Statins

Targeting Inflammation by Lowering Low-Density Lipoprotein?*

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The pivotal role of low-density lipoprotein cholesterol (LDL-C) in the pathogenesis of atherosclerosis and its ischemic complications are well established. Epidemiologic studies demonstrate a linear relationship between levels of LDL-C and the prospective risk of cardiovascular events (1). In animal models, the administration of cholesterol decreases levels of LDL-C and promotes the formation of lesions (2). As a result, considerable effort has been devoted to the development of therapeutic strategies that lower levels of LDL-C to reduce cardiovascular risk. The finding that decreasing LDL-C with a range of agents in placebo-controlled clinical trials is associated with lower event rates (3–8) has resulted in the incorporation of LDL-C reduction as a cornerstone of therapeutic guidelines aimed at cardiovascular prevention. More recent evidence of incremental clinical benefit by reducing LDL-C to very low levels (9–11) provides a compelling argument for the use of intensive lipid lowering in the high-risk patient.

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At the same time, increasing evidence supports the concept that atherosclerosis is a chronic inflammatory process (12). The accumulation of inflammatory cells within the arterial wall contributes to the formation of the mature atherosclerotic plaque. The plaque’s inflammatory composition influences its propensity to undergo fibrous cap rupture, the typical pathological trigger of acute ischemic events. This relationship between inflammatory activity and plaque rupture is highlighted by reports that systemic levels of markers of inflammation, including C-reactive protein (CRP) (13) and myeloperoxidase (14), predict the prospective risk of acute ischemic events in subjects with and without established coronary artery disease. An extensive search is underway to identify new therapeutic strategies that modulate inflammation within the arterial wall.

Recent attention has focused on the possibility that functional properties, in addition to lowering levels of LDL-C, may contribute to the unequivocal clinical benefit of statins. This concept has gained popularity, despite the demonstration of a direct relationship between the degree of LDL-C lowering and clinical benefit in trials of statin therapy (15). A number of lines of evidence support the potential for clinically significant pleiotropic properties of statins. In a national registry of patients with acute myocardial infarction, early initiation of statins is associated with increased survival in the following year (16). Furthermore, early initiation of more potent statins results in an early reduction in clinical event rates in randomized controlled trials of patients with a recent acute coronary syndrome (9,17). The early separation of event curves observed in these reports is thought to precede the full extent of LDL-C lowering that ultimately is achieved with therapy. Statins modify levels of other lipids and possess a number of in vitro properties that may contribute to a direct protective influence on the arterial wall in vivo (18). These pleiotropic properties appear to be derived from inhibition of isoprenylation of the Rho kinase pathway. In support of their potential contribution to clinical efficacy, it has been observed that the greatest impact of high-dose atorvastatin on both clinical events (19) and atheroma progression (20) is observed in patients who achieved substantial lowering of levels of both LDL-C and CRP, rather than just LDL-C alone. This information complements data that suggest the beneficial impact of high-dose atorvastatin on the rate of plaque progression cannot be completely accounted for by superior LDL-C lowering (21). These findings provide further support that anti-inflammatory properties of statins are of potential significance in humans.

In the current issue of the Journal, Kinlay (22) uses novel meta-analysis techniques to demonstrate a strong relationship between changes in LDL-C and CRP in healthy and stable subjects with coronary artery disease (CAD) who were treated with LDL-lowering interventions in placebo-controlled trials (22). A major limitation of interpreting such data in clinical trials involves the marked intra-individual variability of CRP measurements. To control for this variability, the current analysis was performed using mean levels of LDL-C and CRP in each trial. Multivariate analysis in the range of LDL-C reduction typically seen with statins revealed that almost all of the observed change in CRP was related to decreasing levels of LDL-C. These findings support a previous meta-analysis that demonstrated that nearly all of the clinical benefit in lipid-lowering trials can be attributed to the degree of LDL-C reduction (23). In addition, they provide important insights into the mechanism that translates LDL-C lowering to clinical benefit.
Although these findings provide further impetus for the concept that lowering levels of LDL-C play an important role in reducing cardiovascular risk, a number of important caveats should be noted. More than 80% of the trials in the meta-analysis involved administration of a statin, which resulted in more effective lowering of LDL-C and CRP than nonstatin interventions. Assessing the impact of statins on CRP beyond their LDL effect would have been more robust had this study included more nonstatin trials. The current analysis excluded clinical trials performed in patients with unstable ischemic syndromes. Given the association of plaque inflammation with its propensity to rupture, it is possible that potential anti-inflammatory properties of statins may play a more important role in this clinical setting. Furthermore, it has been reported that CRP levels typically are much greater in the setting of acute coronary syndromes than in the patients studied in the current analysis (24). This distinction is highlighted by the finding of an early separation of event curves only in statin trials of patients with unstable ischemic syndromes. In contrast, clinical benefit in trials of patients with stable CAD is typically not observed for more than 12 months. This early window of protection during which there is a lack of a relationship between LDL-C reduction and clinical benefit suggests that pleiotropic properties of statins may contribute to their efficacy, which is highlighted by the observation that substantial lowering of CRP, in addition to LDL-C, results in the greatest clinical benefit of high-dose atorvastatin in patients with an acute coronary syndrome (19).

The primary analysis by Kinlay (22) excluded nonplacebo-controlled trials, which results in the omission of recent trials that involved a comparison of low- and high-dose statin therapy. It was of interest to note that in further analysis of trials that directly compared statin doses, a similar relationship was demonstrated. However, it should be noted that given the increasing enrollment of patients with an acute ischemic syndrome in these clinical trials, the majority of studies were not included. It therefore remains to be fully established whether the current findings do occur with high-dose statin therapy in patients with unstable symptoms. This information has important implications given the increasing use of high-dose statin therapy in high-risk patients with established CAD. In fact, comparison of the A to Z (Aggrastat to Zocor) and PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) studies provides preliminary evidence to suggest that anti-inflammatory properties of intensive statin therapy may be of clinical importance. The finding of an early separation in event curves only in PROVE IT was accompanied by a smaller difference in LDL-C but greater difference in CRP between the intensive and moderate statin arms (25).

The current findings report the relationship between changes in LDL-C and CRP, not inflammatory events. They do not provide the opportunity to distinguish between causation or association. Although the current findings suggest that, in patients with stable CAD, lowering CRP with lipid-lowering interventions appears to be primarily driven by lowering levels of LDL-C, it remains possible that these interventions do have a significant and independent effect on inflammatory pathways. C-reactive protein is a relatively nonspecific marker of inflammatory activity, and considerable debate has focused on whether it plays a direct role in atherosclerosis. Reports that recombinant CRP stimulates a number of pathological pathways implicated in atherogenesis are confounded by its potential contamination with endotoxin (26). It would be of interest to perform the current analysis with additional inflammatory markers that involve factors with well-established pathological roles in atheroma formation and rupture. This analysis would provide further insight into the possibility that lipid-lowering interventions possess anti-inflammatory properties. In addition, the current analysis does not investigate the impact of these lipid-modifying interventions on other lipid parameters, such as high-density lipoprotein cholesterol, which may itself possess anti-inflammatory properties, or lipoprotein particle size. Given the increasing importance of lipoprotein functionality and their influence on the arterial wall, it is imperative to gain further insight into how lipid-modifying interventions modulate both the quantity and quality of circulating lipid particles.

What are the implications of the findings of Kinlay (22) for the management of patients at an increased risk of cardiovascular events? Lowering levels of LDL-C remains a central component of all strategies designed to reduce cardiovascular risk, and this strategy is likely to have a secondary benefit in modifying inflammatory activity within the arterial wall. This strategy also is consistent with the objective of the JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) study, which aims to determine the clinical utility of triage of high-risk patients, on the basis of increased CRP levels, to lipid lowering with a statin (27). It will be of interest to investigate the findings of such a strategy on the results of the current analysis. Development of therapeutic strategies that inhibit cholesterol synthesis but preserve isoprenylation of the Rho kinase pathway should provide further insight into the relative contribution of LDL-C and CRP lowering to clinical benefit. Regardless, it has been well established that use of lipid-lowering interventions is associated with a substantial residual risk of clinical events.

It should be emphasized that the findings of this mechanistic study do not diminish the potential link between inflammation and associated biomarkers in atherosclerosis and cardiovascular risk prediction. In particular, the current observations in no way detract from the concept that the patient with low levels of LDL-C but an elevated CRP may be at greater risk than the patient with low LDL-C and low CRP. Accordingly, there is an ongoing need to develop new therapies to complement existing prevention strategies. The findings of the study by Kinlay (22) provide further impetus to continue to strive to
discover new therapies that act to directly modify pathological events in the arterial wall.

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