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ORIGINAL ARTICLE

Five-year follow-up of intracoronary autologous cell therapy in acute myocardial infarction: the REGENERATE-AMI trial

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Abstract

Aims The long-term outcomes of the intracoronary delivery of autologous bone marrow-derived cells (BMCs) after acute myocardial infarction are not well established. Following the promising 1 year results of the REGENERATE-AMI trial (despite it not achieving its primary endpoint), this paper presents the analysis of the 5 year clinical outcomes of these acute myocardial infarction patients who were treated with an early intracoronary autologous BMC infusion or placebo.

Methods and results A 5 year follow-up of major adverse cardiac events (defined as the composite of all-cause death, recurrent myocardial infarction, and all coronary revascularization) and of rehospitalization for heart failure was completed in 85 patients (BMC n = 46 and placebo n = 39). The incidence of major adverse cardiac events was similar between the BMC-treated patients and the placebo group (26.1% vs. 18.0%, P = 0.41). There were no cases of cardiac death in either group, but an increase in non-cardiac death was seen in the BMC group (6.5% vs. 0%, P = 0.11). The rates of recurrent myocardial infarction and repeat revascularization were similar between the two groups. There were no cases of rehospitalization for heart failure in either group.

Conclusion This 5 year follow-up analysis of the REGENERATE-AMI trial did not show an improvement in clinical outcomes for patients treated with cell therapy. This contrasts with the 1 year results which showed improvements in the surrogate outcome measures of ejection fraction and myocardial salvage index.

Keywords Myocardial infarction; Stem cells; Percutaneous coronary intervention

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Introduction

Cardiovascular disease, and specifically acute myocardial infarction (AMI), is the leading cause of morbidity and mortality worldwide.[1] While the advent of reperfusion therapy, especially primary percutaneous coronary intervention (PCI),[2] has dramatically improved survival rates in patients with AMI, a significant percentage of patients still develop post-myocardial infarction (MI) ventricular remodelling and subsequent ischaemic heart failure, leading to adverse long-term clinical outcomes.[3,4]

Cell-based therapy has emerged as a promising therapeutic option for patients with AMI, and autologous bone marrow-derived cells (BMCs) have been those most commonly utilized in clinical trials.[5,6] A meta-analysis of 16 studies including 1641 patients with ST-segment elevation MI (STEMI) showed a modest but significant improvement in left ventricular (LV) function and remodelling 3–6 months after

BMC administration.[7] However, the long-term outcomes of these patients have not been established. The REPAIR-AMI (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction) (BMC therapy 3–7 days after PCI)[8] trial showed that cell therapy was associated with improved LV function and more favourable clinical outcomes at 5 years.[9] However, the BOOST (Bone Marrow transfer after Myocardial Infarction) (BMC 4.8 ± 1.3 days after PCI) trial only observed an improvement in LV ejection fraction (LVEF) at 6 months,[10] failing to show a sustained effect on LV function at 18 months[11] or 5 years.[12]

In the context of these studies, REGENERATE-AMI was a multicentre, double-blind, randomized, placebo-controlled trial designed to determine for the first time whether the early delivery (<24 h, within the normal length of a hospital stay) of an intracoronary infusion of BMCs after AMI was feasible, safe and efficacious in the improvement of LV function.[13] Despite not achieving its primary endpoint (a between-group difference in ejection fraction at 1 year: 2.2%; 95% confidence interval [CI] −0.5 to 5.0; P = 0.1), the trial showed a within-group improvement in ejection fraction of 5.1% (from 47.5 ± 9.2% at baseline to 52.6 ± 10.5% at 1 year; $P < 0.0001$), alongside a higher myocardial salvage index (MSI) in patients treated with BMCs (0.1%; 95% CI: 0.0–0.20; P = 0.048).

This paper analyses the 5 year clinical outcomes of the patients from the REGENERATE-AMI trial in order to establish whether the clinical event rate was lower in the BMC-treated patients as suggested by the change in ejection fraction and MSI seen at 1 year.[13,14]

Methods

Study design and participants

This multicentre, double-blind, randomized, placebo-controlled trial was performed in five centres, and the study protocol has been described in detail previously.[13,15] In brief, patients were eligible for inclusion if they had a diagnosis of acute anterior MI (ST-segment elevation in at least two contiguous anterior leads ≥0.2 mV), resultant significant anterior wall motion abnormality on LV angiography and had undergone successful primary PCI within 24 h of symptom onset. Successful primary PCI was defined as Thrombolysis in Myocardial Infarction (TIMI) 3 flow in the infarct-related artery. Bone marrow harvest was performed as soon as possible after index primary PCI (<18 h), and the amount of bone marrow harvested was standardized at 100 mL. The BMC or placebo product (0.9% saline) was infused into the infarct-related artery in three fractions during stop flow conditions within 6 h of bone marrow harvest.[8]

The ethics review board of each participating centre approved the protocol and the study was conducted in accordance with the Declaration of Helsinki. The trial was approved by an independent ethics committee and registered at approved registries (ClinicalTrials.gov: NCT00765453 and EudraCT: 2007-002144-16). Patients consented to the use of their data at 5 years.

Endpoints and definitions

The 5 year analysis of major adverse cardiac events (MACE) included all-cause death, recurrent MI (defined as the recurrence of symptoms or the presence of electrocardiogram changes in association with a rise in cardiac markers occurring after the index PCI for STEMI), repeat revascularization with PCI (target vessel or non-target vessel) and coronary artery bypass grafting. Rehospitalization for heart failure was also recorded. All adverse events were reported to 5 years, and trial safety was monitored by an independent Data and Safety Monitoring Board. All endpoints were reviewed by two independent members of the trial clinical events committee to determine the nature and type of event.

Statistical analysis

Baseline variables are summarized for each group (*Table 1*). Continuous variables are presented as mean ± standard deviation or median ± inter-quartile range, and categorical variables are presented as percentages. Within-group comparisons were performed using the paired t-test and repeated measures analysis of variance adjusted for multiple comparisons. Between-group comparisons were performed using the unpaired t-test. Time-dependent event rates were estimated by Kaplan–Meier survival curves for the randomization status and P-values were determined by the use of log-rank statistics. Unadjusted Cox regression analysis was used to assess the hazard ratios (HRs) and 95% CIs of the randomization status related to the clinical endpoint to be assessed. P-values are two sided with a value of <0.05 considered to indicate statistical significance. All statistical analysis was performed using Stata Version 15.1 (StataCorp, College Station, TX, USA).

Results

Patients and baseline characteristics

A total of 100 patients were randomized to an intracoronary delivery of BMCs (n = 55) or placebo (n = 45). As previously reported, 92 patients reached 1 year follow-up.[13] Eighty-five patients completed 5 year follow-up (BMC n = 46 and placebo n = 39, *Figure 1*). Of those lost to the 5 year follow-up, one

Table 1 Baseline characteristics of the study population

	Placebo (n = 39)	BMC (n = 46)
Age (years), mean ± SD	56.3 ± 10.0	56.6 ± 9.6
Sex (M/F), *n*	37/2	39/7
Ethnicity (Caucasian), *n* (%)	31 (79.5%)	35 (76.1%)
Medical history		
Hypertension, *n* (%)	10 (25.6%)	19 (41.3%)
Hypercholesterolaemia, *n* (%)	10 (25.6%)	16 (34.8%)
Diabetes mellitus, *n* (%)	4 (10.3%)	6 (13.0%)
Active smoker, *n* (%)	19 (48.7%)	22 (47.8%)
Previous MI, *n* (%)	0 (0.0%)	1 (2.2%)
Previous PCI, *n* (%)	0 (0.0%)	1 (2.2%)
Family history, *n* (%)	10 (25.6%)	14 (30.4%)
Medical therapy		
Aspirin, *n* (%)	39 (100%)	46 (100%)
Clopidogrel, *n* (%)	34 (87.2%)	43 (93.5%)
Prasugrel, *n* (%)	4 (10.3%)	2 (4.4%)
Ticagrelor, *n* (%)	1 (2.6%)	1 (2.2%)
Heparin, *n* (%)	35 (89.7%)	41 (89.1%)
Bivalirudin, *n* (%)	4 (10.3%)	4 (8.7%)
GP IIb/IIIa inhibitors, *n* (%)	30 (76.9%)	37 (80.4%)
DES used, *n* (%)	30 (76.9%)	36 (78.3%)
Concomitant PCI performed, *n* (%)	1 (2.6%)	2 (4.4%)
Baseline observations		
Blood pressure (systolic/diastolic), mean	135.4/82.6	136.5/82.1
Pulse (b.p.m.), mean ± SD	83.1 ± 22.3	77.9 ± 15.3
Body mass index (kg/m^2), mean ± SD	27.2 ± 4.5	26.5 ± 3.0
Canadian Cardiovascular Society >1, *n* (%)	1 (2.6%)	3 (6.5%)
New York Heart Association >I, *n* (%)	3 (7.7%)	4 (8.7%)
Angiographic findings		
APPROACH score (%)	31.8 (29.7–44.5)	41.3 (31.3–44.5)
Thrombolysis in Myocardial Infarction flow <2, *n* (%)	30 (76.9%)	30 (65.2%)
Timings		
Chest pain to PCI (min), median (IQR)	176 (128–318)	232.5 (155–358.5)
Door to PCI time (min), median (IQR)	37 (26–58)	39.5 (29.8–58.3)
PCI to bone marrow aspiration time (min), median (IQR)	253 (122–972)	227 (107.3–993.5)
PCI to reinfusion (min), median (IQR)	567 (458–1297)	631 (402.3–1381)
Bone marrow aspiration to infusion (min), median (IQR)	313 (281–372)	321.5 (282.3–372.8)
Baseline LV function (CMR/CT)		
Left ventricular ejection fraction (%)	49.5 (43–56)	50.3 (41.4–53.6)
Left ventricular end diastolic volume (mL)	166 (138.5–185)	152.5 (130.8–176.3)
Left ventricular end systolic volume (mL)	76 (66–99)	75 (60–96.1)

APPROACH, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease score; BMC, bone marrow-derived cell; CMR, cardiovascular magnetic resonance; CT, computed tomography; DES, drug eluting stent; GP, glycoprotein; IQR, inter-quartile range; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

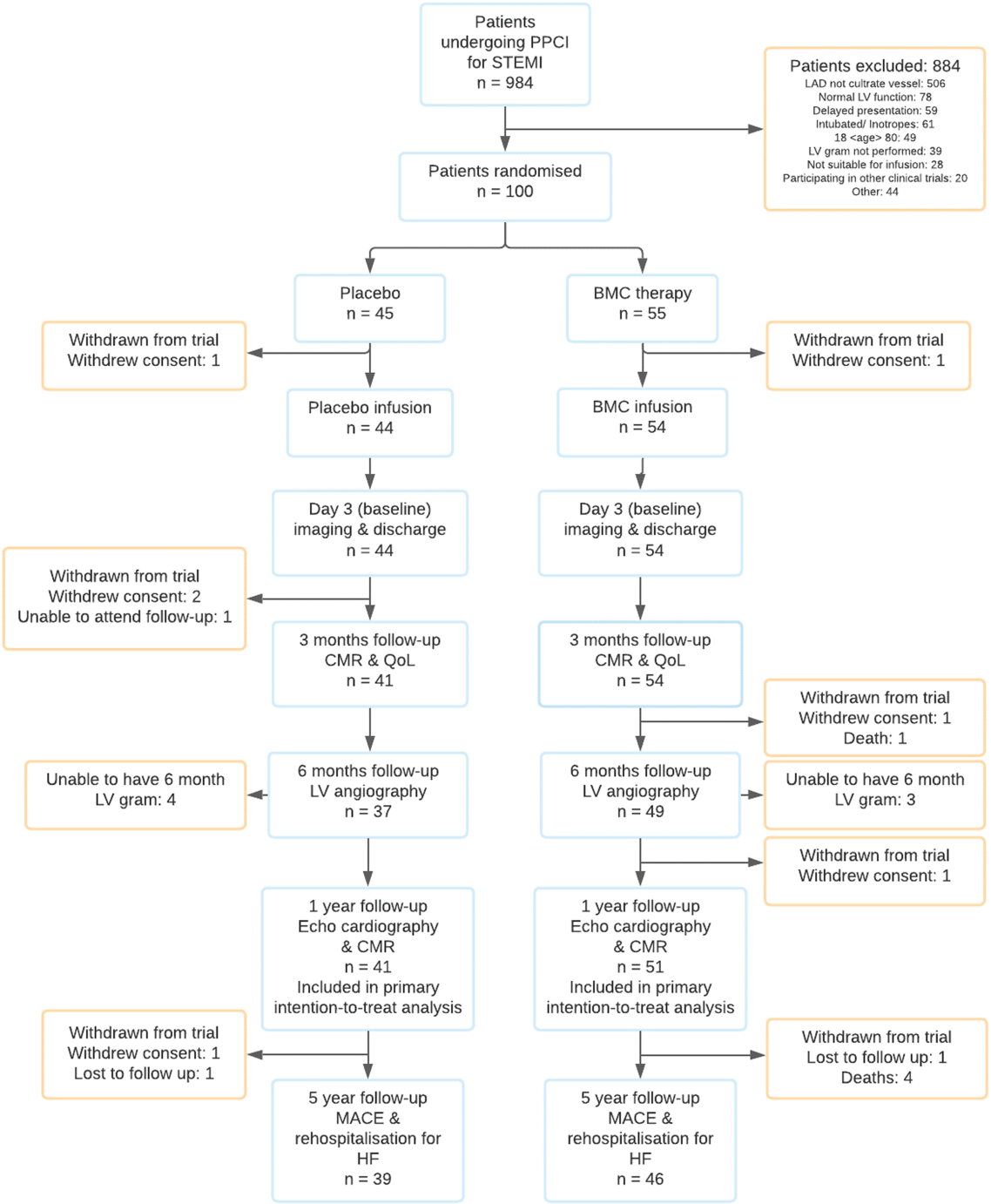
patient assigned to placebo withdrew after 1 year and another was lost to follow-up after 4 years. Five patients randomized to BMC therapy were also lost to follow-up: one patient after 1 year and four patients after 4 years.

Table 1 shows the baseline characteristics of the 85 patients included in this 5 year analysis. These characteristics were similar between both groups, consistent with the findings in our previous report.[13]

Clinical outcomes at 5 year follow-up

The overall adverse clinical events at 5 years are presented in *Table 2*, and *Figure 2* shows Kaplan–Meier survival curves for MACE, all-cause mortality, recurrent MI and repeat revascularization at 5 years. The rate of MACE was similar between the BMC-treated patients and the placebo group (26.1% BMC vs. 18.0% placebo, HR 1.48, 95% CI 0.58–3.76, P = 0.41, *Figure 2A* and *Table 2*). The two groups also had similar rates of recurrent MI (10.9% BMC vs. 7.7% placebo, HR 1.46, 95% CI 0.35–6.10; P = 0.60, *Figure 2C* and *Table 2*) and repeat revascularization (17.4% BMC vs. 18.0% placebo, HR 0.97, 95% CI 0.35–2.67; P = 0.95, *Figure 2D* and *Table 2*). Interestingly, although all the patients showed LV dysfunction at randomization, there were no cases of rehospitalization for heart failure in either group. There were also no cases of cardiac death in either group, but there was an increase in non-cardiac death in the BMC group—from intracerebral haemorrhage at 580 days, chronic obstructive pulmonary disease at 1095 days and kidney failure at 1453 days from admission (6.5% BMC vs. 0% placebo; P = 0.11, *Figure 2B* and *Table 2*).

Figure 1 Consort diagram.



Discussion

This retrospective 5 year analysis of the randomized, placebo-controlled, multicentre REGENERATE-AMI trial did not demonstrate a clinical benefit of BMC infusion despite the within-group increase in ejection fraction and the higher MSI at 1 year compared with controls.[13] Although the study was not powered to definitively address the impact of BMC therapy on clinical outcomes at 5 years, the overall clinical event rates were similar between the two groups. The increase in the incidence of MACE in the BMC-treated group was driven by cases of non-cardiac mortality, which, due to their timing and nature (from intracerebral haemorrhage at 580 days, chronic obstructive pulmonary disease at 1095 days,

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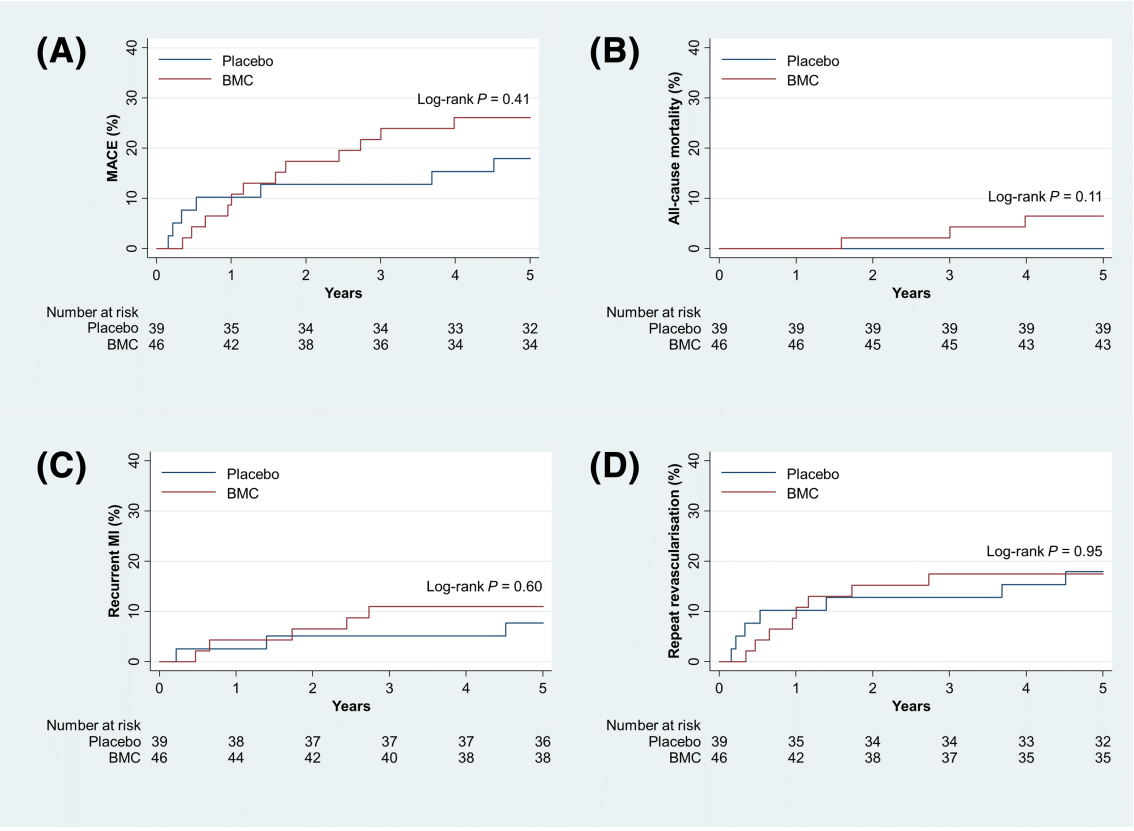
Table 2 Clinical outcomes at 5 years

	Placebo (n = 39)	BMC (n = 46)	Time from admission to death (days)	HR (95% CI)	P-value
Major adverse cardiac events (%)	7 (18.0)	12 (26.1)	—	1.48 (0.58–3.76)	0.41
All-cause mortality (%)	0 (0)	3 (6.5)	—	—	0.11
Cardiac mortality (%)	0 (0)	0 (0)	—	—	—
Non-cardiac mortality (%)	0 (0)	3 (6.5)	—	—	0.11
Intracerebral haemorrhage	0 (0)	1 (2.2)	580	—	—
COPD exacerbation	0 (0)	1 (2.2)	1095	—	—
Kidney failure	0 (0)	1 (2.2)	1453	—	—
Recurrent myocardial infarction (%)	3 (7.7)	5 (10.9)	—	1.46 (0.35–6.10)	0.60
Repeat revascularization (%)	7 (18.0)	8 (17.4)	—	0.97 (0.35–2.67)	0.95
Target vessel revascularization (%)	3 (7.7)	7 (15.2)	—	1.97 (0.51–7.63)	0.32
Non-target vessel revascularization (%)	4 (10.3)	1 (2.2)	—	0.21 (0.02–1.88)	0.12
Coronary artery bypass grafting (%)	0 (0)	0 (0)	—	—	—
Rehospitalization for heart failure (%)	0 (0)	0 (0)	—	—	—

BMC, bone marrow-derived cell; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

Figure 2 Kaplan–Meier curves for (A) MACE, (B) all-cause mortality, (C) recurrent myocardial infarction, and (D) repeat revascularization at 5 years.



and kidney failure at 1453 days from admission—*Table 2*), are arguably unrelated to cell therapy.

Cell-based therapy provides the potential to further improve LV function and clinical outcomes after AMI on top of standard post-PCI medical treatment. Meta-analyses of BMC therapy for AMI have shown mixed results. A meta-analysis of 16 studies including 1641 patients with STEMI showed a modest, but significant, improvement in LVEF of 2.55% and indices of LV remodelling at 3–6 months after intracoronary BMC administration.[7] Patients with a younger age (<55 years) and reduced baseline LVEF (<40%) derived more benefit. In contrast, the multinational ACCRUE (Meta-Analysis of Cell-based Cardiac Studies) meta-analysis reviewed 12 studies (1252 patients) and concluded that there was no significant difference in terms of change in LVEF or clinical events at 6–12 months.[16]

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More importantly, the question remains as to the long-term effects of intracoronary BMC administration on clinical outcomes and LV function and remodelling. A systematic review from 33 clinical trials of BMC therapy post-MI showed a lasting improvement on LVEF during the follow-up period from 12 to 61 months, but this did not translate into decreased morbidity or mortality.[17] Studies with long-term follow-up, however, remain scarce, and the results are conflicting. The REPAIR-AMI trial randomized 204 patients to receive either placebo or intracoronary BMC therapy 3–7 days following successful primary PCI for STEMI.[8,9] The primary endpoint of change in global LVEF at 4 months was significantly higher in the BMC group than controls (5.5% vs. 3.0%, $P = 0.01$).[8] Subsequent analysis of the data at 5 years showed a significant reduction in the composite endpoint of death, recurrent MI and any revascularization in patients that had received BMC therapy.[9] The BOOST trial randomized 60 patients to receive either BMC therapy 4.8 ± 1.3 days after primary PCI for STEMI or standard post-PCI AMI care. The primary endpoint of change in global LVEF at 6 months improved significantly in BMC-treated patients compared with the control group (6.7% vs. 1.4%, $P = 0.026$).[10] However, sustained benefit was not observed at 18 month follow-up[11] or at 5 years.[12] The ASTAMI (Autologous Stem-Cell Transplantation in Acute Myocardial Infarction) study randomized 100 patients to either intracoronary BMC infusion (delivered 4–7 days after PCI for STEMI) or control.[18] The primary endpoint of improvement in global LVEF at 6 months was similar (3.1% BMC vs. 2.4% control, $P = 0.70$). Long-term follow-up at 3 years identified no significant effects of cell therapy in terms of the primary endpoint or adverse clinical events.[19]

In summary, existing trials are conflicting; some show early improvements in surrogate markers in response to cell therapy, while others do not. Few studies have gone on to show sustained long-term benefit, and those that have were not adequately powered to definitively address this.

There could be several possible explanations for the inconsistent outcomes of BMC therapy in clinical trials. Firstly, BMCs are a heterogeneous population including monocytes, lymphocytes, mesenchymal stem cells, haematopoietic stem cells and endothelial progenitor cells. Hence, it can be difficult to determine which cell populations led to the clinical benefits.[20] Furthermore, few trials have assessed the functional capacity of the BMCs (e.g. REPAIR-AMI[9]), thereby making it difficult to compare the potency of cells used in different studies. Given the general perception that there isn't a clear signal for the use of autologous BMCs to improve cardiac function in patients with heart failure,[21,22] the field has moved to other cell types (e.g. mesenchymal stem cells[23] and cardiac stem cells[24]) and combination therapies.[25] Secondly, some of the important variables in methodologies (such as cell number, preparation and storage, and the isolation and infusion procedure[26–28]) could have influenced the outcomes observed. Thirdly, differences in clinical risk factors (such as age, gender, and co-morbidities[29]) may have also played a role.

REGENERATE-AMI was designed to understand whether an early cell infusion would improve outcomes in patients with AMI. Importantly, this therapy was delivered within a normal length of hospital stay in order to minimize the impact (cost and efficiency) on existing healthcare services.[13] Although Phase II trials[8] and metanalyses[30] have shown an increased efficacy of cell therapy delivered 3–7 days after AMI, the specific aim of REGENERATE-AMI was to deliver cell therapy within a shorter time frame, in keeping with the current management and length of stay for AMI patients.

The trial demonstrated that cell therapy could be given within 12 h of primary angioplasty and that patients could be discharged 2 days after admission. This was accompanied by a within-group improvement in ejection fraction (more so at 3 months that reduced at 1 year), and an increased MSI and reduction in scar size compared with controls. These results are similar to those of the BOOST trial, which observed an early benefit with improvement in LVEF at 6 months, but no significant sustained effects at 18 months[11] and 5 years.[12] However, as previously suggested,[14] the increased MSI and reduced infarct size in REGENERATE-AMI should have led to a longer-term clinical signal suggesting improved outcomes. Even though REGENERATE-AMI was not designed to demonstrate differences in clinical outcomes between the placebo and BMC-treated groups, the data collected at 5 year follow-up did not show a reduction in adverse outcomes as defined by overall clinical events. Taken together, these findings suggest that although an early autologous cell delivery approach is feasible, the potential benefits seen at early time points in surrogate markers do not translate to improvements in clinical outcome.

This 5 year analysis of the REGENERATE-AMI data, therefore, adds further important information to the existing small number of clinical trials addressing the role of cell-based therapies in AMI and should be included in further meta-analyses. These are not a substitute for a definitive Phase III clinical trial but are useful in planning these studies as they evidence clinical efficacy and safety signals.

Recently, the results of the first Phase III clinical trial of autologous cell therapy in AMI (BAMI) were published.[31] Despite a rigorous trial design and methodology, this study failed to recruit enough patients (375 out of a target of 3000) to address the primary endpoint of all-cause mortality at 2 years. No difference was seen between patients treated with cells and the placebo group and the study identified a very low overall rate of all-cause mortality (3.5%). This suggests that a much larger study (over 10, 000 patients) would be needed to identify a meaningful difference in outcome. The logistics of such a large study are challenging and makes it unlikely. Thus, the ongoing analyses of the existing Phase II clinical trials (e.g. as are presented here) are important and

will guide decisions about the future of this field of research. Interestingly, the event rates in this 5 year analysis and the BAMI trial are both much lower than expected—suggesting that current treatments for AMI are increasingly effective.

Limitations

There are several limitations to this 5 year analysis of the REGENERATE-AMI study. Firstly, it is important to state that the sample size was not powered to definitively address whether BMC administration can modify mortality and morbidity after AMI. However, previous similarly sized studies have also reported results in patients at 5 years.[32,12] Therefore, this long-term follow-up is an important addition and will help the field to better understand the questions around the sustainability of the early effects seen with cell-based therapy.

Secondly, the number of events is relatively small (an important point when designing future studies in the setting of AMI). Thirdly, due to the limited number of patients and events, we were unable to perform subgroup analysis according to factors deemed predictive of further cardiovascular events, including baseline LVEF and age.[7] Finally, we were unable to take into account any changes in the medication of these patients over the 5 year period.

Conclusions

Despite the REGENERATE-AMI trial's promising 1 year surrogate endpoint results, the 5 year analysis did not demonstrate a long-term benefit on clinical outcomes. These results can be used in further pooled analyses to better understand the role of autologous cell-based therapy in the treatment of AMI.

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Conflict of interest

None declared.

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