Women, Acute Ischemic Heart Disease, and Antithrombotic Therapy
Challenges and Opportunities

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There now exists an extensive and growing literature examining gender-based differences in the pathobiology, presentation, treatment patterns, and clinical outcomes of ischemic heart disease (IHD). IHD is a dominant mode of death for women, and, for >20 years, more women than men die annually from IHD. The first manifestation of IHD in women is frequently myocardial infarction or sudden cardiac death. A better understanding of the spectrum of issues—from pathophysiology through implementation of evidence-based care—among women with IHD is a public health imperative.

Recently, many observations have converged around a common set of themes in the care of women with IHD, especially acute IHD. Lansky et al have pointed out that women with degrees of obstructive coronary artery disease comparable to those of men receive less revascularization. From the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE) registry, we know that women presenting with high-risk non–ST-segment–elevation acute coronary syndromes (primarily myocardial infarction) are less likely than men to undergo an early invasive management strategy despite being at a higher baseline risk. Women with non–ST-segment–elevation acute coronary syndromes are less likely than men to receive recommended evidence-based medications and cardiac procedures, again despite being at higher baseline risk.

However, there are also challenges in evaluating and deciding on treatments for women presenting with acute coronary syndromes. Roe and colleagues have shown that women presenting with non–ST-segment–elevation acute coronary syndromes have a greater likelihood of nonobstructive disease than do men, and the Women’s Ischemia Syndrome Evaluation (WISE) investigators have compiled a substantial body of work suggesting that the pathobiology of IHD differs in women compared with men. All of this makes it imperative that we perform enough research in women to properly ascribe both the benefits and potential risks to any therapy that might be used in a particular disease setting.

Because antithrombotic therapy is considered cornerstone therapy for all acute ischemic coronary syndromes (ST-segment elevation and non–ST-segment elevation), understanding these drugs, including measuring their benefits and risks, is critical. In the setting of non–ST-segment–elevation acute coronary syndromes, a systematic overview of glycoprotein IIb/IIIa inhibitors suggested heterogeneity of treatment effect in women compared with men, raising questions about the appropriateness of treating women with a potentially harmful group of drugs. However, additional analyses of men and women who were troponin positive as well as men and women undergoing percutaneous coronary intervention suggested that in patients with “proven” obstructive coronary artery disease as the cause of their acute syndrome, there was in fact a consistent treatment effect when women were compared with men.

In women, there is an added wrinkle to the story about quantifying harm. Alexander et al, in a series of studies from the CRUSADE registry, have pointed out that antithrombotic therapy is frequently overdosed; this issue is particularly problematic in women, directly translating into worse bleeding outcomes, including a need for transfusion. Because women are typically older, lighter, and have more associated comorbidities, including chronic kidney disease, that may contribute to bleeding risk, this is not surprising. Given the potential differences in pathobiology and presentation that may affect treatment choices and, subsequently, clinical outcomes, enrolling sizable numbers of women in research studies is critical to help clinicians to properly understand differential treatment effects.

Among patients presenting with ST-segment–elevation myocardial infarction who are to be treated initially with lytic therapy for reperfusion, adjunctive anticoagulation is a class I recommendation. Alternatives to unfractionated heparin have now been well investigated and include low-molecular-weight heparins, factor Xa inhibitors, and direct thrombin inhibitors. The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 trial demonstrated the superiority of enoxaparin, a low-molecular-weight heparin, over unfractionated heparin as adjunctive therapy for patients receiving fibrinolysis for ST-segment–elevation myocardial infarction. Overall, the primary end point of death or nonfatal recurrent myocardial infarction through 30 days was reduced by 17%. Bleeding

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was more common with enoxaparin than with unfractionated heparin, although there were similar rates of intracranial hemorrhage.\textsuperscript{15}

In this issue of \textit{Circulation}, Mega and colleagues report on the population of women enrolled in ExTRACT.\textsuperscript{19} As in other clinical trials of ST-segment--elevation myocardial infarction, the vast majority of patients enrolled in ExTRACT were men, but because of the overall large trial size there is information on \textgreater{}4000 women in this trial. Consistent with other reports, they were older, had more comorbidities, and received fewer evidence-based medications than men in the trial. The use of cardiac procedures in the trial was low overall, reflecting the practice patterns seen in a mostly non-US population, and was significantly lower in women than in men. Again, as has been previously and consistently noted, the risk of ischemic outcomes was worse in women, with a reported adjusted risk of mortality 25\% higher than in men. This finding was consistent across age groups, with the greatest absolute risk for women relative to men being in the oldest age population.

The treatment effect with enoxaparin was similar in both sexes. Enoxaparin reduced the 30-day risk of the composite of death and recurrent myocardial infarction by 16\% (relative risk, 0.84; 95\% CI, 0.75 to 0.95) and of death by a nonsignificant 12\% (relative risk, 0.88; 95\% CI, 0.76 to 1.02).

The “cost” to this ischemic benefit was an increased risk of bleeding. Major bleeding, minor bleeding, and the composite of major or minor were all significantly increased among women treated with enoxaparin compared with women treated with unfractionated heparin. Intracranial hemorrhage was directionally, but not significantly, increased (relative risk, 1.43; 95\% CI, 0.81 to 2.51). However, there was insufficient power to reliably detect a difference in this subgroup of women, again pointing to the need for large enough experience in key populations to be able to make meaningful treatment recommendations regarding novel therapies. It should be noted that the investigators report that bleeding was similar among men and women receiving enoxaparin.

A very important feature of ExTRACT was the attention given to the dosing of enoxaparin. The investigators were particularly careful in recommending the dosing of enoxaparin among the elderly, a critical feature given the diminished renal function of many elderly patients and the fact that enoxaparin is a renally excreted drug. In the group of patients aged \textgreater{}75 years, no bolus dose of enoxaparin was given, and the maintenance dose was decreased by 25\%. Major differences were noted in creatinine clearance in women compared with men in ExTRACT. Their median creatinine clearance of 66 mL/min (interquartile range, 51 to 84) suggests that almost one half of the women in the trial had stage III chronic kidney disease.\textsuperscript{20} Although Mega and colleagues do not provide data on compliance to this enoxaparin dosing strategy among their investigators or on the relationship between protocol compliance and bleeding, the fact that there was comparable major bleeding with enoxaparin in women and men despite this marked difference in renal function suggests that the investigators were successful with this dosing strategy; this reinforces the imperative to dose-adjust potent antithrombotics among patients with chronic kidney disease. Success with this protocol dosing is a major accomplishment of the ExTRACT investigators.

Several broader research issues are worth highlighting. Although there was no specification as to the number of women to be enrolled in the trial, the large sample size allowed recruitment of a large number of women, permitting reasonable insight into the risks and benefits of treating women with enoxaparin versus unfractionated heparin. Large trials are critical to advancing our understanding of new therapies because most future advances in acute care cardiovascular medicine are expected to be incremental. As trials become increasingly global, efforts need to be focused on including a spectrum of patients with characteristics such as advanced age and comorbidities such as chronic kidney disease, which are particularly problematic among women.\textsuperscript{21}

Equally important is to make certain that the patterns of care, including angiography and its timing, are reflective of the areas of the world where the therapy will ultimately be used. ExTRACT had very little enrollment inside the US because of its focus on using fibrinolysis. Given the interplay among antithrombotic drugs, invasive cardiac procedures, and patient characteristics, understanding these relationships is critical.

ExTRACT should serve as an example of the benefits that can be realized with careful dosing of antithrombotic therapy both in practice and in clinical trials. High-risk patients typically have the most to gain from aggressive implementation of evidence-based prescribing because their baseline risk is higher, but, paradoxically, they are typically treated less aggressively.\textsuperscript{22} Efforts such as those described in the article in this issue of \textit{Circulation} by Mega et al are invaluable in allowing confident estimates of both risks and benefits so that clinicians and patients can make quantitatively informed treatment decisions. Finally, although knowledge of evidence-based medicine has moved into the mainstream,\textsuperscript{23} the practice of evidence-based prescribing remains suboptimal. Despite an accumulating amount of data linking evidence-based performance to outcome,\textsuperscript{24} we continue to see lower use of evidence-based prescribing, particularly among subgroups such as women, as demonstrated by the current report. We know the challenges; now we have the opportunity to look at the data, understand the gaps, and make appropriate changes to our implementation of proven therapies.\textsuperscript{25}

\section*{Disclosures}

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\section*{References}


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