Alarming Increasing Trends in Hospitalizations and Mortality With Heyde's Syndrome: A Nationwide Inpatient Perspective (2007 to 2014)

Rupak Desai, MBBS[a], Tarang Parekh, MBBS, MSc[b], Sandeep Singh, MBBS[c], Upenkumar Patel, MD, MPH[d], Hee Kong Fong, MD[e], Dipen Zalavadia, MBBS[f], Sejal Savani, MPH[g], Rajkumar Doshi, MD, MPH[h], Rajesh Sachdeva, MD[a,i,j], and Gautam Kumar, MD[a,j,*]

We studied the trends and outcomes of patients with intestinal angiodysplasia-associated gastrointestinal bleeding (Heyde's syndrome [HS]) with aortic stenosis (AS) who underwent surgical aortic valve replacement (SAVR) versus transcatheter aortic valve implantation (TAVI). The National Inpatient Sample (2007 to 2014) and International Classification of Diseases, Ninth Revision, Clinical Modification codes were used to identify HS hospitalizations, pertinent co-morbidities, and outcomes of SAVR versus TAVI from 2011 to 2014. The incidence of HS with AS was 3.1%. The trends in hospitalizations and all-cause inpatient mortality showed relative surges of 29.16% (from 48 to 62 per 100,000) and 22.7% (from 3.7 to 4.54 per 100,000) from 2007 to 2014. HS patients were older (mean age ~80 vs 77 years) females (54.3% vs 52.2%) compared with AS without HS. The all-cause mortality (6.9% vs 4.1%), length of stay (LOS) (~7.0 vs 5.8 days), and hospitalization charges ($58,519.31 vs $57,598.67) were higher in HS (p < 0.001). No differences were reported in all-cause mortality and hospital charges in HS patients who underwent either SAVR or TAVI. However, the TAVI cohort showed lower rates of stroke (1.7% vs 10.0%) and blood transfusion (1.7% vs 11.7%), a shorter LOS (18.3 vs 23.9 days; p < 0.001), and more routine discharges (21.7% vs 14.8%, p = 0.01). An older age, male gender, Asian race, congestive heart failure, coagulopathy, fluid and/or electrolytes disorders, chronic pulmonary disease, and renal failure raised the odds of mortality in HS patients. In conclusion, we observed increasing rates of hospitalizations with HS and higher inpatient mortality from 2007 to 2014. The HS patients who underwent TAVI had fewer complications without any difference in the all-cause mortality compared with SAVR.   © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:1149−1155)

Aortic stenosis (AS) is one of the prevalent valvular heart diseases in the United States and its prevalence rises with age, 1% to 2% at 75 years and reaches up to 6% at the age of 85 years.[1] Similarly, angiodysplasia is a gastrointestinal condition present mostly in elder age groups. It is the second most common cause of lower gastrointestinal bleeding (GIB) in elderly patients.[2,3] Since 1958, many studies have outlined the different clinical criteria in support of the discovery of Heyde's syndrome (HS).[4] AS leads to the destruction of high-molecular-weight multimers of von Willebrand factor (vWF). This creates states of acquired vWF deficiency,[5] which is a rare phenomenon and therefore, the association of bleeding dysplasia among AS patients.[3,6−9] Discrepancies lie in the association of the GIB and the AS with varying incidence among different studies.[3,6,7] However, resolution of GIB has been reported after aortic valve replacement.[3,6,9] Lack of any large-scale data on outcomes of surgical aortic valve replacement (SAVR) vs transcatheter aortic valve implantation (TAVI) in this condition promoted us to look at the nationwide cohorts of AS hospitalizations with and without angiodysplasia-associated GIB.

Methods

Data were acquired from the National Inpatient Sample (NIS; 2007 to 2014) databases, funded by the Agency for Healthcare Research and Quality as a part of Healthcare Cost and Utilization Project. The NIS is the largest all-payer inpatient healthcare dataset in the United States, which can be accessed from the Healthcare Cost and

[a]Department of Cardiology, Atlanta VA Medical Center, Decatur, Georgia; [b]Department of Health Administration, George Mason University, Fairfax, Virginia; [c]Department of Clinical Epidemiology, Biostatistics, and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [d]Department of Internal Medicine, Nassau University Medical Center, East Meadow, New York; [e]Department of Internal Medicine, University of Missouri-Columbia, Columbia, Missouri; [f]Department of Internal Medicine, The Wright Center for Graduate Medical Education, Scranton, Pennsylvania; [g]Department of Public Health, New York University, New York, New York; [h]Department of Internal Medicine, University of Nevada School of Medicine, Reno, Nevada; [i]Department of Cardiology, Morehouse School of Medicine, Atlanta, Georgia; and [j]Department of Cardiology, Emory University School of Medicine, Atlanta, Georgia. Manuscript received October 30, 2018; revised manuscript received and accepted December 19, 2018.

See page 1154 for disclosure information.

*Corresponding author: Tel: (404) 321-6111 ext. 7359

E-mail address: gautam.kumar@emory.edu (G. Kumar).

Utilization Project website (https://www.hcup-us.ahrq.gov/nisoverview.jsp). More than 7 million hospital inpatient stays are included in each year's NIS dataset. It represents a nationally stratified 20% sample of discharges from >1,000 US community hospitals of 44 states. This data represents nearly 95% of the US population. Discharge weight included in this dataset was used to produce national estimates of hospital inpatient stays. Patients' identifications are not revealed in this data. Thus, an institutional review board approval was not required for this study.

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) code 424.1 was used to identify AS hospitalizations in adults. Then, ICD-9 CM such as 569.84, 569.85, 578.1, and 578.9 applied to recognize intestinal angiodysplasia-associated GIB, which constituted the study cohort of HS hospitalizations as documented and validated in previous studies.[3] Co-morbidities associated with AS and HS (https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/Table2-FY2010-V3_5.pdf), SAVR and TAVI procedures, and related complications were identified either by previously validated or used ICD-9 CM diagnostic and procedure codes.[10]

The primary outcome was the all-cause in-hospital mortality in HS hospitalizations. Secondary outcomes were the mean LOS, total hospital charges, and disposition of patients with HS. Secondary co-outcomes were to assess predictors of in-hospital mortality in HS and trends of in-hospital mortality and hospital admissions in HS.

Continuous and categorical variables were evaluated by Student's *t* test and Pearson's chi-square test, respectively. Continuous and categorical variables were expressed as mean $\pm$ standard deviation and percentages, respectively. A 2-tailed p value ≤ 0.05 was set as the cutoff for the statistical significance. A 2-way hierarchical multivariate logistic regression analysis was performed to assess the predictors of in-hospital mortality in HS after adjusting possible confounding variables such as age, gender, race, median household income national quartile for patient zip code and payer status. The results of a multivariable regression were expressed by adjusted odds ratio (OR), 95% confidence interval, and p value. Linear-by-linear association test was used to assess the trends. Missing data of all variables were excluded in all statistical analysis. For a subgroup analysis, we assessed outcomes of SAVR versus TAVI in HS hospitalizations using a propensity-score-matched analysis on a caliper scale of 0.01 adjusting all above-mentioned confounders between 2011 and 2014. All imbalances between the cohorts were removed postmatching, which was confirmed by the absolute standardized difference of <10% postmatching. SPSS version 24 (IBM Corp, Armonk, New York) was used to analyze the study cohort.

Results

The study cohort comprised of 4,161,869 AS hospitalizations. Of these, 130,487 AS hospitalizations (3.1%) were associated with HS and GIB. Patients with HS with GIB were older (mean age ~80 vs 77 years), more often black (8.2% vs 7.7%), females (54.3% vs 52.2%), and Medicare enrollees admitted nonelectively compared with the AS without GIB (p < 0.001) cohort. Over one-third of HS cases were elderly patients ≥ 85 years. The hospitalizations with HS were observed higher in Northeast region and nonteaching hospitals compared with AS only (Table 1).

Overall all-cause inpatient mortality in HS with GIB was 6.9%. The hospitalizations with HS demonstrated higher all-cause in-hospital mortality (6.9% vs 4.1%), prolonged hospitalization (7.0 $\pm$ 7.8 vs 5.8 $\pm$ 5.0 days), higher hospitalization charges ($58,519.31 vs $57,598.67) and discharges to short-term facilities (3.8% vs 3.4%) compared with AS without GIB (p < 0.001), as reported in Table 2.

After excluding cases with missing data, we could match 299 patients with HS who underwent TAVI to a 1:1 propensity-matched control group of 299 patients who underwent SAVR between 2011 and 2014. The imbalances between the groups were adjusted postmatching, except for diabetes, which was higher in the TAVI group, in the matched cohorts. There were no differences in the SAVR and TAVI groups for all-cause mortality (11.7% vs 10.0%, p = 0.51) and hospital charges ($400,816 vs $381,065, p = 0.48); however, TAVI cohort had significantly lower rates of stroke (1.7% vs 10.0%, p < 0.001), periprocedural myocardial infarction (3.3% vs 6.7%, p = 0.06), and blood transfusion (1.7% vs 11.7%, p < 0.001). Furthermore, patients who underwent TAVI had shorter LOS (18.3 vs 23.9, p < 0.001) and more routine discharges (21.7% vs 14.8%, p = 0.01; Table 3).

A gradual increase in the number of HS-related hospitalization (48 to 62 per 100,000) has been noted between 2007 and 2014 (29% relative increase, p_{trend} < 0.001). A gradual increase (2007 to 2014, 3.70% to 4.54%; p < 0.001) in the all-cause inpatient mortality was seen over the 8 years (Figure 1).

Among patients with HS, an older age, male gender, Asian and Pacific Islander race and elective admissions predicted a higher risk of mortality. Compared with the rural hospitals, HS hospitalizations at urban hospitals had higher mortality odds. Cardiovascular co-morbidities linked to increased risk of mortality among the HS hospitalizations were congestive heart failure, coagulopathy and fluid, and electrolytes disorders. Noncardiovascular co-morbidities associated with increased risk of mortality were chronic pulmonary disease, renal failure, metastatic cancer, lymphoma, and solid tumor without metastasis. Traditional cardiovascular risk factors such as dyslipidemia, smoking, diabetes, hypertension, and obesity did not predict higher odds of in-hospital mortality in HS (Table 4).

Discussion

The key findings reported in this nationwide study are as follows. A total of 3.1% AS hospitalizations were associated with HS. The all-cause inpatient mortality in HS was 6.9%. A gradually increasing trend in hospitalizations with HS and in-hospital mortality were noted over the study period. The hospitalizations with HS had a significantly worse impact in terms of higher all-cause mortality and resource utilization. The HS cohort who underwent TAVI showed superior outcomes compared with SAVR.

We determined increasing trends in HS and mortality in the US over the period of 2007 to 2014. A study by Alqahtani et al[11] has reported an increase in the

TABLE 1

Baseline characteristics of hospitalized aortic stenosis patients with versus without intestinal angiodysplasia-associated gastrointestinal bleeding (Heyde's syndrome)

Variables	Intestinal angiodysplasia-associated gastrointestinal bleeding				p value*
	No (n = 4,031,382)		Yes (n = 130,487)		
Age (years) at hospitalization					**<0.001**
Mean (±SD)	77.4 (±12.4)		80.2 (±10.0)		
18-64	586,643	(14.6%)	10,095	(7.7%)	
65-84	2,105,929	(52.2%)	68,538	(52.5%)	
≥85	1,338,809	(33.2%)	51,853	(39.7%)	
Sex					**<0.001**
Male	1,927,689	(47.8%)	59,583	(45.7%)	
Female	2,103,479	(52.2%)	70,894	(54.3%)	
Race					**<0.001**
White	2,948,912	(82.2%)	96,517	(82.1%)	
Black	276,713	(7.7%)	9,603	(8.2%)	
Hispanic	200,370	(5.6%)	6,409	(5.4%)	
Asian or Pacific Islander	59,207	(1.7%)	1,978	(1.7%)	
Native American	16,645	(0.5%)	454	(0.4%)	
Other	83,934	(2.3%)	2,655	(2.3%)	
Type of admissions					**<0.001**
Non-elective	3,159,662	(78.6%)	118,027	(90.6%)	
Elective	862,702	(21.4%)	12,203	(9.4%)	
Primary expected payer					**<0.001**
Medicare	3,296,160	(81.9%)	114,693	(88.0%)	
Medicaid	121,327	(3.0%)	2,876	(2.2%)	
Private including HMO	499,576	(12.4%)	10,331	(7.9%)	
Self − Pay/no charge/others	108,824	(2.6%)	2402	(1.9%)	
Bed size of hospital					**<0.001**
Small	523,639	(13.0%)	17,710	(13.6%)	
Medium	994,637	(24.8%)	32,720	(25.2%)	
Large	2,494,365	(62.2%)	79,510	(61.2%)	
Location/teaching status of hospital					**<0.001**
Rural	432,942	(10.8%)	16,043	(12.3%)	
Urban - non teaching	1,632,393	(40.7%)	55,012	(42.3%)	
Urban - teaching	1,947,306	(48.5%)	58,885	(45.3%)	
Region of hospital					**<0.001**
Northeast	940,929	(23.3%)	32,404	(24.8%)	
Midwest	981,505	(24.3%)	31,471	(24.1%)	
South	1,367,247	(33.9%)	43,379	(33.2%)	
West	741,700	(18.4%)	23,233	(17.8%)	

GI = gastrointestinal bleeding; HMO = health maintenance organization.

* p < 0.05 (bold letters) indicates clinical significance.

TABLE 2

In-hospital outcomes of aortic stenosis hospitalizations with versus without intestinal angiodysplasia-associated gastrointestinal bleeding (Heyde's syndrome)

Outcomes	Intestinal angiodysplasia-associated GIB				p
	No (n = 4,031,382)		Yes (n = 130,487)		
All-cause in-hospital mortality	166,265	(4.1%)	8,944	(6.9%)	**<0.001**
Disposition of patient					**<0.001**
Routine	1,743,762	(43.3%)	55,538	(42.6%)	
Transfer to short-term hospital	136,980	(3.4%)	4,983	(3.8%)	
Other transfers (SNF, ICF, other)	1,144,824	(28.4%)	36,570	(28.0%)	
Home health care	819,661	(20.3%)	23,613	(18.1%)	
Against medical advice	14,914	(0.4%)	654	(0.5%)	
Length of stay mean (±SD)	5.8 (±6.0)		7.0 (±7.8)		**<0.001**
Total hospital charges mean (±SD)	$57,598.67 (±$80,989.84)		$58,519.31 (±$100,434.530)		**0.001**

ICF = intermediate care facility; GIB = gastrointestinal bleeding; SNF = skilled nursing facility.

p < 0.05 (bold letters) indicates clinical significance.

TABLE 3
Outcomes of SAVR versus TAVI in aortic stenosis hospitalizations with angiodysplasia-associated gastrointestinal bleeding: a propensity-matched analysis

Variable	SAVR (n = 299)	TAVI (n = 299)	p
Age (years) at hospitalization			
Mean ± SD	78.8 ± 7.3	78.8 ± 9.0	0.98
18-64	<11*	30 (10.0%)	**<0.001**
65-84	224 (74.9%)	170 (56.8%)	
≥85	65 (21.9%)	99 (33.2%)	
Sex			0.12
Male	168 (56.4%)	150 (50.0%)	
Female	130 (13.6%)	149 (50.0%)	
Type of admission			0.70
Non-elective	129 (43.3%)	134 (44.8%)	
Elective	169 (56.7%)	165 (55.25%)	
Race			0.15
White	254 (85.1%)	244 (81.7%)	
Black	20 (6.7%)	35(11.7%)	
Hispanic	15 (4.9%)	<11*	
Co-morbidities			
Hypertension	209 (69.9%)	209 (70.0%)	1.0
Diabetes, uncomplicated	55 (18.4%)	80 (26.8%)	**0.01**
Diabetes, complicated	<11*	<11*	1.0
Dyslipidemia	129 (43.1%)	124 (41.4%)	0.67
Obesity	60 (20.0%)	55 (18.3%)	0.64
Smoker	79 (26.4%)	89 (29.8%)	0.36
Peripheral vascular disease	70 (23.4%)	60 (19.9%)	0.32
Congestive heart failure	40 (13.5%)	50 (16.7%)	0.26
Liver disease	20 (6.6%)	25 (8.4%)	0.43
Renal failure	134 (44.8%)	129 (43.2%)	0.68
In-hospital outcomes			
All-cause in-hospital mortality	30 (10.0%)	35 (11.7%)	0.51
Postoperative hypotension/shock	20 (6.7%)	20 (6.7%)	1.0
Blood transfusion	35 (11.7%)	<11*	**<0.001**
Postoperative myocardial infarction	20 (6.7%)	<11*	0.06
Perioperative stroke	30 (10.0%)	<11*	**<0.001**
Disposition			**0.01**
Routine	44 (14.8%)	65 (21.7%)	
Transfer to short-term hospital	20 (6.7%)	15 (5.0%)	
Other transfers (SNF, ICF, other)	145 (48.5%)	109 (36.6%)	
Home health care	60 (20.0%)	75 (24.9%)	
Mean length of stay (days)	23.9	18.3	**<0.001**
Mean hospital charges	$381,065	$400,816	0.48

ICF = intermediate care facility; SAVR = surgical aortic valve replacement; SNF = skilled nursing facility; TAVI = transcatheter aortic valve implantation. p < 0.05 (bold letters) indicates clinical significance.

Propensity-score-matched analysis was performed adjusting for baseline demographics, patient-level and hospital-level characteristics, and all relevant baseline co-morbidities on a caliper width of 0.01 after excluding missing data.

* Cell values ≤11 were not reported as per the guidelines by HCUP.

AS-related hospitalization both in white and African-American between 2003 and 2014. In addition, Solanki et al[12] have reported an increase in the angiodysplasia-related hospitalizations and mortality over the last decade in the United States. Because both disorders are prevalent in the older population, a growing number of the older population could be a potential reason for the observed trend. Patients of AS with GIB had higher all-cause in-hospital mortality compared with the AS patients. Cody et al[13] reported around the 100-fold increase in the risk of GIB among patients with calcific AS in comparison to the general population. This added that burden of GIB could be a reason for increased risk of in-hospital mortality and morbidity among the AS with GIB cohort.

Our analysis reports an incidence of 3.1% of GIB among AS hospitalizations. However, varying frequencies of AS and GIB have been reported previously.[6,7] Although AS hospitalizations with GIB consisted of older population compared with the non-GIB group, age has been suggested as a major confounder.[14] An advanced age was an independent predictor of mortality in our multivariable analysis. The prevalence was higher among females; however, the mortality was higher among males as reported previously.[15] We observed a higher prevalence of HS among African-Americans as reported previously.[3,6,16] We found a higher mortality among Asians. The racial disparity in resource utilization could be a reason for observed higher mortality in Asians.
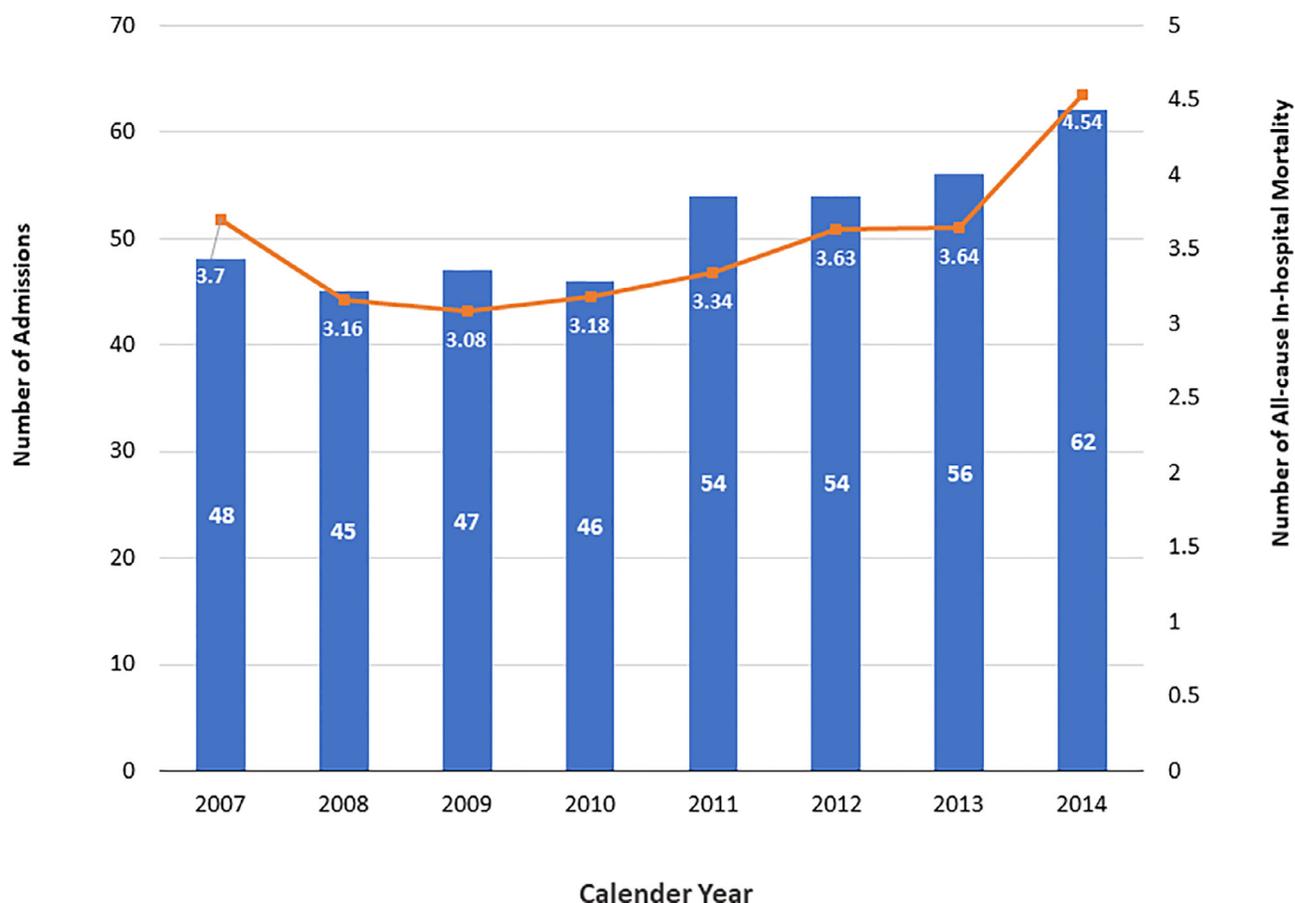
FIGURE 1. Trends in Heyde's syndrome (aortic stenosis and gastrointestinal bleeding attributed to intestinal angiodysplasia) hospitalizations and in-hospital mortality per 100,000.

Pathophysiology of HS is multifactorial.[17,18] Congestive heart failure could add up the hypoxemic state created by AS and potentiate the risk of angiodysplasia among AS patients.[19] Moukarbel et al[20] reported that patient with worse NYHA class, representative of heart failure, had higher odds of GIB and mortality. This could be a potential reason for increased mortality among AS patients with GIB and CHF. Previous studies have reported a strong association of chronic renal failure and hospitalizations with HS,[21,22] because patients with these degenerative disorders are at risk of acquired type-2A vWF syndrome.[4] There is limited data on the prevalence and impact of the cancerous condition in patients with HS.[17,18] However, the presence of a cancerous condition in these population could impose an additive effect on the GIB owing to the increased risk of coagulopathy.[17,23] Patients with HS and fluid-electrolyte disorder had the highest odds of in-hospital mortality. Akinseye et al[24] reported that fluid and electrolyte disorder was a significant predictor of mortality in patients who underwent TAVI. Because it is a modifiable predictor, it should be managed exclusively in this patient population.

Aortic valve replacement has been reported to restore the coagulation abnormality and improve long-term outcomes in HS.[25] SAVR, an established treatment modality for degenerative AS, has been reported to normalize vWF multimers and correct bleeding episodes among AS patients.[26,27] However, SAVR always bears a high risk of bleeding complications. The PARTNER I trial reports higher bleeding complications and overall worse outcomes among high-risk AS patients who underwent SAVR.[28] In the light of the above-referenced reports, TAVI could be an alternative choice for patients with HS; however, the data remain nonexistent in regards to the superiority of TAVI in this patient population. In our study, we reported lower complications and outcomes despite no difference in the all-cause mortality between SAVR and TAVI. Stroke has been reported to be higher in the patients who underwent TAVI in comparison to the SAVR.[29,30] However, we observed that the TAVI group had a lower periprocedural stroke, required fewer blood transfusions, and had more routine discharges compared with the SAVR group. TAVI can be a promising alternative in patients with HS to curtail bleeding risk as this population already has GIB or at a higher risk of GIB.[28,30] Godino et al[4] also reported the abolishment of recurrent GIB after TAVI in patients with HS.

The study bears a few potential limitations. Because the NIS is an administrative database, coding errors and selection bias are likely. The severity of disease and outcomes on follow-up could not be measured with or without interventions (SAVR or TAVI). Owing to the retrospective nature of data, the persistence of angiodysplasia after valve replacement could not be identified. Due to the unavailability of the laboratory parameters, we were unable to associate the findings in terms of vWF, which is being considered

TABLE 4

Independent predictors of in-hospital mortality in Heyde's syndrome hospitalizations

Predictors	Adjusted odds ratio	95% CI lower-upper	p*
Age 65-84 vs 18-64 years	1.16	1.05-1.28	**0.003**
Age ≥85 vs 18-64 years	1.27	1.15-1.41	**<0.001**
Male vs Female	1.14	1.09-1.20	**<0.001**
Asian and Pacific Islander vs white	1.51	1.30-1.75	**<0.001**
Elective vs non-elective admission	1.16	1.07-1.26	**<0.001**
Bed size of hospital small vs large	1.18	1.09-1.27	**<0.001**
Urban non-teaching vs rural hospital	1.35	1.23-1.47	**<0.001**
Urban teaching vs rural hospital	1.42	1.30-1.55	**<0.001**
Northeast vs West region hospitals	0.86	0.80-0.92	**<0.001**
Midwest vs West region hospitals	0.74	0.68-0.80	**<0.001**
South vs West region hospitals	0.93	0.87-0.99	**0.035**
Co-morbidities			
Dyslipidemia	0.81	0.77-0.85	**<0.001**
Smoking	0.78	0.73-0.83	**<0.001**
Deficiency anemias	0.84	0.80-0.89	**<0.001**
Chronic blood loss anemia	0.52	0.48-0.56	**<0.001**
Congestive heart failure	1.34	1.28-1.41	**<0.001**
Chronic pulmonary disease	1.08	1.03-1.14	**0.003**
Coagulopathy	1.98	1.86-2.11	**<0.001**
Diabetes, uncomplicated	0.79	0.75-0.84	**<0.001**
Hypertension	0.75	0.71-0.78	**<0.001**
Hypothyroidism	0.86	0.81-0.92	**<0.001**
Lymphoma	1.26	1.03-1.53	**0.023**
Fluid and electrolyte disorders	2.47	2.35-2.59	**<0.001**
Metastatic cancer	1.83	1.59-2.11	**<0.001**
Other neurological disorders	1.33	1.24-1.44	**<0.001**
Obesity	0.83	0.75-0.91	**<0.001**
Paralysis	1.64	1.45-1.85	**<0.001**
Renal failure	1.32	1.25-1.39	**<0.001**
Solid tumor without metastasis	1.44	1.29-1.62	**<0.001**

Multivariable regression model was adjusted for baseline demographics, patient-level and hospital-level characteristics, and all relevant baseline co-morbidities.

* p < 0.05 (bold letters) indicates clinical significance.

an integral part of the pathogenesis of HS. However, the large sample size representative of the nationwide US population may help to overcome a few of these limitations.

Concisely, we observed alarming increasing trends in hospitalizations and mortality with HS. The TAVI group disclosed fewer complications compared with SAVR without any difference in the all-cause mortality, which suggests TAVI as a promising alternative in patients with HS.

Disclosures

The authors have no conflicts of interest to disclose.

1. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol* 2011;8:162–172.
2. Regula J, Wronska E, Pachlewski J. Vascular lesions of the gastrointestinal tract. *Best Pract Res Clin Gastroenterol* 2008;22:313–328.
3. Pate GE, Chandavimol M, Naiman SC, Webb JG. Heyde's syndrome: a review. *J Heart Valve Dis* 2004;13:701–712.
4. Godino C, Lauretta L, Pavon AG, Mangieri A, Viani G, Chieffo A, Galaverna S, Latib A, Montorfano M, Cappelletti A, Maisano F, Alfieri O, Margonato A, Colombo A. Heyde's syndrome incidence and outcome in patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol* 2013;61:687.
5. Panzer S, Badr Eslam R, Schneller A, Kaider A, Koren D, Eichelberger B, Rosenhek R, Budde U, Lang IM. Loss of high-molecular-weight von Willebrand factor multimers mainly affects platelet aggregation in patients with aortic stenosis. *Thromb Haemost* 2010; 103:408–414.
6. Pate GE, Mulligan A. An epidemiological study of Heyde's syndrome: an association between aortic stenosis and gastrointestinal bleeding. *J Heart Valve Dis* 2004;13:713–716.
7. Bhutani MS, Gupta SC, Markert RJ, Barde CJ, Donese R, Gopalswamy N. A prospective controlled evaluation of endoscopic detection of angiodysplasia and its association with aortic valve disease. *Gastrointest Endosc* 1995;42:398–402.
8. Oneglia C, Sabatini T, Rusconi C, Gardini A, Paterlini A, Buffoli F, Graffeo M. Prevalence of aortic valve stenosis in patients affected by gastrointestinal angiodysplasia. *Eur J Med* 1993;2:75–78.
9. Henne S, Denzer U, Seitz U, Gottsche J, Soehendra N, Lohse A. Recurrent gastrointestinal bleeding and aortic valve stenosis (Heyde syndrome): need for valve replacement? *Z Gastroenterol* 2007;45: 245–249.
10. Doshi R, Shah J, Patel V, Jauhar V, Meraj P. Transcatheter or surgical aortic valve replacement in patients with advanced kidney disease: a propensity score-matched analysis. *Clin Cardiol* 2017;40:1156–1162.
11. Alqahtani F, Aljohani S, Amin AH, Al-Hijji M, Ali OO, Holmes DR, Alkhouli M. Effect of race on the incidence of aortic stenosis and outcomes of aortic valve replacement in the United States. *Mayo Clin Proc* 2018;93:607–617.
12. Solanki SD, Haq KF, Farkas Z, Khan Z, Chakinala RC, Kifayat A, Khan MA, Bhurwal A, Nabors C, Lebovics E. Temporal trends and demographic variations in hospitalizations with angiodysplasia of the intestine: a U.S. population based study. *Electron J Gen Med* 2018;15:em80.
13. Cody MC, O'Donovan TPB, Hughes RW. Idiopathic gastrointestinal bleeding and aortic stenosis. *Am J Dig Dis* 1974;19:393–398.

14. Massyn MW, Khan SA. Heyde syndrome: a common diagnosis in older patients with severe aortic stenosis. *Age Ageing* 2009;38:267–270.
15. Toyofuku M, Taniguchi T, Morimoto T, Yamaji K, Furukawa Y, Takahashi K, Tamura T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Miyake M, Mitsuoka H, Kato M, Hirano Y, Matsuda S, Inada T, Murakami T, Takeuchi Y, Yamane K, Ishii M, Minamino-Muta E, Kato T, Inoko M, Ikeda T, Komasa A, Ishii K, Hotta K, Higashitani N, Kato Y, Inuzuka Y, Maeda C, Jinnai T, Morikami Y, Saito N, Minatoya K, Kimura T. Sex differences in severe aortic stenosis- clinical presentation and mortality. *Circ J* 2017;81:1213–1221.
16. Batur P, Stewart WJ, Isaacson J. Increased prevalence of aortic stenosis in patients with arteriovenous malformations of the gastrointestinal tract in Heyde syndrome. *Arch Intern Med* 2003;163:1821–1824.
17. Olsson M, Hultcrantz R, Schulman S, Wallgren E. Acquired platelet dysfunction may be an aetiologic factor in Heyde's syndrome—normalization of bleeding time after aortic valve replacement. *J Intern Med* 2002;252:516–523.
18. Ramachandran R, Uqdah H, Jani N. A case of recurrent obscure gastrointestinal bleeding: Heyde's syndrome—case report and review. *J Community Hosp Intern Med Perspect* 2018;8:127–129.
19. Ledingham D. Heyde's syndrome: exploring the link between aortic stenosis and an acquired bleeding disorder. *BMJ Case Rep* 2013;2013: bcr2013009306.
20. Moukarbel GV, Signorovitch JE, Pfeffer MA, McMurray JJV, White HD, Maggioni AP, Velazquez EJ, Califf RM, Scheiman JM, Solomon SD. Gastrointestinal bleeding in high risk survivors of myocardial infarction: the VALIANT Trial. *Eur Heart J* 2009;30:2226–2232.
21. Giovannini I, Chiarla C, Murazio M, Clemente G, Giuliante F, Nuzzo G. An extreme case of Heyde syndrome. *Dig Surg* 2006;23:387–388.
22. Karagiannis S, Goulas S, Kosmadakis G, Galanis P, Arvanitis D, Boletis J, Georgiou E, Mavrogiannis C. Wireless capsule endoscopy in the investigation of patients with chronic renal failure and obscure gastrointestinal bleeding (preliminary data). *World J Gastroenterol* 2006;12: 5182–5185.
23. Pereira J, Phan T. Management of bleeding in patients with advanced cancer. *Oncologist* 2004;9:561–570.
24. Akinseye OA, Shahreyar M, Nwagbara CC, Nayyar M, Salem SA, Morsy M, Khouzam RN, Ibebuogu UN. Modifiable predictors of in-hospital mortality in patients undergoing transcatheter aortic valve replacement. *Am J Med Sci* 2018;356:135–140.
25. Hudzik B, Wilczek K, Gasior M. Heyde syndrome: gastrointestinal bleeding and aortic stenosis. *CMAJ* 2016;188:135–138.
26. Panzer S, Eslam RB, Schneller A, Kaider A, Koren D, Eichelberger B, Rosenhek R, Budde U, Lang IM. Loss of high-molecular-weight von Willebrand factor multimers mainly affects platelet aggregation in patients with aortic stenosis. *Thromb Haemost* 2010;103:408–414.
27. Thompson JL 3rd, Schaff HV, Dearani JA, Park SJ, Sundt TM 3rd, Suri RM, Blackshear JL, Daly RC. Risk of recurrent gastrointestinal bleeding after aortic valve replacement in patients with Heyde syndrome. *J Thorac Cardiovasc Surg* 2012;144:112–116.
28. 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.
29. Miller DC, Blackstone EH, Mack MJ, Svensson LG, Kodali SK, Kapadia S, Rajeswaran J, Anderson WN, Moses JW, Tuzcu EM, Webb JG, Leon MB, Smith CR. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg* 2012;143:832–843.
30. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–2198.