Response to 'Correspondence on 'Impact of rheumatoid arthritis on major cardiovascular events in patients with and without coronary artery disease' by Jong *et al*

We appreciate the interest and comments by Jong *et al*¹ concerning our study: 'Impact of rheumatoid arthritis on major cardiovascular events in patients with and without coronary artery disease'.² We would like to clarify and discuss the issues raised by Jong *et al*.¹ The comments by our colleagues highlight many inherent limitations of an epidemiological study that may provide considerations for a future prospective randomised trial.

First, Jong *et al*¹ note that that low-density lipoprotein cholesterol (LDL-C) level was not part of the baseline characteristics. The reason is that biochemical data are currently not available from the national Danish Registries. While we do agree with our colleagues that LDL-C is a player in the pathogenesis of coronary artery disease (CAD) and that LDL-C is an independent predictor of cardiovascular events, there are several more important factors that were included. These are age, gender, heart failure, hypertension, diabetes, smoking and most importantly, the presence or absence of CAD.^{3–5} Further, most of those with CAD were subsequently treated with statins, which reduces the baseline LDL-C levels and modifies the influence of this baseline characteristic.⁶ We used statin treatment as a proxy for hypercholesterolaemia in the adjusted multivariate regression analysis.

Second, Jong *et al*¹ raise an interesting question regarding the impact of high-intensity versus low-intensity statins. Simvastatin was the primary statin used among all patients with rheumatoid arthritis (RA) in this study (44%, median dose 40 mg/daily), followed by high-intensity statins, atorvastatin (19%, median dose 40 mg/daily) and rosuvastatin (3%, median dose 10 mg/daily). It remains an open question whether early initiation of statin treatment will affect long-term outcomes in patients with RA and no CAD, and whether high-intensity versus low-intensity statin treatment will make a difference.⁷ In the presence of CAD, however, statin treatment will aim to reach the levels dictated by the guidelines issued by scientific societies.

Third, Jong *et al*¹ speculate that treatment compliance rates for patients with RA may have been suboptimal. However, the baseline medical treatment, based on prescription dispensations, did not show any significant differences in filling of prescriptions of aspirin, ADP-inhibitor and statins.²

The fourth and final comment address that our study was based on a coronary angiography cohort. We agree, as also stated in our original publications,^{2 8–10} that this is a potential limitation. Since we aimed to assess the impact of CAD on long-term future events, we needed to look at patients who had undergone coronary angiography. This may have introduced selection bias, since patients with RA are more likely to be referred to coronary angiography. However, compared with the general population, patients with no CAD by coronary angiography have a lower risk of myocardial infarction and similar mortality.¹¹ Propensity score matching is one way of adjusting for potential baseline differences but it is only prospective randomised clinical trials that has the potential to remove unmeasured confounding.

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