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EDITORIAL COMMENT

# Lipid Biomarkers and Cardiovascular Risk

## Which Path to Take at the Fork in the Road?*

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Since Anitschkow's seminal observation of aortic atherosclerosis formation in response to feeding a high-cholesterol diet, abundant evidence has affirmed the pivotal role of lipids in cardiovascular disease (CVD) (1). Subsequent randomized controlled trials have unequivocally demonstrated that lowering atherogenic cholesterol levels reduces cardiovascular (CV) event rates in both the primary and secondary prevention setting (2). The demonstration of greater benefit in patients who achieve more intensive lipid lowering has stimulated treatment guidelines throughout the world to promote more aggressive intervention in high-risk individuals (3). The finding that many patients continue to experience clinical events, despite using statin therapy, suggests that there is an ongoing need to develop novel strategies to achieve more effective risk reduction in our patients.

In parallel, increasingly, insights from pre-clinical and pathology studies have highlighted the important role of oxidation and inflammation in the pathogenesis of atherosclerotic disease. In addition to their role in endothelial activation, the earliest abnormality of the artery wall, oxidation and inflammation are implicated in the formation of foam cells, the cellular hallmark of atherosclerotic plaque and in disease progression. Although vitamin and pharmacological strategies with purported antioxidant properties have so far failed to reduce CV risk in large outcome trials, there continues to be immense interest in approaches that target the oxidation component of CVD.

Oxidized phospholipids (oxPL) impart a direct influence on inflammatory pathways within the artery wall and have received considerable attention as targets for biomarker and therapeutic development. The murine monoclonal antibody E06 binds to the phosphocholine head group of oxidized, but not nonoxidized, phospholipids. These antibodies have been employed to demonstrate oxPL species within atheroma samples (4) and to develop blood-based assays that have been shown to predict the risk of CV events in community-based cohorts (5). Still, to date, this assay's predictive capacity has not been evaluated in patients with established coronary artery disease (CAD).

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In this issue of the *Journal*, Byun et al. (6) have evaluated this assay in a random sample of patients who participated in the TNT (Treating to New Targets) study, in which low- and high-dose atorvastatin were directly compared in the secondary prevention setting. Following an 8-week run-in treatment period with atorvastatin 10-mg daily, baseline levels of oxPL-apolipoprotein B (apoB) were higher in patients who subsequently experienced a CV event. This persisted on multivariable analysis, controlling for other clinical and biochemical parameters. Interestingly, this relationship was only observed in patients treated with atorvastatin 10-mg daily, not those treated with the higher 80 mg dose. Further analysis failed to demonstrate an association between follow-up oxPL-apoB levels or their serial change with cardiovascular events.

These are intriguing findings. They extend the published data demonstrating an association between

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oxPL assays and CV risk in patients with established CVD. The finding that oxPL is predominantly carried by the enigmatic lipoprotein(a) and that there is a direct relationship between their levels and CV events may provide further mechanistic rationale for the role of lipoprotein(a) in the pathogenesis of CVD.

However, there remain many unanswered questions. All patients in this substudy had undergone 8 weeks of treatment with low-dose atorvastatin before baseline oxPL-apoB levels were measured. Thus, the relationship between oxPL-apoB levels and CV risk in statin-naïve CAD patients remains to be tested. The finding that the relationship is only observed in patients treated with the lower atorvastatin dose is notable. It is unknown whether this is related to greater lowering of atherogenic cholesterol or potentially more pleiotropic effects on oxidative and inflammatory pathways with high-intensity atorvastatin. The lack of association between serial measures of oxPL-apoB and CV events requires further investigation. The finding that oxPL-apoB levels rise with statin therapy and plaque regression has been postulated to reflect the removal of oxPL from the artery wall to the circulation and may influence interpretation of serial changes and CV risk.

Also, the lack of significant improvement of receiver-operating curve analysis in this study, in contrast to prior reports in primary prevention, requires further consideration. Whether this reflects limited statistical power or the influence of other factors in patients with established CAD is unknown. Finally, it is acknowledged that the oxPL-apoB assay identifies some, but not all, oxPL populations. Whether the other unmeasured oxPL species are more or less important in terms of influencing CV risk remains to be established.

The current analysis is but 1 step in the development pathway of a novel CV biomarker. Further steps along that path will require ongoing elucidation of what is precisely measured by this assay, both in static and serial studies. Applying this assay to additional cohorts will be important to provide further validation of its predictive capacity and its ability to reclassify cardiovascular risk beyond currently-employed algorithms. Ultimately, implementation studies will be required to delineate how to most optimally use this assay, how it changes management, and its cost effectiveness. Accordingly, a considerable amount of work remains to be done.

In addition, the development of a novel lipid biomarker must be considered in the landscape of current approaches to predicting CV risk. Despite the emergence of new approaches to quantify atherogenic lipids, including non-high-density lipoprotein cholesterol, particle-based parameters, and now measures of oxidized lipid species, we still face considerable uncertainty as to how to use these factors that go beyond simply measuring low-density lipoprotein or total cholesterol. Recent updates to treatment guidelines for dyslipidemia have highlighted the need to use more intensive lipid lowering for the highest-risk patients, yet these documents often provide little guidance on how to use these novel lipid biomarkers to refine our risk stratification to identify the individual patients most likely to derive clinical benefit from intensification of lipid-lowering therapy (3). Such stratification is likely to be of increasing importance as additional therapies come to clinical practice, and careful, cost-effective patient selection will be mandatory. More clinical trials specifically testing the utility of novel biomarkers, such as oxPL, to predict baseline and on-treatment risk in various populations will be needed.

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