DRUG REVIEW

Non-lipid Actions of Statins

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Introduction

HMG CoA reductase inhibitors (statins) promote reduction in plasma levels of Low Density Lipoprotein (LDL) cholesterol, a primary risk factor in coronary artery disease. Numerous primary and secondary prevention trials confirm clinical benefits with this class of agents (1-4). The mechanisms involved have largely been attributed to the ability of these agents to inhibit cholesterol biosynthesis (2), leading to up- regulation of hepatic LDL receptors and corresponding reductions in circulating levels of LDL and very high density lipoprotein (VLDL) particles by increasing catabolism (2). Additionally, significant increase in high density lipoprotein (HDL) is produced which ultimately results in favourable lipid ratio (2,4). All these lipid actions have been strongly suggested to result in higher percentage of patients to achieve National Cholesterol Education Program and European LDL cholesterol goals (2, 3). However, a growing body of evidence suggest that some of the clinical benefits of statin therapy may be attributed to mechanisms independent of their cholesterol lowering effects.

Non Lipid Actions Of Statins

1.Endothelial Dysfunction and Statins

Hypercholesterolemia is associated with endothelial dysfunction (5). Increased vascular oxidative stress in hypercholesterolemia contributes to impaired endothelial function and atherogenesis (6). Reactive oxygen derived free radicals may promote LDL oxidation in the vascular wall and attenuate endothelium dependent vasodilatation (7). Therefore, we can say oxidation of LDL cholesterol is critical to the pathogenesis of endothelial dysfunction. Endothelial dysfunction is also known to be associated with diminished Nitric Oxide [NO] (8) and inflammatory process in the vascular wall (9).

Initial trials with HMG CoA reductase inhibitors (statins) suggested that improvement in endothelial function co-relate with lipid lowering actions (10). However, several subsequent trials suggest that this improvement in endothelial dysfunction is also additionally contributed by the pleotrophic (non-lipid) effects of statins (11-13). Both lovastatin and simvastatin can stabilize the gene responsible for endothelial nitric oxide, reduce the level of intermediates involved in cholesterol synthesis and reactive oxygen species generation, decreasing LDL oxidation, decreasing inflammatory mediators and preventing lipid per-oxidation (10,11), thereby potentially impairing atherogenesis process. Atorvastatin also have been shown to possess anti-oxidant effects (14). It has been shown to prevent lipid per-oxidation which is involved in oxidative modification of low density lipoprotein, which ultimately results in formation of atheroselerotic lesions (15). Recently introduced statin, rosuvastatin also have been shown to possess non-lipid, anti-oxidant properties more in comparison to other statins and has been claimed to provide stability to atherosclerotic plaque (16). By all these pleotrophic actions, statins have been shown to improve endothelial dysfunction as well as mortality

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from cardio-vascular death independent of lipid lowering effect (10,11).

2. Anti-inflammatory Role of Statins.

Statins induced reduction in acute phase reactant proteins such as C-reactive proteins (CRP) provide strong evidence for an anti-inflammatory effect of these agents, independent of their cholesterol lowering effects (17). Statins have been related to an early benefits among patients with acute coronary syndrome or to those undergoing percutaneous coronary interventions, a state of vascular injury and inflammation by reducing high sensitivity C-reactive protein (17).

3. Statins and Coagulation

Statins may impede thrombogenesis by inhibiting activation of extrinsic coagulation pathway, by inhibiting platelet adhesion and aggregation and improving rheologic profile (18). They also support fibrinolysis thus maintain a favourable balance between prothrombotic and fibrinolytic mechanisms (19, 20).

4. Normalization of Sympathetic Outflow

Statins have been shown to produce beneficial effects in hypertension, after myocardial infarction and after cerebral ischemia possibly by normalization of sympathetic outflow (21-23). Most recently, one study has supported this hypothesis by showing that non-lipid lowering effects include normalization of sympathetic outflow and reflex regulation in CHF (24).

5. Statins in Peripheral Arterial Disease (PAD)

Stains by increasing production of nitric oxide ,inhibiting platelet function and inhibiting function of endothelin-1, a potent vasocostrictor and mitogen have been suggested recently to improve lower extremity functioning in PAD by retarding the deleterious effects of atherosclerosison leg arteries independent of lipid lowering actions (25).

Conclusion

Therefore, we conclude that these pleotropic (non-lipid)actions like anti-oxidant , anti-inflammatory effects,increase of Nitric Oxide , favourable coagulation,plaque stability, normalisation of sympathetic outflow and in overall by improving endothelial dysfuction, statin therapy may in the future prove to be a useful intervention for the preservation of vascular health in addition to their known favorable lipid actions.Moreover, coronary heart disease, ischemic cerebrovascular disease and peripheral vascular disease still account for the majority of morbidity and mortality among middle aged and other adults. Hyperlipidemia (hypercholesterolemia) is a major cause of increased atherogenic risk (26). Although a wide number of drugs are available today for effective treatment of hypercholesterolemia,the growing evidences of pleiotropic effects of statins establish their supermacy over other available lipid lowering agents, as they are most effective, best tolerated and can provide additional cardioprotective effects independent of their lipid lowering actions.

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