INNOVATION

*I*mpact of Primary versus Deferred Ste*n*t Impla*n*tation on I*n*farct Size and Micr*o*vascular obstruction in Patients with ST-segment Ele*va*tion Myocardial Infarc*tion*

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On behalf of Je Sang Kim[2], Hyun Jong Lee[2], Yang Min Kim[2], Soon Jun Hong[1], Jae Hyoung Park[1], Rak Kyeung Choi[2], Young Jin Choi[2], Jin Sik Park[2], Tae Hoon Kim[2], Ho Joon Jang[2], Hyung Joon Joo[1], Won Heum Shim[2], Youn Moo Rho[2] and Do-Sun Lim[1]

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Disclosure Statement of Financial Interest

Within the past 36 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

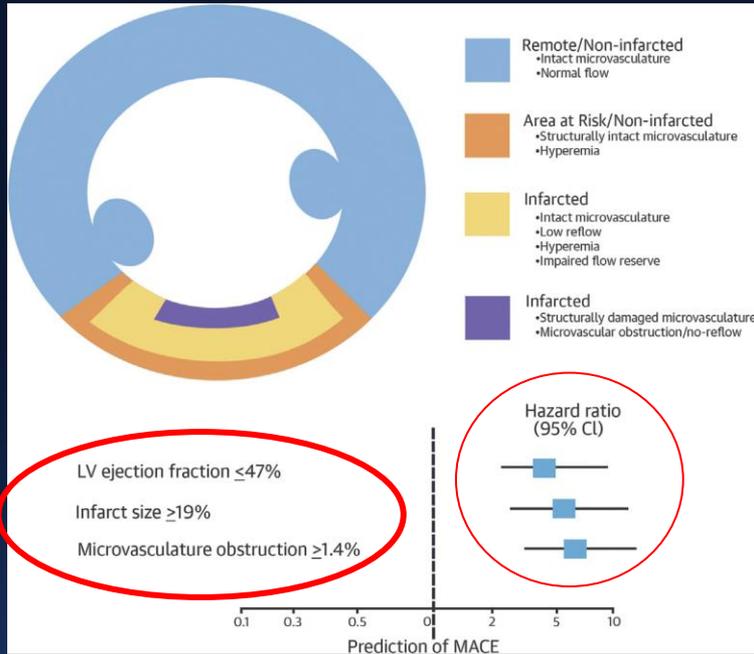**Affiliation/Financial Relationship**

- Grant/Research Support

- Korean Society of Interventional Cardiology
- Sejong Medical Research Institute
- Terumo corporation
- ISU ABXIS CO., LTD.

Backgrounds (I)

- Even after reopening of infarct-related artery, considerable number of patients have perfusion abnormality of myocardium, which is called as myocardial no-reflow.

- The myocardial no-reflow is produced by microvascular obstruction (MVO) secondary to distal embolization of clot, microvascular spasm, infarct tissue edema, and thrombosis.

- Primary PCI with immediate stenting is the current standard of care for STEMI but may have additional injury to myocardium by increasing distal embolization of clot.

Backgrounds (II)

Different Regions of Microvascular Flow After Acute Reperfused STEMI

Remote/Non-infarcted
• Intact microvasculature
• Normal flow

Area at Risk/Non-infarcted
• Structurally intact microvasculature
• Hyperemia

Infarcted
• Intact microvasculature
• Low reflow
• Hyperemia
• Impaired flow reserve

Infarcted
• Structurally damaged microvasculature
• Microvascular obstruction/no-reflow

Hazard ratio
(95% CI)

LV ejection fraction $\leq$47%

Infarct size $\geq$19%

Microvasculature obstruction $\geq$1.4%

0.1 0.3 0.5 0 1 2 5 10
Prediction of MACE

Bekkers SC, et al. J Am Coll Cardiol 2010;55:1649–60.

- MVO size%LV, infarct size%LV, and EF are well known prognostic factor after reperfused STEMI and well assessed by cardiac magnetic resonance imaging   .

- Several studies demonstrated that MVO size has the best prognostic value of all CMR parameters.

- As a result ,treatment strategies, including both pharmacological and non-pharmacological strategies have begun to target MVO.

- However, there is currently a few definitive proof that any agent or intervention at the time of reperfusion reduces MVO and thus results in improved prognosis.

Objectives

- **The aim of this study is to assess whether deferred stenting reduce infarct size and MVO (incidence and size) compared with immediate stenting in primary PCI for STEMI**

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INNOVATION Trial Design

Symptoms of STEMI within 12 hours
ST-segment elevation ≥2 mm in ≥2 continuous ECG leads
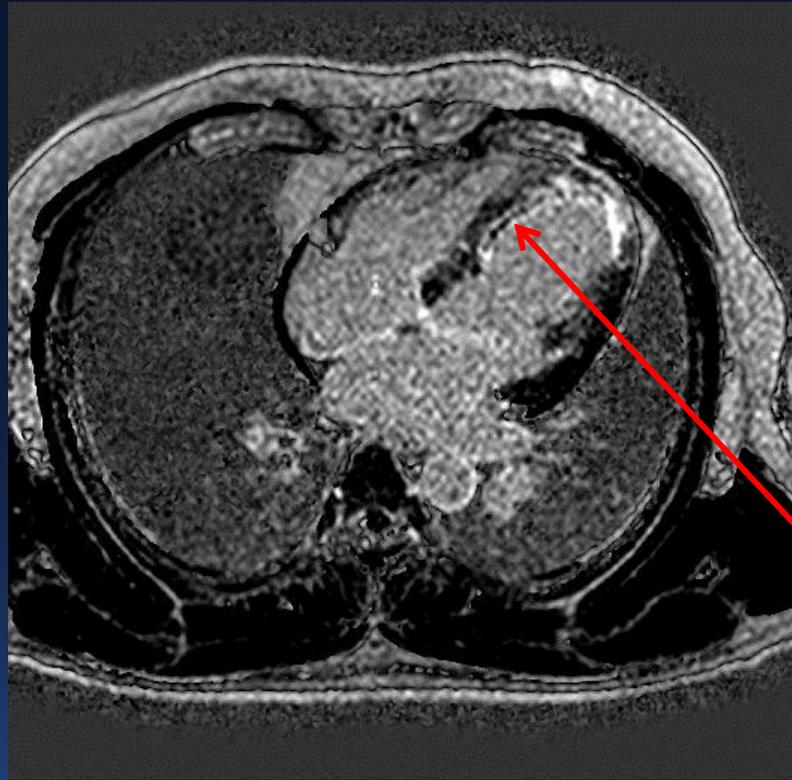Achieving TIMI III flow after initial procedure for STEMI

Randomize 1:1

Immediate stenting

Deferred stenting
with intention-to-stent 3 to 7 days later

**Cardiac MRI at 30 to 35 days after primary reperfusion
Evaluation for CMR parameters; IS%LV, MVO, MVO/IS ratio, and EF at Core lab**

Contrast cardiac magnetic resonance imaging protocols and analysis

- Same Machine and protocol at 2 centers:1.5-T whole body scanner (Intera CV,Philips Medical Systems, Best, The Netherlands) equipped with a dedicated 5-channel phase-array surface cardiac coil

- Infarct tissue: an area of hyperenhancement on LGE images

- MVO : an area of hypoenhancement within the hyperenhanced infarct tissue.

- Quantitative core-lab measurements for infarct and MVO sizes were performed with manual planimetry using extended MR workspace 2.6.3.1 (Philips Healthcare, Best, The Netherlands) by a cardiac radiologist blinded to random assignment.

Endpoints

- **The primary endpoint**
  - **Infarct size % LV** at 30 to 35 days after primary reperfusion assessed by cardiac magnetic resonance (CMR) imaging.

- **The secondary endpoints**
  - The incidence and size of MVO%LV and the ratio of MVO volume/infarct size by CMR

The other secondary endpoints

- **Peak CK-MB**

- **Complete ST resolution (>70%)**

- **Corrected TIMI frame count**

- **Incidence of slow or no reflow**

- **Myocardial brush grade 3**

- **TIMI myocardial perfusion grade 3**

Exclusion criteria

- 12 Presentation 12hr after onset of chest pain
- 34 Initial TIMI 3 flow
- 33 Cardiogenic shock
- 18 Previous history of myocardial infarction
- 1 Previous history of coronary artery bypass graft
- 2 Rescue PCI after fibrinolysis
- 1 Acute left main occlusion
- 9 STEMI due to stent thrombosis
- 1 Major coronary dissection (type D~F) before randomization
- 26 TIMI 3 flow was not achieved before randomization
- 42 Physician did not want randomization because of safety issue.
- 4 Vasospasm
- 7 Others

Baseline Characteristics

	Primary stenting n = 57	Deferred stenting n = 57	P Value
Age, years	59.2 ± 10.3	59.9 ± 13.2	0.770
Male	47 (82.5)	48 (84.2)	0.999
DM	17 (29.8)	18 (31.6)	0.999
HTN	18 (31.6)	36 (63.2)	0.008
Dyslipidemia	17 (29.8)	23 (40.4)	0.327
PAOD	1 (1.8)	0	0.999
Previous PCI	0	2 (3.5)	0.496
Previous CVA	3 (5.3)	3 (5.3)	0.999
Chronic renal failure	3 (5.3)	3 (5.3)	0.999
Anterior wall MI	37 (64.9)	32 (56.1)	0.399
LVEF	46 ± 13	45 ± 10	0.576

Baseline Characteristics

	Primary stenting n = 57	Deferred stenting n = 57	P Value
Killip class on admission			0.986
1	55 (96.4)	54 (94.7)	
2 or 3	2 (3.6)	3 (4.3)	
Systolic blood pressure	131 ± 25	128 ± 20	0.530
Diastolic blood pressure	79 ± 20	79 ± 12	0.969
Aspirin	57 (100)	56 (98.2)	0.999
Thienopyridine	57 (100)	56 (98.2)	0.999
Intensive Statin tx	57 (100)	54 (94.7)	0.243
ACEI or ARB	38 (66.7)	42 (73.7)	0.539
Beta-blocker	48 (84.2)	48 (84.2)	0.999

Angiographic and procedural characteristics

	Primary stenting n = 57	Deferred stenting n = 57	P Value
Infarct- related artery			0.199
Left anterior descending artery	37 (64.9)	32 (56.1)	
Left circumflex artery	4 (7.0)	1 (1.8)	
Right coronary artery	16 (28.1)	24 (42.1)	
Number of diseased vessels			0.275
1	17 (29.8)	24 (42.1)	
2	25 (43.9)	20 (35.1)	
3	15 (26.3)	13 (22.8)	
TIMI flow before PCI			0.907
0~1	47 (82.5)	45 (78.9)	
2	10 (17.5)	12 (21.1)	

Angiographic and procedural characteristics

	Primary stenting n = 57	Deferred stenting n = 57	P Value
TIMI flow before randomization			**0.560**
0-1	0	0	
2	1 (1.8)	2 (3.5)	
3	56 (98.2)	55 (96.5)	
TIMI thrombus grade			**0.675**
1	1 (1.8)	2 (3.5)	
2	1 (1.8)	0	
3	5 (8.8)	5 (8.8)	
4	6 (10.5)	9 (15.8)	
5	44 (77.2)	41 (71.9)	

Angiographic and procedural Characteristics

	Primary stenting n = 57	Deferred stenting n = 57	P Value
Door to TIMI 3 flow time (min)	56 [42-84]	58 [44-70]	0.993
TIMI 3 flow to stenting time (min)	8 [5-12]	4358 [3118-5816]	<0.001
Abciximab use	40 (70.2)	44 (77.2)	0.524
Stenting in culprit lesion	57 (100)	53 (92.9)	0.118
Stent diameter in IFA	3.1 ± 0.4	3.4 ± 0.4	0.011
Stent length in IFA	24 ± 7	24 ± 7	0.716
Total stent number	1.2 ± 0.4	1.1 ± 0.6	0.197
Total stent length	27 ± 13	25 ± 13	0.306
Complete revascularization	47 (82.5)	45 (78.9)	0.813

Strategies to achieve TIMI 3 flow
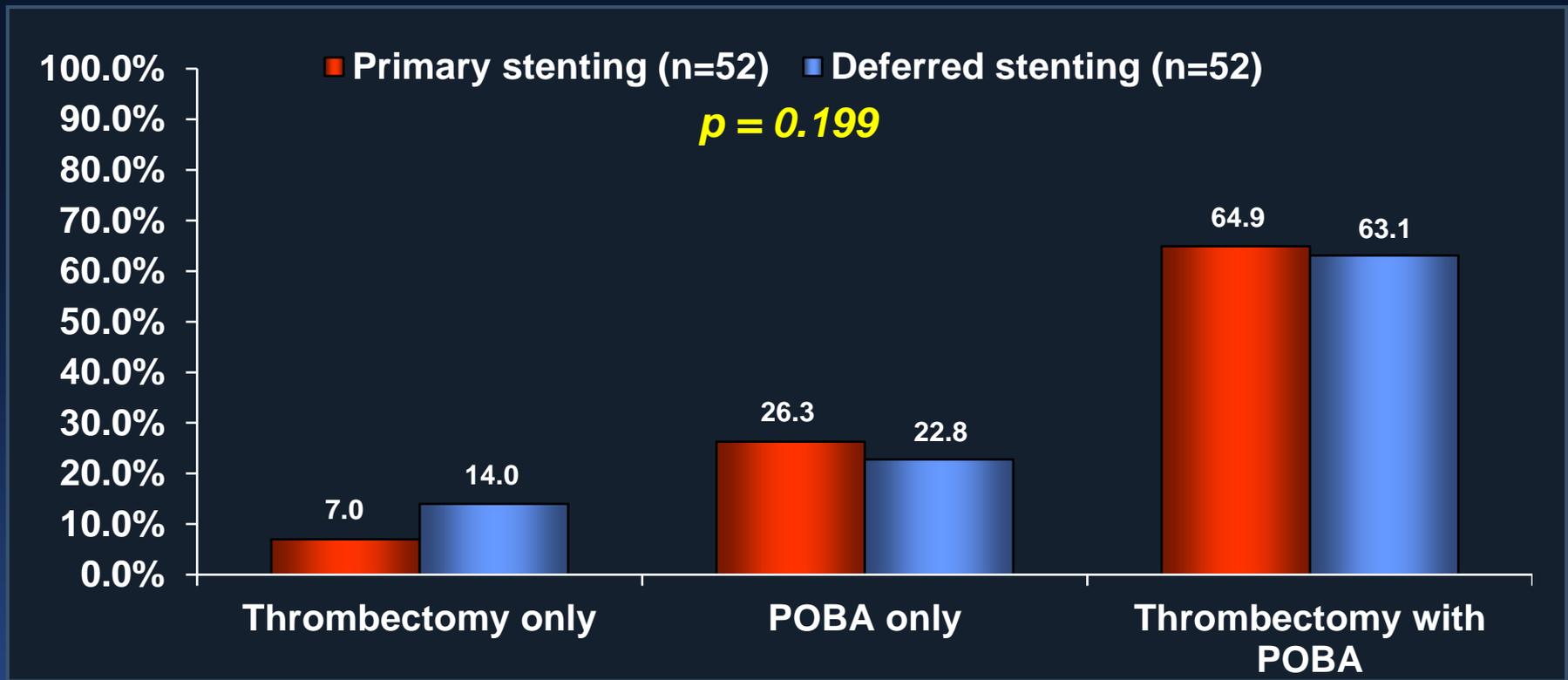
CMR parameters after stent implantation (ITT)

Overall Patients

	Primary stenting (n=52)	Deferred stenting (n=52)	P-value
Reperfusion to C-MRI time (days)	31 [28-34]	31 [28-34]	0.440
Left ventricular mass (g)	89 ± 17	93 ± 24	0.340
Infarct mass (g)	16.7 ± 11.0	14.9 ± 12.5	0.443
MVO mass (g)	0.6 ± 0.7	0.3 ± 0.6	0.041
MVO to infarct ratio	2.5 ± 3.0	1.3 ± 1.9	0.019
LVEF (%)	50 ± 10	53 ± 10	0.213

Infarct size%LV and MVO size %LV by CMR after stent implantation (ITT)
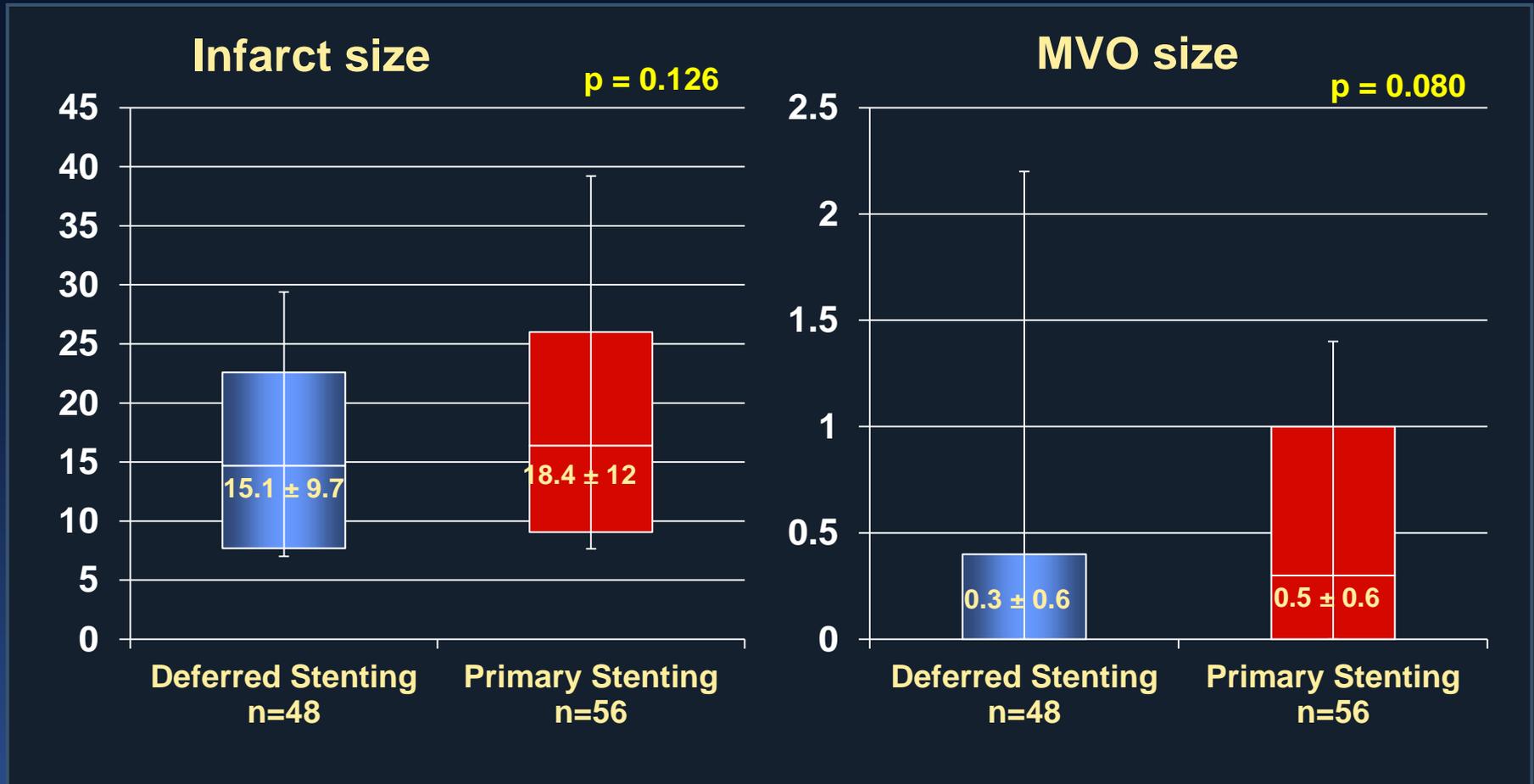

Infarct size

p = 0.069
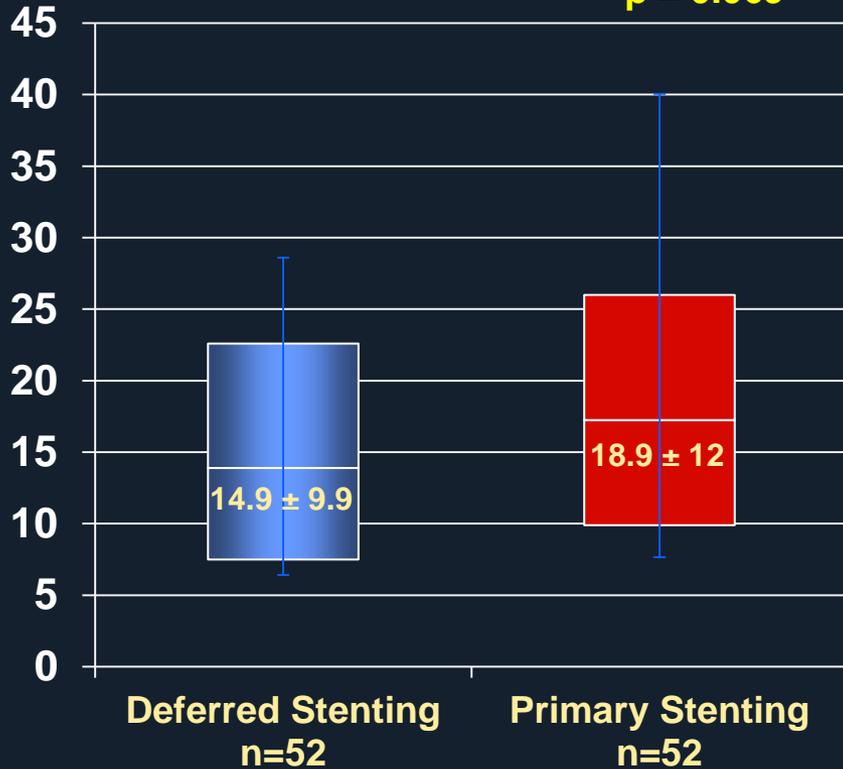
Deferred Stenting: 14.9 ± 9.9
Primary Stenting: 18.9 ± 12

Deferred Stenting n=52
Primary Stenting n=52

MVO size

p = 0.051

Deferred Stenting: 0.3 ± 0.6
Primary Stenting: 0.6 ± 0.7

Deferred Stenting n=52
Primary Stenting n=52
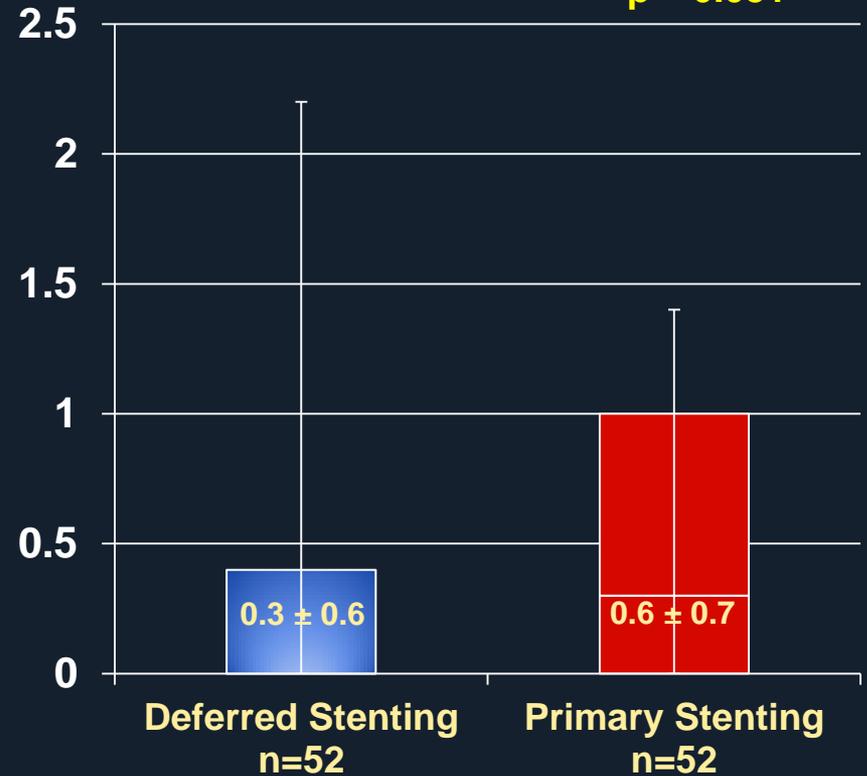
Overall patients

Infarct size % LV and MVO size %LV by CMR after stent implantation (ITT)
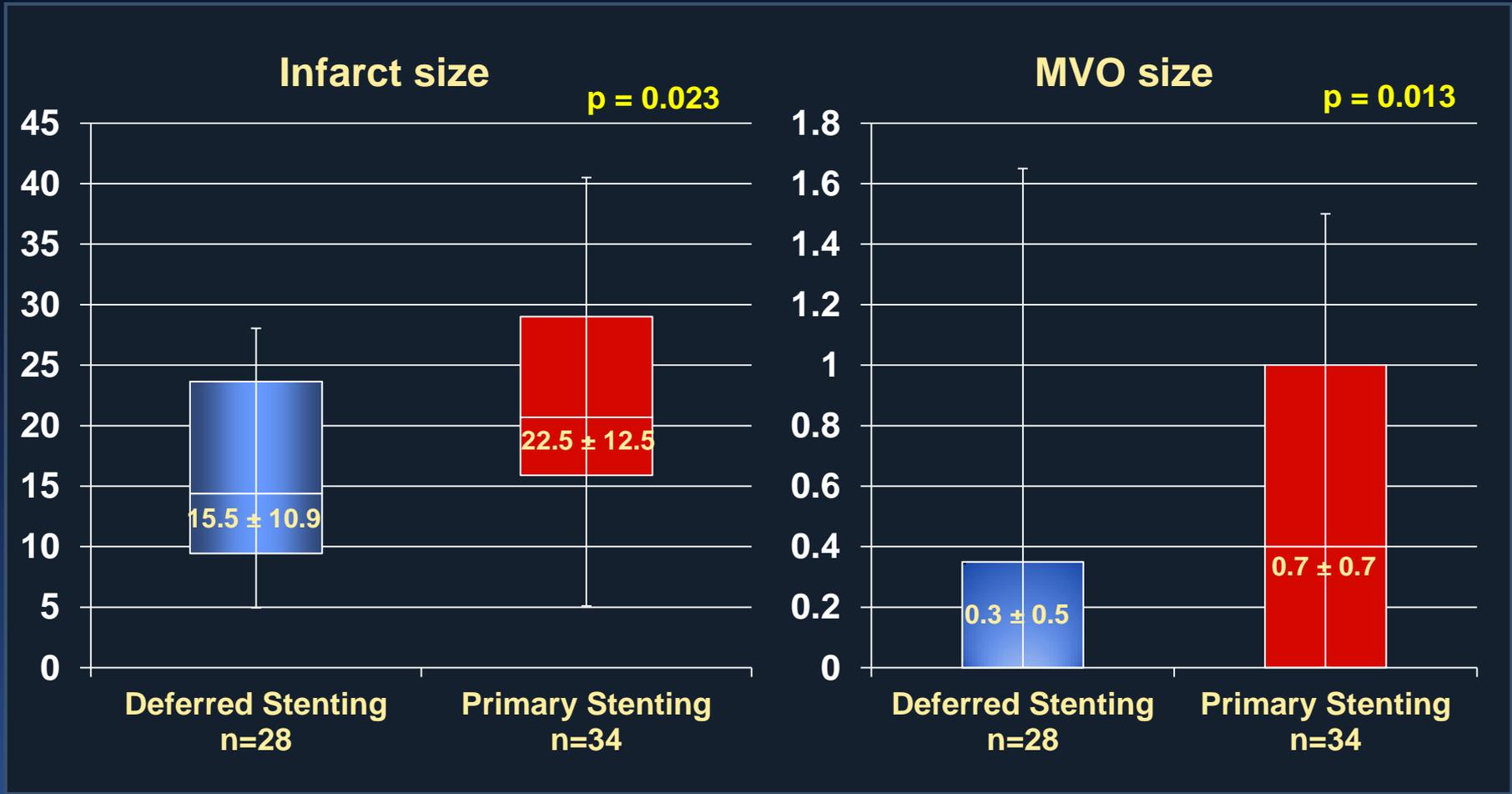
Ant Wall MI patients

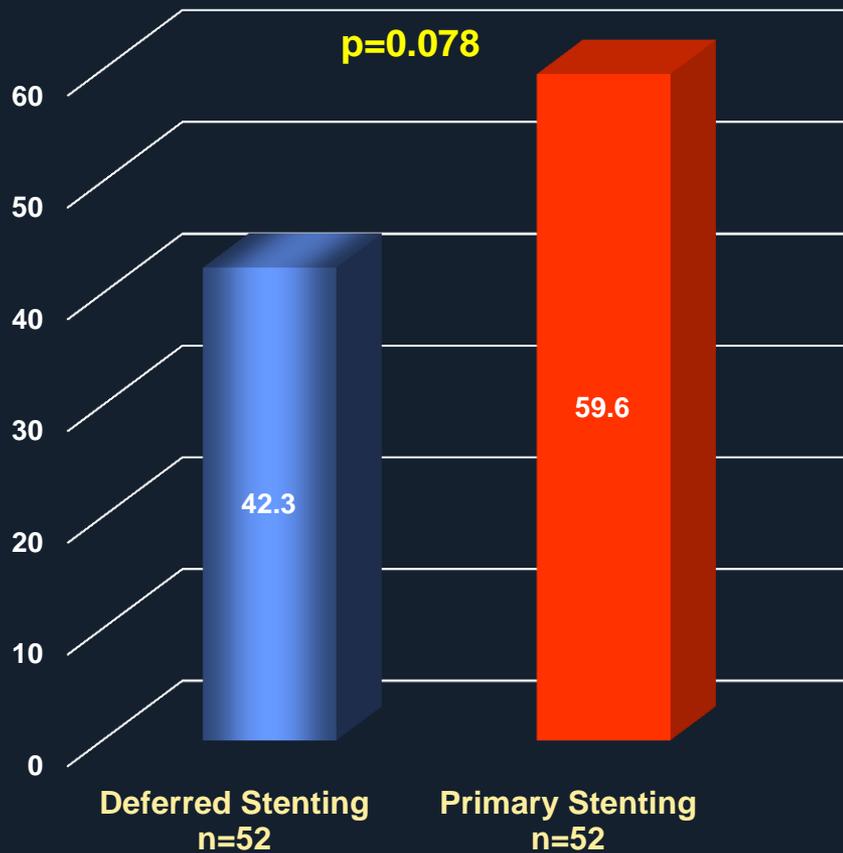# Infarct size%LV and MVO size%LV by CMR after stent implantation (As-treated)

Overall patients

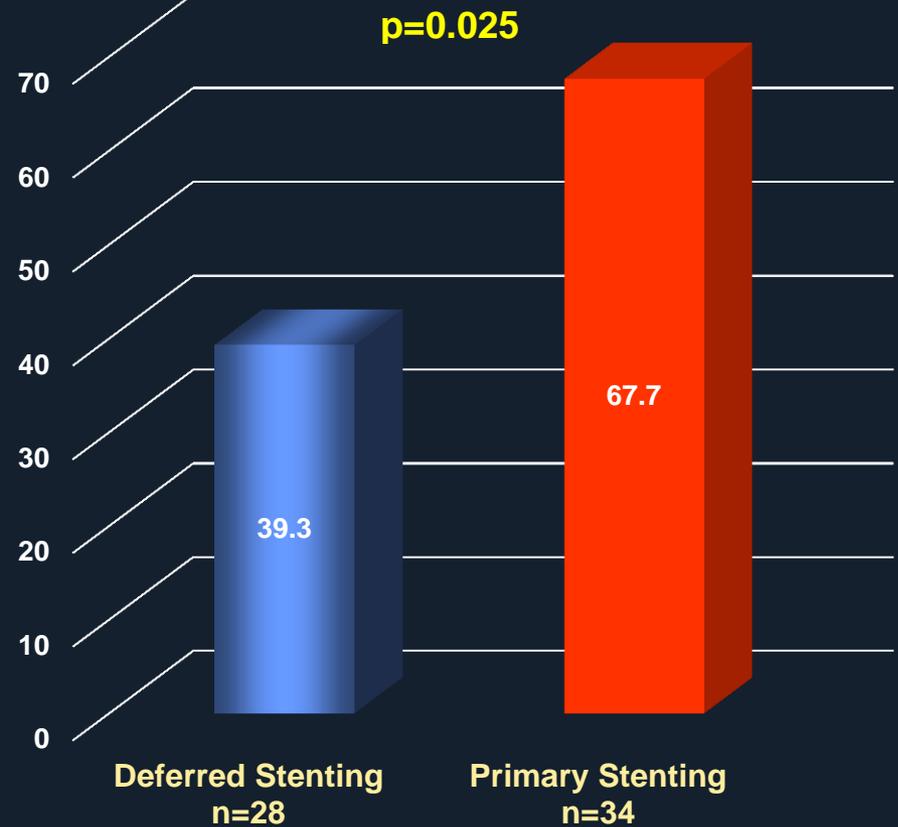# Infarct size and MVO size by CMR after stent implantation (As-treated)

Infarct size

p = 0.013

Deferred Stenting
n=27 — 15 ± 10.4

Primary Stenting
n=35 — 22.7 ± 12.6

MVO size

p = 0.006

Deferred Stenting
n=27 — 0.2 ± 0.5

Primary Stenting
n=35 — 0.7 ± 0.7
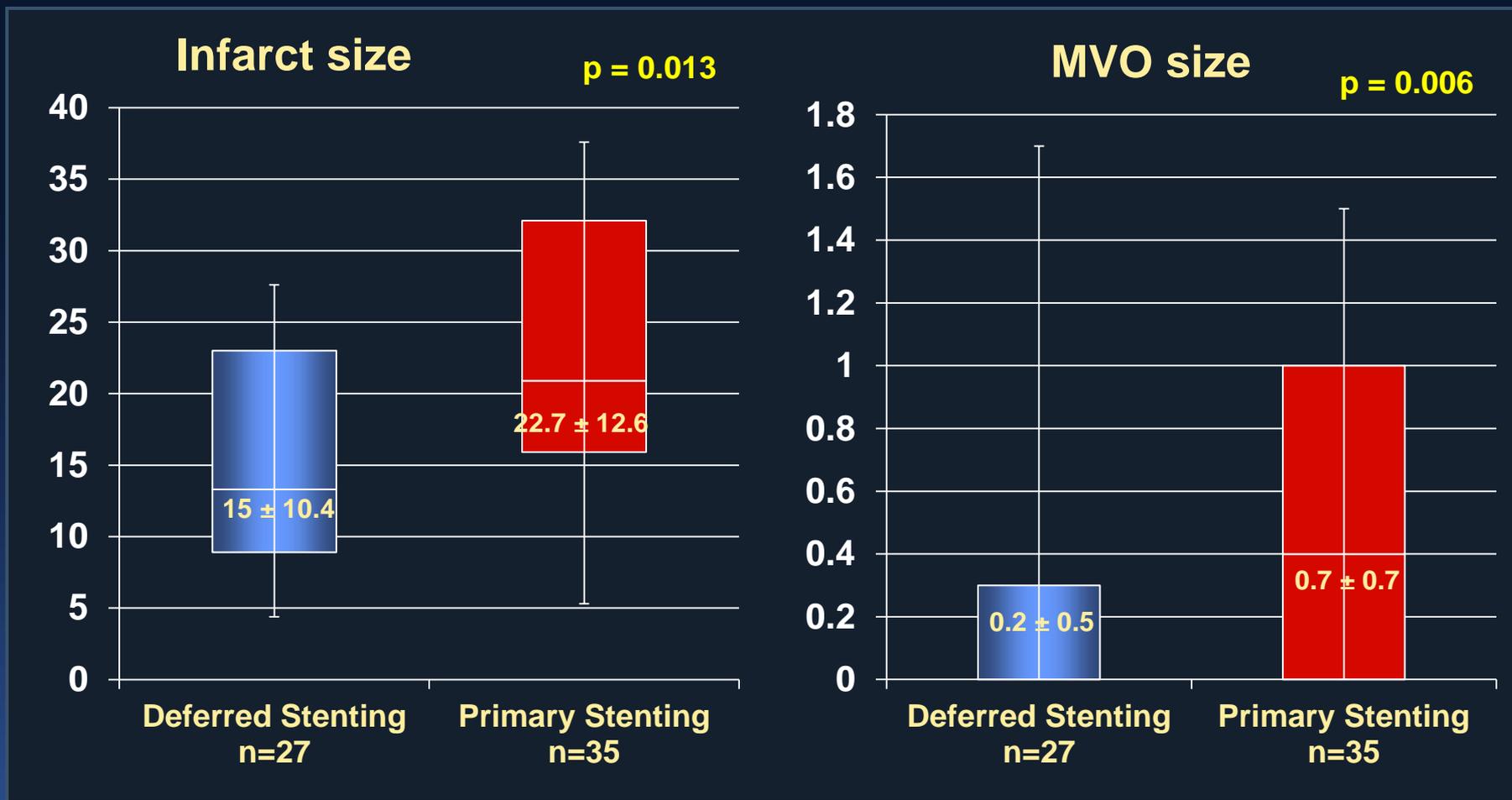
Ant Wall MI patients

MVO incidence (ITT)

Overall patients

Ant wall MI patients

MVO incidence (As-treated)

# 2nd endpoints after stent implantation (ITT)

Overall Patients

	Primary stenting (n=57)	Deferred stenting (n=57)	P-value
Peak CK-MB	260 ± 173	199 ± 136	0.039
Complete ST resolution (>70%)	21 (36.8)	25 (44.6)	0.447
Corrected TIMI frame count	28 ± 23	25 ± 11	0.384
Incidence of slow or no reflow	20 (35.1)	13 (22.8)	0.148
Myocardial brush grade 3	28 (49.1)	39 (68.4)	0.057
TIMI myocardial perfusion grade 3	18 (31.6)	28 (49.1)	0.085

Safety of deferred stenting

Residual stenosis

Coronary dissection
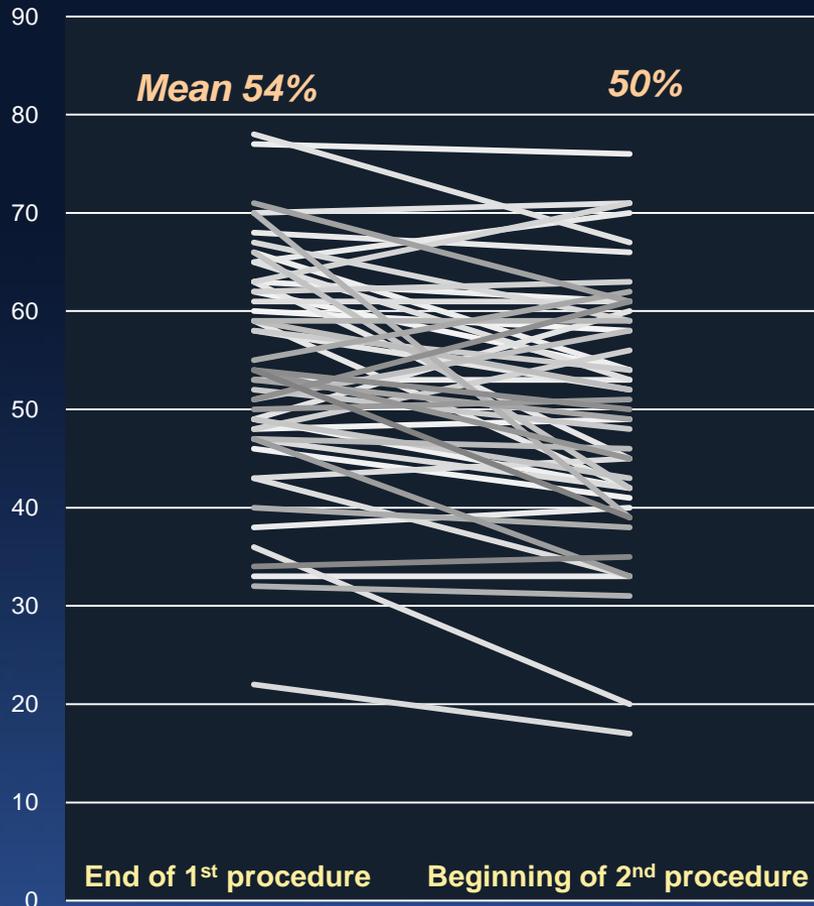
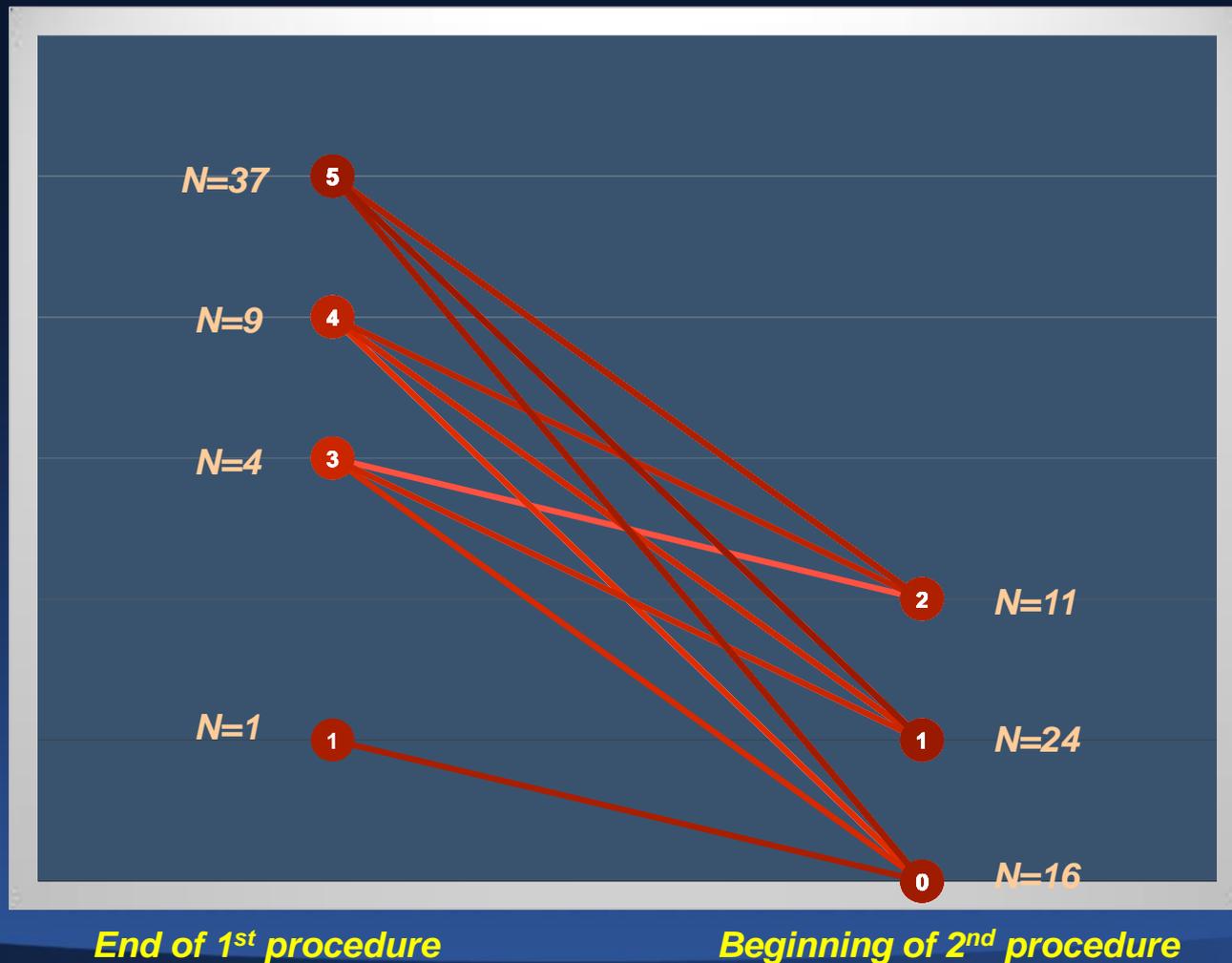
>10% progression of RS in only 2 (3.9%) among 51 patients with deferred stenting

Progression of dissection in only 2 (3.5%) among 51 patients who randomized to deferred stenting (type A->B)

Safety of deferred stenting

TIMI thrombus grade
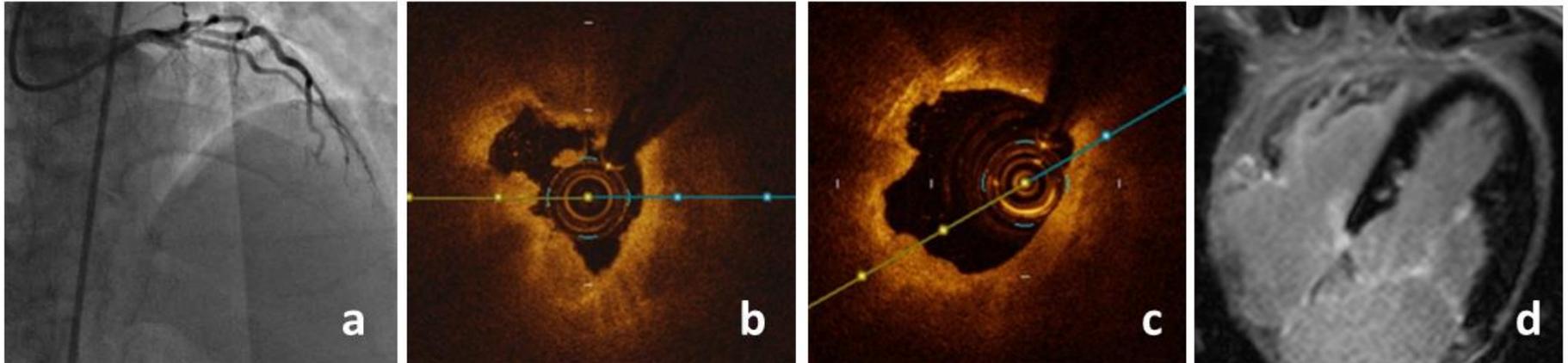*51 patients with deferred stenting*

N=37 — 5
N=9 — 4
N=4 — 3
N=1 — 1

2 — N=11
1 — N=24
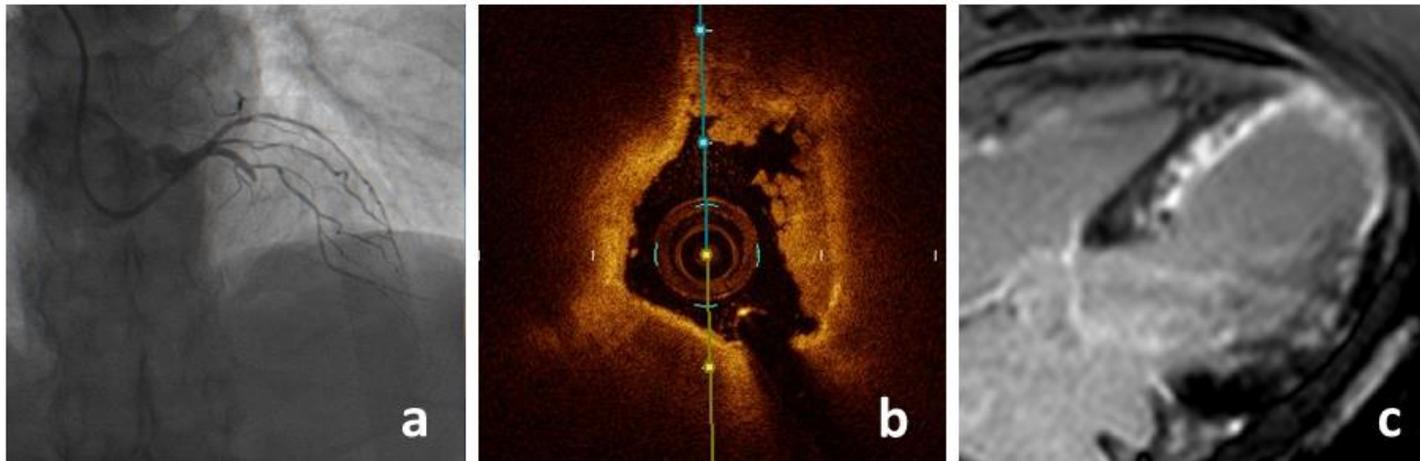0 — N=16

End of 1st procedure   *Beginning of 2nd procedure*

Deferred vs. Immediate stenting examples

Limitations

- **Modest sample size, not powered for efficacy.**

- **Investigators and patients were unblinded but primary and 2nd endpoints underwent independent analysis blind to random assignment.**

- **Because high crossover rate in deferred stenting group was observed during initial procedure, it may have effect on absence of recurrent ischemia or ungent revascularization.**

- **Therefore, risk and benefit of deferred stenting strategy should be delineated.**

Conclusion

- **Deferred stenting showed a strong tendency to reduce infarct size, size & incidence of MVO, and statistically significant reduction of MVO/infarct ratio in overall patients.**

- **Especially in anterior wall MI patients, deferred stenting reduced all CMR parameters very significantly.**

- **Deferred stenting could be performed without additional risk of adverse events with meticulous monitoring during initial procedure, compared with immediate stenting.**

Thank you for your attetion!

- **Why slow/no reflow is not different btw 2groups despite of difference of MVO?**

- **-> Extreme manifestion of MVO was slow or no reflow. Many patients with MVO show normal flow.**

- **Only 33% of patient with normal epicaridal artery flow after reperfused STEMI have normal micorvascular perfusion.**