

New Trends in Lipid Management: Eight Cases to Consider

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Abstract

Eight case histories with differing clinical presentations and lipid abnormalities are presented to illustrate new trends in lipid management. Issues discussed include the use of coronary artery calcium scores to assess coronary heart disease risk for individuals who are asymptomatic, lower LDL-cholesterol goals, new lipid measurements that may be clinically helpful in patient management, and the use of combined lipid-altering agents.

Key Words: Anticholesterolemic drugs, coronary disease, lipids, drug therapy, cardiovascular diseases, lipoproteins, cholesterol, triglycerides, drug therapy, mortality, prevention, control.

IN THE 1990s, at the Mount Sinai Cardiology Clinic and Cardiology Faculty Practice, only 5% of patients with proven coronary heart disease were on two or more lipid-altering medications (1). Since that time, several provocative studies have been published which suggest that low-density-lipoprotein cholesterol (LDL-C) guidelines should perhaps be more demanding for patients with coronary heart disease (CHD) (2–4) and that combination therapy with two different classes of lipid-altering agents may produce more beneficial clinical outcomes than might be expected from studies using only a single agent (5).

In 2001 the Adult Treatment Panel III (NCEP ATP III) of the National Cholesterol Education Program (NCEP) (6) suggested the possible utility of measuring nontraditional CHD risk factors such as ultrasensitive C-reactive protein and

lipoprotein (a) (Lp(a)) to help better estimate CHD risk for those patients without a history of CHD. In addition, they proposed that surrogate measures of atherosclerosis, such as intima-media thickness of the carotid artery, ankle brachial index, and ultrafast or multi-detector computer tomographic (UFCT) scanning of coronary arteries for coronary calcium scores, could also be performed for sharpening CHD risk estimates. LDL-C goals were lowered to less than 100 mg/dL for those with diabetes and for those with a CHD risk equivalent, i.e., more than a 20% 10-year-risk of a myocardial infarction (MI) or CHD death as determined by a Framingham risk algorithm. Non-high-density-lipoprotein cholesterol (non-HDL-C) goals were recommended for those with triglycerides over 200 mg/dL, to estimate all atherogenic apolipoprotein B (Apo B) lipoproteins in one number. Triglyceride goals were set optimally as less than 150 mg/dL.

More recently another paper from the Coordinating Committee of the NCEP (7) has recommended an LDL-cholesterol goal of < 70 mg/dL as a therapeutic option, based on clinical trial evidence in those persons at *very high risk*. Such persons include those with established cardiovascular disease and a recent acute coronary syndrome, or multiple risk factors (especially diabetes), or severe and poorly controlled risk factors such as continued cigarette smoking, or multiple risk factors

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of the metabolic syndrome (especially triglycerides ≥ 200 mg/dL plus non-HDL-cholesterol ≥ 130 mg/dL with low HDL-cholesterol < 40 mg/dL). This report also suggested as a therapeutic option a primary-prevention LDL-cholesterol goal of < 100 mg/dL in persons with an LDL-cholesterol > 100 mg/dL and a moderate 10-year risk of 10–20% with several other risk factors such as hypertension, advancing age, continued smoking, a strongly positive family history of premature atherosclerotic cardiovascular disease, lipids consistent with the metabolic syndrome as stated above, or with a C-reactive protein > 3 mg/L, or a coronary calcium score > 75 th percentile for a person's age and sex. This recommendation was based on evidence from the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (8), in which the use of 10 mg of atorvastatin for 3.3 years reduced the risk of MI and CHD death by 36% and stroke by 27% in the 10,300 participants age 40 to 79 years without coronary heart disease but with hypertension and 3 other risk factors. The report emphasizes that a standard dose of a statin be used to reduce the LDL-cholesterol by at least 30–40% and minimally to a level < 100 mg/dL.

It takes some time for more aggressive guidelines to be implemented, and studies showing the inability of physicians to obtain guideline lipid goals have been discouraging (9). But change does occur. For example, the percentage of patients with CHD who had LDL-C of less than 100 mg/dL increased from 23% to 53% between 1994 and 1999 at the Mount Sinai Cardiology Clinic and Cardiology Faculty Practice (10). The same results will surely occur elsewhere as the clinical evidence for more aggressive lipid-altering therapy mounts. This article will present cases to illustrate several clinical points that may be helpful to the practicing physician in assessing CHD risk and preventing cardiovascular events through the treatment of atherogenic lipids.

A. Be suspicious of patients with family histories of early CHD: Consider using non-invasive imaging studies to assess individual risk in order to lower atherogenic lipids sufficiently.

Case 1: 52-Year-Old Male (Fig. 1)

How many CHD risk factors are there? What is the LDL-C goal? In order to determine an LDL-C goal, one first establishes that the patient has 3 of 5 potential CHD risk factors used in the ATP-III algorithm:

- Age: over 45 in males, over 55 in females
- Positive family history (FH) of CHD: < 55 years old in first-degree male, < 65 years old in first-degree female
- HDL-C < 40 mg/dL

Case 1 52-year-old male

Negative history of CVD, DM, HTN, and smoking.

Father MI at 63, brother MI at 47.

HT: 5'7" WT: 158lbs IW: 145lbs
BP: 104/82

Lipid profile (mg/dL)

TC	TG	LDL-C	HDL-C	T/HDL-C ratio
232	152	37	165	6.3

Fig. 1. Case 1: 52-year-old male

BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HT = height; HTN = hypertension; IW = ideal weight; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TC = total cholesterol; TG = triglycerides; WT = weight; T/HDL ratio = TC divided by HDL-C.

His NCEP ATP-III LDL-C goal is thus < 130 mg/dL.

The patient then began what was supposed to be a 2-month trial of dietary therapy, which involved lowering animal saturated fats and trans fatty acids, and consuming soluble fiber and stanol ester margarines. This could have lowered his LDL-C by 10–15%. He only returned 2 years later because a brother had suffered a heart attack at a family reunion. He panicked and was afraid to move quickly for fear of precipitating a heart attack. While waiting to get a stress test, he obtained an electron-beam computed tomography (EBCT) coronary artery calcium score (CACS) and repeated his lipids levels. The following were the results (Fig. 2).

Given his EBCT coronary artery calcium score and Bruce stress echocardiographic results, what now is his LDL-C goal? How can it be accomplished?

The use of electron beam or multi-detector CT scanning for coronary artery calcium scoring has become one method of assessing CHD risk for patients with no history of clinical CHD (11). This patient's high coronary artery calcium score (CACS) would predict a substantially increased risk of nonfatal MI or CHD death over the next 8.5 years (12). In fact, it would push him into a CHD risk equivalent state. Thus, although he had no symptomatic CHD, my goal for his LDL-C was lowered to less than 100 mg/dL, a 40% decrease in his current LDL-C level, a therapeutic option now suggested by the NCEP committee (7). This goal could most probably be achieved with rosuvastatin 10 mg qd, atorvastatin 20 mg qd, or simvastatin 40–80 mg qd (13).

Case 1 52-year-old male 2 years later

Brother 53 sudden MI at family reunion.
Onset atypical chest pain.
Fears any movement.

Lipid profile (mg/dL)

TC	TG	HDL-C	LDL-C	T/HDL ratio
227	140	32	167	7.1

EBCT: Agatston Score = 1140,
> 90th percentile for age, gender.
Bruce stress echo: Peak HR 155, SBP 120 to 170, no ECG
changes. LV wall motion normal with diffuse hyperdynamic
changes and increase in EF. No evidence of ischemia.

Fig. 2. Case 1: 52-year-old male 2 years later
EBCT = electron-beam computed tomography; ECG = electrocardiogram; EF = ejection fraction; HR = heart rate; LV = left ventricle; SBP = systolic blood pressure.
For all other abbreviations, see Fig. 1.

The question that remains in terms of lipid altering for this man with asymptomatic coronary vascular disease, or for someone with symptomatic or documented obstructive coronary heart disease, is how low to push LDL-C levels. Although many LDL-C lowering trials can show primary or secondary prevention effects of 25–35% in CHD event rates, this still leaves a substantial number of persons with CHD events (2, 14–17). One trial, to be reported in the spring of 2005, may help answer this question. Treating to New Targets (TNT) is a randomized, double-blind study funded by Pfizer, assigning 10,000 participants with known CHD to 10 vs. 80 mg of atorvastatin (18). To qualify, a participant must have been able to lower LDL-C to 100–130 mg/dL with atorvastatin 10 mg per day. Participants were then randomized to remain on atorvastatin 10 mg or to increase to 80 mg qd to attain an LDL-C level in the 50–80 mg/dL range. The hypothesized result would be an improvement in event rate reduction on the higher dose with the lower LDL-C levels. Results from a similar secondary prevention trial, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) (19), comparing simvastatin 20 vs. 80 mg qd for 12,000 participants, should be available by 2006.

A recent intravascular ultrasound trial has been somewhat enlightening in regard to the matter of target LDL-C for patients with CHD. Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL), recruited 654 patients with symptomatic CHD, and at least one coronary vessel with > 20% stenosis and LDL-C baseline values of 125–210 mg/dL, and randomized them to pravastatin 40 mg

or atorvastatin 80 mg for 18 months (3). LDL-C levels were reduced to 110 mg/dL or 79 mg/dL, respectively. Intravenous ultrasound studies to evaluate atherosclerotic plaques in 30 mm segments of coronary arteries with 20–50% stenoses demonstrated that patients on atorvastatin had no increase in atheroma volume (–0.4%) compared with an increase in those on pravastatin (+2.7%, $p=0.02$ between the two groups). This would suggest that an LDL-C of 80 mg/dL or lower would be required for those persons not wishing coronary plaque growth.

Such a clinical difference in cardiovascular (CV) events for patients using the same medications and dosages was recently published by the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) group (4). This study enrolled 4,162 patients hospitalized with acute coronary syndromes and randomly assigned pravastatin 40 mg vs. atorvastatin 80 mg. After a follow-up period of 18–36 months (mean 24 months), patients on atorvastatin compared with those on pravastatin had a 16% reduction in the primary end point of all-cause death, MI, unstable angina requiring rehospitalization, revascularization and stroke (26.3% vs. 22.4% respectively, $p=0.005$). Trial LDL-C values were 95 and 62 mg/dL, respectively. This study pertains only to the approximately one million persons who have MIs and unstable angina in this country annually, and there were some subgroups whose results were not significantly different for patients on the two drugs (those ≥ 65 years, with MI with ST-segment elevation, previously on a statin, and with LDL-C < 125 mg/dL). Whether equivalent levels of LDL-C will be associated with similar decreases in coronary event rates in the much larger part of the population with a history of stable CHD awaits the larger TNT and SEARCH clinical trials mentioned above, with thousands of patients. My LDL-C goal for this man at this point would certainly be < 100 mg/dL, and preferably < 70 mg/dL.

Case 2: 66-Year-Old Woman (Fig. 3)

How should she be treated?

It was unclear whether this patient's LDL-C of 209 mg/dL was atherogenic, given her high HDL-C of 70, which produced a TC/HDL-C ratio of 4.2 (near the ideal range of < 4.0). Her only NCEP ATP III risk factor was age (> 65 years in women), which was offset by her high HDL-C level. Thus, with zero risk factors in the NCEP ATP III algorithm for determining coronary disease risk, her LDL-C goal was < 160 mg/dL. The history of a heart condition in a brother of approximately the same age, however, sent a warning signal that demanded further attention to her CHD risk. The

Case 2 66-year-old woman

Brother with "heart condition."
 Neg history of DM, HTN, smoking
 On hormone replacement therapy x 10yrs
 Atorvastatin 20mg - AST 70 U/L / ALT 103 U/L

PE: 5'2" WT: 126 lbs IW: 120 lbs
 BP: 136/75

Lipid profile (mg/dL)

TC	TG	HDL-C	LDL-C	T/HDL-C ratio
292	65	50	209	4.2

EBCT coronary calcium score 334 Agatston units, 90th percentile for age, gender

Fig. 3. Case 2: 66-year-old woman

ALT = alanine aminotransferase (normal ≤ 60 U/L); AST = aspartate aminotransferase (normal ≤ 50 U/L).
 For all other abbreviations, see Figs. 1 and 2.

EBCT score at the 90th percentile for a woman her age suggested that the HDL-C was in fact not that helpful and certainly did not override the unknown family history risk. Given the high coronary calcium score, her LDL-C goal decreased from < 160 mg/dL to < 100 mg/dL and justified the effort to search for lipid-altering medications that would lower LDL-C to that level without giving the abnormal liver function tests (LFT) produced by atorvastatin 20 mg qd. Alternatives included a lower dose of atorvastatin or rosuvastatin, combined with a bile acid binder or a cholesterol receptor inhibitor, as illustrated in the following cases.

B. Combine therapies to reduce LDL-cholesterol further into the good range.

Case 3: 53-Year-Old Postmenopausal Female (Fig. 4)

This patient's only ATP III CV risk factor is hypertension, which is offset by a negative risk factor of having high high-density lipoprotein cholesterol (HDL-C), which was > 60 mg/dL. Thus, by NCEP ATP III criteria, her LDL-C goal is < 160 mg/dL. To reduce LDL-C from 428 to 160 mg/dL in a patient with familial heterozygous hypercholesterolemia, would almost certainly require, at a minimum, the use of a statin. Although the original fluvastatin preparation, even at 80 mg per day, had the least potency of all the statins, its reformulation into a gel matrix form, fluvastatin XL 80 (Lescol XL 80), has increased its ability to lower mean LDL-C by 37%. By combining fluvastatin with hydrophilic polymers which absorb water on ingestion and form a gelatinous outer coat, the gastrointestinal absorption of fluvastatin is extended to more than 8 hours,

Case 3 53-year-old female

Hypercholesterolemia for years.
 Negative exercise stress test
 HTN, on angiotensin II receptor blocker and diuretic.
 While on simvastatin (Zocor) or atorvastatin (Lipitor): experienced aches so each was discontinued

FH: Brother MI at age 87

HT: 5' 3" WT: 205 lbs IW: 135 lbs BP: 164/90, 145/88 mm Hg

TC TG HDL LDL T/HDL

TC	TG	HDL	LDL	T/HDL
326	60	65	249	5.0
514	70	72	428	7.1
314	76	72	227	4.4
244	47	75	160	3.3

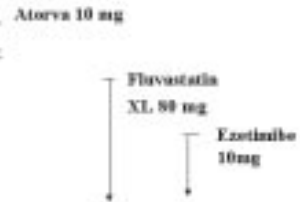


Fig. 4. Case 3: 53-year-old female

Atorva = atorvastatin (Lipitor), Ezetimibe (Zetia).
 For all other abbreviations, see Fig. 1.

causing a lower maximum serum peak level after administration compared to other statins. A report of the pooled clinical trial data using fluvastatin 20, 40, and XL 80 showed a low and equivalent (< 1%) percentage of people of all ages with creatine phosphokinase (CPK) elevations greater than 5 times the upper limit of normal compared to placebo (20). This may validate fluvastatin as a statin that can be tried in patients who have myalgias as a result of usage of other statins. Although other studies have essentially reported no differences in CPK elevations among all the statins (21), our "case 3" patient was started on fluvastatin XL 80, with a remarkable (47%) reduction in LDL-C, producing an LDL-C of 227 mg/dL, without myalgias.

Since fluvastatin XL 80 mg is a single-dose drug, this patient is someone for whom combined therapy—adding either a bile acid binder such as colestevlam hydrochloride (Welchol) (22) or an intestinal cholesterol receptor inhibitor such as ezetimibe (Zetia) (23, 24)—can further reduce LDL-C levels by another 18–40% on average. She was placed on ezetimibe 10 mg, and her LDL-C dropped 30% to 160 mg/dL, our goal for her. She is a hyperresponder to LDL-C-lowering therapy with both fluvastatin XL and ezetimibe. Her situation illustrates the fact that many persons with higher LDL-C levels at baseline will respond better to therapy than those with lower levels. Thus, what would at first seem an impossible lipid-altering task turns out not to be so.

Case 4: 66-Year-Old Woman (Fig. 5)

The first step in this case is simply to maximize the strength of the drug that she is on; fortu-

Case 4 66-year-old woman

Angina at age 55
Coronary angioplasty with stent at age 65

Pravastatin, lovastatin, and fluvastatin not potent enough
Atorvastatin 40 mg caused severe myalgias
On simvastatin 40 mg when first seen in referral

TC	TG	HDL-C	LDL-C	T/HDL-C	
288	227				Atorva 40 Simva 40
201	123	50	126	4.2	
230	146	48	153	4.8	Simva 80
175	113	46	106	3.8	Colesevelam (Welchol) 3 tabs BID
172	132	56	90	3.1	

Fig. 5. Case 4: 66-year-old woman
Atorva = atorvastatin (Lipitor) mg qd, Simva = simvastatin (Zocor) mg/qd
For all other abbreviations, see Fig. 1.

nately, 80 mg of simvastatin did not elicit the myalgias seen with other statins she had used. Like ezetimibe, bile acid binders can be used to increase the LDL-C lowering of a statin. In this case, it decreased LDL-C another 25%, into the LDL-C goal range desired for someone with known CHD. Colesevelam has become a welcome anion binder in the gut, because it is in pill rather than powder form and is more specific for binding bile acid anions than other medications in anionic form. Hence, patients no longer need to worry about decreased absorption of thyroid hormone, digoxin, some antibiotics, and some vitamins when using less specific bile acid binders such as cholestyramine and colestid. However, patients still must take 6 large tablets daily. The cost of bile acid binders is approximately twice the cost of ezetimibe for the same LDL-C-lowering power. On the other hand, bile acid binders are truly nonsystemic, because there is no gastrointestinal absorption, they have been shown to reduce coronary heart disease events, and they have shown no long-term toxicity in randomized, controlled trials. Since ezetimibe is absorbed and excreted through the biliary tree, there are low plasma levels and the predicted long-term safety of this medication awaits confirmation.

C. Be cautious with patients with severely reduced HDL-C levels and use combined therapy to raise HDL-C and lower LDL-C levels.

Case 5: 54-Year-Old Male (Fig. 6)

Case 5 54-year-old male

Healthy, sedentary

Father had MI in his early 60's

Discontinued smoking 16 years earlier
No history of diabetes
Hypertension for 13 years on a calcium channel blocker
History of uric acid stones on Allopurinol 150 mg qd

Lipid/laboratory values (mg/dL)							
TC	TG	HDL-C	LDL-C	T/HDL-C	Glucose		
				ratio			
600	147	213	85	7.7	77		
801	145	160	97	9.1	150		
902	145	134	100	8.1	150		
Lp(a) = 30 mg/dl		Homocysteine = 11.4 mm/L					

Fig. 6. Case 5: 54-year-old male
For all abbreviations, see Figs. 1 and 2.

What are the risk factors? What is the LDL-C goal? How should he be treated?

This patient originally had the metabolic syndrome but subsequently developed the hyperglycemia of type 2 diabetes. Without lipid-altering medications, he already has an LDL-C < 100 mg/dL. Should the physician add a statin to reduce LDL-C further? This question has been answered by the Heart Protection Study (2), an important randomized, controlled trial of simvastatin 40 mg qd vs. placebo in patients at high risk for subsequent cardiovascular events. ("At high risk" is defined here as having CHD, cerebrovascular disease, or peripheral vascular disease; hypertension; or diabetes, with a baseline total cholesterol > 135 mg/dL.) Major coronary events of MI and cardiovascular disease death were reduced by 25% in those patients placed on simvastatin 40 mg, even with baseline levels of LDL-C < 100 mg/dL.

But what about the low HDL-C? Should it be increased? There is growing evidence for increasing HDL-C to add a further preventive effect to the lowering of LDL-C. The HDL-Atherosclerosis Treatment Study (HATS) (25) was a three-year quantitative coronary angiographic trial of simvastatin 40 mg plus niacin to increase HDL-C by approximately 10 mg/dL, compared with placebo, in 160 persons with CHD. Qualifying HDL-C had to be < 35 mg/dL in men with triglycerides < 400 mg/dL, levels that would qualify our patient. In the placebo and simvastatin/niacin groups not on antioxidant vitamins, mean LDL-C levels were 116 and 75 mg/dL and mean HDL-C levels were 34 and 40 mg/dL, respectively. In the placebo group, the mean percentage of stenosis from 9 proximal

lesions increased 3.9% compared with a decrease of 0.4% in those on the simvastatin-niacin combination ($p < 0.001$). More remarkable for a trial not powered to show differences in clinical events, 9 of 34 patients in the placebo group experienced CV death, MI, or revascularization compared with only 1 patient in the combination group, an 89% decrease ($p = 0.04$). Such a small trial provides no definitive clinical evidence but serves to strongly promote the hypothesis that the HDL raising may be very important clinically and may add to the preventive effects of simply lowering LDL-C.

The cardiovascular preventive benefits of niacin were first demonstrated in 1975 in the Coronary Drug Project, in which men who had a history of previous myocardial infarction and were taking 3 grams of niacin daily, showed a 27% decrease in MI at 5 years (from 12.2% to 8.9%, $p < 0.005$) compared with those on placebo (26). The same study demonstrated an 11% decrease in all-cause mortality measured 9 years later, after the formal study had ended (52.0% vs. 58.2%, $p < 0.001$) (27).

Niacin comes in immediate-release and sustained-release forms, the former causing more flushing reactions, the latter less-beneficial lipid effects and more hepatotoxicity, especially at high doses (28). An intermediate-release form, niacin SR (Niaspan), is also available and seems to give the excellent lipid effects of immediate-release niacin without the hepatotoxicity of the sustained-release forms (29). Unfortunately, it is significantly more expensive. No-flush inositol preparations are ineffective because they contain none of the active free nicotinic acid (30). Niacin can raise uric acid levels and precipitate gout, but hopefully this patient would not be affected, since he is already on allopurinol.

In the course of being evaluated for his lipid abnormalities, the patient sustained an inferior wall MI. He was lost to follow-up, but hopefully he is currently on a statin and a niacin preparation, as in the following case.

Case 6: 62-Year-Old Male (Fig. 7)

Hypertension for 20 years; atypical chest pain; positive thallium stress test; mild claudication.

For this patient, niacin reduced triglycerides and LDL-C somewhat and increased HDL-C significantly. The statin was added to reduce LDL-C into our goal range of < 100 mg/dL. Niacin will also increase the size of LDL particles (31), making them less atherogenic. Niacin is also one of the few medications we have which reduce Lp(a). However, there have been no clinical trials to show that reducing Lp(a) will additively reduce risk. The Scandinavian Simvastatin Study (4S) demon-

Case 6 62-year-old male
Hypertension for 20 years
Atypical chest pain, positive thallium stress test
Mild claudication

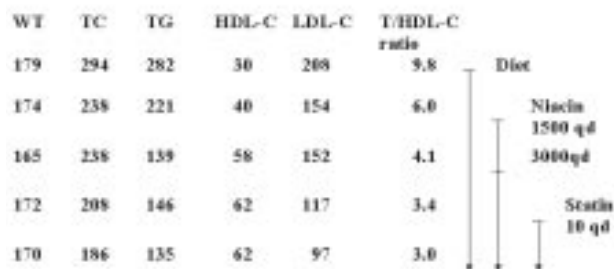


Fig. 7. Case 6: 62-year-old male
For all abbreviations, see Figs. 1 and 2.

strated that the adverse predictive value of increasing quartiles of baseline Lp(a) for future MI and cardiovascular death tended to be lost when the high levels of LDL-C in that trial (150–250 mg/dL, mean baseline 188 mg/dL) were lowered with simvastatin to an average level of 122 mg/dL (32). A similar loss of adverse predictive value of Lp(a) was shown with substantial reduction of LDL-cholesterol in the Familial Atherosclerosis Treatment Study (33). Hence a prudent management for cardiovascular risk associated with an elevated Lp(a) level > 30 mg/dL (highest quintile of population) and an elevated LDL-cholesterol based on the cited clinical evidence is simply to reduce the LDL-cholesterol by 30 to 40% to a value < 130 mg/dL.

D. For patients with diabetes mellitus, and potentially those with the metabolic syndrome, strongly consider the use of fibric acid therapy alone or in addition to statin therapy.

Case 7: 36-Year-Old Male, Referred for Eruptive Xanthoma (Fig. 8)

This young man was referred by a dermatologist when, at the sudden onset of severe hypertriglyceridemia secondary to the hyperglycemia of type 2 diabetes, the patient developed eruptive xanthoma. The most effective pharmacologic therapies for severe hypertriglyceridemia are fibric acid and niacin (6). Triglyceride values above 1000 mg/dL often represent the presence of chylomicrons and indicate increased risk for chylomicron-induced pancreatitis. While lowering triglycerides with gemfibrozil, the patient also eliminated concentrated sweets from his diet, began exercising, and was also started on metformin. This regimen increased insulin sensitivity, reduced glucose levels and hemoglobin A_{1c} (HbA_{1c}) into a more

Case 7 36-year-old Hispanic male

Father: has diabetes, no CHD in family
No smoking

HT: 5'5" WT: 171 lbs TW: 137lbs
Waist-hip ratio: 1.1 BP: 100/74 mm Hg
Many eruptive xanthomas on back and thighs

WT	TC	TG	HDL-C	LDL-C	non-HDL-C	HbA1c
171	471	3885				13.5
156	178	36	53	68	3.4	7.5
151	149	117	39	87	3.3	11.0
155	159	79	44	99	3.6	11.5
156	180	189	37	113	5.1	15.1
160	167	294	32	94	5.4	13.5

Fig. 8. Case 7: 36-year-old Hispanic male
Non-HDL-C = TC minus HDL-C, HbA1c = glycosylated hemoglobin (%), gemf = gemfibrozil (mg qd), metfmin = metformin (mg qd).

For all other abbreviations, see Fig. 1.
All lipid values in mg/dL.

normal range, and helped with weight loss, thereby reducing triglyceride levels.

Fortunately, the patient was quite compliant with the regimen and immediately began losing weight, with remarkable corrections in triglyceride levels and steady drops in hemoglobin A1c, even as both gemfibrozil and metformin were decreased and then stopped. In his case, the NCEP ATP goal for non-HDL-C (30 mg/dL greater than the LDL-C goal) was < 130 mg/dL (6). As he gets older, and his control of diet, weight and activity backslides a bit, he will inevitably be back on these medications. Because of his low HDL-C and moderately increased triglycerides, giving him a total cholesterol (TC)/HDL-C ratio > 5.0, one cannot feel very confident about his long-term prevention of CHD and could easily argue for restarting a fibric acid or starting a statin to prevent premature atherosclerosis.

The Veteran's Administration High Density Lipoprotein Intervention Trial (VA-HIT) (34) demonstrated that gemfibrozil therapy 600 mg bid reduced CHD death plus nonfatal MI by 22% in men with previously documented CHD and TG < 300 mg/dL, HDL-C \leq 40 mg/dL and LDL-C \leq 140 mg/dL over a 5-year period. An important finding in this study was that the effects were more dramatic in those with diabetes than in those without it (35). The number of patients needed to treat in order to prevent one CHD death or MI in the overall population was 23, but in the diabetic population it was only 12. In addition, in those without diabetes, gemfibrozil was effective in reducing CHD risk in the top quartile of insulin resistance, but not in the three lower quartiles of insulin resistance. Gemfibrozil would seem to be most effective

in preventing CHD in those with the insulin resistance/diabetic dyslipidemia secondary to high triglycerides, low HDL-C, and small LDL particle size.

To prevent CHD, the American Diabetes Association (ADA) recommends that statins be the first drug of choice for patients with diabetes (36). ATP III recommends an LDL-C goal of less than 100 mg/dL. But in this case the use of gemfibrozil resulted in an LDL-C < 100 mg/dL, and the VA-HIT study showed that gemfibrozil is cardioprotective in persons with type 2 diabetes or insulin resistance. Had his triglycerides remained elevated at greater than 400 mg/dL even with glucose control, one could argue that a fibric acid would be the more efficacious drug for his lipid abnormalities. But his triglycerides and glucose seem in fairly good control with lifestyle changes, and thus it is reasonable in his case to follow the evidence-based guidelines of the ADA and the recent NCEP guidelines, and place him on a moderate-dose statin for long-term CVD prevention.

Case 8: 63-Year-Old Woman (Fig. 9)

This patient has well-controlled diabetes, and coronary heart disease, and is on a reasonable statin dose with hypertriglyceridemia still inadequately treated (367 mg/dL). Investigators in the Diabetes Atherosclerosis Intervention Study (DAIS) randomly assigned 418 persons with type 2 diabetes and moderate elevations in LDL-C (135–175 mg/dL) and triglycerides (150–465 mg/dL), and with at least one visible coronary angiographic lesion, to the fibric acid, fenofibrate (Tricor), and followed them for 3 years (37). The fenofibrate group, compared with the placebo group, showed significant decreases in coronary lesions, with a smaller increase in percentage diameter stenosis (2.11 vs. 3.65%, $p=0.02$) and a significantly smaller decrease in minimum lumen diameter (–0.06 vs. –0.10 mm, $p=0.029$). Participants taking fenofibrate had fewer CHD clinical events (death, MI, percutaneous transluminal coronary angioplasty [PTCA], coronary artery bypass graft [CABG]) than those taking placebo (38 vs. 50), but the study was not powered to show this as a statistically significant difference.

The clinical issue for this woman is whether to increase her statin dose to achieve a total cholesterol of 204 mg/dL and triglycerides of 367 mg/dL, add a fibric acid to her statin, or do both. In this case the addition of fenofibrate to atorvastatin vastly improved her lipid profile, but even with the results above one wonders whether she is adequately protected. Results of REVERSAL and PROVE-IT (3, 4) would suggest that her LDL-C is

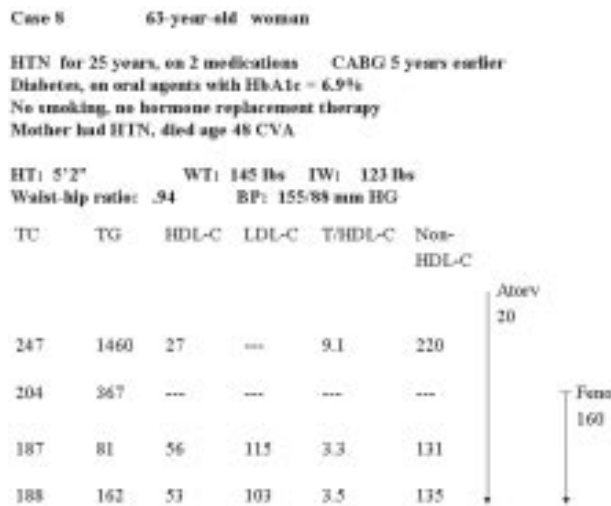


Fig. 9. Case 8: 63-year-old woman
 Atorv = atorvastatin (Lipitor), Feno = fenofibrate (Tricor), non-HDL-C = TC minus HDL-C, HbA1c = glycosylated hemoglobin (%).
 For all other abbreviations, see Fig. 1.

inadequately controlled and that an increase in atorvastatin is needed, along with the addition of fenofibrate.

Can one achieve additional beneficial effects for patients with diabetes and CHD, or at high risk for CHD because of other risk factors, by adding a fibric acid to a statin? The question will be answered in several years in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (which will not finish recruitment until mid-2005 and is expected to have an average follow-up of 4.5 years). Six thousand subjects in the lipid arm of the trial will be randomly assigned to simvastatin 20 mg or simvastatin 20 mg combined with fenofibrate 160 mg qd. The diabetic subgroups of the TNT and SEARCH trials should provide evidence on how low the LDL-C should be targeted when a statin is used alone.

With this patient, there is also the issue of how we determine the adequacy of treatment for someone with diabetes and CHD. Since such patients often have lipid patterns based on small LDL particles, an LDL-C < 100 mg/dL may indicate someone with excess small LDL particles, still at risk for further plaque progression (38). One could set a goal of approximately 70 mg/dL for LDL-C, as discussed in Case 1 above and as recommended as a treatment option for persons with diabetes and CHD. And yet for someone with diabetes or the metabolic syndrome and CHD, this may be inadequate lipid-altering therapy.

Three newer lipid parameters to assess adequacy of treatment have been suggested: non-

HDL-C, LDL particle number and Apo B. Non-HDL-C as a measure of Apo B in all fasting atherogenic lipoprotein particles has been suggested by NCEP ATP III as a secondary target of therapy in those patients with triglyceride levels > 200 mg/dL. In persons with established CHD in the Bypass Angioplasty Revascularization Investigation (BARI) trial, non-HDL-C was shown to be a better predictor of nonfatal MI and angina over 5 years than total, HDL and LDL cholesterol levels (39). In American Indians with diabetes, but without cardiovascular disease, in the Strong Heart Study, non-HDL-C was also shown to be a better predictor of combined fatal and nonfatal cardiovascular disease and coronary heart disease than LDL-C and triglycerides (40).

Another measure of atherogenic particles is the level of Apo B. One Apo B is associated with each LDL, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and Lp(a) particle. Since the half life in the circulation of LDL particles is substantially greater than that of the other Apo-B-containing particles, Apo B levels are a good surrogate for LDL particle numbers. Apo B levels have been better predictors of long-term risk for vascular disease in several large prospective studies, and on-trial Apo B levels have been better predictors of subsequent coronary events than LDL-C levels in several statin-versus-placebo, randomized controlled clinical trials (41). A recent study comparing non-HDL-C and Apo B, suggests that non-HDL-C is equivalent to Apo B in diabetic persons with triglycerides higher than 200 mg/dL, but substantially underestimates risk in those with lower triglyceride levels (42, 43).

The Canadian lipid guidelines for persons with CHD target an Apo level < 90 mg/dL, this being the 20th percentile of the Canadian population (44). The Chairman of the NCEP ATP III has also suggested an Apo level < 90 mg/dL (45). The approximate 20th percentile for men and women in the Framingham Offspring population (46) and the NHANES sample of the United States population is < 80 mg/dL (47). Thus, depending on one's aggressiveness in Apo B lowering, one could aim for < 90 or < 80 mg/dL.

Liposcience measures LDL particle number by nuclear magnetic resonance spectroscopy of lipid particles, giving both an LDL size and particle number. LDL-C < 100 mg/dL and LDL particle number < 1100 nmol/L represent the lowest quintile in the Framingham Offspring Study (48). Thus, in those with type 2 diabetic dyslipidemia consisting largely of excessive small LDL particles, an LDL particle number < 1100 nmol/L may represent a better target than an LDL-C goal of 100 mg/dL,

and < 800 nmol/L may represent a more aggressive target than an LDL-C goal of < 70 mg/dL. Yet none of these newer lipid goals have been compared in clinical prevention trials. Thus, one is left with several highly suggestive but unproven approaches if one wishes to go beyond the newer ATP III goal of an LDL-C < 70 mg/dL in a diabetic patient with coronary heart disease.

In conclusion, we have considered several cases with common but provocative cardiovascular and lipid histories and findings, and attempted to expand our thinking about their management. The future of preventive lipid management will probably include better assessment of risk for those patients without clinical CHD, more sophisticated lipid testing with clearer and more evidence-based therapeutic goals, increased use of combined lipid-altering agents, and better methods for improving patient compliance with such regimens.

Reference

- Harnick DJ, Cohen JL, Schechter CB, et al. Effects of practice setting on quality of lipid-lowering management in patients with coronary artery disease. *Am J Cardiol* 1998; 81:1416–1420.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360:7–22.
- Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004; 291:1071–1080.
- Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350:1495–1504.
- Brown BG, Zhao XQ, Chait A, et al. Niacin plus simvastatin, but not antioxidant vitamins, protect against atherosclerosis and clinical events in CAD patients with low HDLC [abstract]. *Circulation* 2000; 102(Suppl II):506.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285(19):2486–2497.
- Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110:227–239.
- Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361:1149–1158.
- Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000; 160:459–467.
- Smith DA, Harnick D, Kilaru R. Comparison of physician-managed lipid-lowering care in patients with coronary heart disease in two time periods (1994 and 1999). *Am J Cardiol* 2001; 88(12):1417–1419, A6.
- Wilson PW, Smith SCJ, Blumenthal RS, et al. 34th Bethesda Conference: Task force #4C How do we select patients for atherosclerosis imaging? *J Am Coll Cardiol* 2003; 41:1898–1906.
- Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004; 291:210–215.
- Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003; 92:152–160.
- Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; 333:1301–1307.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/Tex-CAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279:1615–1622.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344:1383–1389.
- LIPID Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; 339:1349–1357.
- Waters DD, Guyton JR, Herrington DM, et al. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol* 2004; 93:154–158.
- MacMahon M, Kirkpatrick C, Cummings CE, et al. A pilot study with simvastatin and folic acid/vitamin B12 in preparation for the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). *Nutr Metab Cardiovasc Dis* 2000; 10:195–203.
- Benghozi R, Bortolini M, Jia Y, et al. Frequency of creatine kinase elevation during treatment with fluvastatin. *Am J Cardiol* 2002; 89:231–233.
- Brewer HBJ. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol* 2003; 92:23KB29K.
- Hunninghake D, Insull WJ, Toth P, et al. Coadministration of colesvelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis* 2001; 158:407–416.
- Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002; 40:2125–2134.
- Jeu L, Cheng JW. Pharmacology and therapeutics of ezetimibe (SCH 58235), a cholesterol-absorption inhibitor. *Clin Ther* 2003; 25:2352–2387.
- Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001; 345(22):1583–1592.
- Clofibrate and niacin in coronary heart disease. *JAMA* 1975; 231:360–381.
- Canner PL, Berge KG, Wenger NK, et al., Coronary Drug Project Research Group. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *JACC* 1986; 8:1245–1255.

28. Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. *Metabolism* 1985; 34:642–650.
29. Knopp RH, Alagona P, Davidson M, et al. Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism* 1998; 47:1097–1104.
30. Meyers CD, Carr MC, Park S, Brunzell JD. Varying cost and free nicotinic acid content in over-the-counter niacin preparations for dyslipidemia. *Ann Intern Med* 2003; 139:996–1002.
31. McKenney JM, McCormick LS, Schaefer EJ, et al. Effect of niacin and atorvastatin on lipoprotein subclasses in patients with atherogenic dyslipidemia. *Am J Cardiol* 2001; 88:270–274.
32. Berg K, Dahlen G, Christophersen B, et al. Lp(a) lipoprotein level predicts survival and major coronary events in the Scandinavian Simvastatin Survival Study. *Clin Genet* 1997; 52:254–261.
33. Maher VM, Brown BG, Marcovina SM, et al. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). *JAMA* 1995; 274:1771–1774.
34. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999; 341:410–418.
35. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* 2002; 162:2597–2604.
36. Haffner SM. Dyslipidemia management in adults with diabetes. *Diabetes Care* 2004; 27 Suppl 1:S68–S71.
37. Steiner G. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 2001; 357:905–910.
38. Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Ann Intern Med* 2001; 135:447–459.
39. Bittner V, Hardison R, Kelsey SF, et al. Non-high-density lipoprotein cholesterol levels predict five-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 2002; 106:2537–2542.
40. Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. *Diabetes Care* 2003; 26:16–23.
41. Sniderman AD, Furberg CD, Keech A, et al. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet* 2003; 361:777–780.
42. Wagner AM, Perez A, Zapico E, et al. Non-HDL cholesterol and apolipoprotein B in the dyslipidemic classification of type 2 diabetic patients. *Diabetes Care* 2003; 26:2048–2051.
43. Sniderman AD. Non-HDL cholesterol versus apolipoprotein B in diabetic dyslipoproteinemia: alternatives and surrogates versus the real thing. *Diabetes Care* 2003; 26:2207–2208.
44. Genest J, Frohlich J, Fodor G, McPherson R. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. *CMAJ* 2003; 169:921–924.
45. Grundy SM. Low-density lipoprotein, non-high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. *Circulation* 2002; 106:2526–2529.
46. Contois JH, McNamara JR, Lammi-Keefe CJ, et al. Reference intervals for plasma apolipoprotein B determined with a standardized commercial immunoturbidimetric assay: results from the Framingham Offspring Study. *Clin Chem* 1996; 42:515–523.
47. Bachorik PS, Lovejoy KL, Carroll MD, Johnson CL. Apolipoprotein B and AI distributions in the United States, 1988–1991: results of the National Health and Nutrition Examination Survey III (NHANES III). *Clin Chem* 1997; 43:2364–2378.
48. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol* 2002; 90:22i–29i.