Outcome of Transcatheter Aortic Valve Implantation in Patients with Peripheral Vascular Disease

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Peripheral vascular disease (PVD) is common in patients referred for transcatheter aortic valve implantation (TAVI). We sought to investigate the impact of PVD on patients who underwent TAVI. Using data from the National Inpatient Sample database 2011 and 2014, we identified patients who had undergone TAVI. We studied the clinical characteristics and procedural outcomes in patients with PVD who underwent TAVI compared with those patients without PVD using propensity score matching score matching. *Results*: A total of 42,215 patients underwent TAVI; of which 1,388 patients were matched using propensity score matched scores to 694 in each (PVD vs no PVD) patients. The population had a mean age of 81 years old and 55.8% were of female gender. African-Americans constituted 4.3%. PVD patients who underwent TAVI were found to have higher rates of vascular complications (11.8% vs 5.9 % p <0.001) compared with non-PVD patients and tended to have higher mortality (5.5% vs 3.6%, p = 0.121) and post-TAVI bleeding (13.5% vs 12% p = 0.143). In conclusion, PVD patients have higher in-hospital mortality and higher incidence of in-hospital overall complications compared with patients who have no PVD. **(Am J Cardiol 2019;124:416−422)**

One of 8 people aged 75 years and older have moderate to severe aortic valve stenosis (AS).[1] Transcatheter aortic valve implantation (TAVI) has evolved as a new treatment option for inoperative patients initially, then an alternative for high-risk and now intermediate-risk patients.[2] Given the overlap in risk factors between peripheral vascular disease (PVD) and TAVI, it is not uncommon to encounter PVD as a co-morbidity in patient who has been referred for TAVI procedure.[3] TAVI has evolved as procedure of choice as it has less post-op complications. However, vascular complications are more common in TAVI compared with surgical aortic valve replacement (SAVR) (11% vs 3.2%),[4] particularly in (PVD) patients.[5] Owing to the large diameter of current devices and generalized atherosclerotic disease in patients with PVD. Indeed, multiple reports demonstrated the prevalence of PVD in patients referred for TAVI ranges from 20% to 30%.[6,7] PVD is associated with worse outcomes in the general population and in TAVI,[8] however, the prognostic impact of PVD in patients with severe AS who underwent TAVI is not well established. Hence, we sought to investigate the association of PVD with clinical outcomes in patients with severe AS who underwent TAVI in a national cohort of patients.

Methods

This is a retrospective study using the National Inpatient Sample (NIS) database from 2011 to 2014. The NIS is a publicly available identified database of hospital discharges in the United States, containing data from approximately 8 million hospital stays in each year 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. We included all patients, regardless the access site, who were ≥18 and underwent TAVI. PVD patients were identified with diagnoses of atherosclerosis of the extremities with intermittent claudication, resting pain, ulceration and/or gangrene. We identified 42,215 patients who undergone TAVI as a primary procedure using the International Classification of Disease, Ninth Edition, Clinical Modification (ICD-9-CM) codes (35.05 and 35.06), out of which 3,930 patients with PVD diagnosis using the codes (093.0, 437.3, 440.x, 441.x, 443.1 - 443.9, 447.1, 557.1, 557.9, and V43.4) (Figure 1), supplemental Table 1S summarizes ICD-9 codes used for other co-morbidities. The primary outcome was in-hospital mortality. Secondary outcomes were in-hospital

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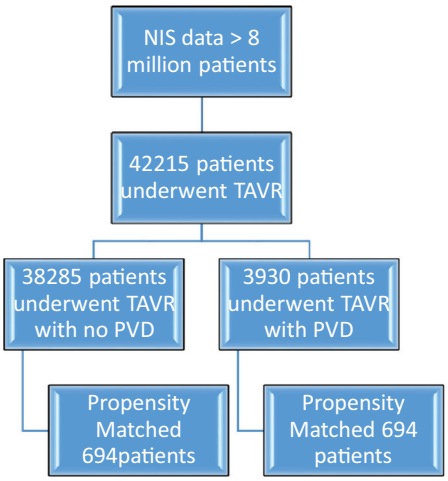


Figure 1. Inclusion criteria and exclusion criteria.

complications which included: (1) hemorrhage requiring blood transfusion; (2) vascular complications (injury to blood vessels, accidental puncture, injury to retroperitoneum, vascular complications requiring surgery); (3) hemopericardium, cardiac tamponade, pericardiocentesis, permanent pacemaker implantation; (4) respiratory complications (postprocedural pneumothorax, postprocedural pulmonary edema, pulmonary collapse, prolonged mechanical ventilation >96 hours, tracheostomy); (5) postprocedural stroke; and (6) acute kidney injury (AKI; Table 1). Data were expressed as weighted mean values ± standard deviation or median with interquartile range and frequencies with percentages for categorical variables. Independent *t* tests were used for the comparison of continuous variables measurements, whereas chi-square test for categorical variables. Weighted values of patient level observations were generated to produce a nationally representative estimate of the entire US population of hospitalized patients. Univariate and multivariate logistic regression analysis were used to study the association between the PVD and outcomes after TAVI. A stepwise logistic regression analysis including all variables with p value <0.2 in the univariate analysis was used to determine the predictive factors of the primary outcome. The following variables were included in the model for the prediction of demographics (age, race, and gender), urgency of TAVI (elective vs emergent), Elixhauser co-morbidities, TAVI access (endovascular or transapical), insurance type, and socioeconomic status. We performed a subgroup analysis by further stratifying patients for TAVI access for all outcomes. To further explore the validity of our findings, we performed propensity score-matching analysis between PVD and non-PVD groups. All patients in both groups were matched for baseline characteristics, hospital characteristics, patients' socioeconomic status and insurance, and urgency of the procedure in 1:3 propensity score matching analysis, using nearest neighbor method. For the trend analysis, Cochrane-Armitage test was used to determine the presence of a linear trend between PVD and TAVI utilization over the studied calendar years. SPSS version 25 software (IBM Corp, Armonk, New York) was used for all statistical analyses.

Table 1
Studied primary and secondary outcomes

Primary outcome	Secondary outcomes
In-hospital mortality	Hemorrhage requiring blood and Vascular complications (injury to blood vessels, accidental puncture, injury to retroperitoneum, vascular complications requiring surgery Transfusion (hemopericardium, cardiac tamponade, pericardiocentesis, permanent pacemaker (PPM) implantation, and conversion to open-heart surgery Respiratory complications (postprocedural pneumothorax, postprocedural pulmonary edema, pulmonary collapse, prolonged mechanical ventilation >96 hours, tracheostomy) Postprocedural stroke Acute kidney injury (AKI)

Results

A total of 42,215 patients underwent TAVI procedure between 2011 and 2014. There were 3,930 patients with PVD and 38, 285 with no significant-PVD. Both groups were of comparable age. Patients characteristics are summarized in Table 2. In the multivariate regression model, we used non-PVD as a reference. Patients with PVD had a significantly higher in-hospital mortality compared with the non-PVD group (5.2% vs 4.1% odds ratio [OR] 1.29, 95% confidence interval [CI] 1.12 to 1.51, p = 0.001). Furthermore, PVD patients were found to have more need for blood transfusion post-TAVI (14.2% vs 11.7% OR 1.23, 95% CI 1.12 to 1.35, p <0.001). Similarly, PVD patients had a higher rates of vascular complications (11.8% vs 5.5% OR 2.30, 95% CI 2.05 to 2.56, p <0.001) cardiac complications (12.2% vs 9.1% OR 1.39, 95% CI 1.25 to 1.52, p <0.001) and postprocedural stroke (1.9% vs 1.3% OR 1.45, 95% CI 1.14 to 1.85, p = 0.003), AKI (20.4% vs 18.6% OR 1.23, 95% CI 1.03 to 1.21, p = 0.005) and respiratory complication (14.9% vs 13.4% OR 1.13, 95% CI 1.03 to 1.24, p = 0.008) Table 4. After propensity matching (Table 3) we included a total of 1,388 patients who had similar co-morbidities divided into 2 equal groups of 694 patients each. Analysis showed mortality rate tended to be higher in the PVD group compared with non-PVD (5.5% vs 3.6% OR1.55, 95% CI 0.925 to 2.59, p = 0.09). PVD group also had higher rates of post-TAVI vascular complications (11.8% vs 5.9% OR 1.07, 95% CI 1.44 to 3.15, p <0.001) compared with non-PVD patients Table 5. There were 33,684 (80%) patients who underwent endovascular access. Only 3,029 patients had PVD (8.9%) versus 30,655 (91.1%) non-PVD. In contrast, 8531 (20%) who underwent transapical access, 901 patients (10.6%) with PVD versus 7630 (89.4%) had no PVD. Patients with PVD who had undergone TAVI through transapical access had similar in-hospital mortality compared with patients without PVD with no statistical differences observed (5.4% vs 5.4%, OR 1.19, 95% CI 0.82 to 1.71 p = 0.361.

Table 2
Patients characteristics who underwent transcatheter aortic valve implantation stratified by peripheral vascular disease status

Variable	PVD group (n = 3930)	Non-PVD group (n =38285)	p value
Age (years)	80.97 ± 8.214	81.15 ± 8.876	0.054
Women	47.1%	48.9%	<0.001
White	87.2%	87.2%	
Black	3.6%	3.8%	
Hispanic	3.8%	3.8%	
Asian	1.1%	1.1%	
Native American	0.3%	0.2%	
Other	1.0%	3.9%	
Endovascular access	3029	30,655	
Transapical access	901	7,630	
Atrial fibrillation	45.9%	44.1%	0.001
Coronary artery disease	75.9%	65.1%	<0.001
Alcohol disorders	1.4%	1.1%	0.008
Anemia	28.3%	26.7%	0.001
Congestive heart failure	74.6%	73.6%	0.030
Chronic lung disease	34.0%	25.0%	<0.001
Coagulopathy	25.4%	23.4%	<0.001
Mood disorders	7.9%	7.6%	0.360
Diabetes, uncomplicated	31.7%	31.0%	0.164
Diabetes, complicated	9.4%	7.2%	<0.001
Drug abuse	1.0%	0.6%	<0.001
Hypertension	84.4%	80.3%	<0.001
Hypothyroidism	18.7%	20.9%	<0.001
Liver Disease	4.4%	4.3%	0.846
Lymphoma	2.1%	2.3%	0.212
Metastatic cancer	0.0%	0.1%	0.222
Chronic kidney disease	42.2%	35.8%	<0.001
Pulmonary disorders	23.5%	22.5%	0.019
Psychosis	0.9%	1.0%	0.544
Peptic ulcer disease	2.5%	1.7%	<0.001
Severe malnutrition	7.0%	6.5%	0.070
Hyperlipidemia	70.1%	62.0%	<0.001
Current smoking	4.0%	2.7%	<0.001

Table 3
Propensity matched patients characteristics who underwent transcatheter aortic valve implantation stratified by peripheral vascular disease status

Variable	PVD group (n = 694)	Non-PVD group (n = 694)	p value
Age	80.63	80.73	0.822
Women	50.6%	51%	<0.914
White	86.6%	87.5%	
Black	3.9%	3.7%	
Hispanic	4.2%	3.3%	
Asian	1.3%	1.4%	
Native American	0.1%	0.4%	
Other	3.9%	3.6%	
Elective hospitalization	75.5%	75.6%	0.950
Atrial fibrillation	45.0%	45.5%	0.871
Coronary artery disease	74.1%	74.4%	0.951
Alcohol disorders	1.3%	1.6%	0.823
Deficiency Anemia	25.4%	25.2%	0.631
Congestive heart failure	11.7%	10.2%	0.493
Chronic lung disease	34.9%	38.5%	0.181
Coagulopathy	25.6%	25.4%	0.951
Mood disorders	6.5%	5.6%	0.574
Diabetes, uncomplicated	25.5%	28.1	0.303
Diabetes, complicated	8.6%	8.1%	0.771
Drug abuse	0.1%	0.0%	0.239
Hypertension	79.4%	77.8%	0.513
Hypothyroidism	18.0%	18.8%	<0.001
Liver Disease	3.0%	2.6%	0.746
Lymphoma	1.2%	1.3%	<0.001
Chronic kidney disease	37.8%	37.2%	0.868
Pulmonary disorders	3.7%	3.3%	0.717
Psychosis	2.4%	2.6%	<0.001
Hyperlipidemia	65.4%	66.3%	0.777
Smoking	3.0%	2.9%	<0.001

Patients with PVD who underwent transapical access had higher vascular complications (12.6% vs 6.6% OR 2.34, 95% CI 2.06 to 2.65, p <0.001) and cardiac complication (14.9% vs 11.4% OR 1.34, 95% CI 1.06 to 1.67, p = 0.015). Patients with PVD who underwent TAVI with endovascular access had high in-hospital mortality compared with patients without PVD (5.3% vs 3.8% OR 1.32, 95% CI 1.09 to 1.59, p = 0.003), had higher rates of vascular complications (3.8% vs 5.8% OR 1.63, 95% CI 1.35 to 1.97, p <0.001), Hemorrhage that required transfusion (13.1% vs 10.4% OR 1.20, CI 1.07 to 1.36, p = 0.003), cardiac complications (11.4% vs 8.5% OR 1.45, CI 1.28 to 1.64, p <0.001) and postprocedure stroke (2.2% vs 1.3% OR 1.54, 95% CI 1.12 to 2.12, p = 0.007) were all higher in patients with PVC. All outcomes are summarized in Figure 2. The stratified model for either the transapical access or endovascular access had no statistically significant difference in hemorrhage requiring transfusion, postprocedure stroke, respiratory complications, permanent pacemaker placement, and AKI when compared with non-PVD patients. The total number of aortic valve implantation patient increased from 2011 to 2014 Figure 3. Mortality over those years is also shown in Figure 4.

Discussion

The main findings of the current study are: (1) patients with PVD who underwent TAVI have higher in-hospital mortality compared with those who have no PVD. (2) PVD patients were more likely to have higher rates of overall complications particularly vascular and post-TAVI hemorrhage. Regardless the access type, vascular complications were higher in PVD group compared with non-PVD. The presence of PVD had significant impact on developing post-TAVI complications especially vascular complication. Multiple previous reports showed that vascular complications were the most common complications in patients who underwent percutaneous catheter interventions with a 30-day mortality of 16.9% compared with 6.6% in patients without vascular complications.[9] Furthermore, having PVD was associated with increased 30 day and in-hospital mortality in small series.[10,11] Hayashida et al, in a cohort that included 285 patients, reported that female gender, Sheath to femoral artery ratio, center experience and femoral calcification played an important role in predicting occurrence of vascular complication in patients who underwent transfemoral access. The authors suggested that applying a cut-off value of 1.05 for sheath to femoral artery ratio may decrease the rate of vascular complications.[11] Also, in our study, PVD patients were noted to have higher risk of bleeding post-TAVI compared

Table 4
Outcomes stratified by presence or absence of peripheral vascular disease

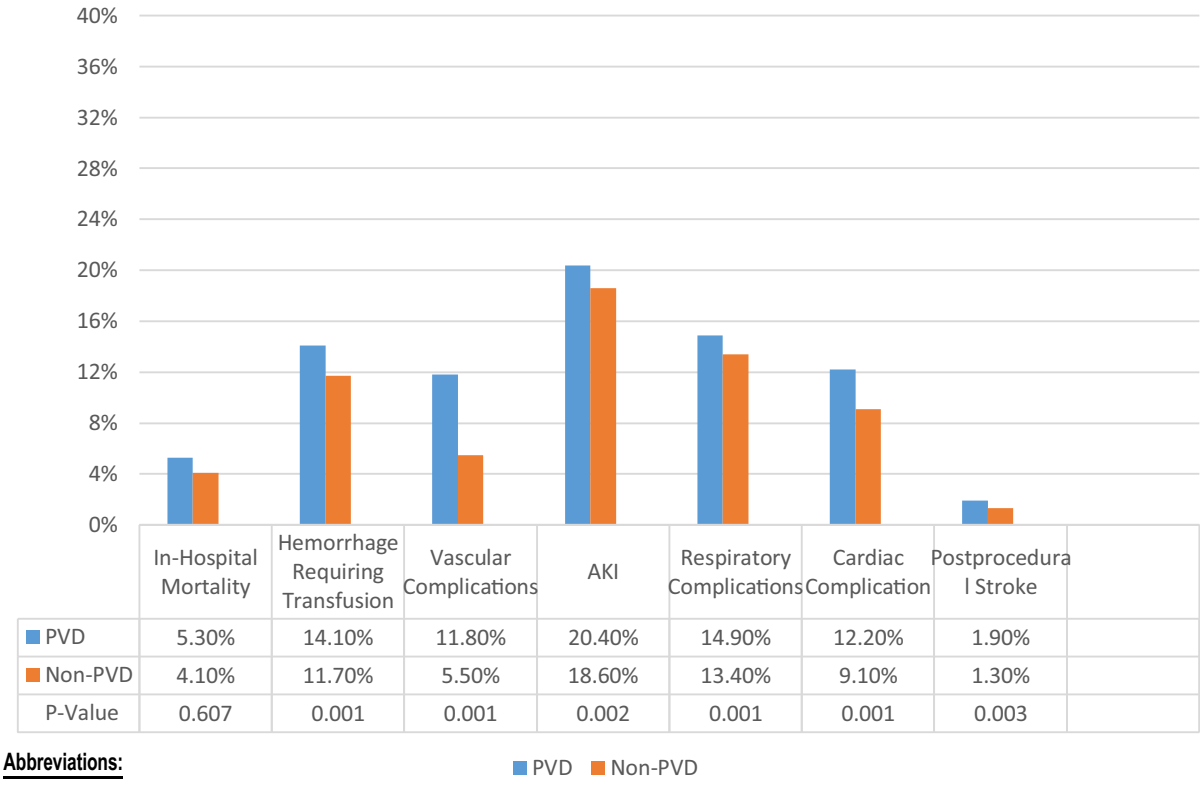
Outcome	PVD (n = 3930)	Non-PVD (n = 38285)	Unadjusted odds ratio (95% CI)	Unadjusted p value
In-hospital mortality	5.3%	4.1%	1.03 (0.92-1.14)	0.607
Endovascular	5.3%	3.8%	1.42 (1.20-1.68)	0.979
Transapical	5.4%	5.4%	1.04 (0.77-1.40)	0.430
Hemorrhage requiring transfusion	14.1%	11.7%	1.23 (1.12-1.35)	<0.001
Endovascular	13.8%	10.4%	0.27 (1.16-1.46)	<0.001
Transapical	17.5%	17.1%	1.02 (0.085-1.23)	0.785
Vascular complications	11.8%	5.5%	2.30 (2.07-2.56)	<0.001
Endovascular	12.6%	6.6%	2.23 (1.99-2.51)	<0.001
Transapical	8.9%	3.2%	2.90 (2.23-3.78)	<0.001
Cardiac complications	12.2%	9.1%	1.39 (1.25-1.53)	<0.001
Endovascular	11.4%	8.5%	1.39 (1.23-1.56)	<0.001
Transapical	14.9%	11.4%	1.36 (1.12-1.66)	0. .002
Permanent pacemaker implantation	9.6%	10.2%	0.93 (.83-1.04)	0.242
Endovascular	10.3%	11.2%	0.91 (0.80-1.03)	0.151
Transapical	7.8%	6.3%	1.24 (0. 95-1.61)	0.099
Respiratory complications	14.9%	13.4%	1.134 (1.03-1.24)	0.008
Endovascular	12.9%	11.2%	1.17 (1.05-1.31)	0.005
Transapical	22.2%	22.3%	0.99 (0.84-1.17)	0.921
Postprocedural stroke	1.9%	1.3%	1.45 (1.14-185)	0.003
Endovascular	2.2%	1.4%	1.67 (1.28-2.75)	<0.001
Transapical	1.1%	1.4%	0.77 (0.40-1.48)	0.304
Acute kidney injury	20.4%	18.6%	1.23 (1.03-1.21)	0.005
Endovascular	19.3%	17.1%	1.16 (1.06-1.28)	0.002
Transapical	23.7%	24.6%	0.95 (0.81-1.12)	0.574

Table 5
Outcomes after propensity match scoring stratified by presence or absence of PVD

Outcome	PVD (n = 694)	Non-PVD (n = 694)	Odds ratio (95% CI)	p value
In-hospital mortality	5.5%	3.6%	1.55 (0.92-2.59)	0.121
Hemorrhage requiring transfusion	13.5%	12.0%	0.14 (0.84-1.58)	0.143
Vascular complications	11.8%	5.9%	2.13 (1.44-3.15)	<0.001
Cardiac complications	12.4%	10.7%	1.18 (0.85-1.64)	0.178
Permanent pacemaker implantation	9.8%	11.4%	0.84 (0.60-1.19)	0.383
Respiratory complications	14.3%	15.7%	0.11 (0.66-1.19)	0.499
Postprocedural Stroke	1.9%	1.6%	1.18 (0.52-2.66)	0.837
Acute kidney injury	20.3%	21.2%	0.95 (0.73-1.23)	0.741

with non-PVD. Post-TAVI bleeding may be due to different etiologies. Baumann et al reported that overall Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol (HAS-BLED) score was higher in patients who have PVD to begin with which put them at higher risk of bleeding.[12] Another paper by Piccolo et al showed that higher Society of Thoracic Surgery (STS) score had association with non-access site bleeding.[13] However, regardless the bleeding site, postprocedure bleeding was associated with increased in-hospital mortality. It is not surprising that patients who undergo TAVI have a high prevalence of renal insufficiency, as most of patients who underwent TAVI often had multimorbid conditions that precluded them from SAVR. In our study, this was relevant in PVD group as they had more Chronic Kidney Disease (CKD) compared with non-PVD patients (42.2% vs 35.8%). Our results are supported by a meta-analysis that showed the CKD burden in PVD patients was high and estimated to be 25%,[14] and in another study renal failure and end stage renal disease were associated with worse in-hospital outcomes.[15] Minor differences in the rates of postprocedural stroke, respiratory and cardiac complications all contributed to worse in-hospital outcome in PVD group.

Our study analyses 4-year data from the NIS data which is the largest publically available database. To our knowledge, this is the largest TAVI population studied for the effect of PVD on patients who underwent TAVI which increase the generalizability of the results. The study has limitations as it was a retrospective observational study, which poses a possible selection bias and unmeasured confounding factors as there was no follow-up beyond the same hospital admission. Further, NIS is an administrative database which could be subject to inaccurate coding and underreporting of co-morbid diagnoses. Also, the inability to determine the severity of peripheral vascular disease was also one of the major limiting factors. There is lack of a validated measure of operative risk such as Society of Thoracic Surgeon score due to the lack of available information but this was compensated by performing an extensive



	In-Hospital Mortality	Hemorrhage Requiring Transfusion	Vascular Complications	AKI	Respiratory Complications	Cardiac Complication	Postprocedural Stroke
PVD	5.30%	14.10%	11.80%	20.40%	14.90%	12.20%	1.90%
Non-PVD	4.10%	11.70%	5.50%	18.60%	13.40%	9.10%	1.30%
P-Value	0.607	0.001	0.001	0.002	0.001	0.001	0.003

Abbreviations:

PVD: Peripheral Vascular disease; AKI: Acute Kidney Injury.

Figure 2. Outcome of transcatheter aortic valve replacement in patients with and without peripheral vascular disease.

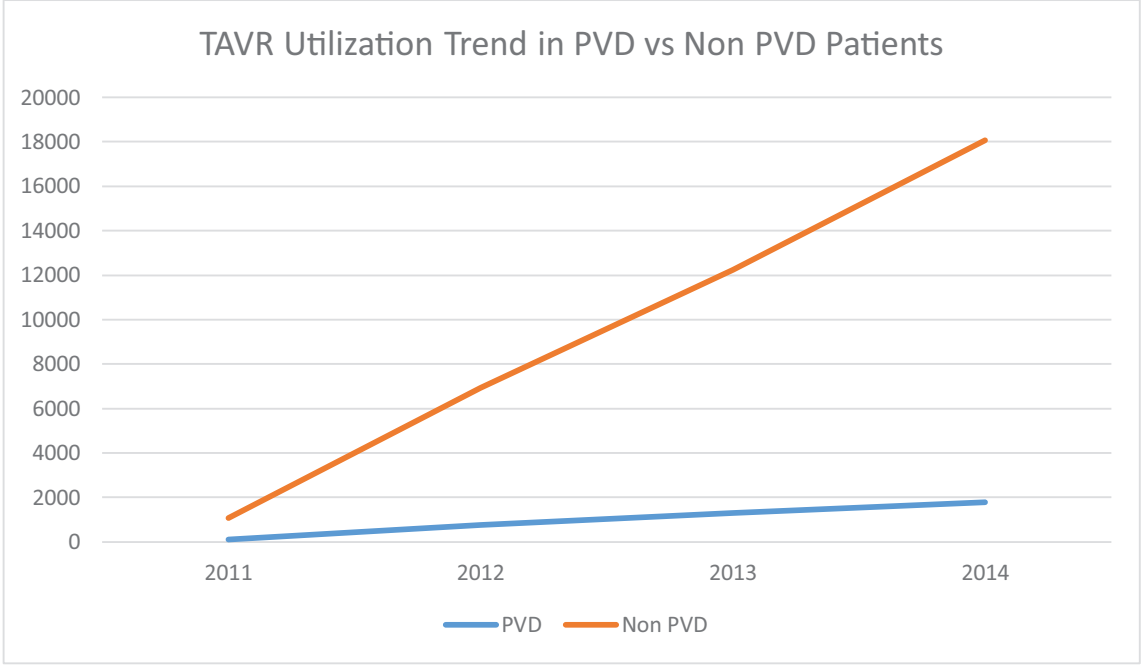


Figure 3. TAVR utilization trend from 2011 to 2104, PVD versus non-PVD.

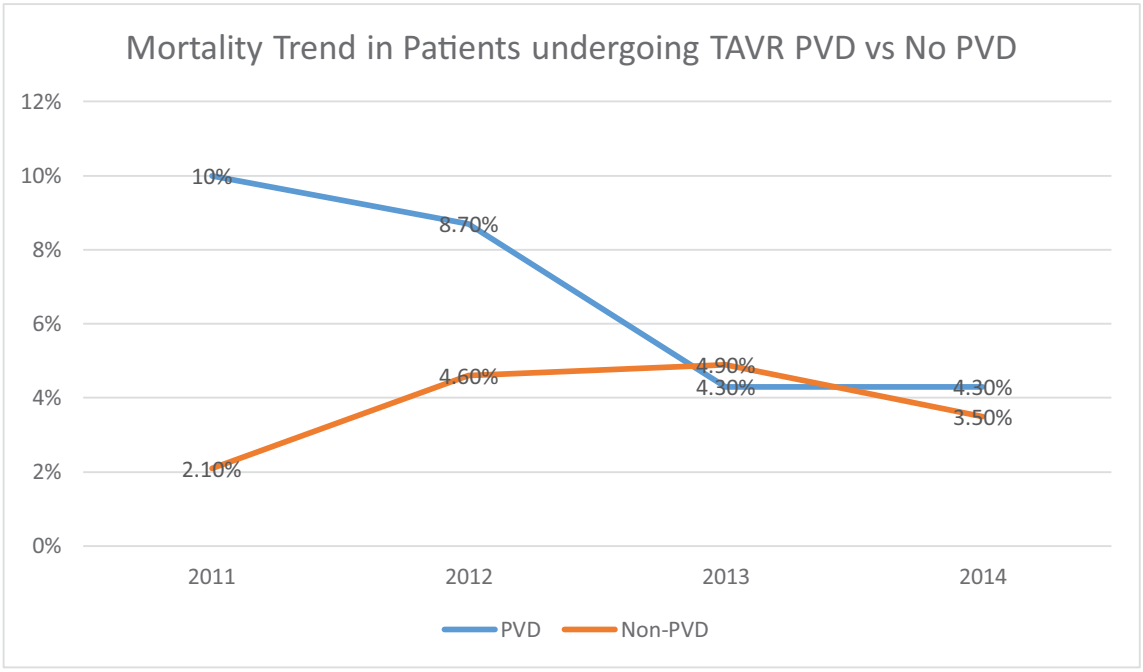


Figure 4. Mortality trend inn TAVR from 2011 to 2014, PVD versus non-PVD.

regression model adjusting for the effect of co-morbidities and other relevant factors. There is missing information on the type of device used, anesthesia type and the amount of contrast used which pose possible cofounding factors. Given that the data used was between the years of 2011 and 2014, the assumption of the use of Edwards SAPIEN Valve (Edwards Lifesciences, Irvine, California) could be valid as the Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) received Food and Drug Administration approval in January 2014. Nonetheless, our analyses were not adjusted for those missing factors.

In conclusion, this analysis of nationally representative cohort that included roughly 42,000 patients who underwent TAVI in the United States. We found that PVD patients have more co-morbid condition, higher in-hospital mortality and higher incidence of in-hospital overall complications compared with patients who have no PVD. The popularity of TAVI is increasing and nowadays moderate risk patients are also being offered to undergo TAVI which translated into increase of TAVI utilization over the last few years (Figure 3), parallel to this trend, we can see the decrease of mortality in patients who underwent TAVI. However, PVD patients continue worse when compared with non-PVD patients (Figure 4).

Conflict of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.04.047.

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005–1011.
2. Nishimura RA, O'Gara PT, Bonow RO. Guidelines update on indications for transcatheter aortic valve replacement. *JAMA Cardiol* 2017;2:1036–1037.
3. Rogers T, Thourani VH, Waksman R. Transcatheter aortic valve replacement in intermediate−and low−risk patients. *J Am Heart Assoc* 2018;7:e007147.
4. Leon Martin B MD, Smith Craig R M.D., Mack Michael M.D., Miller D Craig M.D., Moses Jeffrey W M.D., Svensson Lars G MD, Ph.D., Tuzcu E Murat M.D., Webb John G M.D., Fontana Gregory P M.D., Makkar Raj R MD, Brown David L M.D., Block Peter C M.D., Guyton Robert A M.D., Pichard Augusto D MD, Bavaria Joseph E M.D., Herrmann Howard C M.D., Douglas Pamela S M.D., Petersen John L MD, Akin Jodi J M.S., Anderson William N Ph.D., Wang Duolao Ph.D., Pocock Stuart PD. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
5. Olin JW, Sealove BA. Peripheral artery disease: current insight into the disease and its diagnosis and management. *Mayo Clin Proc* 2010;85:678–692.
6. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 2011;110:946533. CIRCULATIONAHA.
7. Thomas M. A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2010;122:62–69.
8. Fanaroff AC, Manandhar P, Holmes DR, Cohen DJ, Harrison JK, Hughes GC, Thourani VH, Mack MJ, Sherwood MW, Jones WS. Peripheral artery disease and transcatheter aortic valve replacement outcomes: a report from the society of thoracic surgeons/american college of cardiology transcatheter therapy registry. *Circ: Cardiovasc Interv* 2017;10:e005456.
9. Kamath Ashvin R, BA RG, PMF. Risk factors for progression of calcific aortic stenosis and potential therapeutic targets. *Int J Angiol* 2008;17:63–70.
10. Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrøm T, Clemmensen P. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers

NOTION randomized clinical trial. *J Am Coll Cardiol* 2015;65:2184–2194.
11. Hayashida K, Lefèvre T, Chevalier B, Hovasse T, Romano M, Garot P, Mylotte D, Uribe J, Farge A, Donzeau-Gouge P. Transfemoral aortic valve implantation: new criteria to predict vascular complications. *JACC: Cardiovasc Interv* 2011;4:851–858.
12. Baumann F, Husmann M, Benenati JF, Katzen BT, Del Conde I. Bleeding risk profile in patients with symptomatic peripheral artery disease. *J Endovasc Ther* 2016;23:468–471.
13. Piccolo R, Pilgrim T, Franzone A, Valgimigli M, Haynes A, Asami M, Lanz J, Räber L, Praz F, Langhammer B. Frequency, timing, and impact of access-site and non−access-site bleeding on mortality among patients undergoing transcatheter aortic valve replacement. *JACC: Cardiovasc Interv* 2017;10:1436–1446.
14. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UKA, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;382:1329–1340.
15. Gupta T, Goel K, Kolte D, Khera S, Villablanca PA, Aronow WS, Bortnick AE, Slovut DP, Taub CC, Kizer JR. Association of chronic kidney disease with in-hospital outcomes of transcatheter aortic valve replacement. *JACC: Cardiovasc Interv* 2017;10:2050–2060.