Acute Coronary Syndromes
Does Sex Matter?

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In 1960, the American Heart Association (AHA) sponsored a conference in Portland, Ore about women and cardiovascular disease (CVD) entitled “How I Can Help My Husband Cope With Heart Disease.” Today, recognizing that cardiovascular disease is the leading cause of death for women older than 50 years, the AHA now routinely holds conferences about heart disease in women, and the National Heart, Lung, and Blood Institute and the National Institutes of Health Office of Research on Women’s Health devote substantial attention to this area.

Do women and men respond to cardiovascular therapies in the same way? For the most part, yes. However, biological differences, down to the cellular level, might account for different therapeutic effects and adverse responses. For example, women are at greater risk from drugs that prolong cardiac troponin T. These findings are consistent with the recent study that suggested digitalis use was associated with excess risk of death in women but not in men.

In this issue of The Journal, Glaser and colleagues report an important observation from the TACTICS-TIMI 18 (Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction 18) study—that an early invasive strategy in women with non–ST-segment elevation acute coronary syndrome (ACS) results in similar benefits to men so treated. This observation stands in contrast to the findings of 2 previously reported studies testing an invasive strategy for non–ST-segment elevation ACS, the FRISC II (Fragmin and Revascularization during Instability in Coronary artery disease II) and RITA-3 (Randomized Intervention Trial of unstable Angina 3) studies. These studies reported benefit for men and a suggestion of harm for women. Why the different results?

In TACTICS-TIMI 18, 2220 patients with non–ST-segment elevation ACS, including myocardial infarction (MI) and unstable angina, were randomly assigned to receive either an invasive strategy (routine coronary angiography, percutaneous coronary intervention [PCI], or coronary artery bypass graft [CABG] surgery) or a conservative strategy (medical therapy, with revascularization reserved for patients with spontaneous or inducible ischemia). One third of the participants were women; they were older than the men and had higher rates of hypertension and diabetes, and lower rates of prior MI and revascularization. Women had higher rates of no significant coronary artery stenoses compared with men, and less often had elevated levels of cardiac troponin T. These findings are consistent with the results from other trials and registries of patients with ACS. Earlier studies have also reported more nonspecific electrocardiographic changes and atypical symptoms in women with ACS. Women more often have coronary spasm with minimal coronary stenoses, as well as cardiac syndrome X (ie, abnormal coronary vasodilator reserve). However, young women with acute MI inexplicably are at markedly increased risk of death compared with age-matched men in a model that adjusts for comorbidities and treatment.

In TACTICS-TIMI 18, women with elevated levels of cardiac troponin T benefited from an early invasive strategy, similar to men, and the graded benefit based on other risk markers (eg, ST-segment depression and TIMI risk scores) was similar for women and men. However, it appeared that women at lower risk and those with negative troponin levels tended to have excess events with an invasive strategy.

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Although this excess did not approach statistical significance, it is disturbingly consistent with the findings in FRISC II and RITA 3.

An invasive strategy balances early procedural risks with potential early and long-term reduction of cardiac events. For patients at higher risk of cardiovascular events, the balance is favorable provided the procedural risks are not excessive. Patients at lower risk may not derive as much benefit from an aggressive strategy, but they are still subjected to a procedural risk. The disparate results reported in the TACTICS-TIMI 18, FRISC II, and RITA 3 subgroup analyses may be related to differences in the procedural risks and risk profile of enrolled patients. The inclusion criteria for both FRISC II and RITA 3 allowed patients to be enrolled if they had symptoms in the preceding 48 hours, while TACTICS-TIMI 18 mandated symptoms within 24 hours of enrollment. This more lenient criterion for enrollment in the former 2 studies may have selected for patients at lower risk. As Glaser et al note, the event rates were higher for women in the conservative strategy group of TACTICS-TIMI 18 than in the RITA 3 trial, implying a higher-risk group of women enrolled in the former study.

Although the event rates for women in the conservative strategies of FRISC II and TACTICS-TIMI 18 were similar, the higher rate of insignificant coronary disease in women enrolled in FRISC II, despite similar age and proportion with positive troponin levels, implies they had overall lower baseline risk. In the conservative strategy group of FRISC II, women had significantly better outcomes than men. In contrast, in the invasive group, female sex was independently associated with excess death and MI at 12 months, and the interaction between sex and treatment strategy was significant (P = .008). Few details are available for RITA 3, but here too a significant interaction was observed between sex and treatment strategy at 1 year—death or MI for women in the intervention vs conservative groups (8.6% vs 5.1%), in contrast to death or MI for men (7.0% vs 10.1%), respectively.

In other words, in both FRISC II and RITA 3, women in the conservative strategy group appeared to be at lower risk of death or MI, thus rendering the procedural risk more important in determining the ultimate outcome for those assigned to invasive therapy. In FRISC II, the excess risk was attributable to an unusually high event rate in the women who underwent CABG surgery, with 9.9% death and 12.0% MI at 1 year, compared with 1.2% and 5.0% for men. Comparable data are not available for RITA 3.

What is the risk of death for women who undergo CABG surgery? United States data reflect a steady decline in the mortality rate over time despite an increasing risk profile among women undergoing cardiac surgery. Although the absolute improvement in mortality over time is higher in women than in men, female sex is still associated with excess risk. The rates of complications during PCI, and PCI success rates in women, have also improved over time. The event rates were low for women who underwent PCI in TACTICS-TIMI 18. Diabetes confers substantial risk of complications after bypass surgery or PCI. In FRISC II women in the invasive group who underwent CABG surgery had double the rate of diabetes (26%) compared with men who underwent CABG and compared with women and men treated conservatively or with PCI. The rates of CABG surgery for women were lower in TACTICS-TIMI 18 compared with FRISC II, despite similar rates of 3-vessel coronary artery disease (CAD). CABG was used less often for women compared with men in TACTICS-TIMI 18 despite similar rates of 3-vessel CAD. The rates of death and MI for women who underwent CABG surgery in TACTICS-TIMI 18 were low and similar to the rates for men. In summary, the rate of CABG surgery and the associated outcome for women may be a factor in the different trial findings.

In both ST-segment elevation and non–ST-segment elevation ACS trials, women are at increased risk for hemorrhagic events. This was also noted in TACTICS-TIMI 18. Female sex is an independent risk factor for a high activated partial thromboplastin time and bleeding in patients treated with antithrombotic or thrombolytic therapy.

Women are also at increased risk of bleeding after PCI and CABG surgery. This complicating factor will undoubtedly contribute to increased procedural risk, thus tilting the balance between benefit and harm for women enrolled in the invasive strategy. Clinicians must pay careful attention to dose adjustments of antithrombotic medications based on creatinine clearance, weight, and age. Further investigation is needed to define the variables that contribute to the apparent independent risk for bleeding that female sex confers.

Another difference between TACTICS-TIMI 18 on the one hand, and FRISC II and RITA 3 on the other, is the protocol mandated early use of a small-molecule platelet glycoprotein IIb/IIIa (Gp IIb/IIIa) receptor antagonist, tirofiban, in both groups in TACTICS-TIMI 18, followed by intervention within 48 hours in those patients randomized to undergo an invasive strategy. Gp IIb/IIIa antagonists have been demonstrated to reduce MIs associated with PCI in women and men. For patients with ACS, early therapy with Gp IIb/IIIa antagonists also reduces the rate of death and MI following CABG surgery; this may have contributed to the favorable outcomes for women in TACTICS-TIMI 18 who had CABG surgery. The controversy over whether there is a sex interaction with the efficacy of Gp IIb/IIIa antagonists in patients with ACS is a good illustration of the pitfalls of subgroup analysis, the challenges of the correct diagnosis of ACS in women, and international differences. The large PURSUIT (Platelet IIb/IIIa Underpinning the Receptor for Suppression of Unstable Ischemia Trial) study demonstrated an apparent interaction between sex and eptifibatide treatment effect, with a benefit suggested for men but not women. The efficacy of eptifibatide in women was subsequently demonstrated in the ESPRIT (Enhanced Suppression of Platelet IIb/IIIa Receptor with Integrin Therapy)
trial of PCI, paralleling results reported for women receiving abciximab in the PCI setting. Although the large meta-analysis of Gp IIb/IIIa antagonist trials for all patients with non–ST-segment elevation ACS also demonstrated an interaction between sex and treatment effect. Importantly, women with elevated levels of troponin had the same beneficial effect as men treated with Gp IIb/IIIa antagonists. This finding again highlights the challenge of diagnosing non–ST-segment elevation ACS due to a ruptured atherosclerotic plaque vs other etiologies of chest pain in women and the role of risk stratification. Since TACTICS-TIMI 18 had North American patients and FRISC II or RITA 3 did not, international differences in the outcome of an invasive strategy in women vs men may play a role. Prior studies of an invasive strategy in North America, such as TIMI 3B, also showed no interaction between sex and treatment effect. Although the efficacy of low-molecular-weight heparin has been demonstrated for women as well as men, the routine use of this agent for several days of medical stabilization prior to intervention in FRISC II and RITA 3 is a notable difference in trial design compared with TACTICS-TIMI 18.

Women derive the same treatment benefit as men from all of the therapies that receive a Class IA recommendation in non–ST-segment elevation ACS, including antiplalet agents, anticoagulants, B-blockers, angiotensin-converting enzyme inhibitors, and statins, as well as thrombolytic therapy and primary percutaneous transluminal coronary angioplasty for acute ST-segment elevation MI. The report by Glaser et al is reassuring that women with non–ST-segment elevation ACS who are at increased risk of cardiac events, particularly those with elevated troponin levels, derive treatment benefit from a direct invasive strategy. This benefit is the same as for men, and the AHA/American College of Cardiology guidelines recommend a direct invasive strategy for women and men who are at high risk of cardiac events. Evaluation of data from recent trials raises a concern regarding excess events in women at low risk subjected to a routine invasive strategy.

Early coronary angiography may be useful for risk stratification and in suggesting another etiology for symptoms, but should be followed by thoughtful consideration of the role of PCI or CABG surgery in addition to medical therapy, not by reflex intervention for lesions that may be unrelated to the presenting syndrome. In this regard, the demonstration that the benefit of a direct invasive strategy was related to the baseline risk of cardiac events should guide clinical practice. Women with diabetes, as well as men, should have tight glucose control acutely, particularly when undergoing bypass surgery, given the reduced in-hospital mortality demonstrated for the latter. Each institution must assess its outcome following PCI and CABG surgery in women with ACS to ensure that the excellent outcomes in TACTICS-TIMI 18, which led to the beneficial effect of a direct invasive strategy in women, are replicated. Refinement of invasive techniques (PCI and CABG) and attention to comorbidities (diabetes, hypertension, diastolic heart failure) are important for all patients, but may be particularly so for women.

REFERENCES

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Reduction Disability in Older Age

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In this issue of The Journal, Freedman and colleagues1 present encouraging evidence from a number of sources that disability in seniors is decreasing. The authors identified and reviewed 16 articles based on 8 surveys that assessed US trends in the prevalence of self-rated older adult disability and physical, cognitive, and sensory limitations among older adults beginning in 1982 through 1999. Of the studies assessed as having at least fair quality, surveys showed consistent declines in instrumental activities of daily living (IADLs) and in functional limitations. These findings are conservatively presented and all are consistent with the single best study, the report by Manton and Gu,2 which presents the most recent data, has the most detailed end points, surveys the most representative sample of the US population, and shows the most striking findings. Manton and Gu studied trends in disability in the National Long Term Care Surveys (NLTCS) of 1982, 1989, 1994, and 1999 of the Medicare-eligible population aged 65 years and older, which include both institutionalized and noninstitutionalized individuals.

Surveying a sample that includes both institutionalized and noninstitutionalized older adults is important because the proportion of elderly individuals institutionalized declined from 6.8% in 1982 to 4.2% in 1999.3 This increase in the number of persons with relatively greater amounts of disability into the noninstitutionalized population would be expected to decrease observed improvements in noninstitutionalized populations and to underestimate the actual decline, as may have occurred in some of the studies reviewed.1 In the NLTCS, similar declines were observed in those with any disability, IADL disability, and activities of daily living (ADL) disability, with the greater declines seen in IADL. In general, declines in disability are greatest in the studies with the most recent data, and rates of decline appear to have accelerated after 1994, being 1.7% annually over the 17 years of the NLTCS and 2.6% per year from 1994 to 1999. A rapid decline in disability in blacks of nearly 4% per year, not seen previously, occurred from 1994 to 1999. It has been argued that a decline in any disability of 1.5% per year would ensure the long-term solvency of the Medicare and Social Security programs.4 These are important changes.

In 1980, I introduced the compression of morbidity hypothesis, suggesting that if the age of onset of disability could be postponed to a greater degree than senior life expectancy would increase, then lifetime disability could be compressed into a shorter average period and cumulative average lifetime disability could be reduced.4 Furthermore, if decreases in health risk factors such as lack of exercise, obesity, and cigarette smoking could be achieved in seniors, substantial postponement of disability might result and that, in general, preventive approaches to health enhancement and chronic disease prevention held the greatest promise for improving the health of older individuals. At that time, any suggestion that senior health futures could be improved was considered naively optimistic.5,6 Direct proof that morbidity could be compressed would be documentation that age-specific disability rates were declining more rapidly than age-specific mortality rates. The present data indicate that senior mortality rates are declining at about 1% per year7 and disability is declining at about 2% per year.2 Thus, compression of morbidity is occurring nationally, and that certainly is good news.

Reasons for these trends are less clear. Improvements in lifestyle risk factors do not seem adequate to account for much of the change. Over the past 2 decades, the prevalence of obesity has increased,8 and exercise levels have not changed appreciably.9 The decline in cigarette smoking has been estimated to account for as much as 1 percentage point of the decline but cannot account for the complete decline.10 Arguments for major contributions from prostate-specific antigen testing, bone density screening, immunization rates, or other preventive services are not convincing.10 Health promotion and self-management programs have not been broadly adopted, and Medicare has remained reluctant to remunerate for preventive services.

The impact of improvements in medical care on reducing disability is difficult to quantitate. The number of total joint replacements and cataract surgery procedures have doubled over this period, and hypertension, diabetes,