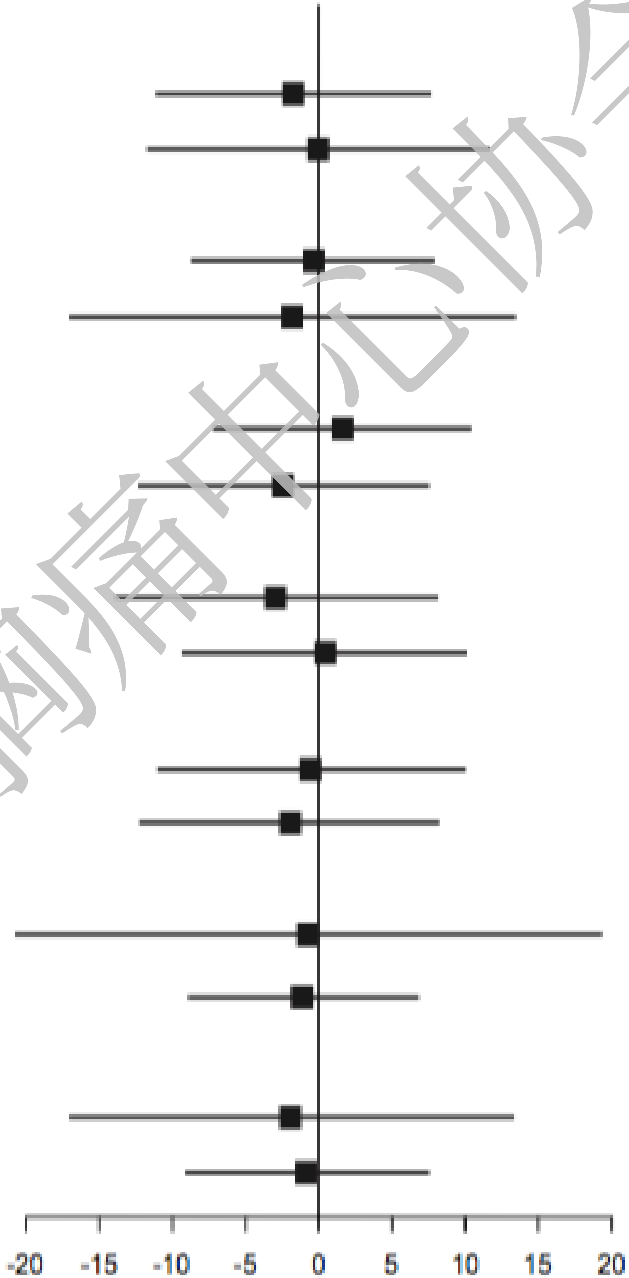
Secondary end points
Included residual ST-segment deviation, TIMI flow after PCI, myocardial blush grade, death, reinfarction, severe heart failure, stent thrombosis, target vessel revascularization, and major adverse cardiac events (a composite of death, myocar- dial infarction, severe heart failure, or stent thrombosis) at 30 days.



Results


A Resolution of ST-Segment Elevation
Percent of Patients
100
80
60
40
20
0
23.5
36.1
40.5
24.2
34.3
41.5
<30%
30-70%
>70%
Post-conditioning
Conventional PCI
B Residual ST-Segment Deviation
Percent of Patients
31.6
16.7
28.1
23.7
30.7
17.6
28.4
23.3
≥6 mm
4-6 mm
1-3 mm
<1mm
Post-conditioning
Conventional PCI

	Postconditioning	Conventional PCI	Difference (95% Confidence Interval)	*P*
	n / total n (%)			
Age				
<65 years	87/211 (41.2%)	88/205 (42.9%)	-1.7 (-11.1 to 7.7)	0.73
≥65 years	51/130 (39.2%)	51/130 (39.2%)	0.0 (-11.7 to 11.7)	0.99
Gender				
Men	105/269 (39.0%)	98/249 (39.4%)	-0.3 (-8.7 to 8.0)	0.94
Women	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



Conventional PCI Better

Postconditioning Better

Outcomes at 30 days

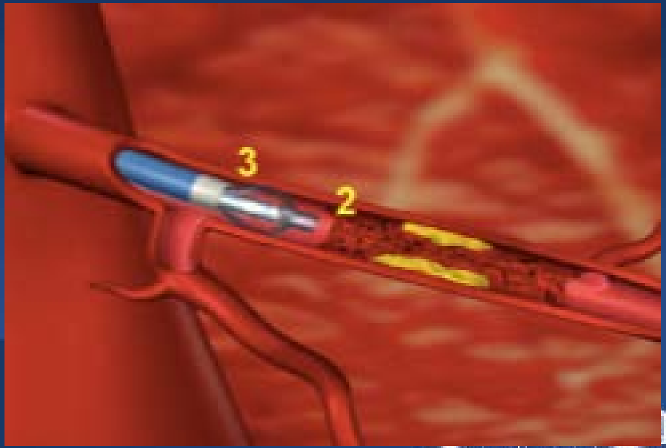
Table 3. Clinical Outcomes at 30 Days

	Postconditioning (n=350), n (%)	Conventional PCI (n=350), n (%)	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)	…	…
Myocardial infarction	2 (0.6)	1 (0.3)	…	…
Severe heart failure	2 (0.6)	5 (1.4)	…	…
Stent thrombosis	7 (2.0)	6 (1.7)	…	…
Target vessel revascularization	3 (0.9)	3 (0.9)	…	…
Major adverse cardiac event†	15 (4.3)	13 (3.7)	1.15 (0.56–2.39)	0.70

1. *Which is the best sequence for ischemic post conditioning ?Whether the repeated balloon inflation- deflation at the site of the culprit lesion might have been responsible for excessive inadvertent thrombus microembolization?*
2. *Although the protocol stipulated post-conditioning within 1 min of STEMI, the high frequency of thrombectomy likely delayed post-conditioning beyond the protective 1-min time-frame, and this might have diluted the benefits of this protective strategy.*

DANAMI3:The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Ischemic postconditioning or deferred stent implantation versus conventional primary angioplasty and complete revascularization versus treatment of culprit lesion only

No Significant!

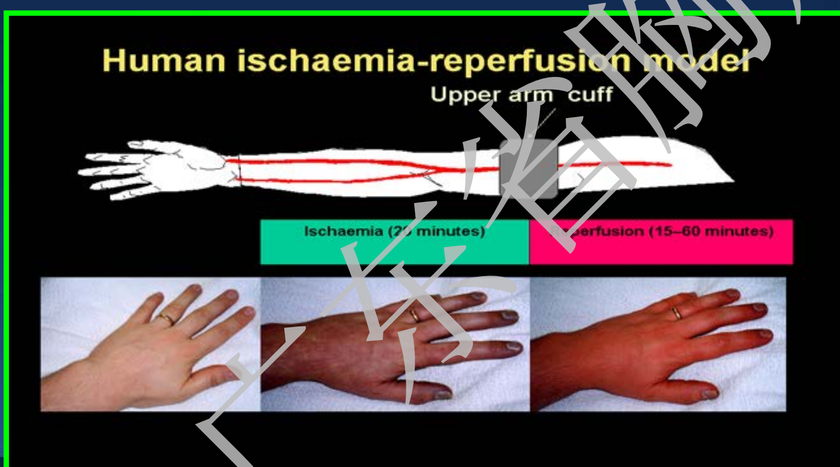


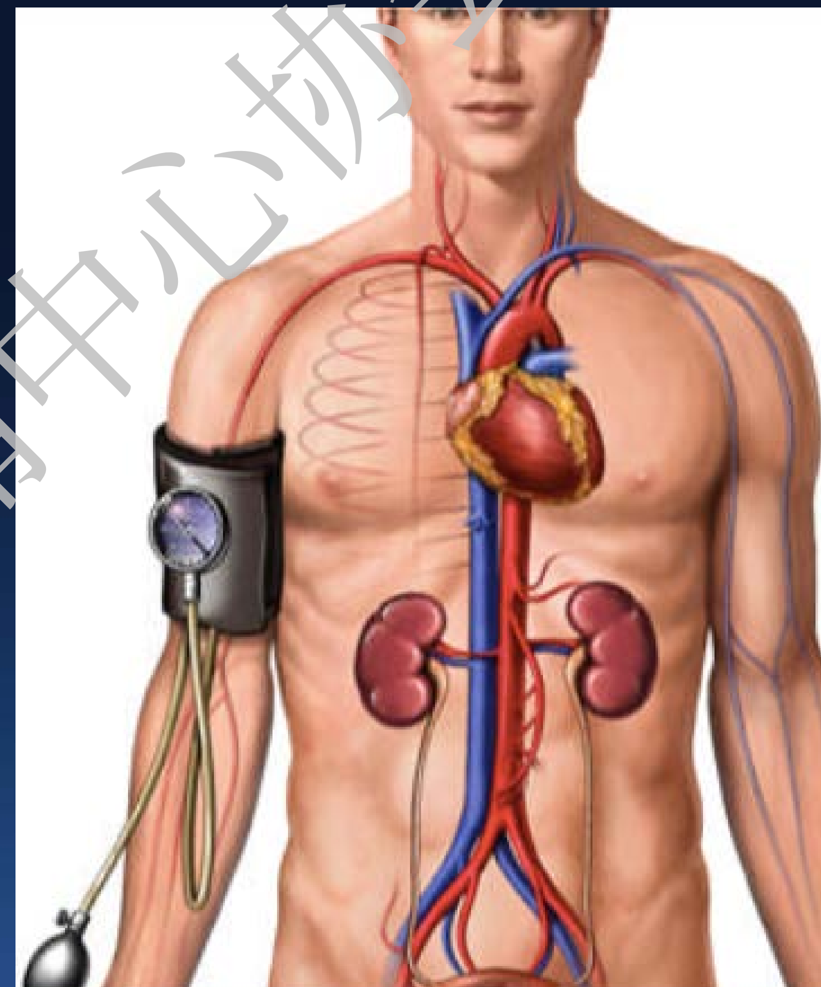
远隔缺血处理（Remote ischemic preconditioning）

• Cycles of brief ischemia/ reperfusion can protect the heart and other organs

• Simple, non-invasive, low-cost intervention

• RIC potentially reduces PMI by 30-40%

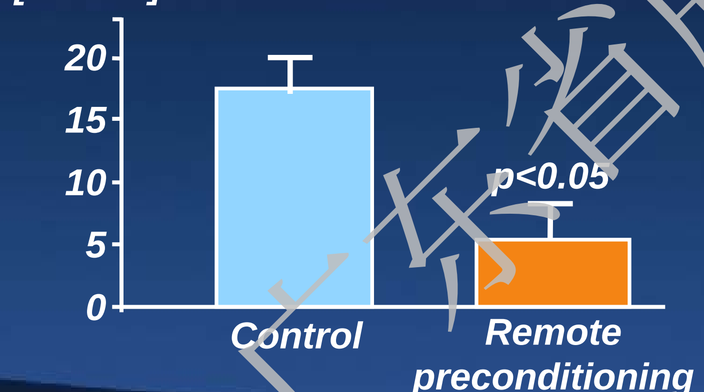




Remote Ischemic preconditioning（RIC）

Experimental

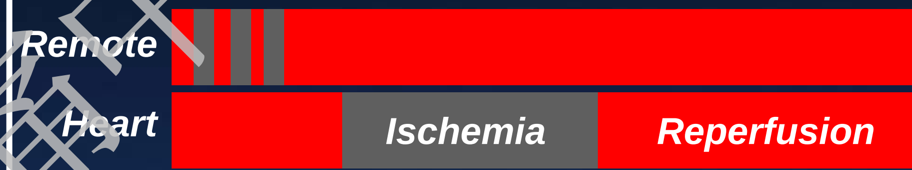
Myocardium

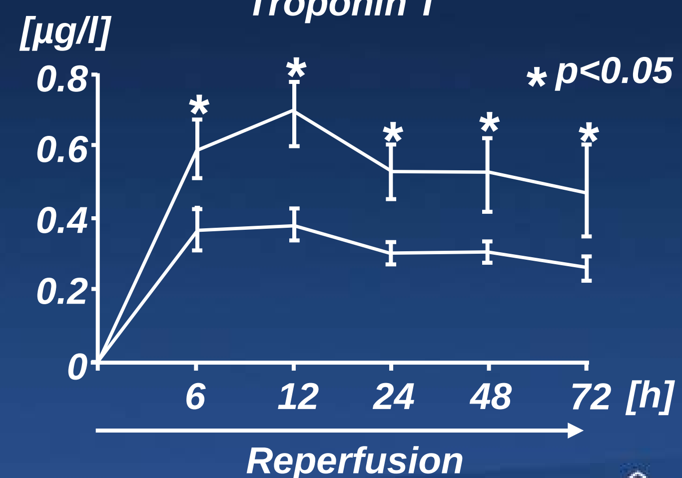


Przyklenk et al., Circulation 87:893-899 (1993)

Clinical

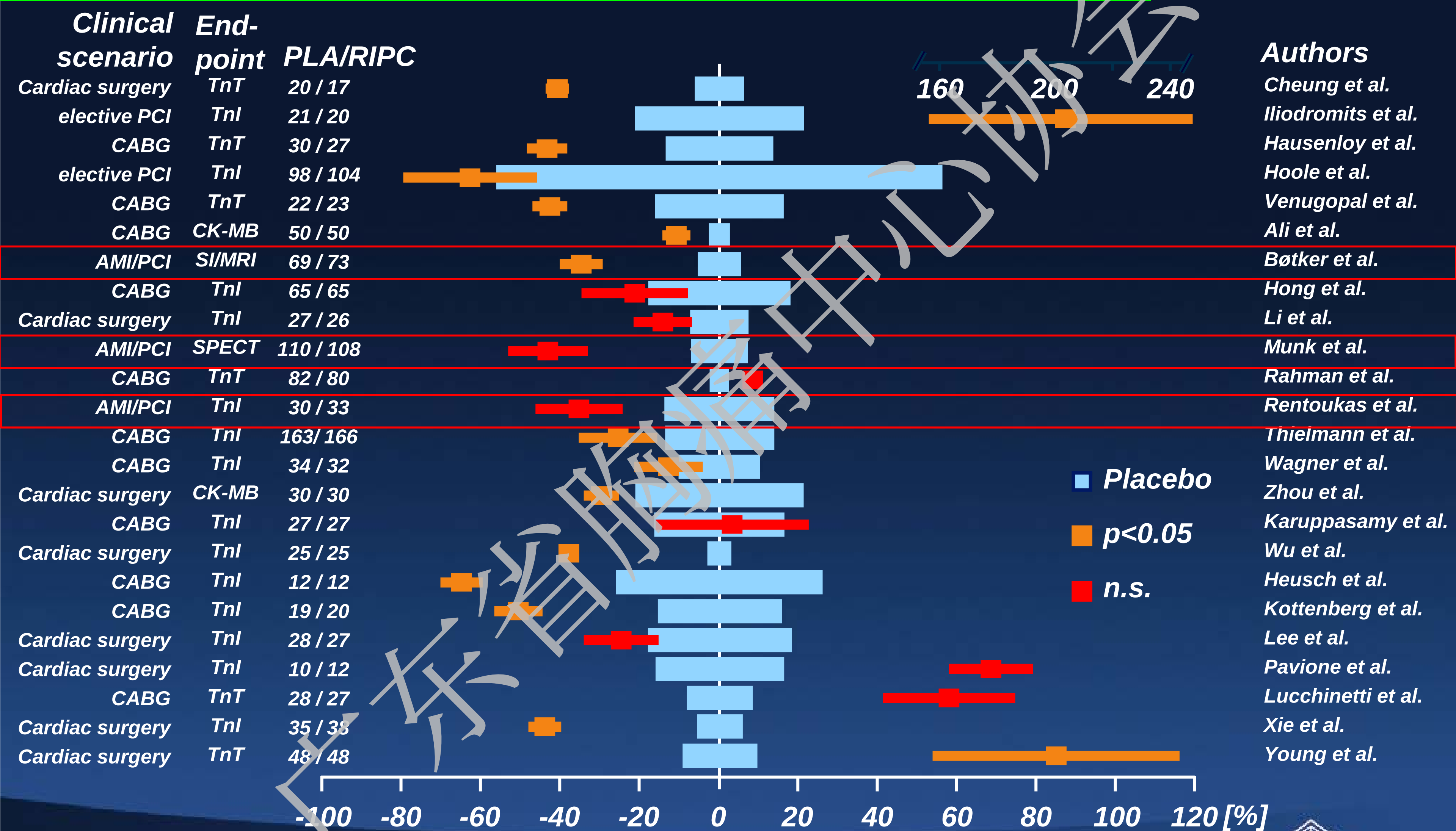
Upper limb





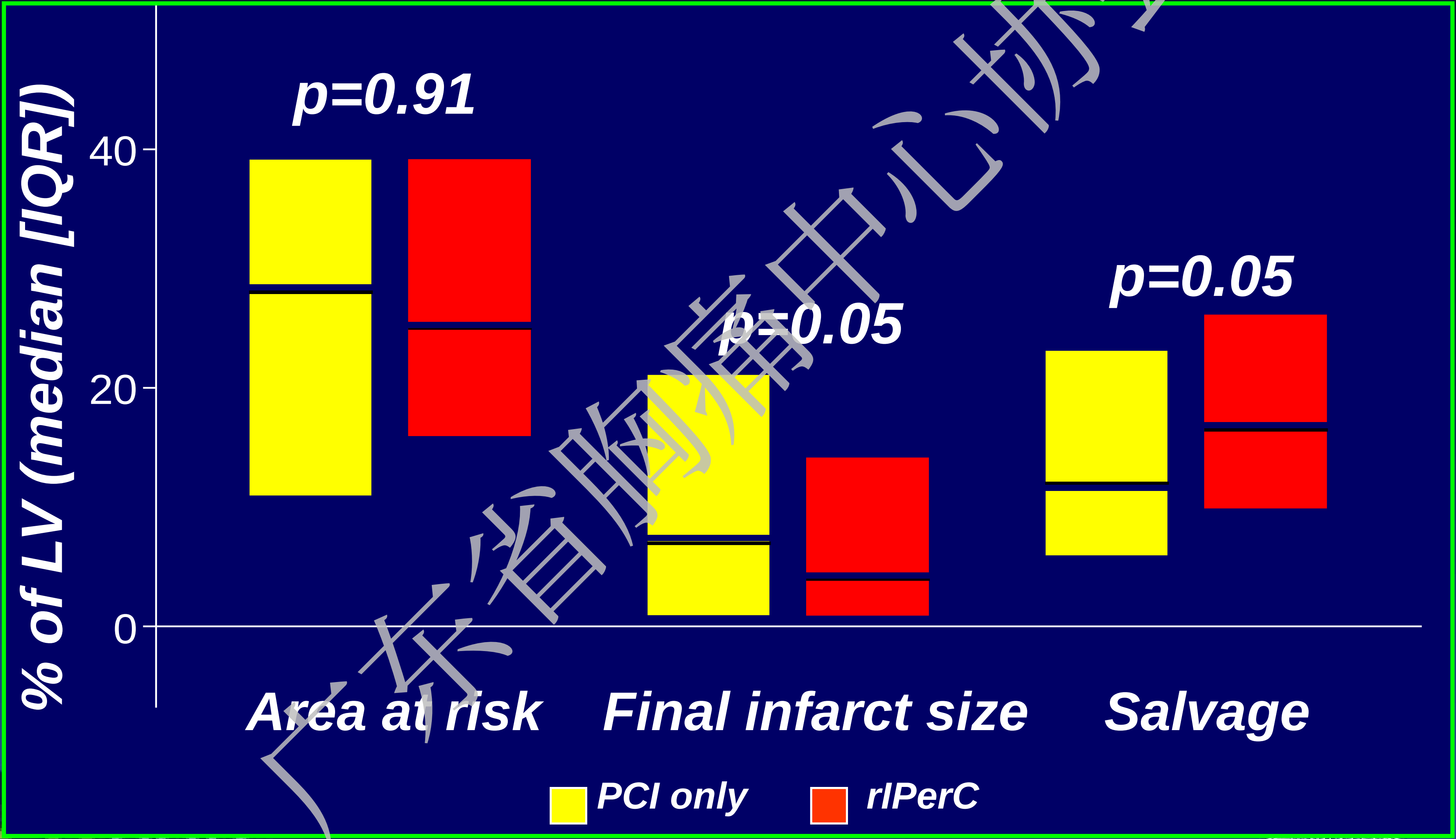
Hausenloy et al., Lancet 370:575-579 (2007)

Remote Ischemic preconditioning



Effect of RIC on Clinical Outcomes in STEMI Patients Undergoing pPCI (CONDI2)

CONDI trial



Bøtker et al. Lancet 2010

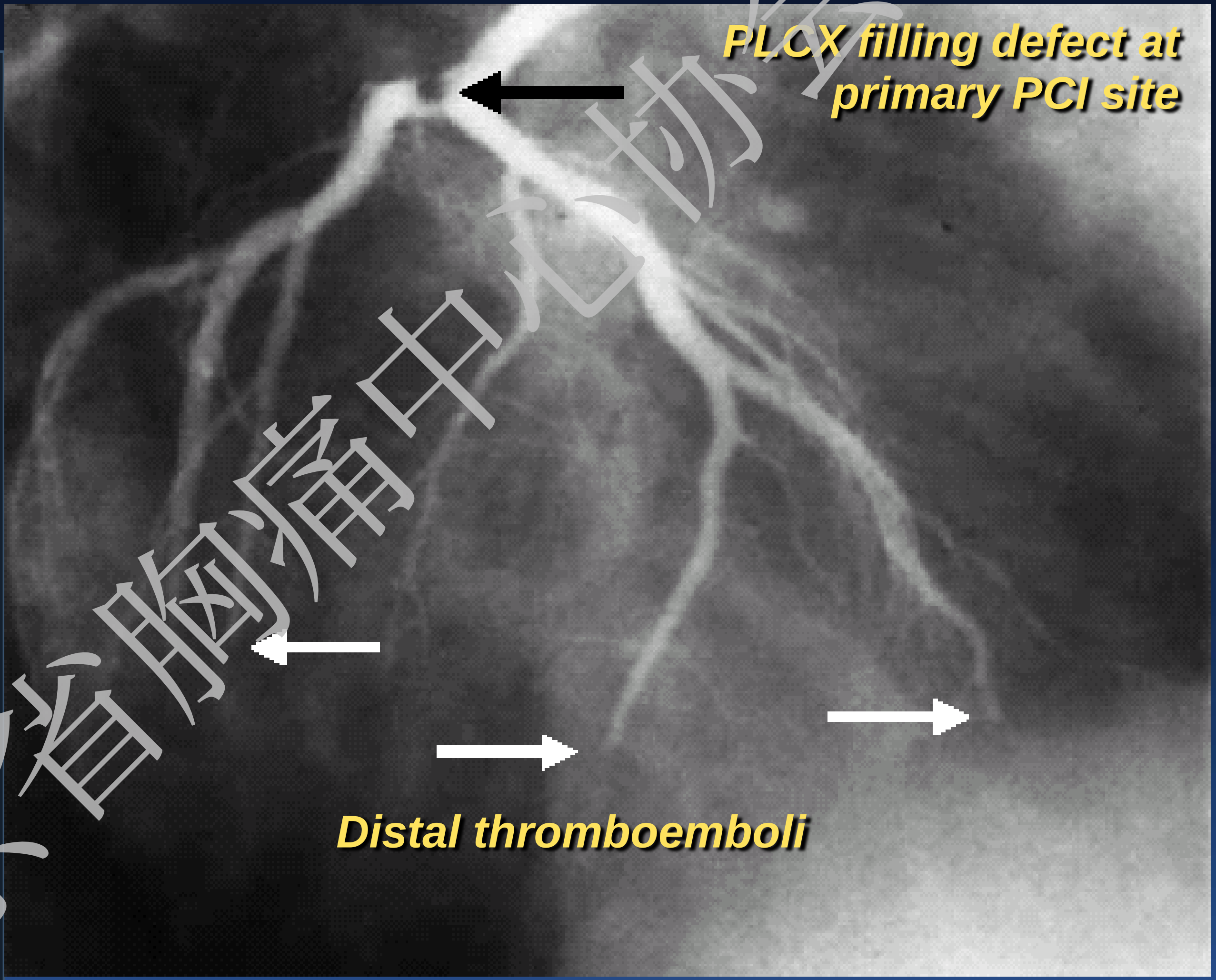
远端栓塞保护（Impact of Macroscopic Distal Emboli）

DE occurred in 27 of 178 (15%) pts after primary PTCA ⇒

↓ ST res

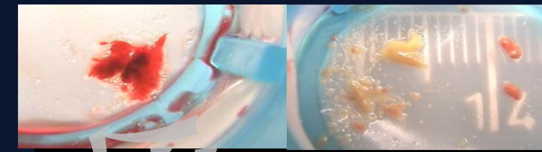
↑ Infarct size

↑ Mortality



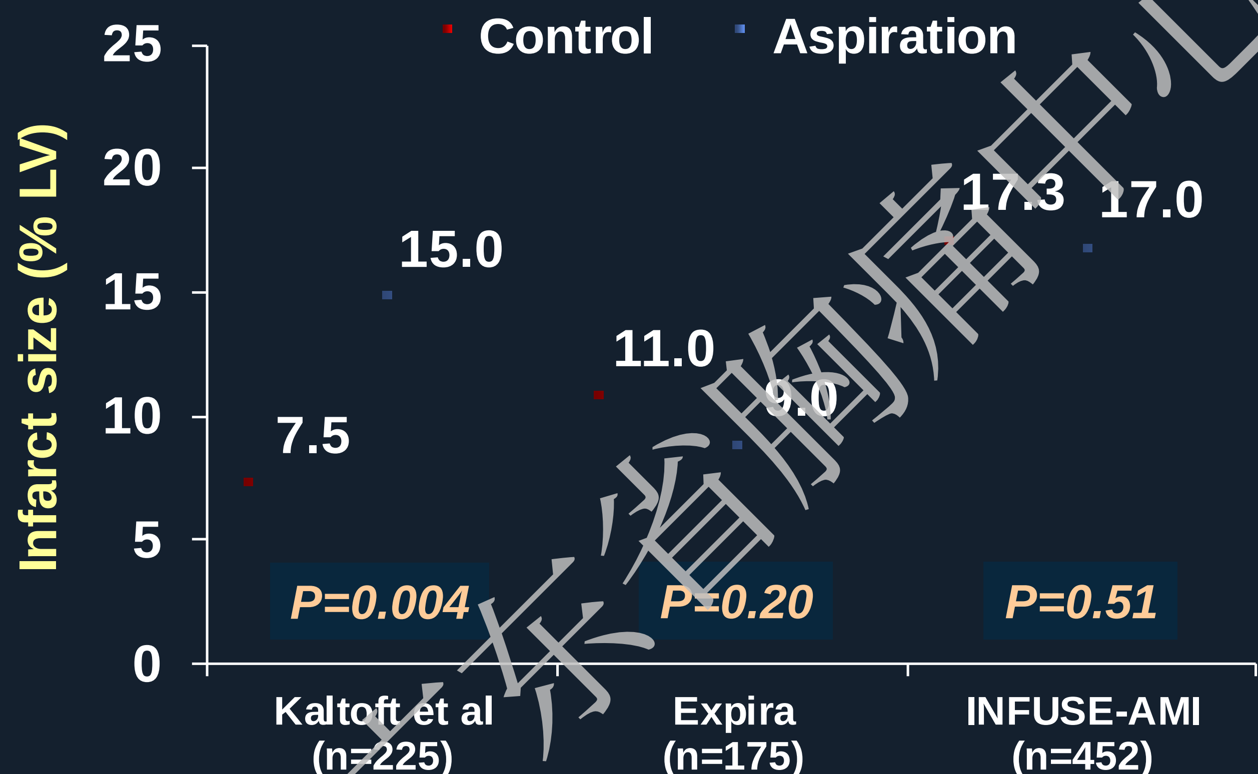
Henriques JPS et al. EHJ 2002;23:1112-7

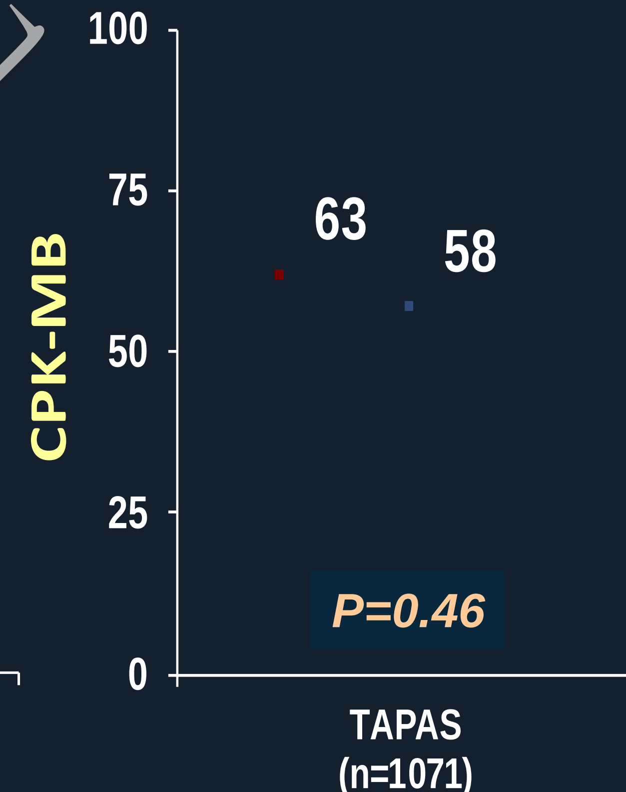
The concept of reducing embolic load



Aspiration Trials to Decrease Infarct Size

Have been negative

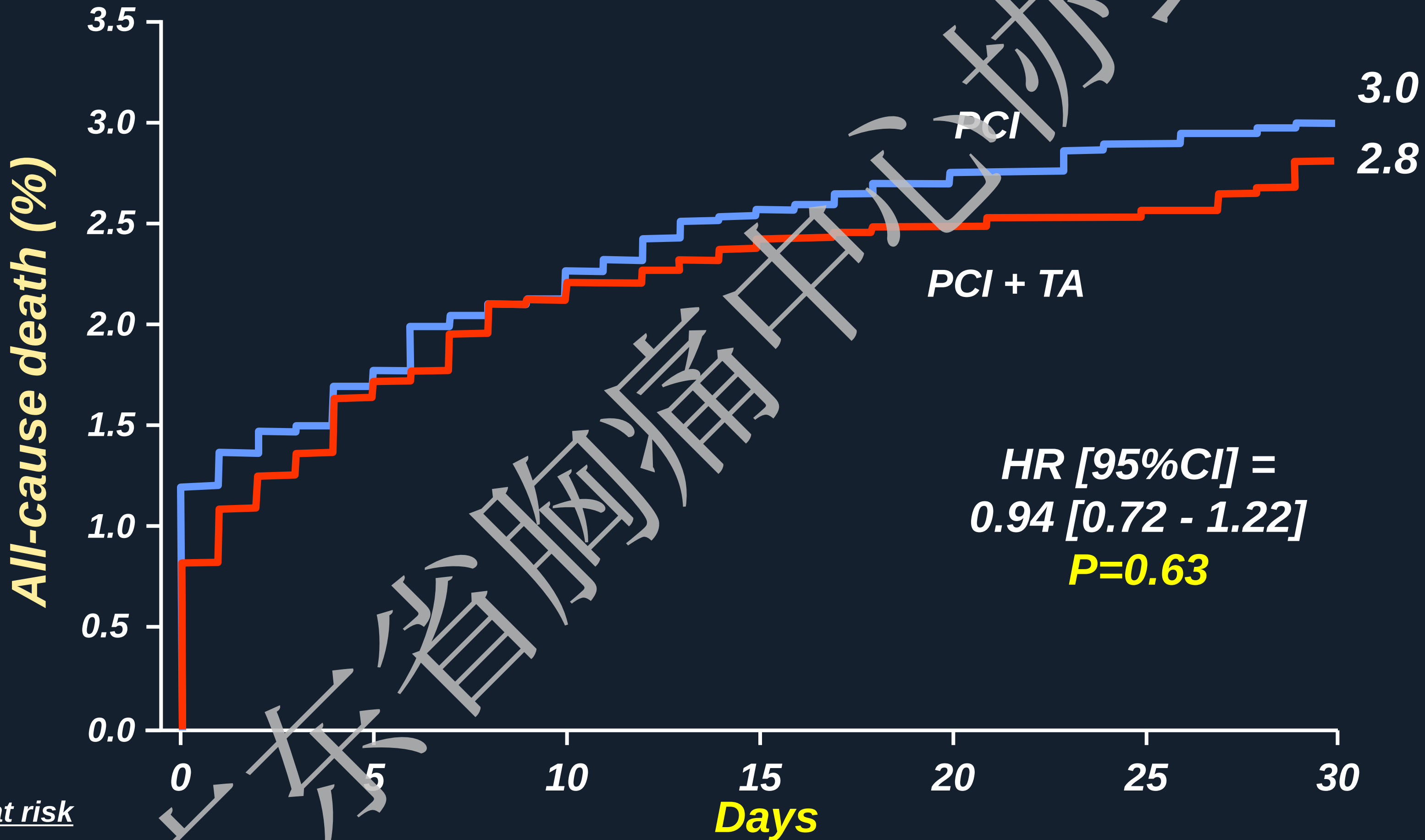




Rescue catheter	Export catheter	Export catheter	Export catheter
Kaltoft A et al. JACC 2006;114:40-47	*Sardella G et al. JACC 2009;53:309–15*	*Stone GW et al. JAMA 2012;307:1817-26*	*Svilaas T et al. NEJM 2008;358;-557-67*

TASTE All-cause Mortality

Primary Endpoint: N=7,244



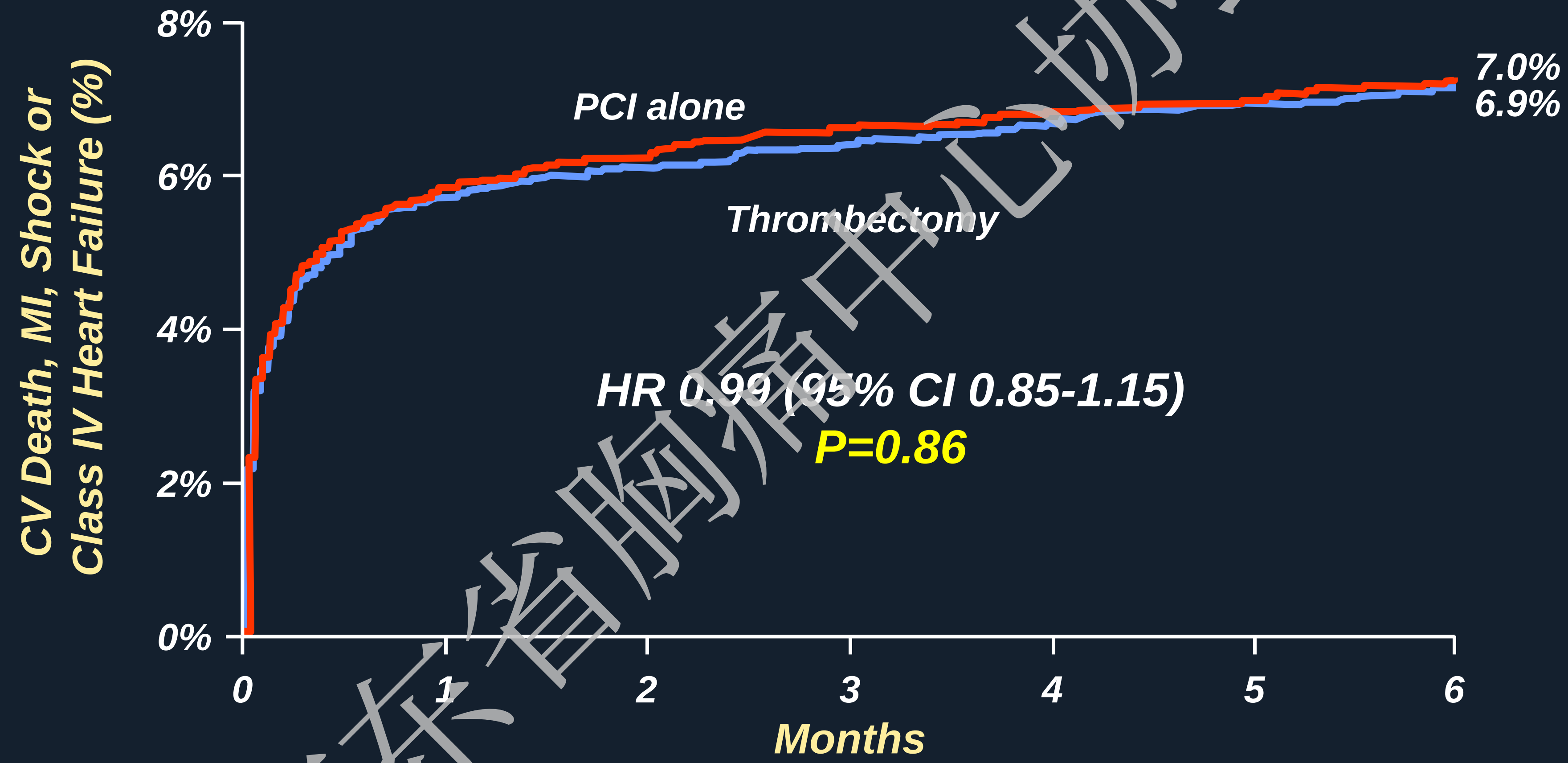
<u>No. at risk</u>

	0	5	10	15	20	25	30
PCI+TA	3621	3568	3540	3532	3526	3524	3519
PCI	3623	3567	3545	3530	3523	3517	3513

Frobert O et al. NEJM 2013:on-line

TOTAL: Primary Endpoint (n=10,063)

CV death, MI, shock or class IV heart failure at 6 months



No. at risk	0	1	2	3	4	5	6
Thrombectomy	5033	4734	4696	4678	4662	4647	4628
PCI alone	5030	4727	4688	4666	4653	4642	4618

Jolly SS et al. NEJM 2015:on-line

Therapeutic Hypothermia/ Hyperoxemia Negetive

Therapeutic hypothermia			
Gotberg et al. 2010 (102); RAPID-MI-ICE	20	Cooling to 35°C prior to PPCI by i.v. infusion of 1–2 liters of cold saline and cooling with Philips InnerCool RTx Endovascular System	Reduction in MI size as % of AAR, as assessed with CMR at 4 days (30% vs 48%); 43% reduction in peak and cumulative Trop-T release
Erlinge et al. 2012 (103); CHILL-MI	120	Cooling to 35°C prior to PPCI by i.v. infusion of 1–2 liters of cold saline and cooling with Philips InnerCool RTx Endovascular System	Ongoing multicenter study investigating whether cooling prior to PPCI reduces MI size (as a % of AAR) on CMR at 4 days
Therapeutic hyperoxemia			
O'Neill et al. 2007 (78); AMIHOT I	269	IC hyperbaric hyperoxemic reperfusion started after PPCI and continued for 90 min	No difference in 14-day MI size as assessed with SPECT; patients with anterior STEMI <6 h showed improvements[A]
Stone et al. 2009 (104); AMIHOT II	281	IC hyperbaric hyperoxemic reperfusion started after PPCI and continued for 90 min	No difference in 14-day MI size as assessed with SPECT[A]

Approach for Prevention of IR injury

Pharmacological	**GLP-1**	**Promising**
	Cycloporine	Negative
	Benvadin	Negative
	Metoprolol	Promising
Nonpharmacological	Ischemic post conditioning	Need more RCTs
	Remote ischemic preconditioning	Need more RCTs
	Aspiration and thrombetomy	Negative
	Therapeutic hypothermia /hyperoxemia	Negative

Conclusion

- **Despite important progress has been made in the quality of phase II trials evaluating protective interventions against reperfusion injury, there is no "magic bullet" for IRI.**
- **The commitment of funding agencies, scientific societies, and industrial partners is needed to achieve this challenging goal.**

Thank you