The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

BY NC SA

Case Report

J Atheroscler Thromb, 2020; 27: 271-277. http://doi.org/10.5551/jat.49239

Disappearance of Angiodysplasia Following Transcatheter Aortic Valve Implantation in a Patient with Heyde's Syndrome:

A Case Report and Review of the Literature

Satoshi Tsuchiya[1], Yasuharu Matsumoto[1], Tsuyoshi Doman[2], Taku Fujiya[3], Jun Sugisawa[1], Akira Suda[1], Koichi Sato[1], Shohei Ikeda[1], Tomohiko Shindo[1], Yoku Kikuchi[1], Kiyotaka Hao[1], Jun Takahashi[1], Waku Hatta[3], Tomoyuki Koike[3], Atsushi Masamune[3], Yoshikatsu Saiki[4], Hisanori Horiuchi[2] and Hiroaki Shimokawa[1]

[1]Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan.
[2]Department of Molecular and Cellular Biology, Institute of Development, Aging, and Cancer, Tohoku University, Sendai, Japan.
[3]Department of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan
[4]Department of Cardiovascular Surgery, Tohoku University Graduate school of Medicine, Sendai, Japan

An 83-year-old woman with severe aortic stenosis was admitted to our hospital due to heart failure with refractory anemia requiring blood transfusions. She had repetitive bleeding episodes from endoscopically proven angiodysplasia in the stomach. Moreover, she repeatedly underwent endoscopic argon plasma coagulation for hemostasis. Importantly, she had a deficiency of the high-molecular-weight (HMW) multimers of von Willebrand factor (VWF), and she was diagnosed with Heyde's syndrome.

After she underwent transcatheter aortic valve implantation (TAVI), aortic valve area and mean left ventricular aorta pressure gradient improved. Notably, endoscopy showed cessation of bleeding at 10 days after TAVI and the disappearance of angiodysplasia at 4 months after TAVI. Even at 2 years after TAVI, follow-up endoscopy showed remaining free of angiodysplasia in the stomach. She experienced no episodes of anemia since TAVI procedure. Additionally, analysis of HMW multimers demonstrated immediate and lasting recovery after TAVI.

Recovery of HMW multimers of VWF with cessation of gastrointestinal bleeding following aortic valve replacement has been previously reported in a patient diagnosed with Heyde's syndrome. To the best our knowledge, this is the first case to demonstrate that angiodysplasia disappears after TAVI for a long term with endoscopic images in a patient with Heyde's syndrome. Here, we summarized case reports of patients with Heyde's syndrome that required aortic valve intervention. Cessation of gastrointestinal bleeding and anemia after aortic valve intervention for severe aortic stenosis may be attributed not only to recovery of HMW multimers of VWF but also to the disappearance of angiodysplasia.

Key words: **Heyde's syndrome, Aortic stenosis, Gastrointestinal angiodysplasia**

Introduction

Aortic stenosis (AS) is sometimes associated with gastrointestinal bleeding. This combined state is referred as Heyde's syndrome[1, 2]. The origin of the bleeding is most often gastrointestinal angiodysplasia that is characterized by focal or diffused venous/capillary lesions presenting as bright red ectatic vessels or pulsatile red protrusions, with surrounding venous dilatation or patchy erythema with or without oozing[3, 4] and is known to easily bleed. Heyde's syndrome has been reported to occur in approximately 20% of

Address for correspondence: Yasuharu Matsumoto, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Seiryo-machi, Aoba-ku, Sendai, Japan 980-8574 E-mail: matsumoto@cardio.med.tohoku.ac.jp

Received: February 8, 2019 Accepted for publication: May 30, 2019

Copyright©2019 Japan Atherosclerosis Society
This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

patients with severe AS[5].

Von Willebrand factor (VWF) is generated and secreted from endothelial cells and megakaryocytes as a giant multimer and shear stress dependently cleaved by its specific protease, ADAMTS13[2, 6]. Among the VWF multimers, the high-molecular-weight (HMW) multimer is critical for its hemostatic function[7]. AS generates unphysiologically high flow at the narrowed valve, thereby generating excessively high shear stress, which causes loss of HMW multimers of VWF. It designates as a hemostatic disorder the acquired von Willebrand syndrome (AVWS)[4]. AVWS also occurs in other conditions requiring left ventricular assist device implantation[8].

The AS-associated AVWS is not rare because the loss of HMW multimers of VWF was already noted in approximately 67% of patients with severe aortic stenosis[6]. Anemia and bleeding can be controlled by the release of the narrowed aortic valve by operation[6]. Nevertheless, it remains unknown whether gastrointestinal angiodysplasia persists or disappears after the valve treatment. This issue is important for evaluating the bleeding risk of patients with AS. Here, we report the case of Heyde's syndrome that shows disappearance of angiodysplasia and recovery of HMW multimers of VWF following transcatheter aortic valve implantation (TAVI).

Case Presentation

In April 2016, an 83-year-old woman with severe AS was admitted to our hospital due to heart failure with repetitive bleeding episodes requiring blood transfusions. She had been diagnosed with AS in 2014, and the severity of AS had progressed up to the mean aortic valve pressure gradient, 81 mmHg; peak aortic flow, 5.61 m/s; and aortic valve area, 0.5 cm^2. She was found to have bleeding from angiodysplasia in the stomach (**Fig. 1A, 1B**). Although she repeatedly underwent endoscopic argon plasma coagulation (APC) for hemostasis, she had repetitive bleeding from angiodysplasia even after APC. In addition, her plasma analysis demonstrated a deficiency of the HMW multimers of VWF, defined as the 11^{th} and the upper bands in the VWF multimer analysis (**Fig. 1C**). Thus, she was diagnosed with Heyde's syndrome.

Because she was frail with a comorbidity of liver dysfunction due to primary biliary cirrhosis, she underwent TAVI with a 23-mm Edwards Sapien 3 valve (Edwards Lifesciences, Irvine, California) (**Fig. 1D**). After the procedure, aortic valve area and mean aortic valve pressure gradient improved from 0.5 cm^2 to 1.5 cm^2 and from 81 mmHg to 10 mmHg, respectively. As an antithrombotic therapy, she was treated with only heparin during perioperative period for TAVI and with clopidogrel 75 mg/day from at 1 week after TAVI. At 10 days after TAVI, an endoscopy presented remaining angiodysplasia but not the cessation of bleeding in the stomach. Since TAVI procedure, she had no more episodes of anemia due to angiodysplasia in the stomach. Notably, there was clear disappearance of angiodysplasia at 4 months after TAVI (**Fig. 1E**). Moreover, HMW multimers of VWF revealed immediate and lasting recovery after TAVI (**Fig. 1C**). While she continued single antiplatelet therapy with clopidogrel after TAVI, neither bleeding nor thromboembolic episode occurred. Even at 2 years after TAVI, follow-up endoscopy showed remaining free of angiodysplasia in the stomach (**Fig. 1F**).

Discussion

To the best of our knowledge, this is the first case to describe that angiodysplasia disappears after TAVI for a long term with endoscopic images and to present the recovery of the loss of HMW multimer in a patient with Heyde's syndrome.

Gastric erosions are defined as endoscopically detectable mucosal breaks that do not penetrate the muscularis mucosae[9]. In contrast, angiodysplasia is characterized by focal or diffused venous/capillary lesions presenting as bright red ectatic vessels or pulsatile red protrusions, with surrounding venous dilatation or patchy erythema with or without oozing[3, 4]. In the present case, the patient suffered oozing not from erosion but from the focal venous/capillary lesions (**Fig. 1A and 1B**). Based on these endoscopic images, the experts in the field of gastroenterology (TF, WH, and TK) diagnosed the patient with angiodysplasia, and she underwent endoscopic APC.

We searched for Heyde's syndrome and aortic valve replacement or implantation in PubMed, which then revealed 74 articles. We excluded 40 articles (1) not written in English (n=11), (2) without treatment intervention for aortic valves (n=6), (3) only abstract (n=3), and (4) original articles including the number of patients over 2 (n=20). We summarized the remaining 34 articles of case reports following aortic valve intervention in patients with Heyde's syndrome, with special references to angiodysplasia and HMW multimers of VWF[10-43] (**Table 1**). To the best of our knowledge, there were seven reports that demonstrated persistence or disappearance of angiodysplasia after aortic valve intervention[10, 11, 16, 30, 31, 35, 41]. Importantly, although gastrointestinal bleeding ceased after aortic valve intervention in many case reports, follow-up endoscopic images to confirm the presence or absence of angiodysplasia and alterations of HMW

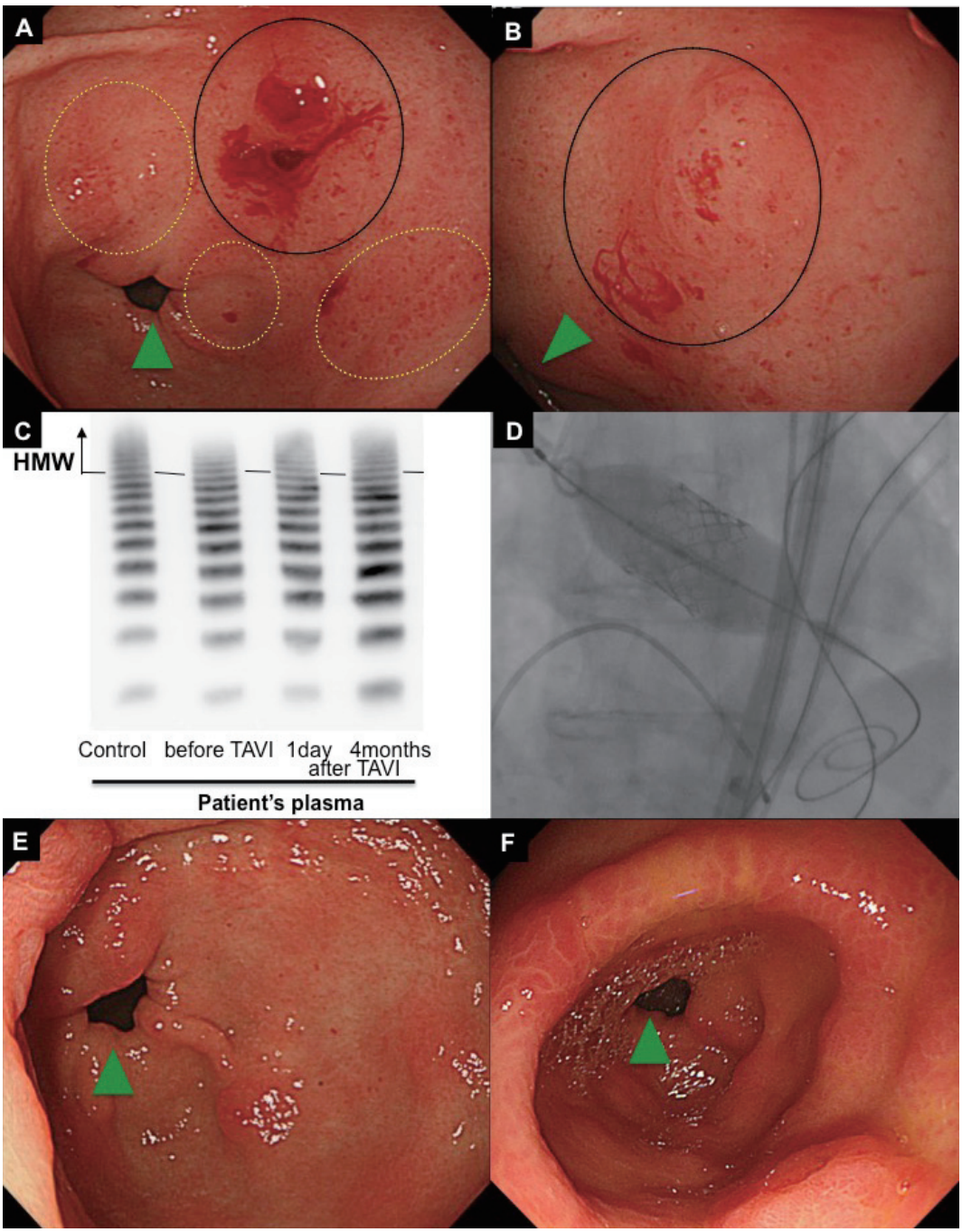

Fig. 1.

(A) Endoscopy before transcatheter aortic valve implantation (TAVI) showed angiodysplasia (yellow circle) and bleeding (black circle) in the stomach. Green arrowhead indicates the pyloric ring.
(B) Endoscopy showed angiodysplasia after washing. The area in the black circle corresponds to that in Fig. 1A. Green arrowhead indicates the pyloric ring.
(C) von Willebrand factor (VWF) multimer analysis. Plasma of the patient was collected multiple times, and sodium dodecyl sulfate agarose gel electrophoresis was used to detect the VWF multimers. Compared with normal plasma, plasma of the patient lacked high-molecular-weight (HMW) of VWF before TAVI. However, the loss of HMW of VWF quickly recovered at 1 day after TAVI and lasted until 4 months.
(D) Angiogram showed TAVI with the balloon expandable Edwards Sapien 3 heart valve system.
(E) Endoscopy showed cessation of bleeding and disappearance of angiodysplasia in the stomach at 4 months after TAVI. Green arrowhead indicates the pyloric ring.
(F) Endoscopy showed that angiodysplasia was not noted in the stomach at 2 years after TAVI. Green arrowhead indicates the pyloric ring.

Table 1. Summary of case reports of a Heyde's syndrome in patients undergoing aortic valve intervention

Reference No.	Age	Procedures	Before procedure			After procedure			
			Bleeding episodes	Angiodysplasia	Loss of VWF HMW	Bleeding episodes	Angiodysplasia	Loss of VWF HMW	Follow-up timing for bleeding
10	67	SAVR	(+)	(+)	(+)	(–)	(+)	(–)	6 months
11	87	SAVR	(+)	(+)	(+)	(–)	(–)	(–)	20 months
12	67	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	N/A
13	68	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	9 months
14	48	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	8 months
15	78	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	9 months
16	67	SAVR	(+)	N/A	N/A	(+)	(+)	N/A	1 month
	68	SAVR	(+)	N/A	N/A	(+)	(+)	N/A	1 month
17	68	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	2 months
18	79	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	9 years
19	74	SAVR	(+)	(+)	(–)	(–)	N/A	(–)	7 months
20	77	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	N/A
	74	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	N/A
21	46	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	12 months
22	78	SAVR	(+)	(+)	(+)	(–)	N/A	(–)	7 days
23	70	SAVR	(+)	(+)	N/A	(+)	N/A	N/A	10 months
24	76	SAVR	(+)	N/A	N/A	(–)	N/A	N/A	4 months
25	71	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	5 months
26	77	SAVR	(+)	(–)	(+)	(–)	N/A	N/A	20 months
27	82	SAVR	(+)	(+)	(+)	(–)	N/A	N/A	1 month
28	67	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	12 months
29	77	SAVR	(+)	(+)	(+)	(–)	N/A	N/A	1 month
30	77	SAVR	(–)	N/A	N/A	(+)	(+)	N/A	3 months
31	80	SAVR	(+)	(+)	N/A	(–)	(+)	N/A	3 months
32	75	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	N/A
33	76	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	42 months
34	79	SAVR	(+)	(+)	N/A	(–)	N/A	N/A	N/A
35	83	SAVR	(+)	N/A	N/A	(+)	(+)	N/A	N/A
36	85	TAVI	(+)	(+)	(–)	(–)	N/A	N/A	6 months
37	81	TAVI	(+)	(+)	N/A	(–)	N/A	N/A	6 months
38	89	TAVI	(+)	(+)	N/A	(–)	N/A	N/A	N/A
39	86	TAVI	(+)	N/A	N/A	(–)	N/A	N/A	3months
40	77	TAVI	(+)	(+)	(+)	(–)	N/A	(–)	10 months
41	75	TAVI	(+)	(+)	N/A	(–)	(–)	N/A	2 months
42	56	TAVI	(+)	(+)	(+)	(+)	N/A	(+)	2 weeks
43	83	BAV	(+)	(+)	N/A	(–)	N/A	N/A	3 months

SAVR: surgical aortic valve replacement, TAVI: transcatheter aortic valve implantation, HMW: high-molecular-weight, VWF: von Willebrand factor, (+): yes, (–): no, N/A: not available.

multimers remained to be examined or presented. To our knowledge, this is the first case to demonstrate that angiodysplasia disappears for a long term after TAVI with endoscopic images and recovery of the loss of HMW multimer in a patient with Heyde's syndrome.

Recovery of HMW multimers of VWF and cessation of gastrointestinal bleeding following aortic valve replacement and left ventricular assist device implantation have been previously reported in patients with Heyde's syndrome[10, 11, 22, 40]. Indeed, the HMW multimers of VWF rapidly recovered at 1 day after surgical aortic valve replacement (SAVR)[44]. Notably, the disappearance of angiodysplasia was noted at 20 months after SAVR[11]. In line with the previous cases, in the present case, the levels of HMW multimers of

VWF rapidly recovered at 1 day after TAVI. However, incomplete recovery of HMW multimers of VWF in the present study may be explained by the presence of aortic regurgitation after TAVI[45]. Notably, we were able to demonstrate that follow-up endoscopy showed cessation of bleeding at 10 days after TAVI and disappearance of angiodysplasia in the stomach at 4 months after TAVI.

Improvement of anemia and sustained lack of blood transfusion following TAVI in this patient may be attributed to the disappearance of angiodysplasia in the stomach. Indeed, several supposed mechanisms of angiodysplasia in AS have been proposed[46, 47]. First, enhanced angiogenesis is caused by increased vascular endothelial growth factor (VEGF)-dependent proliferation due to mucosal and submucosal hypoxia by reduced cardiac output[48]. Second, angiogenesis is also caused by the loss of HMW multimers of VWF by high shear stress in AS[49]. Recent studies indicate that loss of VWF enhances angiogenesis via an Ang-2/Tie-2/VEGFR-2 pathway[50]. Third, the loss of HMW multimers of VWF causes hemorrhage as a result of AVWS[5] because VWF, particularly HMW multimers of VWF, is essential in mediating the adhesion and aggregation of platelets to the sub-endothelium of damaged blood vessels[51]. In the present study, it is possible that angiodysplasia gradually disappeared at 4 months after TAVI through the increased cardiac output and remarkable recovery of the HMW multimers of VWF.

In patients with liver cirrhosis, bleeding in the gut occurs not only from esophageal varices but also from chronic peptic ulcer or erosive gastritis[52]. A previous study reported that the incidence of peptic ulcer in patients with liver cirrhosis was 11.3%[53]. In patients with liver cirrhosis, the levels of VWF are highly elevated due to endothelial damage, increased synthesis of VWF, and increased levels of vasoconstrictors[54-56]; however, those of HMW multimers are reduced[57]. In the present case, regardless of the comorbidity of liver dysfunction due to primary biliary cirrhosis, the loss of HMW multimers was recovered after TAVI.

Angiodysplasia is recognized as an important source of bleeding[46]. In the present case, before TAVI procedure, treatment with endoscopic APC for gastric angiodysplasia was temporarily successful. Unfortunately, the patient again began to have bleeding and anemia. However, after TAVI, angiodysplasia disappeared with a long-term follow-up of endoscopic images and free of bleeding. Based on our and previous study reports that showed rapid recovery of structural VWF and improvement of bleeding following aortic valve intervention, physicians could rather aggressively perform TAVI or SAVR even in patients diagnosed with Heyde's syndrome.

Funding

This work was supported by grants from AMED under Grant Number JP18ek0109370h0001.

COI Statement

H.H received a research funding from Sysmex. Co, Ltd. The other authors have no conflicts of interest to disclose.

References

1) Heyde EC: Gastrointestinal bleeding in aortic stenosis. N Engl J Med, 1958; 259: 196
2) Loscalzo J: From clinical observation to mechanism – Heyde's syndrome. N Engl J Med, 2012; 367: 1954-1956
3) Rider JA, Klotz AP, Kirsner JB: Gastritis with veno-capillary ectasia as a source of massive gastric hemorrhage. Gastroenterology, 1953; 24: 118-123
4) Ge ZZ, Chen HM, Gao YJ, Liu WZ, Xu CH, Tan HH, Chen HY, Wei W, Fang JY, Xiao SD: Efficacy of thalidomide for refractory gastrointestinal bleeding from vascular malformation. Gastroenterology, 2011; 141: 1629-1637. e1-e4
5) Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, Bauters A, Decoene C, Goudemand J, Prat A, Jude B: Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med, 2003; 349: 343-349
6) Tamura T, Horiuchi H, Imai M, Tada T, Shiomi H, Kuroda M, Nishimura S, Takahashi Y, Yoshikawa Y, Tsujimura A, Amano M, Hayama Y, Imamura S, Onishi N, Tamaki Y, Enomoto S, Miyake M, Kondo H, Kaitani K, Izumi C, Kimura T, Nakagawa Y: Unexpectedly high prevalence of acquired von Willebrand syndrome in patients with severe aortic stenosis as evaluated with a novel large multimer index. J Atheroscler Thromb, 2015; 22: 1115-1123
7) Matsumoto M, Kawaguchi S, Ishizashi H, Yagi H, Iida J, Sakaki T, Fujimura Y: Platelets treated with ticlopidine are less reactive to unusually large von Willebrand factor multimers than are those treated with aspirin under high shear stress. Pathophysiol Haemost Thromb, 2005; 34: 35-40
8) Sakatsume K, Saito K, Akiyama M, Sasaki K, Kawatsu S, Takahashi G, Adachi O, Kawamoto S, Horiuchi H, Saiki Y: Association between the severity of acquired von Willebrand syndrome and gastrointestinal bleeding after continuous-flow left ventricular assist device implantation. Eur J Cardiothorac Surg, 2018; 54: 841-846
9) Toljamo K, Niemelä S, Karvonen AL, Karttunen R, Karttunen TJ: Histopathology of gastric erosions. Association with etiological factors and chronicity. Helicobacter, 2011; 16: 444-451
10) Akutagawa T, Shindo T, Yamanouchi K, Hayakawa M, Ureshino H, Tsuruoka N, Sakata Y, Shimoda R, Noguchi

R, Furukawa K, Morita S, Iwakiri R, Kimura S, Matsumoto M, Fujimoto K: Persistent gastrointestinal angiodysplasia in Heyde's syndrome after aortic valve replacement. Intern Med, 2017; 56: 2431-2433
11) Shibamoto A, Kawaratani H, Kubo T, Nishimura N, Sato S, Seki K, Sawada Y, Takaya H, Okura Y, Takeda K, Uejima M, Namisaki T, Moriya K, Mitoro A, Yamao J, Yoshiji H: Aortic valve replacement for the management of Heyde syndrome: a case report. J Nippon Med Sch, 2017; 84: 193-197
12) Capuano F, Angeloni E, Roscitano A, Bianchini R, Refice S, Lechiancole A, Melina G, Comito C, Sinatra R: Blackish pigmentation of the aorta in patient with alkaptonuria and heyde's syndrome. Aorta (Stamford), 2014; 2: 74-76
13) Abi-Akar R, El-Rassi I, Karam N, Jassar Y, Slim R, Jebara V: Treatment of Heyde's syndrome by aortic valve replacement. Curr Cardiol Rev, 2011; 7: 47-49
14) Baciewicz FA Jr, Davis JT: Heyde's syndrome: failure of a mechanical prosthesis and the possibility of a coagulation defect. Ann Thorac Surg, 1987; 44: 554-555
15) Scheffer SM, Leatherman LL: Resolution of Heyde's syndrome of aortic stenosis and gastrointestinal bleeding after aortic valve replacement. Ann Thorac Surg, 1986; 42: 477-480
16) Apostolakis E, Doering C, Kantartzis M, Winter J, Schulte HD: Calcific aortic-valve stenosis and angiodysplasia of the colon: Heyde's syndrome--report of two cases. Thorac Cardiovasc Surg, 1990; 38: 374-376
17) Casson AG, McKenzie NN: Heyde's syndrome. Chest, 1988; 94: 891-892
18) Michot JM, Treton X, Brink C, Fabiani JN, Bouhnik Y: Severe gastro-intestinal angiodysplasia in context of Heyde's syndrome durably cured after aortic valve replacement. Presse Med, 2012; 41: 763-766
19) Undas A, Windyga J, Bykowska K, Dimitrow PP, Stepien E, Sadowski J: Heyde's syndrome without a decrease in large von Willebrand factor multimers: a case of intestinal bleedings reversed by valve replacement in a patient with aortic stenosis. Thromb Haemost, 2009; 101: 773-774
20) Natowitz L, Defraigne JO, Limet R: Association of aortic stenosis and gastrointestinal bleeding (Heyde's syndrome). Report of two cases. Acta Chir Belg, 1993; 93: 31-33
21) İlkeli E, Albeyoğlu Ş, Çiloğlu U, Sabri D: Heyde's syndrome. Asian Cardiovasc Thorac Ann, 2014; 22: 592-594
22) Morishima A, Marui A, Shimamoto T, Saji Y, Tambara K, Nishina T, Komeda M: Successful aortic valve replacement for Heyde syndrome with confirmed hematologic recovery. Ann Thorac Surg, 2007; 83: 287-288
23) Giovannini I, Chiarla C, Murazio M, Clemente G, Giuliante F, Nuzzo G: An extreme case of Heyde syndrome. Dig Surg, 2006; 23: 387-388
24) Saad RA, Lwaleed BA, Kazmi RS: Gastrointestinal bleeding and aortic stenosis (Heyde syndrome): the role of aortic valve replacement. J Card Surg, 2013; 28: 414-416
25) Dos Santos VM, Dos Santos LA, Modesto AA, Amui MO: Heyde syndrome in a 71-year-old man who underwent chest radiotherapy at young age. An Sist Sanit Navar, 2013; 36: 339-345
26) Iijima M, Itoh N, Murase R, Makino Y: A surgical case of aortic stenosis with recurrent gastrointestinal bleeding: Heyde syndrome. Int J Surg Case Rep, 2018; 53: 281-284
27) Takahashi N, Tanabe K, Yoshitomi H, Sato M, Kitamura J, Sato H, Ishibashi Y, Shimada T, Oda T: Successful endoscopic clipping for bleeding from colonic angiodysplasia in a case of Heyde syndrome. Med Sci Monit, 2010; 16: CS107-109
28) Hvid-Jensen HS, Poulsen SH, Agnholt JS: Severe gastrointestinal bleeding in a patient with subvalvular aortic stenosis treated with thalidomide and octreotide: bridging to transcoronary ablation of septal hypertrophy. J Clin Med Res, 2015; 7: 907-910
29) Uchida T, Hamasaki A, Ohba E, Yamashita A, Hayashi J, Sadahiro M: Life-threatening subdural hematoma after aortic valve replacement in a patient with Heyde syndrome: a case report. J Cardiothorac Surg, 2017; 12: 65
30) Iquille J, Nader J, Colpart E, Caus T: Unusual gastrointestinal bleeding after sutureless aortic valve replacement: a word of caution. Ann Thorac Surg, 2017; 103: e225-e226
31) Taguchi T, Watanabe M, Watadani K, Katayama K, Takahashi S, Takasaki T, Kurosaki T, Imai K, Sueda T: A case of Heyde syndrome: resolution following aortic valve replacement. Heart Surg Forum, 2014; 17: e258-e260
32) Ohta S, Watanabe T, Morita S, Ueno S, Tsuji Y, Nakase H, Chiba T: Massive jejunal bleeding due to Heyde syndrome successfully treated with double balloon endoscopy. Clin J Gastroenterol, 2009; 2: 187-189
33) Maor NR: Heyde syndrome: resolution of anemia after aortic valve surgery. Isr Med Assoc J, 2013; 15: 387-389
34) D'Souza PM, Blostein MD: Diagnosis of Heyde's syndrome by abnormal closure times despite normal von Willebrand's activity. Blood Coagul Fibrinolysis, 2011; 22: 622-623
35) Corrêa PL, Felix RC, Azevedo JC, Silva PR, Oliveira AC Jr, Cortes D, Dohmann HF, Mesquita CT: Gastrointestinal bleeding diagnosed by red blood cell scintigraphy in a patient with aortic stenosis: a case of Heyde syndrome. Clin Nucl Med, 2005; 30: 231-235
36) 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
37) Balbo CP, Seabra LP, Galoro VG, Caputi G, Palma JH, Buffolo Ê: Heyde's syndrome and transcatheter aortic valve implantation. Arq Bras Cardiol, 2017; 108: 378-380
38) Pyxaras SA, Santangelo S, Perkan A, Vitrella G, Rakar S, Grazia ED, Salvi A, Sinagra G: Reversal of angiodysplasia-derived anemia after transcatheter aortic valve implantation. J Cardiol Cases, 2012; 5: e128-e131
39) Rashid S, Malkin C, Schlosshan D, Blackman D: Severe aortic stenosis, critical coronary artery disease, and transfusion-dependent angiodysplasia - A management conundrum. J Cardiol Cases, 2015; 13: 87-89
40) Benton SM Jr, Kumar A, Crenshaw M, Fredi JL: Effect of transcutaneous aortic valve implantation on the Heyde's syndrome. Am J Cardiol, 2014; 114: 953-954
41) Gül M, Sürgit Ö, Özal E, Örmeci A, Bakır İ: Treatment of aortic valve stenosis and gastrointestinal bleeding by transcatheter aortic valve implantation in Heyde syndrome. Anadolu Kardiyol Derg, 2012; 12: 691-693

42) Alshuwaykh O, Krier MJ: A case of Heyde syndrome with resolution of gastrointestinal bleeding two weeks after aortic valve replacement. Am J Case Rep, 2018; 19: 924-926
43) Godino C, Pavon AG, Mangieri A, Margonato A: Aortic valvuloplasty as bridging for TAVI in high-risk patients with Heyde's syndrome: a case report. Case Rep Med, 2012; 2012: 946764
44) Yamashita K, Yagi H, Hayakawa M, Abe T, Hayata Y, Yamaguchi N, Sugimoto M, Fujimura Y, Matsumoto M, Taniguchi S: Rapid restoration of thrombus formation and high-molecular-weight von Willebrand factor multimers in patients with severe aortic stenosis after valve replacement. J Atheroscler Thromb, 2016; 23: 1150-1158
45) Van Belle E, Rauch A, Vincent F, Robin E, Kibler M, Labreuche J, Jeanpierre E, Levade M, Hurt C, Rousse N, Dally JB, Debry N, Dallongeville J, Vincentelli A, Delhaye C, Auffray JL, Juthier F, Schurtz G, Lemesle G, Caspar T, Morel O, Dumonteil N, Duhamel A, Paris C, Dupont-Prado A, Legendre P, Mouquet F, Marchant B, Hermoire S, Corseaux D, Moussa K, Manchuelle A, Bauchart JJ, Loobuyck V, Caron C, Zawadzki C, Leroy F, Bodart JC, Staels B, Goudemand J, Lenting PJ, Susen S: Von Willebrand factor multimers during transcatheter aortic-valve replacement. N Engl J Med, 2016; 375: 335-344
46) Sami SS, Al Araji SA, Ragunath K: Review article: gastrointestinal angiodysplasia - pathogenesis, diagnosis and management. Aliment Pharmacol Ther, 2014; 39: 15-34
47) Randi AM, Smith KE, Castaman G: Von Willebrand factor regulation of blood vessel formation. Blood, 2018; 132: 132-140
48) Junquera F, Saperas E, de Torres I, Vidal MT, Malagelada JR: Increased expression of angiogenic factors in human colonic angiodysplasia. Am J Gastroenterol, 1999; 94: 1070-1076
49) Starke RD, Ferraro F, Paschalaki KE, Dryden NH, McKinnon TA, Sutton RE, Payne EM, Haskard DO, Hughes AD, Cutler DF, Laffan MA, Randi AM: Endothelial von Willebrand factor regulates angiogenesis. Blood, 2011; 117: 1071-1080
50) Randi AM, Laffan MA: Von Willebrand factor and angiogenesis: basic and applied issues. J Thromb Haemost, 2017; 15: 13-20
51) Moake JL, Turner NA, Stathopoulos NA, Nolasco LH, Hellums JD: Involvement of large plasma von Willebrand factor (vWF) multimers and unusually large vWF forms derived from endothelial cells in shear stress-induced platelet aggregation. J Clin Invest, 1986; 78: 1456-1461
52) Palmer ED, Brick IB: Sources of upper gastrointestinal hemorrhage in cirrhotic patients with esophageal varices. N Engl J Med, 1953; 248: 1057-1058
53) Tabaqchali S, Dawson AM: Peptic ulcer and gastric secretion in patients with liver disease. Gut, 1964; 5: 417-421
54) Ferro D, Quintarelli C, Lattuada A, Leo R, Alessandroni M, Mannucci PM, Violi F: High plasma levels of von Willebrand factor as a marker of endothelial perturbation in cirrhosis: relationship to endotoxemia. Hepatology, 1996; 23: 1377-1383
55) Hollestelle MJ, Geertzen HG, Straatsburg IH, van Gulik TM, van Mourik JA: Factor VIII expression in liver disease. Thromb Haemost, 2004; 9: 267-275
56) Møller S, Bendtsen F, Henriksen JH: Vasoactive substances in the circulatory dysfunction of cirrhosis. Scand J Clin Lab Invest, 2001; 61: 421-429
57) Lisman T, Bongers TN, Adelmeijer J, Janssen HL, de Maat MP, de Groot PG, Leebeek FW: Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatology, 2006; 44: 53-61