# Beyond Cholesterol Lowering: Effect of Statins on Markers of Cardiovascular Disease

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Our understanding of atherosclerosis has progressed enormously since the days it was defined as part of an aging process and later as a "cholesterol deposit disease." A large body of evidence led to the recognition of inflammation as a major contributor to both the life-long process and its acute-phase complications [1,2]. Inflammation advances by attracting monocytes, other immunocompetent cells, adhesion molecules and bio-active mediators of injury to the endothelial surface. Observations that the classic coronary risk factors do not fully explain the extent and occurrence of the disease have triggered the search for other non-lipid markers of cardiovascular morbidity and mortality. Such markers may target more intensive treatment approaches and identify the patients who will gain most from such treatments.

In this context, the "pleitropic" actions of statins – unrelated to their low density lipoprotein-cholesterol lowering competence – drew much attention. These actions come on top of a radical change in treatment strategies. For instance, studies such as the Heart Protection showed that in 20,536 patients at high risk for cardiovascular disease events, those with LDL-cholesterol below 100 mg/dl (considered the ultimate goal of therapy by the National Cholesterol Education Program guidelines) benefited as much as those with higher LDL-cholesterol levels [3]. The results of other recent clinical trials utilizing statins resulted in a modified NCEP report that introduced a newly created very high risk group requiring LDL-cholesterol reduction to less than 70 mg/dl as a therapeutic option [4].

In this issue of *IMAJ*, Leibovitz et al. [5] demonstrate in a small homogenous group of 54 year old patients with severe hypercholesterolemia (283 $\pm$ 6 mg/dl) but no other major risk factors that beyond the expected significant reduction by 33% (to 192 $\pm$ 8) upon atorvastatin treatment for 24 weeks (at a dose of 10–20 mg daily), fibrinogen levels dropped by 18%, apparently from what is considered a high risk normal value (above 300 mg/dl) from 355 to 275 mg/dl, and C-reactive protein levels dropped from 0.51 to 0.25 mg/dl from the high risk to moderate risk levels, which did not reach statistical significance probably due to the small size of the sample.

Fibrinogen has a pivotal role in the coagulation cascade as the thrombin substrate. Prospective studies investigated the relevance of various hemostatic factors in the prediction of CVD risk. By far, most data exist for fibrinogen [6,7], with a meta-analysis of 18 studies comprising 4,018 CVD cases showing a relative risk of 1.8 when comparing the highest to the lowest fibrinogen measurements. Most of the fibrinogen measurements were within the normal, acceptable reference range (200–450 mg/dl) [8] with a 200 mg/dl difference between low and high risk groups. In a study of 6,075 men aged 45 and above who were followed for 16.5 years [9], a significant interaction was noted between fibrinogen and other markers of inflammation mediating CVD morbidity and mortality. Also, the interaction of fibrinogen with total cholesterol yielded a strong influence on the incidence of acute myocardial infarction and stroke [10]. This trend was even stronger in women in the Scottish Heart Health Study [11]. Moreover, high fibrinogen predicted the occurrence of type 2 diabetes mellitus in the Insulin Resistance Atherosclerosis Study [12].

Potential mechanisms whereby fibrinogen may promote atherosclerosis include mechanisms involving vessel wall, platelets, and plasma viscosity. Therefore, if high fibrinogen serves not only as a marker but also participates in atherogenesis, interventions to lower or counteract its biological function are recommended. This question has been repeatedly discussed and addressed in relation to CRP and cardiovascular events. The issue of screening, identification and intervention related to CRP was recently presented in a scientific statement [13] issued by the American Heart Association and the Centers of Disease Control, which declared that CRP above 3.0 mg/dl may guide the intensification of medical therapy to further reduce risk and improve motivation/compliance with lifestyle modification and medications. Many studies provide unequivocal evidence linking CRP reductions to statin treatment. A Medline search from 1980 to 2003 concluded

LDL = low density lipoprotein
NCEP = National Cholesterol Education Program

CVD = cardiovascular disease
CRP = C-reactive protein

that all statins are effective in lowering CRP that is not dose-dependent [14], with potential cardioprotective effects occurring in very high risk populations such as diabetics [15,16]. There have also been suggestions of early initiation of therapy in patients with the metabolic syndrome where the contribution of a very high risk CRP level has been strengthened by both prospective large-scale studies measuring CVD outcome [17] and in a healthy middle-aged sample with a high incidence of the metabolic syndrome and obesity [18]. In contrast to the straightforward effect of statins on CRP, the response of fibrinogen to statins and other lipid-lowering medications is difficult to summarize due to mixed results. For instance, in the Israeli Bezafibrate Intervention Study, an increase of 75 mg/dl in fibrinogen (1 SD) was found to increase the risk of CVD by 29% [19]. However, a 9% fibrinogen reduction was not followed by CVD reduction. In a randomized study of hypercholesterolemic patients, there were no effects on fibrinogen levels in subjects treated with atorvastatin, fluvastatin, lovastatin or pravastatin [20]. Other large-scale studies confirmed such neutral effects of statins on fibrinogen [21,22], which led to the conclusion that statins do not affect fibrinogen levels [14].

In conclusion, both fibrinogen and CRP represent crucial hemostatic inflammatory markers that undoubtedly stand as strong and independent risk factors for CVD. The research of such markers as part of therapeutic studies on blood lipids and atherosclerosis is very timely and meaningful. However, the routine incorporation of such markers into our analytical panel is premature and has not yet been approved [23], since the cost-effectiveness of altering management on the basis of the results of such screening requires better determinations and correlation with clinical outcome. Meanwhile, further large-scale studies on the stratification of high risk patients (smokers, diabetics, hypercholesterolemics), according to these newly documented markers of subclinical inflammation, will contribute to our understanding and consequently improve the treatment that we offer our patients.

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