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IMPACT OF STATINS IN ISCHEMIC HEART DISEASE

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ABSTRACT

Mortality and morbidity are still high in cardiovascular disease. Myocardial ischemia reperfusion injury leading to myocardial infarction is one of the most frequent causes of the death in human. Atherosclerosis is the major risk factor for cardiovascular disease. Coronary artery disease is a common and serious condition due to an underlying pathology of atherosclerosis, which is caused mainly by increased levels of low-density lipoprotein that accumulate in the walls of the coronary arteries. The main treatment option for high cholesterol levels is a group of cholesterol-lowering drugs called HMG-CoA reductase inhibitors (statins). They act mainly on the liver enzymes responsible for cholesterol synthesis, reducing the production of cholesterol. HMG-CoA reductase inhibitors (statins) have now become one of the most powerful pharmacological strategies in the treatment of cardiovascular diseases. Originally, the cardioprotective effects of statins were thought to be mediated through lipid lowering actions. However, the beneficial effects of statins in heart not only lipid lowering effects, it also having number of pleiotropic actions. Specifically in ischemic heart disease, statins have protective action through increasing the endogenous antioxidant system that can be augmented by inducing another important cellular component called Heat shock proteins (HSP) mediated through BAG-1 Modulation. Statins also have the effects on eNOS induction. In this article, we review the mechanism of cardioprotection of statins and the mechanism of potential beneficial effects of statins in ischemic heart disease.

Keywords: Ischemic reperfusion injury, Statins, HMG-CoA reductase inhibitors, IHD, Lipid lowering drugs

INTRODUCTION

Hypercholesterolemia is a major risk factor in the development of cardiovascular disease. HMG-CoA reductase inhibitors (i.e. statins), originally designed to reduce serum cholesterol levels and thus reduce this risk factor. However, it has become increasingly apparent that the effects of statins extend well beyond their lipid lowering actions, and these pleiotropic effects have a major role in protecting the myocardium against ischemic reperfusion injury. There have been a large number of clinical studies demonstrating the safety and efficacy of statins in reducing total mortality as well as many other secondary endpoint markers in patients with cardiovascular disease [1].

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Coronary artery disease (CAD) is a leading cause of death in the western world. Cardiovascular disease (CVD) is a leading cause of mortality and is responsible for one-third of all global deaths. Nearly 85% of the global mortality and disease burden from CVD is borne by low-income and middle-income countries. In India, for example, approximately 53% of CVD deaths are in people younger than 70 years of age, in China the corresponding figure is 35%. The majority of the estimated 32 million heart attacks and strokes that occur every year are caused by one or more cardiovascular risk factors – hypertension, diabetes, smoking, high levels of blood lipids, and physical inactivity and most of these CVD events are preventable if meaningful action is taken against these risk factors. The prevalence of CAD in urban North India varies from 7% to 10% [2,3] compared to 3% in USA [4] and <1% in Japan [5]. The CAD rates in South India are two folds higher than in North India, with Kerela reporting 14% in urban [6] and

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7% in rural Thiruvananthapuram [7]. Atherosclerotic narrowing of coronary arteries is the primary event leading to coronary artery disease. Atherosclerosis is heterogeneous with diverse causes, natural histories and clinical manifestations. However, contemporary research suggests some fundamental pathobiologic principles that provide a basis for understanding this multifactorial process [8] and there are strong established evidences incriminating cholesterol in atherogenesis. Oxidative modification of low-density lipoprotein (LDL) in the arterial wall is thought to be fundamental to the development of atherosclerosis. Uptake of oxidized LDL by monocytes and macrophages results in the formation of lipid-laden foam cells, which contribute to the formation of "fatty streaks" on the arterial wall [9]. Biochemical and epidemiological studies strongly support the beneficial role of antioxidants in the control of atherosclerosis [10-12] whereas, effect of atorvastatin to inhibit the progression of aortic aneurysm, independent of its lipid-lowering effect. This study suggests new therapeutic aspects of statins to inhibit the progression of aneurysms [13]. There has been a large number of wide reaching clinical studies demonstrating the safety and efficacy of statins in improving survival in patients with cardiovascular disease. Total mortality was significantly reduced by the use of statins, as well as other secondary endpoint markers such as nonfatal myocardial infarction, coronary revascularization procedures, and death caused by coronary heart disease [14]. Furthermore, the use of statins as therapy for heart failure remains controversial, nevertheless, many of the pleiotropic effects of statins are potentially applicable in heart failure. Although early statins trials excluded patients with heart failure because of concerns that lowering serum cholesterol could worsen an already poor prognosis, statin treatments has not been shown to have adverse effects on either cardiovascular events or mortality, and recent experimental and clinical studies have shown promise of benefit. Two large, ongoing trials should provide definitive evidence of the value of statin therapy for patients with heart failure. Pending those results, it is reasonable to follow current National Cholesterol Education Program guidelines in this high-risk population [15].

HMG CoA REDUCTASE INHIBITORS

HMG CoA reductase inhibitors are one of the most effective hypolipidemic agents until date. Formal sterol balance studies found decreases in total body synthesis of cholesterol of less than 20% [16]. Measurements of changes in precursor sterols in serum (which co-relate with cholesterol synthetic rates) indicate a higher degree of suppression [17]. This decrease leads to expression of hepatic LDL receptors as shown in studies on cultured cells and animals [18]. Liver biopsies of patients undergoing cholecystectomy who had been pretreated with pravastatin were studied and a 12-fold increase in HMG CoA reductase activity (determined in an *in-vitro* assay) and a 180% increase in expression of LDL receptors were found [17]. This increase in LDL receptors leads to enhanced removal of LDL and LDL precursors from plasma. These drugs will lower LDL cholesterol levels by 25% to 45% in a dose dependent manner [19]. Triglyceride concentrations also decline by 10% to 30%, reflecting the decrease in VLDL levels. Of great importance is the fact that HDL cholesterol levels typically rise 8% to 10%. After initial drops in plasma LDL cholesterol levels, the lowered LDL levels are maintained at a steady state by compensatory mechanisms of increased (relative) cholesterol synthesis due to induction of HMG CoA reductase levels. This result in reduction of total body cholesterol of less than 20% [20] whereas, HMG-CoA reductase inhibitors inhibit several intracellular signaling systems activated by Ang II (Rho A/Rho kinase and MAPK pathways and redox process) involved in the regulation of connective tissue growth factor (CTGF) [21].

STATINS IN CLINICAL USE

The use of simvastatin in the Scandinavian secondary intervention study (4S) and the use of pravastatin in the WOSCOPS primary prevention trial [14] supported the hypothesis that drugs that lower plasma cholesterol concentration are of benefit to patients with CAD. However, the clinical benefit of the drugs used in these studies is manifest early in the course of lipid lowering therapy before plaque regression could occur, an observation which has triggered a great deal of scientific curiosity, regarding the mechanism of therapeutic benefit, obtained with HMG CoA reductase inhibitors.

Quantitative angiographic assessment of the impact of statins therapy on coronary atherosclerosis have demonstrated that improvement in arterial topographical morphology occurs slowly and only to a small extent. In the multifactorial anti atheroma study (MAAS) there was no significant improvement in arterial morphology with simvastatin after two years, but a statistically significant improvement occurred after four years [22]. Therefore, it is difficult to attribute the time scale of less than two years in which clinical benefit appeared in 4S and WOSCOPS trials, solely to a decrease in LDL cholesterol concentration.

In another interesting study, the program on the surgical control of hyperlipidemias (POSCH) study [23], a comparison between the clinical benefits of statins and lowering of cholesterol (to similar levels) by ileal by-pass surgery was made. This conclusively demonstrated early and substantial clinical benefits by statins, which could not be achieved by only lowering cholesterol (to similar levels) with ileal by-pass surgery [24]. Furthermore, pooled data from four intervention studies using Pravastatin indicates that reductions in cardiovascular events may be more clearly associated with the use of statins, rather than reductions in plasma LDL cholesterol levels [25].

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The cholesterol and recurrent events (CARE) study of 4,159 post-myocardial infarction (MI) patients has extended the benefit of statins to those with "average" lipid levels [26]. The baseline values were TC of 209mg/dl, LDL of 139mg/dl, triglycerides of 155mg/dl, and HDL of 39mg/dl. Therapy with Pravastatin 40mg/dl over a 5-year period resulted in a significant 24% reduction in non-fatal MI and 37% reduction in fatal MI, and 31% reduction in stroke. The incidence of hospitalization for unstable angina was reduced by 13%, and the need for CABG/PTCA by 27%. The results of this study strongly demonstrated the significant benefits of the use of statins in those with CAD but without elevated TC levels. Meanwhile, therapy of simvastatin reduces TNF-α induced invasion of human cardiac myofibroblasts through two distinct mechanisms (i) by attenuating cell migration via Rho-kinase inhibition and subsequent cytoskeletal disruption and (ii) by decreasing MMP-9 secretion via a post-transcriptional mechanism [27]. Whereas newer application of statin resulted as antiproliferative actions, these drugs may find a place in the treatment of glomerulonephritis and cancer. Furthermore, immunosuppressive properties may mean that statins become routinely included in antirejection regimens following organ transplantation [28]. In addition to that, Statins may be used to intervene in earlier stage risk conditions such as postprandial hyperlipidemia or hyperglycemia, insulin resistant state, masked hypertension or metabolic syndrome to further reduce mortality or morbidity of coronary artery disease and heart failure [29].

STATINS THERAPY AND MYOCARDIAL ISCHEMIA–REPERFUSION INJURY

A number of experimental studies have investigated the effects of statins on eNOS and cardiac injury in the setting of ischemia and reperfusion. Using isolated perfused rat hearts [29-31], demonstrated the cardioprotective effects of statins at normal cholesterol levels. Pretreating the rats with simvastatin 18 h prior to the induction of ischemia–reperfusion significantly reduced cardiac dysfunction and improved coronary flow [30]. Confirming the isolated heart findings, *in vivo* experiments with normocholesterolemic mice pretreated with simvastatin found significant reductions in the area of necrosis and reductions in the degree of infiltrating polymorphonuclear neutrophils (PMN) following 30 min of ischemia and 24 hour of reperfusion [32]. In a model of hypercholesterolemia, cholesterol-fed apoE deficient mice, statins again proved to be significantly beneficial in protecting the ischemic myocardium. Decreases in the area of necrosis, PMN infiltration, as well as leukocyte rolling and adhesion in this model of chronic hypercholesterolemia elegantly shows the protective actions of statins without lowering blood cholesterol levels. Furthermore, these effects are dependent on eNOS, as mice deficient in eNOS are completely resistant to the cardioprotective actions of statins treatment [32]. The diabetic myocardium experienced a similar degree of cardioprotection with simvastatin treatment, attenuation of the area of necrosis and diminished PMN infiltration following a period of 30 min of ischemia and 2 hour of reperfusion [30]. Administration of fluvastatin 20 min prior to left coronary artery ligation with a continued intravenous infusion rate of 1 $mg.kg^{-1}h^{-1}$ was sufficient to preserve myocardial blood flow and decrease infarct size following 50 min of ischemia and 60 min of reperfusion [33]. The ability of statins to decrease infarct size continues to be a consistent finding in experiments of ischemia–reperfusion injury. Reductions in infarct size that are observed by statins treatment likely results in the preservation of myocardial function as indicated by a decreased dilatation and a preserved fractional shortening [34]. In addition to this possible mechanism in the preservation of myocardial function, it has been shown that NO has positive inotropic effects at basal endogenous concentrations, which suggest a possible direct role for NO in preserving contractile function [35]. However, in models of heart failure, statins have no effect on the size of the infarct, following permanent ligation of the coronary artery. This is elegantly demonstrated in comparisons of left ventricular infarct size in a murine model of ischemia–reperfusion against permanent coronary occlusion revealing that rosuvastatin reduced infarct size in the reperfusion model. Whereas, it had no effect on the size of the infarct following a permanent occlusion [36]. While statins have no effect on infarct size in models of heart failure, they do attenuate the accompanying myocardial dysfunction associated with heart failure. This preservation of contractile function is evident in a number of studies. Rats subjected to permanent coronary occlusion and subsequently treated with cerivastatin for eleven weeks starting on the seventh postoperative day, experienced significant improvements in all indices of left ventricular systolic and diastolic function [37]. Mice treated with statins for 4 weeks following coronary occlusion experienced a similar degree of benefit [38,39]. Statins treatment also resulted in significant increase in the survival rate during the 4 weeks following the induction of myocardial infarction. Furthermore, statins reduced cardiac myocytes hypertrophy, interstitial fibrosis, as well as preserved left ventricular ejection performance [37-39]. Interestingly, the ability of statins to exert its beneficial effects in models of heart failure also appears to be eNOS dependent as shown by [39] utilizing eNOS deficient mice.

MECHANISMS OF STATINS MEDIATED CARDIOPROTECTION

The resulting increase in circulating NO available in the coronary arteries has a dynamic role in the mechanism responsible for cardioprotection in the presence of developing or established cardiovascular disease. A common cause for the generation of ischemic conditions is platelet activation and aggregation at the site of a developing or damaged atherosclerotic lesion.

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Bioavailability of systemic NO has a vital role in platelet activation. Inhibition of NO production results in increased binding of fibrinogen and increased surface expression of P-selectin, glycoprotein 53, and CD40 ligand. Administration of the NO donor glyceryltrinitrate returned platelet markers of activation to normal, while administration of atorvastatin resulted in a significant suppression of CD40 ligand and P-selectin [40], thus demonstrating that the bioavailability of NO regulates platelet function. Vasodilation by NO provides a rapid method for increasing regional myocardial blood flow under hypoxic conditions. The subsequent increase in NO as a consequence of statins administration has been shown to inhibit the upregulation of many adhesion molecules involved in leukocyte–endothelial cell interactions such as P-selectin [41], VCAM-1, and ICAM-1 [42]. It has also been demonstrated that statins bind to a regulatory site of the β_2 integrin, leukocyte function antigen-1, which serves to block binding to its counter receptor, ICAM-1 [43]. The inhibition of adhesion molecules provides the protective anti-inflammatory effects seen by preventing leukocyte rolling/adhesion and neutrophil infiltration. Reduced monocyte endothelial adhesion was shown to be mediated by inactivation of RhoA, which resulted in a decreased expression of integrins and actin polymerization [44]. Statins inhibit the mevalonate pathway, which not only decreases the hepatic circulation of cholesterol, but decreases isoprenoids as well. Isoprenoids are critical in the post-translational modification of many proteins including Ras and Ras-like proteins such as Rho and Rab, as well as others [45]. Rho is a critical protein in the inflammatory cascade due to its activation of nuclear factor-κB, a proinflammatory transcription factor [46]. Rho has also been shown to downregulate the endothelial production of NO [47]. Therefore, by blocking the prenylation process, statins prevent a secondary pathway in the inflammatory cascade as well as augmenting the NO dependent anti-inflammatory effects. More recently, demonstrated anti-inflammatory effects of statins independent of NO by induction of heme-oxygenase-1 (HO-1). This has been suggested to be protective as the degradation products of heme produce both antioxidant activity as well as an anti-inflammatory effect. Simvastatin induction of HO-1 appears to also mediate anti-inflammatory effects by inhibiting the nuclear translocation of NF-κB subunit p65 [48]. There is also a role for NO in the control of oxygen consumption. Reductions from a physiologic level of the NO: O_2 ratio (as is present in conditions such as endothelial injury or heart failure can result in disinhibition of mitochondria, with an increase in the amount of O_2 consumed relative to the work being performed, i.e., a decreased cardiac efficiency. Returning the NO: O_2 ratio towards more physiologic levels by statin treatment and subsequent restoration of mitochondrial function may very well provide another mechanism for the protective effect. In addition [49], demonstrated that simvastatin preserved mitochondrial membrane potential in response to oxidative stress. Their use of isolated cardiac myocytes demonstrates that simvastatin can exert its effects in the absence of other cell types, i.e., endothelial cells [50]. Furthermore, their findings indicate that the effects of statins on a cardiomyocyte specific system is dependent on NO, as they used the NOS inhibitor N^G-nitrol- arginine methyl ester to block the beneficial effects of statins. Since statins appear to exert their effects on both endothelial cells and in cardiac myocytes, it has been suggested that cardiac myocytes can therefore serve as triggers and effectors of the various effects of statins and that there is perhaps an interaction between the two cells types *in vivo* [49]. These surprising and unexpected observations from the clinical use of statins set the scientific community working in the direction of

Non-lipid lowering properties of statins with varied success. Some positive findings regarding the different mechanisms of action attributed to statins are:

- Decrease in the proliferation of smooth muscle cells by inhibiting synthesis of DNA specifically during S- phase of cell cycle.
- Improving endothelium dependent coronary vasomotion [24].
- Stabilization of atheromatous plaque.
- Prevention of aggregation of platelets.
- Increases fibrinolytic activity of endothelial cells [51].
- Improving diastolic dysfunction [15].
- Decreases oxidative stress [15].

These results though encouraging has not been able to completely explain the results of statin usage in the clinical setup. More work is required to understand the actions of statins. We have seen that oxidant stress plays an important role in the initiation of atherosclerosis, and that statins in all probability have useful non-lipid lowering properties that help in preventing the progress of atherosclerosis. Previous studies have shown that long-term administration of ACE inhibitors enhances the endogenous antioxidant substances (SOD, catalase) in different organs including the heart [52]. It has also been shown that drugs like probucol act like antioxidants themselves and their benefits are partially due to these properties. Therefore, it is proposed that statins may manifest their usefulness by its antioxidant properties or by increasing concentrations of endogenous antioxidants.

Endothelial dysfunction is an essential step in the development of atherosclerosis and coronary artery disease. Impaired endothelium-dependent and nitric oxide dependent and nitric oxide dependent vasodilation is a hallmark of endothelial dysfunction. Moreover, intervention improving endothelial function reduces cardiovascular events in patients with CAD and hypercholesterolemia. In coronary artery disease, the

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impairment of endothelial function is strongly associated with oxidative stress, oxidative stress with cellular angiotensin II type 1 receptor density with low density lipoprotein cholesterol. Increased superoxide production contributes to oxidative stress, reduced NO bioavailability and endothelial dysfunction in animal models of vascular disease. In humans, the contribution of free radicals to endothelial dysfunction is an independent predicator of adverse cardiovascular risk. In human blood vessels including coronary arteries, nicotinamide adenine dinucleotide phosphate reduced form (NADPH) oxidase is the principal source of superoxide and is functionally related to clinical risk factors and systemic endothelial dysfunction. Angiotensin II activates NADPH oxidase, via angiotensin II type 1 receptor (ATIR) stimulation (ATIR blockade and NADPH oxidase inhibition by 3 hydroxyl -3-methylglutaryl coenzyme A inhibitors (Statins) have been shown to inhibit vascular superoxide formation and attenuate endothelial dysfunction in animal models. Previous studies have shown that low density lipoprotein (LDL) mediates ATIR upregulation in isolated vascular smooth muscle cells and that hypercholesterolemic rabbits and men display an enhanced expression of ATIR [53].

In addition, cholesterol – lowering therapy with statins down regulates ATIR in hypercholesterolemic animals. Hypercholesterolemia induces ATIR overexpression that, in turn increase vascular superoxide production, oxidative stress, and the subsequent endothelial dysfunction have not been studied in the same group of patients. The hypothesis that in turn, accounts for enhanced oxidative stress and the subsequent endothelial function. The impairment of endothelial function is strongly associated with oxidative stress, oxidative stress with cellular AT1R density, and the AT1R density with LDL cholesterol, suggesting cause effect relationships between these variables. Whereas, statins therapy reduced LDL-cholesterol also reduced AT1R density and oxidative stress. Low-density lipoprotein reduction by simvastatin is accompanied by angiotensin II type 1 receptor downregulation, reduced oxidative stress, and improved endothelial function in patients with stable coronary artery disease.

In previous human studies, statins therapy has been already reported to downregulated AT1R attenuate oxidative stress and improve endothelial function. AT1R blockade reduced oxidative stress and improved forearm endothelial function in patients with hypercholesterolemia and hypertension. Statins directly increase endothelial NO synthase expression and activity. In addition, in some clinical studies improvement in endothelial function under statin therapy occurred before significant reduction in cholesterol level was evident. Statins were also shown to exert antioxidant effects in rat vascular smooth muscle by cholesterol-independent depression of NADPH oxidase subunit expression and by the upregulation of catalase expression. In humans, the reduction in oxidative stress under statins therapy occurs before significant reduction in LDL-Cholesterol. Finally, statins therapy was shown to directly down regulate AT1R expression in rat vascular smooth muscle. Consistent with its cholesterol-independent activity, 6-week statins therapy in hypercholesterolemic patients exerted greater reduction in AT1R density that could be predicated by the LDL reduction [53].

CONCLUSION

Coronary artery diseases are one of the major causes of morbidity and mortality in humans. The review would reveal that the benefits of statins in reducing the morbidity and mortality of CAD. There is increasing literature concerning the effect of statins on ischemic heart disease commonly observed in the clinical setting. Several clinical trails have firmly established that lipid-lowering drugs reduce the incidence of coronary events. The benefits of statin drugs have been very encouraging. Of interest, in many studies the anti-ischemic effect of statins was independent of their lipid-lowering capacity, while it was highly correlated with several pleiotropic actions of this class of drugs. The ability of statins to regulate NO-dependent endothelial function, decrease oxidative stress and regulation of antioxidants could represent possible mechanisms to explain a potential antiischemic action. Statins seem to have beneficial effect against ischemic heart disease.

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