cular events than is LDL.

This study offers what appears to be a superior risk predictor than LDL; however, it does not have corresponding data to suggest that reducing this risk marker improves cardiovascular outcomes.

Commentary

These two studies both address the question of inflammation in atherosclerotic events. The first finds a correlation between atherosclerosis, unstable angina, and inflammation, the second finds that the inflammatory marker hsCRP is a better risk predictor than our standard marker, LDL. Although these and other data are compelling in identifying hsCRP as a risk predictor and risk marker, hsCRP has yet to reach the status of official "risk factor." Before adopting widespread use of a new risk factor, I believe at least two criteria must be met: 1) the factor in question must be demonstrated to be associated with future cardiovascular events; and 2) there must be data demonstrating that reduction of this factor reduces the occurrence of cardiovascular events. We have ample data that LDL fulfills both of these criteria. Thus far we have data demonstrating that hsCRP fulfills only the first criterion.

Future studies must address the question of whether reducing hsCRP levels will reduce the incidence of future cardiovascular events. The forthcoming JUPITER trial will address precisely this question. It will be a double-blind study that will randomize 15,000 patients with high levels of CRP and low levels of LDL (< 130 mg/dL) to either placebo or 20 mg/day of rosuvastatin to determine whether statin therapy has a primary preventive role in reducing CRP levels and subsequent cardiovascular risk.

In the interim, I believe hsCRP can be used as an additional test to assist the clinician in risk stratification and, if elevated, may prompt the physician to intensify those risk reduction therapies that have been documented to improve cardiovascular outcomes, such as LDL lowering, blood pressure lowering, and use of antiplatelet agents. It must be remembered, however, that we do not yet have definitive data to assure us that the hsCRP value actually helps assess risk on an individual basis. It may be that this assay is more valuable as a population-based clinical research tool.

We must further remember that hsCRP is affected by any inflammatory or infectious state (recent cold, surgery, joint inflammation, etc). Thus, many physicians advocate taking at least two measurements separated by several weeks to minimize the possible influence of these other factors. ■

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Coronary Artery Disease

Gender Differences in Coronary Revascularization: Does Age Make a Difference?

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Numerous and remarkably consistent studies have noted gender differences in the demographic characteristics of patients with acute myocardial infarction.[1] Gender differences have also been found in the clinical, angiographic, and procedural characteristics in patients undergoing coronary revascularization where, in particular, a disturbingly higher mortality rate in women than in men has been noted.[2] Much, although not all, of this difference in mortality rate has been explained by the older age and higher prevalence of comorbid factors in women at the time of presentation. Recently, however, a disparity in gender differences in outcomes has been noted, surprisingly in younger rather than in older women. Two recent studies highlight this finding.

Biology or Bias: Practice Patterns and Long-Term Outcomes for Men and Women with Acute Myocardial Infarction

Alter DA, Naylor CD, Austin PC, Tu JV.
J Am Coll Cardiol. 2002;39:1909–1916.

To determine how age and gender affect the use of coronary angiography and the intensity of cardiac follow-up within the first year after acute myocardial infarction (AMI), and to evaluate the association of age, gender, and intensity of treatment with survival at 5 years after AMI, 25,697 patients hospitalized with AMI in Ontario, Canada,

between 1992 and 1993, were evaluated using linked, population-based administrative data. A Cox proportional hazards model was used to adjust for socioeconomic status, illness severity, attending physician specialty, and admitting hospital characteristics. The cohort was subdivided into four prespecified age groups (ages 20–49, 50–64, 65–74, and ≥ 75 years).

Of the 25,697 patients, 8941 were women and 16,756 were men. Women were, on average, significantly older than men were across the four prespecified age groups. For all patients, the utilization rate of coronary angiography at 6 months was 23.6% and of cardiology follow-up at 1 year was 38.7%; 40.7% of the cohort died within 5 years after AMI. The unadjusted odds ratio of women relative to men receiving coronary angiography and cardiac follow-up specialty care after discharge decreased with advancing age. Despite this inverse relationship between age and treatment in women relative to men, the accrued 5-year mortality rates in women relative to men decreased with advancing age. For each of the three variables examined—coronary angiography within 6 months following AMI, cardiology follow-up within 12 months after hospitalization, and general practitioner only or no physician follow-up within 12 months after hospitalization—younger women were treated more aggressively than younger men were, whereas older women were treated less aggressively than older men were. For every 10 years of increasing age, the risk ratio for coronary angiography in women relative to men fell 17.5% (95% confidence interval [CI], 13.6-21.3, $P < .001$) and for cardiology specialty follow-up dropped 10.2% (95% CI, 7.1-13.2, $P < .001$). Absolute differences in treatments across age groups were greater than the absolute differences in treatments between women and men. Accordingly, although a significant age-gender interaction existed, age was a much stronger predictor of utilization than was gender.

Furthermore, among younger patients, women had lower 5-year adjusted survival rates than men had; among older patients, women had higher 5-year survival rates than men had. The interaction between age and gender was significant. Specifically, for every 10 years of increasing age, the relative hazard chance of death in women compared with men decreased by 14.2% (95% CI, 10.1-17.5, $P < .001$). Moreover, the relationship between age, gender, and mortality was similar for those who received coronary angiography or cardiac specialty care and those who did not. Again, absolute differences in survival across age groups were greater than the absolute differences in survival between men and women. Accordingly, although the age-gender mortality interaction was consistent across subgroups, age again was the stronger predictor of mortality than was gender. The authors concluded that the relationship between age-gender and process-of-care factors was discordant to that between age-gender and outcomes. Survival differences in women improved with increasing age even though women received less aggressive interventions.

Comment

This study demonstrates yet another gender paradox in patients with coronary artery disease—that is, a paradoxical age-gender interaction for long-term treatments and outcomes for patients hospitalized with AMI in Ontario, Canada. Previous studies have noted that women are referred for coronary angiography less often or later in the course of their disease than men are, a phenomenon referred to as "gender bias."[3] Although the results of this study do support the presence of differences in gender-specific treatment for two markers of service intensity, the association is complex and age-dependent and may account for inconsistencies in findings across studies examining for gender variations in treatments and outcomes after AMI. Although these studies routinely adjust for age, few have examined whether gender effects differ according to age at presentation with AMI. Furthermore, this study supports the concept that gender differences in the treatment of patients with coronary artery disease may reflect an issue of "age bias" rather than "gender bias," particularly considering that women present with AMI at older ages than men do. It is reassuring that the interactions demonstrated in this study between age, gender, service patterns, and outcomes support the hypothesis that intrinsic biological and/or psychosocial factors are more likely than gender bias to explain the gender-related outcome differences after AMI.

Although the age-gender mortality interaction was consistent across subgroups, age again was the stronger predictor of mortality than was gender.

It is important to note that in this study, which used population-based administrative data, specific clinical details are lacking. For example, no information was provided on infarct location or left ventricular function. In addition, the perspective of physicians and, most importantly, the gender differences in patient preferences for services, could not be evaluated. It is, however, noteworthy that the age-gender mortality interaction in this study confirms the findings of one recent study performed in the United States.[4]

Sex Differences in Hospital Mortality After Coronary Artery Bypass Surgery: Evidence for a Higher Mortality in Younger Women

Vaccarino V, Abramson JL, Veledar E, Weintraub WS.
Circulation. 2002;105:1176–1181.

The aim of this study was to determine whether younger, but not older, women have a higher rate of in-hospital mortality after coronary artery bypass surgery (CABG) than have men of similar age. Accordingly, 51,187 patients, included in the National Cardiovascular Network database, undergoing CABG at 23 centers, between 1993 and 1999, were evaluated, of whom 30% were women.

In-hospital mortality following CABG was 5.3% in women compared to 2.9% in men, and women were substantially more likely than men to die at younger ages.

The distribution of patient characteristics according to sex in the entire group and within 10-year age subgroups was examined, and the in-hospital mortality rates between women and men according to five age groups (ages < 50, 50–59, 60–69, 70–79, and ≥ 80 years) were determined. A series of logistic regression models assessing the effect of groups of variables on the association of interest (sex and its interaction with age) was used.

As expected, women were older and smaller than men were. Compared with men of similar age, younger women were less often white and had more comorbid conditions and risk factors, including stroke, heart failure, diabetes, renal insufficiency, and angina than men had. These differences became less marked in older patients. Across all age groups, interestingly, women had less severe coronary disease and better left ventricular systolic function than men had. In-hospital mortality following CABG was 5.3% in women compared to 2.9% in men, and women were substantially more likely than men to die at younger ages. In patients aged < 50 years, in-hospital mortality was three times higher for women than for men (3.4% versus 1.1%), and the sex-based differences in in-hospital mortality decreased with increasing age. Among the oldest patients (aged ≥ 80 years), the in-hospital death rate was only slightly higher in women than it was in men (9.0% versus 8.3%). After an adjustment for age, sex, and other patient characteristics, women aged < 50 years were found to be more than twice as likely to die as men of a similar age. In patients aged 50–60 years, women experienced an 86% higher risk of in-hospital death than did men. However, sex differences in in-hospital mortality were less marked in the older age subgroups. Of note, with the exception of bleeding that required re-operation, women tended to suffer more complications after CABG than did men. The gender differences in complications, particularly in renal failure, neurologic complications, and acute myocardial infarction, were more marked at younger ages.

Comment

Although numerous studies have consistently reported higher in-hospital mortality after CABG in women than in men, after adjustment for body-surface area (a surrogate for coronary vessel size), much of the difference disappears.[5] The present study adds to a previous few that have studied mortality data in women and men after age stratification and corroborates the findings of a higher (unadjusted) mortality rate in younger women than in men of the same age.[6-8] Although gender differences are more pronounced in younger than in older women (when women become more like men), adjustment for comorbid conditions and risk factors accounted for < 30% of the mortality difference between women and men at a younger age. Interestingly, similar observations have been made for patients hospitalized with acute myocardial infarction.[1] The reasons for these findings are unknown, but lack of normal protective factors, ovarian dysfunction, abnormalities of the estrogen receptor, and ascertainment and referral bias have been implicated in the higher mortality rate in women with premature coronary disease.[9] ■

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