Sex and Outcome After Myocardial Infarction
A Case of Sexual Politics?

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The concluding decades of the last millennium have brought about a dramatic transformation in the role of women in Western society. Along with a growth in equality in the social and political landscape, there has been an increased awareness of the manifestations of diseases and their diagnosis, management, and outcome in women.

See p 2484

The treatment of women with coronary disease has received particularly intense scrutiny. A multitude of studies have been published from administrative databases, patient registries, clinical trials, and population-based surveys. These have evaluated findings in women with diagnoses of chest pain, stable coronary disease, ST elevation myocardial infarction (MI), and non-ST elevation acute ischemic syndromes. Although the anatomic biological differences are incompletely understood,1 the following 3 key questions have been posed: (1) does the outcome of women with coronary artery disease differ from that of men? (2) Do treatment and management strategies differ between the sexes? (3) Is the effect of treatment and outcome similar for both sexes? The findings in studies have been inconsistent, but nonetheless, several areas of agreement and consensus exist (Table).

The report by Gottlieb et al2 advances our understanding of the relationship between treatment and outcome in the setting of acute MI. This study was derived from a comprehensive national registry of all coronary care units in Israel, and it reports data on hospitalized patients with a diagnosis of acute MI over 2 months during 3 different years. A particular strength of this registry is the inclusion of all patients admitted during this time. Similar to other reports, that by Gottlieb et al2 found that Israeli women were older and had more comorbid conditions at the time of acute MI (eg, heart failure, hypertension, and diabetes) and that they had worse fatal and nonfatal outcomes. Overall, women were less likely to be treated with thrombolysis and other medical therapies, including revascularization, but most of these differences did not persist after multivariate analysis that adjusted for age and other baseline characteristics.

The fact that multivariate adjustment accounts for and “eliminates” treatment differences suggests that age is a major factor in the treatment discrepancies that have been described in many earlier studies.3,4 Because women make up increasing proportions of MI patients as age increases, the demographics of sex and age are inextricably linked. Gottlieb et al2 formally tested for the statistical interplay of age and sex for mortality and found no interaction, but the 100-fold larger National Registry of MI study of Vaccarino et al5 showed a significant interaction. This was particularly true for younger women, who did much worse than men. The outcome differences decreased progressively and were absent in patients ≥70 years old. Why do younger women do worse? Are there estrogen effects on anticoagulation that predispose to poor outcome? Do smaller and thinner arteries somehow influence outcome for MI, as they do for coronary surgery? Do thinner ventricles more often rupture in women after MI? Are there differences in community and social factors that lead to worse outcomes in younger women? These are all questions that must be answered.

Age is an obvious factor that may “account for” sex differences in outcome, because the premenopausal state protects against coronary disease development.1 This essentially shifts the incidence curves for women to the right by 5 to 10 years compared with men. Comorbidities of hypertension and diabetes are also plausible factors to enter into the sex equation, because the protective effects of the premenopausal state can be “overcome” by these other potent causes of atherosclerosis. But how age and sex affect treatment selection is a much thornier question, and it has been the subject of studies and quality improvement efforts, most notably those of the Health Care Financing Administration on behalf of Medicare beneficiaries. On the one hand, older people should enjoy the benefits of proven therapies to prolong quality and duration of life. Older age itself is a high-risk state and treatment benefits of thrombolysis and primary percutaneous transluminal coronary angioplasty (PTCA) are significant in the elderly; therefore, these facts seem to provide more reasons to treat such patients aggressively. On the other hand, older patients are more prone to complications from treatment and because they are less well represented than younger patients in clinical trials, they may derive a lesser degree of benefit at higher clinical and financial cost.6 In the Fibrinolytic Therapy Trialists’ collaboration,7 the relative benefit of thrombolysis decreased in the elderly, perhaps because of an increased incidence of hemorrhagic stroke. However, smaller trials of primary PTCA versus thrombolysis have suggested a relative benefit for primary PTCA, particularly in the elderly. We need a controlled, randomized trial of these 2 treatments in the elderly to
Areas of Agreement and Disagreement in the Literature Regarding Women and Acute MI

**Areas of Agreement**

- Women are older and more likely to have comorbidities (e.g., history of hypertension, heart failure, and/or diabetes) on presentation.
- Multivariate adjustment accounts for some of the differences in procedure use and outcome between men and women.
- Complications from MI and thrombolysis are more common in women than in men.

**Areas of Disagreement**

- Mortality is either similar or higher in women after adjusting for comorbid conditions.
- Thrombolytic and procedure use (i.e., catheterization, revascularization) is either similar or lower in women.

help better understand if we should customize acute MI treatment for the elderly to achieve the best outcome.

Further, studies of treatment selection always face tremendous problems understanding variables that are unmeasured, such as the subtleties of doctor-patient interaction, physician biases regarding who ought to receive or not receive interventions, and age and perhaps sex-influenced patient preferences. Bias is a particularly understudied and charged issue pertaining not only to sex and age, but also, at least in North America, race.6-12

One additional, incompletely understood factor in the sex gap is that differences in manifestations and symptoms of coronary disease exist and may determine treatment.11,13 A delay in presentation or diagnosis or mistaken clinical impressions may influence therapy,12 and less severe or non-classical symptoms may be linked to therapy as well. A decade ago, then-director of the National Institutes of Health Bernadine Healy announced the Women's Health Initiative, which was designed to combat what she described as the “Yentl syndrome”: women are treated as men as long as they—and presumably their symptomatology—resemble men.13 The relationship of clinical presentation to treatment variables and outcome remains incompletely understood, but it is still very much a target for understanding, as is pointed to by the study of Gottlieb et al.2

One important limitation of the Israeli Cardiac Care Unit registry and other studies are the unknown coronary patients who never reach the Cardiac Care Unit or hospital and who are not counted. Some have suggested that men may be disproportionately represented among prehospital deaths,14 leaving a sicker, surviving population of women at the door of the Emergency Department.

Which of Gottlieb et al’s5 findings should find their way to clinical practice? It is unlikely that practice patterns will be altered by the finding that 30-day but not later mortality may be higher among Israeli women or that angiotensin-converting enzyme inhibitors are inexplicably underutilized in this population. Rather, clinicians should be aware that their own perceptions and biases may influence treatment decisions, but little data support the notion that women should be treated with a different therapeutic regimen than men—at least not yet! The remarkable advances in therapy achieved in the past 20 years should be applied as uniformly and completely as possible to all patients.

References

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