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DIABETES AND DYSLIPIDEMIA

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ABSTRACT

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

INTRODUCTION

Cardiovascular disease is the major cause of morbidity and mortality in both men and women with diabetes (approximately 50-70% of deaths) [1-5]. The risk of cardiovascular disease is

increased approximately 2 fold in men and 3-4 fold in women [2-4, 6, 7]. In the Framingham study, the annual rate of cardiovascular disease was similar in men and women with diabetes, emphasizing that woman with diabetes need as aggressive preventive treatment as men with diabetes [2, 6]. In addition, several but not all studies, have shown that patients with diabetes who have no history of cardiovascular disease have approximately the same risk of having a myocardial infarction as non-diabetic patients who have a history of cardiovascular disease, i.e., diabetes is an equivalent risk factor as a history of a previous cardiovascular event [8, 9]. The duration of diabetes and 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 Type 1 diabetes are also at high risk for the development of cardiovascular disease [1, 12-14]. Interestingly, women with type 1 diabetes have twice the excess risk of fatal and nonfatal vascular events compared to men with type 1 diabetes [15, 16]. Additionally, developing type 1 diabetes at a young age increases the risk of cardiovascular disease to a greater degree than late onset type 1 diabetes [16]. While the development of diabetes at a young age increases the risk of cardiovascular disease in patients with both Type 1 and Type 2 diabetes the deleterious impact is greater in patients with Type 2 diabetes [17]. Lastly, in patients with both Type 1 and Type 2 diabetes the presence of renal disease increases the risk of cardiovascular disease [4, 13]. Of note is that the risk of developing cardiovascular events in patients with diabetes has decreased recently, most likely due to better lipid and blood pressure control, which again reinforces the need to aggressively treat these risk factors in patients with diabetes [5, 7, 18].

ROLE OF OTHER RISK FACTORS IN CARDIOVASCULAR DISEASE

Numerous studies have demonstrated that the traditional risk factors for cardiovascular disease play an important role in patients with diabetes [2, 4, 5, 19]. 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, 20]. Other risk factors include obesity (particularly visceral obesity), insulin resistance, small dense LDL, elevated triglycerides, procoagulant state (increased PAI-1, fibrinogen), homocystine, Lp (a), renal disease, microalbuminuria, and inflammation (C-reactive protein, SAA, cytokines) [2, 4, 5, 19, 20]. In the last decade, it has become clear that to reduce the risk of cardiovascular disease in patients with diabetes, one will not only need to improve glycemic control but also address these

other cardiovascular risk factors. In the remainder of this chapter we will focus on the dyslipidemia that occurs in patients with diabetes.

ROLE OF LIPIDS IN CARDIOVASCULAR DISEASE

As in the non-diabetic population, epidemiological studies have shown that increased LDL cholesterol and non-HDL cholesterol levels and decreased HDL cholesterol levels are associated with an increased risk of cardiovascular disease in patients with diabetes [2, 4, 19, 20]. While it is universally accepted that elevated levels of LDL cholesterol and non-HDL cholesterol cause atherosclerosis and cardiovascular disease the role of HDL cholesterol is uncertain. Genetic studies and studies of drugs that raise HDL cholesterol have not supported a causative role of low HDL cholesterol levels as a causative factor for atherosclerosis [21]. Rather it is currently thought that HDL function is associated with atherosclerosis risk and that this does not precisely correlate with HDL cholesterol levels [21]. In patients with diabetes, elevations in serum triglyceride levels also are associated with an increased risk of cardiovascular disease [4, 20, 22]. With regard to triglycerides, it is not clear whether they are an independent risk factor for cardiovascular disease or whether the elevation in triglycerides is a marker for other abnormalities, such as decreased HDL cholesterol levels or increased non-HDL cholesterol levels [4, 20, 22]. Recent Mendelian Randomization studies have provided strong support for the hypothesis that elevated triglyceride levels play a causal role in atherosclerosis [23].

LIPID ABNORMALITIES IN PATIENTS WITH DIABETES

In patients with Type 1 diabetes in good glycemic control, the lipid profile is very similar to lipid profiles in the general population [19]. In contrast, in patients with Type 2 diabetes, even when in good glycemic control, there are abnormalities in lipid levels [24-27]. It is estimated that 30-60% of patients with Type 2 diabetes have dyslipidemia [5, 28]. Specifically, patients with Type 2 diabetes often have an increase in serum triglyceride levels, increased VLDL and IDL, and decreased HDL cholesterol levels. Non-HDL cholesterol levels are increased due to the increase in VLDL and IDL. LDL cholesterol levels are typically not different than in normal subjects but there is an increase in small dense LDL, a lipoprotein particle that may be particularly pro-atherogenic. As a consequence there are more LDL particles, which coupled with the increases in VLDL and IDL, leads to an increase in Apo B [24-27]. Studies have shown that the anti-oxidant and anti-inflammatory functions of HDL isolated from patients with diabetes are reduced, indicating that HDL levels per se may not fully reflect risk [29]. Additionally, the postprandial increase in serum triglycerides is accentuated and elevations in postprandial lipids may increase the risk of cardiovascular disease [24-27]. 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) [30]. Additionally, the ability of HDL to facilitate cholesterol efflux is reduced in patients with Type 2 diabetes [31]. Since a high percentage of patients with Type 2 diabetes are obese, insulin resistant and have the metabolic syndrome, it is not surprising that the prevalence of increased triglycerides and small dense LDL and

decreased HDL cholesterol is common in patients with Type 2 diabetes even when these patients are in good glycemic control.

In both Type 1 and Type 2 diabetes, poor glycemic control increases serum triglyceride levels, VLDL and IDL, and decreases HDL cholesterol levels [25]. Poor glycemic control can also result in a modest increase in LDL cholesterol, which because of the elevation in triglycerides is often in the small dense LDL subfraction. It is therefore important to optimize glycemic control in patients with diabetes because this will have secondary beneficial effects on lipid levels.

Lp (a) levels are usually within the normal range in patients with Type 2 diabetes and do not appear to be greatly affected by glycemic control [32-34]. In patients with Type 1 diabetes Lp(a) levels are also within the normal range but improvements in glycemic control result in decreases in Lp (a) levels [35]. The development of microalbuminuria and the onset of renal disease are associated with an increase in Lp (a) levels [36].

Table 1: Lipid Abnormalities in Patients with Diabetes	
Type 1 Diabetes	Lipid profile is similar to controls if glycemic control is good
Type 2 Diabetes	Increased triglycerides, VLDL, IDL, and non-HDLc. Decreased HDLc. Normal LDLc but increase in small dense LDL, LDL particle number, and apolipoprotein B.
Poor glycemic control	Increased triglycerides, VLDL and IDL and decreased HDLc. Modest increase in LDLc 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. Specifically, insulin, sulfonylureas, meglinitides, DPP4 inhibitors, and alpha-glucosidase inhibitors do not markedly alter fasting lipid profiles other than by improving glucose control (there are data indicating that DPP4 inhibitors and acarbose decrease postprandial triglyceride excursions, but they do not alter fasting lipid levels) [37]. In contrast, metformin, thiazolidinediones, GLP1 agonists, and SGLT2 inhibitors have effects independent of glycemic control on serum lipid levels. Metformin decreases serum triglyceride levels and may modestly decrease LDL cholesterol without altering HDL cholesterol [37]. The effect of thiazolidinediones appears to depend on which agent is used. Rosiglitazone increases serum LDL cholesterol levels, increases HDL cholesterol levels, and only decreases serum triglycerides if the baseline triglyceride levels are high [37]. In contrast, pioglitazone has less impact on LDL cholesterol levels, but increases HDL cholesterol levels, and decreases serum triglyceride levels [37]. 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 [37]. In a randomized head to head trial it was shown that pioglitazone decreased serum triglyceride levels and increased serum HDL cholesterol levels to a greater degree than rosiglitazone treatment [38, 39]. Additionally, pioglitazone increased LDL cholesterol levels less than rosiglitazone. In contrast to the differences in lipid parameters, both rosiglitazone and pioglitazone decreased A1c and C-reactive protein to a similar extent. The

mechanism by which pioglitazone induces more favorable changes in lipid levels than rosiglitazone is unclear, but differential actions of ligands for nuclear hormone receptors are well described. Treatment with SGLT2 inhibitors results in a small increase in LDL cholesterol and HDL cholesterol levels [37]. Finally, GLP-1 receptor agonists, such as exenatide and liraglutide, can favorably affect the lipid profile by inducing weight loss (decreasing triglycerides and increasing HDL cholesterol levels) [37]. Additionally, GLP-1 receptor agonists reduce postprandial triglycerides [37].

Table 2: Effect of Glucose Lowering Drugs on Lipid Levels	
Metformin	Decrease triglycerides and modestly decrease LDLc
Sulfonylureas	No effect
DPP4 inhibitors	Decrease postprandial triglycerides
GLP1 analogues	Decrease fasting and postprandial triglycerides and increase HDLc
Acarbose	Decrease postprandial triglycerides
Pioglitazone Rosiglitazone	Decrease triglycerides and increase HDLc. Small increase LDLc but a decrease in small dense LDL
SGLT2 inhibitors	Small increase in LDLc and HDLc
Insulin	No effect

PATHOPHYSIOLOGY OF THE DYSLIPIDEMIA OF DIABETES

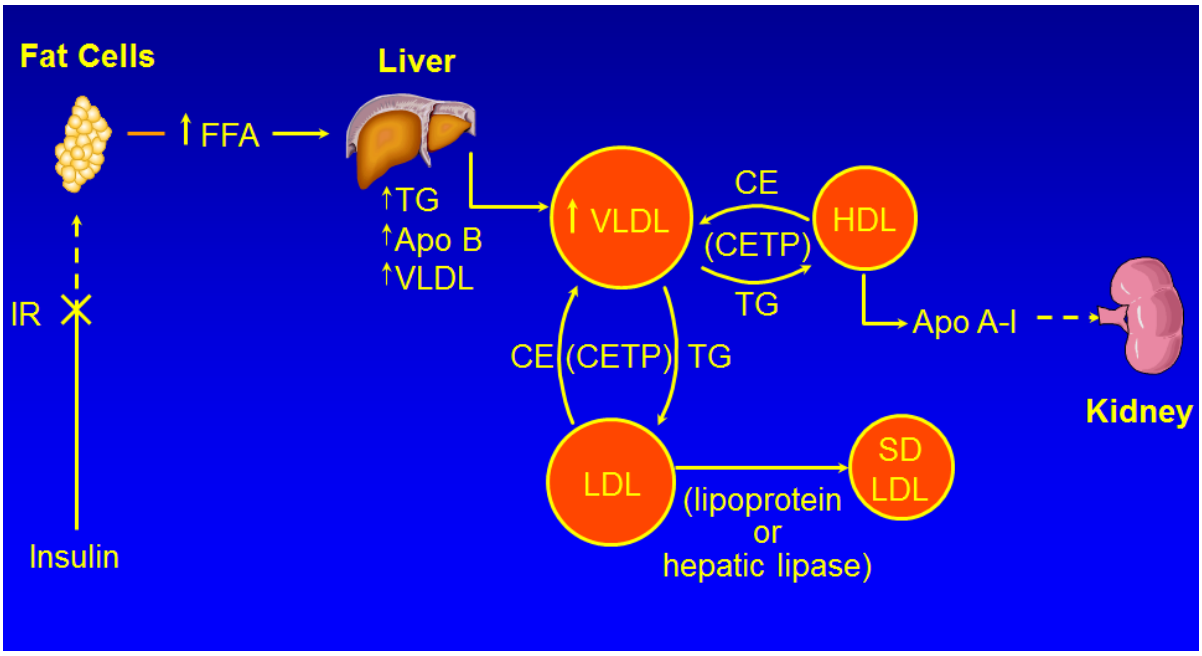

Figure 1. Pathophysiology of the Dyslipidemia of Diabetes

Increase in Triglycerides

There are a number of different abnormalities that contribute to the dyslipidemia seen in patients with Type 2 diabetes and obesity (figure 1) [25-28, 40-42]. A key abnormality is the

overproduction of VLDL by the liver, which is a major contributor to the elevations in serum triglyceride levels. The rate of secretion of VLDL is highly dependent on triglyceride availability, which is determined by the levels of fatty acids available for the synthesis of triglycerides in the liver. An abundance of triglycerides prevents the intra-hepatic degradation of Apo B-100 allowing for increased VLDL formation and secretion. There are three major sources of fatty acids in the liver all of which may be altered in patients with type 2 diabetes. First, the flux of fatty acids from adipose tissue to the liver is increased. An increased mass of adipose tissue, particularly visceral stores, results in increased fatty acid delivery to the liver. Additionally, insulin suppresses the lipolysis of triglycerides to free fatty acids in adipose tissue; thus, in patients with either poorly controlled diabetes due to a decrease in insulin or a decrease in insulin activity due to insulin resistance, the inhibition of triglyceride lipolysis is blunted and there is increased triglyceride breakdown leading to increased fatty acid deliver to the liver. A second source of fatty acids in the liver is *de novo* fatty acid synthesis from glucose. Numerous studies have shown that fatty acid synthesis is increased in the liver in patients with type 2 diabetes. This increase may be mediated by the hyperinsulinemia seen in patients with insulin resistance. While the liver is 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 type 2 diabetes. This increase in chylomicrons leads to the increased delivery of fatty acids to the liver. The increase in hepatic fatty acids produced by these three pathways results in an increase in the synthesis of triglycerides in the liver and the protection of Apo B-100 from degradation resulting in the increased formation and secretion of VLDL. Finally, insulin stimulates the post translational degradation of Apo B-100 in the liver and a decrease in insulin activity in patients with Type 2 diabetes also allows for the enhanced survival of Apo B-100 promoting increased VLDL formation.

While the overproduction of triglyceride rich lipoproteins by the liver and intestine are the main contributors to the elevations in serum triglyceride levels in patients with Type 2 diabetes, there are also abnormalities in the metabolism of these triglyceride rich lipoproteins. First, there is a modest decrease in lipoprotein lipase activity, the key enzyme that metabolizes triglyceride rich lipoproteins. The expression of lipoprotein lipase is stimulated by insulin and decreased insulin activity in patients with Type 2 diabetes results in a decrease in lipoprotein lipase, which plays a key role in the hydrolysis of the triglycerides carried in chylomicrons and VLDL. Additionally, patients with Type 2 diabetes have an increase in Apo C-III levels. Glucose stimulates and insulin suppresses Apo C-III expression. Apo C-III is an inhibitor of lipoprotein lipase activity and thereby reduces the clearance of triglyceride rich lipoproteins. In addition, Apo C-III also inhibits the cellular uptake of lipoproteins. Recent studies have shown that loss of function mutations in

Apo C-III lead to lower serum triglyceride levels and a reduced risk of cardiovascular disease [43, 44]. 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 [45]. 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 Type 2 diabetes, 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 cholesterol levels in patients with Type 2 diabetes.

Role of Glucose and Insulin

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

levels may decrease due to the formation of small HDL that are more susceptible to accelerated clearance. Improvements in glycemic control can markedly lower serum triglyceride levels and may increase serum HDL levels. In patients with very poorly controlled diabetes improvements in glycemic control may also lower LDL levels.

Role of Inflammation

Many if not most patients with Type 2 diabetes are obese. Obesity is a pro-inflammatory state due to the macrophages that infiltrate adipose tissue. The cytokines produced by these macrophages and the adipokines that are produced by fat cells also alter lipid metabolism [46, 47]. The pro-inflammatory cytokines, TNF and IL-1, decrease the expression of lipoprotein lipase and increase the expression of angiopoietin like protein 4, an inhibitor of lipoprotein lipase. Together these changes decrease lipoprotein lipase activity, thereby delaying the clearance of triglyceride rich lipoproteins. In addition, pro-inflammatory cytokines stimulate lipolysis in adipocytes increasing circulating free fatty acid levels, which will provide substrate for hepatic triglyceride synthesis. In the liver, pro-inflammatory cytokines stimulate de novo fatty acid and triglyceride synthesis. These alterations will lead to the increased production and secretion of VLDL. Thus, increases in the levels of pro-inflammatory cytokines will stimulate the production of triglyceride rich lipoproteins and delay the clearance of triglyceride rich lipoproteins, which together will contribute to the increase in serum triglycerides that occurs in obese patients.

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

Pro-inflammatory cytokines also affect HDL metabolism [48, 49]. 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 [50]. In parallel inflammation increases the oxidation of LDL and the small dense LDL that occurs in patients with diabetes is more susceptible to oxidation.

EFFECT OF LIPID LOWERING DRUGS ON CARDIOVASCULAR EVENTS

Monotherapy Studies

STATINS

As shown in Table 3, statin trials, including both primary and secondary prevention trials, have consistently shown the beneficial effect of statins on cardiovascular disease including patients with diabetes, primarily by lowering LDL cholesterol levels. The Cholesterol Treatment Trialists analyzed data from 18,686 subjects with diabetes (mostly Type 2 diabetes) from 14 randomized trials [51]. In the statin treated group there was a 9% decrease in all-cause mortality, a 13% decrease in vascular mortality, and a 21% decrease in major vascular events per 39mg/dl reduction in LDL cholesterol. The beneficial effect of statin therapy was seen in both primary and secondary prevention patients. The effect of statin treatment on cardiovascular events in patients with diabetes was similar to that seen in non-diabetic subjects. Thus, these studies indicate that statins are beneficial in reducing cardiovascular disease in patients with diabetes. Because of the large number of patients with diabetes included in the Heart Protection Study (HPS) and CARDS these two studies will be discussed in greater depth.

Table 3: Effect of Monotherapy with Statins on Cardiovascular Outcomes

Study	**Drug**	**% Decrease**	
		Controls	**Diabetics**
2º Prevention			
4S	Simvastatin	32	55
CARE	Pravastatin	23	25
LIPID	Pravastatin	25	19
LIPS	Fluvastatin	20	43
HPS	Simvastatin	24	26
1º Prevention			
AFCAPS	Lovastatin	37	42
HPS	Simvastatin	24	24
ASCOT	Atorvastatin	44	16
CARDS	Atorvastatin	--	37

The HPS was a double blind randomized trial that focused on patients at high risk for the development of cardiovascular events, including patients with a history of myocardial infarctions, other atherosclerotic lesions, diabetes, and/or hypertension [52, 53]. Patients were between 40 and 80 years of age and had to have total serum cholesterol levels greater than 135mg/dl (thus very few patients were excluded because they did not have a high enough cholesterol level). The major strength of this trial was the large number of patients studied (>20,000). The diabetes subgroup included 5,963 subjects and thus was as large as many other prevention trials. The study was a 2x2 study design comparing simvastatin 40mg a day vs. placebo and anti-oxidant vitamins (vitamin E 600mg, vitamin C 250mg, and beta-carotene 20mg) vs. placebo and lasted approximately 5 years. Analysis of the group randomized to the anti-oxidant vitamins revealed no beneficial or harmful effects. In contrast, simvastatin therapy (40mg per day) reduced cardiovascular events, including myocardial infarctions and strokes, by approximately 25% in all participants and to a similar degree in the diabetic subjects (total cardiovascular disease reduced 27%, coronary mortality 20%, myocardial infarction 37%, stroke 24%). Further analysis of the subjects with diabetes revealed that the reduction in cardiovascular events with statin therapy was similar in individuals with diabetes diagnosed for a short duration (<6 years) and for a long duration (>13 years). Similarly, subjects with diabetes in good control (HbA1c <7%) and those not in ideal control (HbA1c >7%) also benefited to a similar degree with statin therapy. Moreover, both Type 1 and Type 2 diabetic patients had a comparable reduction in cardiovascular disease with simvastatin therapy. The decrease in cardiovascular events in patients with Type 1 diabetes was not statistically significant because of the small number of subjects. Nevertheless, this is the only trial that included Type 1 diabetics and suggests that patients with Type 1 will benefit from statin therapy similar to Type 2 diabetics. In general, statin therapy reduced cardiovascular disease in all subgroups of subjects with diabetes (females, males, older age, renal disease, hypertension, high triglycerides, low HDL, ASA therapy, etc.) i.e. statin therapy benefits all patients with diabetes. Of particular note, even subjects with diabetes whose baseline LDL cholesterol levels were less than 116mg/dl had a reduction in cardiovascular events when treated with simvastatin. Moreover, analysis of all study patients similarly demonstrated that subjects with LDL cholesterol levels less than 100mg/dl benefited from statin therapy. These results were of particular clinical importance because they demonstrated that in high-risk patients with LDL cholesterol levels < 100mg/dl statin therapy would nevertheless result in benefit.

The CARDS trial specifically focused on subjects with diabetes [54]. The subjects in this trial were males and females with Type 2 diabetes between the ages of 40 to 75 years of age who were at high risk of developing cardiovascular disease based on the presence of hypertension, retinopathy, renal disease, or current smoking. Of particular note, the subjects did not have any evidence of clinical atherosclerosis (myocardial disease, stroke, peripheral vascular disease) at entry and hence this study is a primary prevention trial. Inclusion criteria included LDL cholesterol levels less than 160mg/dl and triglyceride levels less than 600mg/dl. It is important to recognize that the average LDL cholesterol in this trial was approximately 118mg/dl, indicating relatively low LDL cholesterol levels. A total of 2838 Type 2 diabetic subjects were randomized to either placebo or atorvastatin 10mg a day. Atorvastatin therapy resulted in a 40% decrease in LDL cholesterol levels with over 80% of patients achieving LDL cholesterol levels

less than 100mg/dl. Most importantly, atorvastatin therapy resulted in a 37% reduction in cardiovascular events. In addition, strokes were reduced by 48% and coronary revascularization by 31%. As seen in the HPS, subjects with relatively low LDL cholesterol levels (LDL <120mg/dl) benefited to a similar extent as subjects with higher LDL cholesterol levels (>120mg/dl). CARDS, in combination with the other statin trials, provide conclusive evidence that statin therapy will reduce cardiovascular events in patients with diabetes. Importantly, the benefits of statin therapy are seen in patients with diabetes in both primary and secondary prevention trials.

A few studies have compared the effect of different magnitudes of LDL cholesterol lowering with statins on the reduction in cardiovascular events in patients with diabetes. The Post-CABG study compared very low dose lovastatin (2.5-5.0mg per day) vs. high dose lovastatin (40-80mg per day) in 1,351 subjects post bypass surgery [55]. Approximately 10% of patients in this trial had diabetes. Baseline LDL cholesterol levels were between 130-174mg/dl. As expected, the high dose of lovastatin reduced LDL cholesterol levels to a much greater degree than the low dose lovastatin (low dose achieved LDL cholesterol levels of approximately 135mg/dl vs. high dose achieved LDL cholesterol levels of approximately 95mg/dl). The main comparison in this trial was the change in atherosclerosis in the grafts measured by comparing baseline angiography to angiography after an average of 4.3 years. In the entire population, the mean percentage of grafts with progression of atherosclerosis was 27 percent in the high dose lovastatin group and 39 percent in the low dose lovastatin group. Additionally, the rate of revascularization was reduced by 29 percent in the high dose lovastatin group. When the patients with diabetes were analyzed separately, similar beneficial effects were observed. These results indicate that lowering LDL cholesterol levels to less than 100mg/dl would slow the angiographic changes to a greater extent than lowering the LDL cholesterol levels to 135mg/dl. Of note though is that even with LDL cholesterol levels less than 100mg/dl progression of atherosclerosis still occurred.

Studies have also compared reductions of LDL cholesterol to approximately 100mg/dl to more aggressive reductions in LDL cholesterol. The Reversal Trial studied 502 symptomatic coronary artery disease patients with an average LDL cholesterol of 150mg/dl [56]. Approximately 19% of the patients in this trial had diabetes. Patients were randomized to moderate LDL lowering therapy with pravastatin 40mg per day or to aggressive lipid lowering with atorvastatin 80mg per day. As expected, LDL cholesterol levels were considerably lower in the atorvastatin treated group (pravastatin LDL= 110mg/dl vs. atorvastatin LDL= 79mg/dl). Most importantly, when one analyzed the change in atheroma volume determined after 18 months of therapy using intravascular ultrasound, the group treated aggressively with atorvastatin had a much lower progression rate than the group treated with pravastatin. Compared with baseline values, patients treated with atorvastatin had no change in atheroma burden (there was a very slight regression of lesions), whereas patients treated with pravastatin showed progression of lesions. When one compares the extent of the reduction in LDL cholesterol to the change in atheroma volume, a 50% reduction in LDL (LDL cholesterol levels of approximately 75mg/dl) resulted in the absence of lesion progression. This study suggests that lowering the LDL cholesterol to levels well below 100mg/dl is required to prevent disease progression as measured by

intravascular ultrasound. Other studies, such as Asteroid, have shown that marked reductions in LDL cholesterol (in Asteroid the mean LDL cholesterol levels were 61mg/dl) can even result in the regression of coronary artery atherosclerosis determined by intravascular ultrasound measurements [57]. Recently the Saturn trial demonstrated that aggressive lipid lowering with either atorvastatin 80mg or rosuvastatin 40mg would induce regression of coronary artery atherosclerosis to a similar degree in patients with and without diabetes if the LDL cholesterol levels were reduced to less than 70mg/dl [58]. Together these trials indicate that aggressive lowering of LDL cholesterol levels to below 70mg/dl can induce regression of atherosclerotic lesions.

The Prove-It trial determined in patients recently hospitalized for an acute coronary syndrome whether aggressively lowering of LDL cholesterol with atorvastatin 80mg per day vs. moderate LDL cholesterol lowering with pravastatin 40mg per day would have a similar effect on cardiovascular end points such as death, myocardial infarction, documented unstable angina requiring hospitalization, revascularization, or stroke [59, 60]. In this trial, approximately 18% of the patients were diabetic. As expected, the on-treatment LDL cholesterol levels were significantly lower in patients aggressively treated with atorvastatin compared to the moderate treated pravastatin group (atorvastatin LDL cholesterol = approximately 62 vs. pravastatin LDL cholesterol = approximately 95mg/dl). Of great significance, death or major cardiovascular events was reduced by 16% over the two years of the study in the group aggressively treated with atorvastatin. Moreover, the risk reduction in the patients with diabetes in the aggressive treatment group was similar to that observed in non-diabetics.

In the treating to new targets trial (TNT) patients with stable coronary heart disease and LDL cholesterol levels less than 130mg/dl were randomized to either 10mg or 80mg atorvastatin and followed for an average of 4.9years [61, 62]. Approximately 15% of the patients had diabetes. As expected, LDL cholesterol levels were lowered to a greater extent in the patients treated with 80mg atorvastatin than with 10mg atorvastatin (77mg/dl vs. 101mg/dl). Impressively, the occurrence of major cardiovascular events was reduced by 22% in the group treated with atorvastatin 80mg ($p<0.001$). In the patients with diabetes events were reduced by 25% in the high dose statin group. Once again, the risk reduction in the patients with diabetes randomized to the aggressive treatment group was similar to that observed in non-diabetics.

Finally, the IDEAL trial was a randomized study that compared atorvastatin 80mg vs. simvastatin 20-40mg in 8,888 patients with a history of cardiovascular disease [63]. Approximately 12% of the patients had diabetes. As expected, LDL cholesterol levels were reduced to a greater extent in the atorvastatin treated group than the simvastatin treated group (approximately 104mg/dl vs. 81mg/dl). Once again, the greater reduction in LDL cholesterol levels was associated with a greater reduction in cardiovascular events. Specifically, major coronary events defined as coronary death, nonfatal myocardial infarction, or cardiac arrest was reduced by 11% ($p=0.07$), while nonfatal acute myocardial infarctions were reduced by 17% ($p=0.02$).

Combining the results of the Heart Protection Study, CARDS, Reversal, Prove-It, TNT, and IDEAL leads one to the conclusion that aggressive lowering of LDL cholesterol with statin therapy will be beneficial and suggests that in high risk patients lowering the LDL to levels well below 100mg/dl is desirable. Recently, the Cholesterol Treatment Trialists reviewed five trials with 39,612 subjects that were designed to determine the effect of usual vs. aggressive reductions in LDL cholesterol [64]. They reported that intensive control (approximately a 19mg/dl difference in LDL cholesterol) resulted in a 15% decrease in major vascular events, a 13% reduction in coronary death or non-fatal MI, a 19% decrease in coronary revascularization, and a 16% decrease in strokes. As will be discussed below most treatment guidelines reflect the results of these studies. 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 cholesterol 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 4. 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 [65]. In this trial, 9795 patients with Type 2 diabetes between the ages of 50 and 75 not taking statin therapy were randomized to fenofibrate or placebo and followed for approximately 5 years. Fenofibrate therapy resulted in a 12% decrease in LDL cholesterol, a 29% decrease in triglycerides and a 5% increase in HDL cholesterol levels. The primary outcome was coronary events (coronary heart disease death and non-fatal MI), which were reduced by 11% in the fenofibrate group but did not reach statistical significance (p= 0.16). However, there was a 24% decrease in non-fatal MI in the fenofibrate treated group (p=0.01) and a non-significant increase in coronary heart disease mortality. Total cardiovascular disease events (coronary events plus stroke and coronary or carotid revascularization) were reduced 11% (p=0.035). These beneficial effects of fenofibrate therapy on cardiovascular disease were observed in patients without a previous history of cardiovascular disease. In patients with a previous history of cardiovascular disease no benefits were observed. Additionally, the beneficial effect of fenofibrate therapy was seen only in those subjects less than 65 years of age. The beneficial effects of fenofibrate in this study may have been muted by the increased use of statins in the placebo group, which reduced the differences in lipid levels between the placebo and fenofibrate groups. If one adjusted for the addition of lipid-lowering therapy, fenofibrate reduced the risk of coronary heart disease events by 19% (p=0·01) and of total cardiovascular disease events by 15% (p=0·004).

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 [66]. Additionally, subgroup analysis of several fibrate trials has also suggested that the benefit of fibrates was greatest in patients with elevated triglyceride levels [66, 67].

The mechanism by which fibrates reduce cardiovascular events is unclear. These drugs lower serum triglyceride levels and increase HDL cholesterol, but it should be recognized that the beneficial effects of fibrates could be due to other actions of these drugs. Specifically, these drugs activate PPAR alpha, which is present in the cells that comprise the atherosclerotic lesions, and it is possible that these compounds directly affect lesion formation and development. In addition, fibrates are anti-inflammatory. In fact, analysis of the VA-HIT study suggested that much of the benefit of fibrate therapy was not due to changes in serum lipoprotein levels [68, 69].

To summarize, while in general the studies to date suggest that monotherapy with fibrates reduce cardiovascular disease in patients with diabetes, the results are not as robust or consistent as seen in the statin trials. Of note fibrate therapy was most effective in patients with increased triglyceride levels and decreased HDL levels, a lipid profile typically seen in patients with type 2 diabetes.

Table 4: Effect of Fibrate Monotherapy on Cardiovascular Outcomes

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

* Not statistically significant

NIACIN

A single randomized trial, the Coronary Drug Project, has examined the effect of niacin monotherapy on cardiovascular outcomes [70]. 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 [71]. 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.

OTHER DRUGS

With regard to ezetimibe, 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 [72, 73]. 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. However, bile acid sequestrants can raise triglyceride levels and therefore must be used with caution in hypertriglyceridemic patients. There are no outcome studies with ezetimibe monotherapy or PCSK9 inhibitor monotherapy in patients with diabetes but given that these drugs reduce LDL cholesterol levels and in combination with statins reduce cardiovascular events one would anticipate that ezetimibe and 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 Type 2 diabetes [74]. In this trial, 5,518 patients on statin therapy were randomized to placebo or fenofibrate therapy. The patients had diabetes for approximately 10 years and either had pre-existing cardiovascular disease or were at high risk for developing cardiovascular disease. During the trial, LDL cholesterol levels were approximately 80mg/dl. There was only a small difference in HDL cholesterol with the fenofibrate groups having a mean HDL cholesterol of 41.2mg/dl while the control group had an HDL cholesterol of 40.5mg/dl. Differences in triglyceride levels were somewhat more impressive with the fenofibrate group having a mean triglyceride level of 122mg/dl while the control group had a triglyceride level of 144mg/dl. First occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes was the primary outcome and there was no statistical difference between the fenofibrate treated group and the placebo group. Additionally, there were also no statistically significant differences between the groups with regards to any of the secondary outcome measures of cardiovascular disease. Of note, the addition of fenofibrate to statin therapy did not result in an increase in either muscle or liver side effects. On further analysis, there was a possible benefit of fenofibrate therapy in the patients in whom the baseline triglyceride levels were elevated (>204mg/dl) and HDL cholesterol levels decreased (<34mg/dl). In the fibrate monotherapy trials,

this same group of patients also derived the greatest benefit of fibrate therapy. Future fibrate statin combination therapy trials will need to focus on patients with high triglycerides and low HDL cholesterol levels. Finally, similar to what has been reported in other trials, fenofibrate had beneficial effects on the progression of microvascular disease [75, 76]. 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.

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 [77]. In this trial 3,314 patients were randomized to Niaspan vs. placebo. Approximately 33% of the patients had diabetes. On trial, LDL cholesterol levels were in the 60-70mg/dl range in both groups. As expected, HDL cholesterol levels were increased in the Niaspan treated group (approximately 44mg/dl vs. 38mg/dl), while triglycerides were decreased (approximately 121mg/dl vs. 155mg/dl). However, there were no differences in the primary endpoint between the control and Niaspan treated groups (Primary endpoint consisted of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization). There were also no differences in secondary endpoints except for a possible increase in strokes in the Niaspan treated group. The addition of Niaspan to statin therapy did not result in a significant increase in either muscle or liver toxicity. Thus, this study does not provide support for the addition of niacin to statins. However, it should be recognized that this was a relatively small study and a considerable number of patients stopped taking the Niaspan during the course of the study (25.4% of patients discontinued Niaspan therapy). In addition, most of the patients included in this study did not have a lipid profile that one would typically consider treating with niacin therapy. In the subset of patients with TG > 198mg/dl and HDL cholesterol < 33mg/dl niacin showed a trend towards benefit (hazard ratio 0.74; p=0.073) in this study, suggesting that if the appropriate patient population was studied the results may have been positive [78].

HPS 2 Thrive also studied the effect of niacin added to statin therapy [79]. This trial utilized extended release niacin combined with laropiprant, a prostaglandin D_2 receptor antagonist that reduces the flushing side effect of niacin treatment. HPS 2 Thrive was a very large trial with over 25,000 patients randomized to either niacin therapy or placebo. Approximately 32% of the patients in this trial had diabetes. The LDL cholesterol level was 63mg/dl, the HDL cholesterol 44mg/dl, and the triglycerides 125mg/dl at baseline. As expected, niacin therapy resulted in a modest reduction in LDL cholesterol (10mg/dl), a modest increase in HDL cholesterol (6mg/dl), and a marked reduction in triglycerides (33mg/dl). However, despite these lipid changes there were no significant differences in major cardiovascular events between the niacin and control group (risk ratio 0.96 CI 0.90- 1.03). It is unknown whether laropiprant, the prostaglandin D_2 receptor antagonist, might have effects that worsen atherosclerosis and increase event rates. Similar to the ACCORD-LIPID and AIM-HIGH studies, the group of patients included in the HPS 2 Thrive trial 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 cholesterol levels coupled with low HDL cholesterol 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 [80]. This was a large trial with over 18,000 patients randomized to statin therapy vs. statin therapy + ezetimibe. Approximately 27% of the patients in this trial had diabetes. On treatment LDL cholesterol levels were 70mg/dl in the statin alone group vs. 53mg/dl in the statin + ezetimibe group. There was a small but significant 6.4% decrease in major cardiovascular events (Cardiovascular death, MI, documented unstable angina requiring 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 and other risk factors [81].

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 cholesterol level of 70 mg/dl or higher who were on statin therapy [82]. Approximately 40% of the patients had diabetes [83]. 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 cholesterol levels were 92mg/dl and evolocumab resulted in a 59% decrease in LDL cholesterol levels (LDL cholesterol 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 cholesterol 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 [84]. Further analysis has shown that in the small number of patients with a baseline LDL cholesterol level less than 70mg/dl, evolocumab reduced cardiovascular events to a similar degree as in the patients with an LDL cholesterol greater than 70mg/dl [85]. Finally, the lower the on-treatment LDL cholesterol levels (down to levels below 20mg/dl), the lower the cardiovascular event rate, suggesting that greater reductions in LDL cholesterol levels will result in greater reductions in cardiovascular disease [86].

It should be noted that that the duration of the FOURIER trial was very short and it is well recognized from previous statin trials that the beneficial effects of lowering LDL cholesterol 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. Thus, long-term benefit may be greater than observed during the study.

Two recent trials examined the effects of bococizumab, another PCSK9 inhibitor, on cardiovascular outcomes [87]. In one trial patients with cardiovascular disease or at high risk for cardiovascular disease with LDL cholesterol levels greater than 70mg/dl on statin therapy were randomized to bococizumab or placebo (SPIRE 1; n= 16,817)). In the second trial, similar patients were studied except LDL cholesterol levels were greater than 100mg/dl and some patients were statin intolerant (SPIRE 2; n= 10,621). Almost 50% of the patients in these trials had diabetes. The primary end point was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death. The trials were stopped early after a median follow-up of 7months in SPIRE 1 and 12 months in SPIRE 2 due to high rates of development of antidrug antibodies, which markedly reduced the magnitude and durability of the decrease in LDL cholesterol levels [88]. In SPIRE 1 baseline LDL cholesterol levels were 94mg/dl while in SPIRE 2 LDL cholesterol levels were 133mg/dl. At 14 weeks LDL cholesterol levels were reduced by approximately 55% in the bococizumab treated groups at 14 weeks. In patients with lower baseline LDL cholesterol levels (SPIRE 1) bococizumab treatment did not reduce cardiovascular events (hazard ratio, 0.99; 95% CI 0.80 to 1.22; P=0.94). However, in patients with higher LDL cholesterol levels (SPIRE 2) cardiovascular disease was reduced by bococizumab treatment (hazard ratio, 0.79; 95% CI, 0.65 to 0.97; P=0.02). Thus, in patients with higher LDL cholesterol levels who were treated for 12 months lowering LDL cholesterol levels with a PCSK9 inhibitor decreased cardiovascular outcomes.

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 cholesterol level of at least 70 mg/dl, a non-HDL cholesterol 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 [89]. 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 cholesterol 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 cholesterol levels in the placebo group was 93-103mg/dl while in the alirocumab group LDL cholesterol 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 cholesterol level greater than 100mg/dl. In patients with an LDL cholesterol 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 cholesterol 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 cholesterol 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.

Support for the benefits of further lowering of LDL cholesterol levels with a PCSK9 inhibitor added to statin therapy is seen in the GLAGOV trial [90]. 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 cholesterol 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 cholesterol and change in PAV (i.e. the lower the LDL cholesterol the greater the regression in atheroma volume down to an LDL cholesterol 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 cholesterol 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 new 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 [91]. 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) [92]. 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 cholesterol, and non-HDL cholesterol 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.

STATINS + HIGH DOSE OMEGA-3-FATTY ACIDS

Japan EPA Lipid Intervention Study (JELIS) was an open label study in patients 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 [93]. 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, LDL, and HDL cholesterol 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 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 cholesterol levels < 40mg/dl there was a 53% decrease in events [94].

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 8179 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 [95]. 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 cholesterol level was 75.0 mg/dl, HDL cholesterol 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 per deciliter). Moreover, the cardiovascular benefits of EPA appeared to occur irrespective of the attained triglyceride level at 1 year (≥150 or <150 mg per deciliter), 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 studies suggest that the addition of EPA to statins in patients with diabetes who have elevated triglyceride levels will reduce cardiovascular events. Whether the decrease in events is due to lowering of triglyceride levels or to other actions of EPA, such as effecting platelet function, remains to be determined.

CURRENT GUIDELINES FOR SERUM LIPIDS

There are several different guidelines for treating lipids in patients with diabetes. The American College of Cardiology and American Heart Association (ACC/AHA) 2013 guidelines recommend that patients with both type 1 and type 2 diabetes between 40 and 75 years of age be treated with statin therapy [96]. If the estimated 10-year risk of developing a cardiovascular event is >

7.5% they recommend intensive statin therapy (atorvastatin 40-80mg or rosuvastatin 20-40mg). If the 10-year cardiovascular risk is < 7.5% they recommend moderate statin therapy (for example atorvastatin 10-20mg, simvastatin 20-40mg, pravastatin 40mg). Cardiovascular risk can be determined using a calculator that is available at **http://my.americanheart.org/cvriskcalculator** or can be downloaded as an app for a smart phone or tablet. If a patient with diabetes has clinical ASCVD they should be treated with intensive statin therapy if less than 75 years of age. Patients with diabetes and clinical ASCVD over 75 years of age should be treated with either intensive or moderate statin therapy depending upon the risks of developing drug toxicity. The ACC/AHA do not recommend any specific LDL goal but rather to just treat with statin therapy. The ACC/AHA guidelines do not recommend the treatment with drugs other than statins, but these guidelines were published before the results of the IMPROVE-IT trial and PCSK9 inhibitor trials were known. The ACC in more recent recommendations acknowledges that one may consider absolute LDL-C or non-HDL-C levels for patients on statin therapy and where appropriate use additional drugs, such as ezetimibe and PCSK9 inhibitors, to lower lipid levels [97].

The 2018 ACC/AHA guidelines recommend the following [98]. “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 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 a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins 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”.

The 2019 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 [99]. This profile includes total cholesterol, HDL cholesterol, triglycerides, and calculated LDL cholesterol. A lipid panel should be obtained immediately prior to initiating statin therapy. Once a patient is on statin therapy testing 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. In patients with elevated triglyceride levels glycemic control is beneficial. Intensive statin therapy should be added to lifestyle therapy in diabetic patients with overt cardiovascular disease or a 10-year risk of a cardiovascular event > 20% (see table 5 for recommendations). In patients without cardiovascular disease over age 40 moderate intensity statin therapy should be added to lifestyle changes. If some patients, high intensity therapy may be used if multiple other risk factors are present. In patients less than 40 years of age with additional risk factors one should discuss with the patient the use of moderate statin therapy. 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 or a PCSK9 inhibitor should be considered to further lower LDL cholesterol levels in patients with atherosclerotic cardiovascular disease if the LDL cholesterol level on statin therapy is greater than 70mg/dl (table 5). The use of fibrates or niacin with statins was generally not recommended. 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 5: ADA Recommendations for Statin and Combination Treatment in Adults with Diabetes

Age	**ASCVD or 10-year risk > 20%**	**Statin Dose***
<40	No	None or moderate intensity if multiple risk factors**
>40	No	Moderate intensity (reduce LDL by 30-50%) or high intensity statin therapy if multiple risk factors**
Any age	Yes	High Intensity (reduce LDLc by > 50%) If LDLc > 70mg/dl despite maximally tolerated statin therapy consider adding ezetimibe or PCSK9 inhibitor

*In addition to lifestyle therapy; ** ASCVD risk factors include LDL cholesterol > 100mg/dl, high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD;

The National Lipid Association (NLA) has treatment goals for patients with diabetes [100]. In patients with Type 1 or Type 2 diabetes 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 cholesterol 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 cholesterol 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 cholesterol < 100mg/dl; Non-HDL cholesterol < 130mg/dl
Diabetes with 2 or more risk factors or end	LDL cholesterol < 70mg/dl; Non-HDL

organ damage	cholesterol < 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

The American Association of Clinical Endocrinologists and American College of Endocrinology guidelines consider individuals with type 2 diabetes to be at high, very high, or extreme risk for ASCVD [101]. Patients with type 1 diabetes 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 type 2 diabetes. 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
Moderate Risk	Two or fewer risk factors and 10yr risk < 10%**	<100	<130	<90
Low Risk	No risk factors	<130	<160	NR

*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.
***Calculate risk using Framingham 10-year risk scoring
NR= not recommended

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

One approach is to combine these recommendations. In patients with diabetes who have pre-existing cardiovascular disease initiate intensive statin therapy. In patients with diabetes 40-75 years of age without pre-existing cardiovascular disease calculate the 10-year risk of developing cardiovascular disease. 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. Eight to twelve weeks after initiating statin therapy obtain a lipid panel to determine if the LDL and non-HDL cholesterol levels are at goal. In patients with pre-existing cardiovascular disease or multiple risk factors the goal should be an LDL cholesterol < 70mg/dl and a non-HDL

cholesterol < 100mg/dl. In patients that are not at high risk the goal should be an LDL cholesterol < 100mg/dl and a non-HDL cholesterol < 130mg/dl. In patients with cardiovascular disease that is progressive or who have multiple risk factors a goal LDL cholesterol of < 55mg/dl and a non-HDL c < 80mg/dl should be strongly considered. If the levels are not at goal either adjust the statin dose or consider adding additional medications. In patients with diabetes less than 40 years of age initiate statin therapy if the patient has overt cardiovascular disease, long standing diabetes, or risk factors for cardiovascular disease and the LDL and non-HDL cholesterol levels are not at goal.

TREATMENT OF LIPID ABNORMALITIES IN PATIENT WITH DIABETES

Life Style Changes

Initial treatment of lipid disorders should focus on lifestyle changes [102]. There is little debate that exercise is beneficial and that all patients with diabetes should, if possible, exercise for at least 150 minutes per week (for example 30 minutes 5 times per week). Exercise will decrease serum triglyceride levels and increase HDL cholesterol levels (an increase in HDL cholesterol requires vigorous exercise) [30, 102]. It should be noted that many patients with diabetes may have substantial barriers to participating in exercise programs, such as comorbidities that limit exercise tolerance, risk of hypoglycemia, and presence of microvascular complications (visual impairment, neuropathy) that make exercise difficult.

Diet is debated to a greater extent. Everyone agrees that weight loss in obese patients is essential [30, 102]. But how this can be achieved is hotly debated with many different "experts" advocating different approaches. The wide diversity of approach is likely due to the failure of any approach to be effective in the *long term* for the majority of obese patients with diabetes. If successful, weight loss will decrease serum triglyceride levels, increase HDL cholesterol levels, and modestly reduce LDL cholesterol [30, 102]. To reduce LDL cholesterol levels, it is important that the diet decrease saturated fat, trans fatty acids, and cholesterol intake. Increasing soluble fiber is also helpful.

It is debated whether a low fat, high complex carbohydrate diets vs. a high monounsaturated fat diet is ideal for obese patients with diabetes [30]. One can find "experts" in favor of either of these approaches and there are pros and cons to each approach. It is essential to recognize that both approaches reduce simple sugars, saturated fat, trans fatty acids, and cholesterol intake. The high complex carbohydrate diet will increase serum triglyceride levels in some patients and if the amount of fat in the diet is markedly reduced serum HDL cholesterol levels may decrease. In obese patients, it has been postulated that a diet high in monounsaturated fats, because of the increase in caloric density, will lead to an increase in weight gain. Both diets reduce saturated fat and cholesterol intake that will result in reductions in LDL cholesterol levels. Additionally, both diets also reduce trans-fatty acid intake, which will have a beneficial effect on LDL and HDL cholesterol levels and simple sugars, which will have a beneficial effect on triglyceride levels.

Recently there has been increased interest in low carbohydrate, increased protein diets. Short-term studies have indicated that weight loss is superior with this diet; however longer studies have demonstrated a similar weight loss to that observed with conventional diets. The major concern with the low carbohydrate, high protein diet is that they tend to be high in saturated fats and cholesterol. Additionally, there may also be an increased risk of progression of kidney disease in patients with pre-existing kidney disease. In the short-term studies during active weight loss this diet has not resulted in major perturbations in serum cholesterol levels, but there is concern that when weight becomes stable these diets might adversely affect serum cholesterol levels.

Thus, the available data do not indicate that any particular diet is best for inducing weight loss and it is essential to adapt the diet to fit the food preferences of the patient. Ultimately no weight loss diet will be successful if the patient cannot follow the diet for the long term.

While it is widely accepted that lifestyle changes will decrease cardiovascular events it should be recognized that the Look Ahead trial failed to demonstrate a reduction in cardiovascular events [103]. In this trial, over 5000 overweight or obese patients with Type 2 diabetes were randomized to either an intensive lifestyle intervention group that promoted weight loss through decreased caloric intake and increased physical activity or to a group that received diabetes support and education (control group). After a median follow-up of 9.6 years there was no difference in cardiovascular events (hazard ratio in the intervention group, 0.95; 95% CI 0.83 to 1.09; P=0.51). A limitation of this study was that while the weight difference between groups was impressive during the first year of the trial, over time the differences greatly narrowed such that at the end of the trial the intensive group had a 6.0% weight loss while the control group had a 3.5% weight loss. This very modest difference demonstrates the difficulty in sustaining long term lifestyle changes. As noted earlier there were no differences in coronary artery calcium scores between the lifestyle and placebo groups in the Diabetes Prevention Program, which also illustrates the difficulty of reducing cardiovascular disease with lifestyle changes [104]. Thus, while weight loss and diet therapy are likely to be beneficial in reducing cardiovascular events, in clinical practice they are seldom sufficient because long-term life style changes are very difficult for most patients to maintain.

In contrast to the failure of lifestyle therapy in the Look Ahead trial to reduce cardiovascular events, the PREDIMED trial employing a Mediterranean diet did reduce the incidence of major cardiovascular disease [105, 106]. In this multicenter trial center trial, carried out in Spain, over 7000 patients at high risk for developing cardiovascular disease were randomized to three diets (primary prevention trial). A Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet. Approximately 50% of the patients in this trial had type 2 diabetes. In the patients assigned to the Mediterranean diets there was 29% decrease in the primary end point (myocardial infarction, stroke, and death from cardiovascular disease). Subgroup analysis demonstrated that the Mediterranean diet was equally beneficial in patients with and without diabetes. The Mediterranean diet resulted in a small but significant increase in HDL cholesterol levels and a small decrease in both LDL cholesterol and triglyceride levels [107]. 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 [108, 109]. 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 [108]. The results of these two trials indicate that we should be encouraging our patients to follow a Mediterranean type diet.

With the currently available weight loss drugs only modest effects on weight and lipid levels have been observed [30, 102]. In some patients, weight loss drugs may be a useful adjuvant to diet therapy. Bariatric surgery can have profound effects on weight and can result in improvements in lipid profiles [30, 102]. Additionally, observational studies have shown a decrease in cardiovascular events following bariatric surgery in patients with and without diabetes [110-114]. For additional information see the chapter entitled “Lifestyle Changes: Effect of Diet, Exercise, Functional Food, and Obesity Treatment, on Lipids and Lipoproteins” [102].

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 [102].

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 type 2 diabetes or patients at high risk for the development of type 2 diabetes [91, 92] (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 [115]. 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 [115]. Additionally, in some patient's high dose fish oil increases LDL cholesterol levels, particularly when serum triglyceride levels are very high [115]. For additional information on fish oil see the chapter on Triglyceride Lowering Drugs [116].

Drug Therapy

The effect of statins, fibrates, niacin, ezetimibe, omega-3-fatty acids, bile acid binders, and PCSK9 inhibitors on lipid levels in patients with diabetes is virtually identical to that seen in the non-diabetic patients (Table 8). For detailed information on lipid lowering drugs see the chapters on Triglyceride Lowering Drugs and Cholesterol Lowering Drugs [116, 117].

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 [118, 119]. 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 [120]. 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 [52, 54, 121]. 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 [122]. In the ACCORD-LIPID Trial the incidence of muscle disorders was not increased in the statin + fenofibrate group compared to statin alone [74]. The dose of fenofibrate needs to be adjusted in patients with renal disease and fenofibrate itself can induce a reversible increase in serum creatinine levels. It should be noted that marked reductions in HDL cholesterol levels can occur in some patients treated with both fenofibrate and a TZD [123].

BILE ACID SEQUESTRANTS

Bile acid sequestrants are relatively difficult to take due to GI toxicity (mainly constipation) [117]. 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 [117]. An additional difficulty in using bile acid sequestrants is their potential for binding other drugs [117]. Many drugs should be taken either two hours before or four hours after taking bile acid sequestrants to avoid the potential of decreased drug absorption. Diabetic patients are frequently on multiple drugs for glycemic control, hypertension, etc., and it can sometimes be difficult to time the ingestion of bile resin sequestrants to avoid these other drugs. Colesevelam (Welchol) is a bile acid sequestrant that comes in pill or powder form, which causes fewer side effects and has fewer interactions with other drugs than other preparations [124]. The usual dose is 3 pills twice a day with meals or 1 packet of powder in water or other liquids once a day with a meal. Of particular note is that a number of studies have

shown that colesevelam improves glycemic control in patients with diabetes resulting in an approximately 0.5% decrease in A1c levels [125].

NIACIN

Niacin is well known to cause skin flushing and itching and GI upset [126]. Additionally, niacin reduces insulin sensitivity (i.e., causes insulin resistance), which can worsen glycemic control [126]. Studies have shown that niacin is usually well tolerated in diabetic subjects who are in good glycemic control [127, 128]. 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 [79]. 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 type 2 diabetes [126]. Additionally recent trials have reported an increased incidence of infection and bleeding with niacin therapy [126]. However, niacin is the most effective drug in increasing HDL cholesterol 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 [115]. Fish oil effectively lowers triglyceride levels but, in some patients, particularly those with significant hypertriglyceridemia, high dose fish oil increases LDL cholesterol levels [115]. It should be noted that fish oil products that contain just EPA (Vascepa) do not adversely affect LDL cholesterol levels [129]. 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

In 2015 two monoclonal antibodies that inhibit PCSK9 (proprotein convertase subtilisin kexin type 9) were approved for the lowering of LDL cholesterol levels; Alirocumab (Praluent) and evolocumab (Repatha) [117]. 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 [117]. A meta-analysis of three trials with 413 patients with type 2 diabetes found that in patients with type 2 diabetes evolocumab caused a 60% decrease in LDL cholesterol compared to placebo and a 39% decrease in LDL cholesterol compared to ezetimibe treatment [130]. In addition, in patients with type 2 diabetes, evolocumab decreased non-HDL cholesterol 55% vs.

placebo and 34% vs. ezetimibe) and Lp(a) (31% vs. placebo and 26% vs. ezetimibe). These beneficial effects were not affected by glycemic control, insulin use, renal function, and cardiovascular disease status. Thus, PCSK9 inhibitors are effective therapy in patients with type 2 diabetes and the beneficial effects on pro-atherogenic lipoproteins is similar to what is observed in non-diabetic patients. Additionally, except for local reactions at the injection sites PCSK9 inhibitors do not seem to cause major side effects.

Table 8. Effect of Lipid Lowering Drugs

	LDLc	HDLc	Triglycerides
Statins	↓ 20-60%	↑ 5-15%	↓ 0-35%*
Bile acid sequestrants	↓ 10-30%	↑ 0-10%	↑ 0-10%**
Fibrates	↓ 0-15%***	↑ 5-15%	↓ 20-50%
Niacin	↓ 10-25%	↑ 10-30%	↓ 20-50%
Ezetimibe	↓ 15-25%	↑ 1-3%	↓ 10-20%
PCSK9 Inhibitors	↓ 50-60%	↑ 5-15%	↓ 5-20%
High Dose Fish Oil	↑ 0- 50%**	↑ 4- 9%	↓ 20- 50%*

***Patients with elevated TG have largest decrease
** In patients with high TG may cause marked increase
*** In 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 cholesterol levels to goal, unless triglycerides are markedly elevated (> 500- 1000mg/dl), which increases the risk of pancreatitis. LDL cholesterol is the first priority because the database linking lowering LDL cholesterol with reducing cardiovascular disease is extremely strong and we now have the ability to markedly decrease LDL cholesterol levels. Dietary therapy is the initial step but, in most patients, will not be sufficient to achieve the LDL cholesterol goals. If patients are willing and able to make major changes in their diet it is possible to achieve significant reductions in LDL cholesterol levels but this seldom occurs in clinical practice [131].

Statins are the first-choice drugs to lower LDL cholesterol levels and the vast majority of diabetic patients will require statin therapy. There are several statins currently available in the US and one should be sure to choose a statin that is capable of lowering the LDL cholesterol to goal. The effect of different doses of the various statins on LDL cholesterol levels is shown in Table 9. Currently four statins are available as generic drugs, lovastatin, pravastatin, atorvastatin, and simvastatin, and these statins are relatively inexpensive. The particular statin used may be driven by price, ability to lower LDL cholesterol levels, and potential drug interactions.

If a patient is unable to tolerate statins or statins as monotherapy are not sufficient to lower LDL cholesterol to goal the second-choice drug is either ezetimibe or a PCSK9 inhibitor. Ezetimibe

can be added to any statin. PCSK9 inhibitors can also be added to any statin and are the drug of choice if a large decrease in LDL cholesterol is required to reach goal (PCSK9 inhibitors will lower LDL cholesterol levels by 50-60% when added to a statin, whereas ezetimibe will only lower LDL cholesterol by approximately 20%). Bile acid sequestrants are an alternative particularly if a reduction in A1c level is also needed. Ezetimibe, PCSK9 inhibitors, and bile acid sequestrants additively lower LDL cholesterol levels when used in combination with a statin, because these drugs increase hepatic LDL receptor levels by different mechanisms, thereby resulting in a reduction in serum LDL cholesterol levels [117]. Niacin and the fibrates also lower LDL cholesterol levels but are not usually employed to lower LDL cholesterol levels (see table 5).

Table 9. Approximate Effect of Different Doses of Statins on LDL Cholesterol Levels

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

Data modified from package inserts

The second priority should be non-HDL cholesterol (non-HDL cholesterol = total cholesterol – HDL cholesterol), which is particularly important in patients with elevated triglyceride levels (>150mg/dl). Non-HDL cholesterol is a measure of all the pro-atherogenic apolipoprotein B containing particles. Numerous studies have shown that non-HDL cholesterol is a strong risk factor for the development of cardiovascular disease [132]. The non-HDL cholesterol goals are 30mg/dl greater than the LDL cholesterol goals. For example, if the LDL goal is <100mg/dl then the non-HDL cholesterol goal would be <130mg/dl. Drugs that reduce either LDL cholesterol or triglyceride levels will reduce non-HDL cholesterol levels.

The third priority in treating lipid disorders is to decrease triglyceride levels. Initial therapy should focus on glycemic control and lifestyle changes including a decrease in simple sugars and ethanol intake. Improving glycemic control can have profound effects on serum triglyceride levels. Fibrates, niacin, statins, and omega-3-fatty acids all reduce serum triglyceride levels (see Table 7). Typically, one will target triglyceride levels when one is trying to lower non-HDL cholesterol levels to goal. Patients with very high triglyceride levels (> 500-1000 mg/dl) are at risk of pancreatitis and therefore lifestyle and triglyceride lowering drug therapy should be initiated early. Note that there is limited evidence demonstrating that lowering triglyceride levels reduces cardiovascular events (see section on effect of lipid lowering drugs on cardiovascular events for details of the various studies). With the recent study demonstrating that adding EPA to statins in patients with elevated triglyceride levels reduces cardiovascular events one can anticipate an increased use of omega-3-fatty acids in patients with elevated triglyceride levels and a non-HDL cholesterol level above goal.

The fourth priority in treating lipid disorders is to increase HDL cholesterol levels. There is strong epidemiologic data linking low HDL cholesterol levels with cardiovascular disease but whether increasing HDL cholesterol levels with drugs reduces cardiovascular disease has not been demonstrated. Life style changes are the initial step and include increased exercise, weight loss, and stopping cigarette smoking. The role of recommending ethanol, which increases HDL cholesterol levels, is controversial but in patients who already drink moderately there is no reason to recommend that they stop unless they are hypertriglyceridemic. The most effective drug for increasing HDL cholesterol levels is niacin (see Table 8), but studies have not demonstrated a reduction in cardiovascular events when niacin is added to statin therapy (see section on the effect of lipid lowering drugs on cardiovascular events for details). Fibrates and statins also raise HDL cholesterol levels but the increases are modest (usually less than 15%). Unfortunately, given the currently available drugs, it is very difficult to significantly increase HDL cholesterol levels and in many of our diabetic patients we are unable to achieve HDL cholesterol levels in the recommended range. Furthermore, whether this will result in a reduction in cardiovascular events is unknown and studies have not demonstrated a benefit.

Many diabetic patients have multiple lipid abnormalities. As discussed in detail above life style changes are the initial therapy. Additionally, improving glycemic control can lead to marked reductions in serum triglyceride levels and modest increases in HDL cholesterol levels. If life style changes are not sufficient in patients with both elevations in LDL cholesterol and triglycerides (and elevations in non-HDL cholesterol), one approach is to base drug therapy on the triglyceride levels (Figure 2). If the serum triglycerides are very high (greater than 500-1000mg/dl), where there is an increased risk for pancreatitis and hyperviscosity syndromes, initial pharmacological therapy is directed at the elevated triglycerides and the initial drug choice is either a fibrate or high dose omega-3-fatty acids (3-4 grams EPA/DHA per day). After lowering triglyceride levels to < 500mg/dl, which may require more than one drug, statin therapy should be initiated if the LDL cholesterol and/or non-HDL cholesterol levels are not at goal. If the serum triglycerides are less than 500mg/dl, statin therapy to lower the LDL cholesterol level to goal is the initial therapy (see Figure 2). Studies have demonstrated that statins are effective drugs in lowering triglyceride levels in patients with elevated triglycerides [117]. In patients with low triglyceride levels statins do not greatly affect serum triglyceride levels. If the non-HDL cholesterol levels remain above goal after one reaches the LDL cholesterol goal, one should then consider combination therapy to lower triglyceride levels, which will lower non-HDL cholesterol levels.

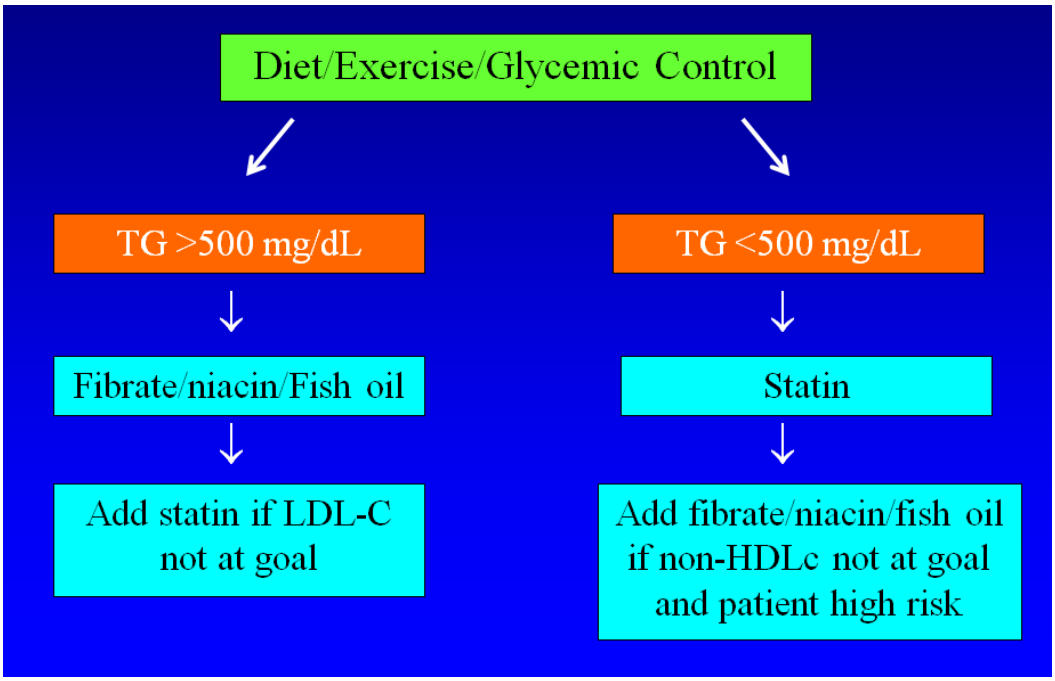

Figure 2. Combined Hyperlipidemia. Increased LDL Cholesterol and TG

Often monotherapy is not sufficient to completely normalize the lipid profile. For example, with statin therapy one may often lower the LDL cholesterol to goal but the non-HDL cholesterol, HDL cholesterol, and triglycerides remain in the abnormal range. Currently, there are no randomized controlled trials demonstrating that combination therapy with fibrates or niacin reduces cardiovascular disease to a greater extent than statin monotherapy. In fact, as noted above, three outcome studies adding either niacin or fenofibrate to statin therapy failed to demonstrate additional benefit while two trials with omega-3-fatty acids showed benefit (see section on the effect of lipid lowering drugs on cardiovascular events for details). Many experts believe that further improvements in the lipid profile will be beneficial and that the studies completed so far should not be considered definitive as they had flaws such as not treating patients with the appropriate lipid profile. When using combination therapy one must be aware that the addition of either fibrates or niacin to statin therapy may increase the risk of myositis [117]. The increased risk of myositis is greatest when gemfibrozil is used in combination with statins. Fenofibrate has a much more modest risk and the FDA approved the use of fenofibrate in combination with moderate doses of statins. Additionally, in the ACCORD LIPID trial the combination of simvastatin and fenofibrate was well tolerated [74]. The increased risk with niacin appears to be very modest. In the AIM-HIGH trial the risk of myositis was not increased in patients on the combination of Niaspan and statin, whereas in the HPS2-Thrive trial myopathy was increased in the group treated with the combination of statin and niacin [77, 79]. The absolute risks of combination therapy are relatively modest if patients are carefully selected; in many patients at high risk for cardiovascular disease combination therapy may be appropriate. Notably, omega-3-fatty acids do not interact with statins or other drugs and hence do not have an increased risk when used in combination therapy. One should be aware of the steps listed in Table 10 that can reduce the potential for toxicity when one uses combination therapy. As with many decisions in medicine one needs to balance the benefits of therapy with the risks of

therapy and determine for the individual patient the best approach. In deciding to use combination therapy a key focus is the non-HDL cholesterol level. When the LDL cholesterol is at goal but the non-HDL cholesterol is still markedly above goal it may be appropriate to resort to combination therapy in patients at high risk.

Table 10. When to Use Combination Therapy

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

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

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