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META-ANALYSIS
Valvular heart disease

Effectiveness of aortic valve replacement in Heyde syndrome: a meta-analysis

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See the editorial comment for this article 'Heyde syndrome: treat aortic valve disease to stop gastrointestinal bleeding?', by L. Waldschmidt and M. Seiffert, https://doi.org/10.1093/eurheartj/ehad277.

Abstract

Aims Heyde syndrome is the co-occurrence of aortic stenosis, acquired von Willebrand syndrome, and gastrointestinal bleeding. Aortic valve replacement has been demonstrated to resolve all three associated disorders. A systematic review and meta-analysis were performed to obtain best estimates of the effect of aortic valve replacement on acquired von Willebrand syndrome and gastrointestinal bleeding.

Methods and results A literature search was performed to identify articles on Heyde syndrome and aortic valve replacement up to 25 October 2022. Primary outcomes were the proportion of patients with recovery of acquired von Willebrand syndrome within 24 h (T1), 24–72 h (T2), 3–21 days (T3), and 4 weeks to 2 years (T4) after aortic valve replacement and the proportion of patients with cessation of gastrointestinal bleeding. Pooled proportions and risk ratios were calculated using random-effects models. Thirty-three studies (32 observational studies and one randomized controlled trial) on acquired von Willebrand syndrome ($n = 1054$), and 11 observational studies on gastrointestinal bleeding ($n = 300$) were identified. One study reported on both associated disorders ($n = 6$). The pooled proportion of Heyde patients with acquired von Willebrand syndrome recovery was 86% (95% CI, 79%–91%) at T1, 90% (74%–96%) at T2, 92% (84%–96%) at T3, and 87% (67%–96%) at T4. The pooled proportion of Heyde patients with gastrointestinal bleeding cessation was 73% (62%–81%). Residual aortic valve disease was associated with lower recovery rates of acquired von Willebrand syndrome (RR 0.20; 0.05–0.72; $P = 0.014$) and gastrointestinal bleeding (RR 0.57; 0.40–0.81; $P = 0.002$).

Conclusion Aortic valve replacement is associated with rapid recovery of the bleeding diathesis in Heyde syndrome and gastrointestinal bleeding cessation. Residual valve disease compromises clinical benefits.

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Structured Graphical Abstract

Key Question

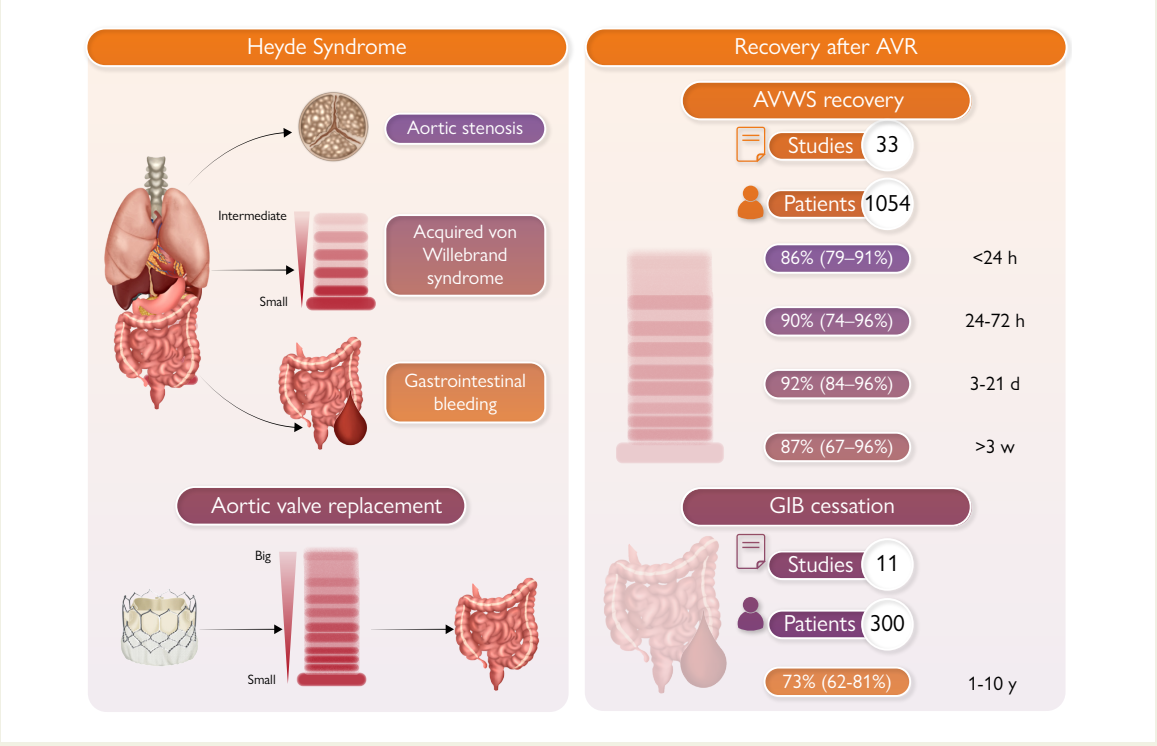
What is the effect of aortic valve replacement (AVR) on Acquired von Willebrand Syndrome (AVWS) and gastrointestinal bleeding (GIB) in patients with Heyde Syndrome?

Key Finding

In this meta-analysis the proportion of patients with AVWS recovery was 87% (95% CI 67–96%) over 3 weeks after AVR. The proportion of patients with GIB cessation was 73% (95% CI 62–81%).

Take Home Message

AVR is associated with rapid recovery of bleeding diathesis in Heyde Syndrome and GIB cessation. Residual aortic valve disease compromises clinical benefits.



Heyde syndrome is effectively treated by aortic valve replacement.

Keywords Heyde syndrome • Acquired von Willebrand syndrome • Gastrointestinal bleeding • Angiodysplasias • Aortic stenosis • Aortic valve replacement

Introduction

Heyde syndrome is the co-occurrence of aortic stenosis (AS) and gastrointestinal bleeding (GIB) caused by angiodysplasias.[1,2] Managing bleeding from these vascular malformations is challenging for gastroenterologists, as patients are often refractory to endoscopic and pharmacologic treatment.[3] Rebleeding can lead to refractory anaemia, with high blood transfusion requirements and subsequent reduced quality of life, increased morbidity, and mortality.[4] In ~2%–10% of patients with AS, angiodysplasias are diagnosed, but the true incidence may be much larger.[5,6]

Acquired von Willebrand syndrome (AVWS) type 2A plays a pivotal role in patients with Heyde syndrome.[7] Von Willebrand factor (vWF) is produced in endothelial cells and megakaryocytes, and undergoes proteolysis in the plasma. High-molecular-weight multimers (HMWM), which comprise 4% of the total protein, are haemostatically active.[8] In AS, the high shear stress around the stenotic valve causes excessive proteolysis of vWF-HMWM, resulting in a bleeding diathesis.[8] Also, AVWS might promote angiogenesis, which ultimately results in angiodysplasia formation.[9] Approximately 80% of AS patients have AVWS.[10]

In patients with Heyde syndrome, aortic valve replacement (AVR) is an effective treatment option for AVWS and angiodysplasia-related GIB.[10,11] Anecdotal evidence suggests that residual valve disease and antithrombotic regimen after AVR may be associated with increased postprocedural bleeding events.[10,11] There is also conflicting evidence on the relationship between Heyde syndrome and periprocedural bleeding.[12,13] Therefore, we performed a systematic review and meta-analysis in which we aimed to assess the effect of AVR on AVWS and GIB in patients with Heyde syndrome. Additionally, we aimed to evaluate which factors are associated with treatment response.

Methods

This project was registered in the International Prospective Register of Systematic Reviews under registration number CRD42020207268 (see *Supplementary material*, page 1). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline.[14]

Search strategy and selection criteria

We performed a literature search for randomized controlled trials (RCTs) and cohort studies on AVWS and GIB related to Heyde syndrome. The following electronic databases were searched: MEDLINE, Embase, and the Cochrane library on 3 June 2020, with an update on 25 October 2022. We also searched the electronic register Clinicaltrials.gov at the indicated dates. A clinical librarian helped create the search syntax. The search terms 'Heyde syndrome' and 'AVR' with synonyms were combined with 'AVWS' or 'GIB'. MeSH terms were used. The full search strategy is provided in the *Supplementary material* (page 2).

All articles were screened based on title and abstract to ensure they reported on the effect of AVR for severe AS on Heyde syndrome-related AVWS or GIB. No language or period restrictions were used. Duplicates were removed. Full-text papers were retrieved from the respective databases or requested from the libraries. The RCTs and cohort studies that reported on the recovery of Heyde syndrome after AVR were included. This encompassed studies that reported on AVWS and/or GIB. Papers that reported on other valvular disorders, interventions, and bleeding disorders were excluded, as well as books, letters, editorials, conference abstracts, published protocols, reviews, case reports, and case series in which patients were not systematically selected. We also excluded studies performed by the same research group that had an overlap in inclusion period and/or follow-up. Studies that did not provide the number or proportion of Heyde patients before and/or after AVR were only included for secondary outcomes, as well as studies on GIB cessation with a follow-up limited to the periprocedural period. The full inclusion and exclusion criteria are provided in Supplementary data online, *Table S1*. We performed a forward citation search on all eligible articles, including scanning and tracking references in footnotes and bibliographies. Two researchers (L.G. and M.R.) executed screening independently. If consensus was not reached, a third researcher got involved (E.v.G.).

Risk of bias and certainty of evidence

The quality of included studies was assessed using the risk of bias in non-randomized studies of interventions tool. This scale consists of seven domains, which are evaluated for low, moderate, or serious risk of bias.[15] Studies with moderate risk of bias in less than three domains were considered to have an overall low risk of bias. Studies with moderate risk of bias in three or more domains were considered to have an overall moderate risk of bias. Studies with serious risk of bias in one or more domains were not included in the primary meta-analyses. The critical appraisal was independently performed by two researchers (L.G. and M.R.). Disagreements were resolved after discussion with a third researcher (E.v.G.). Certainty of evidence was evaluated with the Grading of Recommendations Assessment, Development, and Evaluation approach.[16]

Outcome

Primary outcomes

The primary outcomes were the proportion of Heyde patients with AVWS recovery and Heyde patients with GIB cessation after AVR. We displayed AVWS recovery at four different follow-up times: <24 h after AVR (T1), 24–72 h after AVR (T2), 3 days to 3 weeks after AVR (T3), and >3 weeks after AVR (T4). We selected these time frames because of their clinical relevance, as guidelines advise to resume antithrombotics 24 and 72 h after procedures with minor and major bleeding risks, respectively, and as rapid vWF release from endothelial cells can distort results in the first 3 weeks after AVR.[17–19] We adopted the definition of AVWS used in the respective articles (see *Supplementary material*, page 5). Multiple laboratory tests are utilized to diagnose AVWS, including vWF-HMWM electrophoresis (considered the gold standard), the vWF activity (vWF:Ac) or collagen binding (vWF:CB) to vWF antigen ratio (vWF:Ag), and closure time (CT) adenosine diphosphate (ADP) or bleeding time.[20] If a study deployed multiple tests, we used vWF-HMWM, vWF ratios, or CT-ADP in descending order.[20,21] We displayed GIB cessation as complete cessation after AVR and adopted the definition of GIB used in the respective articles (page S5). Endoscopic small bowel assessment is not part of routine clinical workup.[22] GIB of unknown aetiology after incomplete endoscopic assessment is often considered to be caused by angiodysplasias.[23,24]

Secondary outcomes

Secondary outcomes included differences in haemostasis laboratory tests after AVR and the association between Heyde syndrome and periprocedural bleeding. We reported the various time points after AVR at which laboratory tests were performed. Baseline values were all determined during hospital admission for AVR. We compared the rates of periprocedural bleeding (in-hospital) in Heyde patients with those in non-Heyde patients (controls) from the same cohort. For Heyde patients with GIB, we also compared the rate of periprocedural GIB with the rate in controls. The definition of periprocedural bleeding used in the respective articles was adopted (page S5).

Statistical analysis

Outcomes of this study included pooled proportions of patients and pooled risk ratios (RR). In order to pool proportions, the number of patients with Heyde syndrome (AVWS or GIB) recovery was retrieved from all studies. Derived numbers were used if the number of patients with AVWS/GIB at baseline and after AVR was provided rather than the number with recovery. In order to pool RRs, an RR was calculated for each included study. The RR was calculated by comparing the proportion of AVWS recovery and/or GIB cessation in Heyde patients with the variable to the proportion in Heyde patients without the variable, or by comparing the proportion of Heyde patients with periprocedural bleeding to the proportion of non-Heyde patients (controls) with periprocedural bleeding. Logit transformation was applied for proportions, and the Wilson score interval was used to calculate confidence intervals (CI).[25,26] Analyses were performed using the generic inverse variance method with a random-effects model.[27] Between-study variance was estimated by a restricted maximum-likelihood estimator.[28] Between-study heterogeneity was assessed by determining the I^2 statistic and tested for significance using Cochran's Q-test. Because the Q-test is underpowered to detect moderate degrees of heterogeneity, P-values <0.10 were used.[29] Heterogeneity levels of 30%, 60% and 90% were considered moderate, substantial, and considerable, respectively.[30] To explore heterogeneity, pre-planned subgroup analyses were performed. These included subgroup analyses on AVR procedure (surgical aortic valve replacement [SAVR] or transcatheter aortic valve implantation [TAVI]), residual aortic valve disease (patient–prosthesis mismatch and paravalvular leakage [PVL]), and antithrombotic regimen for patients with GIB. Only studies that provided separate outcomes of Heyde patients with and without residual valve disease and with different antithrombotic regimens were included in order to calculate RRs. The definition of patient–prosthesis mismatch and PVL used in the respective articles was adopted (page S5). Antithrombotics were divided into a restricted (monotherapy or dual antiplatelet therapy) and an intensified (oral anticoagulation combined with single or dual antiplatelet therapy) regimen. We also performed subgroup analyses based on the diagnostic method of AVWS (vWF-HMWM, vWF ratios, or CT-ADP/bleeding time), diagnosis of angiodysplasias (only confirmed cases or both confirmed and suspected cases), number of patients (≥10 for GIB and ≥ 20 for AVWS), and study quality (moderate or high). Omnibus tests of hypothesis were used to compare subgroups.[31] Descriptive statistics were used to display differences in continuous variables after AVR due to the expected large heterogeneity between studies

as values were determined in different laboratories and at varying time points. Publication bias was assessed if the number of studies was ≥10 by constructing a funnel plot and performing Egger's test using a random-effects restricted maximum-likelihood estimator.[32] If a study provided multiple proportions, the longest follow-up time was used (from T4 in descending order). Statistical analyses were performed using the function metaprop and the meta, metafor, and funnel packages in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). For all tests (except for heterogeneity), *P*-values <0.05 were considered statistically significant.

Results

Systematic review

The systematic review yielded 1341 articles (650 from MEDLINE, 623 from Embase, 65 from the Cochrane library, and 3 from Clinicaltrials.gov), resulting in 1112 unique publications (*Figure 1*). We excluded 821 articles based on title and abstract screening. Of the 291 remaining studies, we excluded 249 based on full-text evaluation. Four studies were excluded because they were performed by the same research group and had an overlap in inclusion period.[33–36] One additional article was identified through citation snowballing, yielding 43 studies that met our inclusion criteria.[37]

Thirty-three studies reported on AVWS,[6,10,12,13,38–66] including 32 prospective cohort studies and one RCT.[60] Twenty-five were used for our primary outcome.[6,10,12,38,40–42,44–47,50–54,56–60,62,63,65,66] We included 1054 patients (range: 6–259) who underwent AVR between 2000 and 2022. Eleven observational studies (one prospective) reported on GIB.[5,6,11,37,67–73] Ten of 11 studies were used for our primary outcome.[5,6,11,37,67–72] Nine studies selected consecutive patients with GIB that underwent AVR, and one study selected patients from a cohort of hospitalized AS patients.[71] We included 300 patients (range: 4–72) who underwent AVR between 1968 and 2022. One study ($n = 6$) reported on both AVWS and GIB (see Supplementary data online, *Table S2*).[6]

Risk of bias and certainty of evidence

According to risk of bias in non-randomized studies of interventions, 8/33 studies on Heyde patients with AVWS were scored to have a serious risk of bias.[13,39,43,48,49,55,61,64] These studies did not provide the number of patients with AVWS at baseline or after AVR. Of the remaining studies, 9/25 (36%) were scored to have an overall moderate risk of bias and 16/25 (64%) a low risk of bias (see Supplementary data online, *Table S3A*). Risk of bias was mainly scored for the selection of patients (12/25 [48%]) and measurement of the outcome (14/25 [56%]), as vWF-HMWM was not used in all studies (see Supplementary data online, *Table S3B*). Visual inspection of the funnel plot and Egger's test ($P = 0.020$) for studies on AVWS indicated publication bias (see Supplementary data online, *Figure S1A*). One of 11 studies on Heyde patients with GIB was scored to have a serious risk of bias.[73] This study exclusively reported on periprocedural GIB using a national database. Of the remaining studies, 6/10 (60%) were scored to have an overall moderate risk of bias and 4/10 (40%) a low risk of bias (see Supplementary data online, *Table S4A*). Risk of bias was mainly scored for the selection of patients, as small bowel assessment was not routinely performed (see Supplementary data online, *Table S4B*). The Egger's test ($P = 0.096$) for studies on GIB did not indicate publication bias (see Supplementary data online, *Figure S1B*). The certainty of evidence of our primary outcomes was considered low for AVWS and GIB studies according to the Grading of Recommendations Assessment, Development, and Evaluation approach (see Supplementary data online, *Table S5*).[16]

Primary outcomes

AVR was associated with the recovery of AVWS in 85.9% (95% CI, 79.1%–90.7%; $I^2 = 26\%$) of patients within 24 h after the procedure (T1), in 89.5% (74.1%–96.2%; $I^2 = 80\%$) between 24 and 72 h (T2), in 92.2% (84.0%–96.3%; $I^2 = 58\%$) between 3 and 21 days (T3), and in 87.4% (67.2%–95.9%; $I^2 = 84\%$) between 4 weeks and 2 years (T4). Nine studies assessed AVWS recovery at multiple time points (*Figure 2*).

AVR was associated with complete cessation of GIB in 72.8% (95% CI, 62.2%–81.3%; $I^2 = 59\%$) of patients (*Figure 3*). Follow-up ranged from a median of 12 to 108 months.

Subgroup analyses

Subgroup analyses acquired von Willebrand syndrome

SAVR was performed in 16/25 studies ($n = 352$) and TAVI in 12/25 studies ($n = 695$). In three studies, both procedures were performed.[45,54,57] One did not report separate outcomes ($n = 7$).[57] At T1, AVWS recovery was 91.5% (95% CI, 61.9%–98.6%; $I^2 = 38\%$) after SAVR compared with 85.3% (77.3%–90.9%; $I^2 = 50\%$) after TAVI ($P = 0.092$). At T2, AVWS recovery was 95.0% (87.4%–98.1%; $I^2 = 13\%$) after SAVR compared with 52.7% (47.2%–58.2%; $I^2 = 71\%$) after TAVI ($P = 0.002$). At T3, AVWS recovery was 93.9% (86.1%–97.5%; $I^2 = 0\%$) after SAVR compared with 91.1% (72.5%–97.6%; $I^2 = 76\%$) after TAVI ($P = 0.739$). No TAVI studies performed lab analyses at T4 (see Supplementary data online, *Figure S2*). Subgroup analyses on residual valve disease, which included 11 studies ($n = 181$ with; $n = 1.081$ without), resulted in lower RRs to recover from AVWS. The RR was 0.13 (0.07–0.27; $I^2 = 5\%$) at T1 ($P < 0.0001$), 0.71 (0.46–1.09; $I^2 = 86\%$) at T2 ($P = 0.118$), 0.88 (0.69–1.12; $I^2 = 0\%$) at T3 ($P = 0.311$), and 0.20 (0.05–0.72; $I^2 = 0\%$) at T4 ($P = 0.014$) (*Figure 4*). Subgroup analyses on AVWS diagnosis are provided in the Supplementary data online, *Figure S3*. In 16/25 studies, AVWS was diagnosed through vWF-HMWM ($n = 623$), in 10/25 through vWF ratio abnormalities ($n = 237$), and in 10/25 through CT-ADP or bleeding time ($n = 702$). Multiple assays were used in 8/25 studies.[10,38,40,44,51,54,58,66] The AVWS recovery rates measured through vWF-HMWM, vWF ratios, or CT-ADP/bleeding time did not differ significantly at any time frame (see Supplementary data online, *Figure S3A*). Subgroup analyses on studies with ≥20 patients, which included 14/25 studies ($n = 912$), showed no significant differences in recovery rates (see Supplementary data online, *Figure S4A*). Subgroup analyses on studies with an overall low risk of bias, which included 16/25 studies ($n = 888$), showed a significant difference in recovery rates at T1 compared with studies with a moderate risk of bias (85.0% vs. 100%; $P = 0.020$). There were no significant differences at other time frames (see Supplementary data online, *Figure S4B*).

Subgroup analyses gastrointestinal bleeding

SAVR and TAVI were performed in 6/10 ($n = 103$) and 5/10 studies ($n = 197$), respectively. In one study, both procedures were performed (SAVR in 15/17 patients), but separate cessation rates were not provided.[72] GIB cessation was 82.0% (95% CI, 71.8%–89.1%; $I^2 = 0\%$) after SAVR and 64.2% (49.8%–76.5%; $I^2 = 69\%$) after TAVI ($P = 0.003$) (see Supplementary data online, *Figure S5*). The subgroup analysis on residual valve disease, which included two studies ($n = 58$ with; $n = 59$

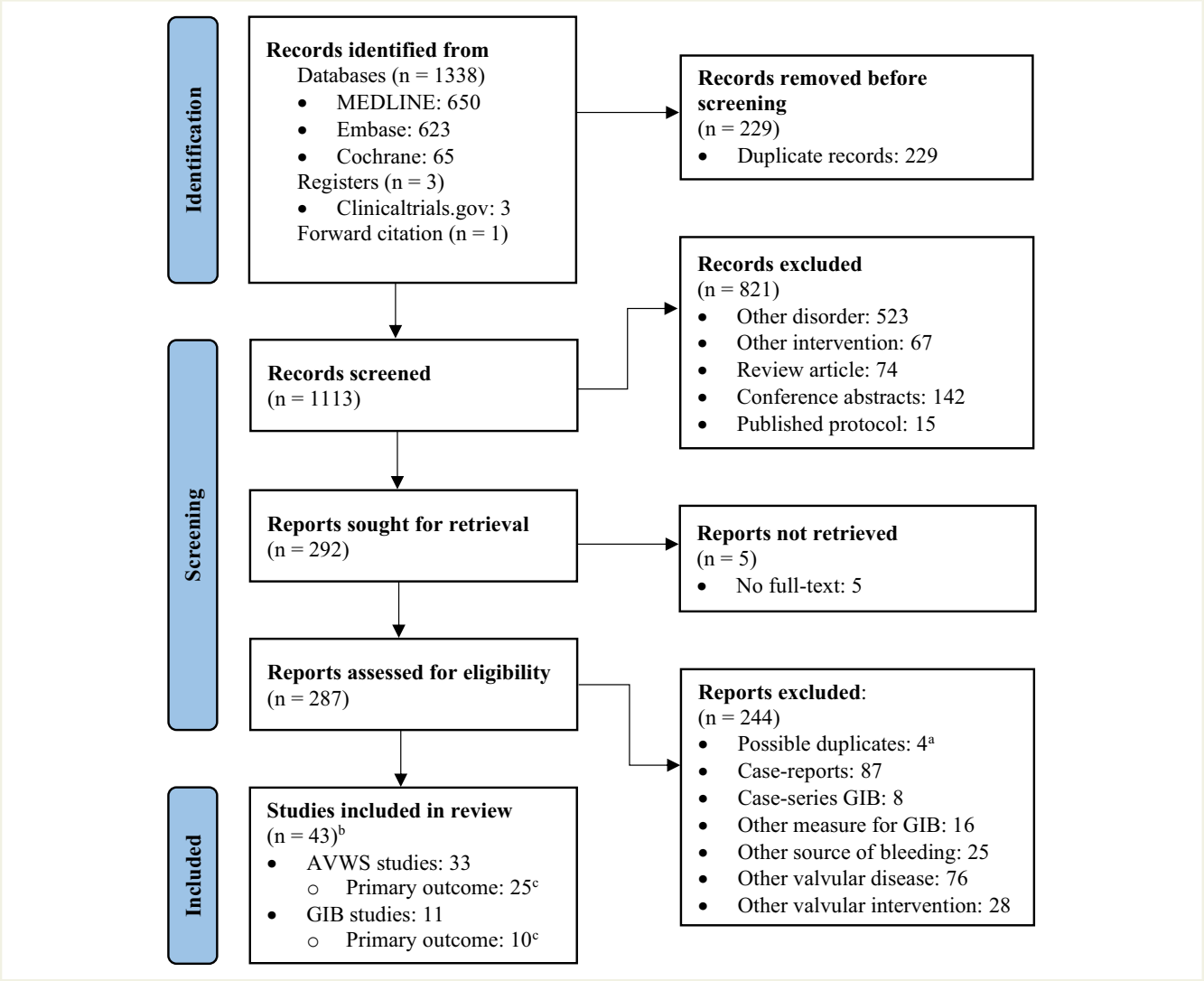


Figure 1 Flowchart of included studies. Adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses. *(A)* Studies were performed by the same research group and had an overlap in inclusion period and follow-up time with one or multiple included studies. *(B)* One study reported on both gastrointestinal bleeding and Acquired von Willebrand syndrome. *(C)* Studies reported on the primary outcome(s). GIB, gastrointestinal bleeding; AVWS, acquired von Willebrand syndrome.

without), resulted in an RR of 0.57 (0.40–0.81; $I^2 = 0\%$) to experience GIB cessation ($P = 0.002$) (see Supplementary data online, *Figure S6A*). The subgroup analysis on intensified antithrombotic regimen use, which included four studies ($n = 54$ with an intensified regimen; $n = 130$ with a restricted regimen), resulted in an RR of 0.94 (0.70–1.27; $I^2 = 19\%$) to experience GIB cessation ($P = 0.704$) (see Supplementary data online, *Figure S6B*). The subgroup analysis on angiodysplasia diagnosis is provided in Supplementary data online, *Figure S7*. In 5/10 studies, only patients with endoscopically confirmed angiodysplasias were included ($n = 199$), and 5/10 studies included confirmed and suspected cases ($n = 101$). Cessation rates did not differ significantly (72.9% vs. 80.8%; $P = 0.405$). The subgroup analyses on studies with ≥10 patients, which included 6/10 studies ($n = 277$), showed no significant difference in cessation rates (see Supplementary data online, *Figure S8A*). Subgroup analyses on studies with an overall low risk of bias, which included 4/10 studies ($n = 246$), showed a significant difference in cessation rates compared with studies with a moderate risk of bias (68.0% vs. 81.1%; $P = 0.017$) (see Supplementary data online, *Figure S8B*).

Secondary outcomes

Differences in haemostasis indices

All 33 studies on AVWS reported on haemostasis indices before and after AVR. Ten studies reported on vWF-HMWM levels, and all showed an increase within 5 min after valve replacement (see Supplementary data online, *Table S6*). Ten studies reported on the vWF:Ac/vWF:Ag or vWF:CB/vWF:Ag ratio, and all showed an increase after AVR. Two studies measured both vWF:Ac/vWF:Ag and vWF:CB/vWF:Ag and reported a significant rise in vWF:Ac/vWF:Ag, but not in vWF:CB/vWF:Ag, in which baseline levels were higher.[42,46] Eight studies reported on CT-ADP or bleeding time, and all showed a decrease after AVR. Two studies performed a subgroup analysis, including those without antiplatelet therapy. Both reported shortened CT-ADP values before AVR.[38,46] Two studies reported on vWF-HMWM, vWF:CB/vWF:Ag, and CT-ADP, and both found a more pronounced difference in values after AVR measured through vWF-HMWM.[44,46] Three studies reported on ADAMTS13. Two measured reduced levels early after

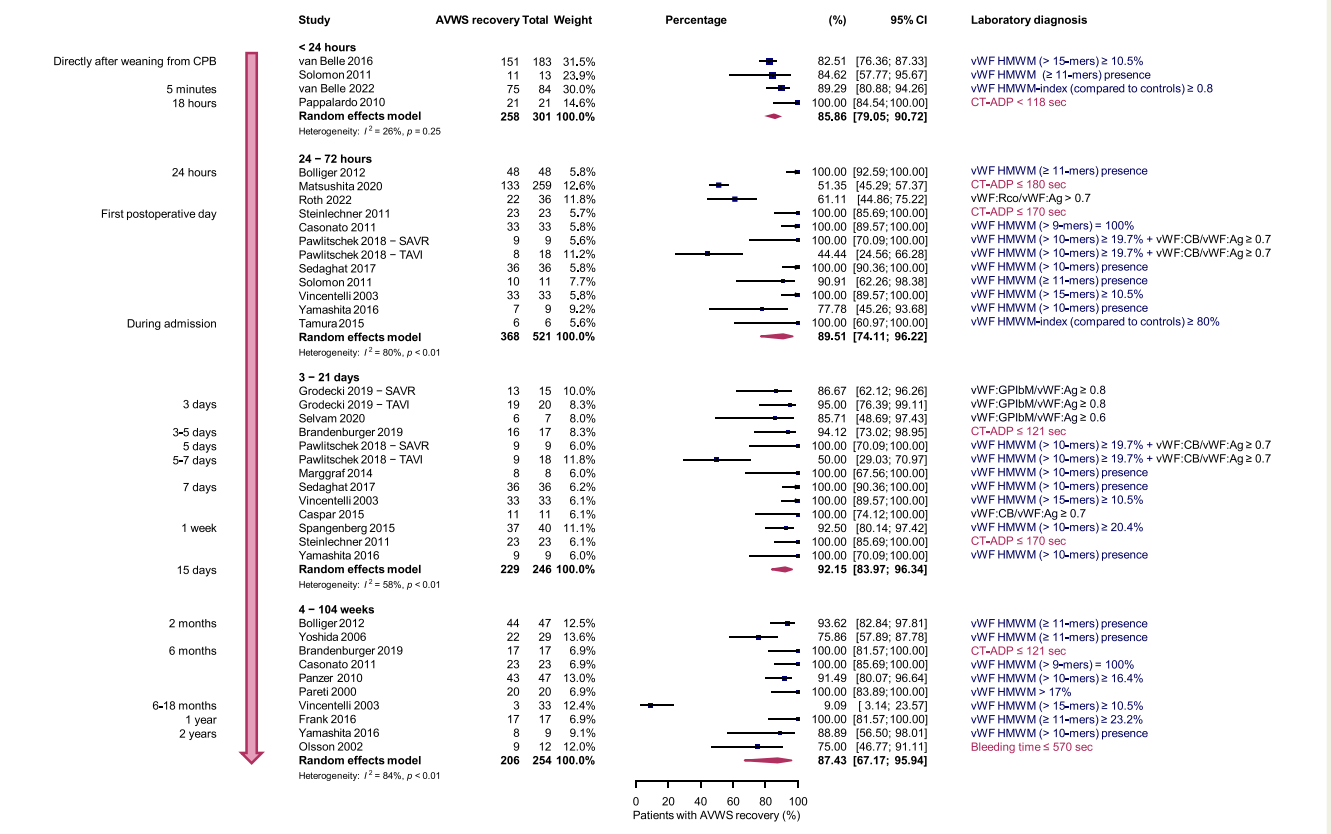


Figure 2 Forest plot on acquired von Willebrand syndrome recovery. Plot shows the proportion of patients with recovery of acquired von Willebrand syndrome after aortic valve replacement. Studies are sorted by follow-up time. Recovery of acquired von Willebrand syndrome is divided into four separate time frames. For studies that analysed recovery of acquired von Willebrand syndrome with multiple laboratory studies, the von Willebrand factor multimer distribution was selected. If not provided, von Willebrand factor ratio normalization was selected over closure time adenosine diphosphate/bleeding time. AVWS, acquired von Willebrand syndrome; vWF, von Willebrand factor; CT-ADP, closure time adenosine diphosphate.

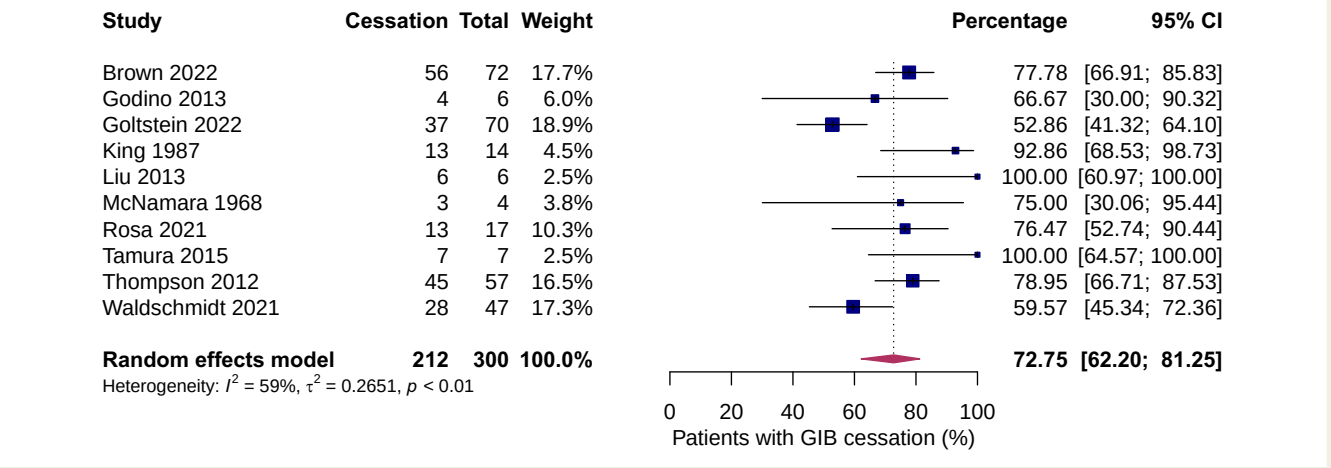


Figure 3 Forest plot on gastrointestinal bleeding cessation. Plot shows the proportion of patients with complete cessation of gastrointestinal bleeding after aortic valve replacement. GIB, gastrointestinal bleeding.

AVR, and two measured above baseline levels between 3 weeks and 6 months.[39,57,62] Fifteen studies reported on platelet levels and thrombogenic activity, which were decreased up to 1 week after AVR. One study reported on Heyde patients with GIB and AVWS, which were both resolved in all six patients after SAVR (see Supplementary data online, *Table S6*).[6]

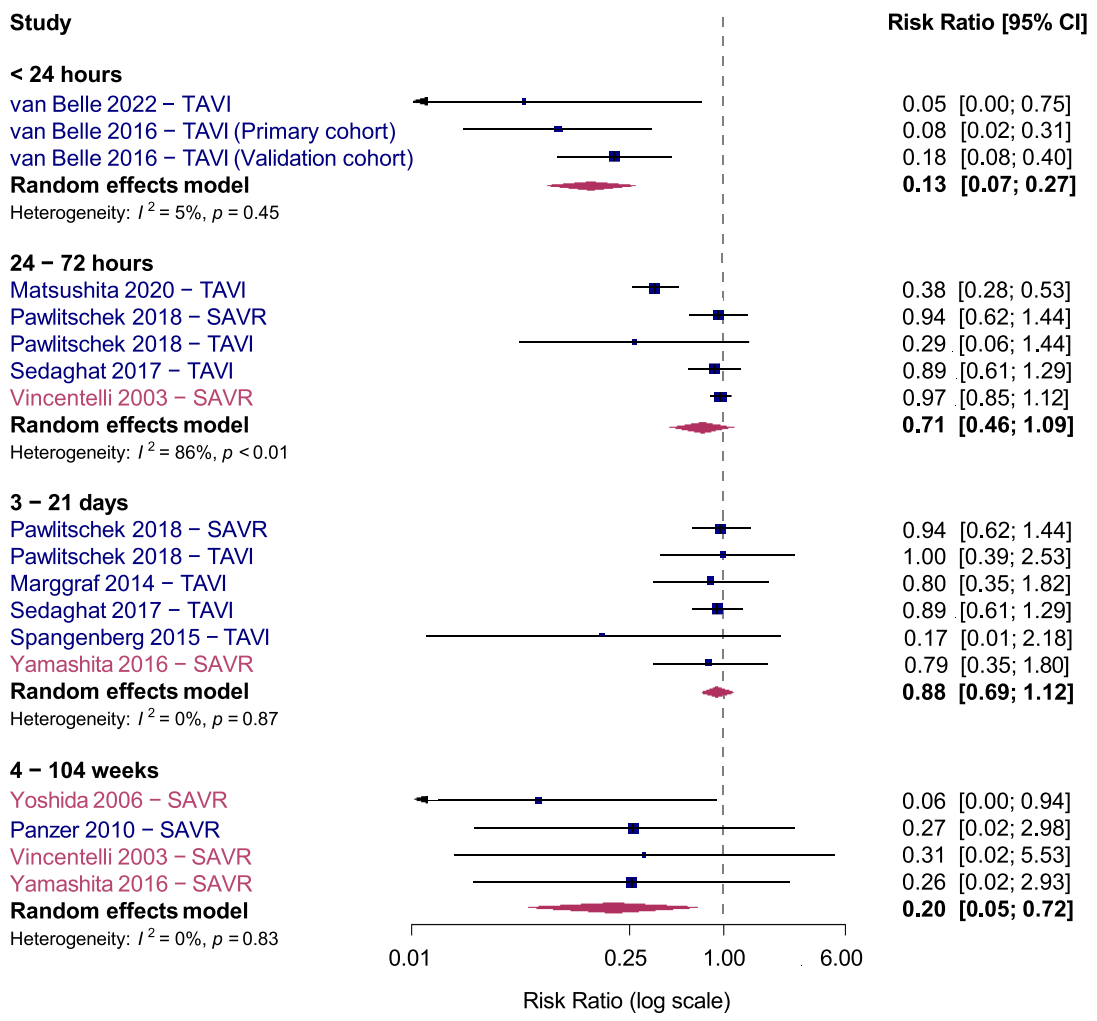


Figure 4 Forest plot on the influence of residual aortic valve disease on acquired von Willebrand syndrome recovery. Plots show the risk ratios of patients with a patient–prosthesis mismatch, in purple, or paravalvular leakage, in blue, to recover from acquired von Willebrand syndrome compared with patients without residual valve disease during four time frames after aortic valve replacement. Three studies looked at the influence of patient–prosthesis mismatch, which was defined as an effective orifice area of <0.8,[10] or <0.85 cm^2/m^2 [62,63] of body surface area. Eight studies looked at the influence of paravalvular leakage, which was mostly defined as >mild or as a circumferential extent of aortic regurgitation >10% measured with transthoracic echocardiography.[38,46,51,56,59,66] One study defined paravalvular leakage as trace to severe.[54] One study defined paravalvular leakage as significant.[47]

Periprocedural bleeding

Fourteen of 33 studies reported on AVWS and periprocedural bleeding. Overall, 6/14 studies found a significant association between periprocedural bleeding rates or blood loss and AVWS, while 8/14 did not (see Supplementary data online, *Table S7*). Five studies included a control group ($n = 273$ patients; $n = 704$ controls). The risk of periprocedural bleeding was greater in patients with AVWS compared with controls (RR 1.97; 0.92–4.22; $I^2 = 50\%$) ($P = 0.081$). One study included patients with AVWS 24 h after TAVI instead of AVWS at baseline ($n = 126$ patients; $n = 439$ controls) with an RR of 1.56 (1.06–2.29) (*Figure 5*).[47]

Four of 11 studies on GIB looked at the rate of periprocedural bleeding; one exclusively reporting on periprocedural GIB (see Supplementary data online, *Table S7*).[73] Two studies compared periprocedural bleeding with a control group ($n = 117$ patients; $n = 353$ controls). The risk of periprocedural bleeding was greater in patients with angiodysplasias compared with controls (RR 1.91; 1.34–2.71; $I^2 = 0\%$) ($P = 0.001$). Three studies compared periprocedural GIB with a control group ($n = 1122$ patients; $n = 213268$ controls). The risk of periprocedural GIB was greater in patients than in controls (RR 7.32; 3.50–15.29; $I^2 = 62\%$) ($P < 0.001$) (*Figure 5*).

Discussion

This meta-analysis on patients with Heyde syndrome shows that AVR is associated with recovery of AVWS and cessation of GIB in 87% and 73%, respectively (*Graphical Abstract*). The VWF levels increase within minutes after valve replacement, and full recovery is established in

86% of patients within 24 h. Maximum recovery is reached within 3 days after SAVR (95%), while it takes 3–7 days after TAVI (91%). Over 3 weeks after AVR, recovery rates fell slightly to 87%. Complete GIB cessation occurred in 82% after SAVR and 64% after TAVI. Residual aortic valve disease negatively impacted the recovery of AVWS and GIB, while antithrombotic regimen did not influence GIB cessation. Periprocedural bleeding was more frequent in Heyde patients and was mainly of gastrointestinal origin.

Heyde syndrome was first recognized in 1958 when a paper reported on 10 patients with unexplained GIB and AS.[1] In 1992, it was suggested that AVWS connects both disorders.[7] Ultra-large vWF propeptide is produced and stored in endothelial cells before being released into the plasma. In patients with AS, high shear stress around the stenotic valve causes vWF to unfold. This enables ADAMTS13 to cleave the protein into various sizes, of which only the larger multimers are haemostatically active.[8,74] The VWF-HMWM and propeptide levels negatively correlate with the valve gradient.[34,39] After AVR, inordinate proteolysis is immediately terminated, which eventually results in AVWS recovery. Interestingly, we found that recovery instantly followed AVR and was already achieved in 85.9% (95% CI, 79.1%–90.7%) of patients within 24 h (T1). The rapid recovery of AVWS after AVR has been attributed to the release of vWF propeptide from endothelial storage pools, as ultra-large multimers are present in the first days to weeks after AVR.[33,34,41,57,62] There are two theories on the release of stored vWF: (i) the change from pathological to physiological shear stress instigates propeptide release; and (ii) the release is secondary to endothelial damage. The first theory was based on the finding that a sudden increase in pulse pressure causes a rise in vWF levels.[75] Supporting the second theory, vWF levels have been reported to increase more rapidly after SAVR with mechanical compared with biological valves and after transapical compared with transfemoral TAVI.[13,46] The AVWS recovery further increased to 89.5% (74.1%–96.2%) after 72 h (T2), reaching a maximum of 92.2% (84.0%–96.3%) after 21 days (T3). Over 3 weeks after AVR (T4), the AVWS recovery rate fell slightly to 87.4% (67.2%–95.9%). This finding could be coincidental, although unlikely, as three studies determined AVWS recovery at multiple time points and reported higher recovery rates earlier after AVR.[10,12,62] The reappearance of AVWS indicates that inordinate proteolysis of vWF-HMWM reoccurs in a subgroup of patients. Prosthesis degeneration would again lead to high shear stress but usually does not arise within the first years after AVR.[76] Alternatively, decreased proteolysis could also occur in a continuous state of high shear stress. Endothelial dysfunction is known to decrease ADAMTS13 activity.[77] Correspondingly, studies that measured ADAMTS13 reported decreased levels in the first days till weeks after AVR.[39,57,62]

Initial studies on the efficacy of AVR to resolve Heyde syndrome were solely based on SAVR. At the beginning of the 21st century, TAVI became available for patients at increased or prohibitive surgical risk, and nowadays, indications are still expanding. Few studies on AVWS have compared both types of AVR with varying results.[43,45,54] We found that AVWS recovery rates were higher after SAVR compared with TAVI at T1 (91.5% vs. 85.2%) and T2 (95.0% vs. 52.7%). Rates did not differ at T3 (93.9% vs. 91.1%). The early difference between both procedures indicates that vWF propeptide release is less noticeable after TAVI, either because of continuous high shear stress or less endothelial damage. Supporting the latter, lower AVWS recovery rates have been reported after TAVI compared with SAVR, which was unrelated to shear stress.[54] Endothelial damage would also elucidate the similarity in outcomes after 3 days, when vWF-HMWM had the chance to replenish, and the low heterogeneity levels of SAVR studies up to T4.[78] Nevertheless, continuous high shear stress plays a pivotal role in AVWS recovery. We found that patients with residual valve disease were less likely to experience AVWS recovery at every time point (RR 0.13 at T1, 0.71 at T2, 0.88 at T3, and 0.20 at T4), which is in line with previous literature, showing that vWF-HMWM and CT-ADP levels could be used to monitor aortic regurgitation during TAVI.[33,38] Again, endothelial damage would explain why T2 and T3 subgroup results were non-significant, as T1 data were solely derived from TAVI studies, and T4 data would no longer be influenced. Unfortunately, there were no TAVI studies with a follow-up longer than 1 week to see if results from both procedures remained comparable without discolouration from endothelial damage.[62] Regardless, results could also be incidental, as no large studies with sufficient follow-up directly compared SAVR with TAVI. Patient and procedural characteristics (including valve type and access site) and diagnostic criteria for AVWS varied greatly, resulting in a low certainty of evidence.

The GIB in Heyde syndrome was denoted idiopathic until 1974 when it was observed that vascular malformations cause bleeding in AS.[79] With the emergence of small bowel assessment in the early 2000s, more cases were confirmed.[22] Although a hallmark of Heyde syndrome, it is not precisely known why the bleeding diathesis in AVWS mainly manifests itself in angiodysplasia-related GIB.[19] A direct causal link is suspected, as angiodysplasias, incidentally found in 1%–5% of the general population, have been reported in 30%–60% of patients with left ventricular assist devices.[2,80] Similar to AS, left ventricular assist devices-induced shear stress causes AVWS.[80] AVWS enhances angiogenesis, which contributes to angiodysplasia formation.[2,81] We found that 72.8% of patients experienced complete GIB cessation after AVR, which was sustained for at least 1–10 years. The results of AVR outperform those of conventional treatment options, raising the question whether valve replacement should be performed solely for GIB in the context of Heyde syndrome.[3,19,69] Cessation rates were higher after SAVR than TAVI (82% vs. 64%). Since AVWS recovers sooner after SAVR, this difference could be partially related to early bleeding. Correspondingly, we previously reported that 13% of Heyde patients exclusively experienced periprocedural GIB after TAVI.[69] Still, studies that compared both procedures at long-term follow-up also found that GIB was less frequent after SAVR.[82] The difference in rebleeding could also be related to the higher prevalence of residual aortic valve disease after TAVI, as patients with PVL were less likely to experience GIB cessation (RR 0.57).[83] Supporting this theory, PVL has been associated with late bleeding events after AVR.[35] We did not find a difference in GIB cessation between patients on an intensified and restricted antithrombotic regimen after AVR (RR 0.94), suggesting that the bleeding diathesis of AVWS outweighs that of antithrombotics. Moreover, as AVWS recovery halts angiogenesis, angiodysplasias have been described to fade in the months following AVR.[84] The influence of antithrombotics on GIB could decrease over time. Interestingly, compared with antiplatelet therapy, rivaroxaban but not apixaban induces a surplus of bleeding complications after AVR.[85–87] From all oral anticoagulant drugs, rivaroxaban causes the highest GIB rate and apixaban the lowest.[88] Personalized antithrombotic regimens might be warranted for those with angiodysplasias and residual valve disease.[89] Of note, results from subgroup analyses could also be incidental, as the type of procedure and antithrombotic regimen started after AVR are not randomly selected, resulting in a low certainty of evidence.

Periprocedural bleeding is a frequent complication of AVR and increases morbidity and mortality.[90] AVWS has been suggested to cause the high rate of periprocedural bleeding, but results are conflicting.[19,56,59] This might be related to the rapid onset of AVWS recovery, as one study measured

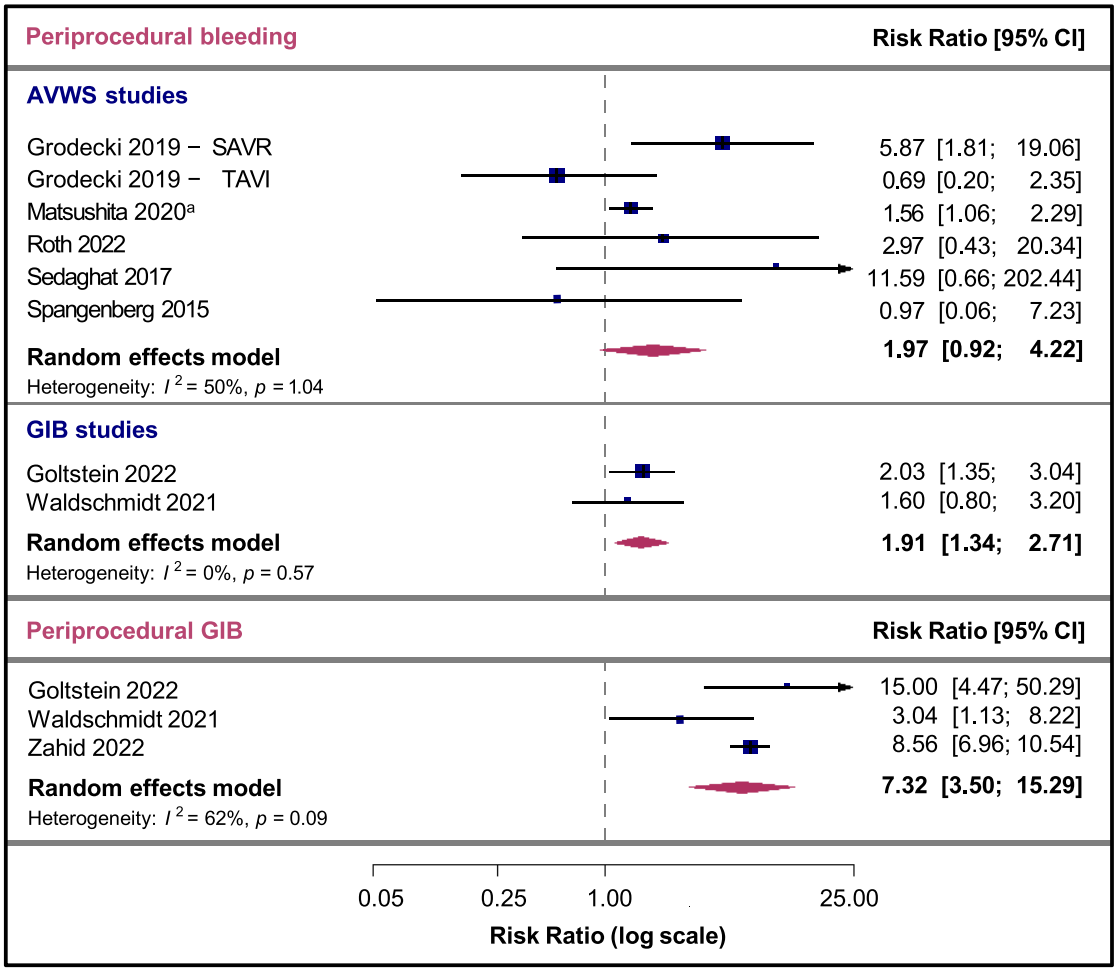


Figure 5 Forest plot on periprocedural bleeding in Heyde syndrome. Plots show the risk ratios of patients with Heyde syndrome to experience periprocedural bleeding and periprocedural gastrointestinal bleeding in comparison to non-Heyde patients (controls). Heyde syndrome consisted of severe aortic stenosis and acquired von Willebrand syndrome (top) or gastrointestinal bleeding (middle and bottom). Periprocedural bleeding was defined as in-hospital access- or non-access-related bleeding. Two studies limited bleeding to ≤24[47] and ≤72 h[69] after AVR, respectively. Bleeding was scored according to BARC[69] or VARC-2 (some excluding minor[5,45,47,56] or minor and major[59] bleeding). GIB, gastrointestinal bleeding

CT-ADP levels 24 h after TAVI rather than before and reported a significant relationship between AVWS and bleeding.[47] Nevertheless, desmopressin administration directly before AVR, which induces the release of vWF propeptide, has been shown to reduce post-operative blood loss.[60,74] We found a trend towards higher periprocedural bleeding rates in Heyde patients with AVWS compared with non-Heyde patients (RR 1.97; 0.92–4.22). Periprocedural bleeding was also more common in Heyde patients with angiodysplasias (RR 1.91; 1.34–2.71) and primarily consisted of periprocedural GIB (RR 7.32; 3.50–15.29). Several case reports describe cessation of periprocedural GIB following desmopressin administration.[23] In addition, Heyde patients have been successfully treated with anti-angiogenic drugs before AVR to prevent bleeding.[23,91] Apart from AVWS, platelet levels and vWF-independent platelet activity were also decreased up to 1 week after AVR, indicating that multiple periprocedural haemostasis disorders might contribute to the high bleeding rate.[19,43,49] Recent guidelines recommend optimizing antithrombotic therapy peri- and post-AVR based on individual bleeding risks.[92]

A strength of our study is that we used proportions of recovery instead of laboratory values as our primary outcome, allowing us to pool data and perform extensive subgroup analyses. Furthermore, we performed a comprehensive search in which we included all items of Heyde syndrome. This study also has several limitations. First, as AVWS is challenging to diagnose, methods and criteria varied between studies.[93] The concentration of vWF:Ag is elevated in patients with AS due to endothelial dysfunction, making diagnosis through vWF ratios less reliable.[46,94] The CT-ADP is not specific for vWF, being modestly influenced by antiplatelet therapy, among others.[95] Therefore, vWF-HMWM is the gold standard, although laborious and requiring expertise.[44] While our subgroup analyses on diagnostic tests did not show any significant differences, the margin of error in all diagnostics could have influenced results. An additive effect of using multiple diagnostic tests should be explored.[44,54,60] Second, we found evidence of publication bias for AVWS studies, which implies an exaggeration of the reported effect size. Third, GIB in Heyde patients was not always confirmed by endoscopy. Small bowel assessment has the highest diagnostic yield in Heyde syndrome but is not part of routine clinical workup.[24] Only including confirmed cases could cause a selection bias based on bleeding severity.[69] However, inclusion of suspected cases could

lead to incorrect results. Nevertheless, we did not find a significant difference in GIB cessation rates between studies that included and excluded suspected cases. Fourth, periprocedural GIB due to oesophageal lesions is not uncommon after AVR, which could have caused an underestimation of the proportion of patients with angiodysplasia-related GIB cessation.[96] Finally, we found no TAVI studies on AVWS with a follow-up longer than 1 week, and there were no studies that directly linked rebleeding of angiodysplasias to AVWS, stressing the need for further research.

In conclusion, the bleeding diathesis in Heyde syndrome recovers in most patients within days after AVR, and patients often experience complete cessation of GIB. Nonetheless, Heyde patients could be at increased risk for periprocedural bleeding. Large prospective studies with adequate follow-up time are required to better understand the influence of AVWS on angiodysplasia-related GIB, confirm the negative influence of residual valve disease on recovery, and establish if Heyde syndrome is indeed related to periprocedural bleeding and associated negative outcomes, justifying preventive treatment.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

The data underlying this article are available in the article and in its online *supplementary material*. The complete datasets and statistical analysis plan will be shared on reasonable request to the corresponding author.

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Ethical Approval

Ethical approval was not required.

Pre-registered Clinical Trial Number

The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) by the National Institute for Health Research (NIHR). PROSPERO 2020 CRD42020207268. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020207268

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