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Letter

Colchicine and coronary inflammation: absence of evidence is not evidence of absence

Commentary on Fiolet et al. Effect of low- dose colchicine on pericoronary inflammation and coronary plaque composition in chronic coronary disease: a subanalysis of the LoDoCo2 trial

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Inflammation has been implicated in the pathophysiology of plaque formation and rupture, while anti-inflammatory treatment with colchicine may be associated with cardiovascular risk reduction (1, 2). However, evidence from large randomized clinical trials remains inconclusive (e.g., the findings of the CLEAR SYNERGY trial) (3) and there is limited data on the direct vascular effects of colchicine. An optical coherence tomography study has indicated that colchicine may stabilize coronary atheromas by increasing fibrous cap thickness (4), while a study that assessed coronary plaques by CCTA showed a reduction in inflammation-driven low-attenuation plaque volume (5).

Pericoronary adipose tissue (PCAT) attenuation captures coronary inflammation by tracking changes in the composition of PCAT (6). The effects of colchicine on PCAT attenuation have not been explored to date. In the present issue of Heart, Fiolet et al (1) published an imaging sub-analysis of the LoDoCo2 study, assessing the effect of low-dose colchicine on PCAT attenuation and plaque morphology. The authors included 151 individuals either on colchicine or placebo arm who underwent coronary computed tomography angiography (CCTA). The analysis showed that the median PCAT attenuation was similar between colchicine-treated patients and patients under placebo, and the results did not change even after adjustment for stented segments. Non-calcified plaque volume was also similar between the two groups, while patients on colchicine had higher calcified plaque volume, irrespective of the statin treatment intensity. No difference was observed in circulating C-reactive protein and interleukin-6 levels between the two groups.

These findings are unexpected, given the anti-inflammatory effects of colchicine and prior imaging evidence indicating its capacity to attenuate plaque inflammation (4, 5). Methodological limitations of the study of Fiolet et al. (1) may obscure any possible anti-inflammatory effects of colchicine. Firstly, the absence of baseline imaging precluded the assessment of comparative changes in PCAT attenuation following colchicine or placebo administration. The study authors also employed an unstandardized metric

of pericoronary inflammation- mean PCAT attenuation- to capture any potential differences between the two arms. The standardized metrics of PCAT i.e. FAI and FAI-Score are derived after adjustment for biological, anatomical and technical factors (6) and have established prognostic value in large cohorts with prospective follow-up (7). The effects of colchicine on FAI were not explored in the present study. In addition, the study population was limited to participants from the European arm of the LoDoCo2 trial. Notably, no significant treatment effect was detected in this study arm in prespecified subgroup analysis. Thus, the failure of the present study to demonstrate any effects of colchicine on PCAT may be largely associated with the absence of a treatment effect within this arm (2). Notable differences were observed between the two groups in terms of statin use, hypertension prevalence, and prior myocardial infarction history. The higher rate of statin use in the placebo arm may have attenuated or masked any additional anti-inflammatory benefits of colchicine on PCAT. Low-density lipoprotein cholesterol levels were inadequately controlled in both study arms (8). This suboptimal control may reflect the underuse of high-intensity statin therapy within the study population and potentially diminish the observable anti-inflammatory effects of colchicine.

Randomized clinical trials on colchicine lack consensus on its effects on reducing cardiovascular events, and its anti-inflammatory potential as assessed by imaging biomarkers such as PCAT attenuation remain inconclusive. Ongoing randomized clinical trials such as the VIRDICT trial (NCT06083337) have the appropriate design with baseline and follow-up scans to address this issue. Until then, absence of evidence on the effects of colchicine on coronary inflammation by PCAT imaging should not be regarded as evidence of absence.

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