Antithrombotic Medication and Major Complications After Mechanical Aortic Valve Replacement

Rikhard Björn, MD, Joonas Lehto, MD, PhD, Markus Malmberg, MD, PhD, Vesa Anttila, MD, PhD, K.E. Juhani Airaksinen, MD, PhD, Jarmo Gunn, MD, PhD, and Tuomas Kiviniemi, MD, PhD*

Patients with mechanical aortic valve replacement (AVR) require lifelong vitamin K antagonist (VKA) therapy for stroke and systemic embolism prevention. However, VKA treatment predisposes patients to various types of bleeding. In the present study, we sought to assess the success of antithrombotic therapy and the occurrence and timing of strokes and bleeding events after mechanical AVR. A total of 308 patients who underwent isolated mechanical AVR were included in the study, and follow-up data were completed for 306 patients (99.4%). The median follow-up time was 7.3 (interquartile range 4.2 to 10.9) years. The risk for major bleeding was 5-fold compared with major stroke (6.2% vs 1.3% and 20.9% vs 4.0%, respectively; events rates 3.1 vs 0.5 per 100 patient-years, respectively) at 30-day and long-term follow-up, indicating good efficacy but inadequate safety of stroke prevention. At the time of the early postoperative major bleeding, the international normalized ratio was under the therapeutic range in 73.7% of the patients. However, most patients were on triple antithrombotic treatment consisting of subcutaneous enoxaparin, VKA, and a tail effect of discontinued aspirin. During the long-term follow-up, the most common site of bleeding was gastrointestinal (41.7%), followed by genitourinary bleeding (23.3%) and intracranial hemorrhage (18.3%). Furthermore, mortality was relatively high, with a 10-year survival estimate of 78.3%. In conclusion, although ischemic stroke is a well-identified adverse event after mechanical AVR, it seems that major bleeding is a frequent clinically relevant complication during perioperative and long-term follow-up. This finding underscores the recognition and management of modifiable bleeding risk factors. **(Am J Cardiol 2023;204:185−194)**

Keywords: surgical aortic valve replacement, bleeding, ischemic stroke

The latest international guidelines for the management of valvular heart disease (VHD) suggest that in patients aged under 60 years requiring aortic valve replacement (AVR), mechanical AVR should be considered instead of biologic AVR.[1,2] Although mechanical valves usually offer a lifelong duration of the prosthesis, they come with increased risks of blood clotting, thus requiring permanent vitamin K antagonist (VKA) therapy guided by the international normalized ratio (INR). Because of the potential disabling and even fatal thromboembolic complications ensuing from inadequate anticoagulation, the focus of VKA therapy has been on preventing thromboembolic events. However, the VKA therapy also increases the risk of major bleeding events. Although ischemic stroke is a well-identified adverse event after mechanical AVR, many studies have shown that during long-term follow-up, the risk of major bleeding could be even higher than that of major stroke.[3−12] Although the risk of bleeding events is known to increase exponentially with INR values >4.5 in patients on VKA generally,[13] less is known how in- and out-of-target range anticoagulation and bleeding events are associated in patients with mechanical aortic valve.[4,5] Moreover, the risk of early perioperative complications after mechanical AVR regarding the success of the early anticoagulation treatment is unknown.

This study aimed to assess the antithrombotic treatment and the success of VKA treatment at the time of major bleeds and thrombotic complications after mechanical AVR, both during the 30-day perioperative period and long-term follow-up. In addition, we sought to evaluate the risk of major bleeding compared with a major stroke.

Methods

The CAREAVR (Consortium of Studies in the Field of Atrial Fibrillation, Stroke and Bleeding in Patients Undergoing Aortic Valve Replacement; *ClinicalTrials.gov* identifier NCT02626871) is a Finnish multicenter retrospective study on the rate of atrial fibrillation (AF), thromboembolic complications, and bleeding events in patients who underwent isolated bioprosthetic or mechanical surgical AVR. The data were collected as part of a broader ongoing protocol in Finland to evaluate the thromboembolic and bleeding

Heart Center, Turku University Hospital and University of Turku, Turku, Finland. Manuscript received June 19, 2023; revised manuscript received and accepted July 14, 2023.

This study was funded by the Finnish Medical Foundation, the Finnish Foundation for Cardiovascular Research, Helsinki, Finland; State Clinical Research Fund (EVO) of Turku University Hospital, Turku, Finland; the Emil Aaltonen Foundation; the Maud Kuistila Foundation; and an unrestricted grant from Bristol-Myers Squibb-Pfizer.

See page 193 for Declaration of Competing Interest.

*Corresponding author: Tel: +358 2 3130787.

E-mail address: tuoski@utu.fi (T. Kiviniemi).

0002-9149/

https://doi.org/10.1016/j.amjcard.2023.07.097

complications of AF management in patients who underwent cardiac procedures. The study population consisted of patients who underwent isolated mechanical AVR at Turku University Hospital's cardiac surgery unit from 2002 to 2014. Patients were excluded from the study if they underwent any other major concomitant cardiac surgery procedure.

Patient records were individually reviewed using standardized structured data collection protocol for pre- and perioperative data, discharge data, and long-term follow-up events such as AF, stroke, transient ischemic attack, bleeding events, and mortality. The data were retrospectively collected from electronic patient records. To obtain reliable and accurate follow-up data, only patients from the catchment area were included. The end points of this prespecified study included the occurrence of major stroke and bleeding events during the early postoperative period and long-term follow-up, the occurrence of new-onset AF, and overall mortality.

The causes of death were derived from Statistics Finland. This government office monitors the time and causes of death in Finland and tracks deaths, even if a patient moved to another hospital region. As such, this resulted in a longer mortality follow-up than the other end points.

After mechanical AVR operation, routine postoperative anticoagulation was enoxaparin 40 mg given subcutaneously once or twice a day, starting on the evening of the day of the surgery and continuing until VKA treatment (routinely begun on the first postoperative day) reached the level of INR 2.0. The INR target was 2.5 to 3.5 for 285 patients (92.5%). Preoperative aspirin was discontinued on the day of the operation. Patients with On-X valves were treated with an INR target of 2.0 to 3.0 for the first 3 months. After 3 months, selected patients with On-X had VKA treatment, with an INR target of 1.5 to 2.0, combined with aspirin 100 mg once daily. All patients were treated with permanent VKA. Beyond the surgery, preoperative β-blocker medication was routinely sustained. No other antiarrhythmic prophylaxis was routinely used.

Major bleeding was described as an overt, actionable sign of hemorrhage that requires diagnostic studies, hospitalization, or treatment by a health care professional (Bleeding Academic Research Consortium types 2 to 5).[14] Ischemic stroke was defined as a permanent focal neurologic deficit adjudicated by a neurologist and confirmed by way of computed tomography. Subtypes of ischemic strokes were categorized by treating physicians using the TOAST (Trial of Org 10,172 in Acute Stroke Treatment) classification system.[15] The study included only patients with ischemic strokes considered definite by the treating neurologist or physician. Major stroke was defined according to the TOAST definitions, excluding lacunar strokes (<20 mm in diameter). The diagnosis of AF was confirmed using a 12-lead electrocardiogram (ECG) recording or telemonitoring, indicating an AF episode of 10 minutes or longer.

An urgent operation was defined as an operation performed during the same in-hospital stay, emergency operation was defined as an operation before the next working day, and salvage procedure was defined as that in which patients require cardiopulmonary resuscitation en route to the operating theater or before the induction of anesthesia. Previous cardiac surgery was defined as 1 or more previous major cardiac operations involving opening the pericardium.

The study protocol was approved by the medical ethics committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare (Finland). Owing to the retrospective, observational nature of the study, written informed consent was not required. The study conformed to the Declaration of Helsinki, as revised in 2002.

Statistical analyses were conducted with R statistics software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported as mean ± SD if normally distributed and median (twenty-fifth to seventy-fifth percentiles) if skewed. The data were tested for normal distribution using the Shapiro−Wilk test and visual inspection. Categorical variables were described as counts and percentages. Pearson chi-square and Fisher's exact test were used in analyses assessing preoperative and perioperative medications, and the Cox regression univariable model was exploited in the analyses of baseline characteristics and operative data. The Cox regression proportional hazards assumption was assessed using graphical methods. A multivariable competing risk analysis was performed by including variables of relevance with a $p < 0.10$ in the univariable analysis. A p value <0.05 was considered statistically significant. Multiple testing correction was not applied owing to the explorative nature of the study.

Results

A total of 308 patients (mean age 57.9 years, 30.2% women) who underwent isolated mechanical AVR were included in the study. In addition, 23 patients (7.5%) received the On-X valve (CryoLife Inc, Kennesaw, Georgia). Follow-up data were complete for 306 patients (99.4%).

Overall, 4 patients (1.3%) experienced a major ischemic stroke, and 19 patients (6.2%) had a major bleed during the postoperative 30-day period. The perioperative anticoagulation treatment and the timing of adverse events in these patients are listed in Figure 1, Table 1. The median time to perioperative major stroke were 11.5 (6.5 to 15.5) and 1.0 (1.0 to 11.0) days from the surgery for major bleeding. The median INR at the time of the major stroke was 1.6 (1.2 to 2.3). In addition, during the major perioperative bleeding, it was 1.6 (1.4 to 2.4), but 26% of the patients were on triple antithrombotic therapy during the bleeding event, consisting of enoxaparin 40 mg subcutaneously, VKA (but mostly under the therapeutic range), and the tail effect of preoperative aspirin. Moreover, over half of the remaining patients were on dual anticoagulation consisting of enoxaparin and VKA. Noteworthy, 78.9% of the perioperative bleeding events were surgical bleedings leading to re-exploration.

The median follow-up time was 7.3 (interquartile range 4.1 to 10.9) years. During the long-term follow-up (after excluding patients experiencing a major stroke or a major bleed during the perioperative period), 12 major strokes (4.0%) and 60 major bleeding events (20.9%) occurred (Figure 2). The cumulative incidence estimates for major stroke at 1, 3, and 5 years were 1.3%, 2.0%, and 3.2%, respectively (Figure 3). The baseline characteristics and

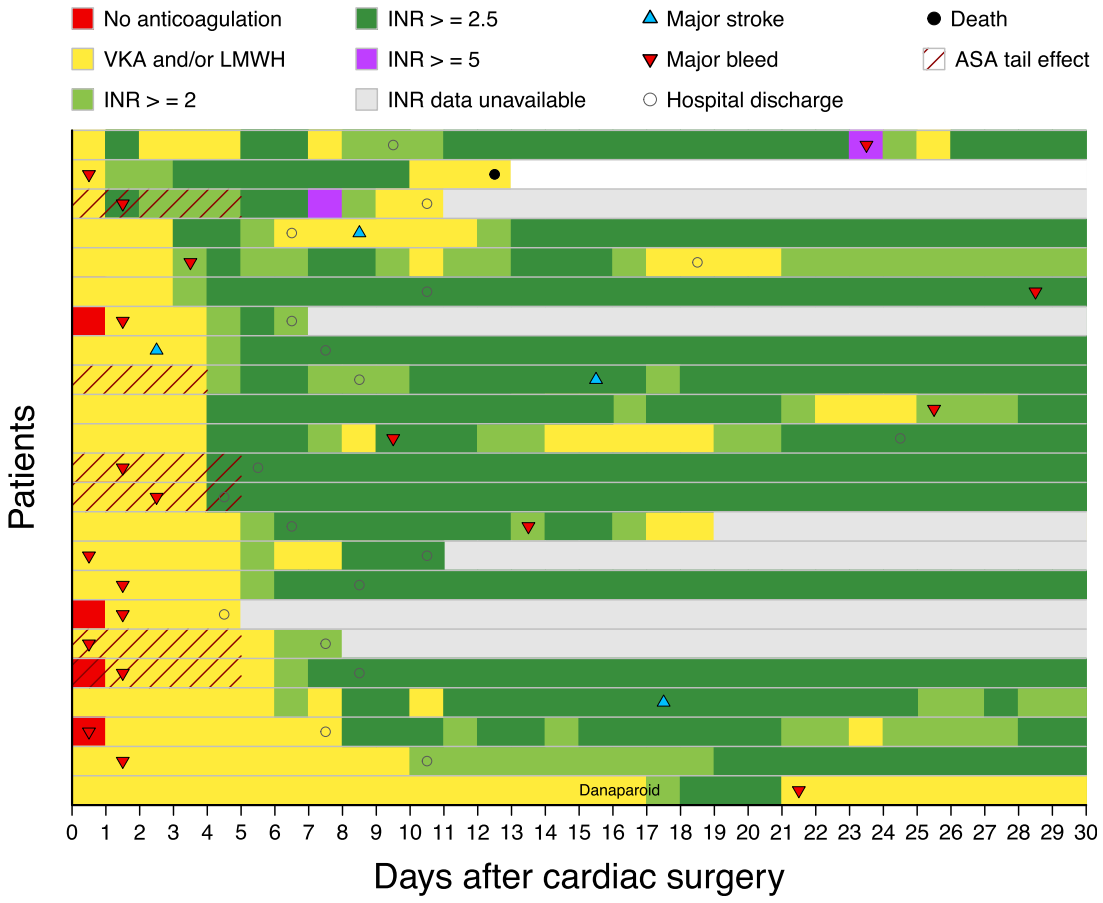

Figure 1. The perioperative antithrombotic treatment of patients experiencing major stroke or major bleeding during 30 days after mechanical isolated aortic valve replacement. ASA = acetylsalicylic acid; LMWH = low molecular weight heparin.

operative data for patients who experienced a major stroke or a major bleed after the 30-day postoperative period are described in Table 2.

The cumulative incidence of major bleeds at 30 days and 1, 3, and 5 years were 6.2%, 7.6%, 13.3%, and 17.3%, respectively (Figure 3). After excluding perioperative major bleeding or stroke episodes within 30 days after AVR, the event rate for major bleeding was 3.1 per 100 patient-years and 0.5 per 100 patient-years for major ischemic stroke. Notably, the ratio of major bleeding events to major strokes was highest in patients with CHA_2DS_2-VASc score 1 to 2 (Figure 4).

Table 1
Preoperative and perioperative medication of patients experiencing major stroke or major bleeding event during the perioperative period after isolated mechanical aortic valve replacement

	Major stroke (n=4)	P1 value	Major bleed (n=19)	P2 value	No major stroke nor bleed (n=283)
Preoperative medication:					
Warfarin	0 (0.0%)	1.000	3 (15.8%)	1.000	45 (15.9%)
Warfarin interrupted	0 (0.0%)	1.000	0 (0.0%)	1.000	42 (14.8%)
Low molecular weight heparin	0 (0.0%)	1.000	0 (0.0%)	1.000	5 (1.8%)
Novel oral anticoagulation	0 (0.0%)	NA	0 (0.0%)	NA	0 (0.0%)
Acetylsalicylic acid	3 (75.0%)	0.058	7 (36.8%)	0.295	73 (25.7%)
ADP receptor inhibitor	0 (0.0%)	1.000	0 (0.0%)	1.000	1 (0.4%)
NSAID	0 (0.0%)	1.000	0 (0.0%)	1.000	2 (0.7%)
Proton-pump inhibitor	1 (25.0%)	0.241	1 (5.3%)	1.000	18 (6.4%)
Perioperative medication:					
LMWH	4 (100.0%)	1.000	17 (94.4%)	0.313	276 (98.2%)
LMWH dose 40 mg once a day	4 (100.0%)	1.000	17 (94.4%)	0.466	272 (96.8%)

Data are reported as n (%).

ADP = adenosine-diphosphate; LMWH = low molecular weight heparin; NSAID = non-steroidal anti-inflammatory drug; P1-value = major stroke vs no major stroke or major bleeding; P2-value = major bleeding vs no major stroke or major bleeding.

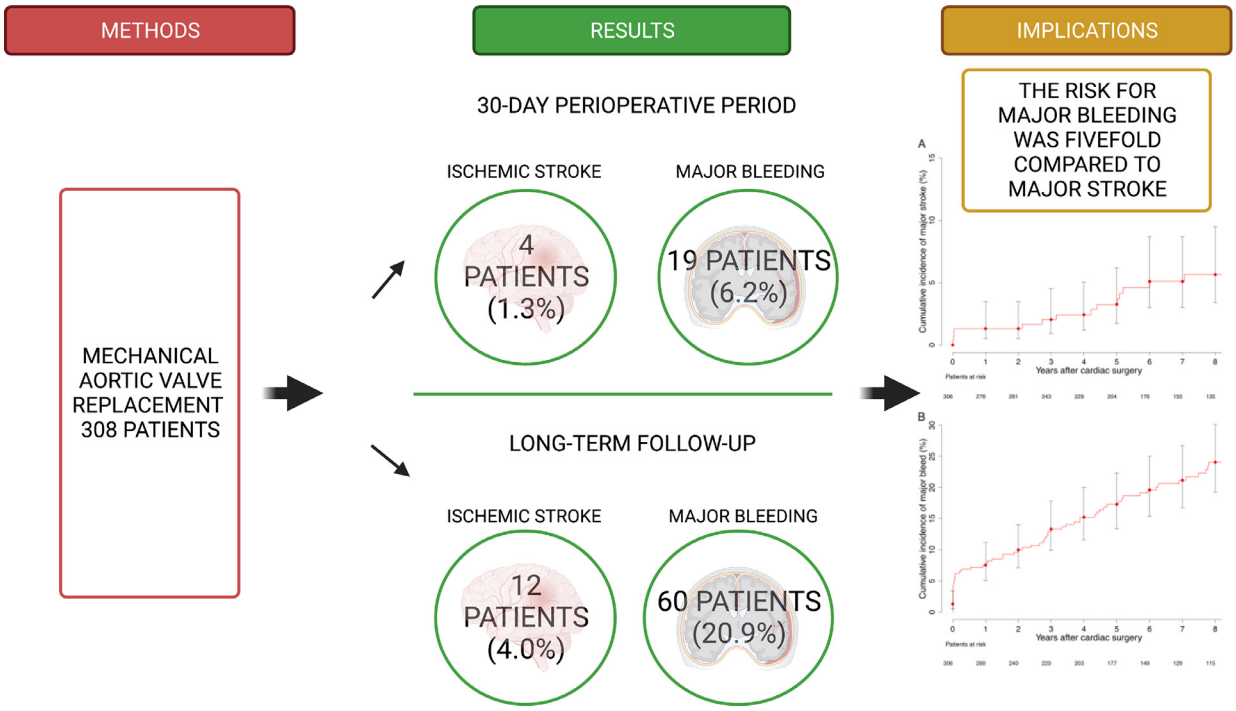

Figure 2. Early postoperative and late incidence of major stroke and major bleeding after mechanical aortic valve replacement.

The major bleeding episode occurred a median of 6.3 (3.4 to 10.2) years after the index operation. The most common bleeding type was gastrointestinal bleeding (n = 25, 41.7%), followed by genitourinary bleeding (n = 14, 23.3%) and intracranial hemorrhage (ICH; n = 11, 18.3%). The median INR value at the time of the first major bleeding event was 3.2 (2.5 to 3.9), and 17 patients (35.4%) had an INR value over 3.5 during the episode (Figure 5). The median INR during the first major stroke was 2.1 (1.3 to 2.9); 7 patients (58.3%) had an INR <2.5, and 4 (33.3%) had an INR value lower than 2.0. The only independent predictor of major bleeding in the multivariable competing risk analysis was lower body mass index (hazard ratio [HR] 0.927, 95% confidence interval [CI] 0.870 to 0.989, p = 0.021), and reoperation for bleeding was the only independent predictor of major stroke (HR 60.8, 95% CI 11.4 to 326.1, p <0.001).

A total of 77 patients (25.2%) without preoperative AF experienced new-onset AF after hospital discharge. In addition, 3 patients with preoperative or new-onset AF experienced major strokes (25% of strokes) during the long-term follow-up. In addition, 2 patients (16.7%) with major stroke had an AF paroxysm during index hospitalization without any later AF paroxysms. In addition, 1 of the patients (8.3%) with stroke developed AF after the stroke. Overall, 50% of patients experiencing major stroke had any AF during the follow-up.

In total, 26 patients (8.5%) received a pacemaker during long-term follow-up, with a median time after the index operation of 3.0 years (interquartile range 116 days to 7.9 years). In addition, 6 of the implantations were conducted during 30 postoperative days.

The median follow-up time for death was 8.8 (5.7 to 12.1) years. Overall, 62 patients (20.3%) died during the follow-up period. The survival rates at 30 days and 1, 5, and 10 years were 96.1%, 95.5%, 91.5%, and 78.3%, respectively (Figure 6). The death certificate diagnoses of death were available in 54 patients (87.1%). Ischemic stroke accounted for 3 deaths, and nontraumatic intracerebral hemorrhage accounted for 1 death during the follow-up period. Significantly, 7 patients (11.7%) died within 30 days after their first major bleeding event. The leading underlying causes of death were coronary artery disease (n = 10, 18.5%) and aortic valve stenosis (n = 10, 18.5%; Supplementary Table 1). Patients who experienced major bleeding events had a tendency for lower survival rate than those without, although it did not reach statistical significance (HR 1.487, 95% CI 0.884 to 2.502, p = 0.135).

Discussion

The main findings of the present study are the following: (1) the risk for major bleeding is 5-fold compared with major stroke during both the early postoperative period and long-term follow-up; (2) postoperative bleeding often associate with the use of triple antithrombotic medication consisting of subcutaneous enoxaparin, oral VKA, and the tail of discontinued aspirin; and (3) the mortality is notably high, considering these patients are assumed to outlive the usual wear-out time of biologic valve prostheses, which is typically 10 to 15 years.[16]

This study offered a novel illustration of major complications during the 30-day perioperative period after isolated AVR (Figure 1). During the perioperative period, major bleeding was significantly more common than an early major stroke, and the bleeding episodes were often encountered during triple antithrombotic therapy consisting of enoxaparin 40 mg subcutaneously, oral subtherapeutic

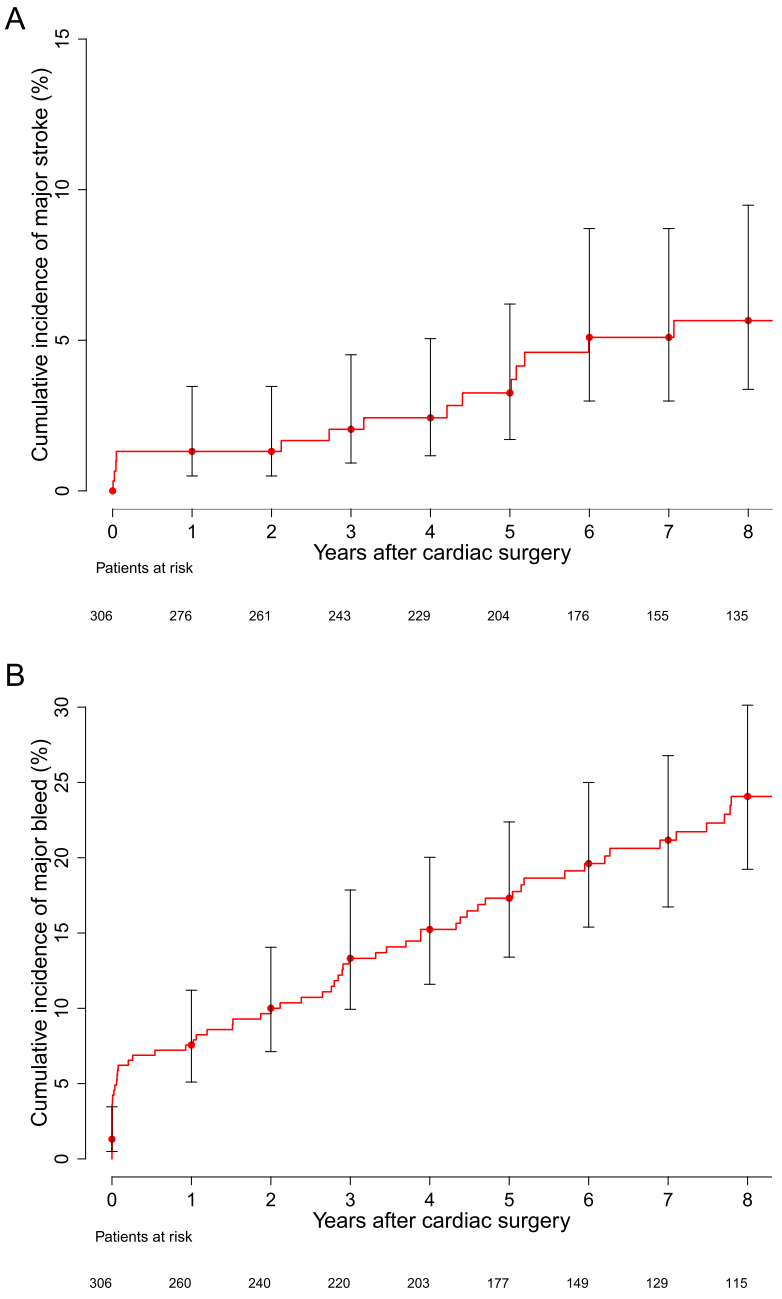

Figure 3. Cumulative incidence of major stroke and major bleeding after mechanical isolated aortic valve replacement.

VKA, and the tail effect of preoperative exposure to aspirin. The effect of aspirin usually lasts 5 to 7 days after discontinuation. Therefore, it is likely that without adequate preoperative interruption, the residual tail effect may predispose the patients to early postoperative surgical site bleeding, often leading to re-exploration. If this safety concern is ignored, the efficacy in stroke prevention was reasonable, given that the incidence of perioperative stroke was relatively low and half of the strokes occurred when the INR was in the therapeutic range.

There is little detailed information on the perioperative anticoagulation treatment in previous studies at the time of the events. Nevertheless, the incidence of bleeds and strokes are consistent with previous studies.[6,10] In the study of Bouhout et al,[10] 5% of the patients entering mechanical AVR experienced early major bleeding and 2% experienced early major stroke. Similarly, in the study of Ram et al[6] concerning mechanical and biologic surgical AVR, 8.5% of the patients experienced early major bleeding, but early stroke episodes were conspicuously absent. In contrast to our study and the previously mentioned studies, the perioperative stroke rate was higher than perioperative bleeding because the cumulative rate of major bleeding was 0.4%. In contrast, the rate of ischemic stroke was 0.5% within 30 postoperative days.[7]

During the long-term follow-up, 1/5 of the patients who underwent mechanical AVR experienced a major bleed. In contrast, only a few major stroke episodes were detected

Table 2
Baseline characteristics and operative data of patients experiencing a major stroke or major bleeding during long-term follow-up after isolated mechanical aortic valve replacement, excluding perioperative events appearing within 30 days after the surgery

	Major stroke (n=12)	P1 value	Major bleed (n=60)	P2 value	No major stroke nor bleed (n=218)
Age	59.0 (45.8−66.0)	0.178	61.5 (55.8−67.0)	0.587	60.0 (52.0−64.0)
Females	2 (16.7%)	0.294	23 (38.3%)	0.231	66 (30.3%)
Diabetes	2 (16.7%)	0.374	6 (10.0%)	0.520	20 (9.2%)
Dyslipidemia	3 (25.0%)	0.386	22 (36.7%)	0.961	83 (38.1%)
Hypertension	6 (50.0%)	0.879	34 (56.7%)	0.574	112 (51.4%)
Coronary artery disease	1 (8.3%)	0.836	6 (10.0%)	0.978	26 (11.9%)
Preoperative atrial fibrillation	2 (16.7%)	0.688	11 (18.3%)	0.281	37 (17.0%)
Chronic atrial fibrillation	2 (16.7%)	0.016	6 (10.0%)	0.001	12 (5.5%)
Paroxysmal atrial fibrillation	0 (0.0%)	0.998	5 (8.3%)	0.538	25 (11.5%)
Chronic lung disease	1 (8.3%)	0.934	4 (6.7%)	0.729	18 (8.3%)
Active smoking	3 (33.3%)	0.139	9 (18.4%)	0.629	26 (16.8%)
Active or ex-smoker	6 (66.7%)	0.159	21 (42.9%)	0.959	68 (43.9%)
Body mass index (kg/m^2)	23.8 (22.8−29.1)	0.576	26.4 (24.0−29.2)	0.057	28.1 (24.6−31.6)
Active endocarditis	1 (8.3%)	0.721	4 (6.7%)	0.864	14 (6.4%)
Previous endocarditis	2 (16.7%)	0.199	4 (6.7%)	0.998	12 (5.5%)
Previous stroke or TIA	1 (8.3%)	0.190	1 (1.7%)	0.839	7 (3.2%)
Previous myocardial infarction	1 (8.3%)	0.284	1 (1.7%)	0.758	5 (2.3%)
Previous percutaneous coronary intervention	1 (8.3%)	0.396	3 (5.0%)	0.576	8 (3.7%)
Previous cardiac surgery	1 (8.3%)	0.277	3 (5.0%)	0.189	6 (2.8%)
CHA_2DS_2-VASc Score	2.5 (0.0−3.0)	0.196	2.0 (1.0−3.0)	0.022	1.0 (1.0−2.0)
EuroSCORE II (%)	1.2 (0.7−1.8)	0.798	1.0 (0.8−1.8)	0.296	0.9 (0.7−1.4)
Modified HAS-BLED Score	1.5 (0.8−2.0)	0.724	1.0 (1.0−2.0)	0.290	1.0 (0.0−2.0)
NYHA Class III or more	5 (41.7%)	0.812	30 (50.0%)	0.201	89 (40.8%)
Echocardiogram:					
Left ventricular ejection fraction	61.7 ± 9.4	0.687	57.8 ± 13.9	0.462	59.2 ± 14.7
Aortic valve peak pressure gradient	98.3 ± 25.5	0.287	82.9 ± 23.2	0.591	83.7 ± 29.5
Aortic valve regurgitation	7 (58.3%)	0.422	42 (71.2%)	0.977	146 (68.7%)
Mitral valve regurgitation	3 (25.0%)	0.432	27 (45.7%)	0.230	78 (36.8%)
Pulmonary artery hypertension	3 (50.0%)	0.212	17 (51.5%)	0.019	36 (28.6%)
Urgent, emergency or salvage procedure	4 (33.3%)	0.092	7 (11.7%)	0.511	33 (15.1%)
Valve prosthesis size (mm)	25.0 (23.0−25.0)	0.139	23.0 (23.0−25.0)	0.879	23.0 (23.0−25.0)
Preoperative laboratory values:					
EGFR (ml/min/1.73 m^2)	85.7 (71.5−96.0)	0.218	78.6 (63.5−91.0)	0.667	82.3 (69.8−95.5)
Discharge drugs:					
Warfarin	12 (100.0%)	0.998	59 (98.3%)	0.873	207 (95.0%)
Low molecular weight heparin	2 (16.7%)	0.546	13 (21.7%)	0.672	57 (26.1%)
Novel oral anticoagulation	0 (0.0%)	NA	0 (0.0%)	NA	0 (0.0%)
Acetylsalicylic acid	0 (0.0%)	0.998	0 (0.0%)	NA	2 (0.9%)
ADP receptor inhibitor	0 (0.0%)	NA	1 (1.7%)	0.182	0 (0.0%)
NSAID	0 (0.0%)	NA	0 (0.0%)	NA	0 (0.0%)
Proton-pump inhibitor	3 (25.0%)	0.096	6 (10.0%)	0.719	22 (10.1%)
AF during index hospitalization	3 (25.0%)	0.685	14 (23.3%)	0.190	62 (28.4%)
Cardioversion during hospitalization	4 (33.3%)	0.146	6 (10.0%)	0.243	32 (14.7%)
Reoperation due to bleeding	2 (16.7%)	<0.001	2 (3.3%)	0.155	0 (0.0%)
Acute de novo dialysis	0 (0.0%)	NA	2 (3.3%)	<0.001	1 (0.5%)
Length of hospital stay	10.5 (9.0−14.3)	0.187	9.0 (7.8 −10.0)	0.381	9.0 (7.0−10.8)

Continuous variables are reported as median (interquartile range) or mean ± SD. Other data are reported as n (%).

AF = atrial fibrillation; CI = confidence interval; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HR = hazard ratio; NYHA = New York Heart Association; P1-value = major stroke vs no major stroke or major bleeding; P2-value = major bleeding vs no major stroke or major bleeding; TIA = transient ischemic attack.

during the same follow-up time. The ratio of major bleeding to major strokes was highest in patients with relatively low CHA_2DS_2-VASc score of 1 to 2 points (Figure 4). The most common reason for major bleeding was gastrointestinal bleeding, which aligns with previous reports.[7,10] Roughly 1/6 of the major bleeding events were ICHs, and the number of ICHs was similar to the number of major strokes.

To the best of our knowledge, there are only 3 studies[9−11] concerning mechanical AVR with equal or longer follow-up than in the present study. Compared with studies by Yuting et al[9] and Bouhout et al,[10] the 5-year cumulative incidence estimate for major bleeding was higher in the present study (5.0% to 7.9% vs 17.3%). This discrepancy is most likely explained by the extensive collection of follow-up data in the present study aiming, in the first place, to avoid the underdiagnosing of the end points. In addition, in the study of Goldstone et al,[11] the 5-year cumulative incidence estimate for major bleeding (approximately 18%) was similar to

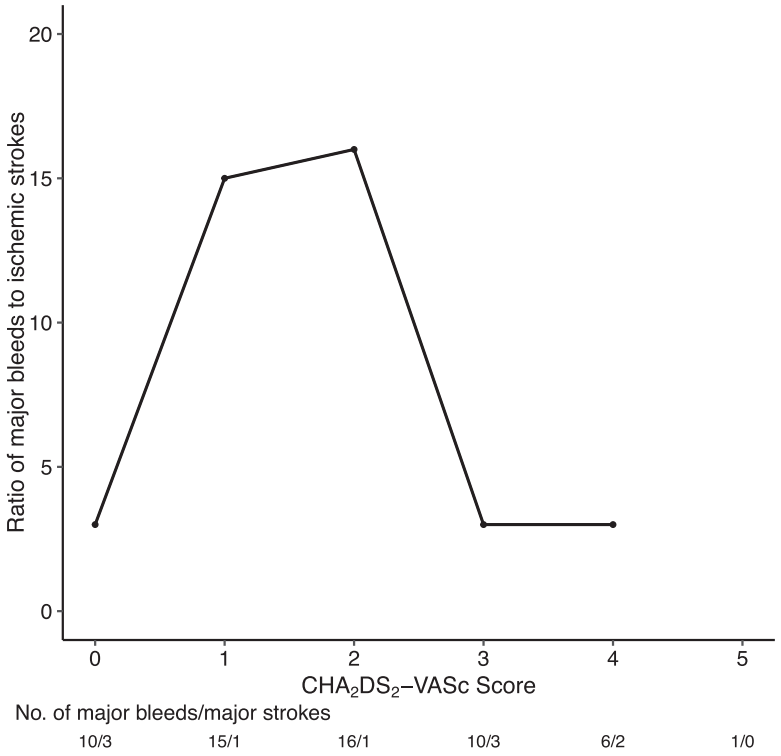

Figure 4. The ratio of major bleeding to major strokes during long-term follow-up in relation to CHA2DS2-VASc score. CHA2DS2-VASc = congestive heart failure; hypertension; age ≥75 (doubled); diabetes mellitus; previous Stroke, transient ischemic attack or thromboembolism (doubled); vascular disease; age 65 to 74; sex category (female).

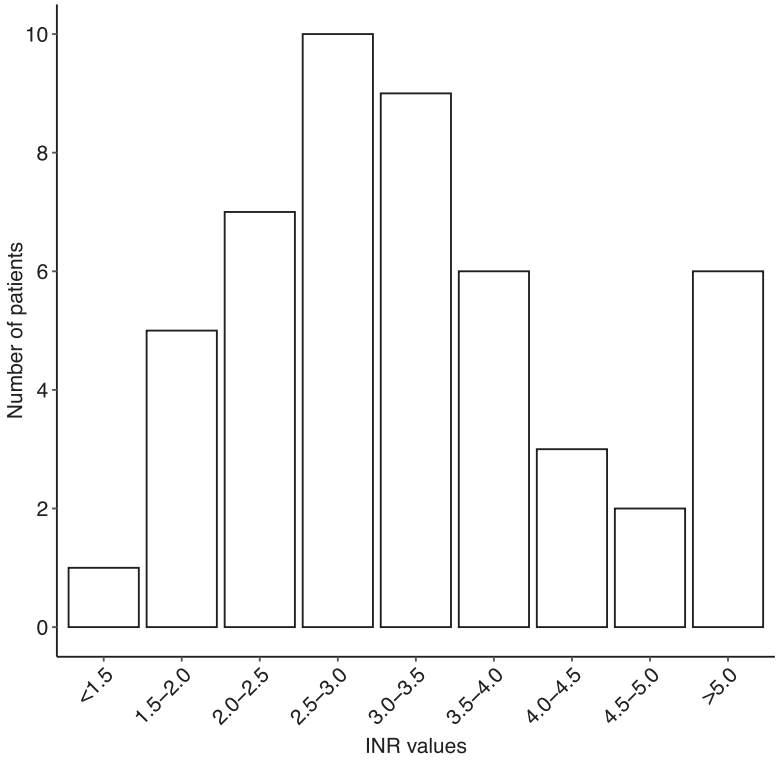

Figure 5. International normalized ratio values during the first major bleeding event.

ours. Comparable to the findings in the present study, the rates of major bleeding events were higher than those of major stroke. Moreover, although the number of ICHs was similar to the number of major strokes in the present study, ICHs are typically weighted higher than strokes in the net clinical benefit analyses of oral anticoagulation. Therefore,

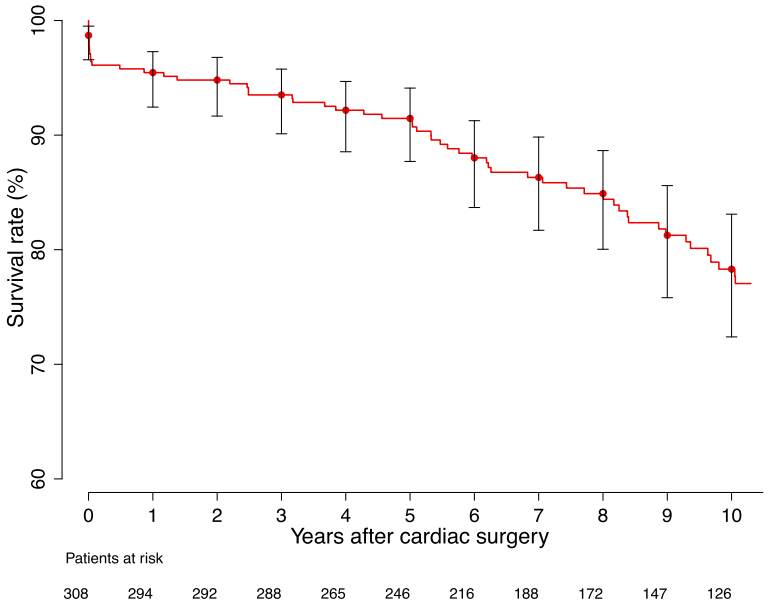

Figure 6. Survival after mechanical isolated aortic valve replacement.

the present ratio seems unbearable. Although ischemic stroke is a feared complication after mechanical AVR, major bleeding appears to be a more clinically relevant complication during long-term follow-up. These results provoke a question: should patients receive biologic AVR at a younger age to reduce the bleeding complications linked to VKA? These data demonstrate the complexity of combining antithrombotic therapies during the early postoperative period. Considering the relatively high rate of early perioperative bleeding episodes from which a notable proportion occurred during the tail effect of aspirin, a policy of sufficient interruption of preoperative aspirin at least 5 to 7 days before the upcoming procedure should be considered.

Patients entering mechanical AVR require lifelong treatment with VKA guided by the INR. It has been shown that in patients receiving VKA, bleeding increases exponentially with INR >4.5.[13] The newest international guidelines for managing VHD:s recommend targeting a median INR value rather than a therapeutic range.[1,2] Based on prosthesis thrombogenicity and patient-related risk factors, the recommended median target value with mechanical aortic valve prosthesis can vary from 2.5 to 4.0. All previous studies concerning lower target INR therapeutic range have demonstrated a lower target INR to be associated with lower bleeding rates, whereas the risk of thromboembolic events is not dissimilar.[4,5,17] Nevertheless, the present study showed that only 1/3 of the bleeding events occur during the long-term follow-up when INR is higher than the defined therapeutic range (Figure 5). In addition, most of stroke events occur when INR is in or over the therapeutic range. Therefore, it seems that only a fraction of the adverse events could theoretically be prevented by altering the VKA treatment. Considering the exceptionally high bleeding occurrence, it appears that the VKA treatment is not the only reason for increased bleeding risk in patients with mechanical aortic valve.

This study showed lower body mass index as an independent predictor of major bleeding. Better outcomes for patients who are overweight and obese after cardiac procedures have also been reported in previous studies.[18,19] However, most studies have focused on coronary artery bypass grafting and transcatheter AVR (TAVR); therefore, data on the influence of obesity on postoperative bleeding after surgical AVR are scarce. Besides the susceptibility to bleeding, our recent report showed that low-weight patients, were prone to get more fluid resuscitation early postoperatively, leading to a higher fluid retention and adverse events postoperatively.[20] These results underline the need for individualized treatment protocols accounting for body weight.

A total of 1/5 of the patients died during the follow-up (Figure 6). The mortality rate was high considering that these patients are relatively young and assumed to outlive the usual wear-out time of surgical and transcatheter biologic valve prostheses, which is typically 10 to 15 years.[16] Compared with the studies by Kytö et al[7] and Bouhout et al,[10] the 10-year survival rate in the present study was lower (87.0% to 81.4% vs 78.3%). In contrast, compared with the study of Yuting et al,[9] the 10-year survival rate was marginally higher in the present study (approximately 75% vs 78.3%). Although major bleeding was notably increased, bleeding was a rare cause of death during the long-term follow-up. The leading underlying causes of death were coronary artery disease (CAD) and aortic valve stenosis, which align with previous reports.[21,22] However, of the patients who died because of CAD, only 1/5 had CAD before the operation. This highlights the importance of effective primary prevention in the mechanical AVR population.

Almost 1/10 of the patients received a permanent pacemaker (PPM) during follow-up. The impact of surgical AVR on the need for a pacemaker has been reported in previous studies.[23–26] In the patients who underwent TAVR, the risk of PPM implantation is known to be higher than

that of patients who underwent surgical AVR[25,27]; typically, the prevalence of PPM implantation after TAVR ranges from 9% to 26%.[25,28] In the present study, the indication for the PPM implantation was typically conduction abnormality involving the AV node (n = 20, 76.9%), which is in line with previous studies.[24]

The main limitation of this study is its retrospective, single-center setting. Nevertheless, the data were collected from electronic patient records in which data on the baseline, operation, and major outcomes are reported in detail. To obtain reliable and accurate follow-up data, only patients from the hospitals' catchment areas were included in this study. A professional third party monitored the data as a quality control of the database. Moreover, data on late mortality were obtained from Statistics Finland, ensuring the quality of survival data of the patients. The small size is another limitation of this analysis and therefore, these findings should be viewed as hypothesis-generating.

In conclusion, the risk for major bleeding was 5-fold compared with major stroke throughout the postoperative period and long-term follow-up. Although ischemic stroke is a well-identified adverse event after mechanical AVR, it seems that major bleeding is a markedly more frequent complication after mechanical AVR.

Declaration of Competing Interest

Dr. Björn received a research grant from Orion Research Foundation and the Vaasa Medical Foundation. Dr. Lehto received research grants from Orion Research Foundation, the Finnish Foundation for Cardiovascular Research, the Finnish Cultural Foundation, Turku University Foundation, and Emil Aaltonen Foundation. Dr. Malmberg has received travel grants and congress sponsorship (Abbott, Boston Lifesciences, Medtronic). Dr. Anttila has no conflicts interest to declare. Dr. Airaksinen received research grants from the Finnish Foundation for Cardiovascular Research, the Clinical Research Fund (VTR) of Turku University Hospital, Turku, Finland and lecture fees from Bayer, and Boehringer Ingelheim. K. E. Juhani Airaksinen is a member in the advisory boards of Bayer, Astra Zeneca, and Bristol-Myers Squibb-Pfizer. Dr. Gunn received research grants from Turku University Research Foundation, Turku, Finland, the Clinical Research Fund (VTR) of Turku University Hospital, Turku, Finland, and an unrestricted grant from Vifor Pharma. Dr. Kiviniemi received lecture fees from Bayer, Boehringer Ingelheim, MSD, Astra Zeneca, St Jude Medical, and Bristol-Myers-Squibb-Pfizer, and research grants from the Finnish Medical Foundation, The Finnish Foundation for Cardiovascular Research, Clinical Research Fund (EVO) of Turku University Hospital, Turku, Finland, Finnish Cardiac Society, the Emil Aaltonen Foundation, the Maud Kuistila Foundation, and an unrestricted grant from Bristol-Myers Squibb-Pfizer. Tuomas O. Kiviniemi is a member of the advisory board of Boehringer Ingelheim, and MSD.

Acknowledgment

The authors would like to thank study coordinator Tuija Vasankari, MS, for her input on data management.

Clinical trial registry number

CAREAVR (Consortium of Studies in the Field of Atrial Fibrillation, Stroke, and Bleeding in Patients Undergoing Aortic Valve Replacement): ClinicalTrials.gov Identifier NCT02626871

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.07.097.

1. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, Bonis M De, Paulis R De, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski W. ESC/EACTS Guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Rev Esp Cardiol (Engl Ed)* 2022;75:524.
2. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM, Thompson A, Toly C. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2021;143:e35–e71.
3. Torella M, Torella D, Chiodini P, Franciulli M, Romano G, Santo L De, Feo M De, Amarelli C, Sasso FC, Salvatore T, Ellison GM, Indolfi C, Cotrufo M, Nappi G. LOWERing the INtensity of oral anticoagulant therapy in patients with bileaflet mechanical aortic valve replacement: results from the "lOWERING-IT" Trial. *Am Heart J* 2010;160:171–178.
4. Labaf A, Svensson PJ, Renlund H, Jeppsson A, Själander A. Incidence and risk factors for thromboembolism and major bleeding in patients with mechanical valve prosthesis: A nationwide population-based study. *Am Heart J* 2016;181:1–9.
5. Puskas JD, Gerdisch M, Nichols D, Fermin L, Rhenman B, Kapoor D, Copeland J, Quinn R, Hughes GC, Azar H, McGrath M, Wait M, Kong B, Martin T, Douville EC, Meyer S, Ye J, Jamieson WRE, Landvater L, Hagberg R, Trotter T, Armitage J, Askew J, Accola K, Levy P, Duncan D, Yanagawa B, Ely J, Graeve A, Puskas J, Gerdisch M, Nichols D, Graeve A, PROACT Investigators. Anticoagulation and antiplatelet strategies after On-X mechanical aortic valve replacement. *J Am Coll Cardiol* 2018;71:2717–2726.
6. Ram E, Amunts S, Zuroff E, Peled Y, Kogan A, Raanani E, Sternik L. Outcomes of isolated surgical aortic valve replacement in the era of transcatheter aortic valve implantation. *J Card Surg* 2020;35:1452–1457.
7. Kytö V, Sipilä J, Ahtela E, Rautava P, Gunn J. Mechanical versus biologic prostheses for surgical aortic valve replacement in patients aged 50 to 70. *Ann Thorac Surg* 2020;110:102–110.
8. Vogt F, Santarpino G, Fujita B, Frerker C, Bauer T, Beckmann A, Bekeredjian R, Bleiziffer S, Möllmann H, Walther T, Beyersdorf F, Hamm C, Böning A, Baldus S, Ensminger S, Fischlein T, Eckner D, GARY Executive Board. Surgical aortic valve replacement in patients aged 50−69 years—insights from the German Aortic Valve Registry (GARY). *Eur J Cardiothorac Surg* 2022;62:1–8.
9. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA* 2014;312:1323–1329.
10. Bouhout I, Stevens LM, Mazine A, Poirier N, Cartier R, Demers P, El-Hamamsy I. Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults. *J Thorac Cardiovasc Surg* 2014;148:1341–1346. e1.
11. Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, Woo YJ. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. *N Engl J Med* 2017;377:1847–1857.
12. Généreux P, Cohen DJ, Williams MR, Mack M, Kodali SK, Svensson LG, Kirtane AJ, Xu K, McAndrew TC, Makkar R, Smith CR, Leon MB. Bleeding complications after surgical aortic valve replacement

compared with transcatheter aortic valve replacement: insights from the PARTNER i trial (Placement of Aortic transcatheter Valve). *J Am Coll Cardiol* 2014;63:1100–1109.
13. Crowther MA, Ageno W, Garcia D, Wang L, Witt DM, Clark NP, Blostein MD, Kahn SR, Vesely SK, Schulman S, Kovacs MJ, Rodger MA, Wells P, Anderson D, Ginsberg J, Selby R, Siragusa S, Silingardi M, Dowd MB, Kearon C. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. *Ann Intern Med* 2009;150:293–300.
14. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736–2747.
15. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE. Classification of subtype of acute ischemic stroke. *Stroke J Cereb Circ* 1993;23:35–41.
16. Kostyunin AE, Yuzhalin AE, Rezvova MA, Ovcharenko EA, Glushkova TV, Kutikhin AG. Degeneration of bioprosthetic heart valves: update 2020. *J Am Heart Assoc* 2020;9:e018506.
17. Gerdisch MW, Sathyamoorthy M, Michelena HI. The role of mechanical valves in the aortic position in the era of bioprostheses and TAVR: evidence-based appraisal and focus on the On-X valve. *Prog Cardiovasc Dis* 2022;72:31–40.
18. Thourani VH, Keeling WB, Kilgo PD, Puskas JD, Lattouf OM, Chen EP, Guyton RA. The impact of body mass index on morbidity and short- and long-term mortality in cardiac valvular surgery. *J Thorac Cardiovasc Surg* 2011;142:1052–1061.
19. van Nieuwkerk AC, Santos RB, Sartori S, Regueiro A, Tchétché D, Mehran R, Delewi R, Brito FS De, Tarasoutchi F, Barbanti M, Kornowski R, Orvin K, Latib A, Pagnesi M, D'Onofrio A, Tarantini G, Ribichini F, Lunardi M, Baan J, Tijssen J, Henriques JPS, Ten F, Dumonteil N, Ghattas A, D'Errigo P, Nogales JM, Modine T, Dangas G. Impact of body mass index on outcomes in patients undergoing transfemoral transcatheter aortic valve implantation. *JTCVS Open* 2021;6:26–36.
20. Koskinen A, Aittokallio J, Gunn J, Relander A, Viikinkoski E, Vasankari T, Jalkanen J, Hollmén M, Kiviniemi TO. Disadvantages of high fluid infusion rate in cardiac surgery. *Eur J Anaesthesiol* 2022;39:963–966.
21. Glaser N, Persson M, Franco-Cereceda A, Sartipy U. Cause of death after surgical aortic valve replacement: Swedeheart observational study. *J Am Heart Assoc* 2021;10:e022627.
22. Thyregod HGH, Ihlemann N, Jørgensen TH, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrøm T, Clemmensen P, Hansen PB, Andersen LW, Steinbrüchel DA, Olsen PS, Søndergaard L. Five-year clinical and echocardiographic outcomes from the nordic aortic valve intervention (notion) randomized clinical trial in lower surgical risk patients. *Circulation* 2019;139:2714–2723.
23. Dawkins S, Hobson AR, Kalra PR, Tang ATM, Monro JL, Dawkins KD. Permanent pacemaker implantation after isolated aortic valve replacement: incidence, indications, and predictors. *Ann Thorac Surg* 2008;85:108–112.
24. Ravaux JM, Van Kuijk SM, Di Mauro M, Vernooy K, Bidar E, Mariani S, Dato GA, Van T Hof AW, Veenstra L, Kats S, Houterman S, Maessen JG, Lorusso R, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration. Incidence and predictors of permanent pacemaker implantation after surgical aortic valve replacement: data of the Netherlands Heart Registration (NHR). *J Card Surg* 2021;36:3519–3527.
25. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–1620.
26. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR, PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–1705.
27. Rück A, Saleh N, Glaser N. Outcomes following permanent pacemaker implantation after transcatheter aortic valve replacement: SWEDEHEART observational study. *JACC Cardiovasc Interv* 2021;14:2173–2181.
28. Reardon MJ, Mieghem NM Van, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PWJC, Kappetein AP, SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376:1321–1331.