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Impact of Intracoronary Cell Therapy on Left Ventricular Function in the Setting of Acute Myocardial Infarction

A Collaborative Systematic Review and Meta-Analysis of Controlled Clinical Trials

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Objectives We aimed to perform a meta-analysis of clinical trials on intracoronary cell therapy after acute myocardial infarction (AMI).

Background Intracoronary cell therapy continues to be evaluated in the setting of AMI with variable impact on left ventricular ejection fraction (LVEF).

Methods We searched the CENTRAL, mRCT, and PubMed databases for controlled trials reporting on intracoronary cell therapy performed in patients with a recent AMI (≤14 days), revascularized percutaneously, with follow-up of ≥3 months. The primary end point was change in LVEF, and secondary end points were changes in infarct size, cardiac dimensions, and dichotomous clinical outcomes.

Results Ten studies were retrieved (698 patients, median follow-up 6 months), and pooling was performed with random effect. Subjects that received intracoronary cell therapy had a significant improvement in LVEF (3.0% increase [95% confidence interval (CI) 1.9 to 4.1]; $p < 0.001$), as well as a reduction in infarct size (−5.6% [95% CI −8.7 to −2.5]; $p < 0.001$) and end-systolic volume (−7.4 ml [95% CI −12.2 to −2.7]; $p = 0.002$), and a trend toward reduced end-diastolic volume (−4.6 ml [95% CI −10.4 to 1.1]; $p = 0.11$). Intracoronary cell therapy was also associated with a nominally significant reduction in recurrent AMI ($p = 0.04$) and with trends toward reduced death, rehospitalization for heart failure, and repeat revascularization. Meta-regression suggested the existence of a dose-response association between injected cell volume and LVEF change ($p = 0.066$).

Conclusions Intracoronary cell therapy following percutaneous coronary intervention for AMI appears to provide statistically and clinically relevant benefits on cardiac function and remodeling. These data confirm the beneficial impact of this novel therapy and support further multicenter randomized trials targeted to address the impact of intracoronary cell therapy on overall and event-free long-term survival. (J Am Coll Cardiol 2007;50:1761–7) © 2007 by the American College of Cardiology Foundation

The treatment of acute myocardial infarction (AMI), especially ST-segment elevation, centers on early revascularization of the infarct-related artery and optimal medical therapy. Although multiple studies have more recently investigated the potential role of intracoronary cell therapy for AMI (1–16), it remains unclear whether intracoronary cell therapy improves left ventricular (LV) function, LV dimensions, infarct size, and other clinical outcomes. Our goal was to systematically review controlled clinical trials appraising the impact of intracoronary cell therapy on post-infarction LV function.

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Methods

We searched (September 2006) the CENTRAL, mRCT, and PubMed databases, as well as years 2000 to 2006

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Abbreviations and Acronyms

AMI = acute myocardial infarction
BMC = bone marrow cell
CI = confidence interval
G-CSF = granulocyte colony-stimulating factor
LV = left ventricular
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
OR = odds ratio
PMC = peripheral mononuclear cell
TVR = target vessel revascularization

American College of Cardiology, American Heart Association, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics conference proceedings without language restriction, using as keywords: "cells AND (intracoronary OR transcoronary)." Initially selected citations were screened at the title/abstract level and, if potentially relevant, retrieved and assessed as complete manuscripts for compliance with these inclusion criteria: 1) prospective comparison of intracoronary cell therapy versus control after AMI in which the infarct-related artery was percutaneously revascularized; 2) intention-to-treat analysis; and 3) follow-up of >3 months. Exclusion criteria were: 1) irretrievable or unclear data; 2) treatment of old MI (>14 days), chronic ischemia, or heart failure; 3) lack of control group; 4) duplicate reports; and 5) ongoing or unpublished studies.

Several study features were extracted, including design, outcome definitions, imaging modalities, patient baseline characteristics, and procedural data. Specifically, the primary end point was the change in left ventricular ejection fraction (LVEF) from baseline to follow-up. Secondary efficacy end points were changes in left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and infarct size. In case a remodeling parameter was reported by more than 1 imaging technique, the 1 with the smaller standard error was chosen for analysis. Secondary safety end points were the incidence of dichotomous clinical events (i.e., death, recurrent AMI, target vessel revascularization [TVR], and rehospitalization for heart failure) evaluated at the longest available follow-up. All of the outcomes analyzed were used as defined in individual trials. In case of missing or unclear data for the primary or secondary end points, at least 2 separate attempts were made to clarify the data by contacting the primary authors at least 3 weeks apart. The internal validity of included trials was appraised separately, addressing the risk of selection, performance, adjudication, and attrition bias. Study search, selection, abstraction, and appraisal were all performed by 2 independent reviewers, with divergences resolved with consensus.

Dichotomous variables are reported as proportions and percentages, continuous variables as mean ± standard deviation or median (interquartile range [IQR]). Binary outcomes from individual studies were combined with the Peto fixed-effect model, unless inconsistency (I^2) >50%, in which case a random-effect model was used to compute odds ratios (ORs) with 95% confidence intervals (CIs). Continuous variables were pooled with a random-effect generic-inverse-variance method, providing summary point estimates (95% CI). Chi-square tests and I^2 were computed to explore statistical heterogeneity and inconsistency, respectively. Small study bias was explored with funnel plots and Egger test. Finally, meta-regression and sensitivity analyses (including exclusion of 1 study at a time) were conducted to explore heterogeneity. Computations were performed using RevMan 4.2 (The Cochrane Collaboration, Copenhagen, Denmark) and SPSS 11.0 (SPSS, Chicago, Illinois), with statistical significance for hypothesis testing set at the 0.05, 2-tailed level.

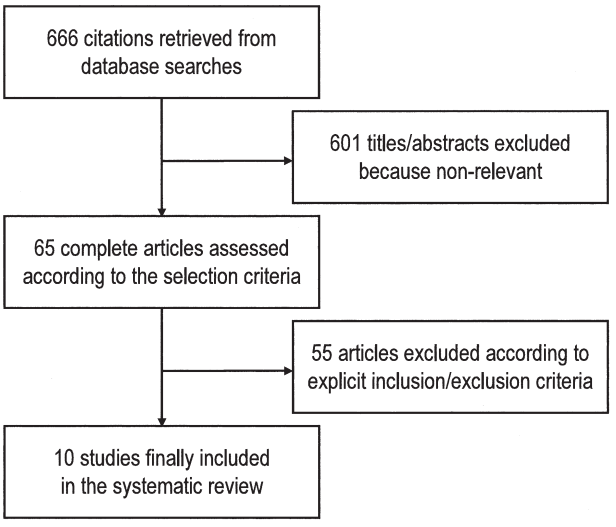

Figure 1 Review Process

This scheme provides a summary of the systematic reviewing process.

Results

From the initial 666 hits, 601 citations were initially excluded at the title/abstract level (Fig. 1). Among the articles retrieved in complete form, 5 were excluded for lack of a control group (3,14), 16 for investigating a different end point, 15 with intracoronary cell therapy for chronic coronary disease or heart failure, 2 because they were ongoing or unpublished, 14 because they were related to surgical delivery or other therapies involving cell therapy, and 1 because the average time from symptom onset to cell injection was >14 days (6). Eventually, 11 articles covering 10 controlled trials were included in the analysis (2,4,5,7,8,10–13,15,16). The 10 included trials allocated 698 patients to intracoronary cell therapy or standard medical therapy (Tables 1 to 4), with a mean follow-up of 6 months (range 3 to 18 months).

Meta-analytic pooling for the primary end point showed that intracoronary cell therapy was significantly superior to standard medical therapy in terms of LVEF improvement, with a clinically and statistically significant difference of

Table 1 Main Features of Included Studies

Study	Year	Design	Patients Enrolled (Patients at Follow-Up)	Cell Type	Follow-Up (Months)	Primary End Point	Imaging Modality for LVEF Assessment
Strauer et al. (10)	2002	Non-RCT	20 (20)	BMC	3	LVEF	LV angiography
Bartunek et al. (11)	2005	Non-RCT	35 (35)	BMC	4	Safety, LVEF	LV angiography, SPECT
Jannsens et al. (8)	2006	RCT	67 (66)	BMC	4	LVEF	Cardiac MRI
BOOST (7)	2006	RCT	60 (60)	BMC	18	LVEF, safety	Cardiac MRI
Zhan-Quan et al. (13)	2006	Non-RCT	70 (58)	PMC	6	LVEF, LV volumes, WMSI	Echocardiography
MAGIC CELL-3-DES (12)	2006	RCT	56 (50)	PMC	6	LVEF	Cardiac MRI
TCT-STAMI (15)	2006	RCT	20 (20)	BMC	6	LVEF	Echocardiography, SPECT
ASTAMI (2,4)	2006	RCT	100 (97)	BMC	6	LVEF, EDV, infarct size	SPECT, MRI, echo
REPAIR-AMI (5)	2006	RCT	204 (187)	BMC	12	LVEF	LV angiography
Meluzin et al. (16)	2006	RCT	66 (66)	BMC	3	Infarct zone systolic function	SPECT

BMC = bone marrow cells; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PMC = peripheral mononuclear cells; RCT = randomized controlled trial; SPECT = single-photon emission computed tomography; WMSI = wall motion score index.

3.0% (95% CI 1.9% to 4.1%; $p < 0.00001$; $I^2 = 73.2\%$). Intracoronary cell therapy was similarly found to have benefit concerning LVESV (average difference −7.4 ml [95% CI −12.2 to −2.7]; $p = 0.002$; $I^2 = 95.8\%$) and infarct size (average difference − 5.6% [95% CI −8.7 to −2.5]; $p = 0.0004$; $I^2 = 92.6\%$). There was a trend for improvement in LVEDV (average difference −4.6 ml [95% CI −10.4 to 1.1]; $p = 0.11$; $I^2 = 95.2\%$) (Fig. 2).

Comparing dichotomous clinical end points (Table 4), intracoronary cell therapy proved to be notably safe, without any increase in the risk of TVR (OR 1.08 [95% CI 0.60 to 1.96]; $p = 0.80$; $I^2 = 25.3\%$). Conversely, intracoronary cell therapy tended to be associated, albeit nonsignificantly, with reductions in the risk of death or rehospitalization for heart failure. In addition, intracoronary cell therapy was associated with a nominally statistically significant decrease in recurrent AMI ($p = 0.04$), but this finding should be regarded as hypothesis-generating only, given the low number of events in all but 1 of the studies (5).

A number of exploratory meta-regression analyses were performed to appraise the impact of the following moderator or covariates on the changes in LVEF associated with intracoronary cell therapy. Specifically, at the overall analysis we did not find statistically significant association between: the benefits of intracoronary cell therapy and follow-up duration ($p = 0.73$), year of publication ($p = 0.54$), baseline LVEF in the experimental group ($p = 0.32$), number of injected cells ($p = 0.69$), time to PCI ($p = 0.40$), and time between symptom onset ($p = 0.72$). However, we found a trend toward a statistically significant association between injected volume and LVEF ($p = 0.066$), suggesting the possible presence of a dose-response relationship (Fig. 3).

No evidence of small-study bias was found either visually at inspection of funnel plots or analytically at Egger test ($p = 0.57$). Computations performed after selecting only randomized trials or high-quality randomized trials (4,5,7,8,11) (Table 3) confirmed the statistically significant improvement of LVEF (respectively: 3.8% [95% CI 2.2 to 5.5]; $p < 0.00001$; $I^2 = 87.8\%$; and 2.8% [95% CI 1.3 to 4.3]; $p < 0.001$; $I^2 = 70.9\%$). Indeed, we found no major differences in LVEF effect size between randomized and nonrandomized studies.

Similarly significant was the effect on LVEF when selecting only studies using a sham intracoronary infusion for the control group (3.0% change [95% CI 0.8 to 5.2]; $p = 0.008$; $I^2 = 79.4\%$). Finally, sensitivity analysis excluding 1 study at a time confirmed in direction and magnitude of statistical significance the results from the

Table 2 Patients and Procedural Characteristics of Included Studies

Study	Mean Age (yrs)	Men (%)	Anterior AMI (%)	Hours to PCI	DES Use (%)	Days to ICT	Average Number of Injected Cells (10^6)	$CD34^+$ Cells (10^6)	Injected Volume (ml)
Strauer et al. (10)	50	92.5	37.5	11.5	0	8	46	NP	20
Bartunek et al. (11)	54	91	94	10	8.6	11.6	NP	15.4	15–20
Jannsens et al. (8)	57	82	63	3.9	NP	1	304	2.8	10
BOOST (7)	56	70	77	8.9	NP	4.8	2,460	9.5	26
Zhan-Quan et al. (13)	60	80	60	24	NP	6	72.5	NP	57
MAGIC CELL-3-DES (12)	60	80	54	9.1	100	4	1,500	7	NP
TCT-STAMI (15)	58	90	70	7.5	NP	0.5	38.7	1.8	16
ASTAMI (2,4)	57	84	100	3.5	5	6	68	0.7	NP
REPAIR-AMI (5)	56	82	78	7.2	14.5	4.4	236	3.6	10
Meluzin et al. (16)	55	92.4	85	7.7	NP	7	55	0.55	21

AMI = acute myocardial infarction; DES = drug-eluting stent; ICT = intracoronary cell therapy; NP = not provided; PCI = percutaneous coronary intervention.

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Table 3 Internal Validity of Included Trials*

Study	Setting	Allocation Concealment	Sham Infusion	Selection Bias	Performance Bias	Adjudication Bias	Attrition Bias
Strauer et al. (10)	Single-center	None (nonrandom allocation)	No	C	C	C	A
Bartunek et al. (11)	Single-center	None (nonrandom allocation)	No	C	C	C	D
Jannsens et al. (8)	Single-center	Likely adequate	Yes	A	A	B	A
BOOST (7)	Single-center	Unclear	No	B	B	A	A
Zhan-Quan et al. (13)	Single-center	None (nonrandom allocation)	No	C	C	C	B
MAGIC-CELL-3-DES (12)	Single-center	Likely inadequate (open table of randomized allocations)	No	B	B	A	A
TCT-STAMI (15)	Single-center	Likely adequate	Yes	A	A	C	D
ASTAMI (2,4)	2 centers	Unclear	No	B	B	D	A
REPAIR-AMI (5)	Multicenter	Likely adequate	Yes	A	A	A	A
Meluzin et al. (16)	Single-center	Unclear	No	A	B	D	A

*The internal validity of included trials was appraised by judging separately the risk for selection, performance, attrition, and adjudication biases, expressed as low risk (A), moderate risk (B), or high risk (C) of bias or incomplete reporting leading to inability to ascertain the underlying risk of bias (D).

overall analysis (all p values <0.001). Analysis comparing the effect of bone marrow cells (BMCs) versus peripheral mononuclear cells (PMCs) could not be performed because of inadequate power due to the low number of studies using intracoronary delivery of peripheral cells (12,13). However, the impact of intracoronary cell therapy on LVEF was investigated for both BMCs and PMCs and demonstrated that intracoronary cell therapy improves LVEF, regardless of whether BMCs (3.3% [95% CI 1.8 to 5.2]; $p < 0.001$; $I^2 = 84.1\%$) or PMCs (5.3% [95% CI 4.1 to 6.7]; $p < 0.001$; $I^2 = 0\%$) were used.

Discussion

The main finding of the present study is that intracoronary cell therapy after AMI results in a modest yet significant increase in LVEF compared with control. In addition, analysis of secondary end points demonstrates that intracoronary cell therapy significantly decreases LVESV and infarct size. This meta-analysis included intracoronary cell therapy derived from both BMCs and PMCs. Although this may be argued as a limitation of the study, intracoronary cell therapy after AMI appears to improve LVEF regardless of whether BMCs or PMCs are employed. It is important to recognize that the outlying study by Chen et al. (6) was excluded, because therapy was initiated >14 days after symptoms.

The question of whether a small increase in LVEF is of clinical significance is an important issue. However, it should be stressed that many of the interventions with an established life-saving effect during or after AMI also provide only moderate yet clinically meaningful increases in LVEF. Several hypotheses have been proposed about how intracoronary cell therapy improves myocardial function. Recent well-conducted studies suggest that bone marrow-derived cells do not transdifferentiate into cardiomyocytes but adopt mature hematopoeitic characteristics (17,18). However, adult peripheral blood $CD34^+$ cells can transdifferentiate into cardiomyocytes, mature endothelial cells, and smooth muscle cells in vivo (19). Another proposed mechanism is that cell therapy may increase angiogenesis and improve blood supply to ischemic regions, potentially aiding in the revascularization of hibernating myocardium (20) and inhibiting cardiomyocyte apoptosis (21).

Table 4 Clinical Events at the Longest Available Follow-Up as Reported by Included Studies and Pooled With Peto Method*

Study	Death	Recurrent Myocardial Infarction	Target Vessel Revascularization	Rehospitalization for Heart Failure
Strauer et al. (10)	—	—	—	—
Bartunek et al. (11)	0/19 vs. 0/16	—	11/19 vs. 4/16	—
Jannsens et al. (8)	1/34 vs. 0/34	0/33 vs. 0/34	2/33 vs. 2/34	—
BOOST (7)	0/30 vs. 1/30	1/30 vs. 0/30	5/30 vs. 4/30	1/30 vs. 3/30
Zhan-Quan et al. (13)	0/35 vs. 0/23	0/35 vs. 0/23	0/35 vs. 0/23	0/35 vs. 0/23
MAGIC-CELL-3-DES (12)	1/27 vs. 1/29	0/27 vs. 1/29	0/27 vs. 1/29	—
TCT-STAMI (15)	0/10 vs. 0/10	0/10 vs. 0/10	0/10 vs. 0/10	0/10 vs. 0/10
ASTAMI (2,4)	0/50 vs. 0/50	—	11/50 vs. 11/50	1/50 vs. 1/50
REPAIR-AMI (5)	2/101 vs. 6/103	0/101 vs. 6/103	16/101 vs. 26/103	0/101 vs. 3/103
Meluzin et al. (16)	0/44 vs. 0/22	0/44 vs. 0/22	6/44 vs. 1/22	0/44 vs. 0/22
OR (95% CI)	0.52 (0.16–1.63)	0.22 (0.05–0.90)	0.97 (0.62–1.52)	0.32 (0.09–1.21)
p value	0.26	0.04	0.90	0.09

*Comparing intracoronary cell therapy versus control event rates (n/N).
CI = confidence interval; OR = odds ratio.

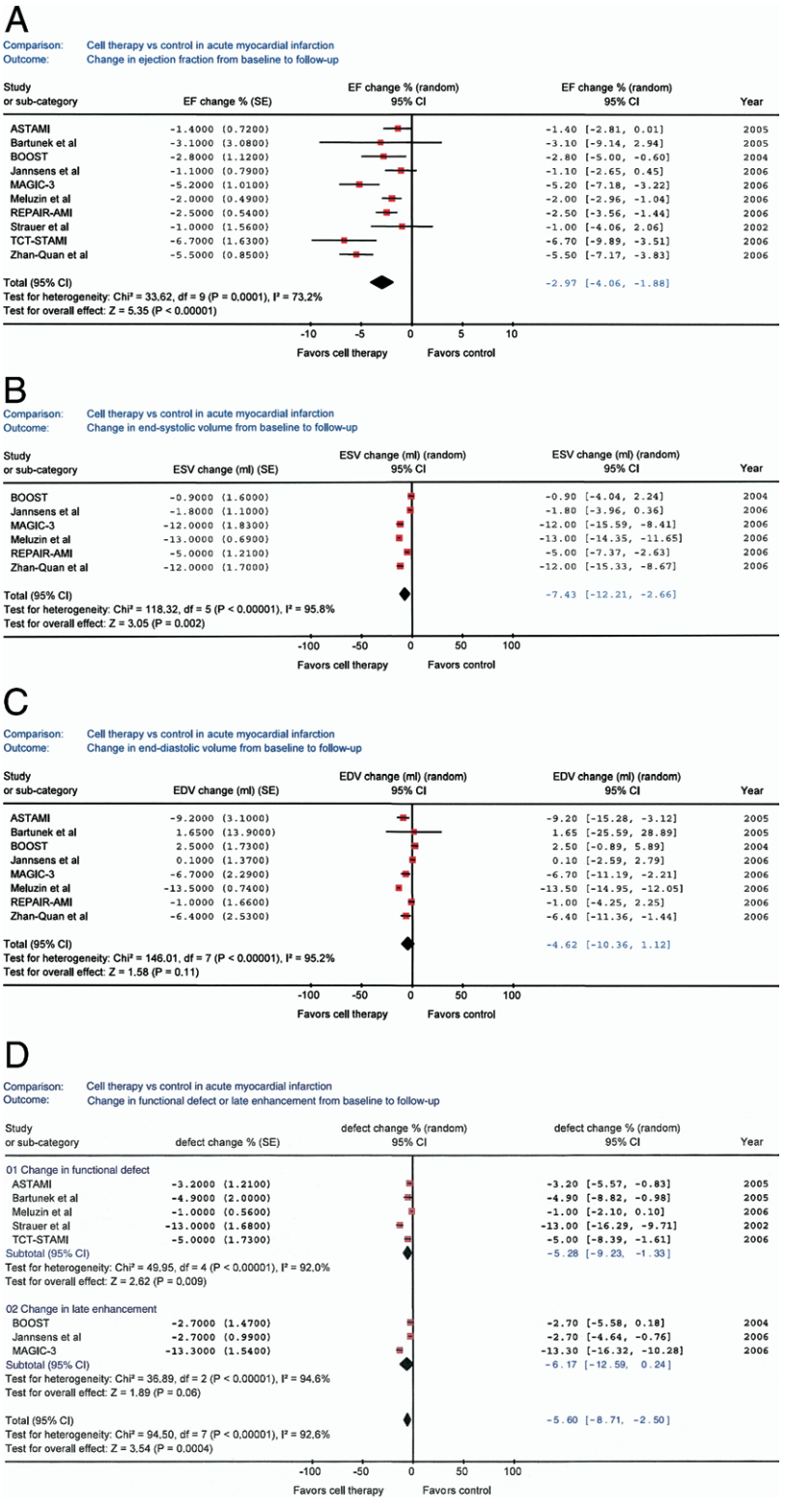

Figure 2 **Impact of Intracoronary Cell Therapy on Left Ventricular Remodeling**

Forest plots show the significantly beneficial impact of cell therapy after myocardial infarction on **(A)** left ventricular ejection fraction (EF), **(B)** end-systolic volume (ESV), **(C)** end-diastolic volume (EDV), and **(D)** infarct size/functional defect at myocardial scintigraphy or late enhancement at magnetic resonance imaging. CI = confidence interval; I^2 = inconsistency; SE = standard error.

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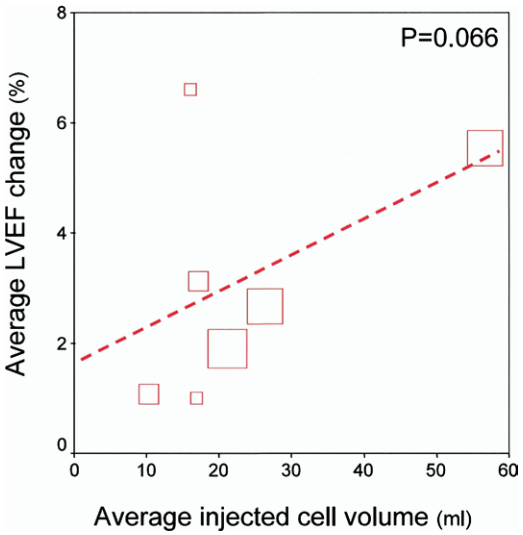

Figure 3 **Metaregression Between Injected Volume and Left Ventricular Remodeling**

L'Abbé plot shows the overall trend toward a statistically significant association between average volume injected in the culprit coronary artery and average change in left ventricular ejection fraction (LVEF) across included studies **(squares)**, with the size of each square proportional to sample size. This trend supports the presence of a dose-response relationship.

Cells were harvested either by bone marrow biopsy or by daily granulocyte colony-stimulating factor (G-CSF) injections for 3 to 5 days followed by apheresis and delivered via an over-the-wire balloon catheter. However, controversy exists as to whether G-CSF injections alone after AMI improve LV function (22). Therefore, the MAGIC Cell-3-DES (Myocardial Infarction With G-CSF and Intra-Coronary Stem Cell Infusion-3-Drug Eluting Stents) trial (12) and the study by Li et al. (13) are inherently different from other studies included in this analysis owing to the use of G-CSF. Additionally, Bartunek et al. (11) primarily delivered $CD133^+$ cells. Cell isolation protocols before delivery have also been shown to have an impact on cell functional activity (23). Finally, Hofmann et al. (24) demonstrated the impact of cell line on cellular retention in the myocardium, with detection of only 1% to 3% of unselected BMCs after intracoronary transfer, whereas 14% to 39% of CD34-enriched labeled cells were detected. Our incomplete understanding of the complex extra- and intracellular signaling that governs cell homing and differentiation is currently a major limitation of this technique. On the other hand, despite previous concerns over a potential increase in in-stent restenosis after cell therapy (14,25), we found that TVR was not increased in cell therapy recipients.

Study limitations. Limitations of systematic reviews are well known. Drawbacks pertinent to the present study include lack of raw and uniform data from included studies, inclusion of papers using intracoronary PMCs and BMCs, variation in imaging techniques and revascularization strategies, and large differences in time from AMI to cell therapy, as well as pooling nonrandomized and randomized trials. However, maintenance of significance when selecting only randomized trials lends support to the robustness of our overall analysis.

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