Samsung Medical Center
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Effect of Postconditioning on Myocardial Reperfusion during Primary Percutaneous Coronary Intervention

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On behalf of the POST Trial Investigators

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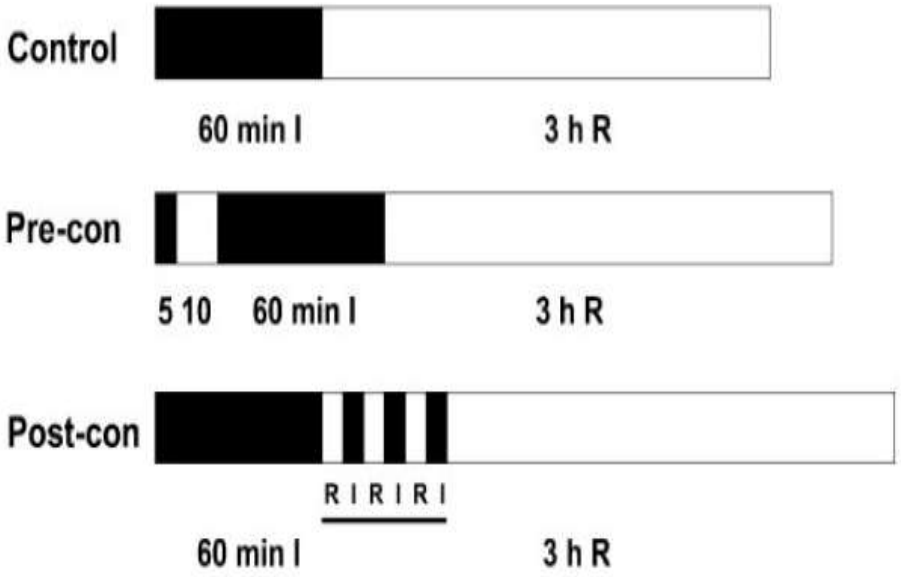
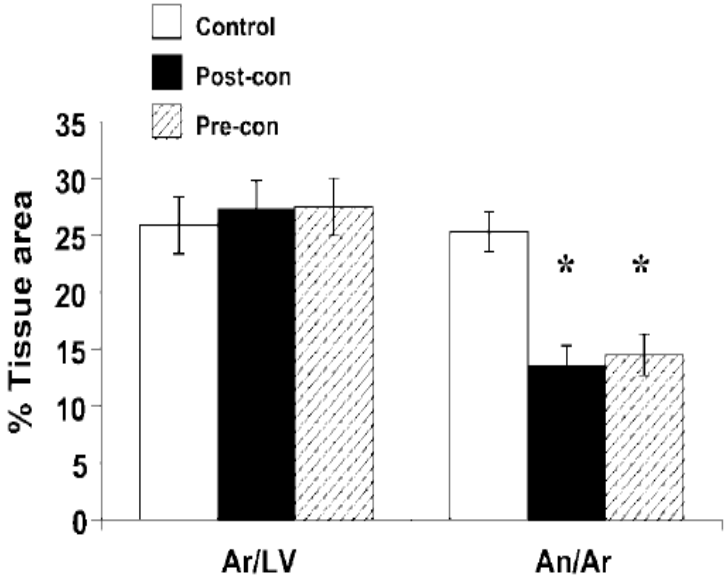
Ischemic Postconditioning

- 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 Heart Circ Physiol 2003





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

  } PostC is Protective!

  - Freixa X et al. Eur Heart J 2012
  - Tarantini G et al. Int J Cardiol 2012

  } PostC is harmful!
- No large scale trials

Objective of Study

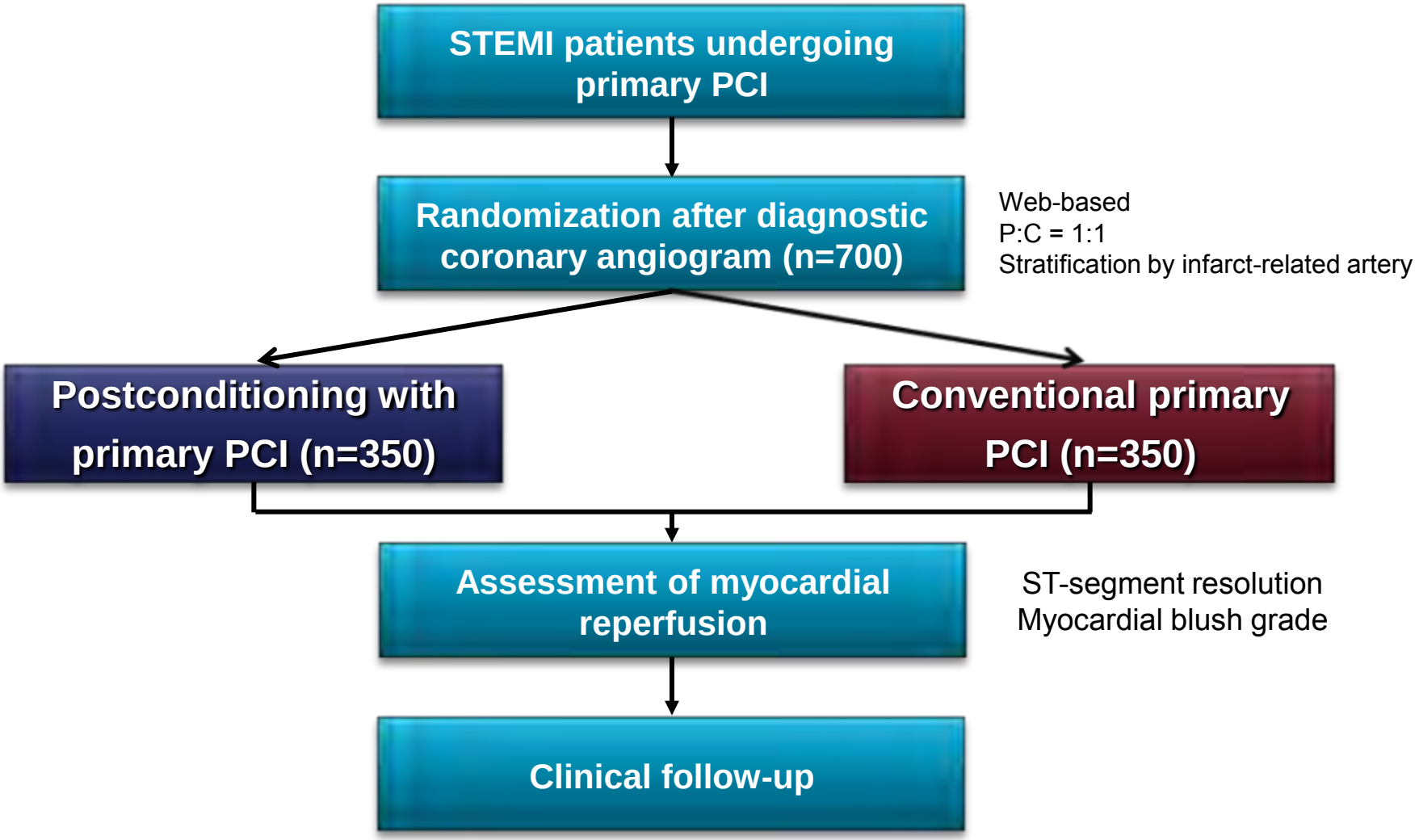
- To evaluate the safety and efficacy of ischemic postconditioning in patients with STEMI undergoing primary PCI.

Hypothesis

Ischemic postconditioning can improve myocardial reperfusion after primary PCI.

Trial Design

A multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) trial



Eligible patients

- Patients with STEMI undergoing primary PCI

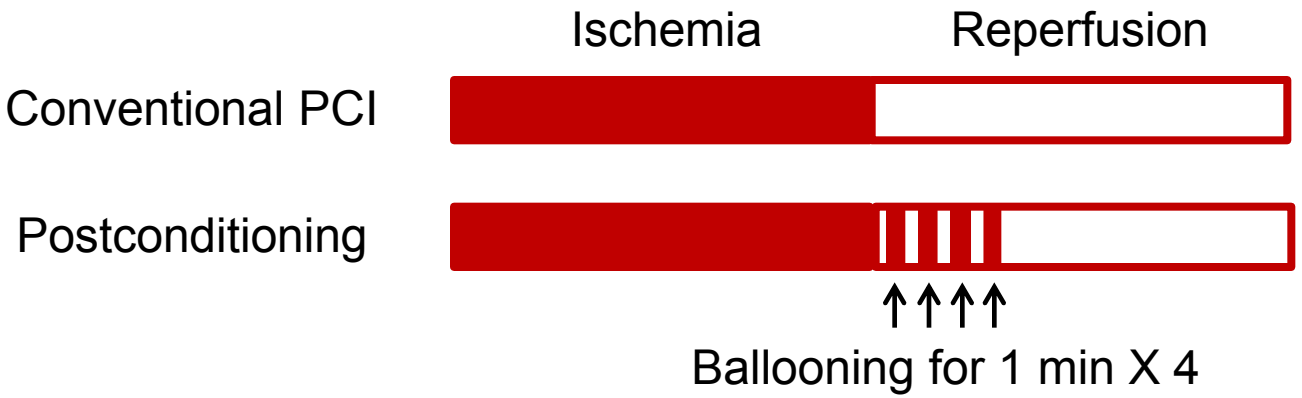
- Inclusion criteria
  - ST-segment elevation more than 1 mm in 2 or more contiguous leads
  - The presence of chest pain for less than 12 hours after symptom onset
  - Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1 in the infarct-related artery
  - Target lesion in a native coronary vessel with reference diameter of 2.25 to 4.25 mm.

Exclusion Criteria

- Hemodynamic instability or cardiogenic shock
- Left bundle branch block on electrocardiogram (ECG)
- Left main lesion
- Rescue PCI after thrombolysis or facilitated PCI
- Non-cardiac co-morbid conditions with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment)
- Female of childbearing potential, unless a recent pregnancy test is negative, who possibly plan to become pregnant any time after enrollment into this study.

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

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

Sample Size Calculation

Primary Endpoint

The rate of complete STR

- **The rate of complete STR in the conventional PCI group: 50%**
- **The expected rate of complete STR in the postconditioning group: 62.5% (relative increase 25%)**
- **Type I error 0.05**
- **Sampling ratio of postconditioning : conventional PCI = 1:1**

A target sample size of 700 subjects would provide 91.7% power.

Independence in Trial Coordination

Steering Committee

17 study investigators

DSMB

Data Safety
Monitoring Board

CTC-SMC

Trial
Coordinating Center

CEAC

Clinical Event
Adjudication Committee

Core Laboratory

ECG and angiographic data analyses

Grant Support

1) The Korean Society of Interventional Cardiology
2) The Sungkyunkwan University Foundation for Corporate Collaboration
3) Medtronic Korea

The sponsors were not involved with the protocol development or the study process, including site selection, management, and data collection and analysis.

Participating Centers

17 Hospitals in Republic of Korea

- Samsung Medical Center
- Samsung Changwon Hospital
- Kyungpook National University Hospital
- Hanil General Hospital
- Konyang University Hospital
- Korea University Anam Hospital
- Gyeongsang National University Hospital
- Eulji University School of Medicine
- Kangbuk Samsung Hospital
- Chungbuk National University Hospital
- Sejong General Hospital
- Daegu Catholic University Hospital
- Chung-Ang University Hospital
- Boramae Medical Center
- Yeungnam University Hospital
- Dankook University Hospital
- Kyung Hee Medical Center

Between July 2009 and June 2012

3916 Patients were assessed

3216 Were not enrolled
- 478 Declined to participate
- 1053 Had TIMI flow grade of 2 or 3
- 412 Had hemodynamic instability or cardiogenic shock
- 47 Had left main lesions
- 36 Underwent rescue PCI or facilitated PCI
- 94 Non-cardiac co-morbid conditions with life expectancy <1 year
- 401 Participated in other studies
- 695 Had other reasons

700 Underwent randomization

350 Were assigned to postconditioning

27 Did not undergo postconditioning per protocol

323 Underwent postconditioning per protocol

341 Were included in analysis of STR

350 Had clinical follow-up

350 Were assigned to conventional PCI

1 underwent coronary artery bypass grafting surgery

349 Underwent conventional primary PCI

335 Were included in analysis of STR

350 Had clinical follow-up

Baseline Clinical Characteristics

	Postconditioning (n=350)	Conventional PCI (n=350)	P Value
Age — yr	60±12	60±12	0.96
Male sex	276/350 (78.9%)	261/350 (74.6%)	0.18
Body mass index*	24.1±3.2	24.4±3.0	0.34
Diabetes mellitus	84/346 (24.3%)	87/346 (25.1%)	0.79
Hypertension	161/341 (46.4%)	159/349 (45.6%)	0.82
Dyslipidemia	139/345 (40.3%)	159/349 (45.6%)	0.16
Current smoking	184/349 (52.7%)	182/348 (52.3%)	0.91
Previous myocardial infarction	10/344 (2.9%)	9/348 (2.6%)	0.80
Previous revascularization	20/346 (5.8%)	16/349 (4.6%)	0.48
Cerebrovascular disease	10/346 (2.9%)	16/348 (4.6%)	0.24
Chronic renal failure	4/345 (1.2%)	2/348 (0.6%)	0.45
Ejection fraction (%)	50·0 (10.9)	50·2 (11.6)	0.88

Angiographic Findings

	Postconditioning (n=350)	Conventional PCI (n=350)	P Value
Number of diseased vessels			0.19
1	189/350 (54.0%)	165/350 (47.1%)	
2	99/350 (28.3%)	115/350 (32.9%)	
3	62/350 (17.7%)	70/350 (20.0%)	
Infarct-related artery			0.90
Left anterior descending	163/350 (46.6%)	157/350 (44.9%)	
Left circumflex	38/350 (10.9%)	40/350 (11.4%)	
Right coronary artery	149/350 (42.6%)	153/350 (43.7%)	
TIMI flow before PCI			0.90
0	328/350 (93.7%)	324/347 (93.4%)	
1	8/350 (2.3%)	7/347 (2.0%)	
2/3	14/350 (4.0%)	16/347 (4.6%)	

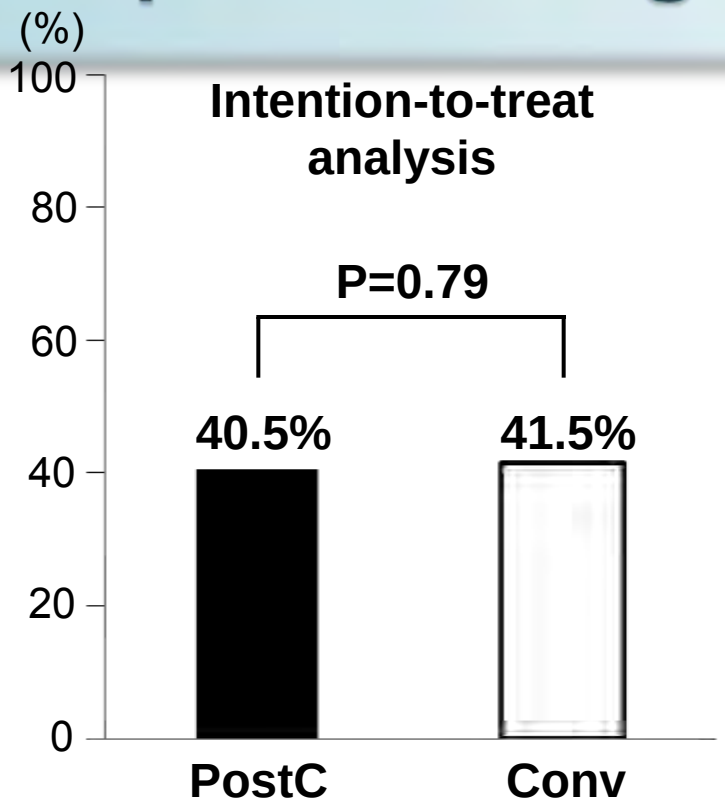
TIMI = thrombolysis in myocardial infarction.

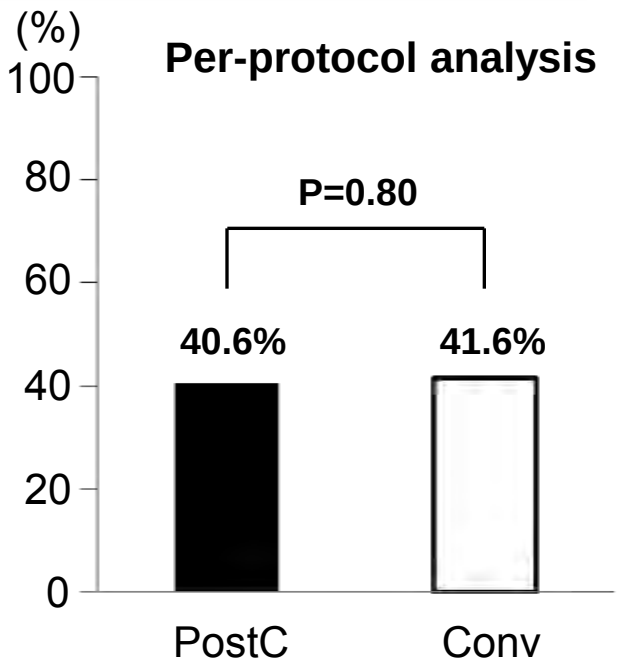
Procedural Findings

	Postconditioning (n=350)	Conventional PCI (n=350)	P Value
Symptom onset-to-reperfusion time — min	196 (123-263)	195 (123-354)	0.91
Door-to-reperfusion time — min	54 (43-73)	56 (44-74)	0.14
Thrombus aspiration	158/350 (45.1)	178/350 (50.9)	0.13
Direct stenting	43/350 (12.3)	51/350 (14.6)	0.38
Obtaining method of reflow			0.69
Wire passage	36/350 (10.3%)	45/349 (12.9%)	
Thrombus aspiration	111/350 (31.7%)	114/349 (32.7%)	
Predilation ballooning	202/350 (57.7%)	189/349 (54.2%)	
Direct stenting	1/350 (0.3%)	1/349 (0.3%)	
Use of glycoprotein IIb/IIIa inhibitor	81/350 (23.1)	80/350 (22.9)	0.93
Stent implantation	337/350 (96.3)	342/350 (97.7)	0.28
Drug-eluting stent	291/337 (86.4)	295/342 (86.3)	0.97
Total stent length, mm	28.2±11.8	28.7±12.6	0.60
Stent diameter, mm	3.3±0.5	3.3±0.5	0.31

1° Endpoint

Complete ST-segment Resolution





	Postconditioning	Conventional PCI	P Value
ECG analysis	341/350 (97.4%)	335/350 (95.7%)	0.21
Time to ECG — min	31 (29-38)	31 (29-37)	0.77
Per-protocol analysis	315/323 (97.5%)	334/349 (95.7%)	0.19

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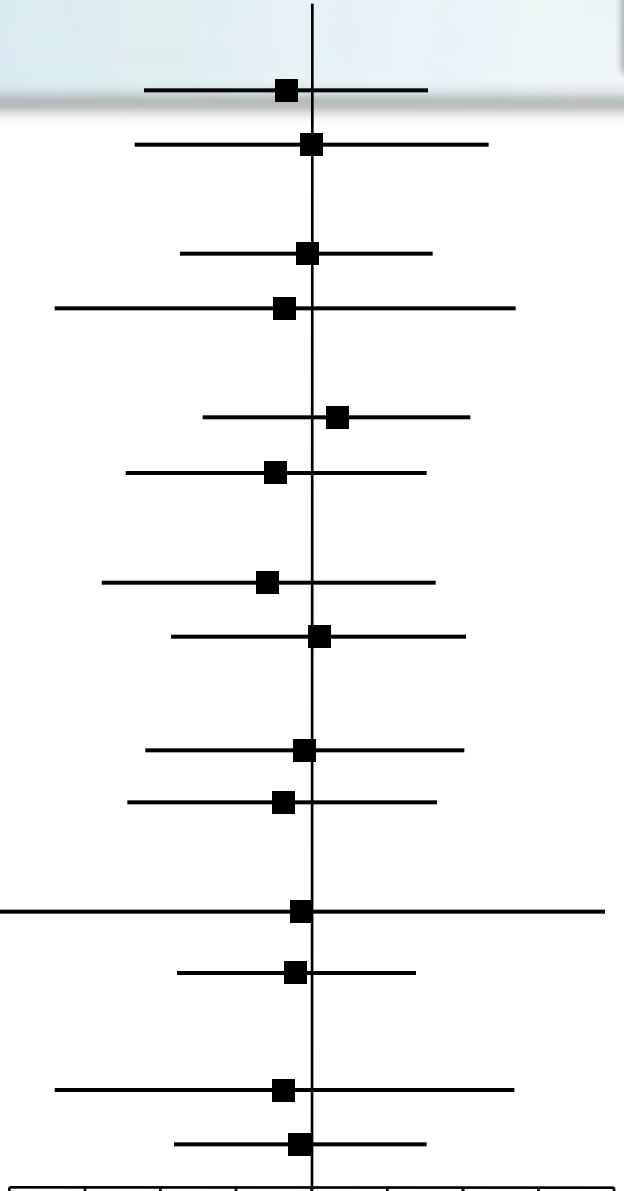
	Postconditioning	Conventional PCI	Difference (95% Confidence Interval)	P value
	n / total n (%)			
Age				
<65	87/211 (41.2%)	88/205 (42.9%)	-1.7 (-11.1 to 7.7)	0.73
≥65	51/130 (39.2%)	51/130 (39.2%)	0.0 (-11.7 to 11.7)	0.99
Sex				
Male	105/269 (39.0%)	98/249 (39.4%)	-0.3 (-8.7 to 8.0)	0.94
Female	33/72 (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.

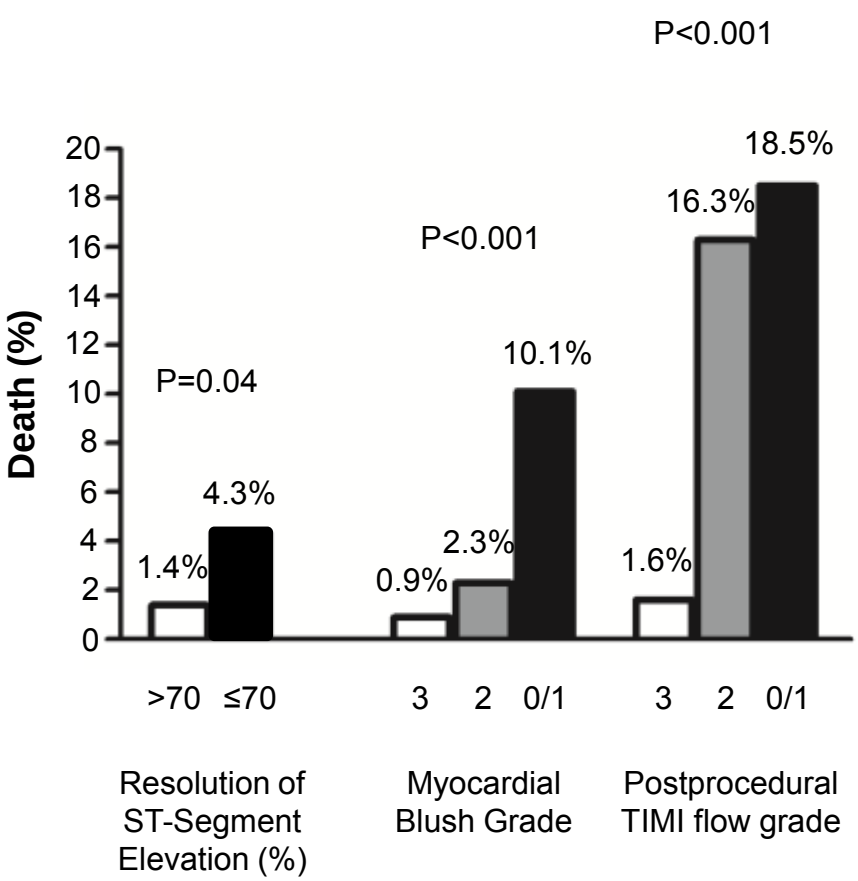
Clinical Outcomes at 1-month

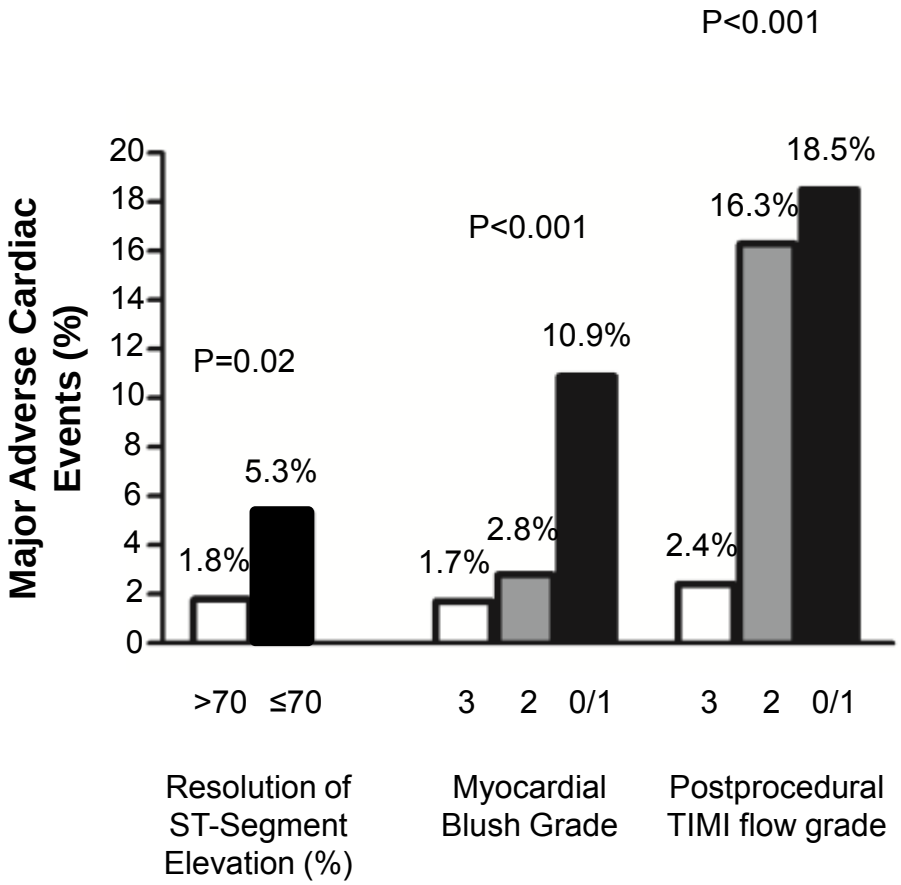
	Postconditioning (n=350)	Conventional PCI (n=350)	Relative risk (95% CI)*	P Value
Death	13 (3.7%)	10 (2.9%)	1.30 (0.58-2.92)	0.53
Cardiac death	10 (2.9%)	9 (2.6%)	1.11 (0.46-2.70)	0.82
Reinfarction	2 (0.6%)	1 (0.3%)	2.00 (0.18-21.74)	0.99†
Severe heart failure	2 (0.6%)	5 (1.4%)	0.40 (0.08-2.05)	0.29†
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.

Figure 2

Outcomes according to STR, postprocedural MBG and TIMI flow grade





Study Limitations

- The sample size was inadequate to make definite conclusion on clinical outcomes.
- This study was not a double-blinded study.
- Postconditioning was not performed per protocol (4 cycles of ballooning) in about 8% of patients in the postconditioning group.
- ECGs before and 30 minutes after the procedure were not available in 3.5% of all patients.
- We excluded patients with hemodynamic instability, cardiogenic shock, or left main lesion who might have lethal reperfusion injury and receive potential benefits from postconditioning.

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 were not significantly different between the randomized groups.
- Cardioprotective effect of ischemic postconditioning was not found in any of prespecified subgroups.