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Aortic stenosis and Heyde's syndrome: A comprehensive review

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Abstract

Heyde's syndrome is an under reported systemic disease of gastrointestinal and cardiac manifestation in older adults. It is characterized by a triad of aortic stenosis, angiodysplasia with bleeding and acquired von Willebrand syndrome. It is characterized by proteolysis of high molecular weight multimers of von Willebrand Factor and loss of platelet mediated homeostasis. Heyde's syndrome is a treatable condition in most cases, especially in the current era of evolution in interventional cardiology and gastroenterology. There are currently no established guidelines in the management of this condition due to paucity of high quality studies, which warrant future trials. High index of suspicion and increasing the awareness of the syndrome among the general practitioners and sub-specialists will improve the diagnostic potential of Heyde's syndrome. Future studies may change the management aspect of Heyde's syndrome and pave a path for drawing specific guidelines and algorithms. The aim of our review article is to summarize the basic pathophysiology, diagnostics and management of Heyde's syndrome with a special attention to Transcatheter aortic valve replacement.

Key Words: Heyde's syndrome; Aortic stenosis; Angiodysplasia; Transcatheter aortic valve replacement; Gastrointestinal bleed; Anti platelet

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Core Tip: We summarize the literature on the aortic valve replacement in aortic stenosis

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and angiodysplasia (Heyde's syndrome). This is a very attractive area of interest for interventional gastroenterologists and cardiologists. Future studies may change the management aspect of Heyde's syndrome and pave a path for drawing specific guidelines and algorithms.

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INTRODUCTION

Heyde's syndrome is a multi-system disorder of the cardiovascular, gastrointestinal (GI) and hematological system that is commonly described as a triad of aortic stenosis, gastrointestinal bleeding from angiodysplasia and acquired von Willebrand syndrome (Figure 1). Dr. Edward Heyde first described the association between aortic stenosis and gastrointestinal (GI) bleeding in 1958[1]. However, it was late in the 1980s to early 1990s that the role of coagulopathy in the form of acquired von Willebrand Disease was hypothesized to be a pathophysiologic mechanism of Heyde's syndrome[2,3]. Angiodysplasia is characterized by abnormal and tortuous small blood vessels in the mucosal and submucosal layers of GI tract (upper GI, small bowel, colon). These are pathologically dilated communications between veins and capillaries[4]. Angiodysplasia is the second leading cause of lower gastrointestinal bleeding in the elderly[5]; accounts for 4%-7% of upper GI bleed and is the most common cause of obscure lower GI bleed in up to 50% of cases[6]. The terms angiodysplasia, arteriovenous malformations (AVMs), vascular ectasia have been used interchangeably. Aortic stenosis is the most common degenerative valvular heart disease in the elderly. Prevalence of aortic stenosis in patients with bleeding angiodysplasia has been shown to be between 7% to 41%[7-9]. The contrary is also true in that, patients with aortic stenosis have a greater potential for gastrointestinal (GI) bleeding. Clinically significant GI bleeding is estimated to occur in 1%-3% of patients with moderate to severe aortic stenosis[10-12]. Controversies exist in this regard, as to whether these two conditions occurring together in elderly, is a mere coincidence or if there is a causal relationship. However, improvement in understanding of the pathophysiology of acquired von Willebrand disease (as described later) and observation of resolution of GI bleed in patients with angiodysplasia who underwent aortic valve replacement strongly support the existence of Heyde's syndrome[13-15]. In this article, we review the epidemiology, pathogenesis and management of Heyde's syndrome in the era of interventional cardiology and gastroenterology.

EPIDEMIOLOGY

Heyde's syndrome predominantly occurs in the elderly population (> 65 years) and is probably under reported. The prevalence of aortic stenosis is around 7% in population aged 75 years or older and increases to 10% in those over 80 years[16,17]. The severity of aortic stenosis also increases with age, with about 1.8% of population over 75 years having moderate to severe aortic stenosis[18,19]. A retrospective study from Cleveland clinic which looked into the association between GI Arteriovenous malformations (AVMs) and Aortic stenosis, showed a 31.7% prevalence of Aortic stenosis in patients with AVMs[8]. Another large single center study from Germany[20] involving a cohort of aortic stenosis patients with transcatheter aortic valve replacement (TAVR) showed that GI bleeding existed in 11% with endoscopically proven bleeding from angiodysplasia in 3% of the study population before TAVR. Angiodysplasia predominantly occurs in people over 60 years[6,21]. Although the true prevalence of angiodysplasia is difficult to estimate, a report from pooled prospective studies showed a prevalence of 0.83% of colonic angiodysplasia in population of healthy asymptomatic adults > 50 years[21]. However, its prevalence is thought to be higher in patients with GI bleed, end stage renal disease and von Willebrand disease[22,23]. Angiodysplasia can also be an incidental finding in healthy older adults without GI bleed during screening



Figure 1 Heyde's clinical triad.

endoscopic procedures or procedures done for other purposes. It is also important to note that while the risk of bleeding in incidentally diagnosed angiodysplasia is not well established, a bleeding angiodysplasia is at increased risk for subsequent bleeding [24].

PATHOGENESIS

Acquired von Willebrand syndrome (vWS) is a key pathogenetic factor in Heyde's syndrome. Acquired vWS encompasses a broad category of syndromes caused by shear induced proteolysis; antibodies to vWF, aberrant vWF binding to tumor cells; decreased vWF synthesis; or drug related [25,26]. vWF is a large glycoprotein, synthesized in megakaryocytes and endothelial cells, and plays a vital role in hemostasis (Figure 2) by mediating platelet adhesion to the sub endothelium and stabilizing factor VIII [27]. Heyde's syndrome is characterized by the loss of the largest multimers of vWF [12,25,28,29]. Shear forces induce structural changes in the vWF while passing through the stenotic aortic valve, making it more sensitive to the action of a specific von Willebrand protease (ADAMTS 13) [2]. This results in proteolysis of high molecular weight multimers of vWF and loss of platelet mediated hemostasis (acquired von Willebrand syndrome vWS) [12,30] (Figure 3). Similar pathophysiology involving shear forces has been observed in hypertrophic cardiomyopathy, Left ventricular Assist Device (LVAD) placement, extra corporeal life support and severe mitral regurgitation [31-33]. Acquired vWS is common in patients with severe aortic stenosis. Decrease in high molecular weight vWF multimers has been shown in up to 68%-79% of cases with severe aortic stenosis [12,34]. vWF is also thought to play a role in suppressing angiogenesis [35,36] through integrin mediated signaling and vascular endothelial growth factor (VEGF) signaling [37,38]. Loss of vWF multimers leads to increased angiogenesis. This is hypothesized to be another mechanism of bleeding from angiodysplasia through increase in angiogenesis with acquired vW syndrome.

CLINICAL FEATURES AND DIAGNOSIS

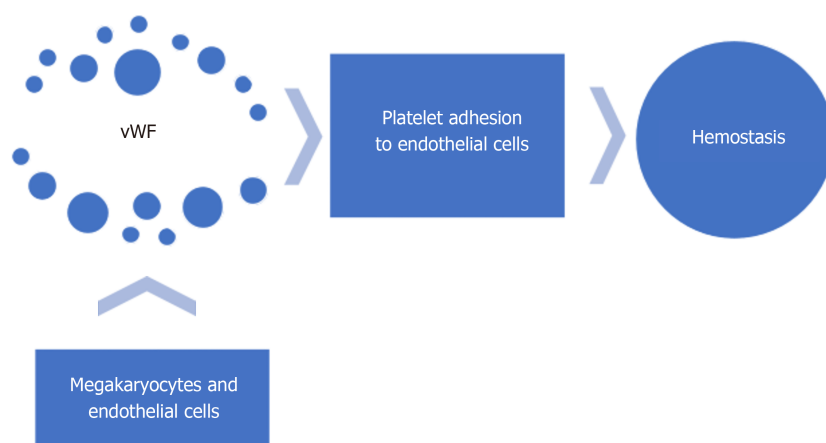
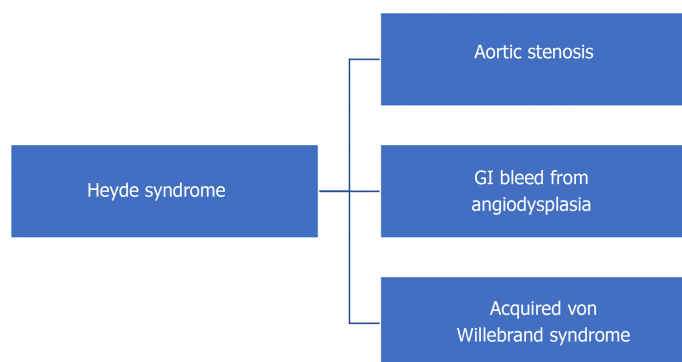
In general, the triad of aortic stenosis, bleeding angiodysplasia and evidence of acquired vWS should be sought for while evaluating suspected Heyde's syndrome. Isolated aortic valve stenosis or GI bleeding in the setting of alternative etiologies including peptic ulcer disease, malignancies, diverticular bleed, *etc.*, are the other differentials to be considered. History and physical exam in a patient with suspected Heyde's syndrome should focus on evidence of aortic stenosis, GI bleeding and impaired hemostasis suggestive of acquired vWS (Table 1). In addition to a complete medical history, prior episodes and etiologies of GI bleeding, use of concomitant drugs that can accentuate GI bleed including NSAIDs, anti-coagulants, aspirin and other anti-platelet agents should be taken into account. Echocardiogram will provide insight into the severity of aortic stenosis (ventricular-aortic gradient and the valve area) and will direct treatment options.

Patients with GI bleed can present with a wide range of clinical symptoms, from asymptomatic to hematemesis, hematochezia, melena, abdominal pain, pallor or blood on digital rectal examination. Acute bleeding with hypotension is rare in Heyde's syndrome. Orthostasis may be present. Bleeding if present is typically painless, and usually chronic or recurrent. Fecal occult blood testing is a useful diagnostic tool in asymptomatic and occult GI blood loss. Symptoms can stem from aortic valve disease. Dyspnea on exertion, syncope, fatigue and exertional chest pain can occur. Physical

Table 1 Clinical features of Heyde's syndrome

Due to	Symptoms	Signs
GI bleed	Hematemesis; Hematochezia; Melena; Abdominal pain	Pallor; Blood on rectal exam; Orthostasis
Aortic stenosis	Dyspnea on exertion; Syncope; Fatigue; Exertional chest pain	Low volume slow rising; carotid pulse; Ejection systolic murmur; Absence of physiologic S2 split
Acquired vWS	Easy bruisability; Mucosal bleeding; Heavy menstrual bleeding	Hemarthrosis; Hematoma

GI: Gastrointestinal; vWS: von Willebrand syndrome.

**Figure 2 Hemostasis.****Figure 3 Pathogenesis of Heyde's syndrome.** GI: Gastrointestinal.

examination should include complete cardiac exam with special note pertinent to features of aortic stenosis such as low volume and slow-rising carotid pulse, a loud mid-to late-peaking systolic murmur in the right intercostal space and a single second heart sound (absence of physiologic splitting of S 2). Easy bruisability and hemarthrosis are suggestive of impaired hemostasis (acquired vWS).

LABORATORY

Labs including complete blood count (CBC) with platelet count and coagulation testing including a prothrombin time (PT) and an activated partial thromboplastin time (aPTT) should be obtained. Metabolic panel and test for fecal occult blood should be included as well. In individuals with acquired vWS, prolonged PTT may be observed as a result of low factor VIII levels. However normal PTT levels do not rule out acquired vWS. Platelets counts are not affected in acquired vWS, however there

may be a coexisting condition or drug use that has to be accounted for.

VWF MULTIMER ASSAY AND PLATELET FUNCTION ASSAY

Reduced levels of large HMW multimers of VWF by gel electrophoresis is a sensitive test for acquired vWS, but is time consuming (7-10 d) and expensive. Another commercially available test of primary hemostasis platelet function assay (PFA)-100 to quantify primary hemostasis (closure time to collagen-ADP) is a useful screening test. VWF antigen and ristocetin cofactor activities are usually normal. PFA is often used as an initial screening test for acquired vWS, as it is completed in a few hours. If abnormal, then VWF multimer assay can be done as a confirmatory test.

MANAGEMENT

Management of Heyde's syndrome basically includes management of the GI bleeding and appropriate consideration for aortic valve repair. In many cases it would mean a multi-team approach coordinated by cardiology, gastroenterology and primary care physician or inpatient hospitalist or geriatrician. There are no specific guidelines drawn for the management of Heyde's syndrome and is rather based on expert consensus. vWF replacement therapies including vWF, factor VIII or octreotide/desmopressin therapy are not found to be of benefit in the management of Heyde's syndrome[39].

MANAGEMENT OF GI BLEEDING

Initial approach to GI bleeding in suspected Heyde's syndrome does not vary from a general approach for any case of GI bleed. Initial resuscitative measures should include intravenous fluids and appropriate blood transfusion to ensure hemodynamic stability prior to identifying the source of bleed or endoscopic interventions. As previously noted, bleeding angiodysplasia is the second most common cause of lower GI bleed in the elderly, however not without diagnostic difficulties or uncertainties. In cases of obscure GI bleeding caused by small bowel angiodysplasia, conventional techniques of upper and lower GI endoscopy might not be sufficient and warrant deep enteroscopy or video capsule studies. CT Angiography may be preferred in the setting of active bleeding, followed by angiography and embolization after localization. Rarely surgical resection or intraoperative enteroscopy might have to be undertaken in life threatening bleed. Actively bleeding angiodysplasia identified during endoscopy should be treated. Argon plasma coagulation (APC) is the most commonly employed non contact technique utilizes energy from ionized argon. Bipolar cauterization can also be effective albeit with a low risk of perforation. Mechanical hemostasis using endoscopic clips, injection sclerotherapy and radio frequency ablation are the other less commonly employed techniques. Non-bleeding angiodysplasia in the setting of occult bleed or severe iron deficiency anemia, unexplained by other etiology should be treated as well. Incidentally found angiodysplasia in asymptomatic patients (without GI bleed or iron deficiency anemia) are usually thought to be low risk for bleeding and are not treated, and they don't fall under Heyde's syndrome.

APPROACH TO AORTIC STENOSIS IN HEYDE'S SYNDROME

Aortic stenosis, if severe can be an independent factor for valve replacement despite the presence or absence of GI bleeding. Cardiology guidelines on management of Aortic stenosis should nevertheless be employed in all cases. Comprehensive echocardiographic evaluation should be performed to assess the disease severity. There is no robust data on aortic valve correction in Heyde's syndrome based on the existing literature. There is a lack of data on randomized trials comparing conservative management *vs* aortic valve correction in suspected or proven Heyde's syndrome. Most of the literature supporting aortic valve replacement in Heyde's syndrome is from case reports, case series and retrospective studies[13,15,40-48] (Table 2). Recurrent and uncontrollable GI bleeding seems to be the most common indication for AVR

Table 2 Aortic valve replacement in Heyde's syndrome

Ref.	Year	Type of study	No of patients	Type of aortic valve replacement	Outcome (Positive)	Outcome (negative)
Love <i>et al</i> [13]	1982	Case series	3	Surgical	Complete resolution of GI bleed	
Scheffer <i>et al</i> [15]	1986	Case report	1	Surgical-porcine	No GI bleeding during 9 mo follow up	
Cappell <i>et al</i> [40]	1986	Case series	2	Surgical	No further bleeding with negative stool guaiac in one pt at 18 mo followup; Disappearance of angiodysplasia by endoscopy with no further bleeding in 2 nd patient at 15 mo follow up	
Abi-akar <i>et al</i> [41]	2011	Case report	1	Surgical- bio prosthetic	No bleeding or blood transfusion at 9 mo follow up	
Thompson <i>et al</i> [42]	2012	Retrospective review (1971-2001)	57	surgical bioprosthetic(47); mechanical(10)	45 patients (79%) had no recurrence of GI bleeding in 15 year followup	12 patients had persistent GI bleeding post AV replacement
Kadkhodayan <i>et al</i> [43]	2012	Case report	1	TAVR	No further episodes of GI bleeding post discharge	
Balbo <i>et al</i> [44]	2016	Case report	1	TAVR	No GI bleeding at 3 and 6 mo of follow up post TAVR	
Alshuwaykh <i>et al</i> [45]	2018	Case report	1	TAVR	No further bleeding with stable Hemoglobin at 6 mo follow up	Melena requiring blood transfusion at 2 wk follow up
Garcia <i>et al</i> [46]	2019	Case report	1	Surgical, mechanical	No new episodes of GI bleeding post valve replacemet	
Famularo <i>et al</i> [47]	2020	Case report	1	TAVR	No GI bleeding at 3 follow up post TAVR	
Godino <i>et al</i> [48]	2012-13	Retrospective (2007-2012)	7	TAVR	During a mean follow-up interval of 22 ± 15 mo, 6 patients (86%) had no recurrence of GI bleeding	One patient had TAVR failure with re hospitalization and blood trasnfusion

GI: Gastrointestinal; TAVR: Transcatheter aortic valve replacement.

in Heyde's syndrome[42].

CORRECTION OF HEMOSTATIC ABNORMALITIES (ACQUIRED VON WILLEBRAND SYNDROME) WITH AORTIC VALVE REPLACEMENT

The severity of vWF abnormality is noted to directly correlate with the severity of aortic stenosis measured by transvalvular gradient[12,49,50]. Correction of valve abnormalities or other conditions associated with high shear force (*e.g.*, ventricular assist device) leads to resolution of GI bleeding[13,14,15,48]. Nevertheless, the hemostatic abnormalities and therefore bleeding can recur if there is a mismatch between the patient and prosthesis, (*e.g.*, paravalvular leak)[12]. TAVR (Transcatheter aortic valve replacement) has also been shown to be effective in this regard, especially in surgically high risk patients, with resolution of GI bleeding[48], and recovery of high molecular weight vWF multimers after successful TAVR[20,48,51].

SURGICAL VALVE REPLACEMENT VS TAVR

Aortic valve stenosis is corrected either by surgical techniques (bio-prosthetic or mechanical) or by TAVR. Bio-prosthetic valve may have an upper hand over mechanical valve in preventing recurrent GI bleed theoretically, as the latter will need anticoagulation. In a retrospective analysis of Heyde's syndrome and surgical aortic valve replacement, recurrent GI bleed was shown to be significantly lower with bioprosthetic when compared to mechanical prosthesis (15% *vs* 50%)[42]. The two most commonly used scores to determine the candidacy for surgical *vs* TAVR are the

STS (Society of Thoracic Surgeons)[52] risk score and the EuroScore[53]. TAVR is currently the treatment of choice in patients with intermediate[52] to high risk for the conventional surgical valve replacement. In a recent randomized control trial with intermediate-risk patients, TAVR was similar to surgical aortic-valve replacement with respect to the primary end point of death or disabling stroke with a significantly lower rate of life threatening bleeding at 30 d in TAVR group (10.4% *vs* 43.4%)[54]. Recent studies have shown that TAVR is non-inferior to surgical valve replacement even in low risk surgical patients[55,56]. TAVR (in the context of angiodysplasia associated GI bleeding) has been shown to have fewer peri-operative complications including myocardial infarction and stroke and decreased rates of blood transfusion than surgical valve replacement[57]. Overall, TAVR is becoming a popular and alternative method to surgery for valvular heart diseases. While it may appear reasonable to consider TAVR or aortic valve surgery for Heyde's syndrome, one cannot make a strong recommendation based on the current available literature. We also proposed an algorithm for management for Heyde's syndrome (Figure 4).

ANTI-PLATELETS/ANTI COAGULANT USE WITH TAVR

Bleeding and thromboembolic complications are the major concerns in the post TAVR period. Several factors can determine the use of anti-platelets and /or anti-coagulants including history of coronary artery disease, cardiac stent, atrial fibrillation, stroke, *etc.* Attempts should be made to minimize the use and/or duration of anti-coagulants and anti-platelet agents in patients with suspected or proven Heyde's syndrome in appropriate situations. Current guidelines recommend a dual anti-platelet therapy (DAPT) of 3-6 mo after TAVR[58,59]. Recent randomized control trials in TAVR have questioned the use of DAPT against single anti platelet therapy (SAPT), with less bleeding risk with SAPT and no difference in thromboembolic events[60-63]. In a recent randomized trial on TAVR in low risk patients, the use of low dose aspirin plus warfarin did not increase short-term bleeding (30 d)[64]. The option of SAPT with TAVR seems to be promising, especially in the setting of Heyde's syndrome.

OUTCOMES OF GI BLEEDING POST AORTIC VALVE REPLACEMENT

Several factors may determine the outcomes of GI bleeding post aortic valve replacement including the duration and number of anti-platelet agents/anticoagulants, age, co-morbidities, frailty and type of aortic valve replacement. Peri-procedural bleeding can also be related to access site bleeding. Theoretically, correction of acquired Von Willebrand syndrome with Aortic valve replacement (as described in above section) can lead to control or resolution of GI bleeding. Current data on the outcomes of GI bleeding post aortic valve replacement in Heyde's syndrome is mostly from case reports and show favorable outcomes[13,15,40,41,43-47] (Table 2). There are a few retrospective studies[42,47] which show favorable outcomes with no recurrence of GI bleed in 79%-86% of patients post TAVR. Thompson *et al*[42], in a retrospective analysis of 57 patients with Heyde's syndrome who underwent AVR, found that in a 15 year follow-up, 79% had no recurrence of GI bleeding.

GI bleeding may complicate TAVR regardless of its existence pre TAVR, and the rates of GI bleeding vary according to literature (1.4%-11.8%). Spiewak *et al*[65], in a retrospective analysis of 482 patients hospitalized for TAVR showed that GI bleed was only 1.4% in the immediate post TAVR period, with 40.6% of the population on DAPT and 29% on oral anticoagulation[65]. However, the risk of GI bleeding post TAVR is may be significantly higher (up to 10 fold, 11.8%) in the setting of triple therapy with DAPT and oral anticoagulant use as shown in a large cohort study by Stanger *et al*[66]. A large retrospective analysis on readmission rates for late GI bleeding following TAVR *vs* surgical aortic valve replacement showed that it was higher in TAVR cohort (3.3%) than surgical cohort (1.5%) with average time to readmission similar in both groups (approximately 90 d)[67]. Another large retrospective study from France, involving a cohort of 372 patients receiving TAVR, showed that major GI bleeding occurred in up to 11.3% of population with a median follow-up of 383 d[68]. For patients with high CHADS₂-VASC score and clinically high risk for bleeding (HAS-BLED score)[69] with anti-coagulants or anti-platelet agents, WATCHMAN device (left atrial appendage closure) is another option. WATCH-TAVR is a prospective, multi-center, randomized controlled trial currently enrolling patients in 32 centers in United States, aiming at the prevention of stroke and bleeding in patients with atrial

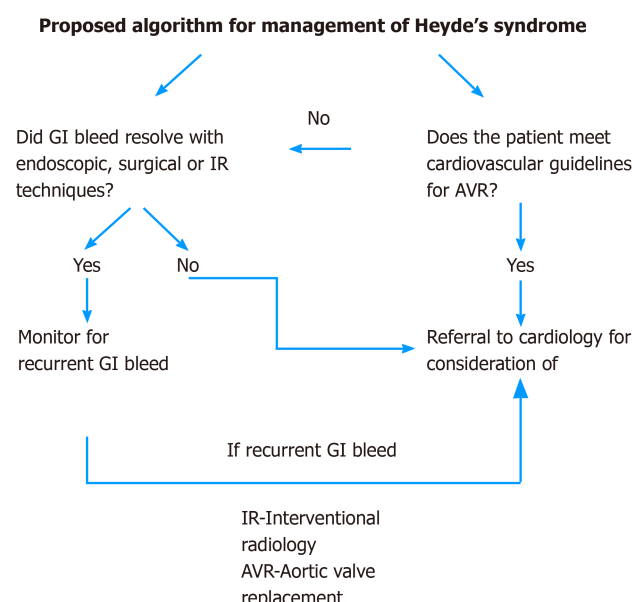


Figure 4 Proposed algorithm. GI: Gastrointestinal; AVR: Aortic valve replacement.

fibrillation undergoing TAVR by using WATCHMAN device.

CONCLUSION

Heyde's syndrome, a complex multi system disorder is often overlooked and under reported, especially in the growing era of geriatric population. Heyde's syndrome should be suspected in patients with intestinal bleeding and aortic stenosis. A high index of suspicion will improve the diagnosis. With evolution in interventional cardiology and gastroenterology the prognosis of this syndrome appears to be excellent. Future randomized controlled trials comparing clinical outcomes with and without aortic valve correction in Heyde's syndrome will help formulate guidelines for aortic valve correction in Heyde's syndrome.

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