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CLINICAL RESEARCH
Clinical trials

Apixaban vs. standard of care after transcatheter aortic valve implantation: the ATLANTIS trial

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See the editorial comment for this article 'Defining optimal antithrombotic therapy post-TAVI: the contribution of ATLANTIS', by F. Andreotti *et al.*, https://doi.org10.1093/eurheartj/ehac139.

Abstract

Aims The respective roles of oral anticoagulation or antiplatelet therapy following transcatheter aortic valve implantation (TAVI) remain debated. ATLANTIS is an international, randomized, open-label, superiority trial comparing apixaban to the standard of care.

Methods and results After successful TAVI, 1500 patients were randomized (1:1) to receive apixaban 5 mg (2.5 mg if impaired renal function or concomitant antiplatelet therapy) ($n = 749$) twice daily, or standard of care ($n = 751$). Randomization was stratified by the need for chronic anticoagulation therapy. Standard-of-care patients received a vitamin K antagonist (VKA) (Stratum 1) or antiplatelet therapy (Stratum 2) if there was an indication for anticoagulation or not, respectively. The primary endpoint was the composite of death, myocardial infarction, stroke or transient ischaemic attack, systemic embolism, intracardiac or bioprosthesis thrombosis, deep vein thrombosis or pulmonary embolism, and life-threatening, disabling, or major bleeding

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over 1-year follow-up. The primary safety endpoint was major, disabling, or life-threatening bleeding. The primary outcome occurred in 138 (18.4%) and 151 (20.1%) patients receiving apixaban or standard of care, respectively [hazard ratio (HR) 0.92; 95% confidence interval (CI) 0.73–1.16] and there was no evidence of interaction between treatment and stratum ($P_{interaction} = 0.57$). The primary safety endpoint was similar in both groups (HR 1.02; 95% CI 0.72–1.44). In Stratum 1 ($n = 451$), an exploratory analysis showed no difference for all endpoints between apixaban and VKA. In Stratum 2 ($n = 1049$), the primary outcome and primary safety endpoint did not differ, but obstructive valve thrombosis was reduced with apixaban vs. antiplatelet therapy (HR 0.19; 95% CI 0.08–0.46), while a signal of higher non-cardiovascular mortality was observed with apixaban.

Conclusion After TAVI, apixaban was not superior to the standard of care, irrespective of an indication for oral anticoagulation.

Structured Graphical Abstract

Key Question

Is apixaban 5mg bid superior to standard-of-care (antiplatelet or VKA) (SOC) after successful TAVI?

Is there an interaction between treatments and outcomes according to the need for oral anticoagulation (OAC) other than TAVI?

Key Finding

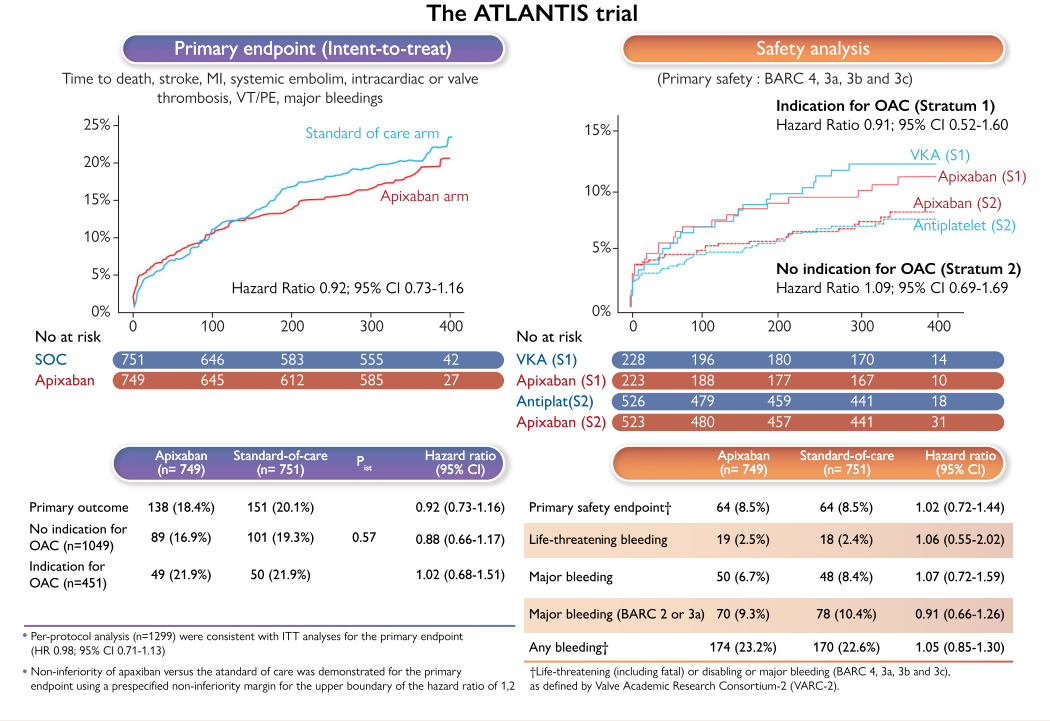
Apixaban:

- was not superior to SOC globally and in each stratum (indication or not for OAC).
- was non-inferior to SOC.
- was as safe as SOC.
- reduced subclinical obstructive valve thrombosis versus antiplatelet therapy alone.

Take Home Message

Apixaban:

- is not the default antithrombotic treatment after successful TAVI.
- can be used instead of VKA after successful TAVI.
- prevents subclinical valve thrombosis.



Primary endpoint and primary safety analysis of the ATLANTIS trial.

Keywords TAVI • Anticoagulation • Valve thrombosis • Stroke

Introduction

Transcatheter aortic valve implantation (TAVI) has become an increasingly used therapeutic option in patients with symptomatic aortic stenosis.[1–8] Although less invasive than surgical aortic valve replacement, peri- and post-procedural thrombotic and bleeding events are frequent and negatively affect short-term survival, especially among patients requiring oral anticoagulants.[9–11] In addition, the risk of thrombus formation on the implanted bioprosthesis and the bleeding risk associated with post-procedural treatment add to the potential hazards of TAVI.[12] Single antiplatelet alone in patients with no need for oral anticoagulation and absence of recent stent implantation is the safest option according to recent evidence.[13–16] Vitamin K antagonists (VKA) alone are also safer than when combined with antiplatelet therapy in patients requiring oral anticoagulation.[17,18] Up to now, there is no evidence that a non-VKA oral anticoagulant (NOAC) could replace antiplatelet therapy or VKA after TAVI in patients without or with an indication for anticoagulation. The recent randomized trials comparing NOAC vs. antiplatelet therapy or VKA following TAVI have suggested more harm than benefit.[19,20]

Apixaban, a reversible inhibitor of human factor Xa, has shown superiority over VKA for the prevention of both ischaemic and bleeding events in patients with atrial fibrillation, with a subsequent mortality benefit.[21] Apixaban was also superior to aspirin in VKA-non-suitable atrial fibrillation patients, with a comparable safety profile.[22] In ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis), we investigated the use of apixaban in all patients, regardless of their need for anticoagulation, when compared with antiplatelet alone or VKA (standard of care) according to the presence or not of an established indication for oral anticoagulation at the time of randomization.[23]

Methods

Study design

ATLANTIS (ClinicalTrials.gov unique identifier: NCT02664649) is an investigator-initiated, international, randomized, open-label, Phase 3, superiority trial comparing standard of care defined as antiplatelet therapy and/or VKA with an apixaban-based strategy after successful TAVI, carried out in 50 hospitals in France, Italy, Germany, and Spain. The primary study objective was to demonstrate the superiority of anticoagulation with apixaban compared with the current standard of care, comprising either antiplatelet or VKA therapy. The main secondary objective was to determine whether there was an interaction between treatment and outcomes according to the presence or absence of an indication other than TAVI for anticoagulation. Details of the trial protocol are available in Supplementary material online, Appendix. The protocol was approved by the relevant national regulatory authorities and ethics committees or institutional review boards in the participating countries. The study was conducted in compliance with the Declaration of Helsinki.

Patients and randomization

All patients provided written informed consent. The 50 participating sites and investigators are listed in Supplementary material online, Appendix. Patients were eligible after a successful TAVI procedure, including valve-in-valve performed with any approved device and defined according to the Valve Academic Research Consortium-2 (VARC-2) criteria[24] in the absence of exclusion criteria.[23] Patients without contraindications to oral anticoagulants were eligible irrespective of the presence of concomitant atrial fibrillation and/or coronary artery disease. A delay of at least 2 weeks between percutaneous coronary intervention and randomization was protocol mandated. Randomization 1:1 was stratified according to the need for oral anticoagulation treatment for a reason other than the TAVI procedure (see Supplementary material online, Appendix *Figure S1*).

Following successful TAVI as defined according to VARC, patients were randomly assigned (1:1) to receive open-label apixaban or standard of care. Randomization was performed centrally using an Interactive Web Response System, with stratification by centre and stratum with random block size, generated according to the procedures of Assistance Publique-Hôpitaux de Paris (AP-HP). A central event committee, composed of physicians not participating in the study, was blinded to the assigned study drug and provided with clinical data in order to adjudicate efficacy and safety endpoints.

The ATLANTIS trial was led by the Allies in Cardiovascular Trials Initiatives and Organized Networks (ACTION) Group (www.actiongroupe.org), an Academic Research Organization based at the Pitié-Salpêtrière Hospital in Paris, sponsored by AP-HP, and funded in part by an unrestricted grant from Bristol Myers Squibb and Pfizer. The ATLANTIS steering committee oversaw the conduct of the trial, in collaboration with representatives of the study sponsor (AP-HP). The trial was monitored by an independent data and safety monitoring board. Data were collected and analysed according to the predefined statistical analysis plan by academic statisticians of the ACTION Group. The chairman and the principal investigator of the study had unrestricted access to the data after the database was locked and statistical analyses were performed.

Procedures

Patients assigned to the apixaban group received open-label apixaban 5 mg tablets, taken orally twice a day for 12 months, started at the time of randomization, irrespective of the pre-existing antithrombotic regimen. A reduced dose of apixaban 2.5 mg was given, according to the product labelling, in case of severe renal insufficiency (creatinine clearance 15–29 mL/min), or in patients requiring concomitant antiplatelet therapy.[23] Patients assigned to the standard-of-care group with an indication for oral anticoagulation (Stratum 1) were given international normalized ratio (INR)-guided VKA therapy for the entire study follow-up, irrespective of the treatment given prior to the TAVI procedure. Patients with no indication for oral anticoagulation were given antiplatelet therapy (Stratum 2). Doses of aspirin and/or clopidogrel were left to the discretion of the physician, but in case of dual antiplatelet therapy (DAPT), a short duration was strongly recommended.[18] Patients in Stratum 2 in whom atrial fibrillation developed were to receive apixaban or INR-guided VKA in the apixaban and standard-of-care groups, respectively. Patients were followed up at 1, 3, 6, and 12 months.[23] Transthoracic echocardiography and four-dimensional computed tomography (4D-CT) were mandated by the study protocol between 3 and 6 months of follow-up.

Outcomes

The primary study endpoint was the composite of death, myocardial infarction (MI), stroke or transient ischaemic attack (TIA), non-central nervous system systemic embolism, intracardiac or valve thrombosis, episode of deep vein thrombosis or pulmonary embolism, life-threatening, disabling or major bleeding [Bleeding Academic Research Consortium (BARC) 4, 3a, 3b, and 3c), defined according to the VARC-2 definitions

over 1 year of follow-up.[24] The main secondary endpoint evaluated the primary assessment criterion according to the presence or not of an indication for anticoagulation. The primary safety endpoint was the composite of life-threatening (including fatal), disabling, or major bleeding. Obstructive valve thrombosis was defined as the mean transprosthetic gradient ≥10 mmHg change from baseline (vs. hospital discharge) or >20 mmHg or reduced leaflet mobility Grade 3 or 4 on at least one leaflet.[24] A 4D-CT scan was to be performed at 3–6 months after randomization in all patients. All components of the primary endpoint were blindly adjudicated by an independent Clinical Event Committee.

Statistical analysis

The sample size was calculated to test the hypothesis of superiority of apixaban over the standard-of-care strategy. Considering an event rate (corresponding to the primary endpoint) of 15% at Day 360 in the standard-of-care group, a sample size of 686 patients per group (total number of events $E = 167$) was determined to allow an 80% power to detect a 33% relative difference in event rate using a log-rank test with a 5% two-sided significance level. Assuming an attrition rate of <10%, a total of 1510 patients had to be included. A pre-specified blinded sample size reassessment was made when 50% of the patients completed a 12-month visit (based on predictive power using the ADDPLAN software) and concluded to continue without any change in sample size.

For the primary endpoint, a test of difference was performed. As *a priori* decided, in the absence of a significant difference between treatments, the interaction was tested according to the need for oral anticoagulation (strata). As pre-specified, non-inferiority of apixaban vs. the standard-of-care strategy was also tested if superiority was not met and was considered to be demonstrated if the upper boundary of the 95% confidence interval (CI) for the hazard ratio (HR) was lower than the *a priori* defined non-inferiority margin equal to 1.2. For secondary efficacy criteria, a hierarchical strategy of testing was used. Tests for significance of difference with a two-sided 5% alpha value were performed only if the primary hypothesis of superiority was verified. In this case, secondary criteria were tested using the following order of (i) death, MI, any stroke; (ii) death, any stroke/TIA, or systemic embolism; and (iii) all-cause death. Each criterion was tested only if a significant difference was found for the previous one; otherwise, only 95% CI of the HR was reported. For each individual parameter of the primary endpoint, no test was performed, and only 95% CI of HR was reported. For safety criteria, *P*-values were reported for each criterion.

Baseline characteristics were tabulated and comparability/differences between the treatment groups were examined by means of descriptive statistics. All variables corresponding to the time to event were analysed using Cox proportional hazards models including treatment, stratum, interaction between treatment and stratum, and age at the time of randomization. In case of a non-significant interaction, this term was omitted from the final Cox model. For composite criteria, the time from randomization to the first event was considered for the analysis and the patient was censored at the end of the study or the date of the last available information. The Kaplan–Meier curves were used to show the incidence of outcomes over time. In addition, a sensitivity analysis on the primary criterion that adjusted the Cox model with variables *a priori* known to possibly affect the outcome (age, gender, body mass index, diabetes, hypertension, peripheral artery disease, previous stroke, and access site) was performed.

All analyses for efficacy were performed in all randomized patients who provided written informed consent according to their group of randomizations [intention-to-treat (ITT) population]. The safety analysis included all patients who received at least one dose of the study drug. An additional analysis of all patients who adhered to the protocol included all patients randomized and treated without major protocol violations/deviations. The outcome of valve thrombosis was assessed at two follow-up visits and the outcome was defined as a binary outcome of thrombosis present at either visit; logistic regression was used to compare treatment, stratum, and treatment-by-stratum interaction. Pre-specified subgroup analyses to evaluate variations in treatment effect were performed by logistic-regression model and with terms for treatment, subgroup, and interaction of treatment with subgroup. All reported subgroup analyses were pre-specified. In case of withdrawal of consent, only data collected before withdrawal were used. All analyses were made using SAS version 9.4 (SAS Institute).

Results

Trial population

From 1 August 2017 to 31 July 2019, 1510 patients were initially enrolled, of whom 10 immediately withdrew consent. A total of 1500 patients were therefore randomized to receive apixaban ($n = 749$) or standard of care ($n = 751$), all of whom were included in the ITT and safety populations (*Figure 1*). The mean time from TAVI to randomization was 3.6 ± 2.6 days (range 0–33). Baseline characteristics were similar between the two groups (*Table 1*). In the standard-of-care group, 228 (30.4%) patients were assigned to Stratum 1 (indication for oral anticoagulation at the time of randomization, mainly because of atrial fibrillation) and 523 to Stratum 2. Patients of Stratum 1 had a higher risk profile than Stratum 2 (see Supplementary material online, Appendix *Table S1*). Very few patients with atrial fibrillation and no indication for oral anticoagulation were in Stratum 2 (32/1049). Follow-up was completed in 97.5% of the patient population. Echocardiography and 4D-CT scans during follow-up were obtained in 89 and 58.6%, respectively.

Low-dose apixaban was used in one-third of patients assigned to apixaban as per-protocol mandated (see Supplementary material online, Appendix *Table S2*). Vitamin K antagonists alone for Stratum 1 and the combination of aspirin and clopidogrel for Stratum 2 were the predominant antithrombotic regimen among patients assigned to the standard of care (*Table 1* and Supplementary material online, Appendix *Table S1*). Apixaban was combined with antiplatelet therapy, mostly aspirin, in more than one-quarter of the apixaban group and irrespective of an indication for oral anticoagulation, while the combination of aspirin and clopidogrel was used in half of the patients in the standard-of-care group, mainly in Stratum 2 (see Supplementary material online, Appendix *Table S3*). Dual antiplatelet therapy (aspirin and clopidogrel) was used in half of the patients assigned to the standard of care, mostly in the patients without an indication for oral anticoagulation, and rarely combined with oral anticoagulation (<5%). The drug regimen was prematurely discontinued in 14% patients in the apixaban group (105 out of 749) (*Figure 1*). Cross-over from apixaban to any standard-of-care treatment and from antiplatelet therapy to oral anticoagulation occurred in 10.7% (80 out of 749) and 13.4% (70 out of 523) of patients, respectively (see Supplementary material online, Appendix *Table S4*). New-onset atrial fibrillation developed in 4.9 and 1.6% of patients in Stratum 1 and 2, respectively.

Primary outcome

In the ITT population, the primary endpoint occurred in 138 (18.4%) of the 749 patients receiving apixaban and in 151 (20.1%) of the

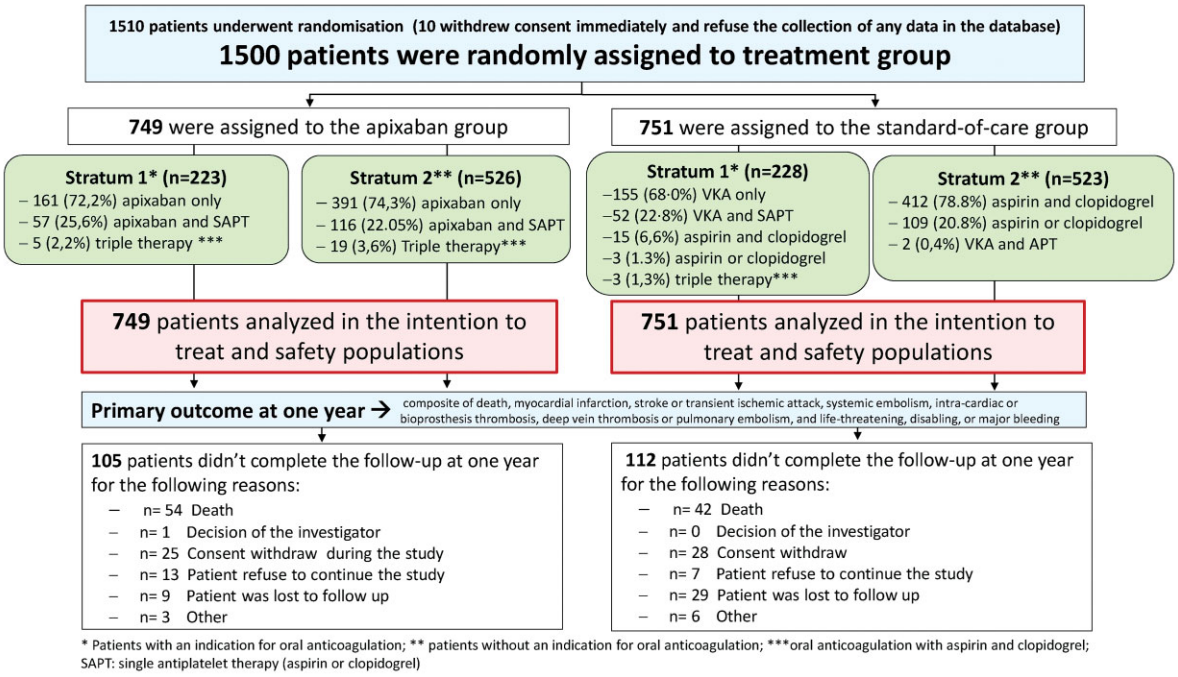


Figure 1 Randomization and follow-up. Stratum 1 and 2 correspond to the need or not for oral anticoagulation treatment, respectively. APT, antiplatelet therapy; VKA, vitamin K antagonist.

Table 1 Baseline patient characteristics in the intention-to-treat population[a]

	Apixaban ($n = 749$)	Standard of care ($n = 751$)
Age, years	81.6 (6.1)	82.3 (6.4)
Sex		
Female	405 (54.1%)	391 (52.1%)
Male	344 (45.9%)	360 (47.9%)
Body mass index, kg/m^2	27.52 (5.45)	27.33 (5.16)
Diabetes mellitus	221 (29.5%)	214 (28.5%)
Hypertension	606 (80.9%)	601 (80.0%)
EuroSCORE II[b]	4.84 (4.11)	5.10 (4.34)
STS risk score[c]	5.14 (5.02)	5.14 (5.38)
Glomerular filtration rate, mL/min	62.87 (30.75)	61.58 (31.00)
NYHA Class III or IV	342 (46.8%)	343 (47.6%)
Congestive heart failure	292 (39.0%)	284 (37.8%)
Prior myocardial infarction	83 (11.1%)	90 (12.0%)
Prior PCI	202 (27.0%)	188 (25.0%)
PCI <1 month	38 (5.1%)	36 (4.8%)
Prior coronary artery bypass grafting	65 (9.1%)	56 (7.8%)
Peripheral artery disease	90 (12.0%)	111 (14.8%)
Prior stroke	78 (10.4%)	89 (11.9%)

Continued

Table 1 *Continued*

	Apixaban ($n = 749$)	Standard of care ($n = 751$)
Prior venous thromboembolic disease	61 (8.1%)	38 (5.1%)
Chronic obstructive pulmonary disease	119 (15.9%)	111 (14.8%)
Atrial fibrillation	212 (28.3%)	199 (26.5%)
CHA_2DS_2-VASc score	4.4 (1.4)	4.3 (1.4)
Pre-TAVI antithrombotic treatment		
VKA	123 (16.4%)	111 (14.8%)
Non-VKA oral anticoagulant	66 (8.8%)	55 (7.3%)
Single antiplatelet therapy	428 (57.1%)	443 (59.0%)
Dual antiplatelet therapy	104 (13.9%)	94 (12.5%)
Antithrombotic treatment at randomization		
VKA only		155 (20.6%)
Apixaban only	552 (73.7%)	
Apixaban 2.5 mg b.i.d.	258 (34.4%)	—
Apixaban 5 mg b.i.d.	491 (65.6%)	—
Aspirin or clopidogrel	—	112 (14.9%)
Aspirin and clopidogrel	—	427 (56.9%)
Dual therapy[d]	173 (23.1%)	54 (7.2%)
Triple therapy[e]	24 (3.2%)	3 (0.4%)
Procedural characteristics		
Type of device		
Self-expanding	395 (52.8%)	386 (51.5%)
Balloon-expanding	353 (47.2%)	363 (48.5%)
Valve-in-valve	40 (5.3%)	35 (4.7%)
Post-TAVI echocardiographic characteristics		
Aortic valvular area, cm^2	1.74 (0.59)	1.80 (0.50)
Mean aortic valve gradient, mmHg	11.2 (6.4)	10.7 (4.9)
Left ventricular ejection fraction, %	59.0 (10.4)	59.0 (10.8)
Paravalvular aortic regurgitation		
Mild	35 (15.4%)	40 (16.6%)
Moderate to severe	3 (1.3%)	1 (0.4%)

Data are mean (SD), unless otherwise indicated. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65–74 years, sex category. NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation; TAVI, transcatheter aortic-valve replacement; VKA, vitamin K antagonist.

[a]Percentages may not total 100 because of rounding.

[b]Scores on the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), which measure patient risk at the time of cardiovascular surgery, are calculated by means of logistic-regression equations. A score of >10% indicates high risk, 5–10% intermediate risk, and <5% low risk.

[c]Society of Thoracic Surgeons (STS) risk scores, which measure patient risk at the time of cardiovascular surgery, are calculated by means of logistic-regression equations. A score of >8% indicates high risk, 3–8% intermediate risk, and <3% low risk.

[d]Combination of VKA or apixaban with aspirin or clopidogrel.

[e]Combination of VKA or apixaban with aspirin and clopidogrel.

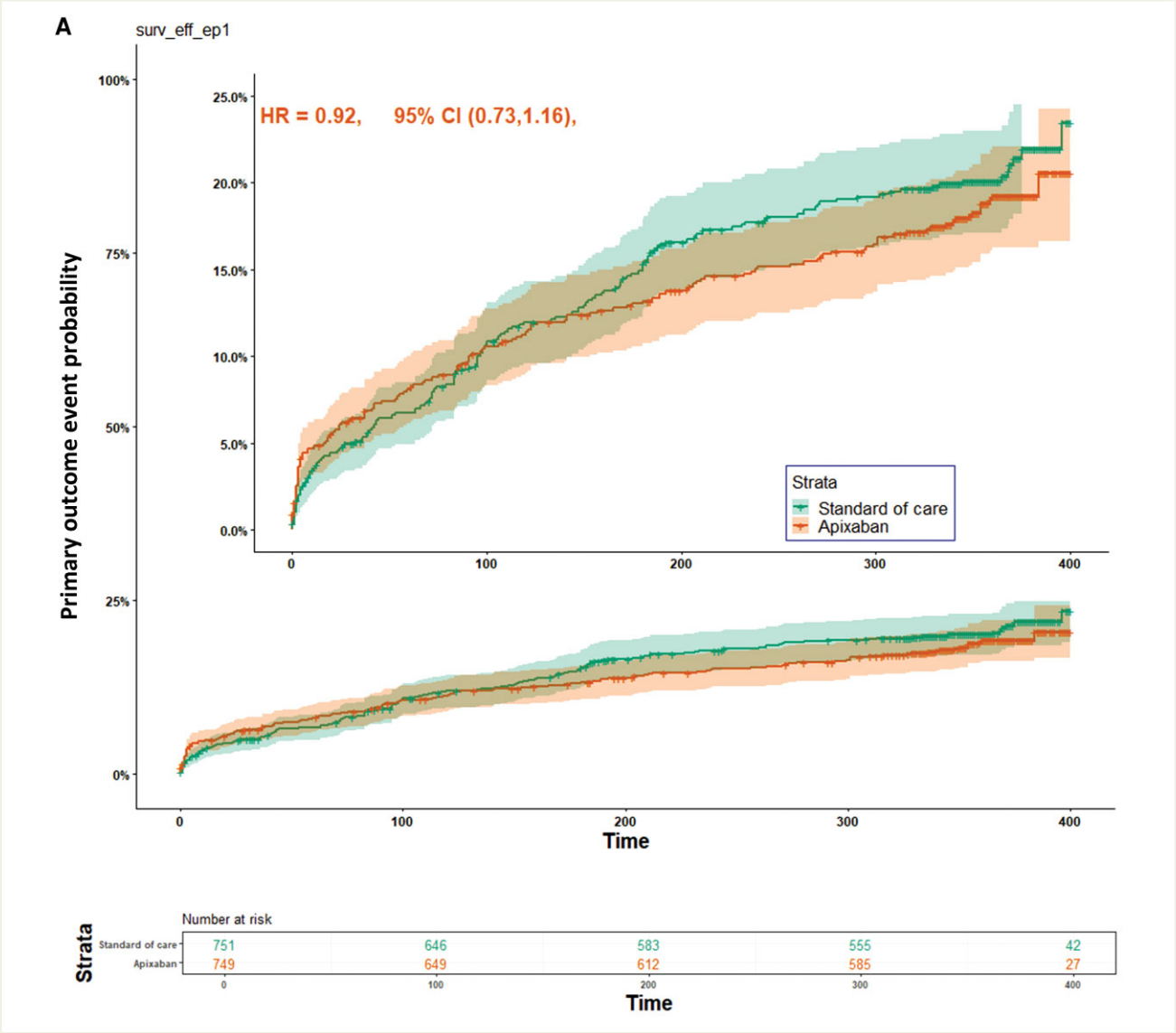


Figure 2 Cumulative risk of the primary outcomes of death from any cause, myocardial infarction, stroke or transient ischaemic attack, systemic embolism, intracardiac or bioprosthesis thrombosis, deep vein thrombosis or pulmonary embolism, life-threatening or disabling or major bleeding events, defined according to the Valve Academic Research Consortium-2 (VARC-2) definitions in the intention-to-treat population in the whole population (*A*) and according to the need (*B*, Stratum 1) or not (*C*, Stratum 2) for chronic oral anticoagulation.

751 patients receiving standard-of-care treatment (HR 0.92; 95% CI 0.73–1.16, $P = 0.43$) (*Figure 2* and *Table 2*). There was no significant interaction according to the need for oral anticoagulation ($P = 0.57$). Results after adjustment for baseline variables potentially affecting the primary outcome were similar (HR 0.93; 95% CI 0.73–1.17). Analysis of patients who adhered to the protocol ($n = 1299$) was consistent with the ITT analyses for the primary endpoint (HR 0.89; 95% CI 0.71–1.13). According to the statistical plan, apixaban was shown to be non-inferior to the standard of care for the primary outcome with a pre-specified margin of HR = 1.2 for all analysed populations. The effect of apixaban on the primary endpoint was consistent across all pre-specified subgroups (see Supplementary material online, Appendix *Figure S2*). A sensitivity analysis without valve thrombosis confirmed the lack of superiority of apixaban over the standard of care (HR 1.13; 95% CI 0.88–1.44) (see Supplementary material online, Appendix *Figure S3*).

Secondary efficacy outcomes

The secondary endpoint of death, MI, or any stroke/TIA occurred in 79 (10.5%) of the 749 patients receiving apixaban and in 62 (8.3%) of the 751 patients receiving standard-of-care treatment (HR 1.33; 95% CI 0.95–1.86) (*Table 2*). Obstructive valve thrombosis, deep vein thrombosis, or pulmonary embolisms were less frequent in the apixaban group than in the standard-of-care group while there were numerically more deaths in the apixaban group. Adjudicated causes of death are presented in Supplementary material online, Appendix

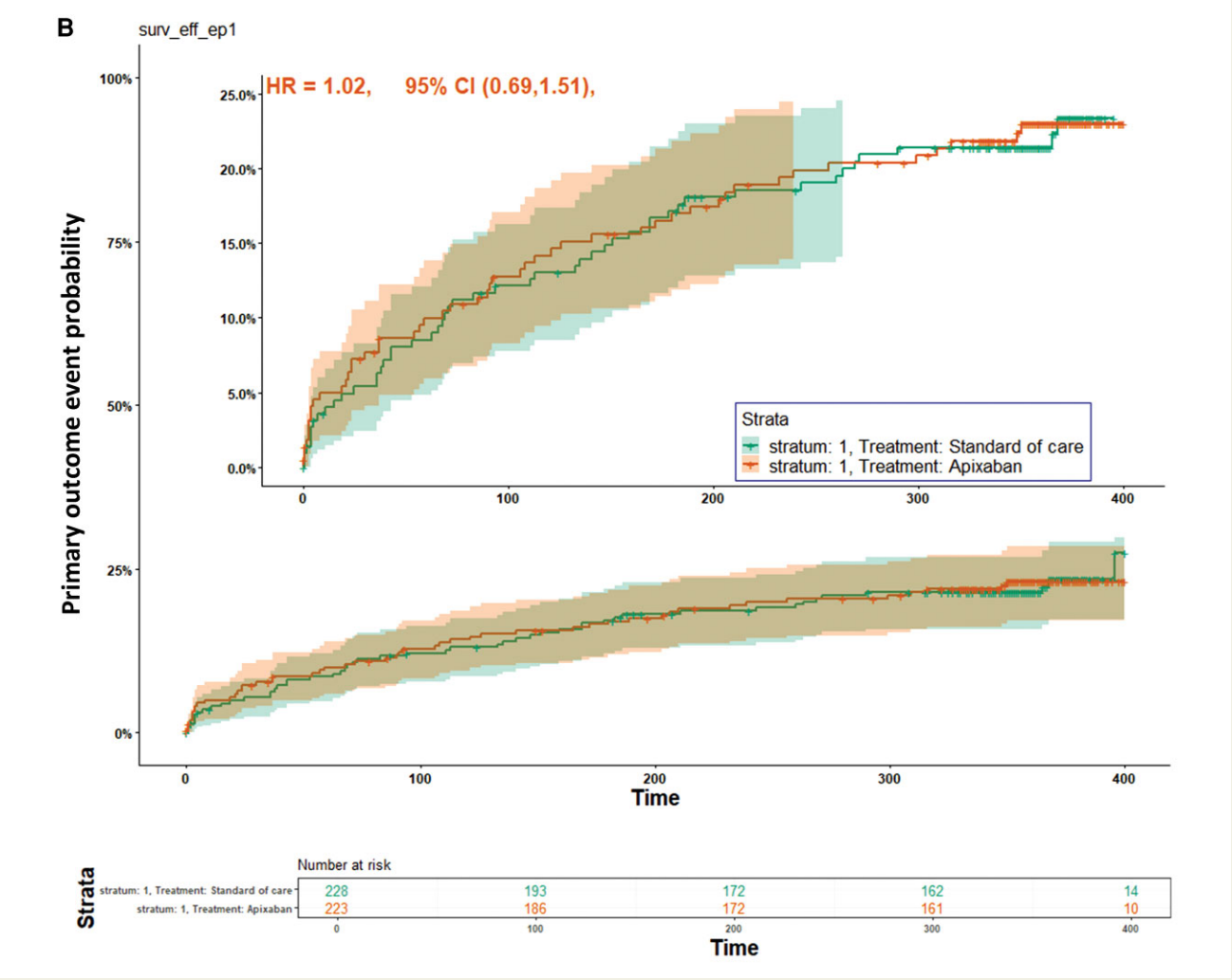


Figure 2 Continued

Tables S5 and S6 and the imbalance is driven by non-cardiovascular death in Stratum 2.

Safety outcomes

Major, disabling, or life-threatening bleeding occurred in 64 (8.5%) patients receiving apixaban and 64 (8.5%) patients receiving standard-of-care treatment (HR 1.02; 95% CI, 0.72–1.44) (*Figure 3*). Life-threatening including fatal bleeding occurred in 19 (2.5%) and 18 (2.4%) patients, respectively (HR 1.06; 95% CI 0.56–2.02). The rates of major and minor bleeding did not differ between groups (*Table 2*). All per-protocol analyses ($n = 1299$) were consistent with the ITT analyses both for safety and for efficacy endpoints.

Outcomes according to strata

Outcomes were more frequently observed among patients with an indication for oral anticoagulation (Stratum 1) than in those without (Stratum 2) (see Supplementary material online, Appendix *Table S5*). The primary outcome and the primary safety endpoint were comparable for each treatment group in each stratum. In Stratum 1, event rates were also similar between apixaban and VKA for all the other endpoints (*Table 3*). In Stratum 2 (*Table 4*), all bleeding endpoints were similar between apixaban and antiplatelet therapy but an excess of non-cardiovascular death was noted with apixaban in this stratum (see Supplementary material online, Appendix *Table S6*). Obstructive valve thrombosis and venous thromboembolic events were largely reduced in patients receiving apixaban vs. antiplatelet therapy (Stratum 2).

Discussion

ATLANTIS demonstrates that apixaban is not superior to the usual standard of care after successful TAVI for the net clinical benefit primary outcome in the global population and each stratum. Apixaban is associated with similar bleeding event rates than the standard of care irrespective of an established indication for oral anticoagulation therapy at the time of randomization. Altogether, ATLANTIS shows non-inferiority of apixaban vs. standard of care after successful

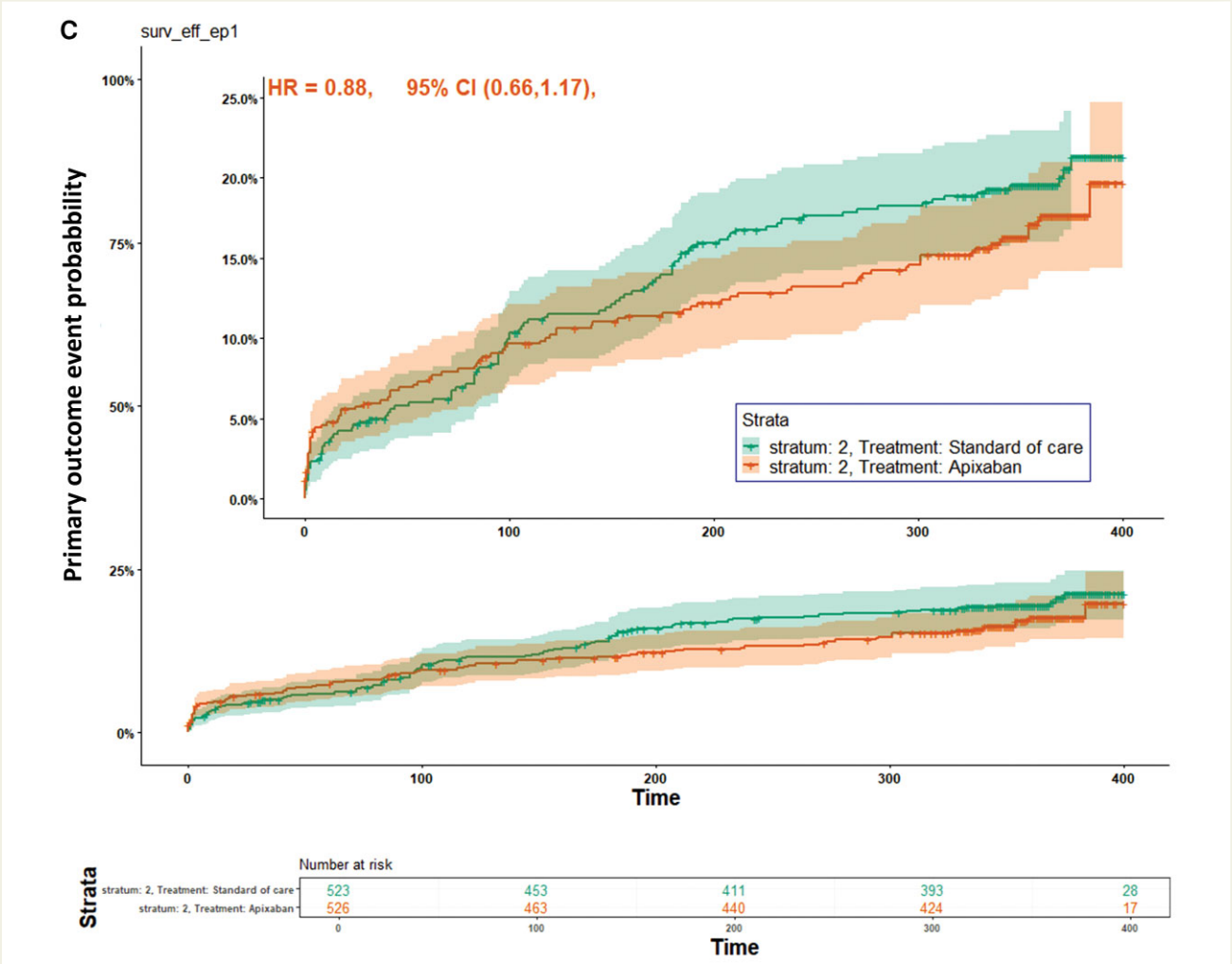


Figure 2 Continued

TAVI for the net clinical benefit primary outcome endpoint (*Structured Graphical Abstract*). Per-stratum exploratory analyses are provided for a better practical guidance but should be considered with caution. They suggest no difference in outcomes between treatment arms among patients with a concurrent indication for anticoagulation. In the stratum of patients without an indication for anticoagulation, obstructive valve thrombosis, deep vein thrombosis, and pulmonary embolism are largely reduced with apixaban vs. antiplatelet therapy (single or dual). In this stratum, the increased rate of the composite of death, any stroke or TIA, and systemic embolism is driven by an excess of non-cardiovascular death.

Our results suggest that new possibilities of antithrombotic treatment are possible after TAVI. The GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial reported higher rates of death, thromboembolic, or bleeding complications in rivaroxaban- vs. aspirin-treated patients without an established indication for anticoagulation.[19] A lower incidence of obstructive valve thrombosis was observed in a limited subset of the GALILEO population, which we confirm here in a larger group of patients.[25] Whether these differences between the two trials are related to the drugs, drug doses (low dose of 10 mg of rivaroxaban vs. usual 5 mg dose of apixaban), early combination with aspirin (in GALILEO but not in ATLANTIS), the study populations (at higher risk in ATLANTIS), or different use of DAPT in the control groups remains unknown. The POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial cohorts demonstrated better safety of single antiplatelet therapy over DAPT in patients without an indication for oral anticoagulation, and of oral anticoagulation alone vs. clopidogrel in addition to oral anticoagulation when indicated.[15,18] In a subgroup analysis of POPular-TAVI, one-quarter of patients with an indication for oral anticoagulation received a NOAC and had a more favourable outcome than patients on VKA. The consensus document of the ESC on post-TAVI antithrombotic therapy as well as the 2021 ESC/EACTS guidelines on the management of valvular heart disease do not give preference to VKA over NOAC when concurrent oral anticoagulation is indicated.[26,27] The American College of Cardiology/American Heart Association guidelines recommend not using low-dose

Table 2 Study endpoints at 1 year in the intention-to-treat population

	Apixaban ($n = 749$)	Standard of care ($n = 751$)	*P*-value	Hazard ratio or odds ratio[a] (95% CI)
Primary outcome[a]	138 (18.4%)	151 (20.1%)		0.92 (0.73–1.16)
No indication for oral anticoagulation ($n = 1049$)	89 (16.9%)	101 (19.3%)	$P_{int} = 0.57$	0.88 (0.66–1.17)
Indication for oral anticoagulation ($n = 451$)	49 (22.0%)	50 (21.9%)		1.02 (0.69–1.51)
	Apixaban ($n = 749$)	**Standard of care ($n = 751$)**		**Hazard ratio (95% CI)**
Secondary efficacy outcomes[b]				
Death, MI, any stroke/TIA	79 (10.5%)	62 (8.3%)		1.33 (0.95–1.86)
Death, any stroke/TIA or systemic embolism	78 (10.4%)	60 (8.0%)		1.36 (0.97–1.90)
Death	54 (7.2%)	41 (5.5%)		1.39 (0.93–2.09)
From cardiovascular causes	38 (5.1%)	28 (3.7%)		1.42 (0.87–2.32)
From non-cardiovascular causes	16 (2.1%)	13 (1.7%)		1.33 (0.64–2.77)
Myocardial infarction	6 (0.8%)	5 (0.7%)		1.22 (0.37–4.00)
Stroke or TIA	28 (3.7%)	21 (2.8%)		1.39 (0.79–2.44)
Systemic embolism	2 (0.3%)	3 (0.4%)		0.66 (0.11–3.95)
Obstructive valve thrombosis[c]	8 (1.1%)	35 (4.7%)		0.23 (0.11–0.50)[a]
Intracardiac thrombus	3 (0.4%)	3 (0.4%)		1.07 (0.22–5.30)
Deep vein thrombosis or pulmonary embolism	1 (0.1%)	11 (1.5%)		0.09 (0.01–0.72)
Safety endpoints				
Primary safety endpoint[a]	64 (8.5%)	64 (8.5%)		1.02 (0.72–1.44)
Life-threatening bleeding	19 (2.5%)	18 (2.4%)		1.06 (0.56–2.02)
Major bleeding	50 (6.7%)	48 (6.4%)		1.07 (0.72–1.59)
Minor bleeding (BARC 2 or 3a)	70 (9.3%)	78 (10.4%)		0.91 (0.66–1.26)
Any bleeding	174 (23.2%)	170 (22.6%)		1.05 (0.85–1.30)

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; TIA, transient ischaemic attack.
[a]Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, 3b, and 3c), as defined by the Valve Academic Research Consortium-2 (VARC-2).
[b]Death, myocardial infarction, stroke or TIA or systemic embolism, intracardiac or bioprosthesis thrombosis, episode of deep vein thrombosis or pulmonary embolism, life-threatening or disabling bleeding or major bleeding (primary endpoint).
[c]Obstructive valve thrombosis was defined as the mean transprosthetic gradient ≥10 mmHg change from baseline (vs. hospital discharge) or > 20 mmHg or reduced leaflet mobility Grade 3 or 4 on at least one leaflet.

rivaroxaban after TAVI when there is no indication for oral anticoagulation, and not to use NOAC during the first 3 months after TAVI when there is a concurrent indication of anticoagulation.[28] The ENVISAGE-TAVI AF (Edoxaban Versus Vitamin K Antagonists After Transcatheter Aortic Valve Implantation in Patients with Atrial Fibrillation) trial compared edoxaban with VKA in patients with an indication for anticoagulation using a non-inferiority margin for the upper boundary of the HR wider than in ATLANTIS (1.38 vs. 1.20). Non-inferiority was demonstrated like in ATLANTIS. However, in contrast to our study, a significant increase in major but not fatal or life-threatening bleedings was observed.[20] High-dose edoxaban and a liberal concomitant use of antiplatelet therapy in 60% of patients vs. 25% and <5% of single antiplatelet therapy and DAPT, respectively, in ATLANTIS, may have led to this unexpected safety issue in ENVISAGE-TAVI AF, mainly driven by an excess in gastrointestinal bleedings. Our results may offer a new option of antithrombotic treatment after TAVI, using apixaban at the usual dose for atrial fibrillation, when anticoagulation is indicated given its ease of use and similar safety or efficacy vs. VKA.

Stratification according to the need for oral anticoagulation was intended in ATLANTIS, a pragmatic clinical trial reflecting real-world clinical practice, to allow all-comers to enter the study. Apixaban was the only NOAC that could be tested in both situations with the same dose given available data against both aspirin and warfarin in atrial fibrillation. Higher overall event rates, including all-cause death, were observed in patients with an indication for oral anticoagulation, reflecting the higher risk of these patients. The similar bleeding event rates of apixaban compared with VKA or antiplatelet therapy is consistent with previous information on atrial fibrillation.[22] It is an

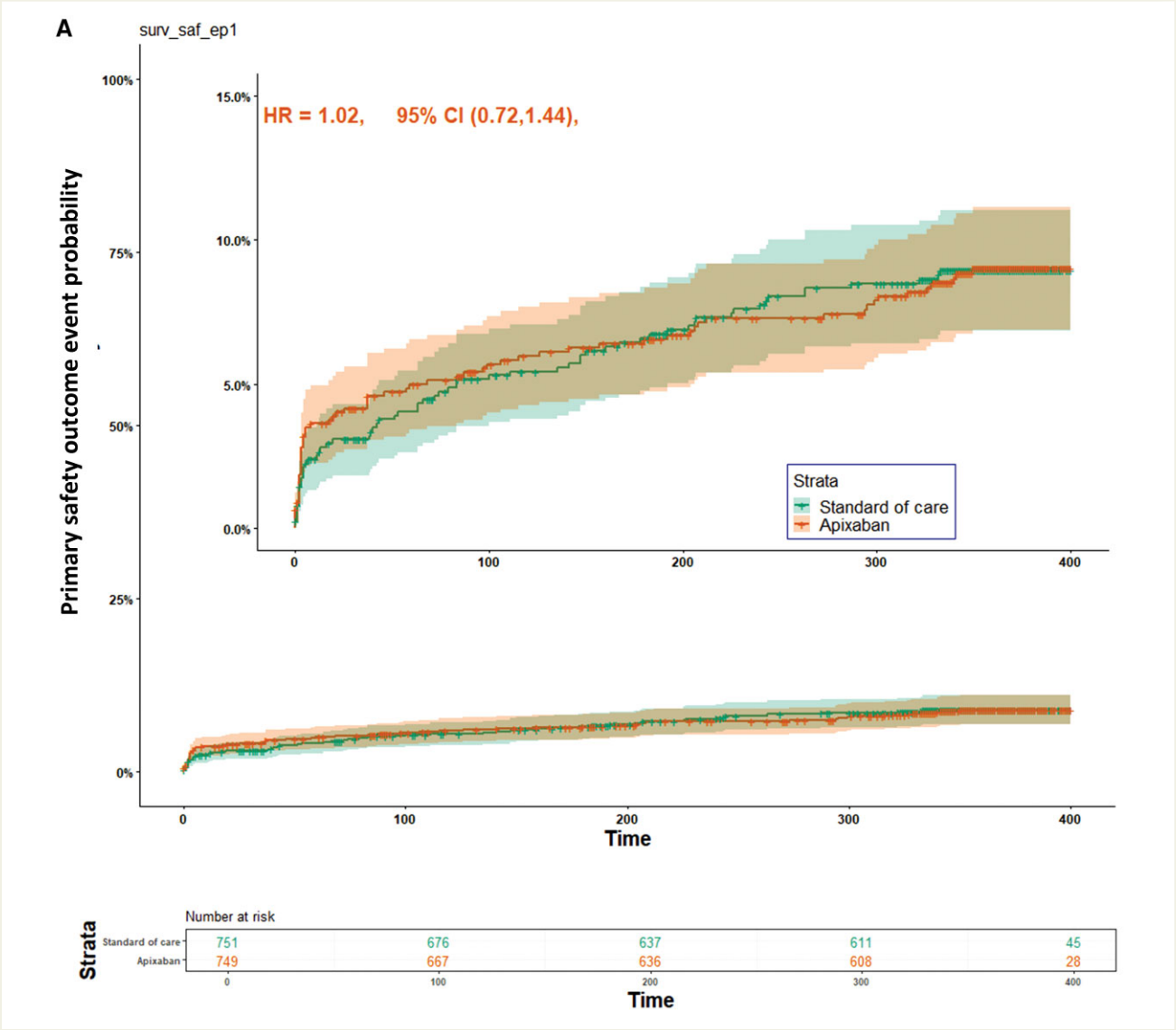


Figure 3 Cumulative risk of the primary safety outcomes of life-threatening (including fatal) or disabling or major bleeding events [Bleeding Academic Research Consortium (BARC) 4, 3a, 3b, and 3c], as defined by the Valve Academic Research Consortium-2 (VARC-2) in the whole population (*A*) and according to the need (*B*, Stratum 1) or not (*C*, Stratum 2) for chronic oral anticoagulation in the safety population.

important finding, knowing that the ATLANTIS population displayed risk scores and event rates higher than anticipated and higher than those observed in previously published trials, considering also that apixaban was combined with antiplatelet therapy in more than one out of four patients.[18,19] The ATLANTIS findings also mitigate registry data that demonstrated better safety of apixaban than VKA or aspirin in the TAVI population.[29] Concerns have been raised towards a potential lack of efficacy of NOAC vs. VKA after TAVI.[30] Although the present results are reassuring in terms of efficacy vs. both antiplatelet and VKA therapy, data in the cohort of patients without an indication for anticoagulation remain insufficient to support clinical use in place of aspirin. Alike the GALILEO trial, we report a signal towards more non-cardiovascular death with apixaban than with antiplatelet therapy in the stratum of patients without an indication for anticoagulation but in contrast to GALILEO without excess bleeding events. Most of the adjudicated causes of death could not be related to cardiovascular events within 30 days prior to death (see Supplementary material online, Appendix *Table S7*).

A 4D-CT scan was protocol mandated in the ATLANTIS study to identify as much as possible obstructive valve thrombosis, a component of the primary endpoint. The lower incidence of obstructive valve thrombosis with apixaban vs. antiplatelet therapy is an advantage in the context of expanding indications towards a declining risk profile population, where a successful procedure and valve durability are even more essential. The magnitude of effect was found to be in the range of that reported with rivaroxaban.[25] However, this reduction of obstructive valve thrombosis at 3 months with apixaban in the cohort of patients without an indication for oral anticoagulation was not associated with a significant clinical benefit at 1-year follow-up (see ATLANTIS_4DCT substudy).

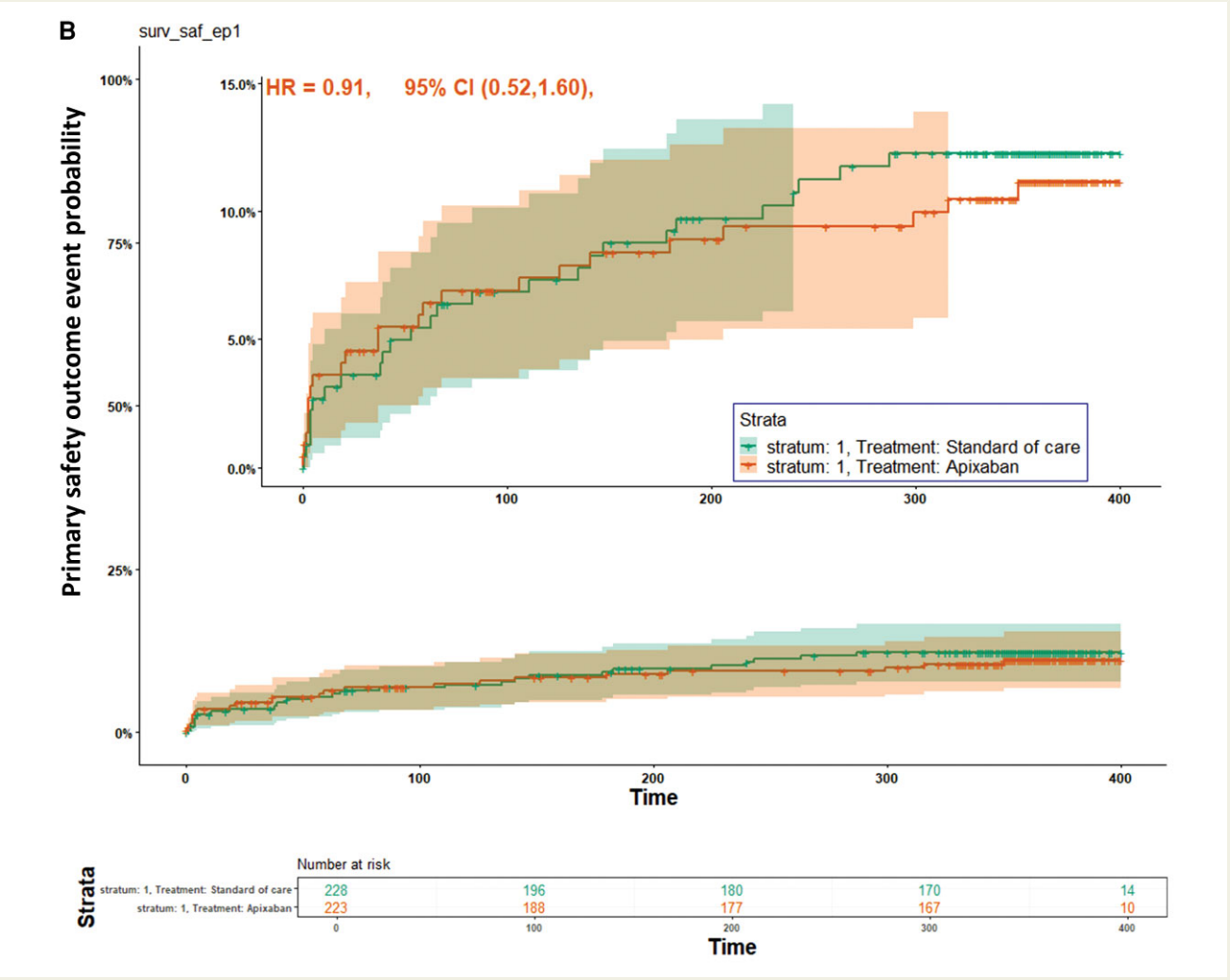


Figure 3 Continued

The ATLANTIS trial has several limitations. First, it was an open-label trial subject to reporting and ascertainment biases. Second, the results of this report apply only to patients who underwent a successful TAVI procedure and not to those scheduled for a TAVI or any other valve procedure. Third, our trial results cannot draw definitive conclusions on efficacy. Fourth, the protocol-driven 4D-CT for the assessment of obstructive valve thrombosis as part of the primary endpoint was adhered to in half of the entire study population. Fifth, interaction analyses according to the need for oral anticoagulation may be seen as a lack of sufficient power for each group considered on its own. However, the sample size calculations were made on the total cohort and the reported adjudicated event numbers were higher than anticipated, even when considering the two strata separately. Sixth, treatment arms may appear heterogeneous, but the overall rate of dual therapy and triple therapy were balanced and low compared to other studies. The difference in the loss to follow-up between treatment arms (9 vs. 29) should be acknowledged as a limitation especially given the reported signal towards more cardiovascular death in the apixaban arm than with antiplatelet therapy in the stratum of patients without an indication for anticoagulation. Finally, whether low-dose apixaban used in one-third of patients would be safer and as effective if used in all patients needs additional investigation.

In conclusion, oral anticoagulation with apixaban after a TAVI procedure was not superior to the standard-of-care antithrombotic treatment with respect to the net clinical benefit over a period of 1 year, irrespectively of a concurrent indication for oral anticoagulation. Non-inferiority was, however, demonstrated. Bleeding event rates with apixaban were similar to those with the current standard of care, in the whole cohort, and in each individual stratum. Some individual endpoints differed in the cohort without an indication for anticoagulation (less valve thrombosis, less pulmonary embolism, more non-cardiovascular death) which need to be interpreted with great caution.

Authors' contributions

The first and last author prepared the first draft of the manuscript and all co-authors revised the manuscript and made the decision

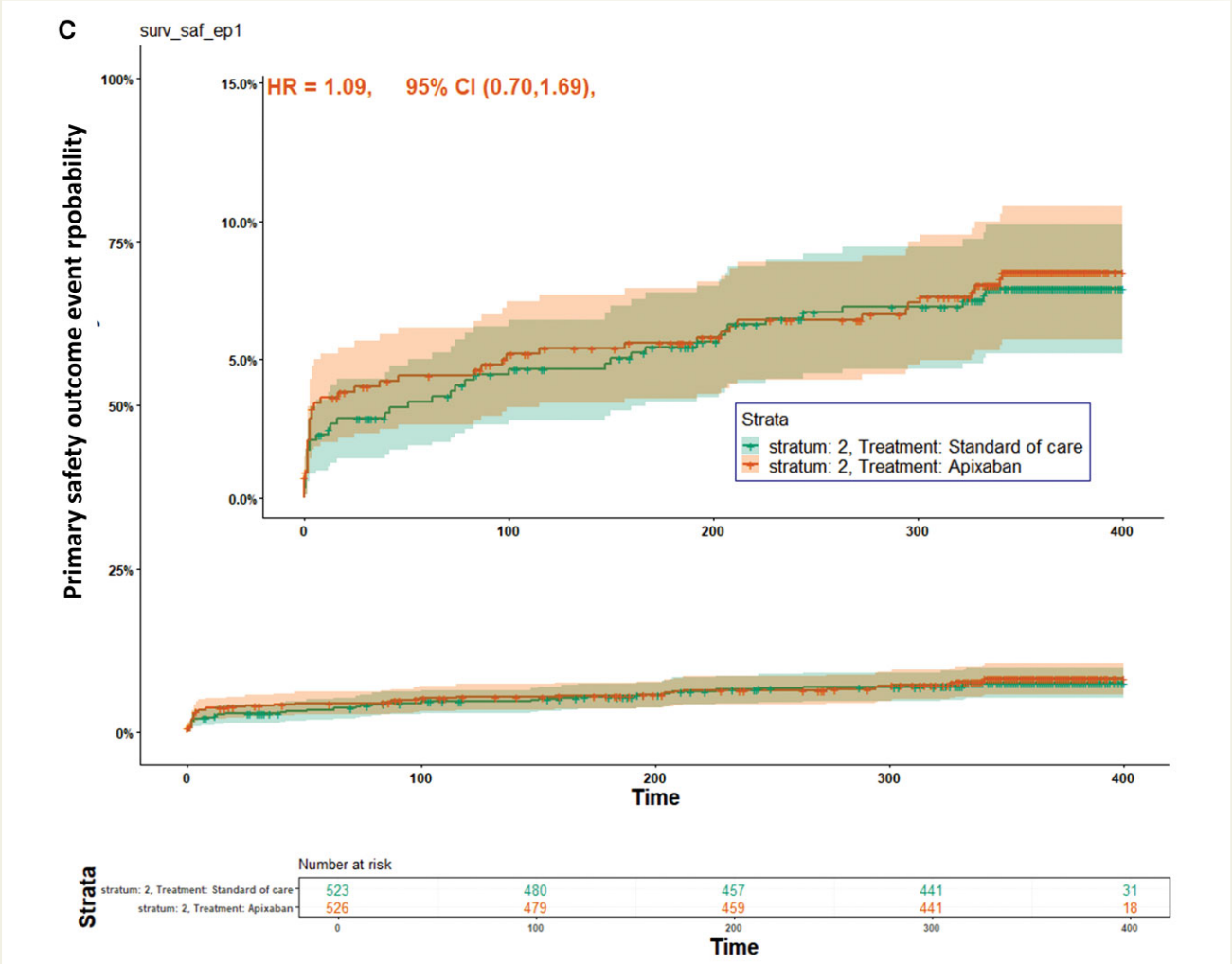


Figure 3 Continued

Table 3 Study endpoints at 1 year in the intention-to-treat population among patients with an indication for oral anticoagulation (Stratum 1)

	Apixaban ($n = 223$)	VKA ($n = 228$)	Hazard ratio or odds ratio[a] (95% CI)
Primary outcome[b]	49 (22.0%)	50 (21.9%)	1.02 (0.69–1.51)
Secondary efficacy outcomes			
Death, MI, any stroke/TIA	29 (13.0%)	27 (11.8%)	1.13 (0.67–1.91)
Death, any stroke/TIA, or systemic embolism	28 (12.6%)	27 (11.8%)	1.09 (0.64–1.86)
Death	23 (10.3%)	23 (10.1%)	1.04 (0.58–1.86)
Safety outcomes			
Primary safety endpoint[a]	23 (10.3%)	26 (11.4%)	0.91 (0.52–1.60)
Minor bleeding (BARC 2 or 3a)	21 (9.4%)	27 (11.8%)	0.79 (0.45–1.40)
Any bleeding	59 (26.5%)	58 (25.4%)	1.05 (0.73–1.51)
Obstructive valve thrombosis[c]	2 (0.9%)	3 (1.3%)	0.68 (0.11–4.08)†

[a]Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, 3b, and 3c), as defined by the Valve Academic Research Consortium-2 (VARC-2).
[b]Death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings.
[c]Obstructive valve thrombosis was defined as mean transprosthetic gradient ≥10 mmHg change from baseline (vs. hospital discharge) or > 20 mmHg or reduced leaflet mobility grade 3 or 4 on at least one leaflet.

Table 4 Study endpoints at 1 year in the intention-to-treat population among patients with no indication for oral anticoagulation (Stratum 2)

	Apixaban ($n = 526$)	Antiplatelet therapy ($n = 523$)	Hazard ratio or odd ratio[a] (95% CI)
Primary outcome[b]	89 (16.9%)	101 (19.3%)	0.88 (0.66–1.17)
Secondary efficacy outcomes			
Death, MI, any stroke/TIA	50 (9.5%)	35 (6.7%)	1.49 (0.97–2.30)
Death, any stroke/TIA, or systemic embolism	50 (9.5%)	33 (6.3%)	1.57 (1.01–2.44)
Death	31 (5.9%)	18 (3.4%)	1.86 (1.04–3.34)
Cardiovascular death	17 (3.2%)	13 (2.5%)	1.42 (0.69–2.95)
Non-cardiovascular death	14 (2.7%)	5 (0.96%)	2.99 (1.07–8.36)
Safety outcomes			
Primary safety endpoint[a]	41 (7.8%)	38 (7.3%)	1.09 (0.70–1.69)
Minor bleeding (BARC 2 or 3a)	49 (9.3%)	51 (9.8%)	0.96 (0.65–1.43)
Any bleeding	115 (21.9%)	112 (21.4%)	1.05 (0.81–1.36)
Obstructive valve thrombosis[c]	6 (1.1%)	32 (6.1%)	0.19 (0.08–0.46)[a]

[a]Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, 3b, and 3c), as defined by the Valve Academic Research Consortium-2 (VARC-2).
[b]Death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, DVT/PE, major bleedings.
[c]Obstructive valve thrombosis was defined as the mean transprosthetic gradient ≥10 mmHg change from baseline (vs. hospital discharge) or > 20 mmHg or reduced leaflet mobility grade 3 or 4 on at least one leaflet.

to submit it for publication. All authors assume responsibility for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol. Bristol Myers Squibb and Pfizer did not have any role in the design, conduct, analysis, results reporting of the study, or medical writing of the article.

Supplementary material

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

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