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Editorial
Type 2 diabetes and cardiovascular risk factors

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Abstract

Diabetes is associated with higher cardiovascular morbidity and mortality. Hypertension, hyperlipidemia and diabetes are independently associated with increased risk of cardiovascular (CV) disease. Subjects with type 2 diabetes are at two- to four-fold increased risk of CV disease compared to those without diabetes. Long-term hyperglycemia is much more closely associated with microvascular complications than macrovascular complications. There is a lack of adequate evidence that improvement in glycemic control decreases CV risk.

Introduction

In the United Kingdom Prospective Diabetes Study (UKPDS) 3867 newly diagnosed type 2 diabetes subjects were randomized to an intensive control group involving the use of sulphonylureas or insulin and a conventional group based on lifestyle management. Over the 10-year period of the trial, intensively treated patients achieved a mean hemoglobin A1c (HbA1c) of 7.0% compared with conventionally treated patients, who achieved a mean HbA1c of 7.9%. Although approximate 1% decrease in HbA1c in the intensive control group showed 16% (relative risk 0.84, 95% CI: 0.71–1.0) reduction in the risk of myocardial infarction (MI) compared to the conventional glucose control group the data did not reach statistical significance ($p = 0.052$). There was also a non-significant (6%) relative reduction in all-cause mortality in the intensive control group[1]. A group of overweight type 2 diabetes subjects in the UKPDS was included in a sub-study that compared intensive glucose control with metformin ($n = 343$) against conventional therapy ($n = 411$) based on lifestyle modification. Although there was no difference in the HbA1c between these two groups, the use of metformin was associated with a 39% relative risk reduction in the risk for MI ($p = 0.01$) and a 36% relative reduction in all-cause mortality ($p = 0.01$) without any effect on microvascular complications[2].

Data from 10-year post-trial monitoring in UKPDS examined the long-term effect on CV outcomes. More than 66,000 person-years of follow-up in this study showed that the benefits of intensive control in patients with type 2 diabetes are sustained for up to 10 years after the cessation of interventions. In the post-trial follow-up period despite loss of glycemic separation, the intensive control group had reduced rates of MI (RR 0.85, 95% CI: 0.74–0.97, $p = 0.01$) and all-cause mortality (RR 0.87, 95% CI: 0.79–0.97, $p = 0.007$). The benefits of metformin treatment that were seen in the randomized trial were also maintained in the post-trial follow-up study. This study suggested that early strict glucose control generates a legacy effect that takes many years before being translated in to cardiovascular protection[3].

In another large trial, Action to Control Cardiovascular risk in Diabetes (ACCORD)[4], 10,251 patients with type 2 diabetes with other risk factors for CV disease were randomized to receive intensive control (targeting HbA1c < 6% and achieving a level of 6.4%) or standard therapy (targeting

HbA1c 7.0–7.9% and achieving a level of 7.5%). The trial was discontinued after 3.5 years of mean follow-up because of unexpected finding of higher CV mortality rate (hazard ratio 1.35, 95% CI: 1.04–1.76, $p = 0.02$) and higher all-cause mortality (hazard ratio 1.22, 95% CI: 1.01–1.46, $p = 0.04$) in the intensive glycemic control group. Despite these increased mortality rates, in the intensive control group there was a non-significant trend towards reduction in the primary outcome of the trial (a composite of non-fatal MI, non-fatal stroke or death from CV causes). Although the exact explanation for the higher mortality remains unknown, there was a higher rate of severe hypoglycemia in the intensive control group[4].

Two other studies, the Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[5] and Veterans Administration Diabetes Trial (VADT)[6] have found that intensive glucose control is not associated with higher CV or all-cause mortality rates. In the ADVANCE trial, 11,140 type 2 diabetes patients were randomized to intensive control (mean HbA1c of 6.5%), or standard control (mean HbA1c 7.3%). After 5 years of follow-up, the incidence of combined major macrovascular and microvascular events was significantly reduced in the intensive glucose control group (hazard ratio 0.90, 95% CI: 0.82–0.98, $p = 0.01$). This study did not show significant CV risk reduction in the intensive control group, but there was a non-significant trend toward a reduction in all-cause mortality (hazard ratio 0.93, 95% CI: 0.83–1.06)[5].

In the VADT study, 1791 veterans with type 2 diabetes were randomized to intensive glucose control (HbA1c 6.9%) or standard control (HbA1c 8.4%). After a median follow-up period of 5.6 years, a composite CV outcome including MI, stroke, CV death, coronary vascularization, and amputation for ischemia was not significantly lower in the intensive control group (hazard ratio 0.88, 95% CI: 0.74–1.05, $p = 0.12$). A secondary analysis of results from VADT suggested a significant benefit of intensive glucose control in subjects with shorter duration of diabetes, lower HbA1c levels and without known CV disease at baseline[6].

It is important to note that the patients in the UKPDS trial had recently diagnosed diabetes and no known pre-existing cardiovascular disease, whereas in the ACCORD, ADVANCE and VADT trials the duration of diabetes was longer and patients had a higher cardiovascular risk profile. This may account for the difference in the results of these trials.

Dyslipidemia in diabetes

The prevalence of dyslipidemia is common in diabetic subjects. However, the clinical importance of dyslipidemia as a cardiovascular risk factor in diabetic subjects was originally downplayed due to the fact that the measurements of total cholesterol levels did not discriminate between subjects with or without evidence of vascular disease. The development of the ability to measure lipid subfractions coupled with the determination of the relation to risk for the initiation and progression of vascular disease clarified the role of dyslipidemia in the diabetic subjects. Cholesterol is distributed in a variety of lipoproteins which demonstrate a variable risk for the development of atherosclerosis. Diabetic dyslipidemia is frequently characterized by a lipid profile which is characterized by a normal total cholesterol level. However, very low-density lipoprotein (VLDL), which is a triglyceride-rich particle endogenously produced by the liver, is frequently elevated. Additionally, the level of high density lipoprotein (HDL) which exhibits anti-atherosclerotic activity is frequently decreased in diabetes. Low-density lipoprotein (LDL) exists in a family of particles with varying dimensions, lipid content, density and impact on the development of vascular disease. The low-density lipoprotein cholesterol level in diabetics is generally within normal limits. However, an increased prevalence of small dense particles which have been associated with an increased risk for the development of atherosclerosis is common in diabetic subjects. The increased cardiovascular risk associated with small dense particles is determined by their inherent cytotoxicity, increased endothelial permeability and enhanced sensitivity to oxidative stress[7].

The cornerstone of the management of dyslipidemia in diabetes is the emphasis on exercise and weight loss. Effective pharmacologic therapy is available in individuals who cannot optimize the lipid profile by hygienic measures alone. The three major pharmacologic agents which had been utilized in the management of diabetic dyslipidemia are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG CoA reductase inhibitors or statins), fibric acid derivatives, and nicotinic acid. The role of pharmacologic therapy has been clarified by an extensive database in prospective clinical trials which examined efficacy and safety. The initial selection of pharmacologic therapy for optimization of the lipid profile is predicated on the lipid phenotype determined on a fasting screening panel.

Statins

Statin therapy modifies the lipid profile utilizing a complex mechanism which involves partial inhibition of the rate limiting enzyme in cholesterol synthesis HMG CoA reductase coupled with an up-regulation of the apolipoprotein B/apolipoprotein E receptor. The combined pharmacologic mechanisms allow increased removal of atherogenic particles from the circulation combined with reduced intracellular cholesterol production. Additionally, statin therapy has been demonstrated to

exhibit a number of non-lipid or pleiotropic effects which have been demonstrated to beneficially alter endothelial function, coagulation, platelet activity and inflammation. The role of statin therapy in the management of diabetic dyslipidemia has been analyzed in a large variety of clinical trials which are beyond the scope of this review. However, several important trials will be reviewed[7].

Collaborative Atorvastatin Diabetes Study (CARDS)
The CARDS randomized 2038 diabetic subjects to receive either placebo or 10 mg per day of atorvastatin[8]. The baseline criteria required that the LDL cholesterol be less than 160 mg/dL and triglycerides could not exceed 600 mg/dL. Atorvastatin therapy resulted in a significant improvement in the lipid profile with reductions in total, LDL, and triglyceride levels of 26%, 40%, and 19% respectively. Additionally, HDL cholesterol was increased by 1%. The primary endpoint was the time to the occurrence of an acute coronary heart disease event. The CARDS trial was terminated early due to a demonstration of a statistically significant reduction in the primary endpoint of 37%.

Heart Protection Study (HPS)
The HPS was a large-scale clinical trial which analyzed 20,536 subjects who had previously been under-represented in earlier trials[9]. The trial analyzed 5963 diabetic subjects in a predefined manner. The administration of simvastatin 40 mg was compared to placebo. Simvastatin reduced LDL cholesterol by 35% which correlated with a reduction of coronary event rates in the diabetic subgroup of 22%. Additionally, simvastatin therapy reduced the risk of a cerebrovascular accident or the necessity of a revascularization procedure in diabetic subjects. The clinical benefits of simvastatin therapy were determined to be independent of the degree of glycemic control or baseline LDL cholesterol.

Ezetimibe

A multicenter, 6-week, randomized, double-blind, parallel-group, clinical trial evaluated the safety and efficacy of ezetimibe (10 mg) added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg in 440 subjects at moderately high to high risk of coronary heart disease with LDL cholesterol levels higher than the National Cholesterol Education Program Adult Treatment Panel III recommendations. Results showed that ezetimibe added to stable rosuvastatin 5 mg or 10 mg reduced LDL cholesterol by 21%. In contrast, doubling rosuvastatin to 10 mg or 20 mg reduced LDL cholesterol by 5.7% (between-group difference of 15.2%, $p<0.001$). Individually, ezetimibe plus rosuvastatin 5 mg reduced LDL cholesterol more than did rosuvastatin 10 mg (12.3% difference, $p<0.001$), and ezetimibe plus rosuvastatin 10 mg reduced LDL cholesterol more than did rosuvastatin 20 mg (17.5% difference, $p<0.001$)[10].

Fibric acid derivatives

Fibric acid derivatives would theoretically provide optimal therapy in diabetic dyslipidemia due to the frequent coexistence of hypertriglyceridemia, low HDL cholesterol and small dense LDL cholesterol. The fibric acid derivatives are part of the peroxisome proliferator-activated receptor alpha (PPAR) family which is a member of the steroid receptor hormone super-family. The major hypolipidemic effect of fibric acid derivatives is modulated by activation of the ubiquitous endothelial bound enzyme lipoprotein lipase. The physiologic effect of activation of lipoprotein lipase results in an enhanced degradation of triglyceride-rich lipoprotein coupled with an increased level of HDL cholesterol. Additionally, fibric acid derivatives modify the average density of LDL by alteration of the particle size due to larger less dense particles. The clinical trial data supporting the use of fibric acid derivatives in diabetic subjects is less robust compared to statin therapy.

Fibric Acid Intervention and Event Lowering in Diabetes (FIELD)
The FIELD trial randomized 9975 diabetic subjects with type 2 diabetes who were not on statin therapy at the beginning of the trial to receive either a placebo or fenofibrate[11]. The FIELD study evaluated 7664 subjects would be classified as primary prevention as they were did not have established cardiovascular disease while the remainder of the cohort had documented atherosclerosis. The primary endpoint was fatal and nonfatal myocardial infarction over the five year duration of the study. Fenofibrate therapy resulted in a significant improvement in lipid parameters which attenuated as the trial progressed. A partial explanation for the loss of relative efficacy was the increased use of statin therapy in the placebo group which approached 20%. The primary endpoint was fatal and nonfatal myocardial infarction. There was a trend to benefit (11% relative risk reduction was noted) which did not reach statistical significance. The FIELD study was initially designed as a placebo controlled study although the increased use of statin therapy in the control group may have played a significant role in the disappointing results.

Action to Control Cardiovascular Risk Factors in Diabetes (ACCORD)
The ACCORD study was designed to evaluate the premise that intensive lipid lowering would reduce the risk for the development of coronary heart disease in diabetic subjects[12]. The ACCORD trial utilized a 2×2 factorial

design in 5518 subjects who were randomized to receive simvastatin plus fenofibrate or placebo over a five-year period. The subjects were selected on the basis of the presence of diabetes rather than the initial lipid phenotype. The lipid criteria included initial LDL cholesterols levels to be between 60 and 180 mg/dL. The levels of fasting triglycerides could not exceed 750 mg/dL at the time of randomization. Additionally, HDL cholesterol was required to be below 55 mg/dL. The administration of combination therapy did not significantly alter the levels of total or LDL cholesterol between the two groups at the end of the trial. However, significant improvement from the initial randomization levels was demonstrated in both the combination and placebo groups. The primary endpoint was the first occurrence of a major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular disease). The primary endpoint was not different between the two groups during the average follow-up of 4.7 years. Prespecified subgroup effects on the primary outcome were analyzed and indicated a possible beneficial effect on the subgroup with high triglycerides and low HDL cholesterol levels. However, the results of the ACCORD trial do not support the use of combination therapy in diabetic subjects.

Hypertension in diabetes

Hypertension is common in diabetic subjects and individuals with risk factor clustering should be aggressively treated in an attempt to reduce the risk of coronary, cerebral, and renal disease. However, the role of antihypertensive therapy is complex due to the frequent coexistence of diabetic nephropathy which alters the pharmacokinetic handling of multiple drugs and may possibly induce metabolic disorders which may negatively impact upon the overall effectiveness of blood pressure lowering.

Treatment guidelines for patients with diabetes and hypertension

Multiple National Organizations have established treatment guidelines for the management of elevated blood pressure in diabetic subjects which are partially based upon the results of landmark clinical trials such as the UKPDS[13] and Hypertension Optimization Trial (HOT)[14]. The various recommendations differ in the definition of specific blood pressure thresholds (Joint National Committee, American Diabetes Association) were the estimation of the subsequent risk of cardiovascular events (European Society of Hypertension/European Society of Cardiology). However, stringent control of blood pressure is a consistent recommendation. The previously recommended targets in earlier guidelines are no longer considered to acceptable and a target blood pressure threshold of less than 130/80 mmHg is recommended in subjects with diabetes and hypertension. However a disappointingly significant proportion of diabetic subjects do not achieve the target blood pressure, which is a significant cause for concern.

Antihypertensive therapy in diabetes

Angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers, diuretics, angiotensin receptor blockers central alpha agonists and direct renin inhibitors have all been shown to be effective in lowering blood pressure in subjects with diabetes. However, diuretics and traditional beta blockers (metoprolol, atenolol, etc.) are generally not recommended as first line antihypertensive therapy in diabetes due to the possibility of an increase in insulin resistance and metabolic abnormalities. However, beta blockers do have definite benefit in subjects with documented cardiovascular disease despite the possible worsening of metabolic parameters. Calcium channel blockers are considered to be metabolically neutral and agents with negative chronotropic effects (diltiazem and verapamil) may have special benefit with the coexistence of atrial fibrillation. Central alpha agonists are very effective blood pressure lowering agents but are associated with a significant side effect profile. Initial therapy has recently been centered upon the use of an angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Clinical trials have demonstrated that these agents demonstrate benefit in diabetic nephropathy and slow the appearance of microalbuminuria. The gradual reduction in glomerular filtration rates may also be beneficially altered by angiotensin-converting enzyme inhibitors or receptor blockers. The role of direct renin in inhibitors such as Aliskerin is being evaluated although promising studies have demonstrated alteration of the progression of microalbuminuria.

Comprehensive management of diabetes includes aggressive treatment of multiple cardiometabolic risk factors. Control of hyperglycemia, hypertension, dyslipidemia and microalbuminuria in type 2 diabetes patients is of utmost importance to improve cardiovascular outcomes.

Transparency

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M.D.S. is a member of the Speakers Bureaus for Boehringer-Ingelheim and Eli Lilly and Co. J.A.F. serves on the Advisory Boards and is a Consultant for Merck and Pfizer. A.G. serves on

the Advisory Boards, Speakers Bureau and is a Consultant for GlaxoSmithKline, Merck, Novo Nordisk and Daiichi Sankyo. He is on the Board of Directors for the American Association of Clinical Endocrinologists.

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