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Forum Review Article

Cardiac Repair with Adult Bone Marrow-Derived Cells: The Clinical Evidence

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Abstract

On the basis of strong evidence from animal studies, numerous clinical trials of cardiac repair with adult bone marrow-derived cells (BMC) have been completed. These relatively smaller studies employed different BMC types with highly variable numbers, routes, and timings of transplantation, and included patients with acute myocardial infarction (MI), chronic ischemic heart disease (IHD), as well as ischemic cardiomyopathy. Although the outcomes have been predictably disparate, analysis of pooled data indicates that BMC therapy in patients with acute MI and chronic IHD results in modest improvements in left ventricular function and infarct scar size without any increase in untoward effects. However, the precise mechanisms underlying these benefits remain to be ascertained, and the specific advantages of one BMC type over another remain to be determined. The long-term benefit and safety issues with different BMC types are currently being evaluated critically in larger randomized controlled trials with a view to applying this novel therapeutic strategy to broader patient populations. The purpose of this review is to summarize the available clinical evidence regarding the efficacy and safety of therapeutic cardiac repair with different types of adult BMCs, and to discuss the key variables that need optimization to further enhance the benefits of BMC therapy. *Antioxid. Redox Signal.* 11, 1865–1882.

Introduction

Approximately 16 million patients suffer from coronary artery disease in the United States alone, with 920,000 episodes of acute myocardial infarction (MI) occurring annually (84). The loss of myocardial tissue during MI results in scar formation, progressive remodeling of the left ventricle (LV), and development of ischemic cardiomyopathy (ICM) (80); and commensurate with the above prevalence of ischemic heart disease (IHD), ~5.3 million patients suffer from heart failure in the United States alone (84). Because of the enormity of the clinical problem and the poor prognosis, a number of medical as well as interventional and surgical approaches have been formulated over the years to alleviate the manifestations and halt the progression of ICM. Although these conventional therapeutic strategies ameliorate the symptoms of heart failure, they fail to reconstitute dead myocardium with functional new cardiomyocytes and vessels, ultimately failing to improve in any major way the overall prognosis of patients with heart failure.

In the incessant scientific pursuit to improve outcomes in patients with acute MI and heart failure, a new approach has gained vigorous momentum in recent years—myocardial repair with cell therapy. Studies from numerous laboratories have shown that therapy with adult stem/progenitor cells can improve LV function, reduce infarct size, and attenuate LV remodeling in animal models of MI and cardiomyopathy. As the mechanisms underlying these benefits of cell therapy continue to unfold, the impressive phenomenological evidence has generated tremendous enthusiasm among clinicians toward translating cell therapy for cardiac repair into clinical practice. As a result, a number of clinical studies primarily using various types of adult bone marrow-derived cells (BMCs) have already been completed and several larger randomized controlled trials (RCTs) are currently in progress.

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The 'first generation' cell therapy trials employed diverse BMC populations injected *via* different routes or mobilized at variable time periods after acute MI and/or percutaneous coronary intervention (PCI) in patients with acute MI, chronic IHD, and ischemic heart failure (1, 2, 95). Moreover, these studies utilized heterogeneous methodology to assess different facets of outcome after relatively short follow-up duration, and often did not report all of the important safety parameters (1). Because of these differences in study design, the results have also been predictably disparate, and the appropriateness of conducting cell therapy trials in humans continues to be questioned. The analysis of pooled data from these smaller trials, however, reveals that BMC therapy in patients with acute MI and chronic IHD is indeed associated with modest improvements in LV function and remodeling (1, 36, 56, 62). Following a summary of data from the controlled clinical trials with different types of BMCs, this review will focus on the evidence emerging from meta-analyses of pooled data from these trials, and the variables that need optimizing in order to improve the outcomes of BMC therapy for myocardial repair.

Controlled Clinical Trials of BMC Therapy for Cardiac Repair

The bone marrow in adults is a complex organ that harbors numerous types of mature and immature hematopoietic and nonhematopoietic cells. Consistent with the notion that various adult organs harbor tissue-specific progenitors that give rise to cells with adult phenotypes continuously or following organ damage, stem/progenitor cells with the potential to repair diverse tissues have been well described in the bone marrow. These include the hematopoietic stem cells (96), mesenchymal stem cells (MSCs) (83), endothelial progenitor cells (EPCs) (4, 103), side population cells (31), multipotent adult progenitor cells (38), and the very small embryonic-like stem cells (VSELs) (49, 109, 110), among others. Because of the relatively greater concentration of stem/progenitor cells, the easy availability, and the efficacy in animal models, numerous clinical trials have already examined the utility of BMCs for myocardial repair in humans (1, 95). Although several earlier trials did not include a control group, a majority of the recent ones compared outcomes in BMC-treated patients with controls who received optimal conventional treatment without cell therapy. Tables 1 and 2 summarize results from controlled clinical trials that examined the feasibility, efficacy, and safety of therapy with various adult BMC populations for cardiac repair in humans. These trials utilized BMCs harvested directly from the bone marrow or the peripheral blood with or without culture or preservation *in vitro*, and may be divided into several categories based on the cell type (Tables 1 and 2).

Bone marrow mononuclear cells

Bone marrow mononuclear cells (BMMNCs) represent a heterogeneous cell population that contains hematopoietic and nonhematopoietic cells with diverse phenotypes. BMMNCs are generally isolated from total BMCs by density gradient centrifugation, which allows separation of BMMNCs relatively easily and quickly. In the first controlled study by Strauer *et al.* (97), intracoronary injection of autologous BMMNCs improved regional contractility and myocardial perfusion, reduced LV end-systolic volume (LVESV), and reduced infarct size in patients with acute MI. The global LV ejection fraction (EF) did not improve significantly. Since then, at least 12 cohort studies or RCTs of BMMNC therapy in patients with acute MI, ICM, or chronic IHD with anginal symptoms have been reported (7, 29, 34, 41, 58, 63, 64, 67, 76–78, 90, 98, 102). However, aside from the differences in patient characteristics, the route of cell transplantation, the number of transplanted BMMNCs, as well as the timing of BMC injection after acute MI or PCI were considerably different among these studies. Importantly, despite this heterogeneity in study design, all of these studies except one (58) reported improvements in one or more parameters of LV contractility, anatomy, and perfusion, including global LVEF, regional wall motion, LVESV, infarct size, and viability. Additional parameters that have been reported to improve with BMMNC therapy include anginal symptoms, exercise capacity, and the New York Heart Association (NYHA) functional class (78, 102).

Besides modest improvements in various outcome parameters, BMMNC therapy offers several other advantages. As mentioned above, BMMNCs are relatively easy to procure in large numbers and do not require complex culture conditions. Moreover, BMMNC therapy has been shown to be efficacious *via* the intracoronary route (90, 97), as well as transepicardial (34, 67) and transendocardial (78, 102) routes. Also, BMMNC therapy has been effective not only in patients with acute MI (29, 90, 97), but also in patients with chronic IHD (98, 102), and ischemic cardiomyopathy (7, 78). Finally, despite these diverse patient subsets and modes of delivery, no significant adverse effect of BMMNC therapy has been reported in the controlled clinical trials.

Unfractionated BMCs

Relatively unfractionated BMCs have been used *via* the intracoronary route in at least three RCTs thus far (37, 66, 87, 92, 106). In the first RCT of BMC therapy in humans, Wollert *et al.* (106) reported significant improvement in global LVEF and regional wall motion in the periinfarct area in BMC-treated patients after 6 months of follow-up. However, after 18 months, the differences in LVEF and other outcome parameters between control and BMC-treated patients were no longer significant (66). Further analysis revealed an accelerated recovery of global LV function in cell-treated patients (66), which was presumably responsible for the early differences in outcomes. Although these observations suggest that the apparent early benefits of BMC therapy merely reflect a hastened recovery following acute MI likely due to a transient paracrine phenomenon, a more sustained nature of improvement in diastolic parameters in these same patients (66) points to a larger spectrum of benefits afforded by BMC therapy. Importantly, despite the injection of a large number of BMCs, no tumors, myocardial calcification, or other forms of cancer were noted during the 18 months of follow-up in the BOOST study (66). In the study by Janssens *et al.* (37), no significant improvement in global LVEF, wall motion, or anatomic parameters were noted despite a reduction in infarct size; while BMC therapy was associated with improvements in several functional and anatomical parameters in the study by Ruan *et al.* (87). The above differences in outcomes certainly call for larger RCTs investigating not only the duration of effects with multiple end-points in humans, but also studies in animal models elucidating the mechanistic underpinnings of BMC treatment effects.

Table 1. Controlled Clinical Trials of Myocardial Repair with Different Types of Bone Marrow-Derived Cells

	Cell type	*Study design*	*Clinical scenario*	*Treated patients*	*Control patients*	*Route of delivery*	*Number of cells (millions)*	*Timing after AMI/PCI*	*Follow-up duration (months)*	*Results*
A. Cells harvested from the bone marrow										
ASTAMI (58, 59)	BMMNC	RCT	AMI	50	50	Intracoronary	87 ± 47.7	6 ± 1.3 days	12	No improvement in LVEF, infarct size, and LVEDV
Hendrikx *et al.* (34)	BMMNC	RCT	ICM	10	10	Intramyocardial (during CABG)	60 ± 31	217 ± 162 days	4	Regional wall thickening ⇑; no improvement in global LVEF, LVESV, and LVEDV
Karpov *et al.* (41)	BMMNC	RCT	AMI	22	22	Intracoronary	89 ± 49	7–21 days	6	No improvement in LVEF, perfusion defect, and quality of life
Meluzin *et al.* (63, 64)	BMMNC	RCT	AMI	40	20	Intracoronary	10 and 100	7 days	12	In high cell dose group: global LVEF ⇑; LVESV ⇓; earlier differences in regional wall motion partially lost at 12 month
Mocini *et al.* (67)	BMMNC	Cohort	ICM	18	18	Intramyocardial (during CABG)	640 ± 463	1–6 months	12	In treated patients compared with baseline, global LVEF ⇑; wall motion ⇑
Penicka *et al.* (76)	BMMNC	RCT	AMI	17	10	Intracoronary	IQR:1,960-3,300	4–11 days	4	No improvement in LVEF, infarct size, and LV volumes
Perin *et al.* (77, 78)	BMMNC	Cohort	ICM	11	9	Transendocardial (EMM-guided)	25.5 ± 6.3	NR	12	Angina ⇓; NYHA class ⇓; exercise capacity ⇑; perfusion ⇑; no improvement in global LVEF
PROTECT-CAD (102)	BMMNC	RCT	CAD with refractory angina	19	9	Transendocardial (EMM-guided)	16.7 ± 3.4 (low dose) 42 ± 28 (high dose)	NR	6	Global LVEF ⇑; infarct wall thickening ⇑; LVESV ⇓; exercise time ⇑; NYHA class ⇓
REPAIR-AMI (25, 90, 91)	BMMNC	RCT	AMI	101	103	Intracoronary	236 ± 174	4.3 ± 1.3 days	12	Global LVEF ⇑; regional wall motion ⇑; LVESV ⇓; coronary flow reserve ⇑; no improvement in LVEDV
Strauer *et al.* (97)	BMMNC	Cohort	AMI	10	10	Intracoronary	28 ± 22	5–9 days	3	Stroke volume index ⇑; regional wall motion ⇑; LV contractility index ⇑; infarct size ⇓; LVESV ⇓

(*Continued*)

Table 1. (Continued)

	Cell type	*Study design*	*Clinical scenario*	*Treated patients*	*Control patients*	*Route of delivery*	*Number of cells (millions)*	*Timing after AMI/PCI*	*Follow-up duration (months)*	*Results*
Strauer *et al.* (98)	BMMNC	Cohort	Chronic IHD (prior MI)	18	18	Intracoronary	60–132	27 ± 31 months	3	Global LVEF ⇑; infarct wall motion ⇑; infarct size ⇓; viability ⇑; $VO2_{max}$ ⇑
TCT-STAMI (29)	BMMNC	RCT	AMI	10	10	Intracoronary	40	1 day	6	In treated patients global LVEF ⇑; infarct size ⇓; LV dilation halted
TOPCARE-CHD (7)	BMMNC CPC	RCT	ICM	35 (BMMNC) 34 (CPC)	23	Intracoronary	205 ± 110 (BMMNC) 22 ± 11 (CPC)	81 ± 72 months (BMMNC) 77 ± 76 months (CPC)	6	Global LVEF ⇑; regional wall motion ⇑ in BMMNC-treated patients
BOOST (66, 92, 106)	BMC	RCT	AMI	30	30	Intracoronary	2,460 ± 940	4.8 ± 1.3 days	18	Early differences in global LVEF and regional wall motion between treated and control patients lost significance at 18 months; persistent improvement in diastolic function; no improvement in LVESV, LVEDV, infarct size
Janssens *et al.* (37)	BMC	RCT	AMI	33	34	Intracoronary	304 ± 128	1 day	4	Infarct size ⇓; no improvement in global LVEF, LVESV, and LVEDV
Ruan *et al.* (87)	BMC	RCT	AMI	9	11	Intracoronary	NR	1 day	6	Global LVEF ⇑; segmental function in the infarct as well as viable area ⇑; LVESV ⇓; LVEDV ⇓
Bartunek *et al.* (10)	AC133 + BMC	Cohort	AMI	19	16	Intracoronary	12.6 ± 2.2	11.6 ± 1.4 days	4	In treated patients compared with baseline, global LVEF ⇑; regional function ⇑; infarct size ⇓; viability ⇑
Chen *et al.* (17)	MSC	RCT	AMI	34	35	Intracoronary	48,000–60,000	18.4 ± 0.5 days	6	Global LVEF ⇑; infarct wall motion ⇑; LVESV ⇓; infarct size ⇓; LVEDV ⇓
Chen *et al.* (16)	MSC	RCT	ICM	24	24	Intracoronary	5/ml	289 ± 168 days	12	Perfusion ⇑; NYHA class ⇓; exercise tolerance ⇑
Katritsis *et al.* (42)	MSC and EPC	Cohort	AMI/ICM	11	11	Intracoronary	2–4	242 ± 464 days	4	Perfusion ⇑; viability ⇑; no improvement in global LVEF, LVESV, and LVEDV

B. Mobilized progenitor cells

Choi *et al.* (18)	PBSC	Cohort	AMI	10	63	Intracoronary	2,030 ± 690	8.3 ± 8.2 days	24	Compared with controls, no additional improvement in LV functional or structural parameters
Erbs *et al.* (24, 45)	CPC	RCT	ICM	13	13	Intracoronary	69 ± 14	7.5 ± 2.9 months	3	Global LVEF ⇑; infarct size ⇓; myocardial perfusion ⇑; coronary flow reserve ⇑
Li *et al.* (55)	PBSC	RCT	AMI	35	35	Intracoronary	72.5 ± 73	7 ± 5 days	6	Global LVEF ⇑; wall motion ⇑; no improvement in LVESV and LVEDV
Losordo *et al.* (57)	CD34 + cells	RCT	CAD with angina	18	6	Transendocardial (EMM-guided)	0.05, 0.1, or 0.5 million/kg	NR	12	Trend toward improved angina frequency, nitroglycerin usage, CCS class, and exercise time in cell-treated patients
MAGIC Cell-3-DES (40)	PBSC	RCT	AMI/ICM	41	41	Intracoronary	1400 ± 500	7 ± 1 (AMI) 517 ± 525 (OMI)	6	In patients with AMI: global LVEF ⇑; LVESV ⇓; infarct size ⇓; coronary flow reserve ⇑. In patients with OMI: coronary flow reserve ⇑
Tatsumi *et al.* (101)	PBMNC	Cohort	AMI	18	36	Intracoronary	4,920 ± 2,820	2.5 ± 0.5 days	6	Global LVEF ⇑; wall motion ⇑; infarct size ⇓; LVESV index tended to be lower
TOPCARE-CHD (7)	BMMNC CPC	RCT	ICM	35 (BMMNC) 34 (CPC)	23	Intracoronary	205 ± 110 (BMMNC) 22 ± 11 (CPC)	81 ± 72 months (BMMNC) 77 ± 76 (CPC)	6	No significant improvement in LVEF or wall motion in CPC-treated patients

AMI, acute myocardial infarction; BMC, unfractionated bone marrow cell; BMMNC, bone marrow mononuclear cell; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CPC, circulating progenitor cell; EMM, electromechanical mapping; EPC, endothelial progenitor cell; ICM, ischemic cardiomyopathy; IQR, interquartile range; LV, left ventricular; LVEF, LV ejection fraction; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; MSC, mesenchymal stem cell; NR, not reported; NYHA, New York Heart Association; OMI, old myocardial infarction; PBMNC, peripheral blood-derived mononuclear cell; PBSC, peripheral-derived blood stem cell; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

Table 2. Adverse Effects Reported in Controlled Clinical Trials of Bone Marrow-Derived Cell Therapy for Myocardial Repair

	Cell type	Follow-up (months)	Cardiovascular death		In-stent restenosis or target vessel PCI		SVT		VT		Recurrent MI/ angina		Comments
			T	C	T	C	T	C	T	C	T	C	
A. Cells harvested from the bone marrow													
ASTAMI (58, 59)	BMMNC	12	0/50	0/50	11/50	9/50	NR	NR	2/50	1/50	1/50	0/50	No difference in signal-averaged ECG variables
Hendrikx *et al.* (34)	BMMNC	4	NR	NR	NA	NA	NR	NR	6/9 (induced)	0/5 (induced)	NR	NR	
Karpov *et al.* (41)	BMMNC	6	NR	NR	4/22	3/22	NR	NR	NR	NR	4/22	3/22	Incidence of arrhythmia was similar in both groups
Meluzin *et al.* (63, 64)	BMMNC	12	NR	NR	9/40	3/20	NR	NR	NR	NR	1/40	2/20	
Mocini *et al.* (67)	BMMNC	12	0/18	0/18	NA	NA	8/18	6/18	6/18	9/18	NR	NR	Cardiac NMR scan did not reveal any abnormal tissue or calcification
Penicka *et al.* (76)	BMMNC	4	2/17	0/10	24%	40%	NR	NR	NR	NR	1/17	NR	Major adverse events in cell therapy group occurred prior to BMMNC injection
Perin *et al.* (77, 78)	BMMNC	12	2/11	0/9	NA	NA	0/11	0/9	0/11	0/9	NR	NR	No change in signal-averaged ECG parameters, BNP level, and WBC count
PROTECT-CAD (102)	BMMNC	6	0/19	1/9	NA	NA	0/19	0/9	0/19	0/9	0/19	2/9	Cardiac MRI did not reveal any tumor or calcification
REPAIR-AMI (25, 90, 91)	BMMNC	12	2/101	5/103	16/101	26/103	NR	NR	5/101	4/103	0/101	6/103	Combined cardiovascular events were significantly reduced in treated patients
Strauer *et al.* (97)	BMMNC	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No side effects were observed at any point of time
Strauer *et al.* (98)	BMMNC	3	NR	NR	1/18	0/18	0/18	0/18	0/18	0/18	NR	NR	
TCT-STAMI (29)	BMMNC	6	0/10	0/10	NR	NR	0/10	0/10	0/10	0/10	0/10	0/10	
TOPCARE-CHD (7)	BMMNC CPC	6	0/35 (BMC) 0/34 (CPC)	1/23	4/35 (BMC) 3/34 (CPC)	0/23	NR	NR	0/35 (BMC) 1/34 (CPC)	1/23	0/35 (BMC) 2/34 (CPC)	0/23	

BOOST (66, 92, 106)	BMC	18	0/30	1/30	5/30	4/30	0/30	0/30	1/30	1/30	1/30	0/30	Echocardiography did not reveal any tumor or calcification; no case of cancer was diagnosed during follow-up
Janssens *et al.* (37)	BMC	4	NR	NR	0/33	1/34	5/33	6/34	0/33	3/34	2/33	1/34	No late potential noted
Ruan *et al.* (87)	BMC	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Bartunek *et al.* (10)	AC133 + BMC	4	NR	NR	9/19	4/16	NR	NR	2/19	0/16	NR	NR	
Chen *et al.* (17)	MSC	6	NR	NR	NR	NR	0/34	0/35	0/34	0/35	NR	NR	
Chen *et al.* (16)	MSC	12	2/24	4/24	NR	NR	NR	NR	NR	NR	NR	NR	
Katritsis *et al.* (42)	MSC and EPC	4	NR	NR	NR	NR	0/11	0/11	0/11	0/11	NR	NR	
B. Mobilized progenitor cells													
Choi *et al.* (18)	PBSC	24	0/10	7/63	1/10	8/63	NR	NR	0/10	0/63	0/10	4/63	
Erbs *et al.* (24, 45)	CPC	3	NR	NR	3/12	3/11	NR	NR	NR	NR	NR	NR	
Li *et al.* (55)	PBSC	6	0/35	0/35	0/35	0/35	NR	NR	1/35	NR	1/35	2/35	
Losordo *et al.* (57)	CD34+ cells	12	0/18	0/6	NA	NA	2/6	2/18	1/6	0/18	3/6	7/18	
MAGIC Cell-3-DES (40)	PBSC	6	0/41	1/41	0/41	4/41	NR	NR	NR	NR	0/41	1/41	No significant increase in coronary restenosis in cell-treated patients
Tatsumi *et al.* (101)	PBMNC	6	0/18	0/36	4/18	NR	NR	NR	NR	NR	NR	NR	The incidence of recurrent MI and in-stent restenosis was similar between groups
TOPCARE-CHD (7)	BMMNC CPC	6	0/35 (BMC) 0/34 (CPC)	1/23	4/35 (BMC) 3/34 (CPC)	0/23	NR	NR	0/35 (BMC) 1/34 (CPC)	1/23	0/35 (BMC) 2/34 (CPC)	0/23	

BMC, unfractionated bone marrow cell; BMMNC, bone marrow mononuclear cell; C, control; CPC, circulating progenitor cell; EPC, endothelial progenitor cell; MSC, mesenchymal stem cell; NA, not applicable; NR, not reported; PBMNC, peripheral blood-derived mononuclear cell; PBSC, peripheral blood-derived stem cell; SVT, supraventricular tachycardia; T, BMC-treated; V, ventricular tachycardia.

AC133+ BMCs

AC133+ BMCs exhibit both hematopoietic and endothelial differentiation potential and therefore, may represent a subpopulation suitable for inducing angiogenesis (13, 75). In the study by Bartunek *et al.* (10), intracoronary delivery of AC133+ BMCs improved global LVEF and regional wall motion, and reduced infarct size in cell-treated patients compared with baseline. However, spontaneous and inducible VT was noted in two cell-treated patients and a higher rate of in-stent restenosis was observed in the cell-treated group during follow-up (10). Meticulous analysis of coronary luminal stenosis during follow-up further revealed greater luminal narrowing in nonstented regions in the infarct-related artery in cell-treated patients (61), indicating a greater risk of atherogenesis with this specific subset of BMCs.

Mesenchymal stem cells

Bone marrow-derived MSCs are the multipotent precursors of various nonhematopoietic lineages and possess the ability to differentiate into adipose, bone, cartilage, skeletal muscle, neural, and other phenotypes (81, 83). Several studies have also documented the ability of MSCs to differentiate into cardiomyocytes *in vitro* and following transplantation into the infarcted myocardium *in vivo* (33, 60, 82). Moreover, MSCs are suitable for preemptive harvest, rapid expansion *in vitro*, and prolonged storage for future use, perhaps as an off-the-shelf product. Despite these advantages, concerns have been raised regarding the intracoronary route of MSC transplantation based on the observations by Vulliet *et al.* (104), who noted microinfarction and fibrosis following intracoronary delivery of relatively large MSCs in healthy dogs. However, in humans, intracoronary injection of a large number of bone marrow-derived MSCs resulted in improvement in global LVEF and regional wall motion, and reduction in infarct size, LVESV, as well as LVEDV in patients with acute MI (17). In a subsequent trial, intracoronary injection of culture-expanded MSCs in patients with ICM improved myocardial perfusion, improved exercise tolerance and NYHA class in treated patients (16). In contrast, in the study by Katritsis *et al.* (42), which included patients with acute as well as old MI and injected relatively small number (2–4 million) of MSCs, no significant improvement in global LVEF, LVESV or LVEDV was noted following intracoronary MSC transplantation despite improved myocardial perfusion and viability. In view of the above, the efficacy and safety of MSC therapy in patients with acute MI are currently being evaluated in larger RCTs.

Mobilized progenitor cells

It is well known that the peripheral blood also contains different types of bone marrow-derived primitive cells (15, 93, 103, 105). Although their precise function and dynamics remain unclear, these progenitors can home to various organs under physiologic circumstances as well as in response to tissue injury, and induce tissue repair *via* differentiation into tissue-specific lineages and other mechanisms. In addition, specific cytokines are able to mobilize large numbers of progenitors into the circulation with minimal adverse effects (53). The use of mobilized progenitors harvested from the peripheral blood *via* apheresis thus obviates the aspiration of bone marrow in patients already incapacitated with MI or heart failure.

Circulating progenitor cells. In the TOPCARE-AMI trial (6, 14, 89), in addition to BMMNCs, the investigators also utilized circulating progenitor cells (CPCs) with endothelial characteristics harvested from patients' peripheral blood followed by expansion *ex vivo*. CPCs were injected *via* the intracoronary route in patients with acute MI and after 4 months, global LVEF increased and LVESV decreased in BMMNC- as well as CPC-treated patients compared with baseline. MRI studies after 1 year of follow-up showed improved LVEF, reduced infarct size, and attenuation of LV hypertrophy in these patients (89). Importantly, the overall benefits noted in CPC-treated patients were similar to those observed in BMMNC-treated patients. In a subsequent RCT (7), these investigators examined the efficacy of CPCs and BMMNCs in patients with previous MI, dysfunctional LV segments, and an open infarct-related artery. Although BMMNC therapy improved global LVEF and regional wall motion in these patients, no such benefit was noted in CPC-treated patients (7). In contrast, in an earlier RCT by Erbs *et al.* (24), intracoronary CPC injection in patients with IHD and chronic total occlusion of coronary artery reduced infarct size, improved regional wall motion and global LVEF, decreased the number of hibernating myocardial segments, and increased coronary flow reserve. These results (24) suggest that the benefits of late reperfusion may be enhanced by concomitant CPC therapy, which improves myocardial perfusion/metabolism mismatch in these patients (45). However, the role of myocardial milieu (acutely infarcted *versus* remodeled myocardium) as a determinant of outcomes following CPC transplantation needs to be examined in future clinical trials.

Peripheral blood stem cells. Several other RCTs and cohort studies have utilized peripheral blood-derived stem cells (PBSCs) (18, 39, 40, 55) or mononuclear cells (PBMNCs) (101) for myocardial repair with or without prior therapy with granulocyte colony-stimulating factor (G-CSF) for BMC mobilization. In the first RCT by Kang *et al.* (39), intracoronary injection of G-CSF-mobilized PBSCs resulted in a high rate of in-stent restenosis, and despite early suggestions of improvement in LV function and perfusion, this trial was stopped prematurely due to safety concerns. In a subsequent RCT from these investigators (40), deployment of drug-eluting stents along with PBSC transplantation *via* the intracoronary route improved global LVEF, decreased LVESV, reduced infarct size, and improved coronary flow reserve in patients with acute MI. However, in patients with ICM, PBSC therapy failed to improve function and remodeling despite improved coronary flow reserve (40). In conjunction with observations from studies with CPCs (7, 24), differential outcomes in the acute *versus* chronic setting (40) indicate that the myocardial environment is an important variable in cell-based cardiac repair.

Improvements in LV functional and structural parameters were also observed in studies by Li *et al.* (55) and Tatsumi *et al.* (101), who injected PBSCs and PBMNCs, respectively, *via* the intracoronary route in patients with acute MI. In contrast, intracoronary delivery of mobilized PBSCs in patients with acute MI failed to confer additional benefits over those achieved with standard therapy in the study by Choi *et al.* (18),

who enrolled a relatively small number of cell-treated patients. In view of these differences in outcomes, and in view of the risk of in-stent restenosis, the true utility of PB-derived unfractionated cell therapy remains to be carefully delineated in larger RCTs.

CD34+ cells. CD34+ cells in the peripheral blood exhibit angiogenic properties and are therefore eminently suitable for the induction of therapeutic angiogenesis in the myocardium (5, 43). In a recent phase I/IIa randomized double-blind controlled trial (57), Losordo *et al.* transplanted peripheral blood-derived autologous CD34+ cells *via* the transendocardial route under electromechanical mapping (EMM) guidance in patients with refractory angina. After 3 months, cell-treated patients exhibited trends toward reduced angina frequency, reduced nitroglycerin usage, improved exercise time, and improvement in Canadian Cardiovascular Society (CCS) class (57). Adverse events were distributed similarly in cell-treated and control patients. Although preliminary, these data support the feasibility and safety of intramyocardial transplantation of CD34+ cells and suggest a beneficial role of such intervention in patients with intractable angina.

Beneficial Effects of BMC Therapy: Analysis of Pooled Data

As is true for any novel treatment strategy, the earlier studies were primarily designed to assess the safety and efficacy of therapy with specific BMC populations. Consequently, these studies enrolled relatively small number of patients each and were sometimes not powered to provide conclusive answers. It is therefore not surprising that results from these trials have often been discordant (1, 85). Since analysis of pooled data offers an excellent means to generate statistically sound conclusions that were unattainable from data in individual studies (51, 68), several meta-analyses of data from clinical trials of BMC therapy have been performed in the recent past (1, 36, 56, 62). Despite the above advantage, meta-analyses are often dependent on reported data and are susceptible to interpretation issues, especially with subgroup analysis. However, while meta-analysis cannot substitute large RCTs, they can effectively provide valid rationale for future RCTs and by identifying specific caveats, guide the formulation of future trials. In this regard, it is important to note that although each meta-analysis of BMC trials included somewhat different sets of studies, the results of these meta-analyses (1, 36, 56, 62) have been generally concordant and show an overall beneficial impact of BMC therapy on cardiac function and structure in patients with acute MI as well as chronic IHD.

Global LV systolic function

The effect of cell transplantation on global LV systolic function and/or regional wall motion was examined in nearly all clinical trials of BMC therapy. Global LVEF is perhaps the most important parameter for any reparative strategy because of its well-known relationship with prognosis in patients with heart failure and major cardiovascular outcomes (19, 88). Because definitive conclusions could not be reached from these smaller individual studies, we performed a comprehensive meta-analysis that included a total of 18 RCTs and cohort studies (a total of 999 patients) of BMC therapy for cardiac repair (1). Our results showed a 3.7% greater increase in LVEF over baseline in BMC-treated patients compared with controls, and the results were similar when data from RCTs and cohort studies were analyzed separately (1). The analysis of interaction indicated similar efficacy of BMC therapy in improving LVEF in patients with acute MI, as well as chronic IHD. However, when data from studies that injected less than 80 million BMCs (the median value) were compared with those from studies with greater number of BMCs, no significant impact of cell number on the improvement in LVEF was noted. Similarly, no significant interaction was noted based on the timing (<5 days *vs*. 5–30 days after acute MI/PCI) of BMC injection (1).

Although the numbers and types of studies included were somewhat different in each, several other meta-analyses have reached similar conclusions regarding the beneficial effects of BMC therapy on LVEF (36, 56, 62). In the meta-analysis by Hristov *et al.* (36), which included five RCTs (a total of 482 patients) of BMC therapy in patients with acute MI, the improvement in LVEF during follow-up was 4.21% greater in BMC-treated patients compared with controls. In the meta-analysis by Lipinski *et al.* (56), which included 10 controlled trials (a total of 698 patients) of BMC therapy in patients with acute MI, cell transplantation was associated with a 3% greater increase in LVEF compared with controls. The meta-analysis of 13 RCTs (a total of 811 patients) in patients with acute MI by Martin–Rendon *et al.* (62) also showed a 2.99% greater improvement in LVEF in BMC-treated patients. Therefore, despite the differences in characteristics of included studies, concordant results from all of the meta-analyses show that BMC therapy is associated with a modestly (2.99–4.21%) greater improvement in LVEF compared with optimal standard treatment alone (1, 36, 56, 62). Although enhanced contractility in the viable LV segments may also play a role, this improvement in global LVEF may directly result from improved wall motion in the infarct territory, which was observed in several studies. Since the precise mechanistic bases of improvement in global LVEF in humans remain largely unknown, systematic and accurate determination of regional LV wall motion in larger RCTs can potentially provide valuable information regarding the true efficacy of BMC therapy in repairing the infarcted myocardium.

LV end-systolic volume

Since a smaller LVESV in the absence of any significant change in LVEDV reflects greater EF, LVESV appropriately serves as a surrogate indicator of global LV systolic performance. A number of studies of BMC therapy assessed LVESV at baseline and during follow-up, albeit with different methods. In our meta-analysis (1), which included patients with acute MI as well as chronic ischemic heart disease, the reduction in LVESV was greater by 4.8 ml in BMC-treated patients compared with controls. Although no significant treatment interaction was observed, this benefit was more pronounced in patients with acute MI, and also when BMCs were injected <5 days after MI or PCI (1). Consistent with these results, greater improvement in LVESV was also noted in BMC-treated patients in the meta-analysis by Lipinski *et al.* (−7.4 ml) (56) and Martin–Rendon *et al.* (−4.74 ml) (62). Importantly, despite a trend in one meta-analysis (56), reduction in LVEDV was generally not significant in BMC-treated patients in these

meta-analyses (1, 56, 62). Therefore, the reduction in LVESV may be interpreted as a valid additional indicator of the efficacy of BMC therapy in improving global LV systolic function.

Infarct scar size

A reduction in infarct size with cell therapy has been reported in a number of animal studies. However, the assessment of infarct size in humans *in vivo* is difficult and the accuracy varies considerably between techniques. In our meta-analysis (1), which included infarct size data from nine studies, a 5.5% greater reduction in infarct size at follow-up was noted in BMC-treated patients compared with controls. Although this benefit was observed in patients with acute MI as well as chronic IHD, the extent of scar size reduction was more pronounced when BMCs were transplanted between 5–30 days after acute MI/PCI compared with transplantation within 5 days (1). In subsequent meta-analyses by Lipinski *et al.* (56) and Martin–Rendon *et al.* (62), which were restricted to RCTs and patients with acute MI only, infarct size reduction was greater in BMC-treated patients by 5.6% and 3.5%, respectively.

Since direct histopathological correlation is not possible in humans, the precise mechanism of scar size reduction remains speculative. The results from studies in animals indicate that BMCs can indeed differentiate into cardiomyocytes (21, 33, 73, 74), however, the extent of new myocyte formation remains highly controversial (8, 69, 73, 86). Other potential mechanisms *via* which BMC therapy may reduce scar size include salvage of native cardiomyocytes (30, 47) or generation of new myocytes *via* the activation of tissue-resident cardiac progenitors (12, 20). Irrespective of the mechanism, that BMC therapy can effectively reduce myocardial scar size is an important observation from a clinical standpoint because a reduction in scar size is likely to impact remodeling favorably with the attendant benefits (79, 80). Aside from the functional improvement, other potential benefits stemming from superior remodeling in terms of LV hypertrophy, diastolic function, and arrhythmia therefore need to be assessed critically during longer follow-up.

LV end-diastolic volume

Following the loss of myocytes during MI, the infarct wall becomes thinner and the LVEDV gradually increases with progressive remodeling (79, 80). The LVEDV is therefore considered an important parameter of LV remodeling and was examined in several BMC trials. In our meta-analysis (1), which included patients with acute MI as well as chronic IHD, BMC therapy was not associated with any significant change in LVEDV compared with controls. When we compared changes in LVEDV in trials in which BMCs were injected <5 days after MI with those with a 5–30 day interval, no significant difference in change in LVEDV based on the time of injection was observed (1). However, in the meta-analysis by Lipinski *et al.* (56), which included trials with BMC therapy within 14 days after acute MI, BMC treatment was associated with a trend toward reduction in LVEDV. Since LV remodeling gradually progresses over time, it is conceivable that transplantation of BMCs early after acute MI is likely to be more effective in preventing the progression of remodeling. Future studies need to be conducted to assess the impact of BMC therapy as a function of the time interval between acute MI and BMC transplantation.

Patient symptoms and functional class

Since the initial clinical trials primarily evaluated efficacy and safety, the end-points were generally limited to the assessment of LV function and anatomy. Although improvement in patient symptoms was recognized in several of these studies (16, 57, 78, 102), analysis of pooled data could not be performed because too few studies included each specific end-point. Nonetheless, from a therapeutic standpoint, improvement in patient symptoms and effort tolerance are highly important indicators of the overall efficacy of infarct repair. In the study by Strauer *et al.* (98) intracoronary injection of BMMNCs improved $VO2_{max}$. In the study by Perin *et al.* (78), transendocardial injection of BMMNCs reduced angina frequency, increased exercise capacity, and improved NYHA class in BMC-treated patients, and these benefits were sustained at least until 12 months. Similar improvement in exercise time and functional class with transendocardial BMMNC therapy was also noted in the PROTECT-CAD trial (102). Intracoronary MSC therapy in the study by Chen *et al.* (16) also resulted in improved exercise tolerance and NYHA class, indicating that the symptomatic benefits are not restricted to a specific type of BMC or patient characteristics. Finally, in the study by Losordo *et al.* (57), transendocardial injection of CD34+ cells in patients with refractory angina showed a trend toward reduced angina frequency, nitroglycerin usage, CCS class, and exercise time in cell-treated patients. Together, these results (16, 57, 78, 98, 102) suggest that the benefits of BMC therapy extend well beyond LV function and remodeling, and a comprehensive assessment of patient symptoms and quality of life parameters in future trials may reveal heretofore underappreciated benefits of BMC therapy impacting critical components of the overall therapeutic goal.

Adverse Effects of BMC Therapy

Every medical and surgical therapeutic strategy comes with variable degrees of inherent risks, and the goal therefore is to optimize the treatment regimen so that the benefits are maximized and adverse effects are reduced to a minimum. In this regard, nearly all of the reports of BMC trials have included safety data and although the reporting has often been incomplete, meta-analyses of these outcomes indicate that BMC therapy does not pose risks beyond those associated with conventional therapy (1, 56, 62).

Major adverse cardiovascular events

Although 'major adverse cardiovascular events' (MACE) is considered an important component of assessment of safety of any therapeutic regimen, its definition remains somewhat variable (46), and only a few BMC trials reported MACE in a comprehensive fashion. However, in meta-analyses performed thus far, the incidence of mortality, recurrent MI, stroke, or hospitalization due to exacerbation of congestive heart failure was similar in BMC-treated and control patients (1, 56, 62).

Arrhythmia

Sustained ventricular tachycardia (VT) has been reported following intramyocardial transplantation of skeletal myoblasts (32, 65), which are unable to connect electrically to the

neighboring myocytes (3, 52). In contrast, BMMNC-derived myocytes express connexin 43 following differentiation *in vitro* (26, 27, 54). After myocardial transplantation or homing in animal models *in vivo*, BMC-derived cardiomyocytes have been shown to express N-cadherin and connexin 43 (21, 73, 86), which are necessary for establishing mechanical and electrical connection, respectively. Consistent with these observations, despite the diversity in BMC types, routes, and doses, no increased incidence of arrhythmia in BMC-treated patients was observed in meta-analyses of studies that included patients with acute MI as well as chronic IHD (1, 36, 56, 62). Nonetheless, in light of the arrhythmogenicity noted with skeletal myoblasts (32, 65), it is imperative that the arrhythmogenic potential of BMCs is monitored closely in future clinical trials.

In-stent restenosis

Although intramyocardial injection obviates this problem, in-stent restenosis is an important consideration when BMCs are injected *via* the intracoronary route. Restenosis is multifactorial in etiology and involves activation of smooth muscle cells in the arterial wall, along with neointimal thickening (11). Several growth factors are also known to play critical roles in restenosis (11), and although coronary stenting eliminates elastic recoil and remodeling, it accentuates neointimal hyperplasia. Although the results of meta-analyses (1, 56, 62) that included trials with several types of BMCs did not reveal an overall increased incidence of restenosis in BMC-treated patients, a higher rate of in-stent restenosis has been reported with intracoronary injection of G-CSF-mobilized peripheral blood cells (39) and AC133+ progenitors (10). In this regard, Schober *et al.* (94) reported a significant correlation between a greater number of circulating CD34+ cells following elective stenting and a higher rate of restenosis in patients with coronary artery disease. Since specific types of BMCs express growth factor systems (100) and are able to differentiate into smooth muscle cells as well as endothelial cells (73, 107), the above observations suggest that the rate of in-stent restenosis may potentially depend critically on the phenotype of injected cells, especially the adhesion molecule expression profile. Irrespective of the inciting factors, the clinical implications of restenosis and *de novo* atherogenesis mandates a careful quantitative monitoring of these potential complications of BMC therapy in future clinical trials of myocardial repair.

Optimizing the Variables

As discussed above, the collective results from the controlled clinical trials completed thus far indicate that BMC transplantation is indeed associated with modest improvements in several parameters of LV function and structure with no significant increase in untoward effects (1, 36, 56, 62). Nonetheless, because of the mixed nature of outcomes from these inherently heterogeneous trials, the utility of BMC therapy in myocardial repair continues to generate controversy, and several key issues remain to be addressed in order to achieve superior myocardial repair.

Finding the ideal BMC

Unfortunately, very few clinical trials have systematically compared the outcomes of therapy with even two BMC types. In our meta-analysis (1), no significant interaction was observed when results from trials that used BMMNCs were compared with those from MSC and CPC trials. Ideally, the optimal BMC for cardiac repair should exhibit several important properties. First, irrespective of the underlying mechanism, transplantation of this BMC should improve cardiac function and structure in a reproducible fashion. Second, the adverse effects of therapy should be minimal. The transplanted BMCs should not give rise to teratomas or other neoplastic lesions *in vivo*, and intracoronary delivery should not trigger cellular hyperplasia involving the arterial wall causing restenosis or *de novo* atheromatous lesions. Third, these BMCs should preferably be able to differentiate into both cardiomyocytes and vascular cells, so that not only new contractile units are formed, but blood supply to these newly formed myocytes is also established. Fourth, the ideal cell should be able to migrate across the vessel wall and home into the myocardium. The expression of various adhesion molecules and CXCR4 may identify BMCs with this capability. This will greatly improve efficacy of cell delivery *via* the intracoronary route, and improve retention of cells following intramyocardial delivery. Finally, these BMCs should be easy to harvest in a timely fashion, and be suitable for long-term storage and use at a future time-point. Although several types of BMCs have been utilized in clinical trials, each with somewhat distinct attributes, the ideal BMC that fulfills all of these criteria remains to be identified in future basic and clinical studies.

Utilizing the most efficacious route

Although intracoronary (7, 10, 16, 17, 29, 37, 40, 55, 64, 87, 90, 97, 98, 101, 106), transepicardial (34, 67), as well as transendocardial (57, 78, 102) routes have all been used successfully for BMC delivery in humans, each route may offer specific advantages based on patient characteristics, the clinical scenario, and the BMC type. In the setting of an acute MI, or in patients with significant coronary artery disease undergoing PCI, BMCs have been injected effectively in the coronary artery following PCI or during an elective catheterization. However, the ability of BMCs to migrate across the vascular barrier is an important consideration with this route, and BMCs that express CXCR4 (for example, VSELs (22, 49)) and other adhesion molecules may be better suited for this mode of delivery. In this regard, Hofmann *et al.* (35) reported greater myocardial retention of CD34+ BMCs compared with unselected BMCs following intracoronary delivery at 5–10 days after PCI following acute MI. In the setting of chronic IHD, intracoronary delivery of CPCs in patients with revascularized chronic total occlusion (24) and BMMNCs in patients with old MI (7, 98) have also resulted in improved LV function. These results suggest that intracoronary route of cell delivery may be utilized even when myocardial microvascular damage is absent and myocardial inflammation has largely subsided.

As an effective alternative, transepicardial injection offers considerable convenience in patients undergoing CABG. With the transendocardial delivery method, the use of an EMM system enables the identification of the scar area and precise cell injection. However, the use of a transendocardial route may potentially be limited by the availability of this system. Nonetheless, the intramyocardial (transepicardial or

transendocardial) route of BMC delivery offers several distinct advantages. First, even large cells can be injected without causing vascular obstruction. This is an important consideration because intracoronary delivery of MSCs in dogs has been reported to cause microinfarction (104). Second, intramyocardial injection eliminates the issues of restenosis and increased atheroma formation. Importantly, intracoronary injection of circulating AC133+ progenitors (10) and G-CSF-mobilized PBSCs (39) have both been associated with a higher rate of restenosis. Finally, the EMM-guided delivery method offers precision in site-directed injection of BMCs (57, 78). In our meta-analysis (1), an effective comparison between different routes could not be performed because of the paucity of clinical trials with the intramyocardial route. However, the above considerations suggest that a careful selection of the delivery method based on patient characteristics and the type of BMC may potentially enhance the outcomes of BMC therapy.

Determining the optimal BMC number

Quantitative data from animal as well as human studies indicate that only a small fraction of injected cells is retained within the myocardium (9, 23, 35, 41). Apart from cell washout, a large number of transplanted cells are also lost *via* cell death in the hostile inflammatory milieu (99, 108). Thus, it only seems logical that injecting a larger number of cells would help achieve superior cardiac repair. Accordingly, several clinical trials have utilized a large number of BMCs (17, 18, 40, 101, 106), and in our meta-analysis (1), the number of transplanted BMCs ranged from 2 to 60,000 million BMCs. However, when outcomes from studies that used less than the median of 80 million BMCs were compared with those from studies that used more, there was no significant difference in outcomes based on BMC numbers (1). In a subsequent meta-analysis restricted to patients with acute MI alone, the improvement in LVEF was noted only with transplantation of >100 million BMCs (62). Consistent with this observation, in the study by Meluzin *et al.* (63, 64), sustained improvement in LVEF was noted only in patients who received a greater number of BMMNCs, indicating a possible dose-response relationship. Interestingly, in a study in mice (44), intramyocardial injection of CD34+ cell enriched fraction yielded superior results compared with unfractionated BMMNCs, and although a high dose of BMMNCs afforded benefits, the incidence of intramyocardial hemorrhage increased. In our laboratory, intramyocardial injection of only 10,000 CD45- VSELs after acute MI in mice resulted in improvement in LV function and structure, while a 10-fold greater number of CD45+ hematopoietic stem cells failed to confer reparative benefits (22). These data from animal studies (22, 44) indicate that injecting a larger number of cells, especially *via* the intramyocardial route, may not always yield superior results, and the outcomes may critically depend on the specific BMC type. Thus, dose-response studies with larger number of patients with specific clinical conditions will be necessary to determine the optimal number of BMCs for myocardial repair.

Selecting the optimal time

For relatively subacute conditions, including chronic IHD and ICM, BMC therapy may be synchronized with a planned PCI or CABG procedure. However, the issue of timing is particularly critical for BMC delivery in patients with acute MI. Although BMC transplantation after acute MI in humans has been efficacious over a rather wide time-range (1, 36, 56, 62), perhaps greater benefits can be achieved with BMC delivery during an optimal timeframe after MI. Conceivably, the increased expression of adhesion molecules (50) and chemoattractants (48) in the infarcted as well as the viable myocardium may improve BMC retention. However, delivery of BMCs during the peak of inflammation shortly after MI may also cause excessive cell death. As an important yet secondary consideration, cell delivery immediately following PCI in the setting of an acute MI necessitates ready availability of BMCs. In our meta-analysis (1), injection of BMCs within the 5-to 30-day window after acute MI/PCI resulted in greater infarct size reduction and the interaction tended to be significant ($p = 0.10$). Although we did not observe any significant interaction of timing with regard to LVEF (1), Martin–Rendon *et al.* (62) noted a greater improvement in LVEF when BMCs were injected >7 days after acute MI. Since the inflammatory reaction persists for a prolonged period of time after acute MI (28, 71), specific information from animal models regarding the kinetics of BMC retention, survival, and differentiation following transplantation at different intervals after MI will be particularly helpful toward the design of future BMC trials in humans.

Tailoring cell therapy for specific patient populations

The collective results from various important trials suggest that patient characteristics are also important determinants of outcomes of cells therapy. While it seems prudent to apply BMC therapy at an earlier time-point after the ischemic cell death and before the remodeling is complete, data from animal models indicate that cell therapy can also improve outcomes in the setting of established cardiomyopathy (70, 72). Although millions of patients with heart failure may potentially benefit from effective BMC therapy, relatively fewer patients with advanced cardiomyopathy have been enrolled in clinical trials thus far. In our meta-analysis (1), the reparative benefits were comparable in patients with acute MI and chronic IHD, and no significant difference was observed in interaction analyses based on the disease entity. Importantly, BMC therapy was associated with enhanced regional wall motion in patients with ICM in several studies (7, 24, 34, 67), perhaps indicating the formation of new myocytes and/or preventing the demise of native myocytes *via* paracrine mechanisms. However, scant information exists regarding the retention, survival, and differentiation of injected cells in humans, and conceivably the myocardial environment (acutely inflamed *versus* remodeled myocardium) may influence these variables in a cell-specific manner. Consistent with this notion, in the TOPCARE-CHD trial, BMMNC therapy but not CPC therapy was able to improve outcome variables in patients with chronic IHD (7). In contrast, in the study by Erbs *et al.* (24, 45), CPC injection was effective in improving both global and regional wall motion in patients with chronic total occlusion. Importantly, compared with the TOPCARE-CHD study (7), Erbs *et al.* (24) injected nearly threefold greater number of CPCs (22 ± 11 *vs.* 69 ± 14 million) within a shorter time window following MI (77 ± 76 *vs.* 7.5 ± 2.9 months). In light of these observations (7, 24), it will be important to

identify whether a specific BMC type is more suitable for cardiac repair in patients with ICM and to examine whether the reparative efficacy is dependent on the chronicity of myocardial pathology.

Conclusions

Myocardial repair with cell therapy remains the 'holy grail' of regenerative cardiology, and the safety and efficacy of BMC therapy for cardiac repair have rapidly been evaluated in numerous clinical trials. Despite the heterogeneity in patient population, BMC type, number, route, and timing of BMC transplantation in these smaller trials, meta-analyses of pooled data indicate that BMC therapy modestly improves LV function and structure in patients with acute MI as well as chronic IHD. Based on their easy availability in large numbers, applicability *via* different routes, phenotypic plasticity, and efficacy in diverse patient populations, BMCs in general appear to be well suited for myocardial repair in humans. Although these meta-analyses also suggest an excellent safety profile, long-term safety remains to be determined in RCTs with longer follow-up duration and uniform reporting of adverse events. Moreover, in order to identify the optimal BMC type, the comparative efficacy and safety profiles of specific BMC subsets need to be characterized *via* direct comparison. A synergistic collaboration between the basic and clinical scientists will be critical for further optimization of BMC number, route, and timing with a view to achieving optimal cardiac repair with minimal adverse effects.

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Abbreviations

AMI, acute myocardial infarction; ASTAMI, Autologous Stem Cell Transplantation in Acute Myocardial Infarction; BMC, bone marrow-derived cell; BMMNC, bone marrow mononuclear cell; BOOST, BOne marrOw transfer to enhance ST-elevation infarct regeneration; C, control; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CD, cluster of differentiation; CPC, circulating progenitor cell; CXCR4, CXC chemokine receptor 4; EF, ejection fraction; EMM, electromechanical mapping; EPC, endothelial progenitor cell; G-CSF, granulocyte colony-stimulating factor; ICM, ischemic cardiomyopathy; IHD, ischemic heart disease; IQR, interquartile range; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; MACE, major adverse cardiovascular events; MAGIC Cell-3-DES, Myocardial Regeneration and Angiogenesis in Myocardial Infarction With G-CSF and Intra-Coronary Stem Cell Infusion-3-Drug Eluting Stents; MI, myocardial infarction; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; NA, not applicable; NR, not reported; NYHA, New York Heart Association; OMI, old myocardial infarction; PB, peripheral blood; PBMNC, peripheral blood-derived mononuclear cell; PBSC, peripheral blood-derived stem cell; PCI, percutaneous coronary intervention; PROTECT-CAD, Prospective randomized trial of direct endomyocardial implantation of bone marrow cells for treatment of severe coronary artery diseases; RCT, randomized controlled trial; REPAIR-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction; SVT, supraventricular tachycardia; T, BMC-treated; TCT-STAMI, transcatheter transplantation of stem cell: for treatment of acute myocardial infarction; TOPCARE-AMI, Transplantation Of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction; TOPCARE-CHD, Transplantation of Progenitor Cells and Recovery of Left Ventricular Function in Patients with Chronic Ischemic Heart Disease; $VO2_{max}$, maximum volume of oxygen consumed; VSEL, very small embryonic-like stem cell; VT, ventricular tachycardia.

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