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A REVIEW ON STATIN THERAPY FOR REDUCTION IN BLOOD PRESSURE

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ABSTRACT

Hypertension and hypercholesterolemia are two of the major risk factors for cardiovascular events (CV) which usually coexist among 40- 60% patients. Data suggests that almost 47% of patients with high cholesterol levels also have high blood pressure. Although antihypertensive and cholesterol lowering drugs are effective separately, a combination of both is much efficacious in reducing major CV events, as it increases compliance. Statin's effect on cardiovascular protection may be beyond just lipid lowering. Statins are known to have pleiotropic effects, which may help in reducing BP along with cholesterol. A number of studies focus on the blood pressure lowering effect of HMG CoA reductase inhibitor. Further studies are need of the hour to better evaluate the benefits of statin therapy in such patients. A widespread literature search was carried out from Pubmed, and articles relevant to the current topic were selected.

Keywords: Hypertension, Hypercholesterolemia, Statin therapy, Cholesterol

INTRODUCTION

Hypertension and hypercholesterolemia are one of the two main contributors in the development and progression of atherosclerotic heart disease. Cardiovascular

risk reduction can be better achieved by joint control of hypertension and hyper-cholesterolemia.

Statin therapy can be initiated in patients who have not yet achieved the target blood pressure (140/90 mmHg). Majority of patients (almost 92%) did not reach the goal BP, even in presence of ongoing anti-hypertensive, either monotherapy or with add ons **[1]**. Statin therapy has gained interest in the field of hypertension due to the potential role of different statin agents in blood pressure (BP) lowering **[2]**.

Statins reduce the lipid levels in body by inhibiting biosynthesis of cholesterol **[3]**. Upto 2/3rd of Cholesterol is endogenously produced by the hepatocytes in human. Reduction in LDL levels in blood can be achieved by increasing uptake of LDL by cells **[4]**. Statins, chemically a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the most effective first line agents for lowering LDL-C **[5]** and total cholesterol levels **[6]**. The management of people at risk of atherosclerotic cardiovascular disease (ASCVD) event has been revolutionized by the availability of Statins **[7]**. Evidence from recent studies suggests that disturbances in the renin–angiotensin–aldosterone system (RAAS) may be a root cause in development of cardiovascular diseases like hypertension, atherosclerosis and heart failure. Therefore drugs that interfere with the RAAS have been successfully used as first-line treatment in for cardiovascular diseases including hypertension **[8]**.

Hypertension is often associated with Arteriosclerosis, thought to result from hypercholesterolemia, inflammation and/or oxidative stress. Statins have established their role in lowering blood cholesterol as well as reduce oxidative stress, inflammation and macrophage-related production of metalloproteinase, hence effective in providing with Hypotensive effects. Drapala *et al* showed that even in the absence of high levels of Low density lipoprotein (LDL), statin therapy may be beneficial. In instances where hypertensive patients benefit from statin, independently of their plasma lipid levels and independently of the influence on their BP, inflammation and atherogenic dyslipidaemia may play contributing factor **[9]**. Several studies show that statins enhance hypotensive effect of ACE-I and ARBs, which is an evidence for the interaction between statins and RAAS **[9]**. Due to statins increased role in protection against cardiovascular events, Pharmacokinetic and pharmacodynamic properties of have been reviewed extensively **[10]**.

HYPOTENSIVE EFFECT OF STATINS:

Hypotensive effect of statin therapy has been controversial, with contradictory results in multiple studies. Even though the mechanism related to BP lowering effect of statin is well known, findings on human studies assessing the statin effects seem rather inconsistent **[11]**.

The following hypotensive effects are attributed to statin- they increase the endothelial nitric oxide (NO) production, and inhibit the production of reactive oxygen species (ROS), like superoxide anion and hydroxyl radicals, which indirectly results in vasodilation **[12]**.

Downregulation of expression of angiotensin type 1 receptors along with decreased expression of NAD(P)H oxidase subunit p22phox, and reduced free radical release in the vasculature to improve arterial compliance, can also be achieved by statin therapy **[13]**.

Statins help in reducing the synthesis of thromboxane A2, a strong vasoconstrictor, and thus improve vasodilation. Statins also produces anti-inflammatory effects. They cause a decrease in the levels of intracellular adhesion molecule (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and others, which in turn inhibits the adhesion of leucocytes to the endothelium. Statins may reduce the activity of chemokines (monocyte chemoattractant protein-1 (MCP-1), interleukin 8 (IL-8), regulated on activation normal T-cell expressed and secreted (RANTES) along with the synthesis of proinflammatory cytokines such as IL-1β, IL-6, tumor necrosis factor alpha (TNF-α) and C-reactive protein, all of which affect cell migration. Statins also tend to hinder the activity of nuclear factor kappa B(NF-κB) which is activated in presence of inflammatory stimuli as well as up-regulate IκBα, which is inhibitor of nuclear factor kappa B(NF-κB) **[14]**.

Other functions of statins which can be regarded pleitropic are:

Improvement of coronary remodeling, decrease in macrophage cholesterol accumulation and decreased expression of Major Histocompatibility Complex Class II antigen is among some of the major functions. Currently, Atorvastatin is one of the most effective statinuses for lowering LDL-C, and has been shown to markedly reduce cardiovascular risk in many patient groups **[14]**.

COMBINATION WITH ANTI-HYPERTENSIVE MEDICINE

A combination of two or more drugs, to improve the efficacy, is usually integrated in a antihypertensive drug regimen. Majority of

patients reach treatment targets with these combinations and with a safety profile that is similar with monotherapy **[15]**.

Experimental evidences establish interaction between low density lipoprotein (LDL-C) and mediators of vasoconstriction. Statins play a role in enhancing the inhibitory effect of ACE inhibitors and angiotensin receptor blockers on atherosclerosis via reduction of malondialdehide and monocyte chemoattractant protein-1 levels. Results from experimental studies suggest a potential benefit in combining an ACE inhibitor and statin for vascular diseases like hypertension **[16]**.

Combination of ACE inhibitors often with a calcium channel blocker (CCB), are highly effective, according to recent studies. This is in comparison to older antihypertensive treatment regimen based on a beta-blocker and a diuretic **[17]**. Modest blood pressure lowering effect of statins is showed in available data, which is most important with not well controlled hypertension patients **[18]**. Statins and the angiotensin-converting enzyme (ACE) inhibitors have noticeably changed the management of patients with cardiovascular risk including hypertension, leading to a significant decrease in morbidity and mortality. The resultant decrease in cholesterol levels is beneficial, along with decrease in blood pressure. Combination therapy with Amlodipine and Atorvastatin in reduction of CV events in hypertensive patients, were reported in Clinical studies **[19]**. The mechanism by which Angiotensin-I-converting enzyme (ACE) inhibitors increases blood pressure is by catalyzing the conversion of angiotensin-I to angiotensin-II. Angiotensin II causes the muscles surrounding blood vessels to contract, thus restricting the blood flow. ACE also reduces the action of the vasodilator bradykinin, thereby increasing the blood pressure. ACE inhibitors act by diminishing the action of this enzyme which causes the blood vessels to dilate with net reduction in blood pressure **[20]**. Angiotensin-converting enzyme (ACE) inhibitors have modified the management of hypertensive patients, leading to a decrease in morbidity and mortality rates in cardiovascular patients **[21]**. Stefan Naydenov Naydenov *et al* reported that Atorvastatin and amlodipine helped in significant reduction of both blood pressure and LDL-C which are the most important indicators of CV risk **[22]**.

CONCLUSION

Multiple studies have reported the mild but significant effect that statin has in reduction of blood pressure. Statin therapy along with antihypertensive medication has hypotensive properties to some extent based on the

various mechanisms. Studies evaluating the magnitude of the hypotensive effects of statins may improve by use of 24-hour ambulatory BP measurements that accurately determines the extent of antihypertensive effects evaluate the effects of different doses of statin and assess possible synergistic actions of statin and other antihypertensive drugs. Future large-scale, randomized trials are required to garner further information on the definite effect of statins in hypertensive patient.

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