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Editorial

Non-statin lipid lowering and coronary plaque composition

Cardiovascular disease (CVD) is the leading cause of death in the United States with coronary artery disease (CAD) accounting for more than 40% of CVD deaths.[1] As our understanding of the pathogenesis of CAD has evolved, it is now apparent that there can be significant inter-person heterogeneity in the progression of coronary atherosclerosis and development of obstructive coronary disease.[2] The composition of individual coronary artery plaques has substantial variation and differing proportions of fibrosis, lipid, calcium, and/or necrotic core.[3] Differences in plaque composition along with specific plaque features such as thin or thick caps[2] can also portend different risks for acute coronary syndrome[3,4]. Importantly, the composition of plaques is not static and they can progress, regress, or alter in composition, although this pathophysiology is still not fully understood.[4] Multiple non-invasive methods to investigate plaque composition and metabolic activity now exist, which include intravascular ultrasound (IVUS), coronary computed tomography angiography (CTA), and positron emission tomography (PET). This has allowed for the study of in vivo changes with increasing granularity and, among these imaging modalities, coronary CTA is uniquely suited to describe plaque composition throughout the entire coronary tree.

1. What does this study show?

Al'Aref et al. investigated the relationship between non-statin therapy (NST) and plaque composition in a cross-sectional evaluation of 4,945 patients with no known history of CAD who were referred for coronary CTA as part of the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry. Plaque composition was characterized as either non-calcified plaque (NCP), partially calcified plaque (PCP) (containing both calcified components and non-calcified components), or calcified plaque (CP). A segment stenosis score (SSS) was also calculated to measure the overall coronary atherosclerosis burden.

In an unadjusted univariate analysis, NST was found to be associated with a higher number of segments with PCP (0.7 vs. 0.6 segments, $p < 0.01$) and CPs (1.5 vs. 1.1 segments, $p < 0.01$) as well as an increased extent of all plaque types. The authors also performed a propensity score analysis to in order to reduce the effect of confounding between those on NST and those not on NST.[5] They found that after propensity score matching there was no statistical association between NST and the number of segments with PCP, NCP, or the SSS. Additionally, in a sub-analysis that excluded patients who were on statins there was also no statistically significant association. Statin therapy, however, was associated with a higher number of segments of PCP and CP. Lastly, over the very short follow up period of 2.6 years, the authors found that there was no significant difference in mortality for patients prescribed NST.

This timely study attempts to better understand the pathophysiology behind the growing clinical evidence supporting non-statin lipid lowering therapies for CVD event reduction. While the results of this study did not show a significant association between non-statin therapy and plaque composition, there are a number of considerations that may help to explain these results. First, the type of NST used was not specified and of the NST included in this analysis only ezetimibe has been shown to have a significant reduction in ASCVD events in the current era of cardiovascular treatment therapies.[6] Additionally, cholesterol medications such as icosapent ethyl—shown to significantly reduced cardiovascular death[7]—and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors—shown to significantly reduce low-density lipoprotein cholesterol and composite cardiovascular outcomes[8]—were not included as the pivotal trials showing their CVD benefit had not been completed. Second, the higher rate of diabetes, hyperlipidemia, statin therapy, and other cardiovascular medication use suggests that the NST patients were at higher cardiovascular risk than those without NST. While the authors performed propensity scoring that included many cardiovascular risk factors to statistically account for confounding by indication, there likely still exists residual confounding not fully accounted by statistical modeling.

2. How does this compare with our current understanding?

Most prior studies that have evaluated plaque composition have looked at statin therapy and those that have examined NST effects on plaque composition have predominantly utilized IVUS. In the coronary CTA literature, statin therapy has generally been shown to reduce total plaque volume and low attenuation or non-calcified plaque, but increase coronary artery calcium scores.[9–11] Additionally, these changes on plaque composition can be detectable in as little as four months of therapy.[4]

Studies investigating the relationship between NST and plaque composition have generally identified plaque regression, which may be mediated through reductions in LDL-C. The OCTIVUS trial, which assessed 87 patients who were randomly assigned to ezetimibe 10mg or placebo in addition to atorvastatin therapy found regressions in the total plaque volume (200.0 mm^3–189.3 mm^3, $p < 0.001$), as well as the percentage atheroma volume (40.1%–39.2%, $p = 0.036$) after a treatment period of 12 months.[12] The Virtual Histology Evaluation of Atherosclerosis Regression During Atorvastatin and Ezetimibe Administration (HEAVEN) study investigated 89 patients who were either on ezetimibe and atorvastatin or atorvastatin only. Over the course of 12 months, there were significant reductions in the percent atheroma volume (−0.4% vs. 1.4%, $p = 0.014$) in the ezetimibe group, as well as significant reductions in LDL-C (23.1%, $p = 0.0003$).[13]

Both of these trials were single center trials with less than 100

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participants, but were able to find significant differences in plaque volume within 12 months. So why might there exist differences between these two trials and the results from this study by Al' Aref and Su et al.?

One such reason is that the CONFIRM registry does not have data on the amount of LDL-C reductions at time of plaque composition assessment and there was only a small difference in baseline LDL between the NST 108.7 mg/dL and statin group 113.1 mg/dL (4% difference). Conversely, in the OCTIVUS trial, the ezetimibe group had a follow-up LDL-C of 54.1 mg/dL compared to 77.2 mg/dL in the placebo group (35.2% difference) and in the HEAVEN study the ezetimibe group had a follow-up LDL-C of 77.2 mg/dL compared to 100.4 mg/dL in the placebo group (26.1% difference).[12,13]

It is also important to consider that changes in plaque composition and subsequent regression are due to a combination of both the absolute baseline LDL-C values and the percentage change in LDL-C. Silverman et al. found that for each reduction in LDL-C of 38.7mg/dL, there was a 23% relative risk reduction of vascular events[14] and this reduction was consistent for non-statin therapy with ezetimibe and bile acid sequestrants. As such, in this study by Al'Aref and Su et al. the NST group may not have reached a sufficient LDL-C reduction from baseline in order to see changes in plaque composition due to the varying lipid lowering sub-types effected by the NST that were included in the registry.

3. What next steps are needed?

Coronary CTA is an ideal non-invasive imaging modality to characterize coronary plaque composition and plaque change, which can further elucidate the pathophysiologic mechanisms for NST in achieving a reduction in CVD. Future studies are needed to focus on specific types of NST in order to better understand the impact of lowering different lipid sub-types and the possible contribution of non-lipid pleiotropic effects.

Conflicts of interest

The authors report no conflict of interest.

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Ramzi Dudum
Johns Hopkins Department of Internal Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

Seamus P. Whelton*
Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins School of Medicine, Baltimore, MD, USA
E-mail address: seamus.whelton@jhmi.edu.

* Corresponding author. 600 North Wolfe Street, Blalock 524 A, Baltimore, MD, 21287, USA.