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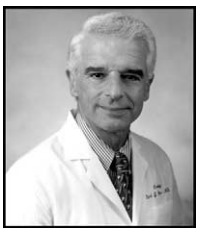
**PLENARY ADDRESS**



# Ischemic Heart Disease in Women: Facts and Wishful Thinking

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I want to share some information on the problem of ischemic heart disease in women. Because of a focus on men, this topic has received inadequate attention, and the general assumption has been that what is true for men is also true for women. In this overview, I will try to separate the facts from the wishful thinking that has evolved on this topic, largely due to deficiencies in our knowledge base. Some questions will help to focus this overview. First, how important is ischemic heart disease in women? I will discuss some differences observed in clinical outcomes of women compared to men and also compared to women without ischemic heart disease. Second, I will deal with some of the diagnoses and management dilemmas in women with ischemic heart disease. Specifically, these include concerns related to the meaning of angina, whether women have more comorbidities, a different disease, or even gender-related bias rather than a different expression of disease. I will use two recent projects as sources of new data to illustrate some important points. Finally, I will suggest what I believe is needed for the future.

## FACTS ABOUT THE IMPORTANCE OF ISCHEMIC HEART DISEASE IN WOMEN

Cardiovascular disease is the leading cause of death in both women and men. Although the number of cardiovascular deaths has declined in men, it has actually increased in women over the past decade. Most of this increase is due to ischemic heart disease and ischemic stroke. And this unfortunate trend is primed to continue, because not only is our population aging, but it is being ravaged by the epidemics of obesity, metabolic syndrome, and diabetes—all of which disproportionately affect women. Considering outpatient and inpatient aspects of the problem, annual cost projections are to be about *$400 billion annually*. Clearly, this is an important issue.

To get a true picture of the burden of ischemic heart disease in American women, it seems appropriate to compare them with non-American women. Certainly, differences in collection and reporting such data exist among countries. However, this cannot fully explain the almost five-fold difference in coronary heart disease (CHD) deaths between France, Korea, or Japan and the U.S. (1). Even women in neighboring countries such as Canada and Mexico seem to have fewer CHD deaths than do American women. The Eastern European countries and the United Kingdom, have higher death rates than do U.S. women.

Let us move to diagnosis and management. First, some facts. Previous reports suggest that, compared with men, clinical manifestations of ischemic heart disease in women appear approximately 10 or more years later. Women demonstrate more symptoms and/or noninvasive findings suggesting ischemic heart disease, yet they have a lower prevalence of luminal obstruction compared to men. Symptoms in women, such as chest discomfort and dyspnea, are difficult to interpret. Sensitivity and specificity of stress testing to predict coronary disease are significantly lower in women. And women ultimately have poorer outcomes. This leads to difficulty with clinical decision-making. However, considering some of the biases that have effectively put women with ischemic heart disease at a disadvantage to men, these last two facts should perhaps not be so unexpected.

Let us look at some of these biases. For those of us who went to medical school or trained from 1969 to the 1980s, a picture from the Netter collection represents what has been viewed as classical angina pectoris (2). It would be unusual to visualize a woman carrying a briefcase up steps in the winter, after eating a meal, clutching her chest, and complaining of angina pectoris. This is not the usual symptom picture for a woman, but it is easy to see how the male bias has been perpetuated. We actually have a very incomplete knowledge base on the topic of "female-pattern" angina.

Even the more recently developed health outcome tools, such as the Seattle Angina Questionnaire, are biased toward men. Consider that among the almost 5,000 patients with angina and coronary disease followed for outcomes in this project, *only 79 were women* (3). Of course, we should not question the conclusion that scores are independently associated with one-year mortality among outpatients with coronary disease. Clearly, these scores serve a valuable risk-stratification role. But how many of you remember the

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principal limitation cited by the investigators that the findings ". . .need to be confirmed in women"? Considering these examples, it is wishful thinking to believe that we have an understanding of what is "angina" in women and how such female-pattern ischemia-related symptoms are linked to adverse outcomes.

More facts: Compared with men, women have worse outcomes once they present with obstructive coronary disease. This clearly is relevant to the need for coronary bypass surgery where mortality rates in women are approximately twice that observed in men. For a woman under 65 years of age, who has a myocardial infarction (MI), the mortality rate is approximately twice that for men. Overall, the one-year mortality rate for women is about 1.5 times the rate for men. For heart failure patients of all ages, the annual incidence rate for women is about twice that of men. In the SOLVD registry, at one-year follow-up, women had higher rates of all adverse outcome rates combined compared to men.

Because time does not permit critical examination of all these areas, I will focus on coronary bypass surgery. It is important to know the limitations of the evidence-based data that we take for granted when making decisions for bypass surgery. In all of the seven randomized trials of coronary artery bypass graft (CABG) surgery versus medical therapy, which included more than 2,600 stable angina patients, there were only 85 *women* (4). The conclusion was that the CABG group had a significantly lower mortality at 5, 7, and 10 years. But the stated limitations that "the exclusion of patients >65 years" and "low numbers of women" are not generally remembered by physicians. It is not surprising, lacking the evidence base to help us make choices for women relative to bypass surgery or medical therapy, that there are low numbers of women relative to men referred for bypass surgery. Nor should it surprise us that women have unusually high adverse outcome rates.

## WHY THE DIFFERENCE?

There have been suggestions about why women have higher adverse outcome rates than men. Is it an incomplete understating of the disease? Is it that women have more comorbidities (e.g., obesity, diabetes, hypertension, increased age), or perhaps is it that ischemic heart disease in women is a different disease with a more prominent microvascular component? Or, is it a bias in patient-care patterns? All of these as well as other factors have been suggested. Although the published literature is extremely limited relative to women, I believe that data from two recent projects, INVEST and WISE, offer some important new insights on these questions.

The INVEST was an international trial where 22,576 coronary artery disease (CAD) patients were randomized to two multi-drug antihypertensive strategies, one anchored by verapamil, the other by atenolol (5). For the first time in a randomized CAD trial, ~50% of the patients were women. The main findings, which I reported at this meeting last year in Chicago, showed that blood pressure control overall was excellent, with more than 70% achieving <140/90 mm Hg. Adverse outcomes were equivalent between strategies, with fewer cases of new-onset diabetes in the verapamil strategy.

Not unexpected, women were older than men and 5% more were older than 70 years. There were also differences in ethnicity, with more Hispanic women than Hispanic men and fewer Caucasian women than Caucasian men. Women had a body mass index higher than men and a lower prevalence of prior MI, which seems consistent with the higher early MI mortality rates in women. Women had more angina, about half of the coronary revascularizations, less unstable angina, less smoking, more diabetes, and less hypercholesterolemia.

Women entered with significantly higher systolic blood pressure levels than did men, and at any time during follow-up they had 2 to 3 mm higher systolic blood pressure levels than did men. Yet women used more medications and at the same or higher doses. However, they showed a lower percentage of blood pressure control.

Despite higher blood pressure and higher prevalence of many comorbidities, women had a lower primary outcome rate—defined as first event among death, MI, or stroke. This was due to lower rates of death and nonfatal MI, but not to stroke compared with men, which was likely related to their higher blood pressure.

Congestive heart failure, residing in the U.S., prior MI, and being female in the U.S. were all significant independent predictors of adverse outcomes (death, MI, or stroke). Interestingly, Hispanic women and multiracial or Asian women had lower adverse outcomes, and women in general had lower adverse outcomes than did men.

However, when the cohort was restricted to the 10,000 patients with prior MI or coronary revascularization, the adverse outcome risks were higher among the women. The rates for death and stroke alone were significantly increased, with a trend for nonfatal MI to also be increased in women.

In the cohort restricted to those with prior MI or revascularization, the multivariate model again identified heart failure and U.S. residency as associated with increased risk and also added diabetes, as well as age, renal impairment, smoking, and peripheral vascular disease to the risk model. Interestingly, in this restricted cohort adjusted for these covariates, the women no longer have a significantly lower adverse outcome compared with men. These findings confirm older and smaller trials relative to more comorbidities in women. Further, they extend those findings to show more difficult-to-control blood pressure and suggest that a large component of the gender difference in outcomes is related to comorbid conditions that are more frequent in women than in men.

I will share with you some new data from the WISE study, a four-center, NHLBI study that evaluated approximately 1,000 women with suspected ischemia referred for

elective diagnostic coronary angiography. Almost all of these women had chest discomfort, and the objectives were to investigate new and diagnostic pathophysiologic mechanisms and to better characterize outcomes in the absence of flow-limiting stenoses by angiography.

Angiographic findings of this cohort of women showed that only 38% of the women had 50% or greater stenosis. These were evenly divided, with 19% having one-vessel obstruction and 19% with two- and three-vessel obstruction. This confirms several prior studies that found the majority of women presenting with symptoms and/or signs suggesting ischemic heart disease have no stenosis or <50% stenosis. It is this subgroup that is of particular interest.

A presentation later this week will summarize four-year, risk-adjusted outcomes by extent of coronary disease (6). There was a *9.4% death or MI rate* (or about 2.7% annually) in the subgroup with no or minimal disease by angiography. This is an unacceptable event rate.

Another presentation will summarize the estimated lifetime cost of care for cardiovascular disease by the angiographic extent of disease (7). Even women with no disease by angiography have in excess of $750,000 for lifetime costs for care. In an era of shrinking health care resources, such a finding also is unacceptable.

We have been particularly interested in the subgroup of women without apparent angiographic obstruction. In a WISE substudy, the arteries of these women were examined using intravascular ultrasound (IVUS). Our findings indicate that >80% of women with so-called "normal angiograms" have plaque lesions by IVUS and the vast majority have multiple lesions.

In a recent report from our institution, a cohort of 163 of these women underwent coronary artery reactivity testing using acetylcholine (8). Women who failed to dilate had more cardiac events over follow-up than did the women who dilated. This persisted in a multivariate model where cross-sectional area response to acetylcholine was an independent predictor of four-year outcome.

These findings illustrate a pervasive myth that I have given the less than eloquent name of "myth of angina with normal coronary arteries in women as a benign syndrome." This myth has contributed to some of the bias related to the management of women with so-called normal coronary arteries and is based upon >3,000 cases in the literature. With few exceptions, long-term follow-up in these studies is too brief to account for the delay in presentation of women compared to men. All of these studies were retrospective, and none used core laboratory angiographic findings. Translated into practice, these studies led to the dismissal of subspecialty care for an important subgroup of women—who were consequently disregarded by primary caregivers as having benign symptoms. The end result was an extremely important missed opportunity for cardiovascular prevention in far too many women.

**Table 1.** Ischemic Heart Disease in Women: Diagnosis and Management

| Some Examples of Wishful Thinking Over the Years: |
|---|
| • What is true for men is also true for women. |
| • Hormone replacement therapy prevents cardiovascular disease. |
| • Seattle Angina Questionnaire scores independently predict morbidity and mortality among women with coronary artery disease. |
| • Women undergoing coronary artery bypass graft surgery have lower mortality than those treated medically. |
| • Women with angina and "normal coronary angiograms" have a benign long-term outcome. |

## RECAPITULATION

From the foregoing it is apparent that much of our thinking relative to ischemic heart disease in women was wishful thinking. This thinking, as summarized by the examples in Table 1, has contributed to our lack of understanding of this problem. Perhaps now that we recognize these limitations we can move forward. Some of the exciting new work relates to diagnostic evaluations in women.

Relative to newer diagnostic techniques, later this week new and innovative data will be presented among WISE women comparing single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) global and regional myocardial perfusion status. Findings in 133 women undergoing evaluation for chest pain as part of the WISE project show a global myocardial perfusion derived from MRI is superior for identifying women at high risk for adverse outcomes compared with SPECT and MRI regional ischemia scar analyses (9). Considerable data link the microvasculature to ischemia among these women without severe obstructive lesions.

New data will be presented on hemoglobin (Hgb) alone and Hgb combined with inflammatory markers, suggesting that a multimarker panel may be useful to identify women at high risk for adverse events (10).

## WHERE DO WE GO FROM HERE?

There are a number of important steps that we all must take to bring this situation under control and ensure that we are giving female patients the highest quality care possible. First, we must increase awareness among women about their risk of heart disease. Second, we must teach—or re-teach—physicians to pay more attention to symptoms and test findings. We must also begin to better understand that there is a "female pattern" of ischemia-related symptoms distinct from that seen in men. We must come to grips with the fact that a "clean" angiogram in a symptomatic woman does not mean her long-term outcome is benign. And more research needs to be done looking at issues like concealed plaque (e.g., remodeling) and inflammation in the vessel wall, the prognostic utility of blood markers, and the role of the microvasculature. Finally, and this is true for all of our patients, it is absolutely imperative that we all apply

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**Figure 1.** Laura Bush accepts an honorary fellowship from Dr. Pepine.

evidence-based prevention strategies to stem the tide of hypertension, obesity, and diabetes.

The first action step I mentioned was the need to raise women's awareness of their risk of heart disease. The ACC intends to play an important role in this effort. Last month I was a guest at the White House when President and Mrs. Bush kicked off American Heart Month. After this session, I will recognize Mrs. Bush's strong support for the awareness campaigns with an honorary fellowship in the ACC (Fig. 1). Just this past week, we held our first community event, the primary aim of which was to bring attention to this very issue. The event was conducted in collaboration with the NHLBI and AHA and their respective women's awareness campaigns, both of which the ACC supports. The event, hosted by our Louisiana ACC Chapter, was an astounding success, attracting hundreds of visitors and generating media coverage to ensure that the message is spread far and wide.

These awareness campaigns could not come at a more important time. Surveys have shown that women do not believe heart disease is something they need to worry about. In one survey, *87%* of women cited cancer as their greatest concern, even though cardiovascular disease kills nearly twice as many women each year as do all forms of cancer combined.

The ACC will continue to support these campaigns and ensure that the Red Dress, the common symbol of these campaigns, becomes as ubiquitous as the pink ribbon of breast cancer awareness. Women must receive the message loud and clear: *Heart disease is not relegated to men. You, too, are at risk.*

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