European Heart Journal Supplements (2020) **22** (Supplement C), C26–C33
The Heart of the Matter
doi:10.1093/eurheartj/suaa007

ESC European Society of Cardiology

Haemorrhagic stroke and major bleeding after intervention with biological aortic valve prosthesis: risk factors and antithrombotic treatment

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KEYWORDS
Aortic valve intervention;
Biological prosthesis;
Antithrombotic treatment;
Haemorrhagic stroke;
Major bleeding event

The majority of patients with severe aortic stenosis are recommended intervention with a surgical biological prosthesis (bioSAVR) or a transcatheter aortic valve intervention (TAVI). The antithrombotic strategies after aortic valve intervention vary and include drugs targeting both platelets and the coagulation cascade. Long-term exposure and changes of antithrombotic treatment influence the risk of both bleeding and thromboembolic events.

The aim was to describe an unselected sample of patients who have experienced haemorrhagic stroke and other major bleeding events after biological aortic prosthesis, their antithrombotic treatment and changes of treatments in relation to the bleeding event.

All patients performing an bioSAVR or a TAVI 2008–2014 were identified in the SWEDEHEART registry and included in the study ($n = 10\,711$). The outcome events were haemorrhagic stroke and other major bleeding event. Information of drug exposure was collected from the dispensed drug registry.

The incidence rate of any bleeding event was 2.85/100 patient-years the first year after aortic valve intervention. Heart failure and atrial fibrillation were present more often in patients with a first haemorrhagic stroke or other major bleeding event compared to without. The proportion of exposure to warfarin was 28.7% vs. 21.3% in patients with and without a haemorrhagic stroke. Comparable figures were 31.2% vs. 19.0% in patients with and without other major bleeding event. During 1 month prior a haemorrhagic stroke or other major bleeding event 39.4% and 38.0%, respectively, of the patients not previously exposed to antithrombotic treatment started warfarin or single antiplatelet therapy.

Major bleeding events are not uncommon after aortic valve intervention with a biological prosthesis. Evaluation of comorbidities and previous bleeding might improve risk stratification for bleeding in these elderly patients. The pattern of change of antithrombotic treatment was similar in the groups with and without a bleeding event and in most patients the antithrombotic regime was unchanged the month before an event.

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PALABRAS CLAVE
prótesis biológica;
tratamiento antitrombótico;
ictus hemorrágico;
episodios hemorrágicos;
importantes

A la mayoría de los pacientes con estenosis de la válvula aórtica grave se les recomienda someterse a una valvuloplastia con prótesis biológica (bioSAVR) o a una valvuloplastia aórtica transcateteral (TAVI). Las estrategias antitrombóticas tras una valvuloplastia aórtica son distintas y, entre ellas, se incluyen fármacos dirigidos tanto a las plaquetas como a la cascada de la coagulación. La exposición prolongada y los cambios en el tratamiento antitrombótico influyen en el riesgo de sufrir complicaciones hemorrágicas y tromboembólicas.
El objetivo es describir una muestra de pacientes sin seleccionar que han padecido ictus hemorrágicos u otros episodios hemorrágicos importantes tras una valvuloplastia aórtica con prótesis biológica, así como el tratamiento antitrombótico y los cambios de tratamientos en relación con la hemorragia.
Todos los pacientes sometidos a bioSAVR o TAVI en 2008-2014 se encontraban en el registro SWEDEHEART y se incluyeron en el estudio (n = 10 711). Los criterios de valoración fueron ictus hemorrágico y otras hemorragias importantes. La información de la exposición al fármaco se recogió del registro de dispensación de fármacos.
En el primer año tras la valvuloplastia aórtica, la tasa de incidencia de cualquier episodio hemorrágico fue de 2,85 por 100 pacientes. La insuficiencia cardíaca y la fibrilación auricular fueron más frecuentes en pacientes con presencia de un primer ictus hemorrágico u otras hemorragias importantes en comparación con el grupo de control. La proporción de exposición a warfarina fue del 28,7% frente al 21,3% en pacientes con presencia y ausencia de un ictus hemorrágico, respectivamente. Cifras comparables fueron el 31,2% frente al 19,0% en pacientes con presencia y ausencia de otros episodios hemorrágicos importantes, respectivamente. Un mes antes de que se produjera el ictus hemorrágico u otras hemorragias importantes, el 39,4% y el 38,0%, respectivamente, de los pacientes que no estaban previamente expuestos a un tratamiento antitrombótico comenzaron un tratamiento con warfarina o antiagregante plaquetario simple.
La presencia de episodios hemorrágicos importantes es frecuente tras una valvuloplastia aórtica con prótesis biológica. La evaluación de comorbilidades y hemorragias anteriores puede mejorar la estratificación de riesgos de sufrir hemorragias en pacientes de avanzada edad. El tipo de cambio del tratamiento antitrombótico fue similar en el grupo de control y en el grupo con presencia de un episodio hemorrágico y, en la mayoría de los pacientes, no se modificó la pauta de administración del antitrombótico en el mes previo al episodio hemorrágico.

关键词
主动脉瓣介入;
生物假体;
抗血栓治疗;
出血性卒中;
重大出血事件

建议大多数患有严重主动脉瓣狭窄的患者采用外科生物假体（SAVR）或经导管主动脉瓣膜介入（TAVI）进行干预。主动脉瓣介入后抗血栓形成的策略各异，包括靶向血小板和凝血级联的药物。长期的抗血栓治疗和抗血栓治疗的改变会影响出血和血栓栓塞事件的风险。
用于描述未经选择的患者样本，这些患者在生物主动脉假体术后经历了出血性卒中和其他主要出血事件，他们的抗血栓治疗和治疗方法的改变与出血事件有关。
在 SWEDEHEART 登记表中识别出 2008-2014 年所有进行过 SAVR 或 TAVI 的患者，并纳入研究 （n = 10711）。结果事件是出血性卒中和其他重大出血事件。药物暴露信息是从配药登记表中收集的。
主动脉瓣介入治疗后第一年任何出血事件的发生率均为2.85/100（患者/年）。初次出血性卒中或其他严重出血的患者心力衰竭和心房颤动的发生率更高。出血性卒中患者华法林暴露的比例为28.7%，而非出血性卒中患者的暴露率为21.3%。有或没有其他重大出血事件的患者可比数字是 31.2% 与 19.0%。在出血性卒中或其他重大出血事件发生前的一个月内，39.4% 和 38.0% 的以前未接受过抗血栓治疗的患者分别开始了华法林或单一抗血小板治疗。
主动脉瓣生物假体介入后的大出血事件并不少见。对合并症和既往出血的评估可能会改善这些老年患者出血的风险分层。在有出血事件和没有出血事件的组中，抗血栓形成治疗的变化模式相似，并且在大多数患者中，在事件发生前一个月抗血栓形成方案没有改变。

Introduction

Antithrombotic treatments targeting platelets and the coagulation cascade have improved ischaemic outcomes and survival in patients with thromboembolic diseases. By exposing patients to long-term oral antithrombotic treatment there is an increased risk of bleeding events and combinations of antithrombotic treatment further increase that risk.[1,2] The number and severity of comorbidities increase with age and frailty is associated with the risk of bleeding during antithrombotic treatment.[3,4] In patients with severe aortic valve disease a biological prosthesis is the first line of treatment in the elderly. Surgical aortic valve intervention is still performed in the majority of the patients even though transcatheter aortic valve intervention (TAVI) has been studied and proved superior as an alternative also in the low-risk group of aortic stenosis patients.[5,6] The guideline recommendations for antithrombotic treatment after a surgical biological aortic valve replacement are based on low level of evidence but include aspirin or warfarin for a shorter time period if there is no other indication for oral anticoagulant treatment.[5,6] Several studies of antithrombotic strategies after TAVI is ongoing and the recommendation today includes single/dual antiplatelet drugs or single antiplatelet combined with warfarin.[7] Non-vitamin K anticoagulant treatment (NOAC) is not recommended the first 3 months after valve intervention. Changes of antithrombotic treatment including combinations of treatment as well as withdraw of treatment can influence the risk of both bleeding and thromboembolic events.[8-10] There are sparse data of how clinical characteristics and changes of antithrombotic treatment affect bleeding risk in patients with biological aortic valve prosthesis.

The aim of the present study was to describe an unselected sample of patients in Sweden who have experienced haemorrhagic stroke and other major bleeding events after biological aortic prosthesis, their antithrombotic treatment and changes of treatments in relation to the bleeding event using a complete national clinical registry.

Methods

Study population and data sources

Surgical aortic valve replacement and TAVI are performed at eight centres in Sweden. All patients undergoing cardiac surgery and TAVI are continuously included in the Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART).[11] The present study cohort included all patients undergoing a biological SAVR or a TAVI, between 1 January 2008 and 31 December 2014 and who were alive at discharge from the index intervention. 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 at index intervention ($n = 55$) were excluded. In total, 10 711 patients were identified and included in the study. The study was approved by the local ethics committee (Log No. 2014/518) and in compliance with the regulations of the Declaration of Helsinki. All patients admitted for surgical aortic valve replacement and TAVI 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 (ICD-10) of all hospital admissions in Sweden since 1987.[12] 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 computerized linkage between the database and the updated census register, the Swedish Cause of Death Register (CDR) 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, atrial fibrillation, myocardial infarction, peripheral artery disease, any thromboembolism (i.e. ischaemic stroke, systemic embolism, pulmonary embolism and venous thromboembolism), and major bleeding event (i.e. haemorrhagic stroke and hospitalization for other major bleeding event). Comorbidities were continuously updated during the follow-up. The International Code of Disease, Tenth Revision (ICD-10) was applied to identify comorbidities and outcome events (Supplementary material online, *eTable 1*).

Outcome events

Outcome events after discharge from the index surgical procedure were haemorrhagic stroke, other major bleeding event. Other major bleeding event was defined as a hospitalization a bleeding event as the primary diagnosis (Supplementary material online, *eTable 1*).

Exposure to oral antithrombotic treatment

Information on the dispension of oral antiplatelet and anticoagulant treatment was collected by computerized 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

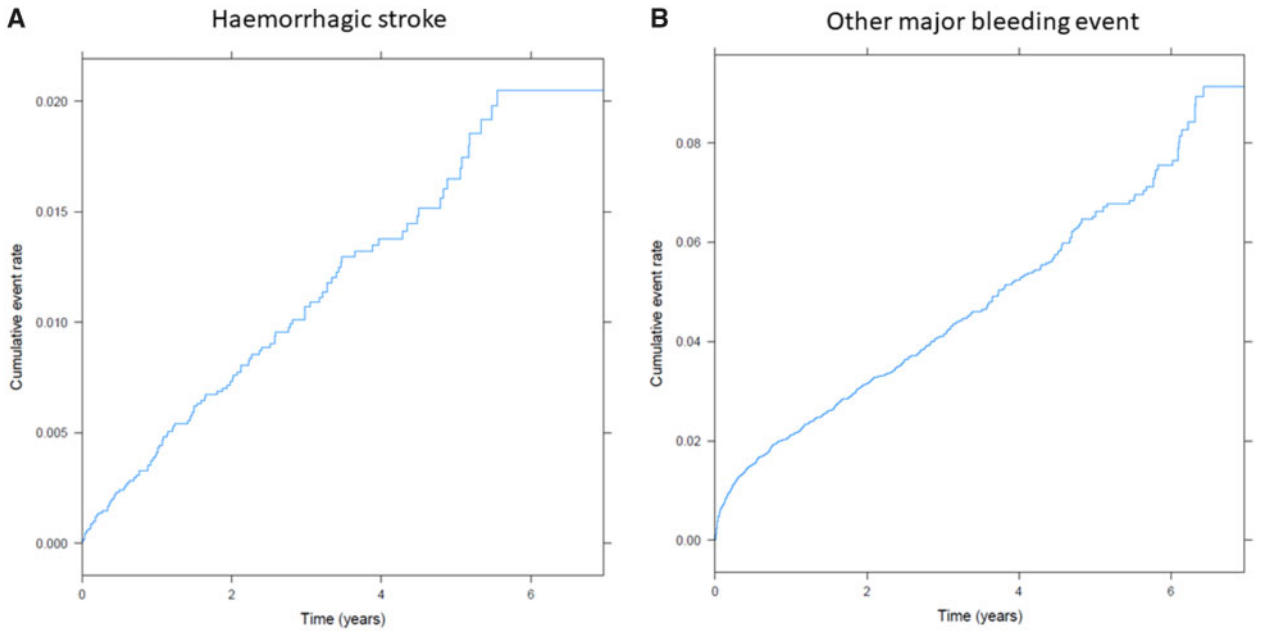

Figure 1 Kaplan–Meier estimate for (*A*) haemorrhagic stroke and (*B*) other major bleeding event in patients discharged alive after an intervention with a biological aortic prosthesis.

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 categorized into five exposure groups: (i) single antiplatelet treatment (SAPT, either aspirin or $P2Y_{12}$-inhibitor), (ii) warfarin, (iii) warfarin plus an SAPT or a dual antiplatelet treatment (DAPT), (iv) DAPT (aspirin and $P2Y_{12}$-inhibitor) only, and (v) no antithrombotic treatment. Information on dispension of non-vitamin K antagonist oral anticoagulant drugs (NOACs) was collected separately, and not included in further analyses.

Statistical methods

Categorical variables were expressed as frequencies and percentages and continuous variables as median and interquartile ranges (Q1–Q3) or mean [standard deviation (SD)]. Kaplan–Meier curves for the outcomes events were created.

To describe patients with outcome events a matched analysis database was created. This was done by including patients with bleeding events ('cases'), as they occur, together with matched patients who have not yet had a bleeding ('controls'). Note that controls can later become cases. This means that patients classified as non-bleeders have identical follow-up time as the bleeders and have not yet had a bleeding during this follow-up time. We performed the matching procedure as follows: at any time point a bleeding event had been registered, all patients without a bleeding event from the index intervention to this time point where identified. From these candidates, 10 random patients were selected as controls. This is performed regardless of whether the patients had already been used as controls, and whether the patients later experienced a bleeding. We repeated the procedure for each type of bleeding event. The matched analysis database consisted of 11 patients for each bleeding event.

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/PY was calculated for each outcome event, started at discharge from the index intervention ending at an outcome event.

For each patient in the matched analysis database, we recorded the number of drug switches before the bleeding event occurred or for controls, the bleeding event of the case to which that patient was matched. The number of switches per year was computed by dividing this number of switches by the follow-up time, i.e. the time from index valve intervention to the bleeding event. If a drug switch occur after a very short observation time, the number of switches per year becomes very large. For this reason, only patients with at least 1-month follow-up time were included in this analysis. The mean and SD of this quantity (number of switches per year) was reported.

The proportion of switches within each pharmaceutical group was recorded 1 month before the occurrence of a haemorrhagic stroke and other major bleeding event.

Results

Outcome events

During a mean follow-up of 3.13 years (median 2.99, maximum 6.97 years), there were in total 141 haemorrhagic stroke (incidence rate 0.45/100 PY) and 526 other major

Table 1 Clinical characteristics in the group with and without a first haemorrhagic stroke

	Haemorrhagic stroke ($n = 111$)[a]	Control group ($n = 1110$)
Age at index intervention, median (Q1-Q3)	76 (69-80)	74 (68-79)
Sex		
Female	23 (20.7%)	422 (38.0%)
Male	88 (79.3%)	688 (62.0%)
Comorbidities		
Diabetes	30 (27.0%)	200 (18.0%)
Hypertension	61 (55.0%)	484 (43.6%)
Heart failure	25 (22.5%)	179 (16.1%)
Atrial fibrillation	33 (29.7%)	181 (16.3%)
Ischaemic stroke	11 (10.0%)	89 (8.0%)
Haemorrhagic stroke	3 (2.7%)	4 (0.4%)
Other major bleeding event	9 (8.1%)	50 (4.5%)
Myocardial infarction	11 (10.0%)	150 (13.5%)
Peripheral artery disease	10 (9.0%)	60 (5.4%)

[a]Description of the group with the first haemorrhagic stroke.

bleeding events (incidence rate 1.66/100 PY) (*Figure 1*). Of all the major bleeding events 269 (whereof 48 haemorrhagic stroke) out of 667 occurred during the first year after the valve intervention resulting in an incidence rate during the first year of 2.85/100 PY.

Clinical characteristics in the groups with major bleeding event

The clinical characteristics of the patients suffering a first haemorrhagic stroke are described in *Table 1*. Diabetes mellitus was present in 27.0% with a haemorrhagic stroke vs. 16.0% in the group without. Comorbidities such as hypertension, heart failure, and atrial fibrillation were also common in the group with a haemorrhagic stroke as were males (*Table 1*). A medical history of a previous haemorrhagic stroke or other major bleeding event was present in 2.7% and 8.1%, respectively, of the patients with haemorrhagic stroke compared to 0.4% and 4.5% in the group without a haemorrhagic stroke.

Among patients with other major bleeding event heart failure and atrial fibrillation were present in 23.6% and 27.3%, respectively vs. 14.2% and 16.0% in the group without (*Table 2*). A medical history of haemorrhagic stroke or previous other major bleeding was present in 0.7% and 8.4%, respectively, in patients with other major bleeding event compared to 0.4% and 3.9% in the group without a bleeding event.

Antithrombotic exposures prior to a bleeding event

The proportion of antithrombotic treatment prior to a haemorrhagic stroke or other major bleeding are described in *Table 3*. Prior to a haemorrhagic stroke patients were exposed to SAPT 38.9% and warfarin 28.7% of the person-time compared to 48.7% and 21.3%, respectively in patients without a haemorrhagic stroke. Comparable figures in patients with other major bleeding event postoperatively were 31.2% for warfarin exposure compared to 19.0% in the group without a bleeding event (*Table 3*).

Changes of antithrombotic exposures before a bleeding event

The number of switches of antithrombotic treatment prior to a bleeding event was 2.3 (SD 1.9)/PY in patients with a haemorrhagic stroke as compared with 2.0 (SD 1.8)/PY in the group without a bleeding event. During 1 month prior to the first haemorrhagic stroke 39.4% of the patients not exposed to any antithrombotic treatment were dispensed warfarin (27.3%) or SAPT (12.1%) (*Figure 2A*). In patients exposed to SAPT 1 month before a haemorrhagic stroke 13.0% intensified antithrombotic treatment with dispension of warfarin. In the group exposed to warfarin the addition of SAPTwas rare (*Figure 2A*).

The number of switches of antithrombotic treatment before the bleeding event was 2.3 (SD 2.0)/PY in patients with a other major bleeding event as compared with 2.0 (SD 2.1)/PY in the group without a bleeding event. During 1 month prior to the first other major bleeding event 38.0% of the patients not exposed to any antithrombotic treatment were dispensed warfarin (18.6%), SAPT (17.1%) or warfarin + SAPT (2.3%) (*Figure 2B*). In patients exposed to SAPT 1 month prior to other major bleeding event 11.2% intensified antithrombotic treatment with dispension of warfarin (9.2%) or an additional antiplatelet drug (2.0%). The majority of the patients exposed to warfarin did not change antithrombotic exposure, however, 25.5% in the warfarin + SAPT group reduced antithrombotic intensity 1 month prior to other major bleeding event (*Figure 2B*).

Discussion

In the present study, we found that traditional cardiovascular risk factors were associated with bleeding events during long-term follow-up in an elderly unselected cohort with a

Table 2 Clinical characteristics in the group with and without a first other major bleeding event

	Other major bleeding event ($n = 450$)[a]	Control group ($n = 4500$)
Age at index intervention, median (Q1–Q3)	76 (71–81)	74 (68–79)
Sex		
Female	142 (31.6%)	1727 (38.4%)
Male	308 (68.4%)	2773 (61.6%)
Comorbidities		
Diabetes	97 (21.6%)	836 (18.6%)
Hypertension	213 (47.3%)	1799 (40.0%)
Heart failure	106 (23.6%)	640 (14.2%)
Atrial fibrillation	123 (27.3%)	721 (16.0%)
Ischaemic stroke	47 (10.4%)	354 (7.9%)
Haemorrhagic stroke	3 (0.7%)	17 (0.4%)
Other bleeding event	38 (8.4%)	175 (3.9%)
Myocardial infarction	68 (15.1%)	555 (12.3%)
Peripheral artery disease	27 (6.0%)	280 (6.2%)

[a]Description of the group with the first other major bleeding event.

Table 3 The proportion of antithrombotic exposure

	Haemorrhagic stroke	Control group
Person-years	210	2129
SAPT	38.9%	48.7%
Warfarin	28.7%	21.3%
Warfarin + SAPT	13.3%	9.0%
Dual antiplatelet treatment	2.4%	1.5%
No antithrombotic treatment	16.7%	19.7%
	Other major bleeding event	Control group
Person-years	775	7832
SAPT	39.3%	51.6%
Warfarin	31.2%	19.0%
Warfarin + SAPT	9.9%	8.4%
Dual antiplatelet treatment	2.3%	1.6%
No antithrombotic treatment	17.3%	19.4%

SAPT, single antiplatelet treatment.

prior aortic valve intervention. The bleeding events were not related to changes of antithrombotic treatment.

Haemorrhagic stroke is a severe bleeding event often with remaining disability and exposure to oral anticoagulant treatment are associated with more severe symptoms as compared with exposure to antiplatelet therapy.[13] In the present study, the number of haemorrhagic stroke cases represented only a minor proportion of all major bleeding events. Several risk factors for cardiovascular disease such as diabetes mellitus, hypertension, and atrial fibrillation were more frequent in the group with a haemorrhagic stroke when compared with controls which is in accordance with previous findings.[14,15] Comorbidities contribute to progression of atherosclerosis and patients with peripheral vascular disease have been found to have a higher risk of bleeding events compared to patients with coronary artery disease.[16] There was also a higher proportion of men in the group with haemorrhagic stroke, in the present study, which might be associated with the occurrence of cardiovascular risk factors.[17] The established risk factors for haemorrhagic stroke might therefore be systematic evaluated in patients with an aortic valve intervention to identify the patients with high risk for a severe bleeding during follow-up.

In the elderly, markers associated with frailty can improve risk prediction for a new bleeding event.[18,19] In the present study, including a representative cohort undergoing aortic valve intervention with a biological prosthesis, a medical history of a previous bleeding was more frequent both in the group with a haemorrhagic stroke as well as in the group with other major bleeding.

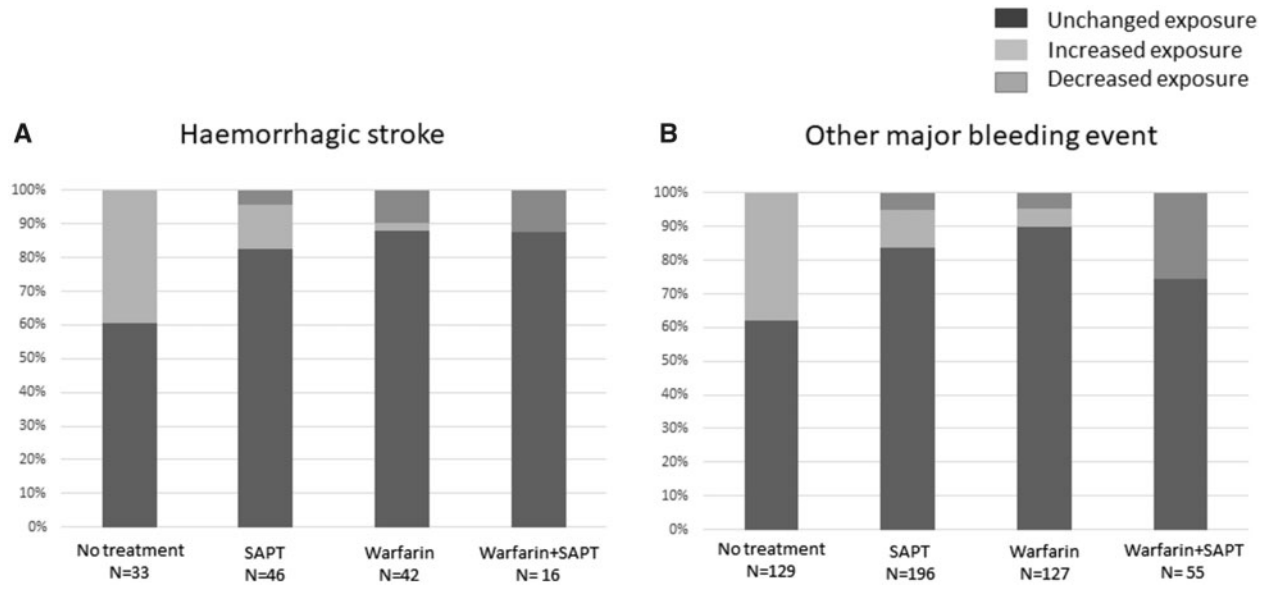

Figure 2 Changes of antithrombotic exposure 1 month before (*A*) a haemorrhagic stroke and (*B*) other major bleeding event. The staples describe the proportions of unchanged, intensified, or decreased treatment separated by the antithrombotic exposure; no antithrombotic treatment, single antiplatelet treatment, warfarin, warfarin + single antiplatelet treatment, 1 month before a bleeding.

The duration of exposure to antithrombotic treatment is important for the risk of bleeding and as expected patients suffering from a haemorrhagic stroke or other major bleeding had been exposed to warfarin during a higher proportion of the time of follow-up. Within the groups with a bleeding event both a haemorrhagic stroke or other major bleeding one-third of previously unexposed started antithrombotic treatment 1 month before the bleeding event occurred, which is in accordance with previous results where changing antithrombotic treatment are associated with increased bleeding risk.[9,10] However, the number of changes of types of antithrombotic treatment was similar in the groups with bleeding events compared to controls and the majority of the patients with a bleeding event did not change antithrombotic treatment the month before occurrence of a haemorrhagic stroke or other major bleeding.

In conclusion, major bleeding events are not uncommon after aortic valve intervention with a biological prosthesis. Evaluation of comorbidities and previous bleeding might improve risk stratification for bleeding in these elderly patients. The pattern of change of antithrombotic treatment was similar in the groups with and without a bleeding event and in most patients the antithrombotic regime was unchanged the month before an event.

Supplementary material

Supplementary material is available at *European Heart Journal-Supplement* online.

Funding

This paper was published as part of a supplement supported by an educational grant from Boehringer Ingelheim.

Conflict of interest: C.C. has received lecture fees from Boehringer Ingelheim and Bristol Myers Squibb. S.J. has received institutional research grants from Astra Zeneca, Jansen and lecture fees from Astra Zeneca, Jansen and Bayer. L.L. and E.S. have nothing to disclose.

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