Impact of Gender Differences on Outcomes of Peripheral Artery Disease Intervention (from a Nationwide Sample)

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We aimed to evaluate the role of gender differences in the outcomes of catheter-based peripheral arterial disease interventions on a national level. We queried the National Inpatient Sample Database and identified all patients who presented with acute or symptomatic long term limb ischemia requiring transcatheter nonsurgical peripheral intervention in the years of 2016 to 2017. The primary outcome was major adverse cardiovascular events (MACE), defined as the composite end point of in-hospital mortality, nonfatal stroke, and acute myocardial infarction. Secondary outcomes were the subject components of the primary end point, vascular complications, major bleeding, acute kidney injury, limb amputation, total cost, and length of stay. A total of 58,165 patients were included. The majority were males (57.2%) and of white race (67.1%). On multivariate analysis, female gender was an independent predictor of MACE with an adjusted odd ratio (a-OR) of 1.36 (95% confidence interval [CI]: 1.12 to 1.65, p = 0.002), mortality (a-OR 1.52; 95% CI: 1.12 to 2.04, p = 0.006), nonfatal stroke (a-OR 2.51; 95% CI: 1.56 to 4.03, p < 0.001), major bleeding (a-OR 1.87; 95% CI: 1.53 to 2.28, p < 0.001), and higher cost with an adjusted mean ratio of 1.03 (95% CI: 1.00 to 1.06, p = 0.033). There was no significant difference in the rates of myocardial infarction, vascular complications, limb amputation, acute kidney injury, and length of stay. In conclusion, females presenting with acute or symptomatic long term limb ischemia requiring transcatheter peripheral intervention have a significantly higher composite risk of MACE. **(Am J Cardiol 2021;141:127−132)**

Peripheral artery disease (PAD) remains one of the most underdiagnosed cardiovascular diseases worldwide.[1] There has been a significant increase in the number of patients diagnosed with PAD over the last few years, with more than 200 million patients diagnosed globally based on existing literature, and approximately 9 millions of those are in the United States.[2,3] Despite a higher burden of PAD in males, females suffered a greater increase in PAD-related morbidity and mortality between 1990 to 2010 when compared with their male counterparts.[4] Most of the existing data on the impact of gender on cardiovascular diseases are derived from coronary artery disease and myocardial infarction outcome studies.[5,6] There is limited data on how gender differences impact PAD intervention outcomes. We aimed to evaluate the role of gender differences in the outcomes of catheter-based PAD interventions on a national level.

Methods

The study was conducted using the National Inpatient Sample (NIS) of the Health Care Utilization Project which is sponsored by the Agency for Healthcare Research and Quality. The NIS is an administrative claim database that combines hospitalization data from all United States community hospital discharges. The NIS database contains data from a 20% sample of inpatient hospitalizations in the United States and provides hospitalization records for over 7 million hospital stays each year with a weighted estimate of more than 35 million hospitalizations annually.[7]

We included all adult patients who were hospitalized for acute or symptomatic long term limb ischemia who received peripheral vascular angioplasty during the years 2016 to 2017. (Figure 1) These patients were identified using the International Classification of Diseases—Tenth Revision, Clinical Modification diagnosis codes (Supplementary Table 1,2). Limb ischemia was defined by the presence of either (1) intermittent claudication pain, (2) extremity with gangrene, (3) extremity with rest pain, (4) extremity with ulceration, (5) arterial embolism and thrombosis of the lower extremities, (6) type 2 diabetes mellitus with a foot ulcer, (7) stenosis of other vascular prosthetic devices, implants, and grafts (Supplementary Table 1).

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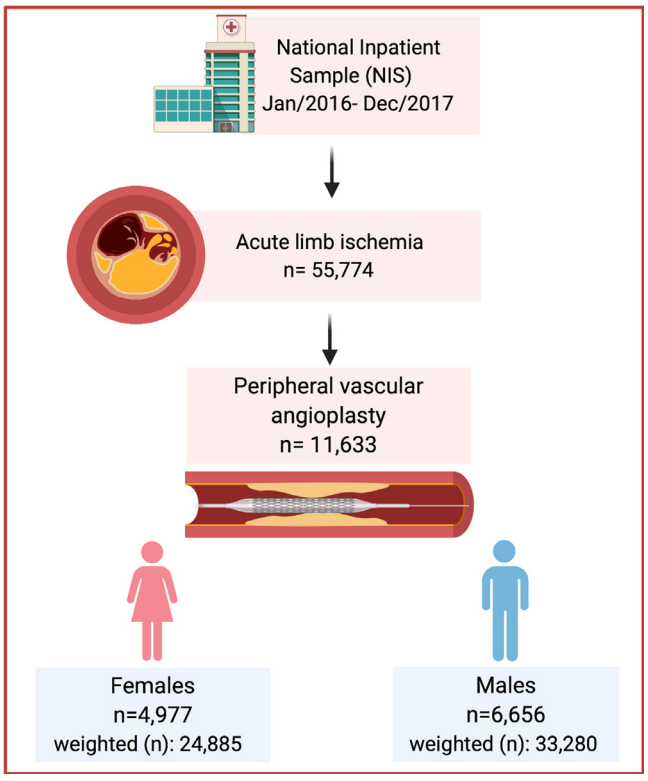


Figure 1. Algorithm for selection of study population. Explain what weighted means here.

This study was conducted to test the hypothesis of weather women are at higher risk for procedural complications after intervention for PAD. The primary outcome of the study was major adverse cardiovascular events (MACE) defined as the composite end point of in-hospital mortality, nonfatal stroke, and acute myocardial infarction. Secondary outcomes were in-hospital mortality, nonfatal stroke, myocardial infarction, vascular complications, major bleeding (postprocedural bleeding requiring blood transfusion), acute kidney injury, limb amputation, total cost, and length of stay. The cost for each inpatient hospitalization record was calculated by multiplying the total hospital charge with the cost-to-charge ratio provided by the NIS database.

Categorical variables were presented as percentages. Continuous variables were expressed as mean ± standard error of the mean or as median with interquartile ranges for approximately symmetric or skewed continuous variables, respectively. The standardized mean difference effect size was obtained for each variable. Effect size is considered large, moderate, small, or trivial for values ≥ 0.5, 0.3 to 0.5, 0.1 to 0.3, and < 0.1, respectively.[8] To account for the complex survey design, data were analyzed considering stratification, primary sampling units, probability sampling discharge weights, and robust variance estimation to all multivariable models as outlined by Health Care Utilization Project NIS analytic guidelines.[9] Binary outcomes were modeled using multivariable logistic regression. Original models included variables for age, gender, race, clinical co-morbidities, health insurance type, and hospital factors including size and teaching status (All variables in Table 1). Nonconsequential variables were removed using backward selection based on their contribution to the Akaike Information Criterion of the model. Continuous variables were modeled using generalized linear models with log link and gamma function for total hospital cost and a quasi-Poisson model with a log link function for the length of stay. Odds ratios with 95% confidence intervals were reported for binary outcomes and prevalence rate ratios (PRR), also referred to as means ratios, with 95% confidence intervals for the numeric outcomes. Calculated mean ratios represent the increase or decrease in percent association with length of stay and cost.[10,11] For example, PRR of 1.1 for the length of stay represents a 10% increase in the mean length of stay. Descriptive analyses and statistical models were carried out using R (R Core Team, 2019)[12] Figure 1.

Results

A total of 58,165 patients (Females = 24,885; Males = 33.280) who presented with PAD-related symptoms were included. The majority of patients were males (57.2%) and of white race (67.1%). Female patients were older with a median age of 71 (IQR: 62 to 81) versus 68 (IQR: 60 to 76) for males, standardized mean difference = 0.2. The most prevalent cardiovascular risk factors were hypertension (79.6%), hyperlipidemia (56%), and diabetes mellitus (47.4%). The top presenting symptoms were intermittent claudication (21.7%), gangrene of an extremity (21%), and rest pain (17%). Tables 1 and 2 summarize the baseline characteristics and reasons for admission of the study population respectively.

The unadjusted in-hospital procedural outcomes are summarized in Table 3. Females had higher prevalence of MACE, all cause in-hospital mortality, nonfatal stroke, and major bleeding. There was no significant gender difference in the rates of myocardial infarction, vascular complications, limb amputation, acute kidney injury, length of hospitalization, and cost. Table 4 summarizes the results of multivariate analysis. Female gender was an independent predictor of MACE with an adjusted odd ratio (a-OR) of 1.36 (95% CI: 1.12 to 1.65, p = 0.002), mortality (a-OR 1.52; 95% CI: 1.12 to 2.04, p = 0.006), nonfatal stroke (a-OR 2.51; 95% CI: 1.56 to 4.03, p < 0.001), major bleeding (a-OR 1.87; 95% CI: 1.53 to 2.28, p < 0.001), and higher cost with an a-MR of 1.03 (95% CI: 1.00 to 1.06, p = 0.033). There was no significant difference in the rates of myocardial infarction, vascular complications, limb amputation, acute kidney injury, and length of stay.

Discussion

In our study, we found that females have a significantly higher risk of acute in-hospital major adverse cardiovascular events, even after adjusting for co-morbidities, using a national sample.

Ramkumar et al studied the impact of gender on the method of lower extremity revascularization and noted that females underwent stenting or atherectomy at lesser rates than males and experienced higher rates of occlusion and reintervention.[13] Results obtained from the K- VIS ELLA

Table 1
Baseline characteristics and reasons for admission of study population

	Total (n = 58,165)	Men (n = 33,280)	Women (n = 24,885)	SMD
Age (years) (IQR)	69 (61, 78)	68 (60, 76)	71 (62, 81)	**0.24**
Race				**0.13**
White	67.1%	69.4%	64.0%	
Black	16.8%	14.9%	19.2%	
Hispanic	8.5%	8.1%	9.1%	
Asian or Pacific Islander	1.3%	1.2%	1.3%	
Deficiency anemia	24.1%	21.9%	27.1%	**0.12**
RA/ collagen/vascular disease	5.4%	3.8%	7.5%	**0.16**
Congestive heart failure	20.8%	20.2%	21.5%	0.03
Valvular heart disease	8.4%	7.9%	8.9%	0.04
Long term pulmonary disease	26.7%	25.6%	28.1%	**0.06**
Diabetes mellitus	47.4%	48.3%	46.2%	0.04
Hypertension	79.6%	79.4%	79.8%	0.01
Hypothyroidism	11.0%	7.1%	16.2%	**0.29**
Alcohol abuse	4.0%	5.9%	1.3%	**0.25**
Drug abuse	2.3%	2.8%	1.6%	**0.09**
Liver disease	2.5%	2.7%	2.1%	0.04
Long term renal failure	29.6%	30.2%	28.7%	0.03
Obesity	12.4%	10.7%	14.6%	**0.12**
Peripheral vascular disease	96.9%	96.7%	97.1%	0.03
Depression	9.2%	7.7%	11.4%	**0.13**
Atrial fibrillation	19.7%	20.0%	19.4%	0.01
Coronary artery disease	43.5%	46.3%	39.7%	**0.13**
Hyperlipidemia	56.0%	56.9%	54.7%	0.04
Obstructive sleep apnea	6.4%	7.5%	4.9%	**0.11**
Previous stroke	11.9%	11.3%	12.6%	0.04
Median household income (percentile)			**0.06**	
0 to 25th	34.5%	33.2%	36.1%	
26th to 50th	25.5%	26.2%	24.7%	
51st to 75th	22.1%	22.5%	21.6%	
76th to 100th	16.5%	16.8%	16.1%	
Insurance category				**0.21**
Medicare	69.6%	66.5%	73.7%	
Medicaid	9.7%	9.5%	10.1%	
Private insurance	16.1%	18.6%	12.8%	
Self-pay	2.0%	2.2%	1.8%	
No charge	0.3%	0.4%	0.3%	
Hospital bed size				0.02
Small	15.0%	15.2%	14.7%	
Medium	28.6%	28.6%	28.7%	
Large	56.3%	56.1%	56.6%	
Hospital location & teaching status		0.02		
Rural	4.8%	4.7%	4.8%	
Urban nonteaching	23.9%	23.6%	24.3%	
Urban teaching	71.3%	71.6%	70.9%	

Data are presented as mean (SD) or median (IQR) for continuous measures, and % for categorical measure
SMD: Standardized mean difference (Effect size) is considered large, moderate, small or trivial for values ≥ 0.5, 0.3-0.5, 0.1-0.3 and < 0.1, respectively.

Table 2
Reasons for admission for patients who underwent peripheral vascular angioplasty according to gender

Variable	Total (n = 58,165)	Men (n = 33,280)	Women (n = 24,885)	SMD
Intermittent claudication	21.7%	23.1%	19.9%	**0.08**
Gangrene	21.0%	21.5%	20.5%	0.02
Rest pain	17.0%	15.1%	19.4%	**0.11**
Ulceration	15.8%	14.8%	17.0%	**0.06**
Arterial embolism & thrombosis	12.5%	12.0%	13.2%	0.04
Diabetic foot ulcer	7.5%	9.0%	5.5%	**0.13**
Stenosis of vascular prosthetic devices, implants and grafts	4.5%	4.6%	4.4%	0.01
Elective vs nonelective admission	41.0%	41.5%	40.4%	0.02

SMD: Standardized mean difference (Effect size) is considered large, moderate, small or trivial for values ≥ 0.5, 0.3-0.5, 0.1-0.3 and < 0.1, respectively.

Table 3
Complications after peripheral vascular angioplasty according to gender.

	Total n = 58,165	Men (n = 33,280)	Women (n = 24,885)	SMD
Major adverse cardiac event	3.9%	3.5%	4.6%	**0.06**
All cause in-hospital mortality	1.7%	1.3%	2.1%	**0.06**
Nonfatal stroke	0.6%	0.4%	0.9%	**0.07**
Myocardial infraction	2.0%	2.0%	1.9%	0.01
Vascular complications	1.4%	1.2%	1.6%	0.03
Major bleeding	3.7%	2.7%	5.0%	**0.12**
Amputation	0.1%	0.1%	0.1%	0.02
Acute kidney injury	14.4%	14.7%	14.1%	0.02
Length of stay, days (IQR)	5.0 (2.0, 9.0)	4.0 (2.0, 9.0)	5.0 (2.0, 9.0)	0.04
Cost of hospitalization, USD (IQR)	24,197 (16,370, 36,353)	24,293 (16,335, 36,470)	24,044 (16,388, 36,165)	0.02

Data are presented as mean (SD) or median (IQR) for continuous measures, and % for categorical measures.
Need to explain what SMD means and what they signify.
SMD: Standardized mean difference (Effect size) is considered large, moderate, small or trivial for values ≥ 0.5, 0.3-0.5, 0.1-0.3 and < 0.1, respectively.

(Korean Vascular Intervention Society Endovascular Therapy in Lower Limb Artery Disease) registry showed that women had higher rates of mortality, myocardial infarction, and procedural complications than men. [14] Our study showed similar results that females had worse intervention outcomes. Our study additionally showed that women had worse MACE than men and support the current literature that female gender is an independent predictor of mortality.[15,16,17]

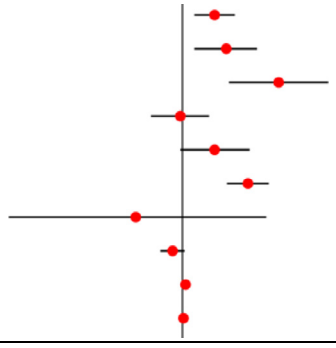
Conversely, another smaller study, evaluating a Michigan state cohort in 2014, did not show significant gender differences in in-hospital mortality, myocardial infarction, and stroke.[18] In addition, Doshi et al investigated the NIS for the years 2012 to 2014 and reported no difference in in-hospital mortality between males and females patients who underwent endovascular peripheral intervention.[19] These outcome differences are likely due to study population size or difference in methodological designs. The higher risk of MACE in females found in our study might be attributed to 'females presenting at a later stage of the disease as we found more females presenting with resting pain and extremity ulceration compared with more males presenting earlier with intermittent claudication. This could be due to higher incidences of arthritis and osteoporosis, smaller calf muscle mass, and less physical activity which all contribute to delayed symptom development.[20,21,22]

Of all the adverse events, female gender was most predictive of periprocedural stroke; females were 180% more likely to develop a cerebrovascular accident during their hospitalization. This association was consistent with previous studies, although more significant in our analysis.[18,15] Of note, females in our study were also more likely to have a history of previous stroke. This could be related to suboptimal preventive strategies as studies have shown that in patients with cardiovascular disease, females were less likely to be on optimal medical therapy including β-blockers or lipid-lowering medication.[23,24] Vouyouka et al found that in patients with baseline cerebrovascular disease, female gender was associated with a 33% increased risk of hospital mortality on multivariable regression analysis. [25]

Regarding the secondary outcomes, females were more likely to have postprocedural bleeding than males, which is consistent with previous studies.[15,16,17,21] One possibility might be related to the diffuse nature of PAD in females and smaller vessel size resulting in multiple access site attempts and higher bleeding risk. Also, since females might present at a later stage of the disease, this may result in complex and prolonged procedures and which further

Table 4
Adjusted complications after peripheral vascular angioplasty according to gender

	Adjustd OR	95% CI	p value
Major adverse cardiac event	1.37	1.13 – 1.66	**0.001**
All cause in-hospital mortality	1.52	1.12 – 2.04	**0.007**
Non-fatal stroke	2.58	1.59 – 4.21	**<0.001**
Myocardial infraction	0.99	0.75 – 1.30	0.924
Vascular complication	1.38	0.98 – 1.93	0.061
Major bleeding	1.85	1.52 – 2.26	**<0.001**
Amputation	0.69	0.17 – 2.91	0.69
Acute kidney injury	0.91	0.81 – 1.02	0.104
Cost of hospitalization	1.03	1.00 – 1.06	**0.025**
Length of stay	1.01	0.98 – 1.06	0.467



p value is significant if < 0.05.

increase complication risk. Another plausible mechanism for the higher bleeding risk in females is that females metabolize heparin, the most commonly used anticoagulant during endovascular procedures, slower than males even after correcting for age and weight differences due to different drug pharmacokinetics.[26,27]

In a 2012 statement by the American Heart Association on females with PAD, female gender was associated with adverse outcomes after PAD intervention but was reported to be inconsistent given the controversy in the literature.[17] Similarly, in a 12 months follow up of 1,084 patients who underwent 1,702 endovascular procedures, compared with males, women had a higher risk for repeat intervention and lower risk of mortality except in those who had superficial femoral artery disease who had a higher mortality rates than men. [28] We believe that our study adds significant large-scale data to the literature and proves that female gender is an independent predictor of adverse outcomes after catheter-based PAD intervention on many levels. This study highlights the need for more aggressive preventive measures, symptom education and awareness, and earlier diagnosis and treatment in females with PAD risk factors.

This study has some limitations. The information studied and analyzed is subject to errors due to incomplete discharge summaries and incorrect or incomplete coding. A second limitation is the inability to include after discharge longitudinal data for follow (e.g. 30-days, 6-months, and 1-year follow-up). The lack of outpatient procedure data also represents a limitation as a significant proportion of the interventions take place in the outpatient setting and this could have added valuable information to our study. Nonetheless, we believe our data is largely generalizable as it is a large-scale, nationwide study that had enough power to detect important conclusions.

In conclusion, in this real-world NIS , we found that women with PAD who presented to the hospital and had endovascular intervention are at significantly higher risk of in-hospital morbidity and mortality than men. Moreover, female gender is an independent predictor of adverse events after-endovascular intervention including MACE, stroke, and bleeding.

Authors' Contributions

Abdalla Hassan MD: Conceptualization, Methodology, Writing- Original draft preparation; Ashraf Abugroun MD: Methodology, Software, Data curation, statistical analysis, Writing- Original draft preparation; Hussein Daoud MD: Writing- Original draft preparation and Validation; Shafaq Mahmoud MD: Writing- Original draft preparation; Saria Awadalla PhD: Statistical analysis, writing- Reviewing and Editing; Annabelle Volgman MD: Writing- Reviewing and Editing; Alvaro Alonso MD: Supervision;

Disclosures

The investigators declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.003.

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