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Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women

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In addition, endorsed by: American Academy of Physician Assistants; American Association for Clinical Chemistry; American Association of Cardiovascular and Pulmonary Rehabilitation; American Diabetes Association; American Geriatrics Society; American Society for Preventive Cardiology; American Society of Echocardiography; American Society of Nuclear Cardiology; Association of Women's Health, Obstetric and Neonatal Nurses; Canadian Women's Health Network; Jacobs Institute for Women's Health; Black Women's Health Imperative; National Women's Health Resource Center; The North American Menopause Society; Partnership for Gender-Specific Medicine; Preventive Cardiovascular Nurses Association; Sister to Sister: Everyone Has a Heart Foundation, Inc.; Society for Women's Health Research; Society of Geriatric Cardiology; The Mended Hearts Inc; WomenHeart the National Coalition for Women With Heart Disease; and Women's Health Research Center.

Significant advances in our knowledge about interventions to prevent cardiovascular disease (CVD) have occurred since publication of the first female-specific recommendations for preventive cardiology in 1999.¹ Despite research-based gains in the treatment of CVD, it remains the leading killer of women in the United States and in most developed areas of the world.²⁻³ In the United States alone, more than one half million women die of CVD each year, exceeding the number of deaths in men and the next 7 causes of death in women combined. This translates into approximately 1 death every minute.² Coronary heart disease (CHD) accounts for

the majority of CVD deaths in women, disproportionately afflicts racial and ethnic minorities, and is a prime target for prevention.¹⁻² Because CHD is often fatal, and because nearly two thirds of women who die suddenly have no previously recognized symptoms, it is essential to prevent CHD.² Other forms of atherosclerotic/thrombotic CVD, such as cerebrovascular disease and peripheral arterial disease, are critically important in women. Strategies known to reduce the burden of CHD may have substantial benefits for the prevention of noncoronary atherosclerosis, although they have been studied less extensively in some of these settings.

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In the wake of the reports of the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study (HERS), which unexpectedly showed that combination hormone therapy was associated with adverse CVD effects, there is a heightened need to critically review and document strategies to prevent CVD in women.⁴⁻⁷ These studies underscore the importance of evidence-based practice for chronic disease prevention. Optimal translation and implementation of science to improve preventive care should include a rigorous process of evaluation and clear communication about the quantity and quality of evidence used to support clinical recommendations. Recently, there has been an increase in the number and proportion of women that have participated in clinical trials, although many early CVD prevention trials did not fully include women and other important subpopulations.⁸ Therefore, it is important to consider the full range of available evidence, including data on men as appropriate, to develop recommendations for diverse populations of women. Furthermore, because many patients seen in clinical practice may have characteristics that are not similar to those of clinical trial participants, it is necessary to draw inferences about the likelihood that data will generalize from research to clinical settings.

The objective of this collaborative effort was to develop the first set of evidence-based guidelines for the prevention of CVD in adult women with a broad range of cardiovascular risk. The technology for identifying CVD in its earliest stages has improved over the past decade, and this has led to a blurring of the distinction between primary and secondary prevention. The concept of CVD as a categorical, "have-or-have-not" condition has been replaced with a growing appreciation for the existence of a continuum of CVD risk. Table 1 illustrates a spectrum of CVD, showing risk groups defined by their absolute probability of having a coronary event in 10

years according to the Framingham Risk Score for women.⁹ Clinical diagnoses and scenarios that broadly group women into categories of high, intermediate, and lower risk also are provided. This scheme allows healthcare providers to match the intensity of risk intervention to the baseline level of CVD risk. A scoring sheet for use in clinical practice to calculate absolute 10-year CHD risk in women is provided in Appendix I. The recommendations herein are designed to assist healthcare providers in optimizing CVD preventive care for all women age 20 years and older. Implementation of these guidelines may differ among countries and regions for cultural, medical, and economic reasons. In addition, application of these guidelines should also take into consideration individual factors such as frailty and life expectancy.

Methods

Selection of Expert Panel Members

The leadership of each of the 13 American Heart Association (AHA) Scientific Councils was asked to nominate a recognized expert in CVD prevention who had particular knowledge about women. The president of the AHA appointed at-large members to fill gaps in specific areas of expertise. The AHA Manuscript Oversight Committee approved the chair of the Expert Panel. On the basis of recommendations of the AHA Expert Panel, major professional or government organizations with a mission consistent with CVD prevention were solicited to serve as cosponsors and were asked to nominate 1 representative with full voting rights to serve on the Expert Panel. Panelists also suggested diverse professional and community organizations to endorse the final document after its approval by the AHA Science Advisory Coordinating Committee and cosponsoring organizations.

TABLE 1. Spectrum of CVD Risk in Women

Risk Group	Framingham Global Risk (10-y Absolute CHD Risk)	Clinical Examples
High risk	>20%	<ul style="list-style-type: none"> • Established CHD • Cerebrovascular disease* • Peripheral arterial disease • Abdominal aortic aneurysm • Diabetes mellitus • Chronic kidney disease†
Intermediate risk	10% to 20%	<ul style="list-style-type: none"> • Subclinical CVD‡ (eg, coronary calcification) • Metabolic syndrome • Multiple risk factors§ • Markedly elevated levels of a single risk factor • First-degree relative(s) with early-onset (age: <55 y in men and <65 y in women) atherosclerotic CVD
Lower risk	<10%	<ul style="list-style-type: none"> • May include women with multiple risk factors, metabolic syndrome, or 1 or no risk factors
Optimal risk	<10%	<ul style="list-style-type: none"> • Optimal levels of risk factors and heart-healthy lifestyle

CHD indicates coronary heart disease; CVD, cardiovascular disease.

*Cerebrovascular disease may not confer high risk for CHD if the affected vasculature is above the carotids. Carotid artery disease (symptomatic or asymptomatic with >50% stenosis) confers high risk.

†As chronic kidney disease deteriorates and progresses to end-stage kidney disease, the risk of CVD increases substantially.

‡Some patients with subclinical CVD will have >20% 10-year CHD risk and should be elevated to the high-risk category.

§Patients with multiple risk factors can fall into any of the 3 categories by Framingham scoring.

||Most women with a single, severe risk factor will have a 10-year risk <10%.

TABLE 2. Summary of Articles Identified From Systematic Literature Review by Topic

Topic	Abstracts Identified	Articles Included for Full-Text Screening	Meta-Analyses Identified	Articles Included for Evidence Tables
Hyperlipidemia	339	119	5	40
Physical activity	950*	95	6	52
Tobacco use	1341	127	6	16
Antiplatelet therapy	753	155	12	31
Blood pressure management	273	112	16	31
β -Blocker therapy	845	136	12	30
Cardiac rehabilitation	950*	69	4	19
ACE/ARB therapy	371	48	7	21
Weight management	158	25	1	6
Diabetes	229	56	2	8
Hormone replacement therapy	373	93	5	41
Diet modification	425	89	4	68
Warfarin in atrial fibrillation	242	49	6	11
Aspirin for primary prevention	25	15	3	10
Depression therapy	45	5	0	2
Antioxidant supplementation	220	43	0	16
Omega-3 fatty acid supplementation	169	45	2	8
Folic acid supplementation	69	10	1	3
Total†	6819	1279	92	399

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*Physical activity and cardiac rehabilitation were combined during the initial literature search. This number reflects the total number of abstracts identified as physical activity OR cardiac rehabilitation.

†Total numbers reflect unique articles. Actual sum of the individual recommendation numbers are higher than total due to the inclusion of some articles under more than one recommendation. The exception is the total articles included for evidence tables, which reflects the number of tables that appear in the report.

Selection of Topics and Candidate Recommendations

The Expert Panel reviewed previously published AHA recommendations for the primary and secondary prevention of CVD and discussed and debated topics that were timely, with the goal of developing a set of candidate recommendations for searching and rating.^{1,10–11} A list of preselected recommendations was circulated to the panel, and experts were asked to independently rate the priority of the recommendation and suggest modifications to the wording. Recommendations were then selected for the systematic literature search.

Systematic Search and Summary of Data

Inclusion and exclusion criteria for studies to be evaluated as part of the evidence-rating process were established according to the Expert Panel recommendation to focus on major CVD clinical end points (death, myocardial infarction, stroke, revascularization procedure, congestive heart failure, or a composite CVD end point) in high-quality studies. The importance of other outcomes, such as quality of life and resource utilization, was recognized, but these were not feasible to include in this version. The purpose of the clinical recommendations is to provide guidance with regard to risk-reducing interventions; therefore, the panel supported the inclusion of studies that were interventional rather than etiologic in nature. For example, studies of the impact of weight loss on major clinical CVD outcomes were included but not studies that simply related obesity to CVD.

Inclusion criteria were randomized clinical trials or large prospective cohort studies (>1000 subjects) with CVD risk-reducing interventions evaluated. Also, meta-analyses that used a quantitative systematic review process were included. All studies had to have at least 10 cases of major clinical CVD end points reported. Studies with surrogate end points were excluded unless they met the minimum number of outcome events. Studies meeting the above criteria were included whether or not there were female participants.

The systematic search was conducted by the Duke Center for Clinical Health Policy Research, Durham, NC. Search terms were constructed for each clinical recommendation, with an “explode” term to include related articles. Three databases were searched electronically on OVID, including Medline (1966 through July 3, 2003), the Cumulative Index to Nursing & Allied Health (CINAHL) (1982 through July 3, 2003), and PsycInfo (1872 through July 3, 2003). More than 99% of the studies were located in Medline. Nearly 7000 titles and abstracts identified through the systematic search were reviewed to exclude those that did not meet obvious eligibility criteria or were not available in English. More than 1200 articles were obtained for full-text screening and reviewed for inclusion/exclusion criteria. A standardized abstraction form was completed to document the study design, end points, and decision to include or exclude. Table 2 lists the number of articles included/excluded for each category of recommendation.

TABLE 3. Classification and Levels of Evidence

Strength of Recommendation	
Classification	
Class I	Intervention is useful and effective
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Intervention is not useful/effective and may be harmful
Level of Evidence	
A	Sufficient evidence from multiple randomized trials
B	Limited evidence from single randomized trial or other nonrandomized studies
C	Based on expert opinion, case studies, or standard of care
Generalizability index	
1	Very likely that results generalize to women
2	Somewhat likely that results generalize to women
3	Unlikely that results generalize to women
0	Unable to project whether results generalize to women

Included articles were abstracted for more detailed information on a standardized form that included study type, number of participants (% female) at baseline, population characteristics (primary prevention, secondary prevention, or mixed), mean age (age range), percentage diabetic, percentage white, intervention(s) (for drug trials, information was listed about dose, schedule, and duration), primary outcomes including numbers of events, subgroup analysis of clinical end points in women (if analysis available), and comments about important methodological or quality issues.

Expert Panel members reviewed the summary evidence tables for completeness. Tables were updated with publications that were inadvertently omitted or included during the systematic search to comprise the final evidence tables. In addition, results of trials or meta-analyses published subsequent to the systematic search that met inclusion criteria were made available to the Expert Panel. A complete listing of references reviewed by the Expert Panel and used to compile the evidence summary tables is listed in Appendix II. The evidence summary tables are located in an online-only Data Supplement at <http://www.circulationaha.org>.

Evidence Rating System

Two primary reviewers from the Expert Panel were assigned to each candidate recommendation to propose an initial evidence rating and suggest modifications to wording on the basis of the results of the systematic evidence search. A series of conference calls was held to discuss the rating and revised wording of recommendations. Each expert received a final copy of the evidence tables and voted independently on the strength of the recommendation (Class I, IIa, IIb, or III) and level of evidence (A, B, or C) as outlined in Table 3. Class I interventions should be administered unless contraindicated. Class III interventions

should not be administered for CVD prevention. The rationale for the rating system is based on methods used in AHA/American College of Cardiology clinical practice guidelines as described.¹² The experts also evaluated the likelihood that data from men would generalize to women with regard to each specific risk-reducing intervention (1, very likely; 2, somewhat likely; 3, unlikely; and 0, unable to project). Criteria to determine generalizability were based on factors such as differences in the epidemiology and pathophysiology of CVD between men and women (eg, the ratio of hemorrhagic stroke to coronary events may alter the risk-to-benefit ratio of aspirin in primary prevention for women versus men). The final rating of evidence was determined by a majority vote.

Clinical Recommendations

Evidence-based recommendations for the prevention of CVD in women are listed in Table 4. Each recommendation is accompanied by the strength of recommendation, level of evidence to support it, and the generalizability index. The strength of the recommendation is based on not only the level of evidence to support a clinical recommendation, but also on factors such as feasibility of conducting randomized controlled trials in women. Recommendations are grouped in the following categories: lifestyle interventions; major risk factor interventions; atrial fibrillation/stroke prevention; preventive drug interventions; and a Class III category, where routine intervention for CVD prevention is not recommended.

Several lifestyle interventions were rated as Class I recommendations, although the supporting evidence was in many cases classified as level B. These decisions reflect the availability of observational studies as evidence to support the recommendation, as well as ethical issues that preclude conducting randomized controlled trials of certain lifestyle interventions. For example, the Expert Panel regarded smoking cessation as a top priority in clinical practice and suggested that the absence of trial data should not preclude a strong emphasis on clinician interventions to help women stop smoking. More detailed information on how to treat tobacco dependence is available at http://www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf (Table 5).

Lifestyle interventions received Class I recommendations from the panel not only because of their potential to reduce clinical CVD, but also because heart-healthy lifestyles may prevent the development of major risk factors for CVD.¹³ Prevention of the development of risk factors through a positive lifestyle approach may minimize the need for more intensive intervention in the future.

Although evidence to support a clinical benefit for CVD event reduction was limited with some interventions (eg, treatment of depression), there may be other important benefits associated with these therapies that are reflected in the strength of the recommendation, such as improved quality of life. Behavioral interventions may have benefits that are not captured by our stringent outcome criteria for clinical CVD events. Weight management via lifestyle and behavioral approaches was rated as a Class I recommendation, level B. The panel suggested there was insufficient evidence to rate more aggressive medical and surgical approaches that generally are limited to a small subset of women.

TABLE 4. Clinical Recommendations

Lifestyle interventions**Cigarette smoking**

Consistently encourage women not to smoke and to avoid environmental tobacco. (Class I, Level B)_{GI=1}

Physical activity

Consistently encourage women to accumulate a minimum of 30 minutes of moderate-intensity physical activity (eg, brisk walking) on most, and preferably all, days of the week. (Class I, Level B)_{GI=1}

Cardiac rehabilitation

Women with a recent acute coronary syndrome or coronary intervention, new-onset or chronic angina should participate in a comprehensive risk-reduction regimen, such as cardiac rehabilitation or a physician-guided home- or community-based program. (Class I, Level B)_{GI=2}

Heart-healthy diet

Consistently encourage an overall healthy eating pattern that includes intake of a variety of fruits, vegetables, grains, low-fat or nonfat dairy products, fish, legumes, and sources of protein low in saturated fat (eg, poultry, lean meats, plant sources). Limit saturated fat intake to <10% of calories, limit cholesterol intake to <300 mg/d, and limit intake of *trans* fatty acids. (Class I, Level B)_{GI=1}

Weight maintenance/reduction

Consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m² and a waist circumference <35 in. (Class I, Level B)_{GI=1}

Psychosocial factors

Women with CVD should be evaluated for depression and refer/treat when indicated. (Class IIa, Level B)_{GI=2}

Omega 3 fatty acids

As an adjunct to diet, omega 3 fatty-acid supplementation may be considered in high-risk* women. (Class IIb, Level B)_{GI=2}

Folic acid

As an adjunct to diet, folic acid supplementation may be considered in high-risk* women (except after revascularization procedure) if a higher-than-normal level of homocysteine has been detected. (Class IIb, Level B)_{GI=2}

Major risk factor interventions**Blood pressure—lifestyle**

Encourage an optimal blood pressure of <120/80 mm Hg through lifestyle approaches. (Class I, Level B)_{GI=1}

Blood pressure—drugs

Pharmacotherapy is indicated when blood pressure is $\geq 140/90$ mm Hg or an even lower blood pressure in the setting of blood pressure-related target-organ damage or diabetes. Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated. (Class I, Level A)_{GI=1}

Lipid, lipoproteins

Optimal levels of lipids and lipoproteins in women are LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL, and non-HDL-C (total cholesterol minus HDL cholesterol) <130 mg/dL and should be encouraged through lifestyle approaches. (Class I, Level B)_{GI=1}

Lipids—diet therapy

In high-risk women or when LDL-C is elevated, saturated fat intake should be reduced to <7% of calories, cholesterol to <200 mg/d, and *trans* fatty acid intake should be reduced. (Class I, Level B)_{GI=1}

Lipids—pharmacotherapy—high risk*

Initiate LDL-C-lowering therapy (preferably a statin) simultaneously with lifestyle therapy in high-risk women with LDL-C ≥ 100 mg/dL (Class I, Level A)_{GI=1}, and initiate statin therapy in high-risk women with an LDL-C <100 mg/dL unless contraindicated (Class I, Level B)_{GI=1}.

Initiate niacin§ or fibrate therapy when HDL-C is low, or non-HDL-C elevated in high-risk women. (Class I, Level B)_{GI=1}

GI indicates generalizability index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

*High risk is defined as CHD or risk equivalent, or 10-year absolute CHD risk >20%.

†Intermediate risk is defined as 10-year absolute CHD risk 10% to 20%.

‡Lower risk is defined as 10-year absolute CHD risk <10%.

§Dietary supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should only be used if approved and monitored by a physician.

TABLE 4. Continued

Lipids—pharmacotherapy—intermediate risk†

Initiate LDL-C-lowering therapy (preferably a statin) if LDL-C level is ≥ 130 mg/dL on lifestyle therapy (Class I, Level A)_{GI=1}, or niacin§ or fibrate therapy when HDL-C is low or non-HDL-C elevated after LDL-C goal is reached. (Class I, Level B)_{GI=1}

Lipids—pharmacotherapy—lower risk‡

Consider LDL-C-lowering therapy in low-risk women with 0 or 1 risk factor when LDL-C level is ≥ 190 mg/dL or if multiple risk factors are present when LDL-C is ≥ 160 mg/dL (Class IIa, Level B) or niacin§ or fibrate therapy when HDL-C is low or non-HDL-C elevated after LDL-C goal is reached. (Class IIa, Level B)_{GI=1}

Diabetes

Lifestyle and pharmacotherapy should be used to achieve near normal HbA_{1c} (<7%) in women with diabetes. (Class I, Level B)_{GI=1}

Preventive drug interventions**Aspirin—high risk***

Aspirin therapy (75 to 162 mg), or clopidogrel if patient is intolerant to aspirin, should be used in high-risk women unless contraindicated. (Class I, Level A)_{GI=1}

Aspirin—intermediate risk†

Consider aspirin therapy (75 to 162 mg) in intermediate-risk women as long as blood pressure is controlled and benefit is likely to outweigh risk of gastrointestinal side effects. (Class IIa, Level B)_{GI=2}

 β -Blockers

β -Blockers should be used indefinitely in all women who have had a myocardial infarction or who have chronic ischemic syndromes unless contraindicated. (Class I, Level A)_{GI=1}

ACE inhibitors

ACE inhibitors should be used (unless contraindicated) in high-risk* women. (Class I, Level A)_{GI=1}

ARBs

ARBs should be used in high-risk* women with clinical evidence of heart failure or an ejection fraction <40% who are intolerant to ACE inhibitors. (Class I, Level B)_{GI=1}

Atrial fibrillation/stroke prevention**Warfarin—atrial fibrillation**

Among women with chronic or paroxysmal atrial fibrillation, warfarin should be used to maintain the INR at 2.0 to 3.0 unless they are considered to be at low risk for stroke (<1%/y) or high risk of bleeding. (Class I, Level A)_{GI=1}

Aspirin—atrial fibrillation

Aspirin (325 mg) should be used in women with chronic or paroxysmal atrial fibrillation with a contraindication to warfarin or at low risk for stroke (<1%/y). (Class I, Level A)_{GI=1}

Class III interventions**Hormone therapy**

Combined estrogen plus progestin hormone therapy should not be initiated to prevent CVD in postmenopausal women. (Class III, Level A)

Combined estrogen plus progestin hormone therapy should not be continued to prevent CVD in postmenopausal women. (Class III, Level C)

Other forms of menopausal hormone therapy (eg, unopposed estrogen) should not be initiated or continued to prevent CVD in postmenopausal women pending the results of ongoing trials. (Class III, Level C)

Antioxidant supplements

Antioxidant vitamin supplements should not be used to prevent CVD pending the results of ongoing trials. (Class III, Level A)_{GI=1}

Aspirin—lower risk‡

Routine use of aspirin in lower-risk women is not recommended pending the results of ongoing trials. (Class III, Level B)_{GI=2}

GI indicates generalizability index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

*High risk is defined as CHD or risk equivalent, or 10-year absolute CHD risk >20%.

†Intermediate risk is defined as 10-year absolute CHD risk 10% to 20%.

‡Lower risk is defined as 10-year absolute CHD risk <10%.

§Dietary supplement niacin must not be used as a substitute for prescription niacin, and over-the-counter niacin should only be used if approved and monitored by a physician.

TABLE 5. Internet Resources With Supporting Materials for Selected Recommendations

Clinical Recommendation	Recommended Web Site	Comments
Cigarette smoking	http://www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf	Treating Tobacco Use and Dependence
Diet	http://www.cfsan.fda.gov/~frf/sea-mehg.html	Mercury Levels in Seafood Species
Weight management	http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm	Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults
Lipids	http://circ.ahajournals.org/cgi/reprint/106/25/3143.pdf	Third Report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)
Blood pressure	http://hyper.ahajournals.org/cgi/content/full/42/6/1206	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)
	http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/index.htm	Dietary Approaches to Stop Hypertension (DASH) Eating Plan
Diabetes	http://www.diabetes.org/home.jsp	American Diabetes Association
	http://circ.ahajournals.org/cgi/content/full/105/18/2231	AHA Conference Proceedings: Prevention Conference VI: Diabetes and Cardiovascular Disease
Atrial fibrillation/stroke prevention	http://www.nhlbi.nih.gov/about/framingham/stroke.htm	Framingham Stroke Risk Scoring System
	http://www.americanheart.org/downloadable/heart/222_ja20017993p_1.pdf	ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation
Absolute CHD risk calculation	http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm	Framingham CHD Risk Scoring System

All sites were accessed on and available as of December 16, 2003.

Our dietary recommendations emphasize intake of a variety of heart-healthy foods. The panel concluded that intake of fish has been associated with a reduced risk of CVD. The benefits of fish seem to result, at least in part, from omega-3 fatty acids. Nonetheless, women of childbearing age, especially pregnant women, should avoid shark, swordfish, king mackerel, and tilefish because the relatively high content of mercury in these fish may impair fetal neurological development. Still, these women can eat other kinds of fish, such as catfish, flounder, and salmon, which have less mercury. For a more complete listing of mercury levels in different types of fish, see the US Food and Drug Administration web site at <http://www.cfsan.fda.gov/~frf/sea-mehg.html> (Table 5). Women who do not eat fish might consider nonmarine sources of omega-3 fatty acids, such as flaxseed oil, walnut oil, canola oil, soybean oil, or walnuts. However, there is less evidence supporting a cardiovascular benefit from these sources of omega-3 fatty acids.¹⁴

TABLE 6. CVD Prevention Strategies for Clinical Practice

1. Assess and stratify women into high, intermediate, lower, or optimal risk categories.
2. Lifestyle approaches (smoking cessation, regular exercise, weight management, and heart-healthy diet) to prevent CVD are Class I recommendations for all women and a top priority in clinical practice.
3. Other CVD risk-reducing interventions should be prioritized on the basis of strength of recommendation (Class I > Class IIa > Class IIb) and within each class of recommendation on the basis of the level of evidence, with the exception of lifestyle, which is a top priority for all women (A>B>C).
4. Highest priority for risk intervention in clinical practice is based on risk stratification: (high risk > intermediate risk > lower risk > optimal risk).
5. Avoid interventions designated as Class III.

Other expert panels and organizations (including the National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III]; the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7], and the American Diabetes Association) have addressed control of major risk factors extensively and can be referred to for more specific information about management approaches (Table 5).^{9,15,16} For example, our recommendation to encourage an optimal blood pressure through lifestyle approaches should be implemented using more detailed information from the JNC 7 report about weight management, adopting a DASH (Dietary Approaches to Stop Hypertension) eating plan, dietary sodium reduction, physical activity, and moderation of alcohol consumption.¹⁵ Similarly, NCEP ATP III provides algorithms for cholesterol management and is updated as new evidence becomes available.⁹ According to NCEP/ATP III, LDL cholesterol is the primary target of lipid-lowering therapy, and intensity of therapy should be matched to the absolute risk of the patient. Glycemic control received a Class I recommendation from the Expert Panel. Treatment of hyperglycemia has been shown to reduce or delay complications of diabetes such as retinopathy, nephropathy, and neuropathy, which underscores the importance of glycemic control in diabetic patients.¹⁶ Moreover, both lifestyle intervention and (to a lesser degree) metformin therapy have been shown to reduce the incidence of diabetes.¹⁷

Although there was good consensus on the use of aspirin (75 to 162 mg) in high-risk women, recommendations for aspirin therapy in intermediate- and lower-risk women were more challenging. The difficulty in developing these recommendations was due to the lack of data from primary prevention trials that included women and the possibility that data on men may not necessarily be extrapolated to women.

TABLE 7. Priorities for Prevention in Practice According to Risk Group

High-risk women (>20% risk)
Class I recommendations:
<ul style="list-style-type: none"> • Smoking cessation • Physical activity/cardiac rehabilitation • Diet therapy • Weight maintenance/reduction • Blood pressure control • Lipid control/statin therapy • Aspirin therapy • β-Blocker therapy • ACE inhibitor therapy (ARBs if contraindicated) • Glycemic control in diabetics
Class IIa recommendation:
<ul style="list-style-type: none"> • Evaluate/treat for depression
Class IIb recommendations:
<ul style="list-style-type: none"> • Omega 3 fatty-acid supplementation • Folic acid supplementation
Intermediate-risk women (10% to 20% risk)
Class I recommendations:
<ul style="list-style-type: none"> • Smoking cessation • Physical activity • Heart-healthy diet • Weight maintenance/reduction • Blood pressure control • Lipid control
Class IIa recommendations:
<ul style="list-style-type: none"> • Aspirin therapy
Lower-risk women (<10% risk)
Class I recommendations:
<ul style="list-style-type: none"> • Smoking cessation • Physical activity • Heart-healthy diet • Weight maintenance/reduction • Treat individual CVD risk factors as indicated
Stroke prevention among women with atrial fibrillation
Class I recommendations:
High-intermediate risk of stroke
<ul style="list-style-type: none"> • Warfarin therapy
Low risk of stroke (<1%/y) or contraindication to warfarin
<ul style="list-style-type: none"> • Aspirin therapy

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Uncontrolled hypertension is not uncommon in women, and aspirin therapy may increase the risk of hemorrhagic stroke in this setting. Moreover, the risk of gastrointestinal bleeding and other side effects may outweigh the potential benefits of aspirin in women at lower risk for CVD. The panel suggested a conservative approach, pending the results of ongoing clinical trials. It was also noted that nonsteroidal antiinflammatory medications should not be substituted for aspirin for CVD prevention. For stroke prevention among women with

atrial fibrillation, a dose of 325 mg of aspirin is needed if there is a contraindication to warfarin therapy or if the risk of a stroke is considered low (<1% annual event rate per year). Tools to determine stroke risk are available at <http://www.nhlbi.nih.gov/about/framingham/stroke.htm> (Table 5).

The Class III recommendations on hormone therapy and antioxidant supplementation were based on recent clinical trials showing no benefit for CVD prevention and possible adverse effects of these interventions. The panel acknowledged that major trials have been limited to specific types and dosages of these agents, and those results may not generalize to compounds not tested in clinical studies. In particular, ongoing trials will give more information about unopposed estrogen therapy and clinical outcomes. However, given the unproven benefit and possible harm associated with postmenopausal hormone therapies, it was suggested that a conservative approach be taken in clinical practice unless further research is available to support use for CVD prevention. The use of hormone therapy for menopausal symptoms has been addressed by other professional societies.^{18,19} Although hormone therapy is not recommended for CVD prevention, women and their healthcare providers should weigh the potential risks of therapy against the potential benefits for menopausal symptom control.

Limitations

The process of developing clinical guidelines has several limitations, even when a systematic approach is undertaken. Most importantly, data used to establish recommendations might be generated from populations that do not reflect the characteristics of the patient being treated, and individual responses can vary significantly. The clinical cardiovascular end points chosen for inclusion in the systematic evaluation do not necessarily reflect the net clinical impact and do not include many end points that are clinically important but often not reported (eg, symptoms, quality of life, functional status, hospitalizations, resource utilization, etc). We simplified the recommendation for each level of risk for purposes of clinical utility and acknowledge that there might be variability in efficacy and effectiveness of various interventions within the same risk intervention category (eg, various doses or types of physical activity or drugs within the same class may yield different results). The Framingham risk score may not apply equally to all populations, but it performs well within subgroups.^{20,21} We may have omitted or included some studies because of the limitations of electronic searching and human error; however, the likelihood that such an inadvertent omission or inclusion would alter a recommendation is small. Our recommendations are based on evidence available to the panel through November 2003, and as science evolves, recommendations may have to be revised. Finally, we do not include a comprehensive plan for implementation of the guidelines in this document. The AHA is developing professional education programs and other initiatives to facilitate the dissemination and implementation of the guidelines.

Conclusions and Future Directions

Overwhelming evidence suggests that CVD can be prevented in both women and men. Clinical recommendations are provided to assist healthcare providers and the public in

efforts to avoid an initial or recurrent cardiovascular event. Strategies to implement these guidelines and prioritize risk-reducing therapies in clinical practice are outlined in Tables 6 and 7. Our systematic search of the literature shows that several prevention strategies are likely to have substantially greater benefit than risk and that some interventions are likely to be associated with greater risk than benefit. It is important that the public be appropriately informed about potentially lifesaving preventive therapies and take action to lower their risk. On the basis of our review of the scientific evidence, it appears the risk of no action is far greater than that of applying knowledge to prevent CVD. Approximately 75% of the original research articles that met our inclusion criteria included female subjects, and very few presented race/ethnic-specific analyses. Moreover, few studies included elderly women, especially those over 80, in whom CVD is common. The results of this project highlight the need to include diverse populations in research studies and to present subgroup analyses so that guidance can be tailored, if appropriate, to subpopulations. These recommendations are meant to assist clinicians on the basis of our current state of evidence and supersede previous AHA prevention guidelines with regard to women.^{1,10,11,22} Because health care is a blend of science and art, we emphasize that guidelines are not a substitute for good clinical judgment.

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Appendix I

Framingham Point Score Estimate of 10-Year Risk for Women

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol (mg/dl)	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥ 280	13	10	7	4	2

Smoking	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dl)	Points
≥ 60	-1
50-59	0
40-49	1
< 40	2

Systolic BP (mmHg)	If Untreated	If Treated
< 120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥ 160	4	6

Point Total	10-Year Risk %
< 9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥ 25	≥ 30

10-Year Risk _____ %

A more precise method of calculating CHD risk in women is available online at <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>. Adapted from the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Final Report (*Circulation*. 2002;106:3143-3421), Table III. 1-6, p 3231.

Appendix II

Original research articles identified through systematic search by topic (summary evidence tables on web).

Hyperlipidemia

- Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized—pravastatin versus usual care: The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT-LLT). ALLHAT Officers and Coordinators for the ALLHAT collaborative research group. *JAMA*. 2002;288:2998–3007.
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Physical Activity

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