Comparison of In-Hospital Outcomes in Patients Having Limb-Revascularization With Versus Without Atrial Fibrillation

Homam Moussa Pacha, MD[a], Yasser Al-khadra, MD[b], Fahed Darmoch, MD[c], Mohamad Soud, MD[d], Anwar Zaitoun, MD[e], Chun Shing Kwok, MBBS, MSc, BSc[f,g], Mamas A. Mamas, MD[f,g], Amir Kaki, MD[e], Santiago Garcia, MD[h], Subhash Banerjee, MD[i], Salman A. Arain, MD[a], George W. Vetrovec, MD[j], James J. Glazier, MD[k], and M Chadi Alraies, MD[k,*]

The impact of atrial fibrillation (AF) on clinical outcomes among patients with peripheral artery disease (PAD) who undergo limb revascularization procedures is not well understood. We aim to compare in-hospital outcomes for patients with and without AF who underwent limb revascularization. We identified patients with PAD aged ≥18 years that underwent limb revascularization using endovascular or surgical approaches in the National Inpatient Sample between 2002 and 2014. Multivariate logistic regression analysis was performed to examine in-hospital outcomes. A total of 2,283,568 patients underwent limb revascularization during the study duration and 294,469 (12.9%) had AF. Patients with AF were older (mean age 76.1 ± 10.0 years), more likely to be women and white, compared with non-AF group. Among patients who had surgical revascularization, AF was associated with a higher rates of in-hospital mortality (6.4% vs 2.5%, adjusted odds ratio [aOR]: 1.09 [95% confidence interval {CI}: 1.05 to 1.12]) and major amputation (5.2% vs 3.8%, aOR: 1.05 [95% CI: 1.02 to 1.08]), compared with non-AF group. Among patients who had endovascular intervention (EVI), AF was associated with a higher rates of in-hospital mortality (3.8% vs 1.6%, aOR: 1.29 [95% CI: 1.24 to 1.33]) and major amputation (5.2% vs 3.9%, aOR: 1.07 [95% CI: 1.04 to 1.10]), compared with non-AF group. Within study period, EVI utilization increased in patients with and without AF (P_{trend} <0.001); whereas, surgical revascularization utilization decreased in patients with and without AF (P_{trend} <0.001). In conclusion, among patients with PAD who undergo limb revascularization, AF appears to be associated with poor in-hospital outcomes. **(Am J Cardiol 2019;124:1540−1548)**

The prevalence of peripheral artery disease (PAD) increases with age and is estimated to affect 10% and 14% of the United States population[1] and more than 200 million persons worldwide.[2] Atrial fibrillation (AF) is frequent in PAD has been associated with decreasing ankle-brachial index (ABI) and worse cardiovascular outcome.[3,4] Patients with AF tend to be older and more likely to have diabetes, hypertension, chronic kidney disease, coronary artery disease (CAD), and heart failure than those with normal sinus rhythm.[4−6] In-hospital complications including myocardial infarction (MI), stroke, infections and death are more frequent in PAD patients with AF.[4−7] PAD patients with AF are more challenging to treat as they have higher comorbidity burden and more complex disease, and are often on anticoagulation.[4] Whereas vascular diseases such as symptomatic PAD and/or previous MI are considered in risk stratification of AF,[8] there is little known about the impact of AF among patients undergoing limb revascularization for PAD. We aimed to examine national trends and in-hospital outcome of limb revascularization in PAD patients with AF compared with those without AF.

Methods

The National Inpatient Sample (NIS) is a publicly available database of hospital discharges in the United States, containing data from approximately 8 million hospital stays that were selected using a complex probability sampling design, and the weighting scheme recommended by the Agency for Healthcare Research and Quality which is intended to represent all discharges from nonfederal hospitals.[9] From 2002 to 2014 and after weighting the data, we

[a]University of Texas Health Science Center, McGovern Medical School, Memorial Hermann Heart & Vascular Institute, Houston, Texas; [b]Cleveland Clinic, Medicine Institute, Cleveland, Ohio; [c]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, Massachusetts; [d]Rutgers New Jersey Medical School, Newark, New Jersey; [e]Ascension St John Hospital, Detroit, Michigan; [f]Keele Cardiovascular Group, Centre for Prognosis Research, Institute of primary Care and Health Sciences, Keele University, Stoke-on-Trent, United Kingdom; [g]Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom; [h]Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, Minnesota; [i]University of Texas Southwestern Medical Center, Dallas, Texas; [j]VCU Pauley Center at Virginia Commonwealth University, Richmond, Virginia; and [k]Wayne State University, Detroit Medical Center, Detroit Heart Hospital, Detroit, Michigan. Manuscript received June 30, 2019; revised manuscript received and accepted July 30, 2019.

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*Corresponding author: Tel: (216) 255-0008.

E-mail addresses: alraies@hotmail.com; calraies@gmail.com (M.C. Alraies).

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used International Classification of Disease, Ninth Edition, Clinical Modification (ICD-9-CM) codes to identify all PAD patients aged ≥18 who had limb revascularization (endovascular intervention or surgical revascularization). We further categorized PAD patients based on clinical presentation into those with IC and CLI. CLI was defined as lower extremity rest pain, ulceration, and/or gangrene due to atherosclerosis of lower extremity arteries. CLI was also identified by the presence of codes for lower extremity chronic ulceration, osteomyelitis, and/or cellulitis along with primary diagnosis codes for PAD. A list of ICD-9-CM diagnosis codes used to identify PAD population is included in supplemental table 1. EVI was defined as angioplasty, atherectomy, and/or stenting of lower limb vessels.[10] Surgical revascularization was identified using ICD-9-CM procedure codes for open bypass, endarterectomy, incision and/or resection of lower limb arteries. A list of ICD-9-CM procedure codes used to identify limb revascularization is included in supplemental table 1. This approach has been used by a previous NIS database study to accurately identify patients with PAD and CLI undergoing limb revascularization procedures.[11] Lastly, we identified patients with AF using the ICD-9-CM diagnoses code 427.31 (Figure 1).

Data were retrieved retrospectively. Baseline patient-level characteristics included demographics (age, sex, race, primary expected payer, median household income for patient's zip code), clinical presentation (IC vs CLI), procedure type (EVI vs surgical revascularization), and relevant comorbidities (smoking, dyslipidemia, diabetes mellitus, hypertension, CAD, carotid artery disease, previous MI, previous percutaneous coronary intervention [PCI], previous coronary artery bypass grafting [CABG], congestive heart failure, previous stroke/transient ischemic attack [TIA], obesity, renal failure, valvular disease, coagulopathy, hypothyroidism, chronic lung disease, pulmonary circulation disorder, fluid and electrolytes disorder, liver disease, neurologic disorder, anemia and metastatic cancer). Hospital-level characteristics were census region, bed size, and teaching status. Comorbidities were identified using the Clinical Classification Software codes provided by the Healthcare Cost and Utilization Project and the Elixhauser Comorbidity Index, and ICD-9-CM codes.[12] A list of ICD-9-CM codes and Clinical Classification Software codes used to identify comorbidities is included in Supplemental Table 2.

The primary outcome was all-cause in-hospital mortality. Secondary outcomes included acute MI, stroke, major bleeding, major vascular complications (injury to blood vessel, accidental puncture, injury to retroperitoneum, other vascular complications, or any vascular complications requiring surgery), major amputation and hospital length of stay (LOS). Major bleeding was defined as hemorrhage leading to hemodynamic instability or requiring blood transfusion. Major adverse cardiovascular events (MACE) were defined as a composite of death, MI, or stroke. Net adverse cardiovascular events (NACE) were defined as a composite of MACE, major bleeding, or major vascular complications. A list of ICD-9-CM codes used to define in-hospital outcomes is included in supplemental table 2. We also examined temporal changes in limb revascularization (endovascular and surgical) utilization and in-hospital mortality among PAD patients with/without AF within study period.

Continuous variables were expressed as weighted mean values ± standard deviation (normal distribution) or median with interquartile range (non-normal distribution), and categorical variables were expressed as percentages. Continuous variables were compared using the unpaired Student *t* test or Mann-Whitney U test as appropriate whereas the chi-square test was used to compare categorical variables. Weighted values of patient level observations were generated to produce a nationally representative estimate of the entire US population of hospitalized patients. Univariable and multivariable logistic regressions were used to estimate

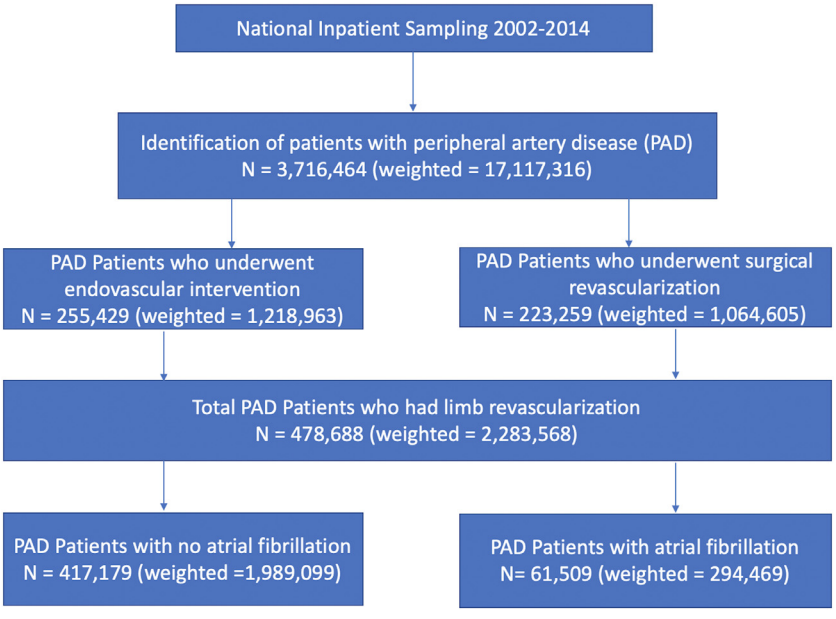

Figure 1. Identification of study population using National Inpatient Sampling Database.

Table 1
Baseline characteristics in all patients with peripheral artery disease and undergoing limb revascularization stratified by the presence of atrial fibrillation

Variable	Atrial fibrillation		p-Value
	No (N = 1,989,099)	Yes (N = 294,469)	
Age (years)	67.1 ± 11.8	76.1 ± 10.0	<0.001
Women	42.4%	45.6%	<0.001
			<0.001
White	73.2%	82.4%	
Black	14.9%	8.4%	
Hispanic	7.9%	5.6%	
Asian or Pacific Islander	1.1%	1.2%	
Native American	0.6%	0.4%	
Other	2.3%	2.1%	
Elective hospitalization	59.1%	31.4%	<0.001
Primary expected payer			<0.001
Medicare	65.4%	85.3%	
Medicaid	7.3%	2.7%	
Private insurance	22.8%	10.1%	
Self-Pay	2.3%	0.8%	
No charge	0.3%	0.1%	
Other	1.8%	1.0%	
Median household income (percentile)			<0.001
0 to 25	29.5%	23.7%	
26 to 50	26.9%	25.9%	
51 to 75	23.5%	25.2%	
76 to 100	20.1%	25.2%	
Location/teaching status			<0.001
Rural	6.8%	6.2%	
Urban nonteaching	40.5%	40.7%	
Urban teaching	52.7%	53.1%	
Hospital region			<0.001
Northeast	18.8%	22.8%%	
Midwest	24.3%	24.6%	
South	40.7%	35.4%	
West	16.2%	17.1%	
Clinical presentation			
Intermittent claudication	25.3%	13.9%	<0.001
Critical limb ischemia	40.0%	45.3%	<0.001
Other	21.4%	18.8%	<0.001
Procedure type			
Surgical revascularization	55.1%	59.2%	<0.001
Endovascular intervention	53.9%	49.7%	<0.001
Comorbidities			
Smokers	24.4%	10.0%	<0.001
Dyslipidemia	41.2%	35.4%	<0.001
DM, uncomplicated	25.6%	23.9%	<0.001
DM, complicated	14.0%	12.9%	<0.001
Hypertension	71.5%	71.2%	0.002
Coronary artery disease	15.5%	13.5%	<0.001
Prior myocardial infarction	10.1%	9.8%	<0.001
Prior percutaneous coronary intervention	7.9%	6.1%	<0.001
Prior coronary artery bypass grafting	13.9%	13.3%	<0.001
Congestive heart failure	6.1%	15.3%	<0.001
Carotid artery disease	4.0%	3.3%	<0.001
Prior stroke/transient ischemic attack	3.7%	4.9%	<0.001
Obesity	6.6%	5.8%	<0.001
Renal failure	18.4%	25.6%	<0.001
Valvular disease	2.2%	5.9%	<0.001
Coagulopathy	3.2%	5.3%	<0.001
Hypothyroidism	7.3%	11.9%	<0.001
Chronic lung disease	24.1%	28.1%	<0.001
Pulmonary circulation disorders	0.7%	1.9%	<0.001
Fluid and electrolytes disorders	14.0%	20.5%	<0.001

(*continued*)

Table 1 (***Continued***)

Variable	Atrial fibrillation		p-Value
	No (N = 1,989,099)	Yes (N = 294,469)	
Liver disease	1.2%	1.0%	<0.001
Neurological disorders	3.8%	5.7%	<0.001
Deficiency anemia	15.7%	20.4%	<0.001
Chronic blood loss anemia	1.2%	1.7%	<0.001
Metastatic cancer	0.6%	0.8%	<0.001

Values are expressed as mean ± SD for continuous variables or percentages for categorical variables.

Table 2
In-hospital outcomes in patients with and without atrial fibrillation and undergoing limb revascularization

	Surgical revascularization N = 1,064,605			Endovascular intervention N = 1,218,963		
	Non-AF group	AF group	p-Value	Non-AF group	AF group	p-Value
In-hospital mortality						
%	2.5%	6.4%		1.6%	3.8%	
Unadjusted OR (95% CI)	Ref.	2.65 (2.59-2.71)	<0.001	Ref.	2.41 (2.33-2.48)	<0.001
Adjusted OR (95% CI)	Ref.	1.09 (1.05-1.12)	<0.001	Ref.	1.29 (1.24-1.33)	<0.001
Myocardial infarction						
%	3.0%	5.7%		3.5%	5.1%	
Unadjusted OR (95% CI)	Ref.	1.96 (1.91-2.00)	<0.001	Ref.	1.46 (1.42-1.50)	<0.001
Adjusted OR (95% CI)	Ref.	1.12 (1.09-1.16)	<0.001	Ref.	1.12 (1.09-1.16)	<0.001
Stroke						
%	6.2%	9.0%		6.7%	8.8%	
Unadjusted OR (95% CI)	Ref.	1.50 (1.47-1.53)	<0.001	Ref.	1.34 (1.32-1.37)	<0.001
Adjusted OR (95% CI)	Ref.	1.42 (1.37-1.48)	<0.001	Ref.	1.19 (1.14-1.24)	<0.001
Vascular complications						
%	3.4%	3.2%		3.0%	3.1%	
Unadjusted OR (95% CI)	Ref.	0.95 (0.92-0.97)	<0.001	Ref.	1.04 (1.01-1.07)	0.02
Adjusted OR (95% CI)	Ref.	0.88 (0.85-0.91)	<0.001	Ref.	1.04 (1.003-1.08)	0.03
Major bleeding						
%	6.2%	10.6%		7.4%	10.1%	
Unadjusted OR (95% CI)	Ref.	1.78 (1.75-1.81)	<0.001	Ref.	1.40 (1.38-1.43)	<0.001
Adjusted OR (95% CI)	Ref.	1.20 (1.18-1.23)	<0.001	Ref.	1.10 (1.07-1.12)	<0.001
Major adverse cardiovascular events						
%	10.9%	19.1%		11.2%	16.5%	
Unadjusted OR (95% CI)	Ref.	1.94 (1.91-1.96)	<0.001	Ref.	1.57 (1.55-1.59)	<0.001
Adjusted OR (95% CI)	Ref.	1.22 (1.20-1.25)	<0.001	Ref.	1.24 (1.21-1.26)	<0.001
Net adverse cardiovascular events						
%	18.3%	28.9%		19.4%	26.4%	
Unadjusted OR (95% CI)	Ref.	1.81 (1.79-1.83)	<0.001	Ref.	1.49 (1.47-1.51)	<0.001
Adjusted OR (95% CI)	Ref.	1.22 (1.20-1.24)	<0.001	Ref.	1.17 (1.16-1.20)	<0.001
Major amputation						
%	3.8%	5.2%		3.9%	5.2%	
Unadjusted OR (95% CI)	Ref.	1.37 (1.34-1.40)	<0.001	Ref.	1.35 (1.32-1.39)	<0.001
Adjusted OR (95% CI)	Ref.	1.05 (1.02-1.08)	0.001	Ref.	1.07 (1.04-1.10)	<0.001

Adjusted for demographics (age, sex, race), hospital characteristics (region, bed size, teaching status), clinical presentation (intermittent claudication vs critical limb ischemia), and all comorbidities listed in Table 1. OR = odds ratio.

the odds of in-hospital outcomes between groups (AF versus no AF). The regression models were adjusted for demographics (age, race and gender), patients' insurance, socioeconomic status, hospital characteristics, clinical presentation, procedure type (endovascular vs surgical), and all comorbidities listed in Table 1. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to report the results of regression models. Linear regression models were used to assess the LOS. Log transformation of LOS was done to adjust for positively skewed data. Sensitivity analysis was performed by stratifying the cohort by IC and CLI and evaluating in-hospital outcomes in each group. Trend over time in limb revascularization utilization and in-hospital mortality was examined using Cochrane-Armitage test. P-value of less than 0.05 was considered statistically significant. SPSS version 25 software (IBM Corp, Armonk, NY) was used for all statistical analyses.

Results

Of 2,283,568 patients who underwent limb revascularization procedures from 2002 to 2014, 1,989,099 had no AF

(87.1%) and 294,469 had AF (12.9%). Baseline characteristics for both groups are summarized in Table 1. Compared with patients with no AF (mean age 67.1 ± 11.8 years), patients with AF were older (mean age 76.1 ± 10.0 years), more likely to be women and white, and less likely to be African American or Hispanic (p <0.001 for all). CLI was more prevalent in AF patients; whereas, IC was more prevalent in patients with no AF (p <0.001). Individuals with AF more frequently underwent surgical revascularization and less frequently underwent EVI (p <0.001), compared with non-AF group. The prevalence of heart failure, previous stroke/TIA, renal failure, valvular disease, coagulopathy, hypothyroidism, chronic lung disease, pulmonary circulation disorders, fluid and electrolytes disorders, neurological disorders, anemia (deficiency and chronic blood loss), and metastatic cancer was higher among patients with AF; whereas, smoking, dyslipidemia, diabetes (complicated and uncomplicated), hypertension, CAD, carotid artery disease, previous MI, previous PCI, previous CABG surgery, obesity, and liver disease were more prevalent in non-AF patients (p <0.001 for all, except for hypertension which is 0.002). Elective admissions were less frequent in patients with AF (31.4% vs 59.1%, p <0.001).

Among PAD patients undergoing surgical revascularization, AF was associated with higher risk of in-hospital mortality (6.4% vs 2.5%, adjusted OR: 1.09 [95% CI: 1.05 to 1.12] and longer length of hospital stay (median LOS = 7 days; Interquartile range [IQR] (4 to 13) vs 5 days; [IQR] (3 to 9); p <0.001), Compared with non-AF group. Patients with AF had higher incidence of MI (5.7% vs 3.0%, p < 0.001), postprocedural stroke (9.0% vs 6.2%, p <0.001), major bleeding (10.6% vs 6.2%, p <0.001), MACE (19.1% vs 10.9%, p <0.001), and NACE (28.9% vs 18.3%, p <0.001). The incidence of vascular complications was lower in patients with AF (3.2% vs 3.4%, p <0.001). After multivariate risk adjustment, patients with AF remained to have higher risk of MI, postprocedural stroke, major bleeding, MACE, and NACE; and lower risk of vascular complication compared with those without AF (Table 2). Patients with AF more frequently underwent major amputation (5.2% vs 3.8%, p <0.001) following surgical revascularization in the same hospitalization compared with those with no AF, and this difference remained significant even with multivariate risk adjustment (adjusted OR: 1.05 [95% CI: 1.02 to 1.08]) (Table 2).

Among PAD patients undergoing endovascular intervention, AF was associated with higher risk of in-hospital mortality (3.8% vs 1.6%, adjusted OR: 1.29 [95% CI: 1.24 to 1.33] and longer length of hospital stay (median LOS = 6 days; [IQR] (2 to 11) vs 3 days; [IQR] (1 to 8); p <0.001), compared with non-AF group. Patients with AF had higher incidence of MI (5.1% vs 3.5%, p <0.001), postprocedural stroke (8.8% vs 6.7%, p <0.001), vascular complications (3.1% vs 3.0%, p = 0.02), major bleeding (10.1% vs 7.4%, p <0.001), MACE (16.5% vs 11.2%, p <0.001), and NACE (26.4% vs 19.4%, p <0.001). After multivariate risk adjustment, patients with AF remained to have higher risk of MI, postprocedural stroke, vascular complications, major bleeding, MACE, and NACE compared with those without AF (Table 2). Patients with AF more frequently underwent major amputation (5.2% vs 3.9%, p <0.001) following EVI in the same hospitalization compared with those with no AF, and this difference remained significant even with multivariate risk adjustment (adjusted OR: 1.07 [95% CI: 1.04 to 1.10]) (Table 2).

Table 3
In-hospital outcomes in patients with intermittent claudication and undergoing limb revascularization

	Atrial fibrillation		p-Value
	No (N = 503,492)	Yes (N = 40,954)	
In-hospital mortality			
%	0.5%	1.5%	
Unadjusted OR (95% CI)	Ref.	3.22 (2.95-3.52)	<0.001
Adjusted OR (95% CI)	Ref.	1.72 (1.55-1.91)	<0.001
Myocardial infarction			
%	1.9%	4.0%	
Unadjusted OR (95% CI)	Ref.	2.21 (2.10-2.33)	<0.001
Adjusted OR (95% CI)	Ref.	1.85 (1.74-1.97)	<0.001
Stroke			
%	5.3%	7.5%	
Unadjusted OR (95% CI)	Ref.	1.44 (1.38-1.49)	<0.001
Adjusted OR (95% CI)	Ref.	1.63 (1.51-1.76)	<0.001
Vascular complications			
%	2.6%	3.3%	
Unadjusted OR (95% CI)	Ref.	1.28 (1.21-1.36)	<0.001
Adjusted OR (95% CI)	Ref.	1.20 (1.12-1.28)	<0.001
Major bleeding			
%	4.9%	8.0%	
Unadjusted OR (95% CI)	Ref.	1.69 (1.63-1.75)	<0.001
Adjusted OR (95% CI)	Ref.	1.34 (1.28-1.40)	<0.001
Major adverse cardiovascular events			
%	7.4%	12.4%	
Unadjusted OR (95% CI)	Ref.	1.76 (1.70-1.81)	<0.001
Adjusted OR (95% CI)	Ref.	1.79 (1.71-1.88)	<0.001
Net adverse cardiovascular events			
%	13.6%	20.8%	
Unadjusted OR (95% CI)	Ref.	1.66 (1.62-1.70)	<0.001
Adjusted OR (95% CI)	Ref.	1.47 (1.42-1.52)	<0.001
Amputation			
%	0.2%	0.4%	
Unadjusted OR (95% CI)	Ref.	1.56 (1.32-1.84)	<0.001
Adjusted OR (95% CI)	Ref.	1.03 (0.84-1.27)	0.80

Adjusted for demographics (age, sex, race), hospital characteristics (region, bed size, teaching status), procedure type (endovascular vs surgical), and all comorbidities listed in Table 1. OR = odds ratio.

In subgroup analysis of patients with IC, individuals with AF had higher risk of in-hospital mortality (1.5% vs 0.5%, adjusted OR: 1.72 [95% CI: 1.55 to 1.91]) than those without AF. Compared with non-AF group, risk-adjusted incidence of MI, postprocedural stroke, major bleeding, vascular complications, MACE, and NACE was higher in patient with AF. Only 0.4% of AF patients and 0.2% of non-AF patients underwent major amputation (p <0.001). However, there was no difference in risk-adjusted incidence of major amputation between both groups (adjusted OR: 1.03 [95% CI: 0.84 to 1.27]) (Table 3).

In subgroup analysis of patients with CLI, individuals with AF had higher risk of in-hospital mortality (4.1% vs 2.0%, adjusted OR: 1.27 [95% CI: 1.22 to 1.32] than those without AF. Compared with non-AF group, risk-adjusted incidence of postprocedural stroke, major bleeding, MACE, and NACE was higher in patient with AF. There was no difference in risk-adjusted incidence of MI or vascular complications between both groups (Table 4). AF patients more

Table 4
In-hospital outcomes in patients with critical limb ischemia and undergoing limb revascularization

	Atrial fibrillation		p-Value
	No (N = 795,082)	Yes (N = 133,363)	
In-hospital mortality			
%	2.0%	4.1%	
Unadjusted OR (95% CI)	Ref.	2.10 (2.03-2.16)	<0.001
Adjusted OR (95% CI)	Ref.	1.27 (1.22-1.32)	<0.001
Myocardial infarction			
%	2.9%	4.0%	
Unadjusted OR (95% CI)	Ref.	1.37 (1.32-1.41)	<0.001
Adjusted OR (95% CI)	Ref.	1.02 (0.98-1.06)	0.33
Stroke			
%	7.4%	8.7%	
Unadjusted OR (95% CI)	Ref.	1.18 (1.16-1.21)	<0.001
Adjusted OR (95% CI)	Ref.	1.23 (1.19-1.27)	<0.001
Vascular complications			
%	1.9%	1.9%	
Unadjusted OR (95% CI)	Ref.	0.96 (0.92-1.01)	0.08
Adjusted OR (95% CI)	Ref.	0.96 (0.92-1.01)	0.12
Major bleeding			
%	6.6%	8.8%	
Unadjusted OR (95% CI)	Ref.	1.37 (1.34-1.40)	<0.001
Adjusted OR (95% CI)	Ref.	1.12 (1.09-1.15)	<0.001
Major adverse cardiovascular events			
%	11.7%	15.7%	
Unadjusted OR (95% CI)	Ref.	1.41 (1.38-1.43)	<0.001
Adjusted OR (95% CI)	Ref.	1.20 (1.17-1.23)	<0.001
Net adverse cardiovascular events			
%	18.5%	24.0%	
Unadjusted OR (95% CI)	Ref.	1.39 (1.37-1.41)	<0.001
Adjusted OR (95% CI)	Ref.	1.17 (1.15-1.19)	<0.001
Major amputation			
%	6.9%	8.0%	
Unadjusted OR (95% CI)	Ref.	1.18 (1.16-1.21)	<0.001
Adjusted OR (95% CI)	Ref.	1.13 (1.10-1.16)	<0.001

Adjusted for demographics (age, sex, race), hospital characteristics (region, bed size, teaching status), procedure type (endovascular vs surgical), and all comorbidities listed in Table 1. OR = odds ratio.

Table 5
In-hospital outcomes in patients with atrial fibrillation and undergoing limb revascularization using surgical revascularization vs endovascular intervention

	Surgical revascularization N = 147,994	Endovascular intervention N = 146,475	p-Value
In-hospital mortality			
%	6.4%	3.8%	
Unadjusted OR (95% CI)	Ref.	0.58 (0.56-0.60)	<0.001
Adjusted OR (95% CI)	Ref.	0.66 (0.63-0.68)	<0.001
Myocardial infarction			
%	5.7%	5.1%	
Unadjusted OR (95% CI)	Ref.	0.89 (0.86-0.92)	<0.001
Adjusted OR (95% CI)	Ref.	0.93 (0.90-0.97)	<0.001
Stroke			
%	9.0%	8.8%	
Unadjusted OR (95% CI)	Ref.	0.98 (0.95-1.00)	0.05
Adjusted OR (95% CI)	Ref.	0.88 (0.84-0.92)	<0.001
Vascular complications			
%	3.0%	3.1%	
Unadjusted OR (95% CI)	Ref.	1.07 (1.02-1.11)	0.003
Adjusted OR (95% CI)	Ref.	1.18 (1.13-1.24)	<0.001
Major bleeding			
%	10.3%	10.4%	
Unadjusted OR (95% CI)	Ref.	0.98 (0.96-1.01)	0.14
Adjusted OR (95% CI)	Ref.	1.04 (1.01-1.07)	0.005
Major adverse cardiovascular events			
%	19.1%	16.5%	
Unadjusted OR (95% CI)	Ref.	0.84 (0.82-0.86)	<0.001
Adjusted OR (95% CI)	Ref.	0.83 (0.81-0.85)	<0.001
Net adverse cardiovascular events			
%	28.4%	26.4%	
Unadjusted OR (95% CI)	Ref.	0.90 (0.89-0.92)	<0.001
Adjusted OR (95% CI)	Ref.	0.93 (0.92-0.95)	<0.001
Amputation			
%	5.0%	5.2%	
Unadjusted OR (95% CI)	Ref.	1.04 (1.01-1.07)	0.03
Adjusted OR (95% CI)	Ref.	0.998 (0.96-1.04)	0.91

Adjusted for demographics (age, sex, race), hospital characteristics (region, bed size, teaching status), clinical presentation (intermittent claudication vs critical limb ischemia), and all comorbidities listed in Table 1. OR = odds ratio.

frequently underwent major amputation (8.0% vs 6.9%, p <0.001) compared with those with no AF, and this difference remained significant even after multivariate risk adjustment (adjusted OR: 1.13 [95% CI: 1.10 to 1.16]) (Table 4).

When AF patients were stratified by procedure type (endovascular vs surgical) (Table 5), the endovascular group had lower risk of in-hospital mortality (3.8% vs 6.4%, adjusted OR: 0.66 [95% CI: 0.63 to 0.68] and shorter length of hospital stay (median LOS = 5 days; [IQR] (2 to 10) vs 7 days; [IQR] (4 to 13); p <0.001) than surgical group. Compared with the surgical group, risk-adjusted incidence of MI, postprocedural stroke, MACE, and NACE were lower in the endovascular group. However, endovascular group had higher risk-adjusted incidence of vascular complications and major bleeding than surgical group. There was no difference in risk-adjusted incidence of major amputation between endovascular and surgical groups (Table 5).

Among PAD patients undergoing limb revascularization, there was a temporal upward trend for EVI utilization in patients with and without AF from 2002 to 2014 (P_{trend} <0.001 for both groups). Conversely, the total number surgical revascularization in PAD patients with and without AF decreased significantly within the study period (P_{trend} <0.001 for both groups) (Figure 2). The peak for change of EVI and surgical revascularization utilization was noticed in year 2006. The incidence of in-hospital mortality decreased significantly within the study period in all PAD patients (including CLI and IC) with and without AF (P_{trend} <0.001 for all groups) (Figure 3).

Discussion

In this study of 2,283,568 patients with PAD undergoing limb revascularization in the United States from 2002 to 2014, we report the following findings: (1) PAD patients with AF had worse cardiovascular and limb outcomes than those without AF; (2) these adverse outcomes in AF patients were seen in patients presenting with IC as well as CLI; (3) among patients with AF, EVI was associated with lower in-

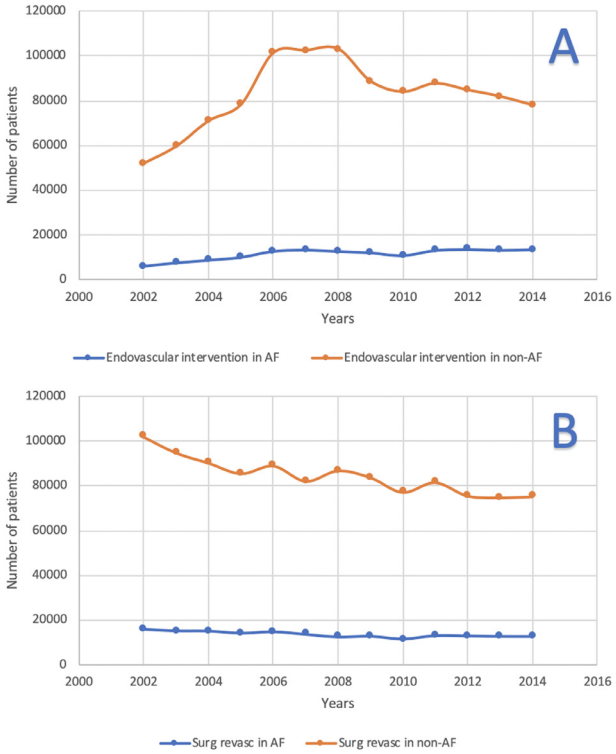

Figure 2. Annual number of endovascular intervention (Panel A) and surgical revascularization (Panel B) utilization among peripheral artery disease patients with and without atrial fibrillation. Abbreviation: AF = atrial fibrillation; Surg revasc = surgical revascularization.
P_{trend} <0.001 for all trends.

hospital mortality but similar risk of major amputation compared with surgical revascularization; (4) during the study period, EVI increased in PAD patients with and without AF; whereas surgical revascularization decreased; (5) in-hospital mortality decreased overtime in all PAD patients undergoing limb revascularization. Our study findings could help inform the consent process and periprocedural risk assessment and may lead to optimization of medical therapies in patients with atrial fibrillation aimed at reducing bleeding and ischemic complications in the perioperative phase.

Among AF patients with symptomatic PAD, low ABI were found to predict vascular death, MI and stroke/thromboembolism.[8,13,14] In the Reduction of Atherothrombosis for Continued Health (REACH) registry, patients with PAD and AF experienced higher risk of cardiovascular death and stroke compared with those without AF.[15] Furthermore, Conway and Lip reported high mortality in patients with symptomatic PAD and AF and considered these patients high-risk individuals.[16] In addition, data from REACH registry reported higher incidence of major bleeding in PAD patients with AF compared with those without AF.[15] In our study, PAD patients with AF had higher risk of major bleeding than those without AF. This might be secondary to the use of anticoagulants in addition to antiplatelet therapy in the periprocedural period. Although dual antiplatelet therapy is often prescribed after EVI, unfortunately, we were unable to adjust for medication use due to limitation of NIS database.

Thromboembolism related to AF may contribute to the high risk of stroke, MI, and major amputation that we observed in PAD patients with AF.[17,18] Thrombogenesis (Virchow's triad)

Figure 3. Annual rate of in-hospital mortality among peripheral artery disease (Panel A), critical limb ischemia (Panel B), and intermittent claudication (Panel C) patients with and without atrial fibrillation. Abbreviations: AF = atrial fibrillation; PAD = peripheral artery disease; IC = intermittent claudication; CLI = critical limb ischemia.
P_{trend} <0.001 for all trends.

secondary to inflammation and endothelial injury, platelet activation, and growth factor changes is important factor that contributes to worse cardiovascular and limb outcomes in PAD patients with AF. [5,19] In addition, established atherosclerosis in the systemic circulation may also contribute to worse cardiovascular outcome associated with AF in this study.[5] Although multiple studies assessed the association between PAD and AF in ambulatory patients,[8,13,14,20,21] our study is the first to examine cardiovascular and limb outcomes of PAD population with AF undergoing limb revascularization procedures.

Over the past decade, the growing utilization of EVI was associated with a significant reduction in the number of open revascularization procedures.[22–24] The current analysis reported similar findings among AF patients over study the duration of the study period with peak change of EVI and surgical revascularization utilization noticed in year 2006. This trend has increased focus toward outcomes of EVI due to high success rate and lower perioperative complications compared with open approach. In our study, EVI in AF patients was associated with lower odds of mortality and adverse outcomes (MI, stroke, MACE, and NACE). Interestingly, our study reported no difference in the rate of major amputation between EVI and surgical revascularization in patients with AF. Another NIS study by Sachs et al reported higher rate of major amputation in EVI when compared with surgical revascularization.[24] However, they examined the difference between both procedures among all PAD patients (our study was on AF patients), and the study was conducted during a different time period (1999 to 2007).

NIS is large, nationally representative database that has been validated multiple times for accuracy. Nevertheless, as with all studies that use routinely collected electronic healthcare data, there are several limitations to our study. Given the retrospective design, the possibility of unmeasured confounding is present due to lack of randomization. The NIS does not capture information about frailty or the severity of comorbid conditions that may preclude intervention. This analysis also relied on ICD-9-CM codes and there were no information on key variables related to limb revascularization such as indication, complexity, duration and success rate of the procedures. The dataset also lacked information on the Trans-Atlantic Inter-Society Consensus Document II classification and target lesion localization (below vs above knee); which could have confounded the outcome analysis. Furthermore, medications are not available in this dataset and the analysis was limited to in-hospital outcomes as follow up after discharge was not available.

In summary, limb revascularization in PAD patients with AF is associated with higher in-hospital mortality, higher risk of adverse cardiovascular and limb outcomes, and prolonged hospital stay compared with patients without AF. Among PAD patients with AF, endovascular intervention is associated with lower in-hospital mortality and similar risk of major amputation compared with surgical revascularization.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.069.

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