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## The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) Trial

### First Randomized Placebo-Controlled Study of Myoblast Transplantation

Philippe Menasché, MD, PhD; Ottavio Alfieri, MD; Stefan Janssens, MD, PhD; William McKenna, MD; Hermann Reichenspurner, MD; Ludovic Trinquart, MSc; Jean-Thomas Vilquin, PhD; Jean-Pierre Marolleau, MD; Barbara Seymour, BS; Jérôme Larghero, PharmD, PhD; Stephen Lake, ScD; Gilles Chatellier, MD, PhD; Scott Solomon, MD; Michel Desnos, MD; Albert A. Hagège, MD, PhD

**Background**—Phase I clinical studies have demonstrated the feasibility of implanting autologous skeletal myoblasts in postinfarction scars. However, they have failed to determine whether this procedure was functionally effective and arrhythmogenic.

**Methods and Results**—This multicenter, randomized, placebo-controlled, double-blind study included patients with left ventricular (LV) dysfunction (ejection fraction  $\leq 35\%$ ), myocardial infarction, and indication for coronary surgery. Each patient received either cells grown from a skeletal muscle biopsy or a placebo solution injected in and around the scar. All patients received an implantable cardioverter-defibrillator. The primary efficacy end points were the 6-month changes in global and regional LV function assessed by echocardiography. The safety end points comprised a composite index of major cardiac adverse events and ventricular arrhythmias. Ninety-seven patients received myoblasts (400 or 800 million;  $n=33$  and  $n=34$ , respectively) or the placebo ( $n=30$ ). Myoblast transfer did not improve regional or global LV function beyond that seen in control patients. The absolute change in ejection fraction (median [interquartile range]) between 6 months and baseline was 4.4% (0.2; 7.3), 3.4% (−0.3; 12.4), and 5.2% (−4.4; 11.0) in the placebo, low-dose, and high-dose groups, respectively ( $P=0.95$ ). However, the high-dose cell group demonstrated a significant decrease in LV volumes compared with the placebo group. Despite a higher number of arrhythmic events in the myoblast-treated patients, the 6-month rates of major cardiac adverse events and of ventricular arrhythmias did not differ significantly between the pooled treatment and placebo groups.

**Conclusions**—Myoblast injections combined with coronary surgery in patients with depressed LV function failed to improve echocardiographic heart function. The increased number of early postoperative arrhythmic events after myoblast transplantation, as well as the capability of high-dose injections to revert LV remodeling, warrants further investigation. (*Circulation*. 2008;117:1189-1200.)

**Key Words:** heart failure ■ myoblasts ■ myocardial infarction ■ stem cells ■ transplantation

The large number of patients suffering from heart failure ( $\approx 5$  million people in the United States), the increasing incidence of this condition because of the aging of the population, and the related economic burden account for the

ongoing search for new therapies in patients who are unresponsive to medications or cardiac resynchronization and are not eligible for heart transplantation. In this context, cardiac cell therapy is generating a growing interest as a means of

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improving left ventricular (LV) function through the repopulation of postinfarct myocardial scars by new contractile cells. Skeletal myoblasts are precursor cells of adult myofibers and feature several advantages, including autologous origin, high in vitro scalability, and lack of tumorigenicity due to myogenic lineage restriction. Experimentally, myoblasts engraft in postinfarction scars, differentiate into myotubes, and improve LV function (reviewed in Dowell et al<sup>1</sup>). The consistency and robustness of these results have paved the way for the first surgical<sup>2-6</sup> or catheter-based<sup>7-9</sup> phase I trials, which have confirmed feasibility but by virtue of design could not fully evaluate efficacy and safety profiles. We therefore implemented the Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial to specifically address these issues. Herein, we report the 6-month results of this clinical trial.

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## Clinical Perspective p 1200

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### Methods

The objectives of the study were to assess both the safety and efficacy of 2 doses of autologous skeletal myoblasts compared with a placebo injection in patients undergoing coronary artery bypass grafting (CABG) operations for multivessel coronary artery disease and severe cardiac dysfunction.

### Study Design

The MAGIC phase II study was a randomized, placebo-controlled, 3-arm, double-blind trial. It was conducted in 21 academic hospitals in France, Germany, Belgium, United Kingdom, and Italy. Although it was initially planned to include 300 patients, the slow rate of recruitment subsequently led to an amendment in which the intended sample size was reduced to 120. The study was approved by the institutional ethics committees of the participating centers. All patients provided written informed consent.

### Patient Selection

Patients were eligible if (1) they were between 18 and 80 years of age, and if they had (2) an indication for CABG, (3) an alteration in LV function, defined by an ejection fraction (EF)  $\geq 15\%$  and  $\leq 35\%$  determined by echocardiography and confirmed by the core laboratory, (4) a history of myocardial infarction that had occurred at least 4 weeks before screening with a residual akinesia affecting  $>2$  accessible contiguous LV segments (of 16) on echocardiography with no viability after stimulation with low-dose dobutamine, and (5) a stable New York Heart Association (NYHA) functional class I to III with optimal contemporary medical management, including angiotensin-converting enzyme inhibitors and  $\beta$ -blockers.

The major exclusion criteria were the need for rapid surgery, the need for an additional surgical procedure (ie, mitral valve repair or LV aneurysmectomy), left or biventricular pacing therapy, insufficient acoustic windows for accurate echocardiographic recordings, contraindication to low-dose dobutamine, and positive serological test results for human immunodeficiency virus and hepatitis.

### Interventions

All treated patients underwent a muscle biopsy of  $\approx 10$  g from the thigh under local anesthesia. The biopsy was then shipped by courier to 1 of the 2 core manufacturing facilities (Hôpital Saint-Louis, Paris, France, and Genzyme Corporation, Cambridge, Mass), where it was cultured and expanded for 3 weeks under Good Manufacturing Practice conditions as previously described<sup>2,3</sup> or kept frozen for patients randomized to the placebo group. The biopsy was expanded to a target of  $400 \times 10^6$  or  $800 \times 10^6$  cells, depending on the random allocation, after which cells were collected by trypsinization, washed, suspended in Dulbecco's modified Eagle's medium supple-

mented with albumin 0.1%, and transferred into a sterile vial. Criteria for product release included a percentage of myoblasts (identified by flow cytometry as CD56-positive cells)  $\geq 50\%$ , a cellular viability (as determined by propidium iodide exclusion)  $\geq 80\%$ , and other quality control test results (ie, endotoxin and sterility testing). The study medication (cell suspension or placebo solution consisting of the suspension medium without skeletal myoblasts) was then shipped back to the transplantation center. During the preclinical phase of the study, care had been taken to tightly harmonize the processing techniques between the 2 laboratories so as to end up with a consistent and reproducible cell therapy product.

After placement of the bypass grafts, cells (at 1 of the 2 select doses) or the placebo solution was transferred into 1-mL vials and injected into an average of 30 sites in and around the echocardiography-identified myocardial akinetic segments for a total injection volume of 6 mL. This was accomplished with the use of a 27-gauge customized prebent needle to make injections parallel to the epicardium and avoid inadvertent delivery of cells into the ventricular cavity. The transplanted/injected segments were marked on a 16-segment map reproducing the echocardiographic division of the LV. In an attempt to limit the inflammatory response generated by the injections themselves, 3 doses of 240 mg of prednisolone were given on induction, at the time of aortic unclamping, and during the first 24 postoperative hours. An implantable cardioverter-defibrillator (ICD) was placed in all patients at the time of muscle biopsy or before postbypass hospital discharge according to local practices. In addition, amiodarone therapy starting at the time of biopsy and continued for 3 months postoperatively was strongly recommended to all investigators.

### Echocardiography

Transthoracic 2-dimensional echocardiography was performed by each center with the use of fundamental and second-harmonic imaging. For a given patient, each examination was identified by a randomization number and recorded on a separate S-VHS videotape that was made anonymous. All examinations were preferentially performed by the same senior sonographer, using the same machine and similar machine settings. Echocardiographic studies were conducted according to a standard protocol, and the following views (with at least 10 beats from each view) were obtained and systematically recorded, taking care to optimize LV endocardial border definition: 1 parasternal long-axis view; 3 parasternal short-axis views at the base, midpapillary, and apex levels; and 3 apical 4-, 2-, and 3-chamber views. At screening, a stress echocardiographic examination was performed to rule out segmental thickening in the infarcted area and included recordings of 4 LV views at each of the 4 stages of a low-dose dobutamine infusion protocol (basal, 5  $\mu\text{g}/\text{kg}$  per minute for 3 minutes, 10  $\mu\text{g}/\text{kg}$  per minute for 3 minutes, recovery) and usually displayed as quad screens, as previously described.<sup>10</sup>

All tapes were sent to a core laboratory at Hôpital Européen Georges Pompidou (Paris, France). At screening, studies were reviewed for quality (excluding patients with poor study quality) and inclusion criteria. Echocardiograms from videotape were then digitized within cine-loops, and analyses were performed with the use of an offline analysis workstation. After the LV was divided into 16 segments as recommended by the American Society of Echocardiography,<sup>11</sup> a semiquantitative assessment of segmental LV contraction was performed visually. Segments were classified as normokinetic, hypokinetic, severely hypokinetic, akinetic, or dyskinetic, and numbers (from 1 to 5, respectively) were attributed to each of those segments; a global and regional wall motion score was then calculated for each patient as the sum of those numbers divided by the number of visualized segments. Serial changes in LV segmental thickening were then classified as unchanged, improved ( $\geq 1$  grade), or worsened ( $\geq 1$  grade).

LV endocardial borders were traced manually at end-diastole and end-systole on the apical 4- and 2-chamber views from 3 separate cardiac cycles. LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) (mL) were derived according to the modified

biplane Simpson's rule in the apical 4-chamber and apical 2-chamber views, and EF was calculated as  $[\text{EF, \%} = 100 \times (\text{EDV} - \text{ESV}) / \text{EDV}]$ . Indexed volumes were obtained by dividing LV volumes by body surface area.

Readings were performed blinded to the treatment group, timing of echocardiography, number and location of coronary bypasses, and sites of cell injections by a single senior echocardiographer. After unblinding of the data, the placebo- or cell-injected segments were identified by analysis of the intraoperative diagram depicting the injection sites.

## Follow-Up and End Points

### Efficacy

The primary efficacy end points were (1) the change from baseline to month 6 in LVEF, which was used to calculate the intended sample size, and (2) the proportion of patients with recovery of contraction in previously akinetic myocardial segments at month 6, defined as improvement in at least 1 segment by 1 grade (according to the 5-grade regional wall motion system described above) and no deterioration in any segment (from akinetic to dyskinetic) in the transplanted area. The secondary efficacy end points were the change from baseline to month 6 in echocardiographic LV volumes, the functional status, and quality of life assessed by the NYHA classification and SF-36 health survey questionnaire, respectively, at the 6-month study point.

### Safety

The safety end points were the 30-day and 6-month rates (1) of major cardiac adverse events (MACE), defined as the composite of cardiovascular- and noncardiovascular-related death, myocardial infarction, congestive heart failure, resuscitated sudden death, and stroke; and (2) of arrhythmias, assessed by interrogation of the ICDs and defined as sustained ventricular fibrillation or polymorphic ventricular tachycardia, sustained monomorphic ventricular tachycardia at a rate  $>120$  bpm, wide complex tachycardia of unclear type, sustained atrial fibrillation or flutter, bradyarrhythmia and shock delivered by ICD, bradyarrhythmia pacing, or antitachycardia pacing. All ICD data were reviewed by an independent expert electrophysiologist blinded to the treatment group.

## Randomization and Blinding

Treatment assignments were determined with the use of a computer-generated randomization list drawn up by the statistician. Randomization was in a 1:1:1 ratio, stratified by center, and involved blocking within each center (with randomly varying block size). Treatment assignments were allocated by each recruiting study site with the use of a centralized telephone randomization system after study eligibility of patients was confirmed.

After discharge from the hospital, a separate and blinded cardiology team provided all subsequent follow-up care. The patients were blinded to treatment assignment, as was the independent Clinical End Point Committee in charge of adjudicating all MACE and arrhythmic events.

## Statistical Analysis

To have a 90% chance of detecting a treatment difference of 5% in LVEF change from baseline to month 6 between the pooled treatment groups and the control group, with an assumed SD of 6.5%, 120 patients in total were required on the basis of a 2-sided, 2-sample *t* test with a type I error risk of 2.5%.

The analyses were performed on patients who underwent CABG surgery and received the study injections (myoblasts or placebo) and were by intention to treat. Each primary efficacy analysis compared the pooled treatment groups with the control group with a type I error risk of 2.5% (Bonferroni adjustment for the primary efficacy end points). When the results were deemed significant, a multiple comparison procedure was performed. Secondary efficacy analyses were performed at the 5% significance level.

Absolute changes from baseline to month 6 in LVEF and LV volumes were compared with the Mann-Whitney test, and an

adjusted probability value was computed with the use of a tied worst-rank score analysis (patients who withdrew or died before the 6-month echocardiography were assigned a rank that represented a "worst-rank score" relative to those actually observed). The Hodges-Lehmann method was used to compute the estimate and the confidence interval (CI) for the difference between the 2 medians.

Proportions of patients with recovered contraction in akinetic cell- or placebo-injected segments were compared with the  $\chi^2$  test and with the assumption that patients who withdrew or died before the 6-month echocardiography had not recovered contraction. Absolute changes from baseline to month 6 in global and regional wall motion scores, calculated on initially akinetic injected segments, were compared with the Mann-Whitney test.

The MACE-free survival and ventricular arrhythmia-free survival distributions were estimated according to the Kaplan-Meier method and compared with the log-rank test. For the analysis of time to first ventricular arrhythmia, death was treated as censored event.

Hazard ratios were estimated with the use of a Cox proportional hazard model with the factor variable for treatment group designation in the model. The analysis was further adjusted post hoc for EuroSCORE.

An independent data safety monitoring board reviewed safety and futility issues at regular intervals, with no predetermined rule for stopping the trial. In January 2006, the safety committee recommended stopping enrollment for reasons of futility at a time when 97 of the 120 planned patients had completed the whole procedure. The study was conducted in compliance with International Conference on Harmonization Good Clinical Practice guidelines.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Patients

From November 2002 to February 2006, 120 patients were randomized, of whom 97 actually underwent CABG surgery and injections. Of these, 34 were assigned to the control group, 33 to the low-dose cell group, and 30 to the high-dose cell group. Patient disposition at each stage of the study is represented in Figure 1.

The 3 groups of patients were well balanced with respect to baseline characteristics, location of injected areas, intraoperative variables, and drug therapies (Table 1). Patients in NYHA class I at the time of inclusion had experienced previous episodes of cardiac failure. Except for 8 patients (2, 4, and 2 in the placebo, low-dose, and high-dose groups, respectively), the bypass grafts were placed in areas remote from the transplanted/injected scars, which were thus not revascularized.

## Characterization of Transplanted Cells

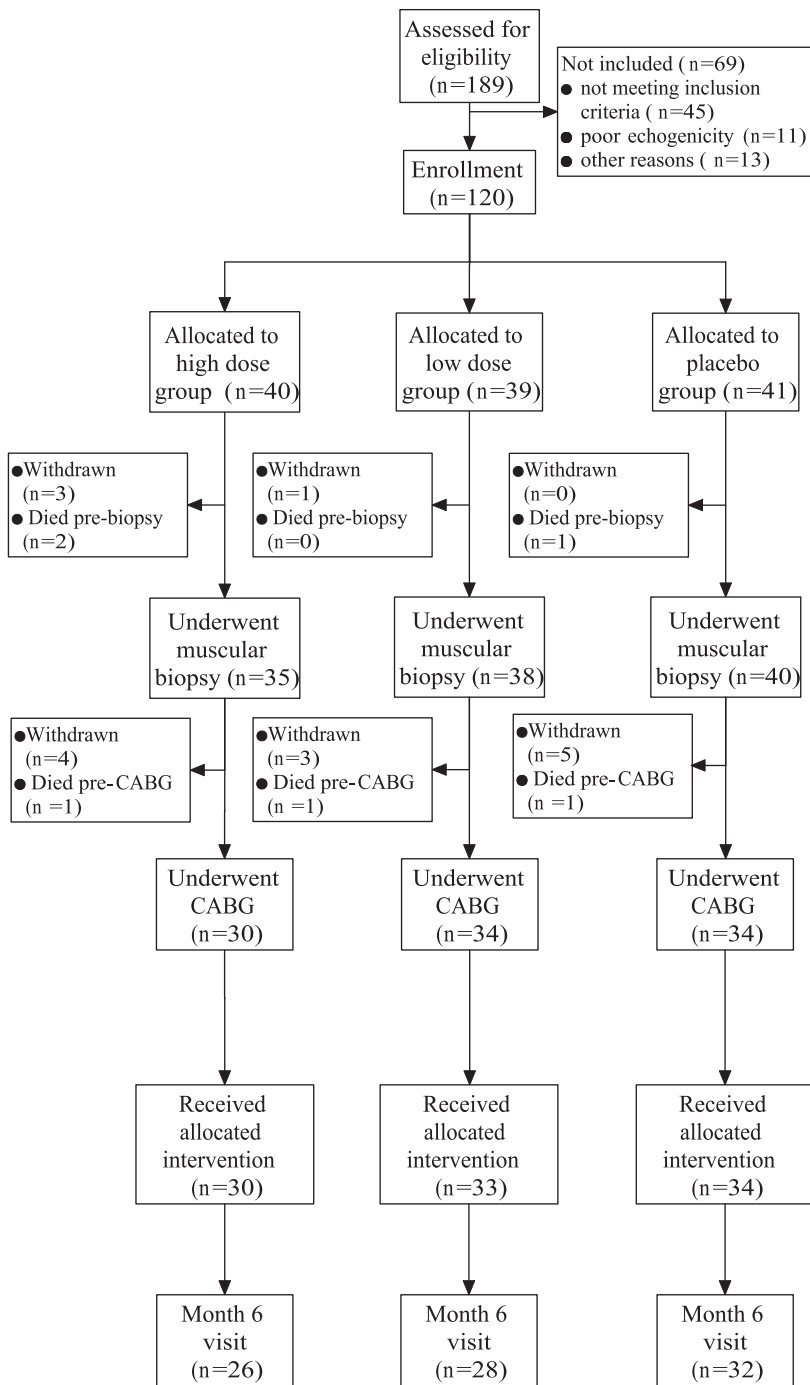
The percentages of cell viability and myoblast purity were 95% and 89%, respectively. In addition, final product shipping stability studies demonstrated that the product was stable for up to 72 hours at  $-1^\circ\text{C}$  to  $6^\circ\text{C}$  when stored in the closed shipping box. Holding cells in a syringe at room temperature for up to 4 hours also showed little difference compared with controls for viability, apoptosis, and subsequent capacity to form myotubes (data not shown).

## Efficacy

### Regional LV Function

The total number of initially akinetic myocardial segments that were injected was 97, 93, and 98 in the placebo,





**Figure 1.** Flow chart of the MAGIC trial. In the low-dose cell group, the difference between the number of patients who underwent CABG (n=34) and that of patients who received treatment (n=33) is due to the fact that 1 patient suffered an intraoperative aortic dissection. The anticipated complexity of the procedure then led the investigators not to proceed with any injection.

low-dose, and high-dose cell groups, respectively. At 6 months, the proportion of patients in whom these segments improved their contraction by 1 grade was not affected by myoblast injections, regardless of the dose (placebo group, 48%; low-dose group, 35%; high-dose group, 40%;  $P=0.66$ ). At the segmental level, the change in the regional wall motion score index from baseline was not significantly different between the 3 groups (Table 2).

**Global LV Function**

Baseline LVEF values were not significantly different between the 3 groups and, at 6 months, had increased to a similar extent in all 3 groups (Table 3 and Figure 2).

Likewise, the absolute decrease in global wall motion score index did not differ among the groups (Table 2).

In contrast, measurements of LV volumes, a prespecified secondary end point, demonstrated significant between-group differences over time (Table 3 and Figure 2). Although baseline LVEDV did not differ between the 3 groups, they subsequently increased in the placebo group, whereas they decreased in the low-dose cell group and to a still greater extent in the high-dose cell group (difference between high-dose and placebo group medians,  $-12.8 \text{ mL/m}^2$ ; 95% CI,  $-25.2$  to  $-3.6$ ;  $P<0.05$ ). Changes in LVESV featured a similar pattern, with a 6-month difference between high-dose and placebo group medians of  $-8.1 \text{ mL/m}^2$  (95% CI,  $-16.8$

**Table 1. Baseline Characteristics by Treatment Groups**

Variables	High Dose (n=30)	Low Dose (n=33)	Placebo (n=34)	<i>P</i>
Age at CABG, y	59 (53; 67)	61 (54; 70)	61 (55; 72)	0.67
Male, n (%)	28 (93)	33 (100)	32 (94)	0.46
Recent myocardial infarction ( $<90$ d), n (%)	2 (7)	5 (15)	6 (18)	0.42
NYHA class II or III (%)	26 (87)	24 (73)	28 (82)	0.36
Logistic EuroSCORE	3.4 (2.5; 6.3)	4.4 (2.9; 11.2)	3.3 (2.0; 6.7)	0.34
No. of grafts, n (%)				
One	7 (23)	5 (15)	5 (15)	0.15
Two	12 (40)	15 (45)	22 (65)	...
$\geq 3$	11 (37)	13 (40)	7 (20)	...
Aortic cross-clamp time, min	59 (47; 75)	64 (49; 80)	61 (52; 72)	0.88
Cardiopulmonary bypass time, min	98 (76; 126)	99 (85; 130)	96 (86; 115)	0.76
Location of treated myocardial infarctions, n (%)	...	...	...	0.80
Anterior	20 (67)	23 (70)	25 (73)	...
Inferior	5 (17)	6 (18)	3 (9)	...
Both	5 (16)	4 (12)	6 (18)	...
Baseline drug therapy, n (%)				
ACE inhibitors	20 (67)	22 (67)	29 (85)	...
$\beta$ -Blockers	22 (73)	23 (70)	19 (56)	...
Diuretics	20 (67)	24 (73)	19 (56)	...

Data are given as median (first quartile; third quartile) unless stated otherwise. ACE indicates angiotensin-converting enzyme.

to  $-2.6$ ;  $P < 0.05$ ). Significant differences between the high-dose and placebo groups were still found when nonparametric ANCOVA was performed with baseline volume data taken as covariates.

The percentage of patients who improved by 1 NYHA class at 6 months was 44%, 29%, and 42% in the placebo, low-dose, and high-dose cell groups, respectively, and did not differ significantly ( $P = 0.43$ ). Likewise, quality of life, as assessed by the SF-36 quality of life questionnaire, was not different among the 3 groups (data not shown).

### Safety Analysis

The time to first MACE was not significantly different between the 3 groups (Figure 3, top panel), and at the 6-month study point, the proportion of patients who had experienced a MACE did not differ significantly between the pooled treatment groups and the placebo group (placebo, 7 patients [21%]; low dose, 13 patients [39%]; high dose, 6 patients [20%]; EuroSCORE-adjusted hazard ratio, 1.5; 95% CI, 0.6 to 3.6;  $P = 0.69$  for the comparison of the pooled treatment groups versus the control group). This composite

**Table 2. Global Wall Motion Score Based on All Assessed Segments and Regional Wall Motion Score Based on Initially Akinetic Injected Segments in Patients Alive at Month 6**

	Placebo	Low Dose	High Dose	<i>P</i>
Global wall motion score, n	32	28	26	...
Baseline	2.78 $\pm$ 0.36	2.85 $\pm$ 0.43	2.77 $\pm$ 0.40	0.74
Six month	2.48 $\pm$ 0.44	2.62 $\pm$ 0.50	2.39 $\pm$ 0.35	0.15
Six-month change from baseline	-0.29 $\pm$ 0.40	-0.22 $\pm$ 0.47	-0.38 $\pm$ 0.36	0.19
Regional wall motion score,* n	29	26	25	...
Baseline	4.00 $\pm$ 0.00	4.00 $\pm$ 0.00	4.00 $\pm$ 0.00	...
Six month	3.53 $\pm$ 0.58	3.56 $\pm$ 0.71	3.78 $\pm$ 0.36	0.24
Six-month change from baseline	-0.47 $\pm$ 0.58	-0.44 $\pm$ 0.71	-0.22 $\pm$ 0.36	0.24
Recovery in at least 1 segment, n (%)	14 (48.3)	9 (34.6)	10 (40.0)	0.66

Data are given as mean $\pm$ SD.

\*In the placebo, low-dose, and high-dose cell groups, 32, 28, and 26 patients reached the 6-month follow-up visit, respectively: Among them, 2, 2, and 1 patients did not receive study injections in initially akinetic segments; 6-month wall motion grades were not available for 1 patient in the placebo group.

**Table 3. Global LV Function**

Variable	Placebo (n=32)	Low Dose (n=28)	High Dose (n=26)	<i>P</i> *	<i>P</i> <sub>adj</sub> †	High Dose vs Placebo	Low Dose vs Placebo
Baseline LVEF, %	29.6 (28.0; 33.1)	25.2 (21.2; 33.1)	28.7 (22.6; 34.1)	0.25	...	...	...
Six-month LVEF, %	35.1 (26.4; 39.3)	32.3 (24.1; 38.8)	32.5 (28.2; 38.5)	0.66	...	...	...
Absolute change in LVEF, %‡	4.4 (0.2; 7.3)	3.4 (−0.3; 12.4)	5.2 (−4.4; 11.0)	0.62	0.95	1.1 (−3.8; 5.4)	1.2 (−3.0; 6.0)
Baseline EDV indexed to BSA, mL/m <sup>2</sup>	86.2 (78.7; 103.2)	93.7 (81.3; 122.4)	96.8 (81.7; 105.2)	0.27	...	...	...
6-month EDV indexed to BSA, mL/m <sup>2</sup>	94.0 (74.8; 108.4)	104.0 (70.0; 127.2)	82.4 (69.3; 96.0)	0.72	...	...	...
Absolute change in EDV, mL/m‡	5.9 (−11.8; 15.2)	−3.9 (−17.0; 12.6)	−12.6 (−19.4; 0.0)	0.11	0.22	−12.8 (−25.2; 3.6)§	−2.0 (−14.9; 6.3)
Baseline ESV indexed to BSA, mL/m	58.9 (54.2; 72.0)	63.3 (53.0; 97.9)	67.0 (54.0; 77.4)	0.35	...	...	...
6-month ESV indexed to BSA, mL/m	62.6 (50.4; 74.3)	68.2 (45.8; 91.3)	50.6 (43.2; 66.5)	0.79	...	...	...
Absolute change in ESV, mL/m‡	−2.1 (−12.2; 5.9)	−6.5 (−16.4; 2.6)	−8.3 (−18.4; −3.4)	0.05	0.34	−8.1 (16.8; 2.6)§	−3.8 (−11.1; 3.4)

Data are given as median (first quartile; third quartile). BSA indicates body surface area. In the high-dose, low-dose, and placebo groups, 26, 28, and 32 patients reached the 6-month follow-up visit, respectively. Among them, telediastolic and telesystolic volumes were not available for 1, 1, and 3 patients, respectively, and LVEF values were not available for 0, 1, and 2 patients, respectively.

\*Wilcoxon test comparing pooled treatment groups vs placebo group.

†Adjusted *P* value computed with use of a tied worst-rank score analysis (patients who withdrew or died before the 6-month echocardiography were assigned a rank that represented a worst-rank score relative to those actually observed).

‡The median absolute change is not the same as the difference between medians at baseline and month 6. An absolute median decrease is not inconsistent with a 6-month median greater than the baseline median.

§*P*<0.05 by multiple comparison with use of the Dunn procedure. Significant differences between the high-dose and placebo groups were still found when nonparametric ANCOVA was performed with baseline volume data as covariates.

index was driven partly by deaths occurring during the first postoperative month, none of which could be attributed directly to the procedure (in the low-dose group, 1 cardiac failure after a major postbypass peripheral vascular surgery and 1 pulmonary edema; in the high-dose group, 1 acute cardiac failure in a redo patient with a logistic EuroSCORE of 15%, 1 ischemic stroke, and 1 multiorgan failure after a reexploration for bleeding originating from a vein graft). No patient experienced bleeding from the injections.

Likewise, the time to first arrhythmia did not differ significantly between the 3 groups (Figure 3, bottom panel), whereas the distribution of amiodarone therapy was balanced equally among the 3 groups (59%, 75%, and 73% in the placebo, low-dose, and high-dose cell groups, respectively; *P*=0.36). No death occurred that was attributable to an arrhythmic event. The comparison of hazard ratios (low dose versus placebo, 2.2 [95% CI, 0.4 to 12.2]; high dose versus placebo, 3.3 [95% CI, 0.6 to 16.9]) was not significant (*P*=0.35 and *P*=0.16, respectively) and as such did not support a dose-response increase in arrhythmic episodes. The main safety data are summarized in Table 4.

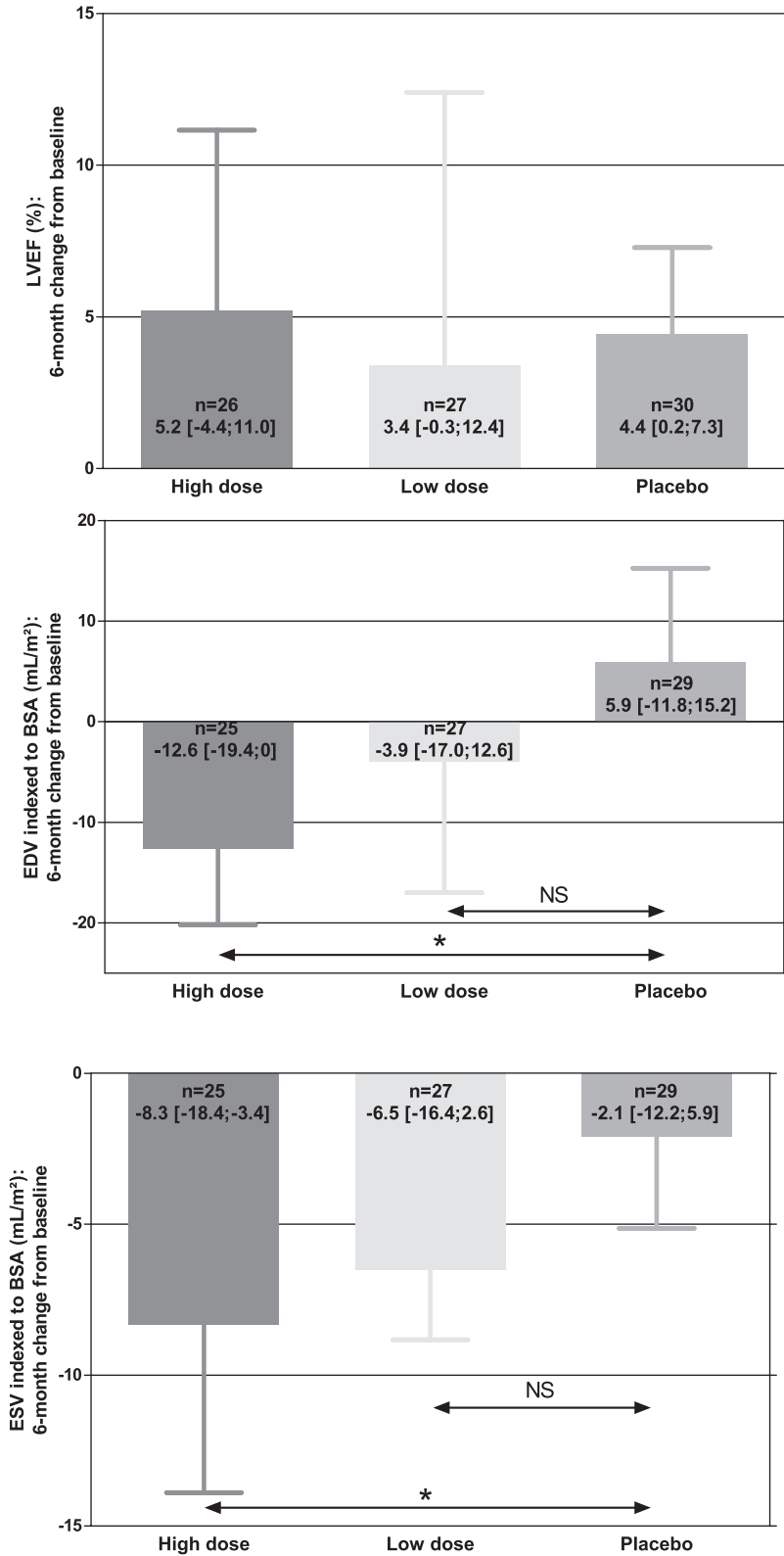
## Discussion

This first randomized controlled trial of autologous myoblast transplantation in patients with severe ischemic heart disease

failed to detect an incremental improvement in regional or global LV function over that provided by CABG alone.

## Interpretation of Efficacy End Points

The study failed to meet its primary efficacy end point because myoblast-treated patients did not show an incremental improvement in regional or global LV function. Because the functional efficacy of myoblast transplantation seems tightly dependent on graft volume,<sup>12</sup> a possible cause for failure could be an insufficient rate of engraftment<sup>13</sup> due to initial cell leakage<sup>14</sup> and subsequent cell death.<sup>15</sup> This loss of injected cells is largely caused by apoptosis due to cell detachment from the extracellular matrix and by ischemia of the cellular graft.<sup>16</sup> In the MAGIC study, the latter factor was certainly critical in that the myoblast-injected areas were not vascularized because of the unsuitability of most of the infarct-related arteries for direct revascularization. Furthermore, in contrast to intracoronary infusions of bone marrow stem cells that can be easily standardized, multiple epicardial echo-guided needle injections are more difficult to control, particularly in the context of a multicenter trial. In the interpretation of our negative findings, one should also take into account that low-dose dobutamine echocardiography has a negative predictive value for assessing preoperative myocardial viability in the range of 70%.<sup>17</sup> This is consistent with



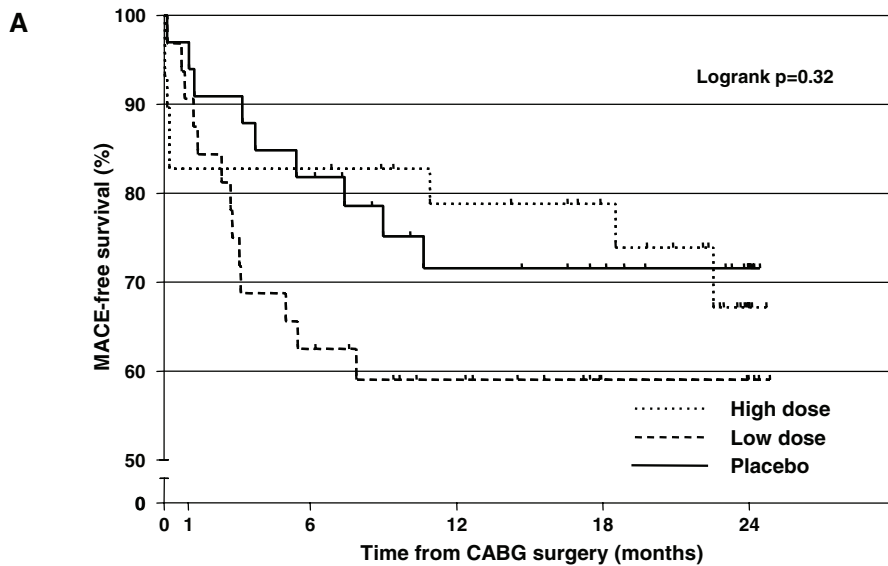
**Figure 2.** Six-month change from baseline in LVEF (top), indexed EDV (middle), and indexed ESV (bottom). Data are given as median and interquartile range. The pooled treatment groups and the placebo group were compared with a Wilcoxon test. The associated probability value was 0.62, 0.11, and 0.05 for LVEF, indexed EDV, and indexed ESV indices, respectively. An adjusted probability value was computed with a tied worst-rank analysis (patients who died before the 6-month echocardiography were assigned a rank that represented a worst-rank score relative to those actually observed). The adjusted probability value was 0.95, 0.22, and 0.34 for LVEF, indexed EDV, and indexed ESV, respectively. \* $P < 0.05$  in a multiple comparison with the use of the Dunn procedure. BSA indicates body surface area.

our finding that approximately one third of the initially akinetic segments injected with the placebo medium improved functionally after the operation, which suggests that some of them may have been mistakenly identified as nonviable preoperatively, whereas they still harbored hibernating tissue that recovered after bypass grafting of the

neighboring myocardial territories through collaterals.<sup>18</sup> Together with the small sample size, this relatively high rate of segmental recovery in the placebo group might have obscured a potential treatment effect.

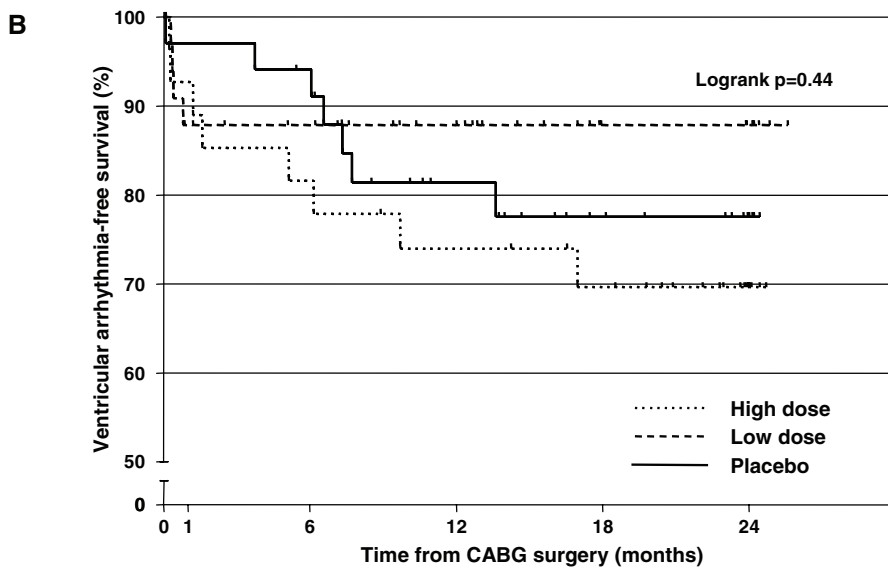
An interesting finding of this study was that patients receiving the highest dose of cells experienced a significant





# at risk	High dose 30	24	24	20	16	3
	Low dose 33	29	20	14	5	3
	Placebo 34	32	27	20	17	8

**Figure 3.** A, Time to first MACE.  
B, Time to first ventricular arrhythmia.



# at risk	High dose 30	24	24	20	16	3
	Low dose 33	29	20	14	5	3
	Placebo 34	32	27	20	17	8

reversal of LV remodeling compared with the control group, whereas no between-group differences existed in medications. The magnitude of the reduction in LV volumes was actually close to that obtained with the 2 most powerful antiremodeling therapies (ie, cardiac resynchronization<sup>19</sup> and  $\beta$ -blockers<sup>20</sup>). These changes in LVEDV and LVESV are in agreement with experimental data showing the beneficial effects of myoblast engraftment on LV dimensions.<sup>21</sup> The underlying mechanism remains, however, incompletely clarified. Passive changes due to the mere injection of compliant materials<sup>22</sup> are unlikely because patients of all groups received the same intramyocardial volume of injectate. Con-

versely, skeletal myoblasts are known to secrete factors that may affect the composition of the extracellular matrix,<sup>23</sup> and in view of the inability of myogenic cells to convert into cardiomyocytes,<sup>24</sup> it has been assumed that these paracrine effects could account for the reported benefits of experimental myoblast transplantation. In sheep<sup>21</sup> and pig<sup>25</sup> models of myocardial infarction, skeletal myoblasts reduced fibrosis, and this effect might have contributed to the reversed remodeling seen in our high-dose group. This view is indirectly supported by the mechanistic link reported between changes in levels of some metalloproteases and those of ventricular volumes.<sup>26</sup> Although a dissociation between EF and ventric-

**Table 4. Safety End Points**

	Placebo (n=34)	Low Dose (n=33)	High Dose (n=30)	HR (95% CI)	<i>P</i> *	EuroSCORE-Adjusted HR (95% CI)	<i>P</i> †
Six-month MACE,‡ n (%)	7 (21)	13 (39)	6 (20)	1.6 (0.7; 3.8)	0.29	1.5 (0.6;3.6)	0.69
Six-month mortality, n (%)	2 (6)	5 (15)	4 (13)	2.6 (0.6;12.1)	0.20	2.5 (0.5;11.4)	0.25
Six-month ventricular arrhythmias, n (%)	2 (6)	4 (12)	5 (17)	2.7 (0.6; 12.6)	0.18	2.8 (0.6; 12.8)	0.19
Sustained VF or polymorphic VT	...	1	...	...	...	...	...
Sustained monomorphic VT	1	2	4	...	...	...	...
Sustained monomorphic VT and sustained VF or polymorphic VT	1	1	1	...	...	...	...

HR indicates hazard ratio of pooled treatment groups to placebo group; VF, ventricular fibrillation; and VT, ventricular tachycardia.

\*Log-rank test comparing pooled treatment groups vs placebo group.

†Wald test in a Cox regression model including the treatment group and the logistic EuroSCORE.

‡Includes cardiovascular- and noncardiovascular-related death, myocardial infarction, congestive heart failure, resuscitated sudden death, and stroke.

ular enlargement has been reported,<sup>27</sup> an expected benefit of reversed remodeling is an improvement of LV function<sup>28</sup> due to reduced wall stress on remote myocardium. This benefit, however, was not demonstrated in our study, possibly because it was outweighed by the advanced degree of LV dysfunction or fell beyond the detection limits of echocardiography in these markedly dilated and distorted hearts. Finally, our negative results may point out that lineage-restricted skeletal myoblasts,<sup>29</sup> as used in this protocol, are not the optimal candidates for improving the severe LV dysfunction of chronically infarcted hearts in which a successful outcome likely requires implantation of contractile and electromechanically integrated cells, fostering a true regeneration of the grafted myocardium.

**Interpretation of Safety End Points**

One of the major concerns raised by the early-phase studies of myoblast transplantation was that it could increase the risk of ventricular arrhythmias,<sup>2,4</sup> a complication attributed to the slowing of conduction velocity by the electrically isolated islet-like clusters of myoblasts<sup>30</sup> and the subsequent occurrence of reentries.<sup>31</sup> However, animal experiments performed in rat<sup>32</sup> and dog<sup>33</sup> have yielded divergent results. As shown in Table 4, our results show that at the 6-month study point, the proportions of patients who had experienced arrhythmias did not differ significantly between the pooled treatment groups and the placebo group. Nevertheless, the actual number of arrhythmias was 2 times greater in each of the myoblast-treated groups than in the placebo group, which clearly calls attention to a proarrhythmic risk of myoblast implantation. Our data also confirm the survival benefit conferred by ICDs in this high-risk heart failure patient population<sup>34</sup> irrespective of cell-based therapy. In the future, although myoblast transfection by connexin 43 has been shown to reduce arrhythmias in coculture experiments,<sup>31</sup> another option could be to avoid myocardial tissue disruption by injected cells and the resulting electric heterogeneity<sup>35</sup> through the use of myoblast-seeded cell sheets simply overlaid onto the infarct areas.<sup>36</sup>

Although mortality outcomes were not significantly different between the individual or pooled treatment groups and the placebo group (with no perioperative death that could be attributed to cell injections), the small sample sizes call for caution in the interpretation of these data, and larger patient

series are required to more conclusively characterize the safety profile of the procedure. However, the occurrence of some serious adverse events after randomization but before intraoperative injections highlights the importance of developing cell expansion techniques that allow shortening of the biopsy-to-surgery time interval in these critically ill and potentially unstable patients.

**Study Limitations**

Although the MAGIC trial is the largest skeletal myoblast study performed thus far, it has limitations. First, both the number of patients enrolled and the number of clinical events were small, which restricts the power of the statistical analyses and the strength of the subsequent conclusions. As such, we need to remain cautious about the conclusions until studies with larger numbers of patients are available. In particular, the significance of the volume changes observed in the high-dose MAGIC patients should be interpreted conservatively because of the known potential for subgroup analyses to overestimate the direction of treatment effects.<sup>37</sup> Second, the follow-up is still limited to 6 months. The transient efficacy of intracoronary infusions of bone marrow cells reported by the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial investigators<sup>38</sup> and the late recurrent LV dilatation in the cardiac resynchronization Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial<sup>26</sup> highlight the importance of a long-term follow-up in cell therapy studies. Finally, because of the presence of an ICD, we were unable to perform magnetic resonance imaging, which would have more accurately depicted changes in regional function and LV volumes because, among surrogate end points, the latter may be more appropriate than EF to assess the effects of combining cell implantation and bypass surgery in patients with chronic LV dysfunction.

Whereas some improvement in EF has been reported after intracoronary infusions of bone marrow cells in patients with acute myocardial infarction,<sup>39</sup> data on surgical implantation of cells combined with bypass surgery in those with advanced LV dysfunction are more scarce and less conclusive. Indeed, neither the present study nor that of Hendriks et al,<sup>40</sup> which was designed similarly except that it entailed transplantation of bone marrow cells instead of myoblasts, has successfully

achieved its primary end point. Furthermore, the potential for myoblast-induced arrhythmias remains a concern. Taken together, these observations emphasize the importance of additional work to address some remaining key issues such as selection of the most suitable cell type, optimization of cell transfer, survival, and integration to set the stage for “second-generation” cells that, it is hoped, will yield more successful results.

## Appendix

### Participating Centers

#### France

Paris, Hôpital Européen Georges Pompidou, Principal Investigator (PI): A.A. Hagège; Toulouse, Hôpital de Rangueil, PI: M. Galinier; Clermont-Ferrand, Hôpital Gabriel Montpied, PI: C. de Riberolles; Grenoble, Hôpital A. Michallon, PI: D. Blin; Lille, Hôpital Cardiologique, PI: C. Bauters; Besancon, Hopital Jean Minjot, PI: F. Schiele; Bordeaux, Hôpital Haut-Leveque, PI: M.A. Billes; Nantes, Hôpital G et R Laennec, PI: D. Duveau; Caen, Hôpital Côte de Nacre, PI: A. Khayat; Rennes, Hôpital de Pontchaillou, PI: A. Leguerrier; Rouen, Hôpital Charles Nicolle, PI: F. Tron.

#### Germany

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#### Belgium

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#### United Kingdom

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#### Clinical Adjudication Committee

Scott Solomon (Boston), William Stephenson (Boston).

#### Data Monitoring Committee

Edouardo Camenzind (Geneva), Philippe Lechat (Paris), Mark A. Pfeffer (Chair, Boston), Jean L. Rouleau (Montreal), P. Gabriel Steg (Paris), Pascale Tubert-Bittner (Paris), Hein Wellens (Utrecht).

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Two days before this article was definitively accepted, Dr Ketty Schwartz passed away. She was a top-ranked scientist and an extraordinarily gifted woman whose commitment to basic and translational science has been relentless. The purpose of this last-minute note is not to summarize her multiple and major scientific contributions but to remind readers that she largely inspired, >10 years ago, the project of using skeletal myoblasts in the treatment of heart failure. She then participated actively in the preclinical development of this project and closely followed its subsequent clinical applications. Many of us are strongly indebted to Ketty Schwartz, and we would like to dedicate this article to her memory.

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## Disclosures

The members of the steering committee (Drs Menasché, Alfieri, Janssens, McKenna, Reichenspurner) and Drs Solomon and Hagège were consultants to Genzyme Corporation. Barbara Seymour and Steven Lake are employees of Genzyme Corporation.

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### CLINICAL PERSPECTIVE

The recognition that heart failure is caused largely by the irreversible loss of a substantial number of cardiomyocytes has led to the concept that implantation of contractile cells in postinfarction myocardium could improve left ventricular function. Preclinical studies showing that skeletal myoblasts met this objective have paved the way for early-phase clinical trials, which were not able to establish the efficacy of the procedure. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial is the first to address this issue. Using the rigorous standards of randomized, controlled, double-blind studies, it enrolled 97 patients with severe left ventricular dysfunction scheduled for bypass surgery and allocated them to receive in-scar injections of a placebo medium or autologous myoblasts. After 6 months, neither global nor regional function improved in treated patients beyond that seen in the placebo group. However, the highest dose of myoblasts was associated with a significant antiremodeling effect. Recordings of internal defibrillators showed that the 6-month incidence of ventricular arrhythmias did not differ significantly among groups despite a trend toward a greater number of early postoperative events after myoblast grafting. These results lead to 3 main conclusions: (1) Implanted myoblasts may exert some therapeutic benefits, possibly through paracrine signaling; (2) it remains uncertain whether these effects have an impact on patient outcomes; and (3) to move the field from proof of concept to active therapy requires the optimization of the best cells matching the target clinical setting (acute infarction or heart failure), their method of delivery, and strategies enabling the enhancement of graft survival and its functional integration.

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