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The effect of diabetes mellitus on aortic valve stenosis and its treatment outcome: A meta-analysis review

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Abstract

BACKGROUND: Given the importance of diabetes mellitus (DM) and its role in the development of aortic valve stenosis (AVS), as well as its association with adverse outcomes after aortic valve replacement (AVR), the present meta analysis aimed to provide a comprehensive review of previous studies in this field.

METHODS: To achieve this objective, a thorough literature search was conducted in PUBMED/MEDLINE, ScienceDirect, CINAHL, EMBASE/SCOPUS, PsycINFO, ClinicalKey, the Cochrane Central Register of Controlled Trials (CENTRAL), ProQuest, Web of Science, and Persian databases such as SID and Magiran. The number of patients, gender ratio, mean age, prevalence of T2DM, AVS, and treatment outcomes after TAVI, TAVR, and SAVR (stroke, early and late mortality) were recorded.

RESULTS: This meta-analysis comprised 22 studies involving a total of 760,287 patients with AVS. The pooled prevalence of DM was approximately 31% (95% CI: 26–36%). DM was associated with a significantly higher risk of early mortality, including both in-hospital mortality (OR: 2.399) and 30-day mortality (OR: 1.45), compared with non-DM patients ($p<0.05$). However, the increase in late mortality (one year or longer) among DM patients was not statistically significant. Additionally, DM patients showed a significantly elevated risk of stroke compared with non-DM patients (OR: 1.15; 95% CI: 1.03–1.28; p=0.009).

CONCLUSION: Overall, DM appears to play a significant role in the development of AVS and is associated with adverse outcomes including mortality and stroke after AVR.

Keywords: Diabetes Mellitus; Aortic Stenosis; Stroke; Aortic Valve Replacement Surgery; Transcatheter Aortic Valve Implantation; Transcatheter Aortic Valve Replacement

Introduction

Type 2 diabetes mellitus (T2DM) is linked to numerous complications and an increased risk of death from cardiovascular diseases globally. A frequently occurring complication of diabetes mellitus (DM) is heart valvular disease[1,2].

Valvular diseases, especially calcified aortic valves with and without stenosis, are progressive conditions associated with increasing age and the presence of cardiovascular risk factors[3,4]. The literature has indicated that T2DM, after hypertension, is the second most common risk factor for aortic stenosis (AS) and can be significantly associated with the development of aortic valve stenosis (AVS)[5].

In histopathological evaluations, higher degrees of calcification have been reported in the aortic valves of DM patients compared with non-DM patients[6]. The effect of hyperlipidemia and hyperglycemia on aortic valve calcification results from a series of cellular and molecular alterations that progressively impair the structure and function of the valve. Valve endothelial cells (VECs), which constitute the first layer in direct contact with circulating blood, are particularly susceptible to hyperglycemia-induced injury. Elevated glucose levels promote oxidative stress, inflammation, and endothelial dysfunction. This dysfunction compromises the protective endothelial barrier, allowing harmful molecules such as oxidized LDL to penetrate the valvular tissue and initiate calcific pathways.

Valve interstitial cells (VICs), the predominant cell type within the valvular stroma, also undergo pathological changes when exposed to hyperlipidemia and inflammatory stimuli. Under these conditions, VICs differentiate into osteoblast-like cells, contributing to extracellular matrix stiffening, leaflet thickening, and progression of valvular calcification[7]. DM may also increase the risk of atherosclerosis due to its association with AS. Activation of the renin–angiotensin–aldosterone system, elevated inflammatory interleukins, generation of free radicals, and protein glycosylation result in enhanced profibrotic and calcific mechanisms contributing to aortic valve calcification and progression to AS[7-9].

Furthermore, patients with DM not only have an increased risk of developing AVS but also experience a higher incidence of recurrent stenosis, which rapidly progresses from mild to severe[10–12].

Currently, no medication exists that can reverse or slow the advancement of aortic valve calcification or halt AVS. Cardiovascular medications such as cholesterol-lowering agents (statins) and renin–angiotensin system inhibitors have been shown to be ineffective in hindering its progression[13–16].

Therefore, despite the similarity of risk factors associated with vascular and valvular calcification, different mechanisms may be involved in their development and progression. Consequently, AVS is classically managed by surgical aortic valve replacement (SAVR) or by less invasive procedures such as transcatheter aortic valve implantation or replacement (TAVI or TAVR)[17,18].

In addition, T2DM is strongly associated with poor in-hospital and short-term prognosis in patients with cardiovascular disease requiring surgical or invasive interventions. The literature has not fully clarified how T2DM may affect the outcomes of SAVR or TAVI[19–23].

Hence, considering the significance of DM and its role in the incidence, severity, and treatment outcomes of AVS and given the availability of numerous previous studies in this field a comprehensive review of these studies and a summary of their findings can be valuable for understanding the role of DM, improving approaches to AVS management, and enhancing the success of therapeutic interventions. For this purpose, the present study was conducted as a systematic review investigating the effect of T2DM on AVS and its treatment outcomes.

Materials and Methods

Protocol and Registration

The protocol of the current study was registered in the PROSPERO registration platform (Approval code: CRD420251046858). The Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) 2020 27-item checklist was employed for identifying, selecting, appraising, and synthesizing the selected studies[24].

Search Strategy and Study Selection

The search was conducted using keywords derived from the Medical Subject Headings (MeSH) database, as well as terms identified from previously published articles in this field, combined using the AND and OR operators. The search was performed using the keywords "Aortic Stenosis," "Calcified Aortic Valve," "Aortic Valve Calcification," "Aortic Valve Stenosis," "Aortic Calcification," "T2DM," "DM-2," "Diabetes," "Surgical Aortic Valve Replacement (SAVR)," "Trans-Catheter Aortic Valve Replacement or Implantation (TAVR or TAVI)," "Outcome," "Stroke," and "Mortality."

To access all published articles in this field, a complete and systematic search of texts published up to January 2025 was performed across the following databases: ScienceDirect, CINAHL, ClinicalKey, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE/SCOPUS, PUBMED/MEDLINE, PsycINFO, Web of Science, ProQuest, and Persian databases such as SID and Magiran.

All articles with full text or, when available, appropriate abstracts and conference abstracts were included in the screening.

The inclusion criteria comprised human studies on patients over 18 years of age; studies evaluating the effect of T2DM on AVS and the outcomes of related treatments; and all types of research studies written in English or Persian, including clinical trials, case series, and cross-sectional, cohort, and case-control studies. The exclusion criteria consisted of studies with non-randomized sample sizes and studies not reporting information required for analysis.

The search process was performed independently by two authors (A.M. and H.KH.), and their results were compared. A reference hand search of all articles was also conducted. The number of relevant articles extracted from each database was entered into EndNote X9 software, and a flowchart was generated. In the first step, unrelated and duplicate studies were removed under the supervision of the corresponding author by reviewing titles and abstracts. In the next step, the remaining articles were carefully evaluated and critiqued. Differences between the two researchers were discussed, and final inclusion was determined based on consensus.

Reviewing the Scientific Validity of Articles and Sources (Scoring Method)

A modified version of the STROBE checklist was utilized for assessing the quality of studies[25]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement provides a set of recommendations to improve the reporting of observational studies. Three chief types of observational studies case–control, cross-sectional, and cohort studies are addressed by STROBE. A 22-item checklist covering all sections of a manuscript (title, abstract, introduction, methods, results, and discussion) is included in the statement.

Moreover, the reporting quality of randomized controlled trials (RCTs) was assessed using the CONSORT statement. The compliance of each RCT with the 25 items of the CONSORT checklist was evaluated. A "yes" or "no" response was assigned to each item and its subsections. If all subsections received a "yes," one point was assigned to the item; if only one subsection was met, a score of 0.5 was awarded. No points were assigned if the item was not applicable[26]. The total score for each study was then calculated.

Data Extraction

To extract data, a checklist was prepared that included the following information: name of the first author, publication year, country/location, ethics committee approval, reasons for inclusion or exclusion, randomization method, nature of the groups (control/placebo, intervention), number of patients, gender ratio, mean age, T2DM, type of study design (interventional, prospective cohort, retrospective, cross-sectional, etc.), AVS, and

treatment outcomes after TAVI, TAVR, and SAVR (stroke, early mortality [in-hospital and 30-day], and late mortality [≥1 year]).

Data extraction from the selected articles was performed independently by two researchers. In cases of discrepancies, discussions were held to reach consensus, and the most accurate data were approved. All collected data were reviewed by a statistician.

Statistical Analysis

Comprehensive Meta-Analysis (CMA) software version 3.7 was used to analyze the data. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated for each endpoint across all studies. A two-sided p-value <0.05 was considered statistically significant.

Thompson's I^2 test was used to assess heterogeneity. An I^2 ≥50% indicated significant heterogeneity. The Mantel–Haenszel random -effects model was used for studies with I^2 ≥50%. If overall effects were consistent and I^2 <50%, a fixed-effects model was preferred; otherwise, a random-effects model with wider CIs was selected.

Meta-regression and subgroup analyses were performed to identify sources of heterogeneity. Sensitivity analysis was conducted by removing one study at a time; a ≥20% change in the overall effect was considered significant. Funnel plots and Egger's test were used to evaluate publication bias.

Ethical Considerations

This study protocol was reviewed and approved by Isfahan University of Medical Sciences (approval code: IR.MUI.MED.REC.1403.322).

Results

Study Selection

In the initial search using keywords, 1,895 studies were identified. After removing 200 duplicate studies, the titles and abstracts of 1,695 articles were screened, and 910 records were excluded. Subsequently, 785 full-text studies were assessed for eligibility. Considering the study objective of evaluating the prevalence of DM in patients with AVS and their treatment outcomes, only 50 studies remained after applying the inclusion and exclusion criteria. Of these, 20 studies were excluded due to incomplete results and 8 due to low quality. Finally, 22 studies 15 single-center and 7 multicenter were included for quantitative evaluation[5,21,27–46] (Fig. 1).

Risk of Bias Within Studies

The risk of bias in the included studies was assessed independently by two authors using the Cochrane Collaboration's risk-of-bias tool. The authors examined domains such as blinding of participants, selective reporting, allocation concealment, incomplete outcome data, blinding of outcome assessment, and allocation sequence generation (Fig. 2). Any discrepancies were discussed and resolved.

Study Characteristics

This meta-analysis included 760,287 patients with AVS, comprising 60.2% male and 39.8% female participants. The mean age of patients across the included studies ranged from 62 to 89 years.

Diabetes Rate

Among the AVS patient population in the 22 studies, 252,945 (33.2%) had DM and 507,342 (66.7%) did not. Most studies reported DM rates between 20% and 36%, with many showing statistically significant findings ($p<0.05$). However, the DM rate in AVS patients was non-significant in studies by Roderburg et al. (2021), Wang et al. (2013), and Lindman et al. (2011) ($p>0.05$).

Based on the random-effects model, the overall DM rate was approximately 31% (95% CI: 26–36%; heterogeneity I^2 = 99.92%) (Fig. 3).

Regarding gender differences among patients with AVS, no significant difference was found between men and women in DM prevalence. In the fixed-effects model, the mean DM rate was 36% for women and 35% for men (heterogeneity I^2 = 14.01%). In some studies, such as Lindman et al. (2011), the DM rate was significantly higher in men (58%) than in women (35%). However, in

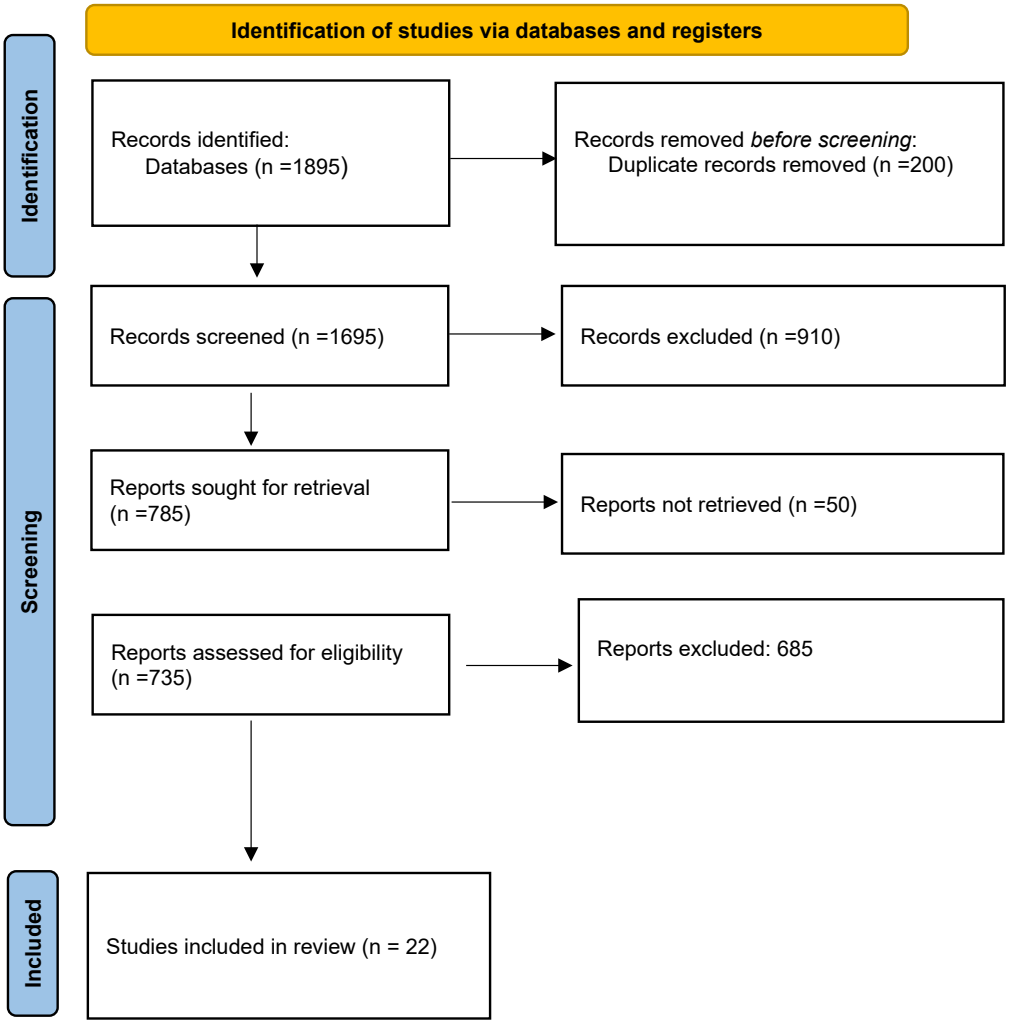

Fig. 1. PRISMA 2020 flow diagram for reviews

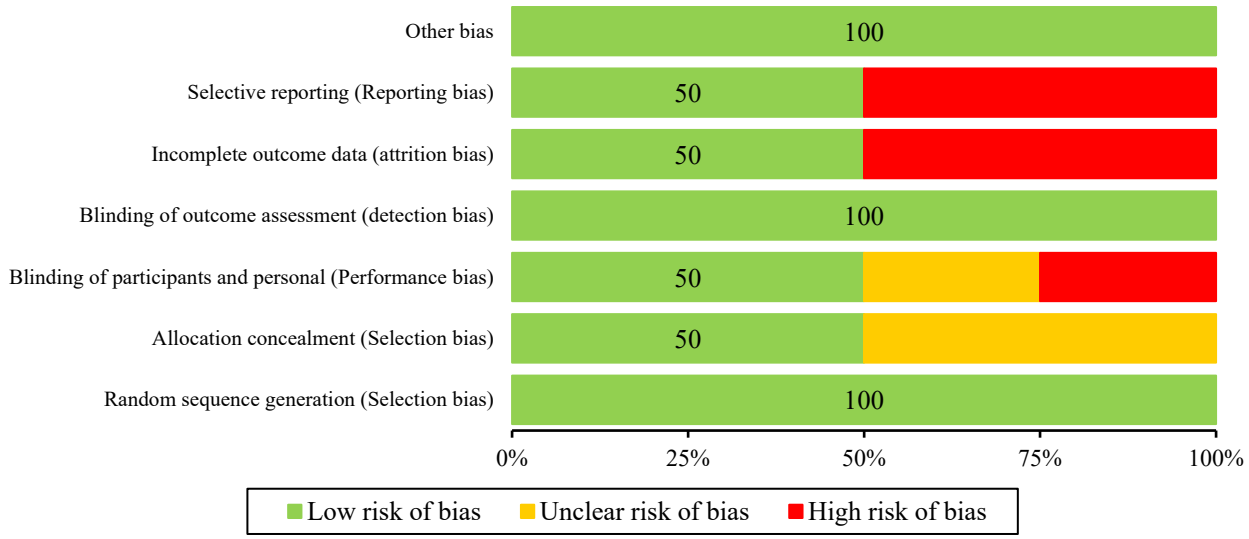

Fig. 2. Risk bias of studies according to the Collaboration's risk of bias tool

most cases, the difference was too small to be statistically significant. Additionally, studies with wide confidence intervals (e.g., Natorska et al. (2012) and Jex et al. (2023)) should be interpreted cautiously due to potential high heterogeneity.

Outcome

In-hospital Mortality

The overall analysis of in-hospital mortality was based on four studies with a total of 90,726 patients. In-hospital mortality was significantly increased in DM patients compared with non-DM patients (OR: 2.399; 95% CI: 2.23–2.59; p<0.001; heterogeneity I^2 = 23.40%) (Fig. 4).

Thirty-day Mortality

The overall analysis of 30-day mortality was based on 12 studies with a total of 599,851 patients. Thirty-day mortality was significantly increased in DM patients compared with non-DM patients (OR: 1.45; 95% CI: 1.03–2.03; p=0.031; heterogeneity I^2 = 93.43%) (Fig. 5).

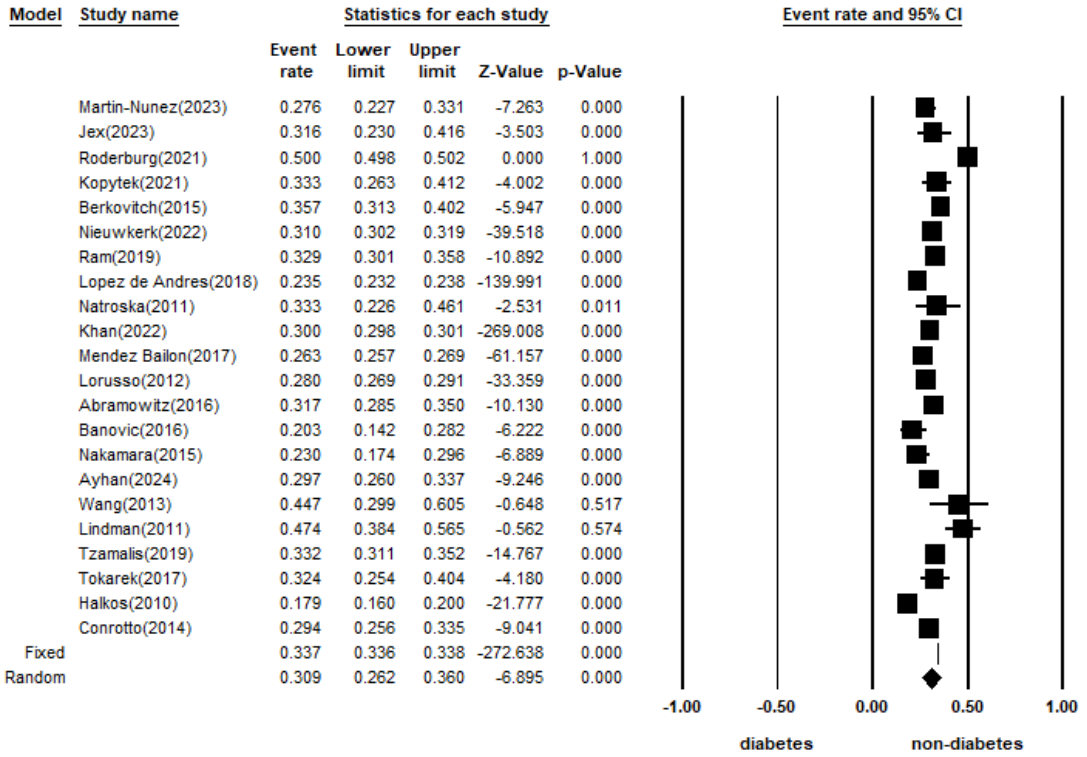

Fig. 3. Forest plot showing the diabetes rate in patients with aortic valve stenosis

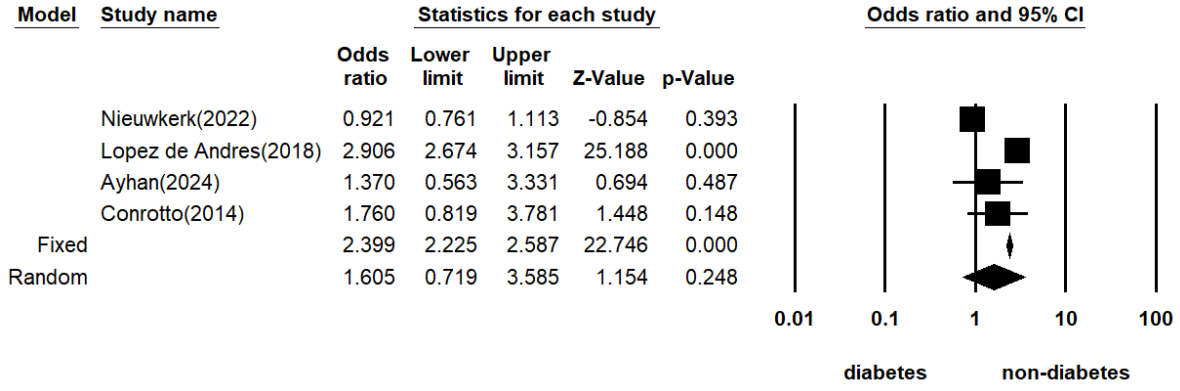

Fig. 4. Forest plot showing the effect of diabetes on in-hospital mortality in patients with aortic valve stenosis

Late Mortality

The overall analysis of late mortality (one year or more) was based on four studies with a total of 2,995 patients. Late mortality was non-significantly increased in DM patients compared with non-DM patients (OR: 1.02; 95% CI: 0.90–1.14; p=0.809; heterogeneity I^2 = 40.25%) (Fig. 6).

Stroke

The overall analysis of stroke was based on four studies with a total of 490,567 patients. Stroke was significantly increased in DM patients compared with non-DM patients (OR: 1.15; 95% CI: 1.03–1.28; p=0.009; heterogeneity I^2 = 10.04%) (Fig. 7).

Discussion

The present meta-analysis aimed to investigate the association between T2DM and AVS, as well as treatment outcomes, by reviewing 22 studies involving a total of 760,287 patients with AVS.

According to the results, approximately one-third of patients with AVS also had DM. The

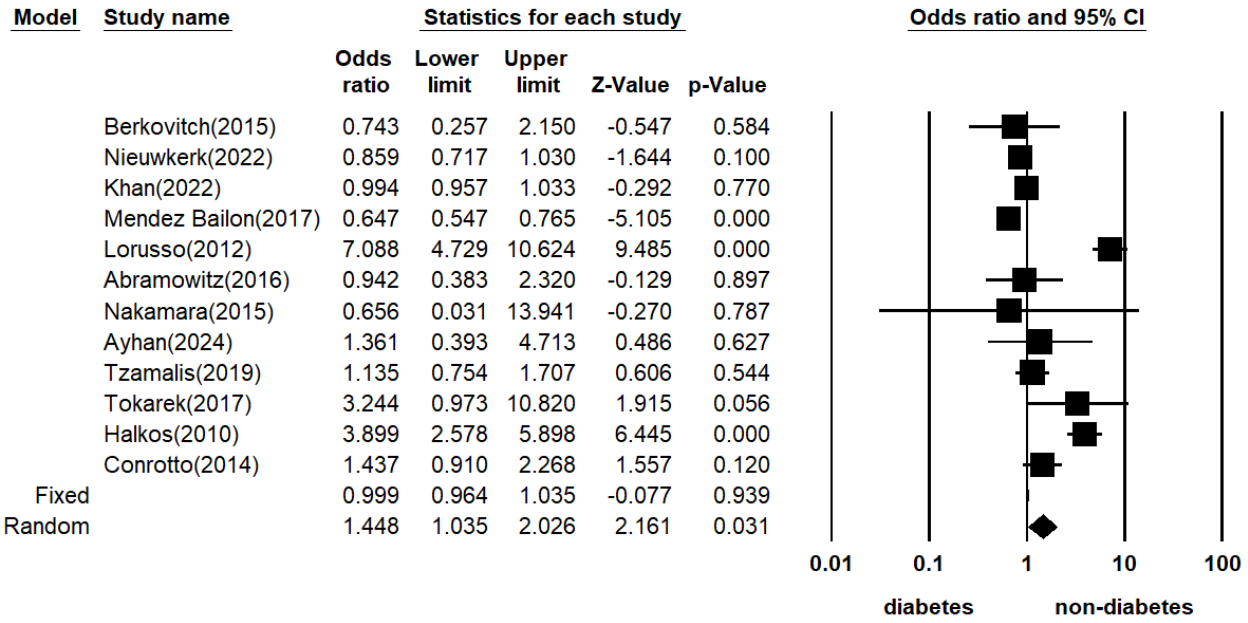

Fig. 5. Forest plot showing the effect of diabetes on 30-day mortality in patients with aortic valve stenosis

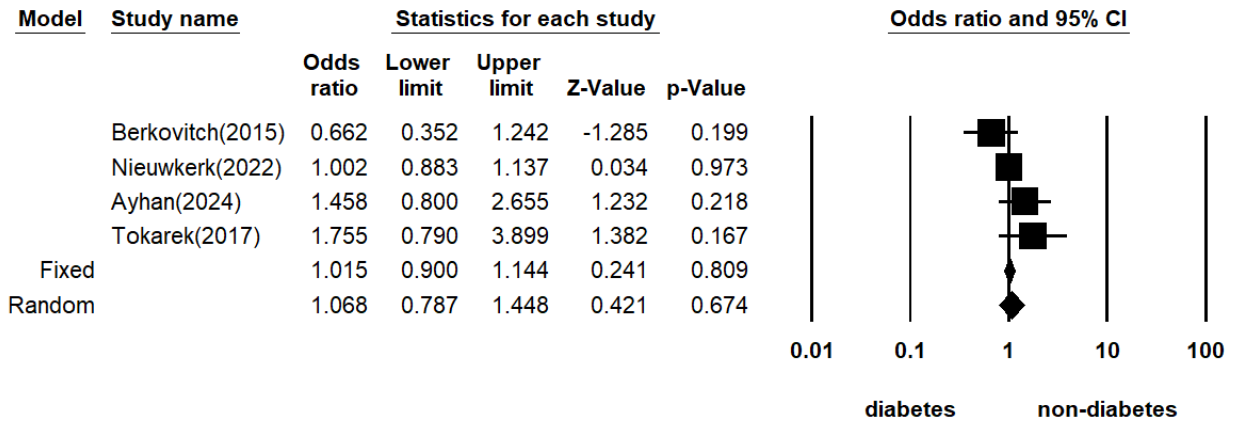

Fig. 6. Forest plot showing the effect of diabetes on late mortality in patients with aortic valve stenosis

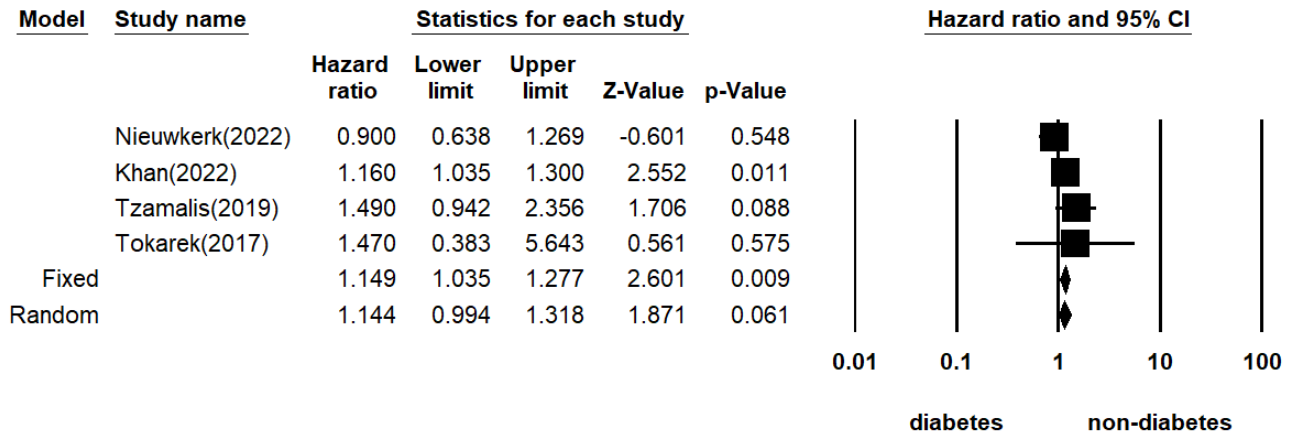

Fig. 7. Forest plot showing the effect of diabetes on stroke in patients with aortic valve stenosis

DM rate was similar between women (36%) and men (35%). Therefore, the presence of DM as a comorbidity in these patients is of great clinical importance. Statistically, in almost all studies, negative Z values and p-values <0.05 indicated that the observed rates were significant compared with reference values. However, some studies such as those by Lorusso et al. (2012) and Roderburg et al. (2021) reported a non-significant association between DM and AVS[29,37], which may be attributable to small sample sizes or high data dispersion.

Nevertheless, the findings of this meta-analysis emphasize the importance of considering DM as a crucial medical condition in the management of AVS. The high prevalence of DM in these patients can play a decisive role in treatment decisions, pharmacological interventions, and prediction of long-term complications. Generally, aggressive treatments for AVS include TAVI, TAVR, and SAVR. As DM accelerates the progression of AS and is a determinant of poor outcomes, close follow-up after treatment is indispensable.

The development of AVS in DM patients is driven by atherosclerosis-like and inflammatory mechanisms. Consequently, the prevalence of AVS is higher in younger DM patients, often accompanied by more comorbidities[34,47]. The inflammatory factor NF-κB shows increased expression in the aortic valve tissue of diabetic patients and is associated with elevated valvular calcification and increased serum HbA1c levels. Furthermore, poorly controlled diabetes is associated with increased valvular expression of coagulation-related factors. Thus, elevated serum glucose may enhance the development of AVS in DM patients[48].

The evaluation of the main outcomes after TAVI, TAVR, and SAVR indicated that early mortality (in-hospital and 30-day) was significantly increased in DM patients compared with non-DM patients; however, DM did not play a significant role in late mortality (one year or more).

Review of the studies revealed a significant role of DM in 30-day mortality in several studies, such as those by Lorusso (2012), Halkos (2010), and Mendez-Bailon (2017)[21,27,37], while other studies including Abramowitz (2016) and Nakamura (2015) reported non-significant associations[38,40].

Regarding late mortality, Berkovitch's study (2015) reported an OR of 0.66, which was not significant and had a wide confidence interval [1.24–0.35], although the OR was less than 1, suggesting a reduced probability of mortality in DM patients[31]. Nieuwkerk's study (2022) found

an OR of 1.00, indicating no difference between DM and non-DM groups[32]. Both Ayhan (2024) and Tokarek (2018) reported trends toward increased delayed mortality in DM patients (OR: 1.46 and 1.76, respectively); however, these findings were not statistically significant due to wide confidence intervals and p-values >0.05[41,45].

Overall, the findings of the present review indicate that although DM is associated with early mortality in these patients, it does not significantly affect long-term survival.

As noted, the results of studies examining the effect of DM on outcomes after TAVI, TAVR, or SAVR are contradictory. Some studies have reported increased short-term and long-term mortality in DM patients[49], while others have reported similar 30-day and 1-year mortality rates in DM and non-DM patients[46,50].

Other studies have reported significantly lower 1-year mortality after TAVR compared with SAVR, leading to more than one-third of patients being referred for TAVR due to the possibility of better outcomes[21,43]. Based on some findings, survival in DM patients receiving bioprostheses may be worse due to structural valve deterioration or the need for reoperation[33].

It is important to note that many studies did not compare baseline and clinical characteristics between groups, and differences in valve procedures or valve types may have influenced the results.

In addition, according to the present meta-analysis, four studies examined stroke at different time points after therapeutic interventions (TAVI, TAVR, and SAVR) and showed that stroke incidence was significantly higher in DM patients compared with non-DM patients. Nieuwkerk's study (2022) reported a hazard ratio (HR) of 0.90, indicating a relative risk reduction[32]. In contrast, studies by Khan (2022), Tzamalis (2019), and Tokarek (2018) reported HRs of 1.16, 1.49, and 1.47, respectively, indicating an increased relative risk of stroke in DM patients after AVS interventions[36,44,45].

Similarly, other studies have reported an increased risk of stroke after TAVR in both early and late follow-up periods among DM patients[36,51], suggesting that DM increases stroke risk by 30–60%. This may be due to hyper-aggregation commonly observed in DM, which increases the risk of cerebral embolization.

The present study had several limitations. First, minor heterogeneity and publication bias may have affected the results, although fixed- and random-effects models were applied to address this issue. Second, the review included several clinical trials, most of which examined outcomes after TAVI or TAVR, while only three studies reported SAVR outcomes; therefore, results could not be stratified by AVR type. Third, most studies did not specify the type of valve used, which could have added valuable context to the findings. Despite these limitations, this large-scale meta-analysis, including more than 700,000 patients, provides important insights into the association between DM and AVS, as well as early and late outcomes after treatment.

Conclusion

According to the results of the present meta-analysis, more than one-third of patients with AVS also had DM. DM played a significant role in treatment outcomes and was associated with increased in-hospital and 30-day mortality after AVR. However, delayed mortality was not significantly affected by DM. Furthermore, the odds of stroke after AVR were significantly higher in DM patients compared with non-DM patients.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: AH; HKh
Data Acquisition: HKh
Data Analysis or Interpretation: AMM; HKh
Manuscript Drafting: AH; AMM; HKh
Critical Manuscript Revision: AH; AMM; HKh
All authors have approved the final manuscript and are responsible for all aspects of the work.

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