CHAPTER

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Mixed Dyslipidemia

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Mixed dyslipidemia is one in which there is an elevated LDL cholesterol and triglyceride levels combined with decreased levels of HDL cholesterol. This kind of mixed dyslipidemia is commonly seen in patients with diabetes and metabolic syndrome.

The gold standard for treating dyslipidemia in patients with or at high risk for CVD centers on intensive LDL-C lowering with statins[1]. However, even among patients who achieve LDL-C levels < 70 mg/dL, the residual risk for subsequent CHD events remains high.

Table 1 : ADA/AHA 2007: Primary Prevention of CVD in Patients With Diabetes

- Elevated LDL-C is a *primary* target of lipid-lowering therapy
  - LDL-C goal < 100 mg/dL
- TG-rich lipoproteins, especially VLDL, are often elevated in patients with diabetes, appear to be atherogenic, and represent a *secondary* target of lipid-lowering therapy
  - TG goal: < 150 mg/dL; HDL-C goal: males > 40 mg/dL females > 50 mg/dL
  - If TG are 200–499 mg/dL, non–HDL-C goal ≤ 130 mg/dL
  - If TG are ≥ 500 mg/dL, lowering TG is primary target
- Combination therapy of LDL-C–lowering drugs (statins) with fibrates or niacin may be necessary to achieve lipid targets[3]

The role of elevated TG, elevated non–HDL-C, and low HDL-C on residual CHD risk, guidelines for treating beyond LDL-C, and clinical trial evidence supporting the use of TG and HDL-C modifying therapies will be reviewed.

According to the NCEP ATP III[2], elevated TGs are widely recognized as a marker for increased CVD risk. In this context, elevations in serum TG can be considered a marker for atherogenic remnant lipoproteins.

VLDL-C is the most readily available measure of atherogenic remnant lipoproteins for clinical practice. A normal VLDL-C is typically ≤ 30 mg/dL (TG/5) when TGs are < 150 mg/dL. The goal for non–HDL-C is 30 mg above the goal for LDL-C. Non–HDL-C is calculated by subtracting HDL-C from total cholesterol (TC) or adding the LDL-C and VLDL-C (VLDL-C = TG/5). In the presence of high serum levels of TG, non–HDL-C will better represent the concentrations of all atherogenic lipoproteins than will LDL-C alone.

Thus, the guidelines (Table 1) recommend that non–HDL-C be a secondary target of therapy when TG levels are ≥ 200 mg/dL. Non–HDL-C incorporates all of the cholesterol in LDL and VLDL and all of the apolipoprotein-B containing particles.

NCEP ATP III acknowledges HDL-C as an independent risk factor for CHD**,** a finding which has been corroborated by epidemiologic studies and a number of large prospective, population-based studies. An HDL-C less than 40 mg/dL in both men and women is identified as a risk factor for CHD, although no specific target levels for raising HDL-C are provided.

Atherosclerosis is a complex vascular inflammatory process that is in part triggered by lipid accumulation in the blood vessel wall. Lipoproteins play a significant role not only in the transportation of lipids but also in triggering a number of inflammatory processes. Low-density lipoprotein cholesterol (LDL-C) is involved in the transfer of cholesterol to the lining of the vessel wall and, therefore, is considered to be an atherogenic lipoprotein. Epidemiologic evidence has directly linked elevated LDL-C with an increased risk of ischemic events such as MIs. Furthermore, large-scale prospective trials have demonstrated a reduction in cardiovascular events with a reduction of LDL-C levels. There is also evidence to suggest that smaller, denser LDL-C particles may be even more atherogenic than larger, fluffier LDL-C particles. These small, dense LDL-C particles are more common in patients with diabetes, which at least partially explains the high risk of cardiovascular events in this population.

The evidence for an association between elevated TG levels and the risk of cardiovascular disease has been accumulating for close to five decades. In a meta-analysis of 17 population-based prospective studies, Austin and colleagues investigated the relationship between TG levels and the risk of cardiovascular disease.[4] The overall population in this meta-analysis included 46,413 men and 10,864 women. The findings of this study suggested that every 89 mg/dL increase in TG levels was associated with a 36% increased risk of cardiovascular events in men and a 76% increased risk in women.

The Copenhagen Male Study followed 2906 men with elevated triglyceride levels for a span of 8 years. In that study, a high triglyceride level was found to be a significant risk factor for an adverse cardiac event, independent of other risk factors.[5]

The association between TG values and CHD risk was also evaluated in a recent meta-analysis by Sarwar et al(2007).[6] Twenty-nine prospective studies were included, representing the largest and most comprehensive epidemiologic assessment in Western populations (262,525 participants; 10,158 CHD cases). The combined analysis of the 29 studies yielded an adjusted odds ratio of 1.72 (95% CI, 1.56–1.90). The study concluded that a strong and highly significant association exists between TG value and CHD risk.

Elevation in triglyceride levels has been linked to an increased risk of cardiovascular events, and there is evidence to suggest that a decrease in triglyceride levels (with the use of lipid modifying agents) reduces the risk of cardiovascular events.

The role of high-density lipoprotein cholesterol (HDL-C) as a protective lipoprotein has been well established in epidemiologic studies and is evolving in clinical trials focusing on increasing HDL-C levels using lipid-modifying agents.

Managing Mixed Dyslipidemia

When considering using lipid-modifying therapy to decrease the risk of cardiovascular events, it is crucial that one focuses on total lipid control, which includes a reduction in LDL-C and TG levels as well as an increase in HDL-C levels. Focusing only on LDL-C reduction may be a myopic approach that may not provide patients with maximal cardiovascular protection.

Many individuals have mixed dyslipidemia, which includes elevated LDL-C and TG levels, as well as low HDL-C levels. This lipid triad abnormality is often observed in patients with diabetes, as well as those with the metabolic syndrome. In addition to mixed dyslipidemia, component risk factors for the metabolic syndrome include hypertension, insulin resistance (with or without non-insulin-dependent diabetes), and a procoagulant state. It is

Table 2 : ADA Standards of Medical Care in Diabetes: Dyslipidemia Management[17-18]

	First Priority	Second Priority
LDL-C lowering Goal: < 100 mg/dL < 70 mg/dL is an option in patients with overt CVD.	• Life style changes • Statins	• Niacin, ezetimibe, bile acid sequestrants, or fenofibrate
HDL-C raising Goal: > 40 mg/dL > 50 mg/dL in women	• Life style changes	• Niacin or fibrates
TG lowering Goal: < 150 mg/dL	• Life style changes • Glycemic control	• Fibrates (fenofibrate, gemfibrozil) • Niacin • Statins (if also have high LDL-C)
Combined hyperlipidemia	• Glycemic control + high-dose statin	• Glycemic control + statin + fibrate • Glycemic control + statin + niacin

well established that the presence of diabetes or the metabolic syndrome substantially increases the risk of cardiovascular events. Therefore, aggressive and global lipid management becomes of paramount importance in these patients.

Reduction of cardiovascular events has been consistently demonstrated with statins through a large number of prospective, randomized controlled trials in both primary and secondary prevention settings. These trials have demonstrated the ability of statins to reduce the risk of cardiovascular events by 25% to 38%.[7-11] But these data suggest that even with aggressive LDL-C lowering, about two-thirds of major coronary events are not prevented.

The staggering rate of remaining residual cardiovascular events in these statin trials calls for a more global approach to cardiovascular risk reduction.[12] This includes more aggressive lifestyle modification (e.g., exercise, dietary improvement, smoking cessation, and moderation of alcohol consumption) and more intensified therapy to achieve optimal blood pressure as well as lipid control. As evidence continues to demonstrate the significance of reduction of TG levels and increase in HDL-C levels, lipid management should take a more global perspective, perhaps focusing on combination therapy to more effectively reduce LDL-C and TG levels as well as to increase HDL-C levels.

An update to the NCEP-ATP III guidelines highlighted the consideration of combining a fibrate or niacin with LDL-C lowering drugs when a high-risk patient has high TG levels or low HDL-C levels.[13] One potential concern about combination therapy is the risk of myopathy, which may be minimized by combining a low-to-moderate dose of a statin with a fibrate or niacin. One fibrate in particular, fenofibrate, has been recognized as a potentially safer fibrate since it does not seem to interfere with the metabolism of statins.[14-15]

The patient population that would most likely be in need of combination therapy would be those with diabetes or the metabolic syndrome. There is a high rate of lipid triad abnormality (mixed dyslipidemia) in these groups of patients, making the need for combination of fibrate or niacin with a statin an eminent one.

The American Diabetes Association (ADA) guidelines (Table 2) recommend the combination of a statin and a fibrate for patients with diabetes whose lipid abnormality is not corrected by a statin alone; a secondary consideration is given to a niacin and statin combination due to potential glycemic changes that may occur with niacin.[16] Regardless of the choice of combination therapy (e.g., statin + fibrate or statin + niacin), the most important factor to keep in mind is that all atherogenic lipoproteins should be addressed and, after correcting for LDL-C values, one has to focus on the reduction of non-HDL-C levels, potentially with the use of combination therapy, to reduce the global risk of cardiovascular events.

Although NCEP does not suggest a target to which HDL-C should be raised in patients at risk, it does recommend that patients with low HDL-C

Table 3 : Overview of Major HDL-C–Raising Pharmacologic Options [19-20]

Drug Class	Changes in Lipid Parameter			Benefits	Adverse Events/ Comments
	LDL-C	HDL-C	TG		
Statins	↓↓↓	↑	↓	Reduce risk for total and CHD mortality	Well tolerated, no additional risk for non-CHD death seen in large prevention studies
Niacin	↓↓	↑↑↑	↓↓↓	Reduce risk for total and CHD mortality	Flushing, GI discomfort reduce compliance; hyperglycemia restricts use in pts with diabetes
Fibrates	↓	↑↑↑	↓↓↓	Reduce risk for CHD mortality	Raise some concerns over additional risk for non-CHD mortality
Resins	↓↓	↑	↑	Reduce risk for CHD	Decrease absorption of many drugs; may be inconvenient to administer; unpalatable

be treated with lifestyle modification (weight loss, diet, smoking cessation, aerobic exercise) and drug therapy as indicated. The Expert Group on HDL Cholesterol and the European Consensus Panel on HDL-C recommend that HDL be raised to ≥ 40 mg/dL in patients with CAD and those at high risk for CAD (metabolic syndrome, diabetes mellitus, 10 yr Framingham risk > 20%). The American Diabetes Association recommends HDL-C targets of ≥ 40 mg/dL in diabetic men and ≥ 50 mg/dL in diabetic women.

Statins, fibrates, niacin and resins all have varing effects on the different lipid entities. Table 3 gives an overview of major HDL-C raising pharmacological options

Table 4 : HDL-C Response to Pharmacologic Intervention [21]

Monotherapy	**HDL-C Elevation**
Niacin	15%–35%
Fibrates	6%–18%
Statins	4%–10%
Combination Therapy	
Niacin + fibrate	45%–48%
Niacin + statin	17%–30%
Fibrate + statin	14%–28%

Because all of the available drugs that increase HDL-C levels have significant effects on other lipoproteins, it has not been possible to prove in clinical trials the benefit of raising HDL-C in isolation. However, because of the known correlation of low HDL-C levels with increased CHD risk, the magnitude of the HDL-C elevation achievable with pharmacologic treatments has become a point of interest in many trials of lipid-altering therapy. Niacin and fibrates individually increase HDL-C more than the statins and combination of niacin with fibrates gives the maximum increase in HDL-C.(Table 4.)

Some important studies using combination therapies to manage mixed dyslipidemias

The HATS study (HDL-Atherosclerosis Treatment Study) (2001) showed that the addition of niacin to simvastatin therapy in patients with CAD with low HDL-C and "normal" LDL-C resulted in slight regression of coronary atherosclerosis and a significant reduction (90%) in clinical coronary events over 3 years.[22] Niacin/simvastatin combination therapy reduced CHD progression by 90% and cardiovascular events by 40% in patients with metabolic syndrome. These data suggest that patients with metabolic syndrome should be treated more aggressively, and simvastatin plus niacin combination therapy appears to be an effective therapy.[23]

SAFARI trial[24] – (Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia.) (2005) demonstrated that combination therapy with simvastatin plus

fenofibrate was significantly more effective than simvastatin monotherapy at correcting the levels of all the major lipids: TGs, VLDL-C, LDL-C, and HDL-C. The combination therapy substantially reduced TG and increased HDL-C, compared to simvastatin monotherapy.

Statin/Fibrate Combination Therapy Pharmacokinetic Interactions [25-26]

The risk of adverse effects of statin/fibrate combination therapy is dependent on pharmacokinetic interactions that alter statin metabolism and clearance. High levels of statins can cause liver function abnormalities, myopathy, and in rare cases, rhabdomyolysis. A number of studies have investigated the pharmacokinetic interactions between different fibrates and statins to explain the variations in adverse events reported by patients who are receiving particular statin/fibrate combination therapies. These studies have concluded that there is a difference between fibrates in their ability to affect the pharmacokinetics of statins, and among statins in their susceptibility to metabolic interactions with the fibrates.

In patients treated with fenofibrate in combination with statins, the number of cases of rhabdomyolysis reported per million prescriptions dispensed was approximately 15-fold lower for fenofibrate than for gemfibrozil.[27]

ARBITER 1,2,3 [28] (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) (2006) showed that when niacin ER was added to statin therapy, there was a significant regression in atherosclerosis measured by CIMT after 12 and 24 months of treatment. In patients with diabetes or metabolic syndrome ($n = 62$), there was a significant regression of CIMT (-0.046, $P < 0.001$) in statin + niacin ER versus statin monotherapy after 12 to 24 months of treatment.

The COMPELL study- (Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone) (2007).[29] This study evaluated comparative effects on lipid levels of combination therapy with niacin ER and low-to-moderate doses of a statin (atorvastatin and rosuvastatin), simvastatin plus ezetimibe, and a highly potent statin alone (rosuvastatin). Statin/niacin ER combination regimens increased HDL-C and lowered TGs and lipoprotein (a) significantly more than the other regimens ($P < 0.001$ for analysis of variance across groups). In summary, low-to-moderate dose combination therapy with a statin and niacin ER provided broad control of lipids and lipoproteins independently associated with CHD.

The COMPELL study reported 12-week safety data with niacin ER/statin combination therapy, simvastatin/ezetimibe combination therapy, and rosuvastatin monotherapy in patients who qualified for drug therapy based on number of CHD risk factors. All drug regimens were generally well tolerated. All groups had small increases (within the normal range) in liver transaminases and creatinine kinase. No drug-related myopathy or hepatotoxicity was observed. No patient had elevated creatinine kinase > 5 or > 10 times ULN, and only one rosuvastatin patient had liver enzyme elevation > 3 X ULN. Small increases in fasting glucose (3–5 mg/dL) were observed with niacin ER/statin combination therapy, but there were no significant changes in HbA1C levels. Slight increase in uric acid (~ 0.1 mg/dL) were also observed with niacin ER/statin combination therapy versus no change or slight decrease (0.4–0.5 mg/dL) in other 2 groups.

Based on a recent analysis of FDA reports, the overall prevalence of adverse event reports (AERs) with niacin ER/statin combination has been found to be quite low (≤ 1%).

Conclusions

In all of these major statin trials, significant residual cardiovascular risk remains even after reducing LDL-C. According to Libby, in the best of circumstances, the decrease in cardiovascular events due to statin treatment still allows two-thirds of cardiovascular events to occur. Libby concludes, "To address the majority of cardiovascular events that still occur despite our most powerful existing

therapies, we must combine lifestyle change and evaluate new pharmacologic strategies that will move us toward the goal of eradicating cardiovascular disease in the future."[30]

Lipid abnormalities beyond LDL-C (non–HDL-C, TG, HDL-C) should be intensively treated to reduce residual CVD risk. Clinical trial data support the efficacy of lifestyle change, niacin, and fibrates for reducing CVD risk when used alone and in combination with statins. Clinical trial and surveillance data support the safety of Niacin ER and fenofibrate when used alone and in combination with statins.

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