RELATIONSHIP BETWEEN VON WILLEBRAND FACTOR DEGRADATION AND HEYDE SYNDROME DIAGNOSIS

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Abstract: Heyde's Syndrome is a clinical condition characterized by the coexistence of aortic stenosis and gastrointestinal bleeding, typically associated with angiodysplasia. This study reviews recent literature, highlighting the relationship between aortic stenosis and the degradation of von Willebrand factor (vWF), leading to the development of acquired von Willebrand disease (AVWD). The review addresses the key biochemical parameters and diagnostic methods used for identifying the syndrome, emphasizing the importance of echocardiography for detecting aortic stenosis and multimer analysis of vWF for confirming AVWD. The analysis includes discussions on the diagnostic challenges and clinical implications of the syndrome, proposing guidelines that could improve therapeutic management and reduce associated morbidity. It concludes that an integrated, evidence-based diagnostic approach is essential for the early detection and effective treatment of Heyde's Syndrome.

Keywords: Diagnosis; von Willebrand Factor; Heyde's Syndrome

Introduction

Diverticular Disease and angiodysplasia/arteriovenous malformations (AVMs) are the main causes of lower gastrointestinal bleeding (LGIB) in the elderly population. In contrast, Heyde's syndrome, a rare condition more commonly seen in the elderly, is characterized by a unique relationship between aortic stenosis and gastrointestinal bleeding, where the source of bleeding is

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typically angiodysplasia. The most widely accepted hypothesis to explain the pathophysiology of Heyde syndrome is acquired von Willebrand syndrome (AVWS). Specifically, there is evidence in the literature demonstrating the destruction of high molecular weight von Willebrand factor (vWF) multimers on gel electrophoresis, secondary to shear by a stenotic aortic valve, resulting in AVWS and, consequently, gastrointestinal hemorrhage (Tsuchiya, S.; Matsumoto, Y.; Doman, T.; Fujiya, T.; Sugisawa, J.; et al, 2020)

However, this hypothesis remains controversial, as there are cases reported in the literature where no evidence of such destruction was found, raising doubts about the universality of this explanation for all cases of Heyde's syndrome. Since Dr. Heyde's first description in 1958, numerous cases of this unique association have been reported, but to date, no comprehensive systematic review of case reports has been conducted. This study presents a systematic review of this type, summarizing the epidemiology, risk factors, clinical characteristics, diagnostic approach, including the prevalence of AVWS, and the management of Heyde's syndrome according to the cases reported in the literature (Islam, S.; Cevik, C.; Islam, E.; Attaya, H.; Nugent, K, 2011).

In the literature, several parameters have been discussed to aid in the diagnosis of Heyde's syndrome. Among them, the analysis of von Willebrand factor, a glycoprotein crucial for primary hemostasis, whose function is frequently compromised in patients with severe aortic stenosis, stands out. The fragmentation of von Willebrand's factor, induced by the mechanical stress generated by aortic stenosis, is one of the most relevant biochemical markers for the diagnosis of this syndrome, as pointed out by studies such as those by Venerito et al. (2021) and Tsuchiya et al. (2020). The degradation of this factor results in a lower capacity for platelet adhesion, predisposing patients to gastrointestinal hemorrhages.

Despite progress in understanding this syndrome, diagnosis still presents considerable challenges, in part due to the absence of standardized diagnostic criteria and overlapping symptoms with other conditions. Identification of aortic stenosis, often performed by transthoracic echocardiography, is a critical step, but should be complemented by laboratory evaluation of von Willebrand factor and

endoscopic imaging methods for the detection of angiodysplasias.

This study aims to review the recent scientific literature on Heyde's Syndrome, focusing on biochemical parameters and diagnostic approaches that can facilitate the early and accurate identification of this condition. The consolidation of this information aims to contribute to the development of clinical guidelines that improve therapeutic management and reduce the morbidity associated with the syndrome.

This revised introduction provides a clearer and more articulate context on the relevance of Heyde's syndrome in clinical practice, highlighting the importance of diagnostic advances and the need for well-established guidelines for the effective management of this condition.

PATHOPHYSIOLOGY

Aortic stenosis is widely recognized as the most common valvular heart disease and represents the main indication for valve surgery in western regions. Specific risk factors, such as the presence of bicuspid or tricuspid aortic valve, play a significant role, accounting for 50% and 30-40% of cases, respectively. However, degenerative aortic stenosis is best understood as a multifactorial process similar to atherosclerosis, where the risk factors for its development coincide with those already associated with atherosclerosis. Notably, coronary artery disease is present in 30% of patients with mild to moderate aortic stenosis and in 50% of those with severe stenosis (Messika-Zeitoun; Lloyd, 2018; Blackshear et al., 2013).

For valvular areas smaller than 1.5 cm^2, both the transvalvular gradient and maximum velocity tend to increase, often resulting in turbulent or jet flows that increase the shear stress on the aortic valve (Natorska et al., 2016). Under conditions of low shear stress, von Willebrand factor (vWF) circulates in a globular and quiescent form, being activated only in situations of vascular injury. When activated, vWF adopts a linear conformation that facilitates its interaction with platelets, promoting their activation and adhesion. High molecular weight multimers (MEPM) in vWF are considered

highly effective due to their ability to spontaneously bind to both platelets and collagen (Hilligass; Limdi, 2016; Van Belle et al., 2015).

Under normal conditions, the enzyme ADAMTS13, a disintegrin and metalloprotease, regulates the distribution of high molecular weight multimers to prevent thrombus formation. However, in situations of high shear stress, such as aortic stenosis, MEPM undergo dynamic modulations that result in the loss of their globular shape, exposing the sites of attachment to the ADAMTS13 and facilitating their cleavage (Tiede et al., 2008). The decrease in multimers with higher molecular weight, with percentages below 10.5%, is associated with an increased hemorrhagic risk (Hilligass; Limdi, 2016).

The importance of shear stresses in hemostasis has been confirmed by studies using ventricular assist devices. These studies have shown that a high-velocity and shear stress environment results in the progressive loss of MEPM in all patients, with a significant association with bleeding complications, particularly in the gastrointestinal tract, observed in 20-40% of patients (Spangenberg et al., 2015).

When studying 95 patients with moderate to severe aortic stenosis, Spangenberg et al. (2015) observed a reduction in MEPM in 42% of cases. Similarly, Vincentelli et al. (2003) reported that 79% of patients with severe aortic stenosis and 75% of those with moderate stenosis had a significant decrease in MEPM. However, in a study with a comparable sample size, only 20% of patients exhibited a significant reduction in MEPM, and these individuals showed a 34.8% higher maximum transvalvular gradient compared to patients with normal percentages of MEPM (Natorska et al., 2016).

Although these findings support the correlation between aortic stenosis and von Willebrand factor deficit, the disparity in reported rates (42% vs. 79-75% vs. 20%) indicates that this relationship is complex and dependent on individual factors, including age, the presence of comorbidities such as thyroid disease, and the severity of aortic stenosis (Franchini et al., 2004). In patients with thyroid pathologies, for example, approximately 2.6% demonstrate coagulation alterations consistent with acquired von Willebrand disease (Franchini et al., 2004).

Bowen et al. (2003) demonstrated that blood group, especially group O, influences susceptibility to proteolysis and vWF clearance by ADAMTS13. VWF, synthesized in endothelial cells, megakaryocytes and platelets, undergoes a series of modifications until its glycosylation. The study showed that the oligosaccharides present in the VWF structure protect the cleavage site by the ADAMTS13. The presence of blood group O-specific oligosaccharides appears to prevent proteolysis, resulting in lower baseline VWF levels in these individuals compared with those of other blood groups.

Regarding the role of age in Heyde's syndrome, Balaoing et al. (2014) observed that vWF, expressed and secreted by endothelial cells throughout life, tends to accumulate in the valvular subendothelium, promoting the formation of nodules and subsequent calcification. This accumulation of vWF in an older, dispersed, and disorganized extracellular matrix may affect the development and progression of calcification aortic stenosis. In addition, the study indicated that ADAMTS13 expression is not affected by age, suggesting an increasing imbalance in the vWF/ADAMTS13 ratio over time, which may explain the higher hemorrhagic risk in elderly patients (Balaoing et al., 2014).

Acquired von Willebrand factor (vWF) deficit, when associated with episodes of hemorrhage in individuals without a personal or family history of recurrent hemorrhage, is an indication for the diagnosis of acquired von Willebrand disease (VWD). This condition, although rare, with an estimated prevalence of 0.04%, is associated with significant morbidity. It is characterized by a qualitative deficit in vWF, similar to that observed in hereditary von Willebrand disease type 2A (Giannini et al., 2011). Although most patients do not have a history of hemorrhages, about 48% manifest hemorrhagic diathesis, often evidenced by episodes of mucocutaneous bleeding, such as epistaxis, gingival bleeding, and gastrointestinal hemorrhages (Giannini et al., 2011).

In the specific subgroup of individuals with VWD secondary to aortic stenosis, studies indicate that, despite the vWF deficit, only between 9% and 21% of patients have a history of hemorrhage or anemia (Vincentelli et al., 2003). Natorska et al. (2016) suggest that mechanisms intrinsic to aortic stenosis itself may explain why the incidence of hemorrhages or anemia in these patients is lower than expected. In fact, in patients with moderate to severe aortic stenosis and with an elevated transvalvular

gradient, the deficit of high molecular weight multimers (MEPM) is accompanied by an increase in thrombin production and platelet activation. This phenomenon alters the hemostatic balance towards thrombosis, promoting the formation of fibrin-rich thrombi, regardless of the presence of vWF (Natorska et al., 2011).

Thus, understanding the pathophysiology of Heyde's syndrome requires an analysis of the mechanisms that connect aortic stenosis with gastrointestinal bleeding, particularly in elderly patients. This complex clinical picture is mediated by the loss of high molecular weight von Willebrand factor (MEPM vWF) multimers, a condition that leads to acquired von Willebrand disease (VWAD) and is closely related to hemostatic dysfunction.

Aging, a key factor that exacerbates this condition, as it is associated with hypoxia of the gastrointestinal mucosa and progressive venular dilation, which in turn contributes to the incompetence of the precapillary sphincters. These factors create an environment conducive to the development of gastrointestinal (GI) angiodysplasia, one of the main causes of hemorrhage in this population. Recent studies highlight that the interaction between vWF and angiopoietin-2 (Ang-2) in endothelial cells modulates signaling through the VEGFR2 receptor, a process critical for cell proliferation and migration. These interactions are essential in angiogenesis, and the dysregulation of this process, exacerbated by aortic stenosis, results in an anomalous vascularization characteristic of angiodysplasia (Randi, Laffan, 2017; Gragnano et al., 2017).

Also, in vascular smooth muscle cells, vWF plays a significant role in the maturation of vessels, a process that is also affected by its deficiency. This not only contributes to the predisposition to bleeding, but also to the formation of anomalous vessels, which can bleed easily, further aggravating the clinical condition of patients with Heyde's Syndrome (Hudzik, Wilczek, & Gasior, 2016).

DIAGNOSIS

Gastrointestinal Angioplasty

In individuals who experience anemia or gastrointestinal bleeding, it is essential to investigate possible sources of gastrointestinal bleeding, including gastric or duodenal ulcers, diverticular disease, neoplasms, and inflammatory bowel diseases (Hudzik, Wilczek, Gasior, 2016). The first recommended approach is to perform upper GI endoscopy and colonoscopy, to comprehensively evaluate the possible causes of bleeding.

Capsule endoscopy is a valuable method for visualizing the small intestine, and is considered a safe and effective technique for identifying lesions that may go unnoticed in other endoscopic examinations. However, this technique has limitations, such as the difficulty in identifying all lesions, especially those located in the distal small intestine, impaired visibility in cases of active hemorrhage, and the impossibility of direct intervention (Thompson et al., 2012; Michot et al., 2012). To overcome these limitations, balloon enteroscopy, either one or two balloons, can be employed. Although enteroscopy offers better image quality, it also does not allow, in isolation, extensive therapeutic maneuvers (Randi & Laffan, 2017).

Endoscopically, angiodysplasia is characterized by small (usually smaller than 5 mm), flat, cherry-red lesions distributed along the gastrointestinal mucosa. These lesions are often seen in the right colon and cecum, areas where intestinal wall thickness and tension seem to increase the predisposition to the development of these anomalies (Michot et al., 2012). These lesions may also have a paler surrounding mucosa, giving them a “clear halo” appearance, which is characteristic in some cases of angiodysplasia (Hudzik, Wilczek, Gasior, 2016).

The success of any endoscopic procedure depends on several factors, including the operator’s experience, visibility during the procedure, and the location and size of the lesion. Due to the possibility of confusion with areas of inflammation or trauma, repeat upper GI endoscopy or colonoscopy is recommended in cases of high clinical suspicion or when the initial examination is of poor quality,

before considering investigation of the small bowel with additional techniques (Blackshear et al., 2013).

Radiographic techniques, such as angiography, are indicated for patients who have acute gastrointestinal bleeding and whose endoscopies have not identified any lesion, or to confirm the location of suspicious lesions previously visualized by endoscopy. Angiography is particularly useful in the acute diagnosis of angiodysplasia, as it does not require previous bowel preparation, allows precise localization of the hemorrhagic lesion, and enables therapeutic embolization of the lesion. However, the associated risks, such as intestinal ischemia, should be considered, limiting their indication to patients with severe hemorrhage and hemodynamic instability (Michot et al., 2012).

If relevant lesions are not identified, such as neoplasms or other gastrointestinal pathologies, or if angiodysplasia is diagnosed, the possibility of valvular disease, such as aortic stenosis, should be considered, suggesting the presence of Heyde's Syndrome as a differential diagnosis. In this context, Blackshear et al. (2013) recommend performing an echocardiogram to evaluate aortic stenosis, along with von Willebrand factor (vWF) testing, in order to exclude or confirm the presence of VWA.

Aortic Stenosis

Aortic stenosis, one of the main acquired valvular heart disease in elderly patients, is often associated with gastrointestinal angiodysplasia and acquired von Willebrand disease (VWD), thus characterizing Heyde's Syndrome. The diagnosis of this syndrome often begins with the identification of aortic stenosis, usually through a transthoracic echocardiogram.

The transthoracic echocardiogram is the test of choice to assess the presence and severity of aortic stenosis. This examination allows a detailed visualization of the valve leaflets, their movement, the degree of calcification, and the function of the left ventricle. In patients with aortic stenosis, significant calcification of the valve cusps is often observed, which leads to a reduction in the valve area and an increase in the pressure gradient across the valve. This pressure overload, in turn, can

lead to decreased ventricular function over time, exacerbating clinical symptoms and increasing the risk of complications such as gastrointestinal hemorrhages associated with angiodysplasia (Grimard, Safford, & Burns, 2016).

The association between aortic stenosis and gastrointestinal hemorrhage due to angiodysplasia is an important marker of Heyde's syndrome. Calcification of the aortic valve and consequent alteration of blood flow can lead to the degradation of high molecular weight von Willebrand factor (vWF) multimers, resulting in VAWD. This condition predisposes patients to bleeding, especially in the gastrointestinal tract. Early detection of aortic stenosis through echocardiography allows clinicians to consider the possibility of Heyde syndrome in patients with a history of unexplained anemia or episodes of gastrointestinal bleeding (Carità et al., 2016).

Confirmation of the diagnosis of Heyde's syndrome requires not only the identification of aortic stenosis, but also the investigation of laboratory parameters related to vWF. The decrease in high molecular weight vWF multimers, often observed in patients with significant aortic stenosis, is indicative of VWD. This finding, combined with clinical symptoms and endoscopic evidence of angiodysplasia, reinforces the diagnosis of Heyde's Syndrome and guides therapeutic management, which may include aortic valve replacement to resolve both stenosis and associated bleeding complications (Van Belle et al., 2019).

Von Willebrand Acquired

The correct diagnostic approach to Heyde's syndrome, with emphasis on the identification of acquired von Willebrand disease (VWAD), requires the application of sensitive and specific laboratory tests that can confirm changes in hemostasis. Given that VWD is a condition often associated with severe aortic stenosis, it is essential that the initial evaluation includes a panel of coagulation tests.

The diagnostic protocol should begin with basic coagulation tests, including activated partial thromboplastin time (APTT) and prothrombin time (PT). APTT, which measures the intrinsic

and common coagulation pathway, may be normal or slightly increased in patients with VAWD. Prothrombin time, in turn, usually does not show significant changes. Along with these tests, it is recommended to perform the PFA-100, a platelet function analyzer that has high sensitivity in detecting defects in high molecular weight von Willebrand factor (MEPM) multimers, which are often decreased in patients with aortic stenosis. Studies indicate that PFA-100 is prolonged in 92% of patients with severe aortic stenosis and in 50% of those with moderate stenosis, although its use is limited in specific conditions such as anemia (hemoglobin <10 mg/dL), hemolysis, thrombocytopenia, or use of antiplatelet drugs (Hudzik, Wilczek, Gasior, 2016).

If VWD is suspected based on initial tests, it is imperative to order specific tests that allow a definitive diagnosis. Landmark studies suggest that a sensitivity of 86% was achieved in patients with VWD when reductions in at least one of the following parameters were observed (Tiede et al., 2008):

- VWF <50 IU/dL – This test quantifies von Willebrand factor monomers regardless of their polymerization. A significant reduction in this value indicates a global factor deficiency, which is common in VAWD.
- VWF/Ag ratio <0.7 – This ratio reflects the ratio between the activity of the ristocetin cofactor and the vWF antigen, and its reduction may indicate the presence of inhibitory antibodies or a selective loss of high molecular weight multimers.
- WF/Ag ratio <0.8 – This measure, which compares collagen binding with vWF antigen, is a marker of loss or decrease in MEPM. Studies show that this ratio is decreased in 67% of patients with severe aortic stenosis and in 25% of those with moderate stenosis.

Although the combination of tests such as PFA-100, APTT, and PT can provide a preliminary diagnosis of acquired von Willebrand disease (VWA) in most cases, it is important to emphasize that the exclusion of this condition should not be based on these results alone. In situations of high clinical suspicion, it is recommended to perform electrophoresis of von Willebrand factor (vWF) multimers,

which is considered the gold standard for the detection of structural anomalies in multimers. This test allows the detailed identification of multimerized forms of vWF, highlighting reductions or absences of high molecular weight multimers, which are indicative of VWD in patients with aortic stenosis (Tiede et al., 2008).

The use of immunohistochemistry techniques, such as enzyme-linked immunosorbent assay (ELISA), allows the detection of anti-vWF antibodies. Although the presence of these antibodies is not considered a definitive diagnosis of VAWD, studies suggest that their presence may be associated with a higher frequency of bleeding episodes, indicating cases of greater severity. These antibodies, by interfering with normal vWF function, may exacerbate the predisposition to bleeding in patients already vulnerable due to aortic stenosis, making the identification and monitoring of these markers a useful tool for risk stratification and more personalized clinical management (Budde et al., 2008).

Final Thoughts

Heyde Syndrome is a complex and multifaceted condition that presents significant challenges in both diagnosis and clinical management. The association between aortic stenosis and gastrointestinal bleeding, particularly due to angiodysplasia, highlights the importance of a diagnostic approach that combines clinical, laboratory, and imaging methods. The literature reviewed throughout this study underlines the relevance of integrating these tools for a more accurate and timely diagnosis.

The diagnosis of Heyde's Syndrome should begin with the identification of aortic stenosis, usually performed by means of transthoracic echocardiography, which allows a detailed evaluation of valve function and the detection of associated hemodynamic changes. At the same time, laboratory evaluation of von Willebrand factor (vWF), with emphasis on the analysis of high molecular weight multimers, is crucial for the confirmation of acquired von Willebrand disease (VWAD), a hallmark characteristic of this syndrome. The combination of these tests allows not only the confirmation of the diagnosis, but also the stratification of patients according to the risk of bleeding complications.

Although the understanding of the pathophysiology of Heyde syndrome has advanced significantly, there are still gaps in knowledge that require further investigation. Additional studies are needed to explore the clinical variability observed among patients, as well as to develop new therapeutic approaches that can improve clinical outcomes and quality of life for affected patients.

References

BASAK, D. K.; GOMES, R. R.; ARFIN, S., Md. Heyde's syndrome: Rarely heard and often missed. Advanced Research in Gastroenterology & Hepatology, Vol. 2, No. 4, 2017. DOI: 10.19080/argh.2017.02.555592.

BLACKSHEAR, J. L. et al. Indexes of von Willebrand Factor as Biomarkers of Aortic Stenosis Severity (from the Biomarkers of Aortic Stenosis Severity [BASS] Study). The American Journal of Cardiology, v. 111, n. 3, p. 374-381, 2013. DOI: 10.1016/j.amjcard.2012.10.015.

BUDDE, U.; SCHNEPPENHEIM, R. Acquired von Willebrand syndrome in patients with high shear stress: from quantitative loss of von Willebrand factor to qualitative defects. Seminars in Thrombosis and Hemostasis, v. 34, n. 5, p. 520-528, 2008. DOI: 10.1055/s-0029-1145245.

CARITÀ, P.; COPPOLA, G.; NOVO, G. et al. Aortic stenosis: insights on pathogenesis and clinical implications. Journal of Geriatric Cardiology, v. 13, p. 489-498, 2016. DOI: 10.11909/j.issn.1671-5411.2016.06.001.

GIANNINI, S. et al. Acquired von Willebrand syndrome type 2A in a JAK2-positive essential thrombocythemia - affected member of a large von Willebrand disease family with a novel autosomal dominant A1716P mutation. Thrombosis and Haemostasis, v. 105, n. 5, p. 921-924, 2011. DOI: 10.1160/th10-08-0517.

GOLA, W.; LELONEK, M. Clinical implication of gastrointestinal bleeding in degenerative aortic stenosis: an update. Cardiology Journal, v. 17, n. 4, p. 330-334, 2010.

GRAGNANO, F. et al. Von Willebrand Factor as a Novel Player in Valvular Heart Disease: From

Bench to Valve Replacement. Angiology, v. 69, n. 2, p. 103-112, 2017. DOI: 10.1177/0003319717708070.

GRIMARD, B. H.; SAFFORD, R. E.; BURNS, E. L. Aortic stenosis: diagnosis and treatment. American Family Physician, v. 93, p. 371-378, 2016.

HUDZIK, B.; WILCZEK, K.; GASIOR, M. Heyde syndrome: Gastrointestinal bleeding and aortic stenosis. CMAJ, v. 188, n. 2, p. 135–138, 2016. DOI: 10.1503/cmaj.150194.

ISLAM, S. et al. Heyde's syndrome: a critical review of the literature. Journal of Heart Valve Disease, v. 20, n. 4, p. 366-375, 2011.

MICHOT, J. M. et al. Severe gastro-intestinal angiodysplasia in context of Heydes syndrome durably cured after aortic valve replacement. La Presse Médicale, v. 41, n. 7–8, p. 763–766, 2012. DOI: 10.1016/j.lpm.2011.10.012.

MOHEE, A. et al. Aortic stenosis and anemia with an update on approaches to managing angiodysplasia in 2018. Cardiology Journal, v. 27, p. 72-77, 2020. DOI: 10.5603/CJ.a2018.0068.

NATORSKA, J. et al. Increased thrombin generation and platelet activation are associated with deficiency in high molecular weight multimers of von Willebrand factor in patients with moderate-to-severe aortic stenosis. Heart, v. 97, n. 24, p. 2023-2028, 2011. DOI: 10.1136/hrt.2010.217273.

RANDI, A. M.; LAFFAN, M. A. Von Willebrand factor and angiogenesis: basic and applied issues. Journal of Thrombosis and Haemostasis, vol. 15, no. 1, p. 13–20 (2017). doi: 10.1111/jth.13551.

THOMPSON, J. L. et al. Risk of recurrent gastrointestinal bleeding after aortic valve replacement in patients with Heyde syndrome. The Journal of Thoracic and Cardiovascular Surgery, v. 144, n. 1, p. 112-116, 2012. DOI: 10.1016/j.jtcvs.2011.05.034.

TIEDE, A. et al. Diagnostic workup of patients with acquired von Willebrand syndrome: A retrospective single-centre cohort study. Journal of Thrombosis and Haemostasis, vol. 6, no. 4, p. 569–576, 2008. DOI: 10.1111/j.1538-7836.2008.02909.x.

TSUCHIYA, S. et al. Disappearance of Angiodysplasia Following Transcatheter Aortic Valve Implantation in a Patient with Heyde's Syndrome: A Case Report and Review of the Literature.

Journal of Atherosclerosis and Thrombosis, v. 27, n. 3, p. 271-277, 2020.

VAN BELLE, E. et al. von Willebrand factor and management of heart valve disease: JACC Review Topic of the Week. Journal of the American College of Cardiology, v. 73, p. 1078-1088, 2019. DOI: 10.1016/j.jacc.2018.12.045.

VENERITO, M. et al. Gastrointestinal bleeding and cardiovascular diseases: Systematic review and meta-analysis. Journal of Gastroenterology and Hepatology, v. 36, n. 3, p. 746-753, 2021.

VINCENTELLI, A. et al. Acquired Von Willebrand Syndrome in Aortic Stenosis. New England Journal of Medicine, v. 349, n. 4, p. 343-349, 2003. DOI: 10.1056/nejmoa022831.