Managing Diabetic Dyslipidemia: Aggressive Approach

Kelly Anne Spratt, DO

The United States is experiencing a marked increase in rates of diabetes mellitus and metabolic syndrome, almost certainly in part due to the increase in obesity rates. This phenomenon is likely to also result in an increased risk of coronary artery disease as risk factors increase exponentially. This article defines diabetic dyslipidemia, the rationale for aggressive treatment, and options for ongoing management, including nonpharmacologic therapy and medications, alone or in combination, for management of all aspects of the lipid profile.

J Am Osteopath Assoc. 2009;109(suppl 1):S2-S7

Before type 2 diabetes mellitus (T2DM) is clinically diagnosed, the risk of a person's having cardiovascular disease is elevated as much as five times that of a person who does not have diabetes.[1] In their study of 117,629 women followed for 20 years, Hu et al[1] found that 110,227 women did not have diabetes or impaired glucose at baseline. Type 2 diabetes mellitus developed in 5894 of these women during the study period. The researchers documented 1556 new cases of myocardial infarctions (MIs), 1405 strokes, 815 fatal cases of coronary heart disease (CHD), and 300 fatal strokes.

The classic study by Haffner et al[2] supports the concept of T2DM as a CHD equivalent. This group compared the 7-year incidence of MI (both fatal and nonfatal) among 1373 subjects without diabetes with that of 1059 subjects with diabetes. The results of this Finnish population-based study suggest that the risk of MI in patients who have diabetes and no previous MI is as high as that for patients without diabetes who have had a previous MI.[2] Therefore, the rational approach is to look at patients who have T2DM and suspect the presence of yet-to-be-diagnosed CHD, and therefore treat them aggressively for dyslipidemia.

Dyslipidemia Associated With Diabetes

Consider here a typical patient with T2DM and a glycosylated hemoglobin (HbA_{1c}) value of 8.1%. Such a patient's typical serum lipid levels might be the following: low-density lipoprotein cholesterol (LDL-C), 129 mg/dL; high-density lipoprotein cholesterol (HDL-C), 42 mg/dL; triglycerides, 249 mg/dL; and total cholesterol, 234 mg/dL. Such a patient would thus warrant lipid-lowering treatment (*Figure 1*).

Dyslipidemia is prevalent in patients with T2DM in whom low levels of HDL-C and elevated triglyceride concentrations predominate. In their study, Jacobs et al[3] found no significant difference in controlled LDL-C levels of less than 100 mg/dL in patients with diabetes (25.3%) and that of patients without diabetes (24.3%). Contrarily, they found significantly greater proportions of patients without diabetes had controlled HDL-C (60.0%; $P<.001$) and triglyceride levels (74.5%; $P<.001$) than patients with diabetes (36.3% and 38.4%, respectively). Of interest, as patients progress from insulin sensitive to insulin resistant to diabetic, their LDL-C levels increase about 15% while the LDL particle size increases more than 33%.[4,5]

The increased small, dense LDL-C particles in patients with T2DM are a highly atherogenic LDL-C that is significantly associated with progression of coronary artery disease[6] and portends a much lower probability of survival of ischemic heart disease.[7] In patients with T2DM, low levels of HDL-C have been found to be an independent predictor of risk for CHD even when LDL-C levels are low and therefore can be a greater risk factor than high levels of LDL-C.[8] Therefore, it is important that treatment of patients with T2DM include agents that will help to increase their HDL-C to recommended levels (>40 mg/dL in men; >50 mg/dL in women).[9]

Triglyceride concentrations once were not a concern in the treatment of patients with T2DM. They were, however, routinely measured merely as a

Dr Spratt is clinical associate professor of medicine at the University of Pennsylvania School of Medicine in Philadelphia.

Dr Spratt has no conflicts of interest to disclose.

Correspondence to Kelly Anne Spratt, DO, FACC, Penn Presbyterian Medical Center, 51 N 39th St, Philadelphia Heart Institute, Suite 2C, Philadelphia, PA 19104-2640.

E-mail: kelly.spratt@uphs.upenn.edu

This supplement is supported by an educational grant from Merck & Co, Inc.

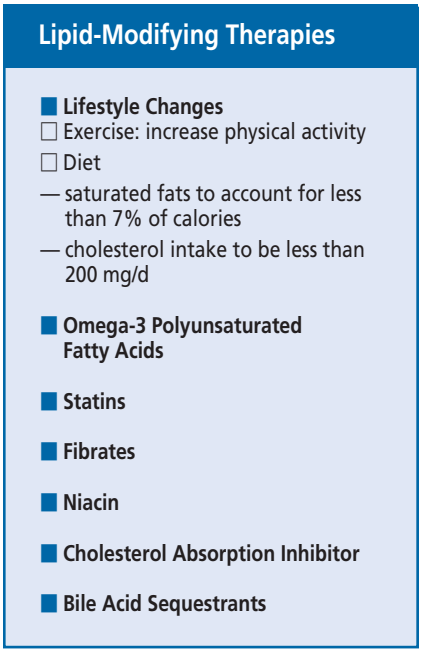

Figure 1. *Source:* Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. *Bethesda, Md: National Cholesterol Education Program. National Heart, Lung, and Blood Institute, National Institutes of Health. NIH Publication No. 02-5215, September 2002.*

component of the lipid profile. We now recognize that triglyceride concentrations may also be highly predictive of mortality in patients with T2DM or impaired fasting glucose.[10]

The Paris Prospective Study (PPS)[11] presented epidemiologic evidence that hypertriglyceridemia is an important predictor of CHD in persons with impaired glucose tolerance or diabetes.

In the PPS, Fontbonne et al[11] looked at the long-term incidence of CHD in 943 men with impaired glucose tolerance or diabetes who were selected from 7038 men aged 43 to 54 years seen at the first follow-up examination for a separate analysis of risk factors for CHD mortality.

Of the 943 men, 26 died of CHD at a mean follow-up of 11 years. These men had significantly higher levels of plasma triglyceride ($P<.006$) and plasma cholesterol levels ($P<.02$) and both fasting and 2-hour post glucose load compared with those who did not die of CHD. Findings of this study suggest that dyslipidemia has a clinically significant role in the occurrence of atherosclerotic vascular disease in these patients with diabetes.

A large meta-analysis of 17 prospective trials found that not only is the triglyceride concentration an independent risk factor for cardiovascular disease, but also increasing the triglyceride concentration by as little as 88 mg/dL increases cardiovascular risk by 75% for women and 30% for men.[12]

Another meta-analysis also supports the risk of elevated triglyceride concentrations as an independent risk factor with up to a sevenfold increase in risk as triglyceride concentrations increase from 131 mg/dL to 299 mg/dL.[13]

Although the increased risk of elevated triglyceride concentrations is independent of HDL-C levels, patients with diabetes and those with impaired fasting glucose often have low HDL-C levels as well. Elevated triglyceride levels reduce the effect of lipoprotein lipase and that reduces production of HDL-C.[14] In addition, the HDL-C produced is small, dense, and has decreased antiatherogenic activity. The kidney more readily clears this smaller HDL-C particle, leading to a further reduction of the HDL-C level.[15,16]

In summary, the dyslipidemia associated with diabetes or impaired fasting glucose involves atherogenic, dense LDL-C, low levels of HDL-C with reduced antiatherogenic activity, and elevated concentrations of triglycerides, each of which markedly increases the risk of mortality.

Treatment Options

Diet and Exercise

Diet and exercise are the fundamental and first considerations in patients with T2DM. They should constitute the starting point of physicians' conversations with these patients to provide guidance and instructions about a diet constructed to avoid complications of diabetes mellitus and limit dyslipidemia. Even low levels of exercise improve insulin sensitivity, maintain glycemic optimization, and reduce hypertriglyceridemia. The American Heart Association has recommended a minimum of 30 minutes of physical activity 5 days a week.[17] Moderately vigorous activity performed as part of daily activity, including gardening, brisk walking, or housecleaning done in 10-minute bouts may count toward this recommendation.

The initial approach for patients with T2DM is to minimize their consumption of high-glycemic-index foods (bread, rice, potatoes, pasta, and sugar) and to maximize their consumption of whole grains, fruits, and vegetables (red, yellow, green, orange). A diet that is high in low-fat protein and includes fish rich in omega-3 oils is important as the cornerstone of nutritional guidance.

Many patients benefit from including increased levels of fiber, foods that are rich in stanol and sterol esters, and supplementation with at least 1 g of fish oil daily. Use of this supplement has been shown to reduce risk of sudden death in patients who have coronary disease through cardiac electrical stabilization benefits. Fish oil supplementation also is effective in dramatically lowering triglyceride levels.[18] Neither garlic supplements nor policosinol has been found to augment lipid lowering, and neither is recommended specifically to treat patients with dyslipidemia or hypercholesterolemia.[19,20]

Statins

Despite lifestyle changes, most patients with T2DM require medication to lower their lipid levels. The most potent medications to reduce LDL-C levels are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), and they are considered a first-line treatment for patients with diabetic dyslipidemia.

Statins may decrease the LDL-C level by as much as 50% and have additional benefit on HDL-C and triglyceride levels. These medications may be used in monotherapy, or they may need to be used in combination for the patient with multiple lipid abnormalities. Remember that many derangements of the lipid profile in patients with diabetes involve triglycerides and HDL-C.

Statin medications are the mainstay for treatment of patients with diabetes who have dyslipidemia because of their pleotropic effects, including anti-inflammatory properties and potential to increase nitric oxide and enhance vasodilation. These medications have years of patient evaluations that have shown a decrease in cardiovascular mortality as

well as in total mortality. Data from both primary and secondary prevention trials strongly support starting lipid-lowering therapy with a statin in most patients with diabetes and that the benefit of statins increases in patients with low levels of HDL-C.[21-23]

Use of statins in both primary and secondary prevention confers a strong benefit to patients who have diabetes. Costa et al[10] conducted a systematic review and meta-analysis of 12 studies to evaluate the clinical benefit of lipid-lowering drug treatment in primary and secondary prevention in patients with and without diabetes mellitus. They found that lipid-lowering treatment with statins was as effective in patients with diabetes as in patients who did not have diabetes (21% vs 23% risk reduction for major coronary events, respectively, in primary prevention; and 21% vs 23% in secondary prevention, respectively). However, when the results were adjusted for baseline risk, patients with diabetes had greater benefit in both primary and secondary prevention of death due to coronary artery disease, nonfatal MI, revascularization, and stroke.

A meta-analysis for the American College of Physicians on lipid-lowering therapy in T2DM evaluated primary and secondary prevention in a wide variety of patients. This study concluded that there was a reduction of events of 22% in primary prevention and 24% in secondary prevention.[24]

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[23] was a primary prevention study that examined the relationship between percent reduction from baseline and on-treatment lipid values. The study investigated use of lovastatin in healthy patients and assessed coronary risk and lipid levels.

Of note, the lower the baseline HDL-C level, the greater the cardiovascular benefit in the group receiving lovastatin. Thus, primary prevention through lipid modification may confer clinically significant cardiovascular benefit to persons with average LDL-C levels and low HDL-C levels.

For some patients who cannot tolerate statins, red yeast rice, a Chinese herb that is similar to lovastatin, may be an alternative. Data are available on both primary and secondary prevention populations. In their 12-week, open-label primary prevention study, Becker et al[25] compared the lipid-lowering effects of lifestyle changes, red yeast rice, and fish oil (alternative treatment) with those of simvastatin (40 mg/d). They enrolled 74 patients with hypercholesterolemia and randomly assigned all participants to receive the alternate treatment or simvastatin. Both groups had a statistically significant reduction in LDL-C levels ($P<.001$). In the group receiving the alternate treatment, triglyceride levels were significantly reduced (29% vs 9.3% in the treatment group; $P=.003$) as was weight (5.5% vs 0.4% in the treatment group; $P=.001$).

The second study was a multicenter secondary prevention trial conducted in a Chinese population. Lu et al[26] examined the effects of a partially purified extract of red yeast rice on lipoprotein and cardiovascular end points (major coronary event including nonfatal MI and death from CHD) in patients who had average LDL-C levels at baseline and who had had a previous MI. They randomly assigned patients to receive the red yeast rice extract or placebo. The red yeast rice extract treatment substantially decreased cardiovascular and total mortality by 30% and 33%, respectively, as well as the need for coronary revascularization procedures by one third. This treatment also reduced total cholesterol and LDL-C levels and increased HDL-C levels.

For patients who have myalgias during statin therapy, the use of coenzyme Q10 may be beneficial to decrease myalgias in patients intolerant of statin medications.[27]

Fibric Acid

Fibric acids are beneficial for diabetic dyslipidemia, lowering triglyceride levels, and raising HDL-C levels, though with minimal impact on LDL-C. Outcome studies show that fibric acid/fibrates are especially effective drugs in decreasing cardiovascular events in patients with diabetes given the lipid derangements in triglyceride and HDL-C levels.

The Helsinki heart study, a double-blind, placebo-controlled primary prevention trial among 4081 men with dyslipidemia, tested the efficacy of gemfibrozil in preventing CHD.[28] In the 18-year follow-up, the researchers compared the CHD, cancer, and all-cause mortality in the original gemfibrozil group with those in the original placebo group. Gemfibrozil therapy at 1200 mg/d in 2046 men resulted in a 35% decrease in triglyceride concentrations, an 11% reduction in total cholesterol levels, and an 11% increase in HDL-C levels. Gemfibrozil therapy also resulted in a 34% reduction in CHD events overall but an astounding 68% reduction in patients with diabetes.

The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA HIT), a multicenter, randomized, double-blind, placebo-controlled, secondary prevention study, sought to determine if the reduction in major CHD events with gemfibrozil could be attributed to changes in plasma lipid levels.[29] Triglyceride concentrations were reduced 31%, total cholesterol levels were unchanged, and HDL-C levels increased 6%. Patients with diabetes had a 41% reduction in CHD events and a 40% decrease in cerebrovascular events compared with an overall decrease of 22% and 31%, respectively, in these events in the cohorts without diabetes.

In the Diabetes Atherosclerosis Intervention Study (DAIS), 418 subjects with T2DM were randomly assigned to receive 200 mg of micronized fenofibrate daily or placebo.[6] Fenofibrate therapy resulted in improved serum triglyceride, HDL-C, and LDL-C concentrations as well as decreased LDL particle size. It also resulted in 40% reductions in focal coronary disease and cardiovascular disease rates.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study assessed the effect of fenofibrate (200 mg/d) compared with placebo on cardiovascular disease events in patients with T2DM.[30] Although fenofibrate did not significantly reduce the risk of the primary outcome, it did reduce total cardiovascular events, mainly because of fewer nonfatal MIs. Thus, use of fenofibrate offers some benefits in patients with diabetes and should be considered

either alone or in combination for diabetic dyslipidemia.

Combination Therapy

Statin Plus Fibrate—The use of the combination of statin and fibrate would seem ideal in managing diabetic dyslipidemia. A safety and tolerability study of this combination is the Study of Artial Fibrillation Reduction (SAFARI), which enrolled 619 patients with T2DM and LDL-C levels greater than 130 mg/dL and triglyceride concentrations between 150 mg/dL and 500 mg/dL to receive simvastatin alone or in combination with fenofibrate.[31] This combination was found to be safe and effective at reducing LDL-C and triglyceride levels while increasing HDL-C levels. Additionally, there was a shift in LDL-C particle size to the more favorable subclass pattern A.[31] The large lipid portion of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a randomized study involving more than 5000 patients, is in progress to assess if this combination results in fewer cardiovascular events. Findings are expected to be released later in 2009.[32]

The Diabetes and Combined Lipid Therapy (DIACOR) study, looked at the effects of adding fenofibrate (160 mg/d) to simvastatin (20 mg/d) in patients with T2DM and no history of CHD who had mixed dyslipidemia plus two or more of the following: low HDL-C levels, elevated triglyceride concentrations, and elevated LDL-C levels.[33]

The DIACOR study comprised 300 enrolled patients (mean age 61 years; 55% men) who met the enrollment criteria. After a washout period of all lipid-lowering medications, the patients were randomly assigned to receive monotherapy with simvastatin (20 mg/d) or fenofibrate (160 mg/d), or combination therapy with both medications.[33]

In patients with baseline triglyceride concentrations of 170 mg/dL or greater, the combination therapy resulted in the greatest reductions in levels of the atherogenic LDL-C pattern B and in dense very low-density lipoprotein cholesterol levels as well as the greatest increases in HDL-C.[33]

Thus, the combination of fenofibrate and statin appears to be well tolerated, safe, and effective with outcomes data soon to be available. This combination may be an excellent option for diabetic dyslipidemia.

Statin Plus Niacin—Brown et al[34] compared the cardiovascular protection of a combination of simvastatin and niacin with a combination of simvastatin plus niacin and antioxidant vitamin therapy. Their 3-year trial documented greater clinical and angiographically measurable benefits with the simvastatin-niacin combination than would be expected with simvastatin monotherapy.

Patients receiving the simvastatin-niacin combination therapy had regression of stenosis (0.4%), as compared with progression of stenosis in the groups receiving placebos (3.9%) and antioxidant vitamins (1.8%). At the end of the 3 years, 91% of the patients treated with the simvastatin plus niacin had not had a cardiovascular event (coronary death, MI, stroke, or revascularization) compared with 78% of the patients treated with niacin monotherapy.[34]

Thus, the statin-niacin combination therapy improves freedom from clinical events, reducing death, MI, stroke, or revascularization. Niacin provides benefit by raising the HDL-C level, while the statin provides benefit by reducing the LDL-C level.[34]

The later HDL Atherosclerosis Treatment Study (HATS) showed that the combination of simvastatin and niacin at mean daily doses of 13 mg and 2.4 g, respectively, was effective, safe, and well tolerated in 25 patients with and 135 patients without diabetes mellitus.[35] These 160 patients had coronary artery disease, mean LDL-C levels of 128 mg/dL, HDL-C levels less than or equal to 35 mg/dL, and mean triglyceride concentrations of 217 mg/dL. They were randomly assigned to receive combinations of antioxidant vitamins or their placebos or simvastatin plus niacin or their placebos.

The simvastatin-niacin combination therapy was found to slow progression of angiographically measurable atherosclerosis, resulting in a 60% reduction in major cardiovascular events.[35]

Patients with diabetes in the simvastatin-niacin-treated group had an initial slight decline in glycemic control, which subsequently returned to pretreatment levels at 8 months and remained stable thereafter.[35]

Statin Plus Ezetimibe—Because ezetimibe monotherapy reduces LDL-C, raises HDL-C, and lowers triglyceride concentrations, it would seem intuitive that this agent combined with statin would be ideal.

Results of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial were released in April 2008.[36] Kastelein et al[36] conducted a 24-month double-blind randomized study to compare the effects of simvastatin (80 mg/d) combined either with placebo or ezetimibe (10 mg/d). They enrolled 720 patients with familial hypercholesterolemia and randomly assigned them to receive either the simvastatin-ezetimibe combination formulation or the simvastatin alone.

At the end of the ENHANCE study, the group receiving the simvastatin monotherapy had a mean LDL-C level of 192 mg/dL; the group receiving the simvastatin-ezetimibe combination had a mean LDL-C level of 141 mg/dL (a between-group difference of 16.5%, ($P<.01$). The group receiving the combined therapy had a 25% reduction in triglyceride concentration ($P<.01$) and a 6.6% decrease in C-reactive protein ($P<.01$).[36]

However, the primary outcome in the ENHANCE trial was the mean change from baseline in the thickness of the carotid intima media thickness (CIMT) as measured by B-mode ultrasonography. The group receiving the combination therapy had a slight, not significant increase in CIMT ($P=.29$).[36]

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial[37] was conducted to look at the effect of ezetimibe on progression of aortic stenosis. This trial concluded that this combination did not affect aortic stenosis, but the trial raised the possibility that the addition of ezetimibe to statin therapy led to an increase in the incidence of cancer.

Peto et al[38] analyzed cancer data from the SEAS trial as well as from two ongoing trials evaluating the use of ezetimibe: the Study of Heart and Renal Pro-

tection (SHARP),[39] a trial assessing renal progression, and the Improved Reduction of Outcomes Vytorin Efficacy International Trial (IMPROVE-IT), an acute coronary syndrome trial.[40] Although both of these trials are ongoing, information regarding cancer incidence was gleaned from these large randomized trials. In neither trial was the incidence of cancer greater with combination therapy of ezetimibe and statin.

Additionally, a meta-analysis of 90,000 patients in statin trials using the ezetimibe-statin combination found no increased risk of cancer.[41] Thus, combining a statin with ezetimide appears to be safe, lowers LDL-C levels effectively but does not have outcomes data at this point.

Treating the Patient

In terms of the order of priorities in treating our previously described patient who has diabetes and an LDL-C level of 129 mg/dL, the initial priority is to lower the LDL-C level, so first institute statin therapy (*Figure 2*). The outcomes and data support the effectiveness of statins in this patient population with benefit in reducing cardiovascular events and total mortality. The next priority is to increase the HDL-C level, so next prescribe diet (ie, consuming fewer carbohydrates) and more exercise, which help in achieving and maintaining glycemic control.

Combination therapy with a statin is often required. The statin may be combined with either niacin in patients who can tolerate it or with a fibrate. Both agents have been shown to be safe when combined with a statin. Also, both combinations have the ability to reduce cardiovascular events in patients with diabetes. These combinations, together with lifestyle changes and the use of fish oil, are helpful in controlling triglyceride levels, a common derangement in diabetic dyslipidemia.

References

1. Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care*. 2002;25:1129-1134.

2. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from CHD in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-234. Available at http://content.nejm.org/cgi/content/abstract/339/4/229. Accessed March 1, 2009.

3. Jacobs MJ, Kielsil T, Pio JR, Malik S, L'Italien GJ, Chen RS, Wong ND. Prevalance and control of dyslipidemia among persons with diabetes in the United States. *Diabetes Res Clin Pract*. 2005;70:263-269.

4. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC Jr, et al. LDL particle subclasses, LDL particle size and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192:211-217.

5. Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, et al. Effect of insulin resistance and Type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. *Diabetes*. 2003;52:453-462. Available at: http://diabetesjournals.org/cgi/content/full/52/2/453. Accessed May 7, 2009.

6. Vakkilainen J, Steiner G, Anaquer J-C, Aubin F, Rattier S, Foucher C, et al. Relationship between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: the Diabetes Atherosclerosis Intervention Study (DAIS) [published online ahead of print March 4, 2003]. *Circulation*. 2003;107:1733-1737. Available at http://circahajournals.org/cgi/content/full/107/13/1733. Accessed February 20, 2009.

7. St-Pierre A, Cantin B, Dagenais GR, Mayrièe P, Bernard P-M, Després J-P, et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Québec Cardiovascular Study [published online ahead of print December 23, 2004]. *Arterioscler Thromb Vasc Biol*. 2005;25:553-559. Available at: http://atvb.ahajournals.org/cgi/content/full/25/3/553. Accessed March 1, 2009.

8. Castelli WP. Cholesterol and lipids in the risk of coronary artery disease—The Framingham Heart Study.*Can J Cardiol*.1998;4(suppl A):5A-10A.

9. *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Choles-*

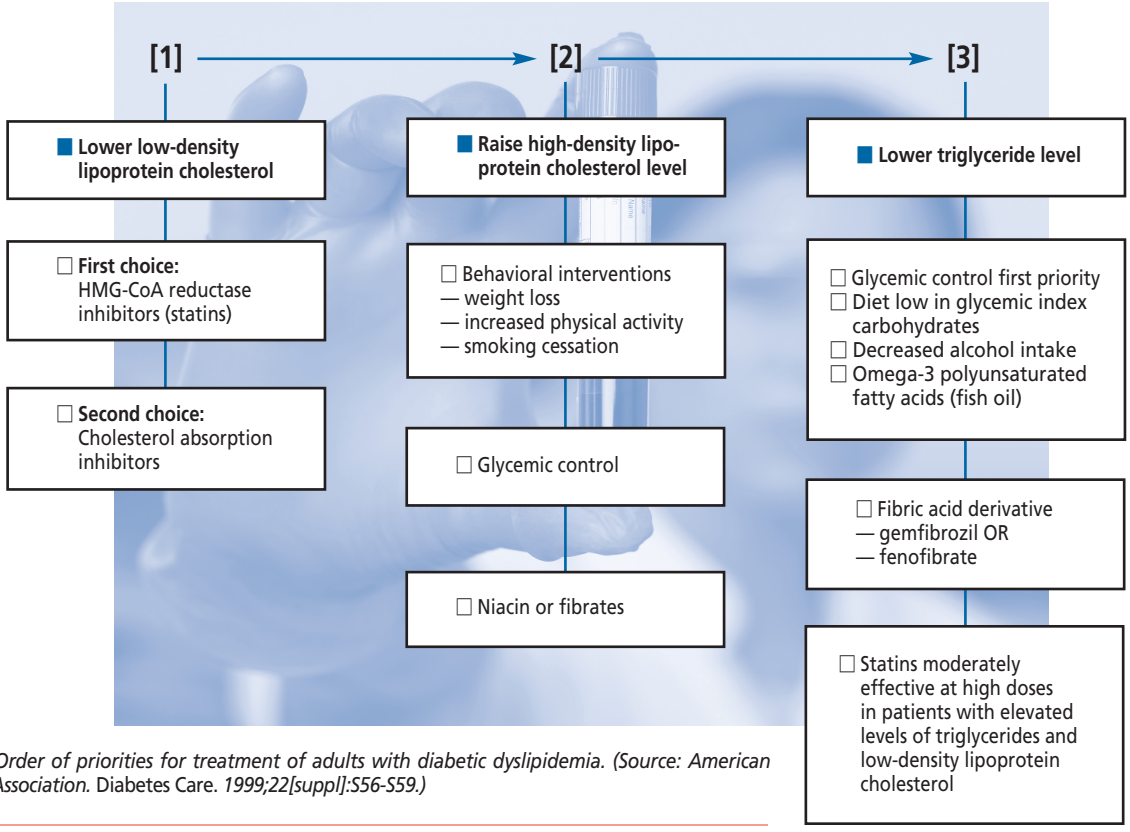

Figure 2. *Order of priorities for treatment of adults with diabetic dyslipidemia. (Source: American Diabetes Association.* Diabetes Care. *1999;22[suppl]:S56-S59.)*

terol in Adults (Adult Treatment Panel III). Final Report. Bethesda, Md: National Cholesterol Education Program. National Heart, Lung, and Blood Institute, National Institutes of Health. NIH Publication No. 02-5215, September 2002.

10. Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials [published online ahead of print April 3, 2006]. *BMJ*. 2006;332:1115-1124.

11. Fontbonne A, Eschwè E, Cambien E, Richard JL, Ducimetière P, Thibult N, et al. Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes. Results from the 11-year follow-up of the Paris Prospective Study. *Diabetologia*. 1989;32:300-304.

12. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213-219.

13. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 western prospective studies. *Circulation*. 2007;15:450-458. Available at: http://circ.ahajournals .org/cgi /content/full/115/4/450. Accessed April 14, 2009.

14. Ginsberg HN. New perspectives on atherogenesis: role of abnormal triglyceride-rich lipoprotein metabolism. *Circulation*. 2002;106:2137-2142. Available at: http://circ.ahajournals.org/cgi/reprint/106 /16/2137. Accessed April 14, 2009.

15. Haskell WL, Lee I-M, Pate rr, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007; 116:1081-1093.

16. Kontush A, Chapman MJ. Antiatherogenic small dense HDL: guardian angel of the arterial wall? *Nat Clin Pract Cardiovasc Med*. 2006;3:144-153.

17. Haskell WL, Lee I-M, Pate RR, Powell KE, Blair SN, Franklin BA, et al; american College of Sports Medicine, American Heart Association. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association [published online ahead of print August 1, 2007]. *Circulation*. 2007;116:1081-1093. Available at: http: //circ.ahajournals.org/cgi/reprint/116/9/1081. Accessed April 14, 2009.

18. GISSI Prevenzione Investigators (Gruppo Italiano per to Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999;354:447-455.

19. Berthold HK, Unverdorben S, Degenhardt R, Bulitta M, Gouni-Berthold I. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: A randomized controlled trial. *JAMA*. 2006;295:2262-2269. Available at: http://jama.ama-assn.org/cgi /content/full/295/19/2262. Accessed April 14, 2009.

20. Gardner CD, Lawson LD, Block, Chatterjee LM, Kiazand A, Balise RR, et al. Effect of raw garlic or garlic supplements on plasma lipid concentrations in adults with hypercholesterolemia: a randomized clinical trial. *Arch Intern Med*. 2007;167:346-353. Available at: http://archinte.ama-assn.org/cgi /content/full/167/4/346. Accessed April 14, 2009.

21. 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.

22. Sherpherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, et al; for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307. Available at: http://content .nejm.org/cgi/content/abstract/333/20/1301. Accessed April 14, 2009.

23. Gotto AM Jr, Whitney E, Stein EA, Shapiro DR, Clearfield M, Weis S, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCaps). *Circulation*. 2000;101:477-484. Available at: http://circ.ahajournals.org/cgi /content/full/101/5/477. Accessed April 14, 2009.

24. Vijan S, Hayward RA. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. *Ann Intern Med*. 2004;140:650-658.

25. Becker DJ, Gordon RY, Morris PB, Yorko J, Gordon YJ, Li M, et al. Simvastatin vs therapeutic lifestyle changes and supplements: randomized primary prevention trial. *Mayo Clin Proc*. 2008;83: 758-764. Available at: http://www.mayoclinic proceedings.com/content/83/7/758.long. Accessed April 14, 2009.

26. Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, et al; Chinese Coronary Secondary Prevention Study Group, Li S. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction [published online ahead of print April 11, 2008]. *Am J Cardiol*. 2008;101:1689-1690.

27. Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme q10 on myopathic symptoms in patients treated with statin medications [published online ahead of print April 3, 2007]. *Am J Cardiol*. 2007;9:1497-1498.

28. Tenkanen L, Mäntiäri M, Kovanen PT, Virkkunen HM, Manninen V. Gemfibrozil in the treatment of dyslipidemia. An 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med*. 2006;166: 743-748. Available at: http://archinte.ama-assn.org /cgi/reprint/166/7/743. Accessed March 4, 2009.

29. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, et al; VA-HIT Study Group. Veterans Affairs High-Density Liporotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events. *JAMA*. 2007;285:1585-1591. Available at: http: //jama.ama-assn.org/cgi/content/full/285/12/1585. Accessed April 14, 2009.

30. Keech A. Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial [published corrections appear in *Lancet*. 2006; 368:1415; 2006;368:1420]. *Lancet*. 2005;366: 1849-1861.

31. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J, et al. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). *Am J Cardiol*. 2005;5:462-468.

32. Ginsberg HN, Bonds DE, Lovato LC, Crouse JR, Elam MB, Linz PE, et al; ACCORD Study Group. Evolution of the lipid portion of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am J Cardiol*. 2007;99:56-67.

33. May HT, Anderson JL, Pearson RR, Jensen JR, Horne BD, Lavasani F, et al. Comparison of effects of simvastatin alone versus fenofibrate alone versus simvastatin plous fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study [published online ahead of print December 26, 2007]. *Am J Cardiol*. 2008;101:486-489.

34. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583-1592. Available at: http://content .nejm.org/cgi/content/abstract/345/22/1583. Accessed April 14, 2009.

35. Zhao XQ, Morse JS, Dowdy AA, Heise N, DeAngelis D, Frohlich J, et al. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). *Am J Cardiol*. 2004;93:307-312.

36. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al; ENHANCE Investigaators. Simvastatin with or without ezetimibe in familial hypercholesterolemia [published online ahead of print March 30, 2008]. *N Engl J Med*. 2008;358:1431-1443. Available at: http://content .nejm.org/cgi/content/abstract/358/14/1431. Accessed April 14, 2009.

37. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al; SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis [published online ahead of print September 2, 2008]. *N Engl J Med*. 2008;359:1343-1356. Available at: http://content .nejm.org/cgi/content/abstract/359/13/1343. Accessed April 14, 2008.

38. Peto R, Emberson J, Landray M, Baigent C, Collins R, Clare R, et al. Analysis of cancer data from three ezetimibe trials [published online ahead of print September 2, 2008]. *N Engl J Med*. 2008;359:1357-1366. Available at: http://content .nejm.org/cgi/content/abstract/359/13/1357. Accessed April 2009.

39. Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney Int Suppl* . May 2003 (84):S207-S216.

40. Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, et al; IMPROVE-IT Investigators. Rational and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with coronary syndromes [published online ahead of print September 2, 2008]. *Am Heart J*. 2008;156:826-832.

41. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists' (CTT) collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins [published online ahead of print September 27, 2005] [published corrections appear in *Lancet*. 2005;366:1358, 2008;371:2084]. *Lancet*. 2005;366:1267-1278.