Review

DIABETES MELLITUS AND CORONARY HEART DISEASE RISK: FOCUS ON DYSLIPIDEMIA

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ABSTRACT

Diabetic patients are at 2-5 fold increased risk for coronary heart disease (CHD) compared to their non-diabetic counterparts. Traditional CHD risk factors contribute to this increased risk. There are clinical trial data to suggest favorable effects of glucose lowering, blood pressure lowering and aspirin use to reduce the CHD risk. Angiotensin converting enzyme use is also associated with reduced CHD risk. The most compelling data for CHD risk reduction has been shown in post hoc analyses of randomized clinical trials using lipid lowering agents including both statins and fibrates. There is a single large clinical trial that has recently confirmed the results of these post hoc analyses. Thus statin therapy has become an accepted strategy to reduce CHD risk in diabetic patients. Combination trials using both statins and fibrates are underway.

KEY WORDS: Diabetes mellitus; Dyslipidemia; Atherosclerotic vascular disease.

DIABETES MELLITUS AND CARDIOVASCULAR RISK FACTORS

The insulin resistance syndrome is characterized by a number of cardiovascular risk factors. These include central obesity, hyperglycemia (including diabetes mellitus), hypertension, dyslipidemia (characterized by elevated triglycerides, low HDL cholesterol and elevated small, dense LDL cholesterol) as well as procoagulant milieu and inflammatory markers. More than 90% of patients with diabetes mellitus have insulin resistance as a phenotypic association. Insulin resistance reflects a state in which there is impaired insulin action, usually defined as impaired glucose disposal. However, insulin is not only a glucose lowering hormone, but is also a lipid lowering hormone. Therefore insulin resistance is also manifest as impaired handling of lipid moieties such as free fatty acids and triglyceride carrying lipoproteins.

When several features of the insulin resistance syndrome cluster together (obesity, hyperglycemia, hypertension, dyslipidemia), this has been described as the metabolic syndrome. Although there is not perfect concordance between the insulin resistance syndrome and the metabolic syndrome, for practical purposes, these terms are often used interchangeably. When components of the metabolic syndrome cluster together, there is a corresponding increase in the risk for coronary heart disease (CHD). Therefore modulation of these risk factors should be associated with a reduction in cardiovascular disease risk. This article will provide a brief overview of the current understanding of modulation of several non-lipid risk factors followed by a more detailed description of clinical trials that have evaluated lipid lowering in diabetic patients.

Treatment of Metabolic Abnormalities in Diabetes Mellitus and Effect(s) on Cardiovascular Disease Risk (data from clinical trials)

Hyperglycemia

Whereas several observational studies have reported an association between hyperglycemia and atherosclerotic vascular disease risk, there are limited intervention trial data. The United Kingdom Prospective Diabetes Study (UKPDS) compared a glucose lowering approaches in which an intensive policy using insulin and sulfonylureas was compared to a conventional policy. The mean in trial HbA_{1c} delta was about 0.9%. Using an intention to treat analyses, the UKPDS showed a 16% reduction in MI risk (p=0.052) over the duration of the study. In obese patients treated with metformin there was a more favorable effect in reducing the risk for MI (2). When these data were analyzed as an observational study

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relating in trial HbA1c concentrations for all participants, for every 1% reduction in HbA1c there was a reduction in both the risk for MI and stroke (3). Whether intensive glycemic control will be associated with significant reduction in CHD risk is the goal of the large NIH trial being carried out with a study population of 10,000 type 2 diabetic patients in the USA and Canada (ACCORD trial)(4).

Hypertension

Several studies of hypertension with diabetic subsets have demonstrated a favorable effect on cardiovascular outcomes, especially stroke. The UKPDS showed a reduction in stroke in the intensive treatment group, but no significant reduction in MI with the intention to treat analyses (5). However, using these same patients in observational analyses, reduction in systolic BP was associated with favorable effects on atherosclerotic disease outcomes (6).

ACE inhibitor therapy

Modulation of the rennin angiotensin system with angiotensin converting enzyme inhibitors may have a favorable effect on not only blood pressure, but also insulin resistance, endothelial cell dysfunction and lipid oxidation. Two large trials (HOPE, EUROPA) have demonstrated that the use of angiotensin-converting-enzyme-inhibitors (ACE-I), ramipril and perindopril respectively, have reduced the risk for cardiovascular disease in diabetic patients (7-9). Some of the favorable effect was attributable to blood pressure reduction, but most of the effect was attributable directly to the use of an ACE-inhibitor. In fact, a post hoc analysis from the HOPE study suggested that ramipril might have a favorable effect to reduce the risk to develop new onset diabetes mellitus (10,11).

Aspirin Therapy

The largest single trial of aspirin use in diabetic patients was the Early Treatment Diabetic Retinopathy Study. The primary purpose of this study was to determine whether aspirin (650 mg/day) vs. placebo would reduce the risk for progression of retinopathy. Whereas there was no effect on retinopathy there was a reduction in cardiovascular outcomes—a composite of cardiovascular and cerebrovascular events (12). These data are supported by the large observational study in screenees from the Bezafibrate Infarction Prevention Study (BIPS) Aspirin which showed a favorable effect of aspirin in diabetic patients; diabetic patients were a greater risk for CHD events, but aspirin had a comparable risk reduction to that seen in non-diabetic subjects (13). Further support for aspirin use in diabetic patients is reviewed in the technical review published by Cowell (14).

Other risk factors associated with insulin resistance

Interventions that improve insulin resistance, including exercise and the insulin sensitizers, are associated with favorable effects on inflammatory and pro-coagulant risk factors. However, these interventions are also associated with favorable effects on body fat, glucose, lipids and hypertension. Therefore, it is not yet clear whether modulation of these "non-traditional" risk factors will have a favorable effect on cardiovascular outcomes in diabetic patients.

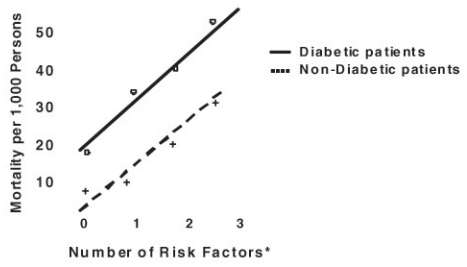
DYSLIPIDEMIA

The typical dyslipidemia associated with insulin resistance and diabetes mellitus is one that is characterized by increased concentrations of triglyceride rich lipoproteins (especially VLDL) and reduced concentrations of HDL cholesterol compared to subjects without diabetes mellitus/insulin resistance. Concentrations of LDL cholesterol are comparable between diabetic/insulin resistance subjects and their non-diabetic/non-insulin resistant counter parts. However, the composition of LDL is more likely to be a small dense LDL—a composition that is associated with increased atherogenicity.

There are several observational studies that have shown a continuous and graded relationship among TC and the risk for coronary heart disease (CHD) (15, 16). One of the largest observational studies is comprised of more than 300,000 screened from the Multiple Risk Factor Intervention Study (MRFIT) (16). The diabetic subjects in this cohort have also been analyzed. Three important observations can be made from this observational study. First, diabetes mellitus increases the risk for CHD by about 3-fold (Fig 1). Second, traditional risk factors for CHD in non-diabetic subjects such as smoking, hypertension and dyslipidemia also contribute to the risk for CHD in diabetic subjects. Third, the relationship between TC and CHD Risk can be shown for both diabetic and non-diabetic subjects. In each of the latter 2 cases, diabetic patients have the 3-fold increase in risk over their non-diabetic counterparts. In the UKPDS analysis of risk factors that contributed to

cardiovascular risk in the diabetic participants in that trial, both LDL cholesterol and HDL cholesterol were important contributors to CHD risk (17).

Fig 1: Relationship of Coronary Disease Mortality and Number of Risk Factors in Diabetic and Non-Diabetic Patients



* Risk factors analyzed were smoking, dyslipidemia, and hypertension

Adapted from Diabetes Care 1989;12:573-579

Lipid Lowering Trials

Several lipid lowering trials have included subsets of diabetic patients (details and references below). Most of these trials have used either statin or fibrate therapy. In post hoc analyses of the diabetic subsets, each of these trials has shown favorable effects on atherosclerotic vascular disease outcomes. The results of a lipid lowering trial carried out exclusively in diabetic patients have also recently been reported. Key outcomes in diabetic patients from among these trials will be discussed below. It should be noted that large trials of combination therapy (to modify each of the lipid abnormalities associated with the metabolic syndrome) have not been performed. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is currently underway in the United States and Canada. This trial will evaluate the effects of adding fibrate therapy to diabetic patients who are being treated with a statin on cardiovascular outcomes.

Early Cholesterol Lowering Studies

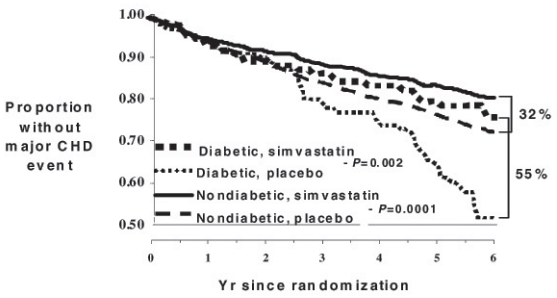
The first major randomized, double blind, cholesterol lowering trial, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) excluded patients with diabetes mellitus (14). The LRC-CPPT compared questran to placebo in men without known CHD and demonstrated that an 11% reduction in LDL-C was associated with a 19% reduction in CHD risk. The general interpretation was that the results of this trial would be applicable to patients with diabetes. The second large clinical trial, the Helsinki Heart Study compared the effects of gemfibrozil to placebo in patients with elevated non-HDL cholesterol. The reduction of CHD events in this study was also demonstrated in the patients with diabetes mellitus (n = 135), but because of the small number of subjects this result did not reach statistical significance. These 2 trials were the underpinning for the multiple trials published since that time.

Lipid Lowering Trials That Included Diabetic Patients

Statin Therapy Trials

Since the mid 1990's most of the cholesterol lowering trials have included some diabetic subjects. The first LDL-cholesterol lowering trial to demonstrate a reduction in all cause mortality (in addition to a reduction in coronary events) was the Scandinavian Simvastatin Study of Survival (4S). From among the 4,444 participants in this trial, there were 202 patients with known diabetes at the time of the trial (21, 22). The benefits of cholesterol lowering were comparable in diabetic subjects compared to their diabetic counterparts; however, even in the statin treated diabetic subjects their risk for cardiovascular events was greater than subjects without diabetes (Fig 2).

Fig 2: The Relationship of Coronary Heart Disease Mortality in Diabetic and Non-diabetic Subjects from the Scandinavian Simvastatin Survival Study (21).



Adapted from Pyörälä K et al. *Diabetes Care*. 1997;20:614-620.

In the CARE trial there were 586 patients with a clinical diagnosis of diabetes mellitus and 3573 subjects without diabetes mellitus (23). Baseline and in-trial LDL-c concentrations were comparable in the diabetic and non-diabetic subjects. In this trial the reduction in risk for diabetic subjects was 23% and

the reduction in risk was 25% for non-diabetic subjects. The Heart Protection Study was a study of more than 20,000 subjects randomized to simvastatin 40 mg vs. placebo. This study had 5,963 subjects with diabetes mellitus (24). In the intention to treat analyses, the reduction in risk for CHD events was 24% for the trial as a whole. In diabetic patients collectively, the results were comparable. In diabetic patients without prior vascular disease (n = 2912), the primary prevention of CHD was 33%. In several other trials, the beneficial effects of LDL-cholesterol lowering were comparable in the diabetic subjects and non-diabetic subjects (25-29). In many of these trials the number of diabetic subjects was too small for the favorable reduction in atherosclerotic disease events to be statistically significant.

There is a single trial in which lipid lowering therapy in diabetic subjects did not favor the statin therapy. The PROSPER trial was comprised of 5804 men and women aged 70-82 years were treated with pravastatin for 3 years (30). There were 623 patients with clinically diagnosed diabetes. There was a 19% reduction in CHD events when all participants were analyzed. In the diabetic subjects the risk ratio for the pravastatin group compared to placebo was 1.27 (95% CI 0.90-180).

Recently a cholesterol lowering trial was completed that was performed exclusively in patients with diabetes mellitus. The Collaborative Atorvastatin Diabetes Study (CARDS) was comprised entirely of patients with diabetes mellitus (n = 2838) (31). Patients were randomized to atorvastatin 10 mg daily (vs. placebo) and followed for a mean of 3.9 years. The risk for cardiovascular events was reduced by 37%, the risk for acute coronary disease events was reduced by 36 % and the risk for stroke was reduced by 48%.

Fibrate Therapy Trials

Gemfibrozil, a fibric acid derivative, (compared to placebo) has been studied in 2 major cholesterol trials (20, 21, 32). Fibrates do not have much effect to reduce LDL cholesterol, but do lower triglycerides and raise HDL-cholesterol. Diabetic and non-diabetic subjects on fibrates in these trials had less coronary events and strokes compared to those on placebo. This benefit was not associated with reduced LDL concentrations. There were 135 diabetic patients in the Helsinki Heart Study. Although the relative risk reduction in the diabetic patients was greater than in the trial as a whole (RR = 0.32, 95% CI 0.07-1.46), the small numbers precluded statistically significant differences. In the Veterans Administration study (VA-HIT) comprised of 2351 men, there were 627 diabetic subjects. There was a 24% risk reduction in both diabetic and non-diabetic subjects.

Summary of Statin/Fibrate Trials in Diabetic Subjects

What can we say about the reduction in risk for heart disease from these trials? Statin agents (usually compared to placebo) have been used in most of these studies and the major lipid effect has been a reduction in LDL-cholesterol. Diabetic patients in the statin trials generally had more heart disease than their non-diabetic counterparts. Whereas diabetic subjects got comparable (or even greater) *relative* benefit, the diabetic patients on statins still have a greater risk for heart disease than their non-diabetic counterparts. A summary of trials published over the past 20 years has recently been published (Table 1) (33). (This summary was published before the CARDS trial). Based on all of these studies statins are now considered standard therapy for coronary heart disease risk reduction in most patients with diabetes mellitus. Of note is the observation that LDL cholesterol lowering not only is associated with a reduced risk for heart disease, but also a reduced risk for stroke.

Fibrates have most of their effects to reduce triglycerides and raise HDL cholesterol. They have little effect on LDL-cholesterol. In the Helsinki Heart Study patients were recruited because they had elevated non-HDL cholesterol. However, the subjects who got the greatest benefit were those who had elevated VLDL cholesterol (triglyceride carrying moiety) concentrations. In the VA-HIT study, triglycerides were reduced by ~ 30%, and the HDL-C was increased by about 7%. The investigators have interpreted the increase in HDL-C as being responsible for the favorable outcomes in this study.

Table 1: Coronary Heart Disease Events for Subjects with Type 2 Diabetes Mellitus in Randomized, Double-Blind, Lipid Lowering Trials (33).

a. Primary Prevention Studies

Study	Treatment	Control (n/n)	Intervention (n/n)	RR (95% CI)	ARR (95% CI)	NNT
AFCAPS/TexCAPS	lovastatin (± resin) vs. placebo	6/71	4/84	0.56 (0.17–1.92)	0.04 (-0.04–0.12)	27.1
ALLHAT-LLT	pravastatin vs. usual care	Not reported	Not reported	0.89 (0.71–1.10)	Not reported	Not reported
HHS	gemfibrozil vs. placebo	8/76	2/59	0.32 (0.07–1.46)	0.07 (-0.01–0.15)	14.0
HPS	gemfibrozil vs. placebo	367/1976	276/2006	0.74 (0.64–0.85)	0.05 (0.03–0.07)	20.8
PROSPER	pravastatin vs. placebo	28/205	32/191	1.23 (0.77–1.95)	-0.03 (-0.10–0.04)	-32.3
ASCOT-LLA	atorvastatin vs. placebo	46/1274	38/1258	0.84 (0.55–1.29)	0.01 (-0.01–0.02)	169.5
Pooled*		—	—	0.78 (0.67–0.89)	0.03 (0.01–0.04)	34.5**

** Meta-analysis; due to no heterogeneity between 1° prevention studies (P=0.18), fixed-effects model used. ** ‡Number needed to treat for benefit is for 4.3 years.*

b. Secondary Prevention Studies

Study	Treatment	Control (n/n)	Intervention (n/n)	RR (95% CI)	ARR (95% CI)	NNT
4S	simvastatin vs. placebo	44/97	24/105	0.50 (0.33–0.76)	0.23 (0.10–0.35)	4.4
CARE	pravastatin vs. placebo	112/304	81/282	0.78 (0.62–0.99)	0.08 (0.01–0.16)	12.3
HPS	simvastatin vs. placebo	381/1009	325/972	0.89 (0.79–1.00)	0.04 (0.00–0.09)	23.1
LIPID	pravastatin vs. placebo	88/386	76/396	0.84 (0.64–1.11)	0.04 (-0.02–0.09)	27.7
LIPS		31/82	26/120	0.53 (0.29–0.97)	0.16 (0.03–0.29)	6.2
Post-CABG	Lovastatin 40-80 mg (± resin) vs. lovastatin 2.5-5 mg (± resin)	14/53	9/63	0.53 (0.18–1.60)	0.12 (-0.03–0.27)	8.2
PROSPER*	pravastatin vs. placebo	31/115	38/112	1.26 (0.85–1.87)	-0.07 (-0.19–0.05)	NA
VA-HIT	gemfibrozil vs. placebo	116/318	88/309	0.76 (0.57–1.01)	0.08 (0.01–0.15)	12.5
Pooled†		—	—	0.76 (0.59–0.93)	0.07 (0.03–0.12)	13.8‡

** Meta-analysis; due to substantial between-study heterogeneity (P=0.026), random-effects model used. ** Number needed to treat for benefit is for 4.9 years.*

CONCLUSIONS

Although both statins and fibrates are commonly used to treat cholesterol and triglyceride abnormalities in patients with diabetes mellitus, two large studies are underway that will refine our understanding of lipid altering therapy in patients with diabetes. The FIELD study will be the first large study comparing another fibrate, fenofibrate, in a clinical outcomes study. Since no large studies have been carried out to answer the question about whether the combination of a statin and a fibrate will improve the results seen with either agent used by itself, a study to answer this question is also underway. Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (4). ACCORD is funded by the National Institutes of Health (NIH) and will include 10,000 diabetic patients from among whom ~5,200 are projected for enrollment in the lipid arm. In the lipid arm all subjects will be treated with a statin and then randomized to fenofibrate or a placebo. Until the results of the ACCORD trial are available, statins will continue to be the mainstay of therapy. Fibrates may be used either alone or in combination in selected diabetic patients.

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