

## Review Article

### Women and Heart Disease: Gender Differences and Similarities

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#### Introduction

Cardiovascular disease (CVD) is the leading cause of death in women (Figure 1). Women

Compared to men women have; Lower LV mass, greater contractility, preserved mass

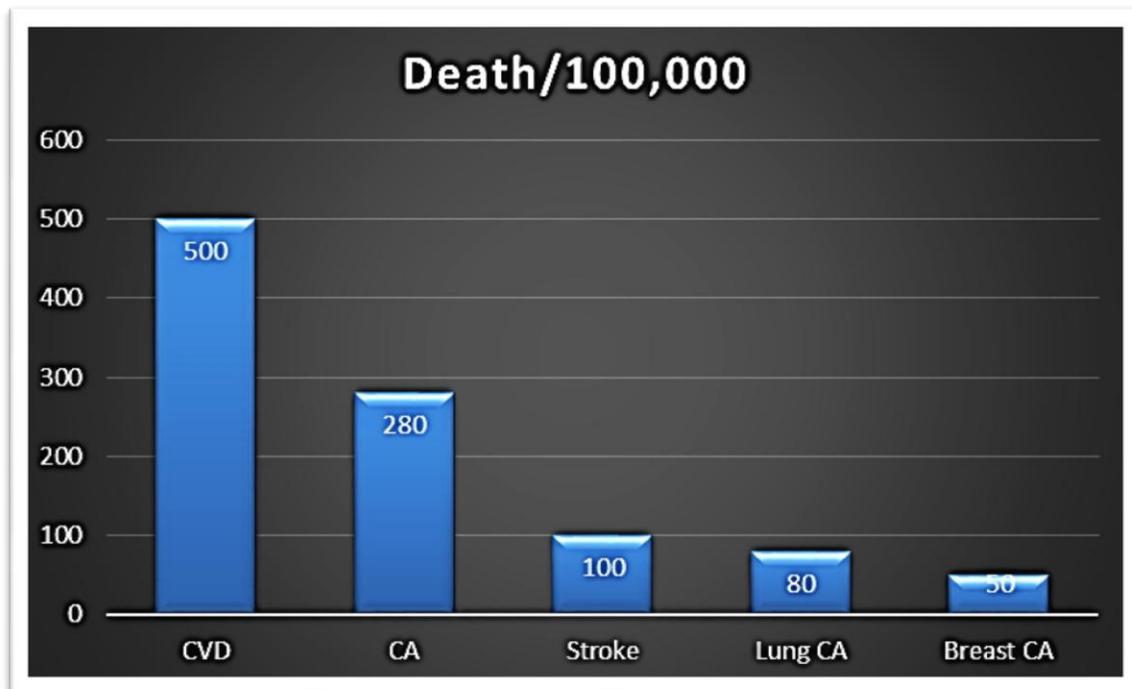


Figure 1: Mortality in women shown as death/100,000. CVD ranks as the leading cause of death among women. CA = Cancer. Source AHA 2013.

constitute 401,000 deaths/year from cardiovascular disease (CVD) compared to 386,000 in men, and 176,255 deaths/year from coronary artery disease (CAD) versus 39,520 deaths from breast cancer.<sup>1</sup>

It is popular among women groups to campaign against breast cancer and publicize it as a common cause of mortality in women. Such beliefs do not conform to available data and may lead to serious complacency in following prevention policies.

with aging, small coronary vessels, lower blood pressure, faster resting heart rate and less catecholamine mediated vasoconstriction<sup>2</sup>.

Women are roughly 10 years older than men when they present, and have more comorbidities Young women also develop CAD and have a worse prognosis than men<sup>3</sup>. Women are more likely to wait before presenting to medical attention and are referred less often for appropriate testing or treatment. Women with MI are more likely to have complications and increased

mortality. Fewer women have been included in studies; consequently there is less data to use for accurate comparison<sup>4</sup>. There is also lack of awareness to CVD among women; a survey of 2500 women of less than 25 years, in 1997-2012, showed that although awareness among whole study population nearly doubled (30 to 56%), but was still low among minorities in the US, 36 in African Americans and 34% in Hispanic women<sup>5</sup>.

In a study of 515 women with MI Mc-Sweeney reported that females clinically present differently from males and that chest pain is absent in 43% while the most common symptoms are: dyspnea in 58%, weakness in 55% and fatigue in 43%. Female show prodromal symptoms to heart attack in the form of fatigue in 71%, sleep disturbance in 48% and dyspnea in 42%<sup>6</sup>.

### Heart failure

As emerging epidemiologic data reveal a growing prevalence and burden of heart failure among women, it is important that treating physicians and researchers recognize sex-based differences in relation to heart failure. Despite the overall incidence of heart failure being lower in women compared with men, the magnitude of improvement in survival over the last several decades has been less apparent in women. While clinical trials have demonstrated improved outcomes among heart failure patients, they have predominantly included men, yielding results that are sometimes inadequately powered to detect a benefit for women.

Multiple studies demonstrate that women diagnosed with heart failure are more likely to be older, hypertensive, have preserved systolic function, and have less coronary artery disease, when compared with their

male counterparts.<sup>7,8</sup> The apparent lower mortality in women with heart failure may be related to the relatively preserved left ventricular function, which is more common in women than in men.

In the Cardiovascular Health Study, the 6-year mortality among patients with reduced ejection fraction was almost double that of those with preserved systolic function, findings confirmed by the Framingham Heart Study<sup>9,10</sup>. While most data support an overall improved survival in women with heart failure, the survival trends between genders over time are less consistent across cohorts. In the Framingham Heart Study cohort, the 5-year survival improved by approximately 30% between 1950 and 2000, a significant trend that was similar for both genders, with most of the improvement after 1990<sup>11</sup>. While the Olmsted County participants also showed improved survival over time, the 5-year survival for women improved to a lesser degree than for men (10 vs 25% decrease in mortality in the 1996-2000 time period compared with 1979-1984 in women and men, respectively)<sup>12</sup>. Data from the Kaiser Permanent registry mimic the Olmsted cohort, with a 14% improvement in 1- and 5-year mortality rates for men between 1970 and 1994, but stable mortality rates for women<sup>13</sup>.

### Risk factors

Risk factors for CVD in women above 55 include dyslipidemia: both high LDL and/or low HDL, family history of premature CAD, diabetes, smoking, hypertension and Peripheral Arterial Disease (PAD). In addition to obesity, high triglycerides, metabolic syndrome, collagen vascular disease, autoimmune disease, and chronic kidney disease are common among females. Menopause needs special mention as low

levels of estrogens pose significant risk for developing cardiovascular disease in the smaller blood vessels (coronary microvascular disease) of females. Early termination of the Women's Health Initiative (WHI) hormone-replacement therapy trials and data from HERS Study, have drawn much attention to the relationship between estrogen and cardiovascular health<sup>14</sup>. Clinical data are equivocal with regard to estrogen and heart failure. In a subgroup analysis of the BEST trial, which included patients with ejection fraction less than 35%, postmenopausal women taking hormone-replacement therapy had improved survival compared with those who were not. Interestingly, this benefit was most prominent in patients with non-ischemic heart failure<sup>15</sup>.

Broken heart syndrome is a cardiomyopathy brought on by stressful situations that can cause severe, but usually temporary, heart muscle failure. This condition may also be called Takotsubo cardiomyopathy, apical ballooning syndrome or stress cardiomyopathy. Women are nine times more likely than men to get Takotsubo cardiomyopathy (TTC) says a new study of 1,750 people with the disease<sup>16</sup>. However, cardiac complications appeared to be more common in male than female patients with TTC during their hospitalization<sup>17</sup>.

Pregnancy related risk factors are also identified which include pre-eclampsia, eclampsia, gestational diabetes, stillbirth, miscarriages, especially multiple, history of cancer treatments (XRT), Depression and stress.

Among the risk factors in women low HDL is more predictive than high LDL. Additionally Lp (a) is more predictive in younger women, while TG can be more

predictive in older women, especially if >400 mg/dL<sup>18</sup>. Diabetes mellitus almost double the risk of fatal CAD while smoking is associated with 50% of all coronary events in women<sup>19,20</sup>.

### Diagnosis and Treatment

The diagnosis of CAD is similar in both sexes: Treadmill stress testing, nuclear stress testing, Stress echo, CT calcium score, coronary CT angiography, cardiac catheterization with coronary angiography. Unlike in men treadmill stress testing results in inconclusive and incomplete test duration. Treatment of cardiovascular disease in women requires the adoption of preventive strategy in addition to treatment protocols. Risk factors may double, quadruple or even result in tenfold increase of the patient risk. It is important that women should follow a healthy lifestyle e.g. exercise, quit smoking eat healthy diet and attain a BMI <25 and waist circumference <35 inches. Risk factor: Hypertension, Diabetes mellitus, dyslipidemia should receive serious attention. Women should receive treatment for depression whenever diagnosed. It is recommend that women older than 65 years take a daily 81-milligram aspirin to help prevent heart disease if their blood pressure is controlled and the risk of digestive bleeding is low. Aspirin might also be considered for at-risk women younger than 65 years for stroke prevention.

Among the different pharmacological therapies tested,  $\beta$ -blockers have the most data to support their use in women with heart failure and reduced ejection fraction. In a subgroup analysis of the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial, investigators found that metoprolol succinate significantly decreased the risk of

hospitalizations and mortality in women; however, their mortality alone was not significantly different, irrespective of the use of metoprolol succinate<sup>21</sup>. Pooled data from the MERIT-HF trial,<sup>22</sup> the second Cardiac Insufficiency Bisoprolol Study (CIBIS-II)<sup>[53]</sup> and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial,<sup>23</sup> yielded a mortality benefit with  $\beta$ -blockers in women similar to that recorded in men. The relative risk of death was decreased by 31% in women compared with 34% in men, which are both significant findings<sup>21</sup>.

As advised in NHLBI: "Heart Truth" campaign; by doing just 4 things: eating right, being physically active, not smoking, and keeping a healthy weight, the risk of heart disease in women may be considerably lowered, by as much as 82 percent.

### Conclusion

Contrary to common beliefs among females, CVD is the leading cause of morbidity and mortality in women.

Gender differences and similarities are common and should be realized and highlighted in treatment guidelines. While clinical trials have demonstrated improved outcomes among heart failure patients, they have predominantly included men, yielding results that are sometimes inadequately powered to detect a benefit for women.

Preventive strategies seem to work well in females when compared to curative means.

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