Evaluation of the American Heart Association Cardiovascular Disease Prevention Guideline for Women

Judith Hsia, MD; Rebecca J. Rodabough, MS; JoAnn E. Manson, MD, DrPH; Simin Liu; MD, ScD; Matthew S. Freiberg, MD, MSc; William Graettinger, MD; Milagros C. Rosal, PhD; Barb Cochrane, PhD; Donald Lloyd-Jones, MD, DrPH; Jennifer G. Robinson, MD, MPH; Barbara V. Howard, PhD; for the Women’s Health Initiative Research Group*©2010 American Heart Association, Inc.

Background—The 2007 update to the American Heart Association (AHA) guidelines for cardiovascular disease prevention in women recommend a simplified approach to risk stratification. We assigned Women’s Health Initiative participants to risk categories as described in the guideline and evaluated clinical event rates within and between strata.

Methods and Results—The Women’s Health Initiative enrolled 161 808 women ages 50 to 79 years and followed them prospectively for 7.8 years (mean). Applying the 2007 AHA guideline categories, 11% of women were high risk, 72% at-risk, and 4% at optimal risk; 13% of women did not fall into any category, that is, lacked risk factors but did not adhere to a healthy lifestyle (moderate intensity exercise for 30 minute most days and <7% of calories from saturated fat). Among high risk, at-risk, and optimal risk women, rates of myocardial infarction/coronary death were 12.5%, 3.1%, and 1.1% per 10 years (P for trend <0.0001); the event rate was 1.3% among women who could not be categorized.

We observed a graded relationship between risk category and cardiovascular event rates for white, black, Hispanic, and Asian women, although event rates differed among ethnic groups (P for interaction=0.002). The AHA guideline predicted coronary events with accuracy similar to current Framingham risk categories (area under receiver operating characteristic curve for Framingham risk, 0.665; for AHA risk, 0.664; P=0.94) but less well than proposed Framingham 10-year risk categories of <5%, 5% to 20%, and >20% (area under receiver operating characteristic curve for Framingham risk, 0.724; for AHA risk, 0.664; P<0.0001).

Conclusions—Risk stratification as proposed in the 2007 AHA guideline is simple, accessible to patients and providers, and identifies cardiovascular risk with accuracy similar to that of the current Framingham algorithm.

Clinical Trial Registration—clinicaltrials.gov Identifier: NCT00000611.
(Circ Cardiovasc Qual Outcomes. 2010;3:00-00.)

Key Words: women ■ prevention ■ risk factors

© 2010 American Heart Association, Inc.

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org

DOI: 10.1161/CIRCOUTCOMES.108.842385
The 2007 American Heart Association guidelines for cardiovascular disease prevention in women recommended categorizing women as high risk, at-risk, or optimal risk on the basis of prevalent medical conditions, conventional coronary risk factors, diet, and physical activity.

WHAT THE STUDY ADDS

- In the Women’s Health Initiative, a large, diverse cohort of postmenopausal women, prediction of cardiovascular risk by the American Heart Association guidelines did not differ from Adult Treatment Panel III modified Framingham categories of <10%, 10% to 20%, and >20%, but the American Heart Association guidelines were less accurate than the Framingham categories of <5%, 5% to 20%, and >20 (P<0.0001).
- Whether the American Heart Association guidelines will be used by practitioners and whether its use would improve clinical decision-making and patient outcomes remain to be demonstrated.

Variables

Women reporting prior myocardial infarction (MI) or coronary revascularization were considered to have established coronary disease and those with prior stroke to have established cerebrovascular disease. Women reporting carotid or peripheral arterial revascularization were considered to have established peripheral arterial disease. Diabetes mellitus requiring dietary or pharmacological therapy (excluding gestational diabetes), high cholesterol requiring drug treatment, family history of coronary disease (male first-degree relative with MI before age 55 or female relative before age 65), and cigarette smoking were assessed by self-report at baseline. Hyper-tension included both measured high blood pressure and self-reported high blood pressure requiring pills. If a woman had missing data for a given risk characteristic, she would be classified on the basis of other reported factors; in their absence, she would be considered to have no risk factors. Lipid profiles and fasting glucose levels were not available for most women, so for this analysis, body mass index (BMI) ≥30 kg/m² with waist circumference ≥35 inches was used as a surrogate for the metabolic syndrome. The American Heart Association guideline includes several criteria that are not explicitly defined. For this analysis, poor exercise capacity was identified by self-report of being limited “a lot” in climbing multiple flights of stairs or walking several blocks. Total physical activity was assessed by questions on a frequency and duration scale for walking and other types of activity. We defined physical inactivity as the lowest quintile, <1.25 metabolic equivalent (MET)-hours/week. For the optimal risk category, we defined the physical activity component of a healthy lifestyle as ≥10 MET-hours/week, which approximates 30 minutes of walking, 6 days per week, consistent with the physical activity component of healthy lifestyle as described in the 2007 American Heart Association diet and hormone trials. The protocol and consent forms were approved by institutional review boards of the participating institutions; all trial participants provided written informed consent.

WHAT IS KNOWN

- The 2007 American Heart Association guidelines for cardiovascular disease prevention in women recommended categorizing women as high risk, at-risk, or optimal risk on the basis of prevalent medical conditions, conventional coronary risk factors, diet, and physical activity.

Table 1. Risk Categories in 2007 AHA Cardiovascular Prevention Guidelines for Women

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Established cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>End-stage or chronic renal disease</td>
</tr>
<tr>
<td></td>
<td>10-y Framingham global risk &gt;20%</td>
</tr>
<tr>
<td>At risk</td>
<td>&gt;1 major risk factor of cardiovascular disease including</td>
</tr>
<tr>
<td></td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td></td>
<td>Poor diet</td>
</tr>
<tr>
<td></td>
<td>Physical inactivity</td>
</tr>
<tr>
<td></td>
<td>Obesity, especially central adiposity</td>
</tr>
<tr>
<td></td>
<td>Family history of premature cardiovascular disease (&lt;55 y in male relative or &lt;65 y in female relative)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>Evidence of subclinical vascular disease</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise</td>
</tr>
<tr>
<td>Optimal risk</td>
<td>Framingham global risk &lt;10% and a healthy lifestyle with no risk factors</td>
</tr>
</tbody>
</table>

“poor diet” as at risk for cardiovascular disease without an explicit definition. For this analysis, we defined poor diet as consuming >10% of calories from saturated fat. For a healthy diet, the guideline recommends a diet rich in fruits and vegetables, whole-grain, high-fiber foods, fish at least twice weekly, saturated fat <10% of energy, and if possible, <7% cholesterol <300 mg/day, alcohol <1 drink/day, sodium <2.3 g/day, and trans fat <1% of energy. In view of (1) the limited dietary assessment likely to be available to practitioners using this guideline and (2) the fact that very low saturated fat consumption (<0.61% of calories) was required to demonstrate cardiovascular event reduction in the dietary modification trial, we elected to use the AHA guideline saturated fat criterion (<7% of total calories) as shorthand for a healthy diet. In prior analyses, WHI participants adhering to saturated fat restrictions generally met recommendations for fruit and vegetable and dietary cholesterol consumption.

Framingham Algorithm

The Framingham algorithm at baseline was calculated in the random subsample of women with fasting lipid profiles: 1% of observational study, 8.6% of hormone trial, and 4.3% of dietary modification trial participants, oversampled for minority women. High-sensitivity C-reactive protein was not measured in these samples. The Framingham algorithm assigns points for each of the following factors: age, total and high density lipoprotein cholesterol levels, systolic blood pressure, treatment for hypertension, and current cigarette smoking. Each calculated point total is assigned a corresponding 10-year risk for MI/coronary heart disease (CHD) death. The high-risk category includes those with 10-year risk >20%; prior MI, stroke coronary revascularization procedure, or diabetes mellitus.

Outcomes Ascertainment

Participants reported emergency room visits, overnight hospital stays, and outpatient coronary revascularization procedures at least annually. Medical records for all deaths, overnight hospitalizations, and outpatient coronary revascularization procedures were scrutinized for potential outcomes of interest. Centrally trained physician adjudicators classified outcomes on the basis of medical record review. MI was categorized using an algorithm that included symptoms, ECG findings, and cardiac enzymes. Stroke required
rapid onset of a persistent neurological deficit not due to trauma, tumor, infection, or other cause.22

Statistical Analysis
Differences in baseline characteristics across risk strata were evaluated with ANOVA F tests for continuous covariates and χ² tests for categorical covariates. Annualized event rates were compared across subgroups using likelihood ratio testing from generalized linear models with a Poisson distribution and log-link function. Hazard ratios, 95% confidence intervals, and associated probability values were from Cox proportional hazards models. Areas under receiver operating characteristic curves (AUCs) were computed using logistic regression. Curves were compared using nonparametric methods for correlated AUCs.23 Analyses were performed using SAS for Windows version 9 (SAS Institute, Cary, NC) and R version 2.7.2 (R Foundation for Statistical Computing). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
The cohort included 161,808 women ages 50 to 79 years at study entry, with follow up of 7.8 ± 1.6 years (mean ± standard deviation). High risk, at-risk, and optimal risk women constituted 11%, 72%, and 4% of the cohort, respectively. A considerable proportion of women (13%) did not fall into any category, that is, they lacked risk factors but did not adhere to a healthy lifestyle. The uncategorized women consumed 7% to 10% of calories in the form of saturated fat and performed 1.25 to <10 MET-hours/week of physical activity, thus meeting neither our definition of “poor diet” (>10% of calories from saturated fat) nor physical inactivity (<1.25 MET-hours/week), either of which would have placed them in the at-risk category. Neither did they meet our definition of healthy lifestyle (not smoking, <7% of calories from saturated fat, and ≥10 MET-hours/week of physical activity), which would have qualified them for the optimal risk category.

The number and percentage of women with each risk characteristic are shown in descending order of frequency within each risk stratum (Table 2). Among women in the high-risk category, self-reported diabetes mellitus was the most common qualifying characteristic (6%), followed by prevalent CHD (3%). Among women in the at-risk category, “poor diet,” defined in this analysis as >10% of calories from saturated fat, was the most common characteristic (43%), followed by hypertension (26%) and obesity (25%).

Among high-risk women, the rate of MI/CHD death ranged from 12.3% to 20.3%/10 years. Women with at-risk characteristics had coronary event rates ranging from 3.0% to 5.4%/10 years, whereas optimal risk women had the lowest coronary event rate, 1.1%/10 years. The event rate among women who could not be categorized was similar to that of optimal risk women (1.3%/10 years). Clinical event rates for individual risk characteristics did not overlap between categories.

Selected baseline characteristics are shown by risk category (Table 3). Age and ethnicity differed between risk categories (P < 0.0001 for each); women in lower-risk categories were younger and more likely to be white or Asian.

The number of cardiovascular events and annualized event rate are shown by risk category (Table 4). Among women in the high-risk category, the rate of MI/CHD death was 12.5%/10 years and of MI/CHD death/stroke was 19.0%/10 years. In contrast, these events occurred at ~1/10th that frequency among optimal risk women, whereas at-risk women had intermediate event rates (P for trend < 0.0001 across risk strata). Women who did not fall into any risk category had event rates similar to the optimal risk group.

Cardiovascular event rates were examined among women from different ethnic groups by risk category (Table 5). The numbers of events in the low-risk categories are small for ethnic minority women. A graded increase in event rate across risk groups was consistently observed in all ethnic groups, although the absolute event rates differed between groups (P for interaction = 0.002). For each risk category, event rates were higher among white and black women compared with Hispanic or Asian women.

In a random subsample of women with measured lipids at baseline, the numbers of women with and without MI/CHD death are shown by risk category for the 2007 AHA guideline and Framingham algorithm (Figure). Mean calculated Framingham 10-year risk was 2% for the entire subsample, with 80%, 6% and 14% in the low-, intermediate-, and high-risk categories, respectively (including assignment to the high-risk group on the basis of clinical characteristics). Among women in the AHA at-risk category, Framingham 10-year risk was <10% for 3640 (92%) and 10% to 20% for 322 (8%). AUC for prediction of CHD events was no different for
the 2 approaches to risk stratification ($P=0.94$). We also considered Framingham categories of <5%, 5% to 20%, and >20% (Figure 1). Among women in the AHA at-risk category, Framingham risk was <5% for 3695 (68%) and 5% to 20% for 1267 (32%). These modified Framingham categories more accurately predicted CHD events; AUC was 0.724 for the Framingham algorithm compared with 0.664 for the AHA guideline ($P<0.0001$).

### Table 3. Baseline Characteristics by AHA Risk Category

<table>
<thead>
<tr>
<th>Category</th>
<th>High Risk</th>
<th>At Risk</th>
<th>Optimal Risk</th>
<th>Not in Any Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening, y</td>
<td>17 578</td>
<td>116 626</td>
<td>6784</td>
<td>20 820</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>17 409</td>
<td>115 630</td>
<td>6713</td>
<td>20 611</td>
</tr>
<tr>
<td>Waist circumference, inches</td>
<td>17 514</td>
<td>116 205</td>
<td>6764</td>
<td>20 744</td>
</tr>
<tr>
<td>Physical activity quintiles</td>
<td>16 890</td>
<td>111 848</td>
<td>6784</td>
<td>18 818</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>12 696</td>
<td>96 547</td>
<td>6024</td>
<td>18 266</td>
</tr>
<tr>
<td>% of calories from saturated fat</td>
<td>16 763</td>
<td>113 741</td>
<td>6784</td>
<td>19 771</td>
</tr>
</tbody>
</table>

### Table 4. No. and Percent (per 10 Years) of Women With Cardiovascular Events by AHA Risk Category

<table>
<thead>
<tr>
<th>Category</th>
<th>High Risk</th>
<th>At Risk</th>
<th>Optimal Risk</th>
<th>Not in Any Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>1141</td>
<td>2224</td>
<td>47</td>
<td>178</td>
</tr>
<tr>
<td>CHD death</td>
<td>631</td>
<td>747</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>Stroke</td>
<td>936</td>
<td>2366</td>
<td>63</td>
<td>235</td>
</tr>
<tr>
<td>Hospitalized angina</td>
<td>1902</td>
<td>3011</td>
<td>69</td>
<td>267</td>
</tr>
<tr>
<td>MI/CHD death</td>
<td>1568</td>
<td>2749</td>
<td>59</td>
<td>217</td>
</tr>
<tr>
<td>MI/CHD death/stroke</td>
<td>2342</td>
<td>4922</td>
<td>119</td>
<td>441</td>
</tr>
<tr>
<td>MI/CHD death/angiina</td>
<td>3204</td>
<td>5575</td>
<td>125</td>
<td>473</td>
</tr>
</tbody>
</table>

### P value

P value is from ANOVA for continuous variables (age, body mass index, waist circumference, physical activity, calories from saturated fat), or $\chi^2$ test for categorical variables.

### HRs

HRs are from Cox proportional hazards analyses, where the “Optimal” group is the referent for risk category. P value for each individual or composite event was <0.0001. This was the case whether “Not in any category” women were omitted, combined with “Optimal” or with “At risk” women or included as a separate category. HR indicates hazard ratio.
Discussion

We classified a large, diverse cohort into optimal, at-risk, and high-risk categories as proposed in the 2007 update of the Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women. Most women were at risk, but a significant proportion (13%) could not be categorized. Incident cardiovascular events increased across risk strata (P for trend <0.0001); this relationship was apparent among white, black, Asian, and Hispanic women, although absolute event rates varied among ethnic groups (P for interaction=0.002). Event rates did not overlap for individual characteristics defining at-risk versus high risk women. The 2007 AHA guideline and Framingham 10-year risk categories (<10%, 10% to 20%, >20%) predicted coronary events with similar accuracy. In contrast, modified Framingham 10-year risk categories of <5%, 5% to 20%, and >20%, predicted coronary events more accurately than the 2007 AHA guideline (AUC, 0.724 versus 0.664; P<0.0001).

Strengths of this analysis include the large, diverse population, careful prospective collection and adjudication of cardiovascular events, and richness of the baseline dataset including dietary and physical activity variables. Limitations include the lack of available data on renal function, the fact that lipoproteins were only measured in a random subsample of participants and the potential inaccuracy of self-reported medical conditions such as diabetes mellitus or hypercholesterolemia. High-sensitivity C-reactive protein was not measured in the random sample, precluding assessment of the Reynolds risk score.

Age is not a specified criterion for risk categorization in the 2007 AHA guideline. The prevalence of several high-risk and at-risk criteria such as diabetes, hypertension, and dyslipidemia increase with age, thereby incorporating, at least in part, the cardiovascular risk associated with aging. Further, this approach focuses on long-term effects of risk factors, potentially avoiding the false reassurance that a low 10-year Framingham risk may provide to younger individuals with clinically important risk characteristics.

The 2007 AHA guideline for women recommends a diet rich in vegetables and fruits, whole-grain, high-fiber foods, oily fish at least twice weekly, limiting alcohol, salt <2.3 g/day, saturated fat <7% of calories, trans fats <1% of calories, and dietary cholesterol <300 mg/day, an assessment well beyond the scope of most practitioners’ office visits. Applying just the salt, beverage, saturated and trans fat, and dietary cholesterol criteria to the WHI, fewer than 1% of women fell into the optimal risk category and 16% could not be categorized, that is, had no risk criteria but did not adhere to a healthy lifestyle. For this analysis, we chose saturated fat <7% of calories as shorthand for a healthy diet (1) to reflect a feasible degree of dietary assessment in community practice, (2) with knowledge that WHI participants adhering to the saturated fat restriction generally are consuming at least 5 daily servings of fruits/vegetables and <300 mg/day of cholesterol, and that (3) cardiovascular event reduction in the dietary modification trial was only observed at very low levels of saturated fat consumption (<6.1% of calories).

A shortcoming of the 2007 AHA guideline in this analysis was its inability to classify all women. Certainly the 13% of women who remained uncategorized could be addressed by changing our definition of “optimal lifestyle,” which included consuming <7% of calories from saturated fat and performing physical activity equivalent to 30 minutes of walking, 6 days per week. On the other hand, the no man’s land, or no woman’s land, between poor diet/physical inactivity and optimal lifestyle warrants scrutiny. In our analysis, this encompasses women consuming between 7% and 10% of calories from saturated fat and/or with physical activity levels...
between 1.25 and 10 MET-hours per week. In fact, the event rates among the uncategorized women were similar to the optimal risk women, from which limited cardiovascular benefit from prudent lifestyle could be inferred. One approach to resolving the problem of unUncategorizable women would be to combine them with the optimal risk group because their event rates are similar. This could lead to the inference that lifestyle does not matter. Alternatives would be to combine them with the at-risk group or to eliminate the gap between definitions of optimal lifestyle and poor diet/sedentary lifestyle.

Risk stratification permits providers and payors to efficiently direct attention and resources toward patients likely to benefit from initiation or intensification of preventive therapies. An at-risk label may also focus patients’ attention on adherence to lifestyle or other interventions. For risk stratification to be effective, it must be (1) used and understood by providers, (2) comprehensible to patients, and (3) valid across a spectrum of individuals.

Incorporation of ATP III into clinical practice has lagged behind provider awareness of the guideline. Doubtless many factors contribute to the gap between what clinicians do and what scientific evidence supports; one potential obstacle to risk stratification using ATP III is its complexity. The 2007 AHA prevention guideline for women requires no mathematical calculation but does require knowledge of a list of qualifying risk characteristics. The idea that specific characteristics or behaviors increase an individual’s likelihood of having a cardiovascular event may be more accessible to both providers and patients than concepts of global risk and extrapolation from population to individual risk.

Another advantage of the AHA guideline is that a qualifying risk characteristic directly pinpoints the target for intervention. Broadly recommended healthy behaviors such as physical activity, attainment and maintenance of ideal body weight, avoidance of cigarette smoking, and consumption of a prudent diet are directly addressed in laymen’s terms, so that a woman told she was at risk because of physical inactivity could undertake appropriate remedial action.

If validity is the property of a measurement method to measure what it is intended to measure, then the 2007 AHA risk stratification scheme is valid. Our findings support its predictive accuracy among older women from a variety of ethnic groups. Accuracy among younger women or among men remains to be demonstrated.

The ultimate measure of a guideline is whether it improves clinical decision-making, thereby enhancing efficiency and reducing clinical events. Global risk assessment appears to improve risk factor management only modestly in practice. The impact of the risk stratification approach proposed in the 2007 AHA prevention guideline for women will need to be demonstrated in the field.

Sources of Funding

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, United States Department of Health and Human Services, through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. The sponsor participated in design and management of the WHI and reviewed the manuscript but had no role in data analysis or interpretation, preparation, or approval of the manuscript.

Disclosures

Dr Hsia is employed by and owns stock in AstraZeneca. The other authors report no conflicts.

References

14. Lager RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women’s Health Initiative Observational Study: baseline character-
28. Sheridan SL, Crespo E. Does the routine use of global coronary heart disease risk scores translate into clinical benefits or harms? A systematic review of the literature. BMC Health Serv Res. 2008;8:60.
Evaluation of the American Heart Association Cardiovascular Disease Prevention Guideline for Women

Judith Hsia, Rebecca J. Rodabough, JoAnn E. Manson, Simin Liu, Matthew S. Freiberg, William Graettinger, Milagros C. Rosal, Barb Cochrane, Donald Lloyd-Jones, Jennifer G. Robinson, Barbara V. Howard and for the Women's Health Initiative Research Group

Circ Cardiovasc Qual Outcomes. published online February 16, 2010;
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/early/2010/02/16/CIRCOUTCOMES.108.842385