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Advances in Cardiovascular Health in Women over the Past Decade: Guideline Recommendations for Practice

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Abstract

Cardiovascular disease (CVD) remains the number one cause of death in women. It is estimated that 44 million women in the United States are either living with or at risk for heart disease. This article highlights the recent significant progress made in improving care, clinical decision-making, and policy implications for women with CVD. We provide our perspective supported by evidence-based advances in cardiovascular research and clinical care guidelines in seven areas: (1) primary CVD prevention and community heart care, (2) secondary prevention of CVD, (3) stroke, (4) heart failure and cardiomyopathies, (5) ischemia with nonobstructive coronary artery disease, (6) spontaneous coronary artery dissection, and (7) arrhythmias and device therapies. Advances in these fields have improved the lives of women living with and at risk for heart disease. With increase awareness, partnership with national organizations, sex-specific research, and changes in policy, the morbidity and mortality of CVD in women can be further reduced.

Keywords: cardiovascular health, health disparity, stroke, coronary artery disease, heart failure, arrhythmias

Introduction

ALTHOUGH CARDIOVASCULAR DISEASE (CVD) remains the leading cause of death of women, there have been many important advances in research, clinical care, and guideline updates over the past 10 years. This perspectives article was prepared following a White House series entitled, ''Making Healthcare Better: Cardiovascular Health'' held September 9, 2016. *WomenHeart*: The National Coalition for Women with Heart Disease, worked with the White House and the American Heart Association (AHA) to invite panelists representing patients, providers, and hospitals to discuss the impact of heart disease on individuals, families, communities, and the healthcare system. Federal officials, over 50 *WomenHeart Champions* (women living with heart disease), WomenHeart's Board and Scientific Advisory Council members, and heart health advocates highlighted achievements in heart health for women during this important meeting. We herein summarize for medical professionals and women's health specialists, key accomplishments in women's heart care over the past decade and provide current practice guideline-directed medical therapy recommendations, including Class I (recommended therapies) and Class III (therapies not recommended due to no benefit and possible harm).

Background

It is estimated that 44 million women in the United States are either living with or at risk for heart disease.[1] This article highlights the significant progress made in improving care, clinical decision-making, and policy implications for women with CVD. We provide our perspective supported by evidence-based advances in cardiovascular research, and guided by both the quantity and high-quality science in seven areas: (1) primary CVD prevention and community heart care, (2) secondary prevention of CVD, (3) stroke, (4) heart failure and cardiomyopathies, (5) ischemia with

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nonobstructive coronary artery disease, (6) spontaneous coronary artery dissection, and (7) arrhythmias and device therapies. Advances in these fields, among others, are improving the lives of women living with and at risk for heart disease and offering hope for a future in which mortality from CVD in women continues to decline. Similarly, sex-specific statements and guidelines for practice provide opportunities for increasing awareness of CVD in women and improving women's healthcare.

Primary CVD Prevention, Awareness, and Comprehensive Heart Care

Cardiovascular (CV) death remains the leading cause of mortality in women.[2] Awareness of CVD in women has increased from 24% in 1997 to 56% in 2012 due to media attention, government support, education and national organizations such as *WomenHeart*, the AHA, and the American College of Cardiology (ACC).[3] Although awareness has improved, CVD continues to present a serious threat to the health of women due, in part, to the prevalence of traditional risk factors, including obesity (159.2 million Americans; 49% women),[2] hyperlipidemia (LDL-cholesterol ≥130 mg/dL; 73.5 million Americans; 53% women),[2] and diabetes mellitus (21.1 million Americans, 50% women).[2] Advances in science over the past decade include greater recognition of nontraditional risk factors for CVD, including autoimmune disorders, obstructive sleep apnea, and radiation-induced myocardial injury.[4] Pregnancy-associated conditions such as gestational diabetes and hypertension, preeclampsia, and eclampsia are now also recognized as additional risk factors for the development of CVD.[5–7] Most importantly, comprehensive preventive healthcare has now been proven to be effective for reducing CV risk factors in women.[8–14] As a result, many tertiary hospitals have a women's heart center.

The efficacy of comprehensive heart care programs for increasing awareness and improving prevention, outcomes, and CVD profiles has been clearly demonstrated.[9,10,12] Similarly, community-based approaches for risk prevention and management of cardiovascular risk factors are critical to address health disparities and empower communities to adopt heart-healthy lifestyles. The efficacy of model systems for CVD risk prevention has been shown for several minorities, including Latinas and African American women in community organizations.[8,11,13,14] In addition, use of a systems approach to community engagement can increase awareness, modify risk behaviors, improve clinical risk profiles, and reduce serum inflammatory CV risk markers in high-risk women.[13] Furthermore, for women with the greatest knowledge gaps, including those in rural communities, a brief educational and awareness interaction by a health professional in the course of a clinical encounter can result in significant knowledge gains.[13] Therefore, research demonstrating effectiveness of culturally relevant and community participatory models for raising awareness of CVD risk and therapeutic lifestyle changes is an essential tool for empowering women to initiate primary prevention of their leading killer.

Recommendations for practice

- AHA/ACC effectiveness-based guidelines for the prevention of cardiovascular disease in women[15]:
  - Avoid tobacco smoke, engage in aerobic activity, eat healthy foods (fruit, vegetables, whole grain, high fiber, and fish), control blood pressure with goal <120/80 mmHg, and maintain good lipid profile (Class I).
  - No hormone therapy or selective estrogen receptor modulators for prevention of CVD (Class III).
  - No antioxidant vitamin supplements for CVD prevention (Class III).
  - No aspirin for primary prevention of myocardial infarction (or stroke) in healthy women age <65 (Class III).
- AHA/ACC guideline on the assessment of cardiovascular risk[16]:
  - Race- and sex-specific Pooled Cohort Equations should be used to predict 10-year risk of atherosclerotic CVD event in blacks and non-Hispanic whites 40–79 years old, Class I.
  - Routine measurement of carotid intima-media thickness for risk assessment of atherosclerotic CVD is not recommended, Class III.
- AHA consensus statement on the use of noninvasive cardiac testing in women with suspected ischemic heart disease[17]:
  - Summarizes diagnostic accuracy in women, risk stratification and risk scores, cardiorespiratory fitness, chronotropic/heart rate/blood pressure and ST segment response, application of specific diagnostic studies, radiation exposure, radiation dose-reduction techniques, testing in women with functional disabilities, and myocardial perfusion imaging with positron emission tomography (PET) or magnetic resonance imaging (MRI).

Secondary Prevention of CVD

In the United States, there is a high prevalence of CVD and its risk factors as evidenced by 80 million Americans with hypertension (52% women), 15.5 million Americans with coronary heart disease (43% women), 5.5 million Americans with heart failure (53% women), and 6.6 million Americans with stroke (55% women). Over the last decade, there has been a decline in cardiovascular death in women. However, the global burden remains high and CVD is the leading cause of death in women with mortality higher than cancer, diabetes mellitus, and chronic lower respiratory disease combined.[2]

Most secondary prevention of CVD includes the use of pharmacotherapy (*e.g.*, aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors) and recommendations for therapeutic lifestyle therapy, including weight management, physical activity, and tobacco cessation. Since 2008, a few sex-specific studies have focused on effectiveness of drugs, side effects from medications, and utilization of guideline therapy in women with CVD. For example, studies have shown that aspirin reduces cardiovascular mortality in postmenopausal women with stable CVD[18] and statins reduce CV events and all-cause mortality.[19] Despite these known benefits, women often receive less aggressive care than men.[20] The reason remains unclear but may be due to poor compliance with and tolerance to drugs such as statins[21] and/or underutilization of these therapies by health professionals in women.[20]

Cardiac rehabilitation is a cost-effective and multidisciplinary intervention that aims to reduce coronary risk factors and optimize patients' physical and psychological function. It

is recommended for those who recently had a myocardial infarction, revascularization therapy (surgical or percutaneous), stable angina, symptomatic peripheral vascular disease, chronic heart failure, heart or heart/lung transplantation, and cardiac valve replacement or repair. Despite the proven hemodynamic and survival benefits, gender disparities exist and women are less likely to be referred and less likely to attend cardiac rehabilitation when compared with men. Minority women are especially affected and often have financial barriers.[22,23] Important steps in broadening the referral rate for all patients include educating eligible patients while hospitalized regarding the benefits, evaluating inpatients to determine eligibility, educating health professionals on guideline recommendations for cardiac rehabilitation, and utilizing all healthcare providers (nurses, physicians, physical therapist, dieticians, and clinical exercise physiologist) to increase referral and participation rates to outpatient cardiac rehabilitation centers.[24]

Recommendations for practice

- AHA scientific statement for the management of acute myocardial infarction in women[25]:
  - Percutaneous coronary interventions for ST-segment elevation myocardial infarctions (STEMI) are preferred for women over thrombolytics for revascularization.
  - Coronary stenting of target vessel during STEMI is preferred over angioplasty.
  - No sex-specific recommendations on coronary artery bypass grafting for STEMI.
  - Early invasive strategy should be pursued for high-risk women with non-STEMI.
  - Aspirin usage to reduce risk of recurrent ischemic events is recommended.
  - Same pharmacologic therapy for women and men with non-STEMI and STEMI.
  - Smoking cessation and cardiac rehabilitation are recommended for women.
- AHA/ACC guideline for the management of patients with non-ST elevation acute coronary syndromes.[26]
  - Women with non-ST elevation acute coronary syndrome should be given the same treatment as men, but may need dose adjustment for weight and renal function to reduce bleeding risk from antiplatelet and anticoagulation therapy.
  - Women should undergo early invasive strategy for treatment of non-ST elevation acute coronary syndrome if they had elevated serum troponin levels.

Stroke in Women

Stroke is the third leading cause of death for women in the United States. Mortality rates have declined over time; however, women have had less reduction in age-adjusted stroke mortality than men.[2] A recent study noted women to be less likely than men to have traditional stroke symptoms such as focal neurologic deficits. Mental status changes were the most common presentation in women.[27] Sex differences in stroke risk factors included older age, hypertension, atrial fibrillation, congestive heart failure, preeclampsia, pregnancy-related hypertension, and metabolic syndrome in women, while cardiovascular disease, hyperlipidemia, and tobacco usage were more likely stroke risk factors in men.[2,28–30] Sex disparities in treatment have also been noted. Women are less likely than men to receive aspirin, statins, or thrombolytics and more likely to have a delay in care.[29–31] Women have also been noted to be less independent, more disabled, and have a higher likelihood of being discharged to an assisted living facility after a stroke than men.[32–34] Therefore, quality of life and functional status after a stroke are often worse in women than men.

Recommendations for practice

- AHA and American Stroke Association (ASA) guidelines for prevention of stroke in women[28]:
  - Low-dose aspirin from 12th week of gestation until delivery for primary stroke prevention in pregnant women with hypertension (Class I).
  - Calcium supplementation during pregnancy to prevent preeclampsia for patients with calcium intake <600 mg/day (Class I).
  - Severe hypertension in pregnancy should be treated with therapy deemed safe and effective (methyldopa, labetalol, nifedipine) with consideration of maternal/fetal side effects (Class I).
  - Laboratory testing (complete blood count, chemistry, prothrombin time, activated partial thromboplastin time) for patients suspected of having cerebral venous thrombosis (CVT) (Class I).
  - Screening for prothrombotic conditions for patients with CVT (Class I).
  - Full anticoagulation therapy for women with CVT during pregnancy and continuing >6 weeks postpartum (Class I).
  - Blood pressure measurement before oral contraceptives (OCs) (Class I).
  - OCs may be harmful with a history of thromboembolic events or smoking (Class III).
  - Not useful to screen for prothrombotic mutations before OCs (Class III).
  - No hormone therapy in postmenopausal women for stroke prevention (Class III).
  - Healthy lifestyle for women with CVD risk factors (Class I).
  - Active screening for AF and age-/sex-specific risk stratification tools when determining management to prevent stroke (Class I).
  - New anticoagulation therapy as alternative to warfarin in women with AF and risk factors for stroke except for prosthetic heart valves, severe renal failure, and advanced liver disease (Class I).
  - No anticoagulation for AF when <65 years of age with no other risk factors for stroke (Class III).
  - Assessment for CVD risk factors and initiate primary prevention for women with asymptomatic carotid stenosis (Class I).
  - Carotid endarterectomy (CEA) for women with transient ischemic attack (TIA) or stroke <6 months and ipsilateral 70%–99% carotid stenosis (Class I).
  - CEA for women with TIA or stroke and 50%–69% ipsilateral carotid stenosis if surgical risk is <6% (Class I).

- Aspirin for women who undergo CEA (Class I).
- Clopidogrel as substitute for aspirin if deemed high risk for stroke (Class I).

Heart Failure and Peripartum Cardiomyopathy

There are 5.7 million Americans with heart failure and about 50% of them are women.[2] For more than a decade we have known that women with heart failure are more likely to be older, have hypertension, and have heart failure with preserved ejection fraction (HFpEF) when compared to men. Women are also less likely than men to have coronary artery disease as the underlying cause of their heart failure. Survival from heart failure is better for women than men based on population studies that included patients with reduced and preserved ejection fraction.[35] Over the last decade, there have been several advancements for women with heart failure, including more sex-specific data on the impact of heart failure, research focused on peripartum cardiomyopathy, and studies focused on the higher prevalence of HFpEF in women.

Advances in the heart failure field include more sex-specific data in heart failure cohorts,[36–38] improved usage of guideline therapy for women,[39] and sex differences in response to medical/device therapy.[40–44] In 2009, we learned from the Cardiovascular Health Study that women compared to men ≥65 years old have better survival rates.[38] In-hospital mortality for patients admitted with acute decompensated heart failure was very low (<3%) with no significant sex differences.[36] However, for as yet unclear reasons, women with end-stage heart failure awaiting heart transplantation had worse survival rates than men.[37]

Sex-specific data for heart failure therapy over the last decade included new and previously used medical/device therapy. During this time period, there was FDA approval of sacubitril/valsartan for symptomatic heart failure with ejection fraction ≤40% and FDA approval of two continuous-flow left ventricular assist devices (HeartMate II and HeartWare) whose smaller size make them suitable for a wider range of patients, including women and those of smaller stature. In a subgroup analysis of the sacubitril/valsartan versus enalapril study (PARADIGM-HF), women taking sacubitril/valsartan had reduced cardiovascular death and heart failure hospitalization compared to the control.[41] As for left ventricular assist devices, data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) showed no sex difference in survival but a higher risk of stroke in women compared to men even after adjustment for many confounding factors, including type of device.[40]

Data from the Registry to Improve the Use of Evidence-Based Heart Failure Therapies (IMPROVE HF) showed similar clinical effectiveness for both women and men receiving biventricular pacemakers.[43] A meta-analysis demonstrated that biventricular pacemakers had additional survival/hospitalization benefits in women with left bundle branch block and QRS 130–149 ms but not men with similar electrocardiography findings.[44] Multiple implantable cardioverter–defibrillator (ICD) studies showed no sex differences in survival.[43] However, Santangeli et al. noted in a meta-analysis that women were less likely than men to receive appropriate ICD firings for ventricular fibrillation or rapid ventricular tachycardia (VT). Therefore, the true benefit of an ICD in women appeared less than men.[42] Supporting this was a study by Rho et al. noting women to have a lower rate of sudden death when compared to men.[45] Finally, an exercise trial called HF-ACTION noted a reduced combined endpoint of death and hospitalization with exercise training in women with heart failure and reduced ejection fraction.[46] Exercise duration was the strongest cardiopulmonary stress test predictor for death in women, while peak oxygen consumption was the best predictor in men.[47]

Peripartum cardiomyopathy

Peripartum cardiomyopathy is a rare complication of pregnancy with the development of left ventricular systolic dysfunction in the peripartum period. It is estimated to occur in 1 of 7,500 pregnancies in the United States. Known risk factors include age ≥30 years, hypertension, preeclampsia/eclampsia, multiple births, and African American race. Over the last decade, we have learned that anemia, reactive airway disease, autoimmune diseases, and drug abuse are additional risk factors.[48] In 2012, the first prospective study (IPAC) in the United States enrolled 100 women diagnosed with peripartum cardiomyopathy within 13 weeks of delivery. In this study, 72% women recovered cardiac function over 12 months and 13% had persistent ejection fraction <35% and/or a major event (death, heart transplantation, or left ventricular assist device). Risk factors for persistent cardiomyopathy were black race, late presentation of heart failure after delivery, initial ejection fraction <30%, and significant dilation of the heart at initial diagnosis (left ventricular end diastolic dimension ≥6.0 cm).[49] Genetic analysis identified a link between black race and polymorphisms, more common among women with persistent left ventricular systolic dysfunction.[50] Finally, in a larger peripartum study ($n = 172$) that included the IPAC participants, about 15% of peripartum cardiomyopathy patients shared genetic mutations with women and men who had idiopathic dilated cardiomyopathy.[51]

Heart failure with preserved ejection fraction

The prevalence of HFpEF is increasing according to a population study published in 2011.[52] It remains a disease more common in women and associated with comorbidities such as hypertension, chronic obstructive lung disease, and diabetes mellitus.[53] Natriuretic peptides are biomarkers used to help diagnosis acute heart failure episodes when the cause of shortness of breath is unclear. Serum levels are lower in HFpEF compared to heart failure with reduced ejection fraction and higher in women than men for any given ejection fraction.[53] There remains no specific therapy for HFpEF beyond diuretics and treatment for hypertension.[54]

Recent pathologic data have shown that HFpEF patients have more cardiac hypertrophy, more cardiac fibrosis, and lower microvascular density when compared to control.[55] The low microvascular density called microvascular rarefaction and the presence of fibrosis supported a hypothesis that HFpEF was due to coronary microvascular inflammation. This new paradigm, based on many national and international studies, suggested that chronic inflammation from comorbidities such as diabetes mellitus resulted in generation of reactive oxygen species that altered nitric oxide-cyclic GMP-protein kinase G signaling. This in turn lead to endothelial dysfunction, myocardial fibrosis and stiffness, and

myocardial hypertrophy.[56] Supporting this hypothesis was a study noting that inflammatory markers such as interleukin-6 and tumor necrosis factor-alpha were strongly associated with the development of HFpEF.[57] However, more research is needed to understand the pathophysiology since an exercise tolerance study in HFpEF failed to show a change in peak oxygen consumption with administration of a phosphodiesterase inhibitor, a drug that improves the nitric oxide-cyclic GMP-protein kinase G signaling.[58]

Recommendations for practice

- ACC/AHA updated heart failure guidelines provide recommendations and relevant information regarding women[54,59]:
  - Aldosterone receptor antagonists contraindicated if serum creatinine is greater than 2.0 mg/dL in women.
  - More women than men have HFpEF and Takotsubo cardiomyopathy (broken-heart syndrome).
- Heart Failure Society of America's consensus statement summarizes available heart failure research in women and addresses the limitations in our current sex-specific data.[60]

Ischemia with Nonobstructive Coronary Artery Disease

Chest pain in the absence of obstructive coronary artery disease (CAD) still remains an underrecognized and underdiagnosed condition. Women are more likely than men to have chest pain associated with ischemia on stress testing and no significant coronary artery disease by cardiac catheterization. The true prevalence is unknown, but based on earlier research, about 50% of women undergoing cardiac catheterization for ischemia have nonobstructive disease compared to only 17% of men.[61] This is of clinical significance as symptomatic women with ischemia and nonobstructive (<50% stenosis) coronary artery disease have a higher mortality than asymptomatic women with no known coronary heart disease. Based on the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study cohort, 5-year annualized cardiovascular events (myocardial infarction, heart failure hospitalization, stroke, cardiac death, and all-cause death) in women with nonobstructive symptomatic coronary artery disease and ≥4 cardiac risk factors (smoking, diabetes mellitus, dyslipidemia, obesity, hypertension, and family history of coronary artery disease) were 25.3% compared to 6.5% in asymptomatic women ($p = 0.003$).[62] Thus, ischemia with nonobstructive coronary artery disease is a concern and women should be properly counseled that they may still have cardiac ischemia and need additional workup despite obstructive coronary disease not being demonstrated by cardiac catheterization.

The pathophysiology for ischemia and nonobstructive coronary artery disease is under investigation, but the findings of several recent studies have contributed to our understanding of this disease. Intravascular ultrasound analysis has demonstrated that the majority of women with nonobstructive coronary artery disease have significant atheroma within the vessel wall. Traditional cardiovascular risk factors such as age, hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease, and hormone therapy correlated with atheroma burden.[63] In a subgroup of women, abnormal coronary reactivity was predictive of cardiovascular events (*i.e.*, higher risk of death, nonfatal myocardial infarction, nonfatal stroke, and heart failure hospitalization).[64] Therefore, coronary microvascular dysfunction was associated with poor outcome and remains important to recognize. Additional options for noninvasive evaluation for women with chest pain but no obstructive CAD include cardiac MR stress testing to assess for subendocardial ischemia or cardiac myocardial perfusion PET imaging, which may provide information on coronary flow reserve abnormalities due to microvascular ischemia.[65]

Other predictors of mortality in women with chest pain and nonobstructive coronary disease include triglyceride/high-density lipoprotein (HDL) ratio even after adjusting for possible confounders.[66] In another study using the WISE database and a severity score derived from angiographic analysis, Sharaf et al. demonstrated a progressive nonlinear increase in 10-year cardiovascular death or myocardial infarction based on the severity of the coronary artery disease.[67]

Recommendations for practice

- No guidelines for optimal therapy exist because of insufficient research in this field.
- Experts recommend traditional antianginal therapy and drugs to reduce oxidative stress, improve endothelial dysfunction (angiotensin-converting enzyme inhibitors, aspirin, statins, and biguanides), and manage ischemia. Also suggest tricyclic agents to improve chest pain control.[61]

Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection (SCAD) is a nonatherosclerotic cause of acute coronary syndrome in which obstruction of a coronary lumen is secondary to dissection or intraluminal hematoma and not plaque rupture. SCAD appears in less than 5% of patients undergoing coronary artery catheterization and is more common in young women.[25] The largest registry of SCAD patients in the United States is the Mayo Clinic Virtual Registry and DNA Biorepository established in 2011 and organized initially by a *WomenHeart Champion* through the use of social media.[68,69] Extracoronary vascular abnormalities, such as fibromuscular dysplasia, are common in patients with SCAD.[70] In-hospital mortality is low, but patients are at risk for recurrence and major adverse cardiac events.[68,71]

Multiple risk factors have been associated with SCAD such as extreme emotional stress, extreme exertion, pregnancy, and fibromuscular dysplasia.[69] Traditional cardiovascular risk factors such as obesity, diabetes mellitus, hyperlipidemia, and tobacco are less likely to be present.[68,70] Patients often present with an acute coronary syndrome in their fourth decade of life.[71] The diagnosis is made at the time of coronary angiography. The left anterior descending artery is the most common involved vessel[71] with about 23% of SCAD patients having multivessel SCAD.[68] Hallmark angiographic features include corkscrew appearance (78% vs. 17% in controls, $p < 0.05$) of the coronary vasculature. Other findings include extracoronary vascular abnormalities such as fibromuscular dysplasia (80%), extracoronary artery dissection (8%), aneurysms (4%), and tortuous carotid arteries (5%).[70]

Recommendations for practice

- No guideline-directed therapies for SCAD patients exist.[25]
- Experts recommend conservative therapy and nonpercutaneous intervention for acute coronary syndromes when possible, given the information below.[71]
  - Percutaneous coronary interventions have a high failure rate with risk of propagation of the coronary artery dissection.
  - Coronary artery bypass graft surgeries have a high failure rate with only 24% of patients having patent graft vessels, 3.5 years following revascularization.

Arrhythmias and Device Therapy

Sex differences in cardiac electrophysiology can substantially affect the epidemiology, presentation, and prognosis of various arrhythmias as well as their management. Women have higher resting heart rates, longer QT intervals (which increase their risk for drug-induced torsades de pointes VT), less clear survival benefits with ICDs and significantly underutilization of devices in women[72] despite recent studies suggesting women may even have a better response to cardiac resynchronization therapy (improved survival), reduced numbers of hospitalizations, and more robust reverse ventricular remodeling when compared to men.[44,73] Over the last decade, there have also been several advancements for women with atrial fibrillation (AF) and ablation therapy although women remain grossly underrepresented in landmark device trials.

Atrial fibrillation

AF currently affects more than five million Americans and is expected to reach a prevalence of nearly 16 million in the United States by 2050.[74] AF is more common in men, but after age 75, almost 60% of people with AF are women. Moreover, women are at higher risk for both stroke and death from AF, independent of other risk factors. The Stroke Prevention in AF and Framingham Heart Studies demonstrated this higher risk in women and, consequently, the CHADS-VASc scoring systems included ''female gender'' as an important parameter for stroke risk assessment.[75–77] Studies have shown that women are more likely than men to experience symptomatic AF, a higher frequency of recurrences, and significantly higher heart rates during AF. Despite this, treatment for AF is less aggressive in women than men, with women less likely than men to receive anticoagulation, ablation procedures, rhythm control, and electrical cardioversion despite similar success rates with cardioversion to normal sinus rhythm. Over the last decade, there has been more targeted research in women and an increased awareness of sex differences in the clinical presentation of AF.[78,79]

Anticoagulation is a key component in the management of AF, given the substantially increased risk of associated thromboembolic events. The introduction of the novel oral anticoagulants had perhaps one of the greatest impacts in this area. Dabigatran, the first to receive FDA approval in 2010, was studied in the RELY trial and showed no sex interaction with outcomes or efficacy. Similarly, rivaroxaban, apixaban, and edoxaban were evaluated in the ROCKET-AF, ARISTOTLE, and ENGAGE-AF trials, respectively, and none reported any differences in sex-related efficacy or adverse events.[80–82] The overall bleeding risk as a result of anticoagulation therapy is similar between women and men although women benefit from a greater reduction in thromboembolic events.[83,84] The availability of these new drugs provides an opportunity to further reduce strokes in women with AF.[85]

Radiofrequency catheter ablation is a therapeutic option for AF as first-line treatment or for patients failing arrhythmia control.[86] Several studies analyzed sex differences in outcomes and complications after AF ablation, with inconsistent results. A European cohort study found no sex differences regarding freedom from AF following ablation.[87] In contrast, a larger U.S. cohort study concluded that women had higher complication rates postprocedure.[82] However, studies consistently demonstrate that women are referred for ablation much later in the course of their AF than men, and referral rates are lower.[82,88] Earlier studies have not produced consistent findings with respect to sex differences in longer term procedural success. In 2015, the largest AF ablation study in the United States examining procedural outcomes by sex found that women were more likely to be rehospitalized for AF within 1 year after an ablation procedure but less likely to undergo cardioversion or repeat ablation.[89]

Implantable cardioverter defibrillators

Sudden cardiac death (SCD) accounts for about 25% of the 17 million deaths due to CVD every year in the world. Heart failure with reduced left ventricular ejection fraction is a major risk factor for SCD due to the increased association of ventricular arrhythmias. Studies have previously shown that women are at lower risk for SCD compared with men.[90] Data from multiple randomized controlled trials have shown that the use of ICDs has a mortality benefit for both primary and secondary prevention.[91] However, women were markedly underrepresented in these landmark trials. Accordingly, the existence of sex-related differences in outcomes among ICD recipients is still controversial and women are less likely to receive this therapy compared with men.[72]

A recent analysis of the clinical effectiveness of ICD therapy by sex using patients enrolled in IMPROVE HF trial demonstrated that the clinical benefits associated with ICD were similar between men and women. Additionally, there was no significant sex interaction for 24-month mortality.[43] It is important to note that studies of sex differences in clinically meaningful long-term outcomes following ICD placement have been conflicting, largely due to heterogeneity in study design, population, and length of follow-up. Specifically, variable sex differences in mortality have been observed with most recent studies demonstrating either reduced mortality in women or no difference between sexes.[42,90,92,93] More consistently, women have been shown to have higher risk for ICD-related complications.[90,93] In addition, researchers have found that women compared to men with ICD for primary prevention are more likely to have nonischemic cardiomyopathy, less likely to have myocardial scar, and less likely to experience appropriate ICD-delivered therapy.[93–96] Thus, women seem to be the minority of ICD recipients, more likely to have nonischemic cardiomyopathy, and experience higher rates of device-related complications and lower incidence of appropriate therapies compared to men.

Catheter ablation

Among patients with structural heart disease, catheter ablation has been demonstrated in randomized trials to be an effective treatment for VT.[97,98] Similar to primary prevention trials, previous studies of VT ablation have insufficiently enrolled women. Thus, gaps in knowledge persist regarding significant differences in the clinical presentation, electrophysiologic substrate, and outcomes. A recently published large, multicenter study evaluated patients with structural heart disease undergoing VT ablation and found that women had higher rates of VT recurrence long term following ablation versus men despite more favorable baseline clinical characteristics.[99] Although the mechanisms are unclear, there are several potential considerations. Women may be undertreated during ablation since the total ablation time was shorter in women, and clinical VT was more likely to be inducible at the end of ablation, which is a predictor of recurrence.[99,100] In addition, women may receive less therapy before or after ablation. Consistent with this, fewer women were treated with β-blockers or ICDs before ablation. Despite this, a nonsignificant trend toward lower mortality was observed among women following ablation.[99]

Table 1. Summary of Recent Cardiovascular Research in Women

Science fields	*Highlights*
Primary CVD Prevention and Community Heart Care	New risk factors for CVD include gestational diabetes and hypertension, preeclampsia, eclampsia, autoimmune disorders, obstructive sleep apnea, and radiation-induced myocardial injury[4–7] Comprehensive preventive healthcare screening and interventions reduced CV risk factors in women[9,10,12] AHA/ACC sex-specific guidelines published in 2011[15]
Secondary Prevention of CVD	Aspirin and statins reduced mortality in women with CVD[18,19] AHA published in 2016 a scientific statement for the management of acute myocardial infarction in women[25] AHA/ACC 2014 guidelines for non-ST elevation acute coronary syndromes included sex-specific recommendations[26]
Stroke	Risk factors for women included older age, hypertension, atrial fibrillation, congestive heart failure, preeclampsia, pregnancy-related hypertension, and metabolic syndrome[28–30,105] Women frequently presented with mental status changes[27] AHA/ASA published 2014 prevention of stroke in women[28]
Heart Failure and Cardiomyopathies	Women more likely than men to have HFpEF and hypertension[35] Mortality higher in women versus men awaiting heart transplantation[37] Similar survival in women as men with left ventricular assist devices, reduced cardiovascular death/HF hospitalization with sacubitril/valsartan, and reduced death/hospitalization with biventricular pacemakers in women with left bundle branch block and QRS 130–149 ms[40,41,44] Peripartum cardiomyopathy had mostly good prognosis, blacks more likely to have persistent cardiac dysfunction, and genetic mutations identified were similar to other cardiomyopathies[49–51] New HFpEF paradigm for pathophysiology: chronic inflammation from comorbidities caused endothelial dysfunction, myocardial fibrosis, and myocardial hypertrophy[56]
Ischemia with Nonobstructive Coronary Artery Disease	Higher mortality in symptomatic women with ischemia and nonobstructive coronary artery disease than asymptomatic[62] Most women had significant atheroma detectable by IVUS[63] Risk factors same as known for CVD[63]
Spontaneous Coronary Artery Dissection	More common in young women[25] Risk factors: extreme emotional stress/exertion, pregnancy, and fibromuscular dysplasia[69] In-hospital mortality low but risk of recurrence and major adverse cardiac events[68,71]
Arrhythmia and Device Therapies	Higher risk of stroke and death with AF and lower risk of SCD in women vs men[75–77,90] Similar safety and benefit with NOACS for AF[80–83] Efficacy of ablation therapy for AF controversial[87,89] High recurrence rate of VT after ablation in women vs men[99] Inappropriate ICD therapy more likely in women vs men[93]

AF, atrial fibrillation; ACC, American College of Cardiology; AHA, American Heart Association; ASA, American Stroke Association; CV, cardiovascular; CVD, cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; IVUS, intravascular ultrasound; NOACS, novel oral anticoagulants; SCD, sudden cardiac death.

Recommendations for practice

- ACC/AHA updated guidelines on arrhythmias and device therapy recommend clinical management irrespective of sex.

Conclusion and Future Directions

Over the last decade, there were many significant advances for women living with heart disease, including sex-specific research, reporting of sex-specific referral and utilization of therapy, and sex-specific cardiovascular disease management guidelines (Tables 1 and 2). Registries such as IPAC for peripartum cardiomyopathy and the Mayo Clinic's Virtual Registry and DNA Biorepository for SCAD have helped propel the study of cardiovascular conditions that occur primarily or exclusively in women. New risk factor associations have been defined for CVD in women, including autoimmune disorders, obstructive sleep apnea, and pregnancy-associated conditions such as gestational hypertension, gestational diabetes mellitus, preeclampsia, and eclampsia. Community-based CV education and awareness programs have also been demonstrated to improve primary prevention in women, including those at high risk due to race/ethnicity/rurality. Meta-analyses and large studies demonstrated benefit of aspirin and statins for secondary prevention in women and defined the highest risk treatment groups. In addition, cardioembolic events were found to be more likely in women with AF than men, and symptomatic ischemia with nonobstructive disease in women was associated with high plaque burden by intravascular ultrasound and adverse CV outcomes. In concert, advances in our knowledge of epidemiology, pathophysiology, and clinical outcomes have contributed to the issuance of key sex-specific guidelines in CVD for women.

Advances in CVD healthcare for women have also been propelled via unique partnerships between researchers, advocacy groups, and policy makers that have resulted in high-impact actions. One such example is the Society for Women Health Research and *WomenHeart's* ''10 Q Report for Advancing Women's Heart Health through Improved Research, Diagnosis and Treatment,'' presented at a Congressional briefing in 2011. This report summarized the top 10 most important cardiovascular concerns in women.[101] Similarly, responding to the underrepresentation of women and those from ethnic/racial minority groups in clinical trials, in 2012, Congress directed the FDA (Section 907 of the Food and Drug Administration Safety and Innovation Act) to re-evaluate the clinical trial participation and safety and efficacy of drugs, biologics, and devices by sex, race, ethnicity, and age. Specifically, it required the FDA to determine the extent of appropriate analysis required for subgroups to determine safety and effectiveness, FDA applications to include this information, and an FDA plan on how information will be provided to the public, including what will be written on the label for approval.[102] Then, in 2014, the FDA released an action plan consisting of 27 points to enhance the collection and availability of subgroup data, including sex-specific data. These included a plan to work with sponsors to improve the data obtained during applications, education and training of FDA reviewers regarding the importance of subgroup analysis, development of a new women's health research plan to answer specific sex-specific concerns, collaboration with NIH, industry, and other stakeholders to improve enrollment of a diverse population, and improvement in the communication of results with the public.[103] That same year the NIH announced a policy to balance sex as a study variable in *in vitro* and animal studies to further understand sex differences, given the paucity of female cell and animal data.[104]

The advances over the last decade in biomedical research, those facilitated by unique academic/private partnerships, and the efforts of national, professional, patient, and governmental organizations summarized here have significantly impacted research and improved cardiovascular healthcare in women. This momentum should be continued as work still

Table 2. Guidelines and Scientific Statements

Guidelines	*Weblink*
Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: A guideline from AHA[15]	http://circ.ahajournals.org/content/123/11/1243.long
ACC/AHA guideline on the assessment of cardiovascular risk: A report of the ACC/AHA task force on practice guidelines[16]	www.sciencedirect.com/science/article/pii/S0735109713060312
Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: A consensus statement from the AHA[17]	http://circ.ahajournals.org/content/130/4/350.long
Acute myocardial infarction in women: a scientific statement from AHA[25]	http://circ.ahajournals.org/content/133/9/916.long
AHA/ACC guidelines for the management of patients with non-ST elevation acute coronary syndromes: A report of the ACC/AHA task force on practice guidelines[26]	http://circ.ahajournals.org/content/130/25/e344.long
Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the AHA/ASA[28]	http://stroke.ahajournals.org/content/45/5/1545.long
ACCF/AHA 2013 guidelines for the management of heart failure: A report of the ACC/AHA[54]	www.sciencedirect.com/science/article/pii/S0735109713021141
An update of the ACCF/AHA 2013 guidelines for the management of heart failure: A report of the ACC/AHA task force on clinical practice guidelines and the Heart Failure Society of America[59]	www.sciencedirect.com/science/article/pii/S0735109716330248
Toward Sex-Specific Guidelines for Cardiac Resynchronization Therapy?[106]	https://journals.ohiolink.edu/pg_240?::NO:240:P240_JOURNALID:249343592

needs to be done to close remaining gender gaps in CV healthcare through new knowledge, advocacy, community education, and the inclusion of greater numbers of women in clinical trials. Working together, researchers, healthcare professionals, advocates, and women living with heart disease can contribute to further progress in prevention, early detection, accurate diagnosis, and proper treatment for women with or at risk for CVD.

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