LITERATURE HIGHLIGHTS

Sex-Related Outcome Disparities for CLTI and Lifestyle-Limiting Claudication Interventions

With Pallavi Manvar-Singh, MD, and Elizabeth A. Genovese, MD

In a scoping literature review of sex-based outcomes in patients who underwent endovascular peripheral intervention for lifestyle-limiting claudication (LLC) or chronic limb-threatening ischemia (CLTI), Manvar-Singh et al determined that female patients were associated with bleeding complications, higher rates of reintervention, reduced rates of primary patency postintervention, and elevated risk of nonfatal stroke. Results were published in *Seminars in Vascular Surgery*.[1]

Studies have suggested that peripheral artery disease (PAD) is more prevalent in women than men in certain populations (eg, octogenarians) and that women with PAD often have inferior outcomes and more adverse events after revascularization. Despite this, published evaluations of sex-specific outcomes after endovascular interventions for PAD are lacking.

Investigators first determined that there were no published systematic reviews relevant to the topic. A systematic search of keywords was then conducted in the PubMed, Embase, Web of Science, and Cochrane Library databases, and relevant articles were uploaded to Covidience for further screening. After articles were excluded (eg, not measuring and/or reporting outcomes of interest, incorrect indication), investigators narrowed down to 16 articles related to endovascular procedures and outcomes evaluation in adult women with LLC or CLTI.

The objective was to evaluate sex-related outcomes after endovascular intervention for LLC or CLTI, and the analysis focused on five major outcomes: risk of major bleeding events, mortality, amputation, reintervention/major adverse limb events (MALEs), and major adverse cardiac events (MACE). A meta-analysis was not conducted due to the heterogeneity of the 16 studies in this review.

KEY FINDINGS

- Female patients undergoing endovascular intervention for LLC or CLTI may be at increased risk of bleeding complications, reintervention, and nonfatal stroke.
- Female patients with LLC or CLTI do not experience higher rates of amputation or conclusively higher mortality risk after endovascular intervention.
- Comprehensive, sex-inclusive research is needed to properly address disparities in outcomes and develop tailored treatment recommendations.

Women were found to experience increased bleeding complications after endovascular interventions, with six studies reporting statistically significant increased bleeding events compared to men.

Increased mortality and female sex were not conclusively associated with increased mortality; however, an increased mortality rate among female patients was reported in five studies. Female sex was also not associated with a higher amputation rate, and one study found that men were more likely to undergo minor amputation.

Reintervention/MALEs were more prevalent in women, with a statistically higher rate of reintervention reported in women in five studies. Although five of seven studies addressing MACE rates did not see an increased risk in women, there was evidence pointing to an increased stroke risk in women.

Limitations of this review include the inability to qualify for a systematic review or meta-analysis due to the lack of peer-reviewed articles, difference in studied outcomes, and presence of case-controlled or cohort studies with selection and researcher bias.

These findings not only reveal important sex-related disparities but also indicate the need for further research and trials focusing specifically on female patients. With the ability to consider the risk profiles and physiologic differences at play among male versus female patients with LLC and CLTI, physicians will be able to provide more tailored treatment recommendations.

1. Manvar-Singh P, Folk A, Genovese EA. A scoping review of female sex-related outcomes after endovascular intervention for lifestyle-limiting claudication and chronic limb-threatening ischemia. Semin Vasc Surg. 2023;36:541-549. doi: 10.1053/j.semvascsurg.2023.10.001

ENDOVASCULAR TODAY ASKS…

Pallavi Manvar-Singh, MD, and Elizabeth A. Genovese, MD, share insights into the study's findings and how they may inform future treatment decisions.

While mortality risk and female sex did not have a conclusive connection, some studies in your review did note increased mortality in women. What is the takeaway from this finding? What would further research regarding a potential link between sex and mortality look like?

Mortality risk in patients diagnosed with CLTI has been found to be as high as 35% at 3 years in a recently published randomized controlled trial.[1] Our review failed to conclusively demonstrate increased amputation or mortality rates in female patients, and this may be explained by stricter adherence to medical therapy, such as statins, P2Y12 inhibitors, and factor Xa inhibitors. However, a few studies in our review did note that female sex was an independent predictor of mortality. This is perhaps explained by the fact that female patients tend to present for evaluation and intervention later than their male counterparts with severe symptoms of ischemia. This trend has been observed in other sex-based studies and reviews. Female patients also tend to be older than male patients at initial presentation, which can result in worse outcomes and survival rates. Future clinical research examining matched cohorts by disease severity with equal enrollment of both sexes, including subgroup analyses, may control for potential confounding variables.

One obstacle encountered in your review is the relatively low number of published studies meeting the search criteria. How did this impact the choice of outcomes chosen for the study, and are there other outcomes that would be beneficial to pursue if there were more studies available? How might future trial/outcome designs be more standardized to collect poolable—and actionable—data?

Unfortunately, inadequate recruitment of female patients and insufficient sex-based reporting and analysis in clinical trials continue to be a problem. A major consequence of this disparity is a "one-size-fits-all" approach to treating patients that is irrespective of sex. Our study and similar studies evaluating sex-based differences in outcomes demonstrate that this strategy may contribute to higher rates of adverse events in women compared with men. Our choice of study outcomes included clinically impactful endpoints (such as amputation rates or MALE, MACE, mortality, bleeding, and reintervention rates) that were documented within the articles reviewed, despite significant heterogeneity.

Additionally, freedom from target lesion revascularization (TLR) should be included as a future study endpoint. This may provide further insight as to why female patients experienced increased revascularization rates after endovascular intervention. It is possible that significant disease was overlooked or that there was a procedural complication such as vessel dissection or thrombosis during the index intervention.

Future study design should ensure comparison of matched cohorts. Most studies analyzing outcomes of endovascular interventions in PAD combine patients with claudication and CLTI to increase the power of the study. It has long been recognized that the natural history of each disease process is different, and therefore the groups should not be analyzed together. To improve standardization, treatment details and outcomes should

be documented. In addition to demographics and comorbid conditions, variables to consider and document in future study design include the following: smoking cessation status; level of arterial disease treated (eg, aortoiliac, infrainguinal, infrapopliteal); use of atherectomy or intra-arterial lithotripsy devices; type of balloon (plain or drug-coated); type of stent (eg, covered, bare-metal, drug-coated); details regarding heparin dosing and use of protamine; use of closure device; sheath size; bleeding complication requiring operative intervention; postprocedure compliance with medication; adherence to outpatient follow-up; minor or major amputation (MALE); freedom from TLR; minor or major bleeding complication; stroke or myocardial infarction (MACE); and mortality

These variables and study outcomes can then be analyzed by sex.

Although future trials focusing specifically on female patients with severe symptoms are needed to make definitive conclusions, the study still reveals crucial insights about how women with LLC or CLTI fare after endovascular intervention. How does this factor into your decision-making now? As a field, how should we be considering patient sex when making treatment plans?

Several past studies evaluating complications after endovascular interventions found that women had an increased risk of access site or bleeding complications, which is consistent with our study findings. This increased risk is thought to be a result of the relatively small body surface areas and vessel diameters in female versus male patients. Our study and studies with similar findings have influenced my treatment decisions, heightening my awareness of technique and device size relative to vessel diameter. Intraoperatively, I routinely use adjuncts to objectively guide my decisions for sheath and device selection and sizing, such as ultrasound guidance for arterial access with a micropuncture needle and sheath and intravascular ultrasound. Having a better understanding of plaque morphology and true vessel diameter may help reduce bleeding complications or need for reintervention by using appropriately sized balloons and stents and limiting use of larger-profile devices when possible.

Our study concluded that female patients were found to have higher risk of bleeding than male patients, which may result in reintervention and potential failure to rescue. I routinely use activated clotting time and/or partial thromboplastin time to direct dosing of anticoagulation and reversal agents, acknowledging the increased risk of postprocedure bleeding complications. If available, thromboelastography may be used as well. Additionally, it is important to treat hypertension prior to use of a closure device, maximizing device success and postprocedural hemostasis.

Although each study does not provide granular details necessary to explain why female patients experienced higher reintervention rates after endovascular intervention, the argument can be made that female patients with small vessel diameters may benefit from open peripheral artery revascularization as first-line treatment. However, without vigorous evidence available supporting improved outcomes and patency rates with decreased reinvention rates in female patients undergoing open versus endovascular treatment, that suggestion remains speculative. ■

1. Farber A, Menard MT, Conte MS, et al; BEST-CLI Investigators. Surgery or endovascular therapy for chronic limb-threatening ischemia. N Engl J Med. 2022 ;387:2305-2316. doi: 10.1056/NEJMoa2207899

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