Heart failure remains a major and growing public health problem, with its prevalence in the United States estimated to be 5.7 million. Although survival after diagnosis of heart failure has improved, overall mortality remains high: approximately 50% of people diagnosed with heart failure will die within 5 years. Despite recent advances in medical and device management of heart failure, a significant proportion of patients reach end-stage heart failure; for these patients, heart transplantation still remains the treatment of choice. In the past 5 years, the distribution of diagnoses in patients undergoing heart transplantation has changed significantly: nonischemic dilated cardiomyopathy (DCM) is now the leading cause of heart disease for adult heart transplant recipients (53.3% of recipients), followed by ischemic cardiomyopathy (37.7%), adult congenital heart disease (2.9%), and valvular heart disease (2.7%). These trends indicate that patients with nonischemic DCM may represent the largest subpopulation of heart failure patients with a significant need for alternative treatment modalities.

HEART FAILURE AND NONISCHEMIC DCM

Heart failure progression is accompanied by the activation of neurohormonal and cytokine systems, as well as a series of adaptive changes within the myocardium, collectively referred to as left-ventricular remodeling. The unfavorable alterations may be categorized broadly into those that occur in the cardiac myocytes vs. changes that occur in the volume and composition of the extracellular matrix. There is increasing evidence that cardiac dysfunction and left-ventricular remodeling may occur due to progressive myocyte loss, via both necrotic and apoptotic cell death. Failing human cardiac myocytes also undergo a number of structural and functional changes that might be expected to lead to a progressive decline in contraction force generation and transmission defects, metabolic abnormalities, and disturbed calcium homeostasis of cardiomyocytes, decreased α-myosin heavy-chain and increased β-myosin heavy-chain gene expression, progressive loss of myofilaments, alterations in cytoskeletal proteins, alterations in excitation–contraction coupling, and desensitization of β-adrenergic signaling. Principal changes in the extracellular matrix consist of perivascular fibrosis around intramyocardial blood vessels, replacement fibrosis, and progressive activation of matrix metalloproteinases, which degrade extracellular matrix and cause mural realignment of myocytes, leading to left-ventricular wall thinning and dilation.

Nonischemic DCM is characterized mainly by left-ventricular or biventricular dilation and systolic dysfunction in the absence of coronary artery disease, arterial hypertension, valvular heart disease, or congenital heart disease. This disorder can develop at any age, in either sex, and in people of different ethnic origins. The etiology of nonischemic DCM is multifactorial, and it may develop due to genetic factors, infectious causes, mechanical stress, or toxicity-related causes. Macroscopic inspection usually reveals an enlargement of all four chambers, with relatively more pronounced dilation of the ventricles than the atria. Microscopic examination typically shows areas of...
perivascular and interstitial fibrosis and occasionally areas of cardiomyocyte necrosis/apoptosis and inflammatory cell infiltrates. Cardiomyocytes may vary significantly in size and may be either atrophied or hypertrophied. Abnormal shapes, sizes, and numbers of mitochondria have also been reported in nonischemic DCM. The exact pathophysiologic mechanisms that underlie these changes remain poorly understood. The interactions among specific sarcomeric and cytoskeletal proteins; direct pathogen infection; postinfection immune, organ-specific immune, and autoimmune mechanisms; and free oxygen radical species are thought to play pivotal roles in development and progression of nonischemic DCM. In addition to alterations in myocytes and cytoskeletal proteins, patients with nonischemic DCM also have defective vascularization and impaired vasculogenesis and angiogenesis. 5 Although the exact underlying mechanisms remain to be defined, they appear to be related to impaired myocardial homing and survival of CD34-positive (CD34 +) cells. 6,7

**CD34 + CELLS**

CD34 was first identified as an antigen expressed on hematopoietic progenitors in screens of monoclonal antibodies generated against human hematopoietic precursors. Subsequently, the CD34 + cell fraction of bone marrow was shown to successfully engraft in both baboons and humans and to be free of most of the malignant tissues, which represents a major advantage over the other stem cell selection criteria. 8 Owing to its clinical utility, the use of CD34 became widely accepted as a marker of hematopoietic stem cells. However, the function of the CD34 antigen remains to be fully elucidated. Current evidence indicates that it may be involved in hematopoiesis, trafficking of hematopoietic cells, and promoting the proliferation of hematopoietic progenitor cells. 9 CD34 + cells can stay either in the bone marrow or in the peripheral blood pool, depending on the homing signals of the microenvironment.

The CD34 antigen is expressed on both endothelial progenitor cells and fully differentiated endothelial cells. 9 The likelihood that these cells could eventually adopt an endothelial role suggests that CD34 + cells might contribute to the formation of new blood vessels from existing vascular structures in ischemic tissues. Although the exact nature of the beneficial course taken by CD34 + cells in ischemic conditions is undefined, it is thought to involve either the direct incorporation of injected cells into the newly developing vasculature or the production and secretion of angiogenic cytokines that support an ischemia-induced angiogenic response. 10

A key prerequisite for the therapeutic use of peripheral CD34 + cells is successful mobilization. This is performed by granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or as shown more recently, a C-X-C motif receptor 4 (CXCR4) inhibitor, plerixafor. The use of granulocyte colony-stimulating factor alone or in conjunction with chemotherapy at a dose of 10 μg/kg daily for 5 days, followed by leukapheresis on day 5, is the most commonly used approach. Side effects are typically mild and tolerable. The target dose of subcutaneous injection is 5 × 10^6/kg body weight, with a minimal target dose of 2 × 10^6/kg body weight. 11,12 However, up to 30% of donors and patients undergoing mobilization based on granulocyte colony-stimulating factor fail to mobilize adequate numbers of CD34 + cells to proceed to leukapheresis. Clinical risk factors for poor mobilization include previous high-dose chemotherapy (e.g., fludarabine, melphalan, and lenalidomide), underlying comorbid diseases, radiotherapy encompassing bone marrow, low steady-state platelet counts and peripheral blood CD34 + levels, low steady-state tumor necrosis factor-a levels, and increasing age. In this group of patients, a risk-adaptive protocol for mobilization, which usually involves the addition of plerixafor, is used. 13 Other nonhematological adverse factors influencing circulating CD34 + levels observed in different populations are smoking, alcohol abuse, and severity of cardiovascular disease. 14-17 In addition, physiologic and pathophysiologic conditions, such as peripheral or myocardial ischemia, are known to stimulate endogenous CD34 + cell mobilization. 18,19

**CD34 + CELL THERAPY IN ISCHEMIC HEART DISEASE**

Several clinical studies have investigated the safety and efficacy of stem cells in the setting of acute myocardial infarction, ischemic heart failure, and angina pectoris (Table 1). However,

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Baseline LVEF (%)</th>
<th>Follow-up (months)</th>
<th>Cell dose</th>
<th>Delivery route</th>
<th>LVEF change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTAMI (ref. 38)</td>
<td>100</td>
<td>46.3</td>
<td>6</td>
<td>68 × 10^6</td>
<td>IC</td>
<td>+3.1%</td>
</tr>
<tr>
<td>REPAIR-AMI (ref. 39)</td>
<td>204</td>
<td>47.6</td>
<td>12</td>
<td>2.4 × 10^8</td>
<td>IC</td>
<td>+2.5%</td>
</tr>
<tr>
<td>TOPCARE-CHD (ref. 40)</td>
<td>121</td>
<td>39.9</td>
<td>3</td>
<td>205 × 10^6</td>
<td>IC</td>
<td>+1.8%</td>
</tr>
<tr>
<td>BOOST (ref. 41)</td>
<td>60</td>
<td>50.7</td>
<td>6</td>
<td>2.5 × 10^5</td>
<td>IC</td>
<td>+6.7%</td>
</tr>
<tr>
<td>STAR-heart (ref. 42)</td>
<td>391</td>
<td>32.8</td>
<td>60</td>
<td>6.6 × 10^7</td>
<td>IC</td>
<td>+6.2%</td>
</tr>
<tr>
<td>REGENT (ref. 20)</td>
<td>200</td>
<td>37.0</td>
<td>6</td>
<td>1.9 × 10^6</td>
<td>IC</td>
<td>+3.0%</td>
</tr>
<tr>
<td>FOCUS-HF (ref. 43)</td>
<td>30</td>
<td>37.0</td>
<td>6</td>
<td>484 × 10^6</td>
<td>IM</td>
<td>+3.0%</td>
</tr>
<tr>
<td>FOCUS-CCTRN (ref. 21)</td>
<td>92</td>
<td>32.4</td>
<td>6</td>
<td>100 × 10^6</td>
<td>IM</td>
<td>+1.4%</td>
</tr>
<tr>
<td>TIME (ref. 44)</td>
<td>120</td>
<td>45.2</td>
<td>6</td>
<td>146.6 × 10^6</td>
<td>IM</td>
<td>+3.1%</td>
</tr>
<tr>
<td>LATE-TIME (ref. 45)</td>
<td>87</td>
<td>48.7</td>
<td>6</td>
<td>147 × 10^6</td>
<td>IC</td>
<td>+0.5%</td>
</tr>
</tbody>
</table>

IC, intracoronary; IM, intramyocardial; LVEF, left-ventricular ejection fraction.
In the majority of these studies, CD34+ cells were injected as a part of unselected bone marrow mononuclear cells (BMCs), which makes it very difficult to evaluate the direct effects of the CD34+ cell subpopulation. Despite this limitation, there is increasing evidence that the clinical efficacy of unselected BMCs may indeed correlate with the proportion of CD34+ cells within the BMC mixture.

In patients who underwent BMC therapy after acute myocardial infarction in the Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) trial, there was a significant inverse correlation between the baseline left-ventricular ejection fraction (LVEF) and its change after cell therapy in patients treated with selected CD34+ cells, but not in the unselected BMC group. Furthermore, subgroup analysis revealed that in patients with severely reduced LVEF (<37%), the use of a relatively small number of selected CD34+ cells was associated with a trend for improvement of LVEF similar to that with the use of a 100× higher number of unselected BMCs. A similar trend was observed in the First Mononuclear Cells Injected in the United States trial, conducted by the Cardiovascular Cell Therapy Research Network (FOCUS-CCTRN), a randomized double-blind, placebo-controlled trial of ischemic heart failure patients with an LVEF <45%. In this study, all patients underwent bone marrow aspiration (isolation of BMCs using a standardized automated system) and transendocardial injection of 100 million unselected BMCs or placebo. Although the study failed to reach its primary end points (i.e., changes in left-ventricular end-systolic volume, maximal oxygen consumption, and reversibility on single-photon emission computed tomography), it found that the improvement in left-ventricular function was correlated directly with the number of CD34+ cells within the unselected BMC population: each 3% higher level of CD34+ cells was associated with an average of 3.0% greater absolute unit increase in LVEF. In accordance with these findings, the results of the Autologous Cellular Therapy CD34–Chronic Myocardial Ischemia (ACT34-CMI) trial demonstrated that patients who received intramyocardial injections of autologous CD34+ cells (10^5 cells/kg) experienced significant improvements in angina frequency and exercise tolerance.

Although the reasons for the apparent superiority of selected CD34+ cells over unselected BMCs remain poorly defined, it is tempting to speculate that they may be partly related to differences in the angiogenic potency. In a preclinical model of myocardial infarction, the injection of selected CD34+ cells was associated with a significantly higher myocardial capillary density, lower fibrosis area, greater echocardiographic fractional shortening, and greater regional wall motion than injection of unselected BMCs. These findings led the authors to conclude that CD34+ cells exhibited superior efficacy for preserving myocardial integrity and function after myocardial infarction than unselected BMCs.

When tracking the fate of human CD34+ cells in a preclinical model of ischemic heart failure, bioluminescence imaging showed that injected CD34+ cells survived in the hearts for longer than 12 months. In this murine model, anti–vascular endothelial growth factor treatment, which abolished the formation of paracrine effect mediated by vascular endothelial growth factor, abrogated the improvement in cardiac function. This suggests that paracrine effects play an important role in determining the long-term improvement in cardiac function after CD34+ cell therapy. In contrast to the studies discussed above, which indicated that CD34+ cells incorporate into newly formed vasculature, these findings suggest that they promote vascular angiogenesis in a paracrine manner via secretion of angiogenic factors. Thus, based on the current evidence, the two mechanisms appear to act synergistically to produce the observed outcomes.

EVIDENCE OF MYOCARDIAL ISCHEMIA IN NONISCHEMIC DCM

In patients with ischemic heart disease, hibernating myocardium has been defined as a blood flow–metabolism mismatch in the presence of contractile dysfunction and is thought to represent the adaptation of the myocardial tissue to chronic or repetitive ischemia. Similarly, regions with flow abnormalities, increased glucose metabolism, and decreased aerobic metabolism have also been found in patients with nonischemic DCM.

Using electroanatomical mapping, hibernation is defined as viable myocardium using voltage thresholds with significantly impaired linear shortening. Previous studies in ischemic cardiomyopathy have shown a good concordance in identifying hibernating segments using electroanatomical mapping, single-photon emission computed tomography, positron emission tomography–computed tomography, and postmortem autopsies. In a pilot study of electroanatomical mapping in patients with nonischemic DCM, we were able to demonstrate the existence of significant hibernating myocardial segments in nearly half of the patients. On average, it occupied 28% of the left ventricle, with comparable distributions in the anterior, lateral, septal, and posterior walls. By contrast, scar segments had a preferential basal distribution. The distribution of hibernating and scar segments was consistent with preclinical and clinical studies. Using left-ventricular mapping in a sheep model of nonischemic DCM, hibernation was present in up to 44% of all segments and had a more diffuse distribution pattern in comparison with scar segments, which had a preferential basal distribution.

Although epicardial coronary arteries are not obstructed in patients with nonischemic DCM, coronary flow reserve is often impaired both globally and regionally. Moreover, studies have described defective vascularization and impaired vasculogenesis and angiogenesis in nonischemic DCM, possibly caused by impaired survival of endothelial cells due to increased expression of vascular endothelial (VE)-cadherin/β-catenin. These areas of perfusion defects in DCM may contribute to hibernation. Based on the current preclinical and clinical evidence, the progression of nonischemic DCM appears to be related not only to structural and functional changes in the myocytes but also to cardiac endothelial dysfunction, marked vascular derangements, and impaired vasculogenic and angiogenic responses.

Therefore, therapeutic strategies aimed at repairing the vasculogenesis and angiogenesis also may benefit patients with nonischemic DCM.
In contrast to ischemic heart disease, very few trials to date have focused on the effects of stem cell therapy in nonischemic DCM (Table 2). In the Transplantation of Progenitor Cells and Recovery of Left Ventricular Function in Patients with nonischemic Dilated Cardiomyopathy (TOPCARE-DCM) trial, intracoronary BMC infusion into the left anterior descending coronary artery was performed in 33 patients with DCM by using over-the-wire balloon catheter. After 3 months, such therapy resulted in regional wall motion of the target area and global LVEF increase of regional wall motion was directly related to the functionality of the infused cells. At 1 year after the infusion, the investigators also found a significant decrease in N-terminal pro–brain natriuretic peptide (NT-pro-BNP) levels. In the Autologous Bone Marrow Cells in Dilated Cardiomyopathy (ABCD) trial, the investigators enrolled 81 patients with DCM, who were randomized to either intracoronary injection of BMCs in both left and right coronary systems (n = 41) or the control arm (n = 40). During the 3-year follow-up, they found no significant difference in mortality between the groups. The LVEF improved in the treatment arm by 5.9%, with a reduction in end-systolic volumes and no change in end-diastolic volumes. Similarly, in a study of patients with refractory DCM, infusion of BMCs into the left main coronary artery was associated with improved LVEF, maximal oxygen consumption, New York Heart Association (NYHA) functional class, and quality of life.

Collectively, these data suggest that stem cell therapy using unselected BMCs also may benefit patients with nonischemic DCM. Furthermore, based on the data in ischemic heart disease, it is possible that this therapeutic approach could be further improved by the use of selected CD34+ cells.

**CLINICAL TRIALS OF UNSELECTED BMC THERAPY IN NONISCHEMIC DCM**

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**CLINICAL TRIALS OF CD34+ CELL THERAPY IN NONISCHEMIC DCM**

On the basis of the positive results of the unselected BMC therapy, we have performed the first prospective, randomized trial investigating the long-term effects of CD34+ cell therapy in patients with nonischemic DCM. Of 110 patients with dilated cardiomyopathy, 55 were randomized to CD34+ cell transplantation (SC group), and 55 patients did not receive stem cell therapy (controls). In the SC group, peripheral blood CD34+ cells were mobilized by the granulocyte colony–stimulating factor and collected via apheresis. All patients who underwent
myocardial scintigraphy and CD34+ cells were injected in the coronary artery supplying the segments with reduced viability. At 5 years, stem cell therapy was associated with an increase in LVEF (from 24.3 ± 6.5 to 30.0 ± 5.1%; \( P = 0.02 \)), an increase in 6-min walk distance (from 344 ± 90 to 477 ± 130 m; \( P < 0.001 \)), and a decrease in NT-pro-BNP (from 2,322 ± 1,234 pg/ml to 1,011 ± 893 pg/ml; \( P < 0.01 \)). During follow-up, 27 (25%) patients died and 9 (8%) underwent heart transplantation. Of the 27 deaths, 13 were attributed to pump failure, and 14 were attributed to sudden cardiac death. Total mortality was lower in patients receiving SC therapy (8/55, 14%) than in controls (19/55, 35%; \( P = 0.01 \)). The same pattern was true in terms of pump failure (3/55 (5%) vs. 10/55 (18%), \( P = 0.03 \)) but not for the sudden cardiac death (5/55 (9%) vs. 9/55 (16%), \( P = 0.39 \)).

On the basis of these findings, we concluded that intracoronary CD34+ therapy is indeed associated with improved ventricular remodeling, better exercise tolerance, and improved long-term survival in patients with nonischemic DCM (Figure 2). Furthermore, we have shown that the response to intracoronary CD34+ cell therapy is dependent on the degree of myocardial cell retention, suggesting that the efficacy of intracoronary cell therapy may be limited by the number of cells retained in the myocardium. This may be particularly important in patients with nonischemic DCM, who have been shown to have a significant downregulation of several stem cell–homing factors, including stromal cell-derived factor-1. 

In an attempt to improve myocardial cell retention, we performed a follow-up study investigating whether transendocardial CD34+ cell delivery is associated with greater retention rates and clinical improvement than intracoronary cell delivery in patients with nonischemic DCM. Of 40 patients with nonischemic DCM, 20 were randomized to receive intracoronary injection (IC group) and 20 received transendocardial CD34+ cell delivery (TE group). In both groups, CD34+ cells were mobilized by filgrastim, collected via apheresis, and labeled with technetium-99m radioisotope for single-photon emission computed tomography imaging. In the IC group, cells were injected by the intracoronary route into the artery supplying segments of greater perfusion defect as shown on myocardial perfusion scintigraphy. In the TE group, electroanatomical mapping was used to identify viable but dysfunctional myocardium, and transendocardial cell injections were performed. At baseline, groups did not differ in age, gender, LVEF, or NT-pro-BNP levels. The numbers of CD34+ cells were also comparable (105 ± 31 × 10^6 in the TE group vs. 103 ± 27 × 10^6 in the IC group, \( P = 0.62 \)). At 6 months, LVEF improved to a greater extent in the TE group (+8.1 ± 4.3%) than in the IC group (+4.2 ± 2.3%, \( P = 0.03 \)). The same pattern was observed for the 6-min walk test distance (+125 ± 33 m in the TE group vs. +86 ± 13 m in the IC group, \( P = 0.03 \)) and the NT-pro-BNP levels (−628 ± 211 vs. −315 ± 133 pg/ml, \( P = 0.04 \)). These results show that in patients with nonischemic DCM, transendocardial CD34+ cell transplantation is associated with better improvement in ventricular function, NT-pro-BNP levels, and exercise capacity as compared with the intracoronary route (Figure 3).

Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Baseline LVEF (%)</th>
<th>Follow-up (months)</th>
<th>Cell dose</th>
<th>Delivery route</th>
<th>LVEF change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bocchi et al. (ref. 35)</td>
<td>8</td>
<td>21.8</td>
<td>15</td>
<td>N/A</td>
<td>IC</td>
<td>+8.8%</td>
</tr>
<tr>
<td>Fischer-Rasokat et al. (ref. 33)</td>
<td>33</td>
<td>30.2</td>
<td>3</td>
<td>259 × 10^6</td>
<td>IC</td>
<td>+3.2%</td>
</tr>
<tr>
<td>Seth et al. (ref. 34)</td>
<td>41</td>
<td>22.5</td>
<td>36</td>
<td>168 × 10^6</td>
<td>IC</td>
<td>+5.9%</td>
</tr>
</tbody>
</table>

IC, intracoronary; LVEF, left-ventricular ejection fraction; N/A, not available.

Figure 2 Survival and causes of death in patients with nonischemic DCM treated by CD34+ cell therapy (stem cell group) and controls. Five-year survival as evaluated by Kaplan–Meier analysis was 2.3 times higher in the stem cell group than in controls. DCM, dilated cardiomyopathy.
CONCLUSIONS
On the basis of current evidence, CD34+ cell therapy appears to offer an important new therapeutic strategy to improve left-ventricular function and exercise capacity in patients with nonischemic DCM. Further studies should be performed to better define the underlying mechanisms and the long-term effects of such therapy. Our preliminary data on nonischemic DCM warrant further research to be conducted on whether a similar approach using selected CD34+ cells would also improve left-ventricular perfusion and function in patients with ischemic heart failure.

ACKNOWLEDGMENTS
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CONFLICT OF INTEREST
The authors declared no conflict of interest.

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Figure 3 Changes in left-ventricular dimensions and function after intracoronary and transendocardial CD34+ cell therapy in patients with nonischemic DCM. Figure displays the changes in left-ventricular ejection fraction (LVEF, a), wall motion score index (WMSI, b), left-ventricular end-diastolic dimension (LVEDD, c) and left-ventricular end-systolic volume (LVESV, d) in patients undergoing intracoronary (IC) vs. transendocardial (TE) cell therapy. Although LVEF increased in both groups, the change (6 months vs. baseline) was significantly higher in the TE group than the IC Group. Similarly, WMSI decreased more in segments receiving TE injection than those treated by IC injection. LVEDD did not change significantly in any of the groups; in the case of LVESV, changes were more favorable in the TE than in the IC group. DCM, dilated cardiomyopathy.


