Management of Dyslipidemia in Women in the Post-hormone Therapy Era

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OBJECTIVE: Cardiovascular disease (CVD) is the leading cause of death for women in the United States and is largely preventable. The American Heart Association has recently released evidence-based guidelines for the prevention of CVD in women; these include gender-specific recommendations for the management of dyslipidemia. This article reviews these recommendations and the evidence supporting them.

DESIGN: This was a qualitative review of a systematic literature search related to lipid guidelines for women and discussion of rationale and evidence for new clinical recommendations.

MAIN RESULTS: Lifestyle modifications are the cornerstone of lipid management. Substantial evidence from randomized clinical trials supports the use of low-density lipoprotein cholesterol-lowering therapy (primarily statins) in all high-risk women and the use of niacin or fibrates when high-density lipoprotein cholesterol is low or non-high-density lipoprotein cholesterol is elevated. Fewer data are available for women at lower or intermediate risk.

CONCLUSIONS: Encouragement of lifestyle modification and appropriate use of lipid-altering therapy will have a substantial impact on reducing the burden of cardiovascular disease in women.

KEY WORDS: lipids; women; cardiovascular disease; prevention guidelines.

DOI: 10.1111/j.1525-1497.2005.40239.x

J GEN INTERN MED 2005; 20:297-305.

Cardiovascular disease (CVD) is the leading cause of death for women in the United States and a major cause of disability.¹ More women die from CVD than from the next 7 causes of death combined. Women are more likely than men to die as a result of their first myocardial infarction, underscoring the importance of primary prevention.² In addition, should they survive, women are approximately twice as likely as men to be subsequently disabled with heart failure or to suffer a second myocardial infarction.¹

One important difference between men and women involves the role of lipids in CVD. Gender differences in lipoprotein levels become apparent at puberty.³ While low-density lipoprotein cholesterol (LDL-C) is a major risk factor in all adults, other lipids and lipoproteins have been shown to be especially potent predictors of risk in women. Gender bias in the awareness, evaluation, and management of dyslipidemia, as well as other cardiovascular risk factors, has also impacted women's health. Moreover, until very recently, hormone ther-

apy was believed to be cardioprotective, based on data from epidemiologic studies and biologic plausibility. However, in the Heart and Estrogen/Progestin Replacement Study (HERS), although hormone therapy reduced LDL-C levels by 11% and increased high-density lipoprotein cholesterol (HDL-C) levels by 10%, it failed to significantly affect any of the cardiovascular outcome measures in women with coronary heart disease (CHD).⁴ Also, in the Women's Health Initiative trial, combination hormone therapy significantly increased the risk of total CVD (hazard ratio, 1.22; 95% confidence interval [CI], 1.09 to 1.36), and estrogen alone conferred no benefit in women without CHD.^{5,6} Consequently, hormone therapy is no longer recommended for managing dyslipidemia or reducing cardiovascular risk in women.⁷

As a result of the gender-specific features of CVD and the changing therapeutic landscape, in 2004 the American Heart Association (AHA) updated its guidelines for CVD prevention in women (first published in 1999).^{7,8} This article reviews the evidence and recommendations concerning the management of dyslipidemia in women.

METHODS

Sources for this review included the 2004 AHA guidelines for CVD prevention in women and its systematic literature search that referenced 40 original research articles and 5 meta-analyses of lipid treatment trials.⁷ Selective searches were also done in MEDLINE for English language articles using key terms *women/sex/gender*, *coronary heart disease*, and *lipids*. In addition, other dyslipidemia treatment guidelines were reviewed and primary and secondary articles known to the author were included.

Lipids Predict Cardiovascular Disease in Women

LDL-C is the major atherogenic lipoprotein in both men and women.⁹ In the United States, mean LDL-C levels are higher in men than women until age 55, at which point they become higher in women. Based on numerous observational and clinical trials, LDL-C can be used to predict the risk of CVD and is the primary target for intervention in either gender. Cohort studies have suggested a 3% decrease in CHD risk for each 1% reduction in total cholesterol,¹⁰ while statin trials have demonstrated a 1% decrease in risk for each 1% reduction in LDL-C.⁹ The CHD reductions achieved in LDL-C-lowering trials, however, still leave absolute rates of CHD events that are well above those observed in populations with low risk.

Triglyceride (TG) and HDL-C levels are also significantly associated with cardiovascular risk. Mean TG levels are higher in men than women, although the difference tends to decrease with increasing age.⁹ However, the association between TG level and risk is stronger in women than in men. In a meta-analysis of 17 population-based studies, a 1 mmol/L (89 mg/dl) increase in TG levels was associated with a 76% increase in the risk of CVD in women, compared with a 32% increased risk in men.¹¹ Even after adjustment for other risk factors, includ-

Accepted for publication July 1, 2004

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ing HDL-C, TGs remained significantly associated with increased risk in women (37%) and men (14%). Moreover, analyses from the Lipids Research Clinic showed that TG was a better predictor of CVD risk than LDL-C in women¹² and that non-HDL-C was a better predictor in both genders, although this association was stronger in men than in women.¹³

HDL-C levels are higher in adult women than men for each decade of life,³ and are strongly associated with CHD risk in women. The Framingham Heart Study showed a significant 6-fold difference in risk of myocardial infarction between the upper and lower quartiles of HDL-C in women ($P < .001$), but only an insignificant, 1.7-fold difference in men.¹⁴ Similarly, in a pooled analysis of 22 population studies, low levels of HDL-C remained a significant predictor of risk in older women but not in older men.¹⁵ Studies have also found that HDL-C is the most powerful predictor of CVD risk in women.^{12,16,17} These results suggest the importance of the total lipid profile, and not just LDL-C alone, to evaluate risk in women.

Other emerging risk factors may also contribute to CVD risk in women. In a prospective case-control study involving 28,263 postmenopausal women, cardiovascular risk was 4.4-fold higher (95% CI, 2.2 to 8.9) in women in the highest, as compared with the lowest, quartile for C-reactive protein.¹⁸ In the placebo arm of HERS, the baseline level of lipoprotein Lp(a) correlated significantly with the risk of subsequent cardiovascular events.¹⁹ In addition, LDL particle size decreases and particle number increases following menopause; these variables also correlate with CVD risk.^{3,20} Determining levels of these emerging risk factors may be beneficial in some women who fall into an intermediate-risk category, but the value of routine screening has not been established.

Randomized Clinical Trial Evidence for Beneficial Effects of Dyslipidemia Therapy

In early clinical studies of dyslipidemia therapy, women were either excluded or largely underrepresented.^{21–24} It was not until the 1990s that women were routinely included in clinical studies, although even then they were frequently underrepresented.^{25–35} Nonetheless, the new AHA guidelines are based on the best available evidence from randomized clinical trials and large prospective cohort studies evaluating CVD risk-reducing interventions, whether or not women were included.⁷ The summary evidence tables (published online at <http://www.circulationaha.org>) include results from 40 original studies of lipid-altering therapies, 52 studies of physical activity, and 68 dietary studies, with gender-specific information provided when available.

Lifestyle Changes. Observational studies of lifestyle therapies suggest the potential to reduce the development and progression of CVD as well as the development of major CVD risk factors, which might limit the need for future interventions.⁷ For example, the Nurses' Health Study remains the largest cohort study of women ($N=84,129$) who had no evidence of CHD initially. Fourteen years later, diet, exercise, and smoking status were each independently associated with risk for developing CHD.³⁶ The vast majority of coronary events (82%) were primarily attributed to deviations from a heart-healthy lifestyle. However, an inherent limitation of observational studies is the potential for unmeasured confounders to affect outcomes,

particularly when looking at health care behaviors. Although there are far fewer randomized controlled trials of lifestyle interventions, 2 secondary prevention studies demonstrated significant reductions in coronary events with diet and smoking interventions.^{37,38}

Pharmacotherapy. Subgroup analyses from landmark statin trials—including the Air Force/Texas Coronary Atherosclerosis Prevention Study, the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) study, and the Long-term Intervention with Pravastatin in Ischaemic Disease trial—suggested that dyslipidemia therapy in women produced reductions in cardiovascular risk similar to those observed in men (Table 1).^{25–35,39} Absolute risk reductions varied from study to study, depending on the specific population evaluated and the variables assessed; also, some of the studies lacked sufficient power to determine the significance of risk reductions in women.^{25–28} However, a meta-analysis of these primary and secondary prevention trials that included nearly 4,000 women found that overall relative risk of major coronary events was reduced by 29% in women and 31% in men.⁴⁰ Similarly, in the Heart Protection Study (HPS), which included more than 5,000 women, statin therapy reduced major vascular events by 20% in women and 25% in men.²⁹

In contrast, the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm did not show a significant benefit of statin therapy in women. However, this was likely due to the small sample size, the small number of CHD events observed, and the fact that the primary outcomes were restricted to fatal and nonfatal CHD events.³⁴ Because the ratio of stroke to CHD events is greater in women than men,¹ it is important to evaluate all cardiovascular events, especially in women. Moreover, women are more likely to present with unstable angina than myocardial infarction compared with men.¹ Two other trials, one in elderly individuals and another in hypertensive patients, also showed little benefit in either men or women.^{33,35} Despite these results, the totality of evidence from statin trials demonstrates significant and comparable benefits in both men and women.

Similar reductions in cardiovascular risk have been reported in trials with other lipid-altering agents, although the evidence is primarily in men. The first large-scale prevention trial, the Coronary Drug Project, included 1,119 men with CHD who were treated with niacin monotherapy.²² After 6 years, they showed a 14% reduction in coronary events (nonfatal myocardial infarction and CHD death) compared with the placebo cohort. At follow-up 9 years after study end, there was an 11% relative reduction in total mortality among the original niacin cohort, primarily due to a reduction in CHD deaths.⁴¹ In another secondary prevention trial, the Veterans Affairs High-density Lipoprotein Intervention Trial, gemfibrozil reduced the relative risk of coronary events by 22% among 1,264 men with CHD, low levels of HDL-C, and mildly elevated levels of LDL-C.⁴² In the Helsinki Heart Study, a primary prevention trial, treatment with gemfibrozil reduced the relative incidence of coronary events by 34% in 2,051 men with hyperlipidemia.²¹

Combination studies with niacin and fibrates have also been shown to reduce cardiovascular risk in both men and women.^{24,43,44} For example, in the Stockholm Ischaemic Heart Disease Secondary Prevention Study, in which approximately 20% of the study subjects were women ($n=113$), the combination of clofibrate and niacin reduced CHD and total mortal-

Table 1. Gender Effects in Large Statin Trials

Study	Population (N)		Primary End Point	Relative Risk (95% CI) in Men and Women	Relative Risk (95% CI) in Women
	Total	Women (%)			
Primary prevention					
AFCAPS/ TexCAPS ^{2 8,30}	6,605 adults with average TC	997 (15)	Sudden cardiac death, MI, or unstable angina	0.63 (0.50 to 0.79)	0.54 (0.22 to 1.35)
Secondary prevention					
4S ^{27,31}	4,444 Adults with MI/angina and elevated TC	827 (19)	All-cause mortality CHD death, MI, or resuscitated arrest	0.70 (0.58 to 0.85) 0.66 (0.59 to 0.75)	1.16 (0.68 to 1.99) 0.66 (0.48 to 0.91)
CARE ^{26,32}	4,159 Adults with MI and average TC	576 (14)	CHD death or MI	0.76 (0.64 to 0.91)	0.57 (0.34 to 0.96)
LIPID ²⁵	9,014 Adults with MI/angina and average TC	1,516 (17)	CHD death or MI	0.76 (0.68 to 0.85)	0.89 (0.67 to 1.18)
Mixed primary and secondary prevention					
HPS ²⁹	20,536 adults with CHD, other vascular disease, or diabetes	5,082 (25)	CHD death or MI, stroke, or revascularization	0.76 (0.72 to 0.81)	0.80 (0.70 to 0.92)
PROSPER ³³	5,804 adults aged 70–82 years with vascular disease or diabetes	3,000 (52)	CHD death or MI, or stroke	0.85 (0.74 to 0.97)	0.96 (0.79 to 1.18)
ASCOT-LLA ³⁴	10,305 adults with HTN + 3 CV risk factors	1,942 (19)	CHD death or MI	0.64 (0.50 to 0.83)	1.10 (0.57 to 2.12)
ALLHAT-LLT ³⁵	10,355 adults with average TC, HTN, and 1 additional CHD risk factor	5,051 (49)	All-cause mortality CHD death or MI	0.99 (0.89 to 1.11) 0.91 (0.79 to 1.04)	0.98 (0.83 to 1.17) 1.02 (0.81 to 1.28)
PROVE-IT ^{39*}	4,162 adults with ACS	911 (22)	CHD death, MI, stroke, revascularization, and unstable angina with hospitalization	0.84 (0.74 to 0.95)	0.75 (0.60 to 0.95)

*PROVE-IT was an active-control trial that evaluated moderate versus intensive statin therapy over 2 years compared with the other trials which evaluated statin monotherapy versus placebo over ~5 years.

AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm; CARE, Cholesterol and Recurrent Events Trial; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HPS, Heart Protection Study; HTN, hypertension; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease Study; MI, myocardial infarction; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy Study; 4S, Scandinavian Simvastatin Survival Study; TC, total cholesterol.

ity by 36% and 26%, respectively, compared with placebo among the total study population.²⁴ The High-density Lipoprotein Atherosclerosis Treatment Study was an angiographic study in which 13% of 160 patients were women ($n=27$). The combination of niacin plus simvastatin produced a mean regression in coronary stenoses and reduced the risk of the clinical end point of coronary death, myocardial infarction, stroke, or revascularization for worsening ischemia by 90% ($P=.03$) compared with placebo.⁴³

Although the quantity of clinical trial data supporting the efficacy and safety of lipid-altering therapy in women is not as great as in men, the evidence demonstrates that the effects are generally comparable. Thus, the data and results obtained from clinical trials of dyslipidemia therapy involving men should also be generalizable to women.

American Heart Association Clinical Guidelines for Women

Based on the accumulating epidemiologic and clinical trial data, the AHA has developed the first evidence-rated guidelines for CVD prevention specifically in women.⁷ The guidelines include recommendations for risk assessment, optimal lipid levels, and treatment strategies for women. A basic principle of National Cholesterol Education Program Adult Treatment Panel III (ATP III) and the new AHA guidelines is that dyslipidemia treatment is tailored to each individual's global cardiovascular risk. Major risk factors in women include smoking, hypertension, dyslipidemias, diabetes, obesity, sedentary lifestyle, an atherogenic diet, and a family history of premature CHD. Sim-

ilar to ATP III, women are stratified into 3 risk groups—high, intermediate, and lower—based on clinical diagnoses (e.g., established CHD) and on absolute 10-year CHD risk using the Framingham Risk Score for women (Table 2).⁷ In addition, a new group—optimal risk—was created for women who have desirable levels of risk factors and who engage in a heart-healthy lifestyle. Optimal lipid and lipoprotein levels for women include LDL-C < 100 mg/dl, TG < 150 mg/dl, non-HDL-C < 130 mg/dl, and HDL-C > 50 mg/dl. Last, while LDL-C remains the primary target of dyslipidemia therapy, the guidelines also include secondary targets for non-HDL-C, TG, and HDL-C, dependent on a woman's risk status.

Management of Dyslipidemia

The primary goal of dyslipidemia therapy is to provide for optimal cardiovascular health. The first step in meeting this goal should be lifestyle changes, including smoking cessation, healthy diet, and exercise.^{7, 9} A heart-healthy diet that is well balanced, diversified, low in saturated fat, and high in fiber should be recommended. Overweight women should be encouraged to gradually lose weight and can benefit from formal nutrition counseling. In addition, all women should be encouraged to perform at least 30 minutes of moderate-intensity exercise per day.

For women with LDL-C levels above goal, a stricter diet is recommended, with fat intake limited to 25% to 35% of total calories and < 7% from saturated fats, cholesterol intake limited to < 200 mg/day, and reduced intake of *trans* fatty acids.⁷ Diet can be readily assessed using MEDFICTS, a simple ques-

Table 2. Global Risk, and Thresholds for Pharmacotherapy⁷

Risk Level	Clinical History	Initiate Pharmacotherapy
High 10-yr risk > 20%	CHD CHD risk equivalents Diabetes Chronic kidney disease	LDL-C < 100 mg/dl Statin concurrent with TLC LDL-C ≥ 100 mg/dl Statin, concurrent with TLC Non-HDL-C ≥ 130 and/or HDL-C < 50 mg/dl Niacin or fibrate
Intermediate 10-yr risk 10%–20%	Subclinical CHD Metabolic syndrome 2+ RFs or 1 very elevated RF First-degree relative with premature CHD	LDL-C ≥ 130 mg/dl Statin after TLC Non-HDL-C ≥ 160 and/or HDL-C < 50 mg/dl Niacin or fibrate after LDL-C goal achieved
Lower 10-yr risk < 10%	Metabolic syndrome 2+, 1, or 0 RFs	LDL-C ≥ 190 mg/dl Statin after TLC Non-HDL-C ≥ 220 and/or HDL-C < 50 mg/dl Niacin or fibrate after LDL-C goal achieved

Adapted from the American Heart Association evidence-based guidelines for cardiovascular disease prevention in women.⁷

CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RF, risk factor; TLC, therapeutic lifestyle changes. To convert LDL-C to mmol/L: mg/dl × 0.02586.

tionnaire designed to evaluate fat intake (available in ATP III).⁹ Plant stanols and sterols, such as enriched margarines and spreads, can also be incorporated into dietary changes to augment LDL-C reduction. Ingestion of 2 to 3 g/day of plant stanol or sterol esters typically reduces LDL-C by 6% to 15%.⁹ Fish oils/omega-3 fatty acids have been shown to reduce TG levels, and epidemiologic studies suggest a beneficial effect on CVD.^{45–48} Although clinical trials have yielded mixed results, the new guidelines recommend increased consumption of fish, at least 2 servings per week.^{7,45} Supplements can be considered for women who do not eat fish who are at high risk of CVD. It is important that these lifestyle changes be continually reinforced at all patient encounters.

Pharmacotherapy should be instituted when lifestyle changes alone do not achieve lipid goals and, in high-risk women, may be initiated simultaneously. Currently there are 5 classes of drugs for lipid lowering—statins, bile acid sequestrants, cholesterol absorption inhibitors, niacin, and fibrates—with each class having differing effects on the lipid profile (Table 3).^{49,66} When used appropriately as monotherapy or in combination, these drugs can control most lipid abnormalities.

Statins. Statins are the most effective class of drugs currently available for reducing LDL-C. Decreases of 30% to 40% are seen at standard daily doses used in clinical studies (atorvastatin 10 mg, fluvastatin 40 to 80 mg, lovastatin and pravastatin 40 mg, rosuvastatin 5 to 10 mg, and simvastatin 20 to 40 mg), with larger reductions available at higher doses.⁶⁷ In addition, they reduce TGs to moderate degrees and produce modest increases in HDL-C. Of the 5 classes of lipid-altering drugs, statins have the strongest specific evidence for efficacy in women (Table 1). In addition, statins are safe and well tolerated. Their use has been associated with hepatotoxicity and myopathy, but these occur at very low rates.⁶⁸ Elevated serum transaminases occur in ≤ 2% of patients and progression to more severe liver disease is very rare.

Rhabdomyolysis is a safety issue in both men and women that has been a recent topic of concern. Cerivastatin was withdrawn from the market in August 2001 because of an increased risk of fatal rhabdomyolysis, especially when cerivastatin was combined with gemfibrozil.⁶⁹ Other medica-

tions that can enhance the risk of myopathy when given concurrently with a statin include fibrates (especially gemfibrozil), niacin, verapamil, amiodarone, nefazodone, cyclosporine and some azole antifungals, macrolide antibiotics, and HIV protease inhibitors.⁶⁸ However, statins used alone and in combination have proven to be extremely safe in the vast majority of patients.^{68,70} Fatal rhabdomyolysis is a rare event, reported in < 1 per million statin prescriptions.^{68,71} This risk can be further reduced by attention to factors that increase the risk of myopathy, such as advanced age (particularly in women), the presence of multisystem disease, and the use of multiple medications or specific concomitant medications. The incidence of myopathy is < 0.1% in patients not receiving concomitant medications that may enhance risk.⁷² Additional preventive steps include counseling patients to immediately report muscle discomfort, muscle weakness, or brown urine.⁶⁸

Statins are preferred as first-line therapy to lower elevated LDL-C levels in women (Table 2). In high-risk women, statin therapy should be begun concurrently with lifestyle changes if LDL-C is ≥ 100 mg/dl. Furthermore, statin therapy is also recommended for high-risk women with LDL-C < 100 mg/dl, unless contraindicated. This recommendation is bolstered by recent trials showing incremental angiographic and outcome benefits in CHD patients at LDL-C levels well below 100 mg/dl.³⁹ Because of these data, a recent update from the NCEP ATP III panel has suggested an LDL-C goal of < 70 mg/dl is optimal among very high-risk patients.⁷³

Bile Acid Sequestrants. Bile acid sequestrants primarily lower LDL-C, have only a minimal effect on HDL-C, and can actually increase TG levels. When used alone or in combination with other lipid-altering agents, bile acid sequestrants have been shown to reduce CVD events in men.^{74,75} In the Familial Atherosclerosis Treatment Study, which enrolled 146 men with known coronary disease, the combination of lovastatin and colestipol produced angiographic improvement and a 70% reduction in CVD outcomes compared with placebo.⁷⁵

Bile acid sequestrants are not absorbed and thus lack systemic toxicity and are an excellent option for women of child-bearing age who are not using oral contraceptives.^{9,76} Granular preparations are bulky and inconvenient to use

Table 3. Current Pharmacologic Therapy for Dyslipidemia

Drug	FDA-approved Daily Dosage	Percent Lipid Change				Major Side Effects
		TC	LDL-C	HDL-C	TG	
HMG-CoA reductase inhibitors (statins)*						
Atorvastatin— <i>Lipitor</i> ^{®49}	10–80 mg qd	–29 to –45	–39 to –60	6 to 5	–19 to –37	Myopathy Increased liver enzymes
Fluvastatin <i>Lescol</i> ^{®50}	20 mg qd to 40 mg bid	–17 to –27	–22 to –36	3 to 6	–12 to –18	
<i>Lescol</i> ^{® XL} (extended-release) ⁵¹	80 mg qd	–25	–35	7	–19	
Lovastatin— <i>Mevacor</i> ^{®52}	10–40 mg bid	–17 to –29	–24 to –40	7 to 10	–10 to –19	
Pravastatin— <i>Pravachol</i> ^{®53}	20–80 mg qd	–24 to –27	–32 to –37	2 to +3	–11 to –19	
Simvastatin— <i>Zocor</i> ^{®54}	20–80 mg qd	–28 to –36	–38 to –47	8 to 8	–19 to –24	
Rosuvastatin— <i>Crestor</i> ^{®55}	5–40 mg qd	–33 to –46	–45 to –63	13 to 10	–35 to –28	
Bile-acid sequestrants						
Cholestyramine granules <i>Questran</i> [®] powder ⁵⁶	8–12 g bid	–9 to –13	–15 to –20	2 to 6	11 to 17	GI distress Constipation Decreased absorption of other drugs
Cholestyramine Light packets						
<i>Questran Light</i> [®] granules ⁵⁶	8–12 g bid	–9 to –13	–15 to –20	2 to 6	11 to 17	
<i>Prevalite</i> [®] packets ⁵⁷	8–12 g bid					
Colestipol						
<i>Colestid</i> [®] granules ⁵⁸	5 g qd or bid	–8 to –15	–12 to –25	–0.4 to 1.5	7 to 25	
<i>Colestid</i> [®] tablets ⁵⁹	2–16 g qd or divided					
Colesevelam—<i>Welchol</i>[™]						
tablets ⁶⁰	3.8 g qd	–7	–15	3	10	
	4.5 g bid	–10	–18	3	9	
Cholesterol absorption inhibitors						
Ezetimibe— <i>Zetia</i> ^{™61}	10 mg qd	–13	–18	1	–8	GI distress Fatigue Musculoskeletal System disorders
Niacin[†]						
Immediate-release— <i>Niacor</i> ^{®62}	0.5–2 g tid	–10 to –20	–10 to –20	20 to 35	–30 to –70	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity
Extended-release— <i>Niaspan</i> ^{®63}	1–2 g qhs	–5 to –12	–7 to –16	14 to 22	–16 to –38	
Fibrates						
Gemfibrozil— <i>Lopid</i> ^{®64}	600 mg bid	–11	–7	8	–35	GI distress Gallstones
Fenofibrate— <i>Tricor</i> ^{®65}	160 mg qd	–19	–21	11	–30	Myopathy
Multiclass agents						
Niacin extended-release/ lovastatin— <i>Advicor</i> ^{™66}	1000/20–2000/ 40 mg qhs	—	–30 to –42	20 to 30	–39 to –44	(See niacin and statins)
Ezetimibe/simvastatin— <i>Vytorin</i> ^{™94}	10/10–10/80 mg qhs	–34 to –43	–46 to –59	10 to 12	–26 to –35	(See ezetimibe and statins)

*For initial treatment of patients with only modest elevations of LDL-C or a history of poor tolerance for these drugs, some physicians use lower doses.

[†]Some niacin products are available as OTC preparations.

Bid, twice daily; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OTC, over the counter; qd, once daily; TC, total cholesterol; TG, triglycerides; tid, three times daily.

and produce various gastrointestinal symptoms, including constipation. However, 2 tablet formulations (colestipol and colesevelam) are also available. Bile acid sequestrants reduce the absorption of a number of other drugs, and concomitant medications should be administered at least 1 hour before or 4 hours after dosing. Of the available sequestrants, colesevelam is the most potent and appears to have a lower likelihood of adverse effects.^{77–79} Bile acid sequestrants, alone or combined with a statin, are useful in the treatment of women with elevated LDL-C.

Cholesterol Absorption Inhibitors. Ezetimibe is the first specific cholesterol absorption inhibitor approved for use in the United States. Ezetimibe produces a moderate reduction in LDL-C, a mild reduction in TGs, and a mild increase in HDL-C.^{80,81} Its

efficacy appears to be similar in men and women. Safety data are principally limited to short-term clinical trial experience, in which adverse effects and discontinuation rates among treated patients were similar to those in the placebo group.⁶¹ Ezetimibe can be administered as monotherapy or in combination with a statin to augment LDL-C lowering. In one study, the addition of ezetimibe 10 mg/day to a statin produced additional changes in LDL-C of –21%, TG of –11%, and HDL-C of +2%.⁸² However, the effects of ezetimibe on cardiovascular morbidity and mortality have not been established in controlled clinical trials.

Niacin. Niacin, a water-soluble B vitamin, is the most effective drug available for raising HDL-C levels.⁹ It also decreases TGs, lipoprotein Lp(a), and a modest effect on LDL-C levels. The re-

duction in LDL-C appears to be greater in women than in men.^{83,84} The most common side effect of niacin is flushing of the skin.^{9,85} This effect occurs equally in men and women and can be reduced by taking aspirin or ibuprofen 30 to 60 minutes prior to taking niacin and by starting with a low dose and gradually titrating to the desired response.⁸⁶ Over time, most individuals develop tolerance to this effect. Niacin can also cause gastrointestinal symptoms, hepatotoxicity, hyperuricemia and gout, and hyperglycemia. These latter reactions appear to be dose related, occurring more frequently at doses ≥ 2 g.⁹ Certain adverse effects are also formulation dependent: immediate-release niacin is associated more with flushing, and some long-acting preparations are associated with increased hepatotoxicity.⁸⁷ A once-daily extended-release niacin has been shown to produce less flushing than plain niacin, without increased hepatic effects.^{9,88}

In the new AHA guidelines, niacin is recommended for the treatment of low HDL-C and elevated non-HDL-C in women at high risk. Treatment of these abnormalities can be started concurrently with LDL-C-lowering therapy, while in women with lower levels of risk, treatment should be considered once the LDL-C goal is reached. Three niacin preparations are available by prescription and approved by the U.S. Food and Drug Administration (FDA) for the treatment of dyslipidemia^{62,63} (Table 3). Some niacin preparations are available over the counter (OTC) as dietary supplements. These preparations are not regulated by the FDA, may vary in their pharmacologic characteristics and therapeutic effects, and should not be substituted for prescription niacins.^{7,89} All niacin preparations should be used only under the supervision of a health care provider.

Fibrates. Fibric acid derivatives, or fibrates, produce large reductions in TG levels and moderate increases in HDL-C levels.^{9,90} Fibrates also produce a modest reduction in LDL-C levels in patients with primary hypercholesterolemia, although levels may increase in patients with hypertriglyceridemia. Fibrates are generally well tolerated, with predominantly gastrointestinal side effects. They can increase the lithogenicity of bile, raising the risk for cholesterol gallstones. They also bind strongly to albumin and can displace other drugs, such as warfarin.

Both statins and fibrates carry a small risk of myopathy, which is increased when they are used in combination.⁹¹ However, even this combination can be used safely in the majority of patients. Of nearly 600 patients receiving a statin-fibrate combination in controlled clinical trials, only 1% developed a creatine kinase level greater than 3 times the upper limit of normal without muscle symptoms, and only 1% withdrew from therapy because of muscle pain.⁹ In the new AHA guidelines, fibrates are also recommended for the treatment of elevated non-HDL-C and low HDL-C in women at high risk. Treatment can be started concurrently with LDL-C-lowering therapy. In women with intermediate levels of risk, treatment should be considered once the LDL-C goal is reached.

The choice between adding niacin or a fibrate to statin therapy will depend on the type of dyslipidemia being treated and side effect profiles. Niacin is particularly useful for patients with low HDL-C who may also require further moderate reductions in TG and LDL-C, while fibrates are more useful for those with high TG who may also require moderate increases in HDL-C. Statin-niacin combinations are contraindicated in patients with chronic liver disease and severe gout and should be used with care in those with hyperuricemia and diabetes.

Flushing, particularly with immediate-release preparations, can also impact tolerability. Statin-fibrate combinations are contraindicated in patients with severe liver or kidney disease and should be used with care in those at risk of myopathy.⁹

Single-pill Combination Therapy. Combination therapy may be necessary to achieve intensive and/or multiple lipid goals, especially in individuals who have severe forms of hyperlipidemia or mixed dyslipidemia. Combination products may also improve patient compliance. A once-daily tablet containing extended-release niacin plus lovastatin is available for the treatment of mixed dyslipidemia.⁹² In a long-term study, extended-release niacin-lovastatin reduced LDL-C, TG, lipoprotein Lp(a), and C-reactive protein levels and increased HDL-C levels in a dose-dependent manner.⁹³ Flushing was the most common adverse effect.^{92,93} No serious hepatotoxicity or myopathy was reported; however, niacin in combination with a statin has been rarely associated with myopathy.⁶⁸ Other adverse effects causing discontinuation were similar to those seen with statin monotherapy. This drug combination can correct most forms of complex dyslipidemia and should be useful in women because of the strong associations between cardiovascular risk and abnormalities in HDL-C and TGs.

Most recently, a once-daily combination containing ezetimibe and simvastatin has been approved for the treatment of high LDL-C.⁹⁴ In a placebo-controlled study, ezetimibe-simvastatin reduced TC, LDL-C, and TG levels in a dose-dependent manner.⁹⁵ Increases in HDL-C were similar across doses. The combination was more effective at lowering TC, LDL-C, and non-HDL-C than simvastatin⁹⁵ or atorvastatin⁹⁶ alone. In a pooled analysis, the incidence of liver enzymes $>3 \times$ ULN was 1.7% and was dose related.⁹⁴ This drug combination can correct elevations of LDL-C $>50\%$, and should be a useful option in women with primary hypercholesterolemia. Other combination products for dyslipidemia are also in development.⁹⁷

Herbal Medications/Dietary Supplements. Approximately 14% of people in the United States take herbal medications and approximately 40% take dietary supplements for their "health,"^{98,99} with rates of use higher in women than in men.⁹⁹ Because many patients may be using supplements without the knowledge of their health care provider, it is important to inquire about such use. Although herbal therapy and diet supplements are often perceived as natural and harmless, it is important to discuss potential side effects with patients.

High intake of soy protein has well-documented efficacy in lowering LDL-C and TG levels,¹⁰⁰ although soy's effects on cardiovascular events in postmenopausal women have not been proven.¹⁰¹ ATP III guidelines recommend soy protein as an acceptable replacement for animal proteins, with their higher saturated fat content.⁹ Phytoestrogens are found in soybean, rather than soy protein, and their benefits and risks are uncertain.¹⁰²

Antioxidants were thought to potentially lower CVD risk, as oxidative changes are an important component of the pathophysiology of atherosclerosis. Numerous clinical trials, however, have not supported this assumption.¹⁰³⁻¹⁰⁶ Consequently, antioxidants are not recommended for CVD prevention in women.⁷

Cholestin, a product related to the red yeast rice that has been used for centuries in China as a food colorant and flavor enhancer, has been promoted as a dietary supplement to re-

duce cholesterol.¹⁰⁷ However, cholestin contains approximately 0.4% statins by weight, and it is these statins that appear to account for the product's cholesterol-lowering effect.¹⁰⁷ Consequently, the FDA has categorized cholestin not as a supplement but as an unapproved drug.¹⁰⁷ It is still being marketed to patients, however, from sites outside of the United States via the Internet.

Missed Opportunities and Barriers to Prevention

Although data clearly demonstrate the beneficial effects of lifestyle changes and pharmacotherapy in patients with dyslipidemia, opportunities to promote such strategies are frequently missed in clinical practice. Furthermore, multiple studies demonstrate a serious underutilization of lipid-altering therapy, particularly among women. The Lipid Treatment Assessment Project, a large multicenter study, found that only 37% of women and 39% of men overall achieved their LDL-C goal; among high-risk patients, women were still significantly less likely than men to achieve goal.¹⁰⁸ Similarly, among CHD patients enrolled in the Prospective Evaluation of the Vascular Events of Norvasc Trial, although LDL-C levels improved during the study, only 31% of men and 12% of women were at goal at the end of the study.¹⁰⁹ In a recent evaluation of lipid management among high-risk women in a managed care setting, only one third were on recommended drug therapy and only 12% had optimal levels of lipids.¹⁰⁹ A national study showed that women may have received less prevential care than men because they are perceived to be at lower risk, despite similar calculated risk levels.

Other barriers to lipid management include the general lack of understanding among women about their actual risks for CHD. A 2003 survey assessed contemporary awareness, perceptions, and knowledge about CVD risk among American women.¹¹¹ Only 46% of respondents spontaneously identified heart disease as the leading cause of death in women, although this awareness represents an increase from 30% in 1997 ($P < .05$) and 34% in 2000 ($P < .05$). Furthermore, only 38% of women recalled discussing CVD prevention with their health care providers. To reduce the growing burden of CHD in women, multiple strategies to improve awareness and manage risk factors will be necessary. Physicians who educate women patients about the risk of CVD and then follow through with appropriate evaluation and treatment can greatly improve the management of dyslipidemia and cardiovascular risk. Additional interventions include the use of electronic supports (phone or web-based), case management, collaborative care models, and specialized lipid clinics.⁹

Conclusion

Compelling evidence demonstrates that CVD risk can be significantly reduced by appropriate management of dyslipidemia in women. Despite this, utilization of lipid-altering therapy in women remains suboptimal. Lifestyle changes are a cornerstone of therapy, yet often are not maximally employed. Currently available pharmacotherapy can address a variety of lipid disorders and, when used appropriately, may have a substantial impact on the burden of CHD in women.

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