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REVIEW ARTICLE OPEN ACCESS

Utilization of Statins in Reducing Comorbidities of Diabetes Mellitus: A Systematic Review

Mudasir Maqbool*, Imran Gani

Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006, Jammu and Kashmir, INDIA.

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***Correspondence to:**

Mr. Mudasir Maqbool,

Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006, Jammu and Kashmir, INDIA. Email: bhatmudasir.scholar@kashmiruniversity.net

Abstract

Background: Medical care for the patients with diabetes, especially medication regimens, has become more complex over time, producing a barrier to achieving evidence-based goals of treatment. National and international clinical guidelines in the prevention of cardiovascular risk in diabetics advocate the utilization of statin therapy in appropriate patients. In this review, we will systematically review about utilization of Statins in reducing Comorbidities of Diabetes Mellitus. **Methods:** We searched the various electronic databases such as: PUBMED, BMJ, LANCET, WHO Website, Unicef Website and Google Scholar for studies related about utilization of Statins in reducing Comorbidities of Diabetes Mellitus. We also checked reference lists of reviews and retrieved articles for additional studies. By systemic searches, we reviewed each paper and retrieved potentially relevant references. **Results:** Many landmark studies across the world like the Heart Protection Study (HPS), the largest trial to date, confirmed the findings of earlier primary and secondary across a wide range of patients, including those with diabetes mellitus. In diabetic patients, statin therapy was associated with a significant 22% reduction in the risk of a first vascular event. The collaborative Atorvastatin diabetes study (CARDS) a study that involved over 2,800 men and women with type 2 diabetes (aged 40-75 years) and at least one other CHD risk factor, was stopped early when patients in the statin group showed significant reductions in myocardial infarction, stroke, angina and revascularization. Various Clinical trials such as MRC/BHF Heart Protections Study, Collaborative Atorvastatin Diabetes Study (CARDS) etc. showed evidence for the benefits of statins in diabetes. **Conclusion:** An overwhelming amount of data that confirm the morbidity and mortality benefit of statin therapy in diabetes mellitus have been reported, both in primary and secondary prevention settings. National and international clinical guidelines in the prevention of cardiovascular risk in diabetics advocate the utilization of statin therapy in appropriate patients.

Key words: Diabetes Mellitus, Statins, Cardiovascular risk, Comorbidities.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, action or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.[1] The prevalence of diabetes, constituted chiefly by type 2 diabetes continues to rise and is a global public health threat. The prevalence among adults aged 20-70 years is expected to rise from 285 million in 2010 to 438 million by the year 2030.[2] The largest increases will take place in the regions dominated by developing economies.[3] The global increase in the prevalence of diabetes is due to population growth, ageing, urbanization and an increase in obesity and physical inactivity. The primary determinants of the epidemic are the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity. Unlike in the West, where older populations are most affected, the burden of diabetes in Asian countries is disproportionately high in young to middle- aged adults.[4] This could have long-lasting adverse effects on a nation's health and economy, especially for developing countries. By 2030, the worldwide healthcare expenditures on diabetes are projected to exceed some USD 490 billion.[3] In India, diabetes is fast gaining the status of a potential epidemic with more than 62 million diabetic individuals currently.[5] Mohan *et al.* provided estimates from a nationwide surveillance study of T2DM and found that in urban areas there was a prevalence of 7.3% of known T2DM and a prevalence of 3.2% in peri- urban / slum areas.[6] Diabetes does not even spare the young Indians as 11.1% adult males and 10.8% adult females are suffering from it.[5] It is predicted that by 2030 diabetes mellitus may afflict upto 79.4 million individuals in India, while China(42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease.[7,8]

Atherosclerotic cardiovascular (ASCVD) risk is increased to 2-to 4- fold in T2DM and outcomes are worse for these patients after myocardial infarction or stroke.[9] Atherosclerosis accounts for approximately 80% of all mortality in diabetic subjects, with 75% due to coronary atherosclerosis and 25% due to cerebral or peripheral vascular disease[10] and more than 75% of all hospitalizations for diabetic complications. It is estimated that more than 50% of patients with newly diagnosed T2DM have coronary heart disease. Indeed, several studies suggest that high- risk patient with T2DM and no history of Clinical coronary heart disease have rates of new events similar to those of non- diabetic subjects with coronary heart disease.[11,12] Furthermore, in several major trials of lipid –altering therapy, subjects with diabetes had higher event rates than those without diabetes during both placebo and treatment.[13,14] Such data prompted the National Cholesterol Education Program Adult Treatment Panel III to define diabetes as a coronary heart disease risk –equivalent disorder. Although several lipid- altering therapies have been shown to benefit patients at risk of CVD, lowering of low-density lipoproteins (LDL) cholesterol with 3-Hydroxy-3-Methylglutaryl Co-enzyme A reductase inhibitors (statins) have shown the most striking results.[15] In addition to lowering of abnormal Lipid levels, statins have certain pleiotropic properties like atherosclerotic plaque stabilization, beneficial effects on vascular endothelium, platelet anti-aggregatory action and anti-inflammatory

action which have a direct role in the progression of CVD in diabetics.[16]

Statins are among the most widely prescribed classes of medicines in the world.[17] Since their restricted entry into clinical practice in 1984 and the public release of Lovastatin in 1987, statins have ranked among the best studied medications. Clinical trials over more than 2 decades have shown that statins are safe and prevent cardiovascular (CV) deaths, major CV events like stroke, myocardial infarction and total mortality.[18-20] Cholesterol lowering to prevent coronary artery disease (CAD) and total cardiovascular disease has been credited with some of the gains made in the reduction of CVD incidence worldwide.[21] Since diabetes leads to a 2-to 8-fold risk in CVD and is recognized as a cardiovascular disease equivalent, there is considerable evidence that statins have very important role in reducing such risk.

Many landmark studies across the world like the Heart Protection Study (HPS), the largest trial to date, confirmed the findings of earlier primary and secondary across a wide range of patients, including those with diabetes mellitus.[22] In diabetic patients, statin therapy was associated with a significant 22% reduction in the risk of a first vascular event. The collaborative Atorvastatin diabetes study (CARDS) a study that involved over 2,800 men and women with type 2 diabetes (aged 40-75 years) and at least one other CHD risk factor, was stopped early when patients in the statin group showed significant reductions in myocardial infarction, stroke, angina and revascularization.[23] Compared with placebo, Atorvastatin 10mg reduced LDL-C by 40% (p<0.0001) and triglycerides by 19% (p<0.0001). These improvements were associated with a 37% reduction (p=0.001) in major coronary events and a 48% reduction in stroke. The justification for the use of statin in prevention: An intervention trial evaluating Rosuvastatin (JUPITER) study which involved 17,802 patients without evidence of heart disease found that patients with low-to-normal LDL cholesterol receiving Rosuvastatin had a lower rate of major cardiovascular events.[19] Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm,[24] A subgroup analysis of the Scandinavian Simvastatin Survival Study,[25] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group,[26] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)[27] have confirmed that statin therapy significantly reduces cardiovascular complications in patients at high risk and/or having type 2 diabetes mellitus. Although there is a wealth of clinical data showing that patients with diabetes mellitus benefit greatly from statin therapy to prevent cardiac events but careful review of findings from many trials combined does show that statins can modestly raise blood sugar and more non-diabetic patients who are on statin therapy are diagnosed with new onset diabetes mellitus compared with those not on statins.[28] Statins might disrupt insulin signaling pathways in such patients and may reduce insulin secretion and/or systemic insulin sensitivity.[29] In a meta-analysis of 32,756 non diabetic patients, statin therapy was associated with 2 new cases of DM per 1000 patients treated with high dose statin therapy for 1 year (number need to harm 498; however, therapy was also associated with 6.5 fewer CV events per 1000 patients per year) (number needed to treat 155).[30] Similarly a recent meta-analysis also confirmed that different types and doses of statins have different capacities to increase the incidence of DM.[31] However the current data do not support discontinuing statins if the patient is already having diabetes mellitus.[28] Similarly from a clinical standpoint there is no current evidence suggesting that the elevations in blood glucose seen while on lipid lowering therapy are associated with an increased risk of CV events or that they attenuate the beneficial effects of the therapy. Until further studies are carried out, statins should continue to be used, after careful assessing the risks and benefits for individual patients.[32]

Diabetes and cardiovascular disease risk

Diabetes Mellitus has been found to be a major cause of heart disease, stroke and death. Patients with diabetes have heart disease, death rates and risk for stroke about 2 to 4 times higher than adults without diabetes.[33] It is estimated that between 60% and 80% of persons with diabetes will develop cardiovascular disease.[34] LDL cholesterol is considered the most important factor in determining CHD risk and lowering elevated cholesterol levels has been the most important factor in decreasing CHD mortality.[35] Therefore, the foremost goal of therapy in type 2 diabetes should be preventing cardiovascular disease through optimization of risk factor modification. This includes aggressive treatment of hypertension, smoking cessation, aspirin therapy and aggressive use of lipid-lowering therapy.[36] For the majority of type 2 diabetes patients, LDL-C lowering remains a primary goal in the treatment of dyslipidaemia.[37] Moreover, a total cholesterol, HDL-C and TG values should also be used to guide treatment choice.[38]

However, the latest guidelines issued by American diabetes Association recommend that statin treatment that statin treatment should be started in all diabetics aged between 40-75 and having LDL-C levels of 70 mg/dl or more.[39] The guideline further issues that for those 40-75 years of age with risk factors; the potential benefits of LDL-C lowering with a high –intensity statin are substantial. Because those with diabetes often have lower LDL-C levels than those without diabetes, "goal" directed therapy often encourages use of a lower statin dose than is supported by the randomized clinical trials (RCTs) and non-statin drugs may be added to address low HDL-C or high triglycerides, for which RCT evidence of an ASCVD event reduction is lacking. Giving a maximally tolerated statin intensity should receive primary emphasis because it most accurately reflects the data that statins reduce the relative risk of ASCVD events similarly in individuals with and without diabetes and in primary and secondary prevention in those with diabetes, along with evidence that high-intensity statins reduce ASCVD events more than moderate-intensity statins.[39]

Evidence for the benefits of statins in diabetes from clinical trials

The publication of the study, MRC/BHF Heart Protections Study of Cholesterol-lowering with Simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial, also known as The Heart Protection Study (HPS) in 2003, helped initiate lipid-lowering therapy as a standard of care in patients with diabetes.[34] The researchers for the HPS trial in the United Kingdom sought to determine if patients with diabetes would benefit from a substantial reduction in LDL cholesterol. Prior to this study, a total of 1500 patients with both CVD and diabetes had been included in various trials of cholesterol lowering statin therapy. Although subgroup analysis suggested that patients with diabetes would also benefit from the cardiovascular effects of cholesterol lowering therapy, diabetes in itself did not appear to be a compelling indication for treatment. In the Heart Protection Study, 5,963 adults with diabetes and 14,573 patients with occlusive arterial disease (no diabetes diagnosis) in the United Kingdom were randomly allocated to receive Simvastatin 40mg daily or a placebo over a 5-year period. The primary end-points included non-fatal myocardial infarction, major coronary event, stroke or revascularization. There was a definite 22% reduction in the event rate in the Simvastatin treated patients versus the placebo treated patients. These results were similar in the patient group with occlusive arterial disease. The researchers concluded that patients with diabetes similar to those enrolled in the study, with 5 years of treatment, can prevent about 45 patients per thousand from experiencing one major vascular event. The researchers also concluded that cholesterol lowering therapy is indicated in patients with

diabetes irrespective of a diagnosis of coronary disease or cholesterol levels. The conclusion drawn by the researchers initiated changes in treatment guidelines for patients with diabetes: to treat and prevent CVD by statin therapy in those patients.[40]

In 2004, the researchers for the Collaborative Atorvastatin Diabetes Study (CARDS) presented their results of a study aimed to determine cardiovascular benefits of treating 2838 patients with type 2 diabetes without high LDL levels. The patients were given either Atorvastatin 10mg or Placebo. According to the study, patients treated with Atorvastatin had overall reduced rates of one major cardiovascular event by 37%. Acute coronary heart disease events were reduced by 37%, the rate of stroke was decreased by 48% and the death rate was reduced by 27%. The researchers concluded that patients with T2DM should receive statins to reduce the risk of cardiovascular disease, irrespective of LDL levels.[23]

Researchers for the Rosuvastatin to prevent vascular events in men and women with elevated C - reactive protein (JUPITER) trial published results in the New England Journal of Medicine in 2008. In this study, 17,802 patients were randomized at 1,315 sites in 26 countries. The patients chosen for the study were healthy men and women with LDL<130 mg/dl and C-reactive protein (an inflammatory marker for cardiovascular events) levels of 2.0 mg/l or greater. Patients were randomized to receive either placebo or Rosuvastatin 20 mg daily. Rosuvastatin reduced LDL levels by 50% and C-reactive protein levels by 37%. Overall mortality was reduced by 20% and strokes reduced by 50% in the patients receiving Rosuvastatin.[20]

In 2010, the researchers for the action to control cardiovascular risk in diabetes (ACCORD) Study Group announced the results of the lipid therapy arm in the tri- phase study. The researchers sought to learn whether combination therapy with a statin plus a fibrate would reduce the risk of cardiovascular disease in patients with type 2 diabetes, as compared to the use of a statin alone. In this trial, 5,518 patients with type 2 diabetes were randomly assigned to receive Simvastatin plus either Fenofibrate or Placebo. The conclusion drawn from the results are that the combination of Fenofibrate and Simvastatin did not reduce the rate of fatal cardiovascular events, non-fatal myocardial infarction or non fatal stroke compared to Simvastatin alone. However, subgroups within the study showed varying results. Patients with initial triglyceride levels of ≥204 mg/dl and HDL≤34mg/dl, benefitted from the inclusion of Fenofibrate in the study regimen. The primary outcome rate in the Simvastatin plus Fenofibrate group was 12.4% versus 17.3% in the statin only group. The sub group made up of women, showed differing results. The rate for primary outcomes was 9.1% for the Fenofibrate plus Simvastatin group and 6.6% in the Simvastatin alone group.[41]

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **ASCVD:** Atherosclerotic cardiovascular disease; **LDL:** Low density Lipoproteins; **CVD:** Cardiovascular disease; **CV:** Cardiovascular; **CAD:** Coronary artery disease; **HPS:** Heart Protection Study; **CARDS:** Collaborative Atorvastatin Diabetes Study; **HDL:** High density lipoproteins; **ACCORD:** Action to control cardiovascular risk in diabetes; **ALLHAT-LLT:** Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

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