Preoperative Anemia and Postoperative Mortality in Patients with Aortic Stenosis Treated with Transcatheter Aortic Valve Implantation (TAVI): A Systematic Review and Meta-Analysis

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Background: Patients with severe aortic stenosis who have comorbidities that prevent general anesthesia and open cardiothoracic surgery are candidates for transcatheter aortic valve implantation (TAVI). However, TAVI can result in patient mortality following the procedure. This systematic review of the literature and meta-analysis aimed to determine the relationship between preoperative anemia and postoperative mortality in patients following TAVI.

Material/Methods: PubMed, EMBASE, the Cochrane Library, and the Web of Science were systematically searched from their inception to February 2019 for relevant published studies that included patients with bicuspid aortic valve stenosis and tricuspid aortic valve stenosis who underwent TAVI and who had preoperative data on hemoglobin levels. The pooled odds ratios (OR) and 95% confidence interval (CI) were calculated using a random-effects generic inverse variance method.

Results: Six published studies that involved 6,406 patients with aortic stenosis were included in the meta-analysis. There was no significant difference observed for the final pooled result for patients with and without anemia for the short-term 30-day postoperative mortality (OR, 1.34; 95% CI, 0.77–2.35). However, long-term mortality rates were significantly worse in patients with preoperative anemia compared with those without anemia (OR, 1.77; 95% CI, 1.34–2.35).

Conclusions: Systematic review of the literature and meta-analysis showed that pre-procedural anemia reduced long-term mortality following TAVI. This finding supports the need to correct preoperative anemia in patients with aortic stenosis to improve patient outcome following TAVI.

MeSH Keywords: Anemia • Aortic Valve Stenosis • Hospital Mortality

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META-ANALYSIS

Background

With the global aging population, the incidence of degenerative cardiac valvular disease in the elderly is increasing, and aortic stenosis has gradually become the most common type of valvular heart disease in this population [1,2]. Surgical aortic valve replacement (SAVR) was once the only treatment for severe aortic stenosis, but it was often contraindicated in elderly patients because of their age, the severity of aortic stenosis, and comorbidities [3]. Data from developed countries have shown that about one-third of patients with severe aortic stenosis are unable to undergo surgical thoracotomy because of their high surgical risk, or because of contraindications to surgery and anesthesia [4-5].

Transcatheter aortic valve implantation (TAVI) was first used in 2002 and is now used routinely as an effective treatment for patients with contraindications for cardiac surgery. In 2017, updated guidelines for the management of patients with valvular heart disease recommended that TAVI is a reasonable alternative to surgical aortic valve replacement (SAVR) for symptomatic patients with severe aortic stenosis (Stage D) who have an intermediate surgical risk, depending on patient-specific procedural risks, cardiac function, and patient preferences [6]. Furthermore, TAVI is associated with a significant survival benefit throughout during 2-year follow-up compared with SAVR for the treatment of severe aortic stenosis [7]. However, it has previously been shown that in low-risk and intermediate-risk patients, TAVI carries higher rates of vascular complications when compared with SAVR [8]. Recent studies have also shown that TAVI can reduce the mortality rate by 46% and significantly improve the quality of life in patients with severe aortic stenosis who tolerate SAVR [9-11].

During the procedure for TAVI, the artificial heart valve is delivered to the aortic valve through the femoral artery route and undergoes artificial valve implantation to restore the function of the aortic valve [12,13]. The TAVI procedure does not require a thoracotomy, there is minimal trauma, and recovery is rapid. However, interventional surgery is complex and requires the cooperation of cardiology, cardiac surgery, medical imaging, anesthesiology, and intensive care department to make a thorough diagnosis and treatment plan in advance. Diabetes mellitus, renal dysfunction, and fracture have been reported to be risk factors for reduced outcome in patients with TAVI [14-16]. Patients who have aortic stenosis may have chronic anemia, and there have been some small studies that have shown that anemia may also be a poor prognostic factor for outcome following TAVI [17]. Therefore, this systematic review of the literature and meta-analysis aimed to determine the relationship between preoperative anemia and postoperative mortality in patients following TAVI.

Material and Methods

Systematic review and meta-analysis protocol

The systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table 1) [18].

Literature search

A systematic review of the literature was performed for all clinical studies published before February 2019 that evaluated the association between anemia and the clinical outcome following transcatheter aortic valve implantation (TAVI). Retrieval databases included PubMed, EMBASE, the Cochrane Library, and the Web of Science. The searched combination of keywords included: anemia OR anaemia OR hemoglobin AND transcatheter aortic valve implantation OR aortic valve replacement OR transcatheter aortic valve replacement OR TAVI OR TAVR. The studies selected included only those published in the English language. References were consulted to increase the number of published studies retrieved.

Inclusion and exclusion criteria for the systematic review of the literature

Published studies were included if they met the criteria of involving adult patients with aortic stenosis who underwent successful TAVI. Patients with anemia or without anemia were required to be clearly identified in the methods section of the publication, and the definition of anemia was required to be clearly given. Prospective or retrospective studies that analyzed the association between anemia and the short-term and long-term prognosis were included and postoperative mortality was the main outcome measured.

The exclusion criteria included the inability to extract data or failure to find the full text of the literature. High-quality or the most recently published study from the same author or research team were chosen when duplicate publications were identified. Review articles, correspondence, comments, letters, practice guidelines, case reports, and editorials were excluded.

Data collection and quality evaluation

Two reviewers independently read the title, abstract, and full text of the publication. Risk of bias of data extraction and evaluation included in the study was cross-checked. In case of disagreement, the two reviewers discussed the publication with a third reviewer to reach consensus. In some cases, the lack of key data was clarified by email and telephone contact with the original author. The content extracted from the publications included the first author, year of publication, sample size, patient age, and gender. Baseline characteristics and
Table 1. Characteristics of the systematic review of the literature for studies on preoperative anemia and postoperative mortality in patients with aortic stenosis treated with transcatheter aortic valve implantation (TAVI).

| Authors                     | No. of patients/ patients with anemia (%) | Age (years) | Definitions of Anemia | Mean/peak gradient (mmHg) | Aortic valve area (cm²) | Main outcomes | Adjusted factors | Duration of follow-up | NOS score |
|-----------------------------|-------------------------------------------|-------------|------------------------|---------------------------|-------------------------|---------------|-------------------|----------------------|-----------|
| Rheude et al. (2017) [24]   | 549/45%                                   | 81±6        | Hb level <12 g/dl in women, <13 g/dl in male | 44±16/71±24              | 0.73±0.21               | 1-year mortality | Age, EF, mean aortic gradient, EuroScore, renal function, AF, MI, PCI | 1 year | ********* |
| Seiffert et al. (2017) [25] | 1210/59%                                  | 82±5        | Hb level <12 g/dl in women, <13 g/dl in men | NA/NA                    | NA                      | 30-day mortality | Periprocedural variable including MI, stroke, AKI, transfusion, access, bleeding, AF | 3 years | ********* |
| Hellhammer et al. (2016) [26] | 376/63%                                   | 81±6.1      | Hb level <12 g/dl in women, <13 g/dl in male | NA/NA                    | 0.73±0.2                | 30-day mortality | NA                  | 30 days | ********* |
| Arai et al. (2015) [27]     | 2137/62% (Moderate to severe anemia)      | 82.7±7.7    | Mild, moderate, and severe anemia | 48.2±16.5/NA             | 0.67±0.18               | 1-year mortality | COPD, BMI, age, pulmonary hypertension, EF, AF, EuroSCORE, Drop in Hb, bleeding | 1 year | ********* |
| De Larochelliere et al. (2015) [28] | 438/64%                                | 79±8        | Hb level <12 g/dl in women, <13 g/dl in male | 41±16/67±25              | 0.64                     | 30-day mortality | 1-year mortality | NA                  | 1 year | ********* |
| Nuis et al. (2013) [29]     | 1696/57%                                  | 81±7        | Hb level <12 g/dl in women, <13 g/dl in male | NA/72±25                 | 0.68±0.20               | 30-day mortality | AKI, AF, post-operative AR, gender, malignancy, PAD, transfusion, EF, BMI, EuroSCORE | 1 year | ********* |

Hb – hemoglobin; COPD – chronic obstructive pulmonary disease; BMI – body mass index EF – ejection fraction; AF – atrial fibrillation; AKI – acute kidney injury; MI – myocardial infarction; PAD – peripheral arterial disease; PCI – percutaneous coronary intervention; NOS – Newcastle-Ottawa Scale (NOS); NA – not available.

Variables for data extraction and analysis included authors, countries, study design, number of patients with or without anemia, patient age, definitions of anemia, the mean and peak gradient of the aortic pressure, aortic valve area, the main

intervention measures of the study subjects were recorded, study type and key elements of bias analysis and evaluation, and outcome indicators and outcome measurement data were recorded. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies [20].
outcomes, adjusting factors, follow-up duration, and NOS score for the study quality assessment in each study.

Definitions

Anemia was defined with a gender-specific cut-off value in various studies. The main outcome assessments were the short-term postoperative mortality and the long-term postoperative mortality. Short-term postoperative mortality was defined as death within one month following TAVI. Long-term postoperative mortality was defined as death from any cause within one year later following TAVI.

Statistical methods

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) software version 2.0 [21]. Firstly, study heterogeneity was tested by a formal Q statistical test and $I^2$ statistical test (test level=0.1). If there was a P-value $>0.1$ and $I^2 <50\%$, this showed that the included studies were homogeneous [19]. Meta-analysis was performed using the Mantel-Haenszel fixed effects model. If there was heterogeneity between the studies, after excluding the influence of obvious causes of heterogeneity, the DerSimonian and Laird random-effects model was used for meta-analysis. Subgroup analysis, sensitivity analysis, or descriptive analysis was used for the studies with apparent heterogeneity, [22,23]. The pooled odds ratio (OR) with a 95% confidence interval (CI) were selected for combined statistics. The test level of the meta-analysis was $\alpha=0.05$. Publication bias was assessed by the asymmetry of the funnel plots. Begg’s test and Egger’s test were also performed to determine the presence of publication bias.

Results

Selection of publications from the systematic review of the literature

Figure 1 shows the flow diagram of the systematic review of the published literature. Initially, we retrieved 298 publications from the databases using the relevant search terms and search strategies, of which seven publications were manually retrieved. After removing 163 duplicated publications in the major databases, we screened the titles and abstracts of the remaining 142 publications. There were then 107 publications with unrelated or incomplete data that were excluded. We downloaded and reviewed the remaining 35 publications as full text, but 28 publications that did not meet the inclusion criteria were subsequently excluded. Finally, six studies [24–29] were included in the meta-analysis that included 6,406 patients with aortic stenosis who underwent transcatheter aortic valve implantation (TAVI).

Baseline characteristics

Table 1 shows the baseline characteristics of the six identified studies published from 2013 to 2017. Overall, patients with anemia accounted for 45–64% of the patients in the included studies. Anemia was defined as a hemoglobin level of $<12$ g/dl for women and hemoglobin of $<13$ g/dl in men. The mean peak gradient of the aortic pressure through the aortic valve were also identified. Adjusted factors were age, ejection fraction (EF), mean aortic gradient, renal function, atrial fibrillation (AF), myocardial infarction (MI), and percutaneous coronary intervention (PCI). Hellhammer et al. reported the 30-day mortality [26], while Seiffert et al. reported the most prolonged follow-up period for patient mortality, which was 3 years [25]. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included studies [20]. Selection (4 stars), comparability (2 stars), and outcome assessment (3 stars) were the three key points for scoring the studies. All study qualities were scored as medium to high.

Meta-analysis of short-term mortality following TAVI

Postoperative 30-day mortality was defined as the short-term prognostic outcome for the preoperative anemia status for patients undergoing TAVI. Figure 2 shows four studies reported the short-term analysis. Non-significant difference was observed for the final pooled result in patients with and without

![Flow diagram of the systematic review of the published literature](https://example.com/flow_diagram.png)
Preoperative anemia was associated with worse long-term survival (Figure 3B), and the pooled adjusted OR was 1.43 (95% CI, 1.22–1.69; P=0.052). Using the random-effects model, when we used the values in the adjusted analysis from each study, the pooled OR still indicated a significantly reduced mortality rate in patients with preoperative anemia compared with those without anemia (OR, 1.34; 95% CI, 0.77–2.35; P=0.30; I²=73%) using the random-effects model.

### Meta-analysis of long-term mortality following TAVI

For the long-term outcomes, we pooled the results in the unadjusted and adjusted outcomes to investigate the final effects of anemia on patient prognosis. Figure 3A shows that there was a significantly reduced mortality rate in patients with preoperative anemia compared with those without anemia as a comorbidity (OR, 1.77; 95% CI, 1.34–2.35; P=0.00; I²=73%) using the random-effects model. When we used the values in the adjusted analysis from each study, the pooled OR still indicated that anemia was associated with worse long-term survival (Figure 3B), and the pooled adjusted OR was 1.43 (95% CI, 1.22–1.69; P=0.00; I²=33%) in the random-effects model.

### Publication bias

Figure 4A shows the shape of the funnel plot for the association between preoperative anemia and short-term postoperative mortality. The P-values for Begg’s and Egger’s tests were 0.497 and 0.934, respectively, which indicated no publication bias. As for the long-term outcomes, no significant bias was observed (Figure 4B) (Begg’s test, P=0.174; Egger’s test P=0.070).

### Discussion

The results of this systematic review of the published literature and meta-analysis showed that although anemia was not a risk factor for short-term mortality within 30 days following transcatheter aortic valve implantation (TAVI), the long-term mortality following TAVI was significantly associated with preoperative anemia status. The same conclusion was also consistent with the adjusted analysis when other potential confounding factors were excluded (Figure 3B). Therefore, anemia in patients with aortic stenosis before undergoing TAVI was associated with an increase in long-term mortality after the TAVI procedure.

Previous studies have shown that the degree of anemia is associated with the degree of severity of aortic stenosis, and anemia (OR, 1.34; 95% CI, 0.77–2.35; P=0.30; I²=74%) using the random-effects model.

### Meta-analysis of long-term mortality following TAVI

| Study name          | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---------------------|------------|-------------|-------------|---------|---------|
| A                   |            |             |             |         |         |
| Arai                | 1.440      | 1.176       | 1.764       | 3.525   | 0.000   |
| Nuis                | 1.694      | 1.352       | 2.122       | 4.587   | 0.000   |
| Rheude              | 5.288      | 2.489       | 11.234      | 4.332   | 0.000   |
| Seiffert            | 1.568      | 1.717       | 2.100       | 3.019   | 0.003   |
|                    | 1.771      | 1.335       | 2.349       | 3.963   | 0.000   |
| B                   |            |             |             |         |         |
| Arai                | 1.440      | 1.280       | 1.620       | 6.077   | 0.000   |
| Nuis                | 1.420      | 1.121       | 1.801       | 2.901   | 0.004   |
| Rheude              | 2.421      | 1.311       | 4.470       | 2.834   | 0.005   |
| Seiffert            | 1.130      | 0.789       | 1.617       | 0.667   | 0.505   |
|                    | 1.427      | 1.220       | 1.668       | 4.448   | 0.000   |

Figure 2. Forest plot shows the meta-analysis of the relationship between preoperative anemia and short-term postoperative mortality after transcatheter aortic valve implantation (TAVI).

Figure 3. Forest plot shows the meta-analysis of the relationship between preoperative anemia and long-term postoperative mortality (A) and in the adjusted method (B) following transcatheter aortic valve implantation (TAVI).
patients with severe aortic stenosis and severe anemia have a higher mortality rate [30,31]. Nagao et al. assessed the impact of anemia on cardiovascular and bleeding outcomes in 3,403 patients enrolled in the CURRENT aortic stenosis registry, and they found that moderate and/or severe anemia was associated with a significantly increased risk for this primary outcome measure as well as for major bleeding [32]. Therefore, improved management of anemia may lead to better clinical outcomes in patients treated for aortic stenosis. In the present study, most patients with TAVI had different degrees of anemia, and the prevalence of anemia in patients included in the study ranged from 45–64%. The mechanism for anemia may be coagulation dysfunction in patients with aortic stenosis, which may increase bleeding [32]. Also, pre-procedural and post-procedural anemia in TAVI patients is closely associated with acute renal injury and with increased 1-year mortality, as shown in the French Registry [27]. Preoperative anemia is also associated with poor aortic valve function after surgery, which increases the probability of patients returning to hospital for repeat treatment.

In our combined outcomes analysis, preoperative anemia was only associated with increased long-term mortality, but not with short-term mortality. These findings were also consistent with those from studies on traditional thoracotomy for surgical aortic valve replacement (SAVR), as anemia before thoracotomy was not associated with short-term mortality after SAVR [25]. In the present study, it was found that most of the follow-up times included in the adjusted long-term analysis were for more than one year. However, the only three-year follow-up study did not suggest that preoperative anemia was associated with increased long-term mortality after surgery [25]. Given that patients who undergo TAVI are a high-risk group, the long-term mortality rate should theoretically increase for patients with and without anemia, which might affect the analysis of the association between anemia and long-term life expectancy.

In the present study, from the published literature, it was not possible to find the exact mechanism to explain why preoperative anemia was associated with increased long-term mortality after TAVI. It was noted that for patients with severe anemia before TAVI, blood transfusion was often performed a few days before the start of the TAVI procedure [33], to ensure that patients could undergo the perioperative period smoothly with reduced postoperative complications, resulting in earlier discharge from hospital. However, blood transfusion may increase the risk of acute renal injury after surgery. Also, anemia is a risk factor for bone fracture, which is also a risk factor for patient mortality after TAVI [34]. Moderate anemia as a sign of poor prognosis after surgery has been confirmed in several large population studies [35–37].

This systematic review of the literature and meta-analysis had several limitations. The heterogeneity of the combined effect values was large, which was also evident in the meta-analysis of short-term mortality and unadjusted mortality. The number of identified publications that underwent meta-analysis was small, so there may have been publication bias. However, there were strict inclusion and exclusion criteria, and the definitions of anemia in the studies were consistent, and we combined the corrected adjusted values and excluded other risk factors, which may increase the validity of the study findings.

**Conclusions**

This systematic review of the literature and meta-analysis aimed to determine the relationship between preoperative anemia and postoperative mortality in patients following transcatheter aortic
valve implantation (TAVI). Preoperative anemia was associated with long-term mortality after TAVI, but not with short-term mortality. This finding supports the need to correct preoperative anemia in patients with aortic stenosis to improve patient outcome following TAVI. Future well-designed large-scale prospective clinical studies are required to validate these findings.

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Conflict of interest

None.