ESC European Society of Cardiology

European Heart Journal Open (2021) **1**, 1–11
https://doi.org/10.1093/ehjopen/oeab036

ORIGINAL ARTICLE
Valvular heart disease

Academic Research Consortium High Bleeding Risk Criteria associated with 2-year bleeding events and mortality after transcatheter aortic valve replacement discharge: a Japanese Multicentre Prospective OCEAN-TAVI Registry Study

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Received 3 June 2021; revised 27 September 2021; editorial decision 8 November 2021; accepted 10 November 2021; online publish-ahead-of-print 15 November 2021

Handling Editor: Magnus Bäck

Aims To investigate the ability of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria and ARC-HBR score to predict 2-year bleeding and mortality in patients undergoing transcatheter aortic valve replacement (TAVR).

Methods and results We enrolled 2514 patients who underwent successful TAVR during 2013–17. In this study, we used the ARC-HBR score for further HBR-risk stratification, and the ARC-HBR score was calculated as follows: each major criterion was 2 points and each minor criterion was 1 point. The impact of the ARC-HBR criteria and increasing ARC-HBR score on the incidence of moderate/severe bleeding events, mortality, and ischaemic stroke in the first 2 years were evaluated. We used survival classification and regression tree (CART) analysis for 2-year moderate or severe bleeding events, and patients were statistically classified into HBR low- (ARC-HBR score ≤1), intermediate- (ARC-HBR score = 2–4), or high-risk (ARC-HBR score ≥5) groups, and 91.4% were at HBR (ARC-HBR score ≥2). The rates of 2-year moderate/severe bleeding events and all-cause mortality were higher in the ARC-HBR group and highest in the HBR high-risk group. An increased HBR score was significantly associated with moderate/severe

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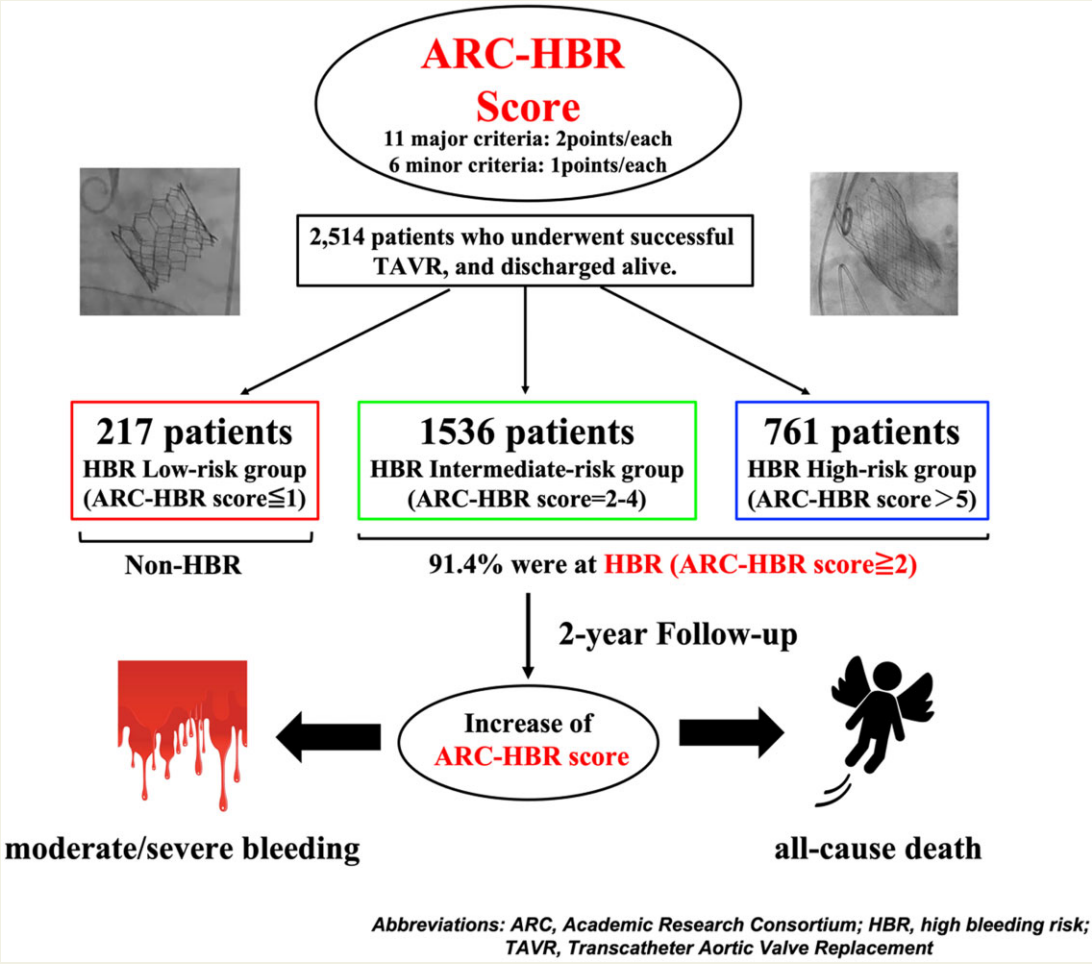
bleeding events [hazard ratio (HR) 1.19, 95% confidence interval (CI) 1.07–1.31; $P = 0.001$] and all-cause mortality (adjusted HR 1.24, 95% CI 1.17–1.32; $P < 0.001$).

Conclusions The ARC-HBR criteria identify patients at HBR after TAVR; an increased ARC-HBR score is associated with 2-year moderate/severe bleeding events and mortality.

Graphical Abstract



Keywords All-cause mortality • High-bleeding risk • Transcatheter aortic valve replacement • Aortic stenosis

Introduction

Transcatheter aortic valve replacement (TAVR) is a feasible therapeutic option for patients who require a valve replacement, regardless of the patient's surgical risk, and provides satisfactory mid-term clinical outcomes.[1–5] This trend is similar to that of percutaneous coronary intervention (PCI) using new-generation drug-eluting stents, which improved clinical outcomes as an alternative therapy for coronary artery bypass grafting in patients with ischaemic heart disease.[6]

The bleeding risk after PCI has been studied extensively, and several studies have reported that post-PCI bleeding negatively affected survival as significantly as the occurrence of thrombotic events.[7–11] Following these reports, the Academic Research Consortium for High-Bleeding Risk (ARC-HBR) standardized the definition of high-bleeding risk (HBR) through a literature review and the consensus of experts.[12] HBR was defined as a ≥ 4% risk of Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding at 1 year or a ≥ 1% risk of an intracranial haemorrhage at 1 year.[13] Several studies

regarding the validation of the ARC-HBR criteria after PCI in real clinical settings have verified that the definition of HBR accurately identifies patients at an increased risk not only for bleeding but also for thrombotic events.[14–16] On the other hand, antithrombotic therapy is recommended after TAVR as well as after PCI, and TAVR is typically performed for older patients with a high surgical risk[17,18] who are frail and have multiple comorbidities associated with HBR.[19,20] Therefore, further information on the bleeding risk, and bleeding events on mortality after TAVR is warranted, although the balance between bleeding and thrombotic risks in patients who undergo TAVR has also been studied.[19] However, the prevalence, expected bleeding event rate, and expected ischaemic event rate of patients with HBR, and the association of HBR and mortality after TAVR are rarely reported except post hoc analysis from POPular TAVI trial.[21] Since there is no bleeding risk stratification model for TAVI patients, we applied the ARC-HBR criteria to patients who underwent TAVR to investigate the prevalence of bleeding events, ischaemic events, and mortality in the first 2 years after discharge. Furthermore, we stratified the patients based on the ARC-HBR score, as we hypothesized that nearly all of the patients who underwent TAVR would be at HBR.

Methods

Study population

We analysed data from 2514 patients who were enrolled in the Optimized Transcatheter Valvular Intervention-Transcatheter Aortic Valve Implantation (OCEAN-TAVI) registry and discharged after a successful TAVI between October 2013 and May 2017. The OCEAN-TAVI is a prospective, multicentre, observational registry of patients with severe aortic stenosis who underwent TAVR at 1 of the 14 collaborating hospitals located in Japan.[18] This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-ID: 000020423). The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital. All patients provided written informed consent prior to participation in this study.

Definition of the Academic Research Consortium for High Bleeding Risk criteria and scoring

There are 11 major ARC-HBR criteria and 6 minor criteria.[12] Patients are considered to be at HBR if they meet at least one major criterion or two minor criteria. In this study, we assigned each major criterion 2 points and each minor criterion 1 point. A patient's ARC-HBR score was the sum of the points of the criteria that the patient met. The study population was classified into three groups according to the ARC-HBR score. Patients with ARC-HBR score ≥2 were considered to be at HBR, as this indicates the presence of at least one major criterion or two minor criteria. In this study, two major criteria (spontaneous bleeding event requiring hospitalization or transfusion in the past 6 months or at any time if recurrent and chronic bleeding diathesis) and one minor criterion (spontaneous bleeding event requiring hospitalization or transfusion within the past 12 months) were not captured from the registry dataset. Therefore, the major criteria were severe chronic kidney disease [estimated glomerular filtration rate (eGFR) <30 mL/min], thrombocytopenia (platelet count $<100 \times 10^9$/L), severe anaemia (haemoglobin <11 g/dL), liver cirrhosis, prior haemorrhagic stroke or moderate or severe ischaemic stroke within the past 6 months, active malignancy, and anticipated use of long-term oral anti-coagulation. The minor criteria were age ≥75 years, mild anaemia [haemoglobin (men vs. women) = 11.0–12.9 vs. 11.0–11.9 g/dL], prior ischaemic stroke, and moderate chronic kidney disease (eGFR = 30–59 mL/min).

Data collection and statistical analysis

All data were collected from the OCEAN-TAVI database. During the study period, the Edwards SAPIEN-XT and SAPIEN-3 (Edwards Lifesciences, Irvine, CA, USA) as balloon-expandable prosthesis and the Medtronic CoreValve and Evolut-R System (Medtronic, Minneapolis, MN, USA) as self-expandable prosthesis were available in Japan. Indication and decision for the approach route of TAVR were decided on the individual local heart team members. Dual antiplatelet therapy (DAPT) is usually recommended for 3–6 months, followed by indefinite single antiplatelet therapy (SAPT) after TAVR in patients who are not eligible for anti-coagulation, and combination therapy of oral anticoagulants (OAC) and SAPT, followed by indefinite OAC after TAVR in patients eligible for anti-coagulation. The specific antithrombotic regimen selected including when to reduce the regimen to single agent was at the discretion of each operator who considered the individual patient's risk. The primary study endpoint was a moderate or severe bleeding event in the first 2 years after discharge, defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO).[13] The secondary study endpoints were 2-year all-cause mortality and 2-year ischaemic stroke rates after hospital discharge.

Continuous variables are presented as the median and interquartile range (IQR), and categorical variables are presented as number and percentage. First, we used survival classification and regression tree (CART) analysis for 2-year moderate or severe bleeding events.[22] We used the ctree function of the party package with moderate or severe bleeding events as the outcome measure and the ARC-HBR score as an independent variable to determine the cut-off values of the ARC-HBR score that define low-, intermediate-, and high-risk HBR. The study population was divided into three HBR groups: high-risk, intermediate-risk, and low-risk. We used a univariable Cox regression model to determine the impact of the ARC-HBR score on the study endpoints. Variables that were found to be significantly different between the three groups were included. We did not include variables that were already included in the ARC-HBR score (age, a history of ischaemic stroke, liver cirrhosis, or malignancy), laboratory data on admission (haemoglobin, platelet count, and eGFR), or STS score [the presence of atrial fibrillation or peripheral artery disease and New York Heart Association (NYHA) heart failure functional class]. The variables with $P < 0.05$ in the univariate analysis were included in the multivariate model, and the Akaike information criteria were used to select the best predictive Cox model. The incidence of each endpoint was estimated using the Kaplan–Meier method and was reported with the 95% confidence interval (CI). Differences among the three groups were evaluated using the log-rank test. Differences in continuous and categorical variables among the groups were compared using the Wilcoxon rank-sum test or the chi-square test, respectively. Statistical analyses were performed using R software packages (version 3.6.3; R Development Core Team). Statistical significance was set at $P < 0.05$.

Results

The patient characteristics, procedural information, and periprocedural clinical outcome data are listed in *Table 1*. The median ARC-HBR score was 4. Patients with ARC-HBR score ≤1, 2–4, and ≥5 were included in the HBR low- ($n = 217$), intermediate- ($n = 1536$), and high-risk ($n = 761$) groups, respectively, according to the survival

Table 1 Patient characteristics

	Total $n = 2514$	Low-risk $n = 217$	Intermediate-risk $n = 1536$	High-risk $n = 761$	*P*-value
HBR	2297 (91.4)	0 (0.0)	1536 (100.0)	761 (100.0)	<0.001
ARC-HBR score	4 (2–5)	1 (1–1)	3 (2–4)	6 (5–6)	<0.001
Age (years)	85 (81–88)	82 (79–86)	85 (82–88)	85 (81–88)	<0.001
Male sex	768 (30.6)	75 (34.6)	455 (29.6)	238 (31.3)	0.293
BSA (m^2)	1.42 (1.30–1.54)	1.47 (1.33–1.59)	1.41 (1.30–1.53)	1.41 (1.31–1.53)	<0.001
Atherosclerotic risks					
Hypertension	1930 (76.8)	167 (77.0)	1170 (76.2)	593 (77.9)	0.644
Dyslipidaemia	1079 (42.9)	112 (51.6)	683 (44.5)	284 (37.3)	<0.001
Diabetes mellitus	541 (21.5)	47 (21.7)	297 (19.3)	197 (25.9)	0.002
Current smoking	61 (2.4)	8 (3.7)	32 (2.1)	21 (2.8)	0.276
Atrial fibrillation	500 (19.9)	0 (0.0)	122 (7.9)	378 (49.7)	<0.001
History of coronary stenting	324 (12.9)	20 (9.2)	212 (13.8)	92 (12.1)	0.124
History of coronary artery bypass grafting	157 (6.3)	17 (7.8)	89 (5.8)	51 (6.7)	0.419
History of myocardial infarction	159 (6.3)	9 (4.1)	94 (6.1)	56 (7.4)	0.200
History of ischaemic stroke	272 (10.9)	2 (0.9)	122 (7.9)	148 (19.4)	<0.001
History of haemorrhagic stroke	12 (0.5)	0 (0.0)	4 (0.3)	8 (1.1)	0.020
Peripheral vascular disease	350 (13.9)	21 (9.7)	197 (12.8)	132 (17.3)	0.002
Pulmonary dysfunction	589 (23.4)	49 (22.6)	355 (23.1)	185 (24.3)	0.778
Liver cirrhosis	75 (3.0)	0 (0.0)	11 (0.7)	64 (8.4)	<0.001
Malignancy	124 (4.9)	0 (0.0)	35 (2.3)	89 (11.7)	<0.001
NYHA class					<0.001
Class II	1150 (45.7)	126 (58.1)	739 (48.1)	285 (37.5)	
Class III	1092 (43.4)	68 (31.3)	648 (42.2)	376 (49.4)	
Class IV	177 (7.0)	7 (3.2)	89 (5.8)	81 (10.6)	
Clinical Frailty Scale	4 (3–5)	3 (3–4)	4 (3–4)	4 (3–5)	<0.001
STS score	6.5 (4.5–9.4)	4.6 (3.0–6.6)	6.2 (4.4–8.7)	8.1 (5.4–12.5)	<0.001
Long-term use of steroids or NSAIDs	128 (5.1)	2 (0.9)	49 (3.2)	77 (10.1)	<0.001
Laboratory data on admission					
Haemoglobin (mg/dL)	11.2 (10.1–12.4)	13.2 (12.6–13.7)	11.4 (10.4–12.5)	10.3 (9.4–11.2)	<0.001
Platelet count ($\times 10^4/\mu L$)	17.6 (14.3–21.4)	19.1 (16.0–21.8)	17.9 (14.9–21.6)	16.4 (11.9–20.6)	<0.001
e-GFR (mL/min/1.73 m^2)	50.6 (38.0–63.1)	70.9 (64.9–80.8)	52.7 (42.4–63.5)	38.0 (27.2–50.3)	<0.001
BNP (pg/mL)	268 (118–563)	127 (58–309)	252 (109–525)	352 (176–703)	<0.001
TAVR procedure					
Transfemoral approach	2154 (85.7)	191 (88.0)	1307 (85.1)	656 (86.2)	0.456
Valve type					0.970
Edwards SAPIEN XT valve	1349 (53.7)	118 (54.4)	829 (54.0)	402 (52.8)	
Edwards SAPIEN 3 valve	834 (33.2)	72 (33.2)	506 (32.9)	256 (33.6)	
Medtronic Corevalve	189 (7.5)	13 (6.0)	117 (7.6)	59 (7.8)	
Medtronic EvolutR	142 (5.7)	14 (6.5)	84 (5.5)	44 (5.8)	
Valve size (mm)	23 (23–26)	26 (23–26)	23 (23–26)	23 (23–26)	0.231
Procedure time (min)	69 (52–94)	70 (52–92)	68 (52–93)	72 (52–97)	0.607
Periprocedural complications					
Coronary occlusion	23 (0.9)	1 (0.5)	15 (1.0)	7 (0.9)	0.757
Ischaemic stroke	48 (1.9)	3 (1.4)	28 (1.8)	17 (2.2)	0.667
Permanent pacemaker implantation	210 (8.4)	14 (6.5)	133 (8.7)	63 (8.3)	0.544

Continued

Table 1 *Continued*

	Total $n = 2514$	Low-risk $n = 217$	Intermediate-risk $n = 1536$	High-risk $n = 761$	*P*-value
Acute kidney injury	241 (9.6)	9 (4.1)	123 (8.0)	109 (14.3)	<0.001
Major bleeding	268 (10.7)	20 (9.2)	153 (10.0)	95 (12.5)	0.141
Minor bleeding	224 (8.9)	4 (1.8)	116 (7.6)	104 (13.7)	<0.00
All bleeding	492 (19.6)	24 (11.1)	269 (17.5)	199 (26.1)	<0.001
New-onset atrial fibrillation	93 (3.7)	11 (5.1)	62 (4.1)	20 (2.6)	0.124
Transthoracic echocardiography after TAVR					
LVEF by modified Simpson's or Teichholz (%)	63 (55–68)	63 (56–67)	64 (56–68)	62 (54–67)	0.001
Mean aortic valve pressure gradient (mmHg)	10 (8–13)	11 (8–14)	10 (8–13)	10 (7–13)	<0.001
Peak aortic valve pressure gradient (mmHg)	19 (15–25)	21 (15–27)	20 (16–26)	19 (14–25)	0.006
Effective orifice area index with Doppler (cm^2/m^2)	1.15 (0.97–1.35)	1.20 (1.02–1.43)	1.14 (0.97–1.34)	1.15 (0.96–1.34)	0.008
Perivalvular leakage grade ≧ moderate	44 (1.8)	4 (1.8)	25 (1.6)	15 (2.0)	0.744
Anti-thrombotic medications at discharge					<0.001
Anti-platelet therapy					
Clopidogrel alone	109 (4.3)	7 (3.2)	68 (4.4)	34 (4.5)	
Aspirin alone	328 (13.1)	21 (9.7)	200 (13.0)	107 (14.1)	
Clopidogrel and aspirin (DAPT)	1361 (54.1)	151 (69.6)	951 (61.9)	259 (34.0)	
Oral anti-coagulation therapy					
Warfarin alone	82 (3.3)	4 (1.8)	34 (2.2)	44 (5.8)	
DOAC alone	110 (4.4)	6 (2.8)	54 (3.5)	50 (6.6)	
Combination therapy					
OAC and anti-platelet therapy	384 (15.3)	17 (7.8)	142 (9.2)	225 (29.6)	
Triple therapy (OAC and DAPT)	35 (1.4)	1 (0.5)	17 (1.1)	17 (2.2)	
None	105 (4.2)	10 (4.6)	70 (4.6)	25 (3.3)	
Proton pump inhibitor	1610 (64.0)	118 (54.4)	950 (61.8)	542 (71.2)	<0.001
H2-blocker	148 (5.9)	17 (7.8)	88 (5.7)	43 (5.7)	0.808

Categorical variables are shown as numbers (percentages) and continuous variables are shown as medians (25–75 percentiles).
ARC, Academic Research Consortium; BNP, brain natriuretic peptide; BSA, body surface area; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; e-GFR, estimated glomerular filtration rate; HBR, high bleeding risk; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NSAIDs; non-steroidal anti-inflammatory drugs; OAC, oral anticoagulant; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

CART analysis results. The majority of the patients (91.4%) met the definition of HBR. The evaluation items for ARC-HBR scoring are listed in Supplemental material online, *Table S1*. The median patient age was 85 years, and 30.6% of the patients were men. The majority of the participants (96.1%) presented with NYHA Class II or higher. The median Canadian Study of Health and Aging's Clinical Frailty Scale score was 4. The median STS score was 6.5%. The median plasma brain natriuretic peptide level on admission was 268 (IQR 118–563) pg/mL. The majority of patients (86.9%) received the SAPIEN XT or SAPIEN 3 valve (Edwards Lifesciences, Irvine, CA, USA) with a median valve size of 23 mm. The transfemoral approach for TAVR was used in 85.7% of patients. Acute kidney injury after TAVR occurred in 9.6% of patients. Echocardiography revealed that the mean post-procedural left ventricular ejection fraction (LVEF) was 63%, the mean aortic valve pressure gradient was 10 mmHg, and the mean effective orifice area index was 1.15 cm^2/m^2. Over half of

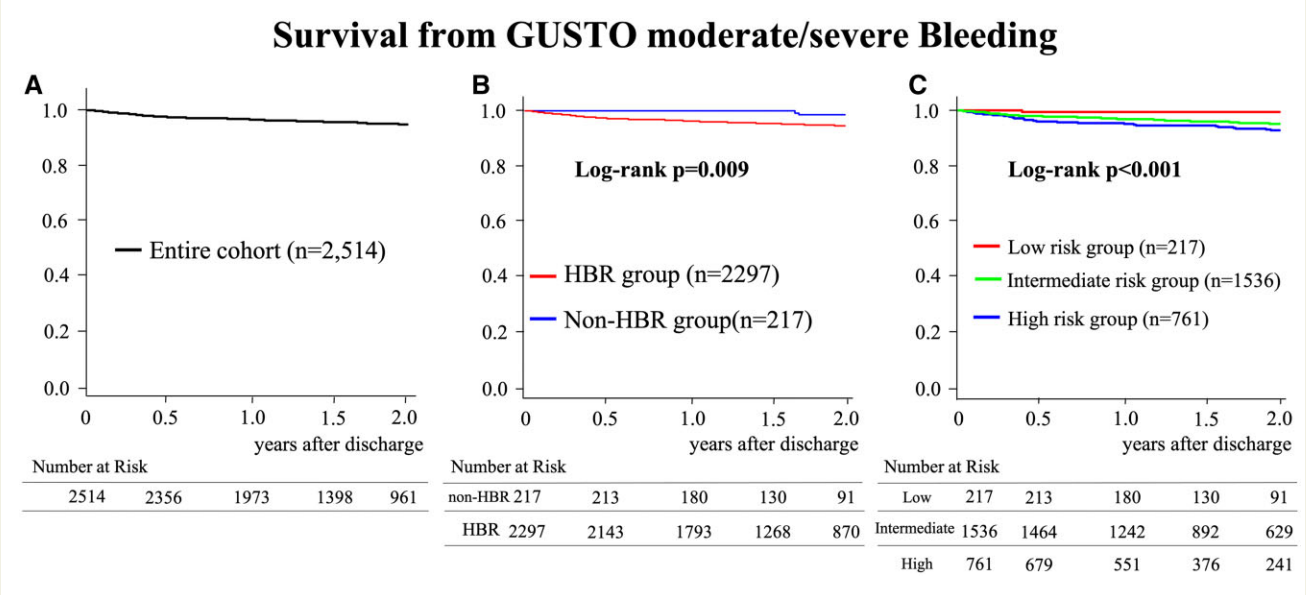


Figure 1 Incidence of bleeding events. (*A*) The rate of moderate/severe bleeding events in the entire patient population is shown. (*B*) The rates of moderate/severe bleeding events are compared between patients at high-bleeding risk (HBR; HBR group) and the non-HBR group. (*C*) The rates of moderate/severe bleeding events are compared between patients in the HBR low-, intermediate-, and high-risk groups.

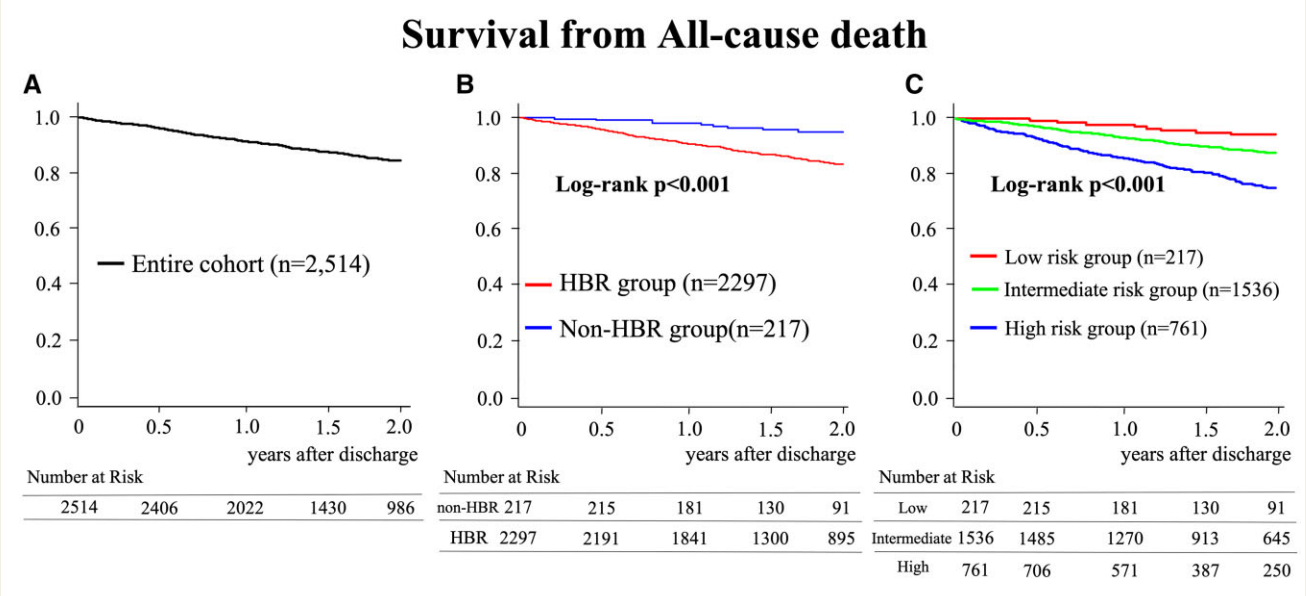


Figure 2 Incidence of mortality. (*A*) The mortality rate in the entire patient population is shown. (*B*) The mortality rates are compared between patients at high-bleeding risk (HBR; HBR group) and the non-HBR group. (*C*) The mortality rates are compared between patients in the HBR low-, intermediate-, and high-risk groups.

the patients (54.1%) were administered dual anti-platelet therapy (DAPT) (clopidogrel and aspirin) after TAVR.

The HBR high-risk group was significantly older ($P < 0.001$) with significantly higher clinical frailty ($P < 0.001$) and STS ($P < 0.001$) scores and a significantly lower LVEF ($P = 0.001$) than the other two groups. The HBR-high-risk group had a significantly higher incidence of acute kidney injury, periprocedural minor bleeding, and all (minor or major) bleeding events after TAVR ($P < 0.001$) than the other two groups. The number of anti-thrombotic medications at discharge was significantly different among the three groups ($P < 0.001$).

During the 2-year follow-up, 106 bleeding events, 328 deaths, and 42 ischaemic stroke events were noted. The rate of moderate/severe bleeding events was 3.3% (95% CI 2.5–4.0) at 1 year and 5.1% (95% CI 3.1–6.0) at 2 years (*Figure 1*). The all-cause mortality rate was

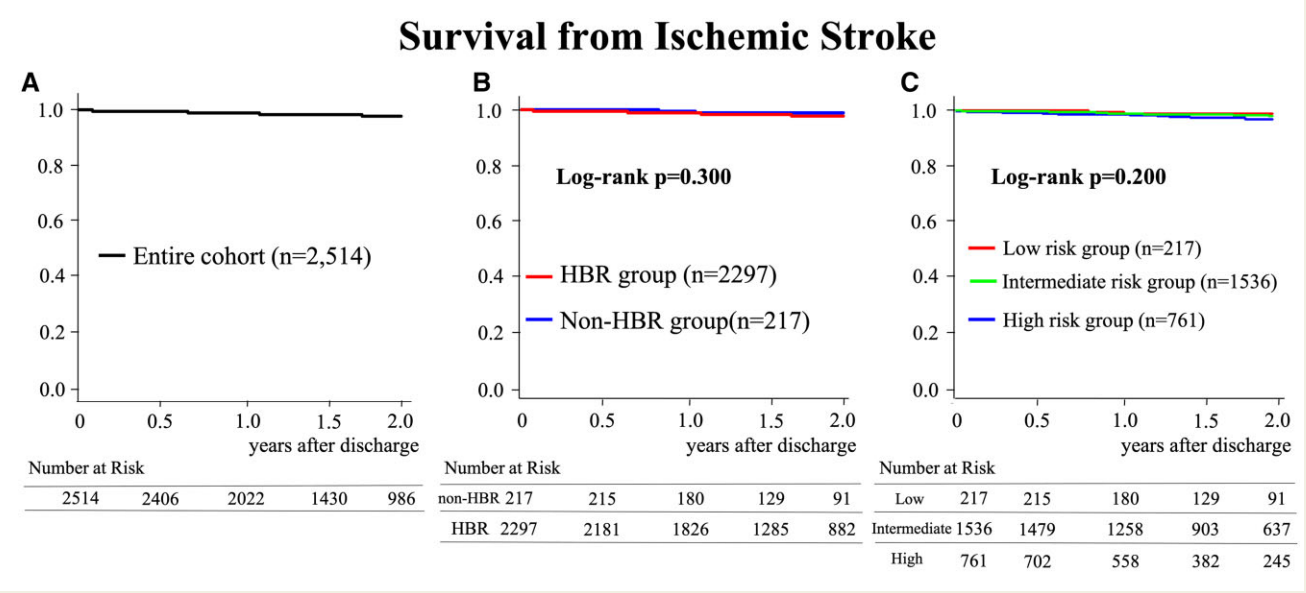


Figure 3 Incidence of ischaemic stroke. (*A*) The rate of ischaemic stroke in the entire patient population is shown. (*B*) The rates of ischaemic stroke are compared between patients at high-bleeding risk (HBR; HBR group) and the non-HBR group. (*C*) The rates of moderate/severe bleeding events are compared between patients in the HBR low-, intermediate-, and high-risk groups.

8.4% (95% CI 7.3–9.5) at 1 year and 15.5% (95% CI 13.9–17.1) at 2 years (*Figure 2*). The rate of ischaemic stroke was 1.2% (95% CI 0.7–1.6) at 1 year and 2.1% (95% CI 1.5–2.8) at 2 years (*Figure 3*).

The rates of moderate/severe bleeding events and all-cause mortality were higher in the patients at HBR (*Figures 1B* and *2B*) and significantly higher in the HBR high-risk group than in the other two groups ($P < 0.001$) (*Figures 1C* and *2C*). The rate of moderate/severe bleeding events at 1 and 2 years was 4.6% (95% CI 3.0–6.1), 3.1% (95% CI 2.2–4.0), and 0.7% (95% CI 0.0–2.1) and 7.2% (95% CI 5.0–9.4), 4.6% (95% CI 3.3–5.8), and 1.4% (95% CI 0.0–3.4) in the HBR high-, intermediate-, and low-risk groups, respectively. The all-cause mortality rate at 1 and 2 years was 14.2% (95% CI 11.7–16.7), 6.5% (95% CI 5.2–7.7), and 1.8% (95% CI 0.0–3.6) and 24.8% (95% CI 21.2–28.2), 12.6% (95% CI 10.7–14.4), and 5.0% (95% CI 1.7–8.3) in the HBR high-, intermediate-, and low-risk groups, respectively. The rate of ischaemic stroke was not significantly different between patients at HBR and those not at HBR or between the three groups (*Figure 3B,C*). The ARC-HBR group (the HBR intermediate- or high-risk group) had a higher risk of moderate/severe bleeding [hazard ratio (HR) 10.43, 95% confidence interval (CI) 1.46–74.77; $P = 0.020$] and death (HR 3.14, 95% CI 1.67–5.89; $P < 0.001$) than the non-HBR group (the HBR low-risk group) (*Table 2*). Furthermore, each 1-point increase in the ARC-HBR score was associated with an increased risk of moderate/severe bleeding events (adjusted HR 1.19, 95% CI 1.07–1.31; $P = 0.001$) and all-cause mortality (adjusted HR 1.23, 95% CI 1.15–1.31; $P < 0.001$) although it was not associated with an increased risk of ischaemic stroke (HR 1.16, 95% CI 0.99–1.36; $P = 0.072$) (*Table 2*). In addition, each 1-point increase in the clinical frailty scale was also associated with an increased risk of moderate/severe bleeding events (adjusted HR 1.19, 95% CI 1.07–1.31; $P = 0.001$) and all-cause mortality (adjusted HR 1.23, 95% CI 1.13–1.34; $P < 0.001$), the occurrence of AKI was associated with an increased risk of all-cause mortality (adjusted HR 1.77, 95% CI 1.32–2.36; $P < 0.001$), and increased STS risk score was associated with an increased risk of ischaemic stroke events (adjusted HR 1.04, 95% CI 1.01–1.06; $P = 0.004$) (*Table 2*).

Discussion

Our study found that 91% of patients who underwent TAVR were at HBR. Meeting the criteria for HBR and an increased ARC-HBR score, and clinical frailty scale were both associated with an increased 2-year risk of moderate/severe bleeding events and all-cause mortality after TAVR. This is the largest study to report the long-term bleeding risks after hospital discharge of patients who undergo TAVR and the effects of HBR on the incidence of bleeding events, mortality, and ischaemic events, as most previous studies focusing on TAVR were short-term and did not include the effects of bleeding risk.[1–5,17,19]

The ARC-HBR criteria have been evaluated in patients who underwent PCI;[14] however, they have rarely evaluated in patients who have undergone TAVR except post hoc analysis from popular TAVI trial.[21] They reported that a total of 78.5% had an ARC-HBR Score 2, and thus were considered at HBR according to the ARC-HBR definition of the 978 patients in the cohort, and there was no statistically significant increase of all bleeding, nor of major and life-threatening bleeding, associated with this definition (non-HBR 19.7% vs. HBR 24.1%; $P = 0.22$; and 6.6% vs. 10.8%; $P = 0.08$, respectively).[21] Of course, the patient background for this study was quite different from that of POPular TAVI trial. In particular, median age (85 years old vs.79.5–81.0) and STS scores (6.5 vs. 2.4–3.2) were higher in patients in our study compared to patients in Popular TAVI,[23,24] which may have contributed to the higher HBR rate in our study

Table 2 Cox regression analysis for each endpoint

	Univariable			Multivariable			AIC model		
	HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
GUSTO moderate/severe bleeding									
ARC-HBR (the HBR intermediate- or high-risk group vs. low-risk group)	10.43	1.46–74.77	<0.001						
HBR score (per 1 point increase)	1.20	1.09–1.33	<0.001	1.19	1.07–1.31	0.001	1.19	1.07–1.31	0.001
Clinical Frailty Scale (per 1 point increase)	1.23	1.06–1.42	0.006	1.19	1.03–1.38	0.020	1.19	1.03–1.38	0.020
STS risk score	1.02	0.99–1.04	0.162						
BNP on admission	1.00	1.00–1.00	0.897						
Acute kidney injury	1.05	0.55–2.01	0.883						
All-cause mortality									
ARC-HBR (the HBR intermediate- or high-risk group vs. low-risk group)	3.14	1.67–5.89	0.020						
HBR score (per 1 point increase)	1.30	1.23–1.38	<0.001	1.23	1.15–1.31	<0.001	1.24	1.17–1.32	<0.001
Clinical Frailty Scale (per 1 point increase)	1.31	1.21–1.42	<0.001	1.18	1.07–1.30	0.001	1.23	1.13–1.34	<0.001
STS risk score	1.04	1.03–1.04	<0.001	1.01	1.00–1.03	0.032	1.01	1.00–1.03	0.009
BNP on admission	1.00	1.00–1.00	0.015	1.00	1.00–1.00	0.658			
Acute kidney injury	2.45	1.86–3.23	<0.001	1.91	1.40–2.61	<0.001	1.77	1.32–2.36	<0.001
Ischaemic stroke									
ARC-HBR (the HBR intermediate- or high-risk group vs. low-risk group)	1.98	0.48–8.17	0.348						
HBR score (per 1 point increase)	1.16	0.99–1.36	0.072						
Clinical Frailty Scale (per 1 point increase)	1.08	0.85–1.38	0.513						
STS risk score	1.04	1.01–1.06	0.004						
BNP on admission	1.00	1.00–1.00	0.744						
Acute kidney injury	1.71	0.72–4.07	0.221						

Categorical variables are shown as numbers (percentages) and continuous variables are shown as medians (25–75 percentiles).
AIC, Akaike information criteria; ARC, Academic Research Consortium; BNP, brain natriuretic peptide; CI, confidence interval; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HBR, high-bleeding risk; HR, hazard ratio; STS, Society of Thoracic Surgeons.

population (91.4% vs. 78.5%). However, this study from POPular TAVI trial included TAVR perioperative bleeding events as TAVR 1-year events, and did not truly assess the long-term bleeding risk after successful TAVR discharge, because TAVR has more perioperative bleeding events compared to PCI because it uses a large calibre catheter. Therefore, we evaluated the long-term prognostic impact of the ARC-HBR criteria after TAVR discharge using the data of the patients in the OCEAN-TAVI registry. The prevalence of patients at HBR was 91%, and the ARC-HBR criteria accurately identified patients with a higher risk of moderate/severe bleeding events after TAVR discharge in our study, although the previous study considered that the ARC-HBR criteria proposed for PCI patients may not be accurately assessed in TAVR patients, since the background of TAVR patients is very different from that of PCI patients.[21] Furthermore, the 2-year mortality after TAVR discharge in patients who met the ARC-HBR criteria was significantly higher than that in patients who did not meet the ARC-HBR criteria. These results are consistent with those of a previous report that showed that late-onset bleeding occurring >30 days after TAVR is related to an increase in mortality.[25]

In addition, since most of the patients in this study met the ARC-HBR criteria, we stratified them by scoring the factors that make up the ARC-HBR criteria. As a result, patients with ARC-HBR score ≥5 had significantly higher risks of bleeding events and mortality; an increase in the ARC-HBR score significantly affected both endpoints. Patients with ARC-HBR score ≥5 had more comorbidities that are known to be associated with poor clinical outcomes after TAVR.[20,26] However, an increased ARC-HBR score was independently associated with higher risks of bleeding events and mortality during the 2 years after TAVR discharge in this study, which is consistent with a previous study that reported that meeting more items of the ARC-HBR criteria was associated with an incrementally higher incidence of major bleeding events in patients who underwent PCI.[14] In addition, this study showed that an increase in the clinical frailty scale was also associated with an increase in bleeding events and mortality at 2 years after TAVR. Although Frailty is not included in the ARC-HBR criteria, a recent Japanese guideline on antithrombotic therapy for ischaemic heart disease adopted frailty as bleeding risk factors that are specific to Japanese patients on the basis of the results of previous studies in

East Asian patients underwent PCI.[27,28] The results of our study indicate that the assessment of frailty is also important for the prediction of bleeding events in Japanese patients undergoing TAVR.

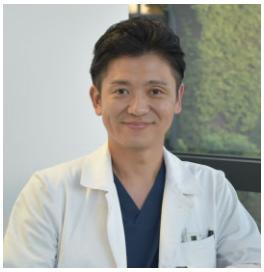
Although risk prediction models for in-hospital mortality after TAVR have been reported,[29,30] these models do not include long-term clinical outcomes. The ARC-HBR criteria were developed for the long-term risk stratification of major bleeding events and include factors that have been reported to be associated with long-term mortality after TAVR, including chronic kidney disease, liver cirrhosis, and active cancer.[31–33] We believe that the adaptation of the ARC-HBR criteria for patients who undergo TAVR and further risk stratification using the ARC-HBR score will help physicians predict the long-term bleeding events and mortality after TAVR. Our results suggest that patients with higher ARC-HBR scores should be carefully monitored after TAVR discharge. Furthermore, the optimal anti-thrombotic therapy after TAVR is controversial, although the use of DAPT was recommended in practice guidelines until recently.[34,35] On the other hand, POPular TAVI trial showed that antithrombotic therapy after TAVR could reduce the risk of bleeding events with monotherapy.[23,24] The specific anti-thrombotic medication administered was not associated with bleeding events or mortality in this study, and the specific medication used was determined on a case-by-case basis by the attending physician. More studies are required to determine the association of the ARC-HBR score and specific anti-thrombotic therapies in patients who underwent TAVR. Furthermore, blood disorders such as von Willebrand disease have also been reported as a risk of bleeding after TAVR and should be considered.[36]

This study has some limitations. First, some ARC-HBR criteria data were not available as the OCEAN-TAVI registry was not designed to investigate the impact of the ARC-HBR criteria. As a result, two major criteria (spontaneous bleeding event requiring hospitalization or transfusion in the past 6 months or at any time if recurrent and chronic bleeding diathesis such as von Willebrand disease) and one minor criterion (spontaneous bleeding event requiring hospitalization or transfusion within the past 12 months) were not available from the registry dataset in this study. Therefore, the prevalence of HBR and the ARC-HBR score may be underestimated in this study. Second, the GUSTO moderate/severe criteria were used to define major bleeding events, while the ARC-HBR initiative defined major bleeding as BARC type 3 or 5 bleeding events. We decided to use the GUSTO criteria based on the data available in the OCEAN-TAVI database, which does not include data regarding haemoglobin drop or the units of red blood cells transfused after each bleeding event. However, some previous PCI trials have reported that the rates of major bleeding were similar when the GUSTO criteria and BARC type 3 or 5 bleeding events were used to define major bleeding.[7,37,38] Third, the specific antithrombotic regimen selected including when to reduce the regimen to single agent was at the discretion of each operator who considered the individual patient's risk. Therefore, it is difficult to interpret the risk of bleeding and mortality with different antithrombotic regimens in this study.

Finally, this study includes only Japanese patients, whose bleeding risk may differ from that of patients in Western countries.[21,27,28] It has been reported that haemorrhagic events after PCI treatment are more common in Asians treated with DAPT compared to Westerners.[39] Furthermore, the risk of intracranial haemorrhage from anti-coagulation has also been found to be higher in East Asians.[40,41] Therefore, the results of this study do not directly apply to Westerners and require careful interpretation.

In conclusion, the ARC-HBR criteria accurately identify patients at HBR after TAVR, and an increased ARC-HBR score is associated with 2-year GUSTO moderate/severe bleeding events and mortality after TAVR, even in cohorts that include many patients at HBR.

Lead author biography



Ka zuki Mizutani is a Japanese cardiologist, and expert of catheter interventions (percutaneous coronary intervention, structural heart disease intervention). He has reported several articles regarding transcatheter aortic valve replacement.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements:

We would like to express our heartfelt gratitude to the Japan Society of Clinical Research for their dedicated support and to the investigators and institutions that participated in the OCEAN-TAVI registry.

Funding

The OCEAN-TAVI registry is supported by grants from Edwards Lifesciences, Medtronic, Boston Scientific, Abbott Medical, and Daiichi-Sankyo company.

Conflict of interest: Drs Yamamoto, Tada, Naganuma, Shirai, Mizutani, Tabata, Ueno, and Watanabe are clinical proctors for Edwards Lifesciences and Medtronic. Drs Takagi and Hayashida are clinical proctors for Edwards Lifesciences. The remaining authors have no conflicts of interest to disclose.

Consent: All patients provided written informed consent prior to participation in this study.

Data availability statement

The data underlying this paper cannot be shared publicly because [the data can only be provided to institutions approved by the Ethics Committee]. Upon reasonable request to the corresponding author, the data will be shared.

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