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Stem cells for cardiac repair—should we be cautious?

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We read the Review by Behfar *et al.* (Cell therapy for cardiac repair—lessons from clinical trials. *Nat. Rev. Cardiol.* **11**, 232–246; 2014)[1] with great interest. We would like to highlight some important studies and meta-analyses that were not discussed in the original Review.

Many clinical trials using bone marrow-derived stem cells (BMSCs) for cardiac repair have been published in the past decade,[1] and thousands of patients have been enrolled in such trials.[2] Whereas the safety and feasibility of BMSC-based treatments has been established, the efficacy has been inconsistent.[3–6] Only a small number of participants have been enrolled into most studies, but some meta-analyses have, nevertheless, been performed to evaluate the benefit of BMSC therapy for cardiac repair.[7–9] For example, in one meta-analysis the investigators included 50 studies (a total of 2,625 patients), and reported that BMSCs improved left ventricular ejection fraction (LVEF), reduced infarct size, and limited remodelling in patients with ischaemic heart disease (IHD), and that these benefits seemed to persist during long-term follow-up.[8] Similarly, the authors of a 2014 Cochrane Systematic Review, which included 23 randomized controlled trials involving 1,255 participants, reported that BMSC treatment can improve LVEF, mortality, and performance status in the long term (after at least 1 year) in individuals with IHD and heart failure.[9] Meta-analyses are considered the highest level of evidence and might have a major effect on future health policy decisions; therefore, ensuring their accuracy is of paramount importance. Although these studies were not discussed in the Review by Behfar *et al.*[1] many clinical researchers interested in this field will refer to these meta-analyses and feel optimistic about the results. However, these results might be misleading.

First, the quality of meta-analysis depends on the quality of the trials included in the study. However, many of studies of BMSC-based cardiac repair were statistically underpowered, preliminary, and suboptimally designed (for example, nonrandomized, open label, or non-controlled).[4,6,8] Furthermore, substantial differences exist between these trials, in that the investigators used different cell types, delivery methods, cell injection numbers, study designs, baseline characteristics of patients, and cardiac imaging modalities. Results of meta-analyses can be misleading if these differences are not accounted for.[10] Secondly, many trials of BMSCs for cardiac repair have unexplained discrepancies that cast doubt on their validity.[11] For example, in one analysis the investigators reported >600 discrepancies (defined as two or more facts that are logically or mathematically incompatible) in 133 reports from 49 different trials.[12] More importantly, a significant association between the number of discrepancies and improvement in LVEF was reported.[12] Only 10% of the trials included in the meta-analysis had no discrepancies, and these showed no improvement in LVEF.[12] Avoiding discrepancies in clinical trial reports is difficult; however, these findings remind us that many studies in the field might have inflated effect sizes, and trials with more unexplained discrepancies seem to have a greater improvement in LVEF than those with fewer discrepancies.[13] For example, in trials with 1–10 discrepancies, LVEF was improved by 2.1%; with 11–20 discrepancies, LVEF improved by 3.0%; with 21–30 discrepancies, LVEF improved by 5.7%; and in trials with >30 discrepancies, LVEF improved by 7.7%.[13] Unfortunately, this situation is not limited to BMSCs, but is also observed with stem cells from other sources. For example, the integrity of the data in the SCIPIO study, in which encouraging results were reported for cardiac stem cell therapy in patients with heart failure, was also questioned by the institution at which the trial was conducted.[14]

In conclusion, we believe that preliminary clinical trials of BMSC therapy for heart disease might be flawed and have inflated effectiveness. Consequently, clinicians should be cautious in their interpretation of these results, and large, appropriately designed, placebo-controlled studies are needed. We look forward to the results of the ongoing BAMI trial, in which investigators aim to include 3,000 patients with acute myocardial infarction and will provide more reliable evidence.[15]

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Competing interests
The authors declare no competing interests.

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