Preventing Cardiovascular Complications of Type 2 Diabetes: Focus on Lipid Management

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Prevention of cardiovascular complications of diabetes must be considered a national public health goal in light of the increasing prevalence of the disease and the high frequency and seriousness of its complications. According to current estimates, more than 13 million people in the United States have physician-diagnosed diabetes, and another 5.4 million may have undiagnosed diabetes.[1] Recent figures from the Centers for Disease Control and Prevention (CDC) confirm that the prevalence of diabetes is growing at an alarming rate. For example, among people in their 30s, there was a 70% increase from 1990 to 1998. In this same time period, the prevalence of diabetes increased 33% among people of all ages and ethnic groups.[2]

Prevalence of diabetes varies to some degree by sex and ethnicity. Among people who are 20 years of age or older, diabetes occurs somewhat more commonly in white men than in white women (4.7% of women, 5.4% of men). Conversely, the disease affects women more frequently than men among African Americans (9.5% of women, 7.6% of men), Mexican Americans (11.4% of women, 8.1% of men), and American Indians/Alaska Natives (12% of women, 9.7% of men). Remarkably, the mortality rate among African-American men and women is at least twice that of whites.[1]

Diabetes is well recognized as an independent risk factor for cardiovascular disease (CVD) in men and women.[3] CVD is up to four times more common in people with diabetes than in those without, and 50% of diabetic people have evidence of CVD at the time of their diagnosis.[4] In addition, the risk of myocardial infarction (MI) and death from coronary disease is the same for diabetic people without a history of MI as for nondiabetic people with such a history.[5] Moreover, postinfarction mortality is significantly higher in people with diabetes than in those without.[6] It is estimated that between 75 and 80% of diabetes-related deaths are attributable to the macrovascular complications of the disease—primarily CVD, cerebrovascular disease, and peripheral vascular disease.[7]

IN BRIEF

Because type 2 diabetes can be considered a cardiovascular disease in its own right, current American Diabetes Association and National Cholesterol Education Program guidelines recommend aggressive treatment of dyslipidemia in people with diabetes, particularly for elevated LDL cholesterol levels. Use of appropriate treatment as determined by the pattern of lipid abnormalities can substantially reduce the risk of macrovascular disease. Institution of tight glycemic control will be beneficial to most patients, but the majority of people with diabetes will also require diet therapy, weight reduction when necessary, and intensive lipid-lowering therapy, which commonly involves one of the statins or fibric acid derivatives.

Pathogenesis of Diabetes-Associated CVD

The pathogenesis of CVD associated with diabetes is not yet fully understood. However, because atherosclerotic macrovascular complications occur at an earlier age and with greater severity in people with diabetes, it is likely that its pathogenesis is directly influenced by the diabetic state.

Long-term exposure to elevated glucose levels alone can contribute to the endothelial cell dysfunction observed in diabetes.[8] Increasing evidence suggests that endothelial dysfunction may play a central role in the development of atherosclerosis.[9] Endothelial dysfunction is characterized by inhibited vasodilation, increased vascular smooth-muscle proliferation, increased thrombogenesis, and proatherogenic cellular processes.[10] Abnormal endothelium-dependent vasodilation also occurs in the microcirculation of diabetic patients, where it may contribute to ischemia and its sequelae.[11] In addition to accelerated atherosclerosis, endothelial dysfunction has been linked with increased thrombosis, hypertension, and dyslipidemia, all of which contribute to the pathogenesis of vascular disease in diabetes.[8]

Hyperglycemia might contribute to atherosclerosis in type 2 diabetes in a number of other ways. For example, hyperglycemia causes glycosylation of proteins in a process that induces cross-linking of collagen and other extracellular matrix proteins in the arterial wall.[12,13] The end products of glycation modify LDL cholesterol, prolonging its half-life and producing changes in the artery ren-

dering it more susceptible to atherosclerosis.[14] Among other proposed biochemical pathways in the pathogenesis of diabetic macrovascular disease are glucose-induced activation of protein kinase C isoforms and increased intracellular oxidative stress.[15]

Patterns of Lipid Abnormalities

According to the CDC, 97% of adults with diabetes have one or more lipid abnormalities.[16] The central characteristic of dyslipidemia in patients with type 2 diabetes is an elevated triglyceride level, particularly triglyceride-rich VLDL levels and decreased HDL cholesterol levels. In diabetic patients, the concentration of LDL cholesterol is usually not significantly different from that seen in nondiabetic individuals. However, patients with type 2 diabetes typically have a preponderance of smaller, denser, oxidized LDL particles, which may increase atherogenicity,[17] even if the absolute concentration of LDL cholesterol is not elevated.[18]

This lipid triad, referred to as atherogenic dyslipidemia, is usually present in patients with premature coronary artery disease. When this characteristic lipid profile is seen in type 2 diabetes, it is referred to as diabetic dyslipidemia and confers a risk of CVD that equals or exceeds that of a high-risk LDL cholesterol concentration of 150–220 mg/dl.[19]

According to the American Diabetes Association (ADA), the presence of increased triglyceride and decreased HDL levels is the best predictor of CVD in patients with type 2 diabetes.[18] Other predictive factors include a history of cigarette smoking and hypertension.

The evidence regarding the predictive value of elevated LDL cholesterol is still accumulating. Most recently, results of the Strong Heart Study indicate that LDL cholesterol is an independent predictor of CVD in patients with diabetes, along with age, albuminuria, fibrinogen, HDL cholesterol (inverse predictor), and percent body fat (inverse predictor).[20] Starting with LDL levels as low as 70 mg/dl, every 10 mg/dl increase in LDL cholesterol was associated with a 12% increase in risk of CVD. This finding is supported by results of prospective, long-term clinical trials in which reduction of LDL levels was associated with a significantly reduced risk of cardiovascular events in both diabetic and nondiabetic participants.[21,22]

Role of Concomitant Risk Factors in Diabetes

A clustering of risk factors, which has been labeled the metabolic syndrome, occurs commonly in type 2 diabetes and simultaneously affects the development of CVD and diabetes.[3] Insulin resistance is present, usually in association with features such as hypertension, elevated triglycerides, low HDL cholesterol, increased small dense LDL particles, endothelial dysfunction, a prothrombotic state and abdominal or visceral obesity. Often, these risk factors may be exacerbated by lifestyle choices, such as a high-fat diet, a sedentary lifestyle, and smoking.

The central feature of the metabolic syndrome is insulin resistance, defined as the impaired ability of insulin to lower blood glucose. Insulin resistance is common among people with impaired glucose tolerance (IGT) and characteristically precedes the onset of type 2 diabetes.[3] Recently, the National Cholesterol Education Program (NCEP) identified the metabolic syndrome as a secondary target of therapy beyond LDL lowering.[23] The risk determinants for clinical identification of the metabolic syndrome are shown in Table 1. According to new NCEP Adult Treatment Panel guidelines (NCEP ATP III), the presence of three or more of these risk determinants establishes the diagnosis of the metabolic syndrome.

Most patients with type 2 diabetes have insulin resistance. Early in the course of type 2 diabetes, fasting plasma insulin levels are often elevated. This is a response to insulin resistance and elevated postprandial plasma glucose levels. Later in the disease course, when pancreatic β-cell function is severely impaired, the insulin secretory response to glucose becomes increasingly deficient, resulting in fasting hyperglycemia and overt diabetes.

Hyperglycemia is a well-established independent risk factor for CVD,[3,6,24] and intensive treatment of hyperglycemia has been shown to prevent or slow the progression of long-term microvascular complications of type 2 diabetes. However, whether tight glycemic control influences the development of macrovascular complications remains to be determined. The VA Cooperative Study on the control of hyperglycemia and development of CVD in type 2 diabetes is a 5- to 7-year study recently initiated to address this issue.

Regardless of whether overt diabetes is present, insulin resistance appears to

Table 1. Clinical Identification of the Metabolic Syndrome*

Risk Factor	Defining Level
• Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
• Triglycerides	≥150 mg/dl
• HDL cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
• Blood pressure	≥130/≥85 mmHg
• Fasting glucose	≥110 mg/dl

*Modified from ref. 23.

induce other metabolic disturbances included in the metabolic syndrome: atherogenic dyslipidemia and impaired glucose tolerance, as previously noted, along with hypertension and a prothrombotic state.[3,24] In addition to lipid abnormalities and hyperglycemia, which are independently atherogenic, hypertension is also known to be a major risk factor for CVD in all populations.[25] Although a causal connection between insulin resistance and hypertension has been debated, the evidence to support this possibility is increasing.[26] Together, hypertension and overt diabetes substantially and synergistically increase the risk of CVD, as well as of microvascular complications.[27]

Accordingly, intensive treatment of dyslipidemia, high blood pressure, and hyperglycemia is now considered essential in the treatment of diabetes, as has been shown by numerous reports from the U.K. Prospective Diabetes Study.[28] A recent study found that lipid values, hypertension, and other CVD risk factors were even more strongly associated with coronary disease than glucose status per se in patients with diabetes.[29]

In addition to physical inactivity and advancing age, obesity, and particularly abdominal or visceral obesity, contribute to insulin resistance and hyperinsulinemia.[3,30] In its own right, obesity is associated with atherogenic changes in lipids as well as with hypertension.[7,31]

The most recently identified component of the metabolic syndrome is a prothrombic state. Elevated levels of plasminogen activator inhibitor-1, for example, are strongly linked with an increased cardiovascular risk of atherothrombosis.[32] Increased fibrinogen levels and platelet abnormalities are also attendant abnormalities of insulin resistance.[33,34]

In addition to the components of the metabolic syndrome, hyperhomocysteinemia (>14 μmol/l) has recently been recognized as an independent risk factor for CVD. As recently reviewed, in people with type 2 diabetes, hyperhomocysteinemia is associated with a 5-year mortality risk almost double that in nondiabetic people. Furthermore, hyperhomocysteinemia may exert an atherothrombotic effect via increasing oxidative stress and, thus, endothelial dysfunction.[35]

Management of Dyslipidemia

Aggressive screening and management of lipid abnormalities is essential for patients with type 2 diabetes in order to slow the progression of atherosclerotic disease. Levels of LDL, HDL, total cholesterol, and triglycerides should be measured when diabetes is first diagnosed. The ADA recommends that screening be repeated yearly in most adult patients because frequent changes in glycemic control may affect lipoprotein levels. In some patients whose levels remain in the low-risk category, assessment may be repeated every 2 years.[6]

Increasingly, the approach to diabetes management is predicated on the principle that diabetes itself is a CVD. Consequently, there is less distinction between primary prevention of CVD and secondary prevention in people with type 2 diabetes.[36] Because patients with diabetes have a higher case fatality rate and are more likely to die than nondiabetic patients before they reach the hospital, a preventive strategy based solely on secondary prevention is not likely to be sufficient as a means of preserving lives.[6] Therefore, patients with diabetes but no established CVD should be treated as aggressively as nondiabetic patients with established CVD.

Goals of therapy

According to current ADA recommendations, the major emphasis for treating diabetic dyslipidemia should be placed on lowering LDL cholesterol levels to <100 mg/dl, even in patients with no history of CVD.[6] These updated ADA recommendations concur with the recent NCEP ATP III guidelines.[23] LDL was selected as the primary lipid parameter for intervention based on results of clinical trials in which reductions in LDL were associated with significant decreases in morbidity and mortality from CVD.

In some diabetic patients, however, therapy may appropriately stress increasing HDL levels. Among the 627 diabetic patients included in the VA-HIT trial of the fibric acid derivative gemfibrozil for the secondary prevention of coronary disease, there was a 24% relative risk reduction compared with placebo-treated patients. This rate increased to 35% among those with the metabolic syndrome. The primary lipid abnormality in this patient population was a low HDL cholesterol level, and treatment with gemfibrozil raised HDL by a mean of 6% and reduced triglyceride level by 31% after 1 year's treatment.[37] Thus, we now have the pharmacological tools to treat all lipid abnormalities in people who are at very high risk for CVD.

The trials assessing the benefits of treating lipid abnormalities have generally focused on the use of statin therapy for lowering LDL levels (Table 2). Because outcome in subpopulations of diabetic patients was determined in post hoc analyses, the therapeutic implications of these studies must be considered preliminary. Nevertheless, they do provide some guidance.

The benefits of secondary prevention with simvastatin were demonstrated in the Scandinavian Simvastatin Survival Study (4S), which followed diabetic and nondiabetic patients with a history of MI and elevated LDL cholesterol levels.[38] Subgroup analysis of patients with diabetes (who made up <5% of the study population) showed that treatment to lower cholesterol significantly improved outcome, with a 55% risk reduction in major coronary events. Death from coronary disease was also reduced, although the results were not significant due to the small sample size of diabetic patients.[22,38] The Cholesterol and Recurrent Events (CARE) study confirmed these results for pravastatin even in those diabetic patients without grossly elevated LDL levels.[21]

The benefits of lipid lowering as *primary prevention* in studies of patients with diabetes have not been as clearly documented. As in the secondary prevention trials, patients with diabetes

Table 2. Overview of Controlled Clinical Trials Evaluating Effects of Lipid-Lowering Agents in Diabetic Patients

Study	Total No. of Diabetic Patients	Mean Duration (years)	Design	Mean Baseline Lipid Levels in Treated Patients (mg/dl)	Percent Reduction of LDL	Percent Reduction in Risk of CVD Events
CARE[21]	586	5	Secondary prevention: pravastatin vs. placebo	TG: 164 HDL: 37.6 LDL: 136	–27	25 (P = 0.05)
4S[38]	202	5.4	Secondary prevention: simvastatin vs. placebo	TG: 149 HDL: 43 LDL: 184	–36	(CHD death or nonfatal MI) 55 (P = 0.002)
LIPID[43]	782	6.1	Secondary prevention: pravastatin vs. placebo	NA	NA	19 (NS)*
Helsinki Heart Study[39]	135	5	Primary prevention: gemfibrozil vs. placebo	TG: 214 HDL: 45 LDL: 200	~ –10	>60 (NS)*
VA-HIT[37]	627	5.1	Secondary prevention: gemfibrozil vs. placebo	Entry criteria: HDL: ≤40 LDL: ≤140	NA	24 (P = 0.05)*

CHD = coronary heart disease; CVD = cardiovascular disease; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; MI, myocardial infarction; NA = not available; NS = not significant; TG = triglycerides.

*Study not powered adequately to detect effects of treatment reliably in subgroups.

formed a small subset of the study populations (usually <5%), and efficacy in diabetes was determined only in post hoc analyses.

The Helsinki Heart Study showed that treatment with gemfibrozil was associated with a nonsignificant reduction in CVD events in the subset of diabetic patients with no prior history of CVD.[39] In addition, analysis of a small subpopulation of patients with diabetes but no clinical history of CVD, average total cholesterol and LDL levels, and low HDL levels participating in the AFCAPS/TexCAPS study did not yield statistically significant results. These patients were treated with lovastatin for a mean of 5.2 years.[40]

A number of primary prevention clinical end point trials are currently underway in patients with diabetes. These include the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study; the Lipid in Diabetes Study (LDS), which is studying fenofibrate and cerivastatin alone or in combination; the Atorvastatin as Prevention of CHD Endpoints in Patients with Non-Insulin-Dependent Diabetes Mellitus (ASPEN) study; the Collaborative Atorvastatin Diabetes Study (CARDS); and the 4D trial, which also is studying atorvastatin in type 2 diabetes patients with end-stage renal disease. The results of these studies should clarify the role of statins in primary prevention of CVD in patients with type 2 diabetes.

The ADA recommends that adults with type 2 diabetes have HDL cholesterol levels >45 mg/dl and triglyceride levels <200 mg/dl. For women, the optimal HDL levels should be above 55 mg/dl, since nondiabetic women tend to have higher HDL cholesterol levels than do men.[6] Indeed, as previously noted, the placebo-controlled VA-HIT trial suggests that diabetic patients whose major lipid abnormality is a low HDL level may benefit from secondary prevention with gemfibrozil therapy, although the study was not powered to detect this end point.[37]

Lipid and lipoprotein treatment goals are not met very frequently, largely because the need to treat diabetic patients even more aggressively than nondiabetic patients is not yet widely appreciated. In fact, the CDC recently reported that despite the widespread prevalence of lipid abnormalities among people with diabetes, only 32% are receiving treatment with diet, exercise, or drugs to reduce lipid levels. Furthermore, among those who are being treated, only 1% have reached the ADA goal of LDL <100 mg/dl.[16]

Nonpharmacological strategies

Diet and exercise are the cornerstones of therapy for all people with dyslipidemia, including those with diabetes. Similar to the NCEP recommendations, the current ADA recommendations emphasize weight loss and decreased intake of saturated fats.[6]

However, the ADA permits either a high-carbohydrate diet or a higher-fat diet enriched in polyunsaturated or

monounsaturated fat. Yet, there is controversy as to the merits of either. As recently reviewed, the controversy revolves to some extent around the fact that weight loss is more difficult to attain with a higher-fat diet, and a high-carbohydrate diet is associated with higher triglyceride and lower HDL levels than a higher-fat diet.[6,36] Therefore, patients' degree of obesity should probably guide dietary choices. In addition, a diet high in fiber, particularly soluble fiber, may improve glycemic control and concomitantly lower plasma lipid concentrations in patients with type 2 diabetes.[41]

Most patients should also be encouraged to increase their regular physical activity to meet currently recommended levels, after undergoing an exercise test to assess the level of risk.[3] Obviously, patients should be encouraged to stop smoking, since tobacco use and diabetes are synergistic risk factors for atherosclerotic disease.[42]

Pharmacological therapy

Generally, pharmacological therapy should follow when a 3- to 6-month trial of lifestyle modifications alone fails to lower LDL cholesterol levels adequately. For diabetic patients without preexisting CVD, the ADA currently recommends initiation of a lipid-lowering agent if LDL cholesterol level remains ≥130 mg/dl despite a regimen of diet and exercise (Table 3). NCEP recommends initiating lipid-lowering therapy in this patient group simultaneously with intensive lifestyle modifications.[23] Patients without preexisting CVD may require a more aggressive strategy of lifestyle modifications and pharmacological therapy if LDL levels are between 100 and 130 mg/dl. Any diabetic patient with established CVD or with a very high LDL cholesterol level (≥200 mg/dl) at diagnosis should receive pharmacological therapy at the same time as lifestyle modifications.[6]

Statins are the drug of first choice for reducing LDL levels and may be required in type 2 diabetic patients with even "normal" LDL levels, since these levels may be atherogenic because of their markedly smaller, denser nature.[6] Bile-acid binding resins may be used as second-line therapy for reducing LDL cholesterol, although they may aggravate hypertriglyceridemia and are associated with unpleasant gastrointestinal side effects.

The choice of statin depends on the degree of LDL cholesterol reduction needed to bring the level to <100 mg/dl (Table 4), the initial LDL cholesterol level, concomitant use of other drugs that undergo hepatic metabolism, and the judgment of the treating physician.[6] Usually, the dose should be low initially and titrated upward, if necessary. The lipid profile should be monitored every 3 months for the first 6 months, then every 6–12 months thereafter. With high-dose statin therapy, the LDL cholesterol levels may be brought as low as 80 mg/dl or

Table 3. Pharmacological Management of Lipid Abnormalities in Type 2 Diabetes

Lipid Abnormality	Target Patients	Pharmacological Options	Comment
Elevated LDL	<100 mg/dl	*First choice*: statin therapy *Second choice*: bile-acid binding resin or fenofibrate	Reducing LDL is the first priority.
Low HDL	>45 mg mg/dl in men >55 mg/dl in women	Glycemic control Nicotinic acid or fibrates	Nicotinic acid is relatively contraindicated.
Elevated triglycerides	<200 mg/dl	Improved glycemic control Fibric acid derivative High-dose statin, if LDL is also elevated	
Combined hyperlipidemia	As above	*First choice*: Improved glycemic control plus high-dose statin *Second choice*: Hypoglycemic therapy plus high-dose statin plus fibric acid derivative *Third choice:* Hypoglycemic therapy plus statin plus nicotinic acid	Combination therapy with a statin and nicotinic acid or with gemfibrozil or fenofibrate may increase risk of myositis.

HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.
Adapted from ref. 6.

less. However, very high-dose therapy (i.e., simvastatin, 80 mg, or atorvastatin, 40 or 80 mg) should only be used to achieve therapeutic goals when absolutely necessary because of the statins' greater association with side effects at these dosages.[6]

Pharmacological intervention to reduce triglyceride levels begins with tight glycemic control.[6] Fibric acids are the drugs of first choice for treating elevated triglyceride levels. For patients with levels in the range of 200–400 mg/dl, the decision to start pharmacological therapy to reduce triglyceride levels is best made individually. For patients with levels >400 mg/dl, pharmacological treatment is strongly advised.

Despite the observation that a low HDL cholesterol level is a powerful predictor of CVD in diabetic patients,[24] the evidence for using pharmacological therapy to increase HDL cholesterol is less clear, particularly because of its relationship to triglycerides. Lifestyle modifications, including weight loss, smoking cessation, and increased physical activity, may increase HDL cholesterol somewhat. Nicotinic acid, which is the most effective agent for increasing HDL levels, is relatively contraindicated due to its adverse effects on glycemic control. However, both statins and fibric acids variably raise HDL levels.

Combination therapy. Higher doses of statins may reduce triglyceride levels moderately, as well as slightly increase HDL cholesterol levels, thereby reducing the need for combination therapy. However, combination therapy with statins and fibric acids may be required if aggressive statin therapy does not achieve lipid and lipoprotein goals. Although the risk of myositis is in-creased with this combination, the risk of clinical myositis, as opposed to elevated creatinine phosphokinase levels, appears to be low.[6]

Bile-acid binding resins may be used in combination with a fibric acid derivative as a third-line choice for high LDL levels. An alternative third-line choice is the combination of a statin with nicotinic acid, which is extremely effective in modifying diabetic dyslipidemia. This combination, however, may significantly worsen hyperglycemia and should be used cautiously in a regimen involving <2 g nicotinic acid per day and frequent monitoring of glucose levels.[6]

Antidiabetic agents. Although the link between hyperglycemia and macrovascular disease has not been fully delineated, optimizing glycemic control through glucose-lowering agents is essential to improve dyslipidemia in diabetic patients. Several antidiabetic agents lower triglyceride levels and some reduce LDL cholesterol levels as well. However, except for the thiazolidinediones (glitazones), oral antidiabetic agents do not change or have only minimal effects on raising HDL cholesterol levels.[6] With use of thiazolidinediones in type 2 diabetes, increases in HDL of up to 19% have been reported.[43]

Table 4. Effects of Statins on Lipid and Lipoprotein Levels: Percent Change From Baseline

Statin	LDL Cholesterol	Triglycerides	HDL Cholesterol
Atorvastatin			
10 mg qd	–39	–19	+6
20 mg qd	–43	–26	+9
40 mg qd	–50	–29	+6
80 mg qd	–60	–37	+5
Cervistatin			
0.2 mg qd	–25	–16	+9
0.3 mg qd	–31	–16	+8
0.4 mg qd	–34	–16	+7
0.8 mg qd	–42	–22	+9
Fluvastatin			
20 mg qpm	–22	–12	+3
40 mg qpm	–25	–14	+4
40 mg bid	–36	–18	+6
Lovastatin			
20 mg qpm	–24	–10	+6.6
40 mg qpm	–30	–14	+7.2
20 mg bid	–34	–16	+8.6
40 mg bid	–40	–19	+9.5
Pravastatin			
10 mg qpm	–22	–15	+7
20 mg qpm	–32	–11	+2
40 mg qpm	–34	–24	+12
Simvastatin			
5 mg qpm	–26	–12	+10
10 mg qpm	–30	–15	+12
20 mg qpm	–38	–19	+8
40 mg qpm	–41	–18	+9
80 mg qpm	–47	–24	+8

Source: *Physicians' Desk Reference,* 54th ed. Montvale, N.J., Medical Economics Company, 2001

Conclusion

In addition to being at risk of microvascular disease, patients with diabetes are at very high risk of macrovascular disease, particularly CVD. Because diabetic patients without previous MI have as high a risk of MI as nondiabetic patients with previous MI, all diabetic patients

should be treated aggressively for the prevention of CVD.

Current ADA and NCEP guidelines recommend aggressive treatment for dyslipidemia in diabetic patients, particularly in those with elevated LDL cholesterol levels. Tight glycemic control achieved with diet, exercise, and some antidiabetic agents may substantially improve the lipid profile and reduce the risk of CVD in some patients. However, most patients will require the use of intensive lipid-lowering therapy to reduce their cardiovascular risk, most commonly with one of the statins or fibric acid derivatives.

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