Preventing Cardiovascular Disease in Women: An Update

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ABSTRACT

Coronary heart disease (CHD) continues to be the leading cause of death among women in the United States. Evidence-based guidelines of the American Heart Association (AHA) offer clinicians recommendations for preventing CHD in women delineating particular lifestyle, risk factor, and pharmacologic interventions. Cigarette smoking, physical inactivity, inappropriate diet, dyslipidemia, hypertension, diabetes mellitus, and metabolic syndrome contribute to the risk of CHD in women, as in men. Lifestyle interventions substantially reduce that risk. Many women, however, require pharmacotherapy to control hypertension, dyslipidemia, and diabetes to levels required for decreasing risk. New findings from clinical trials featuring women may enhance their CHD risk prediction and treatment. However, high coronary risk in many women continues to be underrecognized, and women remain undertreated with statins and other therapeutic agents.

Key words: cardiovascular disease, coronary heart disease, prevention, women

Introduction

Contrary to popular perception, the leading cause of death among women in the United States continues to be coronary heart disease (CHD).[1] Mortality from CHD has not declined in women in the last 20 years as it has in men,[2] highlighting the importance of preventive interventions for women; women with diabetes constitute the specific subgroup in whom survival has not improved over time. Most women who die suddenly of CHD had no previous symptoms, but many have a high prevalence of CHD risk factors.[2] Recent data indicate that a comparable number of women are at high risk for CHD today as they were 15 years ago,[3] (also the case for men), suggesting that established risk-reduction strategies are not successfully implemented, and that aggressive efforts are needed to reduce CHD risk in women, as well as in men.

Current Guidelines for the Prevention of Cardiovascular Disease in Women

In 2004, the American Heart Association (AHA) published evidence-based guidelines for the prevention of cardiovascular disease (CVD) in women.[4] These guidelines addressed the needs of women with a range of cardiovascular (CV) risk and encouraged clinicians to stratify women by baseline risk level to determine the appropriate intensity of preventive interventions (Table 1). Guideline recommendations were categorized as follows: lifestyle, major risk factor, and preventive drug interventions. Lifestyle interventions, including increased regular physical activity and a heart-healthy diet, are the initial preventive approaches in all women, regardless of their risk level. Women were advised not to smoke; this is important because more young American women (age 12–17 years) than men initiate smoking;[5] and avoidance of environmental tobacco was also advocated.

Women were encouraged to achieve optimal levels of major CHD risk factors, including <120/80 mm Hg blood pressure, <100 mg/dL low-density lipoprotein cholesterol (LDL-C), >50 mg/dL high-density lipoprotein cholesterol (HDL-C), <150 mg/dL triglycerides, and <130 mg/dL non-HDL-C (non–high density lipoprotein cholesterol).[4] These guidelines were more stringent than the third National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III),[6] but concordant with the 2004 ATP III guideline update.[7] A near-normal (<7%) hemoglobin A_{1c} level was recommended in women with diabetes.[4]

Regarding preventive drug interventions, high-risk women were advised to take either aspirin (75–162 mg) or clopidogrel, if aspirin-intolerant.[4] Beta-blockers indefinitely (unless contraindicated) were advocated for all women after myocardial infarction (MI) or with chronic ischemic syndromes. Angiotensin-converting enzyme (ACE) inhibitors were recommended in high-risk women, and angiotensin II receptor blockers (ARBs) for high-risk women with clinical evidence of heart failure or an ejection fracture <40%, who are intolerant to ACE inhibitors.[4] Initiation of statin therapy along with lifestyle interventions was recommended not only in high-risk women with elevated LDL-C (≥100 mg/dL), but also in high-risk women with optimal LDL-C (<100 mg/dL).[4] Concomitant niacin or fibrates were recommended when HDL-C was low or non-HDL-C (total cholesterol minus HDL-C) was elevated.

Received: March 2, 2007
Accepted: March 6, 2007

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20134

TABLE 1: Priorities for prevention of coronary heart disease in women according to their risk status

High-risk women (>20% risk)
Class I recommendations:
- Smoking cessation
- Physical activity/cardiac rehabilitation
- Diet therapy
- Weight maintenance/reduction
- Blood pressure control
- Lipid control/statin therapy
- Aspirin therapy
- Beta-blocker therapy
- ACE inhibitor therapy (ARBs, if ACE contraindicated)
- Glycemic control in diabetics

Class IIa recommendation:
- Evaluate/treat for depression

Class IIb recommendations:
- Omega 3 fatty-acid supplementation
- Folic acid supplementation
  - Intermediate-risk women (10%–20% risk)

Class I recommendations:
- Smoking cessation
- Physical activity
- Heart-healthy diet
- Weight maintenance/reduction
- Blood pressure control
- Lipid control

Class IIa recommendation:
- Aspirin therapy
  - Lower-risk women (<10% risk)

Class I recommendations:
- Smoking cessation
- Physical activity
- Heart-healthy diet
- Weight maintenance/reduction
- Treat individual CVD risk factors as indicated

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
CVD = cardiovascular disease
Reprinted with permission from Mosca L et al.[4]

Emerging Data for Prevention of Cardiovascular Disease in Women

New data emerging since the publication of the AHA guidelines have become valuable in the treatment of women.

Aspirin for Low-risk Women

The Women's Health Study showed that 100 mg of aspirin taken on alternate days by nearly 40,000 healthy, low-risk women ⩾45 years of age for 10 years did not significantly decrease the risk of CV events.[8] However, this regimen decreased the risk of stroke by 17% ($p = 0.04$) and ischemic stroke by 24% ($p = 0.009$) versus placebo, the first primary prevention trial to show that aspirin can prevent stroke in healthy women. In this study, low-dose aspirin prevented stroke, MI, and CV death in women >65 years old but increased the risk of bleeding, indicating the importance of individualizing aspirin therapy in older women.

Coronary Risk Prediction in Women

To determine which lipid measures best predict CV risk in women, analysis of laboratory data and occurrence of CV events was performed in 15,632 initially healthy women (⩾ 45 years) followed up for >10 years in the Women's Health Study.[9] Non–HDL-C and total cholesterol to HDL-C ratio were most valuable in predicting CV events, and C-reactive protein added prognostic information to all lipid fractions. The addition of C-reactive protein to the Framingham risk score also improved global CV risk prediction in women, especially those at low-to-intermediate risk.[10]

Diabetes and the Metabolic Syndrome in Women

Diabetes doubles the risk of CVD in women,[2] increases risk of cognitive decline in older women,[11] and is the strongest risk factor for heart failure in women with CHD.[12] Lifestyle measures can substantially reduce a woman's risk of developing diabetes. Patients with impaired glucose tolerance in the Diabetes Prevention Program Research Group,[13] who exercised at least 30 min daily and lost at least 5%–7% of body weight had a 58% reduction in incidence of type 2 diabetes over 3.2 years of follow-up; this suggests that patients (68% women in the cohort) who increase weight loss by increasing physical activity and reducing dietary fat could reduce their diabetes risk by >90%.[14]

The metabolic syndrome, with associated increased CHD risk,[6] is highly prevalent among American women. Between the National Health and Nutrition Examination Surveys (NHANES) of 1988–1994 and 1999–2000, the age-adjusted prevalence of metabolic syndrome increased by 23.5% in women ($p = 0.021$), compared with 2.2% in men ($p = 0.831$).[15] Increases among women in prevalence of abdominal obesity (from 45.7% to 51.9%), high triglyceride levels (from 24.6% to 29.9%), and hypertension (27.9% to 37.3%) during the years of the survey may explain this disproportional increase in metabolic syndrome. Women with metabolic syndrome also have a higher relative risk of CVD than men (2.10 versus 1.57).[16]

Folic Acid and Antioxidants

Although the AHA guidelines advised folic acid supplementation, as an adjunct to diet for high-risk women (except following a revascularization procedure where it had been documented to lack benefit) with high levels of

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20134

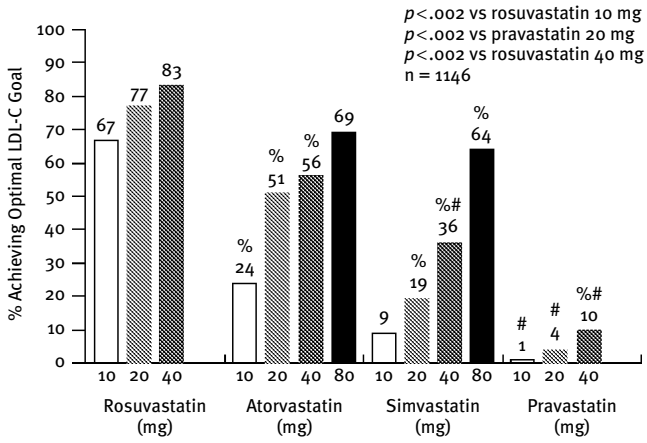

Figure 1: Percentage of women who achieved the optimal LDL-C goal of <100 mg/dL on statin therapy. Adapted from Ford ES et al.[32]

homocysteine, 2 recent trials have demonstrated the lack of efficacy in preventing CVD. The Norwegian Vitamin (NORVIT) study reported that in patients with acute MI within a week of randomization, supplements of folic acid plus vitamins B_{12} and B_6 did not provide any benefit and entailed potential risk.[17] In the Heart Outcomes Prevention Evaluation (HOPE–2) trial, (which enrolled 30% women), the combination of folic acid and vitamins B_{12} and B_6 for 5 years did not reduce the risk of major CV events in patients with vascular disease.[18]

The guidelines did not recommend antioxidant vitamin supplements to prevent CVD pending the results of ongoing trials. Recent data from the Women's Health Study[19] identified that vitamin E failed to provide benefits for either major CV events or MI, except in women >65 years of age, who had significantly fewer major CV events (–26% p = 0.009). The reason for the age-related difference was not apparent.

Menopausal Hormone Therapy

Despite numerous observational trials suggesting coronary protection from menopausal hormone therapy (HT), randomized clinical trials in healthy women failed to show benefit and even rendered harm, including greater rates of MI, stroke, breast cancer, and venous thromboembolism with estrogen plus progestin;[20] and increased stroke risk with unopposed estrogen,[21] as well as nearly twice the rate of gallbladder surgery with unopposed estrogen.[22] A number of questions remain, such as whether earlier initiation[23] or low doses of HT might be beneficial,[24] or whether estrogen and estrogen/progestin combined therapy may provide differential risk or benefit,[24] and whether transdermal rather than oral therapy might be cardioprotective.[24]

Selective estrogen receptor modulators (SERMs) have been proposed for use in cardiac protection. In a recent randomized, placebo-controlled trial,[25] 10,101 menopausal women with documented CHD or at high risk for major coronary events received the SERM raloxifene or placebo and were followed for 5.6 years. Although raloxifene reduced the risk of invasive breast cancer and vertebral fractures, it increased the risks of venous thromboembolism and fatal stroke, and did not significantly affect the risk of CHD, total stroke, or mortality.

Lower LDL-C Goal in High-risk Patients

On the basis of results of recent trials of statin therapy, an update to the NCEP ATP III guidelines recommended a new, lower LDL-C goal of <70 mg/dL as an option for men and women at high risk for CVD.[7] The new, lower goal is also appropriate for patients with established CVD who also have diabetes, severe and poorly controlled risk factors (such as cigarette smoking), multiple risk factors of the metabolic syndrome (especially triglycerides ⩾200 mg/dL, non–HDL-C ⩾130 mg/dL, and HDL-C <40 mg/dL), or acute coronary syndromes.[26]

Statin Therapy and Cardiovascular Disease Risk in Women

Prior to 2004, almost 20,000 women participated in clinical trials of statin therapy, but women constituted only 25% of the study participants. Two exceptions were the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), in which half of the participants were women,[27] and the lipid-lowering arm of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT-LLT), in which 49% were women.[28] The PROSPER trial did not show a statistically significant benefit for women, and ALLHAT-LLT did not report gender-specific results.

Other major primary and secondary prevention trials have shown that statins have a similar impact on reduction of major coronary events in women and men.[29] In the Heart Protection Study, which included the largest number of women (5,082) in a statin trial to date, similar reductions in risk of major vascular events were observed in women (20%) and men (25%).[30] Recent statin trials show that attaining optimal levels of LDL-C is associated with greater reductions in CVD risk.[7] With intensive compared with standard lipid lowering in the TNT (Treating to New Targets) trial, the HR for major cardiovascular events was 0.73 for women and 0.79 for men.[31] A recent posthoc analysis of the Statin

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20134

Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial, which included 1,146 women, suggested that more women could achieve optimal lipid goals if they were prescribed intensive statin therapy (Figure 1).[32]

Despite the Urgency, Women Remain Undertreated

Despite documented benefits of lipid-lowering therapy in women, the 1999–2000 National Health and Nutrition Examination Survey (NHANES) reported that 14% of hypercholesterolemic men received treatment, in contrast to 10.2% of women, and that more men than women attained LDL-C targets.[33] A 2003 national survey comparing LDL-C goal achievement in men and women with dyslipidemia found that significantly fewer high-risk women (those with CHD or CHD risk equivalents) achieved LDL-C goal than high-risk men (50% versus 60%, respectively $p<0.001$).[34] In a study of academic internal medicine practices, women with diabetes received less treatment for modifiable coronary risk factors, including elevated lipids and hypertension, than men, and therefore were less likely to reach LDL-C and blood pressure goals.[35] In a registry of patients with non-ST-segment elevation acute coronary syndromes,[36] 55.9% of women received statins at discharge, versus 63.4% of men. Although these Can Rapid risk stratification of Unstable Angina patients suppress ADverse outcomes with Early implementation (CRUSADE) of the American College of Cardiology (ACC)/AHA Guidelines women with acute coronary syndromes had higher risk characteristics at presentation and higher risk in hospital, they were less aggressively treated than men.

By 2010, 81% of the population >85 years are likely to be women.[1] As the population ages, the incidence of CVD will increase among women, unless successful preventive interventions are instituted across their lifespan. Awareness of high risk of CV in women and attention to the gender-specific features of CV prevention are needed to improve the outlook of women with or at risk for CVD events.

Acknowledgments

With appreciation to Julia C. Wright for assistance in manuscript preparation and reference verification.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20134