Gender-Specific Aspects of Cardiovascular Disease

BARBARA H. ROBERTS, MD, FACC

ABSTRACT

When William Heberden gave his classic description of angina pectoris in 1768, he inadvertently described a gender-specific difference in heart disease when he noted the predominance of men with this condition. It is only in the last few decades that the medical profession has recognized that women are equally afflicted with atherosclerotic cardiovascular disease, albeit with some differences in presentation, risk factors and outcomes. This article will detail the ways in which men and women differ when it comes to the number one killer in the developed, and increasingly the developing, world.

KEYWORDS: Atherosclerotic cardiovascular disease (ASCVD), Myocardial infarction (MI), Risk factors, Coronary artery bypass graft (CABG)

INTRODUCTION

William Heberden gave an address to the Royal College of Physicians in London in 1768 in which he described a new syndrome he called “angina pectoris,” a Latin term for a strangling or choking in the chest. Though he was unable to determine angina’s cause, he unwittingly made the first observation of gender-specific differences in cardiovascular disease when he wrote: “I have seen nearly a hundred people under this disorder, of which number there have been three women, and one boy twelve years old. All the rest were men near, or past the fiftieth year of their age.”

When the epidemic of atherosclerotic cardiovascular disease (ASCVD) occurred in the twentieth century, the myth that this was a man's disease persisted. The prototypical patient with angina or myocardial infarction was described as a middle-aged male. Physicians, and women themselves, were slow to realize that atherosclerosis affected both sexes, albeit with differences that have become more apparent over the last few decades. In this article I will review gender differences in risk factors, symptoms, and outcomes in ASCVD.

RISK FACTORS

Dyslipidemia

Little was known about the etiology of ASCVD before the second half of the twentieth century. Ancel Key’s Seven Countries Study in the 1950s correlated dietary saturated fat intake and serum cholesterol levels with the risk of dying of heart disease in the United States (US), Finland, Greece, Serbia, Japan, the Netherlands and Italy. Unfortunately no women were included in Key’s study. The Framingham Heart Study (FHS) was undertaken by the National Institutes of Health in the late 1940s in response to the epidemic of heart disease. Its objective was to identify the risk factors that contribute to the development of ASCVD.

The study recruited 5,209 men and women between the ages of 29 and 62. The subjects returned every two years for detailed physical examinations, life style interviews and blood tests. FHS and other epidemiologic studies around the world led to the identification of the major modifiable risk factors for ASCVD: smoking, hypertension, hypercholesterolemia, diabetes, obesity and sedentary lifestyle. The unmodifiable risk factors include age and family history.

At that time cholesterol metabolism was poorly understood, but with the groundbreaking work of Drs. Robert Levy, Donald Fredrickson, Michael Brown and Joseph Goldstein, the roles of lipoproteins and of lipoprotein receptors in the pathogenesis of atherosclerosis were slowly unraveled.

The lipoproteins are classified according to their density, and all lipoproteins with the exception of high-density lipoprotein (HDL) are atherogenic. The first hint that low-density lipoprotein (LDL) might not be as atherogenic in women as men arose from the work of Neil Stone in the US and Joan Slack in England on kindred with Type II Familial Hypercholesterolemia. At equivalent markedly elevated LDL-cholesterol levels, affected women in these families developed signs and symptoms of ASCVD on average 10 to 15 years later than affected men.

Cui and his colleagues followed a cohort of 2,406 healthy men and 2,056 healthy women ages 40 to 64 for an average of 19 years. All had measurements of total cholesterol, LDL-cholesterol, non-HDL-cholesterol, and HDL-cholesterol. Elevations in total, LDL-cholesterol, and non-HDL cholesterol, along with low levels of HDL-cholesterol all correlated with an increased risk of cardiovascular disease (CVD) mortality in men. In women, only low levels of HDL-cholesterol and high levels of non-HDL-cholesterol predicted CVD mortality in women and the relative risk was greater in women than in men. Even at LDL-cholesterol levels of over 190 mg/dl, there was only a small and statistically insignificant increase in a woman’s risk of dying of cardiovascular disease (CVD). And at equivalent LDL-cholesterol
levels ranging from under 131 mg/dl to over 160 mg/dl, women with HDL-cholesterol under 50 mg/dl had a 3 to 4 four-fold increase in the risk of dying of CVD.

Other studies have looked at triglyceride (TG) levels and the risk of CVD and found that risk in women is increased more than in men as TG increases. With regard to lipids therefore, it appears that LDL cholesterol is less predictive of risk in women than in men, while elevations of non-HDL cholesterol (with which hypertriglyceridemia is closely linked) and low levels of HDL cholesterol are more predictive of risk.

**Smoking**

There is good epidemiologic evidence that smoking is a stronger risk factor in women than men. In a Danish study of smoking and age at first myocardial infarction (MI), smoking lowered the median age of first MI in women from 79 to 60, and in men from 71 to 64 years of age. Another investigation into smoking risk looked at pooled data from three studies with a total cohort of 11,472 women and 13,191 men who were followed for a mean of 12.3 years. The relative risk of MI in women who were current smokers was 2.24 compared with 1.43 in male smokers. This difference was significant and was unchanged after adjustment for other risk factors. Among women who were under 55, the relative risk of MI was increased almost 7-fold compared to almost 3-fold for same-aged men.

**Diabetes**

Diabetes, like smoking, is a more potent risk factor in women than in men. Kannel and Wilson analyzed Framingham data and found that the age-adjusted relative risk for coronary heart disease (CHD) in diabetic women compared to non-diabetic women was 3.7 [men 1.5], for peripheral arterial disease 6.4 [men 3.4] and for cardiac failure 8.0 [men 4.4]. In a 40-year follow-up of the Rancho Bernardo Cohort Study, Dr. E. Barrett-Connor reported that men who had diabetes by history or fasting plasma glucose had a 2.4-fold excess risk of heart disease compared to men without diabetes, and women who had diabetes had a 3.5-fold excess risk compared to women without diabetes; these differences were independent of many covariates.

In summary, while women and men have the same risk factors for ASCVD, smoking, hypertriglyceridemia, low HDL-cholesterol and diabetes impart greater risk to women than men, while elevations of LDL-cholesterol impart more risk to men than women.

**SYMPTOMS**

Gender disparity in the way ASCVD presents was first noted in the Framingham study. In a 26-year follow-up study of the initial participants, a striking difference was found in the ways men and women presented. There were a total of 1,240 coronary events among the initial cohort; these included MI’s, sudden death, angina pectoris and unstable angina. Despite roughly equal numbers of men and women, 60% of these events occurred in men and 40% occurred in women. Among men, acute MI was the most frequent presentation, comprising 43% of men’s initial coronary events; an additional 10% of first events in men were episodes of sudden death. Among women however, angina was the presenting complaint in 53% of women and MI was the initial event in only 29% of women. The authors also noted that once ASCVD was manifest in women they had a greater risk...
of mortality with an MI than did men. This finding has been found in other studies as well. FHS was first to report on the greater likelihood of silent or unrecognized MIs in women compared to men [34% vs 27% respectively].

The Coronary Artery Surgery Study revealed gender discrepancies in anginal prognosis. Among the study population of 20,391 patients, all of whom had coronary angiograms for the evaluation of chest pain (CP), 50% of women compared to 17% of men were found to have minimal or no atherosclerosis.

Because women with angina were less likely than men to have obstructive coronary artery disease (CAD) the Women’s Ischemia Syndrome Evaluation (WISE) investigations were undertaken to optimize symptom evaluation and testing, to explore the mechanisms for symptoms and ischemia in the absence of angiographic coronary stenosis and to investigate the role of reproductive hormones on symptoms. A total of 159 women (out of 323) who had coronary angiograms for chest pain were found to have minimal or no luminal irregularities. Intracoronary adenosine was used to determine the presence or absence of coronary microvascular dysfunction. Seventy-four (47%) had sub-normal coronary flow velocity reserve suggestive of microvascular dysfunction. The authors concluded that this abnormality was present in about half of women who had chest pain in the absence of obstructive CAD.

Despite the absence of coronary obstruction, the WISE investigators observed a high rate of adverse outcomes in these women. They subsequently undertook an intravascular ultrasound (IVUS) study of 100 women with suspected ischemia without obstructive CAD [≥50% stenosis].

The study showed 69.6% of patients had no (<20% stenosis) and 30.4% had minimal CAD. IVUS investigation in 92 women showed that 21% had no atherosclerosis while in the remaining 79% per cent atheroma volume was 27±8%. The number of risk factors correlated with the percent of atheroma volume and percent of vessel involvement. Seventy-three percent of the women in whom remodeling was assessed had evidence of positive remodeling. These findings were felt to help explain the increased risk of adverse outcomes.

A recent study of sex differences in symptoms in acute coronary syndrome (ACS) among 1,015 patients [30% women] under 55 found that women were significantly more likely than men to have non-ST-segment elevation MI [37.5% vs 30.7%] and to present without chest pain [19.0% vs 13.7%]. Although CP was the most common presenting symptom of ACS, patients without CP were not different from those with CP in type of ACS, troponin level, or coronary stenosis.

Multiple studies have looked at gender differences in symptom presentation with acute MI. In addition to the FHS finding mentioned above, a study from Canada found that women with MI were more likely than men to have atypical symptoms, had a higher prevalence of diabetes and hypertension, and were older. McSweeney and her colleagues administered questionnaires to 515 female survivors of documented MI. Among prodromal symptoms the most common was unusual fatigue, occurring in almost 71% of women. Only 29.7% of women had prodromal chest pain. Acutely, at presentation with MI, the most common symptom was shortness of breath (57.9%). Forty-three percent of women experienced no chest pain and of those who experienced discomfort the most frequent locations were the back (37%) and high chest (27.7%).

Disparate findings were reported from the Myocardial Infarction Triage and Intervention Registry which found no gender differences in symptoms of MI with 99% of 841 men and 99.6% of women presenting with chest pain.

OUTCOMES

Women have a higher mortality than men from MI. Vaccarino and her colleagues abstracted data on over 155,000 women and over 229,000 men entered into the National Registry of Myocardial Infarctions. Overall in-hospital mortality was 16.7% for women and 11.5% for men. Among patients under age 50, women’s mortality was 6.1% compared to 2.9% for same-aged men. The difference in mortality between men and women was no longer significant after age 74. More recent data was reported from 78,254 patients with acute MI in 420 United States hospitals from 2001-2006. In the overall cohort, mortality was 8.2% in women and 5.7% in men. This difference was not statistically significant, but in the ST segment elevation MI cohort, there was a significant difference in mortality, 10.2% in women vs 5.5% in men. In this study, women were less likely to receive early medical and acute reperfusion therapies, timely pharmacological and mechanical reperfusion, and invasive procedures. Women were older than men and had more co-morbidities.

Other studies have found that women have higher operative mortality from coronary artery bypass surgery (CABG). In this retrospective analysis of 15,440 patients who had CABG at 31 Midwestern hospitals, operative mortality (OM) was 4.24% in women and 2.23% in men, p<0.0001. After adjustment for all co-morbidities, even body surface area, female gender remained an independent predictor of increased mortality [risk adjusted OM 3.81% in women and 2.43% in men]. Another review of CABG and percutaneous coronary interventions [PCI] in 2007 examined 23 studies reporting outcomes by gender for CABG and 48 reporting outcomes for PCI. The authors found that the majority of studies noted greater in-hospital mortality in women than men, with mortality differences resolving with longer follow-up.

SUMMARY

Gender differences in ASCVD exist for presenting symptoms, risk factor weighting, and outcomes. More research will hopefully elucidate mechanisms and improve the treatment of women with this disease.
References

Author
Barbara H. Roberts, MD, FACC, is Director, The Women’s Cardiac Center at The Miriam Hospital and Associate Clinical Professor of Medicine, Alpert Medical School of Brown University.

Financial disclosures
None

Correspondence
Barbara H. Roberts, MD, FACC
Director, The Women’s Cardiac Center at The Miriam Hospital
164 Summit Avenue
Providence, RI 02906
bhrroberts@lifespan.org
401-793-3750