In-Hospital Outcomes After Transcatheter Aortic Valve Implantation in Patients With Versus Without Chronic Thrombocytopenia

Marwan Saad, MD, PhD[a]*, Ahmed N. Mahmoud, MD[b,*,**], Amr F. Barakat, MD[c], Amgad Mentias, MD[d], Ayman Elbadawi, MD[e], Islam Y. Elgendy, MD[f], Ahmed Abuzaid, MD[g], Akram Y. Elgendy, MD[h], and Hani Jneid, MD[i]

Patients with chronic thrombocytopenia (cTCP) were excluded from the pivotal transcatheter aortic valve implantation (TAVI) trials. The National Inpatient Sample was queried and propensity score matching was performed to evaluate the prevalence and impact of cTCP on in-hospital clinical outcomes after TAVI. The main outcome was in-hospital mortality in patients with versus without cTCP. Among 38,855 TAVI hospitalizations, 7,105 had a diagnosis of cTCP (18.3%). In-hospital mortality was similar in both groups ($OR_{adjusted}$ 0.79; 95% confidence interval [CI] 0.57 to 1.09); however, cTCP was associated with higher risk of acute kidney injury ($OR_{adjusted}$ 1.29; 95% CI 1.08 to 1.54), vascular complications ($OR_{adjusted}$ 1.99; 95% CI 1.22 to 3.25), perioperative blood product transfusion ($OR_{adjusted}$ 1.69; 95% CI 1.42 to 2.01), cardiac tamponade ($OR_{adjusted}$ 4.04; 95% CI 1.51 to 10.82), cardiogenic shock ($OR_{adjusted}$ 1.52; 95% CI 1.07 to 2.15), and use of extracorporeal membrane oxygenation ($OR_{adjusted}$ 2.32; 95% CI 1.1 to 4.9). In conclusion, cTCP is common in patients who underwent TAVI and is associated with worse postprocedure clinical outcomes, however, with similar in-hospital mortality. **(Am J Cardiol 2019;124:1106−1112)**

Transcatheter aortic valve implantation (TAVI) has offered a viable option for treatment of severe symptomatic AS in high-risk and inoperable patients, and its indications are expanding to include intermediate and low-risk patients,[1−3] resulting in an exponential growth in the numbers of TAVI procedures worldwide.[4] Chronic thrombocytopenia (cTCP) is frequently seen in the elderly and its prevalence increases with aging.[5] cTCP was shown to be an independent risk factor for higher mortality in the elderly population.[6] Patients who underwent TAVI are commonly frail, and the risk of major or life-threatening bleeding complications was reported to be as high as 16% within 1 year after the procedure.[7] The presence of TCP in patients who underwent TAVI is hence a challenging situation especially with the utilization of antiplatelet or anticoagulant therapy.[8−10] Despite the previously mentioned concern, most of the large randomized controlled trials (RCTs) evaluating the outcomes with TAVI have excluded patients with significant baseline cTCP,[1,2] leaving the literature with conflicting data from single-center small observational studies, or studies that were just focused on postprocedure acquired TCP.[8,11−15] The aim of this study was to assess the prevalence and in-hospital outcomes of cTCP in patients who underwent TAVI in a nationwide representative database from the United States, the National Inpatient Sample database (NIS).

Methods

The NIS database is considered the largest publicly available deidentified all-payer inpatient database in the United States, including >100 clinical and nonclinical data elements from around 8 million hospitalization records each year.[16] The NIS is a part of the Healthcare Cost and Utilization Project (HCUP), constructed from billing data of approximately 20% of stratified sample discharges from the United States, and is maintained by the Agency for Healthcare Research and Quality (AHRQ).[16] The NIS data until 2014 include an International Classification of Diseases-9th Edition-Clinical Modification [ICD-9-CM] coding format for a primary (principal) diagnosis which is usually considered the main reason for hospitalization, 24 secondary diagnoses, and 15 procedural diagnoses for each hospitalization record. In addition, each record includes variables such as gender, age, race, insurance status (eg, Medicare, Medicaid, private, or uninsured), hospital characteristics (eg, location, bed size, etc.), median home income, hospitalization outcomes, length of hospital stay, total hospitalization cost, and discharge status (eg, dead or alive). The discharge

[a]Cardiovascular Institute, Warren Alpert Medical School of Brown University, Providence, Rhode Island; [b]Division of Cardiovascular Medicine, University of Washington, Seattle, Washington; [c]UPMC Heart and Vascular Institute, University of Pittsburgh, Pittsburgh, Pennsylvania; [d]Division of Cardiovascular Medicine, University of Iowa, Iowa City, Iowa; [e]Division of Cardiovascular Medicine, University of Texas Medical Branch, Galveston, Texas; [f]Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA; [g]Division of Cardiology, University of California at San Francisco, San Francisco, California; [h]Division of Cardiology, University of Florida, Gainesville, Florida; and [i]Division of Cardiology, Baylor College of Medicine, Houston, Texas. Manuscript received March 30, 2019; revised manuscript received and accepted July 2, 2019.

Funding: None.

*Authors contributed equally.

See page 1111 for disclosure information.

**Corresponding author: Tel: (206) 685-1397; fax: (206) 685-9394.

E-mail address: Ahmoud@UW.edu (A.N. Mahmoud).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.07.011

weights of these variables allow for calculation of national estimates. The NIS data are validated by the AHRQ on annual basis through crosschecking of the data against multiple US hospital registries such as the American Hospital Association Annual Survey Database, the National Hospital Discharge Survey from the National Center for Health Statistics, and the Med-PAR inpatient database from Centers for Medicare & Medicaid Services.[16]

We queried the NIS database years 2012 to 2014 for hospitalizations with ICD-9 procedure codes for TAVI (transfemoral 35.05 and transapical 35.06) and primary or secondary diagnosis of TCP. Using the chronic condition indicator, only records with cTCP (i.e., >1 year) were included. The ICD-9-CM codes used to identify each of these diagnoses and procedures are listed in Supplemental Table 1. The main outcome of the present study was all cause in-hospital mortality among TAVI procedures with or without cTCP in both unadjusted and propensity-matched samples. The secondary outcomes included acute myocardial infarction, acute stroke, cardiac arrest, cardiogenic shock, use of intra-aortic balloon pump, short-term use of ventricular assist device, use of extracorporeal membrane oxygenation (ECMO), hemopericardium, cardiac tamponade, ventricular arrhythmias, advanced heart block, permanent pacemaker placement, vascular complications, periprocedural blood products transfusion, acute kidney injury (AKI), respiratory complications, length of hospital stay, and total charges of hospitalization. Clinical characteristics and inpatient outcomes were reported using ICD-9 codes, Clinical Classifications Software (CCS) codes and Elixhauser co-morbidities as reported by Healthcare Cost and Utilization Project.

The updated weight samples provided with NIS were used to calculate the national estimates in our analyses. Categorical variables were compared using Pearson chi-square test and reported as frequencies. Continuous variables were compared using Mood median test and reported as median and interquartile range. Mantel-Haenszel test for trend was used to generate a linear-by-linear association trend of categorical variables. Odds ratios (ORs) and 95% confidence interval (CI) were used to express outcomes' effect sizes and were considered significant at p value <0.05. A 1:1 propensity score matching analysis was performed to match each case (cTCP) to the closest propensity score control (no cTCP) using the nearest neighbor technique. We evaluated the robustness of the propensity score match through standardized mean differences (bias %) between the unmatched and matched variables with a cut level of 0.1.[17] A list of all variables included in the propensity score matching is illustrated in Table 1. All statistical analyses were performed by SPSS software version 23.0 (IBM, Armonk, New York).

Results

Between 2012 and 2014, there were 38,855 hospitalizations with TAVI procedures identified and included 7,105 of which had diagnosis of cTCP (18.3%). Transfemoral access was the most utilized in both arms (79.8% vs 81.0% in no cTCP and cTCP arms, respectively). Compared with patients without cTCP, patients with cTCP were older (82.0 ± 8.1 vs 80.9 ± 8.8 years), more men (49.0% vs 43.8%, p = 0.001), with more underlying co-morbidities including previous transient ischemic attack (11.8% vs 10.0%, p = 0.03), hypertension (81.6% vs 78.8%, p = 0.03), liver disease (4.3% vs 1.8%, p <0.001), renal failure (42.1% vs 34.2%, p <0.001), lymphoma (2.0 vs 1.3%, p = 0.02), and chronic blood loss anemia (1.7% vs 1.0%, p = 0.04). The prevalence of solid tumors without metastasis or metastatic cancer was similar in both groups (Table 1). After propensity score matching, total of 14,080 hospitalizations were available for analysis (7,040 in each arm). Baseline characteristics were well matched with <10% bias (Table 1 and Figure 1).

After propensity score matching, the primary outcome of in-hospital all-cause mortality was similar in patients with versus without cTCP (4.5% vs 5.7%; $OR_{adjusted}$ 0.79; 95% CI 0.57 to 1.09; p = 0.16). Patients with cTCP had an increased risk of AKI (24.5% vs 20.1%, $OR_{adjusted}$ 1.29; 95% CI 1.08 to 1.54; p = 0.004), vascular complications (3.5% vs 1.8%, $OR_{adjusted}$ 1.99; 95% CI 1.22 to 3.25; p = 0.005), postoperative blood product transfusion (31.2% vs 21.2%, $OR_{adjusted}$ 1.69; 95% CI 1.42 to 2.01; p <0.001), hemopericardium (0.5% vs 0.1%, $OR_{adjusted}$ 7.0; 95% CI 0.86 to 57.2; p = 0.034), cardiac tamponade (1.4% vs 0.4%, $OR_{adjusted}$ 4.04; 95% CI 1.51 to 10.82; p = 0.003), cardiogenic shock (5.4% vs 3.6%, $OR_{adjusted}$ 1.52; 95% CI 1.07 to 2.15; p = 0.018), and use of ECMO (1.6% vs 0.7%, $OR_{adjusted}$ 2.32; 95% CI 1.1 to 4.9; p = 0.023) compared with patients without cTCP. Presence of cTCP was also associated with increased length of hospital stay (7 ± 5 days vs 6 ± 5 days, p <0.001), and total charges of hospitalization (210,605.2 ± 156,781 vs 193,989.9 ± 129,699, p <0.001).

There was no difference between both groups in the risk of cardiac arrest, acute myocardial infarction, acute stroke, advanced heart block, permanent pacemaker placement, ventricular arrhythmias, respiratory complications, and use of intra-aortic balloon pump or short-term ventricular assist device. Table 2 and 3 summarized the unadjusted and adjusted outcomes in no cTCP versus cTCP groups, respectively.

Discussion

In this nationwide propensity-matched cohort of patients, we report important findings (1) cTCP is common in patients at a prohibitive or high risk for surgery who underwent TAVI (18.3%); (2) cTCP in those patients is not associated with an increased risk of in-hospital mortality, but rather with a higher risk of vascular complications, postoperative blood transfusion, AKI, cardiogenic shock, hemopericardium and cardiac tamponade, and hence resulting in longer hospitalizations and increase in total costs.

The interplay between the cardioembolic and bleeding risks is an important determinant of clinical outcomes in patients who underwent TAVI. Not only that these patients have a high baseline cardioembolic risk,[18,19] but also the prevalence of atrial fibrillation can reach up to 30% to 50% in such population.[7] Furthermore, there is an ongoing concern about a significant risk of bioprosthetic valve thrombosis on long-term follow-up especially in patients on dual antiplatelet therapy rather than oral anticoagulation.[20] In contrast, major bleeding is not uncommon after TAVI,[21] and is associated with increased 30-day mortality.[22] Age-related TCP as well as platelet dysfunction in patients with AS play a role in the increased bleeding risk in this

Table 1
Patient and hospital characteristics of patients who underwent TAVI based on the presence or absence of chronic thrombocytopenia before and after propensity matching

Variable	Patient population (non-PS matched)		p Value	Patient population (PS matched)		p Value
	No cTCP (n = 31,750)	cTCP (n = 7,105)		No cTCP (n = 7,040)	cTCP (n = 7,040)	
Calendar year						
2012	18.6 (15.3-22.3)	19.4 (15.7-23.8)		21.0 (17.0-25.6)	19.5 (15.7-23.9)	
2013	32.6 (28.2-37.3)	34.3 (29.2-39.7)	0.44	32.0 (27.0-37.3)	34.2 (29.1-39.6)	0.510
2014	48.8 (43.8-53.9)	46.3 (40.8-51.9)		47.1 (41.5-52.7)	46.4 (40.9-52.0)	
Admission						
Weekend admission	6.3 (5.5-7.3)	5.6 (4.4-6.9)	0.28	6.2 (4.8-8.0)	5.5 (4.4-6.9)	0.479
Elective admission	76.1 (74.1-78.0)	77.2 (73.8-80.2)	0.47	77.2 (74.3-79.9)	77.2 (73.9-80.2)	1.000
Patient demographics						
Age	80.9 (8.8)	82.0 (8.1)	<0.001	84.0 (10)	84.0 (10)	0.574
Sex, female	49.0 (47.6-50.3)	43.8 (41.2-46.6)	0.001	43.0 (40.4-45.6)	44.2 (41.5-46.9)	0.526
Race						
White	87.8 (86.2-89.3)	85.8 (83.7-87.7)		87.0 (84.7-89.0)	86.1 (84.0-87.9)	
African American	3.2 (3.8-4.4)	4.5 (3.5-5.8)		3.6 (2.7-4.7)	4.3 (3.4-5.5)	
Hispanic	3.5 (3.0-4.2)	5.0 (3.8-6.5)		4.9 (3.8-6.4)	4.8 (3,7-6.3)	
Asian/Pacific Islander	1.1 (0.8-1.6)	0.9 (0.5-1.5)	0.07	1.3 (0.9-2.1)	0.9 (0.5-1.5)	0.656
Native American	0.2 (0.1-0.4)	0.4 (0.1-1.1)		0.2 (0.0-1.5)	0.4 (0.1-1.0)	
Other	3.7 (2.6-5.2)	3.5 (2.5-4.8)		3.0 (2.0-4.4)	3.5 (2.5-4.7)	
Median household income						
0 to 25th percentile	21.2 (19.7-22.8)	20.1 (17.8-22.5)		19.1 (17.0-21.4)	20.0 (17.8-22.3)	
26th to 50th percentile	25.1 (23.6-26.7)	25.4 (22.8-28.2)	0.41	24.1 (21.7-26.8)	25.5 (22.9-28.3)	0.510
51st to 75th percentile	25.9 (24.5-27.3)	24.5 (22.3-27.0)		26.9 (24.5- 29.5)	24.5 (22.2-26.9)	
76th to 100th percentile	27.9 (25.5-30.4)	30.0 (26.8-33.5)		29.8 (26.8-33.1)	30.0 (26.9-33.4)	
Primary expected payer						
Medicare	90.1 (89.0-91.0)	91.3 (89.5-92.7)		92.0 (90.4-93.4)	91.5 (89.7-93.0)	
Medicaid	1.1 (0.8-1.4)	0.8 (0.4-1.4)		0.7 (0.4-1.3)	0.7 (0.4-1.3)	
Private insurance	7.0 (6.2-7.9)	6.5 (5.3-8.1)	0.57	6.5 (5.2-8.0)	6.4 (5.1-7.9)	0.553
Self-pay	0.4 (0.2-0.7)	0.5 (0.2-1.1)		0.3 (0.1-0.8)	0.5 (0.2-1.1)	
Other	1.4 (1.0-1.8)	0.9 (0.5-1.6)		0.5 (0.2-1.0)	0.9 (0.5-1.0)	
Smoking history	27.7 (26.3-29.2)	26.0 (23.7-28.4)	0.18	25.9 (23.5-28.5)	26.1 (23.8-28.5)	0.934
Co-morbidities						
Coronary artery disease	68.0 (66.6-69.4)	69.0 (66.4-71.4)	0.51	69.8 (67.3-72.2)	69.0 (66.5-71.5)	0.665
Prior myocardial infarction	13.1 (12.2-14.1)	12.1 (10.5-13.9)	0.30	12.9 (11.2-14.7)	12.1 (10.6-13.9)	0.566
Prior stroke	2.3 (2.0-2.7)	2.0 (1.4-3.0)	0.54	2.5 (1.8-3.5)	2.1 (1.4-3.0)	0.481
Prior TIA	10.0 (9.2-10.7)	11.8 (10.3-13.6)	0.03	11.2 (9.5-13,0)	11.9 (10.3-13.6)	0.554
Prior PCI	18.8 (17.7-20.0)	18.7 (16.6-21.1)	0.92	19.0 (17.0-21.3)	18.8 (16.6-21.2)	0.887
PCI during admission	3.7 (3.2-4.4)	2.7 (1.9-3.9)	0.10	2.6 (1.9-3.7)	2.8 (1.9-3.9)	0.828
Prior CABG	22.3 (21.2-23.5)	22.0 (19.8-21.2)	0.78	20.7 (18.7-22.9)	21.9 (19.8-24.3)	0.432
Prior pacemaker	10.2 (9.4-11.1)	11.4 (9.9-13.1)	0.18	11.4 (9.7-13.3)	11.4 (9.9-13.1)	0.955
Prior ICD	2.9 (2.5-3.4)	3.0 (2.2-4.0)	0.93	2.8 (2.1-3.9)	3.0 (2.2-4.0)	0.827
Carotid artery disease	7.3 (6.6-8.1)	7.7 (6.4-9.2)	0.62	7.0 (5.8-8.5)	7.7 (6.4-9.2)	0.500
Dyslipidemia	35.5 (34.0-37.1)	36.3 (33.9-38.8)	0.58	61.4 (58.6-64.1)	63.8 (61.3-66.3)	0.175
Aortic regurgitation	2.6 (2.1-3.1)	2.5 (1.8-3.5)	0.94	2.1 (1.4-3.0)	2,6 (1.9-3.5)	0.355
Atrial fibrillation	44.0 (42.8-45.3)	45.2 (42.8-47.8)	0.36	44.8 (42.2-47.4)	45.2 (42.8-47.7)	0.811
Alcohol abuse	1.0 (0.8-1.3)	1.4 (0.9-2.1)	0.18	1,7 (1.2-2.5)	1.3 (0.3-2.1)	0.426
Collagen vascular disease	5.0 (4.4-5.5)	4.9 (3.8-6.1)	0.87	5.0 (4.0-6.3)	4.9 (3.9-6.2)	0.858
Chronic blood loss anemia	1.0 (0.8-1.3)	1.7 (1.1-2.5)	0.04	1.8 (1.2-2.7)	1.6 (1.1-2.4)	0.672
Congestive heart failure	12.6 (11.4-13.9)	10.9 (9.3-12.7)	0.08	10.4 (8.7-12.3)	10.9 (9.3-12.8)	0.638
Chronic pulmonary disease	33.9 (32.6-35.2)	30.0 (27.8-32.4)	0.003	30.0 (27.6-32.6)	30.2 (27.9-32.6)	0.933
Depression	7.1 (6.5-7.8)	6.9 (5.7-8.4)	0.79	6.1 (4.9-7.5)	7.0 (5.7-8.4)	0.377
Diabetes, uncomplicated	28.9 (27.8-30.0)	26.6 (24.4-29.0)	0.07	25.3 (23.3-27.8)	26.7 (24.5-29.1)	0.451
Diabetes, complicated	6.1 (5.5-6.7)	5.8 (4.7-7.3)	0.75	5.7 (4.6-7.0)	5.8 (4.6-7.2)	0.933
Drug abuse	0.3 (0.2-0.4)	0.4 (0.1-0.8)	0.59	0.3 (0.1-0.7)	0.3 (0.1-0.7)	1.000
Hypertension	78.8 (77.4-80.1)	81.6 (79.4-83.5)	0.03	82.4 (80.2-84.4)	81.6 (79.5-83.6)	0.596
Hypothyroidism	20.5 (19.4-21.5)	19.6 (17.7-21.5)	0.41	19.7 (17.7-21.9)	19.7 (17.8-21.7)	0.959
Liver disease	1.8 (1.5-2.2)	4.3 (3.3-5.5)	<0.001	3.2 (2.4-4.2)	3.7 (2.8-4.9)	0.483
Lymphoma	1.3 (1.0-1.6)	2.0 (1.4-2.9)	0.02	2.1 (1.4-3.0)	1.9 (1.3-2.7)	0.782
Fluid and electrolyte disorders	24.5 (23.1-25.9)	34.2 (31.6-36.9)	<0.001	33.5 (30.8-36.2)	33.9 (31.3-36.7)	0.787
Metastatic cancer	0.4 (0.3-0.6)	0.3 (0.1-0.8)	0.58	0.5 (0.2-1.0)	0.3 (0.1-0.8)	0.365
Other neurological disorders	6.3 (5.8-7.0)	7.3 (6.1-8.8)	0.18	6.6 (5.4-8.1)	7.2 (6.0-8.7)	0.521

(*continued*)

Table 1 (***Continued***)

Variable	Patient population (non-PS matched)		p Value	Patient population (PS matched)		p Value
	No cTCP (n = 31,750)	cTCP (n = 7,105)		No cTCP (n = 7,040)	cTCP (n = 7,040)	
Obesity	14.5 (13.6-15.6)	12.3 (10.8-14.0)	0.03	11.6 (10.1-13.3)	12.2 (10.7-13.9)	0.285
Paralysis	1.7 (1.4-2.1)	1.8 (1.2-2.7)	0.74	2.4 (1.6-3.5)	1.8 (1.2-2.6)	0.285
Peripheral vascular disease	29.2 (27.7-30.8)	30.8 (28.2-33.6)	0.27	29.6 (27.2-32.2)	30.9 (28.2-33.7)	0.477
Psychosis	1.8 (1.5-2.3)	1.3 (0.8-2.0)	0.14	1.4 (0.9-2.2)	1.3 (0.8-2.1)	0.746
Pulmonary circulation disorders	3.8 (3.3-4.4)	4.2 (3.3-5.3)	0.51	4.1 (3.2-5.4)	4.0 (3.2-5.2)	0.925
Renal failure	34.2 (32.9-35.6)	42.1 (39.3-44.9)	<0.001	41.6 (39.0-44.3)	41.7 (39.0-44.5)	0.969
Solid tumor without metastasis	2.0 (1.7-2.4)	1.8 (1.3-2.6)	0.70	1.8 (1.3-2.7)	1.8 (1.3-2.7)	1.000
Nonbleeding PUD	<0.1	<0.1		<0.1	<0.1	
Weight loss	4.6 (4.0-5.3)	6.6 (5.4-8.1)	0.002	6.8 (5.6 -8.3)	6.5 (5.3-7.9)	0.714
Hospital characteristics						
Bed capacity						
Small	4.9 (3.9-6.3)	4.7 (3.7-6.0)		4.5 (3.3-6.0)	4.8 (3.9-5.8)	
Medium	15.4 (13.5-17.6)	19.6 (16.1-23.6)	0.03	19.2 (16.6-22.1)	19.1 (15.8-22.9)	0.946
Large	79.6 (77.2-81.9)	75.7 (71.7-79.4)		76.3 (73.2-79.2)	76.1 (72.4-79.8)	
Location/teaching status						
Rural	0.9 (0.6-1.2)	0.3 (0.1-0.7)		0.3 (0.1-1.1)	0.3 (0.1-0.6)	
Urban, nonteaching	10.2 (8.7-11.9)	11.1 (9.1-13.6)	0.09	10.7 (8.8-13.1)	11.1 (9.2-13.2)	0.970
Urban, teaching	89.0 (87.2-90.5)	88.6 (86.1-90.7)		89.0 (86.6-91.0)	88.6 (86.5-90.5)	
Region						
Northeast	25.5 (22.5-28.8)	23.0 (19.3-27.2)		22.8 (19.9-26.0)	23.1 (19.6-27.0)	
Midwest/North central	22.4 (19.8-25.2)	21.0 (17.8-24.5)	0.18	20.3 (17.6-23.3)	21.0 (18.0-24.2)	0.965
South	33.9 (30.8-37.1)	37.8 (33.6-42.1)		37.8 (34.1-41.6)	37.6 (33.8-41.6)	
West	18.2 (15.3-21.4)	18.2 (15.1-21.8)		19.1 (15.6-23.1)	18.3 (15.4-21.7)	
Control/ ownership						
Government, non-federal	8.2 (6.8-9.8)	7.2 (5.6-9.3)		5.8 (4.6-7.3)	7.2 (5.8-9.0)	
Private, non-profit	84.5 (82.3-86.4)	85.6 (82.6-88.2)	0.64	86.6 (84.4-88.6)	85.7 (82.9-88.1)	0.389
Private, investor-owned	7.4 (6.1-8.9)	7.1 (5.2-9.7)		7.5 (6.0-9.4)	7.0 (5.2-9.5)	
TAVI access						
Transfemoral	81.0 (79.3-82.5)	79.8 (77.1-82.3)	0.36	79.2 (76.5-81.7)	79.8 (77.1-82.3)	0.688
Transapical	19.2 (17.6-20.9)	20.6 (18.1-23.4)	0.27	20.9 (18.4-23.6)	20.5 (18.0-23.3)	0.823

AIDS = acquired immunodeficiency syndrome; CABG = coronary artery bypass grafting; cTCP = chronic thrombocytopenia; ICD = implantable cardioverter-defibrillator; PCI = percutaneous coronary intervention; PUD = peptic ulcer disease, TAVI = transcatheter aortic valve implantation; TIA = transient ischemic attack.
Categorical variables are presented as % (95% confidence interval), continuous variables are presented as median (interquartile range).

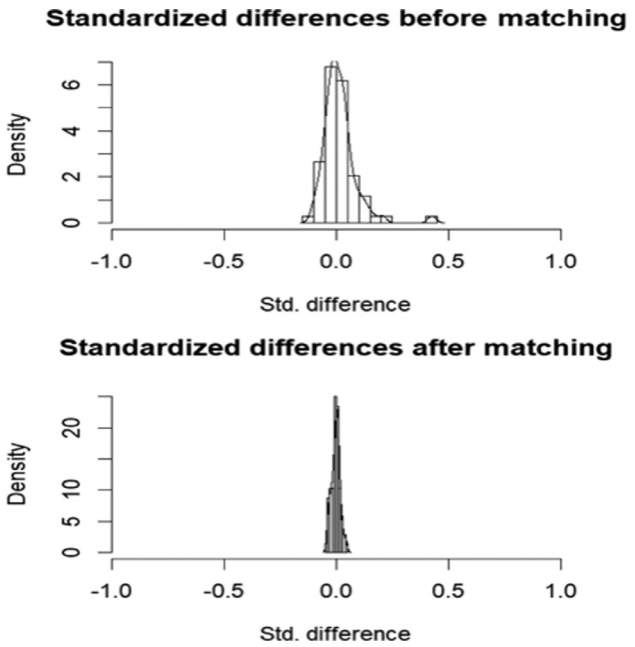

Figure 1. It illustrates the absolute standardized differences in all variables included in the propensity score matching pre- and postmatching.

population.[23,24] The hypotheses behind age-related TCP and platelet dysfunction are the reduction in hematopoietic stem cell reserve as age increases,[23] and the shear effect and disturbed flow in patients with aortic valve disease, respectively.[24] This has made the optimum approach to post-TAVI antithrombotic therapy challenging, and multiple ongoing studies aim at answering the question.[25,26]

Acquired TCP is a commonly reported phenomenon after various cardiovascular procedures including cardiac surgeries,[27] percutaneous coronary interventions,[28,29] and percutaneous closure of congenital heart defects.[11,30] After TAVI, the incidence of acquired moderate/severe TCP was reported to be as high as 36%,[13] being slightly lower when compared with SAVR patients.[15] Although severe persistent TCP after TAVI was associated with worse clinical outcomes in multiple studies,[13,15,31] the prevalence and outcomes of baseline cTCP in patients who underwent TAVI are not well studied in literature. The present study demonstrates that baseline cTCP is a common co-morbidity that needs to be more recognized in patients who underwent TAVI. This goes in line with a retrospective cohort of 732 patients with severe, symptomatic aortic stenosis who underwent TAVI, where the prevalence of baseline TCP (defined as platelet count $<150 \times 10^9$/L) was 21.9%, and that of moderate/severe TCP (defined as platelet count $<100 \times 10^9$/L) was 4.0%.[11]

Table 2
Unadjusted outcomes of patients who underwent TAVI based on the presence or absence of chronic thrombocytopenia

Variable	Patient population		Odds ratio* (95% CI)	p Value
	No cTCP (n = 31,750)	cTCP (n = 7,105)		
Primary outcome				
In-hospital mortality	3.8 (3.4-4.4)	4.8 (3.8-6.1)	1.26 (0.95-1.68)	0.11
Secondary outcomes				
Acute kidney injury	16.8 (15.8-17.8)	24.8 (22.7-27.1)	1.64 (1.44-1.87)	<0.001
Respiratory complications	3.4 (3.0-4.0)	5.6 (4.3-7.4)	1.67 (1.25-2.23)	<0.001
Vascular complications	2.0 (1.6-2.3)	3.4 (2.6-4.5)	1.79 (1.30-2.47)	<0.001
Acute myocardial infarction	2.8 (2.4-3.2)	2.0 (1.4-2.8)	0.71 (0.47-1.06)	0.09
Acute stroke	2.6 (2.2-3.0)	2.6 (1.9-3.6)	1.02 (0.71-1.1.47)	0.91
Advanced heart block	9.7 (8.9-10.5)	10.6 (9.2-12.3)	1.11 (0.92-1.33)	0.29
Ventricular arrhythmia	4.5 (3.9-5.0)	4.9 (3.9-6.0)	1.09 (0.85-1.41)	0.49
Cardiac arrest	3.3 (2.8-3.8)	4.2 (3.2-5.3)	1.28 (0.95-1.73)	0.11
Hemopericardium	0.2 (0.1-0.3)	0.5 (0.2-1.0)	3.14 (1.25-7.91)	0.01
Cardiac tamponade	0.6 (0.5-0.9)	1.5 (1.0-2.2)	2.31 (1.37-3.88)	0.001
Cardiogenic shock	2.9 (2.5-3.4)	5.3 (4.3-6.6)	1.89 (1.46-2.45)	<0.001
Periprocedural blood products transfusion	20.1 (18.5-21.7)	31.2 (28.3-34.2)	1.80 (1.56-2.08)	<0.001
Intra-aortic balloon pump	1.7 (1.4-2.2)	2.7 (2.0-3.6)	1.57 (1.08-2.29)	0.02
Permanent pacemaker placement	10.5 (9.6-11.4)	11.3 (9.6-13.1)	1.08 (0.89-1.32)	0.42
Sort-term VAD	0.2 (0.1-0.4)	0.1 (0.0-0.5)	0.30 (0.04-2.28)	0.21
ECMO use	1.0 (0.7-1.3)	1.6 (1.1-2.4)	1.70 (1.03-2.79)	0.046
Length of stay, d	7.7 (7.2)	8.8 (7.2)		<0.001
Total charges	220,064 (144,585)	256,258 (171,197)		<0.001

CI = confidence interval; cTCP = chronic thrombocytopenia; ECMO = extracorporeal membrane oxygenation; VAD = ventricular-assist device.
Categorical variables are presented as % (95% confidence interval), continuous variables are presented as median and interquartile range.
* Odds ratio are unadjusted

Despite such high prevalence, those patients, especially with platelet count <50,000, are usually excluded from large RCTs,[1,2] hence limited and conflicting data exist regarding outcomes after TAVI in patients with cTCP.[8,11]

This study shows that cTCP is associated with an increased risk of post-TAVI complications, especially those possibly related to increased bleeding risk such as vascular complications, hemopericardium, cardiac tamponade, and

Table 3
Adjusted outcomes of patients who underwent TAVI based on the presence or absence of chronic thrombocytopenia

Variable	Patient population		Odds ratio (95% CI)	p Value
	No cTCP (n = 31,750)	cTCP (n = 7,105)		
Primary outcome				
In-hospital mortality	4.5 (3.6-5.8)	5.7 (4.6-7.0)	0.79 (0.57-1.09)	0.159
Secondary outcomes				
Acute kidney injury	20.1 (18.0-22.4)	24.5 (22.4-26,8)	1.29 (1.08-1.54)	0.004
Respiratory complications	4.0 (3.1-5.6)	5.7 (4.3-7.4)	1.42 (0.98-2.09)	0.066
Vascular complications	1.8 (1.2-2.6)	3.5 (2.6-4.6)	1.99 (1.22-3.25)	0.005
Acute myocardial infarction	2.4 (1.7-3.5)	1.9 (1.3-2.8)	0.79 (0.48-1.29)	0.347
Acute stroke	3.3 (2.5-4.3)	2.6 (1.9-3.5)	0.77 (0.50-1.21)	0.262
Advanced heart block	9.0 (7.6-10.7)	10.6 (9.2-12.2)	1.19 (0.93-1.53)	0.166
Ventricular arrhythmia	5.1 (4.0-6.5)	4.9 (3.9-6.1)	0.96 (0.68-1.34)	0.795
Cardiac arrest	3.6 (2.7-4.7)	4.1 (3.2-5.3)	1.17 (0.79-1.72)	0.435
Hemopericardium	0.1 (0.0-0.5)	0.5 (0.2-1.0)	7.03 (0.86-57.24)	0.034
Cardiac tamponade	0.4 (0.1-0.9)	1.4 (0.9-2.2)	4.04 (1.51-10.82)	0.003
Cardiogenic shock	3.6 (2.8-4.7)	5.4 (4.4-6.7)	1.52 (1.07-2.15)	0.018
Periprocedural blood products transfusion	21.2 (18.9-23.6)	31.2 (28.3-34.3)	1.69 (1.42-2.01)	0.018
Intra-aortic balloon pump	2.3 (1.6-3.2)	2.6 (1.9-3.6)	1.16 (0.71-1.90)	0.553
Permanent pacemaker placement	9.7 (8.2-11.3)	11.0 (9.4-12.9)	1.16 (0.89-1.51)	0.281
Sort-term VAD	0.4 (0.2-1.1)	0.1 (0.0-0.5)	0.17 (0.02-1.45)	0.065
ECMO use	0.7 (0.4-1.3)	1.6 (1.1-2.4)	2.32 (1.10-4.90)	0.023
Length of stay, d	6.0 (5.0)	7.0 (5.0)		<0.001
Total charges	193,990 (129,699)	210,605 (156,781)		<0.001

CI = confidence interval; cTCP = chronic thrombocytopenia; ECMO = extracorporeal membrane oxygenation; VAD = ventricular-assist device.
Categorical variables are presented as % (95% confidence interval), continuous variables are presented as median (interquartile range).

AKI. Another plausible explanation for these complications especially cardiogenic shock and increased ECMO use, is that cTCP likely represents a marker of sickness and frailty,[31] and hence identifies a population at higher risk of such complications. Patients with cTCP in the present study were more likely to be older, with multiple co-morbidities such as liver disease, renal failure, lymphoma, and others. Our results, however, did not show a difference between the 2 groups in in-hospital mortality. This is inconsistent with the results of the study by Sannino et al which showed a correlation between TCP and 30-day and 1-year mortality.[11] This discrepancy can be explained by 2 theories, first, the significantly larger population size examined in our study, and second, due to the nature of NIS data, it is not feasible to determine outcomes with mild versus moderate/severe TCP. In their study, Sannino et al concluded that increased mortality was associated with moderate/severe TCP compared with no or mild TCP, with moderate/severe TCP being an independent predictor of 30-day and 1-year mortality.[11]

The present study has several limitations. First, the NIS is an administrative database that is subject to miscoding errors as well as a potential discrepancy in the criteria and definitions of variables included in our propensity-matched analysis. Second, confounding factors cannot be entirely excluded even after appropriate propensity score matching. Third, the NIS does not provide information regarding important confounding factors such as medical therapy (ie, antiplatelet therapy vs anticoagulation), procedural characteristics (ie, balloon-expandable vs self-expanding valves, sheath size, etc.), or data regarding outcomes after discharge. Fourth, the lack of information about the exact platelet counts in the NIS records precludes more a robust outcome analysis based on the severity of cTCP. Finally, only chronic TCP were included, so our results cannot be generalized for patients with acute TCP.

Conclusions

Patients with cTCP are at higher risk of in-hospital complications after TAVI, however without increase in in-hospital mortality.

Disclosures

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.2019.07.011.

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
2. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–1620.
3. Elgendy IY, Mahmoud AN, Gad MM, Elbadawi A, Rivero F, Alfonso F. Transcatheter or surgical aortic valve replacement for low surgical risk patients: meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2019;12:1399–1401.
4. Carroll JD, Vemulapalli S, Dai D, Matsouaka R, Blackstone E, Edwards F, Masoudi FA, Mack M, Peterson ED, Holmes D, Rumsfeld JS, Tuzcu EM, Grover F. Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT registry. *J Am Coll Cardiol* 2017;70:29–41.
5. Balduini CL, Noris P. Platelet count and aging. *Haematologica* 2014;99:953–955.
6. Msaouel P, Lam AP, Gundabolu K, Chrysofakis G, Yu Y, Mantzaris I, Friedman E, Verma A. Abnormal platelet count is an independent predictor of mortality in the elderly and is influenced by ethnicity. *Haematologica* 2014;99:930–936.
7. Vranckx P, Windecker S, Welsh RC, Valgimigli M, Mehran R, Dangas G. Thrombo-embolic prevention after transcatheter aortic valve implantation. *Eur Heart J* 2017;38:3341–3350.
8. Flaherty MP, Mohsen A, Moore JB, Bartoli CR, Schneibel E, Rawasia W, Williams ML, Grubb KJ, Hirsch GA. Predictors and clinical impact of pre-existing and acquired thrombocytopenia following transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2015;85:118–129.
9. Sherwood MW, Vemulapalli S, Harrison JK, Dai D, Vora AN, Mack MJ, Holmes DR, Rumsfeld JS, Cohen DJ, Thourani VH, Kirtane A, Peterson ED. Variation in post-TAVR antiplatelet therapy utilization and associated outcomes: insights from the STS/ACC TVT registry. *Am Heart J* 2018;204:9–16.
10. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM, Thompson A. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135:e1159–e1195.
11. Sannino A, Stoler RC, Hebeler RF, Szerlip M, Mack MJ, Grayburn PA. Clinical relevance of baseline TCP in transcatheter aortic valve replacement. *J Invasive Cardiol* 2017;29:353–358.
12. Zhu Q, Liu X, He W, He Y, Tang M, Sun Y, Xu X, Shi K, Kong H, Jiang J, Chen L, Chen J, Hu P, Xu Q, Wang J. Predictors of thrombocytopenia after self-expandable transcatheter aortic valve replacement: a single-center experience from China. *Cardiology* 2018;139:151–158.
13. Dvir D, Généreux P, Barbash IM, Kodali S, Ben-Dor I, Williams M, Torguson R, Kirtane AJ, Minha S, Badr S, Pendyala LK, Loh JP, Okubagzi PG, Fields JN, Xu K, Chen F, Hahn RT, Satler LF, Smith C, Pichard AD, Leon MB, Waksman R. Acquired thrombocytopenia after transcatheter aortic valve replacement: clinical correlates and association with outcomes. *Eur Heart J* 2014;35:2663–2671.
14. Gallet R, Seemann A, Yamamoto M, Hayat D, Mouillet G, Monin J-L, Gueret P, Couetil J-P, Dubois-Randé J-L, Teiger E, Lim P. Effect of transcatheter (via femoral artery) aortic valve implantation on the platelet count and its consequences. *Am J Cardiol* 2013;111:1619–1624.
15. Jilaihawi H, Doctor N, Chakravarty T, Kashif M, Mirocha J, Cheng W, Lill M, Nakamura M, Gheorghiu M, Makkar RR. Major thrombocytopenia after balloon-expandable transcatheter aortic valve replacement: prognostic implications and comparison to surgical aortic valve replacement. *Catheter Cardiovasc Interv* 2015;85:130–137.
16. Healthcare Cost and Utilization Project (HCUP). Overview of the National (Nationwide) Inpatient Sample (NIS). Available at: http://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed September 22, 2018. Available from: https://www.hcup-us.ahrq.gov/nisoverview.jsp
17. Stuart EA, Lee BK, Leacy FP. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. *J Clin Epidemiol* 2013;66(8 suppl):S84–S90.

18. Auffret V, Regueiro A, Del Trigo M, Abdul-Jawad Altisent O, Campelo-Parada F, Chiche O, Puri R, Rodés-Cabau J. Predictors of early cerebrovascular events in patients with aortic stenosis undergoing transcatheter aortic valve replacement. *J Am Coll Cardiol* 2016;68:673–684.
19. Nombela-Franco L, Webb JG, de Jaegere PP, Toggweiler S, Nuis R-J, Dager AE, Amat-Santos IJ, Cheung A, Ye J, Binder RK, van der Boon RM, Van Mieghem N, Benitez LM, Pérez S, Lopez J, San Roman JA, Doyle D, Delarochellière R, Urena M, Leipsic J, Dumont E, Rodés-Cabau J. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation* 2012;126:3041–3053.
20. Jose J, Sulimov DS, El-Mawardy M, Sato T, Allali A, Holy EW, Becker B, Landt M, Kebernik J, Schwarz B, Richardt G, Abdel-Wahab M. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv* 2017;10:686–697.
21. Généreux P, Cohen DJ, Williams MR, Mack M, Kodali SK, Svensson LG, Kirtane AJ, Xu K, McAndrew TC, Makkar R, Smith CR, Leon MB. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: insights from the PARTNER I Trial (placement of aortic transcatheter valve). *J Am Coll Cardiol* 2014;63:1100–1109.
22. Stortecky S, Stefanini GG, Pilgrim T, Heg D, Praz F, Luterbacher F, Piccolo R, Khattab AA, Räber L, Langhammer B, Huber C, Meier B, Jüni P, Wenaweser P, Windecker S. Validation of the valve academic research consortium bleeding definition in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *J Am Heart Assoc* 2015;4:e002135.
23. Biino G, Santimone I, Minelli C, Sorice R, Frongia B, Traglia M, Ulivi S, Di Castelnuovo A, Gögele M, Nutile T, Francavilla M, Sala C, Pirastu N, Cerletti C, Iacoviello L, Gasparini P, Toniolo D, Ciullo M, Pramstaller P, Pirastu M, de Gaetano G, Balduini CL. Age- and sex-related variations in platelet count in Italy: a proposal of reference ranges based on 40987 subjects' data. *PLoS One* 2013;8:e54289.
24. Prohaska W, Zittermann A, Lüth JU, Inoue K, Köster-Eiserfunke W, Baller D, Körfer R, Kleesiek K. Prevalent platelet dysfunction in patients with aortic valve disease. *J Heart Valve Dis* 2008;17:542–547.
25. Nijenhuis VJ, Bennaghmouch N, Hassell M, Baan J, van Kuijk JP, Agostoni P, van 't Hof A, Kievit PC, Veenstra L, van der Harst P, van den Heuvel AFM, den Heijer P, Kelder JC, Deneer VH, van der Kley F, Onorati F, Collet JP, Maisano F, Latib A, Huber K, Stella PR, Ten Berg JM. Rationale and design of POPular-TAVI: antiPlatelet therapy fOr Patients undergoing Transcatheter Aortic Valve Implantation. *Am Heart J* 2016;173:77–85.
26. Collet J-P, Berti S, Cequier A, Van Belle E, Lefevre T, Leprince P, Neumann F-J, Vicaut E, Montalescot G. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: the randomized ATLANTIS trial. *Am Heart J* 2018;200:44–50.
27. Matthai WH. Thrombocytopenia in cardiovascular patients: diagnosis and management. *Chest* 2005;127(2 suppl):46S–52S.
28. Ayoub K, Marji M, Ogunbayo G, Masri A, Abdel-Latif A, Ziada K, Vallurupalli S. Impact of chronic thrombocytopenia on in-hospital outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2018;11:1862–1868.
29. De Labriolle A, Bonello L, Lemesle G, Roy P, Steinberg DH, Xue Z, Suddath WO, Satler LF, Kent KM, Pichard AD, Lindsay J, Waksman R. Decline in platelet count in patients treated by percutaneous coronary intervention: definition, incidence, prognostic importance, and predictive factors. *Eur Heart J* 2010;31:1079–1087.
30. Li P, Chen F, Zhao X, Zheng X, Wu H, Chen S, Qin Y. Occurrence and clinical significance of in-hospital acquired thrombocytopenia in patients undergoing transcatheter device closure for congenital heart defect. *Thromb Res* 2012;130:882–888.
31. Hernández-Enríquez M, Regueiro A, Romaguera R, Andrea R, Gómez-Hospital JA, Pujol-López M, Ferreiro-Gutiérrez JL, Brugaletta S, Roura G, Freixa X, Gómez-Lara J, Martín-Yuste V, Gracida M, Cequier Á, Sabaté M. Thrombocytopenia after transcatheter aortic valve implantation. A comparison between balloon-expandable and self-expanding valves. *Catheter Cardiovasc Interv* 2019;93:1344–1351.