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STATE-OF-THE-ART PAPER

Perspectives on Dyslipidemia and Coronary Heart Disease in Women

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Coronary heart disease (CHD) remains the leading cause of death among American women. Numerous differences exist between younger and older women and between women and men with respect to the pathology of CHD and its incidence and prevalence over the life cycle. Differences in lipoprotein levels and lipid fractions play an important role in CHD risk. Hormonal influences on lipoprotein levels in women are complex, change throughout the life span, and are influenced by the administration of oral contraceptives and hormone replacement therapy. Women with obesity, metabolic syndrome, or diabetes have lipid profiles that adversely affect CHD risk. To date, no randomized trials testing the impact of lifestyle changes on lipoprotein levels and subsequent CHD events in non-institutionalized women have been performed, and women have not been well represented in clinical end point trials of pharmacologic lipid-lowering therapy. Available evidence suggests that lipid-lowering therapy with statins does provide benefit in reducing the risk of coronary events in women; however, women remain undertreated, and more data are needed to determine optimal cardiovascular prevention and treatment in this population. (J Am Coll Cardiol 2005;46:1628–35) © 2005 by the American College of Cardiology Foundation

Coronary heart disease (CHD) is the single leading cause of death among American women, as it is among American men (1), even though CHD is less common and occurs later in life in women than men (2). In 2002, the prevalence of myocardial infarction (MI) in women was 3 million, and 3.3 million women had a history of angina pectoris; overall prevalence of CHD was 5.9 million (2). Every year, 345,000 women suffer a new or recurrent MI, and 241,600 women die of an MI (2). From 1970 to 2001, hospital discharges related to CHD for women increased 47% (2). Clearly, women, and particularly postmenopausal women, remain at high risk for coronary events—at least in part because women have been under-represented in clinical outcomes trials, tend to be undertreated in the clinical setting, and might be misdiagnosed when their presenting symptoms differ from those of men (3).

GENDER DIFFERENCES IN PRESENTATION OF CORONARY ATHEROSCLEROSIS

Coronary atherosclerosis starts in early childhood and increases with age (4). A close correlation exists between traditional cardiovascular risk factors and extent of atherosclerotic involvement in male and female children and adolescents that is analogous to that seen among adults. Moreover, atherosclerosis is most pronounced among individuals with multiple coexistent risk factors (4). Autopsy data from the Pathobiological Determinants of Atherosclerosis in Youth Research Group show that girls and young women tend to have less extensive atherosclerotic involvement than their age-matched male counterparts (5). Among young adults, women have lesser degrees of coronary calcification than men (6). Coronary calcification increases with age in both genders, but women lag behind men by about 10 to 15 years (7). Numerous coronary angiographic studies have shown lesser degrees of epicardial coronary artery disease among women than among similarly aged men. This gender discrepancy holds true after stratification by symptoms (typical angina, atypical angina, non-anginal chest pain) (8) and in populations without symptoms of CHD who undergo coronary angiography in preparation for valvular surgery (9).

Angiographic and intravascular ultrasound studies show that women have smaller coronary arteries than men, even after correcting for body surface area (10,11); however, the remodeling that occurs in coronary arteries as atherosclerotic plaque accumulates seems to be similar in women and men (12). The ultrasound appearance of lesions slated for percutaneous intervention is similar in terms of plaque burden, calcium content, and eccentricity (13). Data on gender differences in plaque composition are limited. Eggen et al. (14) reported in 1965 that plaques among women were less calcified than those among men. An intravascular ultrasound study by Rasheed et al. (15) showed a trend toward a greater proportion of hard plaques in men compared with women (47% vs. 33%, $p = 0.06$). In an autopsy study of individuals >40 years of age who died >1 year after

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Abbreviations and Acronyms

ALLHAT = Antihypertensive and Lipid-Lowering Trial to Prevent Heart Attack
ATP III = Third Report of the Adult Treatment Panel
CHD = coronary heart disease
CVD = cardiovascular disease
HDL = high-density lipoprotein
HERS = Heart and Estrogen/progestin Replacement Study
LDL = low-density lipoprotein
Lp(a) = lipoprotein(a)
MI = myocardial infarction
RLP = remnant-like particle

coronary artery bypass graft, women had greater amounts of cellular fibrous tissue and lesser amounts of dense fibrous tissue in both native coronary arteries and saphenous vein grafts, although there were no gender differences in the severity of obstruction or in the amount of intracellular lipid or degree of inflammatory infiltration (16). The same group reported large amounts of lipid-containing foam cells and relative lack of acellular scar tissue in women <40 years of age (17).

Although patients of both genders with MIs tend to present with thrombotic coronary occlusions, the precipitating events might be different. In at least one autopsy series, women were twice as likely as men to have plaque erosion (37% vs. 18%), whereas plaque rupture was more common among men than women (82% vs. 63%) (18). Among sudden death victims, Burke et al. (19) found that acute coronary thrombosis was related to plaque erosion among younger, presumably premenopausal women, whereas plaque rupture with superimposed thrombus or healed infarct without thrombosis was the characteristic finding among older, presumably postmenopausal women. Risk profiles in these women also differed: smoking was associated with plaque erosion, glycosylated hemoglobin with stable plaque and healed infarct, higher total cholesterol with plaque rupture, and hypertension with stable plaque and healed infarct (19). The authors suggested that risk modification might be more effective in younger and older women if it targeted different mechanisms of plaque instability. Whether gender differences in plaque pathology are also present among patients with nonfatal acute coronary syndromes or MIs is unknown.

LIPOPROTEINS THROUGHOUT THE LIFESPAN

Lipoprotein levels in prepubertal girls and boys are similar. The association between lipoprotein levels in childhood and adulthood is strongest for low-density lipoprotein (LDL) cholesterol but also significant for high-density lipoprotein (HDL) cholesterol and triglycerides (20). Gender differences in HDL cholesterol levels and HDL particle size emerge at puberty, and women maintain approximately 10-mg/dl higher HDL cholesterol levels than men throughout their lifetime (21–24). This gender difference in HDL cholesterol levels is maintained even in men and women with CHD, who tend to have lower HDL cholesterol levels than persons without CHD (25). A substantial proportion of women with CHD have HDL cholesterol levels of ≥60 mg/dl, which is considered "protective" against CHD development (23,26). Levels of LDL cholesterol and non-HDL cholesterol are lower in young and middle-aged women than in age-matched men, but the reverse is true after menopause (23,27). Interestingly, LDL particle number remains lower in women than in men throughout their lifetime (28). Paralleling the age-related increase in LDL-cholesterol in women, lipoprotein(a) (Lp[a]) also increases as women grow older, whereas levels remain constant in men (29).

Premenopause. Hormonal influences on lipoprotein levels in women are complex (30). In premenopausal women, lipoprotein concentrations vary throughout the menstrual cycle, with substantial heterogeneity among individuals and studies (31). Parous women tend to have lower HDL cholesterol levels than nulliparous women (32). Effects of contraceptive preparations vary, depending on estrogen dose, progestin dose, androgenicity of the progestin, and route of administration (33–35). Increases in triglycerides up to 57%, accompanied by decreases in LDL particle size, have been reported with oral contraceptives, whereas changes in LDL and HDL cholesterol levels tend to be of smaller magnitude (33–35). Although current oral contraceptive use is associated with increased cardiovascular risk, especially among smokers, such an increase in risk is not apparent among past users of oral contraceptives (36,37).

Postmenopause. It is well known that total cholesterol levels increase at menopause (38–40). The LDL particle distribution shifts toward smaller denser particles and LDL cholesterol levels tend to rise, although this increase is not seen in all studies (41–45). Decreases in HDL_2 particles have been reported, but HDL cholesterol levels overall tend to remain constant (43–45). Postmenopausal women tend to have greater postprandial rises of lipoprotein levels after standardized fat meals than premenopausal women, even after taking the fasting triglyceride concentration into account (46).

Effects of hormone therapy. Oral postmenopausal hormone therapy decreases LDL cholesterol and Lp(a) levels but increases HDL cholesterol and triglyceride levels (47–49). The increase in triglyceride levels is most pronounced with estrogen monotherapy and might be associated with triglyceride enrichment of LDL particles and adverse changes in LDL particle size and atherogenicity (47,50–52). Progestin therapy tends to attenuate this triglyceride rise, but it also blunts the rise in HDL cholesterol associated with oral estrogen supplementation (47). Estrogen receptor polymorphisms are closely linked to the magnitude of the HDL cholesterol response to hormone replacement therapy (53). Apolipoprotein E phenotype might also modulate the response to hormone therapy, but the heterogeneity seen in

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clinical practice is more likely related to differences in the baseline lipid profile, dietary variations, and variable compliance (54). Lipoprotein effects are attenuated when lower-dose formulations are used (55). Changes in lipid profiles with hormone therapy have not translated into beneficial changes in angiographic coronary artery disease nor into improved cardiovascular outcomes, at least in part related to pro-thrombotic and pro-inflammatory effects of hormone therapy (56). Hormone therapy is not recommended for cardiovascular disease (CVD) prevention in women (3).

In short-term studies, transdermal estrogen supplementation is lipid-neutral. Longer-term transdermal therapy might result in LDL cholesterol lowering without significantly affecting HDL cholesterol and triglyceride levels (57). Beneficial changes in the lipid profile have also been reported with transdermal continuous combined therapy; but transdermal therapy did not affect Lp(a) levels (58).

Selective estrogen receptor modulators have less pronounced effects on the lipid profile than oral hormone therapy. In a three-year trial, raloxifene did not affect HDL cholesterol levels, but lowered LDL cholesterol levels by approximately 10% and increased triglyceride levels by up to 8% (59). In the much larger Multiple Outcomes of Raloxifene Evaluation trial, LDL cholesterol levels decreased by 8% to 9% and triglycerides increased by up to 1.5%, whereas HDL cholesterol did not change (60). Although an analysis of safety data in this trial suggested cardiovascular benefits of raloxifene in women at high risk for CVD or with established CHD, the investigators concluded that these findings must be confirmed by an adequately powered, randomized trial with cardiovascular events as predefined outcomes (60).

Lipoproteins in obesity and diabetes. Many studies document adverse changes in the lipid profile among obese women and women with the metabolic syndrome or diabetes mellitus (61). These adverse lipid changes are characterized by a greater prevalence of LDL phenotype B, lower HDL cholesterol levels, and higher triglyceride levels (62). Adverse lipoprotein changes associated with diabetes tend to be more pronounced in women than in men and might mediate the greater adverse prognostic impact of diabetes among women, which has been consistently demonstrated (61,63–65).

IMPACT OF DYSLIPIDEMIA IN WOMEN

Numerous traditional and emerging risk factors contribute to the development of CHD in men and women and have been reviewed in detail elsewhere (3). This review will focus on the impact of dyslipidemia only.

Many observational studies show that CHD risk increases with increases in total and LDL cholesterol levels and decreases with increases in HDL cholesterol levels in both genders, but the relative importance of these lipoprotein fractions might differ by gender (66–71). Levels of HDL cholesterol and triglycerides appear to be more closely related to CHD risk among women than men, whereas LDL cholesterol appears to be a more potent predictor among men (69,70). Non-HDL cholesterol appears to be a better measure of CHD risk in women than in men (72). Although the relative risk of CHD due to lipid abnormalities is higher in younger than older women, the attributable risk is higher in the older age groups (73). Abnormal lipoproteins predict not only incident CHD among previously healthy women, but also recurrent events among those with prevalent CHD (74,75).

Smaller than average LDL particle size and LDL pattern B seem to be associated with the development of premature CHD in younger women, even after LDL cholesterol levels and other risk factors are taken into account; however, the association is not independent of HDL cholesterol levels, triglyceride levels, and body mass index (76). Among older women, LDL size and LDL phenotype might not relate to cardiovascular outcomes (77).

The role of triglyceride-rich remnant particles in the development and progression of CHD in women remains unclear. Remnant-like particle (RLP) cholesterol and triglyceride levels are higher in postmenopausal than in premenopausal women and in women with CHD than in healthy women (78,79). The RLP cholesterol was an independent risk factor for CVD among women enrolled in the Framingham Heart Study (80). Although RLP cholesterol has been linked to progression of coronary and vein-graft atherosclerosis in men (81), such a relationship was not seen for either RLP cholesterol or triglycerides in the Women's Angiographic Vitamin and Estrogen study, an angiographic trial of hormone and antioxidant therapy in postmenopausal women with CHD (82). Remnant levels in this cohort were very high on average but did not relate to progression of CHD or to clinical events (82).

Elevated Lp(a) levels seem to be more strongly related to CHD events than to severity of coronary artery disease in both genders. In the Framingham study, elevated Lp(a) levels in women strongly predicted incident MI but also correlated with claudication and development of cerebrovascular disease (83). Elevated Lp(a) also strongly predicts recurrent events among women with CHD (49). A post-hoc subgroup analysis from the Heart and Estrogen/progestin Replacement Study (HERS) study suggested potential benefit of hormone therapy among women with high Lp(a) levels, but this finding remains to be confirmed in a prospective randomized trial (49).

IMPACT OF LIPID-LOWERING THERAPY IN WOMEN

Stabilization and/or regression of coronary lesions with vigorous lifestyle modification have been shown in men with coronary disease (84,85) but not in women, and, to date, no trials showing the impact of lifestyle changes on CHD events in non-institutionalized women have been published. It is clear, however, that weight management, adherence to a healthy diet, and regular physical activity have beneficial

effects on the lipid profile (and on other risk factors) in women as well as men. Lifestyle modification should thus be recommended to all women with dyslipidemia as outlined in current prevention guidelines (3,86).

Lipoprotein changes in response to pharmacologic lipid-lowering therapy seem to be similar in magnitude and direction in men and women (86,87). The cardiovascular benefits of lipid-lowering therapy in women are less clear than in men, because women make up a minority of study participants in most clinical end point trials, and subgroup results by gender are often not reported. Outcomes data in women with lipid-lowering medications other than statins are exceedingly limited (88).

Comparable angiographic benefit in women and men with familial hypercholesterolemia treated with lovastatin was shown by Kane et al. (89) in 1990. In a meta-analysis by LaRosa et al. (90) of the early statin trials with clinical end points, women and men achieved similar reductions in major coronary events, and the authors calculated that the number needed to treat was 31 for women and 27 for men. An updated meta-analysis of statin end point trials by Walsh and Pignone (88) included newer trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial, and the Heart Protection Study, as well as studies dating back to the early 1970s and 1980s that used colestipol, cholestyramine, and clofibrate as the therapeutic interventions. The Heart Protection Study is particularly important in this context, because it enrolled over 5,000 women, more women than in all the other previous trials combined, and showed that major vascular events were significantly reduced from 17.7% to 14.4% (relative risk reduction: 18.6%) (91). The authors concluded that women with CVD who are treated with statins achieve a 20% to 30% reduction in CHD mortality, non-fatal MI, revascularization, and CHD events, but no reduction in total mortality. The number needed to treat to prevent one event was estimated at 26. In the Treating to New Targets study which compared 10 mg of atorvastatin with 80 mg of atorvastatin in patients with stable CHD and was published after this meta-analysis, major cardiovascular events were reduced 22% in the high-dose group without statistically significant interaction by gender; there was no reduction in total mortality with more intensive therapy (92).

Acute coronary syndromes. Statin trials in patients with acute coronary syndromes were not included in the updated meta-analysis. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy study, a 16% reduction in the combined end point (death from any cause, MI, documented unstable angina requiring re-hospitalization, revascularization, and stroke) was achieved with aggressive lipid-lowering therapy, which lowered LDL cholesterol to an on-trial level of 62 mg/dl (93). Women made up only 22% of study subjects, but a predefined subgroup analysis suggested that the benefit of aggressive lipid lowering in this setting was consistent across gender subgroups (93). The only other randomized trial of statin therapy in this population (the A to Z Trial) did not show a significant benefit of early aggressive therapy, but point estimates (a non-significant 11% reduction in events) were identical in men and women (94).

Primary prevention. Among women without CVD, Walsh and Pignone (88) found no evidence of a mortality benefit or any decrease in CHD mortality, non-fatal MI, revascularization, or CHD events; however, when ALLHAT (which was unblinded and had a 32% drop-in of lipid-lowering therapy in the placebo group) was excluded from the analysis, they found a significant 23% reduction in CHD events (summary risk ratio, 0.77; 95% confidence interval [CI], 0.64 to 0.94). The authors concluded that there was insufficient evidence to determine whether lipid-lowering therapy was effective in reducing CHD events in women without CVD (88). The Collaborative Atorvastatin Diabetes Study, a trial of statin therapy among patients (32% women) with diabetes but without known CVD, was published three months after the meta-analysis (95). The trial was terminated two years earlier than expected, because the prespecified early stopping criterion for efficacy had been met. Cardiovascular events were reduced by 37% (95% CI, −52 to −17; $p = 0.001$) over a median of 3.9 years of follow-up, without heterogeneity by age, gender, baseline lipid profile, hypertension, or smoking.

The Third Report of the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program does not recommend different treatment guidelines for men and women, but their approach to considering drug therapy for middle-aged women with <10% 10-year risk for CHD is somewhat more cautious than it is for middle-aged men in the same risk category (86). The Expert Panel acknowledged that recommendations for women without CVD were based on extrapolation of benefit from men at similar risk (86).

Statin therapy. Consistent with the clinical trials evidence base, the most commonly used drugs for lipid lowering are statins. Comparative efficacy of currently available statins is shown in Table 1 (96–98). Statins are generally well tolerated, with a low incidence of liver abnormalities and muscle toxicity, but important drug interactions between statins and other drugs have been reported, particularly with statins metabolized by the CYP 3A4 system (Table 2) (96–98). Statins should not be used in women who are pregnant, are trying to become pregnant, or who are breast-feeding. The reader is referred to the ATP III guidelines for detailed information on the non-statin drugs currently on the market (86).

UNDERTREATMENT AND TREATMENT DISPARITIES

In the HERS study, which recruited postmenopausal women with CHD from 1993 to 1994, 47% of women were receiving lipid-lowering therapy, but only 37% had met the

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Table 1. Comparative Efficacy and Pharmacology of the Currently Available Statins

Drug	Changes in % ↓TC	↓LDL-C	↑HDL-C	↓TG	Dosage Form Tablets, mg	Standard Dose, mg*	Metabolism	Protein Binding, %	T1/2, h	Hydrophilic
Atorvastatin	25–45	26–60	5–13	17–53	10, 20, 40, 80	10	CYP3A4	98	13–30	No
Fluvastatin	16–27	22–36	3–11	12–25	20, 40, 80	40–80	CYP2C9	98	0.5–3.0	No
Lovastatin	16–34	21–42	2–10	6–27	10, 20, 40	40	CYP3A4	>95	2–4	No
Pravastatin	16–25	22–34	2–12	15–24	10, 20, 40, 80	40	Sulfation	43–67	2–3	Yes
Rosuvastatin	33–46	45–63	8–14	10–35	5, 10, 20, 40	5–10	CYP2C9, CYP2C19	88	19	Yes
Simvastatin	19–36	26–47	8–16	12–34	5, 10, 20, 40, 80	20–40	CYP3A4	95–98	1–3	No

Table 1 is based on composite data from references 96–98. *Standard dose is a dose that will achieve 30% to 40% LDL-C lowering as recommended by Grundy et al. (97).
CYP = cytochrome P; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; T1/2 = half-life.

LDL cholesterol goal of <130 mg/dl as recommended by the 1988 ATP guidelines, and only 9% had met the LDL cholesterol goal of ≤100 mg/dl as recommended by the 1993 guidelines (99). Only 7% of HERS women started statin therapy during the first year of follow-up, despite substantial publicity surrounding the new and more aggressive ATP II LDL cholesterol goals at that time. Undertreatment was more pronounced among black women than among white women enrolled in the trial (100). Miller et al. (101) reported on treatment rates among patients in the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial, who were enrolled between 1994 and 1997. During that period, the proportion of women who achieved an LDL cholesterol goal of <100 mg/dl increased from 6% to 12%, whereas the proportion of men increased from 17% to 31% (101). Data collected from 1998 to 1999 from the National Registry of Myocardial Infarction showed that women were less likely to receive lipid-lowering therapy at hospital discharge than men (multivariate odds ratio for men 1.03, 95% CI, 1.00 to 1.06), but less than one-third of patients of both genders were discharged on treatment (102). In the Women's Ischemia Syndrome Evaluation study, which enrolled patients between 1996 and 1997, only 24% of women with a history of CHD, 56% of high-risk women, and 88% of low-risk women had met their respective LDL cholesterol goals. All women underwent diagnostic coronary angiography, but angiography results did not impact therapy in women with newly diagnosed coronary artery disease or in those whose diagnosis was confirmed (103).

Table 2. Important Drug Interactions With Selected Statins

Lipid-lowering agents
Fibrates (especially gemfibrozil), niacin
Cardiovascular agents
Warfarin, digoxin, verapamil, amiodarone
Immunosuppressive agents
Tacrolimus, cyclosporine
Agents to treat infections
Fluconazole, itraconazole, ketoconazole
Erythromycin, clarithromycin
HIV protease inhibitors
Psychoactive agents
Nefazodone, venlafaxine, fluoxetine, sertraline, benzodiazepines
Others
Antihistamines
Grapefruit juice

Table 2 is based on composite data from references 96–98.
HIV = human immunodeficiency virus.

Reasons for undertreatment are complex and reflect physician and patient preferences as well as environmental factors such as access to care and cost of medication. Current guidelines for cardiovascular risk prevention in women emphasize the importance of achieving recommended lipoprotein goals (3). A recent report from the cardiac rehabilitation setting suggests that treatment rates among women with CHD have improved, because 49% of women who completed cardiac rehabilitation between 1996 and 2003 achieved their LDL cholesterol goal of <100 mg/dl (104). It is not known whether the situation has improved in less-structured care settings or among women without known CVD who, nevertheless, are at high risk for subsequent events.

SUMMARY AND FUTURE DIRECTIONS

Coronary heart disease is the most important cause of death among American women and is responsible for disability and poor quality of life in many women. Dyslipidemia is an important risk factor for the initiation and progression of atherosclerosis and is strongly associated with cardiovascular events. Emphasis on a healthy lifestyle should begin in childhood and continue throughout life. Although the benefits of lipid-lowering therapy appear to be clear in women with CVD, more data are needed for women without CVD. Clinical trials of lipid lowering, to date, have exclusively used a strategy focused on lowering LDL cholesterol, which might not be optimal among those women in whom low levels of HDL cholesterol or elevated triglycerides appear to be as strongly or more strongly related to subsequent CHD. Whether outcomes among women will improve when treatment strategies are geared toward a more aggressive and comprehensive modification of lipoprotein profiles remains to be determined.

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