Lipid Management Strategies for Increasingly Ambitious Goals.

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Interests:

1. Metabolic and genetic determinants of insulin resistance.

2. Management of dyslipidemia, diabetes and obesity.

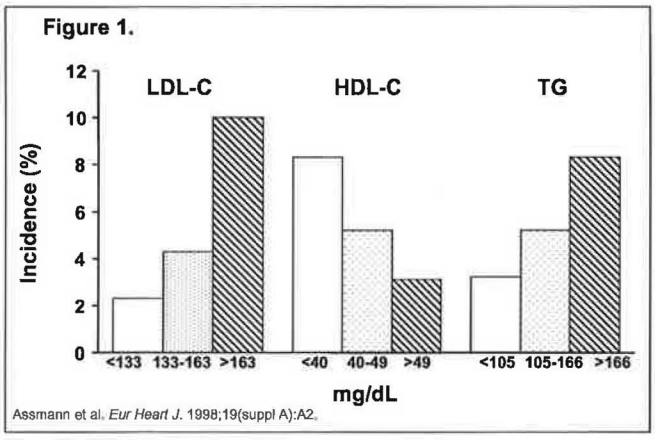
3. Prevention of cardiovascular disease and diabetes.

Introduction.

Over the past three decades, multiple clinical trials have demonstrated the link between cholesterol and cardiovascular disease. In an attempt to synthesize the wealth of data and to integrate the information into clinical practice, several organizations around the world have developed guideline recommendations for the management of dyslipidemia. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) (1) issued a set of recommendations in 2001 incorporating the evidence to date. After 2001, several major clinical trials were completed that affected the recommendations and thus, an update was released in 2004 (2). The update suggested optional more aggressive low-density lipoprotein cholesterol (LDL-c) targets for very high-risk and moderately high-risk patients. These were not official modifications in the recommendations, however, but rather suggested therapeutic options to consider. Since the 2004 update, other clinical trials have been published that add to the wealth of evidence in support for more intense lipid lowering strategies. While serving the goal of reducing CAD morbidity and mortality in our population, these changes in guidelines have also raised the issue of whether intense lipid lowering is realistically attainable in clinical practice. This review will first discuss the latest evidence for intensive lipid lowering goals in certain patient populations and will then focus on practical strategies to effectively implement growingly ambitious goals to lower cholesterol.

Plasma cholesterol, lipoproteins, and cardiovascular risk.

In the US, about half of all men and women have plasma concentrations of LDL>130 mg/dL, a level that is associated with significant CAD risk increase. In several epidemiological studies, other lipid parameters have been shown to predict CAD independent of LDL-C (3-5). Among them, the Munster Heart Study (3) included 17,437 men and 8065 women who were followed for more than 8 years. In that study, the incidence of CAD was positively correlated with increasing plasma concentrations of triglycerides and negatively correlated with increasing plasma concentrations of HDL-cholesterol (Figure 1). More recent epidemiological observations have pointed predictor of risk that would appear to be more useful than LDL-cholesterol. For example, non-HDL-cholesterol, Apolipoprotein B concentrations, and Apo-B/Apo-AI ratios have been proposed to be better predictor of risk and perhaps also better targets of therapy than LDL-C (6-8). This point has recently been emphasized in the Interheart study (9), a large case-control study conducted in 52 Countries, representing every

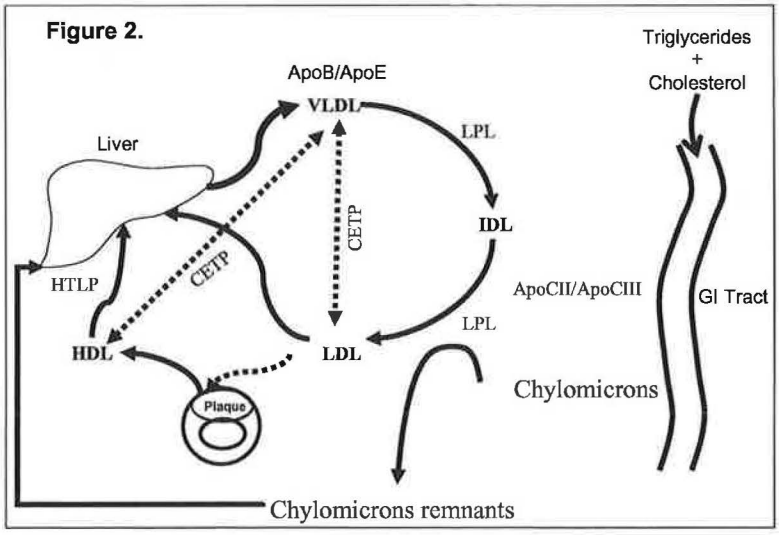


inhabited Continent and included 15152 patients with acute MI and 14820 controls. The study revealed that raised ApoB/ApoAI ratio was associated with more than a three-fold increase in risk for MI worldwide. The findings were similar in all populations studied. The issue of identifying predictors of risk and targets of treatment beyond LDL-C is currently a matter of great discussion and finds its importance in the growing number of patients with obesity, metabolic syndrome and diabetes in our population. These individuals often have average or below average LDL-C despite increased cardiovascular risk. The predominant manifestation of hyperlipidemia in these patients is often that of combined increase in triglycerides and decrease in HDL-C. Therefore, clinicians find it difficult to initiate statin therapy in these patients. Furthermore, intensive lipid lowering is often not pursued in the falsely reassuring accomplishment of LDL-C<100 mg/dL. These patients often have residual increase in non-HDL-C, increase in ApoB, increase in ApoB/ApoAI ratio, and should be intensely managed for adequate reduction of their CAD risk. To understand the reasons underlying these epidemiological observations we will now discuss the main pathways involved in regulation of lipid metabolism and how these pathways are affected by the onset of obesity and type 2 diabetes. Clarifications on the basis of dyslipidemia in patients with obesity, metabolic syndrome and type 2 diabetes will provide the rationale for the need for intensive management of these patients' lipids with focus on non-HDL-C as target of therapy.

Lipoprotein metabolism.

Cholesterol is obtained from 2 sources: diet and "de novo" synthesis in liver and extrahepatic tissues. The total amount of cholesterol that is synthesized or obtained in the diet must be excreted through fecal sterols to maintain stable body cholesterol content. However, a significant portion of cholesterol present in the GI tract from biliary and dietary sources is re-absorbed in the small intestine. Therefore, together with hepatic synthesis, regulation of cholesterol absorption in the GI tract contributes to determine overall cholesterol balance. In the enterocytes, cholesterol esters are assembled with triglycerides and ApoB48 into chylomicrons. Chylomicrons from the lymphatic circulation enter the blood at the junction of jugular and subclavian veins, and during transport to the liver, acquire apoE and ApoC-II. Lipoprotein lipase (LPL), on the surface of capillary endothelial cells hydrolyzes the TG component of chylomicrons to fatty acids, a reaction that requires the presence of apoC. Removal of

Figure 2.



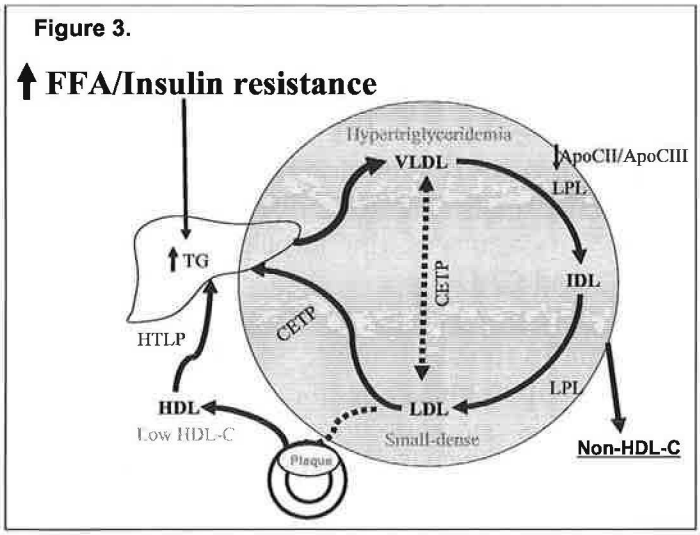
TG creates chylomicron remnants, which are cleared from the circulation by binding of apoE on the chylomicron remnant to the hepatic LDL receptor (LDL-R) or LDL receptor–related protein (LRP). There is also evidence that chylomicron remnants can be taken up by the arterial wall, where they may contribute to atherogenesis.
Cholesterol is transported from extrahepatic tissues to the liver via HDL in a process known as reverse cholesterol transport. ApoA-I derived from the intestine and liver, and cholesterol from extrahepatic tissues (including arterial wall macrophages), are packaged into nascent HDL. The majority of cholesterol export in extrahepatic tissues is mediated by the ABC transporter ABCA1. Cholesterol in nascent HDL is esterified by lecithin-cholesterol acyltransferase (LCAT), resulting in mature HDL. Because cholesterol, but not cholesterol ester, can be transported back to cells, esterification effectively allows a net flux of cholesterol from extrahepatic tissues to HDL and, ultimately, the liver.
Mature HDL can bind to the hepatic SR-BI, which selectively mediates the transfer of cholesterol ester from HDL into the liver. Cholesterol ester is then hydrolyzed to free cholesterol, and there is evidence that this pool of cholesterol from HDL particles is preferentially targeted for excretion into bile. Additionally, random interaction of mature HDL particles with chylomicrons and VLDL/LDL allows the exchange of cholesterol esters for TG, a reaction mediated by the cholesterol ester transfer protein (CETP). TG in HDL are hydrolyzed by hepatic lipase (HL), generating fatty acids (which are transported into the liver cells) and nascent HDL particles. Cholesterol esters transferred from mature HDL to chylomicron and VLDL/LDL are metabolized and taken up by hepatic LDL receptors. Hepatic cholesterol has 2 major fates: Some hepatic cholesterol is reintroduced into the systemic circulation as VLDL particles; VLDL is metabolized to LDL, with most being returned to the liver and some being taken up by extrahepatic tissues. LDL cholesterol can deposit in the intima of the arterial wall through macrophage uptake of modified LDL and foam cell formation. Clearly, ApoB-containing particles (VLDL, IDL and LDL) are all potentially involved in atherogenesis. LDL is usually the particle fraction that contains the highest plasma concentration of cholesterol among ApoB-containing particles and is therefore the best predictor of risk. Conversely, ApoAI-containing particles are responsible for reverse cholesterol transport from the atherosclerotic lesion to the liver and are therefore protective for the plaque progression. Although other mechanisms have been also proposed, the increased concentrations of cholesterol in ApoAI-contaning particle fraction (HDL-C) normally predict reduced cardiovascular risk. This does not apply to all population and does not always substitute a measure of functionality (currently not available for clinical purpose) for HDL-C and CAD risk.

Dylipidemia in insulin resistance and the meaning of non-HDL-cholesterol.

Lipoprotein metabolism is profoundly affected by the onset of insulin resistance. This condition can be defined as a defective biological activity of insulin and predicts CVD, independently of LDL-C and other major cardiovascular risk factors (10). However, the mechanisms linking insulin

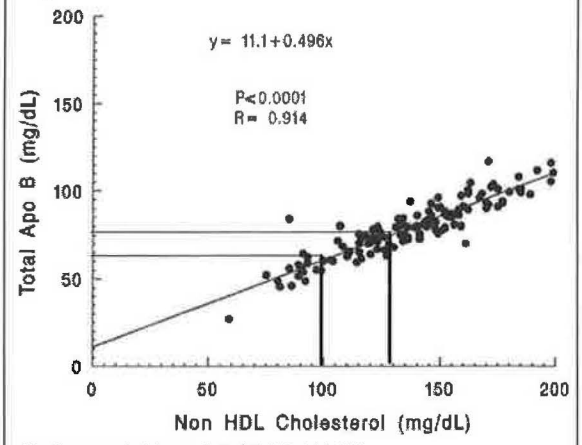
resistance and cardiovascular risk are likely to be found in abnormalities in lipid metabolism. This would create an imbalance between pro-atherogenic particle function (VLDL, IDL, LDL) and anti-atherogenic particle function (HDL). The net effect is a faster atherosclerosis plaque progression and ealier onset of cardiovascular disease. We typically find insulin resistance in patients with obesity (11). However, it is very important to recognize that non-obese patients may also manifest severe insulin resistance and associated metabolic abnormalities in lipid metabolism (12) that could contribute to accelerated atherosclerosis and increased risk for cardiovascular disease. We have carefully studied this problem in a specific population at high risk for cardiovascular disease, the Asian Indian population. Individuals originating from the Indian Subcontinent have 3-5-folds increase in risk for cardiovascular disease (13) and also have susceptibility to insulin resistance and type 2 diabetes (14). We have previously provided evidence of dysfunctional adipose tissue in lean Asian Indians that correlates with excessive insulin resistance in absence of obesity (15). More recently we have provided mechanistic evidence pointing to ENPP1 as a modulator of insulin receptor function and adipogenesis. Increased function of this protein results in defective adipogenesis and increased plasma fatty acids, triglycerides and other associated features of insulin resistance. Genetically induced gain of function appear to predispose individuals to type 2 diabetes and cardiovascular disease, likely as a consequence of reduced ability to new adipocyte formation. Defective adipogenesis and high caloric intake seem to promote dysfunctional adipose tissue. Likely as the result of reduced ability of insulin to promote triglycerides storage in adipose tissue, redistribution of fat in lean tissues, such as skeletal muscle and liver occurs in patients with the metabolic syndrome. Excessive plasma flux to the liver may induce hepatocytes to accumulate triglycerides and increase production of triglycerides-enriched VLDL particles. In addition, insulin resistance is associated with impaired lipoprotein lipase (LPL) activity. The excessive liver output of TG-enriched VLDL particles and the reduced LPL activity will therefore result in a tendency to elevation of plasma triglycerides concentrations in patients with the metabolic syndrome. Likely as a result of increased plasma concentrations of triglycerides, important changes in VLDL, LDL and HDL composition occur in patients with the metabolic syndrome. Specifically, a shift of cholesterol esters is seen from LDL and HDL particles to VLDL, in exchange for triglycerides. This process is mediated by cholesterol ester transfer proteins (CETP)

Figure 3.



and results in an accumulation of TG and loss of cholesterol esters content in both LDL and HDL fractions. These changes explain both the lowering of HDL-C levels and the qualitative shift of the LDL particles towards small-dense LDL. Lower plasma concentrations of HDL-C are also promoted by activation of hepatic lipoprotein lipase associated with insulin resistance. This enzyme contributes to accelerate HDL-C catabolism. Other mechanisms, such as reduced liver production of Apolipoprotein AI and reduced hepatic secretion of nascent HDL may have additional role in the pathogenesis of insulin resistance-related low-HDL-Cholesterol. The changes in lipid metabolism described above explain why patients with obesity, metabolic syndrome and type 2 diabetes typically present with average LDL-C concentrations. It is clear that a profound derangement in lipoprotein metabolism is present in these patients despite the apparent mild changes in plasma lipids concentrations. The shift of cholesterol from the LDL and HDL particles to the VLDL particles makes the non-HDL-C the best predictor of risk in these patients. For the same reasons, non-HDL-C should be considered the goal of treatment. These concepts are included in the ATP III guidelines that suggest using non-HDL-C as a goal of treatment in all patients with plasma triglycerides concentrations above 200 mg/dL. The goal of treatment should be 30 mg above the goal of treatment for LDL-C according to the patient's risk category. As illustrated in figure 4, non-HDL-C is closely related to plasma ApoB concentrations. This is not surprising since each VLDL, IDL or LDL particles, that are all included in the non-HDL-C category, contain only one ApoB particle. It seems that given the approximate equivalence between non-HDL-C and apoB, current guidelines are in line with the epidemiological observations that point to ApoB and ApoB/ApoAI ratio as better predictor of risk when compared to LDL-C. Comparative data between non-HDL-C and apoB levels are not convincingly favoring one versus the other as predictors of cardiovascular risk.

Figure 4.



N. Abate, et al. Atherosclerosis 1993; 104:159

Current clinical guidelines.

Figure 5 summarizes the current evidence in regard to predictor of CAD risk and target of treatment for risk reduction. With some variants, current

Figure 5. Reducing CAD risk in patients with dyslipidemia.

Established

- ⬇ LDL-C and non-HDL-C

Some evidence

- ⬆ HDL-C
- ⬇ Triglycerides

Not established

- ⬇ Lp(a)
- ⬇ Oxidized LDL-C
- ⬇ Small dense LDL
- ⬇ Homocysteine
- ⬇ CRP
- ⬇ Coagulability

clinical guidelines are essentially based on the overall scheme presented in figure 5. The guidelines outlined by the National Cholesterol Education Program Adult Treatment Panel III were recently updated as summarized in Figure 6 (2). In support of the ATP III 2004 update report, five major clinical trials were reviewed. These included the Heart Protection Study (HPS) (16); the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (17); the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial (ALLHAT-LLT) (18); the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-L LA) (19); and the Pravastatin or Atorvastatin Evaluation and Infection – Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial (20). It was determined that these major trials supported the LDL-c goal of less than 100 mg/dl for high- risk patients and the inclusion of patients with diabetes in the high-risk group, as well as confirming the benefits of lipid lowering in older patients. In addition, a new LDL-c goal of less than 70 mg/dl was deemed a therapeutic option in patients determined to belong to a newly defined, very high-risk group. They included established coronary heart disease (CHD) plus multiple major risk factors (especially diabetes); severe and poorly controlled risk factors (especially cigarette smoking); multiple risk factors of the metabolic syndrome; or patients with an acute coronary syndrome. This suggestion was based mostly on the HPS and PROVE-IT trials, which demonstrated further benefit of LDL-c lowering beyond 100 mg/dL, with a median LDL-c of only 62 mg/dl in the intensive arm of PROVE-IT. It was recognized, however, that HPS and PROVE-IT could not be taken as the final word on the benefit of reducing LDL-c to such low levels, and thus the suggestion to reduce the LDL-C goal was left as a therapeutic option instead of a strong recommendation, pending the results of ongoing trials.

Based on the data from ASCOT-LLA and ALLHAT-LLT, a new therapeutic option was also proposed for moderately high-risk patients, which includes patients with two or more risk factors and a 10-year calculated CHD risk of 10–20%. Previously, ATP III did not recommend lipid-lowering therapy for this group of patients in whom LDL-c is less than 130 mg/dl. The 2004 report, however, suggested a LDL-c goal of less than 100 mg/dl for moderately high-risk patients with baseline LDL-c between 100 and 130 mg/dl as a

Figure 6.

Risk Category	LDL-C Goal	Non-HDL-C Goal
High risk: CHD or CHD risk equivalents (10-year risk >20%)	**<100 mg/dL**	**<130 mg/dL**
Very high risk	Optional goal of <70 mg/dL	Optional goal <100 mg/dL
Moderately high risk: ≥2 risk factors (10-year risk 10%–20%)	**<130 mg/dL** (optional goal <100 mg/dL)	**<160 mg/dL** (optional goal <130 mg/dL)
Moderate risk: ≥2 risk factors (10-year risk <10%)	**<130 mg/dL**	**<160130 mg/dL**
Low risk: ≤1 risk factor	**<160 mg/dL**	**<190 mg/dL**

Adapted from Grundy SM et al. *Circulation*. 2004;110:227–239; http://lww.com

therapeutic option based on clinical judgment. No modifications were suggested for the lower risk category.

Review of recent studies (after NCEP guidelines update) with cardiovascular end points.

This section examines Treating to New Targets (TNT) (21), Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) (22), Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis, Anglo-Scandinavian Cardiac Outcomes Trial (23), and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) (24).

-'Treating to New Targets' (TNT).

The TNT clinical trial (21) was carried out in 10 001 patients with clinically evident stable CHD and LDL cholesterol levels at baseline of less than 140 mg/dl while on atorvastatin 10 mg daily. The purpose of this study was to determine if aggressive lowering of LDL-c levels to 80 mg/dl with high-dose statin was associated with better cardiovascular outcomes than a goal LDL-c of 100 mg/dl with moderate statin therapy. Eligible patients were randomly assigned to receive either 10 mg or 80 mg of atorvastatin daily with a median follow-up of 4.9 years. The primary outcome was occurrence of first major cardiovascular event, defined as CHD death, nonfatal myocardial infarction (MI), resuscitation after cardiac arrest, or fatal or nonfatal stroke. The achieved LDL-c levels were 77 mg/dl for the 80-mg group and 100 mg/dl for the 10-mg group. At study end, there was a 22% relative risk reduction (RRR) and 2.2% absolute risk reduction in occurrence of the primary end point. Overall mortality was no different between the groups, although mortality rates were quite low in both groups. As for safety, the group treated with 80 mg of atorvastatin experienced more adverse events leading to discontinuation of study drug (7.2 vs. 5.3%) and more episodes of liver enzyme elevation (1.2 vs. 0.2%) but no difference in myalgia, rhabdomyolysis, or serious adverse events.

-'Incremental Decrease in End Points Through Aggressive Lipid Lowering' (IDEAL)

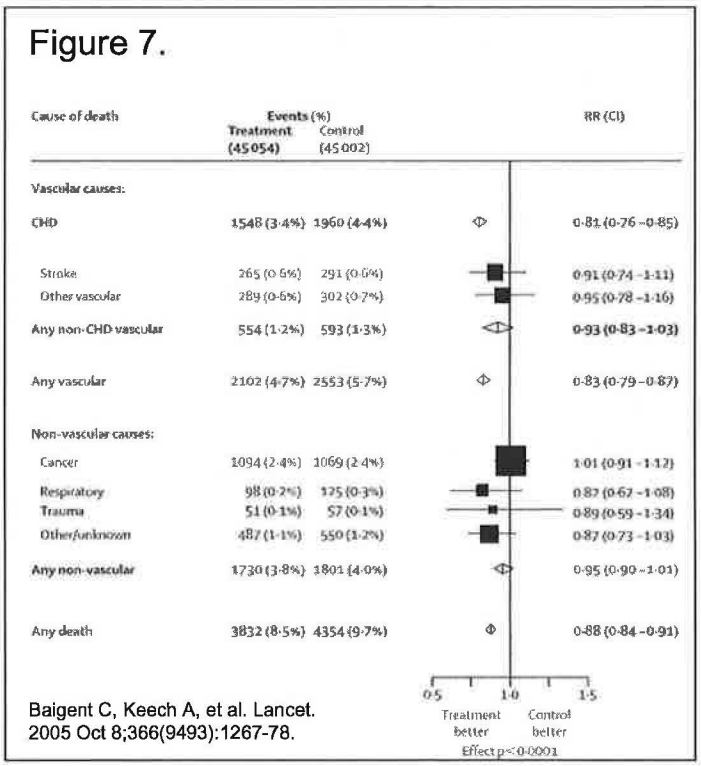
In the prospective, open-label IDEAL trial (22), 8888 patients, all with previous MI and stable CHD, were randomly assigned to high-dose atorvastatin (80 mg daily) or usual-dose simvastatin (20–40 mg daily) and followed for a median of 4.8 years. The primary outcome was occurrence of a major coronary event, defined as CHD death, nonfatal MI, cardiac arrest, or resuscitation – but not stroke. Achieved LDL-c levels were 80 and 108 mg/dl, respectively. The difference in the primary outcome failed to reach statistical significance (hazards ratio 0.89; 95% CI, 0.78–1.01; P = 0.07). Several pre-specified secondary outcomes were statistically different between the groups, however. These included a 13% RRR in major cardiovascular events (primary event plus stroke – the primary end point in TNT); 16% RRR in any coronary event (any primary event, revascularization, or hospitalization for unstable angina); 16% RRR in any

cardiovascular disease (primary event plus congestive heart failure and peripheral arterial disease); and a 17% RRR in nonfatal MI. Again, no difference was demonstrated in mortality. As for safety, more patients in the 80-mg atorvastatin group discontinued medication secondary to adverse events (9.6 vs. 4.2%) and experienced myalgias or elevations in liver enzymes, but it should be noted that this may be as a result of a selection bias as more than 50% of the patients at baseline had previously been treated with simvastatin. No rhabdomyolysis was reported in either group.

-'Cholesterol Treatment Trialists' Collaboration meta-analysis (CTT).

A prospective meta-analysis of data from more than 90 000 patients in 14 randomized trials of statin therapy from 1994–2004 was performed by the CTT Collaboration (23). A 12% RRR in all-cause mortality was demonstrated for every 40 mg/dl reduction in LDL-c over 5 years, due in large part to the 19% RRR in coronary mortality. There were also corresponding reductions in MI or coronary death (23% Relative Risk Reduction), coronary revascularization (24% RRR), fatal or nonfatal stroke (17% RRR), and any major vascular event (21% RRR). Benefits were seen within the first year of treatment but increased over subsequent years. In other words, for every 40 mg/dL reduction in LDL-C achieved, there were 48 fewer major vascular events per 1000 patients for secondary prevention and 25 fewer events per 1000 patients for primary prevention. There was no evidence of reduction in nonvascular mortality and no increase in the incidence of cancer.

Figure 7.



Baigent C, Keech A, et al. Lancet. 2005 Oct 8;366(9493):1267-78.

-The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN).

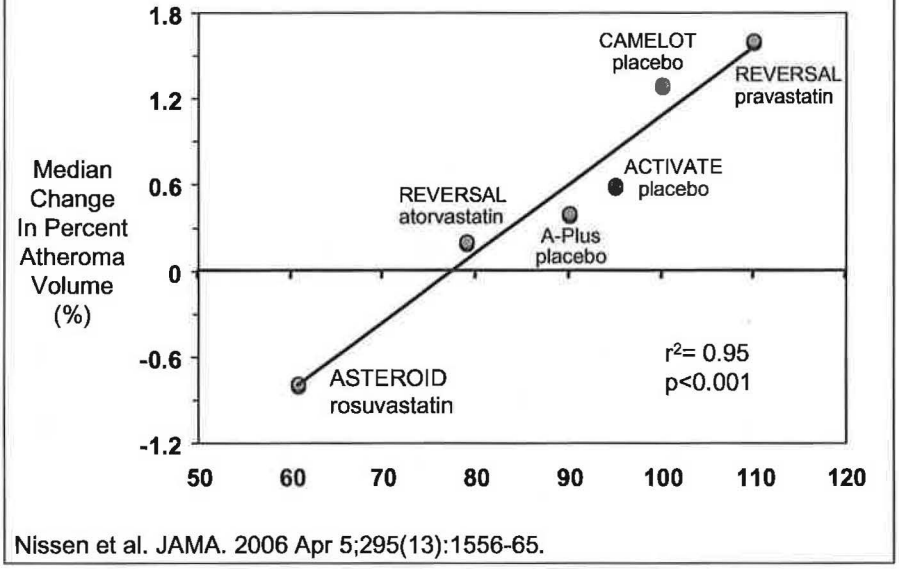
In ASPEN trial (24), patients with type 2 diabetes with or without evidence of CAD, and triglycerides<600 mg/dL were evaluated. A total of 2,410 subjects were randomly assigned to receive atorvastatin 10 mg/day or placebo for 4 years, in a double-blind parallel-group study design. Mean LDL-C reduction was 29% in the active treatment group compared to placebo. Composite primary endpoints (cardiovascular death, nonfatal MI, non-fatal stroke, re-canalization, CABG,

resuscitated cardiac arrest, and worsening or unstable angina) were lowered by 10% (HR 95% CI 0.73-1.12) in the treatment group when compared to placebo. The authors concluded that the study did not confirm the benefit of therapy but do not detract from the imperative that the majority of diabetic patients are at risk of CAD and deserve LDL cholesterol lowering to the currently recommended target.

Review of recent studies with intravascular ultrasound (IVUS) end points.

Recent studies with IVUS technology have suggested regression of plaque with LDL-C concentrations below 70 mg/dL. In the latest of the published clinical trial with an IVUS outcome, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) (25), IVUS was used to assess coronary atheroma burden at baseline and after 24 months of treatment with rosuvastatin 40 mg daily. This was a prospective, open-label blinded end-points trial. 507 patients had a baseline IVUS examination and received at least 1 dose of study drug. After 24 months, 349 patients had evaluable serial IVUS examinations. The mean (SD) baseline low-density lipoprotein cholesterol (LDL-C) level of 130.4 (34.3) mg/dL declined to 60.8 (20.0) mg/dL, a mean reduction of 53.2% (P<.001). The mean (SD) change in percent atheroma volume for the entire vessel was of –0.79% median (P<.001 vs baseline). The significant regression of atherosclerosis was related to the decrease in LDL-C concentrations. Figure 8 illustrates that LDL-C levels achieved correlate linearly with the IVUS progression rates for several studies that used different therapeutic approaches. Therefore it can be inferred that there exists no apparent threshold LDL-C level beyond which the benefits of LDL-C lowering are no longer evident. These conclusions are well in line with the findings of randomized clinical trials using clinical outcome end-points.

Figure 8.



Nissen et al. JAMA. 2006 Apr 5;295(13):1556-65.

Impact of duration of treatment in lipid lowering.

A major issue that remains to be explored is whether and how earlier intervention in LDL-C lowering is cost-effective and safe for more effective reduction of cardiovascular disease morbidity and mortality in our population. On this line, it is of interest that a rare mutation that reduces LDL-C concentrations by increasing the activity of LDL receptor, determines a significant life-time reduction in cardiovascular risk (26). In that study, two sequence variants in PCSK9 gene were associated with LDL-C reduction by about 28% and CHD risk reduction by about 88% in African Americans. The same study provided evidence that another genetic variant of PCSK9 determines a 15% reduction in LDL-C and a 47% reduction in the risk of CHD in whites.

General comments on the impact of cholesterol lowering intervention on cardiovascular disease.

Taken together, the evidence from randomized clinical trials strongly supports safety and effectiveness in outcome improvement with the lowering of LDL-cholesterol and non-HDL-cholesterol, best achieved with statin therapy. In light of the time effect on atherosclerosis progression and risk for cardiovascular event, it seems reasonable to increase the intensity of treatment based on overall risk evaluation. The ten years risk calculation proposed by NCEP ATP III as guidance to initiation of pharmacological treatment and intensity of treatment is, in fact, mainly age-driven and incorporates short term risk evaluation. However, true prevention of cardiovascular disease can be accomplished only by blocking atherosclerosis progression and therefore modifying the natural history of cardiovascular disease. We are gaining evidence that true modification of natural history of atherosclerosis is attainable when LDL-C is maintained below 70 mg/dL. Since atherosclerosis progression starts at young age, early reduction in LDL-C and non-HDL-C has the potential to be more effective in preventing cardiovascular events as compared to more intensive intervention at a later age. Although not yet proven by intervention trials, early intervention is more likely to not require intensive modification of plasma cholesterol concentrations much needed in the high risk population. This can be accomplished with reduced exposure of patients to adverse risks associated with use of higher doses of lipid-lowering agents. On this line, we will now review clinical trials on effectiveness, safety and clinical outcome of lipid-lowering drugs in mono- or combination therapy to satisfy goals set by NCEP-ATP III.

Effectiveness and safety of statin mono-therapy in achieving NCEP goals.

The safety of major statins currently available has been recently reviewed by the National Lipid Association Statin Safety Assessment Task Force (27). Data analysis from published clinical trials and from adverse events reports to the FDA is shown to confirm very low incidence of serious side effects in patients taking statins. On the other hand, effectiveness of statins is widely documented by numerous clinical trials and varies from 18% LDL-C reduction with pravastatin 20 mg daily to 55% LDL-C reduction with rosuvastatin 40 mg daily. Effectiveness of statins is generally greatest at starting doses, for every doubling of statin dose

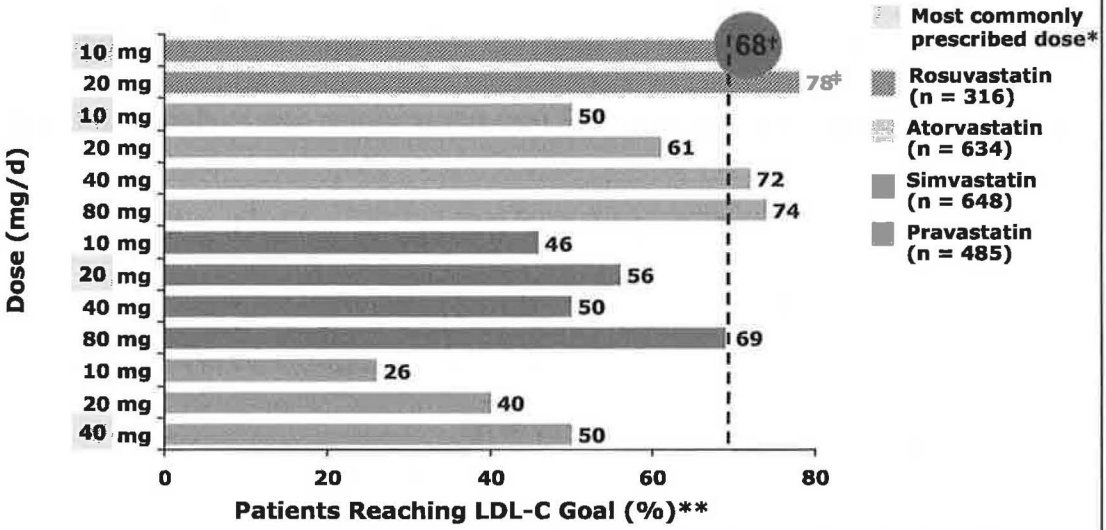
an additional 5-6% reduction in LDL-C is generally expected. Statins are generally more effective in patients with higher baseline plasma LDL-C. Some variability in response to statin therapy is seen in clinical

Figure 9. Pharmacologic Therapy: Statins

- Inhibit cholesterol synthesis, ↑ LDL receptors
- Beneficial effects on lipid parameters
  - LDL-C ↓ 18%-55%
  - HDL-C ↑ 5%-15%
  - TG ↓ 7%-30%
- 24%-40% relative reduction in coronary events
- Potential side effects: myopathy, ↑ liver enzymes
- Contraindications: liver disease
- Precautions: use with certain drugs

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486.

Figure 10 . Patients Reaching ATP III LDL-C Goal



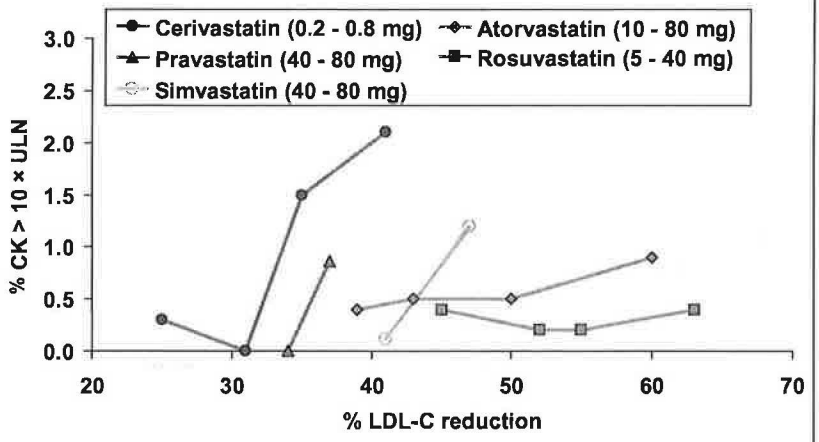
*IMS National Prescription Audit; November 2003–October 2004; **LDL-C goals were <160 mg/dL (low risk), <130 mg/dL (moderate risk), <100 mg/dL (moderately high risk and high risk), or <70 mg/dL (very high risk).
†$P<.001$ vs atorvastatin 10 mg; simvastatin 10 mg and 20 mg; pravastatin 10 mg to 40 mg.
‡$P<.001$ vs atorvastatin 20 mg; simvastatin 20 mg, 40 mg; pravastatin 20 mg, 40 mg.

The 5-mg dose of CRESTOR was not studied in this trial.
Adapted from Jones et al for the STELLAR Study Group. *Am J Cardiol*. 2003;92:152-160.

practice. However, lack of response should be evaluated for possible compliance issues. Recent trials provide information on the ability of statin monotherapy to achieve NCEP ATPIII goals of treatment. Figure 10 compares the most prescribed statins in their ability to achieve goal of treatment in patients at various risk for CAD. Commonly starting dose of 10 mg used for rosuvastatin determined 68% of patients to accomplish goals for LDL-C set by ATP III guidelines revision. The large majority of patients can accomplish goals with sub-maximal doses of atorvastatin or rosuvastatin. A comparison of the effectiveness of maximal vs. submaximal doses of statins should be addressed in view of the increase in risk for side effects seen at maximum statin doses. As shown in figure

11, higher incidence of myopathy is expected with 80 mg of simvastatin or atorvastatin and with 40 mg dose of rosuvastatin. Although the incidence of serious side-effects is small, an important practical implication of indiscriminate use of maximum statin dose is an increase in the number of patients that end-up discontinuing statins altogether in the presence of myalgia manifestation. These patients will be often left without appropriate risk-reducing medications. As we will discuss in more details later, patient education is a powerful tool to reduce the higher risk of non-compliance associated with higher statin doses.

Figure 11.



Brewer HB Jr. Am J Cardiol. 2003 Aug 21;92(4B):23K-29K

Effectiveness and safety of combination therapy in achieving NCEP goals.

Availability of combination therapy should be evaluated to improve effectiveness of lipid lowering intervention. The expected superiority in effectiveness has to be balanced with a discussion on potential increase in side-effects and cost. Figure 12 summarizes the main classes of lipid-lowering agents that increase overall efficacy of treatment and allow more patients to accomplish goals set by NCEP. The overall efficacy of each agent in monotherapy is relatively low as compared to statins. In addition, clinical outcome data are relatively weak in supporting the use of these non-statin agents in monotherapy. Currently, non-statin therapy is reserved as add on to a statin or as alternative to patients who cannot tolerate statins. Combination of non-statin agents can allow

Figure 12.

Main classes of lipid-lowering agents to add to a statin:

- Bile acid sequestrants
- Cholesterol absorption inhibitors
- Plant stanols esters
- Niacin
- Fibrates
- Omega-3 fatty acids

accomplishing goal of treatment but is associated with higher risk for side-effects and cost. We will first discuss bile acid sequestrants as add on therapy to a statin.

Statins+bile acid sequestrants.

Administration of a bile acid sequestrant determines 10-20% reduction in LDL-C. This effect is determined by reduction in bile acid absorption and increased in bile acid synthesis in the hepatocyte to maintain stable pool. Since bile acids are synthesized from cholesterol, this leads to reduction in hepatocyte cholesterol and activation of LDL-receptor. The effect on LDL-C up-regulation is additive to the effect of statins determined by the block of cholesterol synthesis. In clinical trials, addition of a bile acid sequestrant to a statin results in an additional reduction in LDL-C of about 8-10%. This is equivalent to two up-titrations of statin dose. However, the rate of discontinuation due to gastro-intestinal side effects (mainly bloating and constipation) makes bile-acid sequestrants difficult add-on therapy agents.

Figure 13.

Colesevelam HCl	Statin	TC* (%)	LDL-C* (%)	HDL-C* (%)
2300 mg (~4 tablets)	Lovastatin 10 mg	–7	–12 to –10	–3 to –1
2300 mg (~4 tablets)	Simvastatin 20 mg	–6	–8	–3
3750 mg (6 tablets)	Simvastatin 10 mg	–9	–16	+7
3750 mg (6 tablets)	Atorvastatin 10 mg	–4	–10	+3

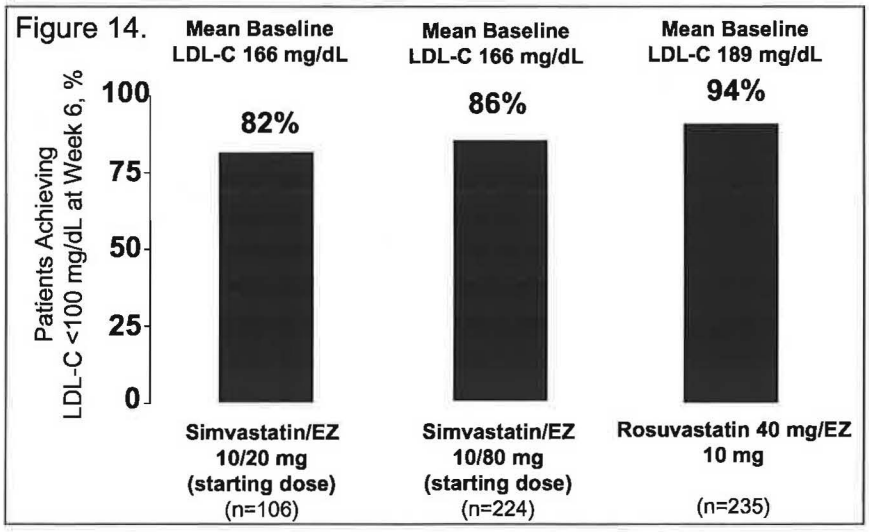
* Change versus statin alone.

Bays H et al. *Expert Opin Pharmacother* 2003;4:779-790.
Davidson MH et al. *Expert Opin Investig Drugs* 2000;9:2663-2671.

Statins+cholesterol absorption inhibitors.

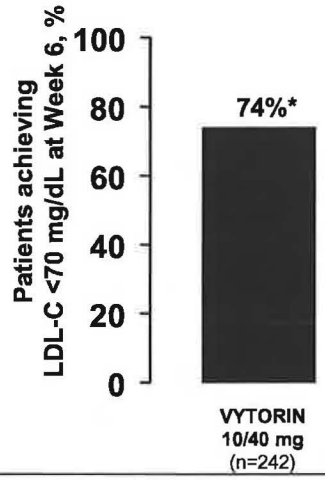
Ezetimibe and stanol esters are two available agents that reduce absorption of cholesterol through two different mechanisms. Ezitimibe appears to inhibit a cholesterol transporter protein (Niemann-Pick C1 Like 1-NPC1L1 is

Figure 14.



a candidate protein) at the plasma membrane of enterocytes. When administered as single agent increases sterol excretion in stools and decreases plasma concentrations of LDL-C by about 15-20%.

Figure 15. Preliminary data from VYTAL study in patients with Diabetes



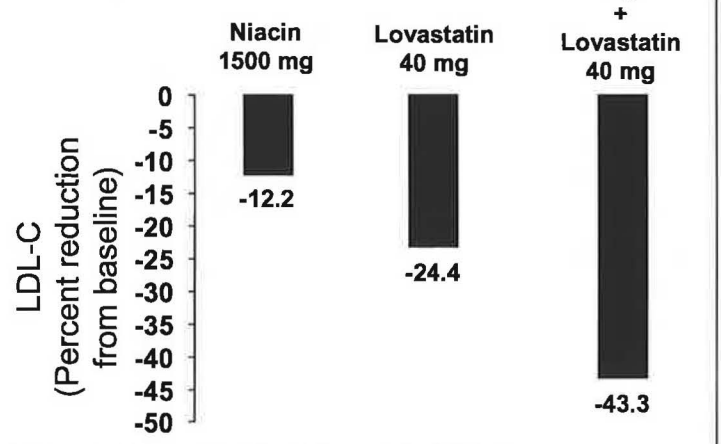
Stanol esters compete with cholesterol in micellar formation with bile acids (required for absorption of cholesterol) and increase sterol excretion in stools. Plasma concentrations of LDL-C decrease up to 10-15% in mono-therapy. As add-on therapy to a statin these two agents are attractive mainly because of lack of significant side effects coupled with additional effectiveness in achieving goals of treatment. In a study that included patients with CAD and baseline LDL-C between 100 and 129 mg/dL, LDL-C was 15% lower and non-HDL-C was 14% lower with combination therapy of stanol esters + statin as compared to statin monotherapy (28).

More data are available on the effects of ezetimibe added to statin therapy. Up to 20-25% additional reduction in LDL-C has been observed when ezitimibe is added to any of the major statins currently used (29-30). Figures 14 and 15 summarize some of the available results. VYTORIN® (ezetimibe/simvastatin) 10/20 mg allowed 82% of patients to achieve LDL-C goal <100 mg/dL (29). LDL-C goal attainment of <100 mg/dL at Week 6 was 94% for Ezetimibe 10 mg+rosuvastatin 40 mg (Figure 14). VYTORIN 10/40 mg allowed 74% of patients with type 2 diabetes to achieve LDL-C goal <70 mg/dL (Figure 15).

-Nicotinic acid+statin.

Nicotinic acid reduces LDL-C up to about 15%. This effect is related to a reduction in VLDL production in hepatocytes. Severe flushing, itching, headache, GI discomfort and liver toxicity are the common reason that makes this drug difficult to tolerate. Discontinuation due to side effects is common. Side-effects are less but still significant with the use of slow-release formulation

Figure 16.



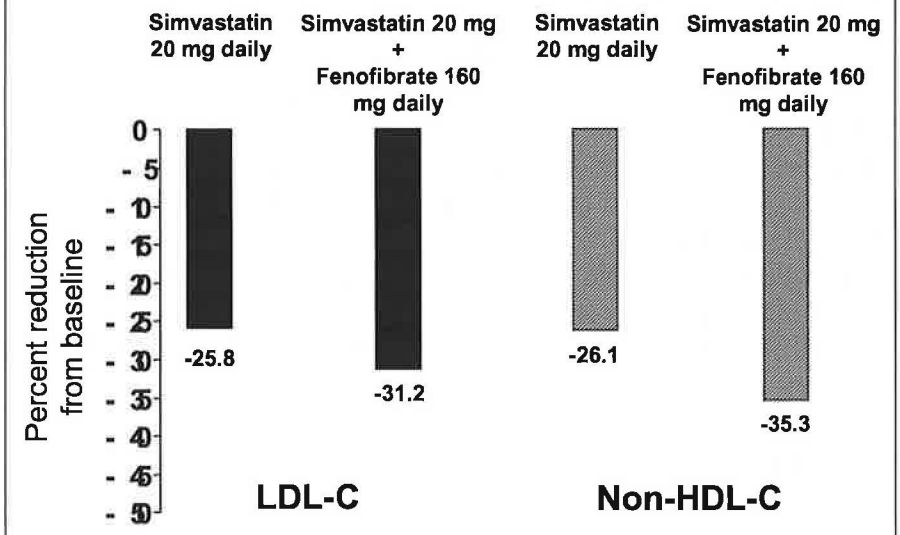
Insull et al. Arch Intern Med. 2004; 164:1121-7.

of niacin. When added to a statin, nicotinic acid increases risk for myopathy and AST/ALT elevation. Usually, slow-release niacin is used in combination to a statin not to exceed the dose of 1500 mg daily. As shown in figure 16, addition of 1500 mg daily of niacin ER determined an additional 19% of LDL-C reduction in patients with type IIa or IIb primary hypercholesterolemia (31).

-Fibrates+statins.

Gemfibrozil and fenofibrate are both effective in reducing plasma triglycerides concentrations. The effects on LDL-C are often of no change or increase in plasma concentrations. However, in combination therapy with a statin, fenofibrate may induce reduction in LDL-C and non-HDL-C. Gemfibrozil but not fenofibrate significantly increases the AUC for plasma statin concentrations. If combination therapy is prescribed, it is therefore prudent to use fenofibrate rather than genfibrozil. Reports of side-effects with fenofibrate + statins are higher than in mono-therapy. As shown in figure 17, in the SAFARI trial (32), patient with mixed hyperlipidemia had 6% additional reduction in LDL-C and 9% additional non-HDL-C reduction when fenofibrate was added to simvastatin as compared to simvastatin mono-therapy. The results on Apo-B containing particles appear therefore modest. However, an additional 23% reduction in plasma triglycerides and 9% increase in HDL-C was also observed. No significant increase in side-effects was observed in that trial. The additional cost related to the use of combination therapy begs the question of whether any advantage is expected on outcome. The clinical trial evidence is at this time inconclusive on the potential beneficial effects of fenofibrate on cardiovascular outcome end-points.

Figure 17.



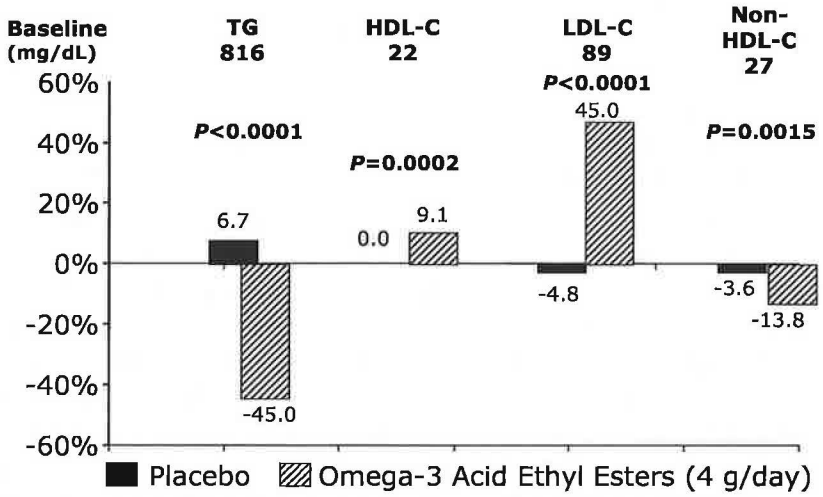
Grundy et al. Am J Cardiol. 2005 Feb 15;95(4):462-8.

-Omega-3 fatty acids+statins.

Omega-3 fatty acids induce reduction in plasma triglycerides concentrations when administered at the dose of > 3 grams a day of EPA and DHEA. Omega-3 fatty acids reduce triglycerides up to 40-50%. The mechanism of action appears to be decreased production of VLDL. Omega-3 fatty acids also

reduce post-prandial lipemia via increased clearance of chylomicron. In a study simvastatin (20 mg) was used alone and in combination with omega-3 fatty acids (4 g/day Omacor) in 41 patients with combined hyperlipidemia. The addition of omega-3 fatty acids provided a significant additional reduction in serum triglycerides levels (28%) and additional reduction in total cholesterol levels, without adversely affecting the LDL-C lowering induced by simvastatin (33). In another study, omacor 4 g/day was added to simvastatin 10 to 40 mg daily (to reduce total cholesterol to <213 mg/dL). Omega-3 fatty acids determined an additional 35% reduction in triglycerides, 40% reduction in VLDL-cholesterol, and 18% reduction in non-HDL-cholesterol (34). When compared to atorvastatin monotherapy, omacor 4 g daily was also observed to have independent and additive effects on dyslipidemia of obese men (35). Compared with baseline values, triglyceride levels were reduced by 26% with atorvastatin monotherapy, 25% with omega-3 fatty acids monotherapy, and 40% with the combination. HDL-C was increased by 4%, 1% and 14%. No significant differences in other lipid parameters were observed.

Figure 18. Omega-3 Ethyl Esters and Lipid Levels in Patients with Triglycerides >500 mg/dL



Pooled analysis: Harris WS et al. *J Cardiovasc Risk* 1997;4:385-391. | Pownall HJ et al. *Atherosclerosis* 1999;143:285-297.

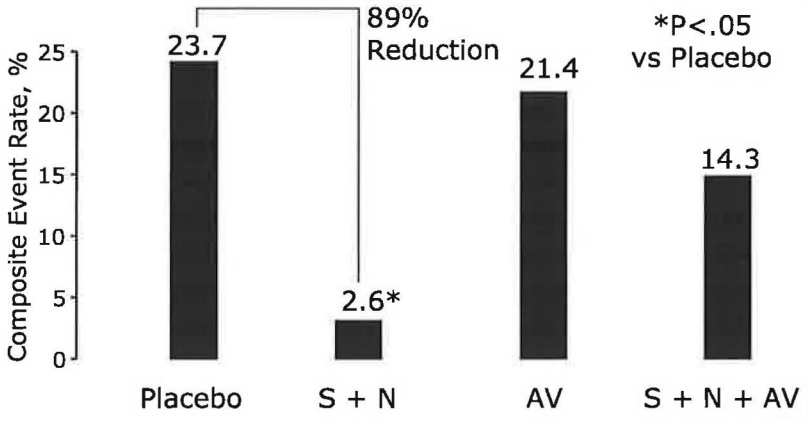
Review of clinical trials using combination therapy with cardiovascular end-points.

-Statins+niacin

The HDL-Atherosclerosis Treatment Study (HATS) (36) enrolled 160 men and women with clinical coronary artery disease and at least 3 stenoses of at least 30% of the luminal diamenter or one stenosis of at least 50%. All had low HDL-C (<35 mg/dL for men and <40 mg/dL for women), and triglyceride below 400 mg/dL. Patients were randomized to receive one of 4 regimen: simvastatin + niacin; antioxidants; simvastatin+niacin+antioxidants; placebo. Treatment with simvastatin + niacin for three years was found to determine a reduction in LDL-C by 42% and an increase in HDL-C by 26%. The average stenosis regressed by -4% with simvastatin + niacin. The frequency of clinical end-point (occurrence of

1st cardiovascular event including death, MI, stroke or revascularization) was decreased by 90% in statin+niacin group as compared to the placebo group.
Despite very low number of treated subjects in each arm (n=33 in the simvastatin+niacin group), the concordance in findings between angiographic changes and events has made this clinical trial the main support for this combination therapy in patients with low HDL-C.

Figure 19. Results from HDL-Atherosclerosis Treatment Study



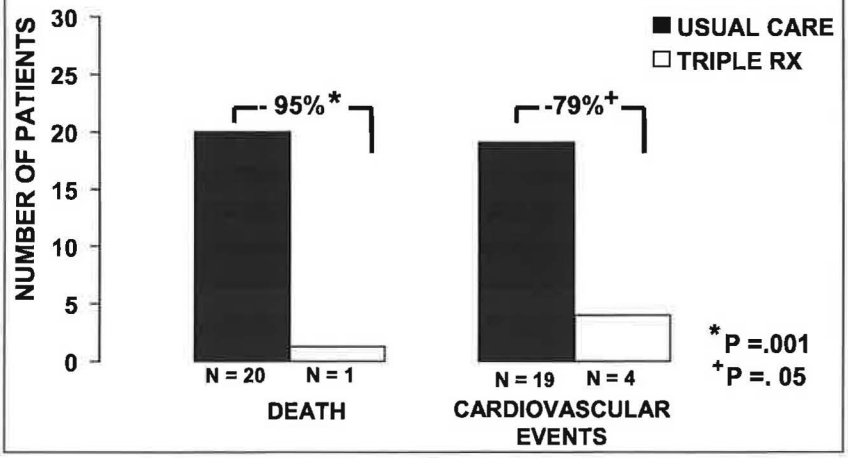
Brown BG et al. *N Engl J Med* 2001;345:1583-1592.

-Statin+BAS

In FATS (37), the effect of intensive lipid-lowering therapy on coronary atherosclerosis among men at high risk for cardiovascular events was assessed by quantitative arteriography in 120 men who had apolipoprotein B levels greater than or equal to 125 mg per deciliter, documented coronary artery disease, and a family history of vascular disease. Patients were given dietary counseling and were randomly assigned to one of three treatments: lovastatin (20 mg twice a day) and colestipol (10 g three times a day); niacin (1 g four times a day) and colestipol (10 g three times a day); or conventional therapy with placebo (or colestipol if the low-density lipoprotein [LDL] cholesterol level was elevated). The levels of LDL and high-density lipoprotein (HDL) cholesterol changed only slightly in the conventional-therapy group

Figure 20. Results from FATS trial.

(10 Year Follow-up of 75 Patients On 40mg of Mevacor, 2.5gm Of Niacin And 20gm. Of Colestipol Daily Versus 101 Patients with"Usual Care".)

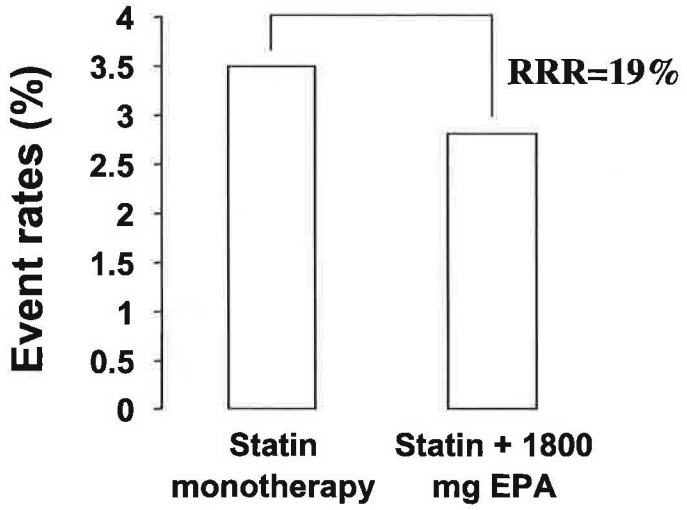


(mean changes, -7 and +5 percent, respectively), but more substantially among patients treated with lovastatin and colestipol (-46 and +15 percent) or niacin and colestipol (-32 and +43 percent). In the conventional-therapy group, 46 percent of the patients had definite lesion progression (and no regression) in at least one of nine proximal coronary segments; regression was the only change in 11 percent. By comparison, progression (as the only change) was less frequent among patients who received lovastatin and colestipol (21 percent) and those who received niacin and colestipol (25 percent), and regression was more frequent (lovastatin and colestipol, 32 percent; niacin and colestipol, 39 percent; P less than 0.005). Clinical events (death, myocardial infarction, or revascularization for worsening symptoms) occurred in 10 of 52 patients assigned to conventional therapy, as compared with 3 of 46 assigned to receive lovastatin and colestipol and 2 of 48 assigned to receive niacin and colestipol (relative risk of an event during intensive treatment, 0.27; 95 percent confidence interval, 0.10 to 0.77).

-Statins+fish oil

Results from the Japan EPA Lipid Intervention Study (38) were presented in November 2005 at the AHA meeting. JELIS was a randomized, open-label, blinded study that incuded 3664 patients with CAD and 14981 without CAD who were taking statins for hypercholesterolemia. The mean baseline total cholesterol was 275 and 180 mg/dL, respectively. Study patients were randomzed to receive either capsules of 1800 mg of highly purified EPA or placebo, and were followed for 4.5 years. The addition of fish oil capsules significantly decreased the incidence of the primary endpoint of major coronary events (sudden cardiac death, fatal and nonfatal MI, unstable angina, and revascularization) from 3.5% in the statin monotherapy group to 2.8% in the combination therapy group (HR, 0.81; RRR, 19%). The results were similar in the primary prevention and secondary prevention groups when they were analyzed separately for relative risk reduction. Likely due to the low event rate in the primary prevention group, the results were not statistically significant in this group analyzed separately. This is the first study in which clinical benefits of combination therapy with omega-3 fatty acids and statins has been reported.

Figure 21. Results from JELIS trial.



Yokoyama M. et al. Am Heart J. 2003;146:613-20.

-Statins+Cholesterol absorption inhibitors.

There are currently no clinical trials available to evaluate clinical outcome benefits related to the use of ezitimibe or plant stanol ester as an add-on to a statin, beyond the proven outcome benefits of a statin. Expected result is that clinical benefit would be determined by the additional LDL-C reduction induced by these agents. Of significance is the consideration that these two agents block GI cholesterol absorption and do not associate with significant increase in side-effect beyond the side effects related to the statin use. This is a clear advantage over the other lipid-lowering agents evaluated in this section and explains the increasingly large use of these agents, particularly ezetimibe, in combination to a statin. The recent availability of vytorin has also given a cost advantage and improved compliance issues related to use of multiple drugs.

Conclusions.

The total annual cost of CAD in the United States is over 100 billion dollars. Although epidemiological studies are showing a progressive reduction in cardiovascular mortality, current clinical practices do not adequately address primary prevention. As a consequence, number of cardiovascular events continues to be high. Need for cardiovascular procedures account for the largest component of CAD cost in the US. What we have learned from epidemiology, mechanistic studies and randomized clinical trials is that, although atherosclerosis is a multi-factorial disease, intervention aimed at reducing plasma cholesterol level is one of the most effective modalities to reduce risk for morbidity, mortality and need for procedures (CABGs and angioplasties). We have also learned that addressing all established major cardiovascular risk factors often associated with hypercholesterolemia, including hypertension and hyperglycemia, results into a compounded benefit that has the potential to significantly impact the natural history of atherosclerosis and reduce burden of coronary artery disease in our population. Contrary to management of hypertension and hyperglycemia, it is increasingly apparent that benefits from plasma cholesterol lowering do not have a lower limit, beyond which adverse events are seen. Whereas the risk of hypoglycemia and hypotension decreases our ability to safely initiate pharmacological intervention early enough and intensively enough to significantly affect the natural history of various diseases associated with these conditions, lowering of plasma cholesterol can be safely pushed to earlier stages of disease, earlier age (even in children) and at the maximum intensity. Therapeutic life-style changes play a primary role in earlier stage of disease progression and pharmacological intervention may not be necessary in younger persons. Diet and exercise play a major role in reducing need for medications at later stages of atherosclerosis progression. Unfortunately, not enough of what we have learned from our clinical experience with lipid lowering intervention is currently applied to practice of medicine. Very often the initiation of treatment is decided too late and is conducted in a non-intensive manner, so that no significant impact on the natural history of atherosclerosis is accomplished.

An important challenge in the management of patients with hyperlipidemia is the growing prevalence of obesity and diabetes that associate with elevation of both cholesterol and triglycerides. Emphasis should be given to the non-HDL-C treatment goals for these patients. The concept of non-HDL-C has not been widely accepted in clinical practice. As a consequence, lipid-lowering therapy for these patients is often either delayed or insufficient in determining adequate reduction of cardiovascular morbidity and mortality.

We have reviewed data that support safe and effective intervention currently available to reduce LDL-C and non-HDL-C concentrations to the intensive goal of treatment proposed by NCEP ATP III. The results intensive lipid lowering are shown to significantly modify the natural history of atherosclerotic disease towards the remarkable results of inducing plaque regression rather than just slowing of progression.

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