Platelet Mapping Highlights Our Burgeoning Understanding of Sex Dimorphism in Vascular Disease—and All That We Have Yet to Learn

Monica Majumdar, MD, MPH; Anahita Dua, MD, MS, MBA, FACS

Division of Vascular and Endovascular Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

The personalization of risk stratification and antithrombotic management in vascular surgery has been discussed widely, but to date we have not produced the science to tailor anticoagulant/antiplatelet therapy individually.[1,2,3] Through our research at Massachusetts General Hospital, we have aimed to identify objective and quantifiable metrics that put patients at highest risk for graft and stent thrombosis, and to leverage those metrics to guide subject-specific thromboprophylaxis. Our recent prospective observational study using the point-of-care, FDA-approved viscoelastic technology of thromboelastography with platelet mapping (TEG-PM) investigated perioperative coagulation profiles in patients undergoing lower extremity revascularization.[4] As we began to learn more about the complex coagulation and platelet environment of the vascular patient, both from our own data and from the robust body of existing cardiovascular literature, an important additional imperative emerged: *Can we delineate objective differences in responsiveness to antiplatelet medications between the sexes, thereby explaining why female patients with peripheral arterial disease (PAD) have fewer risk factors yet higher rates of nonhealing and amputation?*

Emerging research over the past 2 decades has been prescient in recognizing that the time is right to reach beyond our current understanding of sex and its relation to cardiovascular outcomes. Thought leaders across disciplines have illuminated key scientific knowledge gaps relevant to sex differences in cardiovascular risk factors and disease course.[5,6,7]

Through this research, some essential themes have emerged. The first is that phenotypic presentations of cardiovascular disease differ between sexes.[8,9] Female patients are the understudied and often unrecognized cohort in this scenario, and we frequently find ourselves with terms such as *atypical symptoms* making their way into our shared lexicon.[10] The danger in this approach is a potential delay in diagnosis and intervention. In our own cohort of 107 patients, we found this to be true as female patients were significantly less likely to be undergoing surgery for claudication symptoms when compared with males (27% vs 57.1%) and significantly more likely to be undergoing surgery for chronic limb-threatening ischemia (67.6% vs 34.3%) [all $P<.01$].[4]

Another key theme is that known risk factors for cardiovascular disease appear to be less prevalent in females than males, yet female patients are apparently more sensitive to the effects of certain risk exposures.[6,11] In our cohort of PAD patients, females exhibited fewer uncontrolled comorbid conditions, such as hypertension requiring combination pharmacologic therapy (37.8% vs 58.6%), uncontrolled diabetes (2.7% vs 18.6%), coronary artery disease (29.7% vs 57.1%), chronic kidney disease (27.0% vs 51.4%), and history of myocardial infarction (16.2% vs 35.7%) [all $P<.05$].[4] This lack of traditional cardiometabolic risk factors may exacerbate the delayed or missed recognition of female vascular disease.

Finally, and most concerning, is the consistent finding across cardiology and vascular disease types that current available treatment paradigms are less effective in females compared with males.[6,12] There is a growing body of evidence pointing to inadequately measured or yet unidentified key risk factors for cardiovascular disease in female patients. In our analysis of 321 platelet mapping samples we found that female patients had consistently higher platelet reactivity, with greater platelet aggregation and lower platelet inhibition. This was observed overall, across perioperative clinical phases, and, most importantly, ***when comparing within similar antiplatelet regimens.*** In those on monoantiplatelet therapy, female patients exhibited 11.2% higher platelet aggregation as compared with males (80.6% ± 21.0 vs 69.4% ± 25.0, $P<0.01$). In those on dual antiplatelet therapy, female patients exhibited 23.1% greater platelet aggregation than males 67.9% ± 23.8 vs 44.8% ± 31.8, $P<0.01$).[4] In other words, even while being on the same therapy as their male counterparts, women exhibit higher platelet reactivity, which is associated with increased rates of thrombosis. This begs the question: Are we just undertreating women? While both vascular and cardiology society guidelines strongly recommend the use of at least antiplatelet monotherapy for any patient with symptomatic PAD, there is currently no standard recommendation for titration of therapy.[1] The stark differences between the sexes in terms of biologic response to medications found in our cohort suggests that sex-based titration may be vital.

Based on persistently high platelet reactivity across antiplatelet regimens, we worry that available therapies find themselves inadequately matched for the female PAD patient. These data highlight the imperative need to understand sex-specific ranges or thresholds for both established and novel cardiovascular biomarkers. What is left to uncover are the differences in thrombotic risk on a sex-specific level. While greater platelet aggregation was found to be associated with postoperative graft and stent thrombosis in this cohort, our current sample size is too small to distinguish a sex-predictive pattern. Are female patients more likely to thrombose because of their inherent prothrombotic state? Or is their platelet reactivity "tolerance" greater than males? Do

female patients need more frequent prescription of novel P2Y12 inhibitors, such as ticagrelor, to attain the same amount of platelet inhibition as their male counterparts would with aspirin or clopidogrel? Do female patients benefit from the theoretic synergistic effect on platelet physiology that arises from factor Xa inhibition?

To answer these important questions, our coagulation lab is embarking on 2 randomized studies: the first to assess if point-of-care viscoelastic-driven titration of antiplatelet management results in the desired pharmacologic response, and the second will determine if postoperative thrombosis rates can be mitigated through viscoelastic-driven medication management. But as we explore these important questions, we will continue to focus on our female patients. We are at the beginning of our understanding of how and why cardiac and vascular disease can present quite different in females and males, and we find ourselves in the uniquely privileged position to contribute to this evolving narrative. ■

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

Manuscript accepted October 25, 2022.

Address for correspondence: Anahita Dua, MD, MS, MBA, FACS, Massachusetts General Vascular Center: Vascular and Endovascular Surgery, 55 Fruit St., Boston, MA 02114. E-mail: ADUA1@mgh.harvard.edu

REFERENCES

1. Gupta R, Majumdar M, Imran R, Yi J. A comprehensive review on antithrombotic therapy for peripheral artery disease. *Semin Vasc Surg*. 2022;35(2):124-131. doi:10.1053/j.semvascsurg.2022.04.004
2. Lüscher TF, Davies A, Beer JH, et al. Towards personalized antithrombotic management with drugs and devices across the cardiovascular spectrum. *Eur Heart J*. 2022;43(10):940-958. doi:10.1093/eurheartj/ehab642
3. Lüscher TF, Steffel J. Individualized antithrombotic therapy. *Hamostaseologie*. 2016;36(1):26-32. doi:10.5482/HAMO-14-12-0080
4. Majumdar M, McElroy I, Waller HD, et al. Identifying sex dimorphism in peripheral artery disease with platelet mapping. *Ann Vasc Surg*. 2022;S0890-5096(22)00506-4. Online ahead of print September 2, 2022. doi:10.1016/j.avsg.2022.08.006
5. Vaura F, Palmu J, Aittokallio J, Kauko A, Niiranen T. Genetic, molecular, and cellular determinants of sex-specific cardiovascular traits. *Circ Res*. 2022;130(4):611-631. doi:10.1161/CIRCRESAHA.121.319891
6. Pabon M, Cheng S, Altin SE, et al. Sex differences in peripheral artery disease. *Circ Res*. 2022;130(4):496-511. doi:10.1161/CIRCRESAHA.121.320702
7. Nitsche C, Koschutnik M, Kammerlander A, Hengstenberg C, Mascherbauer J. Gender-specific differences in valvular heart disease. *Wien Klin Wochenschr*. 2020;132(3-4):61-68. doi:10.1007/s00508-019-01603-x
8. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. *Eur J Heart Fail*. 2020;22(9):1551-1567. doi:10.1002/ejhf.1902
9. Arnold AP, Cassis LA, Eghbali M, Reue K, Sandberg K. Sex hormones and sex chromosomes cause sex differences in the development of cardiovascular diseases. *Arterioscler Thromb Vasc Biol*. 2017;37(5):746-756. doi:10.1161/ATVBAHA.116.307301
10. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the evaluation and diagnosis of chest pain: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144(22):e368-e454. doi:10.1161/CIR.0000000000001030
11. Rexrode KM, Madsen TE, Yu AYX, Carcel C, Lichtman JH, Miller EC. The impact of sex and gender on stroke. *Circ Res*. 2022;130(4):512-528. doi:10.1161/CIRCRESAHA.121.319915
12. Nguyen LL, Brahmanandam S, Bandyk DF, et al. Female gender and oral anticoagulants are associated with wound complications in lower extremity vein bypass: an analysis of 1404 operations for critical limb ischemia. *J Vasc Surg*. 2007;46(6):1191-1197. doi:10.1016/j.jvs.2007.07.053