Gender-Specific Aspects of Cardiovascular Disease

By Barbara Robert, MD, FACC

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Misconceptions about women and heart disease date back almost 250 years to William Heberden, an eighteenth century British physician who first described the symptom of angina pectoris in 1768. He noted, " Males are most liable to this disease, especially such as have past their fiftieth year. I have seen nearly a hundred people under this disorder, of which number there have been three women." James Herrick in 1912 described the symptoms of acute myocardial infarction (MI) and noted that nearly all cases were in men past middle age[1].

It is only in the last few decades that the medical profession and the public have begun to appreciate the magnitude of the problem of cardiac disease in women. Since 1984 more women than men have died of atherosclerotic cardiovascular disease (ASCVD) each year in the United States.[2] Despite this, women are diagnosed and treated less aggressively than men,[3,4] and are woefully underrepresented in clinical trials.

As more attention has been paid to the problem of ASCVD in women we have learned more about differences in clinical presentation between men and women which have an impact on the way women are approached and treated. We've known since the early publications of the Framingham Heart Study that women tend to present with angina pectoris and men tend to present with either MI or sudden cardiac death. The

Framingham Heart Study was also among the first to note the increased likelihood of "silent myocardial infarction" in women compared to men.

The classic symptoms of MI are severe, substernal chest pain associated with dyspnea, diaphoresis and a feeling of impending doom. However, these symptoms, while typical in men, may not be experienced as frequently in women. A study reported in 2003 on prodromal and acute symptoms in 515 female survivors of acute MI.[5] Prodromal symptoms were present in 95% of women for a month or more pre-infarct and the most frequent were unusual fatigue (70.7%) and sleep disturbance (47.8%). The most frequent acute symptoms were shortness of breath (57.9%), weakness (54.8%), unusual fatigue (42.9%), cold sweat (39%), dizziness (39%), back discomfort (37%) and high chest discomfort (27.7%). 43% of patients in this series experienced no chest discomfort at all and the authors postulated that lack of significant chest pain may be a major reason that women have more unrecognized MI's.

The greater mortality rate of women who have MI's has been attributed to the fact that they tend to be older than men at the time of presentation. However, a retrospective study of 155,565 women and 229,313 men with acute MI enrolled in the National Registry of Myocardial Infarction 2, found that a higher hospital mortality rate occurred only among younger women.[6] Women under age 50 had a 6.1% hospital mortality rate compared to 2.9% for same aged men. The sex difference in mortality rates decreased with increasing age and was no longer significant after age 74. The authors also found more co-morbid conditions, higher pulse rates and lower systolic

blood pressures among younger women than among younger men but not in older women compared to older men. Of interest, despite these findings, younger women were less likely than younger men to present with ST-segment elevation, and while they had similar infarct locations, creatine kinase levels and left ventricular ejection fractions, they had higher rates of hypotension, shock, heart failure and bleeding.

Women undergoing coronary artery bypass grafting (CABG) have also been noted to have a higher mortality than men, and this has traditionally been ascribed to their older age. However, just as is the case with MI, an analysis of 51,187 patients (30% women) who had CABG between 1993 and 1999 found that it was younger women who had higher hospital mortality than men (3.4% versus 1.1% for women and men < 50 years of age and 2.6% versus 1.1% for women and men 50 to 59 years of age).[7] Among patients 80 years of age or older there was no significant difference in mortality (9.0% in women versus 8.3% in men). Younger women undergoing CABG had more risk factors and co-morbid conditions than age-matched men but multivariate analysis found that this explained less than 30% of the mortality difference between younger men and women.

This mortality difference persisted after adjustment for body size and remains largely unexplained. Also, women in this study had angiographically less severe coronary artery disease (CAD) and better left ventricular (LV) function in all age categories..

In contrast, a review of the results of percutaneous coronary intervention (PCI) in 2001[8] found that the apparent gender difference in outcomes was negated after

adjustment for body size. Using data from the National Cardiovascular Network Database on 109,708 patients (33% women) who underwent PCI between 1994 and 1998, researchers found that women had higher risks for stroke, vascular complications and repeat in-hospital procedures, even after risk-adjustment. They had higher unadjusted hospital mortality rates (1.8% versus 1.0%) but after correction for body size gender was not found to be an independent predictor of mortality.

Perhaps the most striking gender disparity with regard to cardiovascular disease is the under-representation of women in clinical trials. Physicians are urged to practice "evidence-based medicine" but when it comes to women, the evidence is often lacking. This is most readily apparent in the area of drug treatment of hyperlipidemia. The current guidelines for treatment of hyperlipidemia take no account of gender (except in the different cut points for the normal level of HDL-cholesterol). But there is reason to believe that they should. Over the past few decades several large, randomized, placebo-controlled trials have shown the benefit of statins (and to a lesser extent fibrates) in both primary and secondary prevention of cardiovascular events.

There were three large primary prevention trials of statin use. Two out of the three trials included women. They are the AFCAPS/TexCAPS[9] and ASCOT-LLA[10] trials. (Overall, women made up 12.5% of the 23,505 subjects enrolled in the three large primary prevention trials of statins. The WOSCOPS[11] trial enrolled only men.) The AFCAPS/TexCAPS trial was undertaken to determine if treatment with lovastatin in subjects without clinically evident ASCVD with average total cholesterol (TC) and LDL-

cholesterol (LDL-C) levels but below average HDL-cholesterol (HDL-C) would lead to a reduction in the risk of first major coronary event. This was defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death. AFCAPS/TexCAPS enrolled 997 women (15% of the study population). The ages of the participants ranged from 45 to 73 years for the men and 55 to 73 years for the women. Overall, the trial found a statistically significant benefit of treatment with a 37% relative risk reduction in the likelihood of first major coronary event. However, on gender-specific analysis, while 13 primary end point events occurred in women on placebo and 7 events occurred in women on lovastatin, this was not a statistically significant difference, given the small numbers of events. (In contrast there were 170 events in men on placebo compared to 109 events in men on lovastatin.)

The ASCOT-LLA was a trial in hypertensive patients without known ASCVD but with at least three other risk factors who were randomized to either placebo or atorvastatin and followed for the occurrence of the composite primary end point of non-fatal MI or fatal coronary heart disease. The age range of the participants was from 40 to 79 years. ASCOT-LLA enrolled 1,942 women (19% of the study population). Overall the trial found a statistically significant 36% relative risk reduction in the likelihood of the primary end point. However, on gender-specific analysis there were 19 primary events in the women on atorvastatin and 17 events in the women on placebo, again, not a statistically significant difference. (In contrast there were 81 primary events in men on atorvastatin and 137 events in men on placebo.) Summarizing the results of these two primary prevention trials of statin use, there were 30 events in 1,461 women

on placebo and 26 events in 1,478 women on statins, a difference that is not statistically significant (p = 0.56).

Despite this lack of evidence for the efficacy of statins in the primary prevention of coronary events in women, both the Adult Treatment Panel III[12] and the more recent "Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women"[13] recommend statin use in women with LDL-C levels above a certain value based on level of risk, even in the absence of diagnosed ASCVD. However, the evidence just presented reveals NO evidence that treating women without clinically apparent vascular disease with statins, even those at high risk, lowers their risk of cardiac events.

When it comes to secondary prevention with statins, the data in women are also not as compelling as they are in men. During the past two decades there have been 5 large secondary prevention trials of statins in coronary heart disease which included men and women. Women made up 25% of the 43, 957 subjects enrolled in the 4S trial[14], the Heart Protection Study[15], the Cholesterol and Recurrent Events Trial[16], the LIPID Trial[17]and the PROSPER Trial[18]. All of these studies showed a statistically significant decrease in the relative risk of coronary events in statin treated compared to placebo treated men. In contrast, gender-specific analysis did not find a statistically significant decrease in risk of cardiac events in women in two of these five trials (LIPID and PROSPER), while the other three did demonstrate benefit in women.

Why the disparity between the findings with regard to the efficacy of statins in men versus women, at least with respect to primary prevention? It might be due to the small numbers of women who have been included in the statin trials. However, there is an alternative explanation. Elevations of LDL-C do not appear to be as potent a risk factor in women as they are in men. Even among kindred with Type II Familial Hyperlipoproteinemia, the onset of coronary artery disease in women lags 10 to 15 years behind that of men with equivalent and very high levels of LDL-C.[19] More than twenty years ago, women were noted to have significantly less cholesterol in small dense LDL and more in large LDL than men.[20] Small dense LDL-C particles are more atherogenic than large fluffy LDL-C particles and since women, at least before the menopause, have more of the latter, it is likely that equivalent levels of LDL-C are less atherogenic in women than men.

In support of this hypothesis, a follow-up study of 2,406 men and 2.056 women enrolled in the Lipid Research Clinics program who were free of vascular disease and aged 40 to 64 years at entry, followed for an average of 19 years, found that only elevated non HDL-C and low HDL-C significantly predicted cardiovascular disease (CVD) mortality in women, whereas TC, LDL-C, non HDL-C and low HDL-C all predicted CVD mortality in men.[21]

More recently, it has been suggested that the LDL-C goal for very high-risk patients be lowered to 70 mg/dl or less[22] based on the findings of the PROVE-IT trial[23] This study enrolled 4162 patients (22% women) with acute coronary syndromes to receive either

40 mg. of pravastatin or 80 mg. of atorvastatin. The subjects in the atorvastatin group, who achieved a median LDL-C level of 62 mg/dl, had a statistically significant 16% relative risk reduction in the rate of the primary end point compared to the pravastatin treated group who achieved a median LDL-C level of 95 mg/dl. The benefit of intensive therapy with high dose atorvastatin was consistent across all prespecified subgroups, including women.

The preventive guidelines for women also recommend treating non-HDL-C and low HDL-C with a fibrate or niacin if they are abnormal once the LDL-C goal is achieved. There is not only a paucity of data to support this, there are no data. The two controlled trials of fibrates (the Helsinki Heart Study[24] and VA-HIT[25]) that showed benefit in reducing cardiac events enrolled only men.

Where do these studies leave us with respect to primary prevention in women? This is an important question to which, unfortunately, we do not have evidence-based answers. It is important to reiterate that for premenopausal women with no other risk factors than an LDL-cholesterol above the current threshold statins have not been shown to decrease the risk of cardiac events. There is clearly no harm in counseling ALL patients on weight control, regular exercise and heart healthy diet. The use of statins in ostensibly healthy young women should probably be reserved for those with Familial Hypercholesterolemia where LDL-C values are in the range of 300 to 400 mg/dl. In addition, their use is contraindicated during pregnancy and lactation; most package inserts state that: "STATINS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO

CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS." While statins have proven to be safe drugs, we know little about their long-term effects. If we are proposing to treat healthy, low-risk women for decades it behooves us to be certain that efficacy is beyond doubt and that benefits outweigh the risks. We simply do not know this with regard to statin (or fibrate/niacin) use in young women who do not have vascular disease.

The recently reported results of the trial of aspirin for primary prevention of cardiovascular disease in women[26] demonstrate the fallacy of assuming that results in men can be generalized to women. Among 39, 875 healthy women 45 years of age or older who were randomized to either 100 mg of aspirin every other day or placebo there was a 24% reduction in the risk of ischemic stroke but no decrease in the risk of fatal or non-fatal MI or death from cardiovascular causes. (However, in women 65 or older aspirin significantly reduced the risk of both ischemic stroke and MI.) These results in women contrast with those of the Physicians' Health Study[27] which found that aspirin significantly reduced the risk of MI in that all-male cohort but had no significant effect on the risk of stroke. The accompanying editorial[28] concludes, "…clinical research…needs always to account for the evolutionary biology of sex."

The Institute of Medicine also noted the importance of taking sex into account: "Sex matters. Sex, that is, being male or female, is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research."[29]

In summary there are gender-specific differences in cardiovascular disease including age at presentation, risk factor weighting, response to medicines, symptoms and mortality. More research needs to be done to elucidate gender differences and to determine the safest, most efficacious preventive strategies and treatments in both sexes.

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