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# Drugs for the Management of Atherosclerosis in Diabetics

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**ABSTRACT**

*Experts once believed that atherosclerosis, or hardening of the arteries, developed when too much cholesterol clogged arteries with fatty deposits called plaques. . When blood vessels became completely blocked, heart attacks and strokes occurred. Today most agree that the reaction of the body's immune system to fatty build-up, more than the build-up itself, creates heart attack risk. Immune cells traveling with the blood mistake fatty deposits for intruders, akin to bacteria, home in on them, and attack. This causes inflammation that makes plaques more likely to swell, rupture and cut off blood flow. Diabetes increases atherosclerosis-related inflammation & diabetic patients are twice as likely to have a heart attack or stroke. Past work has shown that high blood sugar has two effects on cells lining blood vessels as part of atherosclerosis. First, it increases the production of free radicals, highly reactive molecules that tear about sensitive cell components like DNA, causing premature cell death (apoptosis). This process also reduces the availability of nitric oxide (NO), which would otherwise enable blood vessels to relax and blood flow to increase.1*

**KEYWORDS :**

**Coronary Artery Disease ( CAD)**

Diabetes is associated with a 2- to 4-fold increase in the risk of developing coronary artery disease. The risk of a myocardial infarction in patients with diabetes and no evidence of coronary artery disease matches that of patients without diabetes who have had a previous myocardial infarction. In the recent report of the Adult Treatment Panel of the National Cholesterol Education Program, type 2 diabetes mellitus was accorded a coronary artery disease risk-equivalent. In patients with known coronary artery disease and diabetes, the rates of death approach 45% over 7 years and 75% over 10 years. Outcomes are worse in diabetic patients for each manifestation of coronary artery disease. Diabetic patients presenting with unstable angina are more likely to develop myocardial infarction, and diabetic patients with myocardial infarction are more likely to die than are nondiabetic individuals. After myocardial infarction has occurred, the 1-month mortality rate is increased in diabetic patients by 58%. Approximately 50% of diabetic patients die 5 years after a myocardial infarction, double the rate found in nondiabetic patients.[2]

**Cerebrovascular Disease**

Similarly, diabetes increases the risk of stroke. For example, the risk of stroke among patients taking hypoglycemic medications was increased 3-fold among the nearly 350 000 men in the Multiple Risk Factor Intervention Trial. In the Baltimore-Washington Cooperative Young Stroke Study, stroke risk increased more than 10-fold in diabetic patients younger than 44 years of age, ranging as high as 23-fold in young white men. Diabetes also increases stroke-related mortality, doubles the rate of recurrent stroke, and trebles the frequency of stroke-related dementia.[2]

**Peripheral Arterial Disease (PAD)**

Diabetes increases the incidence and severity of limb ischemia approximately 2- to 4-fold. Data from the Framingham cohort and Rotterdam studies show increased rates of absent pedal pulses, femoral bruits, and diminished ankle-brachial indices. As such, patients with diabetes are more likely to develop symptomatic forms of the disease, such as intermittent claudication and critical limb ischemia, and undergo amputation. In the Framingham cohort, the presence of diabetes increased the frequency of intermittent claudication by more than 3-fold in men and more than 8-fold in women.[3] Diabetes is the No.1 cause of nontraumatic amputations .

**Drugs for Management of Atherosclerosis in Diabetes**

The diffuse nature and severity of atherosclerosis in patients with diabetes necessitates aggressive use of established therapies to minimize atherosclerotic risk. Treatment should include correction of the metabolic disturbances and modification of related risk factors, such as hypertension and dyslipidemia. Target-driven, intensive intervention directed at multiple risk factors reduces the risk of cardiovascular events, as well as microvascular events, by 50% in patients with type 2 diabetes.4

**Statins**

Patients with type 2 diabetes are likely to have dyslipidemia characterized by elevated LDL, triglycerides and low HDL cholesterol. Large clinical trials have demonstrated the benefit of LDL lowering therapy in diabetes. The drug class with the most impressive data in diabetic patients is that of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, or statins. Retrospective analyses of the Scandinavian Simvastatin Survival Study and the Cholesterol and Recurrent Events (CARE) trial have demonstrated that statin therapy reduced the risk of cardiovascular events in diabetic patients with coronary artery disease and elevated or average LDL cholesterol by 55% and 24%, respectively. CARDS was the landmark study which demonstrated that 10mg of atorvastatin in diabetics with normal cholesterol also produced significant reduction in atherosclerotic cardiovascular events. Heart Protection Study (HPS) prospectively randomized patients between the ages of 40 and 80 years with diabetes and/or vascular disease and total cholesterol >135 mg/dL to simvastatin or placebo. Among the nearly 3000 diabetic subjects without evidence of atherosclerosis at entry, there was a 34% risk reduction in the combined end point of coronary heart disease, stroke, and revascularization over a 5-year follow-up period.[5]Thus, in patients with type 2 diabetes above the age of 40 years, statin therapy is clearly beneficial and should be instituted.

**Fibrates**

Fibric acid derivatives represent the other major class of lipid modification therapy in diabetes. As PPAR-α agonists, these medications raise HDL and lower triglyceride levels. In the Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), patients with a history of coronary artery disease, normal LDL levels, and low HDL levels were randomized to gemfibrozil or placebo. Over a 5.1-year follow-up period, there was a 24% reduction in death from coronary heart disease, nonfatal myocardial infarction, and stroke in the diabetic and nondiabetic patients. Fibric acid derivatives can be useful in the patient with persistently elevated triglyceride and low HDL levels, despite tight regulation of glycemia. Post-hoc analyses of diabetic subpopulations in lipid intervention trials suggest that correction of lipoprotein abnormalities will lead to a decrease in coronary-artery disease. Diabetes Atherosclerosis Intervention Study ( DAIS) suggests that treatment with fenofibrate reduces the angiographic progression of coronary-artery disease in type 2 diabetes. This effect is related, at least partly, to the correction of lipoprotein abnormalities, even those previously judged not to need treatment. There is a risk of myositis with the joint use of statins and fibric acid derivatives, so this combination requires careful monitoring.6

**Niacin**

The fact that reconstituted HDL improves endothelial function in hypercholesterolemia suggests that drugs capable of elevating the levels of these lipoproteins might be clinically beneficial in diabetics. Niacin increases HDL cholesterol levels more than other available lipid ther-

apies. Several trials have found that treatment of diabetic patients with niacin increases HDL cholesterol and reduces triglyceride levels without adversely affecting glucose control. The effect of niacin on cardiovascular outcomes in patients with diabetes is not known, and it should be considered a second-line agent to be used with caution because of a variety of adverse effects including flushing, hyperuricemia, hyperglycemia, and hepatic dysfunction. Despite the negative outcome of the AIM-HIGH study, several other trials are underway to establish the beneficial effects of niacin on atherosclerotic end points. [7]

**CETP inhibitors**

Elevation of high-density lipoprotein-cholesterol (HDL-C) via inhibiting cholesteryl ester transfer protein (CETP) is an attractive strategy for reducing the risk of atherosclerotic events in high-risk patients. Transfer of triglyceride and cholesteryl ester (CE) between lipoproteins is mediated by CETP; thus inhibition of this pathway can increase the concentration of HDL-C. Torcetrapib was the first CETP inhibitor evaluated in phase III clinical trials. Because of off-target effects, torcetrapib raised blood pressure and increased the concentration of serum aldosterone, leading to higher cardiovascular events and mortality in ILLUMINATE trial.. Two other CETP inhibitors, anacetrapib and evacetrapib, are currently undergoing evaluation in phase III clinical trials. Both molecules have shown beneficial effects by increasing HDL-C and decreasing LDL-C concentration. The success of anacetrapib and evacetrapib remains to be confirmed upon the completion of phase III clinical trials in 2017 and 2015, respectively. . The most crucial role for HDL is cholesterol efflux capacity in which HDL can reverse transport cholesterol from foam cells in atherosclerotic plaques. In view of the heterogeneity in HDL particle size, charge, and composition, the mere concentration of HDL-C may not be a good surrogate marker for HDL functionality. Recent clinical studies have reported that increased HDL functionality inversely correlates with the development of atherosclerotic plaque. Future development of CETP inhibitors may therefore benefit from the use of biomarkers of HDL functionality & more effective treatment of atherosclerosis.[8]

**PCSK-9 inhibitors**

During the past 3 years, monoclonal antibodies that inhibit proprotein convertase subtilisin–kexin type 9 (PCSK9) have emerged as a new class of drugs that very effectively lower LDL cholesterol levels & produce benefits in terms of atherosclerotic end points. Evolocumab, a PCSK9 inhibitor, significantly reduced low-density lipoprotein (LDL) cholesterol levels in short-term studies. OSLER-1 & OSLER-2 studies demonstrated that during approximately 1 year of therapy, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDL cholesterol levels and reduced the incidence of cardiovascular events in a prespecified but exploratory analysis. Similar results were derived from ODYSSEY LONG TERM clinical trial using another PCSK9 inhibitor, Alirocumab over a period of 78 weeks. These drugs might prove useful to treat atherosclerosis in diabetes after successful long term studies.[9]

**ACE inhibitors / ARB**

The ACE/angiotensin II/bradykinin system is inextricably linked to some of the processes that contribute to the generation of atherosclerosis at genetic, molecular, biochemical and pharmacological levels. There is a large body of laboratory-derived experimental data that suggests that inhibition of ACE activity has antiproliferative, anti-inflammatory and vasodilatory effects that can modulate this atherosclerotic process from the earliest form of endothelial dysfunction, to delay of lesion formation in primary atherosclerosis or in myointimal proliferation after PTCA. The clinical evidence for these potential benefits is so far sparse. To the established benefits of ACE inhibitors in left ventricular dysfunction of diabetics, the TREND study explored the interesting possibility that there may be an anti-ischaemic action in these circumstances. In the coming years, there is an urgent requirement for intensive investigation into the ability of ACE inhibitors to modulate the various stages of the atherosclerotic spectrum

It is apparent from the data accumulated to date, that one possible link between risk factors and the development of atherosclerosis is in fact $AT_1$receptor activation. $AT_1$ receptor–evoked oxidative stress has been implicated in all states of atherosclerosis, starting with the development of endothelial dysfunction and ultimately leading to plaque rupture and occlusion of the diseased vessel. Besides the traditional effects of $AT_1$ receptor activation, such as vasoconstriction, water and salt homeostasis, and neurohumoral activation, the interaction of the $AT_1$ receptor with radical-producing systems such as the NAD(P)H oxidase and the eNOS enzyme is thought to be a key event in atherogenesis. Thus, $AT_1$ receptor–elicited oxidative stress has been identified as one key event of the atherosclerotic disease process. Therefore, ACE inhibitors as well as $AT_1$receptor antagonists are potent antiatherosclerotic drugs, which is predominately related to their antioxidative properties. However, large-scale investigations will have to show that $AT_1$ receptor antagonists not only decrease free radicals and improve endothelial dysfunction but also inhibit atherosclerosis-associated mortality and morbidity.[10]

**Antiplatelet Therapy**

Antiplatelet therapy should be implemented in patients with diabetes and atherosclerosis unless contraindicated. The Antiplatelet Trialists' Collaboration analyzed the results of 195 trials of >135 000 patients at high risk of arterial disease and found that platelet antagonists lowered the risk of stroke, myocardial infarction, and vascular death. The Early Treatment Diabetic Retinopathy Study randomized 3711 patients with diabetes and generally no history of myocardial infarction or stroke to aspirin (650 mg daily) or placebo. The relative risk for fatal or nonfatal myocardial infarction among the aspirin-treated patients was 0.83 (99% confidence interval: 0.66 to 1.04), without increased risk for retinal or vitreous hemorrhage. In acute coronary syndromes, platelet antagonists may be more effective in diabetic than nondiabetic subjects. A meta-analysis of the diabetic population of 6 large-scale trials of intravenous platelet glycoprotein (Gp) IIb/IIIa inhibitors in the medical management of acute coronary syndromes demonstrated that these agents reduce mortality by 25% at 30 days in diabetic patients but had no survival benefit in nondiabetic patients. In the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study, the addition of clopidogrel to aspirin led to a reduction in death, myocardial infarction, or stroke in patients with unstable angina/non–ST-segment-elevation myocardial infarction, irrespective of their diabetes status. In the aggregate, these findings underscore the importance of antiplatelet therapy in the short-term and long-term management of diabetic patients with atherosclerosis. It was thought reasonable by some school of thought to start aspirin in diabetic patients who have not had clinical manifestations of atherosclerosis because platelet function is abnormal in patients with diabetes , but multiple reviews failed to show any definite benefit in this subset. So currently, prophylactic administration of aspirin in diabetics is discouraged by many international guidelines.[11]

**Treating Hyperglycemia and Insulin Resistance**

Glycemic control remains a principal intervention for prevention of microvascular disease, including retinopathy and nephropathy. Although the epidemiological link between elevations in glucose and the risk of cardiovascular disease is clear, the impact of glycemic control with the currently used drugs is modest at best. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that strict glycemic control (a hemoglobin $A_{1c}$ of 7% in the intervention group) did not decrease the risk of death, stroke, or amputation, and reached only a trend for myocardial infarction (*P*=0.052). The lack of benefit with glycemic control may have resulted from the small difference between the 2 groups (Δ hemoglobin $A_{1c}$ of 0.9%) . BARI-2D trial highlighted that good glycemic control by either insulin or oral agents can provide better outcomes for treatment of atherosclerotic cardiovascular disease in diabetics.

Improvements in insulin sensitivity may have therapeutic promise. In the UKPDS, one arm of the study demonstrated that enhancing insulin sensitivity with the biguanide metformin decreased macrovascular events. Yet the addition of metformin to a sulfonylurea increased the risk of cardiovascular sequelae. The thiazolidinediones improves insulin sensitivity by binding the peroxisome proliferator–activated receptor-γ (PPAR-γ),a nuclear receptor that participates in the regulation of adipose differentiation. PPAR-γ receptors are expressed in monocyte/macrophages of atherosclerotic lesions. Thiazolidinediones have been reported to improve endothelial function in patients with type 2 diabetes. Despite the controversies surrounding this class of agents, they appeal conceptually to the researchers on atherosclerosis, hence studies evaluating their role in diabetic atherosclerosis are ongoing. [12]

**Treating Hypertension**

In contrast to the management of hyperglycemia, several studies

have found that aggressive management of hypertension decreases the risk of macrovascular disease and death in persons with diabetes. UKPDS was the first study to demonstrate the benefit of tight blood pressure control in achieving a significant decrease in the risk of stroke and death, with equal efficacy of the 2 agents ( Atenolol & Captopril). The majority of subjects required 2 or 3 drugs to control their blood pressure at the completion of follow-up.

More recently, the importance of the renin–angiotensin axis has come into focus & the benefits in terms of nephro-protection is beyond doubt. Despite the contradicting results from the ACCORD & ADVANCE trials , achieving optimal BP with an ACEI/ARB or any combination there of is strongly & uniformly recommended by almost every international guidelines to derive maximum cardiovascular protection for diabetics. [13]

## Conclusion

Diabetes markedly increases the risk of coronary, cerebral, and peripheral atherosclerosis and the clinical consequences of myocardial infarction, stroke, limb ischemia, and death. Aggressive medical management directed at optimizing glucose control, achieving normal blood pressure, correcting dyslipidemia, and inhibiting platelet function reduces the likelihood of these adverse atherosclerotic events. In patients with severe atherosclerosis, revascularizationby either percutaneous or open surgical procedures is often necessary to avert the risk of end-organ damage. Physicians should be aware of the important relationship between diabetes and atherosclerosis and be prepared to institute appropriate medical and interventional treatments to reduce disability and death in these patients. Ongoing research in the field of effective drugs to address atherosclerosis in diabetics is challenging & promising as well.

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