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PCSK9 antagonists and inflammation

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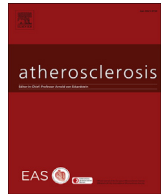
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To the Editor

In their recent contribution to *Atherosclerosis*, Tang et al. [1] have hypothesized that a PCSK9 gene interference could directly suppress atheroma development by decreasing vascular inflammation, suggesting that this might be the protective mechanism of PCSK9 inhibitors (PCSK9i) in coronary patients. The major end-point trials do not clearly indicate that an anti-inflammatory activity of both bococizumab [2] and evolocumab [3] may be responsible for the observed coronary prevention, while in a combined analysis of these trials, the impressive LDL-cholesterol reductions appeared to be definitely responsible for the lower cardiovascular outcomes, with a nearly identical effect on risk as that of statins [4]. An as yet not underlined finding of the bococizumab (SPIRE-1 and SPIRE-2) [2] and evolocumab trials was the absence of changes in high-sensitivity C-reactive protein (hsCRP) levels [3]. These findings confirm the results of a careful meta-analysis from many trials with PCSK9i, showing a lack of activity on CRP levels (evolocumab: weighed mean difference (WMD) 0.002 mg/L; alirocumab WMD 0.15 mg/L) [5]. A similar lack of activity was reported for the RNAi therapeutic agent inclisiran [6].

Interestingly, data from the ODYSSEY COMBO II trial [7] show that PCSK9i may work better in CV patients with residual lipid (LDL-C >70 mg/dL) risk, but not with residual inflammatory risk (CRP > 2 mg/dL). In addition, in this trial, ezetimibe was certainly far less effective on LDL cholesterolemia ($-20.7 \pm 1.9\%$ and $-50.6 \pm 1.4\%$ for ezetimibe and alirocumab, respectively), but it lowered CRP by 25% (baseline, 34.6 nmol/L; week 52, 25.7 nmol/L) vs. no effect of alirocumab (baseline, 34.1; week 52, 33.4 nmol/L) [7]. At both the first [7] and two-year follow-ups, a reduction of coronary procedures with ezetimibe was reported [8]. Obviously, the apo-E knockout mouse in the Tang et al. [1] report provides a distant model from the coronary patient and the acute formation of plaques in this model certainly differs from the slow growth found in the clinical disease.

The lack of activity of PCSK9i on CRP levels is somewhat at odds with the supporting evidence of the importance of CRP reduction in preventing CV risk. This view has been well supported by the successful conclusions of e.g. the JUPITER Study [9], based on the

choice of high-CRP patients, and other similar studies, (e.g. the very recent CANTOS Study with canakinumab) [10].

Finally, the use of PCSK9 inhibitors clearly demonstrated the lack of an association of changes in hs-CRP levels and LDL-cholesterol reduction ($p = 0.697$) [11]; these are usually directly correlated under statin treatment.

Conflict of interest

1. MR, NF and CS have no conflict of interest to declare.
2. AC has received honoraria from Amgen, Sanofi, Regeneron, MSD, Recordati, AstraZeneca and Mediolanum.

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