# Adjunctive Therapy to Reduce Infarct Size: Current and Future Challenges

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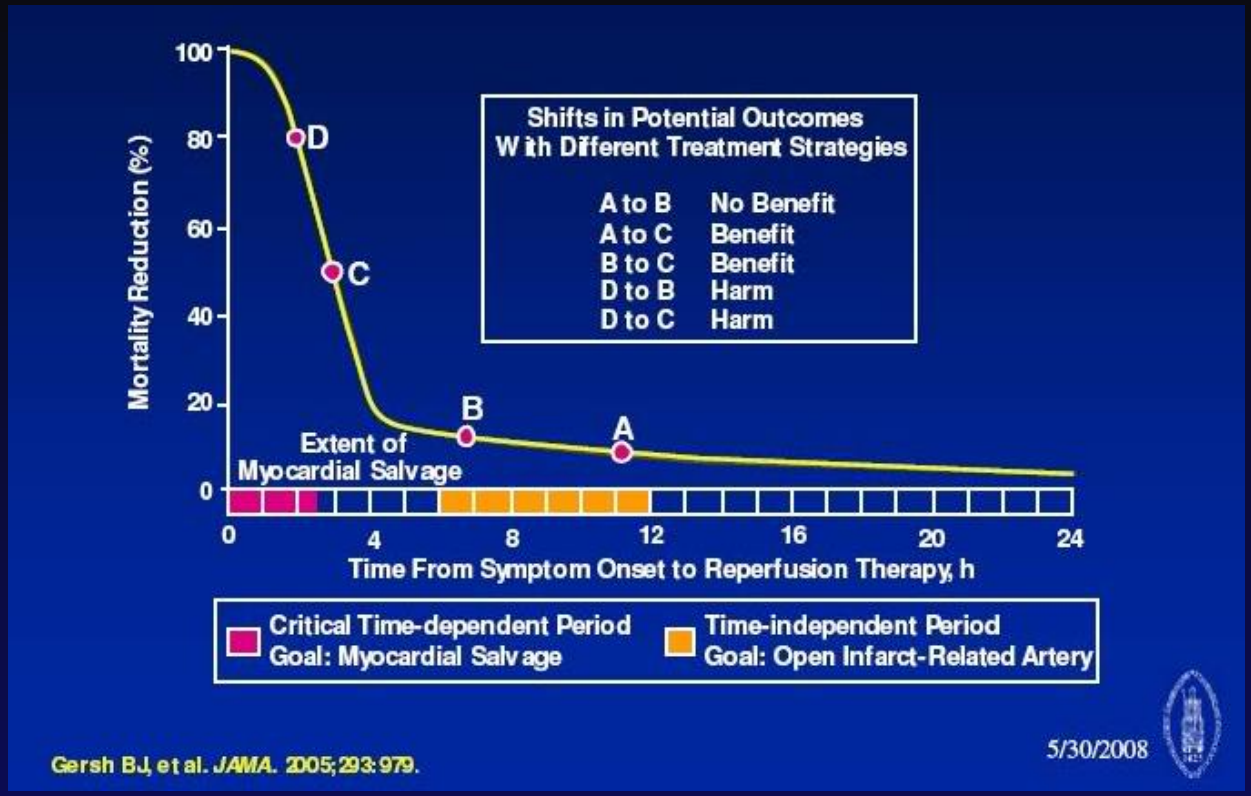
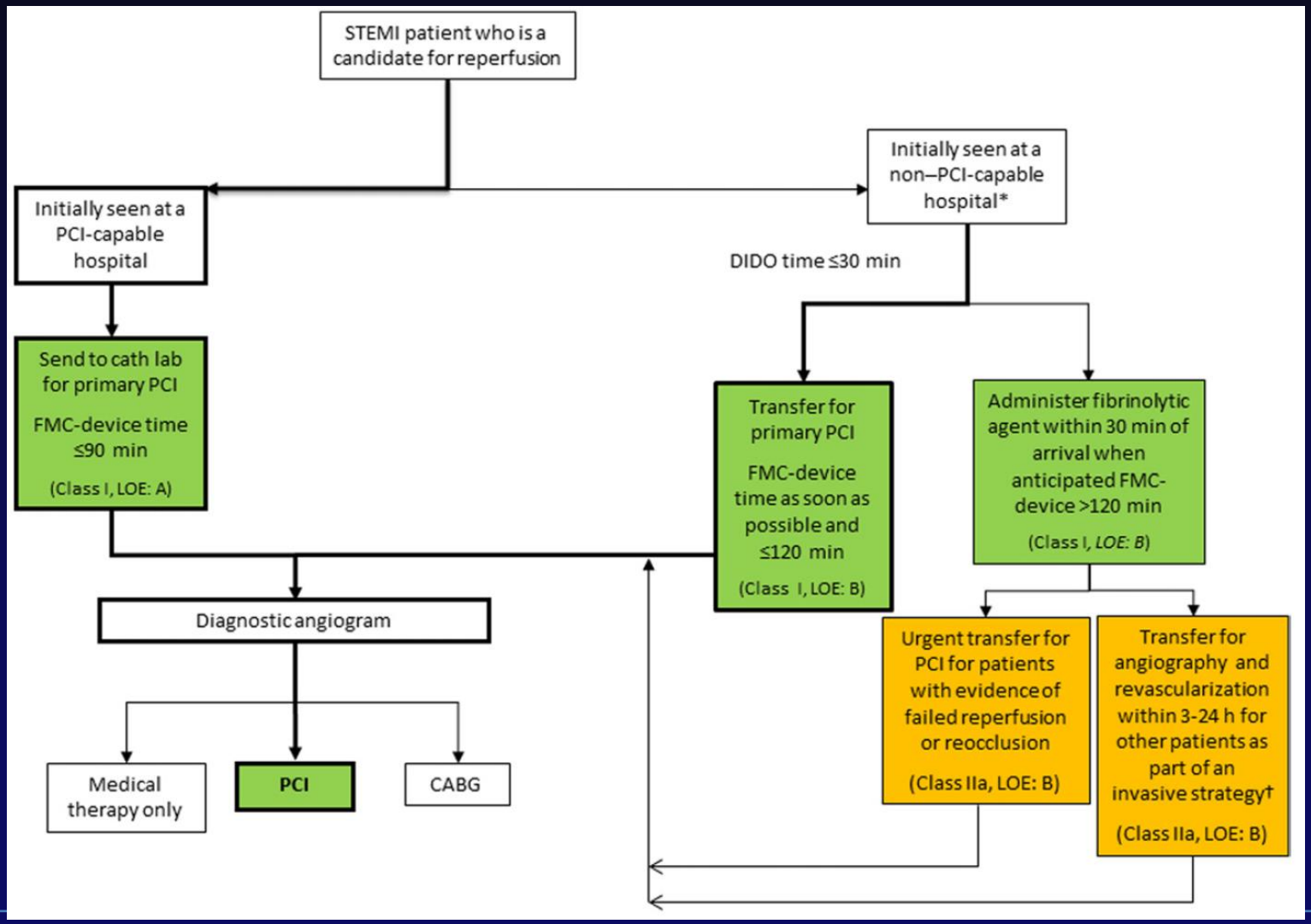

Mortality Reduction (%)
100
80
60
40
20
0
D
C
B
A
Extent of
Myocardial Salvage
Shifts in Potential Outcomes
With Different Treatment Strategies
A to B No Benefit
A to C Benefit
B to C Benefit
D to B Harm
D to C Harm
0
4
8
12
16
20
24
Time From Symptom Onset to Reperfusion Therapy, h
Critical Time-dependent Period
Goal: Myocardial Salvage
Time-independent Period
Goal: Open Infarct-Related Artery
Gersh BJ, et al. JAMA. 2005;293:979.
5/30/2008

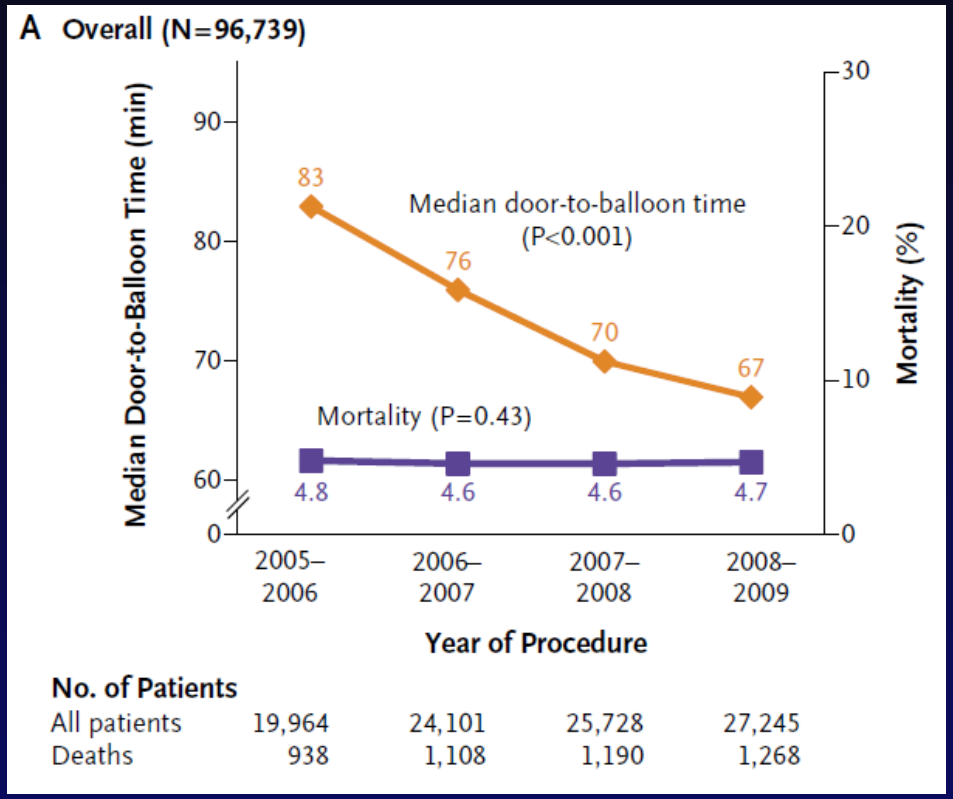
# 1. 빨리 뚫어야 한다

# 2013 ACC/AHA STEMI Guideline



# Reduction of D2B time below 90 min

## Despite improvement of D2B time, no change in in-hospital mortality rate

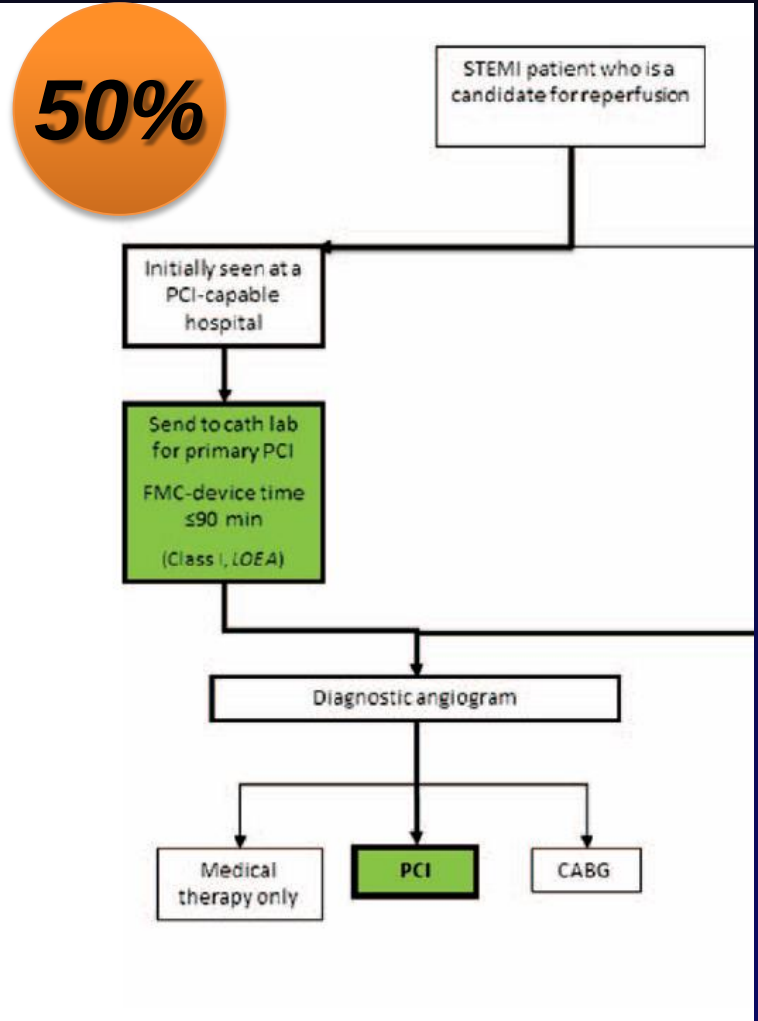



1. *Further decrease of D2B below < 90 min may not be beneficial for STEMI patients presenting directly to PCI-capable hospital.*
2. *But for transferred STEMI patients, it can reduce 1st door-to-device time*



Menees et al. NJEM 2013

# STEMI patient | 50% are transferred

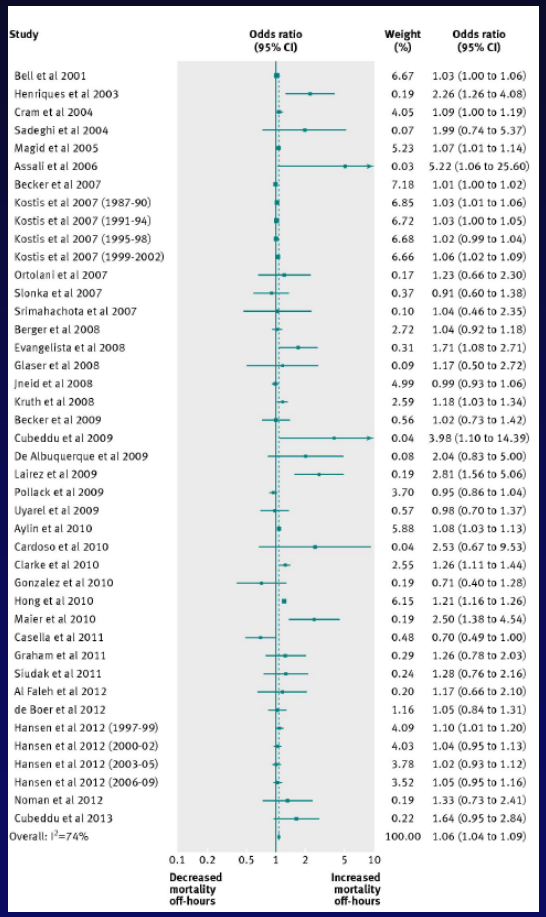


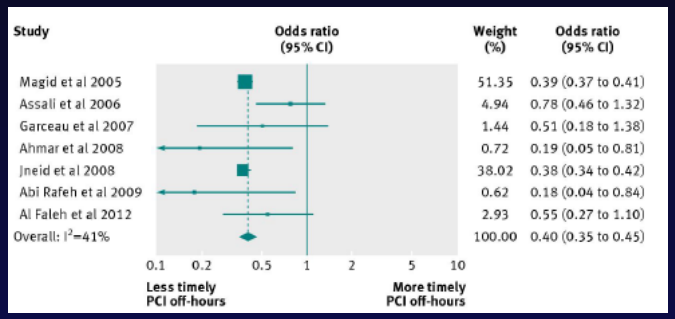
# Off-hour presentation | higher mortality

**Higher short-term mortality**
(OR 1.06, 95% CI 1.04-1.09)

**D2B < 90 min**
**(OR 0.40; 95% CI 0.35 to 0.45)**

**30-day MACE**
**(HR, 2.13; 95% CI, 1.26-3.60)**



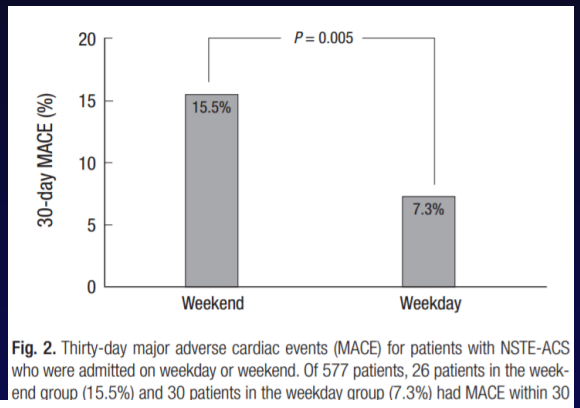




**Fig. 2.** Thirty-day major adverse cardiac events (MACE) for patients with NSTE-ACS who were admitted on weekday or weekend. Of 577 patients, 26 patients in the weekend group (15.5%) and 30 patients in the weekday group (7.3%) had MACE within 30

## The Effect of Admission at Weekends on Clinical Outcomes in Patients with Non-ST-segment Elevation Acute Coronary Syndrome and Its Contributing Factors


Hyun-Jin Kim,[1,2] Kwang-Il Kim,[1] Young-Seok Cho,[1] Jeehoon Kang,[1,2] Jin Joo Park,[1] Il-Young Oh,[1] Chang-Hwan Yoon,[1] Jung-Won Suh,[1] Tae-Jin Youn,[1] In-Ho Chae,[1] and Dong-Ju Choi[1]

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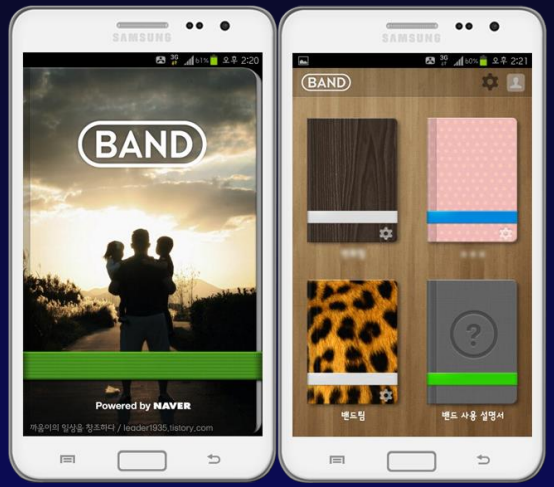
We investigated the effects of weekend admission on adverse cardiac events in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). Patients with NSTE-ACS treated with percutaneous coronary intervention (PCI) were divided into a "weekend group" and a "weekday group" according to the emergency room arrival time. The primary outcome was 30-day major adverse cardiac events (MACE) including cardiac death, recurrent myocardial infarction, repeat revascularization, and urgent PCI. Of 577 patients, 168 patients were allocated to the weekend and 409 patients to the weekday group. The incidence of 30-day MACE was significantly higher in the weekend group (Crude: 15.5% vs. 7.3%, $P = 0.005$; propensity score matched: 12.8% vs. 4.8%, $P = 0.041$). After adjustment for all the possible confounding factors, in Cox proportional hazard regression analysis, weekend admission was associated with a 2.1-fold increased hazard for MACE (HR, 2.13; 95% CI, 1.26-3.60, $P = 0.005$). These findings indicate that weekend admission of patients with NSTE-ACS is associated with an increase in 30-day adverse cardiac event.



**Keywords:** Coronary Artery Disease; Acute Coronary Syndrome; Percutaneous Coronary Intervention

# Smartphone & SNS | better communication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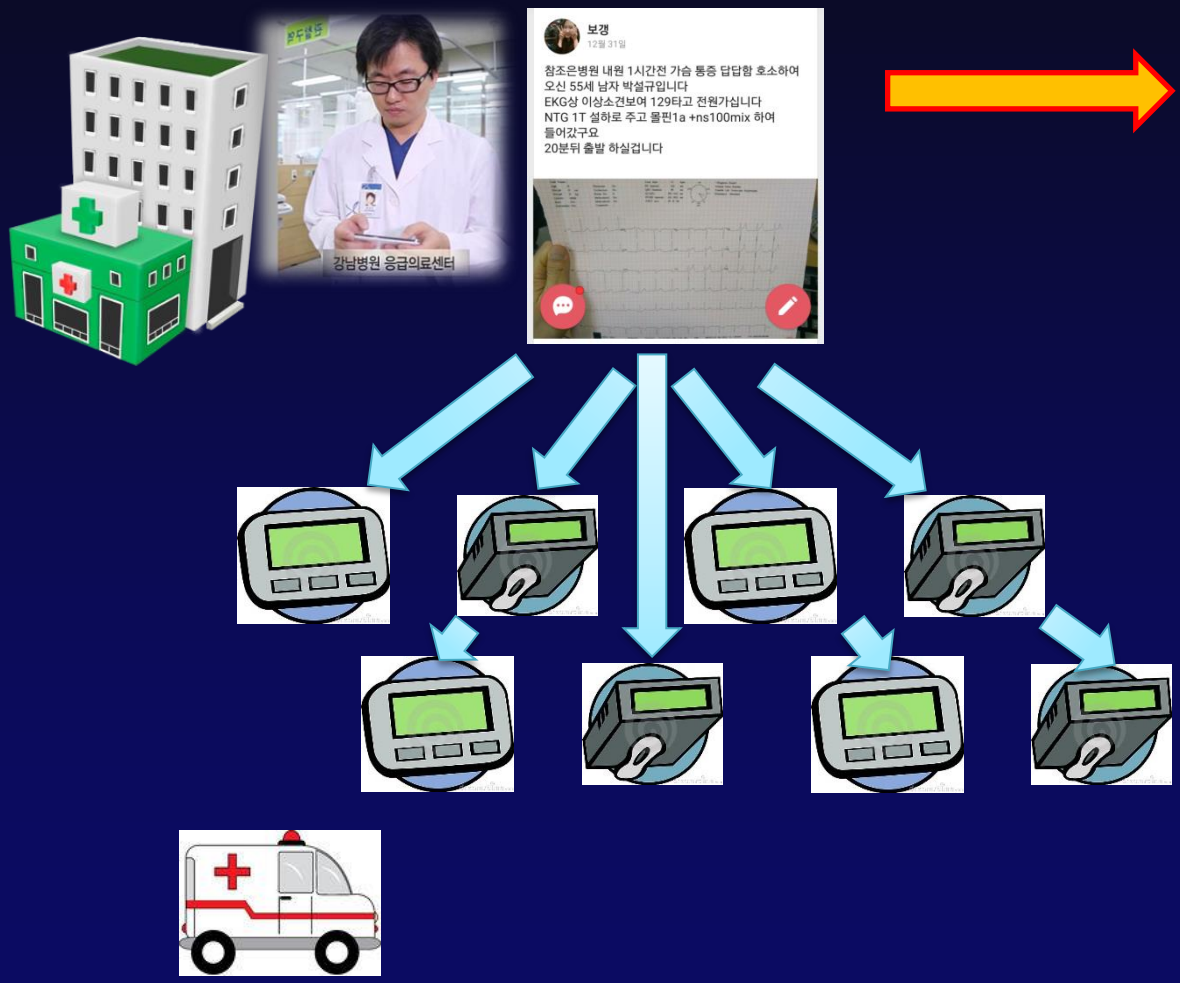
The widespread use of smart-phone and the social network system (SNS) enables an easy and rapid exchange of text and graphic information among the users.

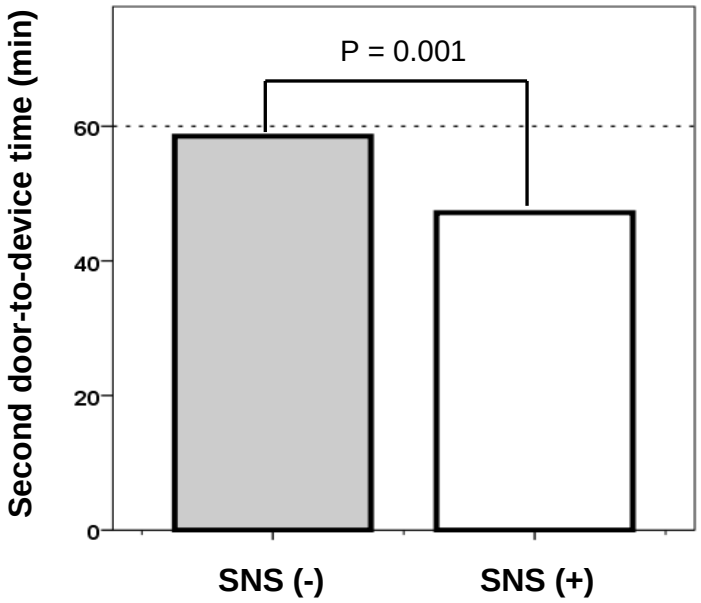
# STEMI activation with SNS use

Non PCI capable hospitals



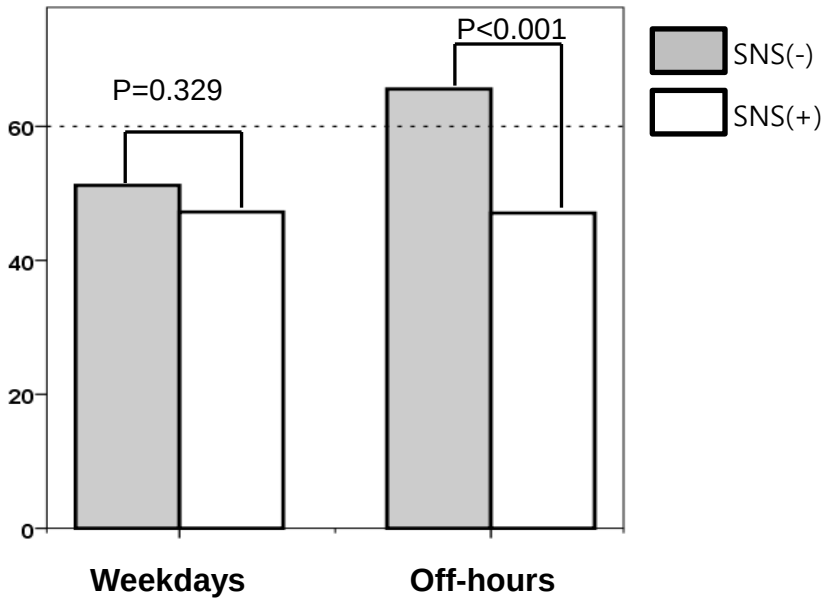
# SNS use reduced D2B time

## (A) All patients




57 min vs. 45 min

## (B) According to ED arrival time

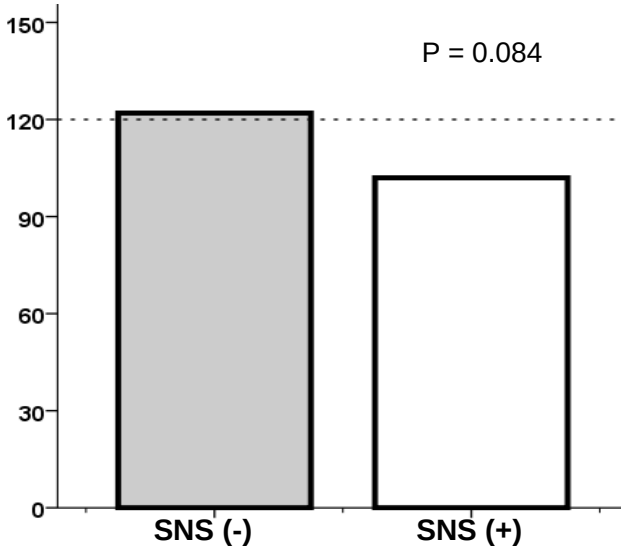



50 min vs. 45 min

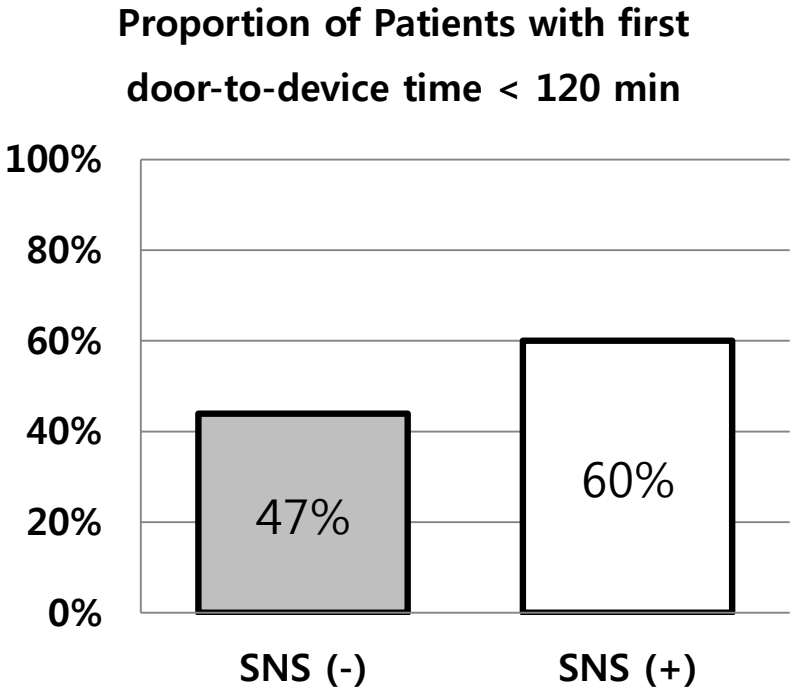
66 min vs. 46 min

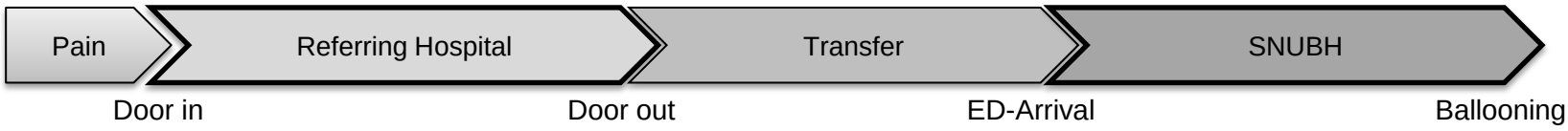
1. *Patients with SNS use had 12 min shorter D2B time.*
2. *During off hour the second D2B time can be reduced to the level of during weekdays.*

# SNS use reduces first door-to-device time




122 min vs. 102 min



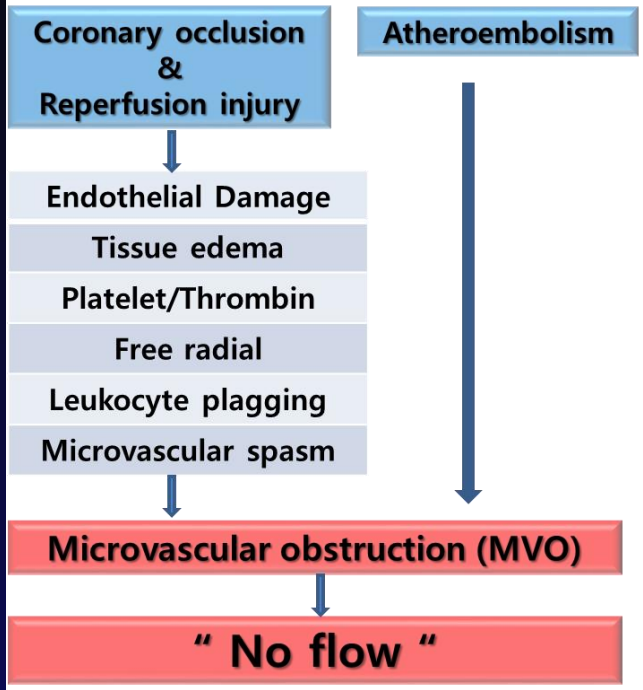



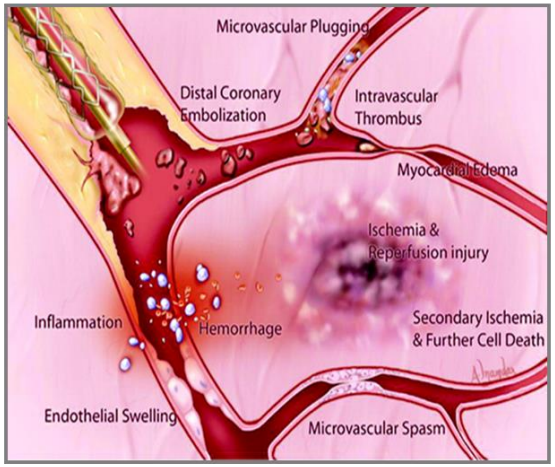

1. *SNS use can reduce the first D2B time by 20 min.*
2. *SNS use can increase the proportion of patients with first D2B by 13%.*



Park JJ, et al. JACC 2016

✓ No flow →" independent predictor of adverse clinical outcome"



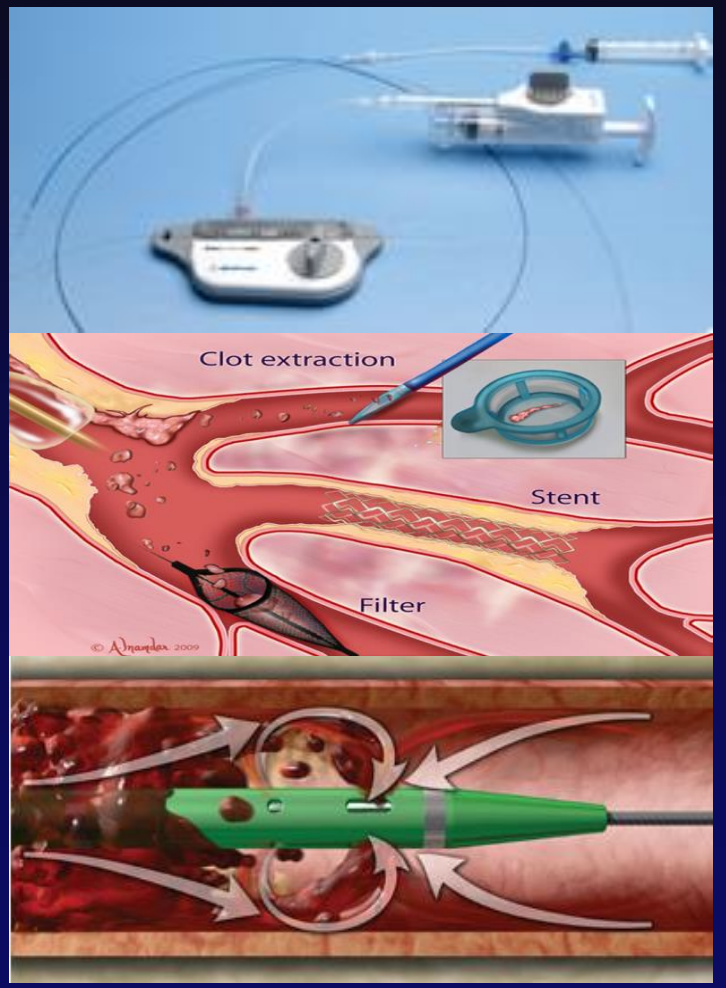




*Ronen Jaffe, et Al: Circulation 2008; 117*

# 2. 잘 뚫어야 한다

# Adjunctive devices for prevention of MVO

- ✓ **Distal protection**
  - GuardWire
  - FilterWire
  - SpideRx
  - Angioguard
- ✓ **Manual aspiration**
  - Export
  - Pronto
  - Driver
  - Rescue
  - TVAC
- ✓ **Mechanical thrombectomy**
  - Angiojet
  - X-sizer



# Effects of balloon-based distal protection during primary percutaneous coronary intervention on early and late infarct size and left ventricular remodeling: A pilot study using serial contrast-enhanced magnetic resonance imaging

Joo-Yong Hahn, MD, PhD,[a] Hycon-Cheol Gwon, MD, PhD,[a] Yeon Hyeon Choe, MD, PhD,[b] Il Rhee, MD,[a] Seung Hyuk Choi, MD, PhD,[a] Jin Ho Choi, MD, PhD,[a] Sang Hoon Lee, MD, PhD,[a] Kyong Pyo Hong, MD, PhD,[a] and Jung Euy Park, MD, PhD[a] *Seoul, South Korea*

**Background** Distal protection devices are effective in preventing distal embolization during primary percutaneous coronary intervention (PCI). We investigated whether balloon-based distal protection could reduce early and late infarct size and left ventricular (LV) remodeling using serial analysis of contrast-enhanced magnetic resonance imaging (CE-MRI).

**Methods** Patients undergoing primary PCI for ST-segment elevation myocardial infarction within 12 hours after symptom onset were randomized to a distal protection group (n = 19) or to a control group (n = 20). The primary end point was infarct size evaluated by the volume of delayed hyperenhancement on CE-MRI at 3 days. The secondary end point included infarct size on CE-MRI at 6 months and LV remodeling assessed by the change between LV end-diastolic volume on CE-MRI at 3 days (baseline) and 6 months (follow-up).

**Results** Percutaneous coronary intervention procedures were fully protected with balloon-based distal protection in all patients of the protection group. Infarct size was similar in the distal protection group and the control group at baseline (25.9 ± 7.8% vs 26.1 ± 8.2%; $P = .93$) and at follow-up (21.4 ± 9.1% vs 18.5 ± 9.1%; $P = .51$). The change in LV end-diastolic volume was 10.5 ± 32.2 mL in the distal protection group and 8.9 ± 40.7 mL in the control group ($P = .86$). There was no significant difference in the 6-month rate of major adverse cardiac events between groups (none in the distal protection group and 4 patients in the control group; $P = .11$).

**Conclusions** Serial CE-MRI showed that the balloon-based distal protection during primary PCI did not reduce early and late infarct size or prevent LV remodeling. (Am Heart J 2007;153:665.e1-665.e8.)

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International Journal of Cardiology

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# Distal protection device aggravated microvascular obstruction evaluated by cardiac MR after primary percutaneous intervention for ST-elevation myocardial infarction

Chang-Hwan Yoon [a], Woo-Young Chung [b], Jung-Won Suh [a], Young-Suk Cho [a], Tae-Jin Youn [a], Eun-Ju Chun [c], Sang-Il Choi [c], In-Ho Chae [a], Dong-Ju Choi [a,*]

[a] Division of Cardiology, Department of Internal Medicine, Seoul National University Bundang Hospital, Republic of Korea
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ABSTRACT

*Background:* Protection of distal embolization by balloon occlusion and thrombus aspiration has not improved microvascular circulation nor decreased myocardial injury during primary percutaneous intervention (PCI) for ST-elevation myocardial infarction (STEMI) in randomized trials. In a prospective randomized trial, we investigated the mechanism of the poor effect of distal protection and thrombus aspiration (DP–TA) in 126 patients with STEMI.

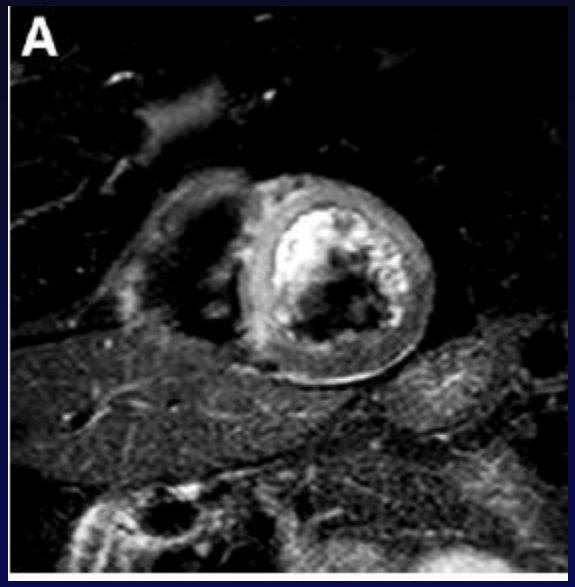
*Methods:* Patients with first-diagnosed STEMI were randomly assigned to DP–TA pretreatment or conventional PCI (c-PCI). Primary endpoint was reduced left ventricular end-diastolic volume (LVEDV) measured by MRI at post-PCI and 6 months after PCI. Secondary end points were infarct ratio (infarct size to entire LV size) by delayed enhancement (DE), area at risk (AAR) ratio (AAR to entire LV size) by T2 high signal, microvascular occlusion index (MVO) ratio (MVO to entire LV size) by DE, and myocardial salvage index (MSI: (AAR − infarct size) * 100/AAR) using cardiac magnetic resonance imaging (MRI) within 3 days after PCI.

*Results:* Baseline characteristics of the patients including cardiovascular risk factors and lesion characteristics were similar between the two groups. DT–PA failed to improve LV remodeling at 6 months (LVEDV 140 ± 39 vs 133 ± 37 in c-PCI group, p = 0.418). Infarct ratio, AAR ratio and MSI were not statistically different between DP–TA group and c-PCI group. However, MVO ratio was significantly larger in DP–TA group than in c-PCI group (2.4 ± 2.7 vs 1.1 ± 1.9, p = 0.045).

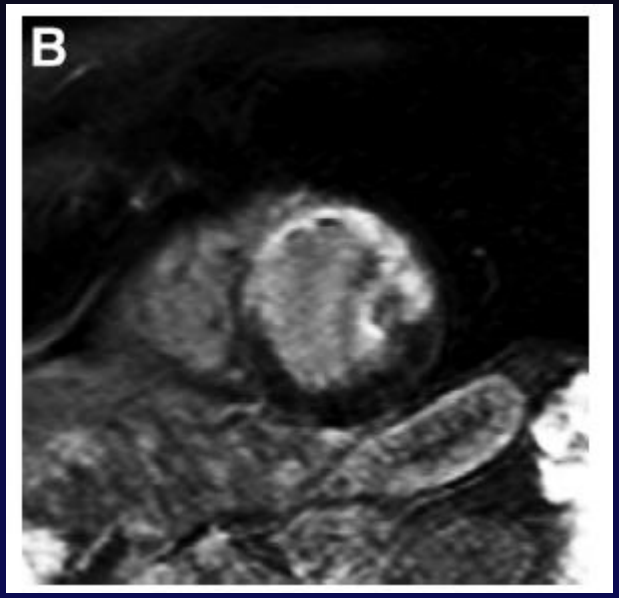
*Conclusion:* DP–TA was potentially hazardous in primary PCI for STEMI by increasing MVO. DP–TA should not be used in STEMI.

# Method to evaluate myocardial salvage

## T2W and DE CMR imaging




✓ T2W CMR : hyperintense
→ area at risk (AAR)




✓ DE CMR : infarct size (IS), MVO

✓ Enabling retrospective evaluation of myocardial salvage

: myocardial salvage index : (AAR-IS)x100 / AAR

ranging from 0% (aborted infarct) – 88%

*Wright J. et al. J Am Coll Cardiol Img 2009;2:825–31)*

# Aspiration thrombectomy X IV Gp IIb/IIIa Rc antagonist

## INFUSE-AMI Trial

**Table 3.** Thirty-Day Cardiac Magnetic Resonance Imaging Results for the Pooled Randomized Groups

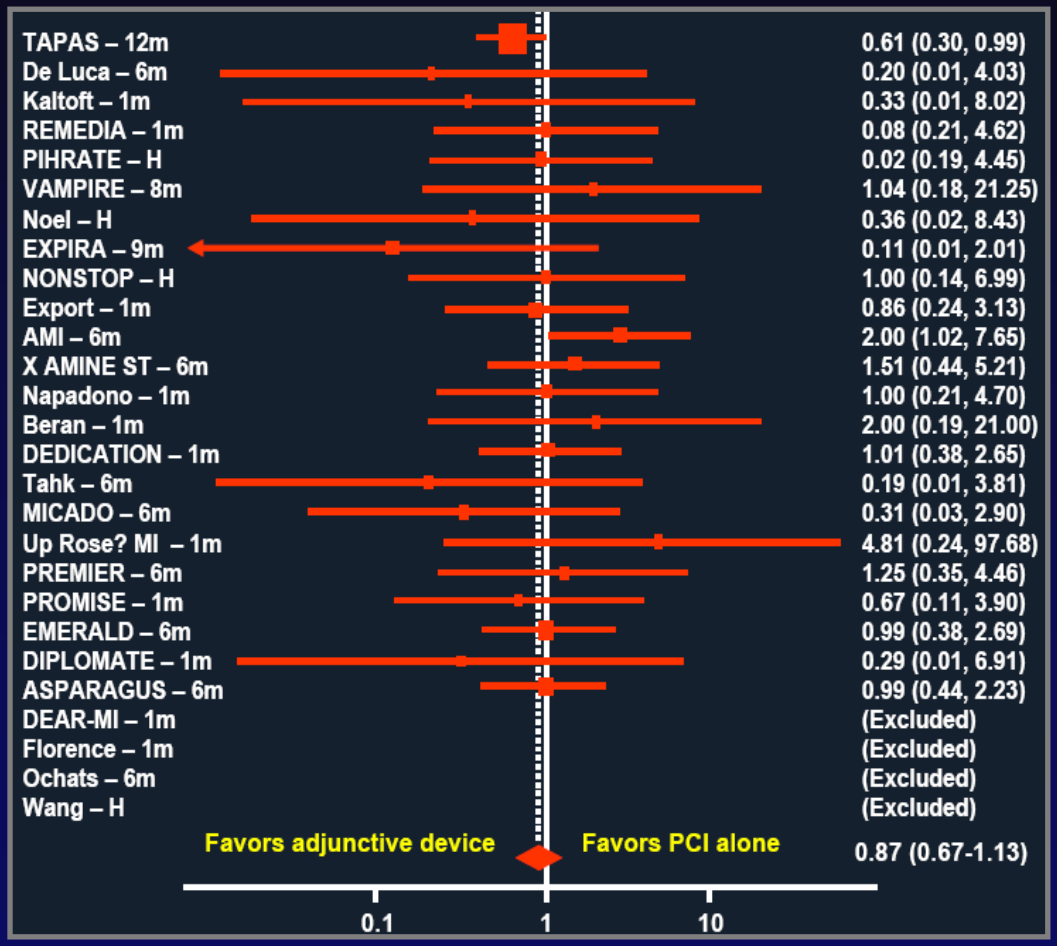
| | Intracoronary Abciximab[a] (n = 188) | No Intracoronary Abciximab[a] (n = 184) | *P* Value | Aspiration Thrombectomy[b] (n = 186) | No Aspiration Thrombectomy[b] (n = 186) | *P* Value |
|---|---|---|---|---|---|---|
| Infarct size, median [IQR], % of total LV mass[c] | 15.1 [6.8-22.7] (n = 181) | 17.9 [10.3-25.4] (n = 172) | .03 | 17.0 [9.0-22.8] (n = 174) | 17.3 [7.1-25.5] (n = 179) | .51 |
| Total LV myocardial mass, median [IQR], g | 128.6 [106.6-152.4] (n = 181) | 130.4 [109.9-155.9] (n = 172) | .55 | 128.3 [108.9-149.8] (n = 174) | 132.0 [107.6-156.1] (n = 179) | .50 |
| Infarct mass, median [IQR], g | 18.7 [7.4-31.3] (n = 184) | 24.0 [12.1-34.2] (n = 175) | .03 | 20.3 [9.7-31.7] (n = 178) | 21.0 [9.1-34.1] (n = 181) | .36 |
| Total abnormal wall motion score, median [IQR] | 7.0 [2.0-10.0] (n = 188) | 8.0 [3.0-10.0] (n = 184) | .08 | 7.5 [2.0-10.0] (n = 186) | 7.5 [2.0-10.0] (n = 186) | .89 |
| Left ventricular ejection fraction, median [IQR], % | 50.2 [44.2-57.9] (n = 182) | 48.9 [42.3-56.7] (n = 179) | .22 | 49.6 [43.3-56.8] (n = 181) | 49.5 [41.8-57.6] (n = 180) | .66 |

Abbreviations: cMRI, cardiac magnetic resonance imaging; LV, left ventricular.
[a] Pooled, either with or without aspiration thrombectomy
[b] Pooled, either with or without intracoronary abciximab.
[c] Primary end point.

*Gregg W. Stone, et al. JAMA. 2012*

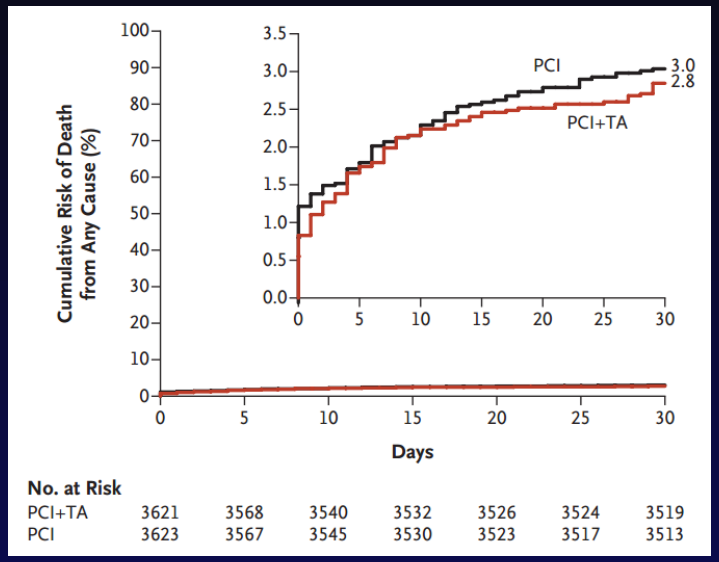
# Studies using adjunctive device in STEMI

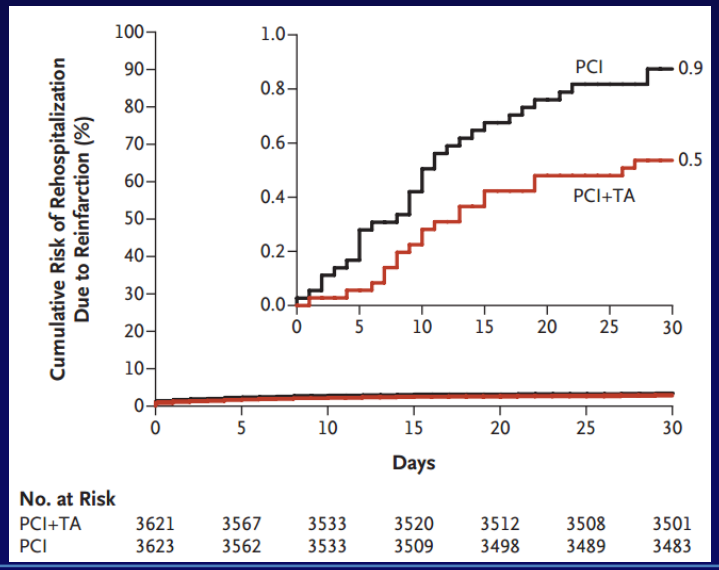
- ✓ **Distal protection**
  - GuardWire
  - FilterWire
  - SpideRx
  - Angioguard
- ✓ **Manual aspiration**
  - Export
  - Pronto
  - Driver
  - Rescue
  - TVAC
- ✓ **Mechanical thrombectomy**
  - Angiojet
  - X-sizer



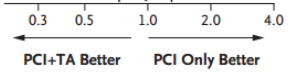

*Anthony A. Bavry, et al. European Heart Journal. 2008*

# TASTE study




| Subgroup | PCI+TA | PCI Only | Hazard Ratio (95% CI) | P Value for Interaction |
|---|---|---|---|---|
| | *no. of deaths/total no. of patients* | | | |
| All patients | 103/3621 | 110/3623 | 0.94 (0.72–1.22) | |
| Sex | | | | 0.51 |
| Female | 37/900 | 45/920 | 0.84 (0.54–1.29) | |
| Male | 66/2721 | 65/2703 | 1.01 (0.72–1.42) | |
| Age | | | | 0.09 |
| >65 yr | 95/1955 | 92/1875 | 0.99 (0.74–1.32) | |
| ≤65 yr | 8/1666 | 18/1748 | 0.47 (0.20–1.07) | |
| Diabetes | | | | 0.55 |
| Yes | 23/448 | 21/453 | 1.11 (0.61–2.00) | |
| No | 78/3155 | 86/3155 | 0.91 (0.67–1.23) | |
| Smoker | | | | 0.46 |
| Yes | 14/1083 | 23/1173 | 0.66 (0.34–1.28) | |
| No | 70/2336 | 76/2211 | 0.87 (0.63–1.20) | |
| Previous myocardial infarction | | | | 0.81 |
| Yes | 13/402 | 14/439 | 1.01 (0.48–2.15) | |
| No | 85/3172 | 92/3138 | 0.91 (0.68–1.23) | |
| Previous PCI | | | | 0.60 |
| Yes | 6/337 | 9/362 | 0.71 (0.25–2.00) | |
| No | 97/3284 | 101/3261 | 0.95 (0.72–1.26) | |
| Time from symptom onset to PCI | | | | 0.98 |
| >2 hr | 73/2308 | 77/2308 | 0.95 (0.69–1.30) | |
| ≤2 hr | 13/800 | 14/805 | 0.94 (0.44–1.99) | |
| Time from ECG to PCI | | | | 0.66 |
| >Median | 61/1765 | 61/1732 | 0.98 (0.69–1.40) | |
| ≤Median | 42/1816 | 49/1843 | 0.87 (0.58–1.31) | |
| Target vessel | | | | 0.73 |
| Left anterior descending artery | 60/1467 | 58/1449 | 1.02 (0.71–1.16) | |
| Left circumflex artery | 10/494 | 13/471 | 0.73 (0.32–1.67) | |
| Right coronary artery | 24/1436 | 28/1443 | 0.86 (0.50–1.49) | |
| Proximal lesion | | | | 0.29 |
| Yes | 94/2903 | 96/2935 | 0.99 (0.74–1.32) | |
| No | 9/718 | 14/688 | 0.62 (0.27–1.42) | |
| Thrombus grade | | | | 0.93 |
| 4–5 | 41/1138 | 41/1078 | 0.95 (0.61–1.46) | |
| 0–3 | 61/2451 | 64/2499 | 0.97 (0.68–1.38) | |
| TIMI grade before PCI | | | | 0.36 |
| 0–1 | 91/2821 | 92/2811 | 0.98 (0.74–1.32) | |
| 2–3 | 12/792 | 18/809 | 0.68 (0.33–1.41) | |
| Bivalirudin therapy | | | | 0.85 |
| Yes | 86/2874 | 92/2835 | 0.92 (0.69–1.24) | |
| No | 17/746 | 18/782 | 0.99 (0.51–1.92) | |
| Glycoprotein IIb/IIIa blocker therapy | | | | 0.36 |
| Yes | 10/558 | 17/630 | 0.66 (0.30–1.44) | |
| No | 93/3063 | 93/2993 | 0.98 (0.73–1.30) | |



# BMS vs DES in STEMI

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## Comparison of drug-eluting versus bare-metal stent implantation in ST-elevation myocardial infarction patients with renal insufficiency: Results from the national registry in Korea

Kyung-Hee Kim [a,1], Bon-Kwon Koo [a,1], Hee-Suk Min [a], Sue K. Park [b], Chi-Hoon Kim [a], Kyung-Woo Park [a], Byung-Joo Park [b], Myung-Ho Jeong [c], Myeong-Chan Cho [d], Sang-Rok Lee [e], Sung-Chull Chae [f], In-Whan Seong [g], Dong-Ju Choi [h], Hyo-Soo Kim [a,*]

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[b] Medical Research Collaborating Center, Seoul National University Hospital, Republic of Korea
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[d] Department of Internal Medicine, Choongbook National University Hospital, Republic of Korea
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ABSTRACT

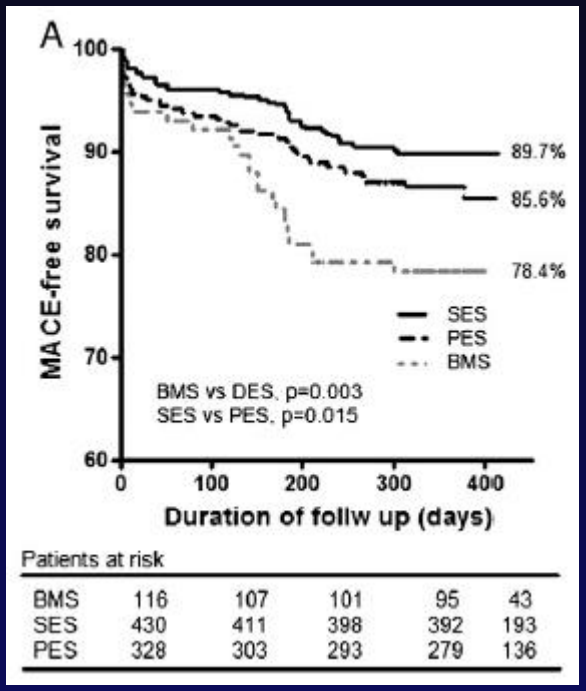
*Introduction:* It is unknown whether drug-eluting stents (DES), in comparison with bare-metal stents (BMS), improve clinical outcomes of ST-elevation myocardial infarction (STEMI) patients with renal insufficiency. We aimed to compare the clinical outcomes of BMS versus DES, as well as sirolimus-eluting stents (SES) versus paclitaxel-eluting stents (PES), in STEMI patients with renal insufficiency.

*Methods:* From the Korea Acute Myocardial Infarction Registry, 874 STEMI patients with renal insufficiency (glomerular filtration rate < 60 ml/min) comprising 116 patients with BMS and 758 patients with DES (430 SES and 328 PES) implantation were selected. Major adverse cardiac events (MACE) within 1 year, defined as composite of all-cause mortality, nonfatal myocardial infarction and target lesion revascularization were compared. In addition to multivariate adjusted analysis, propensity analysis for stent choice was performed.

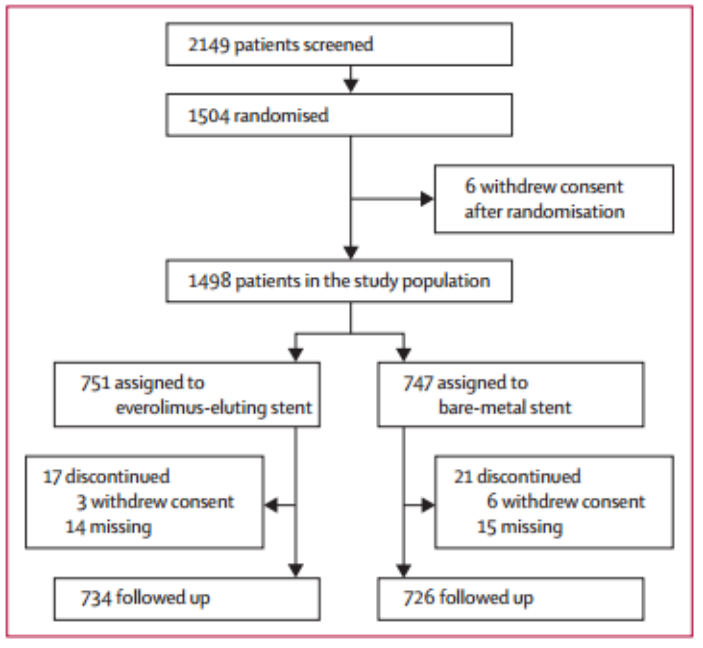
*Results:* With a median follow-up of 342 days, 116 MACE occurred. MACE was more frequent in the BMS group than in the DES group before (HR [95% CI] = 2.3 [1.3–3.8]) and after propensity score matching (HR [95% CI] = 2.0 [1.0–3.8]). The difference of MACE was mainly driven by a higher rate of target lesion revascularization rate in the BMS group. In comparison between SES and PES, there was no significant difference between the 2 groups in propensity score-matched populations (HR [95% CI] = 0.7 [0.4–1.1]).

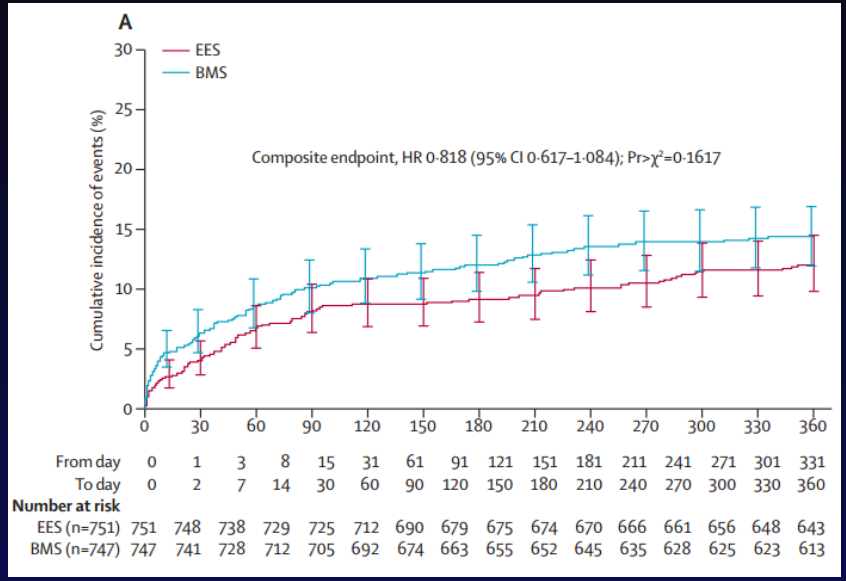
*Conclusions:* In STEMI patients with renal insufficiency, DES implantation exhibits a favorable 1 year clinical outcomes than BMS implantation, however, no difference was found between SES and PES.

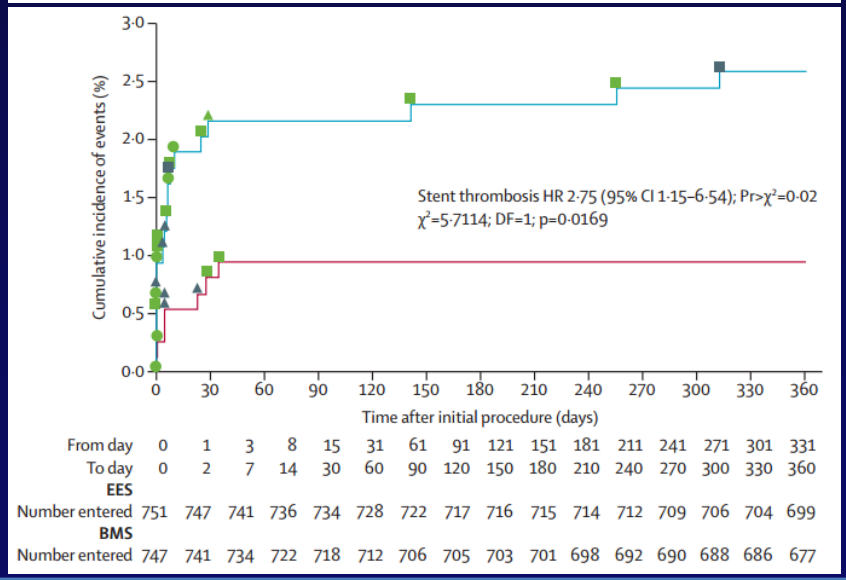




# BMS vs DES in STEMI

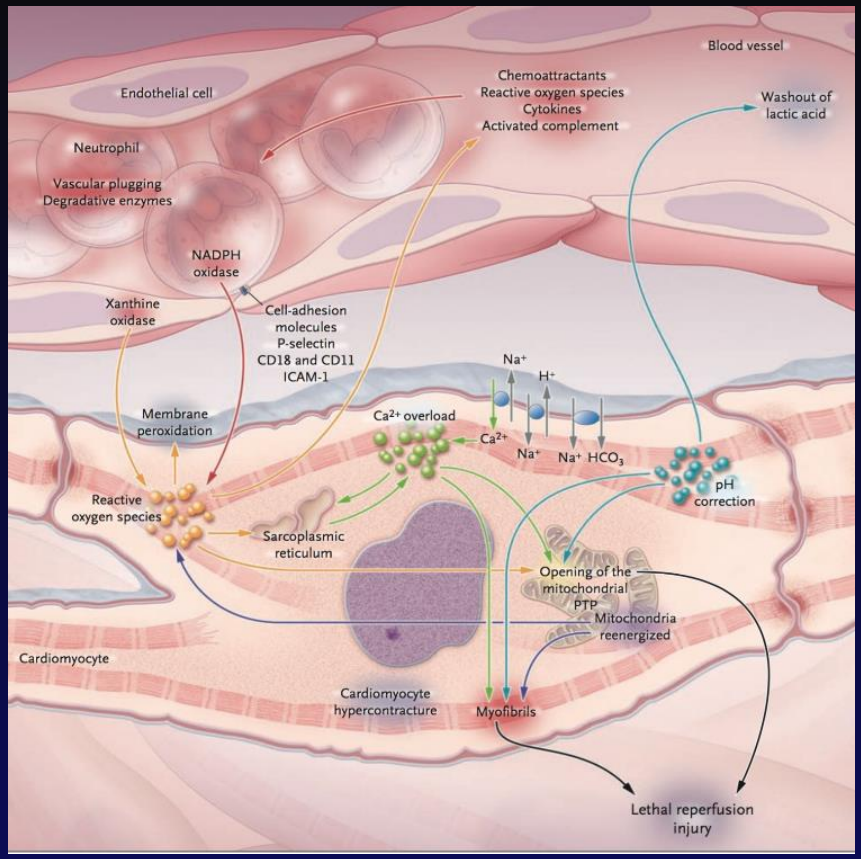




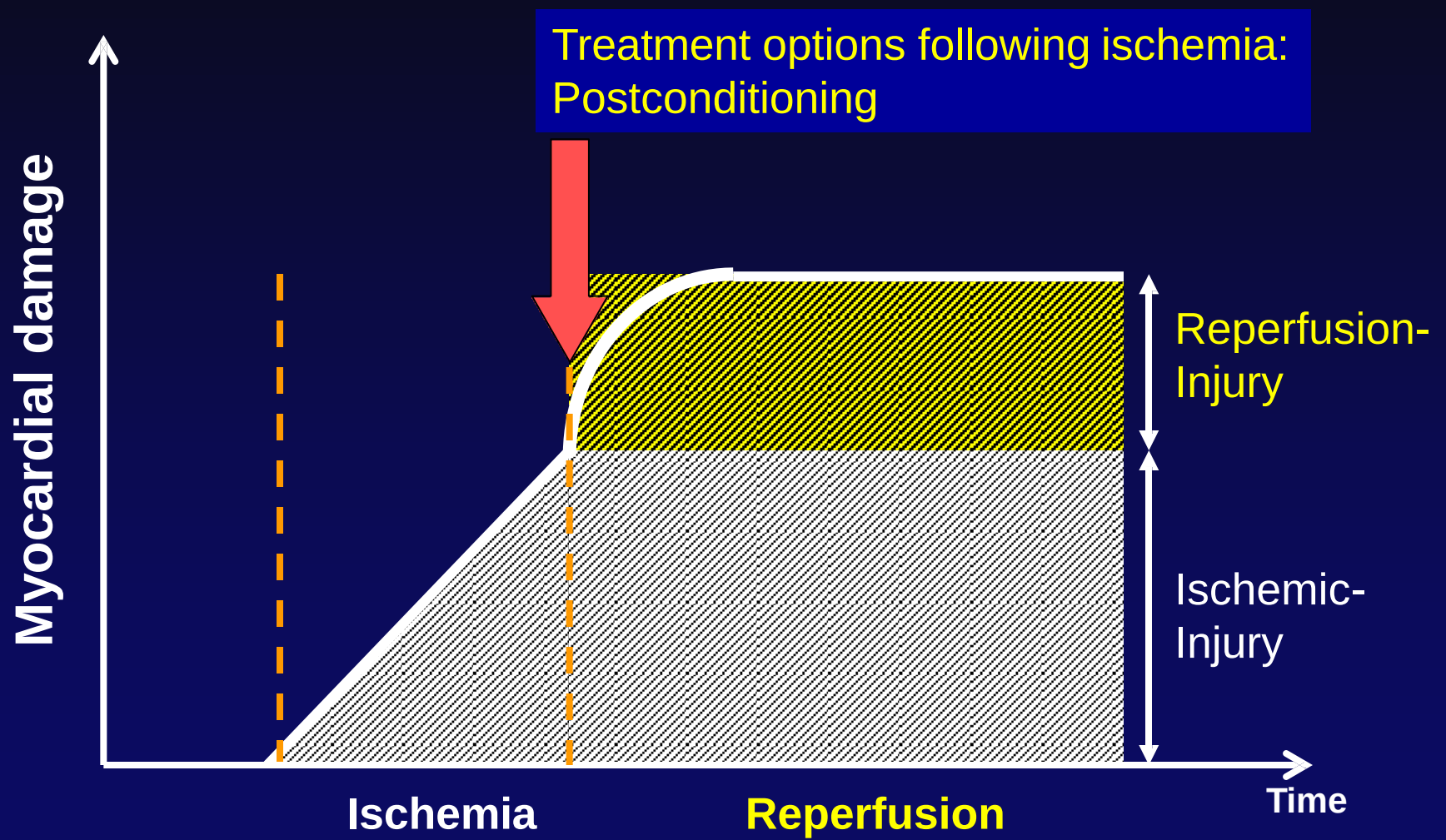

*Sabate M, et al. Lancet 2012*



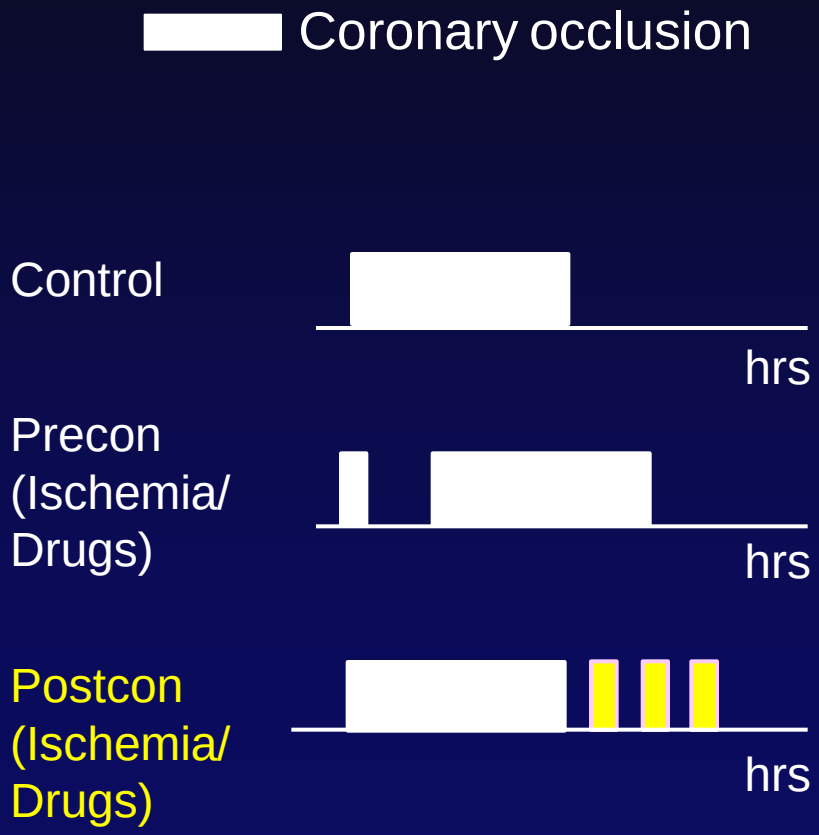

*2008; 117*

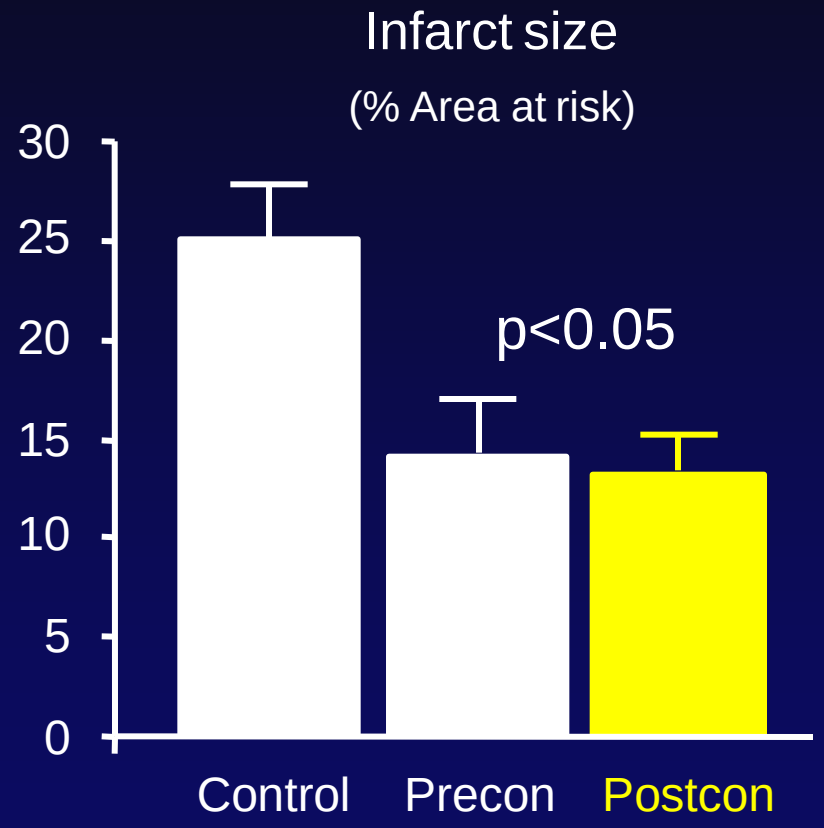
# 3. 허혈-재관류 손상을 줄여 보자

# Ischemia-reperfusion injury

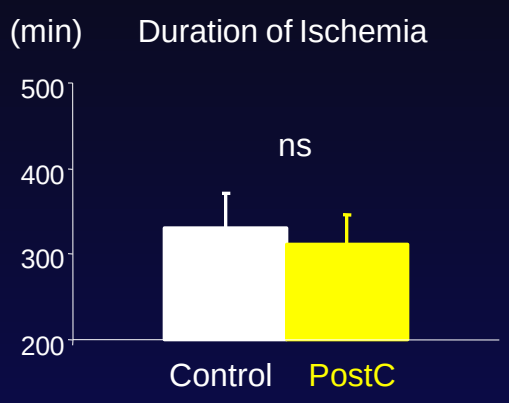


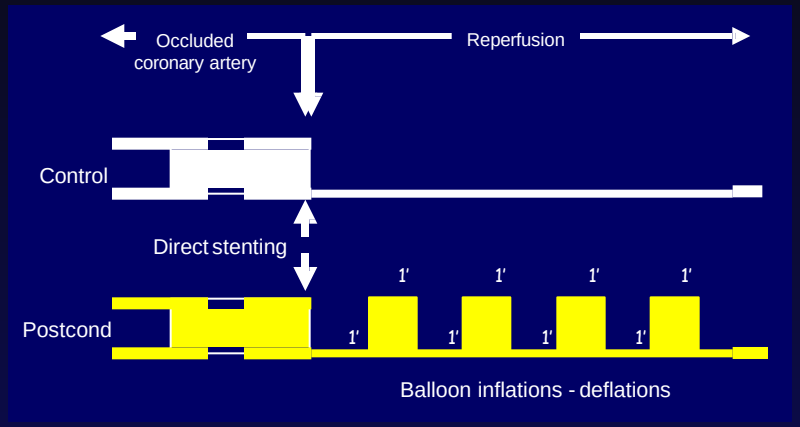
# Pre- and Post-conditioning

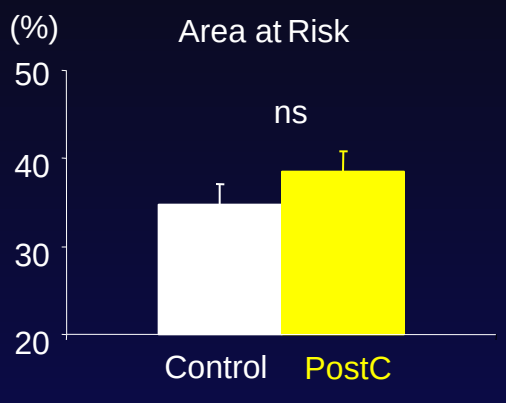


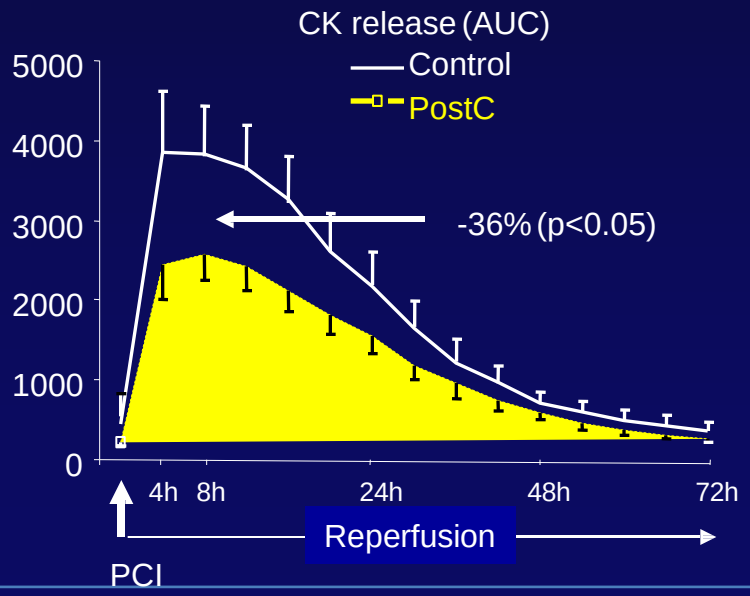



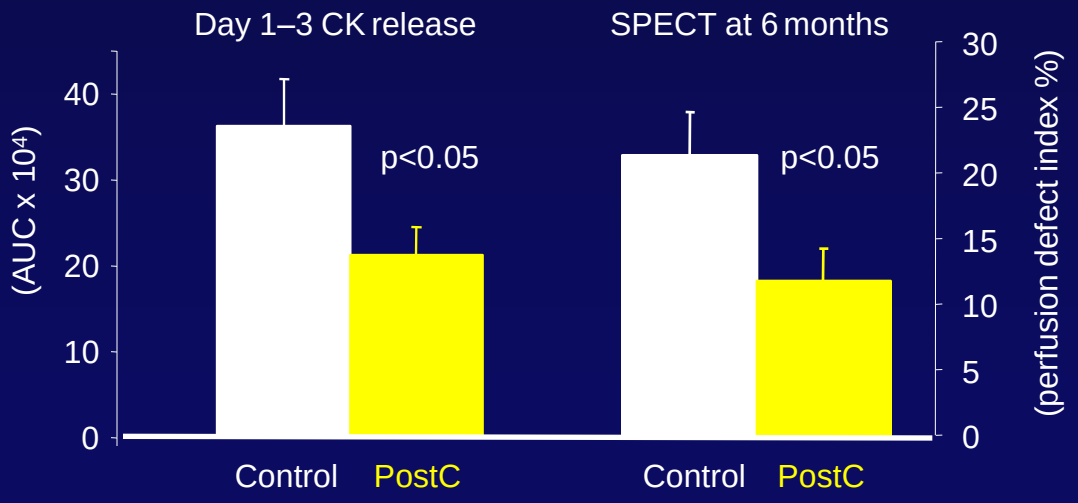
# Ischemic postconditioning






Staat et al., Circulation 112: 2143-2148, 2005
Thibault et al., Circulation 117:1037-44, 2008

# Ischemic post-conditioning

## Ischemic conditioning after PCI shows no benefit in STEMI patients

OCTOBER 26, 2012 Reed Miller



TCT **Miami, FL** - Ischemic postconditioning following PCI of ST-segment-elevation MI patients did not improve outcomes compared with PCI without this extra procedure in the 700-patient randomized **POST** trial [1].

Thirty-day follow-up results from POST, presented by **Dr Joo-Yong Hahn** (Samsung Medical Center, Seoul, Korea) here at TCT 2012, showed that ischemic postconditioning of the target vessel with four one-minute balloon occlusions after primary PCI did not improve myocardial reperfusion compared with conventional primary PCI and that the clinical outcomes one month after the procedure were not significantly different between the 350 patients randomized to postconditioning and the 350 randomized to standard PCI. Also, no cardioprotective effects of ischemic postconditioning appeared in any of the prespecified subgroups, he said.

Dr Joo-Yong Hahn

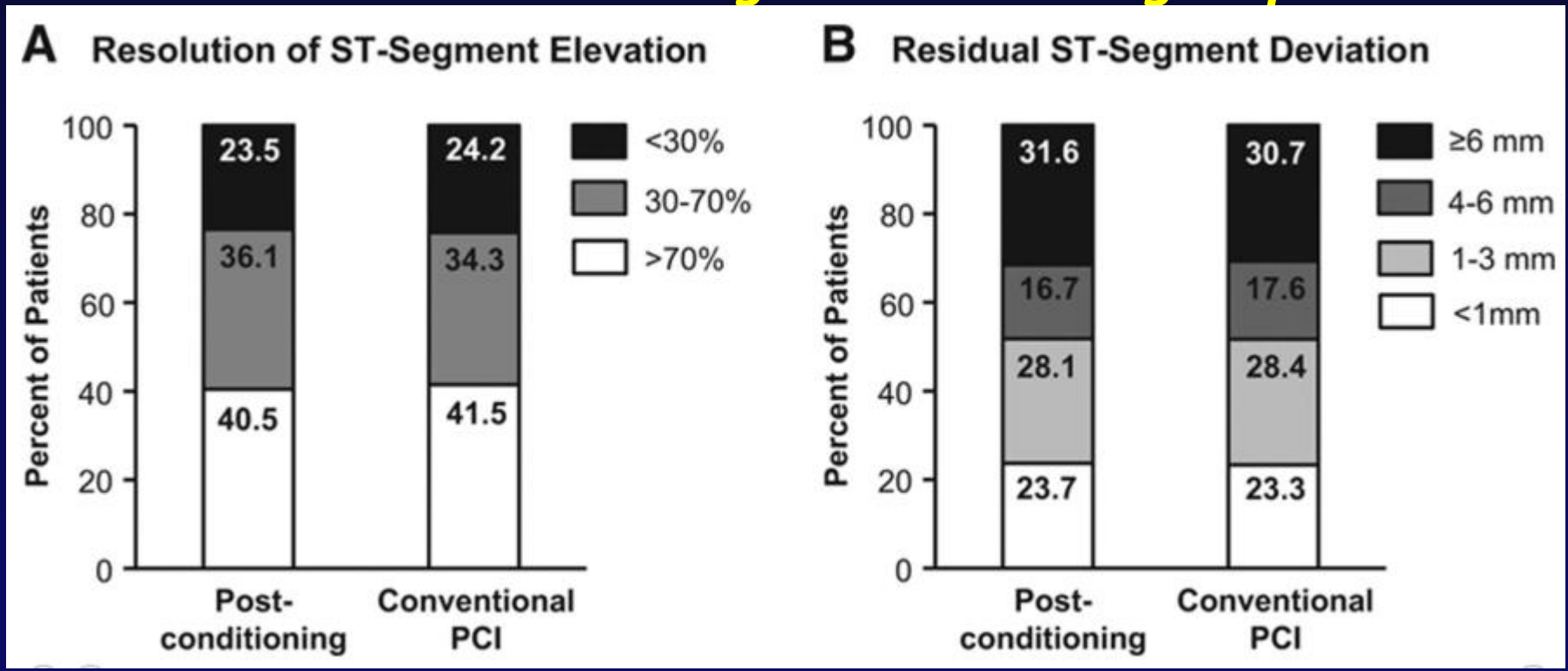
A 2005 study by Staat et al in 30 patients showed that postconditioning reduced enzymatic infarct size in STEMI patients undergoing primary PCI [2]. Previous research suggested that postconditioning inhibits opening of the mitochondrial permeability transition pore, which is involved in reperfusion injury after ischemia reperfusion.

However, subsequent postconditioning studies using contrast-enhanced MRI to examine infarct size have shown inconsistent results. "Previous studies showing the cardioprotective effects of preconditioning have several limitations—they did not reflect current standard practice patterns of primary PCI," Hahn said. "They performed only direct stenting and thrombus aspiration, and glycoprotein IIb/IIIa inhibitors were either not used or used seldom."

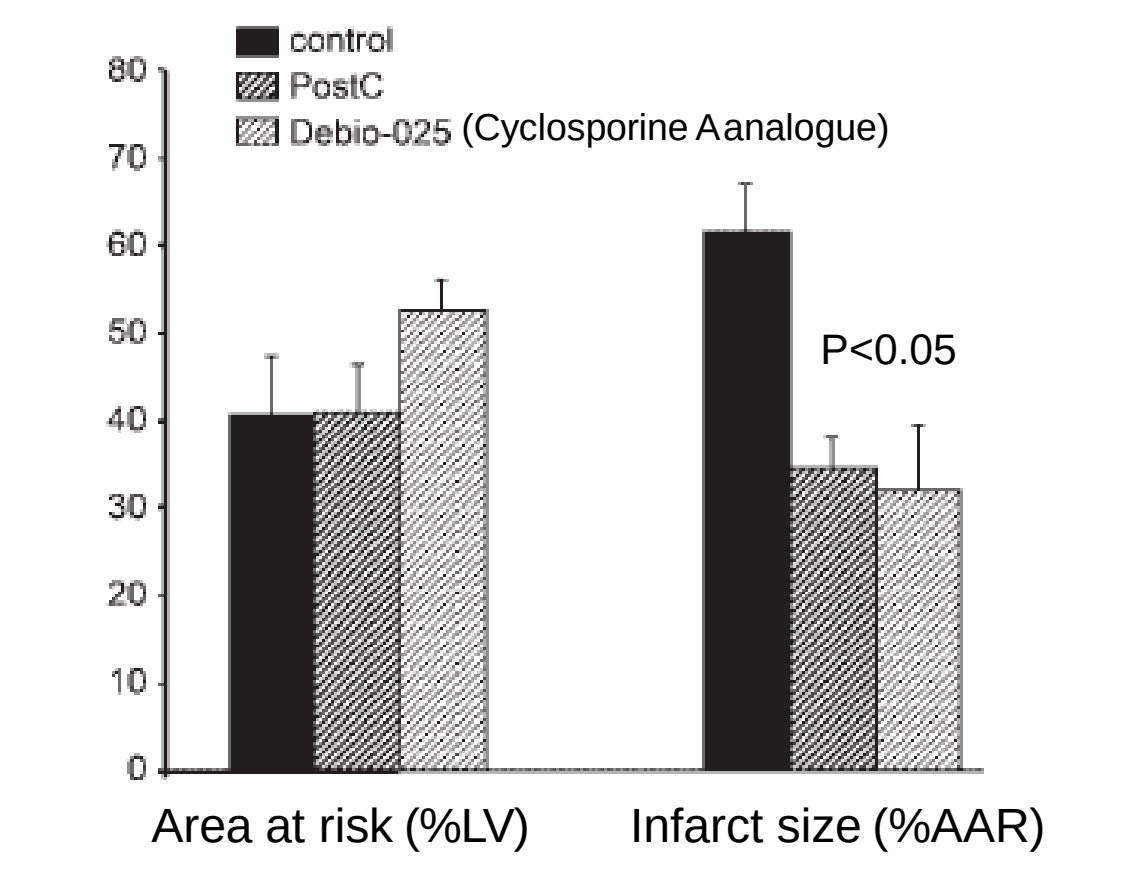
# Ischemic postconditioning during primary percutaneous coronary intervention

**Patient:** STEMI patients who were undergoing PCI within 12 hours after Sx
**Indicator:** balloon occlusion 4 times for 1 minute , separated by 1 minute (n=350)
**Comparator:** without postconditioning (n= 350)
**Outcomes:** complete ST-segment resolution (percentage resolution of ST-segment elevation >70%) measured at 30 minutes after PCI

## *ECG data according to treatment group*



# Phamacologic postconditioning






Gomez et al., Am J Physiol 293: H1654-H1661, 2007

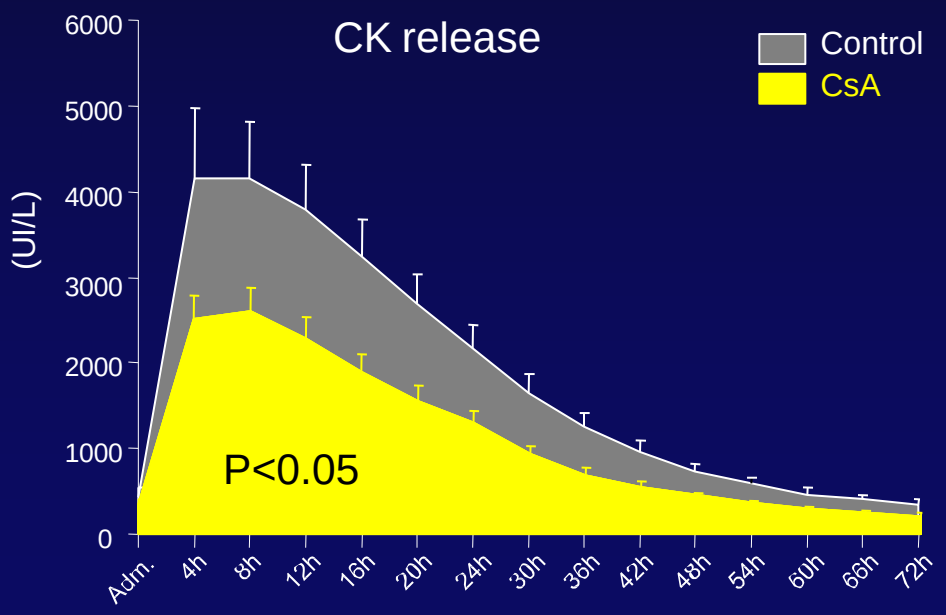
# CyclosporinA and protection of IR injury

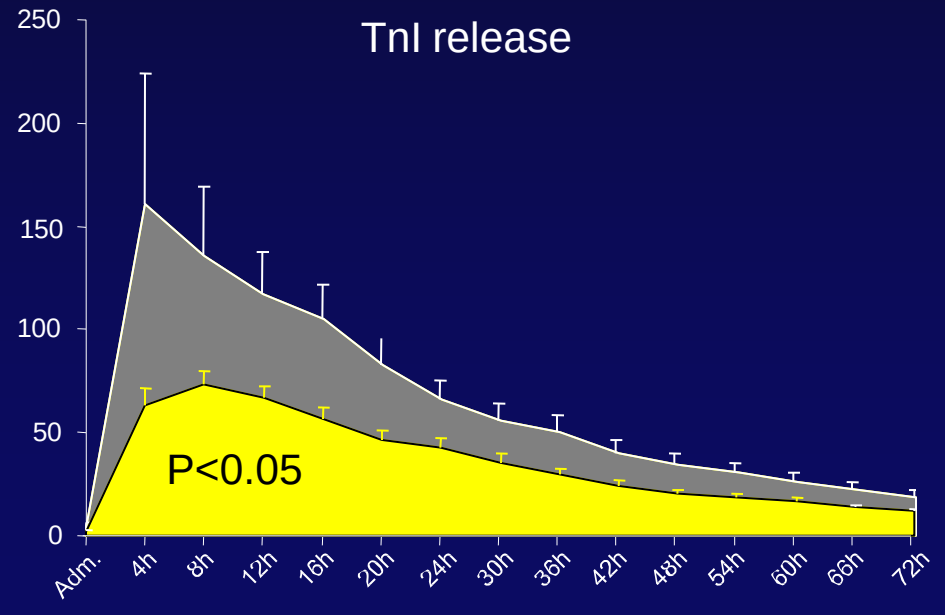
Cyclosporine A (or saline)
(2.5 mg/kg, IV bolus)

Ischemic time

Day 1-3
CK / TnI release

**Infarct size**



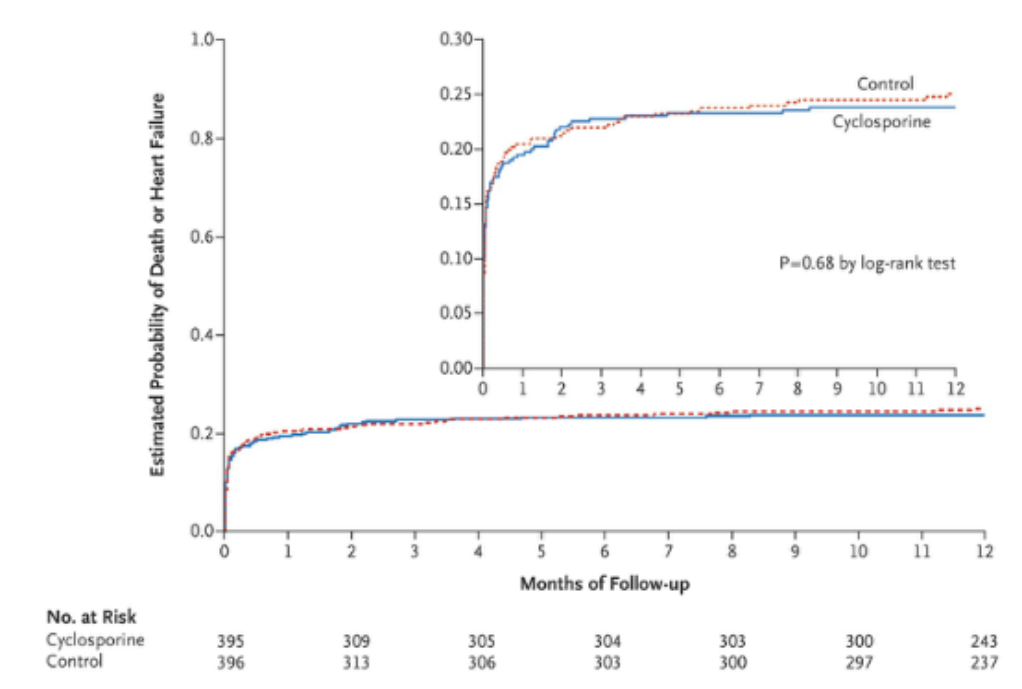



Piot et al., New Engl J Med 359, 473-481, 2008

# Cyclosporine before PCI in Patients with AMI

**Patient:** STEMI patients who were undergoing PCI within 12 hours after Sx
**Indicator:** a bolus iv injection of cyclosporine (2.5 mg/kg) (n=395)
**Comparator:** without cyclosporine (n= 396)
**Outcomes:** a composite of death from any cause, worsening of heart failure during the initial hospitalization, rehospitalization for heart failure, or adverse left ventricular remodeling at 1 year

## *Primary outcome*





N Engl J Med 2015; 373:1021-1031

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journal homepage: www.elsevier.com/locate/ijcard

# The effect of intravenous administration of erythropoietin on the infarct size in primary percutaneous coronary intervention

Jung-Won Suh [a,1], Woo-Young Chung [b,1], Yong-Seok Kim [c], Kwang-Il Kim [b], Eun-Ju Jeon [d], Young-Seok Cho [b], Tae-Jin Youn [b], In-Ho Chae [b], Cheol-Ho Kim [b], Dong-Ju Choi [b,*]

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Acute myocardial infarction
Reperfusion injury

ABSTRACT

*Background:* After an acute myocardial infarction, the early restoration of coronary blood flow is mandatory for reducing infarct size. However, the process of reperfusion itself may also cause irreversible myocardial injury and contribute to the final infarct size. Recent animal studies have suggested that erythropoietin could protect the myocardium when administered after the onset of reperfusion. We investigated whether the administration of erythropoietin at the time of PCI would limit the size of the infarct during acute myocardial infarction by analysis of MRI and cardiac enzymes in this pilot study.

*Methods:* We randomly assigned 57 patients with acute, anterior wall ST-elevation myocardial infarction who were presented within 12 h after the onset of chest pain to one group which was given an intravenous bolus of recombinant human erythropoietin (rhEPO, 50 U/kg) immediately before undergoing PCI or the control group without the IV treatment before PCI. Infarct size was assessed by measuring the release of cardiac enzymes (CK, CK-MB) and by performing MRI on day 4 after infarction.

*Results:* The injection of erythropoietin did not result in thrombotic or hypertensive complications. The release of cardiac enzyme was not different between two groups. On day 4, the absolute infarct volume of the area of hyperenhancement on MRI did not differ between two groups (EPO group $52.4 \pm 23.6$ cm$^3$ vs. control group $54.8 \pm 28.6$ cm$^3$, $p = 0.74$). Two groups did not differ in the percentage of total infarct volume over left ventricle volume (EPO group $34.4 \pm 11.7$% vs. $37.0 \pm 13.8$%, $p = 0.50$).

*Conclusions:* Intravenous administration of erythropoietin was safe and was not associated with thrombotic or hypertensive side effects. However, it did not reduce the infarct size when assessed by MRI and cardiac enzyme. Further studies about the dose or routes of administration of EPO are needed (ClinicalTrials.gov Identifier NCT00882466).

# IV EPO before PCI

- An intravenous bolus injection of erythropoietin (50 U/kg, Epokine Prefilled®, CJ Pharm, Korea

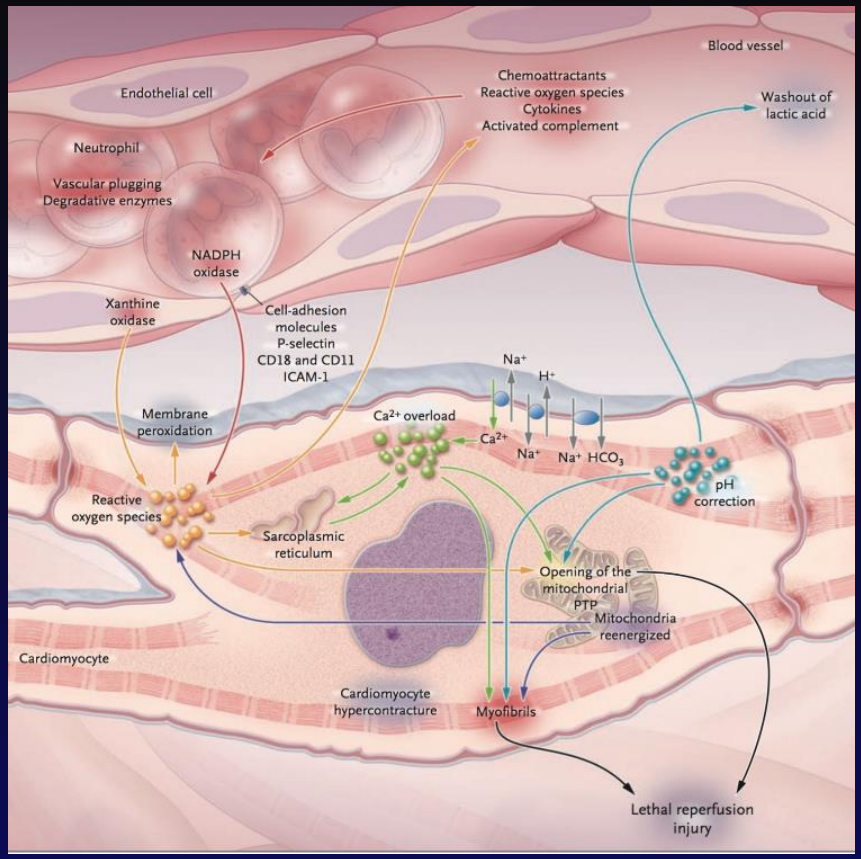
Results of MRI analysis of two groups.

| | EPO group ($n=25$) | Control group ($n=25$) | $p$-value |
|---|---|---|---|
| Ejection fraction, % | 51.5 ± 52.4 | 52.4 ± 14.1 | 0.81 |
| End-systolic volume, mL | 67.3 ± 30.3 | 64.0 ± 32.9 | 0.71 |
| End-diastolic volume, mL | 134.2 ± 32.6 | 127.3 ± 35.6 | 0.48 |
| Total infarct volume, $cm^3$ | 52.4 ± 23.6 | 54.8 ± 28.6 | 0.74 |
| Infarct size, % of LV | 34.4 ± 11.7 | 37.0 ± 13.8 | 0.50 |

LV, left ventricle.



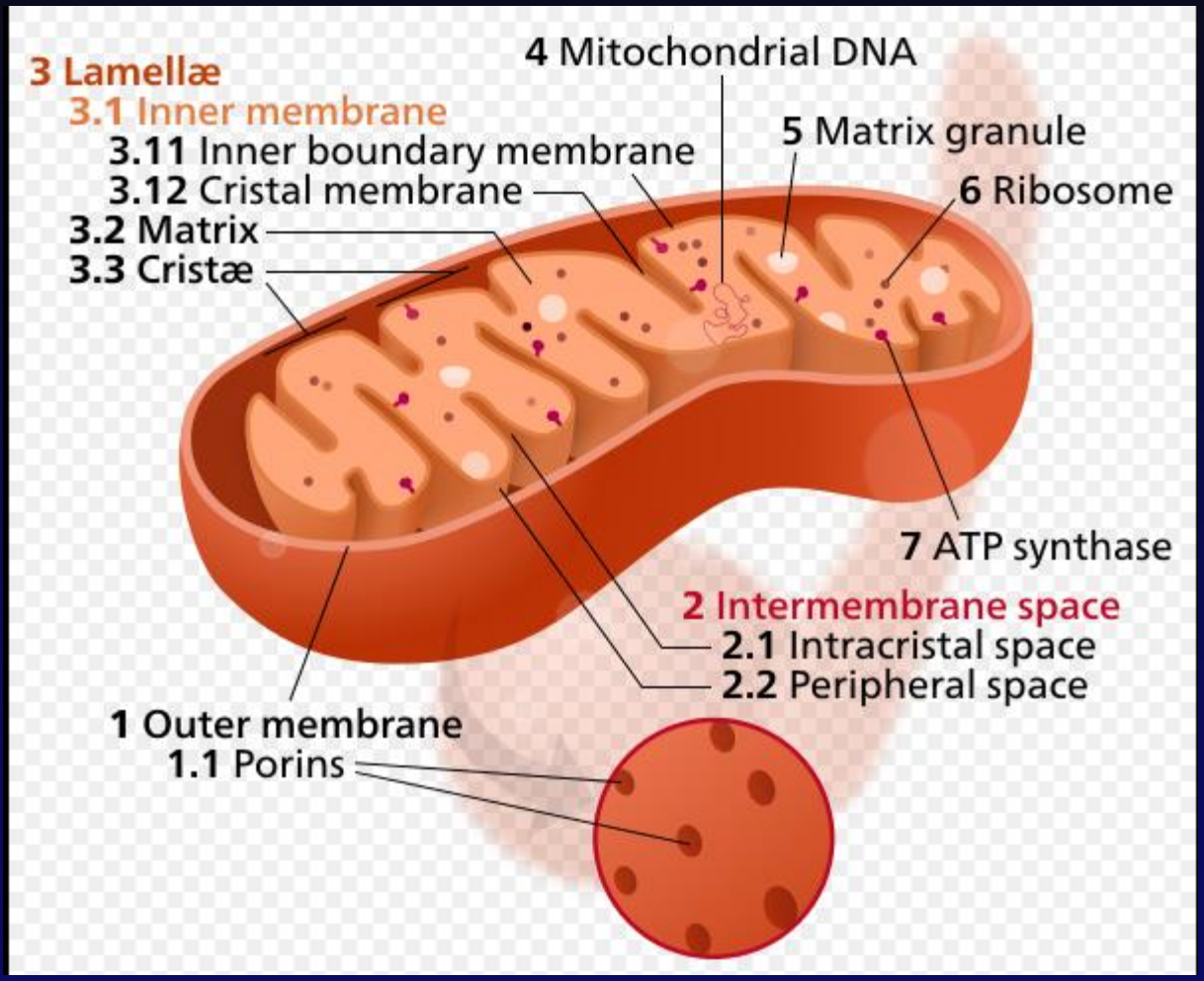
*Suh JW, et al. Int. J. Cardiol. 2011*



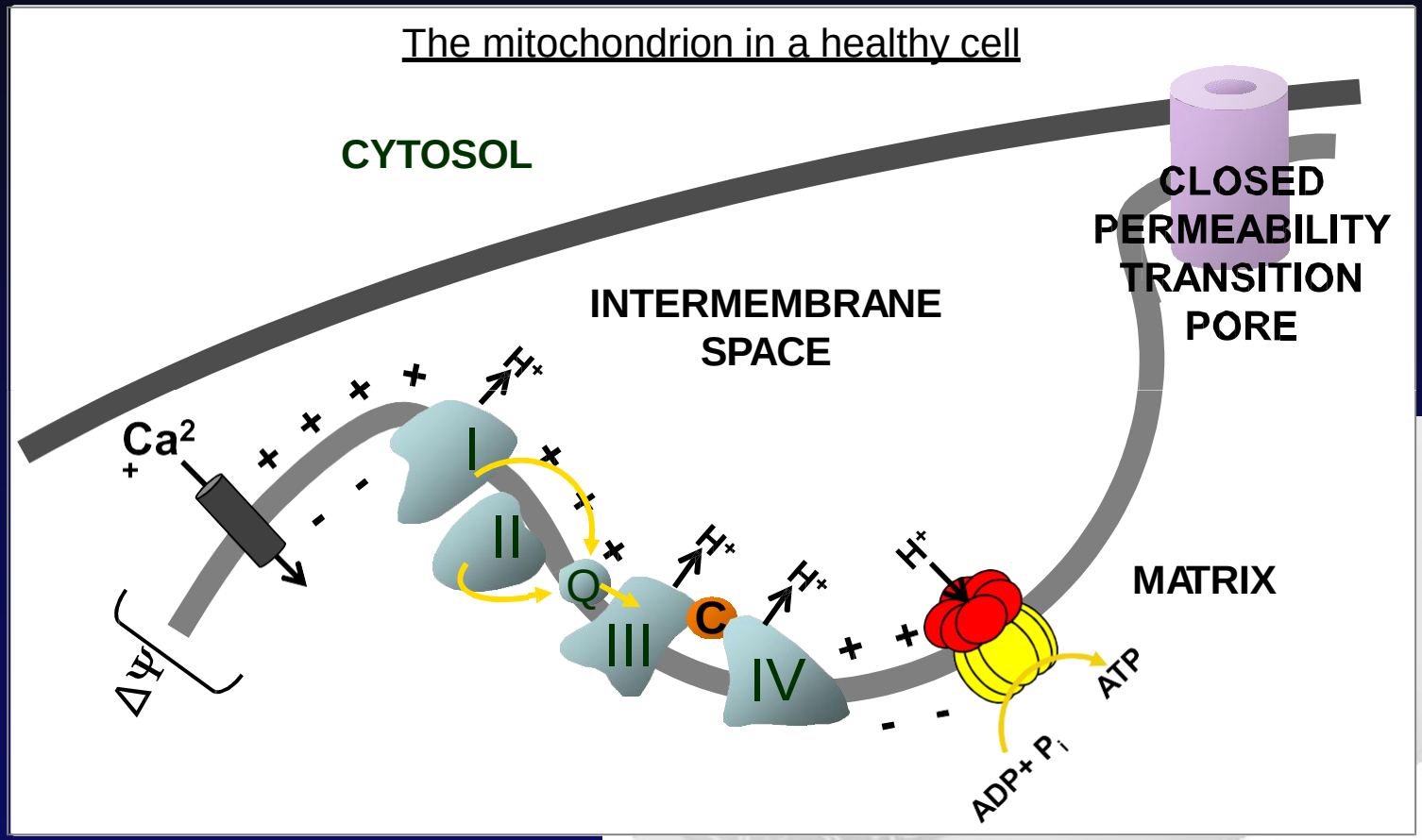

*2008; 117*

# 4. MPTP 를 조절할 수 있을 것인가?

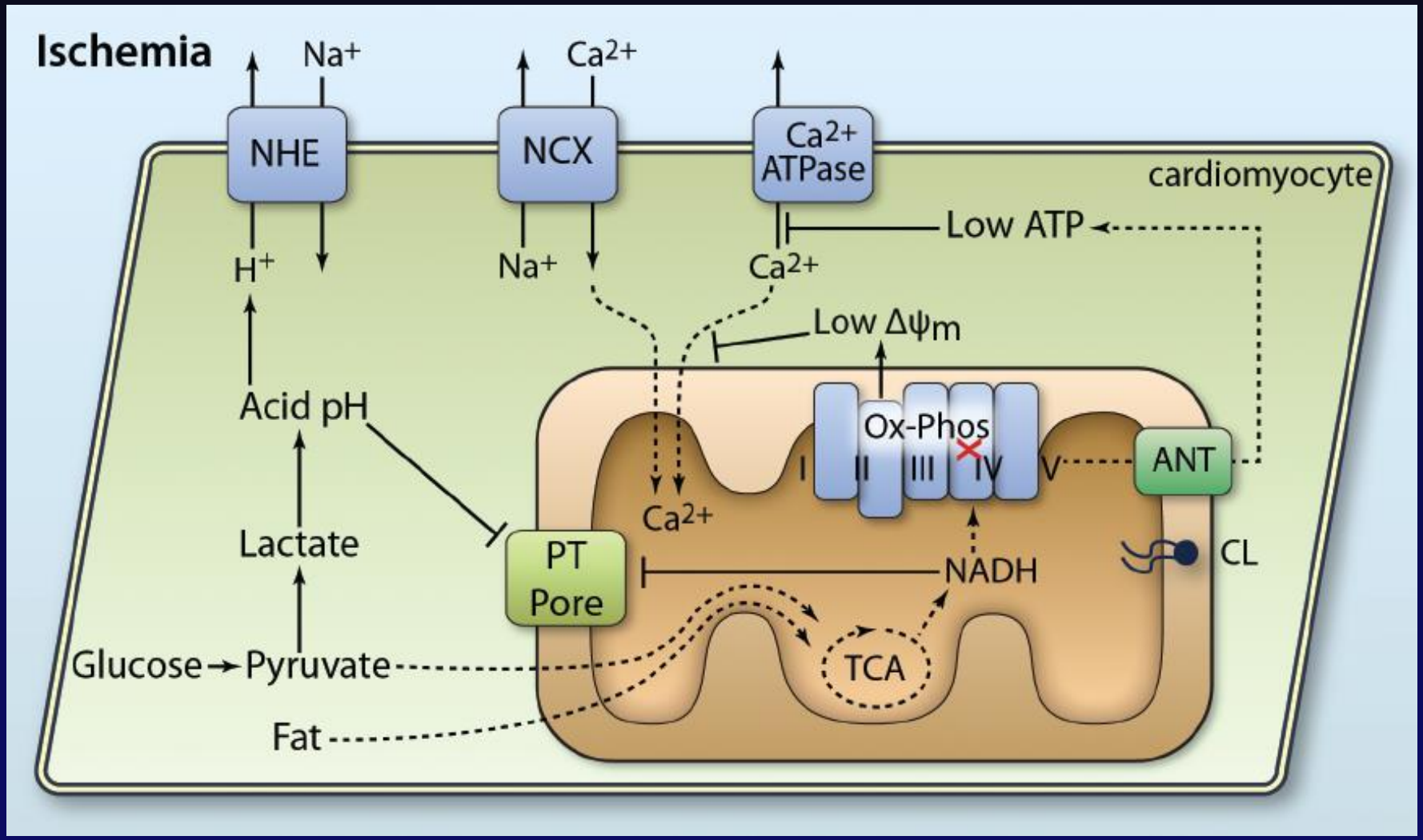
# Mitochondrion 의 구조



# mPTP Mechanism of Action



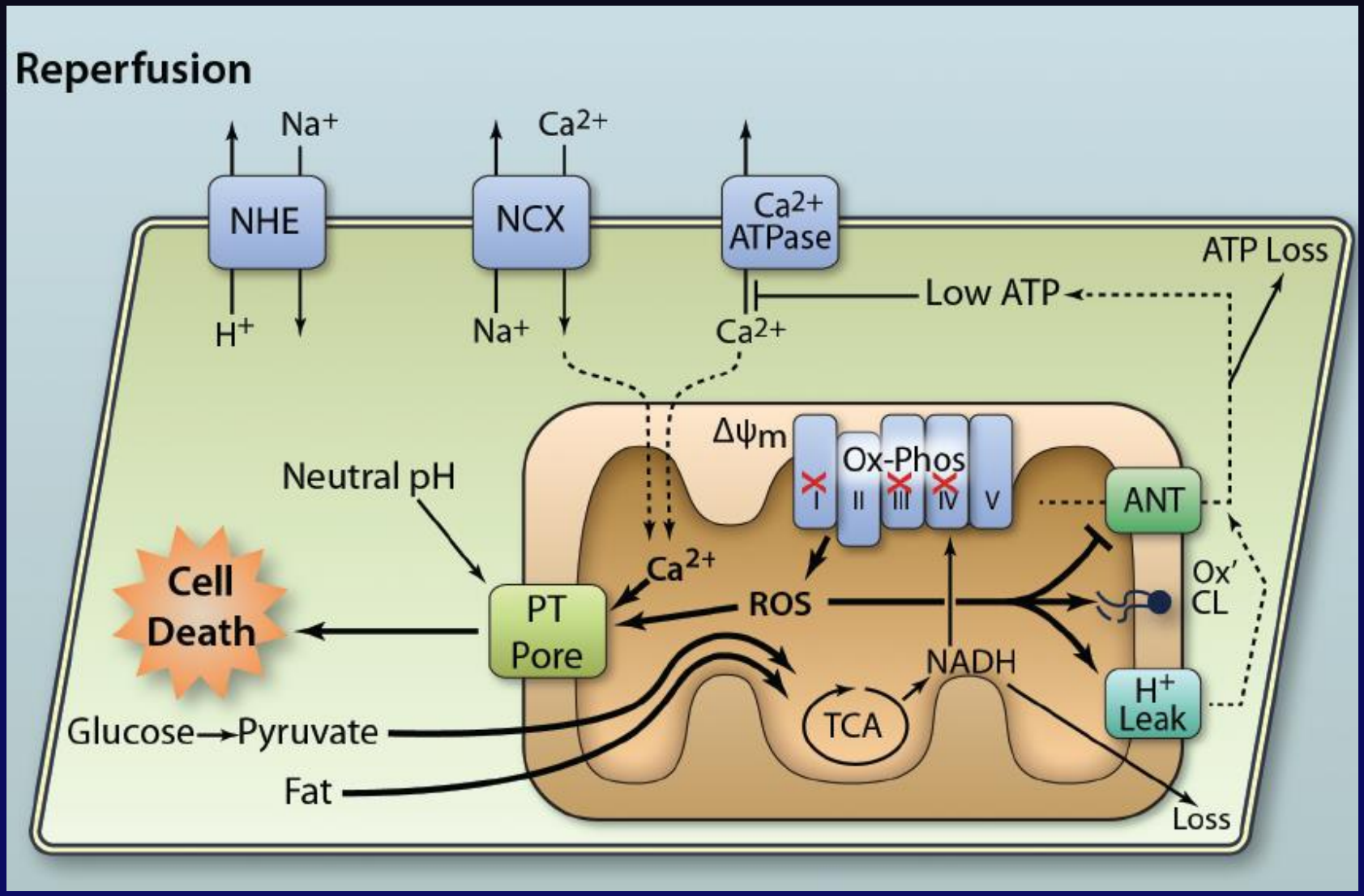
# Mitochondrial pathological events in ischemia






*Circ Res.* 2012;111:1222-1236

# Mitochondrial pathological events in reperfusion

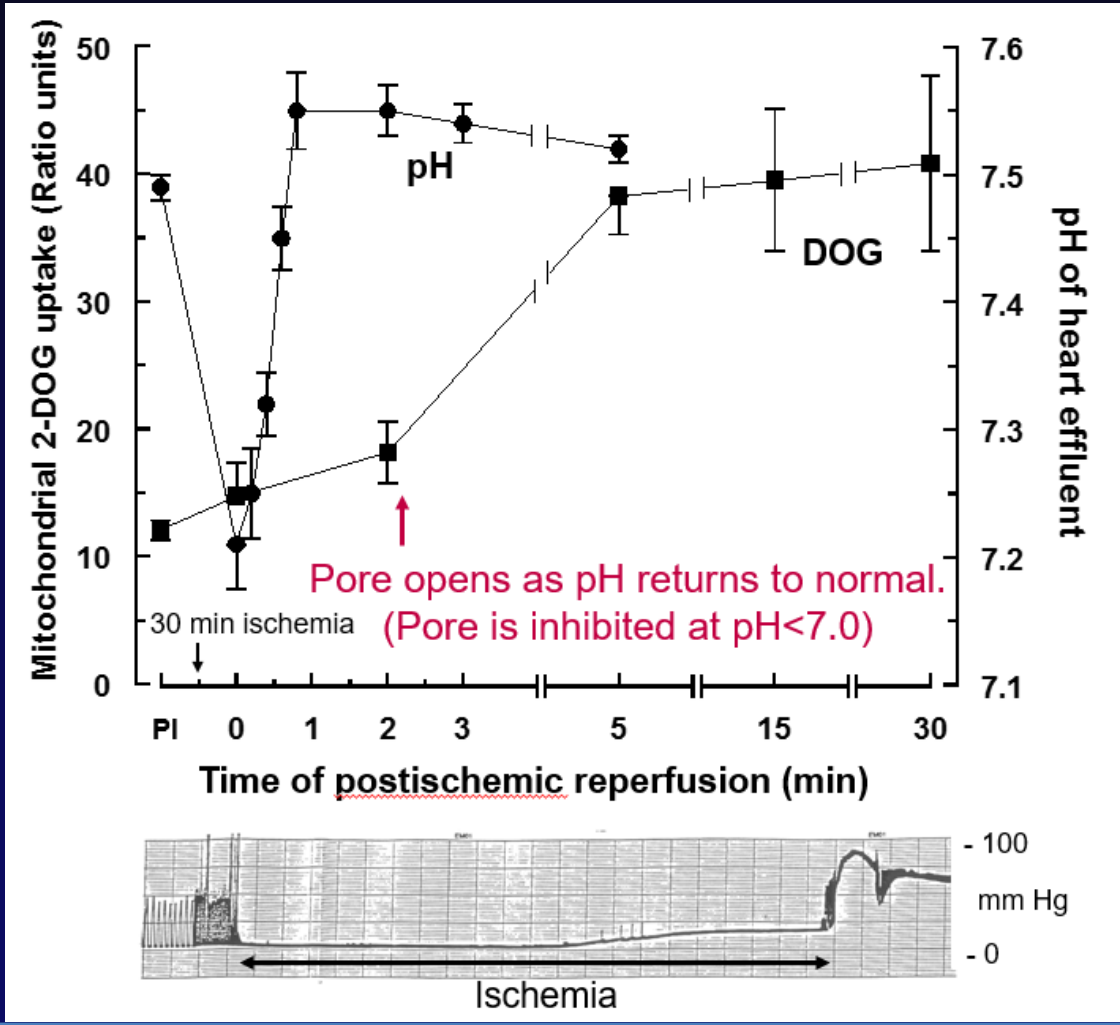





*Circ Res.* 2012;111:1222-1236

# Time dependence of mitochondrial pore opening

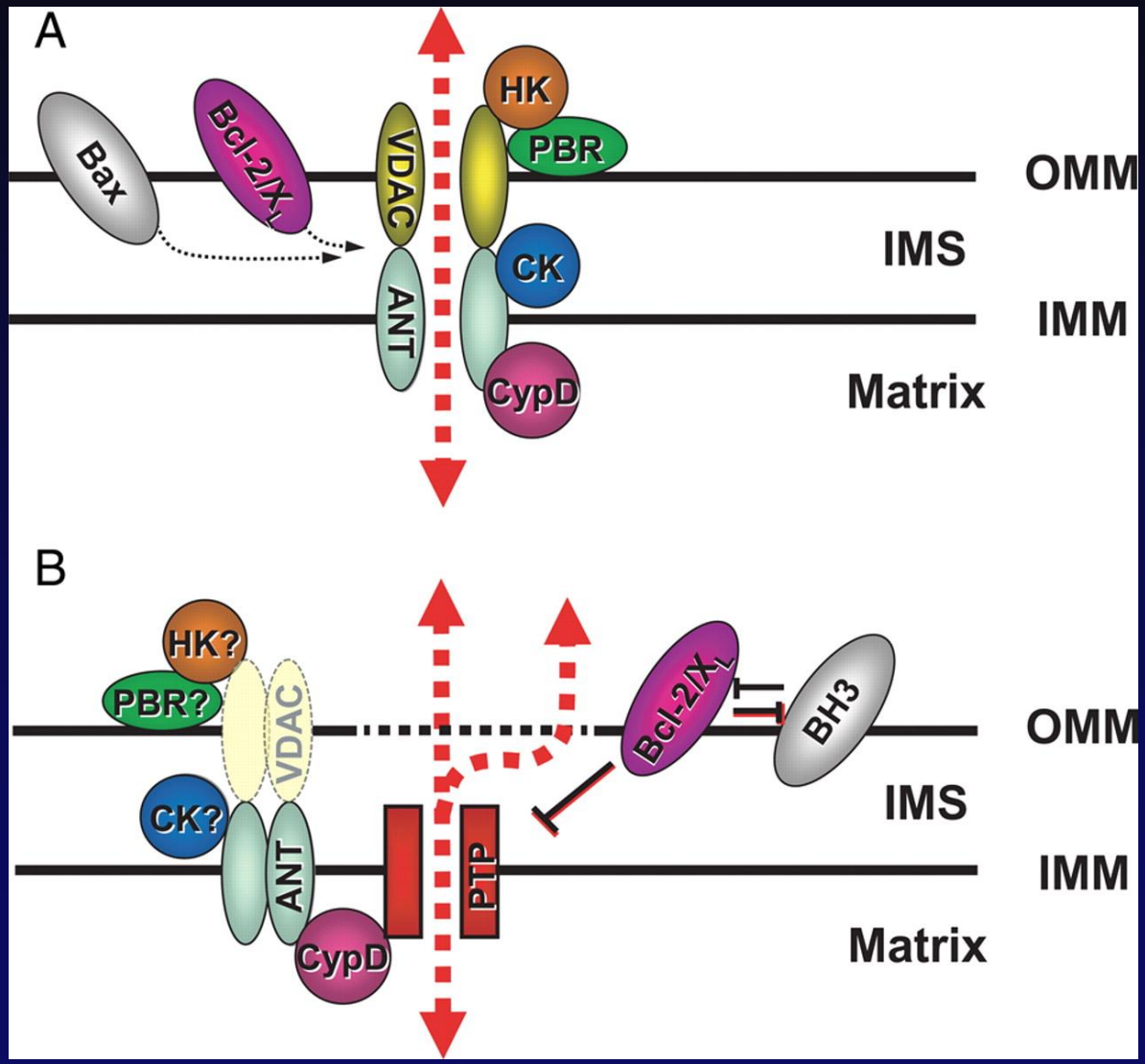
Time dependence of mitochondrial pore opening and pH recovery during reperfusion of hearts after 30 min ischaemia



# Proposed mPTP complex architecture

Classical view

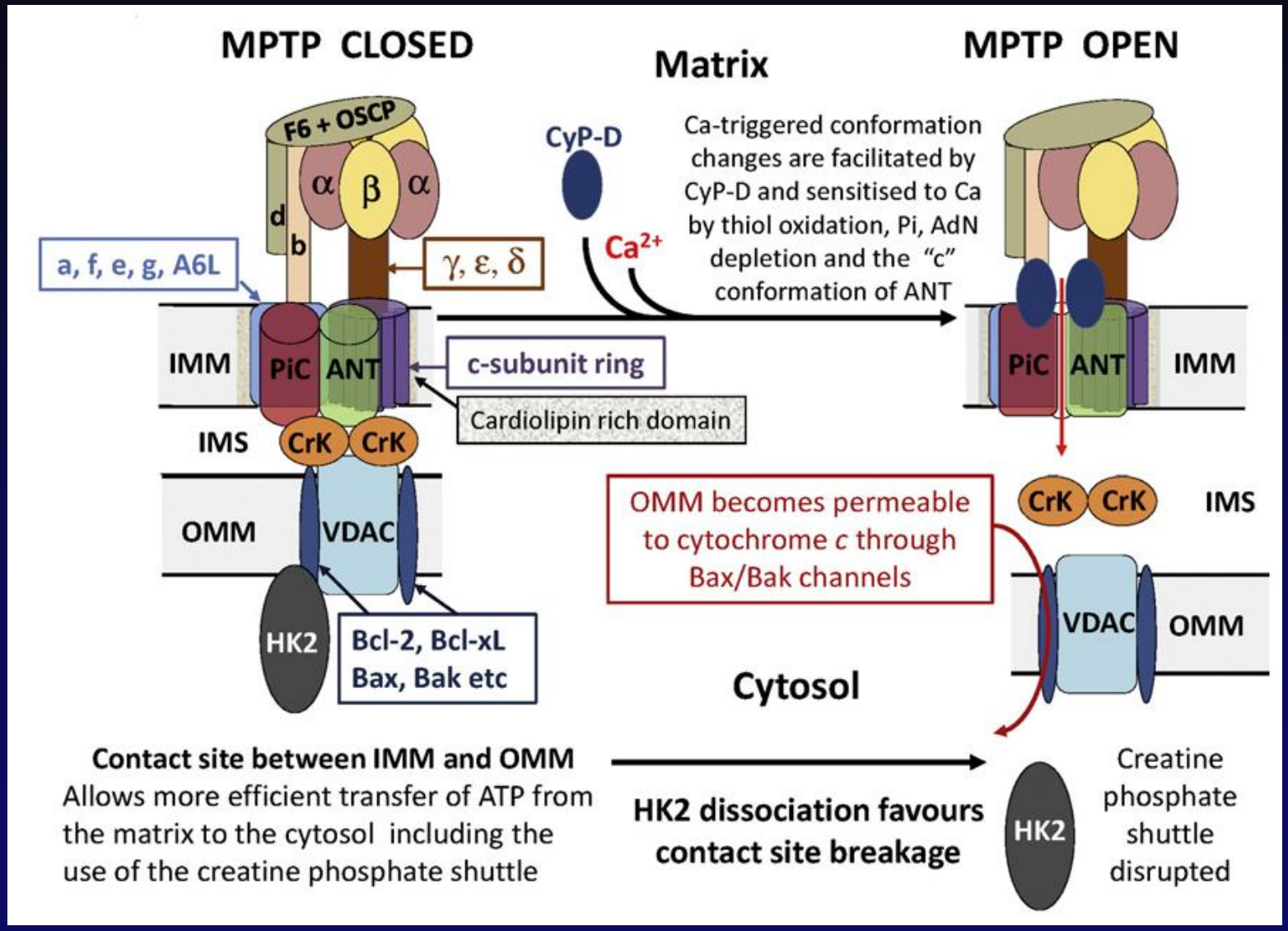
Current view






*Cardiovasc Res.* 2009;83:213-225

# Proposed mPTP complex architecture



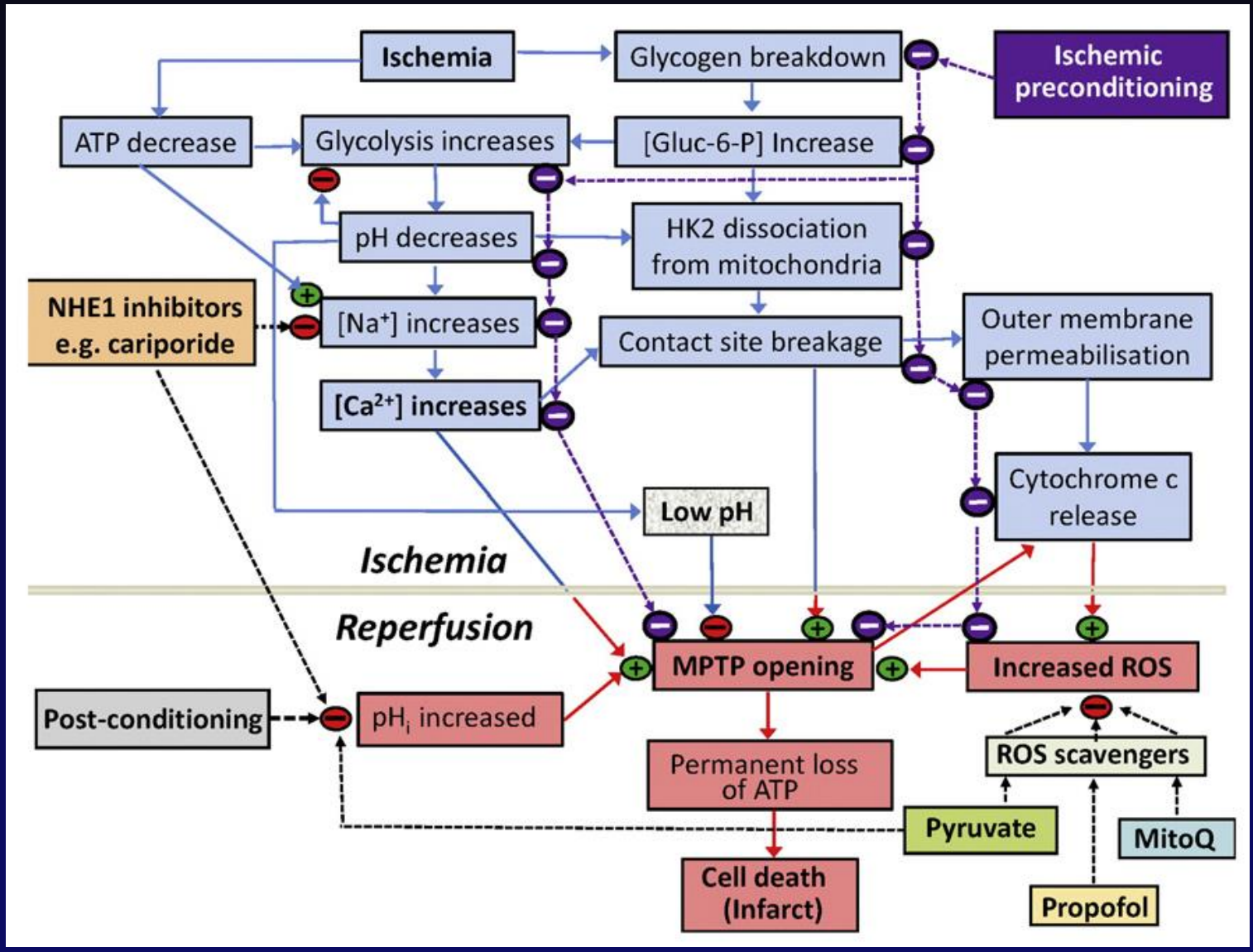



A.P. Halestrap, A.P. Richardson / JMCC 78 (2015) 129–141

# Potential treatments targeting mitochondria

1. *PT pore inhibitors*
2. *NO analogs*
3. *Antioxidants*
4. *Potassium channel openers*
5. *Respiratory chain inhibitors*
6. *RISK pathway modulators*
7. *Aldehyde dehydrogenase 2*
8. *Metabolic modulators*
9. *Others (adenosine, AMP579, beta-blockers, meclizine, …)*

# Various agents involving mPTP opening






A.P. Halestrap, A.P. Richardson / JMCC 78 (2015) 129–141

# Clinical Development of Mitochondrial Therapies for Cardiomyopathy and Ischemic Heart Disease

| Agent | Target/MOA | Clinical Development/ Usage | Status of Cardiac Clinical Development | Clinical Trial |
|---|---|---|---|---|
| PT pore inhibitors | | | | |
| 4′-chlorodiazepam (Ro5-4684) | TSPO | | | |
| CsA | CypD | In-use (immunosuppression) | Phase III (AMI) | NCT01502774 |
| Debio025 | CypD | Phase II (Hepatitis C) | | |
| NIM811 | CypD | Phase II (Hepatitis C) | | |
| Sanglifehrin A | CypD | | | |
| TR040303 | TSPO | | Phase II (AMI) | NCT01374321 |
| NO analogs | | | | |
| MitoSNO1 | | | | |
| Nitrolipids | | | | |
| Nitrite | | In-use (cyanide antidote) | Phase II (AMI) | NCT01584453 |
| SNO-MPG | | | | |
| Antioxidants | | | | |
| Edaravone | | In-use (stroke, Japan) | Phase IV (AMI) | NCT00265239 |
| Glutathione | | Nutriceutical | Cardioplegia additive | |
| HVTP | | | | |
| Imz-$S_N$As | | | | |
| Mangafodipir | | | Phase II (AMI) | NCT00265239 |
| Melatonin | | Nutriceutical | Phase II (AMI) | NCT01172171 |
| MitoE | | | | |
| MitoQ | | Phase II (Hepatitis C, NASH) | | |
| MPG | | | | |
| SOD, catalase | | Various clinical trials | | |
| SS31 (bendavia) | | | Phase II (AMI) | NCT01572909 |

# Clinical Development of Mitochondrial Therapies for Cardiomyopathy and Ischemic Heart Disease

| Agent | Target/MOA | Clinical Development/ Usage | Status of Cardiac Clinical Development | Clinical Trial |
|---|---|---|---|---|
| Potassium channel openers | | | | |
| 3-NP | $mK_{ATP}$ | | | |
| Atpenin A5 | $mK_{ATP}$ | | | |
| Cromakalim | $mK_{ATP}$ | | | |
| BMS-191095 | $mK_{ATP}$ | | | |
| Diazoxide | $mK_{ATP}$ | Various clinical trials | | |
| Malonate | $mK_{ATP}$ | Phase II (osteoporosis) | | |
| Minoxidil | $mK_{ATP}$ | In-use (hypertension, alopecia) | | |
| NS11021 | mBK | | | |
| NS1619 | mBK | | | |
| Pinacidil | $mK_{ATP}$ | In-use (hypertension) | | |
| Respiratory chain inhibitors | | | | |
| Amobarbital | Complex I | In-use (anxiety, sedation) | | |
| Antimycin A | Complex III | | | |
| $H_2S$ | Complex IV | Phase I (renal function) | | |
| Rotenone | Complex I | | | |
| RISK pathway modulators | | | | |
| Lithium | | In-use (bipolar disorder) | | |
| SB216763 | GSK3-β | | | |
| Statins | HMG-CoA reductase | In-use (hyperlipidemia) | Completed phase IV (AMI) | ARYMDA and ARYMDA-ACS |



*Circ Res.* 2012;111:1222–1236

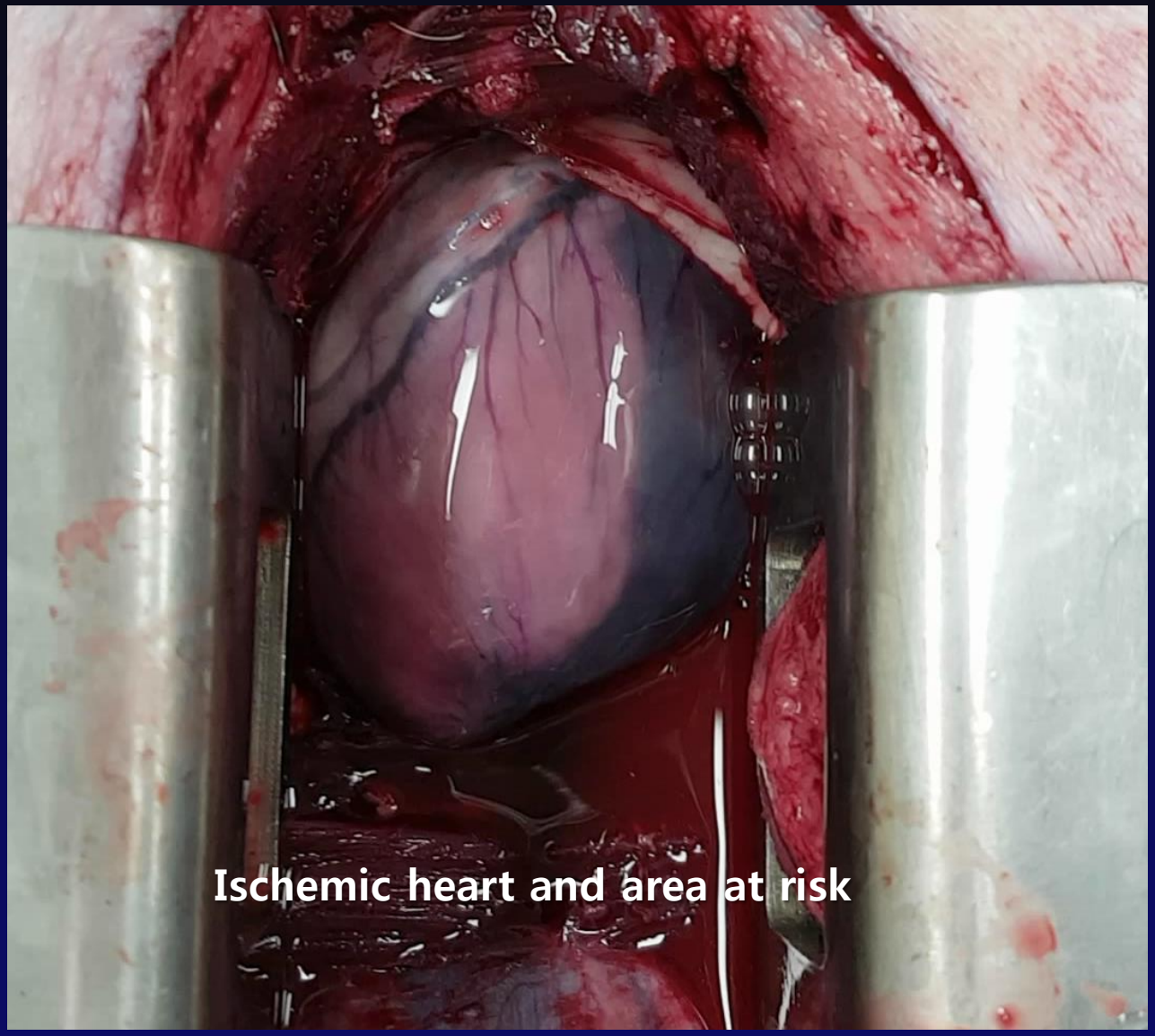
# Clinical Development of Mitochondrial Therapies for Cardiomyopathy and Ischemic Heart Disease

| Agent | Target/MOA | Clinical Development/ Usage | Status of Cardiac Clinical Development | Clinical Trial |
|---|---|---|---|---|
| Metabolic modulators | | | | |
| A-769662 | AMPK | | | |
| Acadesine (AICAR) | AMPK, nonspecific | | Failed phase III (MI) | NCT00872001 |
| Cofactors (carnitine, Co-Q etc) | | Nutriceutical | Various clinical trials (CM) | |
| DCA | Pyruvate dehydrogenase | Failed clinical trials for lactic acidosis, MELAS, Multiple trials in cancer. | | |
| Etomoxir | CPT1 | | | |
| GIK | | | Multiple trials (CABG, noncardiac surgery, AMI) | |
| Idebenone | Respiratory chain | In-use (mitochondrial myopathies) | Phase III (DMD) | NCT01027884 |
| L-Arginine | NOS and TCA cycle substrate | In-use (mitochondrial myopathies) | Failed phase II (MI) | NCT00051376 |
| Oxfenicine | CPT1 | | | |
| Perhexiline | CPT1 | | Clinical (AMI, Aus/NZ) | |
| Ranolazine | Late $Na^+$ channel, specific target unclear | In-use (angina) | Failed phase III (MI)Phase IV (PCI) | NCT00099788 NCT01491061 |
| Trimetazidine | Late $Na^+$ channel, specific target unclear | In-use (angina) | Multiple clinical trials (CM) | |
| Other | | | | |
| Adenosine | Adenosine receptors | | Failed clinical trials (MI, CABG) | |
| AMP579 | Adenosine receptors | | Failed phase III (MI) | ADMIRE I & II |
| Anesthetic preconditioning | | In-use | Phase IV (cardiac surgery) | NCT00364637 |
| β-blockers | β-adrenergic receptors | In-use (patients at risk of MI) | | |
| Cloxyquin/clioquinol | | In-use (antifungal/-protozoal) | | |
| Hypothermia | | In-use | Phase III (AMI) | COOL-MI NCT01379261 |
| Meclizine | Histamine receptors | In-use (antihistamine) | | |
| Preconditioning (IPC, IPoC, RIPC) | | | Multiple clinical trials | |

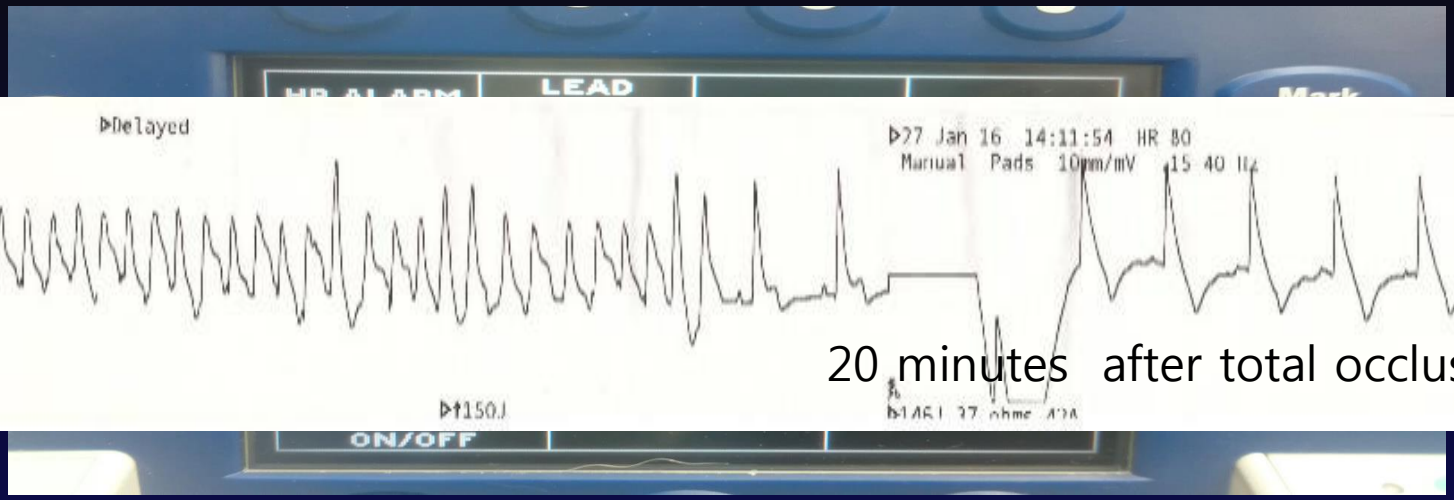


*Circ Res.* 2012;111:1222–1236

# Porcine IR model

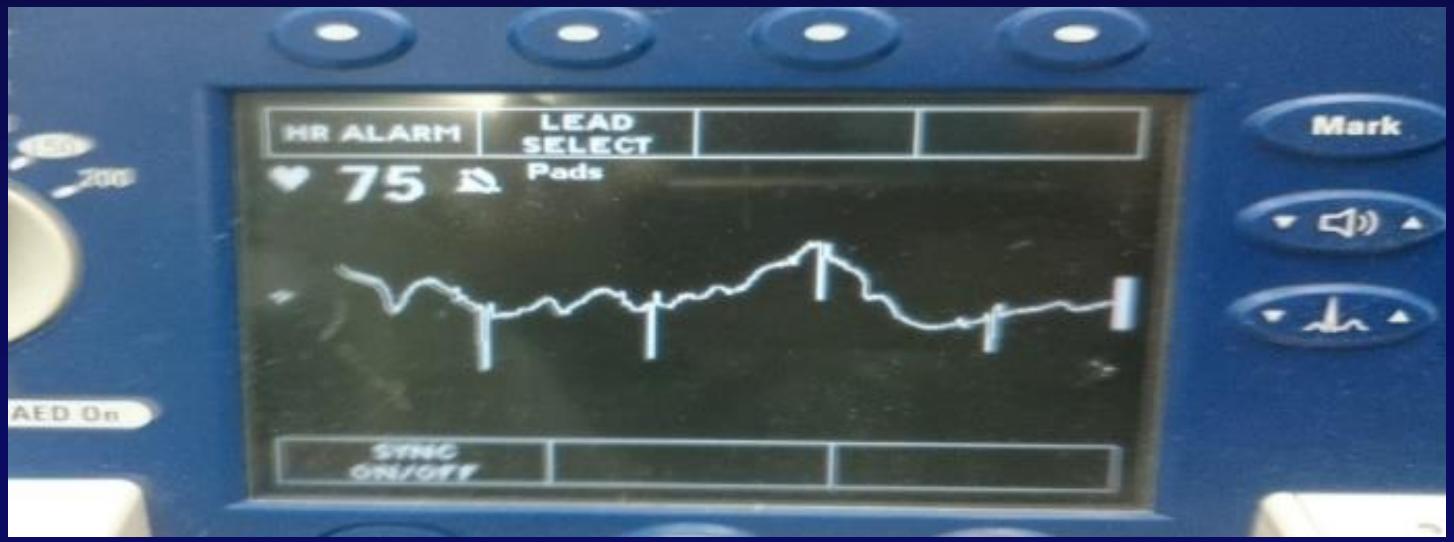


# Porcine IR model




20 minutes after total occlusion

5 minutes after total occlusion

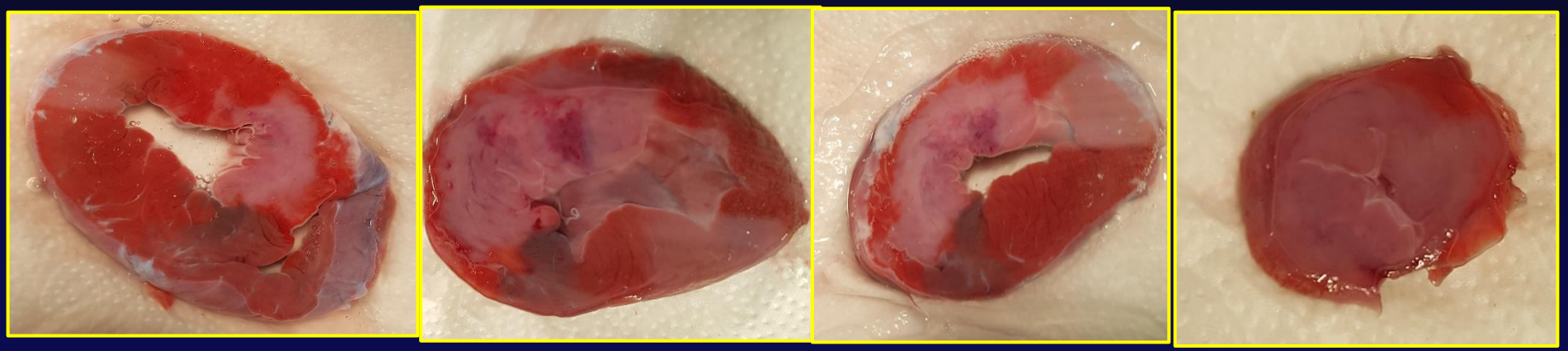



At moment of EDTA solution infusion

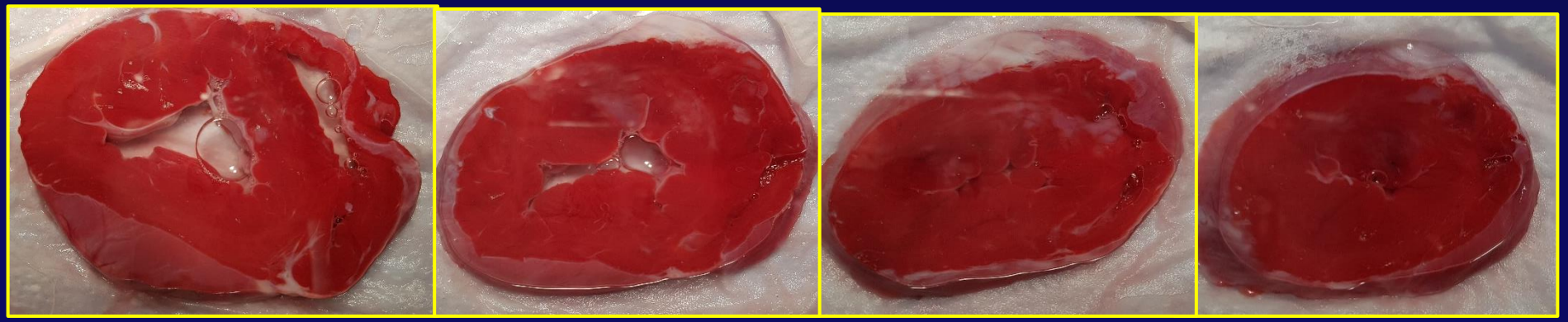
# Viable myocardium after reperfusion(TTC staining)

- EDTA chelating solution has protective effect against reperfusion injury in swine model

Control pig's harvested heart 1 hour after reperfusion



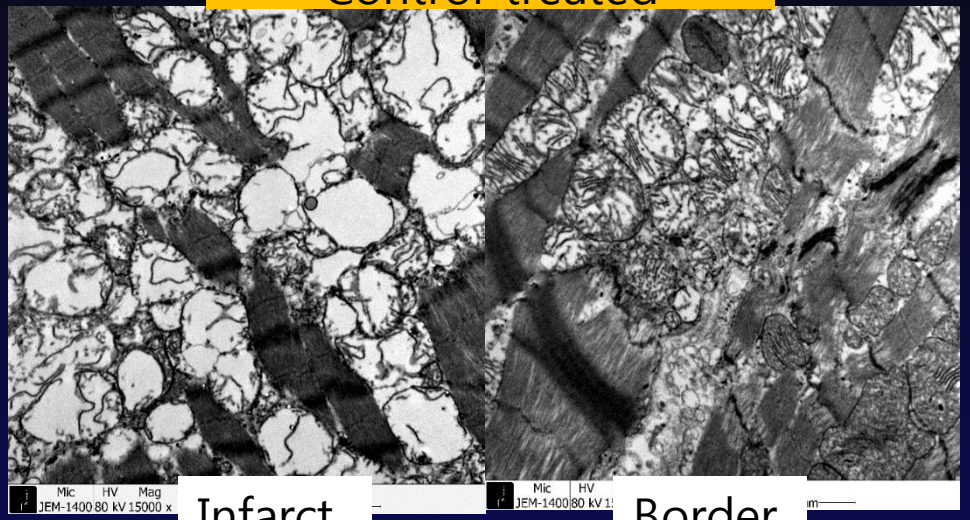
EDTA administrated pig's harvested heart 1hour after reperfusion



# Mitochondria after reperfusion

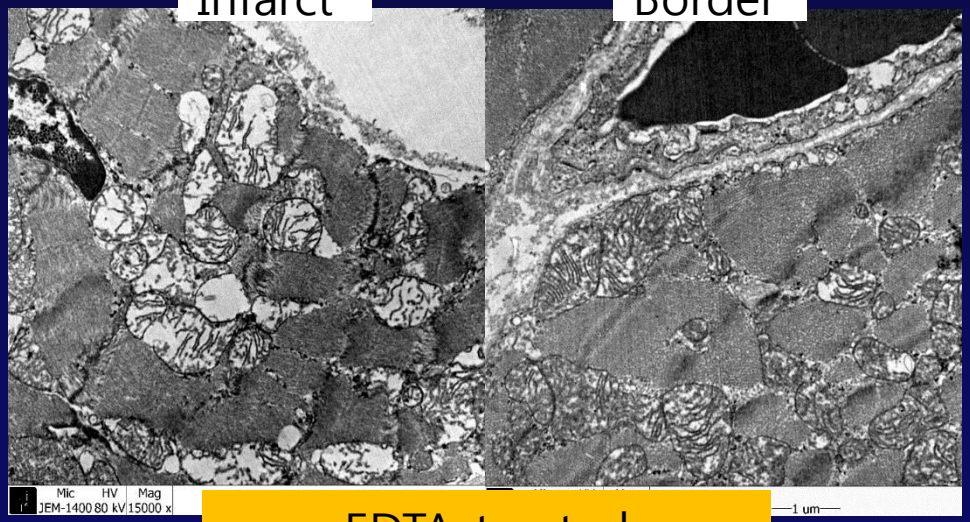

Normal myocardium

Control-treated

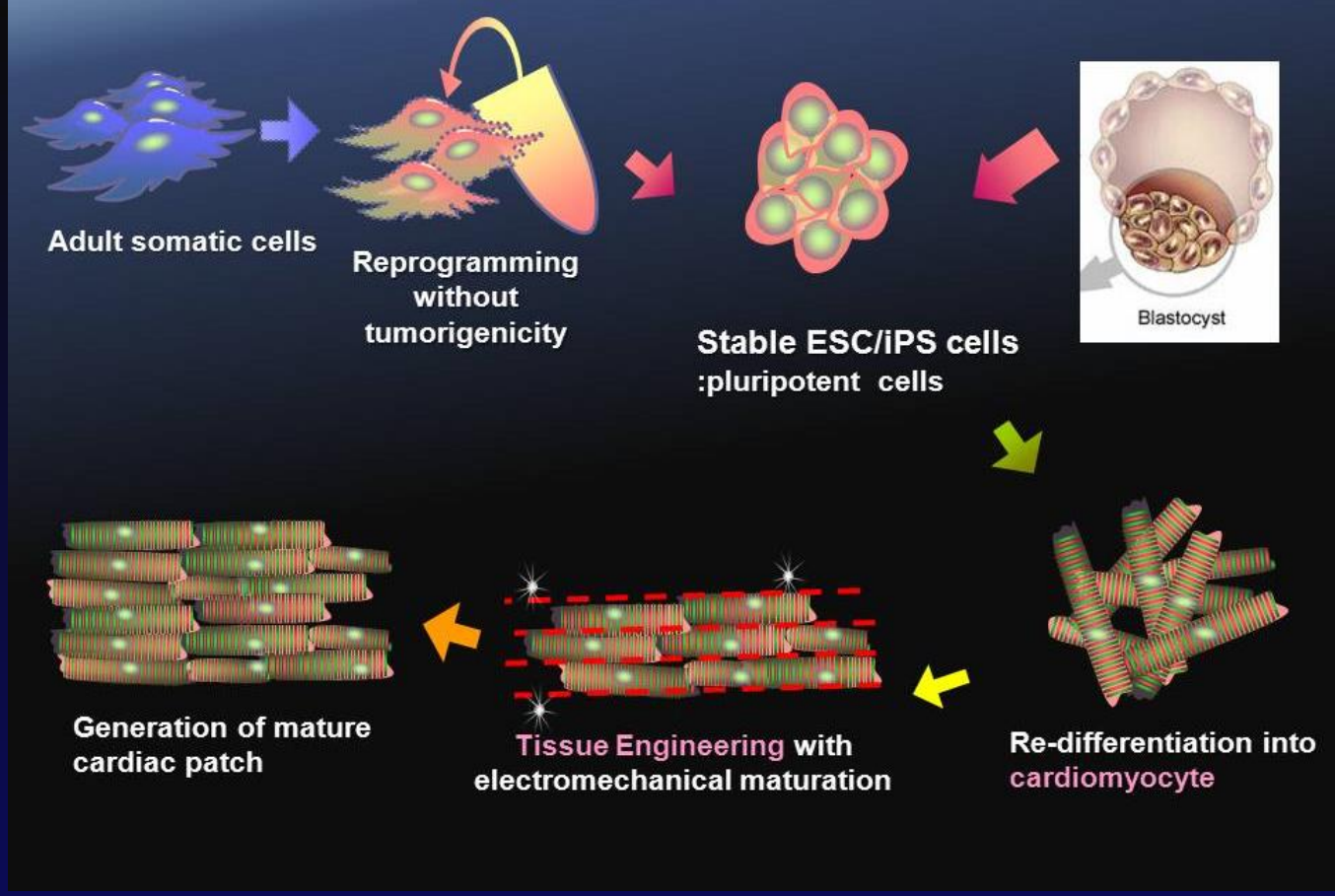



Infarct

Border



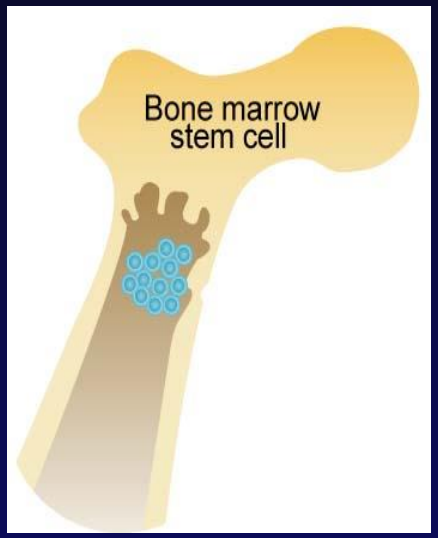

EDTA-treated


Adult somatic cells
Reprogramming without tumorigenicity
Stable ESC/iPS cells :pluripotent cells
Blastocyst
Re-differentiation into cardiomyocyte
Tissue Engineering with electromechanical maturation
Generation of mature cardiac patch

# 5. 줄기세포, 심장재생

# MAGIC cell program:

## Myocardial Regeneration and Angiogenesis in Patient with Myocardial Infarction using G-CSF mobilization and Intra-Coronary Stem Cell Infusion

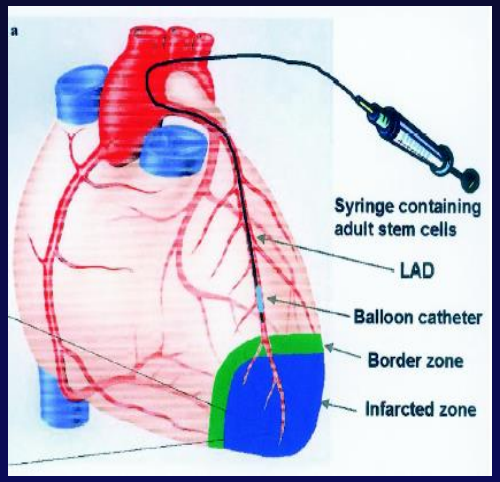



G-CSF injection for 3days

Apheresis

Mob PBSCs

Intracoronary infusion of stem cells





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# MAGIC Cell program in SNUH



**MAGIC Cell-1** : G-CSF vs. Cell infusion vs. control in elective PCI

**MAGIC Cell-2** : G-CSF vs. control in AMI who underwent primary PCI

**MAGIC Cell-3-DES** : Cell infusion vs. control in AMI and OMI with DES

- G-CSF and endothelial function
- Effect of Cell infusion on LV dyssynchrony
- G-CSF and Restenosis, coronary remodeling

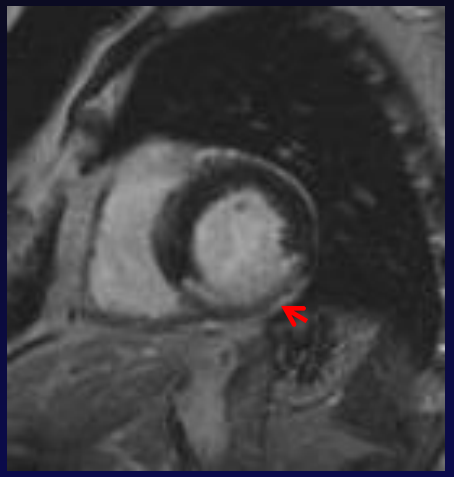
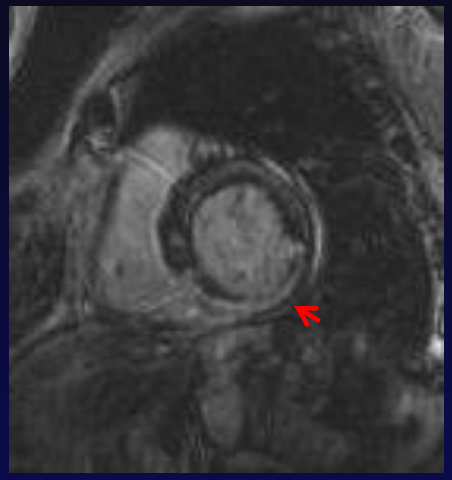
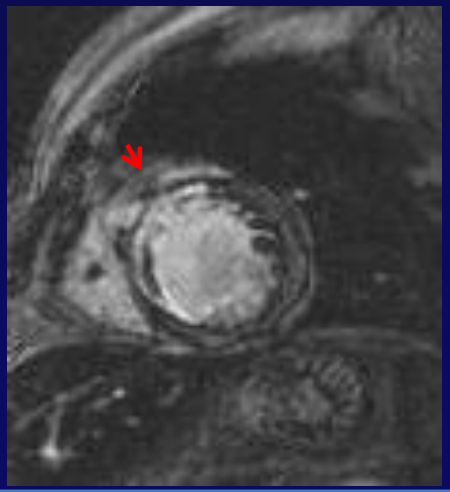
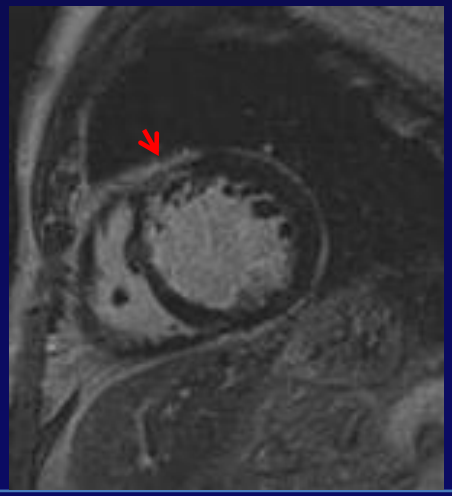
**MAGIC Cell-4-ICMP** : Cell infusion in ischemic CMP without PCI

**MAGIC Cell-5** : cell infusion with combicytokine vs. G-CSF

- 1st generation stem cell therapy
- 1.5th generation stem cell therapy
- 2nd generation stem cell therapy

# Infarct shrinkage

MAGIC-V

| | Baseline | 6 Months | |
|---|---|---|---|
| Control |  |  | No change |
| Combi-cytokine |  |  | Improved |

Articles

# Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial

*Hyun-Jae Kang, Hyo-Soo Kim, Shu-Ying Zhang, Kyung-Woo Park, Hyun-Jai Cho, Bon-Kwon Koo, Yong-Jin Kim, Dong Soo Lee, Dae-Won Sohn, Kyou-Sup Han, Byung-Hee Oh, Myoung-Mook Lee, Young-Bae Park*

## Summary

**Background** Bone-marrow stem-cell transplantation has been shown to improve cardiac function in patients with myocardial infarction. We examined the feasibility and efficacy of granulocyte-colony stimulating factor (G-CSF) therapy and subsequent intracoronary infusion of collected peripheral blood stem-cells (PBSCs) in such patients.

**Methods** We prospectively randomised 27 patients with myocardial infarction who underwent coronary stenting for the culprit lesion of infarction into three groups; cell infusion (n=10), G-CSF alone (n=10), and control group (n=7). Changes in left ventricular systolic function and perfusion were assessed after 6 months. By December, 2003, seven patients from the cell infusion group, three from the G-CSF group, and one from the control group had been assessed.

**Findings** G-CSF injection and intracoronary infusion of the mobilised PBSC did not aggravate inflammation and ischaemia during the periprocedural period. Exercise capacity (mean treadmill exercise time: 450 s [SD 178] at baseline *vs* 578 s [168] at 6 months' follow-up, p=0·004), myocardial perfusion (perfusion defect 11·6% [9·6] *vs* 5·3% [5·0], p=0·020) and systolic function (left ventricular ejection fraction 48·7% [8·3] *vs* 55·1% [7·4], p=0·005) improved significantly in patients who received cell infusion. However, we noted an unexpectedly high rate of in-stent restenosis at culprit lesion in patients who received G-CSF, and therefore we stopped enrolment.

**Interpretation** G-CSF therapy with intracoronary infusion of PBSC showed improved cardiac function, and promoted angiogenesis in patients with myocardial infarction. However, aggravation of restenosis could be a serious problem. In future studies with G-CSF based stem-cell therapy, patients should be carefully monitored for unexpected effects.

*Lancet* 2004; **363:** 751–56. Published online March 2, 2004
http://image.thelancet.com/extras/04art1325web.pdf
*See Commentary page 746*

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**Correspondence to:** Dr Hyo-Soo Kim, Department of Internal Medicine, Seoul National University Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110–744, Republic of Korea
(e-mail: hyosoo@snu.ac.kr)

Bone-marrow stem-cell transplantation has been shown to improve myocardial perfusion and systolic function in patients with myocardial infarction,[1–4] but the invasiveness of bone-marrow cell collection limits its clinical application. Mobilisation of stem cells with granulocyte-colony stimulating factor (G-CSF) and stem-cell factor have been studied as alternative, less invasive approaches in mice,[5] and favourable results have brought attention to the need for such treatments to be assessed in man.

In patients with haematological diseases, G-CSF is a well established stem-cell mobiliser for peripheral-blood stem-cell (PBSC) transplantation, in which CD34 is used as a marker of haemopoietic stem-cells. Likewise, most studies[1–4] of stem-cell transplantation in patients with myocardial infarction have used CD34 as a marker of stem cells for transplantation. The proven efficacy and safety of G-CSF both in healthy donors[6,7] and patients with haematological disease,[8] along with favourable results from studies of CD34+ cell transplantation in patients with myocardial infarction or ischaemia,[1–4] suggest that G-CSF based PBSC transplantation should be assessed in patients with myocardial infarction. However, the feasibility and safety of G-CSF and intracoronary infusion of PBSC mobilised by G-CSF in patients with acute and old myocardial infarction have not been studied. Additionally, no study has compared outcomes with G-CSF alone and G-CSF with additional intracoronary PBSC infusion with regard to cardiac function in patients with myocardial infarction. We aimed to test the feasibility and safety of these treatments in patients with myocardial infarction, and to assess their effectiveness with regard to improvement of cardiac function.

## Methods

### Study protocol

The study was a randomised, controlled phase II clinical trial. The institutional review board of Seoul National University Hospital approved the study protocol. We obtained informed written consent from patients after explaining the procedure and risk. The overall trial profile is shown in figure 1. At least 48 h after onset of acute myocardial infarction, patients underwent coronary angiography. Patients in whom the culprit lesion of the infarct-related artery was eligible for percutaneous coronary intervention (PCI), who were free from chest pain, and showed stable vital signs for at least 24 h, were randomised into one of three groups; cell infusion, G-CSF alone, or control group, by use of a randomisation table. Randomisation was done by a blinded independent co-ordinator; after randomisation, study processes were not blinded. In accordance with the recommendations of the institutional review board, the first three patients were not randomised and were assigned to the cell infusion



# Differential Effect of Intracoronary Infusion of Mobilized Peripheral Blood Stem Cells by Granulocyte Colony–Stimulating Factor on Left Ventricular Function and Remodeling in Patients With Acute Myocardial Infarction Versus Old Myocardial Infarction

## The MAGIC Cell-3-DES Randomized, Controlled Trial

Hyun-Jae Kang, MD; Hae-Young Lee, MD; Sang-Hoon Na, MD; Sung-A Chang, MD; Kyung-Woo Park, MD; Hyung-Kwan Kim, MD; Song-Yi Kim, MD; Ho-Joon Chang, MD; Whal Lee, MD; Won Jun Kang, MD; Bon-Kwon Koo, MD; Yong-Jin Kim, MD; Dong Soo Lee, MD; Dae-Won Sohn, MD; Kyou-Sup Han, MD; Byung-Hee Oh, MD; Young-Bae Park, MD; Hyo-Soo Kim, MD

***Background***—The efficacy of intracoronary infusion of granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells (PBSCs) has not been compared between patients with acute (AMI) versus old myocardial infarction (OMI). In addition, the potential risk of restenosis associated with G-CSF–based stem cell therapy has not been evaluated in the setting of drug eluting stent (DES) implantation.

***Methods and Results***—We randomly allocated 96 patients with myocardial infarction who underwent coronary revascularization with DES for the culprit lesion into 4 groups. Eighty-two patients completed 6-month follow-up; AMI cell infusion (n=25), AMI control (n=25), OMI cell infusion (n=16), and OMI control group (n=16). In cell infusion groups, PBSCs were mobilized by G-CSF for 3 days and delivered to infarcted myocardium via intracoronary infusion. The AMI cell infusion group showed a significant additive improvement in left ventricular ejection fraction (LVEF) and remodeling compared with controls (change of LVEF: +5.1±9.1% versus −0.2±8.6%, $P<0.05$; change of end-systolic volume: −5.4±17.0 mL versus 6.5±21.9 mL, $P<0.05$). In OMI patients, however, there was no significant change of LVEF and ventricular remodeling in spite of significant improvement of coronary flow reserve after cell infusion. G-CSF–based cell therapy did not aggravate neointimal growth with DES implantation.

***Conclusions***—Intracoronary infusion of mobilized PBSCs with G-CSF improves LVEF and remodeling in patients with AMI but is less definite in patients with OMI. G-CSF–based stem cell therapy with DES implantation is both feasible and safe, eliminating any potential for restenosis. (***Circulation*. 2006;114[suppl I]:I-145–I-151.)**

**Key Words:** myocardial infarction ■ stem cell ■ G-CSF

Recent clinical studies[1–6] reported favorable effects of stem cell transplantation in patients with acute myocardial infarction (AMI). However, the outcome has not been adequately evaluated in old myocardial infarction (OMI) patients. Granulocyte colony-stimulating factor (G-CSF)–based stem cell therapy has been proposed as a practical and noninvasive alternative to stem cell therapy using bone marrow stem cells. Because G-CSF alone has only shown equivocal benefits in previous clinical trials,[5,7,8] G-CSF might be considered mostly as a mobilizer to enrich peripheral blood stem cells (PBSCs). Despite the potential adverse effects increasing vascular events,[9–11] short-term use of G-CSF in patients with myocardial infarction (MI) seems safe.

Previously, we reported that, in patients with MI, intracoronary infusion of PBSCs improved cardiac function and exercise capacity, whereas the administration of G-CSF alone did not.[5] Additionally, we suggested the possibility of aggravated restenosis after G-CSF administration. Therefore, in the Myocardial Regeneration and Angiogenesis in Myocardial

From the Cardiovascular Laboratory, Clinical Research Institute (H-J.K., H-Y.L., S-H.N., S-A.C., K-W.P., H-K.K., S-Y.K., H-J.C., B-K.K., Y-J.K., D-W.S., B-H.O., Y-B.P., H-S.K.), Cardiovascular Center (H-J.K., H-Y.L., S-H.N., S-A.C., K-W.P., H-K.K., S-Y.K., H-J.C., B-K.K., Y-J.K., D-W.S., B-H.O., Y-B.P., H-S.K.), Department of Internal Medicine (H-J.K., H-Y.L., S-H.N., S-A.C., K-W.P., H-K.K., S-Y.K., H-J.C., B-K.K., Y-J.K., D-W.S., B-H.O., Y-B.P., H-S.K.), Department of Radiology (W.J.L.), Department of Nuclear Medicine (W.J.K., D.S.L.), and Department of Laboratory Medicine (K-S.H.), Seoul National University Hospital, Seoul, Korea

Drs H-J. Kang and H-Y. Lee contributed equally to this study.

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# Conclusions

1. *Total ischemic time*
2. *Adjunctive device for primary PCI : evidence-based use*
3. *Pre- or post-conditioning to reduce ischemia-reperfusion injury : not yet evidenced*
4. *The mitochondrion and mPTP are a potential untapped target for the future novel adjunctive treatment.*
5. *PostMI myocardial regeneration should be further investigated.*

# Thank You For Your Attention!

Seoul National University Bundang Hospital