CHAPTER

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CAD in Women

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Introduction

The medical community viewed women's health with a bikini approach, focusing essentially on the breast and reproductive system. The rest of women were virtually ignored in considerations of women's health. Traditionally, coronary heart disease (CHD) has been considered as a male problem, but relevant information about CHD in women is rapidly escalating recently.

The onset of clinical manifestations of CHD in women lags behind men by about 10 years and by as much as 20 years for more ominous events. But CHD is not solely a problem for elderly women. More than 9000 US women younger than 45 years sustain a myocardial infarction (MI) each year. The question of why women younger than 65 years of age are more than twice as likely to die from MI than comparably aged men is intriguing. Recent surveys reveal that most women do not appreciate their risk of developing CHD,[1] and, therefore, women may not recognize that certain life style behaviors and physiological factors increase the risk of developing CHD.

Many women are unaware that coronary heart disease is their main killer; their biggest fear is breast cancer. Even more worrying, however, is the apparent lack of awareness of cardiovascular disease in women among healthcare professionals. At the time of presentation with heart disease, women tend to be 10 years older than men, and at the time of their first myocardial infarction they are usually 20 years older[2,3] As coronary heart disease is a disease of the older woman, many women believe that they can postpone attempts to reduce their risk.

Incidence

Worldwide, cardiovascular disease (CVD) is the largest single cause of death among women, accounting for one third of all deaths.[4]

Cardiovascular disease (CVD) is an equal-opportunity killer in men and women over their lifetimes. In Washington state, in 1991, the incidence of CVD death was 42% in women and 39% in men.[5] Nationwide (US), these numbers approach 50%. Among survivors of MI, 25% of men versus 38% of women die within a year after an initial MI.[6] Within 6 years after MI, 18% of men but 35% of women will have a recurrent infarction. Women are more likely to be disabled by heart failure (30% vs. 21%) after MI. Women with unstable angina have a survival advantage compared with men.[6]

In the Indian context the mortality data for coronary artery diseases in women is available from two studies done in 1994 and 1998, JIMI – I

Table 1 : Comparison of mortality

Age	< 44 years		45-70 years		> 70years	
	M	F	M	F	M	F
England and Wales 1993	1.4%	0.3%	17.3%	10.0%	46.5%	72.6%
Scotland 1993	1.5%	0.4%	19.5%	11%	39.8%	66.4%
JIMI-I South India 1994	7.8%	1.8%	13%	23%	37.8%	50.6%
EHIRC North India 1998	7.0%	2%	15%	27%	29%	37.5%

Table 2 : Differences in Cardiovascular Disease Presentation and Outcome in Women(W) versus Men(M)

Presentation	Comparison of W and M
Angina	W > M
Atypical chest pain	W > M
Death from MI	W > M
Sudden death	W > M
Exercise test false +ve	W > M
Angina prognosis for MI	W < M
Consequences	
MI morbidity	W > M
MI morbidity (unadjusted)	W > M
MI mortality (adjusted)	W = to slightly > M
CABG mortality	W = to > M
Angioplasty mortality (adjusted & unadjusted)	W > M
Stenting mortality and MI	W = M (30 days)

& JIMI – II. The comparison of mortality with west in different age group is mentioned in Table – 1.

Differences in CVD Presentation Women vs. Men

The tendency to overlook CHD in women because of its lesser frequency in youth and middle age is compounded by less classical presentation, which is more frequently angina in women and MI in men (Table 2). Obscure symptoms of fatigue or atypical chest pain should be worked up aggressively for potential coronary ischemia, particularly when risk factors for CHD are present.

Table 3 : Classification of CVD Risk in Women

Risk Status	Criteria
High risk	Established coronary heart disease
	Cerebrovascular disease
	Peripheral arterial disease
	Abdominal aortic aneurysm
	Diabetes mellitus
	10-year Framingham global risk > 20%*
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 male relative and < 65 years of age in female relative)
	Hypertension
	Dyslipidemia
	Evidence of sub-clinical vascular disease
	(e.g. coronary calcification)
	Metabolic syndrome
	Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after & topping exercise
Optimal risk	Framingham global risk < 10% and a healthy lifestyle, with no risk factors

CVD indicates cardiovascular disease.

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

Risk Factors

The metabolic syndrome and combined hyperlipidemia are more prevalent in women than in men with arteriosclerosis in middle age. Important risk factors in women are listed in Table 2. Diabetes is particularly more severe risk factor in women than in men. Obesity and physical inactivity are more prevalent in women. The spectrum of CVD risk in women has been shown in Table 3.

Homocysteine in middle-aged women is an independent risk factor for myocardial infarction

and in particular, mortality due to myocardial infarction[7]. Elevated tPA antigen and to a lesser extent D-dimer are independently associated with incident coronary events among postmenopausal women. In analysis stratified by menopausal hormone therapy, tPA antigen remains a consistent marker of increased coronary risk.[10]

The role that novel CVD risk factors (e.g., high-sensitivity C-reactive protein) and novel screening technologies (e.g., coronary calcium scoring) should play in guiding preventive interventions is not yet defined. Further research is needed on added benefits, risks, and costs associated with such strategies before they can be incorporated into guidelines. Unique opportunities to identify women's risk (e.g., during pregnancy) also deserve further exploration. For example, pre-eclampsia may be an early indicator of CVD risk. Women with pre-eclampsia/eclampsia are significantly more likely to develop hypertension and cerebrovascular disease. In addition, maternal placental syndromes in combination with traditional cardiovascular risk factors, such as pre-pregnancy hypertension or diabetes mellitus, obesity, dyslipidemia, or metabolic syndrome, may be additive in defining CVD risk in women.[16] Future research should evaluate the potential for events or medical contact during unique phases in a woman's lifespan, such as adolescence, pregnancy, and menopause, to identify women at high risk and to determine the effectiveness of preventive interventions during critical time periods.

Diagnosis

Recognition of cardiovascular chest pain is difficult in women because of its atypical nature. As a result of atypical symptoms, misdiagnosis as chronic fatigue or a psychiatric disorder is not uncommon. The reason for the lack of classical anginal symptoms in many women, despite having validated myocardial ischemia, is unknown. The greater incidence of silent MI in women may also be related to the atypicality of chest pain presentation.

The exercise tolerance is not as useful in clarifying atypical chest pain in women as in men because it is too susceptible to false-positive and false-negative results. In general, radionuclide or echocardiographic imagings are recommended, if an exercise test is to be done.[11] Nuclear stress perfusion testing in women can be potentially hindered by soft tissue attenuation from breast tissue with the use of thallium, so technetium may be preferred. Many authors prefer stress imaging tests, with their lower false-positive rates, to exercise stress tests for women.[12] A female patient with chest pain with a positive exercise test and a negative angiogram might have arteriosclerotic vasospasm with a normal lumen. Direct referral to cardiac catheterization should occur with a high suspicion of significant CAD that might benefit from intervention or after an abnormal noninvasive stress test. Anginal symptoms are less predictive of abnormal coronary anatomy in women than men.

In patients with UA/NSTEMI, there is a different pattern of presenting biomarkers. Men are more likely to have elevated CK-MB and troponins, whereas women are more likely to have elevated CRP and BNP. This suggests that a multimarker approach may aid the initial risk assessment of UA/NSTEMI, especially in women.[13]

The relationship between the menstrual cycle and vascular spasm is beginning to receive increasing attention.[14]

Acute Coronary Syndrome (ACS)

There are substantial gender differences in the presentation and natural history. After AMI, women have higher mortality during hospitalization, arrived later for evaluation after symptoms began, received less thrombolytic treatment as well as fewer invasive interventions. Women have higher mortality rates than men, even at similar ages or after similar interventions, from cardiogenic shock, sudden death, arrhythmias, myocardial rupture and electromechanical dissociation.

Women subjects with ACS are older and have more comorbid conditions (diabetes, hypertension, angina, congestive heart failure) than the men, who are more likely to be smokers or to have had a prior MI, angioplasty or CABG. With MI, the initial entry ECG in women compared with men is less likely to indicate ST-segment elevation. At presentation, women are more often diagnosed with unstable angina than men.[15] The 30-days mortality after MI is about twice as great for women age 30-50 compared with men of same age and mortality progressively decreases with increasing age until reaching unity at age 75.[16]

Women with elevated troponins benefit from early interventions. If markers are not elevated, this strategy has no benefit and may even be harmful.

Oral Contraceptive (OC) and Hormone Therapy

Young women with high degree of CHD risk should avoid the use of OCs, especially after age of 35 years, unless the risk factors can be modified. It is the standard of clinical practice that OCs not to be prescribed to cigarette smoking women, who are older than 35 years. But, women with a history of oral contraceptive use may be at decreased risk of adverse cardiovascular disease (CVD) outcomes, a recent analysis of data from the Women's Health Initiative (WHI) suggests.[17]

Combined estrogen plus progestin or other forms of menopausal hormone therapy should not be initiated or continued to prevent CHD in postmenopausal women. When treated with postmenopausal hormone therapy (HRT), women with abnormal glucose tolerance (AGT) experience greater atherosclerotic progression than healthy women, new research suggests.

Prognostic Variability and Intervention Results

There are particularly clear sex differences in patients undergoing coronary revascularisation: mortality in women is notably higher. At the time of presentation with coronary artery disease, women are more likely to have comorbid factors such as diabetes mellitus, hypertension, hypercholesterolemia, peripheral vascular disease, and heart failure. In addition, women's coronary vessels tend to be smaller than those of men, which makes them more difficult to revascularise percutaneously as well as surgically. And, because of late presentation, women more often need urgent intervention. Although the absolute mortality for women undergoing percutaneous and surgical revascularisation seems to be improving, it remains higher than for men. Most studies have shown that mortality in hospital is similar in men and women undergoing coronary revascularisation after adjustment for the increase in overall risk among women. The wider use of drug eluting stents and adjunctive medical therapy such as glycoprotein IIb/IIIa inhibitors, as well as improved techniques such as off-pump surgery and minimally invasive coronary surgery, may help to improve outcomes in women having coronary revascularisation. For example, paclitaxel eluting stents reduce clinical and angiographic restenosis in both sexes. And a recent large study found that women who had off-pump coronary artery bypass surgery had 2.6% lower mortality, a 35.1% lower complication rate owing to bleeding, a 118.6% lower rate of neurological complications, and a 49.3% lower rate of respiratory complications than women having on-pump surgery.

Guidelines for Prevention of CVD in Women: Clinical Recommendations AHA 2007 Guidelines[18]

Lifestyle interventions

Cigarette smoking

Women should not smoke and should avoid environmental tobacco smoke. Provide counseling, nicotine replacement, and other pharmacotherapy as indicated in conjunction with a behavioral program or formal smoking cessation program *(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 to 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 program, 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-fiber foods; consume fish, especially oily fish, at least twice a week; limit intake of saturated fat to 10% of energy, and if possible to 7%, cholesterol to 300 mg/d, alcohol intake to no more than 1 drink per day, and sodium intake to 2.3 g/d (approximately 1 tsp 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 behavioral programs 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 to 1000 mg of EPA and DHA) may be considered in women with CHD, and higher doses (2 to 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 mm Hg 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 mm Hg or at an even lower blood pressure in the setting of chronic kidney disease or diabetes (130/80 mm Hg). 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‡ 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 cholesterol) 130 mg/dL *(Class I, Level B)*. If a woman is at high risk or has hypercholesterolemia, intake of saturated fat should be 7% and cholesterol intake 200 mg/d) *(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 or diabetes mellitus or 10-year absolute risk 20% *(Class I, Level B)*. A reduction to 70 mg/dL is reasonable in very-high-risk women's with CHD and may require an LDL-lowering drug combination *(Class IIa, Level B)*.

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% to 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 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 or elevated non–HDL, high-risk women

Utilize niacin 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 or elevated non-HDL, other at-risk women

Consider niacin 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% to 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 HbA1C 7% if this can be accomplished without significant hypoglycemia *(Class I, Level C)*.

Preventive drug interventions

Aspirin, high risk

Aspirin therapy (75 to 325 mg/d) should be used in high-risk women unless contraindicated *(Class I, Level A)*. If a high-risk 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 ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke *(Class IIa, Level B)* and in women 65 years of age when benefit for ischemic 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 mellitus *(Class I, Level A)*. In women after MI and in those with clinical evidence of heart failure or an LVEF 40% or with diabetes mellitus 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 hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and blocker, and have LVEF 40% with symptomatic heart failure *(Class I, Level B)*.

Class III Interventions (Not Useful/Effective and May Be Harmful) for CVD or MI Prevention in Women

Menopausal therapy

Hormone therapy and selective estrogen-receptor modulators (SERMs) 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 beta carotene) should not be used for the primary or secondary prevention of CVD *(Class III, Level A).*

Folic acid

Folic acid, with or without B6 and B12 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

Routine use of aspirin in healthy women 65 years of age is not recommended to prevent MI *(Class III, Level B).*

Conclusion

Coronary artery disease can occur in women of all ages, depending on risk factor burden. Metabolic syndrome, hypertriglyceridemia and low HDL cholesterol are more important risk factor for women. New evidence-based guidelines are available to aid clinicians in improving the preventive, diagnostic and therapeutic management of coronary artery disease in women.

Summary

Emerging data continue to highlight important sex-based differences in coronary heart disease (CHD) prevention and diagnostic testing, in the management of acute coronary syndromes and in the outcome of CHD therapies. Evidence-based guidelines have been developed that offer specific recommendations for clinicians and information for women. These guidelines are buttressed by results that have become available from randomized, controlled clinical trials in women, and data from CHD registries and clinical trials involving both sexes but including adequate numbers of women to enable the reporting of sex-specific results.

Abbreviations

CAD – Coronary Artery Disease,

CHD – Coronary Heart Disease,

MI – Myocardial Infarction,

CVD – Cardio Vascular disease

UA – Unstable Angina,

NSTEMI – Non ST Elevated Myocardial Infarction

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