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

Christina Christersson1*, Elisabeth Ståhle2, Lars Lindhagen3, and Stefan James1,3

1Department of Medical Sciences, Cardiology, Uppsala University, SE 75185 Uppsala, Sweden; 2Department of Surgical Sciences, Thoracic surgery, Uppsala University, SE 75185 Uppsala, Sweden; and 3Uppsala Clinical Research Center, Uppsala University, SE 75185 Uppsala, Sweden

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 a bioSAVR or a TAVI 2008–2014 were identified in the SWEDHEART 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.

*Corresponding author. Tel: +46 18 611 9068, Fax: +46 18 50 66 38, Email: christina.christersson@medsci.uu.se

Published on behalf of the European Society of Cardiology. © The Author(s) 2020.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
A la mayoría de los pacientes con estenosis de la válvula aórtica grave se les recomienda someterse a un valvuloplastia con prótesis biológica (bioSAVR) o a una valvuloplastia aórtica transcateral (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 tromboblémicas.

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 SWEDHEART y se incluyeron en el estudio (n=10711). 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 evolución 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.

建议大多数患有严重主动脉瓣狭窄的患者采用外科生物瓣膜（SAVR）或经导管主动脉瓣膜（TAVI）进行干预。主动脉瓣膜后抗血栓形成的策略各异，包括靶向血小板和凝血cascade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性和血栓栓塞事件的风险。

用于描述未经选择的患者样本，这些患者在主动脉瓣膜术后来过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SWEDHEART登记表中识别出2008-2014年间所有进行过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抗血小板治疗。

主动脉瓣生物瓣膜介入后的重大出血事件并不常见。在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 withdrawal 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 dispersion of oral antiplatelet and anticoagulant treatment was collected by computerized linkage with the Dispensed Drug Register. The register contains information on every prescription and dispersion of drugs in every pharmacy in Sweden. The patient was considered exposed to the corresponding dispensed antithrombotic treatment for 120 days after each dispersion, if no new
Dispensation occurred. Information on dispensation 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 P2Y₁₂-inhibitor), (ii) warfarin, (iii) warfarin plus an SAPT or a dual antiplatelet treatment (DAPT), (iv) DAPT (aspirin and P2Y₁₂-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
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 dispensation of warfarin. In the group exposed to warfarin the addition of SAPT was 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 a haemorrhagic stroke 13.0% intensified antithrombotic treatment with dispensation 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 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%) |

aDescription of the group with the first haemorrhagic stroke.
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. 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. 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. 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. 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. 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.

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

|                                      | Other major bleeding event (n = 450)² | 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%)               |

*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.
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. 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.

**References**

1. Maes F, Stabile E, Ussia GP, Tamburino C, Pucciarelli A, Masson JB, Marsal JR, Barbanti M, Cote M, Rodes-Cabau J. Meta-analysis comparing single versus dual antiplatelet therapy following transcatheter aortic valve implantation. *Am J Cardiol* 2018; 122:310-315.
2. Hess CN, James S, Lopes RD, Wojdyla DM, Neely ML, Liaw D, Hاغstrom E, Bhatt DL, Husted S, Goodman SG, Lewis BS, Verheugt FWA, De Caterina R, Ogawa H, Wallentin L, Alexander JH. Apixaban plus mono versus dual antiplatelet therapy in acute coronary syndromes: insights from the APPRAISE-2 trial. *J Am Coll Cardiol* 2015; 66:777-787.
3. Pavasini R, Maietti E, Tonet E, Bugani G, Tebaldi M, Biscaglia S, Cimaglia P, Serenelli M, Vitali F, Galvani M, Minarelli M, Rubolli A, Bernucci D, Volpato S, Campo G. Bleeding risk scores and scales of frailty for the prediction of haemorrhagic events in older adults with acute coronary syndrome: insights from the FRASER study. *Cardiovasc Drugs Ther* 2019; 33:523-532.
4. Kwok CS, Lundberg G, Al-Faleh H, Sirker A, Van Spall HGC, Michos ED, Rashid M, Bagur R, Mamas MA. Relation of frailty to outcomes in patients with acute coronary syndromes. *Am J Cardiol* 2019; 124:1002-1011.
5. Baumgartner H, Fark V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Jung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017; 38:2739-2791.
6. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod C, O’Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135:e1159-e1195.
7. Nijenhuis VJ, Brouwer J, Sondergaard L, Collet JP, Grove EL, Ten Berg JM. Antithrombotic therapy in patients undergoing transcatheter aortic valve implantation. *Heart* 2019;105:742-748.

8. Merie C, Kober L, Skov Olsen P, Anderson C, Gislason G, Skov Jensen J, Torp-Pedersen C. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA* 2012;308:2118-2125.

9. Jun M, James MT, Ma Z, Zhang J, Tonelli M, McAlister FA, Manns BJ, Ravani P, Quinn RR, Wiebe N, Perkovic V, Wilton SB, Winkelmaier WC, Hemmelgarn BR; Alberta Kidney Disease Network. Warfarin initiation, atrial fibrillation, and kidney function: comparative effectiveness and safety of warfarin in older adults with newly diagnosed atrial fibrillation. *Am J Kidney Dis* 2017;69:734-743.

10. Mahan CE, Spyropoulos AC, Fisher MD, Fields LE, Mills RM, Stephenson JJ, Fu AC, Klagskala W. Antithrombotic medication use and bleeding risk in medically ill patients after hospitalization. *Clin Appl Thromb Hemost* 2013;19:504-512.

11. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart* 2010;96:1617-1621.

12. Ludvigsson JF, Andersson E, Ekborn A, Feychting M, Kim JL, Reuterwall C, Heurgen M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.

13. Romem R, Tanne D, Geva D, Einhorn-Cohen M, Shlomo N, Bar-Yehuda S, Harnof S. Antithrombotic treatment prior to intracerebral hemorrhage: analysis in the National Acute Stroke Israeli Registry. *J Stroke Cerebrovasc Dis* 2018;27:3380-3386.

14. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Golbin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-2222.

15. Rahimi K, Emdin CA, MacMahon S. The epidemiology of blood pressure and its worldwide management. *Circ Res* 2015;116:925-936.

16. Achterberg S, Visseren FL, Kappelle LJ, Pruijsen DM, Van Der Graaf Y, Algra A; Smart Study Group. Differential propensity for major hemorrhagic events in patients with different types of arterial disease. *J Thromb Haemost* 2011;9:1724-1729.

17. Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic review. *Stroke* 2009;40:1082-1090.

18. Christersson C, Lindahl B, Berglund L, Siegbahn A, Oldgren J. The utility of coagulation activity for prediction of risk of mortality and cardiovascular events in guideline-treated myocardial infarction patients. *Ups J Med Sci* 2017;122:224-233.

19. Koller L, Rothgerber DJ, Sulzgruber P, El-Hamid F, Forster S, Wojta J, Golasch G, Maurer G, Niessner A. History of previous bleeding and C-reactive protein improve assessment of bleeding risk in elderly patients (>80 years) with myocardial infarction. *Thromb Haemost* 2015;114:1085-1091.