Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 54, No. 21, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.06.044

EDITORIAL COMMENT

Women Are Like Men . . . Sometimes*

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The impact of sex on the pathophysiology, clinical manifestations, and treatment of cardiovascular disease has been a topic of considerable investigation (1). The issue is an important one because more than 41.3 million women are living with cardiovascular disease. Although progress has been made in reducing the morbidity and mortality of heart disease in both women and men, since 1980 the decrease in mortality has been less for women, and disturbingly, mortality has increased in women younger than 55 years of age (2). Overall cardiovascular disease remains the primary cause of death in women.

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Studies have shown that women with coronary artery disease differ from men with the disease in many regards. Women present more than 10 years older with symptomatic coronary disease and have more risk factors at the time of presentation, including hypertension, hyperlipidemia, and cigarette smoking. The protective effects of sex hormones before menopause have been thought to help explain this observation (3). Women also have a higher incidence of angina with nonobstructive coronary disease. The presenting symptoms of angina are less likely to be chest pain and more likely to be shortness of breath than in their male counterparts (4). They more frequently have symptoms of heart failure with normal left ventricular function. The outcomes of women with acute coronary syndromes (ACS), including ST-segment elevation myocardial infarction (MI) and revascularization with percutaneous coronary intervention (PCI), have been reported to be worse than in men (5–7). In part this can be explained by the older age and greater number of risk factors in women, but it is not entirely accounted for by these factors. On a positive note, the outcomes with PCI have improved recently (6). Others (1) have cited disparities in the delivery of care attributable to either sex bias or lack of access to care as another explanation for the poorer outcome.

The mechanism for these differences in presentation, expression of the disease, and outcome is unclear, but biologic differences are likely to contribute. It is known that the blood vessels in women are smaller, stiffer, more inflamed, and more prone to bleeding (8). Thrombosis is central to the pathophysiology of cardiovascular disease, particularly MI and stroke, and is the basis for the guideline-recommended use of antithrombotic therapy in women at high risk of atherothrombotic events (9). Evidence from both animal studies and human studies has shown sex differences in the development of thrombosis and the response to antithrombotic therapy (10,11). Estrogen has been shown to decrease plasma levels of fibrinogen, antithrombin, protein S, and plasminogen activator inhibitor (12). In a large meta-analysis, women had an increased level of fibrinogen (13). In addition, many studies have shown an increase in platelet reactivity in women. In a study by Becker et al. (14), platelets from women were more reactive to 10 of 12 agonists than those from men. After receiving low-dose acetylsalicylic acid (ASA) for 14 days, platelet function was inhibited in women to an equal degree as in men, but because of the higher baseline reactivity the absolute degree of aggregation was greater in women than men. Clinical studies of ASA for primary prevention have shown a differential benefit in women as compared with men. In a large meta-analysis by Berger et al. (15) of more than 91,000 patients, ASA had no effect on the risk of MI or cardiovascular death in women, but did lower the risk of ischemic stroke. In contrast, men experienced a reduction in the risk of MI but no effect on ischemic stroke. Bleeding was increased to an equivalent degree in both groups.

Sex differences associated with other antiplatelet drugs have also been shown. In a meta-analysis of glycoprotein IIb/IIIa drugs by Boersma et al. (16), women with ACS showed a worse outcome from glycoprotein IIb/IIIa agents, whereas men showed a significant reduction in death and MI at 30 days. When patients with elevated troponin levels were separately evaluated, no sex differences were seen. More recent studies have not shown any sex differences in outcome, possibly because of the use of concomitant clopidogrel. Another potential cause for the differences in outcomes with antithrombotic therapy in women is that they are commonly given excess doses that result in increased major bleeding and a poorer outcome. This is particularly true for the glycoprotein IIb/IIIa agents (17). Excessive bleeding has been linked to a poorer long-term outcome and increased mortality (18).

It would therefore not be unexpected that women might have a less favorable response to clopidogrel as well. Studies have shown sex differences in CYP enzymes that are needed to convert the pro-drug of clopidogrel into its active metabolite. Cytochrome P450 genetic polymorphisms have

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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been shown to reduce the responsiveness to clopidogrel, but it is not known whether these are more common in women (19). Hyporesponsiveness to clopidogrel would be expected to increase thrombotic events, particularly after PCI. In a recent study by Price (20), residual platelet reactivity was assessed by the bedside assay test VerifyNow P2Y12 (Accumetrics Inc., San Diego, California) assay in patients on dual-antiplatelet therapy undergoing PCI. The study showed more platelet reactivity in women compared with men (220 ± 82 U vs. 299 ± 77 U, p = 0.041), and female sex was an independent predictor of high platelet reactivity (odds ratio: 1.91; 95% confidence interval: 1.14 to 3.19; p = 0.014). This would support prior studies suggesting that women are more pro-thrombotic on standard dual-antiplatelet therapy and might need more aggressive antiplatelet therapy than men.

In this issue of the *Journal*, Berger et al. (21) reported a sex-specific collaborative meta-analysis of 79,613 patients enrolled into 5 major trials of clopidogrel. The analysis showed a reduction in the risk of cardiovascular events in both men and women. Although results from women were not statistically significantly different from those of men, they did show a greater reduction in MI with a nonsignificant reduction in stroke and total death. Men seemed to have an equal benefit in the reduction of MI, stroke, and total death. Bleeding was increased in both and was nonsignificantly greater in women. The results of this analysis are reassuring and thus differ from the results seen with aspirin and glycoprotein IIb/IIIa agents. Because these patients were on dual-antiplatelet therapy with ASA and clopidogrel, the additional antiplatelet effect of clopidogrel seemed to reduce adverse events, something not seen previously with ASA alone in primary prevention studies (15). Although this analysis strongly supports the use of clopidogrel in addition to aspirin in women at high risk for cardiovascular events, they also have not closed the book on the issue of sex differences of clopidogrel. The results of a meta-analysis are useful when the individual trials are not adequately powered to look at less frequent events. That is the case here, and the justification for this meta-analysis. This type of analysis is often limited by significant differences among trials in study design, patient inclusion criteria, definitions, end points, and treatment regimens. In this analysis, for example, 2 trials studied patients with acute MI, 1 studied patients undergoing PCI, 1 evaluated patients with ACS, and 1 included patients with stable cardiovascular disease or those at risk for cardiovascular disease. The follow-up time varied from 30 days to 28 weeks, and the baseline characteristics varied significantly among the study populations. Although sensitivity analysis was conducted and heterogeneity among trials was not seen, this analysis does not completely exclude an impact of the differences in the studies on the results. Because the analysis did not include patient-level data, examination of important subgroups was not possible. Overall the differences in the individual cardiovascular events between men and women are provocative and leave the door open for more investigation of this question.

The conundrum is that women have increased thrombotic potential with increased platelet activity but have an increased risk of bleeding. What can be done to reduce ischemic complications while not increasing bleeding? Some have suggested platelet testing as a way to titrate therapy to the effect desired (20). Although an attractive idea, the lack of an accepted standardized test and uncertainty about the optimal level of platelet inhibition needed limits the clinical utility (22). Another approach is to use more potent thienopyridines that do not need conversion in the liver, such as prasugrel. The TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) study showed a significant reduction in ischemic events, particularly stent thrombosis, but was associated with an increased risk of bleeding in those treated with prasugrel as compared with clopidogrel (23). A number of newer, more potent antiplatelet drugs are also in development. Others have suggested that an increased antiplatelet effect can be obtained by the addition of cilostazol to ASA and clopidogrel (24). Cilostazol is an antiplatelet agent that increases intracellular cyclic adenosine monophosphate via selective phosphodiesterase 3 inhibition. Registry studies and randomized trials have suggested benefit in high-risk patients undergoing PCI (24–26). Of note is that in 1 of the randomized trials, women had a substantial benefit, whereas men did not (25).

The cumulative evidence continues to show that women with coronary artery disease differ from men in many important ways, including the response to antiplatelet therapy. The good news is that clopidogrel is an exception. It is also critically important that future studies are designed to adequately address the responses to therapy in women because outcomes cannot be predicted by mostly male-dominated trials. Only then can treatment be optimized for the growing population of women with cardiovascular disease.

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Key Words: sex ■ antiplatelet agents ■ clopidogrel ■ randomized trials.