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Different inflammatory pathways underlying cardiovascular risk in secondary prevention

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This commentary refers to 'Targeted proteomics improves cardiovascular risk prediction in secondary prevention', by N.S. Nurmohamed *et al.*, https://doi.org/10.1093/eurheartj/ehac055 and the discussion piece 'Targeted proteomics improves cardiovascular risk prediction in secondary prevention: the impact of statin treatment?', by P. Giral, https://doi.org/10.1093/eurheartj/ehac329.

Giral raises two questions regarding our recently published manuscript 'Targeted proteomics improves cardiovascular risk prediction in secondary prevention'.[1] First, he notes that there could be a bias introduced by the use of statin therapy which is known to lower C-reactive protein (CRP). Secondly, he questions why lipid lowering therapy (LLT) use was not present in the clinical risk model which was used as comparison to the protein model.

In the exploratory analysis of our study, we assessed inflammatory pathways by dividing patients into high or low residual inflammatory risk profiles based on baseline CRP levels. Patients from the Second Manifestations of ARTerial disease (SMART) were divided in a high CRP (>2 mg/L) and low CRP (≤2 mg/L) group. Since statins reduce CRP, Giral questions whether statin use could have introduced a bias in the exploratory analysis. Therefore, we compared the frequency of statin use in patients with high and low CRP. There were slightly more statin users in the low CRP group (67%) than in the high CRP group (59%) in SMART. This small difference in statin users is unlikely to have impacted our 'additional pathway' analysis, even more so since the vast majority of patients in both groups was using statins. The differences observed between major inflammatory pathways underlying atherosclerotic cardiovascular disease (ASCVD) risk therefore remain insightful. We hope that future studies will further investigate the exploratory finding of neutrophil-signaling related pathways in low CRP patients.

The second question raised by Giral concerns the absence of lipid lowering drug use in the clinical risk model which was compared with the protein model. To ensure a fair comparison of the newly developed protein risk model with currently used clinical risk algorithms in our study, a clinical risk model was composed with variables from the SMART, Reynolds as well as the Framingham risk score[2–4] and was constructed with similar machine learning algorithms as the protein model. Importantly, the SMART, Reynolds as well as the Framingham risk score, were developed with data from very large observational cohorts. Nevertheless, the use of LLT was not included in any of these risk scores, most likely reflecting the fact that the vast majority of, if not all, secondary prevention patients are prescribed LLT. Thus, it is unlikely that LLT use has discriminative value for ASCVD risk, and therefore we did not include this variable in our clinical risk model.

In summary, the major conclusion of our study upholds that a proteomics-based risk model is superior to the traditional clinical models in predicting recurrent ASCVD risk, with a predominant role of neutrophil-related pathways contributing in low CRP patients.

Conflict of interest: N.S.N. and J.M.K. have no conflicts of interest. E.S.G.S. reports adboard/lecturing fees paid to institution by Amgen, Sanofi-Regeneron, Esperion, NovoNordisk, Merck, Akcea-Ionis and Astra-Zeneca; none of which are related to the present research.

Data availability

Data availability from SMART and ATHERO-EXPRESS can be requested via the principal investigators of those study cohorts (respectively f.l.j.visseren@umcutrecht.nl and dkleijn@umcutrecht.nl).

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