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Vitamin K antagonists and structural valve deterioration in bioprosthetic aortic valves

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Abstract

Background: To evaluate the effect of postoperative vitamin K antagonist (VKA) exposure on structural valve deterioration (SVD) after bioprosthetic aortic valve replacement (AVR).

Methods: We retrospectively analysed 123 patients who underwent surgical bioprosthetic AVR between 2010 and 2025 with adequate echocardiographic follow-up. VKA exposure was recorded during follow-up; for the primary time-fixed Cox model, VKA exposure was defined as cumulative postoperative use ≥3 months (yes/no), and VKA was additionally evaluated as a time-varying covariate in a time-dependent sensitivity analysis. The primary endpoint was VARC-3-defined SVD; secondary endpoints were all-cause mortality, bioprosthetic valve failure, and reoperation/valve-in-valve.

Results: Mean age was 71.3±6.1 years; 65% were male. Porcine and bovine bioprostheses accounted for 71.5% and 28.5% of implants. Median SVD-free survival was 2073 days (95% confidence interval [CI]: 0-4212) in VKA users, while the median was not reached in non-users; the difference was significant (log-rank p=0.017). In the adjusted time-fixed Cox model, VKA exposure was associated with higher SVD risk (adjusted hazard ratio [aHR] 2.14; 95% CI 1.08-4.26; p=0.030). In a time-dependent sensitivity Cox model with VKA as a time-varying covariate, periods on VKA were similarly associated with higher SVD hazard (hazard ratio 2.16; 95% CI 1.10-4.23; p=0.025). Porcine bioprostheses were also independently associated with higher SVD risk (aHR 2.71; 95% CI 1.09-6.76; p=0.031).

Conclusion: After bioprosthetic AVR, VKA exposure and porcine bioprostheses were independently associated with SVD. Antithrombotic strategies should consider the potential long-term adverse effects of VKA in the context of prosthesis material and patient characteristics. Prospective multicenter studies are needed to confirm these findings.

Keywords: Heart valve prosthesis, aortic valve, bioprosthesis, warfarin.

The antithrombotic strategy after bioprosthetic aortic valve replacement (AVR) remains uncertain, particularly regarding the effect of vitamin K antagonist (VKA) use on long-term valve durability and structural valve deterioration (SVD). This issue is of critical importance to both surgeons and clinicians, as the longevity of bioprosthetic valves and the need for reoperation directly impact patient prognosis.[1]

The literature reports a dual effect of VKAs. On the one hand, VKA is effective in preventing subclinical leaflet thrombosis and clinical valve thrombosis; recent reviews report that subclinical leaflet thrombosis can occur in 10-20% of patients after transcatheter AVR and can be resolved with anticoagulation.[2] Warfarin treatment has been associated with tissue calcification, as evidenced by 18F-fluoride positron emission tomography uptake, an example of warfarin's pro-calcific effect on valve biology.[3] Furthermore, experimental models have shown that VKA may accelerate vascular and valve calcification by blocking the vitamin K-dependent Matrix Gla protein (MGP) inhibitory pathway.[4] Therefore, the effect of VKA on SVD remains controversial, "the balance between protective and harmful effects".

Findings from clinical studies are also conflicting. Some retrospective cohort studies have shown that VKAs have a positive effect on valve durability,[1] while others have reported that they may increase vascular calcification, leading to adverse outcomes.[5] Some studies have also suggested that switching from VKAs to other anticoagulants, such as rivaroxaban, may reduce the risk of calcification.[6] This discrepancy in the literature is due to methodological differences, patient selection bias, limited follow-up, and lack of standardization in the definition of SVD.[7]

In this context, we aimed to examine the impact of postoperative VKA exposure during follow-up on SVD, bioprosthetic valve failure (BVF), reoperation/valve-in-valve (ViV), and all-cause mortality (VARC-3 criteria),

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in patients undergoing surgical bioprosthetic AVR between 2010 and 2025. Our hypothesis was that VKA use increases the risk of SVD. The single-center, long-term follow-up, exclusion of sutureless valves, event classification using current definitions, and the use of time-dependent analyses for VKA exposure aim to contribute to the evidence base on antithrombotic strategies after bioprosthetic AVR.

Methods

Study Design

This was a retrospective, single-center analysis of patients who underwent bioprosthetic AVR between 2010 and 2025 at the department of cardiovascular surgery. A total of 259 patients were screened. One hundred thirty-six patients were excluded because they had a Perceval sutureless valve, lacked regular postoperative follow-up data, had incomplete echocardiographic examinations, or lacked information on VKA exposure. Ultimately, 123 patients were included in the analysis.

Surgical and Prosthetic Features

Surgical AVR was performed in accordance with institutional standard protocols. Myocardial protection was achieved with central cannulation, aortic cross-clamping, moderate hypothermia, and antegrade cold blood cardioplegia. All AVRs used standard stented, sutured surgical bioprosthetic valves; no stentless or sutureless prostheses were implanted. Porcine bioprostheses included St. Jude Epic and Biocor and Medtronic Hancock II, whereas Sorin/LivaNova Mitroflow was the bovine pericardial bioprosthesis used in this cohort.

Definitions

- VKA exposure: Postoperative VKA use for any indication was recorded throughout follow-up with start/stop dates when available and modeled as a time-varying covariate in time-to-event analyses. For descriptive comparisons and for the primary time-fixed Cox model, cumulative postoperative VKA exposure was dichotomized using a 3-month threshold (≥3 months *vs.* <3 months). The 3-month threshold was selected a priori because contemporary guidelines define the early postoperative antithrombotic window after surgical aortic bioprosthesis implantation as approximately 3 months; therefore, dichotomizing cumulative VKA exposure at ≥3 months distinguishes patients who completed at least this guideline-based early course from those with shorter/no exposure.[8]
- VKA indications: In this cohort, VKA therapy was prescribed mainly for three clinical indications: (i) anticoagulation after surgical bioprosthetic AVR according to local practice, even in the absence of another formal indication, (ii) atrial fibrillation (pre-existing or new-onset postoperative), and (iii) intracardiac thrombus.
- Preoperative VKA use: Patients who were already receiving VKA therapy at the time of the index AVR procedure for an established indication (e.g., atrial fibrillation or intracardiac thrombus).
- Definition of study groups: For descriptive group comparisons, patients were categorized according to whether cumulative postoperative VKA exposure reached 3 months (VKA group) or did not (non-VKA group). Primary time-to-event analyses used a conventional (time-fixed) Cox model. VKA was additionally evaluated as a time-varying covariate in a time-dependent sensitivity analysis.
- SVD: Permanent structural abnormalities detected during postoperative follow-up after exclusion of thrombosis, endocarditis, patient-prosthesis mismatch, and malposition according to VARC-3 criteria and confirmed by echocardiography.[9]
- BVF: Severe hemodynamic deterioration with clinical symptoms according to VARC-3 criteria, reintervention (surgical reoperation or transcatheter ViV), or valve-related death occurring during the postoperative follow-up period.
- Chronic kidney disease: Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m².
- Follow-up period. The interval between the date of surgical bioprosthetic AVR and the last available clinical contact or death; all primary and secondary outcomes were assessed within this period.
- Mortality: All-cause mortality occurring during the postoperative follow-up period.

Outcomes

Primary outcome: Development of SVD according to VARC-3 criteria.

Secondary outcomes: All-cause mortality, BVF, and reoperation/ViV procedures.

Echocardiography Protocol

Echocardiographic follow-up was assessed retrospectively. All transthoracic echocardiograms performed after the index bioprosthetic AVR were retrieved from the institutional digital archive. There was no predefined echocardiographic follow-up protocol; examinations were ordered according to routine clinical care and at the discretion of the treating physicians. For each patient, we recorded the date of the echocardiographic examination used to adjudicate valve-related endpoints, namely SVD and BVF. In patients without any such event during follow-up, the date of the last available postoperative echocardiogram was recorded. Echocardiographic follow-up time was defined as the interval between surgery and this examination.

To describe echocardiographic surveillance in a more standardized way, two additional binary variables were created: "echocardiographic follow-up ≥1 year" and "echocardiographic follow-up ≥3 years", indicating the presence of at least one transthoracic echocardiogram performed ≥1 and ≥3 years after surgery, respectively. These variables were used to summarize the echocardiographic follow-up timeline and to compare echocardiographic surveillance between VKA and non-VKA patients.

Ethical Approval

This retrospective study was approved by the Institutional Review Board of Dokuz Eylül University (approval no: 2025/31-29; date: 17 September 2025) and conducted in accordance with the Declaration of Helsinki. Owing to the retrospective design and the use of de-identified data, the requirement for informed consent was waived.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics v29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normal distribution using the Shapiro-Wilk test. Data not conforming to a normal distribution were analysed using non-parametric methods. Continuous variables were presented as mean ± standard deviation and

median (minimum-maximum); categorical variables were presented as numbers and percentages (%). Comparisons between groups were made using the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Group comparisons were performed between patients in the VKA and non-VKA groups as defined above. Secondary endpoints (BVF, reoperation/ViV, and all-cause mortality) were analysed as binary outcomes over the entire postoperative follow-up period, and event proportions were compared between VKA and non-VKA groups using the chi-square test or Fisher's exact test, as appropriate. Survival analyses were calculated using the Kaplan-Meier method, and groups were compared using the log-rank test. Median potential echocardiographic follow-up was estimated using the reverse Kaplan-Meier method. Median SVD-free survival times with 95% confidence intervals were reported; when the median was not reached within the available follow-up, this was indicated. Multivariate analyses were performed using Cox proportional hazards regression. Results are presented as hazard ratios (HRs) with 95% confidence intervals. For the primary (time-fixed) Cox model, VKA exposure was entered as a binary variable defined as cumulative postoperative VKA use ≥3 months (yes/no). In sensitivity analyses, VKA was additionally evaluated as a time-varying covariate using start-stop intervals. Valve size was entered into the Cox regression models as a continuous predictor, expressed per 1-mm increase in labeled prosthesis diameter; no predefined categorical cut-off for "small" versus "large" valves was used in the primary analyses. The primary multivariable Cox model was prespecified a priori and kept deliberately parsimonious to reduce overfitting and model instability, prioritizing clinically relevant covariates with established mechanistic plausibility for SVD (VKA exposure, prosthesis material, and valve size). With 35 SVD events and 3 covariates in the primary model, the events-per-variable ratio was approximately 11.7. Univariable analyses were used descriptively to summarize unadjusted associations and to inform exploratory sensitivity considerations, rather than to drive automated variable selection. Missing data were limited (LDL 9.8%, creatinine 2.4%, eGFR 2.4%). The primary analyses were performed as complete-case. As a sensitivity analysis to assess potential bias from missingness, we performed multiple imputation using fully conditional specification (chained equations), generating 20 imputed datasets under a missing-at-random assumption. The imputation model included all covariates used in regression models and outcome information (event indicator and time-to-event). Cox models were re-fitted within each imputed dataset and pooled using Rubin's rules. Statistical significance was accepted as two-sided $p<0.05$. Additionally, to address potential immortal time bias related to VKA exposure, we fitted a time-dependent Cox proportional hazards model with VKA as a time-varying covariate. For this analysis, follow-up time was split into start-stop intervals (tstart-tstop; time scale: days since surgery), and a time-dependent variable was coded as 0 before the recorded date of VKA initiation, 1 during the documented VKA treatment period, and 0 again after discontinuation when stop dates were available. When stop dates were unavailable, VKA exposure was assumed to continue until censoring (i.e., the date of the last available echocardiogram/clinical contact used to define follow-up), unless a discontinuation was explicitly documented. The time-dependent model was implemented in IBM SPSS Statistics v29 using the time-varying covariate framework. In all Cox regression analyses, the VKA exposure was defined according to the specified model: as a time-fixed binary variable (cumulative postoperative VKA use ≥3 months) in the primary model, and as a time-varying covariate in the time-dependent sensitivity analysis; definitions were applied irrespective of the clinical indication. To minimize information loss, continuous variables were modeled as continuous predictors in the primary regression analyses whenever applicable (e.g., valve size per 1-mm increase, eGFR as a continuous measure). Clinically used thresholds (e.g., eGFR <60 mL/min/1.73 m²) were reported descriptively and evaluated only in sensitivity analyses, where the corresponding continuous measures were used in the primary models. Baseline group comparisons and secondary endpoint proportion comparisons were considered descriptive; therefore, no formal adjustment for multiple testing was applied. Primary inference was based on the prespecified time-to-event analyses for SVD (Kaplan-Meier and Cox models). Time-to-event was calculated from the date of surgery to SVD adjudication, with censoring at the date of the last available echocardiogram.

Results

A total of 123 patients were included in the study. The mean age was 71.3±6.1 years, and the median age was 71 years (range, 55-86). Overall, 65.0% (n=80) of the patients were male and 35.0% (n=43) were female (Table 1). The preoperative indication was aortic stenosis in 65.0% (n=80), aortic insufficiency in 25.2% (n=31), and mixed aortic valve disease in 9.8% (n=12). All patients received a surgical bioprosthetic aortic valve, most of porcine origin (71.5%, n=88), and the remainder of bovine origin (28.5%, n=35). Isolated AVR was the most common surgical procedure (56.9%, n=70), while concomitant procedures included AVR plus coronary artery bypass grafting (AVR+CABG, 18.7%), AVR plus mitral valve replacement (AVR+MVR, 8.1%), and AVR plus supracoronary ascending aortic replacement (AVR+SCAR, 7.3%). The distribution of specific bioprosthetic valve models is presented in Table 2; Epic was the most frequently implanted prosthesis, followed by Mitroflow, Hancock II, and Biocor.

Baseline demographic and clinical characteristics according to VKA exposure are summarized in Table 1. There were no significant differences between the VKA and non-VKA groups in terms of age, sex, comorbidities, or laboratory parameters. However, cardiopulmonary bypass (CPB) time (p=0.009) and aortic cross-clamp time (p=0.004) were significantly longer in the VKA group.

With regard to anticoagulation, preoperative VKA use at the time of AVR was uncommon: only three patients (2.4%) were already receiving VKA therapy before surgery, two for atrial fibrillation and one for tricuspid valve thrombus. In all remaining cases, VKA was initiated in the postoperative period. Postoperative atrial fibrillation was frequent (70 patients, 56.9%; Table 1), and in 29 of these patients VKA was used as the oral anticoagulant during follow-up. No patients in this cohort received VKA for venous thromboembolism; in patients without atrial fibrillation or intracardiac thrombus VKA was prescribed according to local practice after bioprosthetic AVR.

Overall echocardiographic follow-up time in the cohort was 289 days (interquartile range 98-643 days). Median echocardiographic follow-up time tended to be longer in the VKA group compared with the non-VKA group (424 *vs.* 259 days, respectively), but this difference did not reach statistical significance (Mann-Whitney U test, p=0.059). For descriptive purposes, echocardiography at ≥1 year after surgery was available in 57 patients (46.3%), and follow-up echocardiography at ≥3 years was documented in 20 patients (16.3%).

Table 1. Baseline characteristics of the study population

Feature	VKA (-) (n=72)	VKA (+) (n=51)	p-value
Age (years), mean ± SD[3]	71.4±6.0	71.1±6.4	0.764
Sex (male), n (%)[2]	48 (66.7)	32 (62.7)	0.653
Body weight (kg), median (IQR)[1]	72.5 (67.0-77.0)	72.0 (67.0-77.0)	0.360
Preoperative LVEF (%), median (IQR)[1]	60 (51.5-60.0)	55 (50.0-60.0)	0.242
Valve size (mm), median (IQR)[1]	23 (21.0-23.0)	23 (21.0-23.0)	0.290
Prosthetic material (porcine), n (%)[2]	50 (69.4)	38 (74.5)	0.540
Pathology (AS/AR/mix), n (%)[2]	45/19/8	35/12/4	0.742
CPB duration (min), median (IQR)[1]	98 (72.8-115.5)	115 (86.5-144.5)	0.009*
ACC duration (min), median (IQR)[1]	66.5 (50.0-82.0)	78 (61.0-102.5)	0.004*
Creatinine (mg/dL), median (IQR)[1]	0.87 (0.75-1.04)	0.93 (0.81-1.13)	0.670
GFR (mL/min/1.73 m²), mean ± SD[3]	75.5±19.8	74.7±21.9	0.842
LDL (mg/dL), median (IQR)[1]	105.5 (87.1-133.9)	104.4 (86.1-132.4)	0.895
CKD (eGFR <60 mL/min/1.73 m²), n (%)[2]	19 (26.3)	14 (27.4)	0.667
Hypertension, n (%)[2]	45 (62.5)	33 (64.7)	0.802
Postoperative AF, n (%)[2]	41 (56.9)	29 (56.9)	0.993

*: Statistically significant; [1]: Mann-Whitney U test (continuous variables, not normally distributed); [2]: Chi-square test or Fisher's exact test (categorical variables); [3]: Independent samples t-test (continuous variables, normally distributed); SD: Standard deviation; VKA: Vitamin K antagonist; IQR: Interquartile range; LVEF: Left ventricular ejection fraction; CPB: Cardiopulmonary bypass; ACC: Aortic cross-clamp; GFR: Glomerular filtration rate; LDL: Low-density lipoprotein; CKD: Chronic kidney disease, AF: Atrial fibrillation.

SVD was more frequent in the VKA (≥3 months) group (43.1% [22/51]) than in the non-VKA group (18.1% [13/72]) (relative risk 2.39; 95% CI: 1.33-4.29; p=0.005). In the adjusted time-fixed Cox model, VKA exposure was associated with a higher hazard of SVD (adjusted hazard ratio [aHR] 2.14; 95% CI 1.08-4.26; p=0.030). In a time-dependent sensitivity Cox model with VKA as a time-varying covariate, periods on VKA were similarly associated with higher SVD (HR 2.16; 95% CI 1.10-4.23; p=0.025). Imputation-based sensitivity analyses (20 imputations) yielded materially unchanged estimates compared with complete-case analyses (Supplementary Table S1). Median potential echocardiographic follow-up estimated by reverse Kaplan-Meier was 959 days (range: 11-5259).

In Kaplan-Meier survival analysis, the median SVD-free survival in VKA users was 2073 days (95% CI: 0-4212), while the median was not reached in the non-VKA group because fewer than half of the patients experienced SVD during follow-up (13/72, 18.1%). The difference was significant using the log-rank test (χ^2=5.745, p=0.017) (Figure 1, Table 3).

When secondary outcomes were examined, all-cause BVF was observed in 47 patients (38.2%) in the study overall cohort, reoperation or ViV procedures were performed in 10 patients (8.1%), and 46 patients (37.4%) died during the follow-up period (Table 4). BVF occurred more frequently in the VKA group than in the non-VKA group (51.0% [26/51] *vs.* 29.2% [21/72]; p=0.014). Similarly, all-cause mortality was higher among VKA-treated patients compared with those without VKA exposure (49.0% [25/51] *vs.* 29.2% [21/72]; p=0.025). In contrast, the rate of reoperation or ViV procedures did not differ between VKA and non-VKA patients (7.8% [4/51] *vs.* 8.3% [6/72]; p=0.922).

In univariable Cox regression analysis, VKA use (aHR 2.26; 95% CI: 1.14-4.49; p=0.020) and porcine-derived bioprosthesis (HR 3.16; 95% CI: 1.29-7.72; p=0.012) were significantly associated with an increased risk of SVD, whereas larger valve size showed a protective association (HR per 1-mm increase 0.75; 95% CI: 0.58-0.97; p=0.025) (Table 5).

Table 2. Distribution of implanted bioprosthetic valve models

Valve model	Leaflet material	n	% of total
Epic	Porcine	45	36.6%
Mitroflow	Bovine	35	28.5%
Hancock II	Porcine	29	23.6%
Biocor	Porcine	14	11.4%
Total	-	**123**	**100%**

Percentages are calculated relative to the entire study cohort (n=123). Epic, Hancock II, and Biocor are porcine stented valves, whereas Mitroflow is a bovine pericardial valve.

Table 3. Primary endpoint

Group	n	SVD, n (%)	Median SVD-free survival, days (95% CI)
Non-VKA	72	13 (18.1%)	NR
VKA (≥3 months)	51	22 (43.1%)	2073 (0-4212)
Total	123	35 (28.5%)	N/A

• Log-rank (two-sided) p=0.017; • VKA = (exposure ≥3 months); SVD = (VARC-3 definition); NR = median SVD-free survival not reached in the non-VKA group because fewer than 50% of patients experienced SVD during follow-up; • The ≥3-month VKA definition was used for descriptive comparisons and as the exposure variable in the primary time-fixed Cox model. Time-dependent analyses used VKA as a time-varying covariate; SVD: Structural valve deterioration; CI: Confidence interval, VKA: Vitamin K antagonist.

The multivariable model included prespecified covariates (VKA exposure, prosthesis material, valve size) selected a priori based on clinical plausibility; univariable analyses were reported descriptively. VKA use (HR 2.14; 95% CI: 1.08-4.26; p=0.030) and porcine bioprostheses (HR 2.71; 95% CI: 1.09-6.76; p=0.031) were found to be independent risk factors. Larger valve size, although showing a protective trend, did not reach statistical significance (HR 0.79; 95% CI: 0.61-1.02; p=0.081) (Table 6).

Discussion

This study demonstrated that VKA therapy is a significant risk factor for the development of SVD after bioprosthetic AVR. Kaplan-Meier analysis showed significantly shorter SVD-free survival in patients receiving VKA, and VKA use emerged as a significant predictor of SVD in Cox regression analysis. Because VKA exposure may change over time during follow-up, we additionally performed a Cox regression analysis in which VKA was modelled as a time-varying covariate. In this model, the hazard of SVD during periods on VKA was almost twice as high as during periods without VKA (HR 2.16; 95% CI 1.10-4.23; p=0.025). The fact that VKA exposure remained statistically significantly associated with a similarly increased risk of SVD in this time-dependent Cox model strongly supports that the relationship between VKA use and SVD is a genuine and consistent finding and makes it unlikely that the observed effect is explained solely by immortal time bias. Our results support the notion that VKA use may increase the risk of degeneration in bioprosthetic valves, similar to its adverse effects on native aortic valves.[10]

In our study, BVF was defined according to VARC-3 as a composite endpoint including severe hemodynamic valve deterioration (typically related to SVD), valve-related reintervention (surgical reoperation or ViV), or valve-related death. Interpreted in this context, our secondary outcomes are broadly in line with long-term results reported in contemporary surgical bioprosthetic AVR series. In cohorts of predominantly elderly patients, 5-10-year overall survival after bioprosthetic AVR has generally ranged from approximately 50% to 85%, and structural valve degeneration or valve-related reintervention has been reported in a non-negligible proportion of patients—roughly on the order of 8-20% over a decade of follow-up.[11] For example, Salvini et al.[12] described recipients of the St. Jude/Abbott Trifecta valve, among whom 16% required reoperation for SVD after a mean of 6.3±2.9 years and only 47% were alive at follow-up. Other surgical series have likewise documented meaningful rates of SVD and BVF over long-term follow-up, with variability according to valve design, patient profile, and procedural factors.[13,14] Studies comparing different surgical bioprostheses, such as Trifecta versus Perimount, have shown that leaflet mounting and prosthesis design can markedly influence the need for reintervention and the incidence of BVF,[15] while additional reports highlight the modifying roles of age, comorbidities, and procedural characteristics on BVF risk.[16] Against this background, the BVF rate of 38.2%, the reoperation/ViV rate of 8.1%, and the all-cause mortality rate of 37.4% observed in our elderly cohort over a median follow-up of 959 days appear numerically compatible with the spectrum of outcomes described in these studies, particularly given our use of a broad, VARC-3-based composite definition of BVF. Moreover, prior work has linked early or progressive BVF to adverse survival,[17,18] supporting the prognostic relevance of the BVF and mortality rates observed in our population.

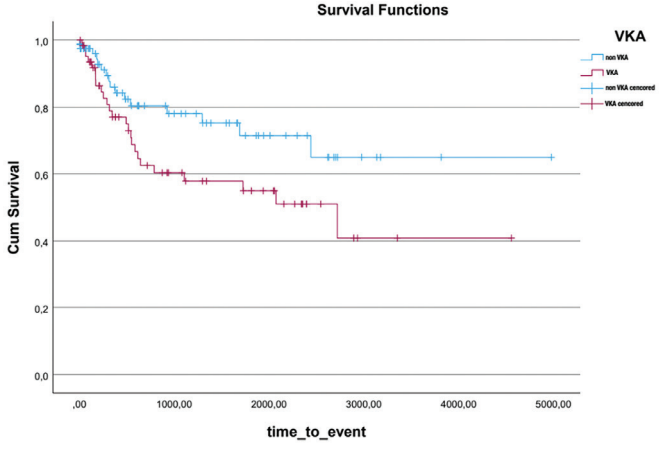


Figure 1. SVD-free survival curves in groups using and not using VKA (Kaplan-Meier analysis). The difference was statistically significant using the log-rank test (χ^2=5.745, p=0.017).

SVD: Structural valve deterioration, VKA: Vitamin K antagonist.

This effect of VKA therapy may be explained by the acceleration of valve calcification by inhibiting the carboxylation of vitamin K-dependent inhibitors, particularly MGP.[19] Studies have shown that levels of dephosphorylated and uncarboxylated MGP (dp-ucMGP) are elevated in VKA-treated individuals, and higher dp-ucMGP levels are associated with higher vascular calcification scores, which may reflect an increased risk of cardiovascular calcification.[20] Furthermore, some studies have suggested that vitamin K supplementation, particularly with the potent derivative menaquinone-7 (MK-7), plays a role in slowing the progression of aortic valve calcification by improving cell viability and upregulating the vitamin K-dependent inhibitor MGP. This indirectly supports a negative role for VKA in the process of valve degeneration.[21]

Some studies on bioprosthetic valve degeneration highlight that there is currently no pharmacological treatment proven to prevent or slow SVD.[22] Furthermore, BVF due to SVD is associated with adverse clinical outcomes ranging from dyspnea to cardiogenic shock, which may require interventional or surgical treatment.[23] In line with the increased risk of SVD, VKA-treated patients in our cohort also showed higher rates of BVF and all-cause mortality during follow-up, whereas reoperation/ViV rates remained low and did not differ between groups. These secondary outcomes, although exploratory and potentially influenced by indication bias and comorbidities, support the overall signal of less favorable long-term valve performance under VKA exposure.

Table 4. Secondary outcomes

Outcome	Non-VKA (n=72) n (%)	VKA (n=51) n (%)	Total (n=123) n (%)	p-value	RR (95% CI)	OR (95% CI)
BVF	21 (29.2)	26 (51.0)	47 (38.2)	0.014*	1.75 (1.12-2.74)	2.53 (1.20-5.34)
Reoperation/ViV	6 (8.3)	4 (7.8)	10 (8.1)	0.922	0.94 (0.28-3.17)	0.94 (0.25-3.50)
Mortality	21 (29.2)	25 (49.0)	46 (37.4)	0.025*	1.68 (1.07-2.65)	2.34 (1.11-4.93)

BVF: Bioprosthetic valve failure; VKA: Vitamin K antagonist; ViV: Valve-in-valve; RR: Relative risk; OR: Odds ratio; CI: Confidence interval; SVD: Structural valve deterioration; *: p-values were calculated using the chi-square test or Fisher's exact test, as appropriate; p<0.05 was considered statistically significant. RR and OR compare the VKA group versus the non-VKA group and are unadjusted, provided for descriptive purposes; primary inference is based on time-to-event analyses for SVD.

Table 5. Univariable Cox regression analyses (for SVD)

Variable	HR (95% CI)	p-value
VKA exposure (≥3 months, time-fixed)	2.26 (1.14-4.49)	0.020*
Age	1.00 (0.95-1.06)	0.883
Male	0.78 (0.39-1.57)	0.466
Prosthesis material (porcine *vs.* bovine)	3.16 (1.29-7.72)	0.012*
Body weight (kg)	0.99 (0.96-1.03)	0.620
CPB duration (min)	1.00 (0.99-1.01)	0.649
ACC duration (min)	1.01 (0.99-1.02)	0.405
Valve size (mm)	0.75 (0.58-0.97)	0.025*
Preoperative creatinine (mg/dL)	0.36 (0.09-1.41)	0.148
Preoperative GFR (mL/min/1.73 m²)	1.01 (0.99-1.02)	0.479
Preoperative LDL (mg/dL)	1.01 (0.99-1.01)	0.236
Preoperative LVEF (%)	1.00 (0.96-1.04)	0.824
Postoperative AF	1.09 (0.56-2.10)	0.810
Hypertension	1.39 (0.65-2.95)	0.399
ASA use	1.18 (0.57-2.45)	0.653
Clopidogrel use	0.58 (0.30-1.12)	0.113
NOAC use	1.19 (0.46-3.07)	0.722

*: Statistically significant (p<0.05); ACC: Aortic cross-clamp; GFR: Glomerular filtration rate; AF: Atrial fibrillation; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; CPB: Cardiopulmonary bypass; VKA: Vitamin K antagonist; HR: Hazard ratio; CI: Confidence interval; SVD: Structural valve deterioration; NOAC: Non-vitamin K antagonist oral anticoagulant.

Table 6. Multivariate Cox regression analyses (time-fixed model for VKA)

Variable	aHR (95% CI)	p-value
VKA exposure (≥3 months, adjusted, time-fixed)	2.14 (1.08-4.26)	0.030*
Prosthesis material (porcine *vs.* bovine)	2.71 (1.09-6.76)	0.031*
Valve size (mm)	0.79 (0.61-1.02)	0.081

*: Statistically significant (p<0.05); VKA: Vitamin K antagonist; CI: Confidence interval; aHR: Adjusted hazard ratio.

Another important finding in our study is that porcine bioprostheses carry a higher risk of SVD compared to bovine pericardial bioprostheses. This is controversial, as some studies support our findings, reporting a significantly higher cumulative incidence of moderate or greater SVD at 10 years in the porcine valve group (29.8%) compared to the bovine valve group (13%).[24] Conversely, there are also publications reporting that SVD is significantly more common in the bovine pericardial valve group and that porcine valves may offer better durability in the context of tricuspid valve replacement.[25]

Additionally, when valve diameter was analysed as a continuous variable, each 1-mm increase in prosthesis size showed a protective association with SVD in the univariable analysis, although this effect did not remain statistically significant in the multivariable model. This trend may reflect the hemodynamic advantages of a larger effective orifice area with increasing valve size, but it needs to be confirmed in larger patient series.

The 2025 ESC/EACTS valve disease guidelines proposed a standardized definition and classification system for SVD in bioprosthetic valves, providing a common language used in research and clinical follow-up in this study. Furthermore, the role of direct oral anticoagulants (NOACs) in anticoagulation was more clearly defined, but no specific recommendations were made regarding the effect of VKA therapy on bioprosthetic valve durability. However, the guidelines emphasized the multifactorial nature of SVD, emphasizing the need for a combined assessment of demographics, comorbidities, valve material, and surgical variables by a multidisciplinary heart team in patient management.

The results of our study are consistent with current guidelines and suggest that greater caution is needed in selecting anticoagulation strategies in bioprosthetic valve patients. Prospective studies evaluating the role of alternative anticoagulation methods (e.g., NOACs) are needed, particularly given the negative effects of VKA use on long-term valve durability.

This study has several limitations that should be acknowledged. Although the primary multivariable model was deliberately parsimonious, the modest sample size and limited number of events contribute to uncertainty, as reflected by relatively wide confidence intervals. Given the retrospective observational design, residual confounding cannot be fully excluded, particularly confounding by indication for VKA (e.g., atrial fibrillation or other clinical reasons for anticoagulation). Therefore, the magnitude of the observed associations should be interpreted as hypothesis-generating rather than causal. First, it was a retrospective, single-center analysis with a relatively small sample size, which may limit the generalisability of the findings and the statistical power, particularly for secondary endpoints. Second, VKA start and stop dates, as well as the indications for VKA therapy, were obtained retrospectively from clinical records; therefore, some degree of exposure misclassification cannot be excluded, and residual immortal time bias may still be present. Third, echocardiographic follow-up was not dictated by a fixed institutional protocol but was driven by clinical practice and physician discretion, which raises the possibility of surveillance bias. To address this concern, we systematically quantified echocardiographic follow-up. Although median echocardiographic follow-up time tended to be longer in the VKA group than in the non-VKA group (424 *vs.* 259 days, respectively), this difference did not reach statistical significance (Mann-Whitney U test, p=0.059). Moreover, the proportions of patients with at least one echocardiogram performed ≥1 year and ≥3 years after surgery were similar between VKA and non-VKA patients (51.0% *vs.* 43.1% and 19.6% *vs.* 13.9%, respectively; p=0.385 and p=0.397). These findings suggest that differential echocardiographic surveillance is unlikely to fully account for the observed association between VKA exposure and structural valve degeneration, although a modest residual effect of surveillance bias cannot be entirely excluded.

This single-center retrospective study examined determinants of SVD after bioprosthetic AVR. VKA exposure and porcine bioprostheses were independently associated with an increased risk of SVD, whereas larger valve size showed a non-significant protective trend. Kaplan-Meier analysis demonstrated significantly shorter SVD-free survival in patients receiving VKA, and this association remained after adjustment for patient and procedural characteristics and was consistent across different analytical approaches.

These findings suggest that the potential adverse effects of long-term VKA therapy should be carefully considered when individualising antithrombotic strategies after bioprosthetic valve replacement, and that the choice of bioprosthetic material is critical for long-term valve

performance. Given the retrospective, single-center design and the possibility of residual confounding, the results should be interpreted as hypothesis-generating and underscore the need for prospective, multicenter studies with long-term follow-up to define the optimal antithrombotic strategy and prosthesis selection in this setting.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Institutional Review Board of Dokuz Eylül University (approval no: 2025/31-29; date: 17 September 2025) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: Owing to the retrospective design and the use of de-identified data, the requirement for informed consent was waived.

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For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.B.D., C.S., T.G., S.B., Ş.B.U.; Concept: O.B.D., C.S., S.B., Ş.B.U.; Design: O.B.D., C.S., S.B., Ş.B.U.; Data Collection or Processing: O.B.D., F.E.K., C.S.; Analysis or Interpretation: O.B.D., F.E.K., C.S., T.G., S.B., Ş.B.U.; Literature Search: O.B.D., F.E.K., C.S.; Writing: O.B.D., F.E.K., C.S., S.B.

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