Optimal lipid modification: the rationale for combination therapy

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Background: An emphasis on more aggressive lipid-lowering, particularly of low-density lipoprotein cholesterol, to improve patient outcomes has led to an increased use of combination lipid-lowering drugs. This strategy, while potentially beneficial, has triggered concerns regarding fears of adverse effects, harmful drug interactions, and patient nonadherence.
Objective: To present key data regarding combination lipid-altering therapy including use, rationale, major trials, benefits, potential adverse effects, compliance issues, and limitations.
Method: Literature was obtained from MEDLINE (1966 – June 2005) and references from selected articles.
Results: A substantial body of evidence from epidemiological data and clinical trials indicates that aggressive lipid modification, especially low-density lipoprotein reduction, is associated with reduced cardiovascular events. Numerous studies utilizing various combinations of cholesterol-lowering agents including statin/fibrate, statin/niacin, statin/bile acid resin, and statin/ezetimibe have demonstrated significant changes in the lipid profile with acceptable safety. Long-term trials of combination therapy evaluating clinical outcomes or surrogate markers of cardiovascular disease, while limited, are promising.
Conclusion: Combining lipid-altering agents results in additional improvements in lipoproteins and has the potential to further reduce cardiovascular events beyond that of monotherapy.
Keywords: combination therapy, coronary heart disease, hypercholesterolemia, lipid-lowering, low-density lipoprotein, statins

Introduction

Coronary heart disease (CHD) continues to be a leading cause of morbidity and mortality in the United States, affecting an estimated 13 million individuals or approximately 7% of the total population (AHA 2005). One of every five deaths was attributed to CHD in 2002. Estimated total costs for CHD in 2005 exceeded $142 billion. Elevated low-density lipoprotein cholesterol (LDL-C) is a major modifiable risk factor for CHD. The National Cholesterol Education Program (NCEP) Adult Treatment Panel's third report (ATP-III) focuses on evidence from clinical trials demonstrating the importance of LDL-C reduction to reduce the risk of CHD (ATP-III 2002). The initial ATP-III report defined target goals for LDL-C based on CHD risk. Lowering LDL-C to less than 100 mg/dL was recommended for those with known CHD or CHD risk equivalents such as diabetes. Since the release of ATP-III in 2001, additional clinical trials have suggested that further reduction of LDL-C to lower targets may provide additional risk reduction. Based on this new evidence, NCEP published the ATP-III Update in 2004, proposing modifications to the guidelines (Grundy et al 2004). For individuals considered to be at very high-risk, a new target LDL-C goal of < 70 mg/dL reflects the potential added benefits of

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aggressive lipid-lowering. Additionally, the document suggested a minimum LDL-C reduction of 30%–40% for those considered to be at moderate to very high risk for CHD, a goal that is not always achievable with monotherapy (Grundy et al 2004). A recent study of patients with dyslipidemia who were risk-stratified based on NCEP guidelines found that less than 60% of patients with CHD or CHD risk equivalents achieved NCEP goals for LDL-C with monotherapy (Davidson et al 2005). To overcome the limited efficacy of single agents and avoid increased toxicity, which is often dose-related, the concept of combination drug therapy has emerged as a potential strategy for the management of dyslipidemia (Worz and Bottorff 2003; Davidson and Toth 2004). However, the use of combined lipid-altering agents is not without safety concerns, especially with certain combinations that warrant close monitoring and patient education. Two combination drug products have received Food and Drug Administration (FDA) approval: Advicor® (lovastatin and extended-release [ER] niacin, Kos Pharmaceuticals, Miami, FL, USA) and Vytorin® (ezetimibe and simvastatin, Merck/Schering-Plough Pharmaceuticals, New Jersey, USA).

The benefits of combination drug therapy are well established for various other cardiovascular risk factors, with hypertension representing perhaps the clearest example. Monotherapy has been shown to be ineffective in approximately 50% of unselected hypertension patients and the majority of those with more advanced stages of hypertension (Materson et al 1993). The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends combination therapy as an option for stage I hypertension when monotherapy is inadequate and also for most stage 2 patients (Chobanian et al 2003).

Similarly, combination therapy has been shown to be advantageous in type 2 diabetes mellitus (DM) resulting in better glycemic control and fewer complications (Bell and Ovalle 2004; Strowig et al 2004).

For patients with dyslipidemia, hesitancy to use combination therapy has centered on concerns that the risk of adverse effects, particularly rhabdomyolysis (Ballantyne, Corsini, et al 2003; Graham et al 2004) could be increased. Theoretically, by combining drugs that target different components of lipid metabolism, greater lipid-lowering can be achieved while still limiting toxicity. This article will review the current literature on combined drug treatment for LDL-C lowering and discuss current implications for practice.

Pharmacologic agents

Potential benefits and risks with combination lipid-altering therapy stem largely from the pharmacology of individual drugs. We will briefly review individual agents that may be considered for combination regimens.

Niacin (nicotinic acid)

Niacin or vitamin B3 has been utilized in high doses as a lipid-modifying agent for 50 years (Altschul et al 1955). This agent favorably alters all major lipoproteins (ie, high-density lipoprotein cholesterol (HDL-C), LDL-C, and triglycerides) and is one of the only cholesterol-lowering drugs to significantly reduce lipoprotein (a) (Lp[a]). Niacin is available as a nutritional supplement in numerous formulations (ie, crystalline immediate-release [IR] and sustained-release [SR]) as well as by prescription as ER (Niaspan®, Kos Pharmaceuticals, Miami, FL, USA). Despite the beneficial impact of niacin on the lipid profile, use is often limited by intolerable side effects.

Although the pharmacology of niacin is not fully understood, the primary effect is inhibition of the synthesis and secretion of hepatic very low-density lipoprotein cholesterol (VLDL-C) which reduces triglycerides and LDL-C (Grundy et al 1981; Knopp et al 1985). Additionally, niacin is the best available agent for raising HDL-C (Knopp et al 1985). This effect is produced by slowing the catabolism of the predominant HDL-C apolipoprotein (apoprotein A-1) and reducing triglycerides (Shepherd et al 1979). Lastly, niacin has demonstrated the capacity to cause a shift in the size of LDL-C (Backes and Gibson 2005), converting the more atherogenic small-dense LDL-C (sdLDL-C) particles to the larger, more buoyant LDL-C.

In high doses, niacin can significantly alter HDL-C, LDL-C, triglycerides, and Lp(a) in a dose-dependent manner. While these lipoprotein effects vary with the formulation utilized (ie, IR, SR, or ER), niacin typically reduces LDL-C (5%–25%), triglycerides (20%–50%) and Lp(a) (30%–39%) while increasing HDL-C (15%–35%) (ATP-III 2002). The IR formulation is generally more effective at raising HDL-C and reducing triglycerides compared with the SR formulation (McKenney 2004). Niacin dosing varies with the product used, but doses of up to 4000 mg daily of the IR and 2000 mg daily of the ER have been studied.

The major limitation of niacin is its side-effect profile. The predominant adverse effect is a prostaglandin-mediated cutaneous flushing that results in discontinuation rates of

5%–50% (Berge 1961; McKenney et al 1994; Guyton et al 1998) depending on the dose and formulation. Flushing can be lessened by aspirin administration (325 mg) 30 minutes prior to the niacin dose or by utilizing a SR or ER product. The SR products cause less flushing, but are associated with hepatotoxicity, especially at doses greater than 2000 mg per day (Knopp et al 1985; McKenney et al 1994). The ER niacin, Niaspan, which has intermediate absorption characteristics compared with the IR and SR, was developed to maintain lipid profile effects comparable to the IR while causing flushing rates similar to the SR. Niacin has also been associated with metabolic effects. Minor blood glucose elevations (eg, 5%) are generally transient, however, some patients may experience larger and more persistent increases (Elam et al 2000). Typically doses < 1500 mg daily have little effect on blood glucose (Elam et al 2000). Because niacin competes with uric acid for renal elimination, mild elevations in uric acid levels have been noted, and niacin should be used with caution in those predisposed to gout. Approximately 10%–30% of patients complain of gastrointestinal (GI) symptoms (eg, nausea, abdominal pain) with niacin; effects are more common with the SR formulation and may be minimized with concomitant food administration. However, those with a previous history of peptic ulcer disease (PUD) should use niacin with caution, and use is contraindicated with active PUD.

Bile acid sequestrants

Once considered first line agents for LDL-C reduction, bile acid sequestrants (BAS) are now primarily utilized as adjunctive therapy with newer agents (eg, statins) for additional LDL-C reduction (PMSG 1993). This class includes cholestyramine, colestipol (both approved in the 1970s), and colesevelam, which has been available since 2000. While the BAS are nonabsorbable resins that generally possess a favorable safety profile, the older agents are associated with drug interactions and numerous GI complaints which limit use.

Bile acid sequestrants bind bile acids in the intestine, interrupting enterohepatic recirculation, resulting in increased fecal bile acid excretion. This stimulates LDL-C receptor activity leading to an increase in uptake of LDL-C from the systemic circulation, thereby reducing LDL-C levels (Grundy et al 1971; Shepherd et al 1980). Because of this reduction in LDL-C, hepatic cholesterol synthesis increases secretion of VLDL-C with a consequential increase in triglycerides and a limited effect on LDL-C levels. The primary use for these agents is therefore LDL-C reduction. Caution should be exercised for those with hypertriglyceridemia since these agents may worsen this disorder (Nestel and Grundy 1976).

The expected reduction in LDL-C with BAS ranges from 15%–30%, with minimal increases in HDL-C and potential increases in triglycerides among those with borderline or elevated levels (ATP-III 2002). Higher doses are required to achieve the upper range of LDL-C reduction, with the strong possibility of nonadherence secondary to poor palatability or side effects. Tolerability is one of the major barriers to BAS use. Common side effects include bloating, constipation, flatulence, epigastric fullness, and nausea (Steiner et al 1991) with discontinuations rates exceeding 40% in clinical practice after one year (Andrade et al 1995). Undesirable formulations represent another barrier. Cholestyramine and colestipol are commonly prescribed as powders or granules which may be mixed with juice to improve palatability. Colesevelam is available in tablet form, but requires six tablets daily to achieve maximum LDL-C reduction. Lastly, the older BAS are associated with numerous potential drug interactions. In addition to binding bile acids, these BAS can sequester many commonly used medications (eg, diuretics, digoxin, amiodarone, thyroxine, acetaminophen, warfarin) (Steiner et al 1991). Concomitant medications should be taken 1 hour before or 4 hours after colestipol or cholestyramine. Because colesevelam has more specificity for bile acids, drug interactions are less of a concern (Aldridge and Ito 2001). Despite potential disadvantages, BAS are still useful in clinical practice particularly for patients with hepatic impairment, those intolerant of statins, children, patients of childbearing potential, and individuals requiring combination therapy to achieve greater LDL-C reduction.

Fibric acid derivatives (fibrates)

While the effects of fibric acid derivatives on the lipid profile primarily involve triglyceride reduction, significant increases in HDL-C, varying effects on LDL-C levels, and improvement in LDL-C particle size have also been observed (Vakkilainen et al 2003). Commonly prescribed fibrates in the United States are gemfibrozil and fenofibrate, and bezafibrate and ciprofibrate are available in Europe. With the rapid increase in patients with mixed dyslipidemia (eg, DM and metabolic syndrome), fibrates may play a greater role in the future for managing these lipid disorders.

The complex mechanism of action for fibrates involves numerous steps in the metabolism of lipoproteins. These agents primarily affect peroxisome proliferator-activated

receptor-alpha (PPAR-α) and lipoprotein lipase (LPL). Stimulation of LPL increases lipolysis, resulting in a clearance of triglyceride-rich lipoproteins (Grundy and Vega 1987). The HDL-C increase produced by fibrates is due not only to the reduction in triglycerides, but also secondary to stimulation of PPAR-α and its effect on increasing synthesis of apolipoprotein A particles (Fruchart et al 1998). Overall, fibrates reduce triglycerides by up to 50%, increase HDL-C 10%–20%, and provide modest reductions in total cholesterol (TC) (ATP-III 2002). The effect of fibrates on LDL-C is dependent on the type of dyslipidemia. Individuals with elevated LDL-C (Type IIa) can experience a moderate reduction in LDL-C levels (10%–20%) with fibrate therapy. For patients with a mixed dyslipidemia pattern (Type IIb), LDL-C effects are less predictable ranging from a modest reduction to possible increased levels. Among those with hypertriglyceridemia (Types IV and V) increases in LDL-C are commonly noted (Knopp et al 1987). In addition, some data suggest fenofibrate and bezafibrate possess better LDL-C-lowering ability compared with gemfibrozil and clofibrate (Blane et al 1986). Similar to niacin, fibrates have been shown to normalize LDL-C composition, shifting from sdLDL-C to the larger and more buoyant particles (Vakkilainen et al 2003; Backes and Gibson 2005), which appears to account for some of the antiatherogenic effects of the class (Vakkilainen et al 2003).

Safety was a concern initially with this class due to the World Health Organization (WHO) trial of clofibrate, which found increased nonCHD mortality secondary to biliary tract disease and cancer (CPI 1978). However, other long-term studies with clofibrate (Anonymous 1975) and other fibrates (Frick et al 1987; DAIS 2001) have not demonstrated an increased risk. While fibrates are generally well tolerated, potential side effects include GI complaints (eg, nausea, abdominal pain), myalgias, increases in serum creatinine levels (fenofibrate), cholelithiasis, and elevated transaminase levels (Brown 1987; Hottelart et al 2002).

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins)

The statins have emerged as the cornerstone for LDL-C lowering since the first agent, lovastatin, was approved in 1987. Five other statins are currently available, including atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. Cerivastatin was approved in 1997 and was voluntarily withdrawn from the market in 2001 because of a significantly higher rate of rhabdomyolysis compared with the other statins (Staffa et al 2002). Nevertheless, the statins' overall safety profile is excellent and numerous clinical trials have indicated significant reductions in cardiovascular events and total mortality.

Several mechanisms account for the pharmacological effects of statins. The two primary modes of activity are competitively inhibiting hydroxymethylglutaryl-coenzyme A reductase (HMG-CoA reductase) (Davignon et al 1992), a precursor to the formation of cholesterol, and upregulating the LDL-C-receptor (Bilheimer et al 1983; Arad et al 1992; Davignon et al 1992), secondary to the reduction in hepatic cholesterol synthesis. In addition to marked LDL-C reduction (20%–55%), statins also moderately reduce triglycerides (8%–30%), via decreased hepatic cholesterol synthesis, and produce minor increases in HDL-C (2%–10%) (Jones et al 2003). It has also been demonstrated that statins possess additional antiatherogenic activity beyond their lipoprotein effects including improved endothelial function (Asberg et al 2001), antiinflammatory properties (Backes et al 2004), and antithrombotic effects (Rosenson and Tangney 1998).

The statins are well tolerated by most patients with a low incidence of adverse effects. The overall discontinuation rate is reported to be <4% (Hsu et al 1995) secondary to such common adverse effects as myalgias, headache, and mild GI complaints. The most concerning adverse events are myopathy and elevation in transaminase levels, both of which are dose-dependent (Ballantyne, Corsini, et al 2003). The incidence of transaminase levels exceeding three times the upper limit of normal occurs in <3% of patients and often improves with a reduction in dosage (Bradford et al 1991; Hsu et al 1995). Liver failure secondary to statins has rarely been reported (Pederson and Tobert 1996). Although the occurrence of nonspecific muscle and joint soreness among patients in placebo-controlled trials (5%) is common, the incidence of myalgias is similar among those receiving placebo or active drug (Pasternak et al 2002). The incidence of statins causing myositis (0.2%) is low (Bradford et al 1991), and even less common for fatal rhabdomyolysis (less than 1 death/million prescriptions) (Staffa et al 2002). Despite these reassuring statistics, practitioners should be cognizant of potential adverse effects, especially an increased risk of muscle toxicity among patients receiving higher statin doses and in combination with other lipid-lowering therapy (eg, fibrates).

Cholesterol absorption inhibitor (ezetimibe)

Ezetimibe, a novel medication, is the most recent addition to the class of cholesterol-lowering medications. This agent primarily targets LDL-C and can be used as monotherapy or as an add-on to statin therapy. Ezetimibe appears to have an excellent safety profile with a low incidence of adverse effects and drug interactions.

Ezetimibe inhibits the absorption of intestinal cholesterol from dietary and biliary sources by approximately 50% (Nutescu and Shapiro 2003), without altering the absorption of fat-soluble vitamins, bile acids, or triglycerides (Gagne et al 2002). This ultimately results in approximately a 20% reduction in LDL-C with minimal changes in HDL-C or triglycerides (Bays et al 2001). When coadministered with a statin, ezetimibe has produced an additional 12%–25% reduction in LDL-C (Figure 1), (Gagne et al 2002; Ballantyne, Houri, et al 2003; Bays et al 2004; Masana et al 2005) and further reductions in high-sensitivity C-reactive protein (CRP) (Ballantyne, Houri, et al 2003) compared with statin monotherapy. Additional potential benefits of ezetimibe include the reduction in intestinal uptake of plant sterols (von Bergmann et al 2005) – a possible contributor to atherosclerotic plaque (Miettinen et al 2005).

An advantage of ezetimibe is its safety profile, which is similar to that of placebo (Bays et al 2001; Brown 2001; Stein 2002). Ezetimibe is primarily metabolized in the intestine and liver, but bypasses the cytochrome P450 system, resulting in no clinically relevant drug interactions (Bauer et al 2001; Keung et al 2001; Kosoglou, Guillaume, et al 2001; Kosoglou, Meyer, et al 2001; Statkevich et al 2001). Ezetimibe is available as a 10 mg tablet and also in a combination formulation with varying simvastatin dosages (ezetimibe 10 mg/simvastatin 10 mg–80 mg) (Bays et al 2004). All dosage forms are administered once daily. Ezetimibe provides a needed option for patients requiring modest monotherapy for LDL-C reduction or further LDL-C reduction with combination therapy, and those intolerant of other lipid-lowering drugs or at risk for drug interactions.

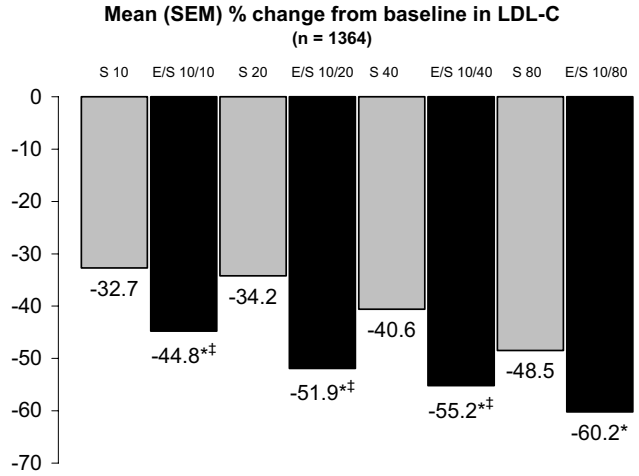

Figure 1 Percent change from baseline in low-density lipoprotein cholesterol (LDL-C) at study end point (12 weeks). * $p < 0.001$ for E/S versus same-dose S; ‡ $p < 0.001$ for E/S versus next highest dose of S. Adapted from Bays et al 2004.
Abbreviations: E, ezetimibe; LDL-C, low-density lipoprotein cholesterol; S, simvastatin; SEM, standard error of the mean.

The rationale for combination therapy

Long-term statin clinical trials have demonstrated significant reductions in cardiovascular death (22%) and total mortality (13%) (Studer et al 2005). While impressive, the findings also demonstrate that despite marked reductions in LDL-C, many patients continue to experience vascular events. Two possible strategies for further reducing events are additional lowering of LDL-C and addressing other abnormalities of the major lipoproteins (ie, low HDL-C, elevated triglycerides).

ATP-III Update

The ATP-III Update was published in the summer of 2004 following the publication of five statin trials (Grundy et al 2004). This document addresses the options of both further lowering LDL-C and targeting other lipoproteins in high-risk persons. The report indicates that a more aggressive LDL-C therapeutic goal of < 70 mg/dL may be appropriate in individuals considered to be very high-risk (eg, CHD, acute coronary syndrome [ACS], CHD-risk equivalent), whose previous recommended LDL-C goal was < 100 mg/dL. While some patients may be able to achieve this goal with monotherapy, many will require adjunctive LDL-C lowering therapy. The ATP-III Update additionally states that the combination of a statin/fibrate or statin/niacin may be considered for elevated triglycerides or low HDL-C in these populations.

The Heart Protection Study

The Heart Protection Study (HPS) was a major contributor to the body of evidence that supports the ATP-III Update. A key point from the HPS was the finding that patients benefit

from statin therapy regardless of the baseline LDL-C (HPSCG 2002). In this trial, patients at high risk for a cardiovascular event were randomized to simvastatin (40 mg daily), or placebo for five years. Event reduction was similar among those receiving statin therapy regardless of whether the baseline LDL-C was < 100 mg/dL or > 135 mg/dL. For individuals with baseline LDL-C levels of < 100 mg/dL, simvastatin further reduced LDL-C to a mean level of 65 mg/dL, well below the previously recommended ATP-III goal of < 100 mg/dL.

Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 and Treating to New Targets trials

While the HPS provided many answers, it did not address whether larger LDL-C reductions resulted in greater event reduction. Two major studies designed to assess this were the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) and the Treating to New Targets (TNT) trials. In the PROVE IT-TIMI 22 study, patients with acute coronary syndrome (ACS) were randomized to moderate (pravastatin 40 mg/day) or intensive (atorvastatin 80 mg/day) lipid-lowering therapy with a mean follow-up of 24 months (Cannon et al 2004). The more intensive atorvastatin therapy resulted in a significant reduction of 16% ($p = 0.005$) in the composite endpoint consisting of all-cause mortality, unstable angina, stroke, myocardial infarction (MI), and revascularization procedures compared with pravastatin. Atorvastatin achieved a mean treatment LDL-C of 62 mg/dL compared with 95 mg/dL with pravastatin. These findings were further reinforced in the TNT trial in patients with stable CHD (LaRosa et al 2005). The TNT trial randomized patients to low (10 mg/day) or high-dose atorvastatin (80 mg/day). A significant 22% ($p < 0.001$) reduction in the composite endpoint of major cardiovascular events was achieved with the high-dose therapy after a median follow-up of nearly 5 years. Despite the substantial reduction in the composite endpoint, overall mortality was not significantly different among the treatment groups. Mean LDL-C levels with the high-dose atorvastatin were 77 mg/dL compared with 101 mg/dL with low-dose therapy. This trial provides additional evidence for the benefit of reducing LDL-C levels considerably beyond the previous threshold of < 100 mg/dL for those with CHD.

Aggressively treating elevated triglycerides and low HDL-C may also reduce cardiovascular events. Epidemiological data indicate that every 1 mg/dL increase in HDL-C is associated with a reduction in cardiac events of 2%–4%, independent of LDL-C (Gordon et al 1989). Low HDL-C remains a predictor of future events in subanalyses of statin trials. Subjects randomized to statins with low HDL-C often experienced higher CHD event rates compared with those with higher HDL-C (Sacks et al 2000). Hypertriglyceridemia is not only associated with numerous risk factors for CHD (eg, low HDL-C, impaired fasting glucose, elevated fibrinogen), but is considered by the ATP-III report to be an independent risk factor for atherosclerosis (ATP-III 2002).

The Veterans Affairs HDL-C Intervention Trial

Although the major focus for the past 10 years has been LDL-C reduction with statins, many other trials have produced impressive results by targeting HDL-C or triglycerides. The Veterans Affairs HDL-C Intervention Trial (VA-HIT) randomized men with CHD to gemfibrozil (600 mg twice daily) or placebo for 5 years (Rubins et al 1999). Gemfibrozil was specifically chosen because of its neutral effect on LDL-C levels. The primary lipid abnormality among the patients was a low HDL-C, with baseline HDL-C, LDL-C and triglycerides values of 32 mg/dL, 111 mg/dL, and 161 mg/dL, respectively. Gemfibrozil significantly increased HDL-C by 6% ($p < 0.001$) and reduced triglycerides by 31% ($p < 0.001$), with no effect on LDL-C. Treatment resulted in a 22% ($p = 0.006$) reduction in the composite endpoint of CHD death and nonfatal MI. The VA-HIT was the first randomized controlled trial utilizing lipid-altering therapy to demonstrate a reduction in CHD events without lowering LDL-C.

Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2 study

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2 trial evaluated the addition of niacin to statin therapy among secondary prevention patients with low HDL-C. Atherosclerosis progression was measured by carotid intimamedia thickness (CIMT) (Taylor et al 2004), a surrogate marker for cardiovascular events. Patients already on statin therapy were randomized to ER niacin (1000 mg/day) or placebo. Carotid intimamedia

thickness was measured at baseline and 12 months. The primary change in the lipid profile with ER niacin was a 21% increase in HDL-C ($p = 0.003$). Patients in the placebo arm showed a significant increase in CIMT after 12 months (0.044 mm ± 0.100 mm; $p < 0.001$) while the niacin group experienced no change (0.014 mm ± 0.104 mm; $p = 0.23$). The authors concluded that the addition of niacin to statin therapy among patients with low HDL-C and CHD slowed the progression of atherosclerosis.

HDL-C-Atherosclerosis Treatment Study

A small trial designed to evaluate the benefits of significantly improving HDL-C and LDL-C was the HDL-C-Atherosclerosis Treatment Study (HATS) (Brown et al 2001). Patients with a previous history of CHD and low HDL-C ($n = 160$) were randomized to a combination of simvastatin and niacin or placebo for three years. The treatment group experienced marked changes in HDL-C (+26%, $p < 0.001$) and LDL-C (–42%, $p < 0.001$) and also demonstrated significant angiographic regression (−0.4%, $p < 0.001$) from baseline. Compared with placebo, those receiving simvastatin and niacin experienced a 90% reduction ($p = 0.03$) in clinical events (ie, CHD death, MI, stroke, revascularization procedure, worsening ischemic symptoms). Additional randomized controlled trials with more subjects are required to confirm these findings.

No large trials have adequately evaluated the clinical outcomes of combined statin and fibrate therapy. The Lipids in Diabetes Study (LDS) using a cerivastatin and fenofibrate regimen was halted early because of the cerivastatin withdrawal. The Action to Control Cardiovascular Risk in Diabetes trial (ACCORD), sponsored by the National Institute of Health (NIH), will evaluate clinical outcomes with this combination. Subjects with a previous history of DM will be randomized to statin monotherapy or combined statin/fibrate therapy. The ACCORD trial, expected to be completed in 2009, should provide valuable long-term safety information on combination therapy and determine whether the addition of a fibrate provides further reduction in clinical events.

A major health concern worldwide is the increasing prevalence of the metabolic syndrome and DM (ATP-III 2002; Wild et al 2004). The typical lipid pattern among these populations is mixed dyslipidemia with a predominance of the more atherogenic sdLDL-C. Angiographic studies have demonstrated sdLDL-C to be a key factor in atherosclerotic progression (Watts et al 1993; Haskell et al 1994) as well as increasing CHD risk by up to sevenfold (Griffin et al 1994; Lamarche et al 1997). In order to meet all lipoprotein goals (ie, LDL-C, HDL-C, triglycerides) and normalize LDL-C distribution among these high-risk populations, the combined use of lipid-altering agents will likely be required.

In summary, the results from recent statin trials suggest that high-risk patients benefit from statin therapy regardless of baseline LDL-C, and that greater LDL-C reductions for those with CHD appear to further reduce cardiovascular events. Studies evaluating long-term outcomes from combination therapy are limited, however, smaller studies and epidemiological findings suggest substantial benefit. The results of these studies will likely increase the use of higher statin doses and also combination therapy to achieve greater LDL-C reductions and improvements in elevated triglycerides, low HDL-C, and LDL-C distribution.

Choosing the optimal regimen

Substantial changes in lipoproteins are seen when combining lipid-altering agents (Table 1). Interpretation is limited, however, because the data are derived from multiple studies using different statins with varying degrees of potency.

A controversy in the lipid community is whether to increase the dose of a statin or add adjunctive therapy for further LDL-C reduction. Proponents of increasing the statin dose argue that keeping the regimen simple will improve adherence, be more cost-effective, and that adjunctive agents may not provide additional pleiotropic effects (eg, CRP reduction) comparable to higher statin doses. Conversely, others argue that doubling the statin dose may result in only a 6% further reduction in LDL-C with increased side effect potential, whereas the addition of ezetimibe or a BAS may result in approximately a 20% reduction in LDL-C. In reality each side of the controversy has valid points. While increasing the statin dose may be the simplest option in certain cases, statins do have dose-dependent side effects particularly when titrated to the highest doses. For example, the incidence rates of myopathy and elevated transaminases increase by approximately 4–5 fold when titrating simvastatin or atorvastatin from 40 mg to 80 mg daily (Davidson 2002). In cases such as this, adding a second agent (ie, ezetimibe, colesevelam) with a different site of action will not only provide more LDL-C reduction but also limit potential side effects.

The use of fixed combination lipid-altering products (ie, ezetimibe/simvastatin and lovastatin/ER niacin) offers potential advantages, and in certain cases, may be

Table 1 Mean lipoprotein changes of various lipid-altering regimens

Regimen	% Change from baseline			
	TC	LDL-C	HDL-C	TG
Statin[a]	−15 to −40	−20 to −55	+2 to +10	−7 to −28
Statin + BAS[b]	−29 to −40	−42 to −56	+4 to +18	−12 to +19
Statin + Niacin[c]	−23 to −31	−29 to −45	+26 to +41	−30 to −42
Statin + Fibrate[d]	−26 to −37	−24 to −50	+14 to +34	−32 to −57
Statin + Ezetimibe[e]	−25 to −49	−39 to −60	+5 to +9	−18 to −40
Statin + BAS + Niacin[f]	−56	−57 to −66	+27 to +32	−45

[a] Jones et al 2003
[b] Malloy et al 1987, Brown et al 1990, Pan et al 1990, Gaw et al 1996, Brown et al 1998, Knapp et al 2001
[c] Stein et al 1996, Guyton et al 1998, Brown et al 2001, Kashyap et al 2002
[d] Athyros et al 1997, Athyros et al 2002, Liamis et al 2002, Derosa et al 2004
[e] Ballantyne, Houri, et al 2003, Melani et al 2003, Ballantyne et al 2005
[f] Malloy et al 1987, Brown et al 1997
Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; BAS, bile acid sequestrant.

preferential to adding a separate second agent or titrating the statin. The attributes of these products compared with statin monotherapy include an overall improved effect on the lipid profile and the possibility of greater cost-effectiveness. These advantages may be especially true when targeting LDL-C with the ezetimibe/simvastatin combination. Numerous studies have demonstrated additional LDL-C reduction when ezetimibe is added to statin therapy (Gagne et al 2002; Melani et al 2003; Ballantyne, Houri, et al 2003; Ballantyne et al 2005; Masana et al 2005). Ballantyne et al (2005) conducted a dose-comparison study of the ezetimibe/simvastatin combination to atorvastatin among 1902 hypercholesterolemic patients. During this 6-week, multicenter, double-blind, parallel-group study, patients not at their ATP-III LDL-C goal were randomized to atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg) or to ezetimibe/simvastatin (10/10 mg, 10/20 mg, 10/40 mg, or 10/80 mg). Ezetimibe/simvastatin therapy resulted in greater reductions compared with atorvastatin when evaluating LDL-C reduction with mean changes across all doses (Table 2). Additionally, ezetimibe/simvastatin produced a significantly greater increase in HDL-C levels and comparable reductions in triglycerides and CRP compared with atorvastatin.

There is less controversy surrounding additional agents for other types of dyslipidemia. Among patients with low HDL-C, attaining the LDL-C goal is the first priority followed by achieving the non-HDL-C goal and maximizing therapeutic lifestyle changes. If HDL-C still remains a concern, therapy with niacin or fibrates may then be considered (ATP-III 2002). Although side effects can limit niacin use, only moderate doses (1000 mg/day) are required to significantly raise HDL-C (24%) while minimizing adverse events, when added to a statin (Wolfe et al 2001). If patients have mixed dyslipidemia, and triglycerides exceed 500 mg/dL, the first objective is to reduce the triglycerides in order to prevent pancreatitis (ATP-III 2002). Many practitioners prefer fibrates for hypertriglyceridemia because of the greater effectiveness, lower incidence of side effects, and lesser need for titration compared with niacin. These individuals may require a statin for LDL-C reduction after the triglycerides are reduced. Additional precautions must be taken with this combination to avoid possible adverse events (see next section).

Table 2 Summary of efficacy results in the modified intention-to-treat population (% change from baseline)

	Atorva 10 mg (n = 235)	EZ/Simva 10/10 mg (n = 230)	Atorva 20 mg (n = 230)	EZ/Simva 10/20 mg (n = 233)	Atorva 40 mg (n = 232)	EZ/Simva 10/40 mg (n = 236)	Atorva 80 mg (n = 230)	EZ/Simva 10/80 mg (n = 224)	All Atorva (n = 927)	All EZ/Simva (n = 923)
LDL-C	−36.1	−47.1*	−43.7	−50.6*	−48.3	−57.4*	−52.9	−58.6*	−45.3	−53.4*
HDL-C	6.9	7.7	5.1	7.2	3.8	9.0*	1.4	7.6*	4.3	7.9*
TC	−21.3	−25.5*	−24.8	−25.4*	−23.6	−27.3*	−32.1	−30.8	−25.5	−27.4*
TG	−21.3	−25.5	−24.8	−25.4	−23.6	−27.3	−32.1	−30.8	−25.5	−27.4

* $p < 0.001$ for between-treatment difference with same dose of atorvastatin. Adapted from Ballantyne et al 2005
Abbreviations: Atorva, atorvastatin; EZ/Simva, ezetimibe/simvastatin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

Problems and pitfalls

The potential for increased adverse events must be considered with the use of more aggressive lipid-altering therapy, including higher statin doses and combination therapy. The risk of additional serious adverse events appears to be extremely low when using agents with excellent safety profiles (ie, cholesterol absorption inhibitor, BAS) in combination with statins (McKenney 2002). However, cases of rhabdomyolysis with ezetimibe alone (Merck/Schering-Plough 2005) or in combination with other agents associated with muscle toxicity (eg, statins) have been reported (Fux et al 2004). Additionally, fibrate monotherapy is associated with a risk for muscle toxicity similar to that of statin monotherapy (Pasternak et al 2002). As a result, concerns regarding an increased incidence of adverse effects are valid and must be monitored appropriately when using statins in combination with other agents (ie, ezetimibe, fibrates, niacin).

Myopathy

Cerivastatin was voluntarily withdrawn from the market in August 2001 because of 31 deaths related to severe rhabdomyolysis (Pasternak et al 2002). Staffa et al (2002) reported fatal rhabdomyolysis to be 16–80 times more frequent with cerivastatin compared with other statins. Later reports from the manufacturer (Bayer AG) indicated that as many as 100 deaths were related to the use of cerivastatin. Twelve of the original cases involved concomitant therapy with the fibrate gemfibrozil. Pharmacokinetic studies evaluating gemfibrozil administered with various statins revealed an increase in serum concentrations of all statins studied, (ie, cerivastatin, pravastatin, rosuvastatin, simvastatin) except fluvastatin (Spence et al 1995; Backman et al 2000, 2002; Pan et al 2000; Kyrklund et al 2001; Davidson 2002; Martin et al 2003; Bergman et al 2004). A recent publication utilizing reports from the FDA from January 1998 to March 2002 showed that the combined use of gemfibrozil and a statin resulted in 590 cases of rhabdomyolysis compared with 16 with fenofibrate and statin therapy (Jones and Davidson 2005). The majority of cases with both gemfibrozil (533) and fenofibrate (14) also involved cerivastatin. When considering the number of prescriptions dispensed during that timeframe, this indicates an approximate 20-fold increase with the gemfibrozil/statin regimen compared with the fenofibrate/statin combination. It should be noted that these findings represent only reported event rates rather than the actual incidence rates. The findings nevertheless strongly suggest a greater rate of rhabdomyolysis with cerivastatin and also the combined use of statin therapy with gemfibrozil. When combining a statin with niacin the risk for myopathy appears to be the same as statin monotherapy (Davidson 2002). No clinically significant drug interactions exist between niacin and statins, and case reports of myopathy involving both agents are extremely limited.

The above information clearly points out the risks, particularly of myopathy, that can be associated with combination therapy. However, the risk of severe myopathy can be greatly reduced if appropriate measures are taken. The American College of Cardiology along with the American Heart Association and the National Heart, Lung and Blood Institute published a clinical advisory shortly after the cerivastatin withdrawal, identifying concomitant medications that may predispose patients to statin-induced myopathy (Table 3).

Hepatotoxicity

The most serious adverse event that occurs with niacin is hepatotoxicity. The frequency is dependent on the dose and formulation utilized. Serious liver toxicity has been reported with the SR formulation in up to 50% of patients receiving ≥2000 mg/day (McKenney et al 1994). The incidence with the IR (3%) (Guyton et al 1998) and ER (1%) (Kashyap et al 2000) formulations is much lower and appears not to be increased with the addition of a statin. Fibrate monotherapy has also been associated with abnormalities in liver function and while it is likely that the incidence is higher with combined statin therapy, data are limited.

Patient focus

Nonadherence

Despite ample evidence from numerous clinical trials and meta-analyses demonstrating that lipid-lowering therapy can

Table 3 Agents increasing risk for statin-associated myopathy

Specific concomitant medications as listed below:
Fibrates (especially gemfibrozil)
Nicotinic acid (rarely)
Cyclosporine
Itraconazole and ketoconazole
Erythromycin and clarithromycin
HIV protease inhibitors
Nefazodone (antidepressant)
Verapamil
Amiodarone

Adapted from Pasternak et al 2002
Abbreviations: HIV, human immunodeficiency virus.

reduce cardiovascular morbidity and mortality (Anonymous 1984; Frick et al 1987; Anonymous 1994; Holme 1995; Furberg 1994; HPSCG 2002; Shepherd et al 2002; Sever et al 2003; Cannon et al 2004), adherence to prescribed therapy is generally poor. For example, in a 5-year, double-blind trial of 4081 dyslipidemic middle-aged men, researchers found that only 36% of men in the active treatment group (gemfibrozil) took more than 90% of the prescribed dose, and adherence declined over time (Maenpaa et al 1992). Long-term compliance is essential because maximal reductions in cardiovascular disease may require 1.5 years of continuous therapy or more (Anonymous 1994; Sacks 2000). However, in the West of Scotland Study, the cumulative rates of withdrawal from pravastatin were 14.9% during the first year and 29.6% at year five (Shepherd et al 1995). While surveys in clinical settings often report that many patients fail to achieve target lipid levels (Pearson 2000; Pearson et al 2000), a very recent study indicates the frequency of achieving lipid goals is improving (Davidson et al 2005).

As outlined by LaRosa and LaRosa (2000), patient noncompliance can be manifested in many ways including outright refusal, taking incorrect doses, forgetting or skipping doses for several days, compliance only before physician visits, and prescriber concern with utilizing the highest statin doses. Various reasons cited for noncompliance include lipid-lowering benefits not compelling enough to change behavior (Horne and Weinman 1999), fear or intolerance of adverse effects, and management difficulties associated with multidrug regimens (Luepker 1993). Other social, cultural, and economic factors reported to be significantly associated with poorer compliance with lipid-lowering medications include unmarried status, gender, lack of insurance, depression, disease state, lack of knowledge about the disease process, cost, and patient–physician relationship (Insull 1997; Maviglia et al 2001; Kaplan et al 2004). Convincing patients of the benefits of primary prevention may be more difficult than secondary prevention because patients are typically asymptomatic and potential harmful effects may be perceived as being far in the future.

Enhancing adherence

For many dyslipidemic patients who cannot achieve LDL-C goals with monotherapy, combination drug therapy has been recommended (Davidson and Toth 2004). Strategies to enhance compliance with lipid-lowering combination therapy can be gained from a recently published study among patients with hypertension and dyslipidemia. Investigators examined the patterns and predictors of adherence with concomitant therapy among 8406 enrollees in a managed-care organization who had been prescribed both antihypertensive (AH) and lipid-lowering (LL) medications within a period of 90 days (Chapman et al 2005). Adherence to both medications declined sharply throughout the study to less than half of patients at 3 months, and one-third at 6 months. After adjustment for age, gender, and other potential predictors, investigators found that patients were more likely to be adherent if they initiated AH and LL therapy on or about the same date, had a history of CHD or congestive heart failure, or took fewer additional medications. The authors suggested that physicians might be able to significantly improve adherence by initiating combination therapy concomitantly and reducing the pill burden. Similarly, ATP-III guidelines recommend simplifying medication regimens, stating that patients are more likely to take once-daily medications and regimens with fewer total drugs.

Several strategies that have been shown to increase patient compliance can be achieved with the use of once daily combination drug products such as ezetimibe/simvastatin (Vytorin) and lovastatin/ER niacin (Advicor). In a recent study, ezetimbe/simvastatin was shown to be a highly efficacious treatment option for hypercholesterolemic patients. The combination was more effective than atorvastatin in lowering LDL-C and provided greater increases in HDL-C at higher dosages (Ballantyne et al 2005). Patient fears about possible adverse effects may be lessened by the finding that the product was well tolerated with a low incidence of adverse effects. Similarly, the lovastatin and ER niacin combination product effectively reduces TC, LDL-C, triglycerides, apo B, Lp(a), increases HDL-C, and has a low incidence of flushing, myopathies, and hepatotoxicity (Gupta and Ito 2002; Moon and Kashyap 2002; Bays et al 2003). With this product, however, the perceived intolerance of niacin may be a barrier to use.

In addition to patient barriers, poor physician compliance with published guidelines (ie, identifying eligible patients, initiating appropriate treatment regimens, and achieving optimal treatment goals) is well documented. For example, data from the National Registry for Myocardial Infarction indicated that only one third of patients discharged from hospital after an acute MI were placed on lipid-lowering therapy (Fonarow et al 2001). Similarly, a study to determine the effectiveness of current lipid management practices in

patients admitted for peripheral vascular surgery found that only a minority achieved the recommended NCEP goal (Cote et al 2003).

Other significant contributors to the treatment gap include prescribing lipid-lowering therapy at insufficient doses or using drugs with limited effectiveness. Several options for improving lipid management include dose titration, initiating treatment with a higher starting dose (Isaacsohn et al 2003), combination therapy, or prescribing a more efficacious statin (Schuster 2004). Yet, numerous studies have demonstrated that physicians are reluctant to modify or titrate the initially chosen therapy, citing tolerability concerns and possible risks of adverse effects. In the Simvastatin Treats Asians to Target (STATT) study, a multicenter, open label trial in patients with CHD and serum LDL-C levels of 115 mg/dL–180 mg/dL and triglycerides levels of ≤ 400 mg/dL, investigators employed a titrate-to-goal protocol to evaluate the efficacy and tolerability of simvastatin (Chung et al 2001). The dose of simvastatin was titrated from 20 mg/dL to 80 mg/dL to achieve the NCEP LDL-C target of ≤ 100 mg/dL. Overall, titration enabled the majority of these patients to achieve target LDL-C levels of ≤ 100 mg/dL and simvastatin was well tolerated across the dose range with no reports of serious adverse effects.

A number of different strategies have been employed to improve physician compliance with NCEP ATP-III guidelines. For example, automatic prescriptions, whereby physicians allow another team member to change lipid-lowering medications (eg, medical director or pharmacist) (Siskind et al 2000) and microelectronic devices which provide adherence feedback to patients (Schwed et al 1999) have been shown to help physicians comply with NCEP guidelines and possibly increase long-term adherence. Additionally, utilizing physician extenders, such as nurses (DeBusk et al 1994) and pharmacists, (Konzem et al 1997; Bluml et al 2000; Faulkner et al 2000) is associated with increased compliance and achievement of lipid goals. Similarly, ATP-III guidelines advocate the use of case management by nurses and the collaborative care of pharmacists as possible strategies that focus on the health delivery system to improve adherence (ATP-III 2002).

In summary, many patients are not achieving LDL-C levels recommended by NCEP ATP-III guidelines. Several strategies that target patients, providers, and health delivery systems are available to help more patients achieve recommended lipid levels and prevent the development or progression of cardiovascular disease.

Conclusion

The use of combination lipid-altering therapy is becoming more commonplace and will likely continue to increase over time. The recent publication of the ATP-III Update supports the use of combination therapy in high-risk individuals for achieving lipoprotein goals, especially LDL-C reduction. While more aggressive treatment with combination therapy is relatively safe, the potential for adverse events increases and additional monitoring and patient education is crucial. Issues of noncompliance with cholesterol drugs continue to be problematic. Focusing on methods to improve patient adherence, including the use of fixed combinations, will be essential to achieve the maximum benefits from these agents. Finally, the completion of ongoing trials evaluating combination therapy should provide valuable additional evidence on the potential benefits of this emerging treatment strategy.

Disclosure

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