LITERATURE HIGHLIGHTS

Exploring Differences in Antiplatelet Therapy Efficacy in Women With PAD

Dr. Anahita Dua and colleagues evaluate platelet aggregation and inhibition in male and female PAD patients on anticoagulation undergoing lower extremity revascularization.

In a prospective, observational study evaluating platelet reactivity in male and female patients with peripheral artery disease (PAD) undergoing revascularization, Majumdar and colleagues found a lower prevalence of traditional cardiometabolic risk factors in females but high platelet reactivity with increased platelet aggregation and diminished platelet inhibition despite similar antiplatelet management between groups. The results were published in *Annals of Vascular Surgery*.[1]

Investigators sought to analyze platelet reactivity between male and female patients with PAD using thromboelastic metrics and platelet mapping to measure clot characteristics and platelet function. Patients were prospectively enrolled between December 2020 and January 2022 if they underwent lower extremity revascularization (open surgical, endovascular, or hybrid) to reestablish inline flow. Patient demographics, comorbidities, and antiplatelet regimens were recorded.

Blood was collected for viscoanalysis within 24 hours preoperatively, 1 to 5 days postoperatively during the inpatient stay, and at the first (1-month) or second (3-month) follow-up visit. Whole blood samples were tested using Thromboelastography (TEG; Haemonetics Corp), and platelet function was quantified using platelet mapping cartridges. Antiplatelet therapy was closely monitored, with patients considered on antiplatelet therapy if the last dose was within 7 days of the platelet mapping blood draw.

Demographics, comorbidities, and antiplatelet regimens were compared by sex using Student's *t* test (continuous variables) and Fisher's exact test (binary variables), and platelet mapping metrics were analyzed by clinical phase of collection, compared by sex, and then stratified by collection phase and antiplatelet regimen (monoantiplatelet therapy [MAPT] or dual antiplatelet therapy [DAPT]).

Patients were followed for up to 1 year. The primary endpoint was occurrence of thrombosis, defined as

KEY FINDINGS

- Female patients had a significantly lower prevalence of cardiometabolic risk factors as compared with male patients, including uncontrolled diabetes, hypertension, CKD, CAD, and history of MI.
- Overall platelet reactivity was higher in female versus male patients, with greater platelet aggregation and lower platelet inhibition.
- The differences in platelet aggregation and inhibition between female and male patients were strongly statistically significant in the postoperative inpatient phase.
- Overall use of anticoagulation was similar between cohorts during platelet mapping blood draws (30% for males vs 29.7% for females); however, female patients had greater platelet reactivity even when samples were analyzed across similar antiplatelet regimens.
- 19.6% of patients experienced a thrombotic event during the study, but there was no significant difference in platelet aggregation between females and males who had an event.

radiographic or clinical evidence of graft/stent failure, need for reintervention to reestablish flow, or need for major limb amputation for graft/stent thrombosis.

One hundred and seven patients were analyzed (70 male, 37 female). The prevalence of uncontrolled diabetes (2.7% vs 18.6%; $P = .03$), hypertension requiring combination therapy (37.8% vs 58.6%; $P = .05$), chronic kidney disease (CKD; 27.0% vs 51.4%; $P = .02$), coronary artery disease (CAD; 29.7% vs 57.1%; $P < .01$), and history of myocardial infarction (MI; 16.2% vs 35.7%; $P = .02$) were lower in female as compared with male patients.

Significantly more female patients underwent intervention for chronic limb-threatening ischemia (Rutherford class ≥ 4), while significantly fewer female patients underwent intervention for claudication (Rutherford class ≤ 3) (67.6% vs 34.3% for males and 27.0% vs 57.1% for males; both $P < .01$).

Investigators analyzed 210 male and 111 female platelet mapping samples (three samples from each clinical phase for each patient). In females, overall platelet reactivity was significantly higher as compared with males, with greater platelet aggregation and lower inhibition (23.8% ± 23.4% vs 36.8% ± 28.9%; $P < .01$). Differences in platelet reactivity were not statistically significant between sexes in the preoperative analysis, but they were strongly statistically significant in the postoperative inpatient phase (platelet aggregation, 74.2% ± 25.0% in females vs 58.8% ± 29.7% in males; platelet inhibition, 25.5% ± 25.1% in females vs 41.2% ± 29.7% in males; both $P < .01$). This pattern continued in the postoperative outpatient phase (in females vs males: platelet aggregation, 75.8% ± 24.9% vs 62.4% ± 27.7%; $P = .02$; platelet inhibition, 25.0% ± 25.0% vs 38% ± 28.0%; $P < .01$).

Overall use of anticoagulation between cohorts did not differ across all time points of platelet mapping sample collection. Most samples were obtained when patients were on MAPT, but the use of DAPT did not differ between groups. Between sexes, the differences in platelet aggregation were 11.2% and 23.1% in the MAPT and DAPT groups, respectively (both $P < .01$).

During the study period, 21 (19.6%) patients had a thrombotic event (14 male, 7 female). Analyzing platelet

ENDOVASCULAR TODAY ASKS…

Study investigators Anahita Dua, MD, MS, MBA, and Monica Majumdar, MD, MPH, with Massachusetts General Hospital/Harvard Medical School in Boston, Massachusetts, provided some background and what the study results might mean for future practice.

Can you give some background into the rationale for the study and your hypotheses? Why was analysis of platelet reactivity of particular interest?

Women are known to have lower risk factors for PAD yet have lower rates of wound healing and higher rates of amputation. This has been traditionally blamed on everything from social factors to innate medical issues, but exploration of the concept that we may be undertreating women has not happened. We know that most PAD studies are done on White males, so it follows that the guidelines we use to treat PAD may be inappropriate for other subsets of the population, such as women. This study aimed to see if the current accepted antiplatelet regimens were indeed having the same impact on the platelet function of men and women.

What do you hypothesize is the reason for the high platelet reactivity in women in this study?

This is a challenging question, as our study did not delve into the why. Initially, there was a thought that this may have something to do with estrogen, but all the women in our study were postmenopausal. Future research should investigate whether high platelet reactivity is generalizable to all women and the underlying causes.

More female patients in this study had more severe PAD (Rutherford ≥ 4) versus male patients despite having a lower prevalence of cardiometabolic risk factors. Is there any potential association between more severe disease and platelet reactivity?

This is an absolute possibility, and our sample size is not large enough to truly answer this question. However, we hypothesize that severe disease is not the primary driver because we have the data for all patients and do not see an uptick in platelet reactivity in men who have more extensive PAD compared to their male counterparts with less extensive PAD.

Although this paper provides support for further analysis of sex-specific coagulation profiling in PAD patients, how have these current findings affected your processes for patient management? Ideally, what does an approach to PAD management that takes sex differences into account look like?

This is a great question—when it comes to a patient's coagulative state, there are myriad factors at play, and sex is just one. We know from our previous research that a platelet inhibition threshold of 30% is associated with a reduced thrombotic rate[1]; hence, we recommend using an objective, point-of-care test (viscoelastic testing) to ensure patients have reached the 30% platelet inhibition threshold. This would mean the patient would initially be started on some combination of antiplatelet agents, and TEG platelet mapping would be performed every 7 days, with medications adjusted until the 30% platelet inhibition threshold is reached. In this fashion, the antiplatelet therapy would move away from "one size fits all" to a personalized approach to therapy.

What are the cost implications of additional viscoelastic testing, and how do you weigh the involved costs against the potential benefits?

After an expensive revascularization procedure, the average time it takes to heal a wound in this population is around 200 days. That means the revascularization must supply an appropriate amount of blood flow without impedence for at least this amount of time or the wound will not heal. The cost of nonhealing diabetic foot ulcers in this country is at $11 billion. When a graft/stent thromboses, the cost of repeated interventions to salvage the revascularization is well into the thousands of dollars, not including the hospital stay and postoperative care. Finally, if a patient undergoes an amputation, the cost to society is extreme, and up to 50% of patients die within 1 year of amputation. Most hospitals have a TEG machine already available, as it is readily used for trauma, organ transplant, and cardiothoracic surgery. The only additional cost would be to buy the cartridges used for TEG platelet mapping. A simple blood sample would be used to confirm the patient was meeting platelet function cut points on the current antiplatelet regimen, and this would in turn optimize the chances that the graft/stent will not thrombose. This personalized approach to antiplatelet therapy would serve to save thousands of dollars by preventing thrombosis and subsequent reintervention and amputation.

Can you give us a preview of how your group plans to expand on these findings in further analyses?

At this point, we are in the midst of a study that is actively using TEG platelet mapping to guide therapy. We start patients on aspirin postrevascularization and then check a TEG platelet mapping in 7 days (the life cycle of a platelet). If the patient does not meet the 30% platelet inhibition cut point, we add further antiplatelet medications in a step-up fashion until the cut point is achieved.

Along with further analysis of sex-specific coagulation profiling, what other actions must be taken to improve outcomes of female patients with PAD?

Recognizing that women have worse outcomes in terms of wound healing and amputation means that, aside from the coagulation optimization, we must also ensure excellent, timely wound care and infectious disease and diabetic management in women to ensure the best outcomes in females with PAD.

1. Majumdar M, Hall RP, Feldman Z, et al. Predicting arterial thrombotic events following peripheral revascularization using objective viscoelastic data. J Am Heart Assoc. 2023;12:e027790. doi: 10.1161/JAHA.122.027790

mapping samples just prior to the thrombotic event, median platelet aggregation was 80.9%. There was no significant difference in platelet aggregation in female versus male patients who experienced a thrombotic event ($P = .26$). There was a difference in aggregation between patients who had a thrombotic events versus those who did not, but this was expected given that there was a difference in platelet inhibition between groups.

These findings build upon prior research demonstrating similar or worse disease prevalence and progression in women with PAD lacking traditional risk factors. The investigators postulated that if female patients are indeed more thrombotic at baseline as compared with male patients, the presence of comorbid conditions may not be necessary for them to have the same disease pathology. As such, this study's findings of sex dimorphism in platelet reactivity may allow for more individualized care for patients with or at risk for vascular disease. ■

1. Majumdar M, McElroy I, Waller HD, et al. Identifying sex dimorphism in peripheral artery disease with platelet mapping. Ann Vasc Surg. 2023;88:42-50. doi: 10.1016/j.avsg.2022.08.006