Application of a sex-specific GRACE score in practice

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Authors' reply

We agree with Giacomo Cafaro and colleagues that comparing different types of cardiovascular outcomes occurring in people with systemic sclerosis to those occurring in patients with other autoimmune diseases would be of interest. However, our study[1] included relatively few participants with systemic sclerosis and even fewer cardiovascular events, precluding a meaningful analysis of individual outcomes.[1]

Satoshi Funada and colleagues also highlight potential differences in types of cardiovascular outcomes across the range of autoimmune diseases studied. Again, although we agree in principle, in practice because we investigated 19 autoimmune diseases and 12 cardiovascular outcomes, this created 228 individual result permutations (456 when one considers adjusted and non-adjusted analyses). Reporting all of these individual findings was simply not practical. However, when preparing our manuscript, we did examine individual disease associations and did not identify major heterogeneity across the range of autoimmune diseases and cardiovascular outcomes examined. As explained for systemic sclerosis, the smaller sample sizes and numbers of events included in any individual analysis made resultant findings less statistically robust than the results from the combined analyses across all cardiovascular diseases. The goal of our analysis was to harness the strength of the large overall cohort of patients with autoimmune diseases to show a clear and consistent association with a broad range of cardiovascular outcomes, accepting that more detail about individual diseases and specific outcomes would be welcome and hopefully will come from the future investigations of other populations.

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Application of a sex-specific GRACE score in practice

We wish to congratulate Florian A Wenzl and colleagues[1] for their important analysis and update of the Global Registry of Acute Coronary Events (GRACE) score to address observed differences in the prediction of in-hospital mortality following non-ST-segment elevation acute coronary syndromes between women and men. If this state-of-the-art prediction model is to reduce sex inequalities in care, then additional information is needed to ensure the GRACE 3.0 score is consistently applied in practice.

In the prediction model cardiac troponin is incorporated as a binary feature, but it was not clear what thresholds were used to define an elevated cardiac troponin. The Universal Definition of Myocardial Infarction recommends the use of a sex-specific 99th percentile as the diagnostic threshold. For most high-sensitivity cardiac troponin assays, the 99th percentile is two times lower in women than men.[2] The implementation of sex-specific thresholds has increased the identification of women with myocardial injury and infarction in practice.[3,4] We seek clarification as to whether an elevated cardiac troponin was defined using the recommended sex-specific diagnostic threshold. If sex-specific thresholds were not used, it would be informative to compare discrimination using a sex-specific and overall troponin threshold separately. Furthermore, the mechanisms of myocardial infarction differ between women and men, with women more likely to have type 2 myocardial infarction due to coronary artery dissection or vasospasm. Given that previous studies have shown that the GRACE 2.0 score does not perform as well in type 2 myocardial infarction as it does in type 1 myocardial infarction,[5] it would be important to report performance stratified by the subtype of myocardial infarction or to publish the prediction model code to enable further external validation.

NLM has acted as a consultant for Abbott Diagnostics, Siemens Healthineers, Roche, and LumiraDx. DMK declares no competing interests.

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Authors' reply

We thank Dorien M Kimenai and Nicholas L Mills for their interest in our Article.[1] Indeed, sex-specific diagnostic thresholds of troponin were introduced into the Universal Definition of Myocardial Infarction in 2012 during the recruitment period of our study and have led to increased diagnostic sensitivity in the decade since.[2]

However, evidence suggests that sex-specific cutoff values for troponin add little to no value to the prognostication of outcomes in patients with acute coronary syndromes.[3–6] Accordingly, there is no recommendation regarding the definition of the 99th percentile of troponin in the Global Registry of Acute Coronary Events (GRACE) scoring system to date. Depending on the time of enrolment, the specific assay used, and the local hospital practice, different thresholds of troponin could have been used in participating study centres across England, Wales, Northern Ireland, and Switzerland. As suggested, we did an exploratory analysis and found no effect of sex-specific (women: 9·0 ng/L, men: 15·5 ng/L) cutoffs on the discriminative ability of GRACE 3.0 compared with a uniform (14·0 ng/L) cutoff value using unseen data from the Swiss SPUM-ACS cohort in which centrally measured high-sensitivity troponin T concentrations (assay produced by Roche Diagnostics, Indianapolis, IN, USA) are available (DeLong's test p=0·4795).

We agree that there are important sex differences in the pathophysiology of non-ST-segment elevation acute coronary syndromes and hope that GRACE 3.0 will improve clinical risk assessment by accounting for sex-specific disease characteristics. Further validation of the updated GRACE score (version 3.0) using its web calculator is encouraged. Regarding analyses in selected subgroups, we note that the main clinical application of the GRACE score is the early stratification of patients towards invasive management thus limiting the value of analyses according to pathophysiological entities, which are typically differentiated via invasive angiography.

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Breast radiotherapy for non-low-risk ductal carcinoma in situ: to boost or not to boost?

For the **GRACE score web calculator** see https://www.grace-3.com/

Radiotherapy and tumour bed boost for ductal carcinoma in situ (DCIS) of the breast is the subject of many debates in tumour boards and radiotherapy departments. We thank Boon H Chua and colleagues[1] for their well designed randomised trial comparing fractionation schedules and boost for non-low-risk DCIS. A boost lowered the 5-year local recurrence rate from 7·3% to 2·9%, resulting in 4% fewer salvage mastectomies compared with the no-boost group; however, this was at the cost of an increase of 15% acute and 11% late grade 2 or more events. Furthermore, a boost increases the intrathoracic dose and a median follow-up of 6·6 years might be too short to detect long-term cardiac events or lung cancer events.[2]

The reported high grade 2 or more acute and late toxicity events, 43% (acute) and 24% (late toxicity) for the no-boost versus 58% (acute) and 35% (late toxicity) for the boost group, might be related to the large boost zone and use of older techniques.[1] The boost area was large: clips and seroma with a 10 mm margin for microscopical extension when surgical margins were less than 10 mm and an additional margin of 5–10 mm for set-up uncertainties and respiration. Advanced treatment techniques[3] or position alterations[4] with a simultaneously integrated photon boost (ie, daily boost dose during whole breast irradiation) have been shown to have a lower toxicity profile, reduced treatment time, and improved patient comfort and health economics.

Further research is needed and gene expression analysis[5] seems promising to personalise breast radiotherapy for DCIS. An individualised treatment approach