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Topic Review

Most Important Outcomes Research Papers on Cardiovascular Disease in Women

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The following articles are being highlighted as part of *the Circulation:Cardiovascular Quality and Outcomes* Topic Review series. This series summarizes the most important manuscripts, as selected by the Editor, that have been published in the *Circulation* portfolio. The objective of this new series is to provide our readership with a timely, comprehensive selection of important papers that are relevant to the quality and outcomes as well as general cardiology audience. The studies included in this article represent the most significant research in the area of cardiovascular disease in women. (*Circ Cardiovasc Quality and Outcomes*. 2013;6:e1-e7.)

Cardiovascular disease (CVD) in women has been historically understudied. For many years, heart disease had been thought to be primarily a "man's disease." Consequently, women have been significantly under-represented in longitudinal studies of disease history and in clinical trials. High-quality data from women at the extremes of age, with multiple co-morbidities, and from racial and ethnic minorities have been particularly rare.

In order to increase awareness of cardiovascular prevention among women, in 1999 the American Heart Association (AHA) published its first women-specific clinical recommendations for the prevention of CVD.[1] In 2004, the AHA and multiple other collaborating organizations subsequently sponsored "Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women," which underwent updates in 2007 and 2011. As a result of these and other related initiatives, the rate of public awareness of CVD as the leading cause of death among US women has increased from 30% in 1997 to 54% in 2009.[2] CVD-associated death among US women has declined significantly over this time period.[3,4]

Yet substantial work still needs to be done to improve women's cardiovascular health. CVD remains the number one killer among women.[4] As the obesity epidemic continues, we are actually finding increases in coronary heart disease (CHD) death among young women 35 to 54 years of age.[2] Morbidity and mortality from stroke and hypertension remain high.[4] In addition, substantial outcomes disparities continue for women from racial and ethnic minorities.[4]

We have therefore dedicated our topic summaries in this issue of *Circulation: Cardiovascular Quality and Outcomes* to CVD in women. We have included only those studies where authors provided a convincing a priori reason to study a particular disease process or clinical intervention in women and reported primary endpoints that were sex-specific. We have included articles on the representation of women in randomized trials of cardiovascular prevention, acute and long-term outcomes of coronary artery stenting in women compared with men, outcomes associated with left ventricular assist device implantation in women, and many other topics.

Gender Bias in Studies for Food and Drug Administration Premarket Approval of Cardiovascular Devices

Summary: Cardiovascular devices can have different safety and effectiveness profiles in men and women. However, the type and quality of sex-specific data reviewed by the Food and Drug Administration (FDA) before approval of these devices are unknown. The authors performed a systematic review of all gender bias comments, demographic reporting with regard to sex, and analysis of results from 123 studies of 78 approved applications for high-risk cardiovascular devices submitted to the FDA between 2000 and 2007. They found that the sex of study enrollees was not reported in the FDA review documentation for 34 of 123 (28%) studies. Among the 89 studies reporting sex distribution, study populations predominantly consisted of men (67%). There was no increase in the enrollment of women over time. To explain the lower representation of women, the applications often stated that the trials reflected the underlying imbalance in the sex distribution of the disease in question and/or differences in referral rates for similar procedures. In addition, only 51 of 123 studies (41%) included a comment or analysis related to sex discrepancies, and only 12 (10%) of these studies reported whether there was a difference in device safety or effectiveness by sex.

Conclusion: Although the FDA requires applications for premarket approval of cardiovascular devices to have comments pertaining to gender bias and analysis for all studies relating to its premarket approval process, the majority of FDA device applications for high-risk cardiovascular devices are missing basic sex-specific data such as the gender of enrollees or data on stratification of outcome by sex. The lack of sex-specific data before device approval may limit the discovery of sex-specific differences in outcomes and therefore mislead interpretations of safety and efficacy.[5]

Lasofoxifene and Cardiovascular Events in Postmenopausal Women With Osteoporosis: Five-Year Results From the Postmenopausal Evaluation and Risk Reduction With Lasofoxifene Trial

Summary: In the Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) trial, lasofoxifene was associated with lower risk of non-vertebral fractures and estrogen-receptor–positive breast cancer.[6] Authors conducted this sub-study to understand the relationship between lasofoxifene use and the occurrence of a comprehensive endpoint encompassing major CHD events including coronary death, nonfatal myocardial infarction (MI), new ischemic heart disease, hospitalization for unstable angina, or coronary revascularization. The trial randomized 8556 osteoporotic women 59 to 80 years of age to lasofoxifene 0.25 mg/d, lasofoxifene 0.5 mg/d or placebo for 5 years. The authors report that lasofoxifene 0.5 mg/d reduced the risk of major

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CHD events by 32% (hazard ratio [HR], 0.68) when compared with placebo, whereas the risk reduction with lasofoxifene 0.25 mg/d did not reach statistical significance. Both the 0.5 mg/d and 0.25 mg/d dosages of lasofoxifene were associated with reduced risk of coronary revascularization (HR 0.56 for both), reduced risk of stroke (HR 0.64 and 0.61, respectively), and increased risk of venous thromboembolism (HR 2.06 and 2.67, respectively). No significant effect of either dosage of lasofoxifene was demonstrated for coronary death or nonfatal MI. The effectiveness of lasofoxifene 0.5 mg/d in reducing CHD events was similar across strata of major cardiovascular risk factors.

Conclusion: In addition to reducing the risk of non-vertebral fractures and estrogen-receptor–positive breast cancer, lasofoxifene 0.5 mg/d may have a favorable effect on the CHD profile of postmenopausal women with osteoporosis. This effect is unique to this drug as compared with other drugs in the same class, including raloxifene and tamoxifen, suggesting that it may be an attractive therapeutic modality in postmenopausal women with osteoporosis. However, findings are limited by the fact that the PEARL trial was not designed to examine primary cardiovascular endpoints, and, accordingly, total CHD events were relatively rare. In addition, the higher risk of venous thromboembolism from lasofoxifene use would likely significantly reduce overall cardiovascular benefit of the agent.[7]

Primary Prevention of CVD

Over the past decade, multiple efforts have been directed toward closing the gender gap in preventive care for cardiovascular disease. As a result of initiatives by the federal government, AHA, and other organizations, the rate of awareness of heart disease as the leading cause of death in women almost doubled between 1997 and 2009; the mortality rate from CVD during the same period decreased by almost half.[2–4] Yet a recent study has shown cardiovascular risk factors among women to have worsened in the past decade.[8] This result is especially troubling in light of the fact that women are often underrepresented in primary prevention trials that test strategies of risk mitigation.[9] It is hoped that the future participation of women in preventive care research will increase following the 2011 report from the Institute of Medicine Committee titled "Women's Health Research: Progress, Pitfalls, and Promise."[10]

Evaluation of the AHA Cardiovascular Disease Prevention Guideline for Women

Summary: The 2007 update to the AHA guidelines for CVD prevention in women recommends a simplified approach to risk stratification. The authors assigned Women's Health Initiative (WHI) participants to risk categories as described in the guideline and evaluated clinical event rates within and between strata. The WHI enrolled 161 808 women 50 to 79 years of age and followed them prospectively for 7.8 years (mean). With reference to the 2007 AHA guideline categories, 11% of women were considered high risk, 72% at-risk, and 4% at optimal risk; 13% of women did not fall into any category, as they lacked traditional risk factors but did not adhere to a healthy lifestyle (moderate intensity exercise for 30 minutes most days and <7% of calories from saturated fat). Among high-risk, at-risk, and optimal risk women, rates of MI/coronary death were 12.5%, 3.1%, and 1.1% per 10 years, respectively (P for trend <0.0001). The event rate was 1.3% among women who could not be categorized. The AHA guideline predicted coronary events with accuracy similar to current Framingham risk categories (area under receiver operating characteristic curve for Framingham risk, 0.665; for AHA risk, 0.664; P=0.94) but less well than proposed Framingham 10-year risk categories of <5%, 5% to 20%, and >20% (area under receiver operating characteristic curve for revised Framingham risk categories, 0.724; for AHA risk, 0.664; P<0.0001).

Conclusion: Given that the 2007 AHA guidelines for cardiovascular disease prevention in women were endorsed by professional organizations representing primary care and specialty providers, the Centers for Disease Control and Prevention, and the National Heart, Lung and Blood Institute, it is concerning that the AHA model was introduced without validation against pre-existing Framingham models. The authors have shown in this study that the AHA guidelines could have utility relative to the traditional Framingham risk score, as it performs similarly yet is easier to implement. However, it does not appear to perform as well as the revised Framingham risk model. The AHA model should also be compared against other commonly used models shown to be prognostic in women such as the Reynold's risk score.[11]

Twelve-year Follow-up of American Women's Awareness of CVD Risk and Barriers to Heart Health

Summary: This study assessed contemporary awareness of CVD risk and barriers to preventive actions including lifestyle interventions and stress management in a nationally representative sample of women. The authors also evaluated trends in these findings since 1997 using triennial surveys. A standardized survey about awareness of CVD risk was completed in 2009 by 1142 women >25 years of age who were contacted through random digit dialing with oversampling for racial/ethnic minorities plus 1158 women who were contacted online. A significantly higher proportion of women was aware that CVD is the leading cause of death in 2009 (54%) compared with 1997 (30%). Black and Hispanic women were significantly less aware than white women, although the gap has narrowed since 1997. In 2009, only 53% of women said they would call 9-1-1 if they thought they were having symptoms of a heart attack. The majority of women cited therapies to prevent CVD that are not evidence-based. Common barriers to preventive behaviors were family/caretaking responsibilities (51%) and confusion about media messages (42%). Community-level changes thought to be helpful in increasing awareness about CVD risk were access to healthy foods (91%), public recreation facilities (80%), and nutrition information in restaurants (79%).

Conclusion: It is concerning that about half of studied women would not have considered calling 9-1-1 on experiencing symptoms of a heart attack and were unaware that heart disease is a leading cause of death among women. "Real-world" understanding is likely to be even worse as study subjects were relatively well educated. While knowledge has improved with time, women continue to struggle to manage their risk factors, as is evident from their increasing Framingham risk scores in the past 2 decades.[8] Using the power of branding and social marketing, "Go Red for Women" and "The Heart Truth" initiatives by the AHA and National Heart Lung and Blood Institute, respectively, can play an enormous role to this end.[2]

Representation of Women in Randomized Clinical Trials of CVD Prevention

Summary: Under-representation of women in cardiovascular studies could impact the accuracy of recommendations for women with cardiovascular conditions. A systematic review by Melloni and colleagues examined the participation of women relative to men in randomized trials that were used to support the AHA recommendations for CVD prevention in women. Overall, of the 156 clinical trials assessed, 135 enrolled both men and women, 20 enrolled only men, and 1 enrolled only women. Sex-specific results were reported in only one-third of the main articles reporting primary study findings. The proportion of women in the trials increased significantly over time, from 9% in 1970 to 41% in 2006. Female representation was better in international trials compared with US trials (32.7% versus 26.7%) and in primary prevention trials as compared with secondary prevention trials (42.6% versus 26.6%). The proportion of enrolled women was comparable in industry-funded versus non-industry–funded clinical trials.

Conclusion: Enrollment of women in cardiovascular trials has increased over time. Nevertheless, several contemporary

cardiovascular trials, including prominent "mega" trials, show suboptimal representation of women. Potential reasons for such under-representation are diverse and include the use of age-based exclusions that predominantly affect women who tend to have later onset of CVD, implicit bias of physicians against screening potential female enrollees, and less motivation to participate among women due to the underestimation of CVD risk.[9] Further efforts including possible over-sampling strategies will be necessary by investigators, funders, and regulating bodies such as the FDA to ensure more equitable representation of women in cardiovascular trials.

Statins for the Primary Prevention of Cardiovascular Events in Women With Elevated High-Sensitivity C-Reactive Protein or Dyslipidemia: Results From the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin and Meta-Analysis of Women From Primary Prevention Trials

Summary: Women have been historically under-represented in trials of primary prevention with statins, and data are inconsistent about the existence of benefit from this therapy in women.[12–14] The authors therefore described results by sex from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), the largest study examining primary prevention with statins. The authors also presented an updated meta-analysis of women in primary prevention trials that included JUPITER participants. In JUPITER, 6801 women and 11 001 men with high-sensitivity C-reactive protein (CRP) ≥2 mg/L and low-density lipoprotein-cholesterol <130 mg/dl were randomized to rosuvastatin or placebo. Although absolute event rates were lower in women, relative risk reduction for the primary endpoint (a composite of MI, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death) was similar for women and men (HR: 0.54; 95% confidence interval [CI]: 0.37–0.8, P=0.002 versus 0.58, 95% CI: 0.45–0.73, P<0.001). Compared with men, a greater proportion of women receiving rosuvastatin had physician-reported diabetes. No other major gender-specific side effects were reported. The accompanying meta-analysis found a marked risk reduction for cardiovascular events (relative risk: 0.63; 95% CI: 0.49–0.82, P<0.001) and a trend toward reduced all-cause mortality among women (relative risk, 0.78; 95% CI: 0.53 to 1.15, P=0.21).

Conclusion: This JUPITER sub study and accompanying meta-analysis confirm similar relative risk reduction with statin therapy for primary prevention in men and women with historically low Framingham risk but elevated CRP. As the authors have clearly discussed, physician-reported diabetes was more frequently seen among women. Given the growing controversy around the significance of statin-induced hyperglycemia, the greater proportion of women with physician-reported diabetes in JUPITER warrants further investigation, especially as women would be expected to have a lower absolute age-adjusted risk of CVD compared with men.[15]

Comparison of the Framingham and Reynolds Risk Scores for Global Cardiovascular Risk Prediction in the Multiethnic Women's Health Initiative

Summary: Framingham-based and Reynolds Risk scores for CVD prediction have not been directly compared in an independent multiethnic validation cohort. The authors therefore selected a case-cohort sample from the Women's Health Initiative Observational Cohort involving 1722 cases of CVD (defined by MI, ischemic stroke, or cardiovascular death) and a random subcohort of 1994 women without prior CVD. Risk was estimated with 3 scores: Framingham Adult Treatment Panel III (ATP III) score, Framingham CVD score, and the Reynolds Risk score. The authors founds that the ATP III and Framingham CVD models overestimated the risk of CHD and CVD, respectively. After recalibration, the Reynolds model demonstrated improved discrimination over the ATP-III model through a positive net reclassification improvement (NRI 4.9%; P<0.02) and positive integrated discrimination improvement (4.1%; P<0.0001). Both the Reynolds and ATP III models demonstrated better discrimination than the Framingham CVD model (NRI=12.9%, P<0.0001 and NRI=5.9%, P=0.0001, respectively). The greatest difference in classification was found for women with 10-year ATP III risks of 5% to 10%. For these subjects, use of the Reynolds Risk calculator reclassified 15% to a lower risk category and 29% to a higher risk category, and 5% were reclassified as having an estimated risk >20%. There was no effect modification by ethnicity.

Conclusion: Study findings support the use of the Reynolds Risk score rather than Framingham risk calculators when calculating cardiovascular risk among women, especially among those with low-intermediate cardiovascular risk per the ATP III model who may benefit from treatment with a statin for primary prevention in the setting of an elevated C-reactive protein.[15] Of note, in contrast to the ATP III score, calculation of the Reynolds Risk score requires that ancillary tests be performed, including measurement of C-reactive protein and hemoglobin A1c, thereby raising questions of cost-effectiveness. In addition, study findings have not been demonstrated in men.[16]

Coronary Artery Disease in Women

Due in large part to the improved treatment of acute coronary syndromes and greater use of efficacious secondary prevention agents such as statins, mortality from coronary artery disease (CAD) has significantly improved over the past half century. However, this reduction in mortality has been less pronounced in women as compared with men.[13,17] Possible reasons for this disparity include fundamental differences in CAD biology among sexes, decreased delivery of evidence-based care for women, and reduced awareness of CAD among women. The studies presented here address related issues, including the natural history and determinants of acute MI (AMI) outcomes among young women, the possible greater influence of social support and depressive symptoms on post-AMI outcomes in women as compared with men and overall sex-specific trends in AMI hospitalization.

Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients Study Design

Summary: Young women with AMI experience an excess risk of mortality from ischemic heart disease. The sources of this elevated risk are not well known. Variation in recovery: role of gender on outcomes of young AMI patients (VIRGO) is an observational study of the presentation, treatment, and outcomes of young women and men from 18 to 55 years of age with AMI. The study will enroll 2000 women with AMI and a comparison cohort of 1000 men with AMI from more than 100 participating hospitals. The aims of the study are to determine sex differences in the distribution and prognostic importance of biological, demographic, clinical, and psychosocial risk factors; to determine whether there are sex differences in the quality of care received by young AMI patients; and to determine how these factors contribute to sex differences in outcomes (including mortality, hospitalization, and health status). Blood serum and DNA for consenting participants will be stored for future studies.

Conclusion: Prior literature has clearly demonstrated that young women with AMI are at an increased risk of dying compared with their

male counterparts. However, efforts to understand the determinants of this difference in outcomes have been limited. VIRGO is the most in-depth prospective study of this relatively vulnerable patient population. Results are expected in the near future.[18]

Benefit of Intensive Statin Therapy in Women: Results From Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction[22]

Summary: Although the effects of statins on reducing future cardiovascular events are well established in men, generalizability to women is less certain because of the relatively few numbers of women included in large, randomized, secondary prevention trials. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, 911 women and 3251 men were randomized to intensive (atorvastatin 80 mg) or standard (pravastatin 40 mg) statin therapy after acute coronary syndrome (ACS) and followed for 18 to 36 months. The primary endpoint was a composite of death, ACS requiring hospitalization, revascularization after 30 days, and stroke. Efficacy endpoints included reduction in LDL and percentage of patients who achieved the target LDL of <70 mg/dL; safety endpoints included elevation in transaminases, creatine kinase, and myalgias/myositis. Women receiving intensive statin therapy versus standard therapy had a reduction in absolute risk of the primary endpoint from 27.0% to 20.3%. This corresponds with a relative risk reduction of 25%, statistically similar to the 14% relative risk reduction in men. Fewer women than men reached efficacy endpoints with intensive statin versus standard therapy. No sex differences were observed in safety endpoints.

Conclusion: This subgroup analysis of PROVE IT-TIMI 22 demonstrates that post-ACS high-dose statin therapy seems to be as effective at preventing a composite cardiovascular outcome in women as in men, thus supporting the widespread use of such therapy. The reasons for the similarity in efficacy by sex are not clear given the better surrogate endpoints among men, including a greater percentage achieving target LDL levels. Further efforts will be needed to improve statin use among women following ACS, as previous studies have found that women are less likely to receive this treatment.[19–21]

The Role of Social Support in Health Status and Depressive Symptoms After Ami: Evidence for a Stronger Relationship Among Women

Summary: Prior studies have associated low social support (SS) with increased readmission and mortality after AMI. However, relatively little is known about the impact of low SS on health status and depressive symptoms and whether this effect varies by sex. Using data from AMI patients enrolled in a 19-center prospective study, the authors examined the association of SS (low, moderate, high) with health status (angina, disease-specific quality of life, general physical and mental functioning) and depressive symptoms after adjusting for site, baseline health status, baseline depressive symptoms, demographic characteristics, and clinical factors. Patients with the lowest SS (relative to those with the highest) had significantly increased (P≤0.05) risk of angina (relative risk, 1.27), lower disease-specific quality of life (mean difference [β], −3.33), lower mental functioning (β, −1.72), and more depressive symptoms (β, 0.94). A non-significant trend toward lower physical functioning (β, 0.87) was observed. In sex-stratified analyses, the relationship between SS and outcomes was stronger for women than for men, with a significant SS-by-sex interaction for disease-specific quality of life, physical functioning, and depressive symptoms (all P<0.02).

Conclusion: In finding that the level of SS is a predictor of multiple patient-centered outcomes, including quality of life and physical functioning, this study identifies a potentially remediable target for intervention. The reasons for the especially important role of SS among women is not clearly known though may relate to sex differences in psychological and physiological pathways modulating responses to stress[22,23] as well as differences in coping behaviors.[24] The role of SS in improving hard outcomes such as mortality remains to be proven.[25,26]

Anderson ML, Peterson ED, Brennan JM, Rao SV, Dai D, Anstrom KJ, Piana R, Popescu A, Sedrakyan A, Messenger JC, Douglas PS. Short- and Long-Term Outcomes of Coronary Stenting in Women Versus Men: Results from the National Cardiovascular Data Registry and Centers for Medicare & Medicaid Services Cohort.[33]

Summary: Although procedural success of percutaneous coronary intervention (PCI) has been shown to be similar in women and men, it is unclear whether in-hospital and long-term outcomes differ by sex in the contemporary era. In addition, sex-stratified outcomes following placement of drug-eluting stents (DES) as compared with bare metal stents (BMS) are not clearly understood. The authors therefore identified 426996 patients ≥65 years of age (42.3% women) enrolled in the National Cardiovascular Data Registry CathPCI Registry (2004–2008) undergoing a PCI and linked them to Medicare inpatient claims for derivation of long-term outcomes. Association of sex with in-hospital mortality and morbidity was studied after adjusting for more than 50 baseline clinical and angiographic factors. Propensity matching was performed for comparison of outcomes by stent type. The authors found that women experienced increased in-hospital mortality (adjusted odds ratio [OR], 1.41; 95% CI, 1.33–1.49), MI (adjusted OR, 1.19; 95% CI, 1.11–1.27), bleeding (adjusted OR, 1.86; 95% CI, 1.79–1.93), and vascular complications (adjusted OR, 1.85; 95% CI, 1.73–1.99). However, at 20.4 months, women had a lower adjusted risk of death (HR, 0.92; 95% CI, 0.90–0.94) but similar rates of MI, revascularization, and bleeding. Relative to bare metal stent use, DES use was associated with improved long-term outcomes in both sexes.

Conclusion: In agreement with previous literature,[27] the findings of this study suggest worse in-hospital outcomes after PCI in women as compared with men. These differences persisted despite controlling for various clinical and angiographic factors. However, it is notable that women were less likely to have died at 20 months despite poorer short-term outcomes. The reasons for this disconnect between short- and long-term outcomes are unknown, although they may relate to potential underuse[28] or misuse[29] of evidence-based therapies in hospitalized women followed by aggressive secondary preventive care such as revascularization in the postdischarge period. Better long-term outcomes among women may also be a peculiarity of the NCDR database, as previous studies have found similar long-term outcomes regardless of sex.[30–33]

Age- and Sex-Specific Trends in the Incidence of Hospitalized Acute Coronary Syndromes in Western Australia

Summary: In this study from Western Australia, the authors sought to examine temporal trends in the hospitalization rates for acute coronary syndromes (ACS), including AMI and unstable angina (UA), by age and sex in a population-based cohort using the Western Australian Data Linkage System, a repository of linked administrative health data. They identified 29421 incident ACS hospitalizations between 1996 and 2007 and used Poisson log-linear regression models to calculate incidence rate changes. Age-standardized incidence rates of ACS declined annually in men by 1.7% (95% CI, −2.1 to −1.3) and in women by 1.6% (95% CI, −2.1 to −1.0). These changes in ACS incidence were driven predominantly by annual declines in UA

incidence of 3.0% in men and 2.5% in women and less so by declines in AMI incidence. However, in age-sex analyses, it was noted that, contrary to the declining trend among other subgroups, ACS incidence increased annually in 35- to 54-year-old women (2.3%; 95% CI, 1.0 to 3.8). This increase was predominantly driven by the greater incidence of AMI over the study period.

Conclusion: The findings of this research are consistent with population-based studies from other countries, including the United States, that demonstrate a decline in rates of acute coronary syndromes in the past decade.[34,35] It is notable that the opposite trend of increasing rates of AMI was observed in 35- to 54-year-old women, which has been mirrored by US AMI data over a similar time.[8] Stroke prevalence also appears to be rising faster among middle-aged women in the United States.[36] These findings may partly be explained by worsening cardiovascular risk profiles among young US women, as suggested by rising Framingham Risk scores.[8] Women in mid-life may therefore comprise a unique population of patients at higher risk of CVD due to clinical, biological, or social factors that will need further explication.[37]

Heart Failure in Women

Heart failure (HF) is the leading cause of hospital admission in the United States, with women comprising almost half of hospitalized patients with HF.[4] The etiology of HF has been shown to have significant differences by sex. Women are more likely to have HF with preserved ejection fraction and less likely to have CAD as the primary etiology of HF.[38] Moreover, other forms of cardiac impairment are exclusively (eg, peripartum cardiomyopathy) or predominantly (eg, apical ballooning syndrome) seen in women. Disease presentation may likewise vary among men versus women, as may patterns of therapy and quality of care.[39,40]

Women have been under-represented in many major HF trials. As a result, significant uncertainty exists about the effectiveness of HF therapies in this population.[39,41] The summaries included in this section describe gender-specific findings related to the medical management of HF with preserved ejection fraction, use of mechanical circulatory support in advanced HF, and use of primary prevention therapies including implantable cardioverter defibrillators.

Should Women Receive Left Ventricular Assist Device Support? Findings from the Interagency Registry for Mechanically Assisted Circulatory Support

Summary: Small studies have reported worse outcomes and more adverse events among women after implantation of a mechanical circulatory support device as compared with men. To further evaluate sex-related differences in outcomes after device placement, the authors included 401 women and 1535 men from 89 institutions undergoing implantation of a left ventricular assist device (LVAD) entered into the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database between June 23, 2006, and March 31, 2010. Seventy-eight out of 401 women (19%) and 402 out of 1535 men (26%) received pulsatile flow devices. With a mean follow-up of 7 months, 67 females (17%) and 250 males (16%) died. The 1-year survival after LVAD implantation was 70% for women and 72% for men with pulsatile-flow devices and 83% for both men and women with continuous-flow devices. There were no statistically significant differences in mortality based on device type. There were also no statistically significant differences in time to first infection, bleeding events, or device malfunction. However, female sex was associated with an increased hazard of a first neurologic event (adjusted HR 1.44; CI, 1.05–1.96).

Conclusion: Comparable efficacy of LVADs in women relative to men and improved mortality rates after either pulsatile- or continuous-flow devices in both sexes are reassuring for the future indications of LVADs. However, given the increased hazard of a first neurologic event among women, a sex-specific study of issues related to thrombosis and bleeding in persons with LVADs, such as that related to the phenomenon of acquired von Willebrand factor deficiency, will be worth further investigation. In addition, greater understanding will be needed to explain why women comprised less than 20% of all LVAD implantations to prevent possible discrimination related to sex.[42]

Important Differences in Mode of Death Between Men and Women With HF Who Would Qualify for a Primary Prevention Implantable Cardioverter-Defibrillator

Summary: Recent studies have shed light on the uncertain benefits received by women as compared with men who undergo treatment with an implantable cardioverter-defibrillator (ICD).[43,44] To understand the possible benefit of ICD therapy in women as compared with men, this study investigates gender differences in modes of death among patients qualifying for ICD therapy based on ACC/AHA/HRS guidelines. The authors studied patients with ambulatory HF with predominantly left ventricular systolic dysfunction from five randomized trials and HF registries. In all, 8377 eligible patients (20% women) met inclusion criteria. Total mortality over a median follow-up of 2.4 years was 26.3% for all patients, with women having a mortality rate of 22.6% versus 27.2% among men. After age adjustment, women had significantly lower rates of all-cause mortality (HR=0.76, CI, 0.68–0.85), sudden death (HR=0.69; CI, 0.58–0.83), and mortality not attributable to sudden death or pump failure (HR=0.73; CI, 0.60–0.90). However, mortality from pump failure alone was similar between sexes (HR=0.95; CI, 0.78–1.14). Overall lower rates of mortality among women persisted after adjustment using the Seattle Heart Failure Model.

Conclusion: Although study results show that women with HF are less likely to die of sudden cardiac death compared with men, these findings do not indicate that ICD therapy should be withheld from women absent further prospective trials designed to test this hypothesis. It is also important to note that data used for this study were derived from a combination of randomized trials with different endpoints as well as HF registries. Improved targeting of ICD therapy may be better obtained by assessment of the underlying cause of systolic dysfunction or assessment of the degree of myocardial fibrosis.[45,46]

Trends in Use of ICD Therapy Among Patients Hospitalized for HF: Have the Previously Observed Sex and Racial Disparities Changed Over Time?

Summary: Previous studies have demonstrated underuse of implantable ICD implantation among patients with HF as well as discrepancies in use based on sex and race.[47–49] This study evaluated the rate of ICD implantation over time among 11 880 patients ≥65 years old of age with a history of HF and LVEF ≤35%. Patients were potentially eligible for ICD therapy and were enrolled in the Get With the Guidelines-Heart Failure (GWTG-HF) program from 2005 through 2009. GWTG-HF records were matched with Medicare claims data. The study also analyzed temporal changes in ICD implantation. Results were stratified by sex and race. Overall, 4739 (39.9%) of patients received an ICD within the study period. ICD use increased from 30.2% to 42.4% between 2005 and 2007 and then remained unchanged from 2008 to 2009. A significant increase in ICD therapy was observed over time in all sex and race groups, with the greatest increase in blacks. The adjusted OR for ICD use comparing blacks versus whites increased from 0.79 (95% CI 0.60–1.03) in 2005–2007 to 0.95 (0.73–1.23) in 2009. However, the adjusted OR for ICD implantation in women versus men decreased from 0.65 (0.52–0.81) in 2005–2007 to 0.63 (0.50–0.78) in 2009.

Conclusion: Quality improvement via GWTG-HF was associated with an overall increase in ICD usage along with the elimination of racial disparities in ICU implantation between blacks and whites over time.

However, sex disparities persisted, as women remained significantly less likely than men to receive ICD therapy. These findings raise questions as to whether imbalances in ICD implantation by sex are due to less frequent consideration of ICD use in women or the more frequent decision among women patients to forgo device implantation. Study results also raise the question of whether clinical practice has more often responded to racial rather than sex-based disparities in care. Importantly, it is unknown whether study findings are reproduced at other centers, as the hospitals participating in the GWTG-HF quality improvement program are more likely in theory to adhere to HF guidelines.[50]

Sex Differences in Clinical Characteristics and Outcomes in Elderly Patients With HF and Preserved Ejection Fraction: The Irbesartan in Heart Failure With Preserved Ejection Fraction Trial

Summary: Previous study of sex differences in outcomes associated with HF and preserved ejection fraction (HFPEF) have been limited by retrospective design,[51] relative under-representation of women, and concerns that patients were not representative of those seen in population-based cohorts.[52] The authors therefore examined data from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial, the largest prospective intervention study to date in HFPEF. I-PRESERVE included a sample population of 60% women with characteristics similar to that described in population-based epidemiologic studies.[53,54] Analysis of sex differences in baseline characteristics and outcomes found that women were more likely to have obesity, chronic kidney disease, and hypertension and were less likely to have CAD compared with men. During a mean follow-up of 49.5 months, women were less likely to die (risk ratio [RR] 0.70; 95% CI, 0.59–0.83) or be hospitalized for any cause (RR 0.77; 95% CI, 0.66–0.89) even after adjustment for demographic characteristics, comorbidities, and clinical factors. These sex-related differences in risk were modified by the presence or absence of several comorbidities in additional analyses for interaction. For example, the improved risk profile among women relative to men tended to disappear in the presence of atrial fibrillation or chronic kidney disease.

Conclusion: These results from a large, prospective, and high-quality database indicate that although HFPEF is more common among women, men may in fact require more intensive or differential follow-up, as they have a higher likelihood of adverse events In addition, effect modification by atrial fibrillation and chronic kidney disease suggests that these conditions may merit special attention as potential causes of destabilization among women with HFPEF as compared with men with this common clinical syndrome.[55]

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