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Mobilization of bone marrow-derived stem cells after myocardial infarction and left ventricular function: simply effects of optimized drug treatment?

We read with interest the recent article by Leone *et al.*[1] regarding the mobilization of $CD34^+$ cells from bone marrow after myocardial infarction (MI) and the effects on left ventricular function.

ACE-inhibitors and statins are administered on a routine basis to patients with acute MI and are likely to contribute to enhance levels of $CD34^+$ cells.[2,3] Indeed, the present paper identifies the use of statins after MI as the best independent predictor of increased mobilization of stem cells. In animal models, however, Nygren *et al.*[4] were unable to detect any increase in peripheral blood progenitor or stem cell activity following MI when animals were without drug treatment. These findings could not be attributed to the trapping of potentially mobilized cells, as no progenitor cells were detected in the infarcted myocardium or in the spleen. Likewise, the findings of Leone *et al.*[1] that 1 year after MI the levels of $CD34^+$ cells were still three-fold higher when compared with the time before MI are difficult to explain by MI or acute release of inflammatory mediators which mobilize stem cells such as VEGF. We postulate that these findings are the result of an optimized drug therapy of patients following MI, including the use of statins, ACE-inhibitors, and other potentially stem cell-mobilizing agents. The finding of Leone *et al.*[1] that the amount of mobilized stem cells is highly variable and does not correlate to the size and severity of MI also points to a multimodal regulation of stem cell mobilization after MI. Interestingly, the finding that $CD34^+$ cell concentration was an independent predictor for global and regional improvement of the left ventricular function 1 year after MI, but not early after MI, may suggest that $CD34^+$ cells could be used as a diagnostic tool to identify patients with a high risk of developing heart failure after MI and who should therefore receive specifically intensive drug therapy.

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Mobilization of bone marrow-derived stem cells after myocardial infarction and left ventricular function: simply effects of optimized drug treatment?: reply

We thank Drs Thum and Bauersachs for their interest in our article.[1] They correctly note that although we found transient mobilization of bone marrow-derived stem cells (BMSCs) after acute myocardial infarction (AMI) in man, Nygren *et al.*[2] failed to find mobilization of BMSCs after AMI in mice. Interestingly, two previous studies in the 'human' model have confirmed our observation of a transient increase in CD34+ cell count following AMI.[3,4] This discrepancy between clinical and experimental data might well be explained by medical treatment given to patients; in particular, statins have been shown to mobilize BMSCs.[5] Accordingly, in our study, statins were independent predictors of BMSCs release after MI at the multivariable analysis. However, the model could explain only 27% of variability, thus suggesting that other, perhaps genetically determined, factors are likely to play an important role in determining the degree of BMSCs mobilization after AMI in man. In addition, among patients with AMI on statins during hospitalization, CD34+ cell count was higher than that observed in patients with stable angina and in patients with AMI reassessed at follow-up (all on statins) (8.80 ± 7.26 vs. 3.80 ± 2.12 cells/μL vs. 3.34 ± 2.70, $P < 0.001$).

On the basis of our observation that CD34+ cell count was an independent predictor of global and regional improvement of LV function at 1 year after AMI, Drs Thum and Bauersachs propose that CD34+ cells could be used as a diagnostic tool for the identification of patients at higher risk of developing heart failure after AMI. We believe that this conclusion is still premature as the results of our study need to be confirmed in much larger populations. The main goals of our study were to confirm BMSCs mobilization after AMI and to establish whether mobilization was associated to changes in left ventricular function after AMI. Our study shows that 'good mobilizers' of BMSCs after AMI exhibit a better evolution of post-AMI dysfunction than that observed in 'poor mobilizers'. These findings represent a strong stimulus to investigate pharmacological strategies which are able to transform 'poor mobilizers' into 'good mobilizers'. Indeed, this approach might turn out to be more

efficient and safer than that based on a single intracoronary or intramyocardial administration of stem cells, which is currently pursued by several groups.[6]

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Critical role of bare-metal stent controls in trials of drug-eluting stents

We have read with interest the randomized trial comparing sirolimus-eluting stents (Cypher, Cordis) to thin-strut bare-metal stents (BMSs) (BeStent 2, Medtronic).[1] Indeed, as the authors have previously pointed out, any novel treatment should be compared with the best performing control treatment, and thus, thin-strut BMS were the only correct benchmark for the thorough appraisal of drug-eluting stents (DESs).

In addition, results of the study from Pache *et al.*[1] provide the first means to accurately test a novel and still controversial analytic tool, the adjusted indirect comparative meta-analysis.[2] We have recently shown that, using their respective BMS control group as reference, different DESs can be indirectly compared by means of meta-analysis.[3] Yet, any such comparison between DESs [namely Cypher vs. Taxus (Boston Scientific)] is based on the assumption that differences between their respective BMS controls [Bx Velocity (Cordis) and

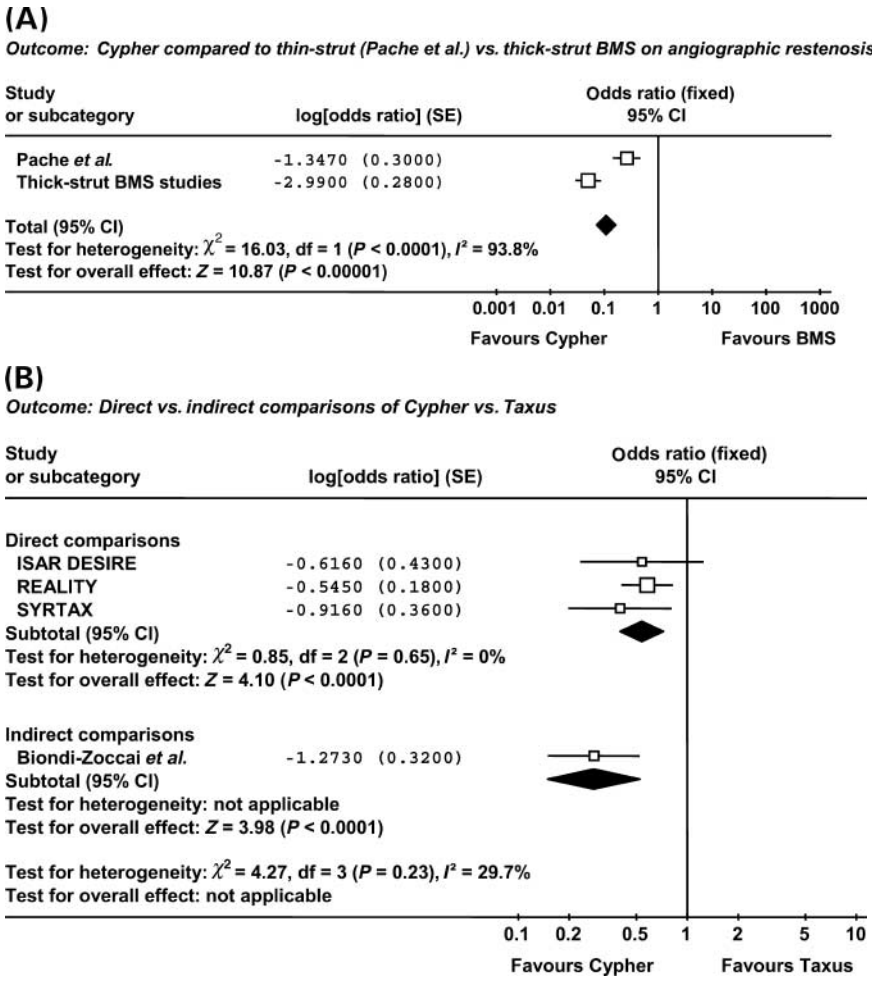

Figure 1 (*A*) Testing the consistency between the odds ratio for the comparisons: (i) Bx Velocity (a thick-strut BMS) vs. Cypher (a polymer-based sirolimus-eluting Bx Velocity) and (ii) BeStent 2 (a thin-strut bare-metal stent) vs. Cypher. Heterogeneity and inconsistency tests suggest a strikingly different beneficial effect when using Cypher vs. Bx Velocity than when using Cypher vs. BeStent 2 [highly significant ($P < 0.01$) for heterogeneity and severe inconsistency ($I^2 > 75\%$)], thus demonstrating that the use of a thick-strut BMS control is likely to overestimate the benefits of Cypher. (*B*) Preliminary results of a meta-analysis on the risk of binary angiographic restenosis with Cypher (a polymer-based sirolimus-eluting stent) vs. Taxus (a polymer-based paclitaxel-eluting stent) and pooling the latest direct head-to-head randomized trials. Combined estimates suggest a significant reduction in angiographic restenosis favouring Cypher ($P < 0.0001$ for the overall effect) and thus, are in agreement with previous predictions based on adjusted indirect comparisons dating back as early as June 2004.[3]