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Comparison of warfarin versus antiplatelet therapy after surgical bioprosthetic aortic valve replacement

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ABSTRACT

Objectives To compare effectiveness of warfarin and antiplatelet exposure regarding both thrombotic and bleeding events, following surgical aortic valve replacement with a biological prosthesis(bioSAVR).

Methods The study included all patients in Sweden undergoing a bioSAVR during 2008–2014 who were alive at discharge from the index hospital stay. Exposure was analysed and defined as postdischarge dispension of any antithrombotic pharmaceutical, updated at each following dispensions and categorised as single antiplatelet (SAPT), warfarin, warfarin combined with SAPT, dual antiplatelet (DAPT) or no antithrombotic treatment. Exposure to SAPT was used as comparator. Outcome events were all-cause mortality, ischaemic stroke, haemorrhagic stroke, any thromboembolism and major bleedings. We continuously updated adjustments for comorbidities with any indication for antithrombotic treatment by Cox regression analysis.

Results We identified 9539 patients with bioSAVR (36.8% women) at median age of 73 years with a mean follow-up of 3.13 years. As compared with SAPT, warfarin alone was associated with a lower incidence of ischaemic stroke (HR 0.49, 95% CI 0.35 to 0.70) and any thromboembolism (HR 0.75, 95% CI 0.60 to 0.94) but with no difference in mortality (HR 0.94, 95% CI 0.78 to 1.13). The incidence of haemorrhagic stroke (HR 1.94, 95% CI 1.07 to 3.51) and major bleeding (HR 1.67, 95% CI 1.30 to 2.15) was higher during warfarin exposure. As compared with SAPT, DAPT was not associated with any difference in ischaemic stroke or any thromboembolism. Risk-benefit analyses demonstrated that 2.7 (95% CI 1.0 to 11.9) of the ischaemic stroke cases could potentially be avoided per every haemorrhagic stroke caused by warfarin exposure instead of SAPT during the first year.

Conclusion In patients discharged after bioSAVR, warfarin exposure as compared with SAPT exposure was associated with lower long-term risk of ischaemic stroke and thromboembolic events, and with a higher incidence of bleeding events but with similar mortality.

INTRODUCTION

After aortic valve replacement (AVR), patients still experience excess mortality compared with the general population.[1] The observed excess mortality can be partly attributed to morbidity related to the prosthesis and associated medication. Biological as compared with mechanical prostheses require less intensive antithrombotic therapy and are therefore the first-line choice in most patients undergoing surgical AVR.

The reported incidence of long-term thromboembolic events after aortic valve surgery with a bioprosthesis (bioSAVR) vary considerably, and generalisation of historical reports to current AVR cohorts must be done with caution.[2 3] Patient characteristics have changed over the years with higher mean age, more atrial fibrillation (AF), concomitant coronary disease and comorbidities that contribute to increased risk of thromboembolic events yet with a lower 30-day mortality.[3 4] There is a substantial amount of data supporting long-term oral anticoagulant treatment (OAC) after valve intervention in patients with AF but whether the majority of patients without prior AF benefit from OAC treatment is not established.[5 6] In the absence of other indications for OAC, current guidelines recommend oral antithrombotic treatment with aspirin or warfarin for 3 months after bioSAVR.[5 6] This recommendation is based on a low level of evidence and should be regarded as expert opinions only.[5 6]

The occurrence of leaflet thrombosis and immobility in bioprostheses with the potential influence on the risk of ischaemic stroke has been increasingly recognised after both transcatheter AVR (TAVI) and bioSAVR.[7 8] However, the true incidence is unclear and the clinical relevance of subclinical leaflet thrombosis is not well established. The incidence of thromboembolic events during the first 3 months after discharge is low and in some series the majority of valve thrombosis cases after SAVR occur >1 year after implantation.[8 9] Altogether, these data suggest that it might be beneficial to prolong the duration and/or intensity of antithrombotic treatment. On the contrary, bleeding risk increases with longer duration. In summary, there are conflicting opinions on the optimal antithrombotic treatment, including strategy and duration of treatment after intervention with a biological prosthesis.[9–12] This study therefore aimed to evaluate the effectiveness of different antithrombotic therapies to identify the antithrombotic regimen that yields highest possible balance between thrombotic and bleeding risks following bioSAVR.

METHODS

Study population and data sources

Surgical AVR is performed at eight centres in Sweden. All patients undergoing cardiac surgery are continuously included in the Swedish Web system for Enhancement and Development of

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Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART).[13] The present study cohort included all patients undergoing a bioSAVR, with or without coronary artery bypass grafting, between 1 January 2008 and 31 December 2014 and who were alive at discharge from the index intervention. The bioSAVR group included all types of biological prosthesis. Patients receiving more than one valve prosthesis (n=332) and patients treated with a mechanical prosthesis (n=2447) were not included. In addition, patients with missing information about previous coronary intervention or left ventricular ejection fraction (LVEF) at index intervention (n=55) were excluded. All patients admitted for bioSAVR are informed of the inclusion in the SWEDEHEART according to ethical approval, and no written informed consent are obtained.

Data collection

The SWEDEHEART registry contains detailed information on the procedures and concomitant diseases. Baseline information from SWEDEHEART was enriched with information from the National Patient Register (NPR), which includes the diagnosis codes (International Code of Disease, 10th Revision (ICD-10)) of all hospital admissions in Sweden since 1987.[14] Linkage was based on the unique 10-digit personal identification number assigned to all Swedish residents at birth or immigration. The National Board of Health and Welfare merged the registries.

All patients were followed through computerised linkage between the database and the updated census register, the Swedish Cause of Death Register and the NPR, all managed by the National Board of Health and Welfare. The start date was 1 day after discharge from the index intervention. The study cohort was followed until death or the end of follow-up (31 December 2014), whichever occurred first.

Baseline information and comorbidities

Information on baseline characteristics and previously diagnosed comorbidities occurring up to 3 years before the valve intervention were defined as hospital admission due to any of the comorbidities as the primary diagnosis in the NPR or collected from the SWEDEHEART registry. Predefined comorbidities at baseline were diabetes, hypertension, congestive heart failure (CHF), AF, myocardial infarction (MI), any thromboembolism (ie, ischaemic stroke, systemic embolism, pulmonary embolism and venous thromboembolism) and major bleeding (ie, haemorrhagic stroke and hospitalisation for other bleeding event). Comorbidities were continuously updated during the follow-up and included in the adjusted models. The ICD-10 was applied to identify comorbidities and outcome events (online supplementary eTable 1).

Exposure to oral antithrombotic treatment

Information on the dispension of oral antiplatelet and anticoagulant treatment was collected by computerised linkage with the Dispensed Drug Register. The register contains information on every prescription and dispension of drugs in every pharmacy in Sweden. The patient was considered exposed to the corresponding dispensed antithrombotic treatment for 120 days after each dispension, if no new dispension occurred. Information on dispension was continuously updated, and patients could be exposed to different pharmaceutical treatment during follow-up and patients changed groups every time a new class of antithrombotic agent was dispensed. The constructed variable regarding exposure to oral antithrombotic treatment at any given time point was categorised into five exposure groups: 1) single antiplatelet treatment (SAPT, either aspirin or $P2Y_{12}$ inhibitor), 2) warfarin, 3) warfarin plus a SAPT or a dual antiplatelet treatment (DAPT), 4) DAPT (aspirin and $P2Y_{12}$ inhibitor) only and 5) no antithrombotic treatment. Information on dispension of non-vitamin K antagonist oral anticoagulant drugs was collected separately, and not included in further analyses.

Outcome events

Outcome events after discharge from the index surgical procedure were all-cause mortality, new hospitalisation for ischaemic stroke, any thromboembolism, haemorrhagic stroke and major bleeding.

Statistical methods

Categorical variables were expressed as frequencies and percentages and continuous variables as median and IQRs (Q1–Q3).

Exposure to a pharmaceutical agent was assessed and updated at every dispension. Consequently, each patient could be exposed to different pharmaceutical categories during follow-up. The sum of periods that patients were exposed to each pharmaceutical category was computed and presented in person-years (PY) for each pharmaceutical category and an incidence rate/100 PY was calculated for each outcome event, started at discharge from the index intervention.

Kaplan-Meier curves for time-dependent exposure, also known as Simon-Makuch curves, were created by restarting patients after a treatment switch.[15]

The association between outcome events and baseline characteristics and continuously updated comorbidities (denominated prior AF, prior thromboembolism, prior major bleeding, prior MI and prior coronary intervention) were explored in unadjusted Cox regression analyses for each variable.

The associations between oral antithrombotic exposure groups and repeated outcome events were analysed using multivariable Cox regression models. To account for data dependency due to recurrent events, robust Huber-White SEs were computed.[16] A crude model that includes only antithrombotic exposure as a time-dependent variable was performed for each outcome event: all-cause mortality, ischaemic stroke, any thromboembolism, haemorrhagic stroke and major bleeding. In addition, adjusted models were fitted, included age, sex, LVEF, diabetes, hypertension, CHF and the continuously updated comorbidities; prior AF, prior thromboembolism (ie, ischaemic stroke, systemic embolism, pulmonary embolism and venous thromboembolism), prior major bleeding, (ie, haemorrhagic stroke and hospitalisation for other bleeding event), prior MI, prior coronary intervention and coronary intervention at index valve replacement.

The results of unadjusted and fully adjusted Cox analysis were presented as HRs with 95% CIs. The proportional hazard assumptions were checked using Schoenfeld residuals.

Interactions between antithrombotic treatment exposure and age or prior AF was tested for using an interaction term in the multivariable Cox model.

A sensitivity analysis was performed of patients without prior AF at the index intervention. In a risk–benefit analysis, the number of prevented ischaemic strokes per caused haemorrhagic stroke due to warfarin treatment instead of SAPT were estimated. This analysis was performed by estimating absolutes risks, separately for each outcome and treatment, using the baseline hazard from the adjusted Cox model as described above. This was done for a random sample of 200 patients, for computer performance reasons, keeping their comorbidities fixed at the baseline values and synthetically setting the antithrombotic treatment to either

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Table 1 Baseline characteristics expressed as frequencies and percentages if not otherwise stated

	bioSAVR n=9539
Age at index intervention median (Q1–Q3)	73 (67–78)
Sex	
Female	3509 (36.8%)
Male	6030 (63.2%)
LVEF	
>0.50	6991 (73.1%)
0.30–0.50	2072 (21.7%)
<0.30	496 (5.2%)
Coronary intervention at index intervention*	3285 (34.4%)
Medical history	
Diabetes	1833 (19.2%)
Hypertension	3736 (39.2%)
Ischaemic stroke	819 (8.6%)
Systemic embolism	314 (3.3%)
Pulmonary embolism and venous thromboembolism	684 (7.2%)
Haemorrhagic stroke	36 (0.4%)
Other bleeding event	355 (3.7%)
Myocardial infarction	1264 (13.3%)
Peripheral artery disease	612 (6.4%)
Heart failure	1234 (12.9%)
Atrial fibrillation	1454 (15.2%)
Previous thoracic surgery	470 (4.9%)
Previous percutaneous coronary intervention	1105 (11.6%)

*Coronary intervention at index intervention; coronary artery bypass grafting or percutaneous coronary intervention within 3 months.
bioSAVR, surgical aortic valve replacement with a biological prosthesis; LVEF, left ventricular ejection fraction at index intervention.

warfarin or SAPT. Finally, these risks were averaged over the 200 patients, and the ratio between the risk differences (SAPT vs warfarin) was computed. CIs were computed based on 2500 bootstrap replicates.

Patient and public involvement

The patients were not involved in the present study.

RESULTS

Clinical characteristics

The study cohort consisted of 9539 patients who had received a surgical biological prosthetic valve in the aortic position. The median age at index intervention was 73 (range 67–78) years and 3509 (36.8%) were females. Prior to intervention, 819 (8.6%) patients had a history of ischaemic stroke and 36 (0.4%) patients had suffered from a haemorrhagic stroke (table 1). At baseline, 1454 (15.2%) patients had experienced AF prior to intervention and another 1064 experienced AF during follow-up. Few patients experienced MI or coronary intervention during follow-up (data not shown).

Outcome events during follow-up

No patient was lost from follow-up. During a mean follow-up of 3.13 years (median 2.99, maximum 6.97 years), 1157 (12.2%) patients died (3.92/100 PY). In total, there were 895 thromboembolic events (3.04/100 PY). Out of these, 405 (45%) were an ischaemic stroke (1.37/100 PY). There were in total 573 major bleeding events (1.94/100 PY) and of these 129 (23%) were a haemorrhagic stroke (0.44/100 PY). Of the outcome events 128 deaths, 157 thromboembolic events and 138 major bleeding events occurred during the first 3 months after discharge.

The association of outcome events with comorbidities

Comorbidities associated with outcome events are presented in online supplementary eTable 2. The most important risk factors of ischaemic stroke and haemorrhagic stroke were prior occurrence of a thromboembolic (HR 3.89, 95% CI 3.12 to 4.86) or a bleeding event (HR 8.86, 95% CI 6.35 to 12.37), (online supplementary eTable 2), respectively.

Antithrombotic exposure

During the total follow-up (29 487 PY), the proportion of exposure in relation to the total person-time to SAPT was 52.7%, to warfarin 19.3%, to warfarin in combination with SAPT 5.8% and to DAPT 1.0%. Patients were without antithrombotic treatment during 21.2% of the total person-time (online supplementary eTable 3). During the first 3 months after discharge, the proportion of exposure to SAPT was 32.6%, to warfarin 31.7%, to warfarin in combination with SAPT 27.1% and to DAPT 1.8%.

The association of outcome events to antithrombotic treatment

The number of outcome events and the corresponding incidence rates of death, ischaemic stroke, any thromboembolism, haemorrhagic stroke and any bleeding by antithrombotic treatment exposure are presented in table 2.

All-cause mortality

The lowest mortality rate was noted during exposure to SAPT (3.04/100 PY) and the highest during periods without oral antithrombotic treatment (6.10/100 PY) (table 2, figure 1A). Warfarin exposure was not associated with higher mortality as compared with SAPT (HR 0.94, 95% CI 0.78 to 1.13) (figure 2A). An additional antiplatelet drug (DAPT 5.74/100 PY) did not influence

Table 2 Antithrombotic exposure and outcome events during follow-up

	Single antiplatelet treatment	Warfarin treatment	Warfarin+SAPT	Dual antiplatelet treatment	No oral antithrombotic treatment
All-cause mortality*	473 (155.5) 3.04	212 (56.9) 3.72	74 (17.1) 4.34	17 (3.0) 5.74	381 (62.4) 6.10
Ischaemic stroke*	215 (155.5) 1.38	57 (56.9) 1.00	29 (17.1) 1.70	6 (3.0) 2.03	98 (62.4) 1.57
Any thromboembolism*	442 (155.5) 2.84	163 (56.9) 2.86	71 (17.1) 4.16	12 (3.0) 4.05	207 (62.4) 3.32
Haemorrhagic stroke*	42 (155.5) 0.27	42 (56.9) 0.74	21 (17.1) 1.23	1 (3.0) 0.34	23 (62.4) 0.37
Major bleeding*	207 (155.5) 1.33	172 (56.7) 3.02	84 (17.1) 4.93	4 (3.0) 1.35	106 (62.4) 1.70

*Expressed as frequencies (person-time) incidence rate/100 patient-years.
SAPT, single antiplatelet treatment.

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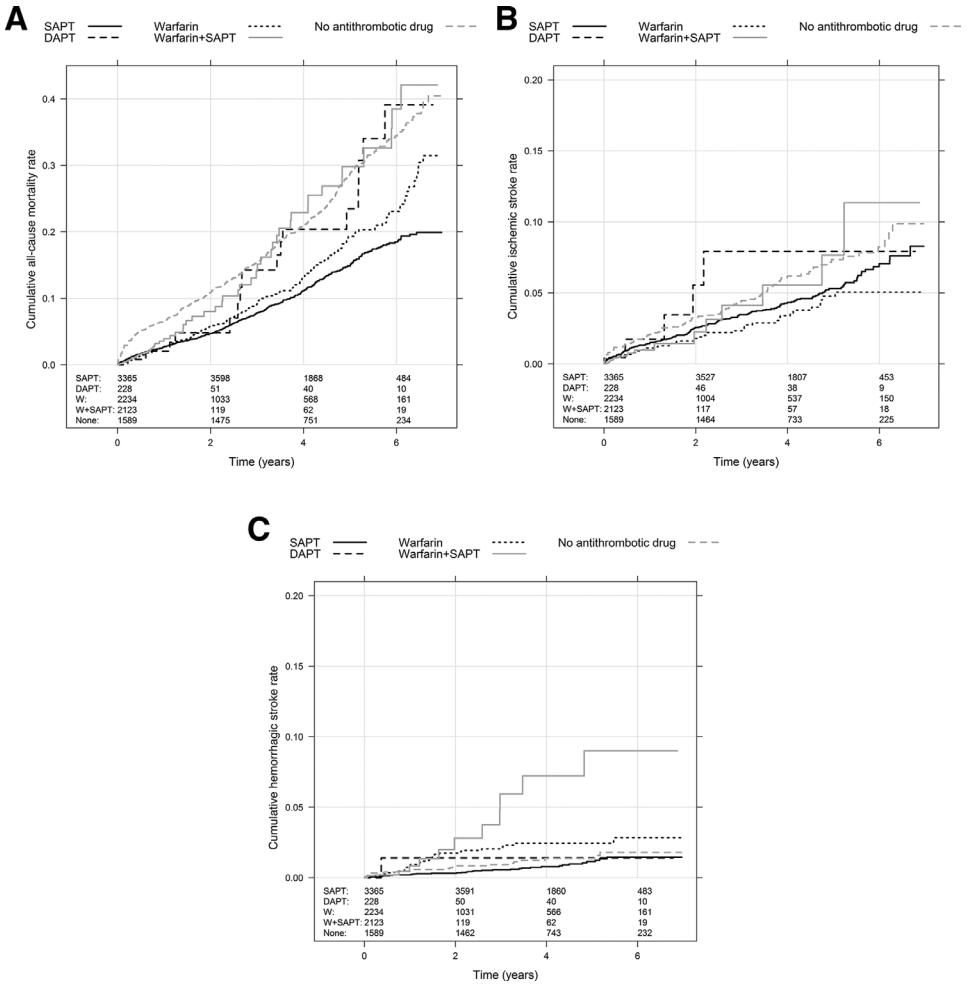

Figure 1 Incidence of outcome events by different antithrombotic exposures Kaplan-Meier estimates for (A) all-cause mortality, (B) ischaemic stroke and (C) haemorrhagic stroke during follow-up. The lines represent different antithrombotic exposures: single antiplatelet treatment (SAPT), warfarin,W+SAPT, dual antiplatelet treatment (DAPT) and no oral antithrombotic treatment.

mortality (HR 1.32, 95% CI 0.81 to 2.15) as compared with SAPT alone (figure 2A). The overall risk of mortality was higher (HR 2.14, 95% CI 1.85 to 2.49) during periods without antithrombotic treatment as compared with SAPT (figure 2A). Similar results were found when the group with AF prior to intervention were excluded from the analyses (online supplementary eFigure 3). No interaction was found between antithrombotic treatment and age (p=0.11) and prior AF (p=0.065).

Ischaemic stroke and any thromboembolism

During SAPT exposure, the incidence rate was 1.38/100 PY for ischaemic stroke and 2.84/100 PY for any thromboembolism (table 2, figure 1B, online supplementary eFigure 1). The incidence rate observed during warfarin exposure indicated a somewhat lower incidence of ischaemic stroke (1.00/100 PY) but not for any thromboembolism (2.86/100 PY) (table 2). In adjusted analysis warfarin exposure gave a lower incidence of ischaemic stroke (HR 0.49, 95% CI 0.35 to 0.70) and any thromboembolism (HR 0.75, 95% CI 0.60 to 0.94) as compared with SAPT (figure 2B, online supplementary eFigure 2). There were no differences between DAPT and SAPT exposure (figure 2B, online supplementary eFigure 2). During time periods without antithrombotic exposure, the incidence of ischaemic stroke was similar, but a higher incidence of any thromboembolism was observed (HR 1.31, 95% CI 1.09 to 1.58) compared with SAPT (online supplementary eFigure 2). Similar results were found when the group with AF prior to intervention were excluded from the analyses (online supplementary eFigure 3).

No interaction was found between antithrombotic treatment and age regarding the incidence of ischaemic stroke (p=0.12) but concerning any thromboembolism (p=0.004). Warfarin was associated with lower incidence of any thromboembolism in older age groups. No interactions were found between antithrombotic treatment and prior AF regarding the incidence of ischaemic stroke (p=0.36) or any thromboembolism (p=0.64).

Haemorrhagic stroke and major bleeding

During SAPT exposure, the incidence rate was 0.27/100 PY for haemorrhagic stroke and 1.33/100 PY for major bleeding (table 2, figure 1C, online supplementary eFigure 1). During warfarin exposure, the incidence rate was 0.74/100 PY for haemorrhagic stroke and 3.02/100 PY for major bleeding (table 2). After multivariable adjustment, warfarin exposure was associated with a higher incidence of haemorrhagic stroke (HR 1.94, 95% CI 1.07 to 3.51) and major bleeding (HR 1.67, 95% CI 1.30 to 2.15) as compared with SAPT (figure 2C, online supplementary eFigure 2). The number of haemorrhagic stroke hospitalisations during DAPT exposure was low (n=1). No difference was found between DAPT or no antithrombotic treatment and SAPT exposure regarding major bleeding (online supplementary

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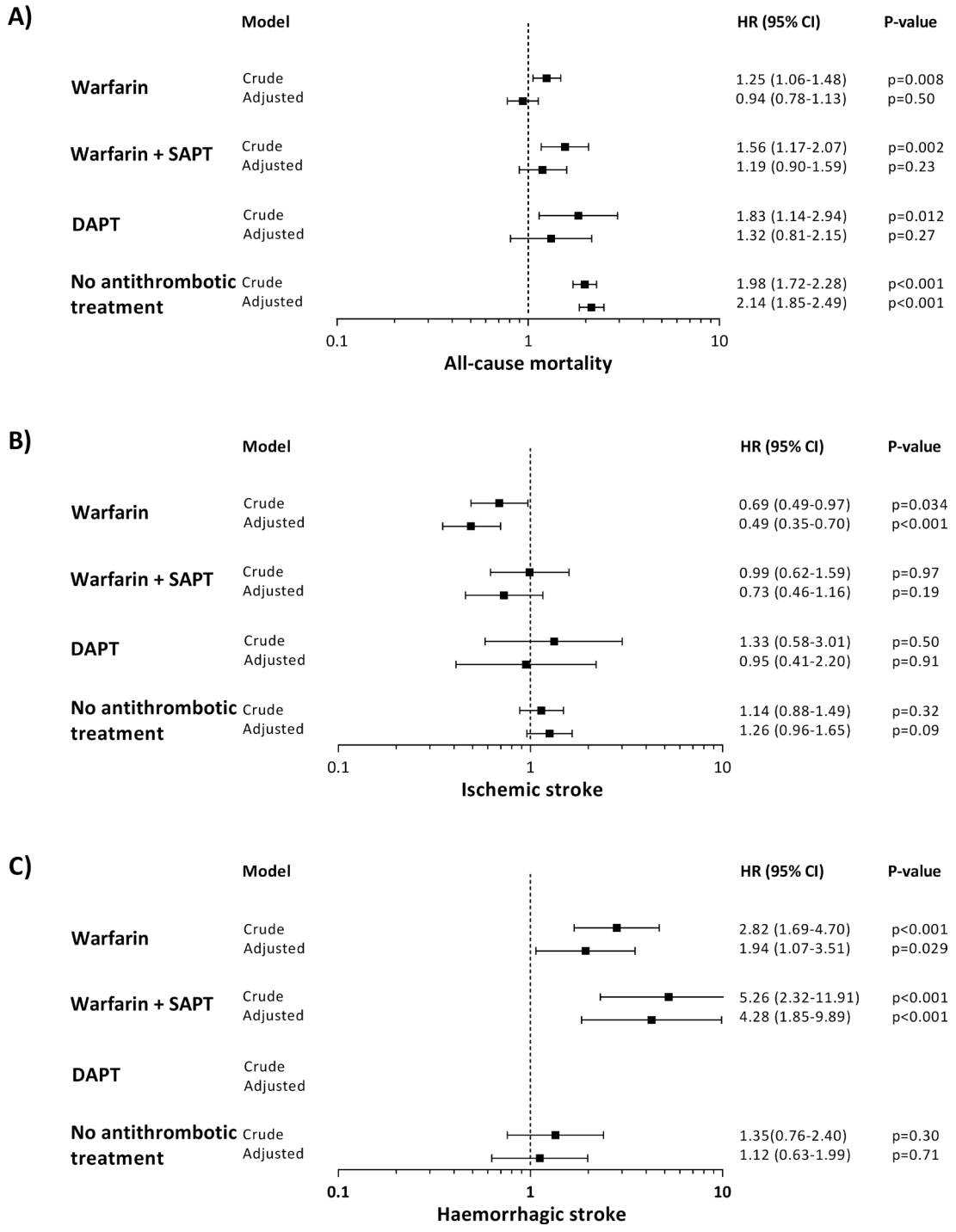

Figure 2 The relative risk of outcome events by different antithrombotic exposures relative to SAPT forest plots describing the relative risk of (A) all-cause mortality, (B) ischaemic stroke and (C) haemorrhagic stroke by warfarin, warfarin+single antiplatelet treatment (SAPT), dual antiplatelet treatment (DAPT) and no antithrombotic treatment relative to SAPT in a crude model. The adjusted model included adjustment for age, sex, left ventricular ejection fraction (<0.30, 0.30–0.50, >0.50), diabetes, hypertension, heart failure and the continuously updated comorbidities; prior atrial fibrillation, prior thromboembolism (ie, ischaemic stroke, systemic embolism, pulmonary embolism and venous thromboembolism), prior major bleeding (ie, haemorrhagic stroke and hospitalisation for other bleeding), prior myocardial infarction, prior coronary intervention and coronary intervention at index valve replacement. The number of haemorrhagic strokes were low during exposure to DAPT (n=1) and no relative risk analysis was performed (C).

eFigure 2). Similar results were found when the group with AF prior to intervention was excluded from the analyses (online supplementary eFigure 4).

There were no interactions for antithrombotic treatment and age regarding haemorrhagic stroke (p=0.90) or major bleeding (p=0.60). No interactions were found between antithrombotic treatment and prior AF regarding the incidence of haemorrhagic stroke (p=0.83) but concerning major bleeding (p<0.001).

Risk-benefit of antithrombotic treatment

Risk-benefit analyses demonstrated that 2.7 (95% CI 1.0 to 11.9) of the ischaemic strokes could potentially be avoided

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per every haemorrhagic stroke caused by warfarin, if patients were exposed to warfarin instead of SAPT during the first year. Similar results were found after 3 years, 2.0 (95% CI. 0.8 to 9.0).

DISCUSSION

After surgical AVR with a biological prosthesis, warfarin treatment was associated with a lower incidence of ischaemic stroke and any thromboembolism without higher mortality as compared with SAPT during long-term follow-up in this study of actual pharmaceutical exposure analysing nationwide complete registries. Furthermore, no tendency towards lower incidence of ischaemic stroke associated with DAPT as compared with SAPT was observed. As expected, exposure to increased intensity of antithrombotic treatment (ie, warfarin) was associated with a higher incidence of haemorrhagic stroke.

Biological aortic prosthesis exposes the patient to increased risk of thromboembolic events.[17 18] This concern has been proposed to be of greater clinical relevance early after an intervention as reflected in current recommendations of antithrombotic treatment for 3 months after biological valve surgery.[5] However, the number of studies supporting this position is limited, and it is increasingly being questioned.[2 8 9 18] A prospective, non-randomised study comparing aspirin with warfarin for 3 months starting 1 day after surgery found no significant differences between the two treatments.[11] Results from retrospective studies are conflicting, describing similar effects of aspirin and warfarin or an increased risk of thromboembolic events after cessation of warfarin during the first 6 months postintervention.[9 12] In our study, ongoing treatment with warfarin, up to 3 years after intervention, was associated with lower incidence of ischaemic stroke, representing a large proportion of all thromboembolic events, compared with SAPT.

In recent years, the issue of valve thrombosis with and without leaflet immobility has been highlighted and proposed to be important for thromboembolic events and structural valve failure.[19] In these studies, most valve thrombosis events occurred >1 year after the intervention, which may indicate a potential benefit of extended antithrombotic therapy.[8 17] Prostheses evaluated by CT exhibits a larger proportion of subclinical leaflet thrombosis than previously known and has been described after both bioSAVR and TAVI, and OAC has been shown to improve valve motion.[20] The importance of these findings remains to be fully comprehended but an association between leaflet thrombosis and stroke or transient ischaemic attack is plausible and has previously been described.[7]

In our large, nationwide, well-described and unselected cohort, 15% of the patients had AF as comorbidity before intervention, and another 6% experienced AF during follow-up, a condition that has previously been shown to be strongly associated with mortality and stroke in AVR.[21 22] For these patients, therapy with OAC is considered a relatively safe option.[3 5] In the present study, representing a bioSAVR cohort, the association between warfarin use and ischaemic stroke was not significantly modulated by prior AF. Therefore, our results support strengthening the indication for OAC regardless of AF as comorbidity or AF during follow-up. Moreover, warfarin exposure reduced the total incidence of thromboembolic events, and the association with OAC exposure remained after adjustment for cardiovascular risk factors, suggesting that conclusions about benefit in this study could be drawn for the entire cohort. However, further studies are warranted to establish the patient groups with the highest benefit of OAC.

Overall warfarin exposure was not related to higher mortality. However, as compared with SAPT, warfarin was associated with a higher risk of haemorrhagic stroke.[23] In the risk-benefit analysis, 2.7 ischaemic strokes could be prevented for each haemorrhagic stroke caused by warfarin. Considering the approximately 2000 patients undergoing bioSAVR in Sweden every year, a substantial number of ischaemic stroke cases might be avoided if patients were consistently shifted to warfarin therapy. There was no interaction between antithrombotic treatment and age on clinical outcomes. Since the incidence of ischaemic stroke increases with increasing age, the relative efficiency obtained by warfarin exposure in the elderly results in a more prominent absolute benefit. Notably, we found no tendency towards increased bleeding risk associated with warfarin in the elderly.

This study confirms an association between warfarin exposure with any major bleeding, of which haemorrhagic stroke only represented a minority of such events.[24] The most important risk factor for a major bleeding event during follow-up was a prior bleeding emphasising the importance of risk stratification of bleeding in bioSAVR.

There was no indication for benefit of DAPT when compared with SAPT in the current bioSAVR cohort, even though exposure to DAPT was low. These results are consistent with previously reported data in TAVI.[10] Prospective randomised trials comparing DAPT and SAPT after bioSAVR are warranted.

Limitations

This study is based on national registries that enable generalisation to European surgical AVR populations.[13] The SWEDEHEART registry has complete national unselected enrolment of patients undergoing bioSAVR and has been subjected to onsite monitoring and validation and shown to produce high levels of agreement between the registry and available data in the electronic health records.[13] The NPR contains data on all hospital admissions in Sweden since 1987, with a validity of cardiovascular diagnosis approaching 95%.[14] Another limitation concerns the potential impact that an unmeasured confounder could have on the study; however, our study included most clinically relevant information that could explain the association between these pharmaceuticals and outcome. The definition of drug exposure after the last dispension of the antithrombotic drug indicates that actual intake is not guaranteed.[25] Furthermore, we had no information on the international normalised ratio of the patients prescribed warfarin. However, the anticoagulant treatment in Sweden is generally of high quality.[26] Pharmaceuticals are involved in a comprehensive reimbursement programme in Sweden, and usage of pharmaceuticals outside this programme can be expected to be marginal also regarding aspirin. The optimal duration of antithrombotic treatment after bioSAVR is not defined in the present study and has to be further evaluated. Despite the limitations noted, our approach, which included a continuous update of pharmaceutical exposure during all follow-ups, should offer an accurate assessment of outcome associated with exposure to prosthesis and related medication. Finally, our study has to be interpreted with caution because of inherent limitations to all observational studies related to confounding by indication.

CONCLUSIONS

Compared with SAPT, antithrombotic treatment with warfarin after surgical intervention with an aortic biological prosthesis was associated with a lower incidence of ischaemic stroke

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Key questions

What is already known on this subject?

- Guidelines for antithrombotic treatment after bioSAVR in patients without other indication for oral anticoagulant treatment recommend aspirin or warfarin for 3 months, based on low level of evidence.
- The risk of leaflet thrombosis and thromboembolism is not limited to the first 3 months.

What might this study add?

- After bioSAVR, exposure to warfarin treatment was associated with a lower incidence of ischaemic stroke without higher mortality as compared with single antiplatelet therapy (SAPT) during long-term follow-up.
- Risk-benefit analyses demonstrated that 2.7 (95% CI 1.0 to 11.9) of the ischaemic stroke cases could potentially be avoided per every haemorrhagic stroke caused by warfarin exposure instead of SAPT during the first year.

How might this impact on clinical practice?

- The association between warfarin exposure and ischaemic stroke was not significantly modulated by prior atrial fibrillation.
- Our results support strengthening the indication for oral anticoagulant treatment in all patients with bioSAVR and underlies the need of thorough risk-benefit analysis regarding antithrombotic treatment not limited to the first 3 months.

and any thromboembolism during long-term follow-up. Warfarin was not associated with higher mortality but with a higher incidence of haemorrhagic stroke. DAPT was not superior to SAPT regarding the risk of ischaemic stroke or any thromboembolism.

Contributors CC, SKJ and ES contributed substantially to the design of the present study. LL performed the statistical analyses. CC and ES provided the first draft of the manuscript. All coauthors participated in the interpretation of data and critically revised the manuscript. All authors have approved the final version of the manuscript. CC, ES and LL had full access to the database and take responsibility for the integrity and of the data and the data analyses.

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