


The striking low cell recoveries reported in the ASTAMI trial, a productive bone marrow harvest may also be critical. Bone marrow usually contains >20,000 total nuclear cells (TNCs)/μL. Ficoll-Hypaque-based density gradient separations at a density of 1.077 g/L are reported to yield TNC recoveries of 20-30%. From 50 mL bone marrow, one would expect about 10⁷ TNCs and 2-3 × 10⁸ TNCs after density gradient separation. With a mean cell number of 2.36 × 10⁸ TNCs, the REPAIR-AMI trial very much is in line with the expected cell recoveries, whereas only one-third of the cells (8.7 × 10⁷ cells) was recovered from identical volumes of bone marrow aspirates in the ASTAMI trial. We believe that it is mandatory to identify the underlying factors of such discrepancies and to establish the quality standards of cellular products for future clinical trials. Ultimately, this will lead to the provision of safe and effective investigational medicinal products to the patients benefit.

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The REPAIR-AMI and ASTAMI trials: cell isolation procedures: reply

It obviously escaped the notion of Egeland and Brinchman that the protocols additionally differ with regard to the washing steps and buffer components used in the density gradient separation of the bone marrow. Our study has been conducted to elucidate factors in the preparation of bone marrow cells for intracoronary application that might influence the cell quality and hence the therapeutic benefit. Using split bone marrow samples, our side-by-side comparison of the REPAIR-AMI and ASTAMI protocols indicates that minor changes like washing steps or the use of sodium chloride solution containing heparinized plasma may result in reduced cell recovery and function. While these factors might in part explain the striking low cell recoveries reported in the ASTAMI trial, a productive bone marrow harvest may also be critical. Bone marrow usually contains >20,000 total nuclear cells (TNCs)/μL. Ficoll-Hypaque-based density gradient separations at a density of 1.077 g/L are reported to yield TNC recoveries of 20-30%. From 50 mL bone marrow, one would expect about 10⁷ TNCs and 2-3 × 10⁸ TNCs after density gradient separation. With a mean cell number of 2.36 × 10⁸ TNCs, the REPAIR-AMI trial very much is in line with the expected cell recoveries, whereas only one-third of the cells (8.7 × 10⁷ cells) was recovered from identical volumes of bone marrow aspirates in the ASTAMI trial. We believe that it is mandatory to identify the underlying factors of such discrepancies and to establish the quality standards of cellular products for future clinical trials. Ultimately, this will lead to the provision of safe and effective investigational medicinal products to the patients benefit.

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Are acute coronary syndromes risk models too complex?

The article by Yan et al. measured the discriminatory performances of the TIMI, PURSUIT, and GRACE risk scores (RS) and suggested that they offered better prediction of in-hospital and 1-year mortality than that of global risk assessment by physicians. Moreover, the study revealed an inverse relationship between estimated risk and early invasive management when patients were stratified by RS, an important finding recently highlighted by Fox et al.in the study by Yan et al., revascularization was more frequently based on physicians’ global assessment, signifying that RS are not being used appropriately for estimating risk. Perhaps, this is because they are too complex.

The Evaluation of the Methods and Management of Acute Coronary Events (EMMACE) risk model is a community-derived risk model for patients presenting with ST-elevation myocardial infarction. It is a simple model that uses patient age, admission heart rate, and systolic blood pressure to predict 30-day mortality [C-index = 0.76 (95% CI 0.72–0.79)]. The EMMACE model has good discriminatory performance because it relies on age and haemodynamic predictors. In the article by Yan et al., RS which included these variables (GRACE and PURSUIT rather than TIMI) also offered improved discriminatory capacity. We have corroborated this using 100,686 patients from the Myocardial Infarction National Audit Project database (MINAP), an extensive community-based cohort of patients hospitalized in UK and Wales with ACS:

- RS for 14-day mortality = 0.58 (0.57–0.59, P < 0.001), GRACE RS for in-hospital mortality = 0.80 (0.80–0.81, P < 0.001), GRACE RS for 6-month mortality = 0.80 (0.79–0.80, P < 0.001), and PURSUIT for 30-day mortality = 0.81 (0.78–0.81, P < 0.001). A concern with the GRACE and PURSUIT RS is that they rely on the collection of multiple variables when it is known that secondary abstraction of difficult-to-obtain key clinical findings adds little to the predictive power of RS. In the article, Yan et al. have inclined to the view that RS complexity may also be prohibitive to their use. Perhaps, RS that rely on a few easily recordable variables may be used more frequently by physicians and also allow as good a risk prediction as more complex scores?

Although the findings by Yan et al. are important, a more appropriate external validation of the RS would have considered their performance over their original risk prediction periods (TIMI, 14 days; PURSUIT, 30 days; and GRACE, in-hospital and 6 months) and outcomes (TIMI—composite of death, revascularization, and re-infarction at 14 days). Second, while the authors identified a significant correlation between the three RS, one would expect this because the authors have compared similar methods (i.e. RS designed to evaluate ACS mortality) over a range of values. The resultant tests of significance are therefore not relevant since it would be unusual that the RS were not related.
References


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Are acute coronary syndromes risk models too complex? reply

We thank Drs Gale and Manda for their interest in our study.1 We believe it is important to explore why validated risk scores are often not applied in the ‘real world’, and concur that their perceived complexity may constitute the greatest barrier to more widespread use. However, our findings should not be construed as promoting one risk score over another—rather, our study highlights the important and inevitable tradeoffs between complexity and accuracy.

We agree that age and haemodynamic variables are the most powerful prognosticators. Although risk scores incorporating only these variables are purported to be ‘simpler’,2 in reality, their application still requires the use of a calculator and a nomogram for conversion into an estimated risk of adverse events. Thus, it remains unclear whether these ‘simpler’ risk scores are necessarily more user-friendly and less time-consuming, compared with the more ‘sophisticated’ ones. For example, the GRACE risk score calculator, which consists of readily available clinical information, is easy to use, and can be readily downloaded onto a PDA or accessible on the website.3

A major strength of the GRACE risk score is its applicability across the full spectrum of acute coronary syndromes. Because reperfusion therapy should be promptly administered to all patients with ST-elevation myocardial infarction in the absence of contraindications (although the optimal type of reperfusion therapy may depend on clinical presentation and local availability), accurate risk stratification is more relevant in the initial management of non-ST-elevation acute coronary syndrome, which represents a more heterogeneous condition with a variable prognosis.

We chose all-cause mortality as our primary study outcome because it was the most robust endpoint. Furthermore, surveillance for myocardial (re-)infarction and the decision to proceed with ‘urgent’ revascularization, especially in the short-term, were probably influenced by physicians’ risk assessment. Finally, randomized controlled trials have shown that an early invasive strategy improves long-term outcome.4 Therefore, risk stratification tools that can identify patients with worse long-term outcome are most useful in guiding treatment decisions. Of note, the TIMI risk score demonstrates better discrimination for mortality than the composite endpoint, even in the original derivation cohort.5 Thus, our conclusions appear to be robust and not critically dependent on the chosen endpoint.

With respect to the correlations among the risk scores and physicians’ assessment, we agree that the highly significant P-values were expected. However, the important point is that there were only weak to moderate correlations—a substantial proportion of patients would be classified into different risk categories, according to these three risk scores and physicians’ assessment. This may account for the treatment-risk paradox observed.6

The most important implication of our study is that systematic application of any validated risk score in routine clinical practice will likely improve risk stratification, and consequently, management decisions and patient care. We believe that it is worth ‘taking the trouble’ to apply these risk scores, which can effectively supplement clinical judgment.

**References**


4. Mehta SR, Cannon CP, Fox KA, Wallentin L, Laden A, Goodman SG. A major strength of the GRACE risk score is its applicability across the full spectrum of acute coronary syndromes. Because reperfusion therapy should be promptly administered to all patients with ST-elevation myocardial infarction in the absence of contraindications (although the optimal type of reperfusion therapy may depend on clinical presentation and local availability), accurate risk stratification is more relevant in the initial management of non-ST-elevation acute coronary syndrome, which represents a more heterogeneous condition with a variable prognosis.

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