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Intracoronary infusion of BM-MNC early or late after AMI - 4 months results of the SWISS-AMI trial

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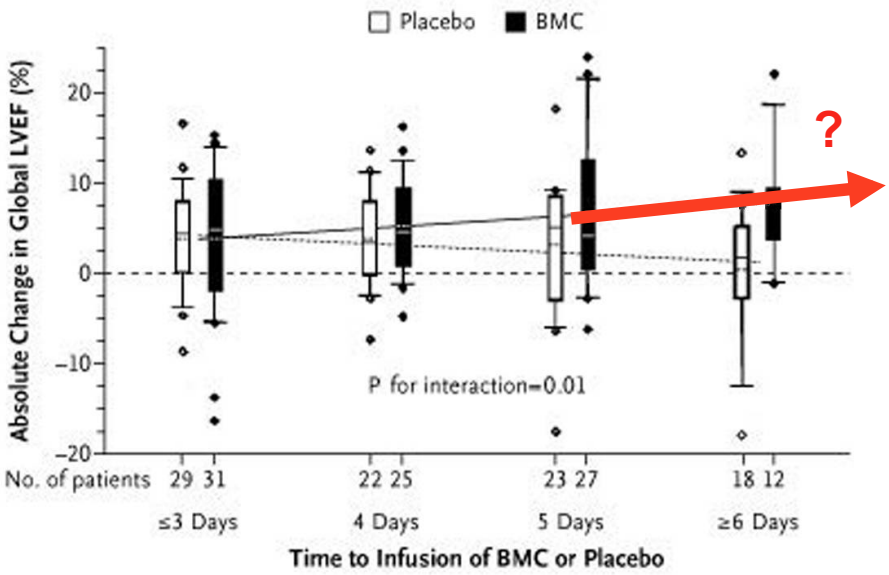
Background

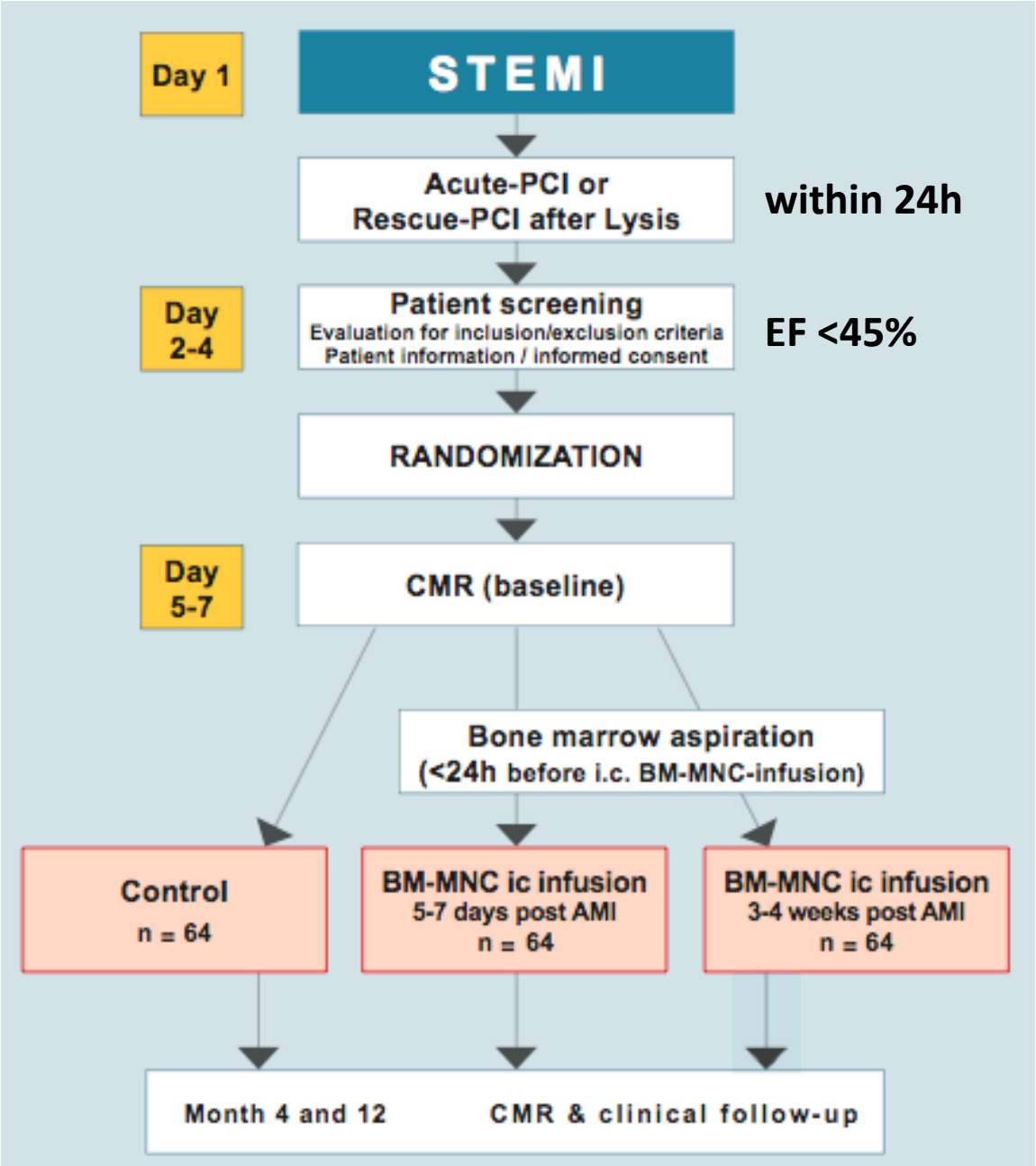
Intracoronary BM-MNC infusion in the infarct related artery after AMI has been shown to be safe; however, its efficacy is still debated.

Optimal timing for cell delivery post-AMI is unknown. Previous studies indicated potential time dependent efficacy in subgroup analyses.



Schächinger V, et al *N Engl J Med* 2006

Study design & Methods



BM-MNC

- BM-Aspiration from the iliac crest (60ml)
- Centralized cell processing using density gradient centrifugation, without adding Heparin *(UTC Lugano)*

CMR

- Standardized protocol including cine and delayed enhancement
- Core-lab analysis *(University Hospital Zurich)*

Sürder et al. *Am Heart J 2010*

Endpoints & sample size

Primary endpoint:

→ Change in global LVEF at 4 mo. vs. baseline

→ *Assumption: Δ LVEF = 3.5%; SD of 6-7%; drop out = 10%*

→ *For a independent sample t-test 58 paired CMR per group are needed - including drop out* → ***n = 64 per group***

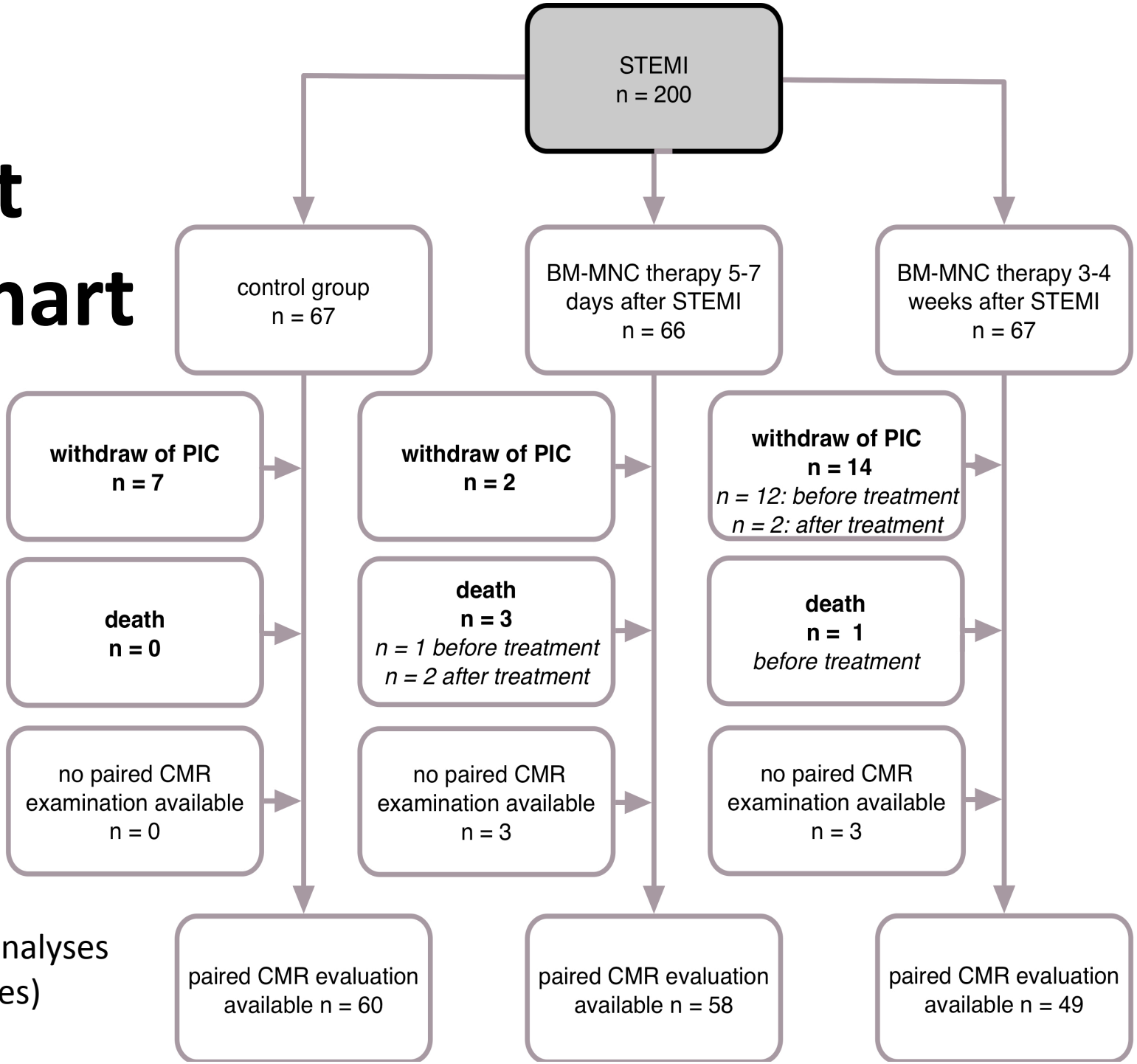
Secondary endpoints:

→ Change in LV volumes, infarct size (DE CMR) and regional myocardial thickening

→ MACE (death, MI, coronary revascularization, stroke)

→ Predictors for efficacy (time to reperfusion, transmurality, microvascular obstruction)

Patient flow chart



Total 345 CMR analyses
(24.430 slices)

Baseline characteristics of the patients

	Control (n = 67)	Early (n = 65)	Late (n = 63)	p-value
Age – years (median; IQR)	56 (14.5)	55 (15)	62 (15)	0.70 * 0.06 ‡
BMI - kg/m2 (median; IQR)	26.7 (4.4)	27.0 (6.1)	27.0 (4.4)	0.92 * 0.89 ‡
Male gender - %	83.6	86.2	82.5	0.18 * 1.00 ‡
Hypertension - %	43.3	49.2	38.7	0.60 * 0.72 ‡
Hyperlipidemia - %	44.8	40.0	41.9	0.60 * 0.86 ‡
Diabetes - %	17.9	7.7	9.7	0.12 * 0.21 ‡
Smoking (active/previous) - %	62.7	67.7	40.3	0.60 * 0.01 ‡
Familiary history of CAD - %	35.8	26.1	24.2	0.26 * 0.18 ‡
1 / 2 / 3 vessel disease %	64/21/15	54/32/14	57/27/16	0.34 * 0.73 ‡
Previous PCI before AMI - %	3.0	3.1	1.6	1.00 * 1.00 ‡

* control vs. early
‡ control vs. late

Characteristics of index AMI

	Control (n = 67)	Early (n = 65)	Late (n = 63)	p-value
Primary PCI – %	94.0	98.5	100.0	0.37 * 0.12 ‡
Concomitant PCI other than infarct related artery – %	18.2	12.3	11.1	0.47 * 0.32 ‡
Infarct vessel LAD/LCX/RCA -%	89/3/8	95/2/3	92/3/5	0.51 * 0.89 ‡
Pain to revascularization time (h)	4.5 (5)	4.8 (5.4)	4.0 (4.8)	0.57 * 0.53 ‡
Stent diameter (mm)	3.5 (0.5)	3.0 (0.5)	3.5 (0.5)	0.73 * 0.89 ‡
Drug eluting stent – %	71.6	80.0	81.0	0.31 * 0.23 ‡
TIMI flow before/after PCI	0/3 (0/0)	0/3 (0/0)	0/3 (0/0)	0.31/0.94 * 0.87/0.81 ‡
Use of Glycoprotein IIb/IIIa inhibitors / bivalirudin - %	71.7	78.5	78.1	0.88 * 0.20 ‡
Maximal creatin kinase - U/l (median;IQR)	3671 (3685)	4314 (3561)	3436 (3813)	0.22 * 0.78 ‡
Baseline nt-pro BNP - ng/l (median;IQR)	1103 (1848)	1450 (1442)	1581 (1912)	0.15 * 0.10 ‡
Baseline LVEF - % (median;IQR)	39.6 (11.2)	34.6 (16.1)	35.6 (11.2)	0.07 * 0.03 ‡
Baseline LVEDV – ml (median;IQR)	154 (44)	153 (49)	149 (47)	0.89 * 0.96 ‡
Baseline LVESV – ml (median;IQR)	94 (35)	94 (41)	97 (38)	0.54 * 0.41 ‡

* control vs. early
‡ control vs. late

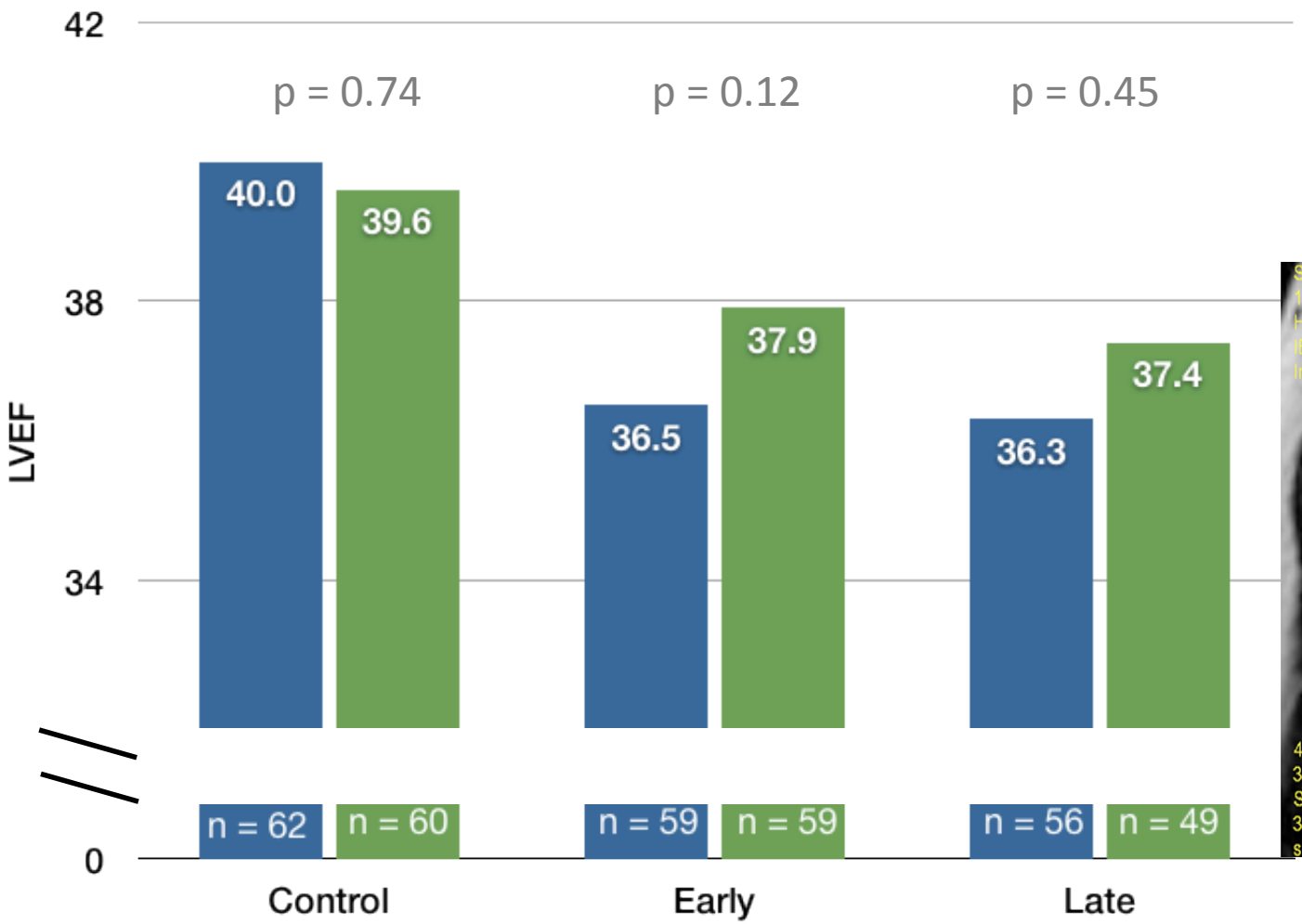
Characteristics of BM-MNC

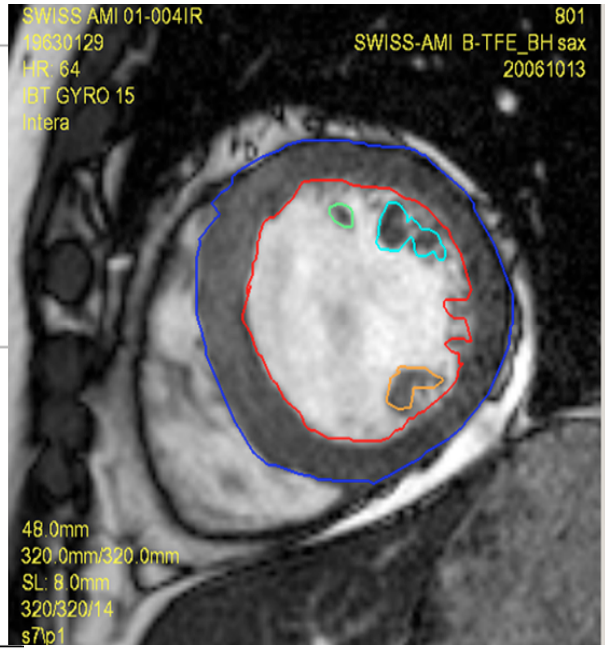
	Early n = 62	Late n = 52	p-value (between group difference)
Cell characteristics (Median, IQR)			
BM aspiration volume (ml)	65 (15)	70 (15)	0.30
Total MNC (10^6 cells)	159.7 (125.8)	139.5 (120.5)	0.18
Viability - %	93.6 (5.55)	93.33 (6.60)	0.98
% CD 34+ cells	1.02 (0.72)	1.31 (0.97)	0.01 #
Total CD 34+ cells (10^6 cells)	1.6 (1.69)	1.45 (2.43)	0.68
% CD 133+ cells	82.65 (28.1)	78.45 (52.83)	0.34
Total CD 133+ cells (10^6 cells)	0.96 (1.46)	0.92 (2.06)	0.77
% Invasion	33 (18) *	26.5 (16.5) **	0.18
Invasion index	50.88 (24.38)*	45.64 (22.10) **	0.21
Timing of BM-MNC treatment			
Days after AMI (Median, IQR)	6 (2)	24 (7)	NA

* n = 29
** n = 30

Results

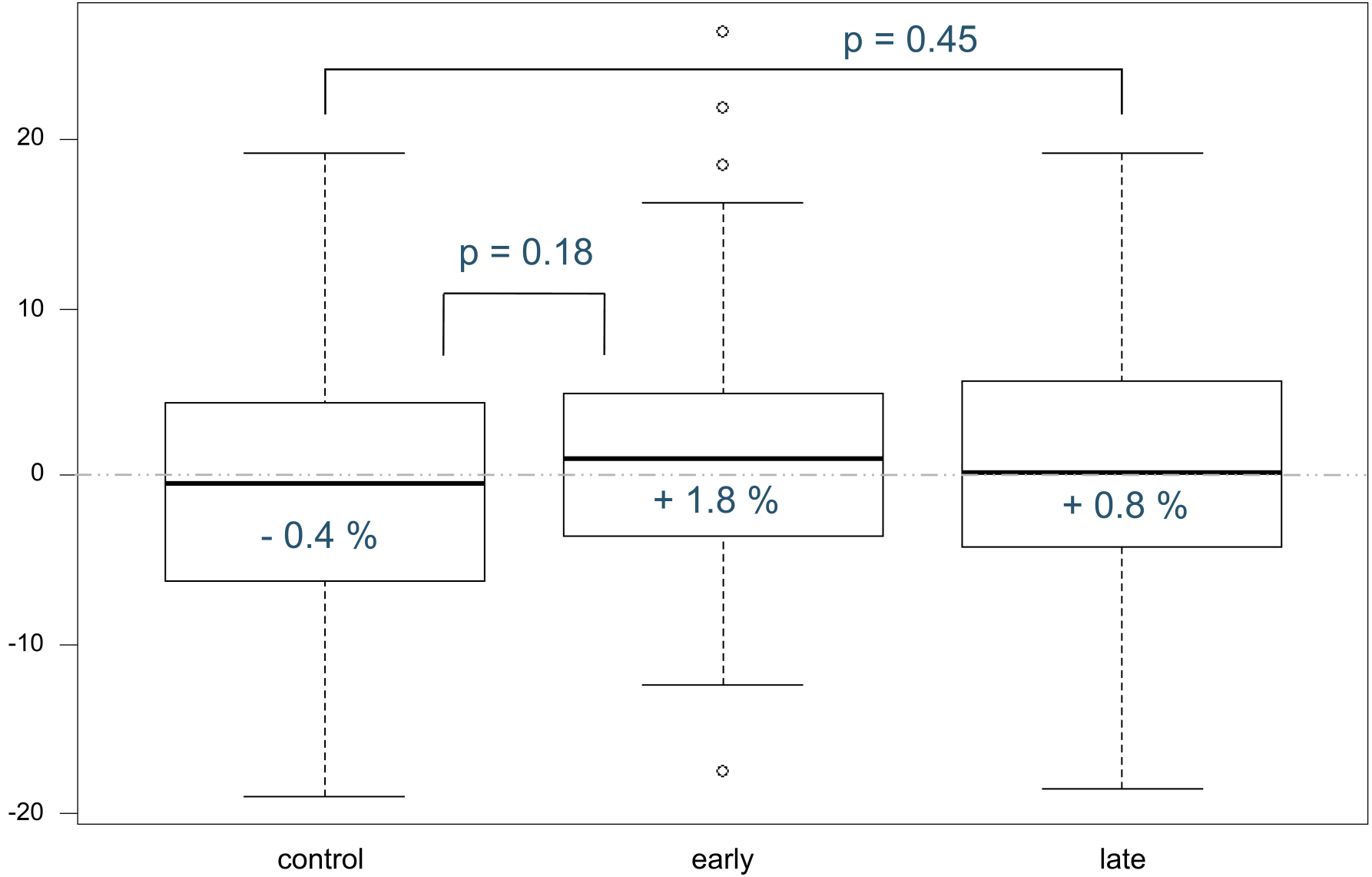
Mean LVEF at baseline and 4 months





Primary Endpoint

Mean change in LVEF 4 months vs. baseline

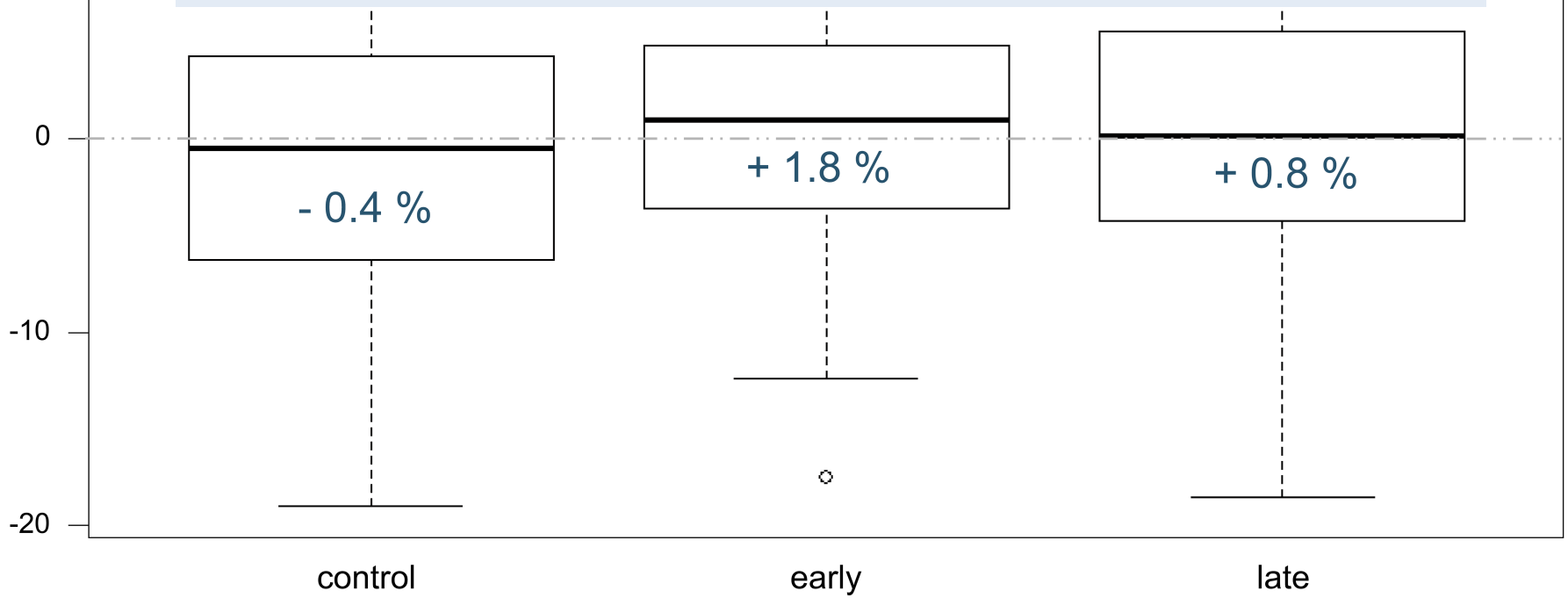


Primary Endpoint

Mean change in LVEF 4 months vs. baseline

Adjusting for baseline LVEF with ANCOVA testing:

Estimate (95%CI)	*p-value*	
1.25 (-1.83 to 4.32)	**0.42**	**early vs. control**
0.55 (-2.61 to 3.71)	**0.73**	**late vs. control**



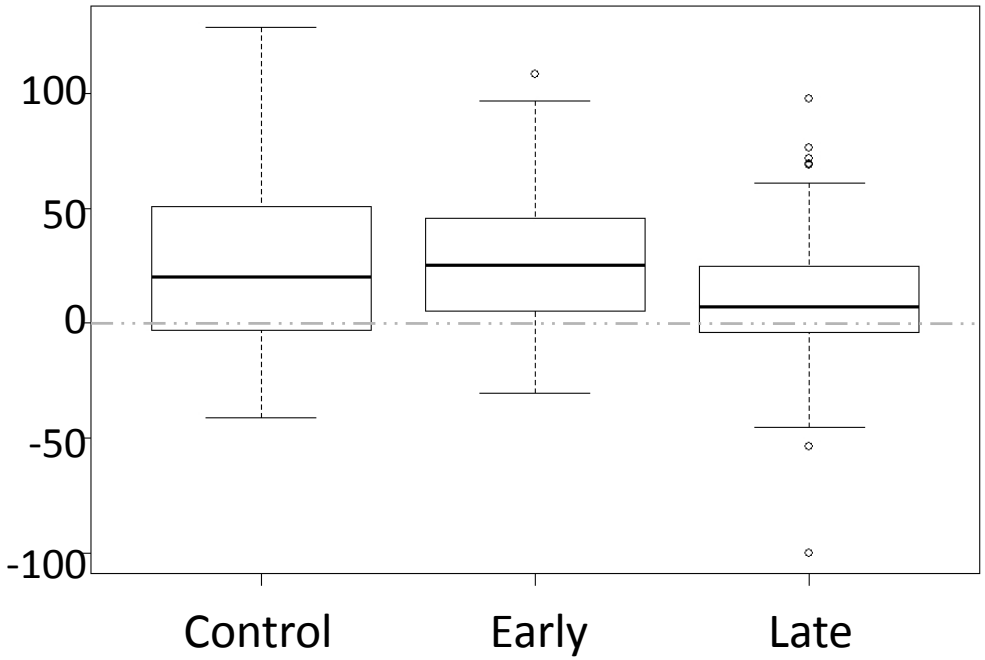
Secondary Endpoints

Change in LV-volumes 4 months vs. baseline

LVEDV (ml)

P = 0.03 vs. control

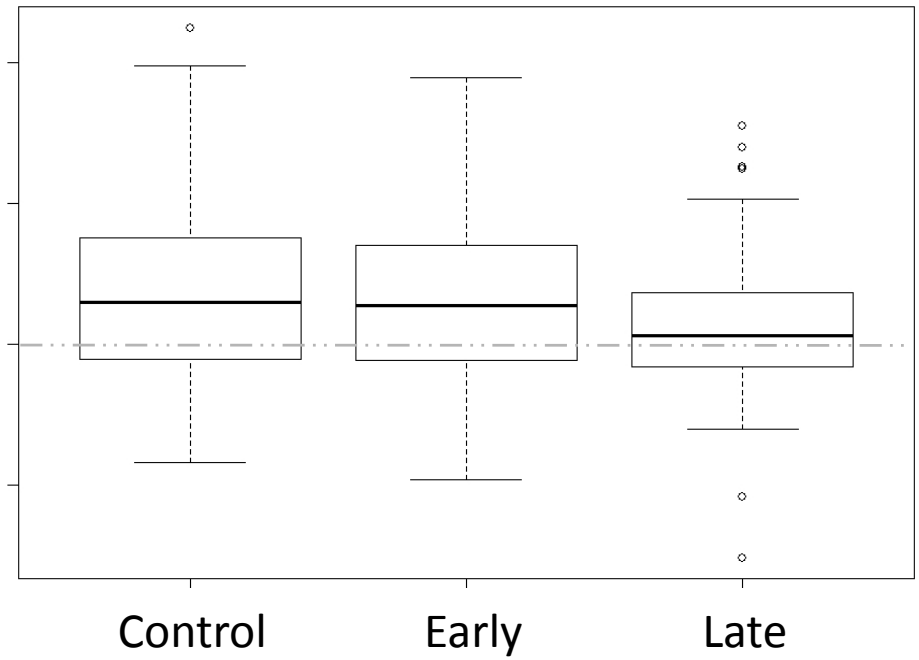
P = 0.89 vs. control



LVESV (ml)

P = 0.07 vs. control

P = 0.79 vs. control



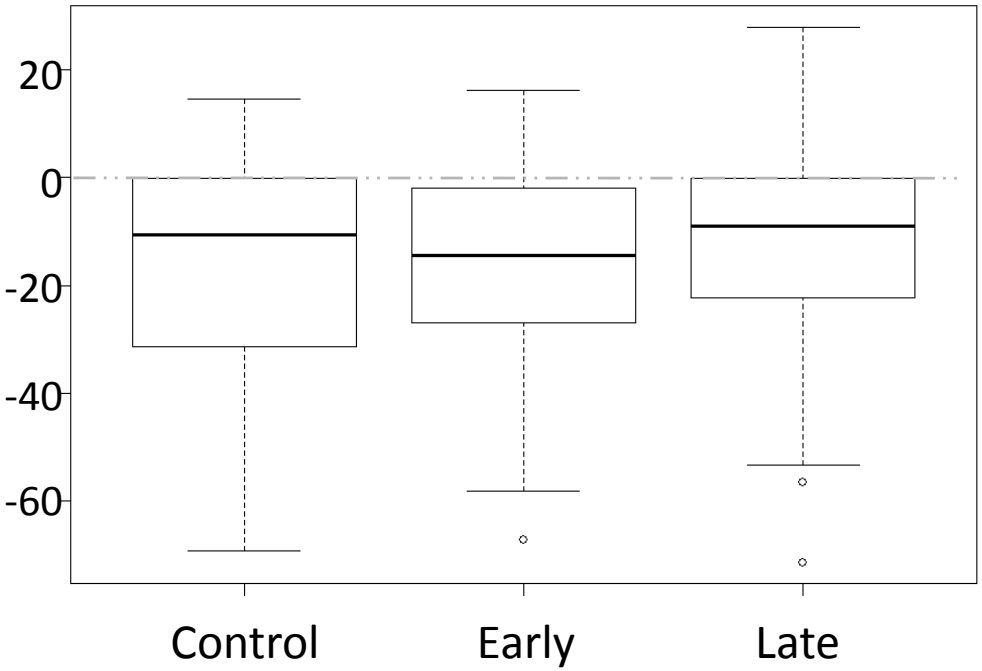
Secondary Endpoints

Change in scar size and regional LV function

Scar size (g)

P = 0.59 vs. control

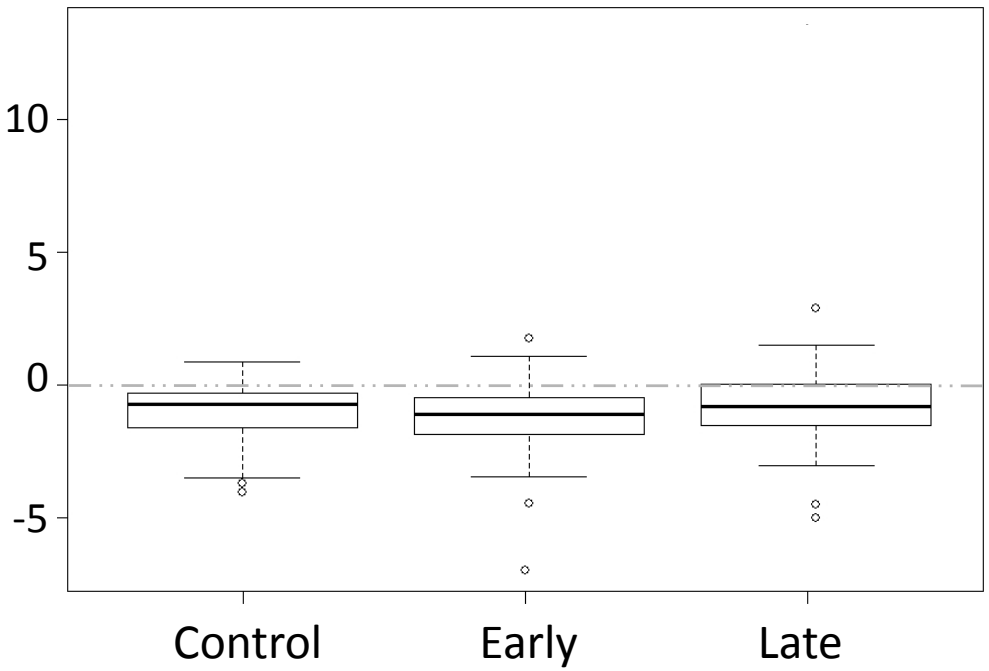
P = 0.82 vs. control



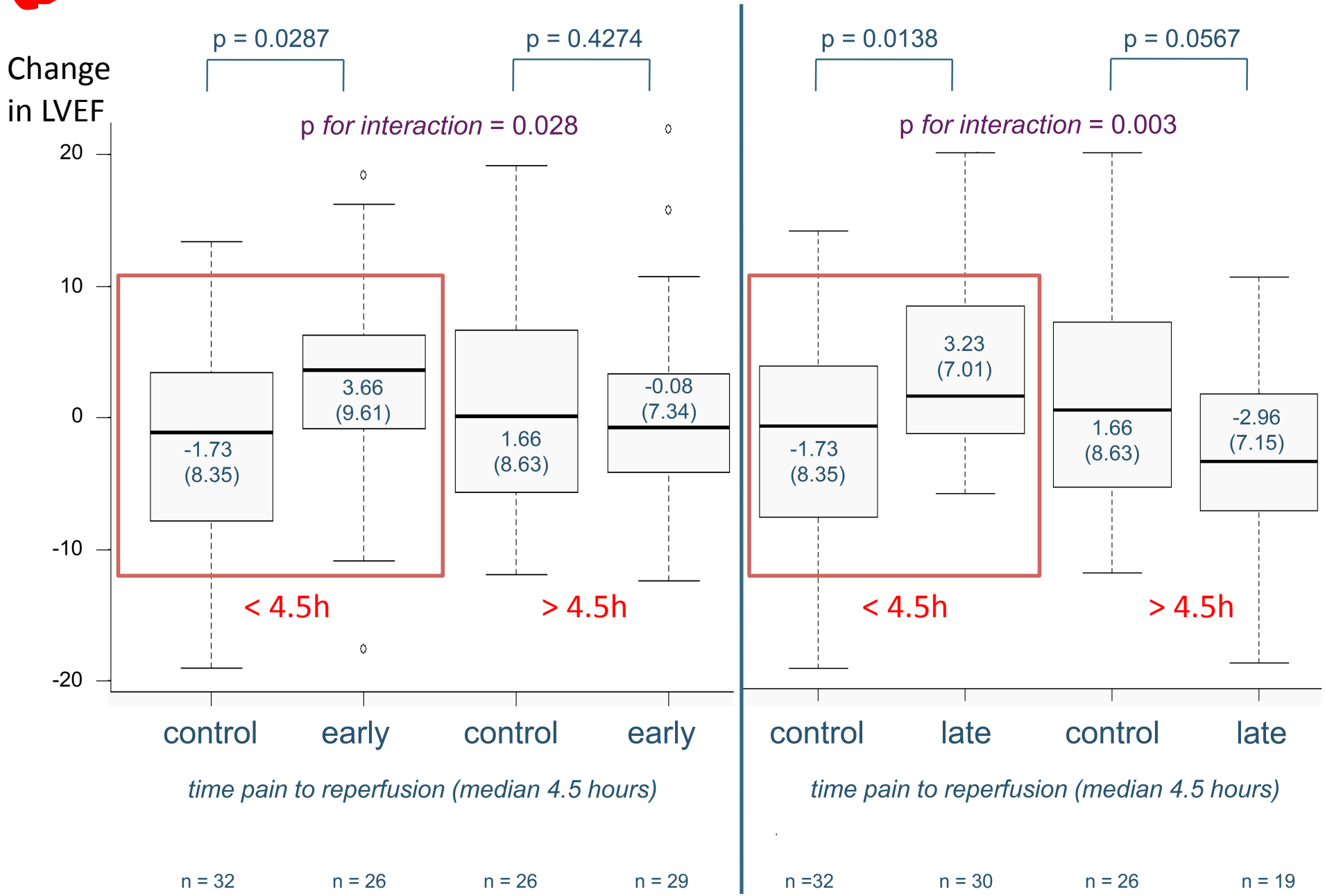
Myocardial thickening in the infarct territory (mm)

P = 0.67 vs. control

P = 0.54 vs. control



Predictors for treatment efficacy



Clinical events during follow up

	Control	Early	Late	p-value
Events between randomization and therapy				
Death	0	1 (3.1%)	1 (1.7%)	0.24 * 0.48 ‡
Events at 4 months follow up (cumulative)				
Death	0	3 (4.8%)	1 (1.7%)	0.24 * 0.48 ‡
Myocardial infarction	1 (1.6%)	1 (1.6%)	0	1.00 * 1.00 ‡
Rehospitalization for heart failure	2 (3.2%)	0	2 (3.6%)	0.50 * 1.00 ‡
Revascularization	3 (4.8%)	3 (4.9%)	2 (3.6%)	1.00 * 1.00 ‡
Cerebral infarction	1 (1.6%)	1 (1.7%)	0	1.00 * 1.00 ‡
Combined events				
Death, myocardial infarction, revascularization, rehospitalization for heart failure	4 (6.4%)	5 (7.9%)	5 (8.8%)	1.00 * 0.74 ‡
Death, myocardial infarction, revascularization, rehospitalization for heart failure, stroke	4 (6.4%)	6 (9.5%)	5 (8.8%)	0.74 * 0.74 ‡

* control vs. early
‡ control vs. late

Summary

Intracoronary infusion of BM-MNC, either 5-7 d or 3-4 wks after primary PCI for STEMI, **did not improve LV-function as assessed by CMR at 4 months compared with control.**

Subgroup analysis indicates potential benefit of i.c. BM-MNC in patients with early reperfusion (within 4.5 h from the onset of pain).

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	Difference in Mean	95% Confidence Interval	*P* for *Z*	*P* for Subgroup Differences
LVEF				
Echo	3.61	2.18 to 5.04	<0.00001	0.001
SPECT	2.60	−0.35 to 5.55	0.08	
MRI	1.17	−0.60 to 2.95	0.20	
LVG	7.08	4.77 to 9.38	0.0001	

SWISS AMI: Δ LVEF early vs. control = 2.1%

Adapted from Jeevanantham et al. Circulation 2012

Subgroup analysis indicates potential benefit of i.c. BM-MNC in patients with early reperfusion (within 4.5 h from the onset of pain).

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