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PAD and the Battle of the Sexes

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It is well known that the United States population will age dramatically over the next 30 to 40 years; the population of people 65 years or older is projected to be 83.7 million in 2050.[1] The majority of the population above 65 years of age are women, and according to the 2010 United States Census Bureau, there are 1.6 women for every man in the octogenarian population.[2] As increasing age is a risk factor for peripheral artery disease (PAD),[3] recognition and effective treatment of this debilitating disease in women will only become more important in the coming years.

Treating PAD in women is challenging, with a noticeable evolution of the standard of care in the past 10 years. There has been a misconception in the medical community for years that lower extremity occlusive arterial disease does not affect women to the same extent as men. This is, in part, correct for younger women because various reproductive and metabolic factors during the reproductive years create an atheroprotective environment.[4] However, once menopause occurs, the atheroprotective hormonal effect gradually dissipates, and after the seventh decade of life, the incidence of arterial occlusive disease becomes equal or even higher in women compared to men.[5] The incidence of PAD in female octogenarians is even higher, ranging from 15.5% to as high as 29%.[6,7]

PAD in women frequently remains underdiagnosed or presents at a more advanced stage compared to men, the reasons for which remain unclear.[8-10] One hypothesis is that physicians tend to misattribute symptoms associated with lower extremity occlusive disease to osteoporosis or other degenerative arthritic syndromes, which are also frequent in this female elderly population.[11,12] In fact, there is an association between osteoporosis and PAD in women, and literature supports that the presence of osteoporosis in women may increase the risk for PAD by threefold.[13] Another possible explanation for the presentation of PAD in women at a later stage is that elderly women have significant socioeconomic challenges that prevent them from seeking appropriate medical care; compared to their male counterparts, elderly women tend to be more socially isolated and have lower income.[14]

Sex-related differences do not only influence the presentation of PAD, they also affect choice of treatment. Historically, women with PAD were more likely than men to undergo a major amputation as first-line therapy and less likely to undergo an arterial reconstruction.[15] When reviewing all PAD-related admissions from 1998 to 2007 in three different states (New Jersey, New York, Florida), the rates of open revascularization and major amputation decreased for both men and women, and there was a significant increase of endovascular procedures for PAD: 144% in men and 150% in women.[8,16] Interestingly, during this same period, women were consistently less likely than men to undergo an open arterial reconstruction during their admission to the hospital for PAD (Figure 1A). Amputation rates per PAD-related admission were initially slightly higher for women (5% vs 4.68%; $P = .0006$).[16] However, during the latter part of the study (after 2003), when the utilization of endovascular procedures began to change, the difference in amputation rates reversed (2.47% in women vs 2.73% in men; $P < .0001$; Figure 1B) On the other hand, endovascular procedures were offered at equal rates to both men and women (Figure 1C).

It is unclear why women with PAD were less likely than men to undergo open reconstruction, but it is likely that the surgeon's decision whether to offer open reconstruction to women was influenced by many biases and historical facts. For one, historically, women have been less likely to be on antiplatelet and statin treatment[17-19] and more likely to have unrecognized and untreated coronary artery disease.[20] Patients who are not on optimized medical therapy are less likely to tolerate major open surgeries and may have higher mortality.[21] Indeed, in the aforementioned study, women had higher overall procedural mortality compared to men, and this difference was more pronounced after open reconstruction (5.49% vs 4%; $P < .0001$).[16] However, the in-hospital mortality after endovascular procedures was overall much lower, and although statistically different ($P < .0001$), it was numerically very comparable between both sexes (2.9% vs 2.1%).[16] Mortality doubled after major amputations, with significant sex-related differences favoring men.

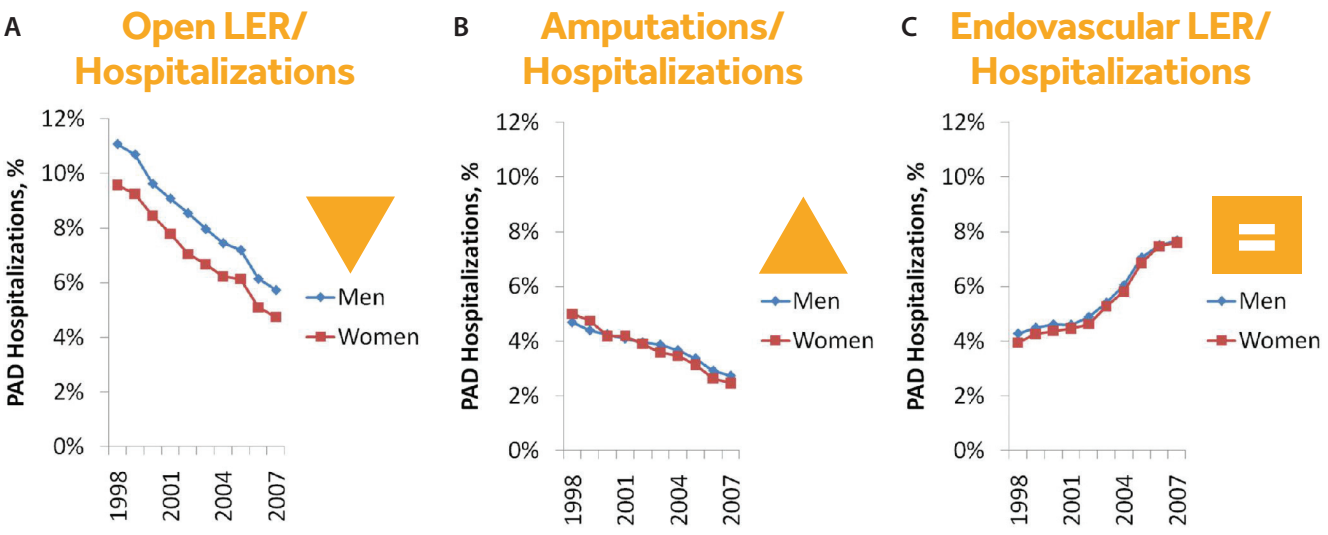

Figure 1. Revascularization and amputation trends per admission in men compared to women with PAD from the New Jersey, New York, and Florida state hospital discharge database from 1998 to 2007: open bypass surgeries (A); amputations (B); and endovascular procedures (C). Abbreviation: LER, lower extremity revascularization. Reprinted from Journal of Vascular Surgery; Vol 51; Egorova N, Vouyouka AG, Quin J, et al; Analysis of gender-related differences in lower extremity peripheral arterial disease; 372-278.e1; Copyright 2010, with permission from Elsevier.

When it comes to lower extremity bypass, there is a bias among surgeons that women do not have sustainable long-term success with their reconstruction as men do. This concept is probably incorrect; although individual reports may be conflicting, when compiled together, there seems to be no significant difference between sexes in long-term patency and limb salvage.[10,22-28] These studies are generally single-institution series in which men and women were not matched for age and comorbidities. In most of these studies, there were more male smokers than females. However, a notable constant finding throughout the published literature was a higher infection rate in women after arterial bypass surgery.[10,22,23] In two separate multivariate analyses, female sex remained a strong independent predictor for wound dehiscence and major wound infection in patients undergoing autogenous bypass grafting after controlling for diabetes, obesity, and other contributing parameters.[29,30] These findings may derive from differences in body habitus, metabolism, and fat content and distribution between the two sexes, because women tend to accumulate fatty tissue mainly in the upper thighs.[31]

The utilization of endovascular procedures could mitigate these differences in wound complications between sexes because endovascular procedures are less invasive. There are no large randomized controlled trials that have confirmed this hypothesis, but the available evidence from two smaller published studies demonstrated equivalent patency and limb salvage rates between men and women after endovascular interventions.[32,33] This equivalency occurred despite women having smaller vessels and more advanced disease. Notably, women required more reinterventions to achieve similar secondary patency to men. In these studies, women who were older were more likely to have tissue loss and more likely to have TransAtlantic Inter-Society Consensus (TASC) C and D lesions. The interventions included balloon angioplasty and/or stenting.

Interestingly, according to existing literature, tibial interventions may be associated with superior 12-month patency in women when compared to men (77.5% vs 58.7%; $P = .032$).[33,34] In one of these studies, female sex remained a positive predictor of superior patency after controlling for TASC lesions and other comorbidities.[34] Similar equivalent outcomes have been reported with the utilization of drug-coated balloons.[35]

Finally, the DURABILITY II trial treated femoropopliteal occlusive disease with the EverFlex™ self-expanding peripheral stent system. The results demonstrated worse postoperative pain and walking scores in women with claudication when compared to men, despite having equivalent 3-year primary (women, 62.5% vs men, 58.8%; $P < .05$), primary assisted, and secondary patency rates, as well as similar ankle-brachial indices for at least the first 2 years.[36,37] This discrepancy between objective and subjective scores in women reflects the complexity of properly addressing claudication in elderly women. As PAD may coexist with other degenerative comorbidities such as osteoporosis, arthritis, and joint disease, leg pain and walking ability may not improve with vascular procedures.

Sex-related differences affect the presentation and management of PAD. In women, PAD is underrecognized, often masked by other comorbidities. Endovascular procedures seem to lessen the gap between men and women in regard to early treatment outcomes, while maintaining similar or possibly better patency rates in women compared to men. ■

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EverFlex™ Self-expanding Peripheral Stent System Brief Statement
Indication

- The EverFlex™ self-expanding peripheral stent system is intended to improve luminal diameter in the treatment of stenotic, restenotic or occluded lesions up to 180 mm in length in the native superficial femoral artery or superficial femoral and proximal popliteal arteries with reference vessel diameters ranging from 4.5 mm – 7.5 mm.
  The EverFlex™ self-expanding peripheral stent system is indicated for improving luminal diameter in patients with atherosclerotic disease of the common and/or external iliac arteries up to and including 100 mm in length, with a reference vessel diameter of 4.5 mm - 7.5 mm.

Contraindications

- Use of the EverFlex™ self-expanding peripheral stent system is contraindicated in patients with known hypersensitivity to nickel titanium and in patients contraindicated for anticoagulant and/or antiplatelet therapy, patients who are judged to have a lesion that prevents complete inflation an angioplasty balloon or proper placement of the stent or stent delivery system.

Potential Adverse Events

- Potential adverse events which may be associated with the use of a stent in the SFA and proximal popliteal arteries, or common and/or iliac arteries include, but are not limited to: Abrupt or sub-acute closure, Allergic reaction to device materials or procedure medications, Allergic reaction to Nitinol, Amputation, Aneurysm, Angina, Arrhythmia, Arterio-venous fistula, Artery injury (e.g., dissection, perforation, or rupture), Bleeding requiring transfusion,
- Bruising, Contrast medium reaction/renal failure, Death, Device breakage, Edema, Embolism, Failure to deploy stent, Fever, Gastrointestinal bleeding due to anticoagulation, Hematoma, Hypertension/Hypotension, Infection, Inflammation, Intraluminal thrombus, Myocardial infarction, Pain, Partial stent deployment, Pseudoaneurysm, Renal failure, Renal insufficiency, Restenosis, Sepsis, Shock, Stent collapse or fracture, Stent migration, Stent misplacement, Stroke, Surgical or endovascular intervention, Thrombosis/occlusion of the stent, Transient ischemic attack, Venous thromboembolism, Vessel spasm, Worsening claudication or rest pain.
- See the Instructions for Use provided with the product for a complete list of warnings, precautions, adverse events and device information.

CAUTION:

- Federal (USA) law restricts these devices to sale by or on the order of a physician.