ORIGINAL ARTICLE

Continuation versus Interruption of Oral Anticoagulation during TAVI

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ABSTRACT

BACKGROUND

One third of patients undergoing transcatheter aortic-valve implantation (TAVI) have an indication for oral anticoagulation owing to concomitant diseases. Interruption of oral anticoagulation during TAVI may decrease the risk of bleeding, whereas continuation may decrease the risk of thromboembolism.

METHODS

We conducted an international, open-label, randomized, noninferiority trial involving patients who were receiving oral anticoagulants and were planning to undergo TAVI. Patients were randomly assigned in a 1:1 ratio to periprocedural continuation or interruption of oral anticoagulation. The primary outcome was a composite of death from cardiovascular causes, stroke from any cause, myocardial infarction, major vascular complications, or major bleeding within 30 days after TAVI.

RESULTS

A total of 858 patients were included in the modified intention-to-treat population: 431 were assigned to continuation and 427 to interruption of oral anticoagulation. A primary-outcome event occurred in 71 patients (16.5%) in the continuation group and in 63 (14.8%) in the interruption group (risk difference, 1.7 percentage points; 95% confidence interval [CI], −3.1 to 6.6; P=0.18 for noninferiority). Thromboembolic events occurred in 38 patients (8.8%) in the continuation group and in 35 (8.2%) in the interruption group (risk difference, 0.6 percentage points; 95% CI, −3.1 to 4.4). Bleeding occurred in 134 patients (31.1%) in the continuation group and in 91 (21.3%) in the interruption group (risk difference, 9.8 percentage points; 95% CI, 3.9 to 15.6).

CONCLUSIONS

In patients undergoing TAVI with a concomitant indication for oral anticoagulation, periprocedural continuation was not noninferior to interruption of oral anticoagulation during TAVI with respect to the incidence of a composite of death from cardiovascular causes, stroke, myocardial infarction, major vascular complications, or major bleeding at 30 days. (Funded by the Netherlands Organization for Health Research and Development and the St. Antonius Research Fund; POPular PAUSE TAVI ClinicalTrials.gov number, NCT04437303.)

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*A list of the POPular PAUSE TAVI investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Transcatheter aortic-valve implantation (TAVI) is an established treatment in patients with symptomatic severe aortic stenosis.[1,2] Despite technical advances over the years, thromboembolic and bleeding complications remain frequent, especially during the periprocedural period.[3-5] Approximately one third of patients undergoing TAVI have an indication for oral anticoagulation owing to concomitant disease, mainly atrial fibrillation.[6-8]

International guidelines advise interrupting oral anticoagulation in patients undergoing interventions with a high risk of bleeding,[9,10] but the appropriate strategy for the management of anticoagulation in patients undergoing TAVI has not been well studied. Interruption of oral anticoagulation during TAVI may decrease the risk of bleeding, whereas continuation may decrease the risk of thromboembolism. Observational studies have suggested a decreased risk of stroke among patients who continued oral anticoagulation during TAVI, without an increased risk of bleeding.[11,12] Therefore, in the Periprocedural Continuation versus Interruption of Oral Anticoagulant Drugs during Transcatheter Aortic Valve Implantation (POPular PAUSE TAVI) trial, we investigated the safety and efficacy of periprocedural continuation as compared with interruption of oral anticoagulation during TAVI with respect to the occurrence of a composite of death from cardiovascular causes, stroke, myocardial infarction, major vascular complications, or major bleeding at 30 days.

Methods

Trial Design and Oversight

The POPular PAUSE TAVI trial was an international, investigator-initiated, open-label, randomized clinical trial with blinded outcome assessment, performed at 22 European sites. The sites and investigators are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. Details of the design of the trial have been described previously[13] and are summarized in Figure S1 in the Supplementary Appendix. The protocol is available at NEJM.org. The trial was funded by the Netherlands Organization for Health Research and Development and the St. Antonius Research Fund; neither had a role in the design or execution of the trial or in the analysis of the data.

The trial protocol was approved by the national authorities and ethics committees and by the institutional review board at each participating site. The first two authors and the last author supervised all aspects of the trial. An independent data and safety monitoring board reviewed the reported outcomes to safeguard the interests of the trial participants. All potential primary-outcome events were adjudicated by a clinical-events committee whose members were unaware of the trial-group assignments; the committee consisted of two interventional cardiologists and one cerebrovascular neurologist (see the Supplementary Appendix for further details).[14] Trial monitoring was performed according to Good Clinical Practice guidelines under the direction of the Research and Development Academy of the St. Antonius Hospital.

The first two authors and the last author prepared the first draft of the manuscript. All the coauthors participated in subsequent revisions of the manuscript. The analyses were performed by the trial statisticians. All the authors reviewed the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Patients who were planning to undergo transfemoral or transsubclavian TAVI, were receiving long-term oral anticoagulants, and had provided written informed consent were eligible for enrollment. The exclusion criteria were the presence of a mechanical heart valve prosthesis, intracardiac thrombus, venous thromboembolism within 3 months before TAVI, or transient ischemic attack or stroke in patients with atrial fibrillation within 6 months before TAVI (Table S1). The representativeness of the trial population is shown in Table S2.

Randomization and Trial Procedures

Patients were randomly assigned before TAVI, in a 1:1 ratio, to either a continued or interrupted oral anticoagulation strategy. Randomization was performed by means of an electronic Web-response system (REDCap eCRF Randomization module), with stratification according to trial site and type of oral anticoagulation (vitamin K antagonist or direct oral anticoagulant).

For the interruption group, guidelines on antithrombotic therapy for patients undergoing a

high-bleeding-risk procedure were followed.[9,10,15] Patients receiving direct oral anticoagulants interrupted the drug regimens 48 hours before TAVI, except for those with concomitant renal insufficiency who were receiving dabigatran. Patients with an estimated glomerular filtration rate (GFR) of 50 to 80 ml per minute per 1.73 m^2 of body-surface area interrupted dabigatran therapy 72 hours before TAVI, and those with an estimated GFR of 30 to less than 50 ml per minute per 1.73 m^2 interrupted dabigatran therapy 96 hours before TAVI. Patients receiving vitamin K antagonists interrupted acenocoumarol therapy 72 hours before TAVI and phenprocoumon or warfarin therapy 120 hours before TAVI. Bridging with heparin or low-molecular-weight heparin was not initiated. Oral anticoagulation was restarted after TAVI, as soon as deemed to be safe by the operator or treating physician. Patients who were assigned to the continuation group continued oral anticoagulation, including on the day of the TAVI procedure. Patients treated with vitamin K antagonists received doses based on their usual target international normalized ratio.[16]

The TAVI procedures were performed according to the local protocol of each participating trial site, including the choice of valve type, whether cerebral embolic protection was used, the amount of heparin and protamine if administered during the procedure, and the type of vascular-closure device. Follow-up visits were performed at discharge and 30 days after TAVI; the 30-day follow-up visit could be performed at the enrolling site or by telephone. If necessary, the patient's primary care physician or treating specialist was contacted for additional information.

TRIAL OUTCOMES

The primary outcome was a composite of death from cardiovascular causes, stroke from any cause, myocardial infarction, major vascular complications, or major bleeding within 30 days after TAVI. Major bleeding was defined as Valve Academic Research Consortium 3 (VARC-3) type 2, 3, or 4 bleeding.[14] Secondary outcomes, which were assessed at discharge and 30 days, included procedure-related components of the primary outcome; procedure-related bleeding complications (VARC-3 type 1, 2, 3, or 4 bleeding); procedure-related thromboembolic complications, defined as stroke from any cause (except hemorrhagic), transient ischemic attack, myocardial infarction, or systemic embolism (vascular complications: distal embolization [noncerebral] from a vascular source); cerebrovascular events (stroke from any cause or transient ischemic attack); death from any cause; and the early safety outcome at 30 days (freedom from death from any cause; stroke from any cause; VARC-3 type 2, 3, or 4 bleeding; major vascular, access-related, or cardiac structural complications; acute kidney injury stage 3 or 4; moderate or severe aortic regurgitation; new permanent pacemaker owing to procedure-related conduction abnormalities; and surgery or intervention related to the device). All definitions were in accordance with the VARC-3 criteria.[14] Bleeding events were also classified according to the Bleeding Academic Research Consortium (BARC) criteria.[17] Full lists of outcomes and definitions are provided in Tables S3 and S4, respectively.

The relationship between the outcome and the procedure was assessed by the clinical-events committee. Given that all outcomes were early events (occurring within 30 days after TAVI), they were in principle considered to be related to the TAVI procedure, unless there was clear evidence of the contrary.[14]

STATISTICAL ANALYSIS

The intention-to-treat analysis included all randomly assigned patients and all events occurring from randomization until 30 days after TAVI. The primary analysis was performed in the modified intention-to-treat population in which the period at risk for any of the outcome events was defined as 5 days before TAVI until 30 days after TAVI. Randomly assigned patients in whom the TAVI procedure was canceled more than 5 days before the planned TAVI date were excluded. We anticipated an incidence of the primary composite outcome of 17.5% in the interrupted oral anticoagulation group and 13.5% in the continued oral anticoagulation group, on the basis of the event rates in cohort B of the POPular TAVI trial[18] and an observational study that evaluated continued as compared with interrupted oral anticoagulation in patients undergoing TAVI.[11] We estimated that a sample of 858 patients would provide the trial with at least 90% power to show noninferiority of continuation to interruption with respect to the primary outcome at a one-sided alpha level of 0.025 and a noninferiority margin of 4.0 percentage points for the absolute be-

tween-group difference.[19] If the noninferiority criterion was satisfied, we planned to test for superiority.

The absolute between-group difference in the occurrence of a primary-outcome event, along with its 95% confidence interval, was calculated and then compared with the prespecified noninferiority margin. Noninferiority was tested according to Blackwelder's method to evaluate hypotheses with a specified difference.[19] This one-sided test was evaluated at an alpha level of 0.025, and the corresponding risk ratios and 95% confidence interval were calculated. Similarly, for the secondary outcomes, the risk differences and risk ratios with their corresponding confidence intervals were calculated, but formal hypothesis testing was not performed. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

Additional analyses of the primary and secondary outcomes were performed in the intention-to-treat-population, including all the patients who underwent randomization. Prespecified subgroup analyses for the primary outcome were performed with the use of risk ratios. In order to use a consistent effect estimate throughout the manuscript, we also performed post hoc subgroup analyses using risk differences.

All primary and secondary outcomes were analyzed according to the prespecified approach outlined in the statistical analysis plan, which is available with the protocol at NEJM.org. There were no missing data for the primary or secondary outcomes. Statistical analyses were performed with the use of R software, version 4.1 (R Foundation for Statistical Computing).

RESULTS

TRIAL POPULATION

From November 2020 through December 2023, a total of 869 patients were randomly assigned to either the continued or interrupted oral anticoagulation strategy. Randomization was performed at a median of 7 days (interquartile range, 5 to 18) before TAVI. Eleven patients were excluded from the analysis, as shown in Figure 1. The main reasons for exclusion were no initiation of TAVI due to death or worsening clinical condition or the need for surgical aortic-valve replacement.

The baseline characteristics of the patients are listed in Table 1. The mean (±SD) age was 81.1±5.9 years, and 34.5% of the patients were

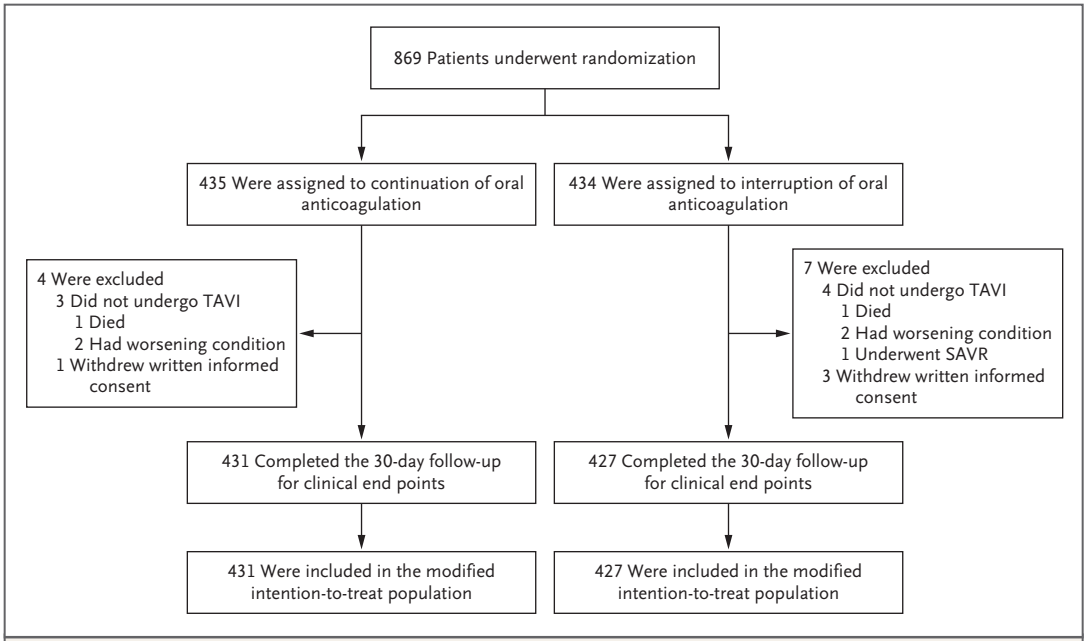

Figure 1. Randomization and Follow-up.

SAVR denotes surgical aortic-valve replacement, and TAVI transcatheter aortic-valve implantation.

women. The indication for long-term oral anticoagulation was atrial fibrillation in 94.9% of the patients, and the mean CHA_2DS_2-VASc score (on a scale from 0 to 9, with higher scores indicating a higher risk of stroke) was 4.5±1.4. In total, 81.9% of the patients were treated with a direct oral anticoagulant, of whom 30.6% had a reduced dose. A total of 12.5% of the patients

Table 1. Baseline Characteristics.*

Characteristic	Continuation Group (N=431)	Interruption Group (N=427)
Age — yr	81.4±5.6	80.9±6.2
Female sex — no. (%)	158 (36.7)	138 (32.3)
Median body-mass index (IQR)†	26.5 (24.2–29.7)	26.9 (24.3–30.8)
Score on the EuroSCORE II — %‡	3.8±3.9	3.9±4.3
NYHA class — no. (%)		
I	11 (2.6)	15 (3.5)
II	152 (35.3)	146 (34.2)
III	241 (55.9)	238 (55.7)
IV	27 (6.3)	28 (6.6)
Atrial fibrillation — no. (%)§	414 (96.1)	406 (95.1)
Paroxysmal — no./total no. (%)	192/414 (46.4)	184/406 (45.3)
CHA_2DS_2-VASc score¶	4.5±1.4	4.4±1.4
Hypertension — no. (%)	339 (78.7)	322 (75.4)
Diabetes — no. (%)		
None	303 (70.3)	304 (71.2)
Non–insulin-dependent	90 (20.9)	87 (20.4)
Insulin-dependent	38 (8.8)	36 (8.4)
Coronary artery disease — no. (%)	207 (48.0)	206 (48.2)
Previous CABG — no./total no. (%)	66/207 (31.9)	72/206 (35.0)
History of myocardial infarction — no. (%)	61 (14.2)	75 (17.6)
Previous cerebrovascular event — no. (%)		
Transient ischemic attack	42 (9.7)	43 (10.1)
Ischemic stroke	39 (9.0)	51 (11.9)
Hemorrhagic stroke	4 (0.9)	4 (0.9)
Undetermined stroke: unknown origin	3 (0.7)	3 (0.7)
Peripheral artery disease — no. (%)	79 (18.3)	85 (19.9)
Chronic obstructive pulmonary disease — no. (%)	68 (15.8)	49 (11.5)
Chronic renal insufficiency — no. (%)	213 (49.4)	221 (51.8)
Previous aortic-valve surgery — no. (%)	36 (8.4)	28 (6.6)
Previous pacemaker implantation — no. (%)	75 (17.4)	88 (20.6)

* Plus–minus values are means ±SD. Shown are patients with periprocedural continuation as compared with interruption of oral anticoagulation during transcatheter aortic-valve implantation. Percentages may not total 100 because of rounding. CABG denotes coronary-artery bypass grafting, IQR interquartile range, and NYHA New York Heart Association.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) estimates the risk of death after cardiac surgery on the basis of 18 variables, with the risk expressed as a percentage.
§ Atrial fibrillation was the indication for oral anticoagulation in 410 patients in the continuation group and in 404 patients in the interruption group (94.9% of all patients).
¶ CHA_2DS_2-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke.

received concomitant antiplatelet therapy, which consisted mainly of clopidogrel. Details on the indication for oral anticoagulation and the types of oral anticoagulant and antiplatelet drugs used are provided in Table S5. In total, 98.7% of the patients were treated through transfemoral arterial access. A cerebral embolic protection device was used in 9.9% of the patients. Procedure-related characteristics are provided in Table S6.

No patients were lost to follow-up, and data regarding the primary and secondary outcomes were complete for 100% of the patients. Adherence to the defined protocol strategy was 94.9% in the continuation group and 91.8% in the interruption group. Oral anticoagulation was restarted at a median of 1 day (interquartile range, 1 to 1) after TAVI in the interruption group. Details on nonadherence to the trial protocol are provided in Table S7.

PRIMARY OUTCOME

A primary-outcome event occurred in 71 patients (16.5%) in the continuation group and in 63 (14.8%) in the interruption group (risk difference, 1.7 percentage points; 95% confidence interval [CI], −3.1 to 6.6; P=0.18 for noninferiority) (Table 2 and Fig. 2). The incidence of each component of the primary outcome at 30 days among patients assigned to continued as compared with interrupted oral anticoagulation was as follows: death from cardiovascular causes, 2.1% and 2.1%, respectively (risk difference, 0.0 percentage points; 95% CI, −1.9 to 1.9); stroke from any cause, 3.2% and 4.4% (risk difference, −1.2 percentage points; 95% CI, −3.8 to 1.4); myocardial infarction, 1.2% and 1.6% (risk difference, −0.5 percentage points; 95% CI, −2.1 to 1.1); major vascular complications, 10.2% and 7.7% (risk difference, 2.5 percentage points; 95% CI, −1.3 to 6.3); and major bleeding, 11.1% and 8.9% (risk difference, 2.2 percentage points; 95% CI, −1.8 to 6.3) (Table 2 and Table S8).

The results of the intention-to-treat analysis of the primary outcome were generally consistent with those of the modified intention-to-treat analysis (Tables S9 and S10). The risk of a primary-outcome event was 16.9% in the continuation group and 14.1% in the interruption group among patients receiving vitamin K antagonists (risk difference, 2.8 percentage points; 95% CI, −8.6 to 14.2) and 16.4% and 14.9%, respectively, among patients receiving direct oral anticoagulants (risk difference, 1.5 percentage points; 95% CI, −3.9 to 6.9). The prespecified subgroup analyses of the primary outcome are shown in Figure 3 and Figure S2.

SECONDARY OUTCOMES

A procedure-related primary-outcome event occurred in 66 patients (15.3%) in the continuation group and in 58 (13.6%) in the interruption group (risk difference, 1.7 percentage points; 95% CI, −3.0 to 6.4). Thromboembolic events occurred in 38 patients (8.8%) in the continuation group and in 35 (8.2%) in the interruption group (risk difference, 0.6 percentage points; 95% CI, −3.1 to 4.4). Cerebrovascular events occurred in 28 patients (6.5%) in the continuation group and in 27 (6.3%) in the interruption group (risk difference, 0.2 percentage points; 95% CI, −3.1 to 3.5). Any bleeding occurred in 134 patients (31.1%) in the continuation group and in 91 (21.3%) in the interruption group (risk difference, 9.8 percentage points; 95% CI, 3.9 to 15.6) (Table 2). Details on BARC classification and bleeding site are provided in Tables S11 and S12, respectively.

SAFETY

The early safety outcome (freedom from death from any cause; stroke from any cause; VARC-3 type 2, 3, or 4 bleeding; major vascular, access-related, or cardiac structural complications; acute kidney injury stage 3 or 4; moderate or severe aortic regurgitation; new permanent pacemaker owing to procedure-related conduction abnormalities; and surgery or intervention related to the device) occurred in 291 patients (67.5%) in the continuation group and in 299 (70.0%) in the interruption group (risk difference, −2.5 percentage points; 95% CI, −8.7 to 3.7) (Table 2).

DISCUSSION

In the POPular PAUSE TAVI trial, we investigated a continued as compared with an interrupted oral anticoagulation strategy among patients undergoing TAVI with an indication for long-term oral anticoagulation owing to concomitant disease, mostly atrial fibrillation. The continued oral anticoagulation strategy was not found to be noninferior to the interrupted oral anticoagulation strategy with respect to the primary com-

Table 2. Primary and Secondary Outcomes.*

Outcome	Continuation Group (N=431)	Interruption Group (N=427)	Risk Difference (95% CI)
	no. (%)		*percentage points*
Primary outcome			
Composite outcome†	71 (16.5)	63 (14.8)	1.7 (–3.1 to 6.6)‡
Components of the primary outcome			
Death from cardiovascular cause§	9 (2.1)	9 (2.1)	0.0 (–1.9 to 1.9)
Stroke from any cause	14 (3.2)	19 (4.4)	–1.2 (–3.8 to 1.4)
Myocardial infarction	5 (1.2)	7 (1.6)	–0.5 (–2.1 to 1.1)
Major vascular complication	44 (10.2)	33 (7.7)	2.5 (–1.3 to 6.3)
Major bleeding: VARC-3 type 2, 3, or 4	48 (11.1)	38 (8.9)	2.2 (–1.8 to 6.3)
Secondary outcomes			
Procedure-related primary-outcome event	66 (15.3)	58 (13.6)	1.7 (–3.0 to 6.4)
Thromboembolic event	38 (8.8)	35 (8.2)	0.6 (–3.1 to 4.4)
Stroke, except hemorrhagic	14 (3.2)	17 (4.0)	
Transient ischemic attack	14 (3.2)	10 (2.3)	
Myocardial infarction	5 (1.2)	7 (1.6)	
Systemic embolism	6 (1.4)	3 (0.7)	
Procedure-related thromboembolic event	37 (8.6)	33 (7.7)	0.9 (–2.8 to 4.5)
Thromboembolic event at discharge	24 (5.6)	22 (5.2)	0.4 (–2.6 to 3.4)
Cerebrovascular event	28 (6.5)	27 (6.3)	0.2 (–3.1 to 3.5)
Ischemic stroke	14 (3.2)	16 (3.7)	
Hemorrhagic stroke	0	2 (0.5)	
Stroke, not otherwise specified	0	1 (0.2)	
Transient ischemic attack	14 (3.2)	10 (2.3)	
Any bleeding	134 (31.1)	91 (21.3)	9.8 (3.9 to 15.6)
VARC-3 type 4	3 (0.7)	4 (0.9)	
VARC-3 type 3	34 (7.9)	25 (5.9)	
VARC-3 type 2	11 (2.6)	9 (2.1)	
VARC-3 type 1	93 (21.6)	55 (12.9)	
Any procedure-related bleeding	122 (28.3)	82 (19.2)	9.1 (3.4 to 14.8)
Any bleeding at discharge	117 (27.1)	77 (18.0)	9.1 (3.6 to 14.7)
Early safety outcome¶	291 (67.5)	299 (70.0)	–2.5 (–8.7 to 3.7)

* All outcomes are reported at 30 days unless stated as being at discharge. VASC-3 denotes Valve Academic Research Consortium 3.
† The primary outcome was a composite of death from cardiovascular causes, stroke from any cause, myocardial infarction, major vascular complications, or major bleeding.
‡ The prespecified noninferiority margin was 4 percentage points. P=0.18 for noninferiority.
§ The incidence of death from cardiovascular causes was the same as that of death from any cause.
¶ The early safety outcome was defined as freedom from death from any cause; stroke from any cause; VARC-3 type 2, 3, or 4 bleeding, major vascular, access-related, or cardiac structural complications; acute kidney injury stage 3 or 4; moderate or severe aortic regurgitation; new permanent pacemaker owing to procedure-related conduction abnormalities; and surgery or intervention related to the device.

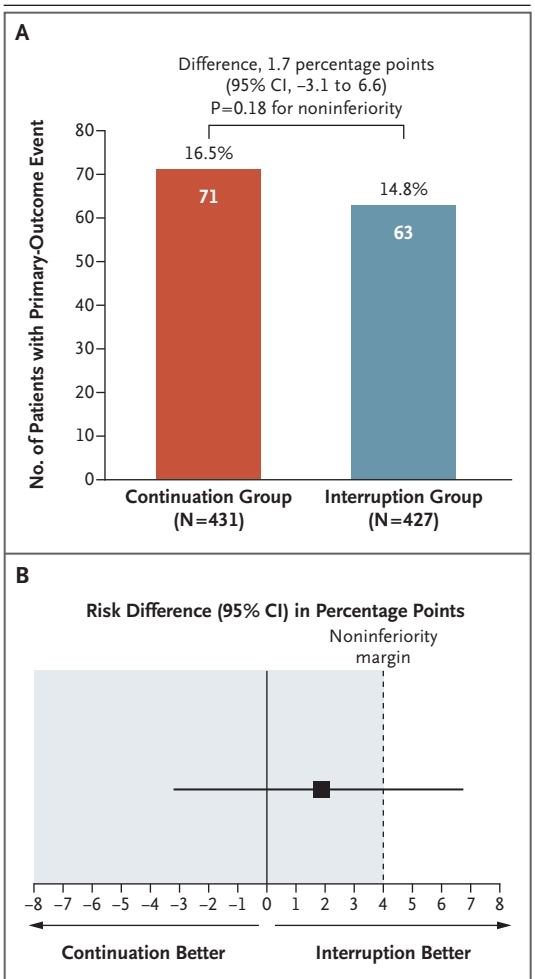

Figure 2. Primary Outcome.

Panel A shows the incidence of the primary outcome among patients with periprocedural continuation as compared with interruption of oral anticoagulation during TAVI. The primary outcome was a composite of death from cardiovascular causes, stroke from any cause, myocardial infarction, major vascular complications, or major bleeding. Panel B shows that the upper limit of the 95% confidence interval for the absolute between-group difference was greater than the prespecified noninferiority margin of 4.0 percentage points, which indicates that the continuation strategy was not noninferior to the interruption strategy.

posite outcome (death from cardiovascular causes, stroke from any cause, myocardial infarction, major vascular complications, or major bleeding at 30 days). This finding was consistent with a numerically higher incidence of major bleeding and major vascular complications in the continued oral anticoagulation group, with no apparent differences in thromboembolic events between the groups.

There were more bleeding complications observed in the continuation group than in the interruption group. These bleeding complications were predominantly minor bleeding (VARC-3 type 1, similar to BARC 2), such as periprocedural bleeding complications that result in manual compression or application of a pressure bandage after discharge from the catheterization laboratory. Furthermore, the incidence of thromboembolic events (composite outcome), as well as the incidence of cerebrovascular events (composite outcome), appeared to be similar in the two groups. However, our trial was not designed to assess the benefit of continued oral anticoagulation with respect to thromboembolic events. Continued oral anticoagulation may be important especially in patients with a high CHA_2DS_2-VASc score or a history of stroke, who might be at increased risk for thromboembolic events because of their underlying vascular or cerebrovascular disease; the risk–benefit ratio may differ as compared with that in the general population of patients undergoing TAVI.[4,20]

The lack of evidence from randomized trials regarding the appropriate periprocedural oral anticoagulation strategy in patients undergoing TAVI has led to a wide variety of approaches in clinical practice.[3] Some centers interrupt oral anticoagulation for a varying duration, whereas others continue oral anticoagulation throughout the periprocedural period. The applied strategies also differ depending on the type of oral anticoagulation used. Therapy with direct oral anticoagulants is often interrupted, whereas therapy with vitamin K antagonists is frequently continued. This difference may be related to the rapid and predictable mechanism of action of direct oral anticoagulants, which makes interruption relatively easy as compared with vitamin K antagonists with a long half-life. The difference may also be related to the lack of readily available reversal agents for direct oral anticoagulants at most centers, whereas these are routinely available for vitamin K antagonists.[12,21] Nevertheless, our findings appeared to be consistent across both subgroups: patients treated with direct oral anticoagulants or with vitamin K antagonists.

There is increasing evidence that for specific cardiac procedures, continuation of oral antico-

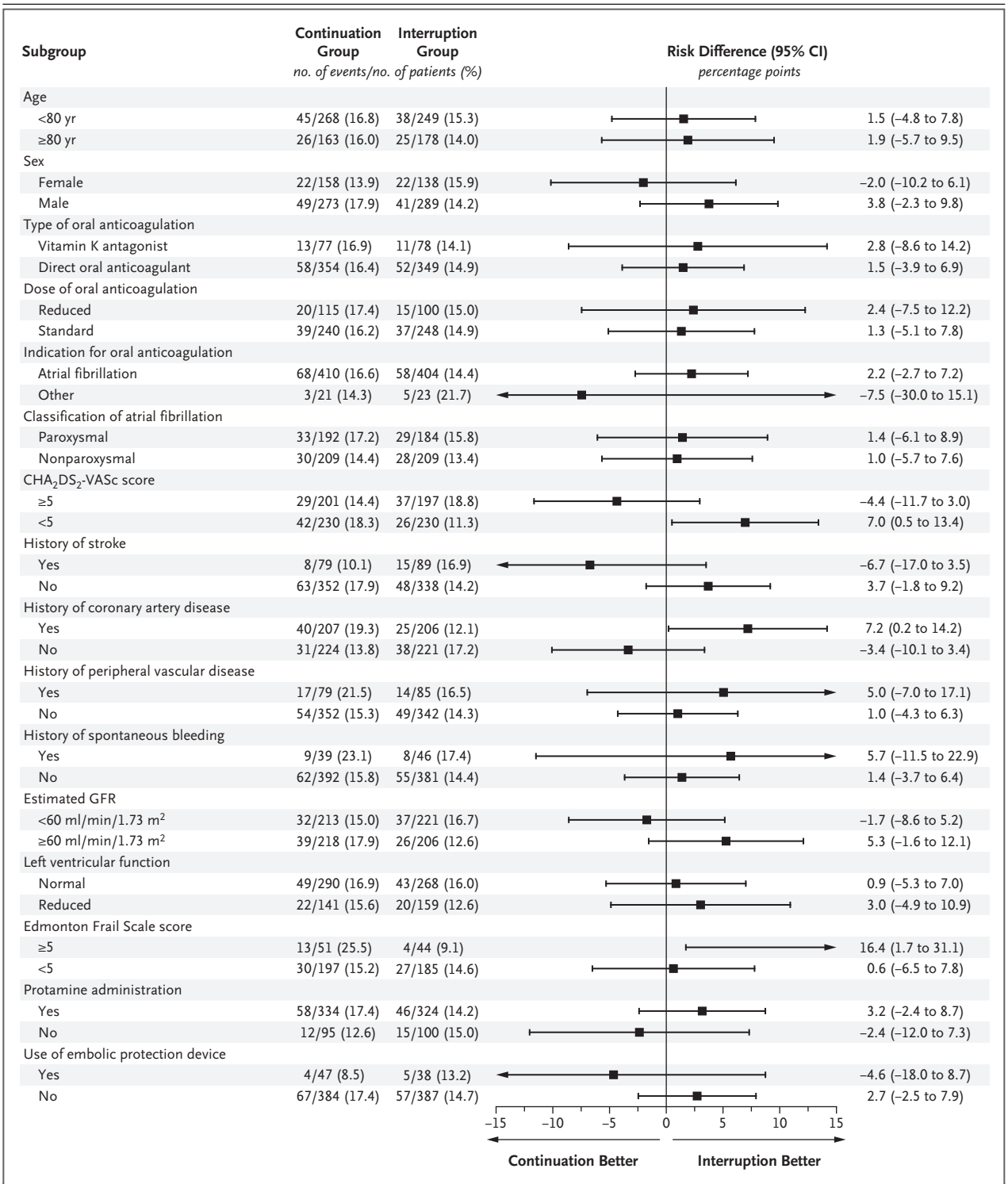

Figure 3. Subgroup Analyses of the Primary Outcome.

CHA_2DS_2-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke. Scores on the Edmonton Frail Scale range from 0 to 17, with higher scores indicating greater frailty. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. GFR denotes glomerular filtration rate.

agulation is at least as safe and effective as interruption. In a randomized trial involving patients undergoing pacemaker or implantable cardioverter–defibrillator implantation, a strategy of continued warfarin therapy reduced the incidence of clinically significant pocket hematoma, as compared with interruption of warfarin therapy combined with bridging with heparin or low-molecular-weight heparin.[22] In a subsequent trial that enrolled patients receiving direct oral anticoagulants, the incidence of clinically significant pocket hematoma was similar in the continuation and interruption groups.[23] In a randomized trial involving patients undergoing catheter ablation for atrial fibrillation, continuation of warfarin therapy was associated with a lower risk of stroke and minor bleeding than interruption of warfarin therapy combined with bridging with heparin or low-molecular-weight heparin.[24] In another randomized trial, ablation of atrial fibrillation with continued use of dabigatran was associated with fewer bleeding complications than with continued use of warfarin.[25] Continuation of oral anticoagulation in patients undergoing coronary angiography with or without percutaneous coronary intervention also appears to be safe.[26]

Accordingly, a series of observational studies have evaluated continued as compared with interrupted oral anticoagulation in patients undergoing TAVI.[11,12,27] Continuation of oral anticoagulation did not seem to be associated with an increased risk of bleeding or vascular complications, and a lower risk of stroke was suggested.[11,12] These findings were, however, not substantiated by our randomized trial. Despite the effort to simplify the periprocedural approach to TAVI, the increase in bleeding complications that we observed may outweigh the convenience of continuing oral anticoagulation throughout the periprocedural period. Our results therefore provide evidence supporting periprocedural interruption of oral anticoagulation in patients undergoing TAVI.

Our findings with respect to bleeding risk are in line with the findings of other randomized trials, which showed that reduced antithrombotic therapy — that is, holding clopidogrel before TAVI — was associated with a reduced incidence of periprocedural bleeding complications.[18,28,29] Interruption of oral anticoagulation may be particularly appropriate in patients undergoing TAVI, because they are at higher risk for periprocedural bleeding than those undergoing other cardiac interventions, owing to older age, more frequent coexisting conditions, greater frailty, and the use of larger devices for vascular access.[3]

Our trial has several limitations. First, this was an open-label trial and was thereby potentially subject to reporting and ascertainment biases. However, trial outcomes were prespecified according to standardized definitions and were adjudicated by a clinical-events committee whose members were unaware of the trial-group assignments. Second, the pragmatic nature of the trial protocol did not include a neurologic examination or neuroimaging in all the patients but relied on clinical events reported by health care professionals. Third, the trial was powered to show noninferiority with respect to a primary composite outcome (which included bleeding or thromboembolic events), rather than two separate thromboembolic and bleeding primary outcomes. Thus, no clinical inferences should be drawn regarding the separate components of the primary outcome or regarding the secondary outcomes. Fourth, the trial protocol allowed for enrollment of patients undergoing TAVI with the use of transfemoral or transsubclavian arterial access. However, almost all the patients enrolled were treated with the use of the transfemoral approach, so the results should not be generalized to other vascular-access approaches for TAVI.

In this randomized trial involving patients undergoing TAVI with an indication for oral anticoagulation owing to concomitant disease, periprocedural continuation was not found to be noninferior to interruption of oral anticoagulation during TAVI with respect to the incidence of a composite of death from cardiovascular causes, stroke, myocardial infarction, major vascular complications, or major bleeding within 30 days.

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APPENDIX

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