In the burgeoning field of cell therapy trials for heart failure (HF), non-ischaemic dilated cardiomyopathy (NICM) has been studied much less frequently than ischaemic cardiomyopathy (ICM), for several reasons. First, the prevalence of ICM is greater than that of NICM. Second, the concept of myocardial regeneration is more readily applicable to ICM, where a well-defined region of myocyte death and scar is usually identified, rather than to NICM, where pathologic examination frequently reveals diffuse fibrosis rather than a confluent scar. Finally, NICM is not one disease, but the final phenotype of many different pathophysiological processes, some of which remain poorly understood, making it difficult to model NICM in animals. Indeed, almost all preclinical studies supporting cell therapy for HF have been conducted in models of post-myocardial infarction HF. While limited preclinical studies of cell therapy have been performed in models of NICM with defined aetiology, such as anthracycline-induced cardiomyopathy and Chagas cardiomyopathy, they are lacking in models of idiopathic dilated cardiomyopathy, which is more prevalent than the former two.

In this issue of the Journal, Martino et al. report the results of the dilated cardiomyopathy arm of the MiHeart Study, a multicentre, double-blind, placebo-controlled phase I–II trial of bone marrow mononuclear cells (BMMNCs) in patients with NICM. A total of 160 patients were randomized to intracoronary administration of placebo or BMMNCs, infused into all coronary arteries without balloon inflation. Subjects had advanced HF with a left ventricular ejection fraction (LVEF) < 35%, New York Heart Association (NYHA) class of III or IV and limited exercise capacity [maximal oxygen consumption (VO2 max) < 15 ml/min/kg]. All patients were on optimal medical therapy for at least 4 weeks prior to randomization and then throughout the study. Consistent with virtually all previous cell therapy studies, administration of BMMNCs was safe and well tolerated. Over a 12-month follow-up, there was no statistically significant benefit of BMMNC treatment with regard to LVEF (assessed by echocardiography), Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, 6-min walk test, VO2 max or NYHA classification.

The MiHeart investigators should be congratulated for this great effort and for conducting the first multicentre, double-blind, placebo-controlled trial of cell therapy in patients with NICM. MiHeart is also the largest study of cell therapy performed thus far in this population. The investigators appropriately excluded known causes of dilated cardiomyopathy, such as Chagas disease, alcohol, hypertension and cardiotoxic drugs, thereby focusing on idiopathic NICM. The cells were administered without balloon inflation, which reduces the risk associated with stem cell administration without compromising efficacy, as has been demonstrated in both experimental and clinical studies.

Unfortunately, MiHeart suffers from a number of significant weaknesses that undermine the conclusions. The attrition of 45 of the 160 patients initially treated, and their exclusion from analysis, nullifies the intention-to-treat design adopted by the investigators. Enrolment took a very long time (6 years) across 11 centres, implying a low procedural volume in at least some centres. Another weakness is the use of echocardiography instead of magnetic resonance imaging (MRI; which has become the modality of choice for assessing cardiac structure and function in cell therapy trials), particularly in the absence of an echocardiography core lab. While echocardiography could be acceptable in a phase I safety study, it is no longer acceptable in phase II efficacy studies. The lack of a central cell preparation facility is another important limitation, because it has been suggested that the beneficial effects of BMMNCs may be related to their functional properties, which in turn are heavily dependent on the cell processing protocol. In this connection, no functional test of the isolated cells was reported (e.g., migration, colony formation), raising the question of whether the cells were functionally intact. Cell viability, in itself, does not necessarily signify functional competence. Given the number and seriousness of these limitations, the results of MiHeart are not conclusive and do not disprove the hypothesis that BMMNCs may be beneficial in NICM.

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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### Table 1  Summary of the largest trials of cell therapy in non-ischaemic cardiomyopathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Cell type</th>
<th>Number of patients</th>
<th>LVEF</th>
<th>NYHA</th>
<th>Number of cells delivered</th>
<th>CD34 content</th>
<th>Delivery</th>
<th>Final assessment time</th>
<th>Final assessment modality</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD trial</td>
<td>RCT</td>
<td>BMMNCs</td>
<td>45 treated, 40</td>
<td>≤35%</td>
<td>≥II</td>
<td>1.68 ± 0.96 × 10⁸</td>
<td>2.7 ± 1.5 × 10⁸</td>
<td>Intracoronary with balloon inflated in the coronary sinus</td>
<td>28 ± 9 months</td>
<td>Echo</td>
<td>†LVEF 5.9% ≤Mortality ≤NYHA ≤QOL ≤WMSI ≤6MWD</td>
</tr>
<tr>
<td>IMPACT-DCM/Catheter-DCM trial</td>
<td>RCT</td>
<td>Cultured BMMNCs (Ixmelyocel-T)</td>
<td>39 (18 NICM) treated, 20 (11 NICM) control</td>
<td>≤30%</td>
<td>≥III</td>
<td>0.35–2.95 × 10⁸</td>
<td>Not reported</td>
<td>Intramyocardial either through mini-thoracotomy or NOGA</td>
<td>1 year</td>
<td>Echo and SPECT</td>
<td>†LVEF †MACE †NYHA †QOL †6MWD</td>
</tr>
<tr>
<td>Vrtovec et al.</td>
<td>RCT</td>
<td>CD34⁺</td>
<td>28 treated, 27</td>
<td>≤30%</td>
<td>≥III</td>
<td>1.23 ± 0.23 × 10⁸</td>
<td>1.23 ± 0.23 × 10⁸</td>
<td>Intracoronary without balloon inflation</td>
<td>1 year</td>
<td>Echo</td>
<td>†LVEF †Mortality and heart transplantation †6MWD</td>
</tr>
<tr>
<td>Vrtovec et al.</td>
<td>RCT</td>
<td>CD34⁺</td>
<td>55 treated, 55</td>
<td>≤30%</td>
<td>III</td>
<td>1.13 ± 0.26 × 10⁸</td>
<td>1.13 ± 0.26 × 10⁸</td>
<td>Intracoronary without balloon inflation</td>
<td>5 years</td>
<td>Echo</td>
<td>†LVEF †Mortality †6MWD</td>
</tr>
<tr>
<td>Vrtovec et al.</td>
<td>RCT</td>
<td>CD34⁺</td>
<td>40 patients randomized to intracoronary (20) or transendocardial (20) routes, no control</td>
<td>&lt;40%</td>
<td>III</td>
<td>1.03 ± 0.27 × 10⁸</td>
<td>1.03 ± 0.27 × 10⁸</td>
<td>Intracoronary without balloon inflation or intramyocardial</td>
<td>Echo</td>
<td>6 months</td>
<td>†LVEF in TE &gt;IC †WMSI in TE &gt;IC †6MWD TC &gt;IC</td>
</tr>
<tr>
<td>INTRACELL trial</td>
<td>RCT</td>
<td>BMMNCs</td>
<td>19 treated, 10</td>
<td>&lt;40%</td>
<td>≥III</td>
<td>1.06 ± 0.43 × 10⁸</td>
<td>1.5 ± 0.7% of cells</td>
<td>Intramyocardial through mini-thoracotomy</td>
<td>Echo</td>
<td>9–12 months</td>
<td>†LVEF †Postoperative mortality †NYHA †QOL †6MWD</td>
</tr>
<tr>
<td>TOPCARE-DCM trial</td>
<td>Treated cohort</td>
<td>BMMNCs</td>
<td>33 treated, no</td>
<td>≤40%</td>
<td>I–III</td>
<td>2.59 ± 1.35 × 10⁸</td>
<td>Not reported</td>
<td>Intracoronary (stop-flow technique)</td>
<td>3 months</td>
<td>Echo</td>
<td>†LVEF 3.2</td>
</tr>
</tbody>
</table>

† increased; ↓ decreased; ↔ no change; BMMNCs, bone marrow mononuclear cells; IC, intracoronary; MACE, major adverse cardiac event; NICM, non-ischaemic cardiomyopathy; NYHA, New York Heart Association class; QOL, quality of life; RCT, randomized controlled trial; 6MWD, 6-min walk distance; TE, transendocardial; WMSI, wall motion score index.
So, what is the current status of cell therapy in patients with NICM? Table 1 summarizes all of the randomised controlled trials (RCTs) of cell therapy conducted to date in this patient population. Most studies were small and non-randomized; only six RCTs have been conducted (as compared with >30 trials in patients with ICM). TOPCARE-DCM was a proof-of-concept cohort study of 33 patients (with no controls) with NICM, LVEF ≤40% and NYHA class I–III who received intracoronary infusion of BMMNCs using the stop-flow technique. At 3 months, there was a significant improvement in LVEF, regional wall motion and microvascular function. In the Autologous Bone Marrow Cells in Dilated Cardiomyopathy (ABCD) trial, 85 patients with NICM, LVEF ≤35% and NYHA class ≥II were randomly allocated to intracoronary infusion of BMMNCs (without the stop-flow technique, but with concomitant balloon inflation in the coronary sinus to slow the transit of cells) or control (standard therapy). At 3-year follow-up, LVEF was increased in the cell-treated group but not in the control group. In the INTRACELL study, 30 patients with NICM, LVEF <35% and NYHA class III or IV were randomized to standard of care or intramyocardial injection of BMMNCs via mini-thoracotomy. MRI showed no improvement in LVEF in the cell-treated group. A recent paper reported the results of the IMPACT-DCM/Catheter-DCM studies, in which a mixed population of ischemic (30 subjects) and non-ischemic (29 subjects) cardiomyopathy patients was treated with BMMNCs enriched in mesenchymal stromal cells (MSCs) and M2-like macrophages or allocated to the control group (standard of care). The cells were administered intramyocardially through a mini-thoracotomy or via catheter-based transcatheter injections. At 1 year there was no overall improvement in major adverse cardiac events in the cell-treated patients and no improvement in LVEF and functional parameters in the cell-treated patients with NICM. Other small, non-randomized studies have mostly reported improvement in functional status but inconsistent results in terms of LVEF.

A series of important studies was conducted by Vrtovec et al.5–7 (Table 1). Their initial report described a RCT of 55 patients with NICM, LVEF ≤30% and NYHA class ≥III assigned to treatment with CD34+ cells or control (optimal therapy). The cells were administered intracoronarily without balloon inflation. At 1 year, the cell-treated group exhibited a significant improvement in LVEF, functional parameters and the combined endpoint of mortality and heart transplantation. In the next trial, the investigators randomized 110 patients with NICM, LVEF <30% and NYHA class III to intracoronary infusion of CD34+ cells (no balloon inflation) or control (optimal therapy). At the 5-year follow-up there was a significant reduction in mortality (14% vs. 35%, P = 0.01) in the cell-treated group, concomitant with a significant improvement in LVEF up to year 3 and in exercise capacity throughout the follow-up period. Finally, in a third study designed to compare intracoronary and transcatheter cell delivery, 40 patients with NICM, LVEF <40% and NYHA class III were randomized to receive the same number of CD34+ cells by either route. At 6 months, LVEF and exercise capacity increased in both groups but the increase was greater in the transcatheterically treated group. It is important to note that in all the above studies, Vrtovec et al. delivered 80–140 million CD34+ cells to the artery or region corresponding to a perfusion defect (reduced tracer accumulation) detected by myocardial perfusion scintigraphy.

There are many potential reasons for the seemingly opposite results of the current study and the work by Vrtovec et al.5–7 In contrast to MiHeart, the studies by Vrtovec et al. were mostly single centre and not blinded or placebo controlled. A major difference is the cell product: Vrtovec et al. administered a pure population of stem cells (CD34+ cells), which have a reported ability to promote angiogenesis in patients with refractory angina and critical limb ischemia, whereas Martino et al.3 administered unfractionated BMMNCs, only a small fraction of which (2–3%) are CD34+. As a result, the number of CD34+ cells administered to patients was ~20–30-fold higher in the Vrtovec et al. studies than in MiHeart. Furthermore, Vrtovec et al. injected the cells selectively into the regions with a perfusion defect, and thus may have delivered higher numbers of effector cells to the target regions, whereas in the MiHeart study, cells were infused throughout the ventricle. In view of these facts, the present study does not disprove the potential therapeutic utility of CD34+ cells. Given the promising results of Vrtovec et al., a rigorous multicentre study is needed to conclusively assess the therapeutic potential of CD34+ cells in patients with NICM.

Other trials are on the horizon. CEP-41750 (NCT02032004) is a large phase III, randomized, double-blind, placebo-controlled trial of allogeneic MSCs in 1730 patients with dilated ischaemic and non-ischaemic cardiomyopathy. This and other ongoing studies will shed light on the efficacy of cell therapy in patients with NICM.

In conclusion, the efficacy of CD34+ cells in NICM remains unknown because a conclusive trial has yet to be performed. Scientific working hypotheses cannot be refuted on the basis of inadequate evidence. As is the case for ICM, therapeutic nihilism is not the way forward. The utility of cell therapy in NICM will not be ascertained by halting clinical research, but by conducting well-designed trials that overcome the limitations of the studies conducted thus far.

Conflicts of interest: The authors have no conflicts of interest.

References


