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EDITORIAL

Heyde syndrome: treat aortic valve disease to stop gastrointestinal bleeding?

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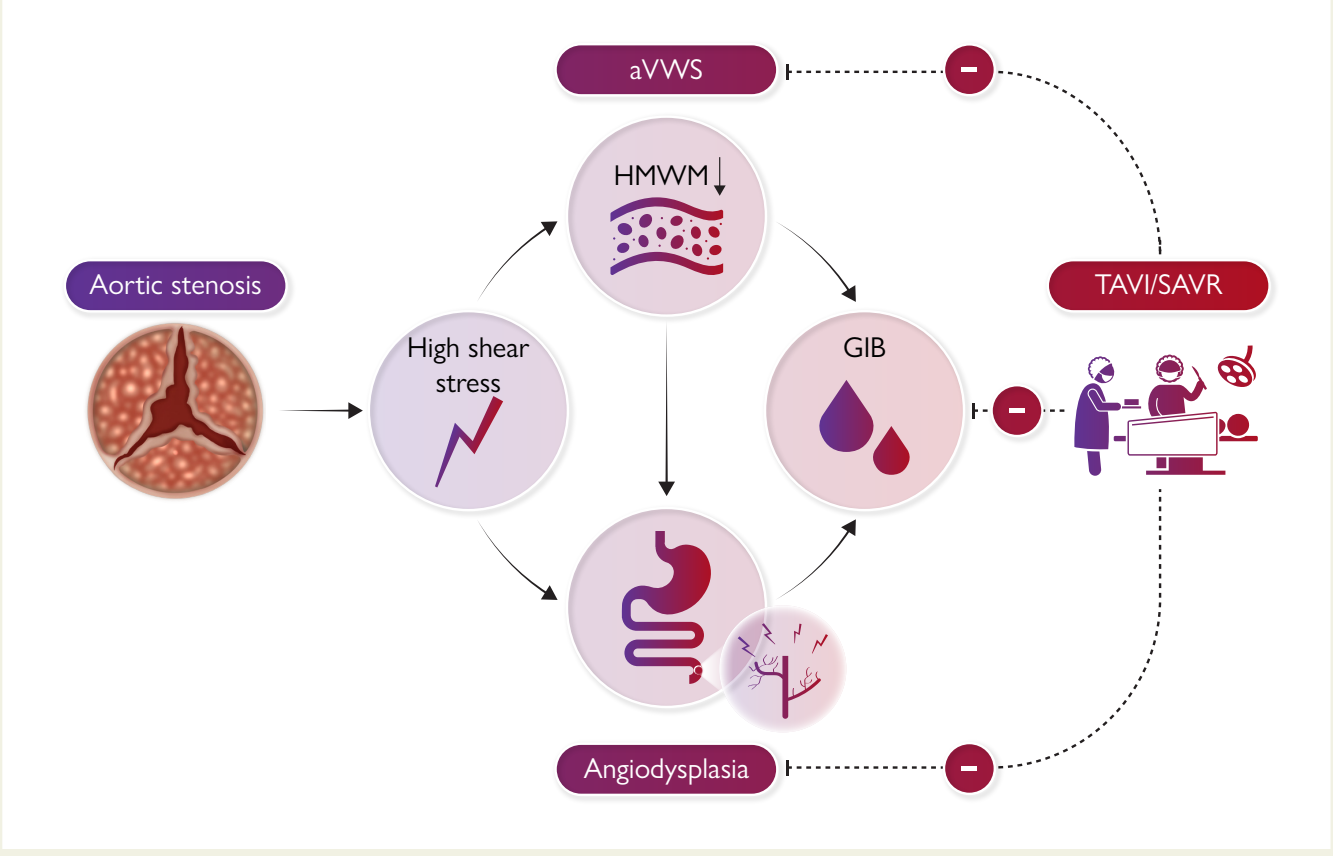
This editorial refers to 'Effectiveness of aortic valve replacement in Heyde syndrome: a meta-analysis', by L.C.M.J. Golstein *et al.*, https://doi.org/10.1093/eurheartj/ehad340.

Graphical Abstract



Heyde syndrome is the association of aortic stenosis and gastrointestinal bleeding (GIB) from angiodysplasia, accompanied by acquired von Willebrand syndrome (aVWS) leading to decreased levels of high molecular weight multimers (HMWMs). The development of angiodysplasia in the gastrointestinal tract remains unclear. Mucosal ischaemia, high shear stress resulting from turbulence caused by the stenotic valve, and the presence of aVWS may be involved. Aortic valve replacement through surgical replacement (SAVR) or transcatheter aortic valve implantation (TAVI) leads to decreased shear stress and may resolve GIB through recovery of aVWS and potentially dissolving angiodysplasias.

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Heyde syndrome is the association of aortic stenosis (AS) and gastrointestinal bleeding (GIB) from angiodysplasia, and it was first described by Edward C. Heyde in 1958.[1] These angiodysplasias are fragile vascular malformations of thin-walled, dilated arterial or venous capillaries in the gastrointestinal mucosa, and their pathogenesis remains unclear.[2] Patients with Heyde syndrome are at increased bleeding risk due to a combination of these vascular malformations and acquired von Willebrand syndrome (aVWS) resulting from high shear stress caused by severe AS. High shear stress leads to unfolding of von Willebrand factor, exposing the cleavage site to ADAMTS 13 (adisintegrin-like and metalloprotease thrombospondin) protease, and leading to decreased levels of the haemostatically active high molecular weight multimers (HMWM).[3] Recurrent bleeding episodes are difficult to manage in these patients. Heyde syndrome is diagnosed in ~3% of patients with AS and is linked to increased all-cause mortality, prolonged hospitalization, and greater healthcare costs.[4] However, the true incidence may be much greater, as chronic anaemia is frequent in elderly individuals with aortic stenosis, and the presence of angiodysplasia in the gastrointestinal tract may be underestimated.

Several smaller studies suggested aortic valve replacement (AVR), performed as transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR), to effectively treat aVWS[5,6] and angiodysplasia-related GIB in Heyde syndrome patients.[7,8] Moreover, residual valve pathologies and antithrombotic regimens were linked to recurrent bleeding complications, albeit limited by the small sample sizes. In the current issue of the *European Heart Journal*, Goltstein *et al.* present a systematic review and meta-analysis to assess the effect of AVR on aVWS recovery and the cessation of GIB in Heyde syndrome patients.[9] To overcome the limitations of previous analyses, they pooled 1054 patients from 33 studies to evaluate the resolution of aVWS using different laboratory assays, and 300 patients from 11 studies to analyse recurrent GIB events in Heyde syndrome patients following AVR. The main findings were as follows: ~87% of patients experienced recovery from aVWS up to 2 years after AVR, and complete cessation from GIB was observed in almost 73%, with higher success rates after SAVR (82%) compared with TAVI (64%). Von Willebrand factor (vWF) levels increased promptly after AVR with slight differences in dynamics between TAVI and SAVR, possibly due to continuous high shear stress or less endothelial damage. Residual aortic valve disease, e.g. paravalvular regurgitation or prosthesis–patient mismatch, negatively affected the recovery of aVWS and GIB, while antithrombotic regimens were not generally found to influence GIB cessation. Heyde syndrome patients were overall at increased risk for peri-procedural (gastrointestinal) bleeding events.

With their systematic review and meta-analysis, the authors contribute significantly to the understanding of treatment effects in patients with Heyde syndrome. The use of recovery rates of vWF as the primary outcome, rather than laboratory values, allowed for pooling of data across studies. However, the lack of utilization of vWF-HMWM electrophoresis, which is considered the diagnostic standard, in many of the included studies and the absence of sufficiently powered randomized trials have to be considered. When comparing treatment effects of TAVI and SAVR in Heyde syndrome, we must keep in mind that the initial studies were limited to SAVR. Long-term follow-up remains scarce after TAVI, and only a few studies examined both SAVR and TAVI in treating aVWS, with in part conflicting results.[10,11] Given the expanding indication and that the number of annual TAVI procedures has surpassed those of SAVR for the treatment of AS in recent years, in-depth analysis of TAVI treatment effects in patients with Heyde syndrome is of paramount interest.

While the previous standard of care for Heyde syndrome involved surgical removal of gastrointestinal tract sections containing angiodysplastic lesions in patients with recurrent bleeding, AVR had been suggested as a treatment option more than three decades ago[6] to improve AS-related symptoms and provide relief from recurrent GIB. Correspondingly, anecdotal evidence suggests the reduction of angiodysplasia in endoscopy following AVR.[12] However, this potential link remains unclear in the absence of systematic endoscopic examinations, and further evidence is required to investigate possible changes in angiodysplasias in Heyde syndrome patients. The association between high shear stress and aVWS in aortic stenosis has been extensively described in the literature.[13] Hence, it appears intuitive that addressing this shear stress by AVR would result in improved haemostasis.[5] It is important to note that this effect may be jeopardized by residual aortic valve pathologies, including paravalvular leakage[7,8] or prosthesis–patient mismatch.[14] Optimal haemodynamic results after AVR seem to play a pivotal role in reducing gastrointestinal bleeding risks and should be particularly considered when planning AVR in patients with Heyde syndrome.

Antithrombotic medication may additionally amplify bleeding risks in these patients. Although Goltstein *et al.* did not find a direct association of restricted vs. intensified antithrombotic regimens and GIB cessation, the debate on the optimal antithrombotic therapy in this vulnerable population remains ongoing.[15] Recent studies suggested a more restrictive approach to reduce bleeding complications after TAVI.[16] However, specific recommendations on antithrombotic regimens after AVR in Heyde syndrome patients are lacking and warrant further investigation.

In conclusion, the present study by Goltstein *et al.*[9] provides persuasive evidence that AVR—whether TAVI or SAVR—effectively restores aVWS and resolves GIB in most patients with Heyde syndrome. Clinicians should consider this association in patients presenting with unexplained anaemia or recurrent GIB and relevant AS. Recurring findings point to the importance of optimal haemodynamic results after AVR to achieve long-term resolution of aVWS and bleeding. This is of particular importance as most of these elderly patients are considered for TAVI rather than SAVR today. Further research is needed to gain a better understanding of the underlying pathophysiology of Heyde syndrome and long-term treatment effects, to optimize therapeutic strategies, ultimately providing patients with the best care available.

Declarations

Disclosure of Interest

M.S. received lecture fees from Abbott Vascular, Abiomed, Amgen, AstraZeneca, Bristol-Myers Squibb, Daichii Sankyo, Edwards Lifesciences, Inari Medical, Medtronic, Pfizer, Philips, Shockwave Medical, and Siemens Healthineers, and lecture fees and research funding from Boston Scientific—all outside the submitted work. LW reports no conflict of interest.

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