The Ever-Humbling Challenge of Peripheral Artery Disease Treatment Seen Across the Sexes

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The area of peripheral artery disease (PAD) is growing on multiple fronts: the prevalence and incidence are increasing[1]; the number of procedures to treat it is increasing[2]; and the number of devices used to treat it sometimes feels as if it is increasing fastest of all. As in all areas of medicine, we grow by understanding what we *can* do, and as this expands, we must continually wrestle with what we *should* do. In the vein of the latter pursuit, the authors have evaluated endovascular treatment patterns and results, specifically looking at how these may differ between men and women.[3] When asking the questions of whether men and women are receiving different endovascular treatment for PAD and whether they are having different results, the great questions of the next level of depth are "Why?" and "Are these differences causally related or secondary to other concurrent differences?"

The notion of sex differences in PAD is not new. Although the prevalence rate was previously reported as higher in men than women, more recent studies show similar rates between men and women, with possibly higher rates of asymptomatic PAD in women relative to men[4]; in the most recent 2016 American Heart Association/American College of Cardiology Guidelines for Management of PAD, male sex is no longer a risk factor of decision-making significance.[5] As expected on the basis of these trends, women represented 41% of the patients evaluated in this retrospective cohort study,[3] which is a better representation of women in proportion to their percentage of those undergoing PAD treatment than many vascular surgery randomized controlled trials.[6] Proposed reasons for this loss of sex difference generally include increased awareness; changes in risk factor rates, such as the reduction of differential smoking rates between men and women; or a combination of the two. Taking the literature in aggregate, the strongest argument can probably be made for the combination, although the nature versus nurture debate continues to flourish in the era of epigenomics and studies on the social determinants of health.

The Society for Vascular Surgery Vascular Quality Initiative database serves as an excellent data source for evaluating the peripheral vascular intervention patterns in real-world practice across a variety of practice types and geographic areas. This database is prospectively maintained by participating institutions, with clinical-level data being placed into the database either by the performing providers or designated data entry personnel who pull data from the record and receive clarifying information from the providers. To participate in the database, all cases for the given module (in this case, the endovascular PAD module) must be put in the database to avoid selection bias. Follow-up is also entered into the database up to 1 year, with specified mandatory follow-up at the 1-year mark. Outcomes are available for review within the participating institution as well as comparison data within the region, although these data are deidentified and participating institutions are prohibited from using comparison data for marketing. These data are not directly shared with the Centers for Medicare and Medicaid Services, but participation has been used to document participation in quality-improvement projects.

Missing data were somewhat of an issue, especially with 17% having a missing Trans-Atlantic Inter-Society Consensus score recorded and 16% having a missing occlusion length recorded; however, the authors used statistical analyses to impute the missing covariate data. In addition, sensitivity analyses with and without the missing data points were reported to be similar. Furthermore, follow-up was recorded in the Vascular Quality Initiative database for only 47% of the cohort. Follow-up data were not imputed, but even the loss of these data for outcomes measurement would still leave >25 000 patients to analyze for outcomes in the cohort.

For the first question of whether men and women are receiving different endovascular treatments, the results of

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analysis in the database indicates that in both univariate and multivariate regression models, the answer is yes. In the authors' words, "factors such as sex, race, lesion location, occlusion length and Trans-Atlantic Inter-Society Consensus score are the strongest drivers of treatment type." On the basis of their supplemental tables, it also appears that practice patterns of the treating center are a sizeable factor with a 9.87 relative risk of tibial stenting per every 1% center stent rate along with a 3.29 and 5.39 relative risk of atherectomy in the femoropopliteal and tibial beds, respectively, related to the center atherectomy rate. To look at the data and immediately write off that the sex and race differences in observed treatment are merely statistical anomalies related to unaccounted covariates is perhaps comforting but nevertheless presumptive. It would be likewise presumptive to conclude from the analysis that conscious or subconscious racism and sexism is the only explanation. Thus, we must look at this finding and ask "Why?" and then be prepared for continued questions rather than answers.

Women in the cohort were older and presented with more severe limitations on ambulatory status, on average, than the men. These factors appear to suggest that women in the study were more frail at baseline, which may have multiple effects weighing on the data. Were some of the patients treated endovascularly deemed "poor surgical candidates" for open revascularization and given a different treatment than their less frail counterparts with otherwise similar clinical and anatomic factors? Alternatively, when deciding whether to add stenting or atherectomy in the endovascular treatment, does the frail patient get everything possible so as to try to avoid reintervention or is the frail patient more often given a "less is more" approach to minimize procedural time and physiologic stress related to the procedure? The latter philosophy is one potential explanation for significantly reduced stenting and atherectomy rates, especially in the femoropopliteal segments.

Occlusion length, Trans-Atlantic Inter-Society Consensus score, and lesion location can be grouped into the anatomic factors that seemed to weigh the most heavily on treatment decision in the cohort. These, along with provider preference, are consistently found in the literature to be key factors guiding treatment decisions in PAD treatment.[2,7] In regard to lesion location, there was no sex difference observed in treating iliac disease, a statistically significant 2% difference in the rate of tibial angioplasty, and a statistically significant 5% difference in the rate of femoropopliteal stenting. Although the factors of race and sex are significant in multivariate analysis, it would be helpful in understanding the scope of the problem to know how much of the treatment variance is explained by provider preference and anatomic factors versus sex and race.

As a secondary analysis, the authors attempted to look at the role of artery diameter in the use of different treatments, which has been previously postulated as a driving factor in sex differences in PAD outcomes in vascular surgery.[8] Because the Vascular Quality Initiative database does not have a record of vessel diameter, we are simultaneously impressed by the authors' use of balloon diameter as a vessel diameter surrogate as well as cautious that this glosses over the potential confounding factor that overdilation/underdilation may play in the outcomes data. The authors note that despite the same median artery diameters, women had statistically smaller arteries than men. Could providers be making the decision to stay with balloon angioplasty alone instead of stenting in a smaller artery at least partially because of concern about the intimal hyperplasia and decreased patency with oversized stents?[9]

In addition to anatomic considerations, provider preference, and vessel size, another area of inquiry on the decision as to whether to stent may be related to how the vessel responds to angioplasty. In their Table 2, the authors show that 37% of the stents were for Trans-Atlantic Inter-Society Consensus A disease.[3] Some may be related to primary stenting of iliac arteries, but how many of these stents were caused by significant recoil or flow-limiting dissection after PTA? Could sex differences in vessel wall response to angioplasty be a factor in the decision in whether to stent secondarily? Could smaller vessel diameter contribute to higher rates of missed significant stenosis after angioplasty?[10] Many things could be theorized, but any unnamed factor, real or perceived, that has a differential proportion among the sexes could contribute to the observed findings of different treatment patterns based on sex.

After tackling the question of whether men and women are treated differently by providers on the basis, at least partially, of sex, the next question evaluated is whether the outcomes in terms of reintervention or occlusion during follow-up were different on the basis of sex. When adjusting for multiple other factors, there were higher rates of reintervention of the femoropopliteal segment in women as well as higher rates of occlusion of the iliac and femoropopliteal segments in women compared with men.[3] These findings are consistent with previous studies demonstrating worse vascular surgery outcomes in women.[8,11] Many of the same factors and questions discussed in the above paragraphs can be applied in evaluating the "why" of this finding, although more advanced disease at presentation and smaller vessel diameter are recurrent explanations.

The authors' analysis of the cohort has demonstrated that sex is a statistically significant factor both in the type of endovascular intervention being performed for PAD as well as in the outcome of those interventions. It is unfortunately a significant logical leap to say that the former causes the

latter. For one thing, there was no significant difference in the management of iliac disease between the sexes and yet women were 42% more likely to find these interventions occluded at follow-up compared with their male counterparts. At least in iliac disease, there is no demonstrated finding that women were getting worse treatment than men and yet had significantly worse results.

Women are getting different treatment than men in the femoropopliteal and tibial segments, which could possibly indicate less efficacious treatment for women in these areas may contribute to the observed poorer outcomes. It is also possible that despite getting "better" treatment, women are having worse outcomes than men when controlling for the other covariates. Of course, this argument first presupposes that we can identify what the better endovascular treatment is. This is why PAD is ever humbling: despite case series, large databases, and even randomized controlled trials, we have still not found that optimal algorithm to serve as the road map for our treatment strategies. In the pursuit of it, we have learned many things along the way, but we have also encountered many more questions, such that full knowledge has stayed elusively out of reach. Hopefully, new lessons will be learned from studies such as BEST-CLI (Best Endovascular Versus Best Surgical Therapy in Patients With Critical Limb Ischemia) and BASIL-2&3 (Bypass Versus Angioplasty in Severe Ischemia of the Limb-2 & 3), along with further exploration of the prospectively maintained databases. We agree with the authors that there is a real need for long-term outcomes data with the added note that, with only a 47% follow-up rate in this sample of the Vascular Quality Initiative database, we have some room for improvement even in short- and medium-term follow-up data.

Perhaps as the analytic software in the endosuite gets more advanced at detecting subtleties commonly overlooked and machine learning is expanded and applied such that thousands of variables get processed proactively and shared real-time, the algorithms generated may help us make that next leap forward in treatment. Until that time, we continue to learn one step at a time. This article adds significant strength to the field, showing that the patient's sex (or its yet unknown significant covariate) needs to be taken into account when counseling patients about treatment as well as keeps us conscious of potential subtle biases in our individual algorithms that may already be materializing.

Disclosures

None.

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