Coronary heart disease (CHD) is the leading cause of death and a significant cause of morbidity among North American women. Because CHD typically develops one to two decades later in females than in males, the importance of cardiovascular disease in this group has been overlooked.

Studies of CHD treatment have shown a bias against the treatment of women with CHD. A recent survey by the Centers of Disease Control and Prevention National Ambulatory Medical Care showed that, during routine office visits, women were counseled less often than men about exercise, nutrition and weight reduction. In the multi-center Heart and Estrogen/progestin Replacement Study (HERS), which enrolled post-menopausal females with documented CHD, only 10% of women had a low-density lipoprotein cholesterol (LDL-C) level below an appropriate target at baseline.

Women with angina or myocardial infarction (MI) often present with atypical symptoms. The recognition and management of CHD in women...
represents a challenge for physicians. This article reviews clinical data evaluating risk factors of CHD in women and how to assess and manage these risk factors. Potential risks and benefits of therapies will be discussed.

Risk Factors For CHD

Post-menopausal state. Women exhibit a steady increase in the incidence of CHD with age (Table 1). Its occurrence is rare before menopause, suggesting the loss of endogenous estradiol plays an important preventive role in CHD. Age-adjusted risk of CHD in post-menopausal women is increased by two- to threefold, as compared to premenopausal women.4

Cholesterol. Hyperlipidemia is an important risk factor in the development of CHD among women. The Framingham study demonstrated total cholesterol increased after menopause.4 This increase was primarily due to an increase in LDL-C with only a slight decrease in high-density lipoprotein cholesterol (HDL-C). Low HDL-C is also a strong predictor of CHD in women over 65 years of age than in men over 65.5

Triglyceride (TG) levels also may be a more significant risk factor in women than in men. A population-based prospective study found a statistically significant increase in the risk of CHD (37%) in women compared to only a 14% increase in risk for men after adjustment for HDL-C and other risk factors.6 A 14-year follow-up study of 1,405 post-menopausal women demonstrated a TG level greater than 4.5 mmol/L was associated with a more than threefold increase in the risk of CHD mortality.7

Smoking. Cigarette smoking is a powerful risk factor that predisposes smokers to CHD in
several ways. Data from the Framingham study revealed that smoking was a powerful risk factor for MI; even stronger than the presence of angina pectoris. Smoking accelerates coronary plaque development and promotes plaque rupture and coronary thrombosis. In women, smoking counteracts the protective effect of estrogen, causing early menopause, decreasing HDL-C and increasing fibrinogen (Table 2).4

Of great importance is the fact that smoking cessation rapidly and markedly reduces the risk of MI, as the risk of CHD returns to baseline within three to four years of cessation.

**Obesity.** Central obesity confers an increased CHD risk in women and predisposes them to diabetes, hyperuricemia and hypertension.4 A waist-to-hip ratio (WHR) of greater than or equal to 0.9 in pre-menopausal woman is an indicator of increased risk of CHD, regardless of the patient’s body mass index.9

**Diabetes.** Diabetes is a powerful risk factor in women, increasing CHD risk three- to sevenfold, as compared to two- to threefold in men.10 This difference may be due to the deleterious effect of diabetes on lipids and blood pressure in women.

**Exercise.** In an eight-year, follow-up prospective study comparing walking with vigorous exercise in the prevention of CHD in 72,448 women, exercise was shown to be inversely associated with the risk of coronary events. Women who walked the equivalent of three or more hours per week at a brisk pace had a 35% reduction in coronary events, as compared to women who walked infrequently. Regular vigorous exercise also was associated with a similar reduction in the risk of developing CHD.11

**Post-menopausal Hormones And Heart Disease**

Multiple observational studies have reported that post-menopausal women who used estrogen had lower rates of CHD events than non-users. Thus, it was surprising when the results of the first large-scale randomized trial assessing the effect of hormone replacement therapy (HRT) in post-menopausal females with CHD demonstrated no benefit in preventing future cardiovascular events.

### Table 1
**Risk Factors For CHD In Women**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Odd ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>4.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.5</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>2.1</td>
</tr>
<tr>
<td>Family history</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.3</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.1</td>
</tr>
<tr>
<td>Estrogen</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Table 2
**Effects Of Smoking On Women**

- Counteracts protective effect of estrogen
- Induces earlier menopause
- Decreases HDL cholesterol
- Increases platelets and fibrinogen
- Risk returns to baseline within three to four years after cessation
The HERS was a multi-center, randomized, blinded clinical trial involving 2,763 post-menopausal women with CHD and an intact uterus. They were randomized to receive HRT (daily conjugated estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg) or placebo. After a four-year follow-up, there was no difference between the groups in the primary composite end point of non-fatal MI and coronary death. There also was no reduction in the risk of stroke.

The HERS investigators found that women assigned to the treatment group had a 50% increased risk of CHD events in the first year of the trial. The risk was highest in the first four months (relative risk [RR] increase of 2.3, 95% confidence interval [CI] 0.9 to 5.6). This risk returned to baseline in two years. The risk was then lower in the treatment group in the third and fourth years of the trial (Table 3). It has been hypothesized that the early adverse effects of estrogen may be due to its procoagulant effect, which may later be offset by an anti-atherogenic benefit. Estrogen also increases the level of C-reactive protein, which is a marker of inflammation. Elevated C-reactive protein has been shown to be an excellent predictor of increased coronary events.

The Coumadin Aspirin Reinfarction Study (CARS) enrolled 8,803 patients for a period of three to 21 days post-MI. Of these, 1,857 were post-menopausal women. They were then further classified as: prior/current users of HRT if they took the drug before enrollment; new users if they began HRT during the study period; or as those who had never used HRT. During a 14-month follow-up, women who began HRT after their MI had a significantly higher incidence of unstable angina (UA), as compared to women who had never used HRT (39% versus 20%, \( P = 0.001 \)). Interestingly, prior/current users had no excess risk of UA or MI when compared with those who had never used HRT. It was also found that users of the estrogen/progestin combination had a lower incidence of death/MI/UA during follow-up, as compared to users of estrogen only (RR = 0.56). The results of the HERS trial and the CARS database only apply to women with pre-existing CHD, and may not be applicable to women free of vascular disease.

The Estrogen Replacement in Atherosclerosis (ERA) trial found that neither estrogen alone, nor estrogen plus progestin, differed from placebo in preventing angiographic progression of CHD over a three-year period.

Primary Prevention Trials

The Woman’s Health Initiative (WHI) study randomized 27,000 women without CHD to receive estrogen plus progesterone versus placebo if they had an intact uterus, and estrogen versus placebo in those without an intact uterus. This trial is now in the third year of a planned nine-year follow-up. After two years of enrollment, the WHI investigators issued a press release saying they had observed an increased risk of CHD events (MI, strokes and thromboembolic events) among patients who received HRT. The final results, however, will not be available until 2005.

Adverse Side Effects Of HRT

In the HERS study, HRT users were at increased risk of venous thromboembolism (RR = 2.7, CI = 1.4 to 5.0, \( p = 0.003 \)) during the four years of follow-up (treating 1,000 post-menopausal women with HRT for four years resulted in 16 episodes of additional deep vein thrombosis or pulmonary embolism). The risk was increased more than fivefold (RR = 5.9, CI = 2.3 to 15.3) during the first 90 days post-MI. In multivariate analysis, the risk for venous thromboembolism also was increased among women who had lower-extremity fractures (RR = 18.1, CI = 5.4
to 60.4) and for 90 days after inpatient surgery (RR = 4.9, CI = 2.4 to 9.8), or non-surgical hospitalization (RR = 5.7, CI = 3.0 to 10.8).16

In addition, among women in the HERS study, treating 1,000 women with HRT for four years resulted in 16 additional episodes of gall bladder disease and the need for cholecystectomy. A meta-analysis of more than 52,000 women with breast cancer found no association with short-term (less than five years) HRT use. The risk of breast cancer, however, was increased by 35% in women who used HRT for more than five years.17

Conclusion

Due to the potential adverse effects and unclear cardiovascular benefits, post-menopausal HRT should not be prescribed solely for the prevention of CHD.

HRT may be appropriate in women at increased risk for CHD if the non-coronary benefits (to alleviate menopausal symptoms or to prevent osteoporosis-related fractures) exceed the risks.

The risks of HRT need to be considered in patients with established cardiovascular disease or those with multiple coronary risk factors. In patients with CHD who have already been on HRT for more than one to two years, and who are doing well, HRT does not need to be discontinued since these patients are past the period of increased cardiovascular risk. Moreover, due to the excessive risk of developing HRT-related venous thromboembolism during the first three months after acute MI, lower-extremity fractures or hospitalization, HRT use should be temporarily discontinued during those periods.

Alternatives to traditional HRT are available, including selective estrogen receptor modulators (SERMS), such as tamoxifen and raloxifene. A meta-analysis of adjuvant tamoxifen in 37,000 women with BC demonstrated no significant reduction in CHD mortality, however, the applicability of these results to women at risk of CHD is not known.18

The Raloxifene for CHD Prevention (RUTH) trial is now ongoing. This trial was designed to assess the possible benefit of raloxifene (a selective estrogen receptor modulator that lowers total cholesterol and LDL-C, and decreases the risk of BC in post-menopausal women) in preventing cardiovascular disease. Ten thousand post-menopausal women older than 55, with docu-

<table>
<thead>
<tr>
<th>Outcomes</th>
<th># of women with events who received estrogen plus progestin</th>
<th># of women with events who received placebo</th>
<th>Relative hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>During four years follow-up</td>
<td>179</td>
<td>182</td>
<td>Not significant</td>
<td>—</td>
</tr>
<tr>
<td>During first year</td>
<td>57</td>
<td>38</td>
<td>1.5</td>
<td>0.03</td>
</tr>
<tr>
<td>During fourth year</td>
<td>40</td>
<td>53</td>
<td>0.75</td>
<td>—</td>
</tr>
</tbody>
</table>
### Table 4

**Guide To Preventive Cardiology In Women**

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>Goal(s)</th>
</tr>
</thead>
</table>
| Cigarette smoking       | • Complete cessation  
                          • Avoid passive smoking                                                                                                                                  |
| Physical activities     | • Accumulate > 30 min of moderate intensity physical activity on most, or preferably all, days of the week  
                          • Women who have had recent cardiovascular events or procedures should participate in cardiac rehabilitation, a physician-guided home exercise program or a comprehensive secondary prevention program |
| Nutrition               | • AHA Step 1 diet in healthy women (< 30% fat, 8% to 10% saturated fat, and < 300 mg/d cholesterol)  
                          • AHA Step 2 diet for women with CVD or if further reduction in cholesterol is needed (< 30% fat, < 7% saturated fat and < 200 mg/d cholesterol)  
                          • Limit sodium chloride (salt) intake to 6 g/d. Women with high blood pressure may require further restriction |
| Weight management       | • Target BMI between 18.5 kg/m\(^2\) to 24.9 kg/m\(^2\)  
                          • Desirable waist circumference < 88 cm (< 35 inches) in women with BMI of 25 kg/m\(^2\) to 34.9 kg/m\(^2\) |
| Blood pressure          | • Less than 140/90 mmHg and lower if tolerated (optimal < 120/80 mmHg)                                                                                                                                      |
| Hormone replacement     | • Initiation or continuation of therapy in women for whom the potential may exceed the potential risks of therapy (short-term therapy is indicated for treatment of menopausal symptoms)  
                          • Minimize risk of adverse side effects through careful patient selection and appropriate choice of therapy |
| Lipid                   | **Primary goal:**  
                          Woman without CHD: Lower risk (< 2 risk factors): LDL goal < 4.1 mmol/L  
                          (optimal < 3.4 mmol/L);  
                          higher risk (< 2 risk factors): LDL goal < 3.4 mmol/L  
                          Woman with CHD: LDL goal < 2.6 mmol/L  
                          **Secondary goal:**  
                          HDL > 0.9 mmol/L; triglyceride < 1.2 mmol/L  
                          †Note: In women, the optimal level of triglyceride may be lower (< 3.9 mmol/L) and HDL higher (> 1.2 mmol/L) |
| Diabetes                | • Maintain blood glucose: preprandial 4.4 mmol/L to 6.6 mmol/L, bedtime 5.5 mmol/L to 7.7 mmol/L  
                          • Maintain Hb A1c < 7%  
                          • LDL 3.4 mmol/L (2.6 mmol/L) if established CHD,  
                          †Note: Many authorities believe LDL should be < 2.6 mmol/L in all patients with diabetes.  
                          • Triglyceride < 3.9 mmol/L  
                          • Control blood pressure |

AHA = American Heart Association; CVD = cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; LDL = low-density lipoprotein; HDL = high-density lipoprotein  
(Adapted From The 1999 AHA/ACC Scientific Statement On Preventive Cardiology In Women)
mented CHD or multiple risk factors, have been randomized to raloxifene versus placebo, and will be followed for six years.19

**Statins (HMG Co A reductase).** These drugs block the synthesis of cholesterol in the liver, resulting in a decrease in plasma cholesterol levels. A meta-analysis of eight clinical trials documented the beneficial effect of statins in reducing CHD in men and women.20 The use of statins in postmenopausal women with hyperlipidemia results in greater reductions in LDL-C levels, but less increase in HDL-C than in men.21

Due to a lack of a clear benefit and the potential adverse effects of HRT, the 1999 American Heart Association and American College of Cardiology (AHA/ACC) guidelines for preventive cardiology in women has replaced HRT with statins as first-line therapy in post-menopausal women with hyperlipidemia.22 Recommendations by the AHA/ACC for coronary risk reduction in women are presented in Table 4.22

**References**


**Suggested Readings**