Women and Coronary Heart Disease: A Century After Herrick
Understudied, Underdiagnosed, and Undertreated

Nanette K. Wenger, MD, MACC, MACP, FAHA

Among the accolades most valued by a clinical cardiologist is to be selected to deliver the annual James B. Herrick Lecture. This lecture honors the legacy of James Herrick as an icon for the cardiac clinician/scientist. I am enormously grateful to the Council on Clinical Cardiology for this singular recognition.

My choice to address “Women and Coronary Heart Disease: A Century after Herrick” will show that this problem remains understudied, underdiagnosed, and undertreated.

James Herrick
First, to James Herrick and his landmark contributions. As we know, in the 1900s, myocardial infarction was considered a uniformly fatal event, and its etiology was largely unknown. Herrick’s scholarly 1912 presentation to the Association of American Physicians, subsequently published in the Journal of the American Medical Association, highlighted that survival could occur after myocardial infarction, albeit often for only a few days. Buttressed by meticulous autopsy data, he documented coronary artery thrombosis as the mechanism for myocardial infarction. Although dismayed by lack of response from colleagues to this carefully detailed scenario, Herrick continued to study and to publish, advocating treatment with digitalis to enhance myocardial contractility and maintain blood pressure, rather than use of nitroglycerin, which did not perform satisfactorily. Always a mentor, he encouraged Dr Fred Smith to explore the diagnostic potential of the newly available precordial ECG for recognition of myocardial infarction, and he documented coronary artery thrombosis as the mechanism for myocardial infarction. Although dismayed by lack of response from colleagues to this carefully detailed scenario, Herrick continued to study and to publish, advocating treatment with digitalis to enhance myocardial contractility and maintain blood pressure, rather than use of nitroglycerin, which did not perform satisfactorily. Always a mentor, he encouraged Dr Fred Smith to explore the diagnostic potential of the newly available precordial ECG for recognition of myocardial infarction in a living patient, and the rest is history. Herrick’s precise case presentations (incidentally all of male patients) and autopsy confirmation established thrombogenesis as pivotal in myocardial infarction, and the way for antithrombotic therapy, coronary thrombolysis, and percutaneous coronary interventions later in the 20th century.

Teaching and Applying Knowledge
In his 1926 article, “The Clinician of the Future,” in the Journal of the American Medical Association, Herrick cited the usefulness of physicians to society as a whole as the physicians’ reason for existence. He advocated improved training of both general practitioners and specialists and cited need for their mutually helpful relationships. Herrick emphasized that there was no substitute for physical examination and careful documentation of a patient’s medical history, reiterating that clinical medicine should be presented to medical students by a clinician, a practicing doctor. He deplored the overestimation of the value of the instrumental and laboratory components of medicine, indicating that laboratory tests should only be incorporated into the history, symptoms, physical examination, and other scientific data for each patient. Exquisitely relevant today is Herrick’s emphasis on the medical history and physical examination; he urged caution in the reliance on the technology of the day, for him the chest x-ray and the ECG. He challenged dependence on laboratory data, identifying its foibles and urging its use as supplementary.

The following quote, cited by a number of previous Herrick lecturers, is noteworthy. It should serve as a guidepost for the contemporary clinician/scientist: “The true physician must possess a dual personality, the scientific toward disease, the human and humane toward the patient.”

Now, a century after Herrick’s publication, what of women and coronary heart disease (CHD)? Remember that Herrick’s prototype patient was a man past the middle period of life.

A wonderful cartoon from the early 1990s is a fitting introduction to this presentation. The physician, seated across the consultation desk from his female patient, says, “We have studies of fruit flies, mice, hamsters, frogs, monkeys, and men with this condition – but medical research using women as subjects just never occurred to anybody.” Fortunately, the ensuing years have witnessed salutary changes in the research landscape. This article reviews the status of CHD in women at the end of 2011; some milestones, stepping stones, and obstructing boulders on the learning journey; the landmark 2010 Institute of Medicine (IOM) Report on Women’s Health Research; what to do when disease discriminates; the question of whether the woman’s heart beats to the tune of a different drummer; awareness/perceptions among women and physicians of women’s CHD risk; and finally our challenges and opportunities.
Status of CHD in Women 2011

Recent decades have witnessed emerging interest in and consequent research studies of CHD in women, with striking salutary results. Once viewed as a man’s disease, CHD remains the leading cause of mortality for women worldwide, in both industrialized nations and developing economies.4 However, changes in US data show major promise.

The striking improvement in cardiovascular disease (CVD) survival documented between 2000 and 2007,5 with a more prominent decline in cardiovascular mortality for women than men (Figure), was equally attributable to the application of evidence-based therapies of established CVD and to preventive interventions for coronary risk factors. These advances were based on research data and advocacy/awareness initiatives, many generated by the cardiac clinician/scientists in attendance this evening. Nonetheless, since 1984, more cardiovascular deaths continue to occur annually among women than men; coronary deaths in women exceed deaths in women from all forms of cancer combined.

Based on research studies responding to this challenge, emerging data have highlighted important sex differences in the pathophysiology and clinical presentation of CHD in women and sex disparities in preventive interventions and diagnostic strategies, in management of acute coronary syndromes, and in the response to therapies, with consequent adverse outcomes of CHD in women.6 Underuse of guideline-based preventive and therapeutic strategies for women substantially contributes to their less favorable CHD outcomes, but the spectrum of sex-based differences likely reflects both biology and bias.

Milestones, Stepping Stones, and Obstructing Boulders
In a review of CHD in women some years ago, I described the journey to explore the state of the science as characterized by “milestones, stepping stones, and obstructing boulders.”7 Let me enumerate, update, and expand on several of these by using the same construct (Table 1).8–21 Among the milestones were the 1992 National Heart, Lung, and Blood Institute (NHLBI) Conference on Cardiovascular Health and Disease in Women; the 2001 IOM Report Exploring the Biological Contributions to Human Health: Does Sex Matter; the Heart and Estrogen/Progestin Replacement Study (HERS); the Women’s Health Initiative (WHI); the Agency for Healthcare Research and Quality Report on Diagnosis and Treatment of Coronary Heart Disease in Women; the Women’s Health Study; and the NHLBI Women’s Ischemia Syndrome Evaluation (WISE) Study.

It was my privilege to chair the initial milestone, the 1992 NHLBI Conference on cardiovascular health and disease in women.8 It derived from a 1986 NHLBI Workshop that first focused attention on this topic, presenting its challenges to the scientific community. The goals of the conference were to highlight new information appropriate for clinical application and to identify knowledge gaps that impeded optimal cardiovascular care for women.

The next milestone was the 2001 IOM report, “Exploring the Biological Contributions to Human Health. Does Sex Matter?”12 that advocated for sex/gender explorations in all aspects of human health from basic science to clinical applications. This landmark report persuasively argued for evaluation of sex-based differences in human disease and in medical research, with translation of these differences into clinical practice.12

Shortly thereafter, the results of 2 randomized clinical trials transformed clinical care for women: the HERS9 and the WHI hormone trials,10,11 which documented that menopausal hormone therapy did not prevent incident or recurrent CVD in women and increased their risk of stroke. HERS and WHI displaced menopausal hormone therapy as the ubiquitous solution to women’s cardiovascular problems, refocusing attention on established cardiovascular preventive therapies.
In 2003, the Agency for Healthcare Research and Quality Report on the Diagnosis and Treatment of CHD in women, a systematic review of relevant research, concluded that most contemporary recommendations for prevention, diagnostic testing, and medical and surgical treatments of CHD in women were extrapolated from studies conducted predominantly in middle-aged men, with resultant fundamental knowledge gaps regarding the biology, clinical manifestations, and optimal management strategies for women.13,14

The Women’s Health Study15 documented lack of aspirin benefit in preventing myocardial infarction (MI) in women <65 years of age, but rather a stroke benefit for women, in sharp contrast to the Physicians’ Health Study results in men wherein aspirin provided MI but not stroke protection.22

I list as the final milestone the NHLBI WISE Study, which identified myocardial ischemia with adverse clinical outcomes in women in the absence of obstructive disease in the epicardial coronary arteries. This added to the spectrum of CHD in women the concept of microvascular disease, currently an area of intense basic and clinical investigation.18

It is noteworthy that these were milestones predominantly of the past decade. Interspersed were pivotal stepping stones to progress, including sections specifically addressing women in many disease-specific American College of Cardiology/American Heart Association (AHA) Clinical Practice Guidelines, which I will not detail in this presentation, but for which I trust expanding sex analyses in clinical research studies will provide further actionable data. Other stepping stones include the AHA Consensus Statement, “Role of noninvasive testing in the evaluation of women with suspected coronary artery disease”;16 the Women’s Antioxidant Cardiovascular Study, and the Women’s Antioxidant and Folic Acid Cardiovascular Study; the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines; WACS, Women’s Antioxidant Cardiovascular Study; WAFACS, Women’s Antioxidant and Folic Acid Cardiovascular Study; CV, cardiovascular; CVD, cardiovascular disease; CHD, coronary heart disease; NSTE-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction; MI, myocardial infarction; Dx, diagnosis; Rx, treatment; QOL, quality of life; †, indicates increased; ‡, decreased; and →, do not provide.

*Milestone.
†Stepping stone.

Table 1. Women and Coronary Heart Disease Milestones and Stepping Stones

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone Description</th>
<th>Note</th>
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<tbody>
<tr>
<td>1992</td>
<td>NHLBI Conference: CV Health and Disease in Women</td>
<td>* New information → clinical application</td>
</tr>
<tr>
<td>1998</td>
<td>HERS</td>
<td>* Menopausal hormone therapy → secondary prevention</td>
</tr>
<tr>
<td>2001</td>
<td>WHS</td>
<td>* Menopausal hormone therapy → primary prevention</td>
</tr>
<tr>
<td>2003</td>
<td>IOM Report</td>
<td>* Evaluate sex differences in human disease, medical research</td>
</tr>
<tr>
<td>2005</td>
<td>AHRQ: CHD in Women</td>
<td>* Dx, Rx, CHD in women extrapolated from studies in middle-aged men</td>
</tr>
<tr>
<td>2005</td>
<td>WHS</td>
<td>* Aspirin prevents stroke, not MI, in women &lt;65 years of age</td>
</tr>
<tr>
<td>2005</td>
<td>AHA: Noninvasive Testing in Women</td>
<td>† Characteristics informing test choice</td>
</tr>
<tr>
<td>2005</td>
<td>CRUSADE: Women with NSTE-ACS</td>
<td>† ACS prognosis worse in women</td>
</tr>
<tr>
<td>2006</td>
<td>NHLBI WISE</td>
<td>† Importance of microvascular disease in women</td>
</tr>
<tr>
<td>2007/2008</td>
<td>WACS/WAFACS cited in21</td>
<td>† Vitamin E, C, beta carotene → CVD prevention in women</td>
</tr>
<tr>
<td>2008</td>
<td>Get with the Guidelines CAD Database</td>
<td>† Folic acid, vitamin B supplements → CVD prevention in women</td>
</tr>
<tr>
<td>2010</td>
<td>IOM Report: Women’s Health Research</td>
<td>† Progress in ↓ CV mortality</td>
</tr>
<tr>
<td>2011</td>
<td>AHA Women’s CVD Prevention Guidelines</td>
<td>† Pregnancy complications → ↑ CV risk</td>
</tr>
<tr>
<td>2012</td>
<td>AHRQ: CHD in Women</td>
<td>† Systemic autoimmune disease → ↑ CVD risk</td>
</tr>
</tbody>
</table>

See future directions Table 2

NHLBI indicates National Heart, Lung, and Blood Institute; HERS, Heart and Estrogen/Progestin Replacement Study; WHI, Women’s Health Initiative; IOM, Institute of Medicine; AHRQ, Agency for Healthcare Research and Quality; WISE, Women’s Ischemia Syndrome Evaluation; WHS, Women’s Health Study; AHA, American Heart Association; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines; WACS, Women’s Antioxidant Cardiovascular Study; WAFACS, Women’s Antioxidant and Folic Acid Cardiovascular Study; CV, cardiovascular; CVD, cardiovascular disease; CHD, coronary heart disease; NSTE-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction; MI, myocardial infarction; Dx, diagnosis; Rx, treatment; QOL, quality of life; †, indicates increased; ‡, decreased; and →, do not provide.
ability to exercise as major determinants informing the choice of noninvasive testing in evaluating chest pain in women. The recently reported Women’s Study further validated this approach as cost effective.

The Women’s Antioxidant Cardiovascular Study (WACS) and the Women’s Antioxidant and Folic Acid Cardiovascular Study (WAFACS) identified that vitamins E, C, and beta carotene and folic acid and B vitamin supplements, respectively, did not prevent incident or recurrent CVD in women, removing ineffective therapies from preventive regimens.

The report on sex disparities in the management of non-ST-elevation ACS from the CRUSADE Quality Improvement registry identified a worse non-ST-elevation ACS prognosis for women than for men. Women had an increased risk of hospital death, reinfarction, heart failure, stroke, and transfusion. It displayed that women were less likely to receive coronary interventions and, at discharge, despite their high-risk status, were less likely to receive guideline-based prescription of aspirin, angiotensin-converting enzyme (ACE) inhibitors, and statin drugs. CRUSADE challenged whether the adverse outcomes of women with ACS reflected their raised baseline risk, their suboptimal admission and discharge therapies, or both, ie, is this biology or bias?

The Get with the Guidelines CAD Database documented increased ST-segment elevation MI mortality for women, 10.2% in comparison with 5.5% for men, predominantly within the initial 24 hours. During this time, women were less likely to receive early aspirin or β-blocker therapy, and they received less reperfusion therapy and less timely reperfusion.

These data suggest that opportunities exist to decrease sex-based disparities in care and to improve clinical outcomes.

Other stepping stones include the serial AHA Guidelines for prevention of CVD in women. Newly added in the AHA Guidelines 2011 Update is the need to ascertain a history of pregnancy complications, including preeclampsia, gestational diabetes mellitus, and pregnancy-induced hypertension. These abnormalities are responses to the cardiovascular and metabolic stress of pregnancy and appear to be early indicators of cardiovascular risk. Coronary risk factor assessment and surveillance is warranted for such women, and a detailed history of pregnancy complications should be part of the routine cardiovascular risk assessment of all women. Evidence of systemic autoimmune collagen vascular disease, because of its association with increase in relative risk for CVD, should prompt screening for coronary risk factors in women with such conditions.

The obstructing boulders, as viewed today, include not only the disproportionately small National Institutes of Health budget addressing CVD (≈4%), despite the enormous magnitude of the clinical problem, but also the lack of participation of women in randomized clinical trials of CVD and its therapies. Despite their burden of CVD, women remain underrepresented in clinical trials (27% of patients in mixed-sex 1997–2006 National Institutes of Health trials); even when included, women are disadvantaged by absence of sex-specific analyses. In CHD research studies, age and presenting symptom inclusion criteria often reflect male rather than female CHD patterns. Nongovernmental research studies, as well, continue to use male models of CHD and to recruit predominantly male participants.

The 2010 IOM Report on Women’s Health Research

In 2008, at the direction of the US Congress, the Department of Health and Human Services requested the IOM to examine what had been learned from research into women’s health in the past 2 decades, how well new knowledge had been translated into practice, and how well research results had been communicated to healthcare providers and to women. The IOM, in Women’s Health Research: Progress, Pitfalls, and Promise, persuasively details some persisting obstructing boulders, revealing that medical research historically neglected the health needs of women, apart from reproductive concerns. I have previously termed this approach bikini medicine, ie, selective research targeting areas covered by the bikini bathing suit, the breasts and the reproductive system. The IOM noted that women’s health involved 2 aspects: sex differences, ie, the biological factors; and gender differences, those affected by broader social, environmental, and community factors. Women remained underrepresented in the design, conduct, and analysis of research studies. Even in basic science studies of diseases more common in women, there was preponderant use of male animal models.

The IOM report cited that, although major progress had been made in reducing cardiovascular mortality, greater research attention was needed regarding quality-of-life issues for women, ie, functionality, mobility, and promotion of wellness. Also noted were disparities in disease burden among subgroups of women, particularly those women who are socially disadvantaged because of race, ethnicity, income level, and educational attainment. Targeted research was recommended on these subpopulations of women with the highest risks and burdens of disease. The IOM report further identified that lack of analysis and reporting of sex-stratified analyses limited the ability to identify potentially important sex/gender differences, including differences in care. The IOM recommended that journal editors require reports of clinical trials to separately present outcomes for female and male participants. This could enhance the needed translation of women’s health research findings into clinical practice and public health policy and effective communication of research-based messages to women. The IOM Report advocated that federally funded studies include plans to disseminate information to the public, to providers, and to policymakers. It further emphasized that, given the multiple and significant roles that women play in US society, maintaining support for women’s health research would enhance its impact.

What to Do When Disease Discriminates

Displaying contributions of biological differences regarding coronary risk factors, a recent systematic review and meta-analysis involving >2 million people uniformly showed a 25% increased coronary risk among women smokers than men smokers. The disproportionately increased coronary
risk for diabetic women versus diabetic men is well known. However, the proportion of women enrolled in prevention clinical trials inadequately reflects their representation in the US population, raising the potential for bias.

Women constituted only 30% of all patients in the clinical trials used to support the 2007 AHA guidelines for the prevention of CVD in women. Representation of women was higher in primary prevention trials and in international (versus United States only) trials. During a comparable time period, the proportion of women enrolled in European randomized controlled trials of coronary prevention varied from 16% to 25%, despite a female prevalence of CHD similar to that of males in the general population. Although women account for 46% of the US population with CHD, they constituted 25% of participants in CHD prevention trials; sex-specific data were cited in only 31% of primary trial publications.

In numerous clinical settings, women with CHD have more unfavorable outcomes than men. Angina is the major initial and subsequent presentation of CHD among women. In comparison with their male counterparts, women with angina have a doubled morbidity and mortality. Anginal equivalents, the nonchest pain symptoms encountered in both sexes but predominating in women, remain underrecognized and understudied. Women with CHD, and, in particular, women <50 years of age, have a doubled mortality after MI, although in recent years younger women have had larger improvements in hospital mortality after MI than did younger men, narrowing the sex gap. The absolute reduction was 3 times greater in women than in men <55 years of age, suggesting a decrease in treatment-related sex bias.

Despite their greater symptom burden of angina and its consequent morbidity and mortality, and despite their older age and higher risk factor burden, women paradoxically have less severe obstructive coronary disease at elective angiography than do men, a biological difference. Yet the male model of coronary disease, ie, obstructive atherosclerosis of the epicardial coronary arteries, constitutes the basis for most diagnostic and therapeutic strategies for both sexes.

Women with stable ischemic heart disease have more MIs than men do. In a Swedish cohort (2006–2008), women with stable ischemic heart disease had lower rates of aspirin and ACE inhibitor use. More women with stable ischemic heart disease had repeat angiography, whereas fewer women than men had angiography in the setting of ACS and, consequently, less percutaneous coronary intervention and coronary artery bypass grafting (CABG) in comparison with their male counterparts; this is illustrative of gender bias. The absence of obstructive coronary disease appears to account for much of the therapeutic underutilization; the Swedish report documents equivalent ACE inhibitor, β-blocker, aspirin, and statin use in women and men with stable ischemic heart disease once there is an angiographic diagnosis of obstructive coronary disease.

Myocardial ischemia with adverse outcomes, in the absence of obstructive coronary disease, is an emerging paradigm for women. Data derived from the NHLBI WISE study add microvascular disease to the spectrum of myocardial ischemia in women. Insights are needed into the underlying biological mechanism(s) and optimal recognition and therapies for microvascular disease. A recent report addressing mechanisms of MI in women without angiographically obstructive coronary artery disease defined occult plaque disruption with distal embolization of atherosclerotic debris or platelet aggregates and/or vasospasm as potentially etiologic. Plaque rupture and ulceration were common in women with MI in the absence of angiographically demonstrable obstructive coronary disease. Intravascular ultrasound and cardiac MRI may permit the categorization of these mechanisms in women. Women in the MERLIN-TIMI 36 trial of non–ST-elevation ACS were more likely than men to report angina, despite having less obstructive coronary artery disease. They had more ischemic periods recorded on continuous ECG, and ECG ischemia was predictive of an unfavorable outcome.

Additional research is mandatory to define the etiologic features in women with nonobstructive ischemic heart disease, which is likely present in almost half as many women with signs and symptoms of myocardial ischemia as obstructive coronary artery disease is likely to present. Guideline-based therapies of ACS must be instituted irrespective of angiographic anatomy. Comparative effectiveness research is requisite to select optimal strategies to evaluate symptoms of suspected myocardial ischemia in women, addressing both obstructive coronary disease and microvascular etiologies.

Women with MI are more likely than men to have recurrent MI and to be subsequently disabled by heart failure. The Canadian Acute Coronary Syndrome Registry assessed the factors influencing the underutilization of evidence-based therapies in women. Canadian women in this 1999–2003 ACS cohort had higher death rates than men. There were lower rates of ACE inhibitor, β-blocker, and statin use among women, which correlated with older age; the consequences of the disease, particularly congestive heart failure; and physician assessment of the patient’s risk as evidenced by the decision for cardiac catheterization. Despite adjustment for these biasing confounders, female sex remained associated with underutilization of ACS guideline-based therapy with lipid-modifying agents and with ACE inhibitors.

Does the woman’s heart beat to the tune of a different drummer? As noted, women with MI are more likely than men to incur heart failure, but women with heart failure far more frequently than men have intact ventricular systolic function. Effective treatments for this diastolic heart failure syndrome remain elusive, likely accounting for its unchanged prognosis, in contrast to the decrease in hospitalizations and improved survival encountered with systolic heart failure. Women with systolic heart failure and ventricular dyssynchrony preferentially benefit from cardiac resynchronization therapy, yet these procedures are underutilized in women.

The safety and efficacy of cardiovascular devices may differ by sex. Lack of sex-specific data for high-risk cardiovascular devices before their Food and Drug Administration approval is widespread, despite a recent IOM recommendation that all medical products evaluated by the Food and Drug Administration present safety and efficacy data separately for women and men. Women comprised only about one-third of participants in 78 clinical trials of cardiovascular devices between 2000 and 2007, with the proportion of women enrolled unchanged over time. Women have not achieved levels of
enrollment in premarket studies adequate to ensure evidence-based sex-specific recommendations. The Heart Disease Education, Analysis and Research, and Treatment for Women Act (HEART for Women Act), currently introduced in Congress, would mandate sex-specific data reporting, ending these disparities.

Women have a doubled operative mortality after CABG surgery, particularly women <50 years of age.\textsuperscript{44} Off-pump CABG procedures have been suggested to narrow the sex disparity.\textsuperscript{45} With all coronary presentations, women sustain an excess of bleeding complications; to date, investigations have failed to elucidate mechanisms of sex differences in blood vessels or in blood function that underlie women’s increased bleeding risk. Depression following MI occurs with increased frequency in women, with the greatest risk in younger women.\textsuperscript{46} Depression may be a component of the increased risk of younger women following both MI and CABG procedures.\textsuperscript{32,44}

An important exception to adverse outcomes is percutaneous coronary intervention, in which the application of stenting and the use of adjunctive pharmacotherapeutic agents seem to selectively benefit women; current percutaneous coronary intervention procedures result in comparable clinical and angiographic improvement for both sexes.\textsuperscript{47–49}

### Awareness/Perceptions of Women’s CVD Risk Among Women and Among Physicians

Concomitant with the widespread US educational and awareness campaigns regarding heart disease in women,\textsuperscript{50} the NHLBI Heart Truth Campaign and its Red Dress icon in 2004 and the AHA Go Red for Women the same year, CVD mortality among US women has decreased dramatically each year since 2000. Abundant evidence exists that increased patient and physician knowledge of the importance of cardiovascular prevention in women has fostered improvement in cardiovascular risk factor awareness, treatment, and control.\textsuperscript{51}

Despite the >6 million US women with known CHD, a disproportionate number of women do not highlight CHD as their major health concern. Although serial surveys have documented increased awareness of CHD as a health threat among women, from 30% to 54%, a substantial proportion of all women surveyed remain unaware of their CVD risk. Lack of awareness is most persistent among the highest-risk populations, women of racial and ethnic minorities.

Furthermore, physicians and other healthcare providers continue to underestimate women’s cardiovascular risk, with consequent underutilization of preventive therapies.\textsuperscript{52,53} A 2004 AHA study of physician awareness and adherence to the AHA women’s prevention guidelines\textsuperscript{34} identified major gaps in knowledge and guideline implementation, and substantial differences in the perception of cardiovascular risk based on the sex of the patient, as well. In an online questionnaire study, physicians assigned a risk status and made specific recommendations for CVD prevention; case studies were constructed such that the risk profiles were comparable for both sexes, but physicians were more likely to assign a lower cardiovascular risk status to women and to suggest fewer preventive interventions. Misperception among physicians of lower cardiovascular risk status for women correlates with suboptimal application of cardiovascular preventive interventions.

### Challenges and Opportunities

Lack of public and professional awareness of women’s coronary risk; knowledge gaps regarding women’s symptom presentation, optimal screening, and diagnostic procedures; and sex disparities in application of evidence-based therapies all contribute to adverse coronary outcomes for women (Table 2).

Surveys, registries, and quality improvement initiatives have documented underuse of evidence-based interventions for women with CHD. Subsequent analyses should enable ascertainment of whether enhanced application of guideline-based therapies to women improves their clinical landscape of CHD.

Future sex-specific basic and clinical CHD research studies and rigorous application of emerging knowledge offer promise to improve CHD outcomes in women, just as Herrick’s scholarly observations constituted the underpinnings for a century of antithrombotic strategies for CHD. This underlies our mandate for exploring sex differences in CHD.

### Summary

Once viewed as a man’s disease, CHD is the leading cause of mortality for US women. Despite their CVD burden, women remain underrepresented in clinical trials and are disadvantaged by absence of sex-specific analyses. Lack of public and professional awareness of women’s coronary risk; knowledge gaps regarding women’s symptom presentation, optimal screening, and diagnostic procedures; and sex disparities in application of evidence-based therapies contribute to adverse CHD outcomes. Adverse outcomes likely reflect both biology and bias. Despite their excess angina and consequent morbidity and mortality, women have less severe obstructive disease at angiography, yet obstructive coronary atherosclerosis, the male model of CHD, constitutes the basis for diagnostic and therapeutic strategies for both sexes. Myocardial ischemia with adverse outcomes without coronary obstructive disease, an emerging paradigm for women, requires assessment for microvascular disease in their CHD spectrum. Women have more unfavorable CHD outcomes than men. Young women (<50 years of age) with CHD, particularly following MI and CABG, have greater mortality than their male peers. Women sustain excess bleeding complications. Women who have CHD with

### Table 2. Major Recommendations to Improve CHD Outcomes in Women

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<tr>
<th>Recommendation</th>
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<tr>
<td>Increase inclusion of women in CHD trials, with analysis and reporting of gender-stratified data</td>
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<tr>
<td>Delineate biological mechanism(s) underlying pathophysiology of ischemic heart disease in women, with emphasis on microvascular disease</td>
</tr>
<tr>
<td>Increase awareness of CHD risk by women and healthcare providers</td>
</tr>
<tr>
<td>Increase application of evidence-based data to guide prevention, recognition, and management strategies for CHD in women, including focus on microvascular disease</td>
</tr>
<tr>
<td>Explore psychosocial/environmental/sociocultural disciplines and their relationships(s) to CHD, CV illness, including differential impacts by sex</td>
</tr>
<tr>
<td>Explore political (including public policy), economic, business, ethical, legal and regulatory, community (global, regional, local), faith-based, and cultural associations and interrelationships with women’s CHD, CV health</td>
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CHD indicates coronary heart disease; CV, cardiovascular.
consequent heart failure, more frequently than men, have intact ventricular systolic function. Effective treatments for diastolic heart failure, the predominant presentation in women, remain elusive. Awareness campaigns and application of evidence-based therapies underlie dramatic decreases in cardiovascular mortality for US women since 2000 because of preventive interventions and improved management of established CHD. Sex-specific basic and clinical research and application of emerging knowledge offer promise to improve CHD outcomes for women.

Acknowledgments

Let me provide appreciation and acknowledgments, first, to my mentors, because mentors are indispensable at every stage of our careers, but I will select just 3: Dr Hermann Blumgart, incidentally the first Herrick lecturer, who introduced me to the excitement and potential frontiers of bedside cardiology during my junior and senior student rotations on Medicine at the Harvard Medical School; Dr Charles Friedberg at the Mount Sinai Hospital in New York City. In the course of my Cardiology Fellowship, he challenged me repeatedly to inquire and to achieve by introducing me to the often famous patients he entrusted to my care as “this physician will guide the care of your children and grandchildren”; and Dr J. Willis Hurst, long-time Chairman of Medicine and Cardiology at the Emory University School of Medicine in Atlanta, also a Herrick lecturer. Teacher, colleague, and cherished friend during our half-century of patient-centered teaching, training, writing, and research. I acknowledge my colleagues, trainees, and students at the Emory University School of Medicine, who continue to teach me daily. In particular, gratitude to our wonderful patients at Grady Memorial Hospital, who have helped us train generations of physicians, who participated in multiple clinical research studies to advance cardiovascular medicine, and who taught me the special tribute embodied in the salutation of “honey, sweetie, or lady doc.” My family merits unique recognition: our 3 daughters, Dr Deborah Wiatrak, Dr Judith Wenger, and Dr Beth Wenger, who mentored me in the art of advancing cardiovascular medicine, and who taught me the potential frontiers of bedside cardiology during my junior and senior careers, but I will select just 3: Dr Hermann Blumgart, incidentally to the often famous patients he entrusted to my care as “this physician will guide the care of your children and grandchildren”; and Dr J. Willis Hurst, long-time Chairman of Medicine and Cardiology at the Emory University School of Medicine in Atlanta, also a Herrick lecturer. Teacher, colleague, and cherished friend during our half-century of patient-centered teaching, training, writing, and research. I acknowledge my colleagues, trainees, and students at the Emory University School of Medicine, who continue to teach me daily. In particular, gratitude to our wonderful patients at Grady Memorial Hospital, who have helped us train generations of physicians, who participated in multiple clinical research studies to advance cardiovascular medicine, and who taught me the special tribute embodied in the salutation of “honey, sweetie, or lady doc.” My family merits unique recognition: our 3 daughters, Dr Deborah Wiatrak, Dr Judith Wenger, and Dr Beth Wenger, who mentored me in the art of rearing both children and grandchildren; and finally, my most cherished advisor, confidant, and best friend, my husband of 54 years, Dr Julius Grady Memorial Hospital, who have helped us train generations of physicians, who participated in multiple clinical research studies to advance cardiovascular medicine, and who taught me the special tribute embodied in the salutation of “honey, sweetie, or lady doc.” My family merits unique recognition: our 3 daughters, Dr Deborah Wiatrak, Dr Judith Wenger, and Dr Beth Wenger, who mentored me in the art of rearing both children and grandchildren; and finally, my most cherished advisor, confidant, and best friend, my husband of 54 years, Dr Julius

References


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Nanette K. Wenger

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