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HEART DISEASE IN WOMEN

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Foreword
Prof (Dr) Muzaffer Elmas

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CHAPTER 2

Prevention of Heart Disease in Women

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An apple a day, keeps the doctor away. But does it prevent heart disease? Is it true that increased consumption of fruits can prevent heart disease? What about antioxidants then? What works? And does it matter? Isn't heart disease a disease of men and women who need not worry about it?

There are many myths about heart disease in women. Let us try to get some clarity on this.

Cardiovascular disease (CVD) is the number one killer of women. CVD kills more women than stroke, lung cancer, breast cancer, and chronic obstructive pulmonary disease (COPD) combined.[1] Statistics state that every third death is from CVD. One in six deaths results from coronary artery disease (CAD). A great deal of progress has been made since 1999 in the prevention and treatment of heart disease in women.[2] The good news is that age-adjusted mortality from heart disease decreased from 1980 to 2002 in men (52%) and women (49%). The bad news is that we are seeing a reversal in that trend. Heart disease death rate among the women of 35–54 years of age in the United States is now increasing. This may be because of the changes in several risk factors leading to CAD.[3] Women all over the world are now entering the work force. More sedentary life style is being adopted, leading to obesity and diabetes. Smoking rates are on the rise. A lot needs to be done to reverse this trend.

To decrease CVD related mortality, it is not enough to work only on prevention. Along with the measures to be taken to prevent heart disease in women, it is also necessary to increase awareness of this leading cause of death. In the United States, for example, public awareness of CVD as the leading cause of death has increased to 54% in 2009. It was only 30% in 1997.[4] It is important that women should call for help at the onset of cardiac symptoms to improve survival from cardiac events. In a recent survey by the American Heart Association (AHA), only 53% of women said that the first thing they would do if they thought they were having a heart attack was to call 911.[4] Women need to be aware of high prevalence of heart disease, symptoms of heart disease, and of the need to seek immediate help at the onset of symptoms.

Prevention of heart disease hinges on understanding the risk factors and then efforts to modulate them. These risk factors are commonly divided into those that can be modified to decrease the risk and those that cannot be modified.

UNMODIFIABLE RISK FACTORS

Age

Prevalence of heart disease increases with age. This is true in men as well as in women. It is seen that the first presentation of CAD occurs approximately 10 years later in women than in men. The INTERHEART study performed in 42 countries around the world shows that a difference of 8–10 years in age at the onset is seen widely around the world (Table 1).[5]

It is thought that before menopause, women are protected from development of atherosclerotic cardiovascular disease (ASCVD) because of the presence of estrogen. This explanation is very attractive but it should be remembered that in clinical practice, the replacement of estrogen after menopause does not prevent cardiovascular events and is a Class 3 indication according to the Effectiveness Based Guidelines for Prevention of Cardiovascular Disease in Women.[6-10]

Table 1: Comparison of age at first myocardial infarction

Region	*Median age women*	*Median age men*
Western Europe	68	61
Central and Eastern Europe	68	59
North America	64	58
South America and Mexico	65	59
Australia and New Zealand	66	58
Middle East	57	50
Africa	56	52
South Asia	60	52
China	67	60
Southeast Asia and Japan	63	55
Ethnic origin		
European	68	59
Chinese	67	60
South Asian	60	50
Other Asian	63	55
Arab	57	52
Latin American	64	58
Black African	54	52
Colored African	58	52
Other	63	53
Overall	**65**	**56**

Source: Modified from Yusuf S et al, the INTERHEART Study.[5]

Family History

Genetic contribution to heart disease is well-known and it is well documented that CAD and death from CVD have a hereditary component.

The genetic transmission in families is rarely monogenic with a Mendelian pattern. More commonly, it is complex reflecting multiple genes, each contributing modestly to a predisposition to atherosclerosis and atherothrombotic events. The statistical association of gene variants with coronary disease differs in men and women, suggesting that different pathways may operate in the manifestation of CVD between men and women. In women, stromelysin 1 (a member of matrix metalloproteinase family of enzymes) and plasminogen activator inhibitor (PAI-1) are thought to be important. In men, two different genes are associated with MI—the gap junction protein Connexin 37 and p22(phox), a component of NAD(P)H redox system.[11] The different manifestations may be because of the presence of circulating estrogens or presence or absence of the Y chromosome. Only limited work has explored sex differences in gene expression, proteomics, or metabolomics. Further work in these areas may provide important insights into the development, diagnosis, and tailored treatment of CVD in the two sexes.[12]

MODIFIABLE RISK FACTORS

Hypertension

High blood pressure (BP) is long known to be associated with risk of development of CVD and CAD. In a meta-analysis of 61 prospective studies published in the journal Lancet in 2002, more than one million healthy adults were studied between the age of 49 and 89 years. CAD risk was slightly higher in women than men. Hypertension (HTN) is increasing in the United States in both sexes but more so in women who have 15% higher prevalence than men.[13,14]

Under the age of 35 years, HTN was more prevalent in men than in women. The prevalence of HTN increases with age in both sexes, but from the age of 45 to 54 years, the rate of rise was greater in women than in men. After the age of 65 years, a higher percentage of women than men have HTN and the gap increases with continued age.[15] The difference in prevalence reaches statistical significance at 75 years of age.

The problem does not stop there. Not only the prevalence increases with age, women are more likely to be undertreated. In the National Health and Nutrition Examination Survey (NHANES) over time (1988–1994 and follow up survey 1999–2000), in men, the treatment rate increased by 9.8% and control rate by 15.3%. In women, the treatment rate increased by a mere 1.9% and control rate by only 0.5%.[16] This lack of improvement is really concerning.

Diabetes Mellitus

Diabetes mellitus (DM) increases the risk of CVD in women. Diabetes is a risk factor for the development and severity of CAD in both men and women but carries a greater risk in women that completely eliminates "the female advantage."[17,18] CVD is twice as common in women with DM compared with those without DM. Diabetic women are four times as likely to be hospitalized as compared with nondiabetics.

Prevalence of DM is increasing rapidly in the United States. Between 1990 and 2001, it rose by 61%.[1] In 2006, out of 17 million patients with known DM, 9.5 million were

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women (more than 50%). It is also seen that women are less likely to be treated to HbA1c goal than men are.[1]

Hyperlipidemia

Hyperlipidemia, a known risk factor for the development of CAD, is not much more common in women at a young age. According to a statistic from the AHA, 47% of the women have total serum cholesterol of 200 mg/dL or more and 31.7% have low-density lipoprotein (LDL) cholesterol level of 130 mg/dL or more. This is similar to the general population. Only 6.7% of women have high-density lipoprotein (HDL) of less than 40 when compared with 15.5% of overall Americans.

Things begin to change around menopause. Total cholesterol and LDL cholesterol increase on an average by about 10% from levels at 6 months before menopause. Menopause affects HDL cholesterol less dramatically. HDL concentration declines gradually in the two years before menopause and then levels off after menopause. The postmenopausal increase in CVD risk may result partly from these lipid profile changes.

LIFESTYLE RISK FACTORS

Obesity and Sedentary Lifestyle

Obesity, described as body mass index (BMI) greater than 30 kg/sq meter, has been rapidly increasing. Prevalence of obesity increased from 12.2% in 1991 to 20.8% in 2001.[19] It increased further to 35.3% in the 2005–2006 NHANES. There is an epidemic of obesity in the United States.

Vigorous physical exercise is needed to modify several risk factors and to decrease risk of heart disease. Prevalence of physical exercise is very low in women. National Center for Health interview survey reported in 2007 that 66.3% women never performed vigorous physical activity and only 9.8% engaged in vigorous physical activity, 5 days or more per week. Objective accelerometer data from NHANES were even more concerning with only 2.5%–3.2% women doing 30 minutes of exercise at least 5 days per week.[20]

Smoking

Smoking is a strong independent risk factor for CAD in both men and women. Estimated prevalence of smoking in women 18 years of age or older was 18%–23% in 2006.[1] Although smoking rates in the United States are falling overall, they are increasing in women.[21] This risk is not improved by low nicotine cigarettes and is present even with minimal exposure.[22] Women using contraceptive pills and smoking are at particularly high risk especially after the age of 35 years.[23] Women find it harder to quit smoking than men, probably because of the weight gain seen with stopping smoking. Smoking can also lead to earlier menopause, a risk factor that is unique to women.[23]

GUIDELINES FOR PREVENTION OF CVD IN WOMEN

Identifying the fact that heart disease in women presents differently, behaves differently, and requires a different consideration for prevention is an important step. In 2004, AHA along with several other organizations sponsored the "Evidence Based Guidelines for Cardiovascular Disease Prevention in Women." Initially, the guidelines challenged the conventional thinking that women should be treated the same as men. Concerns were also raised about lack of representation of women in clinical trials. Since then, over time, more women have participated in clinical trials and more gender-specific analysis has become available. Considering the health implications and economic costs associated with CVD in women, sustained efforts are needed to apply evidence-based therapies that work.

In 2007, the guidelines were updated.[10] A new algorithm for risk classification in women was adopted. This was revised when 2011 AHA guidelines were published.[24] Three risk categories were identified—(1) at high risk, (2) at risk, and (3) at optimal risk (ideal cardiovascular health).

Among the high risk, the rate of MI, CHD death, and stroke was 19%, at risk 5.5%, and at optimal risk 2.2% per 10 years. A major difference from prior guidelines to 2011 updates is that instead of limiting recommendations to evidence based (benefits observed in clinical research), effectiveness-based (benefits and risks observed in clinical practice) recommendations were considered.[24]

The American College of Cardiology (ACC) and AHA in 2013 came up with a new tool to calculate 10 year and lifetime risk for ASCVD.[25] Along with traditional risk factors of age, DM, hyperlipidemia and hypertension, various other parameters like race, and sex were also introduced into the calculations to get to this prediction and determine the need for further work up as well treatment. New recommendations from ACC/AHA guidelines for lipid management came in November 2013.[26] Eighth Joint National Committee (JNC8) guidelines for HTN management came online in December 2013 and

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print published in 2014.[27] It is expected that these will be incorporated in the next AHA update for guidelines for prevention of CVD in women.

Major Risk Factor Interventions

Hypertension

Treatment of HTN can go a long way in helping prevent CVD as well as stroke. JNC8 recommendations set somewhat different targets for BP levels.[27]

- For patients less than 60 years of age, drug therapy should be considered for systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg. The goal is <140/90 mm Hg.
- For patients 60 years or older, drug therapy should be considered for systolic BP ≥150 mm Hg or diastolic BP ≥90 mm Hg. The goal is <150/90 mm Hg.

If pharmacologic treatment for high BP results in systolic BP <140 mm Hg and treatment is well tolerated and without adverse effects, there is no need to adjust therapy.

- For patients with diabetes and patients with chronic kidney disease (CKD), the threshold to initiate drug therapy is 140/90 mm Hg. The goal is <140/90 mm Hg.
- In nonblack patients, including those with DM initial drug-class choices are thiazide-type diuretics, calcium-channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blockers (ARBs).
- In black patients, including those with DM, acceptable initial drug-class choices are thiazide-type diuretics or CCBs.
- Patients with CKD generally should receive ACE inhibitors or ARBs. This is true for all patients with CKD, regardless of race or presence of DM.

Diabetes Mellitus

Lifestyle modifications and pharmacotherapy are recommended in women to achieve HbA1c <7, if this can be achieved without significant hypoglycemia. A lot of literature is available in medical and endocrine journals on this issue. At this point, achieving HbA1c below 6 does not seem to confer extra protection.

Hyperlipidemia

Pharmacotherapy is recommended for LDL-C lowering in high risk women. While prior recommendations set specific levels as targets, new 2013 ACC/AHA guidelines used the intensity of statin therapy as the goal of treatment.[26] Four groups of individuals were identified for whom an extensive body of evidence from randomized controlled trials demonstrated a reduction in ASCVD events with a good margin of safety from moderate- or high-intensity statin therapy:

- Individuals with clinical ASCVD
- Individuals with primary elevations of LDL-C ≥190 mg/dL
- Individuals 40–75 years of age with DM and LDL-C 70–189 mg/dL without clinical
- ASCVD
- Individuals without clinical ASCVD or DM who are 40–75 years of age with LDL-C 70–189 mg/dL and have an estimated 10-year ASCVD risk of 7.5% or higher.

High-intensity statin therapy reduces LDL-C by approximately 50% and includes Atorvastatin 40–80 mg and Rosuvastatin 20–40 mg. Moderate-intensity statin therapy lowers LDL-C by approximately 30%–50%. Low-intensity statin therapy lowers LDL-C on average by 30%. Although high-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy, lower-intensity statin therapy has also been shown to reduce ASCVD events, although to a lesser degree. Therefore, individuals that merit guideline-recommended statin therapy should be treated with the maximum appropriate intensity of a statin that does not cause adverse effects.

Because evidence from randomized controlled trials shows that the absolute benefit of statin treatment is proportional to baseline ASCVD risk, treatment decisions for women should be based on the level of ASCVD risk. This conclusion is a departure from previous approaches that focused on LDL-C levels to guide treatment decisions. Statin treatment based on estimated 10-year ASCVD risk avoids the overtreatment of lower-risk groups such as younger, non-Hispanic White women who, despite moderate elevations in LDL-C, are typically not at significantly increased risk for ASCVD in the next 10 years in the absence of substantial risk-factor burden. However, ignoring the increased ASCVD risk in African American women might result in the under treatment of some individuals who are at significantly higher ASCVD risk at the same LDL-C level. Thus, this guideline recommends statin therapy for individuals in whom it is most likely to provide ASCVD risk reduction based on the estimated 10-year risk of ASCVD.

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Non-statin therapy for hyperlipidemia, with or without statin, may sometimes need to be considered. Use of niacin, bile acid sequestrates, fibrates, omega 3 fatty acids, and agents like Ezetimibe that inhibit cholesterol absorption may be monitored as carefully as in men.

Cigarette Smoking

Smoking cessation is one of the most effective and certainly the least expensive approach to disease prevention. It does not cost anything and may in fact save money. Women should be advised not to smoke and to avoid second hand smoke as well. After smoking cessation, the risk for MI quickly declined and the risk for CAD became similar to nonsmokers at about 3 years. Despite this, not many women who smoke are advised to quit by the health care providers. Data from Centers for Disease Control indicate that only close to 50% smokers who had at least one visit to their health care provider were advised to quit.[28] It has been estimated that each year an additional 1 million smokers could be helped to quit smoking if they got a brief counseling.[29] Brief counseling should include determining whether a patient smokes, advising any patient who smokes to quit, assisting the patient in quitting, for example, by setting a quit date and providing self-help material and scheduling follow-up visits to reinforce adherence.[30,31] Providers should counsel women at each encounter, advise behavioral program or formal smoking cessation program, nicotine replacement, and other pharmacotherapy.

Physical Activity

Physical activity and vigorous regular exercise is a mainstay of staying healthy. Women should be advised to achieve at least 150 min/week of moderate exercise and 75 min/week of vigorous exercise. More benefit is obtained by increasing moderate intensity aerobic physical activity to 5 h per week, 2.5 h of vigorous intensity exercise, or an equivalent combination of both.[24] Women should also be advised to do muscle strengthening exercises 2 or more days of the week. Women who need to lose weight should be advised to do a minimum of 60–90 min of at least moderate intensity exercises on most and preferably all days of the week.[24] Prudent exercise programs are cost effective and have a low potential for adverse effects.[32] Exercise should be individualized to accommodate the patient's level of physical fitness, cardiac status, and preferred activities.

Weight Maintenance/Loss

Women should be advised to maintain or lose weight through a combination of lower caloric intake, physical activity, and formal behavioral programs to achieve an appropriate body weight (e.g. BMI <25 kg/sq meter).[24]

Dietary Intake

Women should consume a diet rich in fruits and vegetables and to choose whole grain high fiber foods (Table 2). They should be advised to eat fish, especially oily fish at least twice a week. They should limit intake of saturated fat, cholesterol, alcohol, salt, sugar, and avoid trans-fatty acids.

Effectiveness-based guidelines in the 2011 update have excellent recommendations[24]

What Does Not Work/May Be Harmful

The effectiveness-based guidelines also came up with recommendations on the things that do not work (Class 3 indication).[24]

Menopausal therapy: Hormone therapy should not be used for primary or secondary prevention of CVD.

Antioxidant supplements: Vitamin C, E, and beta carotene should not be used for primary or secondary prevention of CVD.

Folic acid with or without B6 and B12 supplements should not be used for primary or secondary prevention of CVD.

Aspirin for MI in women <65 years of age: Routine use of Aspirin is not recommended for prevention of MI in healthy women less than 65 years of age.

A very helpful approach to primary and secondary prevention is outlined below as recommended in 2011 update to effectiveness-based guidelines for prevention of CVD in women (Flow chart 1).

Thus, an apple a day may not keep the doctor away but a diet rich in fruits and vegetables and nuts is definitely recommended to prevent heart disease in women. Antioxidants, despite the hype in the last few years, are not. Aspirin, while routinely recommended in the past, is not recommended in women younger than 65 years of age. As the epidemic of obesity is increasing in the United States and as CVD is increasing in some age groups in women, a prevention strategy involving dietary intervention and increasing physical exercise is essential to combat this growing threat.

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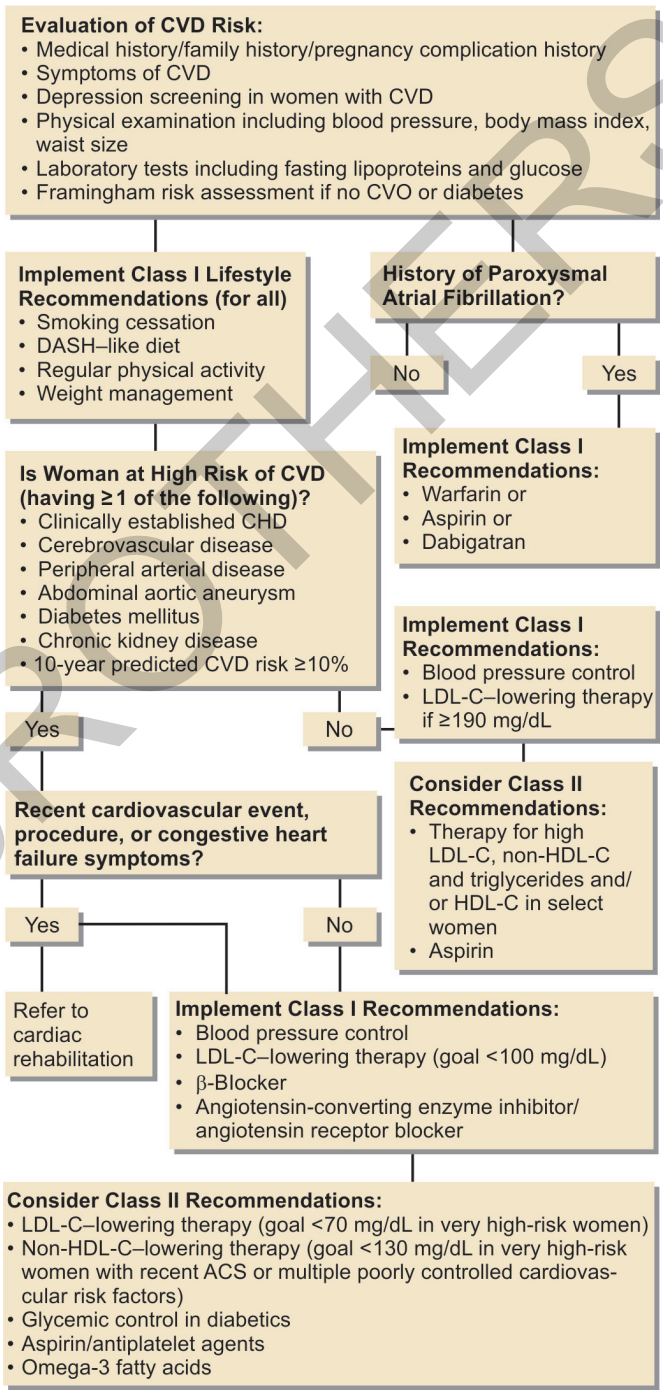
Table 2: Dietary intake recommendations for women

Nutrient	*Serving*	*Serving size*
Fruits and Vegetables	>4.5 cups /day	1 cup raw leafy vegetables, ½ cup cut-up raw or cooked vegetables, ½ cup vegetable juice, 1 medium fruit, ¼ cup dried fruit, ½ cup fresh frozen or canned fruit, ½ cup fruit juice
Fish	2/wk	3.5 oz, cooked (preferably oily types of fish
Fiber	30 g/d (1.1 g/10 g carbohydrate)	Bran cereal, berries, avocado, and so on
Whole grains	3/day	1 slice bread, 1 oz dry cereal, 1/2 cup cooked rice, pasta, or cereal (all whole-grain products)
Sugar	<5/wk (450 kcal/wk from sugar-sweetened beverages	1 tablespoon sugar, 1 tablespoon jelly or jam, 1/2 cup sorbet, 1 cup lemonade
Nuts, Legumes, Seeds	>4/wk	1/3 cup or 1 1/2 oz nuts (avoid macadamia nuts and salted nuts), 2 tablespoons peanut butter, 2 tablespoon or 1/2 oz seeds, 1/2 cup cooked legumes (dry beans and peas)
Saturated fat	<7% total energy intake	Found in fried foods, fat on meat or chicken skin, packaged desserts, butter, cheese, sour cream, and so on
Cholesterol	<150 mg/day	Found in animal meats, organ meats, eggs, and so on
Alcohol	One drink or less	4 oz wine, 12 oz beer, 1.5 oz of 80 proof sprits or 1 oz of 100 proof sprits
Sodium	<1500 mg	
Trans-fatty acids	0	

Flow chart 1: Prevention of CAD in women[24]



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HEART DISEASE
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A paucity of published texts on heart disease in women exists despite the fact that cardiovascular disease represents the most common cause of death in women throughout the world irrespective of the levels of household income and social status and more women die from it than men. Also alarming are the misperceptions prevalent among both the lay public and the medical professionals that cardiovascular disease, especially coronary heart disease, is an uncommon entity in women and this often leads to reduced surveillance and misdiagnosis or delay in diagnosis with consequent undermanagement and undertreatment. This book focuses on all aspects of heart disease in women, discusses all the recent relevant information available in the literature and attempts to dispel the existing misconceptions. The book, therefore, serves to fill an important existing void and by enhancing the awareness of cardiovascular disease in women could encourage more vigorous efforts for both primary and secondary prevention by various local, national and international agencies and organizations. The book consists of 34 chapters written by several nationally and internationally renowned physicians, scientists and cardiologists. It is organized into eight sections dealing with prevention, risk factors, coronary heart disease, non-invasive testing, heart failure, cardiomyopathy, pericarditis, arrhythmias and sudden death, rheumatic heart disease, valvular heart disease, peripheral arterial disease, pregnancy and congenital heart disease. A special chapter provides an update on recent literature on heart disease in women.



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