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ROLE OF GLUCOSE AND LIPIDS IN THE CARDIOVASCULAR DISEASE OF PATIENTS WITH DIABETES

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ABSTRACT

Cardiovascular disease is a major cause of morbidity and mortality in both men and women with Type 1 and Type 2 diabetes. In patients with Type 1 diabetes, intensive glycemic control results in a reduction in cardiovascular disease. However, intensive glycemic control does not have a major impact in reducing cardiovascular disease in patients with Type 2 diabetes. Metformin, pioglitazone, empagliflozin, and certain GLP-1 receptor agonists have been shown to decrease cardiovascular disease in patients with Type 2 diabetes to a greater extent than other treatment modalities. In patients with Type 2 diabetes other risk factors including, hypertension and dyslipidemia, play a major role in inducing cardiovascular disease, and control of these risk factors is paramount. In patients with Type 1 diabetes in good glycemic control, the lipid profile is very similar to the general population. In contrast, in patients with Type 2 diabetes, even with good glycemic control there are frequently lipid abnormalities (elevated triglycerides and non-HDL cholesterol, decreased HDL cholesterol, and an increase in small dense LDL). In both Type 1 and Type 2 diabetes, poor glycemic control increases triglyceride levels and decreases HDL cholesterol levels with only modest effects on LDL cholesterol levels. Extensive studies have demonstrated that statins decrease cardiovascular disease in patients with diabetes. Treatment with high doses of potent statins reduces cardiovascular events to a greater extent than low dose statin therapy. Adding fibrates or niacin to statin therapy has not been shown to further decrease cardiovascular events. In contrast, a recent study has shown that the combination of a statin and ezetimibe does result in a greater decrease in cardiovascular events than statins alone. Current recommendations indicate that most patients with diabetes should be on statin therapy. For complete coverage of all related aeas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

Cardiovascular disease is the major cause of morbidity and mortality in both men and women with diabetes (approximately 50-70% of deaths) [1-5]. The risk of cardiovascular disease is increased approximately 2 fold in men and 3-4 fold in women [2-4, 6, 7]. In the Framingham study, the annual rate of cardiovascular disease was similar in men and women with diabetes, emphasizing that woman with diabetes need as aggressive preventive treatment as men with diabetes [2, 6]. In addition, several but not all studies, have shown that patients with diabetes who have no history of cardiovascular disease have approximately the same risk of having a myocardial infarction as non-diabetic patients who have a history of cardiovascular disease, i.e., diabetes is an equivalent risk factor as a history of a previous cardiovascular event [8, 9]. The duration of diabetes and other risk factors likely determine whether a patient with diabetes has a risk equivalent to patients with a history of previous cardiovascular events [10, 11]. Moreover, numerous studies have shown that patients with diabetes who have cardiovascular disease are at a very high risk of having another event, indicating that this population of patient's needs especially aggressive preventive measures [1, 8]. This increased risk for the development of cardiovascular disease in patients with diabetes is seen both in populations where the prevalence of cardiovascular disease is high (Western societies) and low (for example, Japan) [2]. However, in societies where the prevalence of cardiovascular disease is low, the contribution of cardiovascular disease as a cause of morbidity and mortality in patients with diabetes is reduced [2]. While the database is not as robust, the evidence indicates that patients with Type 1 diabetes are also at high risk for the development of cardiovascular disease [1, 12-14]. Interestingly, women with type 1 diabetes have twice the excess risk of fatal and nonfatal vascular events compared to men with type 1 diabetes [15]. While the development of diabetes at a young age increases the risk of cardiovascular disease in patients with both Type 1 and Type 2 diabetes the deleterious impact is greater in patients with Type 2 diabetes [16]. Lastly, in patients with both Type 1 and Type 2 diabetes the presence of renal disease increases the risk of cardiovascular disease [4, 13]. Of note is that the risk of developing cardiovascular events in patients with diabetes has decreased recently most likely due to better lipid and blood pressure control, which again reinforces the need to aggressively treat these risk factors in patients with diabetes [5, 7, 17].

ROLE OF GLYCEMIC CONTROL

Epidemiological studies have shown an association between the level of glycemic control and the development of cardiovascular disease [1, 4, 5]. However, the association of glycemic control with cardiovascular disease is considerably weaker than the association of glycemic control with the microvascular complications of diabetes, such as retinopathy and nephropathy [4]. Additionally, the association of hypertension and dyslipidemia with cardiovascular disease is stronger than the association of hyperglycemia with cardiovascular disease [2]. It must be recognized that epidemiological studies can only demonstrate associations and that confounding variables could account for the association between poor glycemic control and cardiovascular disease. For example, patients with poor glycemic control may not undertake other preventive measures that could reduce cardiovascular disease such as exercise, healthy diet, etc. Furthermore, the patients with poor glycemic control may have less compliance with therapies that reduce lipids and blood pressure. Therefore, randomized studies are essential in determining the role of glycemic control on cardiovascular disease.

Early randomized studies, such as the UGDP and VA cooperative study, did not demonstrate a reduction in cardiovascular events in patients who were aggressively treated for glucose control [18-20]. In fact, the data suggested that improvements in glycemic control (VA cooperative study) or the use of certain drugs to treat diabetes (oral sulfonylureas in UGDP) may actually increase the risk of cardiovascular disease. More recent studies, the DCCT in patients with Type 1 diabetes and the Kumamoto study in patients with Type 2 diabetes, while demonstrating a decrease in cardiovascular events in the subjects randomized to improved glycemic control did not have enough cardiovascular disease events to demonstrate a statistically significant reduction (DCCT studied a population at low risk for cardiovascular disease and the Kumamoto study had a very small number of subjects) [21-23]. In contrast, both the DCCT and the Kumamoto study clearly demonstrated that improvements in glycemic control resulted in a reduction in microvascular disease [21-23]. However the long term follow-up of the DCCT has demonstrated that those in the intensive glycemic control group had a decrease in cardiovascular disease in subsequent years [24, 25]. The initial DCCT compared intensive vs. conventional therapy for a mean of 6.5 years. At the end of the study a very large proportion of subjects agreed to participate in a follow-up observational study (Epidemiology of Diabetes Interventions and Complications- EDIC). During this follow-up period glycemic control was relatively similar between the intensive therapy and conventional therapy group (glycosylated hemoglobin 7.9% vs. 7.8%) but during the trial there was a large difference in glycosylated hemoglobin levels (7.4% vs. 9.1%). After a mean 17 years of observation, the risk of any cardiovascular event was reduced by 42% and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease was reduced by 57% in the intensive control group. This study demonstrates that being in the intensive glycemic control group (for 6.5 of the 17 years of observation) is sufficient to have long term beneficial effects on the risk of developing cardiovascular disease in patients with Type 1 diabetes. This beneficial effect was not entirely due to the prevention of microvascular complications as the differences between the intensive and conventional treatment groups for cardiovascular disease persisted after adjusting for microalbuminuria and albuminuria. When an outcome of improved glycemic control is seen or persists for years after the trial is over the phenomenon is called a metabolic memory effect.

A similar finding has been reported with regard to Type 2 diabetes. The UKPDS studied a large number of newly diagnosed patients with Type 2 diabetes at risk for cardiovascular disease. In this study improved glycemic control, with either insulin or sulfonylureas, reduced cardiovascular disease by 16%, which just missed being statistically significant (p=0.052) [26]. In the UKPDS the improvement in glycemic control was modest (HbA1c reduced by approximately 0.9%) and the 16% reduction in cardiovascular disease was in the range predicted based on epidemiological studies. The results of a 10 year follow-up of the UKPDS study have been reported (total duration of observation 25 years) [27]. After termination of the study, glycosylated hemoglobin levels became very similar between the control and treatment groups.

Nevertheless, risk reductions for MI became statistically significant for the insulin and the sulfonylurea group compared to controls (15% decrease, p=0.01).

Similarly, the DiGami study, which used insulin infusion during the peri-MI period to improve glycemic control followed by long-term glycemic control, demonstrated that survival post MI was significantly improved by good glycemic control [28]. While this study focused on a highly selected population and time period (patients undergoing a MI), the results are consistent with the hypothesis that improvements in glycemic control will reduce cardiovascular disease. However, the DiGami 2 study did not confirm the benefits of tight glucose control beginning in the peri-MI period on outcomes [29]. It must be noted though that the differences in glucose control achieved in DiGami 2 were much smaller than planned and the number of patients recruited was less than anticipated. Together these deficiencies could account for the failure to demonstrate significant differences in cardiovascular disease events in this study.

Because of the need for more definitive data on the effect of glycemic control on cardiovascular disease in Type 2 diabetes, three large randomized trials, the ACCORD, ADVANCE, and VA Diabetes Trial, have been carried out. Much to everyone's surprise and disappointment, improvement in glycemic control did not clearly result in a reduction in cardiovascular disease in these trials.

The ACCORD study randomized 10,251 subjects with Type 2 diabetes in the US and Canada with either a history of cardiovascular disease or at increased risk for the development of cardiovascular disease [30]. Multiple different treatment protocols were used with the goal of achieving an A1c level < 6% in the intensive group and between 7-7.9% in the standard glycemic control group. During the trial the A1c levels were 6.4% in the intensive group and 7.5% in the standard group. As expected the use of insulin therapy was much greater in the intensive group, as was the occurrence of hypoglycemia and weight gain. After a mean duration of 3.5 years this study was stopped early by the data safety monitoring board due to an increased all-cause mortality in the intensive treatment group (1.41 vs. 1.14% per year; hazard ratio 1.22 CI 1.01- 1.46). The primary outcome (MI, stroke, cardiovascular disease death) was reduced by 10% in the intensive control group but this was not statistically significant (p=0.16). The explanation for the increased death rate in the intensive treatment arm remains unknown, but it has been speculated that the increased deaths might have been due to hypoglycemia, weight gain, too rapidly lowering A1c levels, or unrecognized drug toxicity.

The ADVANCE study randomized 11,140 subjects with Type 2 diabetes in Europe, Asia, Australia/New Zealand and Canada who either had cardiovascular disease or at least one other risk factor for cardiovascular disease [31]. In the intensive group the goal A1c was <6.5%. The achieved A1c levels during the trial were 6.3% in the intensive group and 7.3% in the standard treatment group. Of note is that compared to the ACCORD study, less insulin use was required to achieve these A1c levels. With regards to macrovascular disease (MI, stroke, and cardiovascular death), no significant differences were observed between the intensive and standard treatment groups (HR 0.94, CI 0.84-1.06, p=0.32). In contrast to the ACCORD trial, no increase in overall or cardiovascular mortality in the intensive treatment group was observed in the ADVANCE study. Long term follow-up did not demonstrate a decrease in the risk of death from any cause or major macrovascular events between the intensive-glucose-control group and the standard-glucose-control group [32].

The VA Diabetes Trial randomized 1,791 subjects with poor glycemic control on maximal oral agent therapy or insulin (entry A1c 9.4%) [33]. In the intensive group, the goal A1c was <6.0%. The achieved A1c levels during the trial were 6.9% in the intensive group and 8.5% in the standard treatment group. Similar to the other trials, a significant reduction in cardiovascular disease was not observed in the intensive glycemic control group (HR 0.88, CI 0.74-1.05, p=0.12). Notably there were more cardiovascular disease deaths and sudden deaths in the intensive treatment group, but this increase was not statistically significant. With long-term follow-up, the intensive-therapy group had a significantly lower risk of heart attack, stroke, congestive heart failure, amputation for ischemic gangrene, or cardiovascular-related death than did the standard-therapy group (hazard ratio, 0.83; P=0.04 [34]. However, there was no reduction in cardiovascular or total mortality.

Thus, while the epidemiological data strongly suggests that glycemic control would favorably impact cardiovascular disease the recent randomized trials that were designed specifically to prove this hypothesis have failed to demonstrate a clear link. There are a number of explanations for why these trials may not have worked as planned. First, in the ACCORD, ADVANCE, and VA Diabetes Trial, other cardiovascular risk factors were aggressively treated (lipid and BP lowering, ASA therapy). As a result of these treatments, the actual number of cardiovascular events was considerably less than expected in these trials. The lower event rate may have reduced the ability to see a beneficial effect of glucose control. Additionally, the beneficial effects of glucose control maybe more robust if other risk factors are not aggressively controlled. In this regard it is worth noting that in the earlier UKPDS, which showed that improved glycemic control reduced cardiovascular events, both BP and lipids were not aggressively treated by current standards (systolic BP 135-140mm Hg, LDL cholesterol 135-142mg/dl), which could be why this older trial demonstrated a small benefit on cardiovascular disease.

Second, these three recent trials were comparing relatively low A1c levels in both the intensive and usual control groups (A1c in intensive from ~6.4-6.9% and usual control group from ~7.0-8.4%). It is possible that both levels are on the “flatter” portion of the glycemic control-cardiovascular risk curve and that if one compared patients with higher A1c values one would see more impressive results.

Third, all three trials were carried out by initiating tight control in patients with long standing diabetes who either had pre-existing cardiovascular disease or were at high risk for cardiovascular disease. It is possible that patients with a different clinical profile would be more likely to benefit from intensive glucose control. Subgroup analysis from these trials have suggested that patients with a shorter duration of diabetes, less severe diabetes, or the absence of pre-existing cardiovascular disease actually benefited from intensive control. It may be that glycemic control is most important prior to the development of significant atherosclerosis.

Clearly additional studies on different types of patients (i.e. newly diagnosed without evidence of cardiovascular disease) will be necessary to definitively determine the role of glycemic control in different diabetic populations.

Fourth, the duration of these studies was relatively short and it is possible that a much longer duration of glycemic control is required to show benefits on cardiovascular disease. In the UKPDS study the beneficial effects of intensive glucose control was not statistically significant at the end of the study but with an extended duration of follow-up (15-25 years) became statistically significant.

Fifth, it may be that glycemic control will be more important in patients with Type 1 diabetes where abnormalities in glucose metabolism are the major reason for the increased risk of atherosclerosis. In contrast, patients with Type 2 diabetes have multiple risk factors for atherosclerosis (dyslipidemia, hypertension, inflammation, insulin resistance, coagulation disorders) and glucose may play only a minor role in the increased risk. The differences in other cardiovascular risk factors could account for why intensive glycemic control produced a marked reduction in cardiovascular disease in the DCCT (Type 1 trial) and had only minimal effects in the trials carried out in patients with Type 2 diabetes.

Finally, it is possible that our current treatments have side effects that mask the beneficial effects of glucose control. For example, hypoglycemia and weight gain could counterbalance the beneficial effects of improvements in glycemic control. It is possible that different treatment strategies could lead to more profound benefits (see below).

Thus, the currently available data do not indicate that glycemic control will have major effects on reducing cardiovascular disease in patients with Type 2 diabetes. Furthermore, there are concerns that too tight control in patients with advanced disease could be harmful. In contrast, in patients with Type 1 diabetes intensive glucose control appears to be very beneficial based on the results of the DCCT.

THE EFFECT OF GLUCOSE LOWERING DRUGS ON CARDIOVASCULAR DISEASE

Metformin

In the UKPDS, metformin, while producing a similar improvement in glycemic control as insulin or sulfonylureas, markedly reduced cardiovascular disease by approximately 40% [35]. In the ten year follow-up the patients randomized to metformin in the UKPDS continued to show a reduction in MI and all-cause mortality [27]. Two other randomized controlled trials have also demonstrated cardiovascular benefits with metformin therapy.

A study by Kooy et al compared the effect of adding metformin or placebo in overweight or obese patients already on insulin therapy [36]. After a mean follow-up of 4.3 years this study observed a reduction in macrovascular events (HR 0.61 CI- 0.40-0.94, p=0.02), which was partially accounted for by metformin's beneficial effects on weight. In this study the difference in A1c between the metformin and placebo group was only 0.3%.

Hong et al randomized non-obese patients with coronary artery disease to glipizide vs. metformin therapy for three years [37]. A1c levels were similar, but there was a marked reduction in cardiovascular events in the metformin treated group (HR 0.54 CI 0.30- 0.90, p=0.026).

Together, these results suggest that metformin may reduce cardiovascular disease and that this effect is not due to improving glucose control. Metformin decreases weight or prevents weight gain, lowers lipid levels, etc. and these non-glucose effects may account for the beneficial effects on cardiovascular disease.

Thiazolidinediones

Studies with pioglitazone have also suggested a beneficial effect on cardiovascular disease. The ProActive study was a randomized controlled trial that examined the effect of pioglitazone vs. placebo over a 3 year period in type 2 diabetics with pre-existing macrovascular disease [38]. With regards to the primary endpoint (a composite of all-cause mortality, non-fatal myocardial infarction including silent MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle), there was a 10% reduction in events in the pioglitazone group but this difference was not statistically significant (p=0.095). It should be noted that both leg revascularization and leg amputations are not typical primary end points in cardiovascular disease trials and these could be affected by pioglitazone induced edema. When one focuses on standard cardiovascular disease endpoints, the pioglitazone treated group did demonstrate a 16% reduction in the main secondary endpoint (composite of all-cause mortality, non-fatal myocardial infarction, and stroke) that was statistically significant (p=0.027). In the pioglitazone treated group, blood pressure, A1c, triglyceride, and HDL levels were all improved compared to the placebo group making it very likely that the mechanism by which pioglitazone decreased vascular events was multifactorial.

Recently a multicenter, double-blind trial (IRIS Trial), randomly assigned 3876 patients without diabetes with a recent ischemic stroke or TIA to treatment with either pioglitazone (target dose, 45 mg daily) or placebo [39]. After 4.8 years, the primary outcome of fatal or nonfatal stroke or myocardial infarction occurred in 9.0% of the pioglitazone group and 11.8% of the placebo group (hazard ratio 0.76; P=0.007). All components of the primary outcome were reduced in the pioglitazone treated group. Fasting glucose, fasting triglycerides, and systolic and diastolic blood pressure were lower while HDL cholesterol and LDL cholesterol levels were higher in the pioglitazone group than in the placebo group. Although this study excluded patients with diabetes the results are consistent with and support the results of a protective effect of pioglitazone observed in the ProActive study.

Further support for the beneficial effects of pioglitazone on atherosclerosis is provided by studies that have examined the effect of pioglitazone on carotid intima-medial thickness. Both the Chicago and Pioneer studies demonstrated favorable effects on carotid intima-medial thickness in patients treated with pioglitazone compared to patients treated with sulfonylureas [40, 41]. Similarly, Periscope, a study that measured atheroma volume by intravascular ultrasonography, also demonstrated less atherosclerosis in the pioglitazone treated group compared to patients treated with sulfonylureas [42].

While the data from a variety of different types of studies strongly suggests that pioglitazone is anti-atherogenic, the results with rosiglitazone are different. Several meta-analyses of small and short-duration rosiglitazone trials suggested that rosiglitazone was associated with an increased risk of adverse cardiovascular outcomes [43, 44]. However, the final results of the RECORD study, a randomized trial that was specifically designed to compare the effect of rosiglitazone vs. either metformin or sulfonylurea therapy on cardiovascular events, have been published and did not reveal a difference in cardiovascular disease death, myocardial infarctions, or stroke [45-47]. Similarly, an analysis of patients on rosiglitazone in the BARI 2D trial also did not suggest an increase or decrease in cardiovascular events in the patients treated with rosiglitazone [48]. Thus, while the available data suggests that pioglitazone is anti-atherogenic, the data for rosiglitazone suggests a neutral effect. Whether these differences between pioglitazone and rosiglitazone are accounted for by their differential effects on lipid levels are unknown (see below for information on the effects of these drugs on lipid levels).

DPP4 Inhibitors

Because of the importance of cardiovascular disease in patients with diabetes the FDA is requiring manufacturers of new drugs to treat diabetes to carry out studies addressing cardiovascular endpoints. Recently, the effect of the DPP4 inhibitors saxagliptin, alogliptin and sitagliptin, on cardiovascular endpoints has been reported. In the saxagliptin study, 16,492 patients with Type 2 diabetes who had a history of cardiovascular events or who were at high risk were randomized to saxagliptin or placebo for 2.1 years [49]. Saxagliptin did not increase or decrease cardiovascular death, myocardial infarction, or ischemic stroke. Interestingly more patients treated with saxagliptin were admitted to the hospital for heart failure. In the alogliptin trial, 5380 patients with either an acute myocardial infarction or unstable angina within the previous 15-90 days were randomized to alogliptin or placebo [50]. As seen in the saxagliptin study the rates of cardiovascular events were similar in the alogliptin and placebo groups. The risk of hospitalization for heart failure was not increased in patients treated with alogliptin [51]. Finally, in the sitagliptin trial, 14,671 patients with established cardiovascular disease were randomized to sitagliptin or placebo for 3 years [52]. Sitagliptin did not decrease the risk of major adverse cardiovascular events or increase hospitalization for heart failure. Thus, these results indicate that DPP4 inhibitors do not reduce cardiovascular disease.

SGLT2 Inhibitors

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2 (SGLT2 inhibitor), on cardiovascular morbidity and mortality in patients with Type 2 diabetes has recently been reported [53]. In this study 7020 patients at high risk for cardiovascular disease were randomly assigned to receive 10 mg or 25 mg of empagliflozin or placebo once daily and were followed for 3.1 years. In the combined empagliflozin treated groups there was a statistically significant 14% reduction in the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). As compared with placebo, empagliflozin treatment did not result in a significant difference in the occurrence of myocardial infarction or strokes. However, empagliflozin resulted in a significantly lower risk of death from cardiovascular causes (hazard ratio, 0.62), death from any cause (hazard ratio, 0.68), and hospitalization for heart failure (hazard ratio, 0.65). The beneficial effects of empagliflozin were noted to occur very rapidly and the beneficial effects on congestive heart failure appeared to be the dominant effect compared to effects on atherosclerotic events. The mechanisms accounting for the beneficial effects of empagliflozin in this study are uncertain. Glycemic control was better in the empagliflozin treated patients but it is doubtful that this could account for the observed results. Empagliflozin treatment was associated with small reductions in weight, waist circumference, uric acid level, and systolic and diastolic blood pressure with no increase in heart rate and small increases in both LDL and HDL cholesterol. Whether these changes played a role in reducing events remains to be determined. It is possible that hemodynamic changes secondary to the osmotic diuresis induced by empagliflozin contributed to the beneficial effects. Finally, there may be direct effects of SGLT2 inhibition on myocardial and renal metabolism [54]. Additional cardiovascular outcome studies with other SGLT2 inhibitors (canagliflozin and dapagliflozin) are being carried out and it will be of great interest to see if these studies also demonstrate a reduction in cardiovascular events [55, 56].

GLP-1 Receptor Agonists

Recently, the effect of three GLP-1 receptor agonists on cardiovascular disease has been reported. 6068 patients with Type 2 diabetes and who recently had a myocardial infarction or been hospitalized for unstable angina were randomized to placebo or lixisenatide, a once-daily GLP-1 receptor agonist, and followed for a median of 25 months [57]. The primary end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina was similar in the placebo or lixisenatide groups.

In contrast, a recent study has shown that liraglutide decreased cardiovascular events [58]. In this trial 9340 patients at high cardiovascular risk were randomly assigned to receive liraglutide or placebo. After median time of 3.5 years, the primary outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in significantly fewer patients in the liraglutide group (13.0%) than in the placebo group (14.9%) (hazard ratio, 0.87, $P<0.001$ for non-inferiority; $P=0.01$ for superiority). Additionally, deaths from cardiovascular causes (hazard ratio 0.78, $P=0.007$) or any cause was lower in the liraglutide group than in the placebo group (hazard ratio, 0.85; $P=0.02$). Interestingly patients with established cardiovascular disease or decreased renal function (eGFR < 60) appeared to derive the greatest benefit of liraglutide treatment. As expected weight and blood pressure were decreased in the liraglutide treated group and A1c levels were also decreased by 0.4%.

In support of the beneficial effects of GLP1 receptor agonists to reduce cardiovascular events, semiglutide, a long acting GLP-1 receptor agonist, has recently been shown to also reduce cardiovascular events [59]. In this trial, 3297 patients with Type 2 diabetes with established cardiovascular disease, chronic heart failure, chronic kidney disease, or age >60 with at least one cardiovascular risk factor were randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke occurred in 6.6% of the semaglutide group and 8.9% of the placebo group (hazard ratio, 0.74; $P<0.001$ for non-inferiority, $P = 0.02$ for superiority). In this study, both body weight and A1c levels were decreased in the patients treated with semiglutide.

Thus, two studies have demonstrated that treatment with GLP-1 receptor agonists reduce cardiovascular events. The mechanism accounting for this decrease is uncertain but could be related to reductions in glycated hemoglobin, body weight, systolic blood pressure, or the direct effect of activation of GLP-1 receptors on the atherosclerotic process. Cardiovascular studies using long acting exenatide and dulaglutide are in-progress and will provide additional information on the effect of GLP-1 agonists on cardiovascular events [55, 60].

Acarbose

There are no studies examining the effect of acarbose on cardiovascular outcomes in patients with Type 2 diabetes. However, in the STOP-NIDDM trial 1429 subjects with impaired glucose tolerance were randomized to placebo vs. acarbose and followed for 3.3 years [61]. In the acarbose group a 49% relative risk reduction in the development of cardiovascular events (hazard ratio 0.51; P =.03) was observed. Among cardiovascular events, the major reduction was in the risk of myocardial infarction (HR, 0.09; P =.02). Whether similar results will occur in patients with diabetes is currently being tested [62].

Cycloset

Cycloset is a quick-release bromocriptine formulation (bromocriptine-QR) that activates the D2 dopamine receptor and is approved for the treatment of diabetes. A 52 week, randomized, double-blind, multicenter trial evaluated cardiovascular safety in 3,095 patients with type 2 diabetes treated with bromocriptine-QR or placebo [63]. The composite end point of first myocardial infarction, stroke, coronary revascularization, or hospitalization for angina or congestive heart failure occurred in 1.8% of the bromocriptine-QR treated vs. 3.2% of the placebo-treated patients resulting in a 40% decrease in cardiovascular events (HR 0.60; CI 0.37– 0.96). Clearly further studies to confirm this finding and to elucidate the mechanism of this beneficial effect are required.

Insulin

In patients with Type 1 diabetes the DCCT trial demonstrated that insulin therapy reduced cardiovascular events [24, 25]. With regards to patients with Type 2 diabetes in the Origin Trial

12,537 people with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or Type 2 diabetes were randomized to receive insulin glargine or standard care [64]. The cardiovascular outcomes, which included nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes, revascularization, or hospitalization for heart failure, were similar in the glargine and placebo groups. These studies demonstrate that insulin does not accelerate atherosclerosis and by lowering glucose levels may decrease atherosclerosis, although the protective effects are mainly observed in patients with Type 1 diabetes.

Other Studies

Finally, the Bari 2D study compared the effect of insulin sensitizers (metformin/TZD- mostly rosiglitazone) vs. insulin provision therapy (sulfonylureas/insulin) on cardiovascular outcomes in patients with Type 2 diabetes and coronary artery disease (> 50% stenosis and positive stress test or > 70% stenosis and classic angina) [65, 66]. In this study, no differences in survival or cardiovascular endpoints were observed between metformin/TZD therapy vs. sulfonylurea/insulin therapy for the entire study. However, in the group with more severe coronary artery disease who were selected for coronary artery bypass surgery, the combination of coronary artery bypass and treatment with insulin sensitizers was associated with a lower rate of cardiovascular events. Why the metformin/TZD group only derived an enhanced benefit in the coronary artery bypass patients in this study is unknown. It should be noted that the vast majority of patients on TZD therapy were treated with rosiglitazone and as discussed above the effects of rosiglitazone on cardiovascular disease do not appear to be as beneficial as pioglitazone.

These studies demonstrate that the method by which one improves glycemic control may be very important, with different drugs having effects in addition to glucose lowering that could reduce cardiovascular events.

ROLE OF OTHER RISK FACTORS IN CARDIOVASCULAR DISEASE

Numerous studies have demonstrated that the traditional risk factors for cardiovascular disease play an important role in patients with diabetes [2, 4, 5, 67]. Patients with diabetes without other risk factors have a relatively low risk of cardiovascular disease (albeit higher than similar non-diabetic patients), whereas the increasing prevalence of other risk factors markedly increases the risk of developing cardiovascular disease [2]. The major reversible traditional risk factors are hypertension, cigarette smoking, and lipid abnormalities [2, 4, 5, 13, 68]. Other risk factors include obesity (particularly visceral obesity), insulin resistance, small dense LDL, elevated triglycerides, procoagulent state (increased PAI-1, fibrinogen), homocystine, Lp (a), renal disease, microalbuminuria, and inflammation (C-reactive protein, SAA, cytokines) [2, 4, 5, 67, 68]. In the last decade it has become clear that to reduce the risk of cardiovascular disease in patients with diabetes, one will not only need to improve glycemic control but also address these other cardiovascular risk factors. In the remainder of this chapter we will focus on the dyslipidemia that occurs in patients with diabetes.

ROLE OF LIPIDS IN CARDIOVASCULAR DISEASE

As in the non-diabetic population, epidemiological studies have shown that increased LDL and non-HDL cholesterol levels and decreased HDL cholesterol levels are associated with an increased risk of cardiovascular disease in patients with diabetes [2, 4, 67, 68]. In patients with diabetes, elevations in serum triglyceride levels also are associated with an increased risk of cardiovascular disease [4, 68, 69]. With regards to triglycerides, it is not clear whether they are an independent risk factor for cardiovascular disease or whether the elevation in triglycerides is a marker for other abnormalities, such as decreased HDL cholesterol levels or increased non-HDL cholesterol levels [4, 68, 69].

LIPID ABNORMALITIES IN PATIENTS WITH DIABETES

In patients with Type 1 diabetes in good glycemic control, the lipid profile is very similar to lipid profiles in the general population [67]. In contrast, in patients with Type 2 diabetes, even when in good glycemic control, there are abnormalities in lipid levels [70-73]. It is estimated that 30-60% of patients with Type 2 diabetes have dyslipidemia [5, 74]. Specifically, patients with Type 2 diabetes often have an increase in serum triglyceride levels, increased VLDL and IDL, and decreased HDL cholesterol levels. Non-HDL cholesterol levels are increased due to the increase in VLDL and IDL. LDL cholesterol levels are typically not different than in normal subjects but there is an increase in small dense LDL, a lipoprotein particle that may be particularly pro-atherogenic. As a consequence there are more LDL particles, which coupled with the increases in VLDL and IDL, leads to an increase in Apo B [70-73]. Studies have shown that the anti-oxidant and anti-inflammatory functions of HDL isolated from patients with diabetes are reduced, indicating that HDL levels per se may not fully reflect risk [75]. Additionally, the postprandial increase in serum triglycerides is accentuated and elevations in postprandial lipids may increase the risk of cardiovascular disease [70-73]. It should be recognized that these lipid changes are characteristic of the alterations in lipid profile seen in obesity and the metabolic syndrome (insulin resistance syndrome) [76]. Additionally, the ability of HDL to facilitate cholesterol efflux is reduced in patients with Type 2 diabetes [77]. Since a high percentage of patients with Type 2 diabetes are obese, insulin resistant and have the metabolic syndrome, it is not surprising that the prevalence of increased triglycerides and small dense LDL and decreased HDL cholesterol is common in patients with Type 2 diabetes even when these patients are in good glycemic control.

In both Type 1 and Type 2 diabetes, poor glycemic control increases serum triglyceride levels, VLDL and IDL, and decreases HDL cholesterol levels [71]. Poor glycemic control can also result in a modest increase in LDL cholesterol, which because of the elevation in triglycerides is often in the small dense LDL subfraction. It is therefore important to optimize glycemic control in patients with diabetes because this will have secondary beneficial effects on lipid levels.

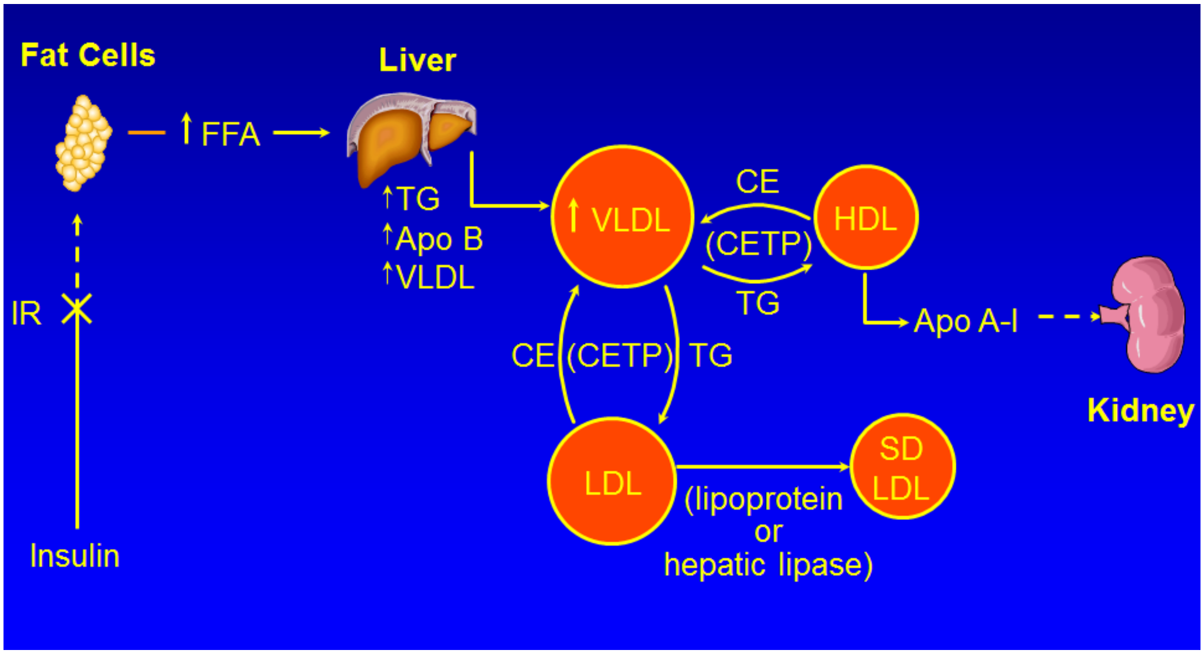
Lp (a) levels are usually within the normal range in patients with Type 2 diabetes and do not appear to be greatly affected by glycemic control [78-80]. In patients with Type 1 diabetes Lp(a) levels are also within the normal range but improvements in glycemic control result in decreases in Lp (a) levels [81]. The development of microalbuminuria and the onset of renal disease are associated with an increase in Lp (a) levels [82].

EFFECT OF GLUCOSE LOWERING DRUGS ON LIPIDS

Some methods used to improve glycemic control may have an impact on lipid levels above and beyond their effects on glucose metabolism. Specifically, insulin, sulfonylureas, meglinitides, DPP4 inhibitors, and alpha-glucosidase inhibitors do not markedly alter fasting lipid profiles other than by improving glucose control (there are data indicating that DPP4 inhibitors and acarbose decrease postprandial triglyceride excursions, but they do not alter fasting lipid levels) [55]. In contrast, metformin, thiazolidinediones, GLP1 agonists, and SGLT2 inhibitors have effects independent of glycemic control on serum lipid levels. Metformin decreases serum triglyceride levels and may modestly decrease LDL cholesterol without altering HDL cholesterol [55]. The effect of thiazolidinediones appears to depend on which agent is used. Rosiglitazone increases serum LDL cholesterol levels, increases HDL cholesterol levels, and only decreases serum triglycerides if the baseline triglyceride levels are high [55]. In contrast, pioglitazone has less impact on LDL cholesterol levels, but increases HDL cholesterol levels, and decreases serum triglyceride levels [55]. It should be noted that reductions in the small dense LDL subfraction and an increase in the large buoyant LDL subfraction are seen with both thiazolidinediones [55]. In a randomized head to head trial it was shown that pioglitazone decreased serum triglyceride levels and increased serum HDL cholesterol levels to a greater degree than rosiglitazone treatment [83, 84]. Additionally, pioglitazone increased LDL cholesterol levels less than rosiglitazone. In contrast to the differences in lipid parameters, both rosiglitazone and pioglitazone decreased A1c and C-reactive protein to a similar extent. The mechanism by which pioglitazone induces more favorable changes in lipid levels than rosiglitazone is unclear, but differential actions of ligands for nuclear hormone receptors are well described. Treatment with SGLT2 inhibitors results in a small increase in LDL and HDL cholesterol levels [55]. Finally, GLP-1 receptor agonists, such as exenatide and liraglutide, can favorably affect the lipid profile by inducing weight loss (decreasing triglycerides and increasing HDL cholesterol levels) [55]. Additionally, GLP-1 receptor agonists reduce postprandial triglycerides [55].

PATHOPHYSIOLOGY OF THE DYSLIPIDEMIA OF DIABETES

(Figure 1):



There are a number of different abnormalities that contribute to the dyslipidemia seen in patients with Type 2 diabetes and obesity (figure 1) [71-74, 85-87]. A key abnormality is the overproduction of VLDL by the liver, which is a major contributor to the elevations in serum triglyceride levels. The rate of secretion of VLDL is highly dependent on triglyceride availability, which is determined by the levels of fatty acids available for the synthesis of triglycerides in the liver. An abundance of triglycerides prevents the intra-hepatic degradation of Apo B-100 allowing for increased VLDL formation and secretion. There are three major sources of fatty acids in the liver all of which may be altered in patients with type 2 diabetes. First, the flux of fatty acids from adipose tissue to the liver is increased. An increased mass of adipose tissue, particularly visceral stores, results in increased fatty acid delivery to the liver. Additionally, insulin suppresses the lipolysis of triglycerides to free fatty acids in adipose tissue; thus in patients with either poorly controlled diabetes due to a decrease in insulin or a decrease in insulin activity due to insulin resistance, the inhibition of triglyceride lipolysis is blunted and there is increased triglyceride breakdown leading to increased fatty acid deliver to the liver. A second source of fatty acids in the liver is *de novo* fatty acid synthesis from glucose. Numerous studies have shown that fatty acid synthesis is increased in the liver in patients with type 2 diabetes. This increase may be mediated by the hyperinsulinemia seen in patients with insulin resistance. While the liver is insulin resistant to the effects of insulin on carbohydrate metabolism the liver remains sensitive to the effects of insulin stimulating lipid synthesis. Specifically, insulin stimulates the activity of SREBP-1c, a transcription factor that increases the expression of the enzymes required for the synthesis of fatty acids. While the liver is insulin resistant to the effects of insulin on carbohydrate metabolism the liver remains sensitive to the effects of insulin stimulating lipid synthesis. Additionally, in the presence of hyperglycemia, glucose can induce another transcription factor, carbohydrate responsive element binding protein (ChREBP), which also stimulates the transcription of the enzymes required for fatty acid synthesis. The third source of fatty acids is the uptake of triglyceride rich lipoproteins by the liver. Studies have shown an increase in intestinal fatty acid synthesis and the enhanced secretion of chylomicrons in animal models of type 2 diabetes. This increase in chylomicrons leads to the increased delivery of fatty acids to the liver. The increase in hepatic fatty acids produced by these three pathways results in an increase in the synthesis of triglycerides in the liver and the protection of Apo B-100 from degradation resulting in the increased formation and secretion of VLDL. Finally, insulin stimulates the post translational degradation of Apo B-100 in the liver and a decrease in insulin activity in patients with Type 2 diabetes also allows for the enhanced survival of Apo B-100 promoting increased VLDL formation.

While the overproduction of triglyceride rich lipoproteins by the liver and intestine are the main contributors to the elevations in serum triglyceride levels in patients with Type 2 diabetes, there are also abnormalities in the metabolism of these triglyceride rich lipoproteins. First, there is a modest decrease in lipoprotein lipase activity, the key enzyme that metabolizes triglyceride rich lipoproteins. The expression of lipoprotein lipase is stimulated by insulin and decreased insulin activity in patients with Type 2 diabetes results in a decrease in lipoprotein lipase, which plays a key role in the hydrolysis of the triglycerides carried in chylomicrons and VLDL. Additionally, patients with Type 2 diabetes have an increase in Apo C-III levels. Glucose stimulates and insulin suppresses Apo C-III expression. Apo C-III is an inhibitor of lipoprotein lipase activity and thereby reduces the clearance of triglyceride rich lipoproteins. In addition, Apo C-III also inhibits the cellular uptake of lipoproteins. Recent studies have shown that loss of function mutations in Apo C-III lead to lower serum triglyceride levels and a reduced risk of cardiovascular disease [88, 89]. Interestingly, inhibition of Apo C-III expression results in a decrease in serum triglyceride levels even in patients deficient in lipoprotein lipase, indicating that the ability of Apo C-III to modulate serum triglyceride levels is not dependent solely on regulating lipoprotein lipase activity [90]. Thus, in patients with diabetes, a decrease in clearance of triglyceride rich lipoproteins also contributes to the elevation in serum triglyceride levels.

The elevation in triglyceride rich lipoproteins in turn has effects on other lipoproteins. Specifically, cholesterol ester transfer protein (CETP) mediates the exchange of triglycerides from triglyceride rich VLDL and chylomicrons to LDL and HDL. The increase in triglyceride rich lipoproteins *per se* leads to an increase in CETP mediated exchange, increasing the triglyceride content of both LDL and HDL. The triglyceride on LDL and HDL is then hydrolyzed by hepatic lipase and lipoprotein lipase leading to the production of small dense LDL and small HDL. Notably hepatic lipase activity is increased in patients with Type 2 diabetes, which will facilitate the removal of triglyceride from LDL and HDL resulting in small lipoprotein particles. The affinity of Apo A-I for small HDL particles is reduced, leading to the disassociation of Apo A-I, which in turn leads to the accelerated clearance and breakdown of Apo A-I by the kidneys. Additionally, the production of Apo A-I may be reduced in patients with diabetes. High glucose levels can activate ChREBP and this transcription factor inhibits Apo A-I expression. Furthermore, insulin stimulates Apo A-I expression and a reduction in insulin activity due to insulin resistance or decreased insulin levels may also lead to a decrease in ApoA-I expression. The net result is lower levels of Apo A-I and HDL cholesterol levels in patients with Type 2 diabetes.

The above described changes lead to the typical dyslipidemia observed in patients with Type 2 diabetes (increased triglycerides, decreased HDL cholesterol, and an abundance of small dense

LDL and small HDL). In patients with both Type 1 and Type 2 diabetes, poor glycemic control can further adversely affect lipid and lipoprotein metabolism. As noted above the expression of lipoprotein lipase is stimulated by insulin. If insulin activity is very low the expression of lipoprotein lipase is severely suppressed and the metabolism of triglyceride rich lipoproteins is markedly impaired. This leads to the delayed clearance of both chylomicrons and VLDL and elevations of triglyceride rich lipoproteins. Additionally, insulinopenia results in a marked increase in lipolysis in adipose tissue, leading to the release of free fatty acids into the circulation. This increase in serum fatty acids results in the increased delivery of fatty acids to the liver, enhanced triglyceride synthesis in the liver, and the increased production and secretion of VLDL. Whereas patients with Type 1 diabetes who are well controlled typically have normal serum lipid profiles, if their control deteriorates they will develop hypertriglyceridemia. In patients with Type 2 diabetes deterioration of glycemic control will further exacerbate their underlying dyslipidemia resulting in greater increases in serum triglyceride levels. If the synthesis of new VLDL is increased sufficiently this can result in an increase in LDL levels. HDL levels may decrease due to the formation of small HDL that are more susceptible to accelerated clearance. Improvements in glycemic control can markedly lower serum triglyceride levels and may increase serum HDL levels. In patients with very poorly controlled diabetes improvements in glycemic control may also lower LDL levels.

Many if not most patients with Type 2 diabetes are obese. Obesity is a pro-inflammatory state due to the macrophages that infiltrate adipose tissue. The cytokines produced by these macrophages and the adipokines that are produced by fat cells also alter lipid metabolism [91, 92]. The pro-inflammatory cytokines, TNF and IL-1, decrease the expression of lipoprotein lipase and increase the expression of angiopoietin like protein 4, an inhibitor of lipoprotein lipase. Together these changes decrease lipoprotein lipase activity, thereby delaying the clearance of triglyceride rich lipoproteins. In addition, pro-inflammatory cytokines stimulate lipolysis in adipocytes increasing circulating free fatty acid levels, which will provide substrate for hepatic triglyceride synthesis. In the liver, pro-inflammatory cytokines stimulate de novo fatty acid and triglyceride synthesis. These alterations will lead to the increased production and secretion of VLDL. Thus, increases in the levels of pro-inflammatory cytokines will stimulate the production of triglyceride rich lipoproteins and delay the clearance of triglyceride rich lipoproteins, which together will contribute to the increase in serum triglycerides that occurs in obese patients.

Adipokines, such as leptin and adiponectin, also regulate lipid metabolism. Obesity increases serum leptin levels and leptin stimulates lipolysis in adipocytes which will increase serum free fatty acid levels. Obesity decreases adiponectin serum levels and studies have shown that the administration of adiponectin to mice decreases serum triglyceride levels. Adiponectin increases lipoprotein lipase and improves the clearance of an exogenous fat load. One would therefore anticipate that the decrease in adiponectin that occurs with obesity would have adverse effects on triglyceride metabolism.

Pro-inflammatory cytokines also affect HDL metabolism [93]. First they decrease the production of Apo A-I, the main protein constituent of HDL. Second, in many tissues pro-inflammatory cytokines decrease the expression of ABCA1 and ABCG1, which will lead to a decrease in the efflux of phospholipids and cholesterol from the cell to HDL. Third, pro-inflammatory cytokines decrease the production and activity of LCAT, which will limit the conversion of cholesterol to cholesterol esters in HDL. This step is required for the formation of a normal spherical HDL particle and facilitates the ability of HDL to transport cholesterol. Fourth, pro-inflammatory cytokines decrease CETP levels, which will decrease the movement of cholesterol from HDL to Apo B containing lipoproteins. Pro-inflammatory cytokines decrease the expression of SR-B1 in the liver. SR-B1 plays a key role in the uptake of cholesterol from HDL particles into hepatocytes. Finally, pro-inflammatory cytokines decrease the expression of ABCG5 and ABCG8 in the liver, which reduces the secretion of cholesterol into the bile, providing more cholesterol for the formation and secretion of VLDL into the circulation. Together these changes induced by pro-inflammatory cytokines result in a decrease in reverse cholesterol transport. Reverse cholesterol transport plays a key role in preventing cholesterol accumulation in macrophages and thereby reduces atherosclerosis. Inflammation also decreases other important functions of HDL, such as its ability to prevent LDL oxidation [94]. In parallel inflammation increases the oxidation of LDL and the small dense LDL that occurs in patients with diabetes is more susceptible to oxidation.

EFFECT OF LIPID LOWERING DRUGS ON CARDIOVASCULAR EVENTS

Monotherapy Studies:

Statins

As shown in Table 1, statin trials, including both primary and secondary prevention trials, have consistently shown the beneficial effect of statins on cardiovascular disease including patients with diabetes, primarily by lowering LDL cholesterol levels. The Cholesterol Treatment Trialists analyzed data from 18,686 subjects with diabetes (mostly Type 2 diabetes) from 14 randomized trials [95]. In the statin treated group there was a 9% decrease in all-cause mortality, a 13% decrease in vascular mortality, and a 21% decrease in major vascular events per 39mg/dl reduction in LDL cholesterol. The beneficial effect of statin therapy was seen in both primary and secondary prevention patients. The effect of statin treatment on cardiovascular events in patients with diabetes was similar to that seen in non-diabetic subjects. Thus, these studies indicate that statins are beneficial in reducing cardiovascular disease in patients with diabetes. Because of the large number of patients with diabetes included in the Heart Protection Study (HPS) and CARDS these two studies will be discussed in greater depth.

Table 1. Statin Trials- Diabetic Subgroups

Study	Drug	% Decrease	
		Controls	Diabetics
2º Prevention			
4S	Simvastatin	32	55
CARE	Pravastatin	23	25

Study	Drug	% Decrease	
		Controls	Diabetics
LIPID	Pravastatin	25	19
LIPS	Fluvastatin	20	43
HPS	Simvastatin	24	26
1º Prevention			
AFCAPS	Lovastatin	37	42
HPS	Simvastatin	24	24
ASCOT	Atorvastatin	44	16
CARDS	Atorvastatin	--	37

The HPS was a double blind randomized trial that focused on patients at high risk for the development of cardiovascular events, including patients with a history of myocardial infarctions, other atherosclerotic lesions, diabetes, and/or hypertension [96, 97]. Patients were between 40 and 80 years of age and had to have total serum cholesterol levels greater than 135mg/dl (thus very few patients were excluded because they did not have a high enough cholesterol level). The major strength of this trial was the large number of patients studied (>20,000). The diabetes subgroup included 5,963 subjects and thus was as large as many other prevention trials. The study was a 2x2 study design comparing simvastatin 40mg a day vs. placebo and anti-oxidant vitamins (vitamin E 600mg, vitamin C 250mg, and beta-carotene 20mg) vs. placebo and lasted approximately 5 years. Analysis of the group randomized to the anti-oxidant vitamins revealed no beneficial or harmful effects. In contrast, simvastatin therapy (40mg per day) reduced cardiovascular events, including myocardial infarctions and strokes, by approximately 25% in all participants and to a similar degree in the diabetic subjects (total cardiovascular disease reduced 27%, coronary mortality 20%, myocardial infarction 37%, stroke 24%). Further analysis of the subjects with diabetes revealed that the reduction in cardiovascular events with statin therapy was similar in individuals with diabetes diagnosed for a short duration (<6 years) and for a long duration (>13 years). Similarly, subjects with diabetes in good control (HbA1c <7%) and those not in ideal control (HbA1c >7%) also benefited to a similar degree with statin therapy. Moreover, both Type 1 and Type 2 diabetic patients had a comparable reduction in cardiovascular disease with simvastatin therapy. The decrease in cardiovascular events in patients with Type 1 diabetes was not statistically significant because of the small number of subjects. Nevertheless this is the only trial that included Type 1 diabetics and suggests that patients with Type 1 will benefit from statin therapy similar to Type 2 diabetics. In general, statin therapy reduced cardiovascular disease in all subgroups of subjects with diabetes (females, males, older age, renal disease, hypertension, high triglycerides, low HDL, ASA therapy, etc) i.e. statin therapy benefits all patients with diabetes. Of particular note, even subjects with diabetes whose baseline LDL cholesterol levels were less than 116mg/dl had a reduction in cardiovascular events when treated with simvastatin. Moreover, analysis of all study patients similarly demonstrated that subjects with LDL cholesterol levels less than 100mg/dl benefited from statin therapy. These results are of particular clinical importance because they demonstrate that in high-risk patients with LDL cholesterol levels < 100mg/dl statin therapy would nevertheless result in benefit.

The CARDS trial specifically focused on subjects with diabetes [98]. The subjects in this trial were males and females with Type 2 diabetes between the ages of 40 to 75 years of age who were at high risk of developing cardiovascular disease based on the presence of hypertension, retinopathy, renal disease, or current smoking. Of particular note, the subjects did not have any evidence of clinical atherosclerosis (myocardial disease, stroke, peripheral vascular disease) at entry and hence this study is a primary prevention trial. Inclusion criteria included LDL cholesterol levels less than 160mg/dl and triglyceride levels less than 600mg/dl. Of note is that the average LDL cholesterol in this trial was approximately 118mg/dl, indicating relatively low LDL cholesterol levels. A total of 2838 Type 2 diabetic subjects were randomized to either placebo or atorvastatin 10mg a day. Atorvastatin therapy resulted in a 40% decrease in LDL cholesterol levels with over 80% of patients achieving LDL cholesterol levels less than 100mg/dl. Most importantly, atorvastatin therapy resulted in a 37% reduction in cardiovascular events. In addition, strokes were reduced by 48% and coronary revascularization by 31%. As seen in the HPS, subjects with relatively low LDL cholesterol levels (LDL <120mg/dl) benefited to a similar extent as subjects with higher LDL cholesterol levels (>120mg/dl). CARDS, in combination with the other statin trials, provide conclusive evidence that statin therapy will reduce cardiovascular events in patients with diabetes. Importantly, the benefits of statin therapy are seen in patients with diabetes in both primary and secondary prevention trials.

A few studies have compared the effect of different magnitudes of LDL cholesterol lowering with statins on the reduction in cardiovascular events in patients with diabetes. The Post-CABG study compared very low dose lovastatin (2.5-5.0mg per day) vs. high dose lovastatin (40-80mg per day) in 1,351 subjects post bypass surgery [99]. Approximately 10% of patients in this trial had diabetes. Baseline LDL cholesterol levels were between 130-174mg/dl. As expected the high dose of lovastatin reduced LDL cholesterol levels to a much greater degree than the low dose lovastatin (low dose achieved LDL cholesterol levels of approximately 135mg/dl vs. high dose achieved LDL cholesterol levels of approximately 95mg/dl). The main comparison in this trial was the change in atherosclerosis in the grafts measured by comparing baseline angiography to angiography after an average of 4.3 years. In the entire population the mean percentage of grafts with progression of atherosclerosis was 27 percent in the high dose lovastatin group and 39 percent in the low dose lovastatin group. Additionally, the rate of revascularization was reduced by 29 percent in the high dose lovastatin group. When the patients with diabetes were analyzed separately, similar beneficial effects were observed. These results indicate that lowering LDL cholesterol levels to less than 100mg/dl would slow the angiographic changes to a greater extent than lowering the LDL cholesterol levels to 135mg/dl. Of note though is that even with LDL cholesterol levels less than 100mg/dl progression of atherosclerosis still occurred.

Studies have also compared reductions of LDL cholesterol to approximately 100mg/dl to more aggressive reductions in LDL cholesterol. The Reversal Trial studied 502 symptomatic coronary artery disease patients with an average LDL cholesterol of 150mg/dl [100]. Approximately 19%

of the patients in this trial had diabetes. Patients were randomized to moderate LDL lowering therapy with pravastatin 40mg per day or to aggressive lipid lowering with atorvastatin 80mg per day. As expected, LDL cholesterol levels were considerably lower in the atorvastatin treated group (pravastatin LDL= 110mg/dl vs. atorvastatin LDL= 79mg/dl). Most importantly, when one analyzed the change in atheroma volume determined after 18 months of therapy using intravascular ultrasound, the group treated aggressively with atorvastatin had a much lower progression rate than the group treated with pravastatin. Compared with baseline values, patients treated with atorvastatin had no change in atheroma burden (there was a very slight regression of lesions), whereas patients treated with pravastatin showed progression of lesions. When one compares the extent of the reduction in LDL cholesterol to the change in atheroma volume, a 50% reduction in LDL (LDL cholesterol levels of approximately 75mg/dl) resulted in the absence of lesion progression. This study suggests that lowering the LDL cholesterol to levels well below 100mg/dl is required to prevent disease progression as measured by intravascular ultrasound. Other studies, such as Asteroid, have shown that marked reductions in LDL cholesterol (in Asteroid mean LDL cholesterol levels were 61mg/dl) can even result in the regression of atherosclerosis determined by intravascular ultrasound measurements [101]. Recently the Saturn trial demonstrated that aggressive lipid lowering with either atorvastatin 80mg or rosuvastatin 40mg would induce regression of coronary artery atherosclerosis to a similar degree in patients with and without diabetes if the LDL cholesterol levels were reduced to less than 70mg/dl [102]. Together these trials indicate that aggressive lowering of LDL cholesterol levels to below 70mg/dl can induce regression of atherosclerotic lesions.

The Prove-It trial determined in patients recently hospitalized for an acute coronary syndrome whether aggressively lowering of LDL cholesterol with atorvastatin 80mg per day vs. moderate LDL cholesterol lowering with pravastatin 40mg per day would have a similar effect on cardiovascular end points such as death, myocardial infarction, documented unstable angina requiring hospitalization, revascularization, or stroke [103, 104]. In this trial approximately 18% of the patients were diabetic. As expected, the on-treatment LDL cholesterol levels were significantly lower in patients aggressively treated with atorvastatin compared to the moderate treated pravastatin group (atorvastatin LDL cholesterol = approximately 62 vs. pravastatin LDL cholesterol = approximately 95mg/dl). Of great significance, death or major cardiovascular events was reduced by 16% over the two years of the study in the group aggressively treated with atorvastatin. Moreover, the risk reduction in the patients with diabetes in the aggressive treatment group was similar to that observed in non-diabetics.

In the treating to new targets trial (TNT) patients with stable coronary heart disease and LDL cholesterol levels less than 130mg/dl were randomized to either 10mg or 80mg atorvastatin and followed for an average of 4.9years [105, 106]. Approximately 15% of the patients had diabetes. As expected LDL cholesterol levels were lowered to a greater extent in the patients treated with 80mg atorvastatin than with 10mg atorvastatin (77mg/dl vs. 101mg/dl). Impressively, the occurrence of major cardiovascular events was reduced by 22% in the group treated with atorvastatin 80mg ($p<0.001$). In the patients with diabetes events were reduced by 25% in the high dose statin group. Once again the risk reduction in the patients with diabetes randomized to the aggressive treatment group was similar to that observed in non-diabetics.

Finally, the IDEAL trial was a randomized study that compared atorvastatin 80mg vs. simvastatin 20-40mg in 8,888 patients with a history of cardiovascular disease [107]. Approximately 12% of the patients had diabetes. As expected LDL cholesterol levels were reduced to a greater extent in the atorvastatin treated group than the simvastatin treated group (approximately 104mg/dl vs. 81mg/dl). Once again the greater reduction in LDL cholesterol levels was associated with a greater reduction in cardiovascular events. Specifically, major coronary events defined as coronary death, nonfatal myocardial infarction, or cardiac arrest was reduced by 11% (p=0.07), while nonfatal acute myocardial infarctions were reduced by 17% (p=0.02).

Combining the results of the Heart Protection Study, CARDS, Reversal, Prove-It, TNT, and IDEAL leads one to the conclusion that aggressive lowering of LDL cholesterol with statin therapy will be beneficial and suggests that in high risk patients lowering the LDL to levels well below 100mg/dl is desirable. Recently the Cholesterol Treatment Trialists reviewed five trials with 39,612 subjects that were designed to determine the effect of usual vs. aggressive reductions in LDL cholesterol [108]. They reported that intensive control (approximately a 19mg/dl difference in LDL cholesterol) resulted in a 15% decrease in major vascular events, a 13% reduction in coronary death or non-fatal MI, a 19% decrease in coronary revascularization, and a 16% decrease in strokes. As will be discussed below most treatment guidelines reflect the results of these studies.

Fibrates

The beneficial effect of monotherapy with fibrates (e.g. gemfibrozil, fenofibrate) on cardiovascular disease in patients with diabetes is shown in Table 2. While the data are not as strong as with statins, the results of these randomized trials suggest that this class of drug also reduces cardiovascular events in patients with diabetes. The largest trial was the Field Trial [109]. In this trial, 9795 patients with Type 2 diabetes between the ages of 50 and 75 not taking statin therapy were randomized to fenofibrate or placebo and followed for approximately 5 years. Fenofibrate therapy resulted in a 12% decrease in LDL cholesterol, a 29% decrease in triglycerides and a 5% increase in HDL cholesterol levels. The primary outcome was coronary events (coronary heart disease death and non-fatal MI), which were reduced by 11% in the fenofibrate group but did not reach statistical significance (p= 0.16). However, there was a 24% decrease in non-fatal MI in the fenofibrate treated group (p=0.01) and a non-significant increase in coronary heart disease mortality. Total cardiovascular disease events (coronary events plus stroke and coronary or carotid revascularization) were reduced 11% (p=0.035). These beneficial effects of fenofibrate therapy on cardiovascular disease were observed in patients without a previous history of cardiovascular disease. In patients with a previous history of cardiovascular disease no benefits were observed. . Additionally, the beneficial effect of fenofibrate therapy was seen only in those subjects less than 65 years of age. The beneficial effects of fenofibrate in this study may have been muted by the increased use of statins in the placebo group, which reduced the differences in lipid levels between the placebo and fenofibrate groups. If one adjusted for the addition of lipid-lowering therapy, fenofibrate reduced the risk of coronary heart disease events by 19% (p=0·01) and of total cardiovascular disease events by 15% (p=0·004).

The mechanism by which fibrates reduce cardiovascular events is unclear. These drugs lower serum triglyceride levels and increase HDL cholesterol, but it should be recognized that the beneficial effects of fibrates could be due to other actions of these drugs. Specifically, these drugs activate PPAR alpha, which is present in the cells that comprise the atherosclerotic lesions, and it is possible that these compounds directly affect lesion formation and development. In addition, fibrates are anti-inflammatory. In fact, analysis of the VA-HIT study suggested that much of the benefit of fibrate therapy was not due to changes in serum lipoprotein levels [110, 111]. To summarize, while in general the studies to date suggest that monotherapy with fibrates reduce cardiovascular disease in patients with diabetes, the results are not as robust or consistent as seen in the statin trials. Of note fibrate therapy was most effective in patients with increased triglyceride levels and decreased HDL levels, a lipid profile typically seen in patients with type 2 diabetes.

Table 2. Fibrate Trials-Diabetic Subgroup

Study	Drug	#Diabetic subjects	% Decrease	
			controls	diabetics
Helsinki Heart Study	Gemfibrozil	135	34	60*
VA-HIT	Gemfibrozil	620	24	24
DIAS	Fenofibrate	418	-	33*
Sendcap	Bezafibrate	164	-	70
Field	Fenofibrate	9795	-	11*

* Not statistically significant

<u>Niacin</u>

A single randomized trial, the Coronary Drug Project, has examined the effect of niacin monotherapy on cardiovascular outcomes [112]. This trial was carried out from 1966 to 1974 (before the introduction of statin therapy) in men with a history of a prior myocardial infarction and demonstrated that niacin therapy reduced cardiovascular events. The results of this study were re-analyzed to determine the effect of niacin therapy in subjects with varying baseline fasting and 1-hour post meal glucose levels [113]. It was noted that 6 years of niacin therapy reduced the risk of coronary heart disease death or nonfatal MI by approximately 15-25% regardless of baseline fasting or 1 hour post glucose challenge glucose levels. Particularly notable is that reductions in events were seen in the subjects who had a fasting glucose levels >126mg/dl or 1 hour glucose levels >220mg/dl (i.e. patients with diabetes). Thus, based on this single study, niacin reduces cardiovascular events both in normal subjects and patients with diabetes.

<u>Other Drugs</u>

With regards to ezetimibe, PCSK9 inhibitors, and bile acid sequestrants, there have been no randomized studies that have examined the effect of these drugs on cardiovascular end points in subjects with diabetes. In non-diabetic subjects bile acid sequestrants have reduced cardiovascular events [114, 115]. Since bile acid sequestrants have a similar beneficial impact on serum lipid levels in diabetic and non-diabetic subjects one would anticipate that these drugs would also result in a reduction in events in the diabetic population. There are no outcome studies with ezetimibe monotherapy in patients with diabetes but given that this drug reduces LDL cholesterol levels and in combination with statins reduces cardiovascular events one would anticipate that ezetimibe monotherapy will also reduce cardiovascular events. Outcome studies with PCSK9 inhibitors are on-going.

Combination Therapy:

The studies with statins have been so impressive that most patients with diabetes over the age of 40 are routinely treated with statin therapy and younger patients with diabetes at high risk for cardiovascular disease are also typically on statin therapy (see Current Guidelines Section). Therefore a key issue is whether the addition of other lipid lowering drugs to statins will result in a further reduction in cardiovascular events. A difficulty with such studies is that the reduction in cardiovascular events induced by statin therapy is so robust that very large trials may be required to see additional benefit.

Statins + Fibrates

The ACCORD-LIPID trial was designed to determine if the addition of fenofibrate to aggressive statin therapy would result in a further reduction in cardiovascular disease in patients with Type 2 diabetes [116]. In this trial, 5,518 patients on statin therapy were randomized to placebo or fenofibrate therapy. The patients had diabetes for approximately 10 years and either had pre-existing cardiovascular disease or were at high risk for developing cardiovascular disease. During the trial, LDL cholesterol levels were approximately 80mg/dl. There was only a small difference in HDL cholesterol with the fenofibrate groups having a mean HDL cholesterol of 41.2mg/dl while the control group had an HDL cholesterol of 40.5mg/dl. Differences in triglyceride levels were somewhat more impressive with the fenofibrate group having a mean triglyceride level of 122mg/dl while the control group had a triglyceride level of 144mg/dl. First occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes was the primary outcome and there was no statistical difference between the fenofibrate treated group and the placebo group. Additionally, there were also no statistically significant differences between the groups with regards to any of the secondary outcome measures of cardiovascular disease. Of note, the addition of fenofibrate to statin therapy did not result in an increase in either muscle or liver side effects. On further analysis there was a possible benefit of fenofibrate therapy in the patients in whom the baseline triglyceride levels were elevated (>204mg/dl) and HDL cholesterol levels decreased (<34mg/dl). In the fibrate monotherapy trials, this same group of patients also derived the greatest benefit of fibrate therapy. Future fibrate statin combination therapy trials will need to focus on patients with high triglycerides and low HDL cholesterol levels. Finally, similar to what has been reported in other trials, fenofibrate had beneficial effects on the progression of microvascular disease [117, 118]. While this was a negative study, it must be recognized that most of the patients included in this study did not have the lipid profile that would typically lead to treatment with fibrates.

Statins + Niacin

The AIM-HIGH trial was designed to determine if the addition of niaspan to aggressive statin therapy would result in a further reduction in cardiovascular events in patients with pre-existing cardiovascular disease [119]. In this trial 3,314 patients were randomized to niaspan vs. placebo. Approximately 33% of the patients had diabetes. On trial, LDL cholesterol levels were in the 60-70mg/dl range in both groups. As expected, HDL cholesterol levels were increased in the niaspan treated group (approximately 44mg/dl vs. 38mg/dl), while triglycerides were decreased (approximately 121mg/dl vs. 155mg/dl). However, there were no differences in the primary endpoint between the control and niaspan treated groups (Primary endpoint consisted of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization). There were also no differences in secondary endpoints except for a possible increase in strokes in the niaspan treated group. The addition of niaspan to statin therapy did not result in a significant increase in either muscle or liver toxicity. Thus, this study does not provide support for the addition of niacin to statins. However, it should be recognized that this was a relatively small study and a considerable number of patients stopped taking the niaspan during the course of the study (25.4% of patients discontinued niaspan therapy). In addition, most of the patients included in this study did not have a lipid profile that one would typically consider treating with niacin therapy. In the subset of patients with TG > 198mg/dl and HDL cholesterol < 33mg/dl niacin showed a trend towards benefit (hazard ratio 0.74; p=0.073) in this study, suggesting that if the appropriate patient population was studied the results may have been different [120].

HPS 2 Thrive also studied the effect of niacin added to statin therapy [121]. This trial utilized extended release niacin combined with laropiprant, a prostaglandin D_2 receptor antagonist that reduces the flushing side effect of niacin treatment. HPS 2 Thrive was a very large trial with over 25,000 patients randomized to either niacin therapy or placebo. Approximately 32% of the patients in this trial had diabetes. The LDL cholesterol level was 63mg/dl, the HDL cholesterol 44mg/dl, and the triglycerides 125mg/dl at baseline. As expected, niacin therapy resulted in a modest reduction in LDL cholesterol (10mg/dl), a modest increase in HDL cholesterol (6mg/dl), and a marked reduction in triglycerides (33mg/dl). However, despite these lipid changes there were no significant differences in major cardiovascular events between the niacin and control group (risk ratio 0.96 CI 0.90- 1.03). It is unknown whether laropiprant, the prostaglandin D_2 receptor antagonist, might have effects that worsen atherosclerosis and increase event rates. Similar to the ACCORD-LIPID and AIM-HIGH studies, the group of patients included in the HPS 2 Thrive trial may not have been the ideal patient population to test for the beneficial effects of niacin treatment added to statin therapy. Ideally, patients with high triglycerides and high non-HDL cholesterol levels coupled with low HDL cholesterol levels should be studied.

Statins + Ezetimibe

Finally, the IMPROVE-IT trial tested whether the addition of ezetimibe to statin therapy would provide an additional beneficial effect in patients with the acute coronary syndrome [122]. This was a large trial with over 18,000 patients randomized to statin therapy vs. statin therapy +

ezetimibe. Approximately 27% of the patients in this trial had diabetes. On treatment LDL cholesterol levels were 70mg/dl in the statin alone group vs. 53mg/dl in the statin + ezetimibe group. There was a small but significant 6.4% decrease in major cardiovascular events (Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization, or stroke) in the statin + ezetimibe group (HR 0.936 CI (0.887, 0.988) p=0.016). Cardiovascular death, non-fatal MI, or non-fatal stroke were reduced by 10% (HR 0.90 CI (0.84, 0.97) p=0.003). These beneficial effects were particularly pronounced in the patients with diabetes. The results of this study have a number of important implications. First, it demonstrates that combination therapy may have benefits above and beyond statin therapy alone. Second, it provides further support for the hypothesis that lowering LDL *per se* will reduce cardiovascular events. Third, it suggests that lowering LDL levels into the 50s will have benefits above and beyond lowering LDL levels to the 70mg/dl range. These new results have implications for determining goals of therapy.

CURRENT GUIDELINES FOR SERUM LIPIDS

There are a number of different guidelines for treating lipids in patients with diabetes. The American College of Cardiology and American Heart Association (ACC/AHA) recommend that patients with both type 1 and type 2 diabetes between 40 and 75 years of age be treated with statin therapy [123]. If the estimated 10 year risk of developing a cardiovascular event is > 7.5% they recommend intensive statin therapy (atorvastatin 40-80mg or rosuvastatin 20-40mg). If the 10 year cardiovascular risk is < 7.5% they recommend moderate statin therapy (for example atorvastatin 10-20mg, simvastatin 20-40mg, pravastatin 40mg). Cardiovascular risk can be determined using a calculator that is available at **http://my.americanheart.org/cvriskcalculator** or can be downloaded as an app for a smart phone or tablet. The ACC/AHA do not recommend any specific LDL goal but rather to just treat with statin therapy. The ACC/AHA guidelines do not recommend the treatment with drugs other than statins, but these guidelines were published before the results of the IMPROVE-IT trial were known.

The 2016 American Diabetes Association (ADA) recommends that adult patients with diabetes have their lipid profile determined at the time of diabetes diagnosis and every 5 years thereafter or more frequently if indicated [124]. This profile includes total cholesterol, HDL cholesterol, triglycerides, and calculated LDL cholesterol. A lipid panel should be obtained immediately prior to initiating statin therapy. Once a patient is on statin therapy testing may be considered on an individual basis to monitor adherence and efficacy. Lifestyle modification including a reduction in saturated fat, trans fat, and cholesterol intake, weight loss if indicated, an increase in omega-3-fatty acids, viscous fiber, and plant stanols /sterol intake, and increased physical activity is indicated in all patients with diabetes. Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, in diabetic patients with overt cardiovascular disease or patients over age 40 who have one or more other cardiovascular risk factors (see table 3 for recommendations). If one follows these recommendations almost all patients with diabetes over the age of 40 will be on statin therapy and many, if not most, under the age of 40 will also be treated with statins. With regards to combination therapy the ADA guidelines make the following statements: 1) statin + ezetimibe- “For people meeting IMPROVE-IT eligibility criteria who can only tolerate a moderate-dose statin the addition of ezetimibe to statin therapy should be considered; 2) statin + PCSK9 inhibitor- “These agents may therefore be considered as adjunctive therapy for patients with diabetes at high risk for ASCVD events who require additional lowering of LDL cholesterol or who require but are intolerant to high intensity statin therapy”; 3) statin + niacin- “Combination therapy with a statin and niacin is not recommended”; statin + fibrate- no firm recommendation was provided. It should be noted that similar to the ACC/AHA guidelines the ADA guidelines do not provide LDL or non-HDL goals.

Table 3: ADA recommendations for statin treatment in people with diabetes

Age	Risk Factors	Statin Dose*
<40	None	None
	CVD risk factors**	Moderate/High
	Overt CVD	High
40-75	None	Moderate
	CVD risk factors	High
	Overt CVD	High
>75	None	Moderate
	CVD risk factors	Moderate/High
	Overt CVD	High

*In addition to lifestyle therapy

** CVD risk factors include LDL cholesterol > 100mg/dl, high blood pressure, smoking, and overweight/obesity

The National Lipid Association (NLA) has treatment goals for patients with diabetes [125]. In patients with Type 1 or Type 2 diabetes with pre-existing atherosclerotic cardiovascular disease, two or more risk factors for atherosclerotic cardiovascular disease (risk factors are age >45 for males, >55 for females; family history of early coronary heart disease; current cigarette smoking; high blood pressure >140/>90 mm HG; or low HDL < 40mg/dl males, < 50mg/dl females), or evidence of end organ damage (retinopathy, albumin/creatinine ratio > 30mg/g, or chronic kidney disease), the goal LDL is <70mg/dl and the goal non-HDL cholesterol is < 100mg/dl. In patients with diabetes with 0-1 risk factors and no end organ damage, the LDL goal is < 100mg/dl and the non-HDL cholesterol goal is < 130mg/dl. The NLA guidelines recommend considering drug therapy if a patient with diabetes is not at goal.

Thus, different organizations have proposed somewhat different recommendations for the treatment of lipids in patients with diabetes. Despite these differences it is clear that the vast majority of patients with diabetes will need to be treated with statins regardless of which guidelines one elects to follow.

One approach is to combine these recommendations. In patients with diabetes who have pre-existing cardiovascular disease initiate intensive statin therapy. In those without pre-exisiting cardiovascular disease begin with the ACC/AHA approach and calculate the 10 risk of developing cardiovascular disease in patients 40-75 years of age without pre-existing cardiovascular disease. Initiate intensive statin therapy if the 10 year risk is > 7.5% or moderate statin therapy if the risk is < 7.5%. Eight to twelve weeks after initiating statin therapy obtain a lipid panel to determine if the LDL and non-HDL cholesterol levels are at goal. In patients with pre-existing cardiovascular disease or multiple risk factors the goal should be an LDL < 70mg/dl and a non HDLc < 100mg/dl as suggested by the NLA. In patients that are not at high risk the goal should be an LDL < 100mg/dl and a non-HDLc < 130mg/dl. If the levels are not at goal either adjust the statin dose or consider adding additional medications. In patients with diabetes less than 40 years of age initiate statin therapy if the patient has overt cardiovascular disease or risk factors for cardiovascular disease and the LDL and non-HDL cholesterol levels are not at goal.

TREATMENT OF LIPID ABNORMALITIES IN PATIENT WITH DIABETES

Life Style Changes

Initial treatment of lipid disorders should focus on lifestyle changes [126]. There is little debate that exercise is beneficial and that all patients with diabetes should, if possible, exercise for at least 150 minutes per week (for example 30 minutes 5 times per week) . Exercise will decrease serum triglyceride levels and increase HDL cholesterol levels (an increase in HDL cholesterol requires vigorous exercise) [76, 126]. It should be noted that many patients with diabetes may have substantial barriers to participating in exercise programs, such as comorbidities that limit exercise tolerance, risk of hypoglycemia, and presence of microvascular complications (visual impairment, neuropathy) that make exercise difficult.

Diet is debated to a greater extent. Everyone agrees that weight loss in obese patients is essential [76, 126]. But how this can be achieved is hotly debated with many different "experts" advocating different approaches. The wide diversity of approach is likely due to the failure of any approach to be effective in the *long term* for the majority of obese patients with diabetes. If successful, weight loss will decrease serum triglyceride levels, increase HDL cholesterol levels, and modestly reduce LDL cholesterol [76, 126]. To reduce LDL cholesterol levels it is important that the diet decrease saturated fat, trans fatty acids, and cholesterol intake. Increasing soluble fiber is also helpful.

It is debated whether a low fat, high complex carbohydrate diets vs. a high monounsaturated fat diet is ideal for obese patients with diabetes [76]. One can find "experts" in favor of either of these approaches and there are pros and cons to each approach. It is essential to recognize that both approaches reduce simple sugars, saturated fat, trans fatty acids, and cholesterol intake. The high complex carbohydrate diet will increase serum triglyceride levels in some patients and if the amount of fat in the diet is markedly reduced serum HDL cholesterol levels may decrease. In obese patients it has been postulated that a diet high in monounsaturated fats, because of the increase in caloric density, will lead to an increase in weight gain. Both diets reduce saturated fat and cholesterol intake that will result in reductions in LDL cholesterol levels. Additionally, both of these diets also reduce trans-fatty acid intake, which will have a beneficial effect on LDL and HDL cholesterol levels and simple sugars, which will have a beneficial effect on triglyceride levels.

Recently there has been increased interest in low carbohydrate, increased protein diets. Short-term studies have indicated that weight loss is superior with this diet; however longer studies have demonstrated a similar weight loss to that observed with conventional diets. The major concern with the low carbohydrate, high protein diet is that they tend to be high in saturated fats and cholesterol. Additionally, there may also be an increased risk of progression of kidney disease in patients with pre-existing kidney disease. In the short-term studies during active weight loss this diet has not resulted in major perturbations in serum cholesterol levels, but there is concern that when weight becomes stable these diets might adversely affect serum cholesterol levels.
Thus, the available data do not indicate that any particular diet is best for inducing weight loss and it is essential to adapt the diet to fit the food preferences of the patient. Ultimately no weight loss diet will be successful if the patient cannot follow the diet for the long term.

While it is widely accepted that lifestyle changes will decrease cardiovascular events it should be recognized that the Look Ahead trial failed to demonstrate a reduction in cardiovascular events [127]. In this trial, over 5000 overweight or obese patients with Type 2 diabetes were randomized to either an intensive lifestyle intervention group that promoted weight loss through decreased caloric intake and increased physical activity or to a group that received diabetes support and education (control group). After a median follow-up of 9.6 years there was no difference in cardiovascular events (hazard ratio in the intervention group, 0.95; 95% CI 0.83 to 1.09; P=0.51). A limitation of this study was that while the weight difference between groups was impressive during the first year of the trial, over time the differences greatly narrowed such that at the end of the trial the intensive group had a 6.0% weight loss while the control group had a 3.5% weight loss. This very modest difference demonstrates the difficulty in sustaining long term lifestyle changes. Thus, while weight loss and diet therapy are likely to be beneficial in reducing cardiovascular events, in clinical practice they are seldom sufficient because long-term life style changes are very difficult for most patients to maintain.

In contrast to the failure of lifestyle therapy in the Look Ahead trial to reduce cardiovascular events, the PREDIMED trial employing a Mediterranean diet did reduce the incidence of major cardiovascular disease [128]. In this multicenter trial center trial, carried out in Spain, over 7000 patients at high risk for developing cardiovascular disease were randomized to three diets (primary prevention trial). A Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet. Approximately 50% of the patients in this trial had type 2 diabetes. In the patients assigned to the Mediterranean diets there was 29% decrease in the primary end point (myocardial infarction, stroke, and death from cardiovascular disease). Subgroup analysis demonstrated that the Mediterranean diet was equally beneficial in patients with and without diabetes. The Mediterranean diet resulted in a small but significant increase in HDL cholesterol levels and a small decrease in both LDL cholesterol and triglyceride levels [129]. A secondary prevention trial of a Mediterranean diet has also demonstrated a reduction in cardiovascular events. The Lyon Diet Heart Study randomized 584 patients who had a myocardial infarction within 6 months to a Mediterranean type diet vs usual diet [130, 131]. There was a marked reduction in events in the group of patients randomized to the Mediterranean diet (cardiac death and nonfatal myocardial infarction rate was 4.07 per 100 patient years in the control diet vs. 1.24 in the Mediterranean diet $p<0.0001$). Unfortunately there is no indication of the number of patients with diabetes in the Lyon Diet Heart Study or whether patients with diabetes responded similar to the entire group. Lipid levels were similar in both groups in this trial [130]. The results of these two trials indicate that we should be encouraging our patients to follow a Mediterranean type diet.

With the currently available weight loss drugs only modest effects on weight and lipid levels have been observed [76, 126]. In some patients weight loss drugs may be a useful adjuvant to diet therapy. Bariatric surgery can have profound effects on weight and can result in improvements in lipid profiles [76, 126]. Additionally, observational studies have shown a decrease in cardiovascular events following bariatric surgery in patients with and without diabetes [132-134].

Ethanol and simple sugars, in particular fructose, increase serum triglyceride levels in susceptible patients. In patients with hypertriglyceridemia efforts should be made to reduce the intake of ethanol, simple sugars, and fructose [126].

Lastly, in the past some "experts" advocated the addition of fish oil supplements to reduce cardiovascular events. However, the recent Origin Trial did not demonstrate that fish oil supplements were beneficial in patients with type 2 diabetes or patients at high risk for the development of type 2 diabetes [135]. In this trial over 12,000 patients were randomized to a 1 gram capsule containing at least 900 mg (90% or more) of ethyl esters of n-3 fatty acids or placebo daily. After a median follow-up of over 6 years, there was no difference in major cardiovascular events. The results of this trial and other trials in patients without diabetes have indicated that routine fish oil supplementation is not protective for cardiovascular disease [126, 136]. However, the Jelis Trial carried out in Japan did demonstrate that adding 1800mg of EPA to statin therapy reduced cardiovascular events by approximately 19%, so it is possible that certain preparations or higher amounts of fish oil will have beneficial effects [137]. Notably, the Jelis trial was an open label trial and the control group did not receive a placebo. It should be recognized that higher doses of fish oil are required to lower serum triglyceride levels (~3-4 grams of DHA/EPA) and are useful in treating patients with high triglyceride levels [138]. Most studies of fish oil in patients with diabetes have demonstrated that this is a safe approach and that worsening of glycemic control does not occur in patients with diabetes treated with fish oil supplements [138]. Additionally, in some patient's high dose fish oil increases LDL cholesterol levels, particularly when serum triglyceride levels are very high [138].

Drug Therapy

The effect of statins, fibrates, niacin, ezetimibe, fish oil, bile acid binders, and PCSK9 inhibitors on lipid levels in patients with diabetes is virtually identical to that seen in the non-diabetic patients (Table 4).

Statins: Statins are easy to use and generally well tolerated by patients with diabetes. However, statins can adversely affect glucose homeostasis. In non-diabetics the risk of developing diabetes is increased by approximately 10% with higher doses of statin causing a greater risk than more moderate doses [139, 140]. The mechanism for this adverse effect is unknown but older, obese patients with higher baseline glucose levels are at greatest risk. In patients with diabetes an analysis of 9 studies with over 9,000 patients with diabetes reported that the patients randomized to statin therapy had a 0.12% higher A1c than the placebo group indicating that statin therapy is associated with only a very small increase in A1c levels in patients with diabetes, which is unlikely to be clinically significant [141]. Individual studies such as CARDS and the Heart Protection Study have also shown only a very modest effect of statins on A1c levels in patients with diabetes [96, 98, 142]. Muscle symptoms occur in patients with diabetes similar to what is observed in patients without diabetes.

Ezetimibe: Ezetimibe is easy to use and generally well tolerated by patients with diabetes.

Fibrates: Fibrates are easy to use and generally well tolerated by patients with diabetes. When combining fibrates with statin therapy it is best to use fenofibrate as the risk of inducing myositis is much less than when statins are used in combination with gemfibrozil, which can inhibit statin metabolism [143]. In the ACCORD-LIPID Trial the incidence of muscle disorders was not increased in the statin + fenofibrate group compared to statin alone [116]. The dose of fenofibrate needs to be adjusted in patients with renal disease and fenofibrate itself can induce a reversible increase in serum creatinine levels. It should be noted that marked reductions in HDL cholesterol levels can occur in some patients treated with both fenofibrate and a TZD [144].

Bile acid sequestrants: Bile acid sequestrants are relatively difficult to take due to GI toxicity (mainly constipation) [145]. Diabetic subjects have an increased prevalence of constipation, which may be exacerbated by the use of bile acid sequestrants. On the other hand, in diabetic patients with diarrhea, the use of bile acid sequestrants may be advantageous. Bile acid sequestrants may also increase serum triglyceride levels, which can be a problem in patients with diabetes who are already hypertriglyceridemic [145]. An additional difficulty in using bile acid sequestrants is their potential for binding other drugs [145]. Many drugs should be taken either two hours before or four hours after taking bile acid sequestrants to avoid the potential of decreased drug absorption. Diabetic patients are frequently on multiple drugs for glycemic control, hypertension, etc., and it can sometimes be difficult to time the ingestion of bile resin sequestrants to avoid these other drugs. Colesevelam (Welchol) is a bile acid sequestrant that comes in pill or powder form, which causes fewer side effects and has fewer interactions with other drugs than other preparations [146]. The usual dose is 3 pills twice a day with meals or 1 packet of powder in water or other liquids once a day with a meal. Of particular note is that a number of studies have shown that colesevelam improves glycemic control in patients with diabetes resulting in an approximately 0.5% decrease in A1c levels [147].

Niacin: Niacin is well known to cause skin flushing and itching and GI upset [148]. Additionally, niacin reduces insulin sensitivity (i.e., causes insulin resistance), which can worsen glycemic control [148]. Studies have shown that niacin is usually well tolerated in diabetic subjects who are in good glycemic control [149, 150]. In patients with poor glycemic control, niacin is more likely to adversely impact glucose levels. In the HPS2-Thrive trial, niacin therapy significantly worsened glycemic control in patients with diabetes and induced new onset diabetes in 1.3% of subjects that were non-diabetic [121]. High doses of niacin are more likely to adversely affect glycemic control. Niacin can also increase serum uric acid levels and induce gout, an abnormality that is already common in obese patients with type 2 diabetes [148]. Additionally recent trials have reported an increased incidence of infection and bleeding with niacin therapy [148]. However, niacin is the most effective drug in increasing HDL cholesterol levels, which are frequently low in patients with diabetes.

Fish oil: A Cochrane review of fish oil in patients with diabetes have demonstrated that this is a safe approach and does not result in worsening of glycemic control in patients with diabetes [138]. Fish oil effectively lowers triglyceride levels but, in some patients, particularly those with significant hypertriglyceridemia, high dose fish oil increases LDL cholesterol levels [138]. It should be noted that fish oil products that contain just EPA (Vascepa) do not adversely affect LDL cholesterol levels [151]. When using fish oil to lower serum triglyceride levels it is important to recognize that one is aiming to provide 3-4 grams of DHA/EPA per day. The quantity of these active omega 3 fatty acids can vary greatly from product to product. Prescription fish oil products contain large amounts of these active ingredients whereas the amount of DHA/EPA in over the counter preparations can vary greatly and in some instances is very low.

PCSK9 inhibitors: In 2015 two monoclonal antibodies that inhibit PCSK9 (proprotein convertase subtilisin kexin type 9) were approved for the lowering of LDL cholesterol levels; Alirocumab (Praluent) and evolocumab (Repatha) [145]. Alirocumab is administered as either 75mg or 150mg subcutaneously every 2 weeks while evolocumab is administered as either 70mg subcutaneously every 2 weeks or 420mg subcutaneously once a month [145]. A meta-analysis of three trials with 413 patients with type 2 diabetes found that in patients with type 2 diabetes evolocumab caused a 60% decrease in LDL cholesterol compared to placebo and a 39% decrease in LDL cholesterol compared to ezetimibe treatment [152]. In addition, in patients with type 2 diabetes, evolocumab decreased non-HDL cholesterol 55% vs. placebo and 34% vs. ezetimibe) and Lp(a) (31% vs. placebo and 26% vs. ezetimibe). These beneficial effects were not affected by glycemic control, insulin use, renal function, and cardiovascular disease status. Thus, PCSK9 inhibitors are effective therapy in patients with type 2 diabetes and the beneficial effects on pro-atherogenic lipoproteins is similar to what is observed in non-diabetic patients.

Table 4. Effect of Lipid Lowering Drugs

	LDLc	HDLc	Triglycerides
Statins	↓ 20-60%	↑ 5-15%	↓ 0-35%*
Bile acid sequestrants	↓ 10-30%	↑ 0-10%	↑ 0-10%**
Fibrates	↓ 0-15%***	↑ 5-15%	↓ 20-50%
Niacin	↓ 10-25%	↑ 10-30%	↓ 20-50%
Ezetimibe	↓ 15-25%	↑ 1-3%	↓ 10-20%
PCSK9 Inhibitors	↓ 50-60%	↑ 5-15%	↓ 5-20%
High Dose Fish Oil	↑ 0- 50%**	↑ 4- 9%	↓ 20- 50%*
***Patients with elevated TG have largest decrease ** In patients with high TG may cause marked increase *** In some patients may increase LDL			

Therapeutic Approach

The first priority in treating lipid disorders in patients with diabetes is to lower the LDL cholesterol levels to goal, unless triglycerides are markedly elevated (> 500- 1000mg/dl), which increases the risk of pancreatitis. LDL cholesterol is the first priority because the database linking lowering LDL cholesterol with reducing cardiovascular disease is extremely strong and we now have the ability to markedly decrease LDL cholesterol levels. Dietary therapy is the initial step but in most patients will not be sufficient to achieve the LDL cholesterol goals. If patients are willing and able to make major changes in their diet it is possible to achieve significant reductions in LDL cholesterol levels but this seldom occurs in clinical practice [153].

Statins are the first choice drugs to lower LDL cholesterol levels and the majority of diabetic patients will require statin therapy. There are several statins currently available in the US and one should be sure to choose a statin that is capable of lowering the LDL cholesterol to goal. The effect of different doses of the various statins on LDL cholesterol levels is shown in Table 5. Currently four statins are available as generic drugs, lovastatin, pravastatin, atorvastatin, and simvastatin, and these statins are relatively inexpensive. The particular statin used may be driven by price, ability to lower LDL cholesterol levels, and potential drug interactions.

If a patient is unable to tolerate statins or statins as monotherapy are not sufficient to lower LDL cholesterol to goal the second choice drug is either ezetimibe or a PCSK9 inhibitor. Ezetimibe can be added to any statin and is now available in a combination pill with simvastatin (Vytorin) or atorvastatin (Liptrozet). PCSK9 inhibitors can also be added to any statin and are the drug of choice if a large decrease in LDL cholesterol is required to reach goal (PCSK9 inhibitors will lower LDL cholesterol levels by 50-60% when added to a statin, whereas ezetimibe will only lower LDL cholesterol by approximately 20%). Bile acid sequestrants are an alternative particularly if a reduction in A1c level is also needed. Ezetimibe, PCSK9 inhibitors, and bile acid sequestrants additively lower LDL cholesterol levels when used in combination with a statin, because these drugs increase hepatic LDL receptor levels by different mechanisms, thereby resulting in a reduction in serum LDL cholesterol levels [145]. Niacin and the fibrates also lower LDL cholesterol levels (see table 4).

Table 5. Approximate effect of different doses of statins on LDL cholesterol levels

% LDL Reduction	Simvastatin (Zocor)	Atorvastatin (Lipitor)	Lovastatin (Mevacor)	Pravastatin (Pravachol)	Fluvastatin (Lescol)	Rosuvastatin (Crestor)	Pitavastatin (Livalo)
27	10mg	-	20mg	20mg	40mg	-	-
34	20mg	10mg	40mg	40mg	80mg	-	1mg
41	40mg	20mg	80mg	80mg	-	-	2mg
48	80mg	40mg	-	-	-	10mg	4mg
54	-	80mg	-	-	-	20mg	-
60	-	-	-	-	-	40mg	-

Data modified from package inserts

The second priority should be non-HDL cholesterol (non-HDL cholesterol = total cholesterol – HDL cholesterol), which is particularly important in patients with elevated triglyceride levels (>200mg/dl). Non-HDL cholesterol is a measure of all the pro-atherogenic apolipoprotein B containing particles. Numerous studies have shown that non-HDL cholesterol is a strong risk factor for the development of cardiovascular disease [154]. The non-HDL cholesterol goals are 30mg/dl greater than the LDL cholesterol goals. For example, if the LDL goal is <100mg/dl then the non-HDL cholesterol goal would be <130mg/dl. Drugs that reduce either LDL cholesterol or triglyceride levels will reduce non-HDL cholesterol levels.

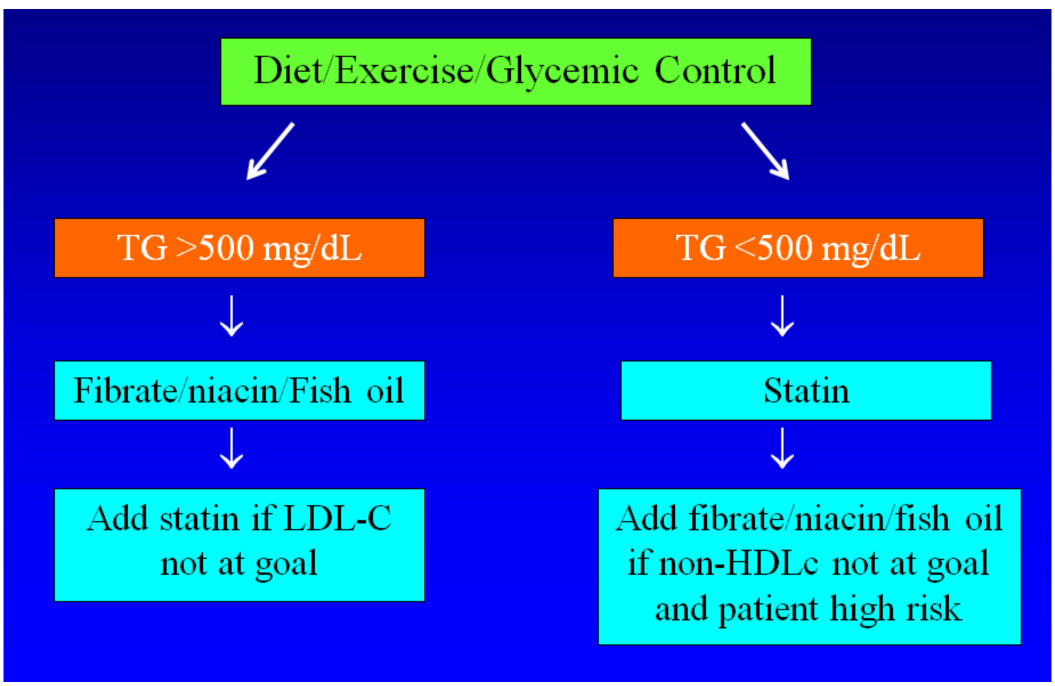
The third priority in treating lipid disorders is to increase HDL cholesterol levels. There is strong epidemiologic data linking low HDL cholesterol levels with cardiovascular disease but whether increasing HDL levels with drugs reduces cardiovascular disease is unknown. Life style changes are the initial step and include increased exercise, weight loss, and stopping cigarette smoking. The role of recommending ethanol, which increases HDL cholesterol levels, is controversial but in patients who already drink moderately there is no reason to recommend that they stop. The most effective drug for increasing HDL cholesterol levels is niacin (see Table 4), but studies have not demonstrated a reduction in cardiovascular events when niacin is added to statin therapy (see section on the effect of lipid lowering drugs on cardiovascular events for details). Fibrates and statins also raise HDL cholesterol levels but the increases are modest (usually less than 15%). Unfortunately, given the currently available drugs, it is very difficult to significantly increase HDL cholesterol levels and in many of our diabetic patients we are unable to achieve HDL cholesterol levels in the recommended range. Furthermore, whether this will result in a reduction in cardiovascular events is unknown.

The fourth priority in treating lipid disorders is to decrease triglyceride levels. Initial therapy should focus on glycemic control and lifestyle changes including a decrease in simple sugars and ethanol intake. Improving glycemic control can have profound effects on serum triglyceride levels. Fibrates, niacin, statins, and fish oil all reduce serum triglyceride levels (see Table 4). Typically, one will target triglyceride levels when one is trying to lower non-HDL cholesterol levels to goal. Patients with very high triglyceride levels (> 500-1000 mg/dl) are at risk of pancreatitis and therefore lifestyle and drug therapy should be initiated early.

Note that there is very limited evidence demonstrating that lowering triglyceride levels or increasing HDL cholesterol levels reduces cardiovascular events.

Many diabetic patients have multiple lipid abnormalities. As discussed in detail above life style changes are the initial therapy. Additionally, improving glycemic control can lead to marked reductions in serum triglyceride levels and modest increases in HDL cholesterol levels. If life style changes are not sufficient in patients with both elevations in LDL cholesterol and triglycerides (and elevations in non-HDL cholesterol), one approach is to base drug therapy on the triglyceride levels (Figure 2). If the serum triglycerides are very high (greater than 500mg/dl), where there is an increased risk for pancreatitis and hyperviscosity syndromes, initial pharmacological therapy is directed at the elevated triglycerides and the initial drug choice is either a fibrate, niacin, or high dose fish oil (3-4 grams EPA/DHA per day). After lowering triglyceride levels to < 500mg/dl, which may require more than one drug, statin therapy should be initiated if the LDL cholesterol and/or non-HDL cholesterol is not at goal. If the serum triglycerides are less than 500mg/dl, statin therapy to lower the LDL cholesterol level to goal is the initial therapy (see Figure 2). Studies have demonstrated that statins are effective drugs in lowering triglyceride levels in patients with elevated triglycerides [145]. In patients with low triglyceride levels statins do not greatly affect serum triglyceride levels. If the non-HDL cholesterol levels remain above goal after one reaches the LDL cholesterol goal, one should then consider combination therapy to lower triglyceride levels, which will lower non-HDLc levels.

Figure 2. Combined Hyperlipidemia. Increased LDL Cholesterol and TG



Often monotherapy is not sufficient to completely normalize the lipid profile. For example, with statin therapy one may often lower the LDL cholesterol to goal but the non HDL cholesterol, HDL cholessterol, and triglycerides remain in the abnormal range. Currently, there are no randomized controlled trials demonstrating that combination therapy with fibrates or niacin reduces cardiovascular disease to a greater extent than statin monotherapy. In fact as noted above, three recent outcome studies adding either niacin or fenofibrate to statin therapy failed to demonstrate additional benefit (see section on the effect of lipid lowering drugs on cardiovascular events for details). However, many experts believe that further improvements in the lipid profile will be beneficial and that the studies completed so far should not be considered definitive as they had flaws such as not treating patients with the appropriate lipid profile. When using combination therapy one must be aware that the addition of either fibrates or niacin to statin therapy may increase the risk of myositis [145]. The increased risk of myositis is greatest when gemfibrozil is used in combination with statins. Fenofibrate has a much more modest risk and the FDA approved the use of fenofibrate in combination with moderate doses of statins. Additionally, in the ACCORD LIPID trial the combination of simvastatin and fenofibrate was well tolerated [116]. The increased risk with niacin appears to be very modest and there is even a combination pill containing lovastatin and niacin available (Advicor). In the AIM-HIGH trial the risk of myositis was not increased in patients on the combination of niaspan and statin, whereas in the HPS2-Thrive trial myopathy was increased in the group treated with the combination of statin and niacin [119, 121]. The absolute risks of combination therapy are relatively modest if patients are carefully selected; in many patients at high risk for cardiovascular disease combination therapy may be appropriate. One should be aware of the steps listed in Table 6 that can reduce the potential for toxicity when one uses combination therapy. As with many decisions in medicine one needs to balance the benefits of therapy with the risks of therapy and determine for the individual patient the best approach. In deciding to use combination therapy a key focus is the non-HDL cholesterol level. When the LDL cholesterol is at goal but the non-HDL cholesterol is still markedly above goal it may be appropriate to resort to combination therapy in patients at high risk.

Table 6. When to Use Combination Therapy

- Clinical Evidence of Arteriosclerosis
- High Risk Patient
    - Hypertension
    - Family History of CAD
    - Cigarettes
    - Proteinuria
    - Microalbuminuria
    - Central Obesity
    - Inactivity
    - Elevated CRP
- No Contraindications
    - Renal or Liver Disease
    - Non-compliant patient
    - Use of other drugs that effect statin metabolism

In summary, modern therapy of patients with diabetes demands that we aggressively treat lipids to reduce the high risk of cardiovascular disease in this susceptible population and in those with very high triglycerides to reduce the risk of pancreatitis.

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