EDITORIAL COMMENT

The Anti-Thrombotic Effects of Statins*

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Several large-scale, multi-centered trials have demonstrated that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or “statins” as they are often called, are effective in lowering total cholesterol and LDL-cholesterol levels by up to 25% and 35%, respectively, and in raising HDL-cholesterol levels by 5% to 10% (1,2). Statins also reduce cardiovascular and overall mortality by up to 42% and 30%, respectively, in patients with significant risk factors for ischemic heart disease, including a previous diagnosis of angina pectoris or myocardial infarction with hypercholesterolemia (1). These beneficial effects extend to patients with hypercholesterolemia but who have no history of coronary artery disease (2). In this setting, a lowering of total cholesterol by 20% and LDL-cholesterol by 26% resulted in a relative risk reduction of coronary events by 31%, a reduction in cardiovascular deaths by 32% and a 22% reduction in deaths from all causes over a follow-up period of almost five years (2).

The effects of “statins” extend to patients with normal/average cholesterol. It is clear that statins also have favorable clinical effects in patients with normal or average cholesterol. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study demonstrated a striking reduction in cardiovascular and all-cause mortality with pravastatin in patients with an acute coronary syndrome, either myocardial infarction or unstable angina, regardless of pre-existing cholesterol levels (3). The reduction in cardiovascular events was greatest in patients whose baseline cholesterol levels were elevated, however, all patients irrespective of the initial total cholesterol level benefited from pravastatin (3). Similarly, in the Cholesterol and Recurrent Events (CARE) study of patients with normal to average serum cholesterol levels and a history of myocardial infarction, there was a significant reduction in cardiovascular deaths, although not in overall mortality, with pravastatin (4).

Statins are more effective in reducing cardiovascular events than previously available lipid lowering agents. Trials of cholesterol-lowering agents other than statins have demonstrated lipid lowering from 6% reduction in total cholesterol levels with clofibrate (in the Coronary Drug Project) (5) to 14% reduction with colestipol (6) compared with dietary treatment plus placebo. The clinical benefits were also limited, with, for example, the Coronary Drug Project demonstrating a 9% reduction in the combined end-point of cardiovascular mortality and non-fatal myocardial infarction (5). With colestipol, there was a 23% reduction in the incidence of all cardiovascular events (6). However, a feature of the majority of these trials before the introduction of the statins is the absence of a reduction in overall mortality. In some instances there was an increase in deaths due to noncardiac causes. These findings extended to trials of both primary and secondary prevention (7).

The apparent clinical superiority of the statins relative to other cholesterol-lowering agents raises the possibility that their beneficial effects reflect pharmacologic activities other than cholesterol lowering. It is worth noting, however, that the statins are far more effective in lowering total cholesterol and LDL-cholesterol than previously studied agents (7). Therefore, their superior effect may be related entirely to their improved efficacy in lowering cholesterol. On the other hand, angiographic studies demonstrate that significant cholesterol reduction is associated with, at best, modest regression of atherosclerosis and luminal narrowing (7). Moreover, coronary thrombosis occurs in many cases on lesions producing less than 50% luminal stenosis (8). Together, these data raise the intriguing possibility that HMG CoA reductase inhibitors reduce cardiovascular events and death by mechanisms other than regression of coronary atherosclerosis.

Biologic activity of HMG CoA reductase inhibitors.

The HMG CoA reductase inhibitors act primarily by inhibiting the rate-limiting enzyme in cholesterol synthesis. This results in up-regulation of hepatic LDL receptor number and removal of total and LDL-cholesterol from plasma. The HMG CoA reductase is also responsible for the generation of isoprenoids, intermediates in the biosynthetic pathway of cholesterol that modify the structure and function of a variety of proteins (9). Statins have been shown to induce vascular smooth muscle cell apoptosis through inhibition of protein prenylation and thus may inhibit vascular neointimal thickening (10). Statins also reduce macrophage cholesterol synthesis and reduce macrophage foam cell formation, thereby stabilizing the atherosclerotic plaque (9).
Antiplatelet effects. Lam et al. have provided direct evidence for an antithrombotic effect of a statin using an experimental model of coronary thrombosis (11). Davi et al. have shown that hypercholesterolemia is associated with platelet activation, in humans, detected as an increase in formation of thromboxane A2, the principle prostaglandin generated by platelets and a potent platelet activator (12,13). There is also evidence that these patients have enhanced platelet aggregation. Treatment with simvastatin at a dose that reduced LDL-cholesterol by 30% to 40% in patients with hypercholesterolemia resulted in normalization of altered platelet aggregation ex vivo and a 50% reduction in thromboxane metabolite excretion when compared with placebo (13).

It is unlikely that a reduction in thromboxane A2 per se explains the antithrombotic effects as the clinical benefits of statins are evident even in patients receiving aspirin (which comprised >80% of patients in the LIPID trial) (4). However, several studies suggest that oxidized LDL can activate platelets directly (14). The antiplatelet activity may also involve reduction in the platelet membrane cholesterol content (15). Recently, a series of isomers of prostaglandins termed isoprostanes have been found in atherosclerotic tissue (16) and oxidized LDL. These are generated nonenzymatically by free radical attack of arachidonic acid in cell membranes and so are insensitive to aspirin (17). Several of these have biologic activity, including 8-epi-PGF2α, which is a potent platelet activator and vascular smooth muscle cell mitogen. Isoprostane formation is increased in patients with atherosclerosis, possibly reflecting an increase in oxidant tone (18). The increase is normalized by treatment with a statin and this in turn may modulate platelet activity.

The HMG CoA reductase inhibitors exert several other effects in patients with atherosclerotic disease and hypercholesterolemia that may indirectly modify platelet activity. These include favorable modification of endothelial function, stabilization of atherosclerotic plaque by reducing lipid content and lipid-laden macrophages and increasing the relative volume of collagen and smooth muscle cells within the plaque (14). This last effect would strengthen the fibrous element of plaque, reducing the risk of plaque rupture, thrombus formation and acute coronary events.

Effects on coagulation? In this issue of the Journal, two articles deal with the potential effects of statins on thrombin generation (19,20). Szczeklik et al. (19) determined the levels of prothrombin fragment 1.2 (F1.2) and fibrinopeptide A, thrombin cleavage products of prothrombin and fibrinogen, respectively, in patients with a total serum cholesterol of >6.5 mmol/liter (19). Patients who failed to respond to simvastatin with a substantial reduction in cholesterol were excluded from the analysis. There was a profound fall in total serum cholesterol in the analyzed patients, with the average pre-treatment cholesterol of 8.0 mmol/liter decreasing to 5.4 mmol/liter on simvastatin. The generation of thrombin cleavage peptides in bleeding time blood (aspirated from the site of a skin incision) was inhibited by simvastatin. Aspirin had a similar effect, and there was no further reduction in thrombin cleavage peptides by the addition of simvastatin to aspirin.

These findings suggest that the reduction in thrombin generation by simvastatin was secondary to an antplatelet effect and specifically inhibition of thromboxane A2, the principle biologic effect of aspirin. Platelets provide a surface for the assembly of enzyme complexes required for thrombin activation. Interestingly, enhanced platelet dependent thrombin generation has been reported in patients with hypercholesterolemia and to normalize on treatment with pravastatin (21). Although Szczeklik could not demonstrate a reduction in plasma levels of FPA or F1.2, this is not surprising because levels of these peptides are usually normal in the absence of an acute coronary syndrome (22).

Likewise, in a second article in this issue of the Journal, Dangas et al. show that plasma concentrations of FPA and F1.2 are unaffected by pravastatin in patients with hypercholesterolemia (20). However, pravastatin reduced thrombus generation in an ex vivo model where the patient’s blood was passed through a perfusion system. The reduction in thrombosis was attenuated in patients on aspirin, again suggesting that aspirin and the statin operate through the same pathway. Thus, in both studies, a statin was effective when thrombosis was provoked and in both studies the effect was attenuated by aspirin.

In conclusion, these studies suggest that statins exert antithrombotic effects largely as a result of an antplatelet activity. The antithrombotic effect was attenuated by aspirin, consistent with the findings of Davi et al., that statins suppress the abnormal generation of thromboxane seen in subjects with hypercholesterolemia. However, the cardiovascular benefits reported with statins are in populations where a high percentage of subjects are on aspirin, and so it is unlikely that this antithrombotic activity contributes to the clinical benefit seen. It is also not clear whether these models reported by Szczeklik and Dangas truly mimic vascular thrombosis. And to complicate matters further, Dangas reports that during the treatment period there was an increase in fibrinogen, a known risk factor for coronary thrombosis (23). But that’s another story.

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