

## Heightened Cardiovascular Risk in Diabetic Women: Can the Tide Be Turned?

The diabetic woman is at heightened risk for all-cause, cardiac, and coronary heart disease (CHD) mortality. So concluded the authors of a 1999 study of sex-specific comparisons of enrollees in the First National Health and Nutrition Examination Survey (NHANES I) (1971–1975) and the NHANES I Epidemiologic Follow-up Survey (1982–1984) (1). The aim of the study was to determine age-adjusted cardiac mortality rates in 2 time periods by using 2 cohorts from the NHANES I national probability sample. One cohort was followed from 1971 to 1974 for a mean of 9.1 years, and the other was followed from 1982 to 1984 for a mean of 8.7 years. Compared with cardiac mortality in the 1971–1974 cohort, cardiac mortality in the 1982–1984 cohort declined by 36.4% in nondiabetic men, 13.1% in diabetic men, and 27% in nondiabetic women—but *increased* by 23% in diabetic women.

An article in this issue (2) underscores the diabetic woman's continued heightened risk for both all-cause and cardiac mortality. Gregg and colleagues compared all-cause and cardiovascular mortality rates in adults with and without self-reported diabetes from the NHANES I (1971–1975), II (1976–1980), and III (1988–1994) cohorts as determined through 1986, 1992, and 2000, respectively. Cardiovascular deaths declined over the 3 decades in diabetic (26.4, 17.1, and 12.8 deaths per 1000 persons per year, respectively) and nondiabetic men (9.6, 6.5, and 4.7 deaths per 1000 persons per year) and in nondiabetic women (4.7, 3.1, and 2.3 deaths per 1000 persons per year) but remained essentially unchanged for diabetic women (10.5, 9.1, and 9.4 deaths per 1000 persons per year). The authors concluded that diabetic women have not benefited from the changes that dramatically improved the cardiovascular disease outlook for others.

The results of these 2 studies are difficult to explain. The decline in CHD deaths in the total U.S. population has been attributed to both major coronary risk factor reduction and evidence-based medical treatments of established CHD (3). Some have attributed the paradoxical increase in deaths in diabetic women to differential application—or differential effects—of risk factor control strategies and CHD therapies. Although the NHANES data set did not contain enough information to test these hypotheses directly, other evidence exists. This editorial discusses this evidence.

Are women with CHD and diabetes less likely to receive appropriate care? The answer appears to be “yes.” Analysis of 2005 Health Effectiveness Data and Information Set (HEDIS) cardiovascular disease and diabetes measures showed sex disparities for ambulatory preventive care. In 2 commercial managed care plan measures and 5 Medicare managed care plan measures, statistically significant disparities disadvantaged women. Suboptimal cholesterol

control after acute cardiac events was common in diabetic and nondiabetic women (4). According to the authors, eliminating sex disparities in cholesterol control in diabetic women could potentially reduce major cardiac events by 4800 events to 10 000 events annually nationwide. The analysis did not include uninsured patients, who are likely to be more vulnerable. Another analysis of quality of cardiovascular and diabetes care in managed care plan enrollees used 11 HEDIS measures to draw the same conclusion about low-density lipoprotein cholesterol control in diabetic persons, which was 19% less likely in women enrolled in Medicare plans and 16% less likely in women enrolled in commercial plans (5). These findings are important at a population level, because elderly women represent the fastest-growing population segment. The rates of prescribing  $\beta$ -blockers after myocardial infarction and angiotensin-converting enzyme inhibitors for heart failure were also lower in women.

Sex disparities disadvantaging women with established CHD are also prominent, regardless of diabetic status. Women receive CHD diagnoses later in their illness, have fewer preventive interventions, and receive fewer guideline-based therapies at hospital admission and at discharge after an acute coronary event. In the northern New England coronary artery bypass graft (CABG) surgery database, diabetes contributed statistically significantly to the sex-based excess of CABG deaths among women (6). In the National Registry for Myocardial Infarction (NRMI) (1994–2002), black persons and women with myocardial infarction received less reperfusion therapy and coronary angiography. The disparity was greatest for black women, who had an 11% excess mortality rate. The NRMI ethnicity and sex gap in treatment has persisted in recent years (7). Younger women (age <50 years) have greater mortality rates than do age-matched men after both myocardial infarction and CABG surgery, which raises a new concern. The age at diagnosis of diabetes is falling in women, perhaps because of the obesity epidemic. Will the progressively longer duration of diabetes further accelerate the adverse clinical outcomes in younger women?

While these sex disparities reflect care of acute CHD, disparities also exist for office-based care, as shown in another study using HEDIS quality measures in commercial managed care settings. Lipid control was worse in women, with disparities of 5% to 9% in women with diabetes, a history of cardiovascular disease, or both. Ethnicity (African American and Latino/a) and lower socioeconomic status also adversely affected cardiovascular care (8). Disparities also exist in Medicare managed care. According to HEDIS quality measures, women had worse cholesterol control than men, and African-American diabetic patients

had greater gaps in care and health outcomes than white diabetic patients (9); African-American diabetic women were at the greatest disadvantage.

These sex disparities have consequences. Diabetic patients have a doubled incidence of myocardial infarction and stroke and less favorable survival rates after cardiovascular events. A 2007 Scientific Statement from the American Heart Association and the American Diabetes Association (10) highlights that treating diabetic patients with established CHD for dyslipidemia, hypertension, and hypercoagulability (as well as percutaneous interventions and cardiovascular surgery for acute coronary syndromes) improves event-free survival. This statement also recommends primary preventive strategies, because up to 80% of diabetic patients develop macrovascular disease and many die of it.

Although sex disparity in access to care and intensity of risk reduction is a plausible explanation for worse cardiovascular disease outcomes in diabetic women, it may not be the entire answer. For example, cardiovascular risk factors might be more common, more likely to cluster, or more severe in diabetic women than in diabetic men. This intriguing possibility is suggested by the more powerful effect of *statistical* risk factor adjustment in women. A meta-analysis of 10 prospective studies (11) of the impact of diabetes on the sex-based differential in CHD risk identified a statistically significant greater relative risk for CHD death for diabetic women versus diabetic men. The increased risk persisted after statistical adjustment for other cardiac risk factors and after exclusion of patients with previous coronary events, suggesting that diabetes per se—not greater risk factor aggregation, severity, or treatment resistance—selectively disadvantaged diabetic women. By contrast, another meta-analysis (12) concluded that statistical adjustment for classic coronary risk factors eliminated the sex-based difference in the impact of diabetes on death, suggesting that differences in risk factors other than diabetes per se are responsible for sex-based differences in outcomes. Clearly, controversy about sex differences in the impact of CHD risk factors persists, but modifiable cardiac risk factors seem to at least partially explain inconsistencies among studies.

Finally, what are postmillennial cardiovascular mortality trends for women? Before 2000, cardiovascular mortality rates decreased serially in the United States in men but not in women (1, 3). However, annual cardiovascular mortality rates declined in women each year from 2000 to 2004. The National Heart, Lung, and Blood Institute (13) attributes this decrease of almost 17 000 deaths from 2003 to 2004 to improved medical and surgical therapies rather than to decreased cardiovascular disease incidence. Pivotal questions remain. Gregg and colleagues' data set ends in 2000. Have diabetic women experienced the favorable cardiovascular survival trend for women since 2000? Do benefits extend to racial or ethnic subsets of women and to younger as well as older women? If so, what interventions

have made a difference? Recent examination of sex-specific effects of diabetes on outcomes of percutaneous coronary interventions showed that diabetic women had greater improvement in percutaneous coronary intervention outcomes than nondiabetic women, such that diabetes is no longer a risk factor for adverse percutaneous coronary intervention outcomes in women (14). A final question: Would more aggressive use of invasive interventions reduce cardiovascular disease mortality rates among diabetic women?

We lack an evidence-based comprehensive strategy for improving cardiovascular outcomes in diabetic women. Until we do, a prudent clinical approach involves 2 steps. First, we must recognize that diabetic women are at excess risk for CHD. Second, we must take an aggressive, guideline-based approach to CHD risk factor management.

Nanette K. Wenger, MD

Emory University School of Medicine, Grady Memorial Hospital,  
and Emory Heart and Vascular Center  
Atlanta, GA 30303

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**Requests for Single Reprints:** Nanette K. Wenger, MD, Emory University School of Medicine, 49 Jesse Hill Jr. Drive, Atlanta, GA 30303; e-mail, nwenger@emory.edu.

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