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EDITORIAL COMMENT

Do Women Really Respond Differently to Antiplatelet Therapies?

The Evidence Just Doesn't Add Up*

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Everything we hear is an opinion, not a fact.
Everything we see is a perspective, not the truth.
—Marcus Aurelius (1)

The whimsical notion that "men are from Mars, women are from Venus" is often used to highlight differences in pathophysiology, epidemiology, clinical presentation, and management of cardiovascular disease in men and women. Since the 2001 Institute of Medicine report, "Exploring the Biological Contributions to Human Health: Does Sex Matter?" (2), a growing body of research has highlighted the importance of considering influences of sex on the pharmacokinetics, pharmacodynamics, safety, and efficacy of numerous medications.

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In this issue of the *Journal,* Lau et al. (3) explore sex-specific heterogeneity of treatment effect (HTE) for potent $P2Y_{12}$ inhibitors by pooling study-level data from 7 active- or placebo-controlled trials in an aggregate-data meta-analysis (ADMA). The key finding is that there is comparable efficacy (reduced ischemic events) and safety (increased bleeding events) among men and women. The authors conclude that "sex should not influence patient selection for the administration of potent $P2Y_{12}$ inhibitors in individuals with appropriate indications for use." Are these conclusions justified? To address this question, several key issues merit consideration.

Principal factors motivating the exploration of sex-specific treatment effects in this meta-analysis are: 1) differences in platelet reactivity and responsiveness to antiplatelet therapy; 2) underuse of antiplatelet therapies in women; and 3) under-representation of women in controlled trials, leading to individual studies being underpowered to examine sex-specific differences. Let us examine carefully these premises.

Sex-specific differences in platelet function have been previously reported, with women exhibiting higher baseline or on-treatment (aspirin or clopidogrel) platelet reactivity compared with men (4,5). It remains unclear whether this is mediated by true biological differences at the platelet level or is confounded by a higher prevalence of comorbidities (older age, diabetes, chronic kidney disease, among others) associated with enhanced platelet reactivity, and whether these differences contribute to increased cardiovascular risk in women (4,5).

Sex-specific HTEs have been claimed for antiplatelet agents, such as aspirin, platelet glycoprotein (GP) IIb/IIIa inhibitors, and clopidogrel. However, careful analysis of the data does not allow one to draw firm conclusions on this point. For example, the results of meta-analyses of controlled trials have been overinterpreted as providing proof of sex-based efficacy of low-dose aspirin in primary prevention, leading to guideline recommendations in support of reduction of myocardial infarction (MI) in men and reduction of ischemic stroke in women (6). An update of the U.S. Preventive Services Task Force guidelines in 2016 eliminated sex-specific recommendations because critical appraisal of the evidence showed that the conclusions of prior ADMA in 2009 relied on subanalyses with serious limitations (i.e., lack of

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pre-specification [only 3 of 11 specified sex as an a priori subgroup], lack of adjustment for confounders [only 5 of 11 adjusted for confounders] or multiple comparison [which increases the propensity of false-positive results from pooled analyses of inconclusive trials], and lack of formal interaction test [although the 95% confidence interval clearly overlapped]) (7). The Antithrombotic Trialists' Collaboration individual-patient data meta-analysis (IPDMA) showed that sex-specific differences in MI or stroke were no longer statistically significant after controlling for multiple comparisons (8). Furthermore, the lack of heterogeneity of treatment effect in secondary aspirin prevention challenges the sex-specific findings in question (8). Thus, on the basis of the totality of data, not only is there insufficient evidence to recommend aspirin for primary prevention—a position supported by the U.S. Food and Drug Administration, the Canadian Cardiovascular Society, and the European Society of Cardiology guidelines—there is even less credible evidence to justify sex-specific recommendations.

A significant, qualitative sex-treatment interaction was observed for trials of GP IIb/IIIa inhibitors with evidence of benefit in men, but harm in women (9). Adjustment for important differences in clinical characteristics that could potentially explain this difference in treatment effect (women were older, had more comorbid conditions, and more frequently had larger infarctions compared with men) did not materially influence the sex differences. However, when risk was further stratified by troponin level, no sex differences were seen. More recent studies with concomitant use of clopidogrel have not shown sex-related differences in outcome. These findings highlight the deficiencies of "one-variable-at-a-time" subgroup analyses, and provide support for multivariable risk-based analyses to reliably explore significant HTEs in clinical trials (10).

In an ADMA of 5 large trials, clopidogrel treatment was associated with a significant reduction in the risk of cardiovascular events in both women and men (11). In women, the overall effect of clopidogrel was driven by a significant reduction in MI, but not stroke or mortality. By contrast, reductions in all 3 endpoints were significant in men. However, there was no evidence of significant sex-treatment interaction, highlighting the importance of appropriate methods to assess heterogeneity between subgroups. Taken together, these results challenge the notion of sex-treatment interaction with antiplatelet therapy.

Underuse of prasugrel in women (23% vs. 77% use in men) has been reported in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network-Get With the Guidelines) analysis, but it is not clear whether sex alone was a determining factor in choice of treatment. Unlike the controlled trials showing greatest benefit in high-risk patients, prasugrel was most frequently used in patients at the lowest predicted risk for bleeding and mortality, reflecting the risk-treatment paradox observed in previous studies. Thus, the limited use of prasugrel in women might be confounded by greater prevalence of characteristics that predict higher risk for bleeding (and mortality), such as older age and medical comorbidities including hypertension, hyperlipidemia, diabetes, chronic kidney disease, and so on.

Results of a meta-analysis are useful when the individual trials are not adequately powered to look at events in subgroups, as is clearly the case here. The investigators justify pooling due to a lack of statistical heterogeneity, a necessary (but not sufficient) criterion for pooling. A major limitation is that the tests for estimating statistical heterogeneity lack power, and therefore frequently do not reject the null hypothesis of homogenous results, even if clinically relevant differences exist (12). One could argue that trials are not poolable, given their substantial clinical heterogeneity in study design, patient inclusion criteria, baseline characteristics, endpoints, treatment regimens, and follow-up. Six trials used an active comparator, and 1 was placebo-controlled (PEGASUS-TIMI 54 [Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54]). Even in the 3 CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trials where clopidogrel was used as an active comparator, the timing of oral clopidogrel treatment (administered either immediately before or after percutaneous coronary intervention [PCI]) was biased in favor of cangrelor, an intravenous $P2Y_{12}$ inhibitor with a rapid onset of action. Because clopidogrel takes at least 2 h to have maximal antiplatelet effect, delaying administration until the time of PCI results in little or no antiplatelet activity during the procedure. Not surprisingly, the outcome benefit observed in the CHAMPION PHOENIX trial was frontloaded during the first 2 h, when antiplatelet effects of clopidogrel were suboptimal. Accordingly, the Food and Drug Administration approved cangrelor *in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor* (13). The label is appropriately silent on a superiority claim relative to clopidogrel. Although the results of sensitivity analyses that excluded data from

PEGASUS-TIMI 54 and the CHAMPION trials did not reveal significant sex-specific HTEs, by excluding more than 52% of the overall cohort (46,282 of 87,850), the analysis lacks the necessary statistical power to capture true positive interactions.

Existing criteria for judging the credibility of subgroup analyses emphasize the importance of prior probability, in addition to the statistical power of the subgroup analysis (14). Even when there is excellent subgroup power, the positive predictive value drops markedly when prior probability for a subgroup effect is low, as is the case here. Furthermore, multivariable risk-based models yield greater insights in detecting HTEs compared with conventional "one-variable-at-a-time" subgroup analyses that are prone to false-negative results (10). Sex-specific differences were not observed in analyses stratified on the basis of age and history of PCI; however, because the analysis did not include individual patient-level data, a deeper exploration into the source of HTE was not possible. Because confounding can be more effectively controlled in subgroup analyses in IPDMA than in ADMA, the former has advantages over the latter in identifying true interactions. In 1 recently published report, the IPDMAs found 14 times more interactions that were statistically significant than the matched ADMAs (15).

Other essential dimensions of evidence derived from a meta-analysis include pre-specification to minimize potential bias, and adjustment for multiplicity to avoid spurious (false-positive) conclusions. Clearly, this pooled analysis was not prospectively planned. Lack of multiplicity adjustment is not a major issue, as no sex-specific interaction was found. Finally, because randomization was not stratified on the basis of sex in any of the individual trials, one cannot exclude the potential impact of confounding (measured or unmeasured) on the overall results. On the basis of these limitations, it is debatable whether this meta-analysis conforms to the criteria that would confer high credibility from a regulatory perspective (16).

Even if one accepts the results of this meta-analysis at face value, it is not clear what new or unique insights are offered by the pooled results that cannot be inferred a priori from the published results of the individual trials. The finding that there is no sex-treatment interaction associated with more potent $P2Y_{12}$ inhibitors relative to clopidogrel replicates previous results with aspirin, GP IIb/IIIa inhibitors, and clopidogrel. The cumulative evidence continues to show that, in terms of response to antiplatelet therapy, what is good for the gander is also good for the goose.

A Cochrane review recently reported that significant sex-treatment interactions are only slightly more common than expected by chance (6%, 8 of 109 topics assessed), and meta-analyses rarely corroborate sex-based subgroup findings from individual randomized trials (17). Statistically significant sex-treatment interactions typically have limited biological plausibility, clinical significance, or policy implications, as reflected in American College of Cardiology/American Heart Association guideline recommendations that do not distinguish between the treatment of men and women. Accordingly, although the whimsical premise that "men are from Mars, women are from Venus" is popular, it might be time to bring such theories down to Earth.

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