ROLE OF GLUCOSE AND LIPIDS IN THE ATHEROSCLEROTIC 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 T1DM and T2DM. In patients with T1DM, 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 T2DM. Metformin, pioglitazone, SGLT2 inhibitors, and certain GLP-1 receptor agonists have been shown to decrease cardiovascular disease in patients with T2DM to a greater extent than other treatment modalities. In patients with T2DM 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 T1DM in good glycemic control, the lipid profile is very similar to the general population. In contrast, in patients with T2DM, even with good glycemic control, there are frequently lipid abnormalities (elevated triglycerides and non-HDL-C, decreased HDL-C, and an increase in small dense LDL). In both T1DM and T2DM, poor glycemic control increases triglyceride levels and decreases HDL-C levels with only modest effects on LDL-C 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, recent studies have shown that the combination of a statin and ezetimibe, a PCSK9 inhibitor, or EPA, an omega-3-fatty acid, does result in a greater decrease in cardiovascular events than statins alone. Current recommendations state that most patients with diabetes should be on statin therapy.

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 the presence of 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 T1DM are also at high risk for the development of cardiovascular disease (1,12-14). Interestingly, women with T1DM have twice the excess risk of fatal and nonfatal vascular events compared to men with T1DM (15,16). Additionally, developing T1DM at a young age increases the risk of cardiovascular disease to a greater degree than late onset T1DM (16). Approximately 50% of patients with T1DM are obese or overweight and between 8% and 40% meet the criteria for the metabolic syndrome, which increases their risk of developing cardiovascular disease (17).

While the development of diabetes at a young age increases the risk of cardiovascular disease in patients with both T1DM and T2DM the deleterious impact is greater in patients with T2DM (18). Lastly, in patients with both T1DM and T2DM 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 (5,7,19).

ROLE OF GLYCEMIC CONTROL

Epidemiological studies have shown an association between the level of glycemic control and the development of cardiovascular disease in both T1DM and T2DM (1,4,5,20). 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). 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 (21-23). In fact, the data from these early studies 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.

DCCT and Kumamoto Studies

More recent studies, the DCCT in patients with T1DM and the Kumamoto study in patients with T2DM, while finding a decrease in cardiovascular events (DCCT 41% decrease) 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) (24-26). In contrast, both the DCCT and the Kumamoto study clearly demonstrated that improvements in glycemic control resulted in a reduction in microvascular disease (24-26). 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 (27,28). 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 T1DM. 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.

UK Prospective Diabetes Study (UKPDS)

A similar finding has been reported with regard to T2DM. The UKPDS studied a large number of newly diagnosed patients with T2DM 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) (29). 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) (30). 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).

DiGami Studies

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 (31). 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 (32). 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.

ACCORD Study

Because of the need for more definitive data on the effect of glycemic control on cardiovascular disease in T2DM, 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 significant reduction in cardiovascular disease in these trials.

The ACCORD study randomized 10,251 subjects with T2DM in the US and Canada with either a history of cardiovascular disease or at increased risk for the development of cardiovascular disease (33). 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). Of note, intensive glycemic control reduced the incidence of any myocardial infarction (i.e. fatal or non-fatal) by 16%, nonfatal myocardial infarction by 19%, coronary revascularization by 16%, and unstable angina by 19% (34).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. Long term follow-up of the ACCORD study did not reveal any beneficial effects on the primary outcome (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death), death from any cause, and an expanded composite outcome that included all-cause death in the intensive glycemic control group (35).

ADVANCE Study

The ADVANCE study randomized 11,140 subjects with T2DM in Europe, Asia, Australia/New Zealand, and Canada who either had cardiovascular disease or at least one other risk factor for cardiovascular disease (36). 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 regard 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 (37).

VA Diabetes Trial

The VA Diabetes Trial randomized 1,791 subjects with poor glycemic control on maximal oral agent

therapy or insulin (entry A1c 9.4%) (38). 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 (approximately 10 years), 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 (39). However, there was no reduction in cardiovascular or total mortality. Furthermore, over a period of 15 years of follow-up the risks of major cardiovascular events or death were not lower in the intensive-therapy group than in the standard-therapy group (40). In a careful analysis it was noted that that the risk of cardiovascular events was 17% lower in the intensive treatment group than in the standard control group during the approximate 10-year period when there was a separation of the glycated hemoglobin curves between the two groups, suggesting that glycemic control was reducing the risk of cardiovascular events (40).

Meta-analyses

In a meta-analysis of 6 randomized studies (UKPDS, Kumamoto, VA Feasibility study, ACCORD, ADVANCE, and VA Diabetes Trial) of intensive vs. conventional glycemic control in patients with T2DM (27,654 patients) there was no significant effect of tight blood glucose control on all-cause mortality (RR 1.03; 95% CI 0.90-1.17), cardiovascular mortality (RR 1.04; 95% CI 0.83-1.29), or nonfatal stroke (RR 1.02; 95% CI 0.88-1.17) but tight glucose control reduced the risk for nonfatal MI (RR 0.85; 95% CI 0.76-0.95) (41). In a meta-analysis of 4 studies (UKPDS, ACCORD, ADVANCE, and VA Diabetes Trial) the primary outcome was the composite of death from cardiovascular causes (including sudden death), non-fatal myocardial infarction and non-fatal stroke, which was decreased by 9% (HR 0.91, 95% CI 0.84–0.99) in the intensive control group (42). Of note the risk of non-fatal/fatal myocardial infarction was reduced by 15% (HR 0.85, 95% CI 0.76–0.94) in the intensive group without significant reductions in the risk of non-fatal/fatal stroke, fatal heart failure, all-cause mortality, or cardiovascular death.

Summary

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 definitively demonstrate a clear link. There are several 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-C 135-142mg/dl), which could be why this older trial demonstrated a small benefit of improving glycemic control 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 likely 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. Additionally, if the difference in A1c levels were great in the intensive and control groups the likelihood of seeing a reduction in cardiovascular events in the intensive group would be enhanced.

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 T1DM where abnormalities in glucose metabolism are a major reason for the increased risk of atherosclerosis. In contrast, patients with T2DM have multiple risk factors for atherosclerosis (dyslipidemia, hypertension, inflammation, insulin resistance, coagulation disorders, etc.) 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 (T1DM trial) and had only minimal effects in the trials carried out in patients with T2DM.

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 definitively indicate that glycemic control will have major effects on reducing cardiovascular disease in patients with T2DM. Furthermore, there are concerns that too tight control in patients with advanced disease could be harmful. In contrast, in patients with T1DM intensive glucose control appears to have a major beneficial effect on cardiovascular disease based on the results of the DCCT.

THE EFFECT OF GLUCOSE LOWERING DRUGS ON ATHEROSCLEROTIC 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% (43). 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 (30). 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 (44). 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 (45). 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).

Further support for the beneficial effects of metformin on atherosclerosis comes from long term follow-up of the Diabetes Prevention Program, which compared the effect of lifestyle changes or metformin in patients at high risk of developing diabetes (46). Coronary artery calcium scores were measured on average 13-14 years after randomization (46). There were no differences in coronary artery calcium scores between the lifestyle and placebo groups. However, in males, coronary artery calcium scores were significantly lower in the metformin group vs. the placebo group. In females treated with metformin coronary artery calcium scores were similar to the placebo group. The absence of a beneficial effect of metformin in women could be due to the lower baseline coronary artery calcium scores making it more difficult to demonstrate a beneficial effect. In HIV-infected patients with the metabolic syndrome metformin similarly reduced the progression of coronary artery calcium scores (47).

Thus, while there are no large cardiovascular outcome trials with metformin, 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 and lowers lipid levels and these or other non-glucose effects may account for the beneficial effects on cardiovascular disease.

Sulfonylureas

Based on the University Group Diabetes Project (UGDP) all sulfonylureas carry a "black box" warning regarding an increased risk of cardiovascular disease (22,23). However, the UKPDS studied a large number of newly diagnosed patients with T2DM at risk for cardiovascular disease and in this study improved glycemic control with sulfonylureas reduced cardiovascular disease by approximately 16%, which just missed being statistically significant (p=0.052) (29). In the UKPDS, A1c was reduced by approximately 0.9% and the 16% reduction in cardiovascular disease was in the range predicted based on epidemiological studies. Thus, the reduction in cardiovascular events was likely due to improvements in glycemic control and not a direct benefit of sulfonylurea treatment. In support of this conjecture is that in the UKPDS, insulin treatment resulted in a similar decrease in A1c levels and reduction in cardiovascular events (29). Additionally, a large randomized cardiovascular outcome study (Carolina Study) reported that linagliptin, a DPP-4 inhibitor, and glimepiride, a sulfonylurea, had similar effects on cardiovascular events (hazard ratio 0.98) (48). Taken together these results suggest that sulfonylureas have a neutral effect on cardiovascular disease.

Meglitinides

The Navigator study was a double-blind, randomized clinical trial in 9,306 individuals with impaired glucose tolerance and either cardiovascular disease or

cardiovascular risk factors who received nateglinide (up to 60 mg three times daily) or placebo (49). After 5 years, nateglinide administration did not alter the incidence of cardiovascular outcomes suggesting that meglitinides do not have adverse or beneficial effect on cardiovascular events.

Thiazolidinediones

Studies with pioglitazone have 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 T2DM with pre-existing macrovascular disease (50). With regard 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-C levels were all improved compared to the placebo group making it very likely that the mechanism by which pioglitazone decreased vascular events was multifactorial.

A multicenter, double-blind trial (IRIS Trial), randomly assigned 3,876 patients with insulin resistance (defined as score of more than 3.0 on the homeostasis model assessment of insulin resistance [HOMA-IR] index) but without diabetes and a recent ischemic stroke or TIA to treatment with either pioglitazone (target dose, 45 mg daily) or placebo (51). 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-C and LDL-C 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.

In contrast, a recent study (TOSCA.IT) compared the effect of pioglitazone vs. sulfonylurea on cardiovascular disease and did not observe a reduction in events with pioglitazone treatment (52). Patient with T2DM (n= 3028), inadequately controlled with metformin monotherapy (2-3 g per day), were randomized to pioglitazone or sulfonylurea and followed for a median of 57 months. Only 11% of the participants had a previous cardiovascular event. The primary outcome, was a composite of first occurrence of all-cause death, non-fatal myocardial infarction, non-fatal stroke, or urgent coronary revascularization and occurred in 6.8% of the patients treated with pioglitazone and 7.2% of the patients treated with a sulfonylurea (HR 0.96; NS) (52). Limitations of this study are the small number of events likely due to low risk population studied and the relatively small number of participants. Additionally, 28% of the subjects randomized to pioglitazone prematurely discontinued the medication. Furthermore, it should be noted that when patients in this study were analyzed based on the risk of developing cardiovascular disease those at high risk had a marked reduction in events when treated with pioglitazone compared to the sulfonylurea (53).Thus,

the results of this study should be interpreted with caution.

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 (54,55). Similarly, Periscope, a study that measured atheroma volume in the coronary arteries by intravascular ultrasonography, also demonstrated less atherosclerosis in the pioglitazone treated group compared to patients treated with sulfonylureas (56).

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 (57,58). 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 as a second oral drug in those receiving either metformin or a sulfonylurea on cardiovascular events, have been published and did not reveal a difference in cardiovascular disease death, myocardial infarctions, or stroke (59-61). 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 (62). 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).

Numerous studies have shown that both pioglitazone and rosiglitazone increase the risk of heart failure (63).

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. The effect of the DPP4 inhibitors saxagliptin, alogliptin, sitagliptin, and linagliptin on cardiovascular endpoints has been reported. In the saxagliptin study (SAVOR-TIMI 53 trial), 16,492 patients with T2DM who had a history of cardiovascular events or who were at high risk were randomized to saxagliptin or placebo for 2.1 years (64). 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 (EXAMINE), 5,380 patients with either an acute myocardial infarction or unstable angina within the previous 15-90 days were randomized to alogliptin or placebo and followed for a median of 18 months (65). 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 statistically increased in the entire subset of patients treated with alogliptin (66). However, the hazard ratio for the subgroup of patients without heart failure at baseline was 1.76, p=0.026) (66). The trend for an increase in heart failure led to the Federal Drug Administration to add the risk of heart failure to the label of DPP4 inhibitors. In the sitagliptin trial (TECOS), 14,671 patients with established cardiovascular disease were randomized to sitagliptin or placebo for 3 years (67). Sitagliptin did not decrease the risk of major adverse cardiovascular events or increase hospitalization for heart failure. Finally, in the

linagliptin trial (CARMELINA), 6,979 patients at high risk for cardiovascular disease were randomized to linagliptin or placebo for a median follow-up of 2.2 years (68). As in the other DPP4 inhibitor studies, linagliptin did not have a beneficial effect on cardiovascular events. Additionally, linagliptin did not increase the risk of hospitalization for heart failure. Thus, these results indicate that DPP4 inhibitors do not increase or decrease cardiovascular disease. The extent to which specific DPP4 inhibitors affect heart failure needs further investigation.

SGLT2 Inhibitors

EMPA-REG OUTCOME TRIAL

The effects of empagliflozin on cardiovascular morbidity and mortality in patients with T2DM has been reported (69). In this study, 7,020 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 non-fatal 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 heart failure appeared to be the dominant effect compared to effects on atherosclerotic events. Decreases in cardiovascular outcomes and mortality with empagliflozin occurred across the range of cardiovascular risk (70). Additionally, the reduction in hospitalizations for heart failure and cardiovascular death were observed both in patients with and without heart failure at baseline (71).

CANVAS TRIAL

The effects of placebo vs. canagliflozin were determined in two combined trials involving a total of 10,142 participants with T2DM and high cardiovascular risk (72). The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke and the mean follow-up was 188 weeks. The primary outcome was reduced in the canagliflozin group (hazard ratio, 0.86; P=0.02). Death from any cause (hazard ratio 0.87; 95% CI 0.74-1.01) and death from cardiovascular disease (hazard ratio 0.87; 95% CI 0.72-1.06) were reduced but were not statistically significant. Similarly, canagliflozin treatment did not result in a significant difference in non-fatal strokes or non-fatal myocardial infarctions (hazard ratio 0.90 for stroke and 0.85 for myocardial infarction). As seen with empagliflozin, hospitalization for heart failure was markedly reduced (hazard ratio 0.67; 95% CI 0.52-0.87) and this beneficial effect occurred rapidly. Notably, there was an increased risk of amputation (hazard ratio, 1.97; 95% CI, 1.41 to 2.75), which were primarily at the level of the toe or metatarsal. The basis for the increase in amputations is unknown. In the empagliflozin study an increase in amputations was not noted.

CREDENCE TRIAL

In a second canagliflozin trial that focused on kidney disease, a decrease in cardiovascular events was also observed (73). In this double-blind trial 4,401 patients with chronic kidney disease and T2DM were randomized to canagliflozin 100mg per day or placebo and followed for a median of 2.62 years. All the patients had an eGFR of 30 to <90 ml per minute per 1.73 m^2 and albuminuria (ratio of albumin [mg] to

creatinine [g], >300 to 5000). In this trial hospitalization for heart failure was reduced by 39%. The relative benefits of canagliflozin for cardiovascular outcomes was similar in individuals across the spectrum of eGFR levels (74). In contrast to the CANVAS trial, an increased risk of amputations was not observed.

DECLARE–TIMI 58 TRIAL

The effect of dapagliflozin on cardiovascular events has also been reported (75). 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease were randomized to dapagliflozin or placebo and followed for a median of 4.2 years. The primary outcome was a composite of major adverse cardiovascular events, defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Dapagliflozin did not result in a lower rate of major adverse cardiovascular events (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; P=0.17) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; P=0.005), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88). Interestingly, in the patients with a history of a previous MI dapagliflozin reduced the risk of a MACE (HR 0.84; P=0.039), whereas there was no effect in patients without a previous MI (76). Additionally, there was not an increase in lower extremities amputations in the dapagliflozin treated group.

VERTIS CV

This trial has not yet been published but was presented at the ADA meeting 2020. Patients with atherosclerotic cardiovascular disease and T2DM were randomized to ertugliflozin 5mg (n=2752), 15mg (n=2747), or placebo (n=2747) and the primary composite outcome of cardiovascular death and non-fatal MI or stroke was determined after a mean duration of follow-up of 3.5 years. This trial did not demonstrate a significant difference in the primary endpoint nor any components of the primary endpoint. However, heart failure hospitalizations were significantly reduced in the patients treated with ertugliflozin (2.5% vs. 3.6%; p=0.006).

SUMMARY

Thus, all five SGLT2 inhibitor studies demonstrated a decrease in heart failure with SGLT2 inhibitor therapy without consistent effects on atherosclerotic cardiovascular events. In a meta-analysis of three of these trials (CASCADE and VERTIS were not included) it was observed that SGLT2 inhibitors reduced the risk of cardiovascular death or hospitalization for heart failure by 23% (p<0·0001), with a similar benefit in patients with and without atherosclerotic cardiovascular disease and with and without a history of heart failure (77). Additionally, greater reductions in hospitalizations for heart failure were observed in patients with more severe kidney disease at baseline. Recently a study examined the effect of dapagliflozin in patients with heart failure and a reduced injection fraction (78). In patients without diabetes dapagliflozin decreased worsening heart failure or cardiovascular death by 27% and in patients with diabetes by 25% further confirming the beneficial effects of SGLT2 inhibitors on reducing the risk of heart failure and extending these findings to patients without diabetes. Additional studies with SGLT2 inhibitors in different patient populations are being carried out and it will be of great interest to see if these studies also demonstrate a reduction in cardiovascular events, particularly heart failure, or an increase in amputations.

The mechanisms accounting for the beneficial effects of SGLT2 inhibitors on heart failure are uncertain

(79). Glycemic control was better in the SGLT2 inhibitor treated patients but it is doubtful that this could account for the observed results (additionally benefit in non-diabetics makes a glucose effect very unlikely). SGLT2 inhibitor 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-C. Whether these changes played a role in reducing events remains to be determined but it is unlikely that these play a major role as other treatments that effect these factors do not markedly diminish the risk of heart failure events. It is possible that hemodynamic changes secondary to the osmotic diuresis induced by SGLT2 inhibitors contributed to the beneficial effects. In an analysis of the EMPA-REG OUTCOME trial, the change in hematocrit (~3% increase), corresponding to ~7% reduction in plasma volume, accounted for approximately 50% of the benefit of the drug on cardiovascular death (80). It should be noted that the increase in hematocrit with SGLT2 inhibitors should not be solely attributed to decreases in plasma volume as studies have shown that SGLT2 inhibitors increase erythropoietin secretion (81). Additionally, SGLT2 inhibitors increase free fatty acid levels and glucagon secretion, which promotes the production of ketone bodies such as beta-hydroxybutyrate that are utilized by the heart for energy production (82). It is possible that this alternative source of energy could be protective for heart function. Finally, there may be direct effects of SGLT2 inhibition on myocardial metabolism (79,83,84). Further studies are required to better elucidate the mechanism of the beneficial effects of SGLT2 inhibitors on heart failure.

GLP-1 Receptor Agonists

The effect of six GLP-1 receptor agonists on cardiovascular disease has been reported.

ELIXA

In the ELIXA trial 6,068 patients with T2DM and who recently had a myocardial infarction or been hospitalized for unstable angina were randomized to placebo or lixisenatide and followed for a median of 25 months (85). The primary end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina was similar in the placebo or lixisenatide groups.

LEADER TRIAL

In contrast, the LEADER trial has shown that liraglutide decreased cardiovascular events (86). In this trial 9,340 patients at high cardiovascular risk were randomly assigned to receive liraglutide or placebo. After a 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=0.01). 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 (87,88). As expected, weight and blood pressure were decreased in the liraglutide treated group and A1c levels were also decreased by 0.4%.

SUSTAIN 6 TRIAL

In support of the beneficial effects of GLP1 receptor agonists to reduce cardiovascular events, semaglutide, a long acting GLP-1 receptor agonist, has been shown to also reduce cardiovascular events (89). In this trial, 3,297 patients with T2DM

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 = 0.02). In this study, both body weight and A1c levels were decreased in the patients treated with semaglutide.

PIONEER 6

In the PIONEER 6 study 3,183 patients with T2DM at high cardiovascular risk (age of ≥50 years with established cardiovascular or chronic kidney disease, or age of ≥60 years with cardiovascular risk factors) were randomly assigned to receive oral semaglutide or placebo (90). After a median time of 15.9 months, major adverse cardiovascular events, the primary outcome, occurred in 3.8% of the subjects treated with oral semaglutide and 4.8% of the placebo group (HR 0.79; 95% CI 0.57 to 1.11). Deaths from cardiovascular causes were 0.9% in the oral semaglutide group and 1.9% in the placebo group (HR 0.49; 95% CI, 0.27 to 0.92) while death from any cause occurred in 1.4% in the oral semaglutide group and 2.8% in the placebo group (HR 0.51; 95% CI, 0.31 to 0.84). It should be noted that the primary outcome was not statistically decreased in this study, which may be due to the relatively small number of subjects studied and the short duration of the study that together resulted in a small number of events. Additionally, more patients in the placebo group received treatment with an SGLT2 inhibitor than in the oral semaglutide group and SGLT2 inhibitors are well recognized to reduce cardiovascular disease events, which could also have diminished the ability to observe a decrease in events in the oral semaglutide group. Because the direction of change in cardiovascular events in PIONEER 6 and glucose lowering, weight loss, and many other effects of oral semaglutide are very similar to injected semaglutide many experts consider the effects on cardiovascular to also be similar.

EXSCEL TRIAL

The effect of once weekly exenatide vs. placebo on cardiovascular outcomes was tested in 14,752 patients, 73% who had cardiovascular disease (91). The primary outcome was the occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. After a median follow-up of 3.2 years (duration of drug exposure 2.4 years) the primary outcome was reduced in the exenatide treated group but this difference just missed achieving statistical significance (hazard ratio 0.91; 95% CI 0.83-1.00; p=0.06). While not statistically significant these results are consistent with the results observed with liraglutide and semaglutide treatment. It should be recognized that a high percentage of patients discontinued exenatide therapy in this trial (>40%) and this could have adversely affected the ability of exenatide treatment to favorably effect cardiovascular outcomes.

HARMONY OUTCOMES TRIAL

The effect of once weekly albiglutide vs. placebo was tested in 9,463 patients with cardiovascular disease (92). The primary outcome was first occurrence of cardiovascular death, myocardial infarction, or stroke. After a median follow-up of 1.6 years a 22% decrease in the primary endpoint was observed in the albiglutide group (hazard ratio 0·78, p<0·0001). It should be noted that albiglutide is no longer available as it was removed from the market due to commercial considerations by Glaxo.

REWIND TRIAL

REWIND was a randomized study of weekly subcutaneous injection of dulaglutide (1.5 mg) or placebo in 9,901 patients with T2DM who had either a previous cardiovascular event or cardiovascular risk factors (approximately 70% of patients did not have prior cardiovascular disease) (93). During a median follow-up of 5.4 years the primary outcome of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes was decreased by 12% in the dulaglutide treated group (HR 0.88, p=0.026). The decrease in events was similar in participants with and without previous cardiovascular disease. In an analysis that focused on stroke it was noted that dulaglutide reduced ischemic stroke by 25% compared to placebo but had no effect on hemorrhagic stroke (94).

SUMMARY

Thus, four studies have clearly demonstrated that treatment with GLP-1 receptor agonists reduces cardiovascular events, two studies has provided data consistent with these results, and one study failed to demonstrate benefit. In a meta-analysis of these seven trials it was observed that cardiovascular death, stroke, or myocardial infarction was decreased by 12% (HR 0.88, p<0.0001), death from cardiovascular causes by 12% (HR 0.88, p=0.003), fatal or non-fatal stroke by 16% (HR 0.84, p<0.0001) and fatal and non-fatal MI by 9% (HR 0.91, p=0.043) (95). Why there are differences in results between these studies is unknown but could be due to differential effects of the GLP-1 receptor agonists, differences in the patient populations studied, or other unrecognized variables. The mechanism accounting for this decrease in cardiovascular disease is uncertain but could be related to reductions in glycated hemoglobin, body weight, systolic blood pressure, postprandial triglyceride levels, or the direct effect of activation of GLP-1 receptors on the atherosclerotic process such as improving endothelial function (96).

Acarbose

In the STOP-NIDDM trial 1,429 subjects with impaired glucose tolerance were randomized to placebo vs. acarbose and followed for 3.3 years (97). In the acarbose group a 49% relative risk reduction in the development of cardiovascular events (hazard ratio 0.51; P =0.03) was observed. Among cardiovascular events, the major reduction was in the risk of myocardial infarction (HR, 0.09; P =.02). In a smaller trial, 135 patients hospitalized for the acute coronary syndrome who were newly diagnosed with IGT were randomly assigned to acarbose or placebo (98). During a mean follow-up of 2.3 years the risk of recurrent major adverse cardiovascular event was decreased significantly in the acarbose group compared with that in control group (26.7% versus 46.9%, P < 0.05).

Despite these favorable observations a large trial failed to demonstrate a beneficial effect of acarbose in Chinese patients with impaired glucose tolerance (99). In a randomized trial acarbose vs. placebo was compared in 6,522 patients with coronary heart disease and impaired glucose tolerance. The primary outcome was cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure and patients were followed up for a median of 5 years. The primary outcome was similar in the acarbose and placebo groups (hazard ratio 0·98; 95% CI 0·86-1·11, p=0·73). No significant differences were seen for death from any cause, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, or impaired renal function.

Thus, whether acarbose favorably affects cardiovascular disease in patients at high risk for

developing diabetes is uncertain. Moreover, the effect of acarbose on cardiovascular disease in patients with diabetes is unknown.

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 T2DM treated with bromocriptine-QR or placebo (100). 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.

Bile Acid Sequestrants

Colesevelam is a non-absorbed, polymeric, LDL-C lowering and glucose lowering agent that is a high-capacity bile acid-binding molecule. This drug was developed primarily to lower LDL-C levels and was later noted to have favorable effects on blood glucose levels and was approved for improving glycemic control in patients with T2DM (101).

There have been no randomized studies that have examined the effect of bile acid sequestrants on cardiovascular end points in subjects with diabetes. In non-diabetic-subjects bile acid sequestrants have reduced cardiovascular events (102,103). Since bile acid sequestrants have a similar beneficial impact on LDL-C 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.

Insulin

As described above in patients with T1DM the DCCT trial and in T2DM the UKPDS trial demonstrated that insulin therapy reduced cardiovascular events by improving glycemic control (27-30). With regard to patients with T2DM, in the Origin Trial 12,537 people with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM were randomized to receive insulin glargine or standard care (104). 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. Extended follow-up also did not demonstrate favorable effects on cardiovascular events in the glargine treated patients (105). Additionally, in patients with T2DM at high risk for cardiovascular events the occurrence of major cardiovascular events was similar in patients treated with degludec insulin or glargine insulin (106). 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 T1DM over a protracted period of time.

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 T2DM and coronary artery disease (> 50% stenosis and positive stress test or > 70% stenosis and classic angina) (107,108). 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.

Summary

These studies clearly 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 reduce cardiovascular events. While previous treatment algorithms have primarily focused on the effect of drugs on glycemic control, current treatment recommendations for patients with diabetes are using the results of these cardiovascular disease trials to decide which drugs should be employed. For example, the ADA is recommending that in patients with high risk or established cardiovascular disease an SGLT inhibitor or GLP1 receptor agonist with proven cardiovascular benefit should be part of the treatment regimen independent of A1c levels (109).

ROLE OF OTHER RISK FACTORS IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Numerous studies have demonstrated that the traditional risk factors for cardiovascular disease play an important role in patients with diabetes (2,4,5,110). 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 (2,4,5,13,111). Other risk factors include obesity (particularly visceral obesity), insulin resistance, small dense LDL, elevated triglycerides, low HDL-C, procoagulant state (increased PAI-1, fibrinogen), family history of early cardiovascular disease, homocystine, Lp (a), renal disease, albuminuria, and inflammation (C-reactive protein, SAA, cytokines) (2,4,5,110,111). 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 I will focus on the dyslipidemia that occurs in patients with diabetes.

ROLE OF LIPIDS IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

As in the non-diabetic population, epidemiological studies have shown that increased LDL-C and non-HDL-C levels and decreased HDL-C levels are associated with an increased risk of cardiovascular disease in patients with diabetes (2,4,110,111). In the UKPDS cohort LDL-C levels were the strongest predictor of coronary artery disease (112). While it is universally accepted that elevated levels of LDL-C and non-HDL-C cause atherosclerosis and cardiovascular disease the role of HDL-C is uncertain. Genetic studies and studies of drugs that raise HDL-C have not supported low HDL-C levels as a causative factor for atherosclerosis (113). Rather it

is currently thought that HDL function is associated with atherosclerosis risk and that this does not precisely correlate with HDL-C levels (113). In patients with diabetes, elevations in serum triglyceride levels also are associated with an increased risk of cardiovascular disease (4,111,114). With regard to triglycerides, it is not clear whether they are a causative factor for cardiovascular disease or whether the elevation in triglycerides is a marker for other abnormalities (4,111,114,115). Recent Mendelian randomization studies have provided support for the hypothesis that elevated triglyceride levels play a causal role in atherosclerosis (115,116).

LIPID ABNORMALITIES IN PATIENTS WITH DIABETES

In patients with T1DM in good glycemic control, the lipid profile is very similar to lipid profiles in the general population (110). In some studies HDL-C levels are modestly increased in patients with T1DM (117). In contrast, in patients with T2DM, even when in good glycemic control, there are abnormalities in lipid levels (118-121). It is estimated that 30-60% of patients with T2DM have dyslipidemia (5,122). Specifically, patients with T2DM often have an increase in serum triglyceride levels, increased VLDL and IDL, and decreased HDL-C levels. Non-HDL-C levels are increased due to the increase in VLDL and IDL. LDL-C 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 apolipoprotein B levels (118-121). Additionally, the postprandial increase in serum triglycerides is accentuated and elevations in postprandial lipids may increase the risk of cardiovascular disease (118-121). 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) (123). Since a high percentage of patients with T2DM 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-C is common in patients with T2DM even when these patients are in good glycemic control.

Studies have shown that the anti-oxidant and anti-inflammatory functions of HDL isolated from patients with T1DM and T2DM are reduced (117,124). Additionally, the ability of HDL to facilitate cholesterol efflux is reduced in patients with T1DM and T2DM (125,126). Together these findings indicate that HDL-C levels per se may not fully reflect risk of cardiovascular disease in patients with diabetes and that HDL function is perturbed in patients with diabetes.

In both T1DM and T2DM, poor glycemic control increases serum triglyceride levels, VLDL, and IDL, and decreases HDL-C levels (119). Poor glycemic control can also result in a modest increase in LDL-C, 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 T1DM and T2DM (127). Some studies have observed no impact of diabetes mellitus on Lp(a) concentrations while other studies reported an elevation or a decrease in Lp(a) concentrations (127). The development of microalbuminuria and the onset of renal disease are associated with an increase in Lp (a) levels (128). Of note low Lp(a) levels are associated with an increased risk of developing T2DM (127). A recent very large case control study found that Lp(a) concentration in the bottom 10% increases T2DM risk (129).

Table 1. Lipid Abnormalities in Patients with Diabetes	
T1DM	Lipid profile is similar to controls if glycemic control is good
T2DM	Increased triglycerides, VLDL, IDL, and non-HDL-C. Decreased HDL-C. Normal LDL-C but increase in small dense LDL, LDL particle number, and apolipoprotein B.
Poor glycemic control	Increased triglycerides, VLDL and IDL and decreased HDL-C. Modest increase in LDL-C with increase in small dense LDL and particle number.

EFFECT OF GLUCOSE LOWERING DRUGS ON LIPIDS

Some therapies used to improve glycemic control may have an impact on lipid levels above and beyond their effects on glucose metabolism. In reviewing the literature, it is often very difficult to separate improvements in glycemic control vs. direct effects of drugs. Additionally, many of the changes induced by drug therapy result in only small changes in LDL-C, HDL-C, and triglyceride levels, are variable from study to study, and are of questionable clinical significance. Insulin, sulfonylureas, meglinitides, DPP4 inhibitors, and alpha-glucosidase inhibitors do not appear to 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 markedly alter fasting lipid levels) (130). In contrast, metformin, thiazolidinediones, GLP1 receptor agonists, bromocriptine-QR, and SGLT2 inhibitors have effects independent of glycemic control on serum lipid levels.

Metformin may decrease serum triglyceride levels and LDL-C levels without altering HDL-C levels (130). In a meta-analysis of 37 trials with 2,891 patients, metformin decreased triglycerides by 11.4mg/dl when compared with control treatment ($p=0.003$) (131). In an analysis of 24 trials with 1,867 patients, metformin decreased LDL-C by 8.4mg/dl compared to control treatment ($p<0.001$) (131). In contrast, metformin did not significantly alter HDL-C levels (131). It should be noted that in the Diabetes Prevention Program 3,234 individuals with impaired glucose metabolism were randomized to placebo, intensive lifestyle, or metformin therapy. In the metformin therapy group no significant changes were noted in triglyceride, LDL-C, or HDL-C levels compared to the placebo group (132). Thus, metformin may have small effects on lipid levels.

The effect of thiazolidinediones appears to depend on which agent is used. Rosiglitazone increases serum LDL-C levels, increases HDL-C levels, and only decreases serum triglycerides if the baseline triglyceride levels are high (130). In contrast, pioglitazone has less impact on LDL-C levels, but increases HDL-C levels, and decreases serum triglyceride levels (130). In the PROactive study, a large randomized cardiovascular outcome study, pioglitazone decreased triglyceride levels by approximately 10%, increased HDL-C levels by approximately 10%, and increased LDL-C by 1-4% (133). 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 (130). In a randomized head to

head trial it was shown that pioglitazone decreased serum triglyceride levels and increased serum HDL-C levels to a greater degree than rosiglitazone treatment (134,135). Additionally, pioglitazone increased LDL-C 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-C and HDL-C levels (130). In a meta-analysis of 48 randomized controlled trials SGLT2 inhibitors significantly increased LDL-C (3.8mg/dl, $p < 0.00001$), HDL-C (2.3mg/dl, $p < 0.00001$), and decreased triglyceride levels (8.8mg/dl, $p < 0.00001$) (136). The mechanism for these increases in LDL and HDL cholesterol is unknown but could be due to a decrease in plasma volume. The decrease in triglyceride levels could be secondary to weight loss.

Bromocriptine-QR (Cycloset) treatment decreases triglyceride levels but has no significant effect on LDL-C or HDL-C levels (137,138). The decrease in triglyceride levels is thought to be due to a decrease in hepatic triglyceride synthesis, likely due to a decrease in adipose tissue lipolysis resulting in decreased blood free fatty acid levels and reduced delivery of fatty acids to the liver for triglyceride synthesis (139).

Colesevelam, a bile acid sequestrant that is approved for glucose lowering, lowers LDL-C levels by 15-20% and has only a modest effect on HDL-C levels (101,140). The effect of bile acid sequestrants on triglyceride levels varies (140). In patients with normal triglyceride levels, bile acid sequestrants increase triglyceride levels by a small amount. However, as baseline triglyceride levels increase, the effect of bile acid sequestrants on plasma triglyceride levels becomes greater, and can result in substantial increases in triglyceride levels (140). In patients with triglycerides > 500mg/dl the use of bile acid sequestrants is contraindicated (140).

Finally, GLP-1 receptor agonists can favorably affect the lipid profile by inducing weight loss (decreasing triglycerides and very modestly decreasing LDL-C levels) (130). In a review by Nauck and colleagues it was noted that GLP-1 receptor agonists lowered triglyceride levels by 18 to 62mg/dl depending upon the specific GLP-1 receptor agonist while decreasing LDL-C by 3-8mg/dl and increasing HDL-C by less than 1mg/dl (141). Additionally, GLP-1 receptor agonists reduce postprandial triglycerides by reducing circulating chylomicrons by decreasing intestinal lipoprotein production (130,141). DPP4 inhibitors have a similar effect on postprandial triglyceride levels as GLP-1 receptor agonists while having minimal effects on fasting lipid levels (141).

Table 2. Effect of Glucose Lowering Drugs on Lipid Levels

Metformin	Modestly decrease triglycerides and LDL-C
Sulfonylureas	No effect
DPP4 inhibitors	Decrease postprandial triglycerides
GLP1 analogues	Decrease fasting and postprandial triglycerides
Acarbose	Decrease postprandial triglycerides
Pioglitazone Rosiglitazone	Decrease triglycerides and increase HDL-C. Small increase LDL-C but a decrease in small dense LDL

SGLT2 inhibitors	Small increase in LDL-C and HDL-C
Colesevelam	Decrease LDL-C. May increase triglycerides
Bromocriptine-QR	Decrease triglycerides
Insulin	No effect

PATHOPHYSIOLOGY OF THE DYSLIPIDEMIA OF DIABETES

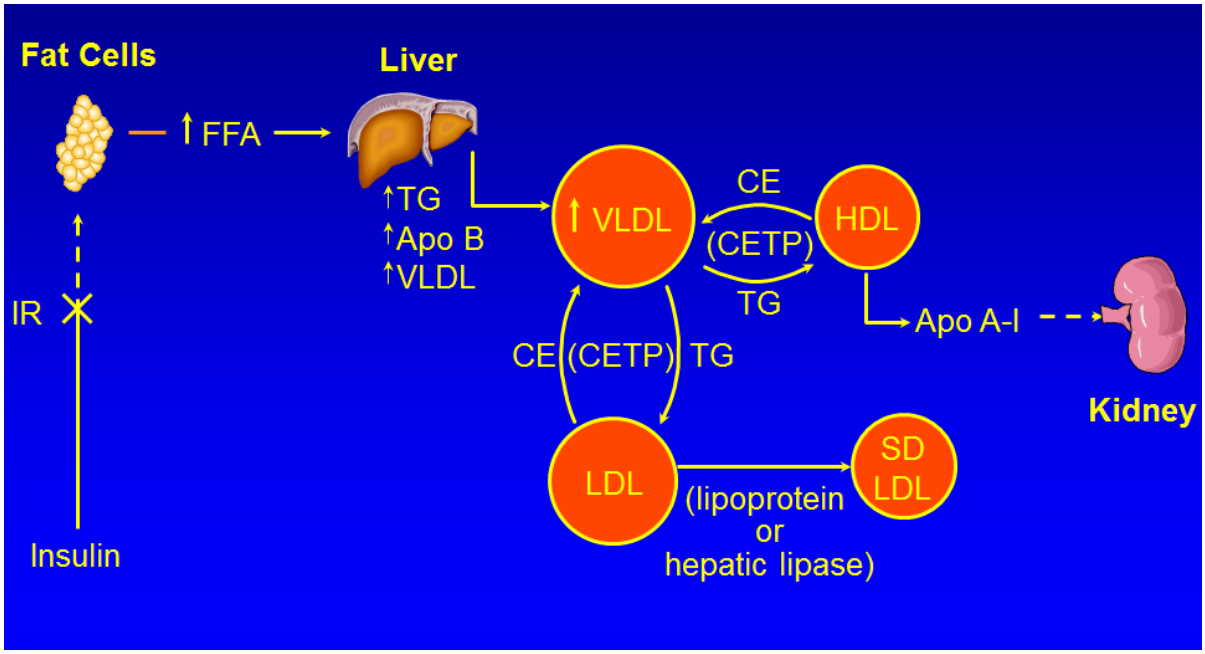

Figure 1. Pathophysiology of the Dyslipidemia of Diabetes

Increase in Triglycerides

There are a number of different abnormalities that contribute to the dyslipidemia seen in patients with T2DM and obesity (figure 1) (119-122,142-144). 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 T2DM. 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. Numerous studies have shown that fatty acid synthesis is increased in the liver in patients with T2DM. This increase may be mediated by the hyperinsulinemia seen in patients with insulin resistance. While the liver is 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. Thus, while the liver is 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 T2DM. 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 T2DM 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 T2DM, 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 T2DM 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 T2DM 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 (145,146). 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 (147). Thus, in patients with diabetes, a decrease in clearance of triglyceride rich lipoproteins also contributes to the elevation in serum triglyceride levels.

Effect on HDL and LDL

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 T2DM, which will also

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-C levels in patients with T2DM.

Role of Poor Glycemic Control

The above described changes lead to the typical dyslipidemia observed in patients with T2DM (increased triglycerides, decreased HDL-C, and an abundance of small dense LDL and small HDL). In patients with both Type 1 and T2DM, 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 T1DM who are well controlled typically have normal serum lipid profiles, if their control deteriorates, they will develop hypertriglyceridemia. In patients with T2DM 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.

Role of Inflammation

Many if not most patients with T2DM 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 (148,149). 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.

Pro-inflammatory cytokines also affect HDL metabolism (150,151). 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 (152). In parallel inflammation increases the oxidation of LDL and the small dense LDL that occurs in patients with diabetes is more susceptible to oxidation.

Role of Adipokines

Adipokines, such as leptin, adiponectin and resistin, regulate lipid metabolism and the levels are altered in obese patients. Obesity increases serum leptin levels and leptin stimulates lipolysis in adipocytes which will increase serum free fatty acid levels (153). The circulating levels of adiponectin are decreased in subjects who are obese (154). Decreased adiponectin levels are associated with elevations in serum triglyceride levels and decreases in HDL-C levels (154). This association is thought to be causal as studies in mice have shown that overexpressing adiponectin (transgenic mice) decreases triglyceride and increases HDL-C levels while conversely, adiponectin knock-out mice have increased triglyceride and decreased HDL-C levels (154). The adiponectin induced decrease in triglyceride levels is mediated by an increased catabolism of triglyceride rich lipoproteins due to an increase in lipoprotein lipase activity and a decrease Apo C-III, an inhibitor of lipoprotein lipase (154). The increase in HDL-C levels induced by adiponectin is mediated by an increase in hepatic Apo A-I and ABCA1, which results in the increased production of HDL particles (154).

Resistin is increased in subjects who are obese and the levels of resistin directly correlate with plasma triglyceride levels (155). Moreover, resistin has been shown to stimulate hepatic VLDL production and secretion due to an increase in the synthesis of Apo B, triglycerides, and cholesterol (155,156). Finally, resistin is associated with a decrease in HDL-C and Apo A-I levels (155).

EFFECT OF LIPID LOWERING DRUGS ON ATHEROSCLEROTIC CARDIOVASCULAR EVENTS

Monotherapy Studies

STATINS

The Cholesterol Treatment Trialists analyzed data from 18,686 subjects with diabetes (mostly T2DM) from 14 randomized trials (157). 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-C. 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.

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 (158,159). 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 T1DM and T2DM patients had a comparable reduction in cardiovascular disease with simvastatin therapy. The decrease in cardiovascular events in patients with T1DM 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 (note this study did not include patients with end stage renal disease but other studies have failed to show benefits of statin therapy in patients with diabetes and end stage renal disease (160).

The CARDS trial specifically focused on subjects with diabetes (161). The subjects in this trial were males and females with T2DM 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-C levels less than 160mg/dl and triglyceride levels less than 600mg/dl. It is important to recognize that the average LDL-C in this trial was approximately 118mg/dl, indicating relatively low LDL-C levels. A total of 2,838 T2DM subjects were randomized to either placebo or atorvastatin 10mg a day. Atorvastatin therapy

resulted in a 40% decrease in LDL-C levels with over 80% of patients achieving LDL-C 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-C levels (LDL <120mg/dl) benefited to a similar extent as subjects with higher LDL-C 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.

Studies have compared reductions of LDL-C to approximately 100mg/dl to more aggressive reductions in LDL-C on atheroma volume. The Reversal Trial studied 502 symptomatic coronary artery disease patients with an average LDL-C of 150mg/dl (162). 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-C 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-C to the change in atheroma volume, a 50% reduction in LDL (LDL-C levels of approximately 75mg/dl) resulted in the absence of lesion progression. This study suggests that lowering the LDL-C 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-C (in Asteroid the mean LDL-C levels were 61mg/dl) can even result in the regression of coronary artery atherosclerosis determined by intravascular ultrasound measurements (163). Additionally, 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-C levels were reduced to less than 70mg/dl (164). Together these trials indicate that aggressive lowering of LDL-C 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-C with atorvastatin 80mg per day vs. moderate LDL-C 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 (165,166). In this trial, approximately 18% of the patients were diabetic. As expected, the on-treatment LDL-C levels were significantly lower in patients aggressively treated with atorvastatin compared to the moderate treated pravastatin group (atorvastatin LDL-C = approximately 62 vs. pravastatin LDL-C = 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-C levels less than 130mg/dl were randomized to either 10mg or 80mg atorvastatin and followed for an average of 4.9years (167,168). Approximately 15% of the patients had diabetes. As expected, LDL-C 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 (169). Approximately 12% of the patients had diabetes. As expected, LDL-C 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-C 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, Saturn, Asteroid, Prove-It, TNT, and IDEAL leads one to the conclusion that aggressive lowering of LDL-C with statin therapy will be beneficial and suggests that in high risk patients lowering the LDL to levels well below 100mg/dl is desirable. Moreover, 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-C (170). They reported that intensive control (approximately a 19mg/dl difference in LDL-C) 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. Additionally, as described in detail below, recent studies of the addition of either ezetimibe or PCSK9 inhibitors to statins further demonstrates that aggressive lowering of LDL-C levels further reduces cardiovascular events

FIBRATES

The beneficial effect of monotherapy with fibrates (e.g. gemfibrozil, fenofibrate) on cardiovascular disease in patients with diabetes is shown in Table 3. 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 (171). In this trial, 9,795 patients with T2DM 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-C, a 29% decrease in triglycerides, and a 5% increase in HDL-C 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).

While the results of fibrate trials have been very heterogeneous it should be noted that fibrate trials in patients with elevated triglyceride levels have reported a greater reduction of cardiovascular events (172). Additionally, subgroup analysis of several fibrate trials has also suggested that the benefit of fibrates was greatest in patients with elevated triglyceride levels (172,173).

The mechanism by which fibrates reduce cardiovascular events is unclear. These drugs lower serum triglyceride levels and increase HDL-C, 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 (174,175).

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 T2DM.

Table 3. Effect of Fibrate Monotherapy on Cardiovascular Outcomes

Study	Drug	#Diabetic subjects	%Decrease controls	% Decrease diabetics
Helsinki Heart Study (176)	Gemfibrozil	135	34	60*
VA-HIT (175)	Gemfibrozil	620	24	24
DIAS (177)	Fenofibrate	418	-	23*
Sendcap (178)	Bezafibrate	164	-	70
Field (171)	Fenofibrate	9795	-	11*

* Not statistically significant

NIACIN

A single randomized trial, the Coronary Drug Project, has examined the effect of niacin monotherapy on cardiovascular outcomes (179). 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 (180). 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 monotherapy reduces cardiovascular events both in normal subjects and patients with diabetes.

EZETIMIBE

A multicenter, randomized trial in Japan examined the efficacy of ezetimibe in patients aged ≥75 years with elevated LDL-C (≥140 mg/dL) without a history of coronary artery disease who were not taking lipid lowering drugs (181). Patients were randomized to ezetimibe (n=1716) or usual care (n=1695) and followed for 4.1 years. The primary outcome was a composite of sudden cardiac death, myocardial infarction, coronary revascularization, or stroke. In the ezetimibe group LDL-C was decreased by 25.9% and non-HDL-C by 23.1% while in the usual care group LDL-C was decreased by 18.5% and non-HDL-C by 16.5% ($p<0.001$ for both lipid parameters). By the end of the trial 9.6% of the patients in the usual care group and 2.1% of the ezetimibe group were taking statins. Ezetimibe reduced the incidence of the primary outcome by 34% (HR 0.66; P=0.002). Additionally, composite cardiac events were reduced by 60% (HR 0.60; P=0.039) and coronary revascularization by 62% (HR 0.38; P=0.007) in the ezetimibe group vs. the control group. There was no difference in the incidence of stroke or all-cause mortality between the groups. Approximately 25% of the patients in this trial had diabetes and the beneficial effects were similar in the diabetic and non-diabetic subjects. It should be noted that the reduction in cardiovascular events was much greater than one would expect based on the absolute difference in LDL-C levels (121mg/dl in ezetimibe group vs. 132mg/dl). As stated by the authors “Given the open-label nature of the trial, its premature termination, and issues with follow-up, the magnitude of benefit observed should be interpreted with caution.” Nevertheless, this study provides evidence that ezetimibe monotherapy can reduce cardiovascular events.

OTHER DRUGS

With regard to PCSK9 inhibitors and bile acid sequestrants there have been no randomized monotherapy 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 (102,103). 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. Additionally, bile acid sequestrants improve glycemic control (101). However, bile acid sequestrants can raise triglyceride levels and therefore must be used with caution in hypertriglyceridemic patients. There are no outcome studies with PCSK9 inhibitor monotherapy in patients with diabetes but given that these drugs reduce LDL-C levels and in combination with statins reduce cardiovascular events one would anticipate that PCSK9 inhibitor monotherapy will also reduce cardiovascular events.

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 T2DM (182). 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-C levels were approximately 80mg/dl. There was only a small difference in HDL-C with the fenofibrate groups having a mean HDL-C of 41.2mg/dl while the control group had an HDL-C 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-C 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-C levels. Finally, similar to what has been reported in other trials, fenofibrate had beneficial effects on the progression of microvascular disease (183,184). 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.

The PROMINENT trial is exploring the effect of pemafibrate, a new selective PPAR-alpha modulator, in reducing cardiovascular outcomes in a large number (approx. 10,000) diabetic patients with atherogenic dyslipidemia on a statin (185). This trial will hopefully provide definitive data regarding the effect of fibrates on cardiovascular disease in patients with diabetes.

STATIN + 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 (186). In this trial 3,314 patients were randomized to Niaspan vs. placebo. Approximately 33% of the patients had diabetes. On trial, LDL-C levels were in the 60-70mg/dl range in both groups. As expected, HDL-C 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-C < 33mg/dl niacin showed a trend towards benefit (hazard ratio 0.74; p=0.073), suggesting that if the appropriate patient population was studied the results may have been positive (187).

HPS 2 Thrive also studied the effect of niacin added to statin therapy (188). 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-C level was 63mg/dl, the HDL-C 44mg/dl, and the triglycerides 125mg/dl at baseline. As expected, niacin therapy resulted in a modest reduction in LDL-C (10mg/dl), a modest increase in HDL-C (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 were not 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-C levels coupled with low HDL-C levels should be studied.

STATIN + EZETIMIBE

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 (189). 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-C 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 re-hospitalization, 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 (Primary endpoint hazard ratio, 0.85; 95% confidence interval, 0.78-0.94) (190,191).

STATIN + PCSK9 INHIBITORS

The FOURIER trial was a randomized, double-blind, placebo-controlled trial of evolocumab vs. placebo in 27,564 patients with atherosclerotic cardiovascular disease and an LDL-C level of 70 mg/dl or higher who were on statin therapy (192). Approximately 40% of the patients had diabetes (193). The primary

end point was cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization and the key secondary end point was cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years. Baseline LDL-C levels were 92mg/dl and evolocumab resulted in a 59% decrease in LDL-C levels (LDL-C level on treatment approximately 30mg/dl). Evolocumab treatment significantly reduced the risk of the primary end point (hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and the key secondary end point (hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL-C levels (median, 74 mg/dl). Of note, a similar decrease in cardiovascular events occurred in patients with diabetes treated with evolocumab and glycemic control was not altered (194). Further analysis has shown that in the small number of patients with a baseline LDL-C level less than 70mg/dl, evolocumab reduced cardiovascular events to a similar degree as in the patients with an LDL-C greater than 70mg/dl (195). Finally, the lower the on-treatment LDL-C levels (down to levels below 20mg/dl), the lower the cardiovascular event rate, suggesting that greater reductions in LDL-C levels will result in greater reductions in cardiovascular disease (196).

The ODYSSEY trial was a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, an LDL-C level of at least 70 mg/dl, a non-HDL-C level of at least 100 mg/dl, or an apolipoprotein B level of at least 80 mg/dl while on high intensity statin therapy or the maximum tolerated statin dose (197). Approximately 29% of the patients had diabetes. Patients were randomly assigned to receive alirocumab 75 mg every 2 weeks or matching placebo. The dose of alirocumab was adjusted to target an LDL-C level of 25 to 50 mg/dl. The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. During the trial LDL-C levels in the placebo group was 93-103mg/dl while in the alirocumab group LDL-C levels were 40mg/dl at 4 months, 48mg/dl at 12 months, and 66mg/dl at 48 months (the increase with time was due to discontinuation of alirocumab or a decrease in dose). The primary endpoint was reduced by 15% in the alirocumab group (HR 0.85; 95% CI 0.78 to 0.93; P<0.001). In addition, total mortality was reduced by 15% in the alirocumab group (HR 0.85; 95% CI 0.73 to 0.98). The absolute benefit of alirocumab was greatest in patients with a baseline LDL-C level > than 100mg/dl. In patients with an LDL-C level > than 100mg/dl the number needed to treat with alirocumab to prevent an event was only 16. It should be noted that similar to the other PCSK9 outcome trials the duration of this trial was very short (median follow-up 2.8 years) which may have minimized the beneficial effects. Additionally, because alirocumab 75mg every 2 weeks was stopped if the LDL-C level was < 15mg/dl on two consecutive measurements the beneficial effects may have been blunted (7.7% of patients randomized to alirocumab were switched to placebo).

It should be noted that that the duration of the PCSK9 outcome trials were relatively short and it is well recognized from previous statin trials that the beneficial effects of lowering LDL-C levels takes time with only modest effects observed during the first year of treatment. In the FOURIER trial the reduction of cardiovascular death, myocardial infarction, or stroke was 16% during the first year but was 25% beyond 12 months. In the ODYSSEY trial the occurrence of cardiovascular events was similar in the alirocumab and placebo group during the first year of the study with benefits of alirocumab appearing after year one. Thus, the long-term benefits of treatment with a PCSK9 inhibitor may be

greater than that observed during these relatively short-term studies.

Additional support for the benefits of further lowering of LDL-C levels with a PCSK9 inhibitor added to statin therapy is seen in the GLAGOV trial (198). This trial was a double-blind, placebo-controlled, randomized trial of evolocumab vs. placebo in 968 patients presenting for coronary angiography. Approximately 20-21% of the patients had diabetes. The primary efficacy measure was the change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures included change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. As expected, there was a marked decrease in LDL-C levels in the evolocumab group (Placebo 93mg/dl vs. evolocumab 37mg/dl; p<0.001). PAV increased 0.05% with placebo and decreased 0.95% with evolocumab (P < .001) while TAV decreased 0.9 mm3 with placebo and 5.8 mm3 with evolocumab (P < .001). There was a linear relationship between achieved LDL-C and change in PAV (i.e. the lower the LDL-C the greater the regression in atheroma volume down to an LDL-C of 20mg/dl). Additionally, evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; P < .001 for PAV and 61.5% vs 48.9%; P < .001 for TAV). The results in the patients with diabetes were similar to the non-diabetic patients.

Taken together these trials demonstrate that further lowering LDL-C levels with PCSK9 inhibitors in patients taking statins will have beneficial effects on atherosclerosis and cardiovascular outcomes.

The results of the ezetimibe and PCSK9 trials have several 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 to much lower levels than usual will have significant benefits. These results have implications for determining goals of therapy.

STATINS + LOW DOSE OMEGA-3-FATTY ACIDS

Origin was a double-blind study in 12,536 patients at high risk for cardiovascular disease who had impaired fasting glucose, impaired glucose tolerance, or diabetes (199). Patients were randomized to receive a 1-gram capsule containing at least 900mg of ethyl esters of omega-3 fatty acids (EPA 465mg and DHA 375mg) or placebo for approximately 6 years. Greater than 50% of the patients were on statin therapy. The primary outcome was death from cardiovascular causes. Triglyceride levels were reduced by 14.5mg/dl in the group receiving omega-3-fatty acids compared to the placebo group (P<0.001), without a significant effect on other lipids. The incidence of the primary outcome was not significantly decreased among patients receiving omega-3-fatty acids as compared with those receiving placebo. The use of omega-3-fatty acids also had no significant effect on the rates of major vascular events, death from any cause, or death from arrhythmia.

A Study of Cardiovascular Events in Diabetes (ASCEND**)** was a randomized, placebo controlled, double blind trial of 1-gram omega-3-fattys acids (400mg EPA and 300mg DHA ethyl esters) vs. olive oil placebo in 15,480 patients with diabetes without a history of cardiovascular disease (primary prevention trial) (200). Approximately 75% of patients were on statin therapy. The primary end point was serious vascular events (non-fatal myocardial infarction, non-fatal stroke, transient ischemic attack, or vascular

death). Total cholesterol, HDL-C, and non-HDL-C levels were not significantly altered by omega-3-fatty acid treatment (changes in triglyceride levels were not reported). After a mean follow-up of 7.4 years the composite outcome of a serious vascular event or revascularization occurred in 882 patients (11.4%) on omega-3-fatty acids and 887 patients (11.5%) on placebo (rate ratio, 1.00; 95% CI, 0.91 to 1.09). Serious adverse events were similar in placebo and omega-3-fatty acid treated groups.

Taken together these studies indicate that low dose omega-3-fatty acids do not reduce cardiovascular events in patients with diabetes.

STATINS + HIGH DOSE OMEGA-3-FATTY ACIDS

Japan EPA Lipid Intervention Study (JELIS) was an open label study in patients on statin therapy with total cholesterol levels > 254mg/dl with (n= 3664) or without cardiovascular disease (n=14,981) who were randomly assigned to be treated with 1800 mg of EPA (Vascepa) + statin (n=9326) or statin alone (n= 9319) with a 5 year follow-up (201). Approximately 16% of the patients had diabetes. The mean baseline triglyceride level was 153mg/dl. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Total cholesterol, LDL-C, and HDL-C levels were similar in the two groups but plasma triglycerides were modestly decreased in the EPA treated group (5% decrease in EPA group compared to controls; p = 0.0001). In the EPA + statin group the primary endpoint occurred in 2.8% of the patients vs. 3.5% of the patients in the statin alone group (19% decrease; p = 0.011). Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group but in this study sudden cardiac death and coronary death did not differ between groups. Unstable angina was the main component contributing to the primary endpoint and this is a more subjective endpoint than other endpoints such as a myocardial infarction, stroke, or cardiovascular death. A subjective endpoint has the potential to be an unreliable endpoint in an open label study and is a limitation of the JELIS Study. The reduction in events was similar in the subgroup of patients with diabetes. In patients with triglyceride levels >150mg/dl and HDL-C levels < 40mg/dl there was a 53% decrease in events (202).

The Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT) was a randomized, double blind trial of 2 grams twice per day of EPA ethyl ester (icosapent ethyl) (Vascepa) vs. placebo in 8,179 patients with hypertriglyceridemia (135mg/dl to 499mg/dl) and established cardiovascular disease or high cardiovascular disease risk (diabetes plus one risk factor) who were on stable statin therapy (203). Approximately 60% of the patients in this trial had diabetes. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. At baseline, the median LDL-C level was 75.0 mg/dl, HDL-C level was 40.0 mg/dl, and triglyceride level was 216.0 mg/dl. The median change in triglyceride level from baseline to 1 year was a decrease of 18.3% (−39.0 mg/dl) in the EPA group and an increase of 2.2% (4.5 mg/dl) in the placebo group. After a median of 4.9 years the primary end-point occurred in 17.2% of the patients in the EPA group vs. 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001), indicating a 25% decrease in events. The beneficial effects were similar in patients with and without diabetes. The number needed to treat to avoid one primary end-point event was 21. The reduction in

cardiovascular events was noted after approximately 2 years of EPA treatment. Additionally, the rate of cardiovascular death was decreased by 20% in the EPA group (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). The cardiovascular benefits of EPA were similar across baseline levels of triglycerides (<150, ≥150 to <200, and ≥200 mg/dl). Moreover, the cardiovascular benefits of EPA appeared to occur irrespective of the attained triglyceride level at 1 year (≥150 or <150 mg/dl), suggesting that the cardiovascular risk reduction was not associated with attainment of a normal triglyceride level. An increase in hospitalization for atrial fibrillation or flutter (3.1% vs. 2.1%, P=0.004) occurred in the EPA group. In addition, serious bleeding events occurred in 2.7% of the patients in the EPA group and in 2.1% in the placebo group (P=0.06). There were no fatal bleeding events in either group and the rates of hemorrhagic stroke, serious central nervous system bleeding, and serious gastrointestinal bleeding were not significantly higher in the EPA group than in the placebo group.

These results demonstrate that EPA treatment reduces cardiovascular disease events. Of note the reduction in TG levels is relatively modest and would not be expected to result in the magnitude of the decrease in cardiovascular disease observed in the JELIS and REDUCE-IT trials. Other actions of EPA, such as decreasing platelet function, anti-inflammation, decreasing lipid oxidation, stabilizing membranes, etc. could account for or contribute to the reduction in cardiovascular events (204). It is likely that the beneficial effects of EPA seen in the JELIS and REDUCE-IT trials are multifactorial.

The Statin Residual Risk Reduction with Epanova in High Risk Patients with Hypertriglyceridemia (Strength) trial is a randomized, placebo controlled, double blind trial of 4 grams per day of omega-3-fatty acids (Epanova) (mixture of EPA and DHA fatty acids) vs. placebo in 13,000 patients on statins with hypertriglyceridemia (180-500mg/dl), optimal LDL-C levels (< 100mg/dl or on maximal statin therapy), low HDL-C (<42mg/dl in men and < 47mg/dl in women), and either cardiovascular disease or high risk for cardiovascular disease (205). The primary outcome is major atherosclerotic cardiovascular events (cardiovascular death, myocardial infarction, stroke, coronary revascularization or hospitalization for unstable angina). The results of this study have not been presented or published but a press release has indicated that the study was stopped due to futility.

CURRENT GUIDELINES FOR SERUM LIPIDS

There are several different guidelines for treating lipids in patients with diabetes. Some guidelines provide specific LDL-C goals while other guidelines do not.

American Diabetes Association Guidelines

The 2020 American Diabetes Association (ADA) recommends that adult patients with diabetes have their lipid profile determined at the time of diabetes diagnosis and at least every 5 years thereafter or more frequently if indicated (206). This profile includes total cholesterol, HDL-C, triglycerides, and calculated LDL-C. A lipid panel should be obtained immediately prior to initiating statin therapy. Once a patient is on statin therapy testing should be carried out 4-12 weeks after initiating therapy and annually thereafter 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. A focus on a Mediterranean style diet or Dietary Approaches to Stop Hypertension (DASH) diet should be encouraged. In patients with elevated triglyceride levels glycemic control is beneficial and

dietary changes and lifestyle changes including weight loss and abstinence from alcohol should be undertaken. Secondary disorders and medications that raise triglyceride levels should be evaluated. The recommendations for lipid lowering therapy are shown in table 4. If one follows these recommendations almost all patients with diabetes over the age of 40 will be on statin therapy and many under the age of 40 will also be treated with statins. The addition of ezetimibe should be considered to further lower LDL-C levels in high risk primary prevention patients. In very high-risk patients with atherosclerotic cardiovascular disease if the LDL-C level on statin therapy is greater than 70mg/dl the use of ezetimibe or a PCSK9 inhibitor should be considered. The use of fibrates or niacin with statins were generally not recommended. However, in patients with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL-C but elevated triglyceride levels (135-499mg/dl) the addition of icosapent ethyl can be considered. Finally, in patients with fasting triglyceride levels greater than 500mg/dl an evaluation for secondary causes of hypertriglyceridemia should be initiated and consideration of drug therapy to reduce the risk of pancreatitis.

Table 4. ADA Recommendations for Lipid Lowering Therapy
Primary Prevention
Age 20-39: With additional risk factors may be reasonable to initiate statin therapy
Age 40-75: Moderate intensity statin therapy*
Age > 75: Moderate intensity statin therapy is reasonable after discussion
Patients at high risk: Multiple risk factors*** or age 50-70 it is reasonable to use high intensity statin therapy**
Patients with 10-year risk > 20%: reasonable to add ezetimibe to maximally tolerated statin to reduce LDL by > 50%
Secondary Prevention
All ages < 75: High intensity statin therapy/maximally tolerated stain
Age >75: Reasonable to continue statin therapy or initiate statin therapy after discussion.
Very High Risk: If LDL > 70mg/dl on maximally tolerated statin consider adding ezetimibe or PCSK9 inhibitor

*Moderate intensity statin- atorvastatin 10-20mg, rosuvastatin 5-10mg, simvastatin 20-40mg, pravastatin 40-80mg, lovastatin 40mg, Fluvastatin XL 80mg, pitavastatin 3-4mg

**High Intensity statin- atorvastatin 40-80mg, rosuvastatin 20-40mg

*** Risk factors include LDL-C > 100mg/dl, high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD

American College of Cardiology and American Heart Association Guidelines

The 2018 American College of Cardiology and American Heart Association (ACC/AHA) guidelines are similar to the ADA guidelines described above and recommend the following (207). “In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50

to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%." In patients with diabetes and cardiovascular disease they recommend "In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDLC levels by ≥50%. In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statins to statin therapy. Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L). In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices." With regards to testing they recommend "Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed". Finally, there are several diabetes specific risk enhancers that are independent of other risk factors that should be considered in deciding a patient with diabetes risk of cardiovascular events (Table 5).

Table 5. Diabetes Specific Risk Enhancers That are Independent of Other Risk Factors in Diabetes
Long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus
Albuminuria ≥30 mcg of albumin/mg creatinine
eGFR <60 mL/min/1.73 m2
Retinopathy
Neuropathy
ABI <0.9

ABI indicates ankle-brachial index

National Lipid Association Guidelines

The National Lipid Association (NLA) has treatment goals for patients with diabetes (208). In patients with T1DM or T2DM with pre-existing atherosclerotic cardiovascular disease, two or more risk factors for atherosclerotic cardiovascular disease or evidence of end organ damage, the goal LDL is <70mg/dl and the goal non-HDL-C is < 100mg/dl (Table 6). In patients with diabetes with 0-1 risk factors and no end organ damage, the LDL goal is < 100mg/dl and the non-HDL-C goal is < 130mg/dl. The NLA guidelines recommend considering drug therapy if a patient with diabetes is not at goal.

Table 6. National Lipid Association Recommendations	
Diabetes with 0-1 risk factors* and no end organ damage**	LDL-C < 100mg/dl; Non-HDL-C < 130mg/dl
Diabetes with 2 or more risk factors or end organ damage	LDL-C < 70mg/dl; Non-HDL-C < 100mg/dl

*Risk factors- 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.
**End Organ Damage- retinopathy, albumin/creatinine ratio > 30mg/g, or chronic kidney disease

American Association of Clinical Endocrinologists/American College of Endocrinology Guidelines

The American Association of Clinical Endocrinologists and American College of Endocrinology guidelines consider individuals with T2DM to be at high, very high, or extreme risk for ASCVD (209). Patients with T1DM and a duration of diabetes of more than 15 years or two or more risk factors, poorly controlled A1c, or insulin resistance with metabolic syndrome should be considered to have an equivalent risk to patients with T2DM. The recommended treatment goals are shown in Table 7.

Table 7. ASCVD Risk Categories and Treatment Goals

Risk Category	Risk Factors/10-year risk	LDL-C mg/dl	Non-HDL-C mg/dl	Apo B mg/dl
Extreme Risk	Diabetes and clinical cardiovascular disease	<55	<80	<70
Very High Risk	Diabetes with one or more risk factors*	<70	<100	<80
High Risk	Diabetes and no other risk factors	<100	<130	<90

*Risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

European Society of Cardiology and European Atherosclerosis Society Guidelines

Finally, the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) has guidelines for the treatment of lipids in patients with diabetes (210). These guidelines classify patients with diabetes as very high risk, high risk, or moderate risk (table 8). The recommended goals of therapy based on risk classification are shown in table 9. As with other guidelines intensification of statin therapy should be considered before the introduction of combination therapy. If the goal is not reached, statin combination with ezetimibe should be considered next.

Table 8. ESC/EAS Classification of Risk in Patients with Diabetes

Very High Risk- target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years)
High Risk- without target organ damage, with DM duration >10 years or another additional risk factor
Moderate Risk- Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE >1 % and <5% for 10-year risk of fatal CVD

Table 9. ESC/EAS Goals of Therapy in Patients with Diabetes			
	LDL-C	**Non-HDL-C**	**Apo B**
Very High Risk	>50% reduction and <55mg/dl (<1.4mmol/L)	<85mg/d;	<65mg/dl
High Risk	>50% reduction and <70mg/dl (<1.8mmol/L)	<100mg/dl	<80mg/dl
Moderate Risk	<100mg/dl	<130mg/dl	<100mg/dl

My Goal Recommendations

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.

The approach I use is to combine these recommendations (Table 10 and 11). In patients with diabetes who have pre-existing atherosclerotic cardiovascular disease I initiate intensive statin therapy. Given the extensive data showing that the lower the LDL-C the greater the reduction in cardiovascular events most secondary prevention patients would benefit from the addition of ezetimibe to maximize LDL-C lowering without markedly increasing costs (211). In patients with diabetes 40-75 years of age without pre-existing cardiovascular disease I calculate the 10-year risk of developing cardiovascular disease (http://www.cvriskcalculator.com/) and identify risk enhancing factors (Table 5). I initiate intensive statin therapy if the 10-year risk is > 7.5% or if there are multiple risk factors or moderate statin therapy if the risk is < 7.5% without multiple risk factors. Six to twelve weeks after initiating statin therapy I obtain a lipid panel to determine if the LDL and non-HDL-C levels are at goal. In patients with pre-existing cardiovascular disease or multiple risk factors (i.e. very high-risk patients) my goal is an LDL-C < 55mg/dl and a non-HDL-C < 80mg/dl. In patients that are at high-risk the goal my goal is an LDL-C < 70mg/dl and a non-HDL-C < 100mg/dl. In patients with moderate risk an LDL-C goal of < 100mg/dl and a non-HDL c < 100mg/dl is appropriate. If the levels are not at goal, I first adjust the statin dose until the patient is taking the maximally tolerated statin dose and then consider adding additional medications. In patients with diabetes who are less than 40 years of age I initiate statin therapy if the patient has overt cardiovascular disease, long standing diabetes, or risk factors for cardiovascular disease and the LDL and non-HDL-C levels are not at goal. In patients over 75 years of age with a reasonable life expectancy I begin moderate statin therapy and adjust based on response. When there is difficulty classifying a patient's risk, I will obtain a coronary calcium score and use the score to help stratify the patient's risk. In all cases the benefits and risks of lipid lowering therapy needs to be discussed with patients and the patient's personnel preferences taken into account.

Table 10. ASCVD Risk Categories and Treatment Goals			
Risk Category	**Risk Factors/10-year risk**	**LDL-C mg/dl**	**Non-HDL-C mg/dl**
Very High Risk	Diabetes and clinical cardiovascular disease or multiple risk factors	<55	<80
High Risk	Diabetes with one or more risk factors	<70	<100
Moderate Risk	Diabetes and no other risk factors	<100	<130

Table 11. Drug Therapy According to Risk Category that is Typically Required	
Very High Risk	Intensive statin therapy + ezetimibe. Add PCSK9 is not close to goal
High Risk	Intensive statin therapy. Add ezetimibe if not at goal
Moderate Risk	Moderate statin therapy. Increase to intensive statin therapy is not at goal

TREATMENT OF LIPID ABNORMALITIES IN PATIENT WITH DIABETES

Life Style Changes

Initial treatment of lipid disorders should focus on lifestyle changes (212). 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-C levels (an increase in HDL-C requires vigorous exercise) (123,212). 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 and for detailed information on nutrition therapy for adults with diabetes see the consensus report by the American Diabetes Association (213). Everyone agrees that weight loss in obese patients is essential (123,212). 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-C levels, and modestly reduce LDL-C (123,212). To reduce LDL-C 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 (123). 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-C 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-C levels. Additionally, both diets also reduce trans-fatty acid intake, which will have a beneficial effect on LDL and HDL-C 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 and therefore the diet needs to be tailored to the specific preferences of the patient.

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 (214). In this trial, over 5000 overweight or obese patients with T2DM 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 (increased monounsaturated fats) did reduce the incidence of major cardiovascular disease (215,216). In this multicenter trial center trial, carried out in Spain, over 7,000 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 T2DM. 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-C levels and a small decrease in both LDL-C and triglyceride levels (217). 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 (218,219). 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 (218). The results of these two trials indicate that we should be encouraging our patients to follow a Mediterranean type diet. It is likely that the beneficial effects of the Mediterranean diet on cardiovascular disease is mediated by multiple mechanisms with alterations in lipid levels making only a minor contribution.

With the currently available weight loss drugs only modest effects on weight and lipid levels have been observed (123,212). 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 marked improvements in lipid profiles with a decrease in triglycerides and LDL-C and an increase in HDL-C (123,212). Additionally, observational studies have shown a decrease in cardiovascular events following bariatric surgery in patients with and without diabetes (220-224). For additional information see the chapter entitled “Lifestyle Changes: Effect of Diet, Exercise, Functional Food, and Obesity Treatment, on Lipids and Lipoproteins” and the chapter entitled “Obesity and Dyslipidemia” (123,212).

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 (212).

Lastly, in the past some "experts" advocated the addition of fish oil supplements to reduce cardiovascular events. However, both the Origin Trial and the ASCEND Trial did not demonstrate that fish oil supplements were beneficial in patients with T2DM or patients at high risk for the development of T2DM (199,200) (see section on effect of lipid lowering drugs on cardiovascular events for details). It should be recognized that higher doses of fish oil are required to lower serum triglyceride levels (~ 3-4 grams of DHA/EPA per day) and are useful in treating patients with high triglyceride levels (225). Additionally, as discussed in detail earlier high dose EPA reduced cardiovascular events. 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 (225). Additionally, in some patient's high dose fish oil increases LDL-C levels, particularly when serum triglyceride levels are very high (225). For additional information on fish oil see the chapter on Triglyceride Lowering Drugs (226).

Drug Therapy

The effect of statins, fibrates, niacin, ezetimibe, omega-3-fatty acids, bile acid sequestrants, bempedoic acid, and PCSK9 inhibitors on lipid levels in patients with diabetes is virtually identical to that seen in the non-diabetic patients (Table 12). Below we will highlight issues particularly relevant to the use of these drugs in patients with diabetes. For detailed information on lipid lowering drugs see the chapters on Triglyceride Lowering Drugs and Cholesterol Lowering Drugs (140,226).

STATINS

Statins are easy to use and generally well tolerated by patients with diabetes. However, statins can adversely affect glucose homeostasis. In patients without diabetes the risk of developing diabetes is increased by approximately 10% with higher doses of statin causing a greater risk than more moderate doses (227,228). 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 (229). 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 (158,161,230). 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 (231). In the ACCORD-LIPID Trial the incidence of muscle disorders was not increased in the statin + fenofibrate group compared to statin alone (182). 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-C levels can occur in some patients treated with both fenofibrate and a TZD (232).

Diabetic Retinopathy

Fenofibrate has been shown to have beneficial effects on diabetic eye disease. The FIELD study, described earlier, was a randomized trial of fenofibrate vs. placebo in patients with T2DM. Laser treatment for retinopathy was significantly lower in the fenofibrate group than in the placebo group (3.4% patients on fenofibrate vs 4.9% on placebo; p=0.0002) (184). Fenofibrate therapy reduced the need for laser therapy to a similar extent for maculopathy (31% decrease) and for proliferative retinopathy (30% decrease). In the ophthalmology sub-study (n=1012), the primary endpoint of 2-step progression of retinopathy grade did not differ significantly between the fenofibrate and control groups (9.6% patients on fenofibrate vs 12.3% on placebo; p=0.19). In patients without pre-existing retinopathy there was no difference in progression (11.4% vs 11.7%; p=0.87). However, in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had a 2-step progression than did those on placebo (3.1% patients vs 14.6%; p=0.004). A composite endpoint of 2-step progression of retinopathy grade, macular edema, or laser treatments was significantly reduced in the fenofibrate group (HR 0.66, 95% CI 0.47-0.94; p=0.022).

In the ACCORD Study a subgroup of participants were evaluated for the progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study Severity Scale or the development of diabetic retinopathy necessitating laser photocoagulation or vitrectomy over a four year period (183). At 4 years, the rates of progression of diabetic retinopathy were 6.5% with fenofibrate therapy (n=806) vs. 10.2% with placebo (n=787) (adjusted odds ratio, 0.60; 95% CI, 0.42 to 0.87; P = 0.006). Of note, this reduction in the progression of diabetic retinopathy was of a similar magnitude as intensive glycemic treatment vs. standard therapy.

Taken together these results indicate that fibrates have beneficial effects on the progression of diabetic retinopathy. The mechanisms by which fibrates decrease diabetic retinopathy are unknown.

Diabetic Nephropathy

The Diabetes Atherosclerosis Intervention Study (DAIS) evaluated the effect of fenofibrate therapy (n= 155) vs. placebo (n=159) on changes in urinary albumin excretion in patients with T2DM (233).

Fenofibrate significantly reduced the worsening of albumin excretion (fenofibrate 8% vs. placebo 18%; P < 0.05). This effect was primarily due to reduced progression from normal albumin excretion to microalbuminuria (fenofibrate 3% vs. 18% placebo; P < 0.001).

In the FIELD trial, fenofibrate reduced urine albumin/creatinine ratio by 24% vs 11% in placebo group (p < 0.001), with 14% less progression and 18% more albuminuria regression (p < 0.001) in the fenofibrate group than in participants on placebo (234). As expected, fenofibrate therapy acutely increased plasma creatinine levels and decreased eGFR but over the long term, the increase in plasma creatinine was decreased in the fenofibrate group compared to the placebo group (14% decrease; p=0.01). Similarly, there was a slower annual decrease in eGFR in the fenofibrate group (1.19 vs 2.03 mL/min/1.73m^2 annually, p < 0.001). End-stage renal disease, dialysis, renal transplant, and renal death were similar in the fenofibrate and placebo groups.

In the ACCORD-LIPID trial the post-randomization incidence of microalbuminuria was 38.2% in the fenofibrate group and 41.6% in the placebo group (p=0.01) and post-randomization incidence of macroalbumuria was 10.5% in the fibrate group and 12.3% in the placebo group (p=0.04) indicating a modest reduction in the development of proteinuria in patients treated with fenofibrate (182). There was no significant difference in the incidence of end-stage renal disease or need for dialysis between the fenofibrate group and the placebo group.

These studies suggest that fibrates may have a beneficial effect on diabetic kidney disease. One should recognize that reducing proteinuria is a surrogate marker and may not indicate a reduction in the development of end stage renal disease. The mechanisms accounting for decreased in proteinuria are unknown.

Amputations

In the FIELD study the risks of first amputation was decreased by 36% (p=0.02) and minor amputation events without known large-vessel disease by 47% (p=0.027) in the fenofibrate treated group (235). The reduction in amputations was independent of glucose control or dyslipidemia. No difference between the risks of major amputations was seen in the placebo and fenofibrate groups. The basis for this reduction in amputations is unknown.

BILE ACID SEQUESTRANTS

Bile acid sequestrants are relatively difficult to take due to GI toxicity (mainly constipation) (140). 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 (140). An additional difficulty in using bile acid sequestrants is their potential for binding other drugs (140). 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. Patients with diabetes 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, powder, or chewable bars and causes fewer side effects and has fewer interactions with other drugs than other preparations (236). The usual dose is 3.75 grams per day and can be given as

tablets (take 6 tablets once daily or 3 tablets twice daily), oral suspension (take one packet once daily), or chewable bars (take one bar once daily). 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 (237).

NIACIN

Niacin is well known to cause skin flushing and itching and GI upset (238). Additionally, niacin reduces insulin sensitivity (i.e., causes insulin resistance), which can worsen glycemic control (238). Studies have shown that niacin is usually well tolerated in diabetic subjects who are in good glycemic control (239,240). 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 (188). High doses of niacin are more likely to adversely affect glycemic control. Niacin can also increase serum uric acid levels and induce gout, both of which are already common in obese patients with T2DM (238). Additionally recent trials have reported an increased incidence of infection and bleeding with niacin therapy (238). However, niacin is the most effective drug in increasing HDL-C levels, which are frequently low in patients with diabetes.

OMEGA-3-FATTY ACIDS

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 (225). Fish oil effectively lowers triglyceride levels but, in some patients, particularly those with significant hypertriglyceridemia, high dose fish oil increases LDL-C levels (225). It should be noted that fish oil products that contain just EPA (Vascepa) do not adversely affect LDL-C levels (241). 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 food supplements can vary greatly and in some levels are very low. Additionally, while prescription omega-3-fatty acid preparations have high levels of quality control, omega-3-fish oil food supplements may have contaminants and the dosage may not be precisely controlled.

PCSK9 INHIBITORS

Two monoclonal antibodies that inhibit PCSK9 (proprotein convertase subtilisin kexin type 9) are approved for the lowering of LDL-C levels; Alirocumab (Praluent) and evolocumab (Repatha). Alirocumab is administered as either 75mg or 150mg subcutaneously every 2 weeks or 300mg subcutaneously every 4 weeks while evolocumab is administered as either 70mg subcutaneously every 2 weeks or 420mg subcutaneously once a month (140). A meta-analysis of three trials with 413 patients with T2DM found that in patients with T2DM evolocumab caused a 60% decrease in LDL-C compared to placebo and a 39% decrease in LDL-C compared to ezetimibe treatment (242). In addition, in patients with T2DM, evolocumab decreased non-HDL-C 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 T2DM and the beneficial effects on pro-atherogenic

lipoproteins is similar to what is observed in non-diabetic patients. Additionally, except for local reactions at the injection sites PCSK9 inhibitors do not seem to cause major side effects.

BEMPEDOIC ACID

The effect of bempedoic acid on LDL-C levels in patients with diabetes are similar to the decreases seen on non-diabetics. Patients with T2DM often have elevated uric acid levels and an increased risk of gouty attacks and a major side effect of bempedoic acid is elevating uric acid levels (140). In clinical trials, 26% of bempedoic acid-treated patients with normal baseline uric acid values experienced hyperuricemia one or more times versus 9.5% in the placebo group. Elevations in blood uric acid levels may lead to the development of gout and gout was reported in 1.5% of patients treated with bempedoic acid vs. 0.4% of patients treated with placebo. The risk for gout attacks were higher in patients with a prior history of gout (11.2% for bempedoic acid treatment vs. 1.7% in the placebo group). In patients with no prior history of gout only 1% of patients treated with bempedoic acid and 0.3% of the placebo group had a gouty attack.

Table 12. Effect of Lipid Lowering Drugs

	LDL-C	HDL-C	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%
Bempedoic Acid	↓ 15-25%	↓ 5-6%	No change
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 patients with high TG may increase LDL

Therapeutic Approach

The first priority in treating lipid disorders in patients with diabetes is to lower the LDL-C levels to goal, unless triglycerides are markedly elevated (> 500-1000mg/dl), which increases the risk of pancreatitis. LDL-C is the first priority because the database linking lowering LDL-C with reducing cardiovascular disease is extremely strong and we now have the ability to markedly decrease LDL-C levels. Dietary therapy is the initial step but, in almost all patients, will not be sufficient to achieve the LDL-C goals. If patients are willing and able to make major changes in their diet it is possible to achieve significant reductions in LDL-C levels but this seldom occurs in clinical practice (243).

Statins are the first-choice drugs to lower LDL-C levels and the vast majority of diabetic patients will require statin therapy. There are several statins currently available in the US and they are available as generic drugs and therefore relatively inexpensive. The particular statin used may be driven by price, ability to lower LDL-C levels, and potential drug interactions. Patients with ASCVD (secondary

prevention patients) should be started on intensive statin therapy (atorvastatin 40-80mg per day or rosuvastatin 20-40mg per day). Given the extensive data showing that the lower the LDL-C the greater the reduction in ASCVD events most secondary prevention patients would benefit from the addition of ezetimibe to maximize LDL-C lowering. Ezetimibe is now a generic drug and therefore this strategy will not markedly increase costs. Similarly, primary prevention patients who are at high risk for cardiovascular events will also benefit from the use of high intensity statin therapy in combination with ezetimibe. Primary prevention patients at moderate risk can be started on moderate intensity statin therapy.

If a patient is unable to tolerate statins or statins as monotherapy are not sufficient to lower LDL-C to goal the second-choice drug is either ezetimibe or a PCSK9 inhibitor. Ezetimibe can be added to any statin. PCSK9 inhibitors can also be added to any statin and are the drug of choice if a large decrease in LDL-C is required to reach goal (PCSK9 inhibitors will lower LDL-C levels by 50-60% when added to a statin, whereas ezetimibe will only lower LDL-C by approximately 20%). Bile acid sequestrants and bempedoic acid are alternatives with the use of a bile acid sequestrant particularly useful if a reduction in A1c level is also needed. Ezetimibe, PCSK9 inhibitors, bempedoic acid, and bile acid sequestrants additively lower LDL-C 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-C levels (140). Niacin and the fibrates also lower LDL-C levels but are not usually employed to lower LDL-C levels.

The second priority should be non-HDL-C (non-HDL-C = total cholesterol – HDL-C), which is particularly important in patients with elevated triglyceride levels (>150mg/dl). Non-HDL-C is a measure of all the pro-atherogenic apolipoprotein B containing particles. Numerous studies have shown that non-HDL-C is a strong risk factor for the development of cardiovascular disease (244). The non-HDL-C goals are approximately 30mg/dl greater than the LDL-C goals. For example, if the LDL goal is <100mg/dl then the non-HDL-C goal would be <130mg/dl. Drugs that reduce either LDL-C or triglyceride levels will reduce non-HDL-C levels. To lower triglyceride levels initial therapy should focus on glycemic control and lifestyle changes including a decrease in simple sugars and ethanol intake. Additionally, if possible, discontinue medications that increase triglyceride levels. If drugs are needed fibrates and omega-3-fatty acids reduce triglyceride levels. As discussed above, studies with the omega-3-fatty acid icosapent ethyl (EPA; Vascepa) added to statin therapy have reduced the risk of cardiovascular events. The National Lipid Association has recommended “that for patients aged ≥45 years with clinical ASCVD, or aged ≥50 years with diabetes mellitus requiring medication plus ≥1 additional risk factor, with fasting TGs 135 to 499 mg/dL on high-intensity or maximally tolerated statin therapy (±ezetimibe), treatment with icosapent ethyl is recommended for ASCVD risk reduction” (245). Alternatively, one could use fenofibrate. As discussed earlier, in the ACCORD-LIPID trial there was a suggestion of benefit with fenofibrate therapy in the patients in whom the baseline triglyceride levels were elevated (>204mg/dl) and HDL cholesterol levels decreased (<34mg/dl) (182). This may be an ideal treatment option in certain patients with diabetes as fenofibrate has also been shown to reduce the risk and/or progression of microvascular disease (226).

Patients with very high triglyceride levels (> 500-1000 mg/dl) are at risk of pancreatitis and therefore lifestyle and triglyceride lowering drug therapy should be initiated early. Treatment is a low-fat diet and glycemic control. Treating secondary disorders that raise triglyceride levels and when possible, stopping drugs that increase triglyceride levels is essential. If

the triglyceride levels remain above 500mg/dl the addition of fenofibrate or omega-3-fatty acids is indicated.

While there is strong epidemiologic data linking low HDL-C levels with cardiovascular disease there is no clinical trials demonstrating that increasing HDL-C levels reduce cardiovascular disease. Thus, the use of drugs such as niacin to raise HDL-C levels is not recommended.

CONCLUSION

Patients with diabetes, particularly T2DM, often have dyslipidemia. 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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