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ORIGINAL PAPER

Adenosine stress perfusion cardiac magnetic resonance imaging in patients undergoing intracoronary bone marrow cell transfer after ST-elevation myocardial infarction: the BOOST-2 perfusion substudy

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Abstract

Aims In the placebo-controlled, double-blind BOne marrOw transfer to enhance ST-elevation infarct regeneration (BOOST) 2 trial, intracoronary autologous bone marrow cell (BMC) transfer did not improve recovery of left ventricular ejection fraction (LVEF) at 6 months in patients with ST-elevation myocardial infarction (STEMI) and moderately reduced LVEF. Regional myocardial perfusion as determined by adenosine stress perfusion cardiac magnetic resonance imaging (S-CMR) may be more sensitive than global LVEF in detecting BMC treatment effects. Here, we sought to evaluate (i) the changes of myocardial perfusion in the infarct area over time (ii) the effects of BMC therapy on infarct perfusion, and (iii) the relation of infarct perfusion to LVEF recovery at 6 months.

Methods and results In 51 patients from BOOST-2 (placebo, $n=10$; BMC, $n=41$), S-CMR was performed 5.1 ± 2.9 days after PCI (before placebo/BMC treatment) and after 6 months. Infarct perfusion improved from baseline to 6 months in the overall patient cohort as reflected by the semi-quantitative parameters, perfusion defect–infarct size ratio (change from 0.54 ± 0.20 to 0.43 ± 0.22; $P=0.006$) and perfusion defect–upslope ratio (0.54 ± 0.23 to 0.68 ± 0.22; $P<0.001$), irrespective of randomised treatment. Perfusion defect–upslope ratio at baseline correlated with LVEF recovery ($r=0.62$; $P<0.001$)

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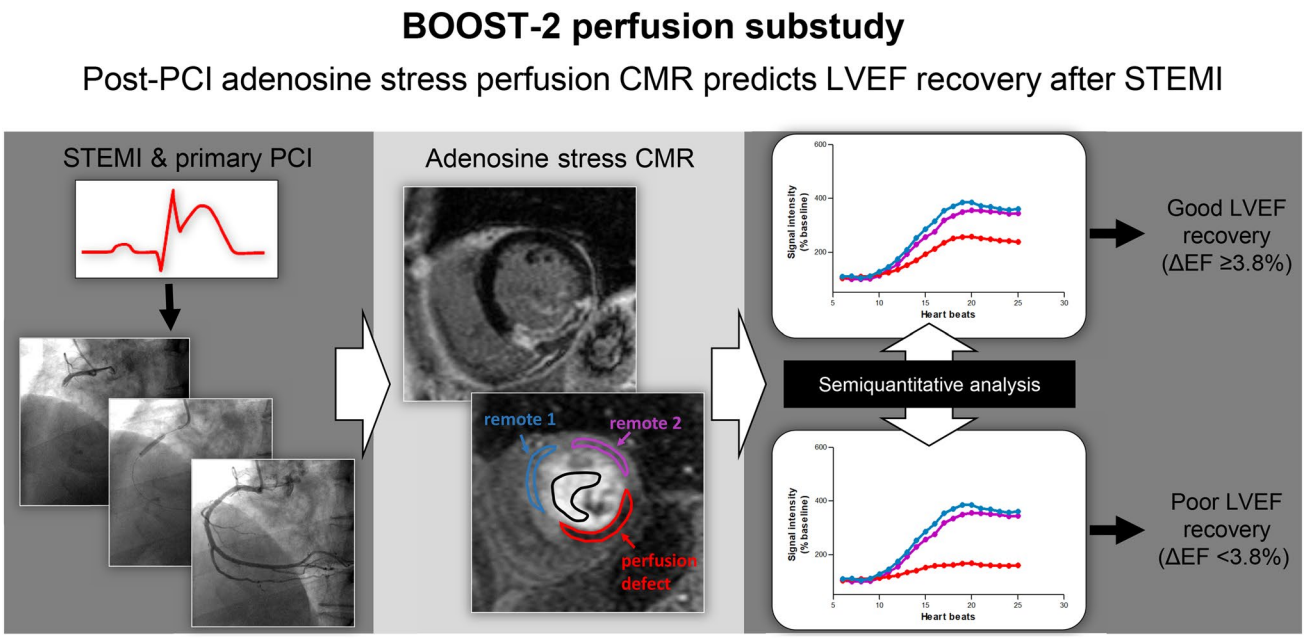
after 6 months, with a threshold of 0.54 providing the best sensitivity (79%) and specificity (74%) (area under the curve, 0.79; 95% confidence interval, 0.67–0.92).

Conclusion Infarct perfusion improves from baseline to 6 months and predicts LVEF recovery in STEMI patients undergoing early PCI. Intracoronary BMC therapy did not enhance infarct perfusion in the BOOST-2 trial.

Graphic abstract



Keywords St-elevation myocardial infarction · Adenosine stress perfusion cardiac magnetic resonance imaging · Bone marrow cell therapy

Introduction

Clinical implementation of evidence-based treatments during the past 20 years has been associated with improved outcomes in patients with ST-elevation myocardial infarction (STEMI) [1, 2]. However, patients with left ventricular (LV) dysfunction after STEMI continue to be at risk of adverse LV remodelling and heart failure [3-5].

Based on studies showing that various bone marrow-derived cell types secrete a broad array of cytokines and growth factors that may promote infarct tissue vascularization and repair [6], intracoronary infusion of autologous bone marrow cells (BMCs) has been explored as an adjunctive strategy to improve heart function after STEMI [7]. A recent review of 41 randomised controlled trials, however, found insufficient evidence for a beneficial effect of BMCs on LV systolic function after myocardial infarction [8]. We recently evaluated the therapeutic potential of BMC therapy in the BOne marrOw transfer to enhance ST-elevation infarct regeneration (BOOST) 2 trial. BMC therapy did not improve LV ejection fraction (LVEF), LV volumes, infarct volume, and regional systolic function as determined by late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) in BOOST-2 [9].

Adenosine stress perfusion cardiac magnetic resonance imaging (S-CMR) is a non-invasive tool to assess myocardial perfusion [10, 11]. We hypothesised that myocardial perfusion in the infarct region as assessed by S-CMR may be more sensitive than global LVEF in detecting BMC treatment effects in BOOST-2. Using the well-characterised BOOST-2 patient cohort, we also re-examined the relationship between regional myocardial perfusion and LV remodelling after STEMI.

Methods

Study design and patient population

BOOST-2 was a randomised placebo-controlled, double-blind trial investigating the effects of intracoronary BMC transfer on LVEF recovery and remodelling in patients with a first STEMI and a moderately reduced LVEF after successful percutaneous coronary intervention (PCI). The detailed

study design has previously been described [9]. In brief, patients were recruited from 10 centres in Germany and Norway and randomly allocated to 6 groups in a 1:1:2:2:2:2 ratio: (i) low-dose bone marrow harvest and placebo cell infusion (loPlacebo) (ii) high-dose bone marrow harvest and placebo cell infusion (hiPlacebo); (iii) low-dose bone marrow harvest and low-dose BMC infusion (loBMC) (iv) high-dose bone marrow harvest and high-dose BMC infusion (hiBMC) (v) low-dose bone marrow harvest and low-dose γ-irradiated BMC infusion (loBMCi), and (vi) high-dose bone marrow harvest and high-dose γ-irradiated BMC infusion (hiBMCi). γ-Irradiation eliminated BMCs' clonogenic potential while retaining cell viability and paracrine function, thereby enabling us to explore mechanisms of action in a clinical context.

CMR was performed 4.4 ± 1.9 days after PCI and after 6 months according to a standardised protocol. BMCs were harvested 7.1 ± 2.6 days after PCI and intracoronarily infused 1 day later [9]. The Robert–Bosch–Medical Centre (Stuttgart, Germany) served as the CMR core lab but was not involved in patient recruitment or follow-up. Change in LVEF from baseline to 6 months was the primary endpoint. Secondary CMR endpoints included changes in LV end-diastolic volume index (LVEDVi), LV end-systolic volume index (LVESVi), and infarct volume. The primary efficacy analysis in BOOST-2 was based on paired CMR studies from 153 patients. None of the four BMC treatment regimens exerted significant effects on change in LVEF or any secondary CMR endpoint in BOOST-2 [9].

Per protocol, centres were encouraged to also perform S-CMR at baseline and 6 months. Paired S-CMR studies were obtained from 56 patients. The core lab excluded S-CMR studies from 5 patients from the analysis due to insufficient image quality, thus leaving 51 paired S-CMR scans for evaluation in the present study (Fig. 1).

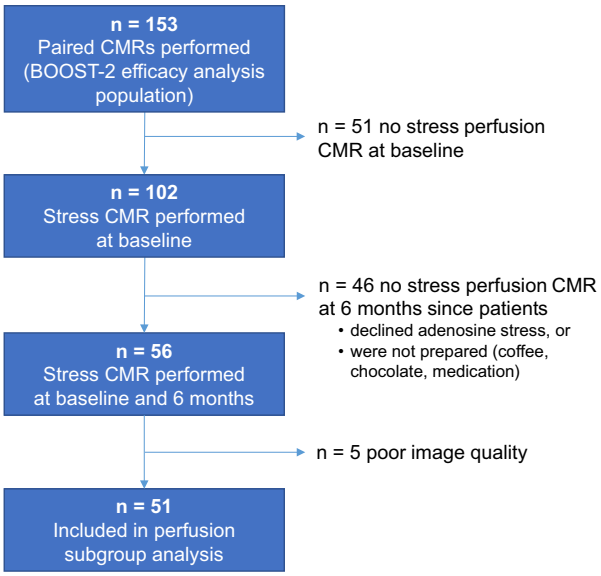


Fig. 1 BOOST 2 patient population flow chart

Cardiac magnetic resonance imaging

All CMR studies were performed according to a standardised protocol [9]. Patients were examined in 1.5 T scanners using ECG-gating and a phased array receiver coil. For the assessment of LV volumes and systolic function, steady-state free-precession cine images were acquired from a stack of short-axis slices covering the left ventricle. After cine imaging, adenosine (140 µg/kg/min) was intravenously (i.v.) infused under continuous ECG and non-invasive blood pressure monitoring for at least 3 min to induce hyperaemia. During adenosine infusion, 0.075 mmol/kg of a gadolinium-based contrast agent were administered i.v. and first-pass perfusion images were obtained from 3 short axis views representing the basal, midventricular, and apical parts of the left ventricle using a saturation-recovery, gradient-echo (GRE) sequence [12]. 15 min later, a second dose of 0.075 mmol/kg gadolinium-based contrast agent was administered and repeat first-pass perfusion images were obtained to determine rest perfusion. 5 min later, corresponding LGE slices were assessed using breath-hold k-space segmented T1-weighted inversion recovery GRE sequences.

Image analysis

CMR studies were analysed by experienced core lab investigators, who were unaware of treatment assignments and any clinical information. Cine and LGE images were analysed using QMass MR 7.6 software (Medis Medical Imaging Systems, Leiden, The Netherlands) as previously described [9]. Perfusion defects within the infarct region were manually contoured on the stress perfusion images and the infarct region was delineated in corresponding LGE short axis slices. Semi-quantitative analysis of first-pass perfusion during hyperaemia was performed using cvi^{42} software (Circle Cardiovascular Imaging Inc., Calgary, Canada) (Fig. 2). In each patient, signal intensity curves were obtained to calculate maximum upslopes in the perfusion defect, remote (noninfarcted) myocardium, and LV blood pool. Maximum upslope of the remote myocardium was averaged from two separate regions of interests placed in non-culprit vessel territories. Perfusion defect–infarct size ratio (range 0–1) was calculated by dividing perfusion defect size by LGE-determined infarct size. Perfusion defect–upslope ratio (range 0–1) was calculated by dividing the maximum upslope of the signal intensity curve of the perfusion defect by the maximum upslope of the signal intensity curve of the remote myocardium during adenosine infusion.

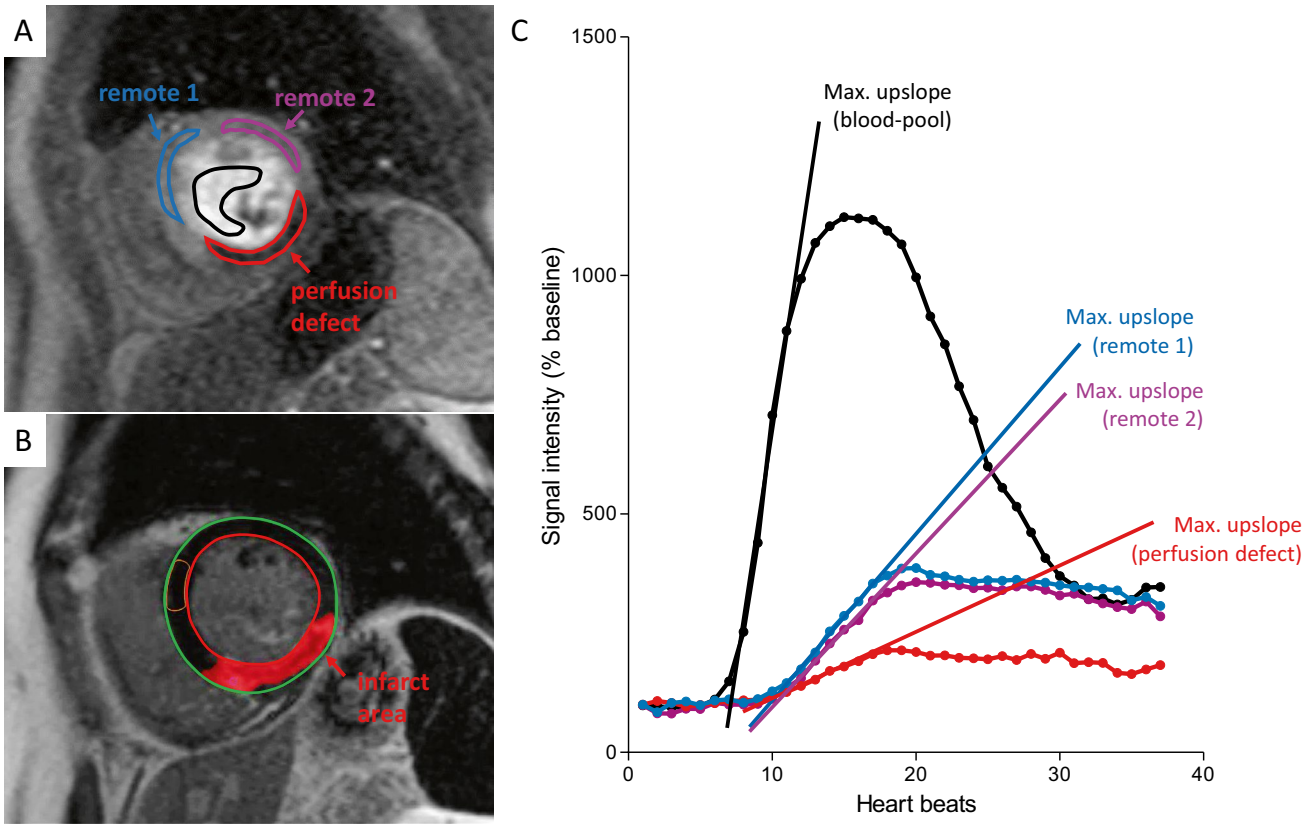


Fig. 2 Exemplary perfusion analysis in a patient with an inferior wall STEMI. **a** Perfusion defects within the infarct region were manually contoured on the stress perfusion images. **b** The infarct region was delineated in corresponding late gadolinium enhancement slices. **c** Semi-quantitative analysis of first-pass perfusion. Signal intensity curves and maximum upslope in the perfusion defect, remote (non-infarcted) myocardium, and left ventricular blood pool

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA) and Prism 5.01 (GraphPad, San Diego, CA, USA). Categorical variables are expressed as numbers and proportions, continuous variables as mean ± SD or median with interquartile range, as appropriate. Changes of S-CMR parameters from baseline to 6 months follow-up and differences between treatment groups (placebo vs. BMCs) were assessed by analysis of covariance (ANCOVA) with the respective baseline values as a covariate. Differences in least-squares mean values and corresponding 95% confidence intervals (CI) were calculated based on the ANCOVA model. Correlations were assessed using Pearson correlation coefficient. The best diagnostic cutoff for predicting LVEF recovery was determined from a receiver-operating characteristic (ROC) curve analysis using Youden's index [13]. *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics

The perfusion substudy population included 51 patients (Table 1). Baseline characteristics of patients randomised to placebo ($n = 10$) or BMC therapy ($n = 41$, all subgroups combined) were well matched. All patients received guideline-recommended therapies. Baseline characteristics of patients from the loBMC ($n = 6$), hiBMC ($n = 8$), loBMCi ($n = 13$), and hiBMCi ($n = 14$) subgroups are shown in Table S1. Patient characteristics in the perfusion substudy population were similar to the entire BOOST-2 study population [9].

Cardiac magnetic resonance imaging characteristics

In the overall perfusion substudy population, baseline LVEF was moderately reduced (47 ± 8%). LVEF significantly increased after 6 months (51 ± 8%, $P < 0.001$)

Table 1 Baseline characteristics

	Placebo ($n=10$)	BMC ($n=41$)	P
Age, years	55 ± 5	57 ± 10	0.74
Male sex [*n* (%)]	9 (90)	36 (88)	0.87
Body mass index (kg/m^2)	28.2 ± 4.0	27.4 ± 3.3	0.48
Hypertension [*n* (%)]	4 (40)	22 (54)	0.45
Diabetes [*n* (%)]	2 (20)	9 (22)	0.91
Family history of CAD [*n* (%)]	4 (40)	14 (34)	0.73
Current smoking [*n* (%)]	8 (80)	18 (44)	0.09
LDL cholesterol (mg/dL)	132 ± 39	125 ± 39	0.26
HDL cholesterol (mg/dL)	45 ± 17	45 ± 10	0.98
Triglycerides (mg/dL)	172 ± 133	105 ± 46	0.13
Previous PCI [*n* (%)]	0	4 (10)	
Thrombolysis prior to PCI [*n* (%)]	0	0	
Drug-eluting stent [*n* (%)]	2 (20)	19 (46)	0.14
Maximum CK concentration (U/L)	2931 ± 1815	3238 ± 2304	0.93
Killip class			
I [*n* (%)]	8 (80)	37 (90)	0.44
II [*n* (%)]	2 (20)	3 (7)	
III [*n* (%)]	0	1 (2)	
Infarct-related artery			
LAD [*n* (%)]	6 (60)	20 (49)	0.79
LCX [*n* (%)]	1 (10)	4 (10)	
RCA [*n* (%)]	3 (30)	17 (41)	
TIMI flow grade before PCI			
0 [*n* (%)]	7 (70)	36 (88)	0.11
1 [*n* (%)]	1 (10)	4 (10)	
2 or 3 [*n* (%)]	2 (20)	1 (2)	
TIMI flow grade after PCI			
1 [*n* (%)]	0	0	0.54
2 [*n* (%)]	1 (10)	2 (5)	
3 [*n* (%)]	9 (90)	39 (95)	
Timing of procedures			
Time symptom onset to PCI (h)	5.6 (3.1–7.8)	5.1 (3.5–13.1)	0.57
Time PCI to baseline CMR (days)	4.0 (3.0–8.0)	4.0 (3.0–5.0)	0.43
Time PCI to cell harvest (days)	6.5 (4.0–9.0)	7.0 (5.0–8.0)	0.81
Medication at primary discharge			
Aspirin [*n* (%)]	10 (100)	41 (100)	
P2Y12 receptor antagonist [*n* (%)]	10 (100)	41 (100)	
Statin [*n* (%)]	10 (100)	41 (100)	
ACE inhibitor or ARB [*n* (%)]	10 (100)	41 (100)	
ß-Blocker [*n* (%)]	9 (90)	39 (95)	
MRA [*n* (%)]	5 (50)	12 (27)	
Medication at 6 months			
Aspirin *n* (%)	10 (100)	38 (93)	
P2Y12 receptor antagonist [*n* (%)]	9 (90)	33 (80)	
Statin [*n* (%)]	10 (100)	39 (95)	
ACE inhibitor or ARB [*n* (%)]	10 (100)	38 (93)	
β-Blocker [*n* (%)]	10 (100)	39 (95)	
MRA [*n* (%)]	3 (30)	7 (17)	

Data are *n* (%), mean ± SD or median (interquartile range)

BMC bone marrow cell, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *LAD* left anterior descending, *LCX* left circumflex, *RCA* right coronary artery, *TIMI* thrombolysis in myocardial infarction, *CK* creatine kinase, *CMR* cardiac magnetic resonance imaging, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *MRA* mineralocorticoid receptor antagonist

Table 2 Cardiac magnetic resonance imaging characteristics

	Baseline	6 months	Change	*P*	Treatment effect (vs. placebo)	*P*
LVEF (%)						
All patients (*n* = 51)	47 ± 8	51 ± 8	3.8 (1.6–6.0)	**< 0.001**	–	–
Placebo (*n* = 10)	49 ± 6	51 ± 7	3.0 (− 0.9 to 7.0)	0.17	–	–
All BMC (*n* = 41)	46 ± 8	51 ± 8	4.6 (2.7–6.5)	**< 0.001**	1.6 (− 2.8 to 6.0)	0.48
LVEDVi (mL/m^2)						
All patients (*n* = 51)	85 ± 14	90 ± 19	5.4 (0.1–10.8)	**0.03**	–	–
Placebo (*n* = 10)	87 ± 14	93 ± 22	6.7 (− 2.9 to 16.4)	0.28	–	–
All BMC (*n* = 41)	85 ± 14	89 ± 19	4.1 (− 0.6 to 8.9)	0.07	− 2.6 (− 13.3 to 8.2)	0.63
LVESVi (mL/m^2)						
All patients (*n* = 51)	46 ± 13	45 ± 13	0.1 (− 4.1 to 4.3)	0.58	–	–
Placebo (*n* = 10)	45 ± 9	47 ± 18	1.8 (− 5.8 to 9.3)	0.66	–	–
All BMC (*n* = 41)	46 ± 14	45 ± 16	− 1.6 (− 5.3 to 2.1)	0.37	− 3.4 (− 11.8 to 5.1)	0.43
Infarct volume (mL)						
All patients (n = 51)	40 ± 23	27 ± 16	− 11.0 (− 14.7 to − 7.3)	**< 0.001**	–	–
Placebo (*n* = 10)	33 ± 18	28 ± 21	− 8.1 (− 14.7 to − 1.5)	0.21	–	–
All BMC (*n* = 41)	42 ± 23	27 ± 14	− 13.9 (− 17.1 to − 10.6)	**< 0.001**	− 5.7 (− 13.1 to 1.7)	0.13

Values at baseline and 6 months are mean values ± SD. Changes from baseline to 6 months and treatment effects are expressed as differences in least-squares mean values with 95% confidence intervals (ANCOVA models with adjustment for baseline values)

Significant p values are in bold ($p < 0.05$)

BMC bone marrow cell, *LVEF* left ventricular ejection fraction, *LVEDVi* left ventricular end-diastolic volume index, *LVESVi* left ventricular end-systolic volume index

(Table 2). Like in the entire BOOST-2 study population [9], BMC transfer (all subgroups combined) did not exert significant effects on 6 months' changes in LVEF, LVEDVi, LVESVi, or infarct volume in the perfusion substudy population (Table 2). Similarly, no treatment effects were observed when the four BMC treatment groups were individually analysed (data not shown).

Perfusion in the infarcted area

S-CMR was well tolerated; only 1 patient reported mild nausea. All 51 patients had perfusion defects in the infarct region at baseline and 6 months. In the overall perfusion substudy population, perfusion defect–infarct size ratio decreased (from 0.54 ± 0.20 to 0.43 ± 0.22; $P = 0.006$) and perfusion defect–upslope ratio increased (from 0.54 ± 0.23 to 0.68 ± 0.22; $P < 0.001$) from baseline to 6 months, suggesting recovery of (hyperaemic) perfusion in the infarcted

Table 3 BMC treatment effect on infarct perfusion

	Baseline	6 months	Change	*P*	Treatment effect (vs. placebo)	*P*
Perfusion defect–size ratio						
All patients (*n* = 51)	0.54 ± 0.20	0.43 ± 0.22	− 0.10 (− 0.17 to − 0.02)	**0.006**	–	–
Placebo (*n* = 10)	0.52 ± 0.21	0.46 ± 0.26	− 0.07 (− 0.21 to 0.07)	0.61	–	–
All BMC (*n* = 41)	0.55 ± 0.20	0.43 ± 0.22	− 0.12 (− 0.19 to − 0.05)	**0.004**	− 0.05 (− 0.20 to 0.11)	0.57
Perfusion defect–upslope ratio						
All patients (*n* = 51)	0.54 ± 0.23	0.68 ± 0.22	0.15 (0.10–0.21)	**< 0.001**	–	–
Placebo (*n* = 10)	0.62 ± 0.23	0.78 ± 0.14	0.19 (0.08–0.31)	**0.02**	–	–
All BMC (*n* = 41)	0.52 ± 0.23	0.66 ± 0.23	0.13 (0.07–0.19)	**< 0.001**	− 0.06 (− 0.19 to 0.07)	0.35

Perfusion defect–size ratio and defect–upslope ratio at baseline and 6 months are mean values ± SD. Changes from baseline to 6 months and treatment effects are expressed as differences in least-squares mean values with 95% confidence intervals (ANCOVA model with adjustment for baseline value)

Significant p values are in bold ($p < 0.05$)

area (Table 3). BMC transfer (all subgroups combined) did not exert significant effects on the changes of both perfusion parameters over time (Table 3). Likewise, no treatment effects emerged when the four BMC treatment groups were individually analysed (Table S2).

Prognostic value of stress perfusion cardiac magnetic resonance imaging after STEMI

Since BMC treatment did not exert any significant effects on LV remodelling [9] or infarct perfusion compared with placebo (Table 3), all patients were combined to explore whether S-CMR early after STEMI can predict changes in LVEF, LVEDVi, and LVESVi after 6 months. Patients were dichotomised using average changes from baseline to 6 months in LVEF (3.8%), LVEDVi (3.6 mL/m^2), and LVESVi (− 0.7 mL/m^2) in the entire study population as cutoffs [9]. Baseline LVEF was lower in patients with LVEF recovery ≥ 3.8% than in patients with LVEF recovery < 3.8% (43 ± 9 vs. 47 ± 8; $P = 0.005$) (Table 4). Baseline LV volumes, infarct volume, and baseline microvascular obstruction were not associated with LVEF recovery from baseline to 6 months (Table 4). Baseline infarct volume was significantly greater in patients with increases in LVEDVi ≥ 3.6 mL/m^2 and LVESVi ≥ -0.7 mL/m^2 than in patients with less-pronounced increases in LV volumes from baseline to 6 months (Table 4).

Table 4 Baseline cardiac magnetic resonance imaging parameters in relation to left ventricular remodeling

	LVEF			LVEDVi			LVESVi		
	LVEF change < 3.8%	LVEF change ≥ 3.8%	*P*	LVEDVi change ≥ 3.6 mL/m^2	LVEDVi change < 3.6 mL/m^2	*P*	LVESVi change ≥ 0.7 mL/m^2	LVESVi change < 0.7 mL/m^2	*P*
Baseline									
LVEF, % (*n* = 153)	47 ± 8	43 ± 9	**0.005**	44 ± 10	46 ± 8	0.40	45 ± 9	45 ± 8	0.81
LVEDVi, mL/m^2 (*n* = 153)	90 ± 15	88 ± 15	0.42	87 ± 15	90 ± 15	0.29	88 ± 16	89 ± 15	0.53
LVESVi, mL/m^2 (*n* = 153)	48 ± 13	50 ± 15	0.22	49 ± 14	49 ± 13	0.81	49 ± 15	49 ± 13	0.79
Infarct volume, mL (*n* = 110)	45 ± 19	40.0 ± 22.5	0.21	48 ± 22	38 ± 19	**0.007**	47 ± 22	39 ± 20	**0.028**
MVO, yes/no (*n* = 110)	38 (49)	39 (51)	0.81	34 (53)	43 (48)	0.56	37 (55)	40 (47)	0.29
MVO, % of infarct (n = 110)	6.6 ± 9.9	7.5 ± 10.8	0.65	8.7 ± 12.2	6.0 ± 8.7	0.15	8.0 ± 10.9	6.4 ± 10.0	0.40
Perfusion defect–size ratio (*n* = 51)	0.51 ± 0.20	0.56 ± 0.19	0.34	0.52 ± 0.20	0.55 ± 0.19	0.55	0.50 ± 0.20	0.57 ± 0.19	0.27
Perfusion defect–upslope ratio (*n* = 51)	0.40 ± 0.19	0.63 ± 0.22	**< 0.001**	0.49 ± 0.27	0.58 ± 0.21	0.20	0.44 ± 0.22	0.61 ± 0.23	**0.011**
Change from baseline to 6 months									
Δ Perfusion defect–size ratio (*n* = 51)	− 0.09 ± 0.27	− 0.12 ± 0.27	0.71	− 0.06 ± 0.26	− 0.14 ± 0.26	0.28	− 0.06 ± 0.27	− 0.14 ± 0.26	0.30
Δ Perfusion defect–upslope ratio (*n* = 51)	0.24 ± 0.20	0.09 ± 0.18	**0.007**	0.16 ± 0.21	0.14 ± 0.20	0.79	0.18 ± 0.20	0.13 ± 0.20	0.35

Data are mean ± SD

Significant p values are in bold ($p < 0.05$)

LVEF left ventricular ejection fraction, *LVESVi* left ventricular end-systolic volume index, *LVEDVi* left ventricular end-diastolic volume index, *MVO* microvascular obstruction, *Myo* myocardium

Baseline perfusion defect–infarct size ratio was similar in both groups ($P = 0.34$), but perfusion defect–upslope ratio was higher in patients with LVEF recovery ≥ 3.8% than in patients with LVEF recovery < 3.8% (0.63 ± 0.22 vs. 0.40 ± 0.19; $P < 0.001$) (Table 4). Likewise, baseline perfusion defect–upslope ratio was significantly higher in patients with a LVESVi change from baseline to 6 months < − 0.7 mL/m^2 than in patients with a LVESVi change ≥ − 0.7 mL/m^2 (Table 4). When analysed as continuous variables, baseline defect–upslope ratio correlated significantly with LVEF at 6 months ($r = 0.45$; 95% CI, 0.20–0.65; $P = 0.001$) and LVEF change from baseline to 6 months ($r = 0.62$; 95% CI 0.41–0.76; $P < 0.001$) (Fig. 3). Based on a ROC curve analysis, a baseline perfusion defect–upslope ratio of 0.54 best discriminated patients with LVEF recovery greater or smaller than 3.8% in our population (sensitivity, 79%; specificity, 74%) (Fig. 4).

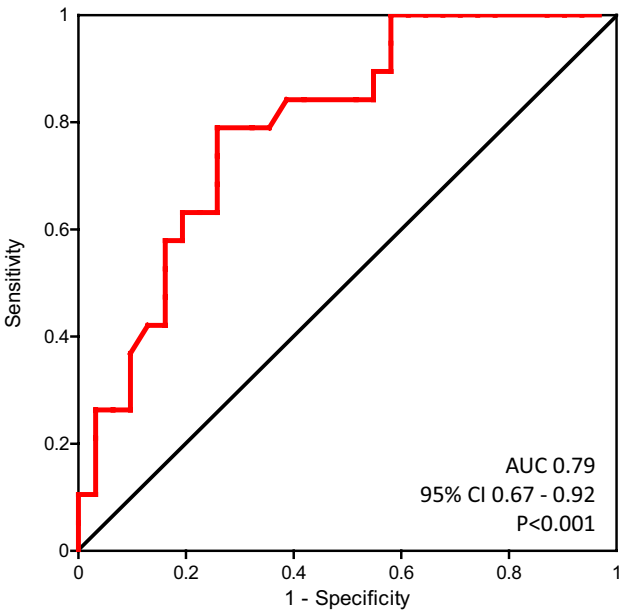


Fig. 4 Baseline perfusion defect–upslope ratio predicts LVEF recovery. ROC curve relating baseline perfusion defect–upslope ratio to LVEF change from baseline to 6 months ≥ 3.8%

Discussion

In the present study, we used serial S-CMR to assess BMC treatment effects on infarct perfusion after STEMI and to explore the prognostic value of infarct perfusion on LVEF recovery over time in patients with STEMI. We analysed patients from the recently completed randomised, placebo-controlled BOOST-2 trial. The BOOST-2 perfusion substudy included patients with a moderately reduced LVEF after first STEMI and successful primary PCI. Patient characteristics and baseline CMR parameters were comparable to the entire BOOST-2 study population [9]. Like in the entire study population [9], BMC transfer did not enhance LVEF recovery in the perfusion substudy.

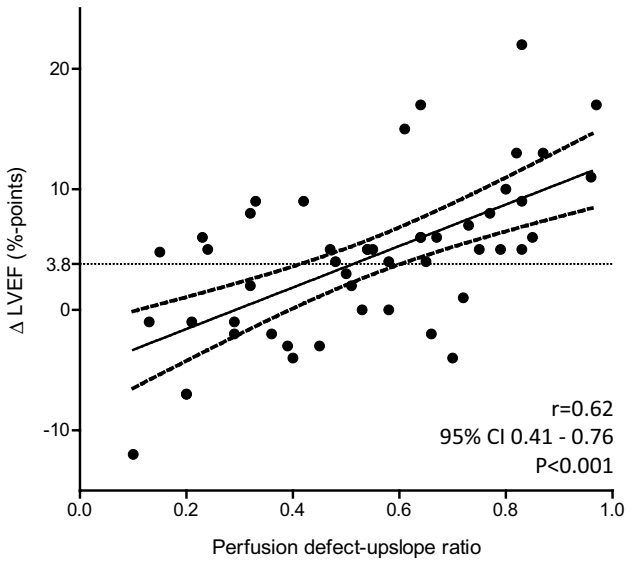


Fig. 3 Baseline perfusion defect–upslope ratio and LVEF change over 6 months. Correlation of baseline perfusion defect–upslope ratio with change in LVEF from baseline to 6 months

S-CMR was safe in our study, no serious adverse events were observed. While concerns about the safety of S-CMR early after STEMI have been expressed by some investigators [14], our experience adds to a growing body of evidence that S-CMR can be safely performed in the first days after STEMI [15, 16].

As shown by serial S-CMR, perfusion defect-infarct size ratio decreased and perfusion defect–upslope ratio increased from baseline (5.1 ± 2.9 days after PCI) to 6 months in the overall substudy population. While previous studies reported improvement of resting infarct perfusion after STEMI [17, 18], our study is the first to document improvements in hyperaemic infarct perfusion over time using serial S-CMR after STEMI.

We did not observe an impact of BMC transfer (all BMC groups combined) on the changes in stress perfusion defect–infarct size ratio or defect–upslope ratio over time in our study. Clearly, the present exploratory analysis is limited by the small number of patients with paired S-CMR examinations, which also precluded meaningful analyses of potential treatment effects mediated individually by the four randomised BMC treatment regimens (loBMC, hiBMC, loBMCi, and hiBMCi). In line with our results, two previous randomised controlled studies concluded that intracoronary BMC therapy does not enhance perfusion recovery in the infarct region after STEMI [18, 19]. These studies, however, assessed rest perfusion only,

using either positron-emission tomography or CMR [18, 19].

Given that BMC transfer, compared with placebo, did not promote recovery of infarct perfusion or LVEF over time, we pooled all patients to evaluate the prognostic value of (S-)CMR variables at baseline for changes in LVEF over time. Baseline LVEF was inversely associated with LVEF recovery, reflecting the greater potential for LVEF improvements in patients with lower baseline LVEF. LGE-determined infarct size at baseline was not significantly associated with LVEF recovery over time in our study [16]. However, patients showing more pronounced increases in LVEDVi and LVESVi after 6 months had significantly greater infarct sizes at baseline than patients with less pronounced increases in their LV volume indices.

Perfusion defect–upslope ratio at baseline, as determined by S-CMR, was significantly associated with LVEF recovery over time: hyperaemic infarct perfusion at baseline was more severely impaired in patients with less-pronounced LVEF recovery (increase of less than 3.8% points) than in patients with greater LVEF recovery. This observation corroborates a previous study that reported greater LVEF at follow-up in patients with better hyperaemic infarct perfusion at baseline [16]. Also, when analysed as continuous variables, baseline perfusion defect–upslope ratio and LVEF change over time were closely correlated in our study; a ROC analysis yielded an AUC of 0.79, suggesting that S-CMR perfusion measurements may help, in the future, to discriminate patients showing a favourable vs. unfavourable LVEF recovery. This is in line with previous data suggesting that microvascular damage following PCI in patients with acute myocardial infarction predicts LVEF recovery and occurrence of major adverse cardiovascular events [20]. Various methods have been used to assess microvascular damage, including both invasive (e.g., measurement of coronary flow and microvascular resistance) and non-invasive techniques (e.g., LGE and perfusion imaging by CMR, PET, SPECT, and contrast echocardiography) [21]. While invasive assessment of the coronary microvasculature has focused on hyperaemic parameters [21], assessment of microvascular obstruction by LGE-CMR has long been the non-invasive gold standard [22-24]. Dynamic myocardial perfusion imaging by CMR in the early postinfarction setting has been proposed as a promising tool to predict patient outcome [17]. The results of the present study suggest that assessment of hyperaemic perfusion defect–upslope ratio by CMR may be a better predictor of LV remodelling than other non-invasive parameters such as infarct size, baseline LVEF, or the presence of microvascular obstruction. However, manual assessment of perfusion defect–upslope ratio is time-consuming, which limits its potential clinical utility. Fully automated perfusion maps that are currently being developed will speed-up quantitative perfusion analysis [25], and should be tested in this indication.

Limitations

The present study represents an exploratory subgroup analysis of a previous trial [9]. We acknowledge that, with only 10 placebo control patients, our study may be underpowered. Hence, the results should be interpreted as hypothesis-generating and larger prospective studies are needed to confirm (or refute) our neutral results.

Conclusion

In conclusion, the BOOST-2 perfusion substudy does not support the use of BMCs to enhance infarct perfusion in patients with STEMI and moderately reduced LVEF. These results add to a growing body of evidence that 'first generation' BMC therapies do not promote functional recovery in STEMI patients treated according to current standards of early PCI and drug therapy [8]. Infarct perfusion, as determined by S-CMR early after PCI, may help to predict LVEF recovery at 6 months.

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