REVIEW ARTICLE

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Drugs for Cardiovascular Disease Prevention in Women

Implications of the AHA Guidelines – 2007 Update

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Abstract

Lifestyle interventions constitute the initial strategy for the primary and secondary prevention of cardiovascular disease in women. However, pharmacotherapy is often indicated for control of major cardiovascular risk factors, and

abundant clinical trial data support the morbidity and mortality benefit of a number of categories of drug therapy following a coronary event. Although women have increasingly been enrolled in clinical trials of pharmacotherapy, under representation of women in most research studies limits the gender-specific assessment of outcomes. Equally importantly, recent randomized clinical trial data have highlighted inappropriate preventive therapies for women (i.e. those lacking effectiveness and potentially imparting harm). Decision-making data for drug therapy for women also derive from a number of clinical trials conducted solely in women.

The drug classes reviewed in this article include omega-3 fatty acids, aspirin, ACE inhibitors and angiotensin II receptor antagonists or blockers, β-adrenoceptor antagonists (β-blockers), aldosterone antagonists, antioxidants, folic acid and vitamins B_6 and B_{12}, and menopausal hormone therapy and selective estrogen-receptor modulators.

Information is sparse regarding specific cardiovascular pharmacotherapies for elderly women, and women of racial and ethnic minorities. Owing to the under representation of the subset of women in many trials, analysis by age, race and ethnicity is not appropriate. This information gap presents a major challenge for future studies, as these subgroups constitute populations of women at high cardiovascular risk.

Coronary heart disease (CHD) remains the leading cause of mortality among women in the US and among women in many countries worldwide. A pivotal issue is that many risk factors for cardiovascular disease (CVD) and CHD are modifiable or preventable, hence, the widespread emphasis on coronary risk reduction as a means to favourably affect both coronary risk factors and clinical manifestations of CHD.

As with the initial 2004 Prevention Guidelines for women,[1] the emphasis focuses on a partnership between women and their healthcare providers, but the 2007 Guideline Update[2] displays a simpler algorithm for ascertaining cardiovascular risk status, defining women as at high risk, at risk or at optimal risk (table I). Furthermore, given the 10-year average delay in onset of clinical manifestations of CHD in women compared with men, the emphasis of the 2007 Guideline Update is on reduction of lifetime risk, rather than the limited viewpoint of 10-year risk. This simplification of the classification of cardiovascular risk status derives from the overview that most studies providing the evidence base for the guidelines were conducted either in apparently healthy women or in women with established CVD.

Given the high lifetime risk of CHD for women, and the documentation that most US women have at least one coronary risk factor,[3] most women are candidates for preventive therapies. The guideline citations are categorized as follows: (i) lifestyle interventions, which are recommended for all women, with virtually all having a class I level of recommendation; (ii) major risk-factor interventions; and (iii) preventive drug interventions (table II). Highly relevant are the class III interventions that have not proved useful or effective and may impart harm (table III). The classifications and levels of evidence are those used in most clinical practice guidelines (table IV).

The studies included in the systematic search for this article were randomized clinical trials or large prospective cohort studies (>1000 subjects) of cardiovascular risk-reducing interventions, meta-analyses that used a quantitative systematic review process or surrogate endpoint studies with at least ten cases of major clinical CVD endpoints reported. A total of 5774 articles were initially identified: 828

were included for full-text screening, and 246 met the inclusion criteria and were included in the evidence tables. This article addresses solely those recommendations that involve pharmacotherapy, such that the bibliography encompassing the evidence base for the guideline recommendations for lifestyle interventions (e.g. smoking cessation, physical activity, cardiovascular or stroke rehabilitation, dietary intake, weight maintenance/reduction or depression screening/referral) is not provided.

The pharmacotherapy bibliography cited includes those references that provided the basis and levels of evidence for the clinical recommendations discussed, and includes a review of trial results and gender-specific outcomes, when available, published up to June 2006.

Table I. Classification of cardiovascular disease (CVD) risk status in women (reproduced from Mosca et al.,[2] with permission, © 2007, American Heart Association, Inc.)

Criteria
High risk
Established coronary heart disease
Cerebrovascular disease
Peripheral arterial disease
Abdominal aortic aneurysm
End-stage or chronic renal disease
Diabetes mellitus
10-Year Framingham global risk >20%[a]
At risk
≥1 major risk factors for CVD, including:
cigarette smoking
poor diet
physical inactivity
obesity, especially central adiposity
family history of premature CVD (CVD at <55 years of age in a male relative and <65 years of age in a female relative)
hypertension
dyslipidaemia
Evidence of subclinical vascular disease (e.g. coronary calcification)
Metabolic syndrome
Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise
Optimal risk
Framingham global risk <10% and a healthy lifestyle, with no risk factors

a Or at high risk on the basis of another population-adapted tool used to assess global risk.

1. Lifestyle Category (Dietary Intake) Omega-3 Fatty Acids

Following guideline recommendations (class IIb, level B), capsules of omega-3 fatty acids (850–1000 mg of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) may be considered, as an adjunct to diet, in women with established CHD. Higher doses (2–4 g) may be used for the treatment of women with high triglyceride levels.[2]

1.1 Primary Prevention

The data regarding omega-3 fatty acids derive from four cohort studies[4-7] and three meta-analyses.[8-10] There was a prospective examination among the 76 763 women in the Nurses' Health Study who completed a dietary questionnaire at baseline (1984) of the association between dietary α-linolenic acid, assessed via this questionnaire, and the risk of sudden cardiac death, other fatal CHD and nonfatal myocardial infarction (MI). After controlling for coronary risk factors and other fatty acids, there was an inverse association between α-linolenic acid intake and the risk of sudden cardiac death, but not the risk of other fatal CHD or nonfatal MI; risk of sudden cardiac death was 38–40% lower in the highest two quintiles of dietary intake. This suggests that increased dietary α-linolenic acid may reduce the risk of sudden cardiac death, but not other coronary events (i.e. it may have antiarrhythmic properties, but provides no information about omega-3 fatty acid supplementation).[4] Association of dietary intake of fish and omega-3 fatty acids, based on a food frequency questionnaire, and the risk of CHD was examined in 41 578 Japanese men and women aged 40–59 years, free of CVD and followed for about a decade.[6] Based on 196 nonfatal and 62 fatal coronary events, multivariable hazard ratios in the highest versus the lowest quintiles of fish intake were 0.63 for total CHD, 0.44 for definite MI and 1.14 for sudden cardiac death. The major reduction was in the risk of nonfatal coronary events, with a strong inverse association between the dietary intake of omega-3 fatty acids, and the risk of definite MI and nonfatal coronary events. Results of these two studies are thus inconsistent.

Table II. Guidelines for the prevention of cardiovascular disease (CVD) in women: clinical recommendations (reproduced from Mosca et al.,[2] with permission, © 2007, American Heart Association, Inc.)

Lifestyle interventions
Cigarette smoking
Women should not smoke and should avoid environmental tobacco smoke. Provide counselling, nicotine replacement and other pharmacotherapy as indicated in conjunction with a behavioural programme or formal smoking cessation programme *(class I, level B)*
Physical activity
Women should accumulate a minimum of 30 minutes of moderate intensity physical activity (e.g. brisk walking) on most, and preferably all, days of the week *(class I, level B)*
Women who need to lose weight or sustain weight loss should accumulate a minimum of 60–90 minutes of moderate intensity physical activity (e.g. brisk walking) on most, and preferably all, days of the week *(class I, level C)*
Rehabilitation
A comprehensive risk-reduction regimen, such as cardiovascular or stroke rehabilitation or a physician-guided home- or community-based exercise training programme, should be recommended to women with a recent acute coronary syndrome or coronary intervention, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease *(class I, level A),* or current/prior symptoms of heart failure and an LVEF <40% *(class I, level B)*
Dietary intake
Women should consume a diet rich in fruits and vegetables; choose whole-grain, high-fibre foods; consume fish, especially oily fish,[a] at least twice a week; limit intake of saturated fat to <10% of energy, and if possible to <7%, cholesterol to <300 mg/day, alcohol intake to no more than one drink per day,[b] and sodium intake to <2.3 g/day (approximately 1 teaspoon of salt). Consumption of trans-fatty acids should be as low as possible (e.g. <1% of energy) *[class I, level B]*
Weight maintenance/reduction
Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake and formal behavioural programmes when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2, and a waist circumference ≤35 in *(class I, level B)*
Omega-3 fatty acids
As an adjunct to diet, omega-3 fatty acids in capsule form (approximately 850–1000 mg of EPA and DHA) may be considered in women with CHD, and higher doses (2–4 g) may be used for treatment of women with high triglyceride levels *(class IIb, level B)*
Depression
Consider screening women with CHD for depression and refer/treat when indicated *(class IIa, level B)*
Major risk-factor interventions
Blood pressure – optimal level and lifestyle
Encourage an optimal blood pressure of <120/80 mmHg through lifestyle approaches such as weight control, increased physical activity, alcohol moderation, sodium restriction, and increased consumption of fresh fruits, vegetables and low-fat dairy products *(class I, level B)*
Blood pressure – pharmacotherapy
Pharmacotherapy is indicated when blood pressure is ≥140/90 mmHg or at an even lower blood pressure in the setting of chronic kidney disease or diabetes mellitus (≥130/80 mmHg). Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated or if there are compelling indications for other agents in specific vascular diseases. Initial treatment of high-risk women[c] should be with β-blockers and/or ACE inhibitors/ARBs, with addition of other drugs, such as thiazides, as needed to achieve goal blood pressure *(class I, level A)*
Lipid and lipoprotein levels – optimal levels and lifestyle
The following levels of lipids and lipoproteins in women should be encouraged through lifestyle approaches: LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL and non-HDL-C (total cholesterol minus HDL-C) <130 mg/dL *(class I, level B).* If a woman is at high risk[c] or has hypercholesterolaemia, intake of saturated fat should be <7% and cholesterol intake <200 mg/day *(class I, level B)*
Lipids – pharmacotherapy for LDL-lowering, high-risk women
Utilize LDL-C-lowering drug therapy simultaneously with lifestyle therapy in women with CHD to achieve an LDL-C <100 mg/dL *(class I, level A)* and similarly in women with other atherosclerotic CVD, diabetes or 10-year absolute risk >20% *(class I, level B)*
A reduction to <70 mg/dL is reasonable in very high-risk women[d] with CHD and may require an LDL-lowering drug combination *(class IIa, level B)*

Continued next page

Table II. Contd

Lipids – pharmacotherapy for LDL-lowering, other at-risk women
Utilize LDL-C-lowering therapy if LDL-C level is ≥130 mg/dL with lifestyle therapy and there are multiple risk factors and 10-year absolute risk 10–20% *(class I, level B)*
Utilize LDL-C-lowering therapy if LDL-C level is ≥160 mg/dL with lifestyle therapy and multiple risk factors, even if 10-year absolute risk is <10% *(class I, level B)*
Utilize LDL-C-lowering therapy if LDL-C ≥190 mg/dL regardless of the presence or absence of other risk factors or CVD on lifestyle therapy *(class I, level B)*
Lipids – pharmacotherapy for low HDL-C or elevated non-HDL-C, high-risk women
Utilize niacin[e] or fibrate therapy when HDL-C is low or non-HDL-C is elevated in high-risk women after LDL-C goal is reached *(class IIa, level B)*
Lipids – pharmacotherapy for low HDL-C or elevated non-HDL-C, other at-risk women
Consider niacin[e] or fibrate therapy when HDL-C is low or non-HDL-C is elevated after LDL-C goal is reached in women with multiple risk factors and a 10-year absolute risk 10–20% *(class IIb, level B)*
Diabetes mellitus
Lifestyle and pharmacotherapy should be used as indicated in women with diabetes *(class I, level B)* to achieve an HbA_{1c} <7% if this can be accomplished without significant hypoglycaemia *(class I, level C)*
Preventive drug intervention
Aspirin, high-risk women
Aspirin therapy (75–325 mg/day)[f] should be used in high-risk[c] women unless contraindicated *(class I, level A)*
If a high-risk[c] woman is intolerant of aspirin therapy, clopidogrel should be substituted *(class I, level B)*
Aspirin – other at-risk or healthy women
In women ≥65 years of age, consider aspirin therapy (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischaemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and haemorrhagic stroke *(class IIa, level B),* and in women <65 years of age when benefit for ischaemic stroke prevention is likely to outweigh adverse effects of therapy *(class IIb, level B)*
β-*Blockers*
β-Blockers should be used indefinitely in all women after MI, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated *(class I, level A)*
ACE inhibitors/ARBs
ACE inhibitors should be used (unless contraindicated) in women after MI and in those with clinical evidence of heart failure or an LVEF ≤40% or with diabetes *(class I, level A).* In women after MI and in those with clinical evidence of heart failure or an LVEF ≤40%, or with diabetes who are intolerant of ACE inhibitors, ARBs should be used instead *(class I, level B)*
Aldosterone blockade
Use aldosterone blockade after MI in women who do not have significant renal dysfunction or hyperkalaemia who are already receiving therapeutic doses of an ACE inhibitor and β-blocker, and have LVEF ≤40% with symptomatic heart failure *(class I, level B)*

a Pregnant and lactating women should avoid eating fish potentially high in methylmercury (e.g. shark, swordfish, king mackerel or tile fish) and should eat up to 12 oz/wk of a variety of fish and shellfish low in mercury, and check the Environmental Protection Agency and the US FDA's websites for updates and local advisories about safety of local catch.

b A drink equivalent is equal to a 12 oz bottle of beer, a 5 oz glass of wine or a 1.5 oz shot of 80-proof spirit.

c Criteria for high risk include established CHD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic renal disease, diabetes, and 10-year Framingham risk >20%.

d Criteria for very high risk include established CVD plus any of the following: multiple major risk factors, severe and poorly controlled risk factors, diabetes mellitus.

e Dietary supplement niacin should not be used as a substitute for prescription niacin.

f After percutaneous intervention with stent placement or coronary artery bypass grafting within the previous year and in women with noncoronary forms of CVD, use current guidelines for aspirin and clopidogrel.

ARB = angiotensin receptor blocker; **BMI** = body mass index; **CHD** = coronary heart disease; **DHA** = docosahexaenoic acid; **EPA** = eicosapentaenoic acid; **HbA_{1c}** = glycosylated haemoglobin; **HDL-C** = high-density lipoprotein-cholesterol; **LDL** = low-density lipoprotein; **LDL-C** = low-density lipoprotein-cholesterol; **LVEF** = left ventricular ejection fraction; **MI** = myocardial infarction.

Among 45 722 men without known CVD, assessment of diet at baseline (1986) and subsequently at 4-year intervals via questionnaire, showed at 14 years that omega-3 polyunsaturated fatty acids

Table III. Class III interventions (not useful/effective and may be harmful) for cardiovascular disease (CVD) or myocardial infarction (MI) prevention in women (reproduced from Mosca et al.,[2] with permission, © 2007, American Heart Association, Inc.)

Menopausal therapy
Hormone therapy and selective estrogen-receptor modulators should not be used for the primary or secondary prevention of CVD *(class III, level A)*
Antioxidant supplements
Antioxidant vitamin supplements (e.g. vitamin E, C, and β carotene) should not be used for the primary or secondary prevention of CVD *(class III, level A)*
Folic acid[a]
Folic acid, with or without vitamin B_6 and B_{12} supplementation, should not be used for the primary or secondary prevention of CVD *(class III, level A)*
Aspirin for MI in women <65 years of age[b]
Routine use of aspirin in healthy women <65 years of age is not recommended to prevent MI *(class III, level B)*

a Folic acid supplementation should be used in the childbearing years to prevent neural tube defects.

b For recommendation for aspirin to prevent CVD in women ≥65 years of age or stroke in women <65 years of age, please see table II.

from both seafood and plant sources appeared to reduce coronary risk, but little influence was evident from the background omega-3 polyunsaturated fatty acid intake.[5] Earlier data from the Cardiovascular Health Study[7] examined the cardiac benefits of fish consumption by the type of fish consumed. In this population, aged ≥65 years (3910 adults at baseline, free of known CVD in 1989–90), consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, was associated with a lower risk of ischaemic heart disease, particularly arrhythmic ischaemic heart disease death.

In addition, the meta-analyses conducted to date relate primarily to dietary intake. The meta-analysis of Brouwer et al.[8] showed that α-linolenic acid consumption might reduce heart disease mortality, but raised concern about the association between high dietary α-linolenic acid and prostate cancer. The meta-analysis by Whelton et al.[9] suggested that fish consumption was associated with a significantly lower risk of fatal and total CHD, and proposed this as an important component of lifestyle modification for CHD prevention.

1.2 Secondary Prevention

The final meta-analysis performed by Yzebe and Lievre,[10] is the sole examination of the efficacy of omega-3 fatty acid supplementation, addressing the results of ten randomized controlled trials in 14 727 adults with recent or acute MI or angina pectoris. Daily intake of omega-3 fatty acids for a mean duration of 37 months decreased all-cause mortality by 16% and MI death by 24%, without significant effect on other outcomes. Data from these studies were considered suboptimal to recommend routine fish oil supplementation, with concern raised regarding the lack of information in patients receiving HMG-CoA reductase inhibitors (statins).

2. Depression

2.1 Secondary Prevention

Although the Guidelines recommend screening women with CHD for depression and referral/treatment when indicated, no specific therapies are addressed.[2] Nonetheless, some information regarding therapy may be relevant. In the ENRICHD trial (see table V for definitions of all study/trial acronyms), overall use of cognitive behavioural therapy and interventions to enhance social support failed to improve outcomes in a depressed, socially isolated, postinfarction population. Two subset studies of ENRICHD provide provocative information. In a *post hoc* analysis, White men, but not other gender or ethnic subgroups, appeared to benefit from the ENRICHD intervention; the total cohort included 973 White men, 424 minority men, 674 White women and 410 minority women.[11] In another ENRICHD analysis, patients whose depression was refractory to cognitive behavioural therapy

and sertraline were at higher risk for late mortality (i.e. not early after acute MI).[12] Finally, a secondary analysis examining the effects of antidepressant medication in the ENRICHD cohort[13] showed benefit of selective serotonin reuptake inhibitors; users had an adjusted hazard ratio of 0.57 for death or recurrent MI, 0.59 for all-cause mortality and 0.53 for recurrent MI. Hazard ratios were 0.72, 0.64 and 0.73 for death or recurrent MI, all-cause mortality or recurrent MI, respectively, for patients taking nonselective serotonin reuptake inhibitor antidepressants compared with non-users. The authors suggested that selective serotonin reuptake inhibitors in depressed patients following MI might reduce subsequent cardiovascular morbidity and mortality, and indicated the need for randomized controlled trial data.

3. Blood Pressure

3.1 Primary Prevention

Lifestyle approaches to hypertension management (including weight control, increase in physical activity, moderation of alcohol use, sodium restriction, and increased consumption of fresh fruits, vegetables and low-fat dairy products) are the initial interventions recommended for blood pressure control, with a goal blood pressure of <120/80 mmHg.

Table IV. Classification and levels of evidence (reproduced from Mosca et al.,[2] with permission, © 2007, American Heart Association, Inc.)

	Strength of recommendation
Classification	
Class I	Intervention is useful and effective
Class IIa	Weight of evidenced/opinion is in favour 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

Pharmacotherapy is indicated when the blood pressure is ≥140/90 mmHg for all women or ≥130/80 mmHg in the setting of chronic kidney disease or diabetes mellitus. The American Heart Association (AHA) currently recommends a goal blood pressure of <130/80 mmHg for those patients at high risk for CHD and <120/80 mmHg when left ventricular dysfunction is present.[14] The pharmacological recommendations for women are those of the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[15] Recommendations of JNC 7 do not differ for women and men. Initial therapy with thiazide diuretics is recommended, save for high-risk women with specific indications for initial use of other drugs including β-adrenoceptor antagonists (β-blockers), ACE inhibitors/angiotensin II receptor antagonists (angiotensin II receptor blockers [ARBs]), with subsequent addition of other drugs such as thiazide diuretics as needed to achieve goal blood pressure. In seven older randomized controlled trials from the INDANA intervention database, subgroup meta-analysis showed significant treatment benefits in the prevention of CVD for women with the use of antihypertensive treatment.

A number of studies regarding treated hypertensive versus nonhypertensive subjects of the same age in the general population examined why cardiovascular mortality was higher in the treated hypertensive population. One study of 8893 treated hypertensive men and women (47% women) concluded that their increased cardiovascular mortality was due mainly to high systolic blood pressure levels while under treatment, i.e. that the excess risk in hypertensive patients may be drastically reduced if systolic blood pressures were better controlled.[16] Similar results were found when women and men were studied separately.

An extensive Cochrane meta-analysis of pharmacotherapy of hypertension in the elderly[17] concluded that randomized controlled trials established the high efficacy of treating healthy older persons with diastolic or systolic hypertension with low-dose diuretics or β-blockers for benefits of cardiovascular

Table V. List of study/trial/database acronyms and definitions

Study/trial/database acronym	Study name
4S	Scandinavian Simvastatin Survival Study
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
ALLHAT	Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial, Lipid Lowering Arm
CAMELOT	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis
CARE	Cholesterol and Recurrent Events
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
CIBIS II	Cardiac Insufficiency BIsoprolol Study II
COPERNICUS	CarvedilOl ProspEctive RaNdomIzed CUmulative Survival study
CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines
ENRICHD	ENhancing Recovery In CHD
EPHESUS	Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUurvival Study
EUROPA	EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease
GREACE	GREek Atorvastatin and Coronary-heart-disease Evaluation
HERS	Heart and Estrogen/Progestin Replacement Study
HOPE	Heart Outcomes Prevention Evaluation
HPS	Heart Protection Study
INDANA	INdividual Data ANalysis of Antihypertensive
INVEST	INternational VErapamil SR-Trandolapril
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
MERIT-HF	MEtoprolol CR/XL Randomized Intervention Trial in Heart Failure
MICROHOPE	Microalbuminuria, Cardiovascular and Renal Outcomes
MIRACL	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
NORVIT	Norwegian Vitamin Trial
PEACE	Prevention of Events with Angiotensin Converting Enzyme inhibition
PERSUADE	PERindopril SUbstudy in coronary Artery disease and DiabEtes
PROSPER	PROspective Study of Pravastatin in the Elderly at Risk
PROVE IT-TIMI 22	PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22
RALES	Randomized ALdactone Evaluation study
RUTH	Raloxifene Use for The Heart
SCAT	Simvastatin/enalapril Coronary Atherosclerosis Trial
Syst-Eur	Systolic Hypertension in Europe
TNT	Treating to New Targets
TRACE	TRAndolapril Cardiac Evaluation
WAVE	Women's Angiographic Vitamin and Estrogen
WHI	Women's Health Initiative

ACC = American College of Cardiology; **AHA** = American Heart Association; **CR/XL/SR** = controlled release/extended release/sustained release; **CHD** = coronary heart disease.

morbidity and mortality, cardiovascular mortality, and total mortality. The meta-analysis encompassed 15 trials that included over 21 000 elderly subjects, most aged 60–80 years.

The ALLHAT study demonstrated superiority of diuretic-based over α-adrenoceptor antagonist-based antihypertensive treatment for the prevention of CVD.[18] 2006 recommendations from the AHA/

American College of Cardiology (ACC) for secondary prevention for patients with defined coronary and other atherosclerotic vascular disease define a goal blood pressure of <130/80 mmHg for those with diabetes or chronic kidney disease. ALLHAT enrolled 42 448 high-risk hypertensive subjects, 19 865 of whom were women. Treatment effects were similar in women and men.

Interesting data are derived from a study of cardiovascular outcomes in high-risk hypertensive patients in ALLHAT related to baseline glomerular filtration rate. Patients in this multicentre study were stratified by baseline glomerular infiltration rate: normal or increased in 8128 patients, mild reduction in 18 109 patients, and moderate or severe reduction in 5662 patients.[19] Women comprised almost half of the cohort, but gender-specific analyses were not reported. Older high-risk hypertensive patients with a reduced glomerular filtration rate were more likely to develop CHD than to develop end-stage renal disease. A low glomerular filtration rate independently predicted increased CHD risk. Neither amlodipine nor lisinopril was superior to chlorthalidone in preventing CHD, stroke or combined CVD, but chlorthalidone was superior to both for preventing heart failure. Based on 4695 patients in the Syst-Eur Trial,[20] with a minimum age of 60 years, the investigators concluded that antihypertensive treatment can successfully control blood pressure in most older patients with isolated systolic hypertension. Women comprised about two-thirds of the cohort and there was no gender heterogeneity in outcome. Underscoring the necessity of early treatment for isolated systolic hypertension was the finding that immediate compared with delayed pharmacotherapy with nitrendipine, with possible addition of enalapril, hydrochlorothiazide or both, prevented 17 strokes or 25 major cardiovascular events per thousand patients followed for 6 years.

3.2 Secondary Prevention

Cardiovascular outcomes were evaluated in coronary patients with diabetes in a diabetic cohort of the INVEST trial;[21] a verapamil sustained-release-based antihypertensive regimen and an atenolol-based regimen resulted in similar cardiovascular outcomes. Women comprised 54% of participants.

4. Lipids: Primary and Secondary Prevention

As with hypertension, lifestyle approaches should be the initial interventions for attaining optimal levels of lipids and lipoproteins in women.[2] The goal levels are a low-density lipoprotein-cholesterol (LDL-C) <100 mg/dL, high-density lipoprotein-cholesterol (HDL-C) >50 mg/dL, triglycerides <150 mg/dL, and non-HDL-C (total cholesterol minus HDL-C) <130 mg/dL. Pharmacotherapy using LDL-C-lowering drug therapy, preferably with statins, is recommended in high-risk women simultaneously with lifestyle interventions to achieve an LDL-C <100 mg/dL, with reduction to <70 mg/dL reasonable for very high-risk women. The Guidelines identify that the latter may require LDL-lowering drug combinations.[2]

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommended statin therapy for women aged 45–70 years;[22] subsequently reported data for women >75 years showed benefit for these elderly women in the HPS[23] but not in PROSPER.[24] Updated NCEP ATP III guidelines[25] for high-risk patients of both genders confirmed the desirability of an LDL-C goal <70 mg/dL, as well as consideration of combining a fibric acid derivative (fibrate) or niacin (nicotinic acid) with an LDL-C-lowering drug for patients with a high triglyceride or low HDL-C level.

Almost 20 000 women were included in the primary and secondary prevention major lipid-lowering trials of statin therapy. AFCAPS/TexCAPS, HPS, ALLHAT and ASCOT-LLA were primary prevention trials. PROSPER involved a combination of primary and secondary prevention patients. 4S, CARE, LIPID, GREACE and TNT were secondary prevention trials. Benefit ranged from 11% in LIPID[26] to 54% in GREACE,[27] without significant benefit evident for women in PROSPER,[24] in the ASCOT-LLA[28] or in ALLHAT. Neither gender showed lipid benefit in ALLHAT.[29] In the TNT

trial,[30] 1902 of 10 001 enrolled patients with stable CHD were women. The comparison was of atorvastatin 10 mg versus 80 mg, with an average follow-up of 4.9 years. Decreases in LDL-C, total cholesterol and triglycerides were comparable by gender.[31] There was a significant comparable decrease in the primary study endpoints of major cardiovascular events, coronary mortality, nonfatal MI, and fatal or nonfatal stroke in both genders affected by intensive compared with standard lipid-lowering therapy; the hazard ratio was 0.73 for women and 0.79 for men. Atorvastatin 80 mg was not associated with documented rhabdomyolysis. More women than men (10% vs 6.5%) discontinued therapy as a result of adverse effects; liver function test abnormalities occurred in 2.5% of women compared with 1% of men. Thus, TNT[31]documented comparable benefit for women and men with high dose compared with standard dose atorvastatin.

Among the total of 19 335 women represented in these clinical trials of statin therapy, the proportion of women averaged 10–20%, except for two trials: PROSPER,[24] a trial of elderly patients, in which half of all patients were women, and the lipid lowering arm of ALLHAT, which enrolled 49% women. In a systematic review of 11 clinical trials that involved almost 16 000 women,[32] the authors considered the evidence insufficient for the benefit of lipid-lowering therapy with statin drugs in women without established CHD; nonetheless, the small number of outcome events limited the power to detect a difference. Statin drugs produced a 26% decrease in coronary mortality, 36% decrease in nonfatal MI and 21% decrease in major coronary events, with insufficient data to determine the effect on revascularization in women with established CHD; no decrease was evident for total mortality.

Specific data for the effects of statins in acute coronary syndromes in the MIRACL trial showed a 16% decrease in death, nonfatal infarction, resuscitated cardiac arrest and recurrent ischaemia requiring hospitalization, but gender-specific data were not reported for the 1074 of the 3086 patients who were women. The endpoint was powered by the reduction in recurrent ischaemia requiring hospitalization.[33] In a substudy of MIRACL,[34] the stroke rate was reduced by half and there was no increase in haemorrhagic stroke.

The PROVE IT-TIMI 22 trial[35] compared pravastatin 40 mg with atorvastatin 80 mg in 4162 patients with acute MI. The resultant mean LDL-C was 95 mg/dL versus 62 mg/dL, respectively. The composite endpoints of all-cause mortality, MI, hospitalization for unstable angina, coronary revascularization and stroke showed benefit for both women and men; 22% of the population were women. The Kaplan-Meier curves separated at 30 days, with a 26.3% occurrence of endpoint events with pravastatin compared with 22.4% with atorvastatin.

In the CRUSADE National Quality Improvement Initiative, 41% of the 35 875 patients were women. Although women had higher risk characteristics at presentation and had greater inhospital risk, their initial and discharge therapies were less aggressive than those for men. Specifically, women were less likely than men to receive statins at discharge: 55.9% versus 63.4%, respectively.[36]

Gender-specific data are not available for most clofibrate trials. There was no benefit for women compared with men in a trial of colestipol versus placebo, and gender-specific data were not reported for a comparison of niacin and clofibrate versus placebo in the Stockholm Ischemic Heart Disease study.[37] Ezetimibe, added to a statin, comparably lowered LDL-C levels in women and men,[38] but clinical outcome data are lacking.

Randomized trial data are similarly lacking for women in regard to lipid-altering dietary supplements (e.g. soluble fibre, soy protein, or sterol or stanol esters).

A recent systematic review of lipid-lowering therapy in women that included data from large multinational statin studies[39] concluded that statin therapy was beneficial in women with established CVD in reducing coronary mortality, nonfatal MI and revascularization, but without effect on total mortality. Evidence remains inconclusive about the effect of lipid lowering on total CHD mortality in women without CVD, although some studies sug-

gest a reduction in coronary events. Highly relevant is the impressive safety profile of statin therapy for both women and men.

The effect of statin therapy at discharge was assessed in an observational study of 23 013 Medicare patients in the US with a principal discharge diagnosis of MI.[40] Statin therapy lowered mortality in patients with acute MI aged <80 years but not in those aged >80 years, raising the question of generalizability of statin benefit to the very old population. The effect of preoperative statin therapy on outcome was evaluated in a retrospective cohort study of patients undergoing coronary artery bypass graft surgery using cardiopulmonary bypass.[41] Preoperative statin use was independently associated with a significant reduction of 7.1% versus 4.6% in the composite endpoint of 30-day all-cause mortality and stroke, respectively.

A meta-analysis of the efficacy and safety of cholesterol-lowering treatment by the Cholesterol Treatment Trialists' Collaborators included over 90 000 participants in 14 randomized trials,[42] where, overall, women comprised 24% of the participants. Major coronary events were reduced in both women and men (i.e. 0.1% vs 7.3% for treated vs control women compared with 7.8% vs 10.6% for treated versus control men). The authors concluded that statin therapy safely reduces the 5-year incidence of major coronary events, coronary revascularization and stroke by about one-fifth per mmol/L reduction in LDL-C, essentially irrespective of the initial lipid profile or other presenting characteristics. Their recommendations provide reinforcement for considering prolonged statin treatment with substantial LDL-C reduction in all patients at high risk of any major vascular event.

Another overview of the use of statins[43] assessed data from 63 410 participants in 15 trials. It similarly concluded that statin treatment reduces the relative risk of coronary events, CVD mortality, nonfatal stroke and all-cause mortality in the secondary prevention setting, with only small and not clinically relevant improvement of cardiovascular morbidity and mortality for primary prevention.

5. Aspirin

Abundant data document that daily aspirin should be used in the preventive management of both women and men with established CHD, other vascular disease, and coronary risk equivalents such as diabetes and chronic kidney disease. However, the use of aspirin for primary prevention in women remained controversial until the publication of data from the Women's Health Study.[44]

5.1 Primary Prevention

In the Women's Health Study,[44] 39 876 healthy women aged ≥45 years were randomized to aspirin 100 mg on alternate days compared with placebo and monitored for 10 years for a first major cardiovascular event (nonfatal MI, nonfatal stroke or death from cardiovascular causes). As background, randomized trials had shown that alternate-day low-dose aspirin decreased the risk of initial MI in men, with little effect on ischaemic stroke. The 44% reduction in the risk of initial MI among the 22 071 apparently healthy men caused the Physicians' Health Study[45] to be terminated prematurely because of this extreme benefit. In the Women's Health Study, aspirin lowered the risk of ischaemic stroke by 24%, with no significant effect on the risk of fatal or nonfatal MI. Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin than the placebo group. Thus, the routine use of aspirin in healthy women aged <65 years is not recommended to prevent MI (a class III recommendation), but it may be considered when the benefit for ischaemic stroke prevention is likely to outweigh the adverse effects of aspirin therapy (class IIb recommendation). In the subgroup of women aged ≥65 years, this aspirin dosage significantly reduced the risk of major cardiovascular events, ischaemic stroke and MI, but this benefit was counter-balanced by an almost comparable occurrence of gastrointestinal bleeding, mandating individualization of therapy for women aged ≥65 years (class IIa).

The conclusion of a recent meta-analysis of six trials that included 95 456 individuals[46] was that aspirin reduced the risk of composite cardiovascular events for both women and men as a result of its

reduction of the risk of ischaemic stroke in women and MI in men; nonetheless, aspirin significantly increased the risk of bleeding comparably among women and men.

5.2 Secondary Prevention

As noted in sections 1 and 5.1, aspirin at a dose of 75–325 mg/day should be used in high-risk women unless contraindicated, with clopidogrel substituted if a high-risk woman is intolerant to aspirin therapy.[2]

In the CHARISMA trial, 15 603 patients (30% women) with clinical manifestations of CVD or multiple risk factors were randomized to clopidogrel 75 mg/day plus low-dose aspirin 75–162 mg/day or placebo plus low-dose aspirin, and followed for a median of 28 months. Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of MI, stroke or death from cardiovascular cause.[47] There was a suggestion of benefit from clopidogrel in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors. No benefit was evident for women.

6. ACE Inhibitors/Angiotensin II Receptor Blockers

6.1 Primary Prevention

A meta-analysis of 28 clinical outcome trials involving a total of 179 122 patients examined the effect of ACE inhibitors and calcium channel antagonists versus diuretics, β-blockers or placebo in hypertensive or high-risk patients on the protection from CHD and stroke. The authors concluded that blood pressure-lowering was fundamental for the prevention of both CHD and stroke; beyond blood pressure reduction, ACE inhibitors appeared superior to calcium channel antagonists for CHD prevention, whereas calcium channel antagonists appeared superior to ACE inhibitors for the prevention of stroke.[48] Gender-specific data were not reported.

6.2 Secondary Prevention

The PEACE trial tested whether patients with stable CHD and normal or slightly reduced left ventricular function would derive therapeutic benefit from the addition of an ACE inhibitor to modern conventional therapy.[49] Trandolapril was randomly administered to 4158 patients and placebo to 4132 patients (18% women); in this population with a lower occurrence of cardiovascular events than in previous trials of ACE inhibition in patients with vascular disease, no added benefit was conferred by ACE inhibition for cardiovascular death, MI or coronary revascularization. Gender-specific outcomes were not provided.

TRACE, another study of trandolapril, examined the effects of this ACE inhibitor on mortality and hospitalization in patients with left ventricular systolic dysfunction following MI: 1749 patients (28% women) were randomized to trandolapril versus placebo.[50] Trandolapril was associated with long-term benefits for all-cause mortality, all-cause hospitalizations and cardiovascular hospitalizations, including those for heart failure. The beneficial effect on mortality and hospitalization rates was maintained for at least 10–12 years. Gender-specific data were not provided.

The PERSUADE substudy of the EUROPA trial examined the effect of perindopril on cardiovascular morbidity and mortality in 1502 diabetic patients (18% women) with CHD but without heart failure. There was a reduction in major cardiovascular events in these diabetic patients, similar in magnitude to the benefit observed in the general population with CHD.[51] Gender-specific data are not available. In the overall EUROPA trial,[52] a low-risk population with stable CHD without apparent heart failure, perindopril significantly improved the outcome of cardiovascular death, MI or cardiac arrest, with 50 patients having to be treated for 4 years to prevent one major cardiovascular event. Fifteen percent of EUROPA participants were female, and benefit was comparable for women and men.

In a retrospective analysis of 1342 Medicare recipients with acute MI and chronic kidney disease, with a derived glomerular filtration rate of

15–89 mL/min/1.73m^2, survival was improved with a β-blocker plus ACE inhibitor, although these patients were less likely to be prescribed combination cardioprotective therapy after acute MI.[53] Although half of the patients were women, gender-specific data were not provided.

A systematic review and meta-analysis of randomized controlled trials addressing ACE inhibitor use in CHD patients with preserved left ventricular systolic function included six trials that involved 16 772 patients randomized to ACE inhibitor therapy compared with 16 728 patients randomized to placebo. The proportion of women varied from 15% in the EUROPA trial to 28% in CAMELOT, but gender-specific information was not provided. A modest favourable effect included a decrease in cardiovascular mortality, in nonfatal MI, in all-cause mortality and in revascularization rates.[54] Similarly, an overview of seven trials that included a total of 33 960 patients followed for a mean of 4.4 years evaluated whether the long-term prescription of ACE inhibitors decreased major cardiovascular events and mortality in coronary patients with intact left ventricular systolic function. The proportion of women participants in the trials analysed varied from 11% in SCAT to 28% in CAMELOT, but once again the overview did not provide gender-specific outcomes. There was a reduction in total mortality (odds ratio [OR] 0.86) and in major cardiovascular endpoints (OR 0.77–0.82).[55]

A third meta-analysis examined the effect of ARBs in 24 trials involving 38 080 patients with chronic heart failure and high-risk acute MI. ARBs were associated with a reduction in all-cause mortality and heart failure hospitalizations compared with placebo; in two comparative trials, there was no difference between ARBs and ACE inhibitors. Comparing ARBs plus ACE inhibitors versus ACE inhibitors alone, all-cause mortality was not reduced but there was a decrease in heart failure hospitalizations with the combination. The authors concluded that ARBs should be regarded as suitable alternatives to ACE inhibitors,[56] but provided no information as to the overall numbers of women studied or gender-specific outcomes.

The timing of use of ACE inhibitors was addressed in 22 trials. Both early and late administration of ACE inhibitors decreased mortality following MI, but the major benefit occurred for long-term mortality.[57] Again, the numbers of women in these trials and the comparative outcomes for women and men were not presented.

The CHARM trial assessed the effect of candesartan in patients with New York Heart Association class II–IV heart failure symptoms; 53% of enrolled patients previously had an MI and 24% currently had angina; 32% were female. Risk reductions in cardiovascular death or nonfatal MI were similar across predetermined subgroups and the component CHARM trials. The authors concluded that, for patients with heart failure, candesartan significantly reduced the composite outcome of cardiovascular death or nonfatal MI.[58] Benefit was comparable for women and men.

7. β-Blockers

7.1 Secondary Prevention

The clinical efficacy of β-blocker therapy was studied in 2894 patients in a cohort study that pooled data from five randomized, controlled trials of abciximab during coronary interventions in patients with acute coronary syndromes.[59] At both 30 days and 6 months, β-blocker therapy was associated with a significant reduction in mortality, similar to the beneficial effects of β-blocker therapy seen in patients with unstable angina and acute MI.

The effect of β-blockers in postinfarction patients with heart failure receiving contemporary management was a prespecified subgroup analysis of the MERIT-HF.[60] In this study, metoprolol reduced total mortality by 40% and sudden death by 50%, extending the profound reduction in morbidity and mortality from β-blockade even in the presence of contemporary management, which included early and late revascularization, ACE inhibitor use, aspirin and statins.

A meta-analysis of β-blockade that included data from MERIT-HF, CIBIS II and COPERNICUS confirmed that carefully titrated metoprolol controlled/extended release could be instituted safely for the majority of patients with clinically stable systolic heart failure. Comparable benefit was seen with bisoprolol in CIBIS II and carvedilol in COPERNICUS.[61] A meta-analysis of mortality results from CIBIS-II, MERIT-HF and COPERNICUS showed very similar survival benefits in women and men; although not all patients in CIBIS-II had an ischaemic aetiology for their heart failure, this was the case for most patients, and mortality and admissions to hospital did not differ significantly between groups for any subgroup of aetiology of heart failure. Finally, in 4304 patients without heart failure but with angiographically confirmed coronary artery disease without acute MI at hospital presentation, discharge β-blocker prescription was associated with an increased event-free survival, showing that the β-blockade benefit evident with heart failure or acute MI extended to patients with confirmed CHD without these conditions, providing approximately the same mortality benefit.[62]

8. Aldosterone Antagonists

8.1 Secondary Prevention

The RALES trial[63] involved 1663 patients with severe heart failure and a left ventricular ejection fraction <35% treated with an ACE inhibitor, loop diuretic and usually digoxin, randomized to spironolactone 25 mg/day versus placebo; 27% of participants were women. The addition of spironolactone to standard therapy reduced both morbidity and mortality in these patients with severe heart failure. Benefit was comparable for women and men. There was minimal serious hyperkalaemia.

The effect of the selective aldosterone antagonist eplerenone was evaluated in 6632 patients with acute MI complicated by left ventricular dysfunction and heart failure (29% female) randomized to eplerenone versus placebo in EPHESUS.[64] The addition of eplerenone 25 mg/day, titrated to a maximum of 50 mg/day, to optimal medical therapy reduced morbidity and mortality in these patients, with a reduction in the primary endpoint of death from cardiovascular causes or hospitalization for cardiovascular events, and the secondary endpoints of death from any cause or any hospitalization. There was also a reduction in sudden cardiac death. Serious hyperkalaemia occurred in 5.5% of the eplerenone-treated patients compared with 3.9% of placebo patients. Survival was improved for both genders, but more so for women, with an interaction term of 0.44, whereas the composite of death from cardiovascular causes or hospitalization for cardiovascular events was better for men than women, with an interaction term of 0.08.

Again from the EPHESUS study,[65] eplerenone reduced mortality at 30 days after randomization in patients following acute MI with left ventricular systolic dysfunction and clinical heart failure. There was a significant decrease in all-cause mortality 30 days after randomization when eplerenone was added to conventional therapy in these patients with a left ventricular ejection fraction <40% and signs of heart failure; eplerenone was initiated on average 7.3 days after MI. Based on the early survival benefit, eplerenone was recommended to be administered during the hospitalization for acute MI.

9. Antioxidants

Reports have been inconsistent on the relationship between the use of antioxidant vitamin supplements and CHD risk.

9.1 Primary Prevention

Based on a detailed food frequency questionnaire to assess the consumption of vitamin C and other nutrients in the Nurses' Health Study,[66] the relationship between total intake of vitamin C and CHD was assessed in 85 118 female nurses followed for up to 16 years. There was a moderate significant inverse association between total vitamin C intake and CHD risk (a relative risk of 0.73). Among the women who did not use supplemental vitamin C or multivitamins, there was a nonsignificant association between dietary vitamin C and CHD incidence. The authors concluded that users of vitamin C sup-

plements appeared to be at lower coronary risk. In the British Heart Protection Study,[67] without separate analysis reported for women and men, there was no evidence of benefit for major coronary events related to the use of vitamin E 600 mg, vitamin C 250 mg or β carotene 12 mg daily.

Similarly, in the WAVE study (a mixed primary and secondary prevention cohort, examining the effect of hormone replacement and antioxidant vitamin supplements on coronary atherosclerosis in menopausal women),[68] vitamin E 400 IU and vitamin C 500 mg daily failed to provide cardiac protection. In the overall HOPE study,[69] as was the case with the diabetic subset in MICROHOPE, vitamin E 400 IU/day failed to affect rates of MI, stroke or cardiovascular death.[69] The St Francis Heart Study examined the effect of vitamins C and E in asymptomatic adults with elevated coronary calcium scores.[70] These antioxidant vitamins, as well as low doses of atorvastatin, did not affect the progression of coronary calcification.

In the 10-year randomized Women's Health Study,[71] there was lack of benefit from 600 IU/day natural-source vitamin E for major cardiovascular events or total mortality. Nonetheless, differing from the totality of evidence for all age groups in this study, among women aged ≥65 years, vitamin E was associated with a 26% reduction in cardiovascular mortality and in major cardiovascular events.

Several meta-analyses warrant mention. Although some epidemiological studies had suggested cardiovascular benefit for vitamin E, the meta-analysis of Eidelman et al.[72] reviewing several large-scale randomized trials failed to show statistically significant or clinically important effects of vitamin E on CVD. A pooled analysis of nine cohorts reported by Knekt and colleagues,[73] including 293 172 individuals free of CHD at baseline, suggested a reduced incidence of major coronary events with high supplemental vitamin C intakes, but a small reduction with high vitamin E or carotenoid intakes. Finally, a review of placebo-controlled randomized trials conducted by Shekelle and associates,[74] addressing 84 eligible trials, failed to find evidence that vitamin E supplementation either beneficially or adversely affected cardiovascular outcomes.

10. Folic Acid, and Vitamins B_6 and B_{12}

10.1 Primary Prevention

There was benefit from whole-grain intake in a cohort study: the Nurses' Health Study,[75] based on a food-frequency questionnaire at baseline (1984) and again in 1986 and 1990 among 75 521 nurses aged 38–63 years. In the same population, examination of the intake of folate and vitamin B_6, again based on a detailed food-frequency questionnaire,[76] suggested that intake of folate and vitamin B_6 above the current recommended dietary allowance may be important in the primary prevention of CHD in women. No specific benefit was evident for vitamin E supplements in these studies.

10.2 Secondary Prevention

The efficacy of homocysteine lowering with B vitamins was evaluated in the secondary prevention setting in patients within a week of acute MI in a randomized controlled trial in Norway (NORVIT).[77] Treatment with B vitamins did not lower the risk of recurrent CVD, but a harmful effect was evident with combined B vitamin treatment (i.e. folate, vitamin B_{12} and vitamin B_6).

In the HOPE study,[78] which involved over 5000 patients aged ≥55 years with vascular disease or diabetes, folic acid 2.5 mg, vitamin B_6 50 mg and vitamin B_{12} 1 mg daily compared with placebo did not reduce the risk of major cardiovascular events.

A combination of folic acid, vitamin B_6 and vitamin B_{12}, designed to lower homocysteine levels, was assessed in a randomized controlled trial in patients following successful coronary stenting.[79] There was a suggestion that, despite the decrease in homocysteine levels, vitamin administration may increase the risk of in-stent restenosis and the need for target vessel revascularization.

In another study of the effect of homocysteine-lowering therapy on percutaneous coronary intervention,[80] 553 patients were randomly assigned to

vitamin therapy compared with placebo after successful percutaneous coronary intervention. In contrast to the prior study, homocysteine-lowering therapy with folic acid, vitamin B_{12} and vitamin B_6 significantly decreased the incidence of major adverse events.

11. Menopausal Hormone Therapy (MHT)/Selective Estrogen Receptor Modulators (SERMs)

Numerous observational studies had suggested that menopausal hormone therapy (MHT) might provide cardiac protection. Indeed, in the National Cholesterol Education Program Adult Treatment Panel II, hormone therapy was the suggested initial intervention for the management of dyslipidaemia in menopausal women.

11.1 Primary Prevention: MHT

The role of MHT in healthy women remained contentious until the publication of the estrogen plus progesterone arm of the WHI trial, using the same hormone regimen, and conducted in over 16 000 initially healthy menopausal women.[81] The trial was terminated prematurely because of an increased risk of heart attack, breast cancer, venous thromboembolism, stroke, dementia and ovarian cancer, counter-balanced by a decrease in hip fracture, colorectal cancer and endometrial cancer. Quality of life was not affected. The unopposed estrogen arm of the WHI trial, conducted in over 10 000 apparently healthy menopausal women with hysterectomy, was again terminated prematurely, due to the excess of risk compared with benefit. There was an increased risk of stroke and probable dementia or memory loss, a decrease in hip fracture, and no effect on breast cancer or heart disease.[82]

A secondary analysis from the WHI combined the data from these two trials (and some would question whether it is appropriate to combine these two studies, given the different characteristics of women in both arms of the study) and sought to explore whether the time of initiation of hormone therapy would influence its effect on cardiovascular disease.[83] The authors concluded that women who initiated hormone therapy close to menopause tended to have a reduced coronary risk compared with the increased risk among women more distant from menopause, but the trend test was not statistically significant. A similar nonsignificant trend was noted for total mortality. Stroke risk was increased regardless of the years since menopause when hormone therapy was initiated.

Further analysis of the estrogen only arm of the WHI,[84] specifically examining the coronary endpoint among these more than 10 000 women, concluded that conjugated equine estrogen did not protect against MI or coronary death, but suggested a lower CHD risk among the women aged 50–59 years at baseline.

Subanalysis of the estrogen/progesterone arm of the WHI[85] confirmed the lack of cardiac protection, but suggested that there might be an increase in risk, particularly during the first year of hormone use, in these >16 000 healthy menopausal women.

Supplementary data are available from cohort studies. In the Nurses' Health Study there was suggestion that the timing of hormone therapy initiation related to onset of menopause or to age might influence coronary risk. Specifically, women beginning hormone therapy near menopause had a significantly reduced risk of CHD, a relative risk of 0.66, whereas among those who initiated hormone therapy at least 10 years following menopause, there was no relationship between such therapy and CHD, with a relative risk of 0.87 for estrogen alone and of 0.90 for estrogen plus progesterone.[86] In a prospective questionnaire cohort of almost 20 000 Danish female nurses, about half of whom were menopausal, there was an increased risk of ischaemic heart disease associated with early ovariectomy, with the suggestion that this risk might be reduced with hormone therapy.[87] The Kuopio Osteoporosis Risk Factor and Prevention study, which collected data from 11 667 women aged 52–62 years, concluded that hormone therapy did not affect overall mortality or coronary mortality in women, but that >5 years of such therapy might increase the risk of breast cancer mortality.[88]

A systematic review and meta-analysis of hormone therapy in CVD,[89] addressing high-quality randomized placebo-controlled trials (seven in total), showed that hormone therapy did not change the risk of all-cause mortality, coronary death and nonfatal MI, but increased the risk of stroke.

A breast cancer study of adjuvant tamoxifen therapy also examined 5-year CHD mortality.[90] There was a favourable effect on breast cancer outcome, but the incidence of endometrial cancer was increased. Coronary mortality was significantly reduced in the 5-year analysis group compared with the 2-year analysis group, without statistically significant increases in mortality from other heart disease, cerebrovascular disease or other vascular disease.

11.2 Secondary Prevention: MHT

The 2004 AHA Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women[1] identified that MHT should not be used for cardiac protection. Specifically cited was HERS, in which 2763 menopausal women with established CHD were randomized to conjugated equine estrogen 6.25 mg and medroxyprogesterone 2.5 mg/day compared with placebo.[91] There was no overall cardiovascular benefit but a trend to early harm was noted. In addition, there was an increased risk for venous thromboembolism.

11.3 Secondary Prevention: SERMs

Finally, a randomized controlled trial of 10 000 women with established CHD or who were at high risk for its occurrence with the selective estrogen receptor modulator raloxifene (the RUTH trial)[92] identified that this agent failed to alter coronary outcome, but was associated with an increased risk of venous thromboembolism. Although there was no increase in stroke risk, stroke mortality was increased. Breast cancer was reduced, as was the risk of clinical vertebral fractures.

12. Conclusion

Data specific to women in a number of randomized clinical trials, data for women from single-gender clinical trials, coupled with cohort studies with gender-specific analyses and meta-analyses of these studies, have provided an initial database to guide the use of pharmacotherapy for coronary prevention and treatment in women. Clearly, these data are valuable in guiding clinical practice, but, equally clearly, substantial gaps in knowledge await clarification.

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