

ORIGINAL ARTICLE

A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement

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ABSTRACT

BACKGROUND

Whether the direct factor Xa inhibitor rivaroxaban can prevent thromboembolic events after transcatheter aortic-valve replacement (TAVR) is unclear.

METHODS

We randomly assigned 1644 patients without an established indication for oral anticoagulation after successful TAVR to receive rivaroxaban at a dose of 10 mg daily (with aspirin at a dose of 75 to 100 mg daily for the first 3 months) (rivaroxaban group) or aspirin at a dose of 75 to 100 mg daily (with clopidogrel at a dose of 75 mg daily for the first 3 months) (antiplatelet group). The primary efficacy outcome was the composite of death or thromboembolic events. The primary safety outcome was major, disabling, or life-threatening bleeding. The trial was terminated prematurely by the data and safety monitoring board because of safety concerns.

RESULTS

After a median of 17 months, death or a first thromboembolic event (intention-to-treat analysis) had occurred in 105 patients in the rivaroxaban group and in 78 patients in the antiplatelet group (incidence rates, 9.8 and 7.2 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.35; 95% confidence interval [CI], 1.01 to 1.81; $P=0.04$). Major, disabling, or life-threatening bleeding (intention-to-treat analysis) had occurred in 46 and 31 patients, respectively (4.3 and 2.8 per 100 person-years; hazard ratio, 1.50; 95% CI, 0.95 to 2.37; $P=0.08$). A total of 64 deaths occurred in the rivaroxaban group and 38 in the antiplatelet group (5.8 and 3.4 per 100 person-years, respectively; hazard ratio, 1.69; 95% CI, 1.13 to 2.53).

CONCLUSIONS

In patients without an established indication for oral anticoagulation after successful TAVR, a treatment strategy including rivaroxaban at a dose of 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy. (Funded by Bayer and Janssen Pharmaceuticals; GALILEO ClinicalTrials.gov number, NCT02556203.)

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*A complete list of investigators in the GALILEO trial is provided in the Supplementary Appendix, available at NEJM.org.

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TRANSCATHETER AORTIC-VALVE REPLACEMENT (TAVR) is indicated in symptomatic severe aortic stenosis.¹⁻⁷ Thromboembolic complications (stroke, systemic embolism, valve thrombosis, and venous thromboembolism) have been observed after TAVR. Observational data suggest that subclinical leaflet thrombosis may occur with bioprosthetic valves and that this phenomenon may be associated with an increased risk of cerebrovascular events and prevented or reversed by anticoagulation.⁸⁻¹³ Current practice guidelines recommend the use of dual antiplatelet therapy early after TAVR,^{14,15} although the recommendation is based mainly on expert consensus.

Rivaroxaban directly inhibits factor Xa and has been shown to reduce the risk of thromboembolism in different clinical settings.¹⁶⁻¹⁸ The 10-mg daily dose has been approved for the prevention of venous thromboembolism in several countries. However, there is a dearth of evidence for routine use of anticoagulation after TAVR for the prevention of thromboembolic events. In addition, patients undergoing TAVR are typically elderly, frail, and at increased risk for both ischemic and bleeding complications. In GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes), we investigated the role of a treatment strategy including anticoagulation with rivaroxaban at a dose of 10 mg daily as compared with an antiplatelet strategy in patients without established indications for anticoagulation after successful TAVR.

METHODS

TRIAL DESIGN AND OVERSIGHT

GALILEO was a randomized, open-label, event-driven, multicenter trial.¹⁹ The trial was conducted in compliance with the International Conference on Harmonisation and the Declaration of Helsinki. The protocol (available with the full text of this article at NEJM.org) was approved by the ethics committees and corresponding health authorities for all participating sites. All the patients provided written informed consent to participate.

The trial was supported by the sponsors, Bayer and Janssen Pharmaceuticals. The sponsors and the academic investigators designed and supervised the trial, which was executed with the assistance of the two clinical research organizations,

Cardialysis (Rotterdam, the Netherlands) and the Center for Interventional Cardiovascular Research and Clinical Trials (Mount Sinai Hospital, New York). The executive committee included members of the academic leadership and the sponsors. Data analyses were conducted by DATAN (Havixbeck, Germany). An independent data and safety monitoring board provided oversight by periodically reviewing all reported serious adverse events. The first, second, and last authors wrote the first draft of the manuscript and made the decision to submit it for publication. All the authors reviewed and critiqued subsequent drafts and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. (Additional information about trial organization is provided in the Supplementary Appendix, available at NEJM.org.)

PATIENT SELECTION AND RANDOMIZATION

Men and women 18 years of age or older were eligible for participation in the trial if they had undergone successful TAVR for treatment of aortic-valve stenosis. Successful TAVR was defined as correct positioning of any single approved transcatheter bioprosthetic aortic valve into the proper anatomical location with the intended valve performance and without periprocedural complications.²⁰ Key exclusion criteria were any established indication for long-term anticoagulation and any absolute indication for dual antiplatelet therapy. (See Supplementary Appendix text and Table S1 for screening procedures and a complete list of the inclusion and exclusion criteria.) After written informed consent had been obtained, eligible patients were randomly assigned (in a 1:1 ratio) through an interactive Web-response system to either the rivaroxaban group or the antiplatelet group 1 to 7 days after TAVR and before hospital discharge.

TRIAL TREATMENT AND FOLLOW-UP

The anticoagulant (experimental) group was assigned to receive rivaroxaban at a dose of 10 mg daily plus aspirin at a dose of 75 to 100 mg daily for 3 months, followed by rivaroxaban monotherapy (10 mg daily). The antiplatelet (control) group was assigned to receive aspirin at a dose of 75 to 100 mg daily plus clopidogrel at a dose of 75 mg daily for 3 months (patients who had not previously received clopidogrel were recommended to receive a single loading dose of ≥ 300 mg), fol-

lowed by aspirin monotherapy (75 to 100 mg daily).

Patients in the rivaroxaban group in whom atrial fibrillation developed were to receive rivaroxaban at a dose of 20 mg once daily (or 15 mg for those with an estimated glomerular filtration rate of 30 to 50 ml per minute per 1.73 m² of body-surface area). In the antiplatelet group, patients in whom new-onset atrial fibrillation developed were to receive vitamin K antagonists (targeting an international normalized ratio of 2 to 3) to replace clopidogrel within 3 months after randomization or to replace aspirin thereafter.

Rivaroxaban was centrally supplied to the sites as trial medication. Clopidogrel, aspirin, and vitamin K antagonists were supplied according to local practice. Patients were followed at 1, 3, and 6 months and every 6 months thereafter. (Details of the follow-up procedures and recommendations for concomitant medications are provided in the Supplementary Appendix.)

OUTCOME MEASURES

The primary efficacy outcome was the composite of death from any cause or thromboembolic events, including any stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism (not involving the central nervous system), deep-vein thrombosis, or pulmonary embolism. The primary safety outcome was the composite of life-threatening, disabling, or major bleeding. The secondary efficacy outcome was defined as the primary efficacy outcome with death from cardiovascular causes replacing death from any cause. The net-benefit outcome included all components of the primary efficacy and primary safety outcomes. All the above outcomes and their components were adjudicated in a blinded manner by an independent clinical-events committee according to Valve Academic Research Consortium definitions.²⁰ (See Table S2 for detailed definitions.)

STATISTICAL ANALYSIS

The primary hypothesis was that the rivaroxaban group would be superior to the antiplatelet group with respect to the time from randomized treatment assignment to the first occurrence of any component of the primary efficacy outcome. The trial was event-driven; we estimated that 440 primary efficacy outcome events would provide the trial with 80% power to detect a 20% lower rela-

tive risk in the rivaroxaban group than in the antiplatelet group. (Details on the power calculation and statistical methods are provided in the Supplementary Appendix.)

No formal interim analyses for efficacy or futility were planned. After review by the data and safety monitoring board on August 7, 2018, immediate termination of the trial was recommended because of safety concerns. The trial leadership and the sponsors accepted this recommendation for trial termination on August 13, 2018 (efficacy cutoff date). Because the trial was terminated early, only 183 patients reached the primary efficacy outcome (42% of the planned 440).

The statistical analysis plan originally specified that the primary efficacy outcome was to be analyzed for noninferiority (with a noninferiority margin for the upper boundary of the hazard ratio of 1.20) in the on-treatment data set; a hierarchical testing strategy specified that no tests for superiority would be performed if noninferiority was not shown. However, it was subsequently decided to present conventional two-sided P values to test for the between-group difference for both the primary efficacy outcome and the primary safety outcome; the approach described below and in the Results section is based on that decision.

The main analyses were performed according to the intention-to-treat principle. For time-to-event analyses, hazard ratios and 95% confidence intervals were generated with Cox proportional-hazards models. The confidence intervals were not adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. Kaplan–Meier curves were used to show the incidence of outcomes over time. The proportionality assumption for the primary efficacy and safety outcomes was not violated.

For the primary efficacy outcome and the primary safety outcome, conventional two-sided log-rank P values were calculated. Prespecified subgroup analyses followed Cox proportional-hazards methods. To describe early and late risks of outcome events, we performed landmark analyses on a post hoc basis with the landmark time point set at 90 days after randomization.

For the on-treatment analyses, trial outcomes were included if they occurred before premature permanent discontinuation of the assigned trial regimen. The time of premature

permanent discontinuation was defined as 2 days after the last ingestion of a trial medication. On-treatment Cox regression analyses were performed by imposing additional censoring at the day of premature permanent discontinuation of the trial regimen.

Characteristic	Rivaroxaban Group (N=826)	Antiplatelet Group (N=818)
Demographic and clinical characteristics		
Age — yr	80.4±7.1	80.8±6.0
Male sex — no. (%)	426 (51.6)	405 (49.5)
Body-mass index†	28.1±5.5	28.2±5.7
Hypertension — no. (%)	720 (87.2)	697 (85.2)
Diabetes mellitus — no. (%)	236 (28.6)	235 (28.7)
EuroSCORE II‡	4.1±3.9	4.1±3.7
EuroSCORE II risk category — no. (%)‡		
High	50 (6.1)	64 (7.8)
Intermediate	139 (16.8)	140 (17.1)
Low	636 (77.0)	613 (74.9)
Missing	1 (0.1)	1 (0.1)
STS risk score§	4.0±3.2	4.3±3.5
STS risk category — no. (%)§		
High	65 (7.9)	74 (9.0)
Intermediate	383 (46.4)	388 (47.4)
Low	378 (45.8)	356 (43.5)
Congestive heart failure — no. (%)	394 (47.7)	380 (46.5)
NYHA class III or IV — no. (%)	250 (30.3)	222 (27.1)
Coronary artery disease — no. (%)¶	325 (39.3)	305 (37.3)
Previous stroke — no. (%)	51 (6.2)	35 (4.3)
Peripheral artery disease — no. (%)	83 (10.0)	82 (10.0)
Previous venous thromboembolism — no. (%)	18 (2.2)	15 (1.8)
Permanent pacemaker — no. (%)	80 (9.7)	80 (9.8)
Chronic obstructive pulmonary disease — no. (%)	110 (13.3)	88 (10.8)
Glomerular filtration rate — ml/min/1.73 m ²	73.4±23.8	73.2±23.2
Procedural characteristics		
Valve type — no. (%)		
Sapien XT, Edwards Lifesciences	13 (1.6)	13 (1.6)
Sapien 3, Edwards Lifesciences	385 (46.6)	346 (42.3)
CoreValve, Medtronic	33 (4.0)	35 (4.3)
CoreValve Evolut R, Medtronic	206 (24.9)	225 (27.5)
Lotus, Boston Scientific	44 (5.3)	40 (4.9)
Portico, St. Jude Medical	44 (5.3)	40 (4.9)
Acurate Neo, Boston Scientific	82 (9.9)	89 (10.9)
Other	19 (2.3)	30 (3.7)
Valve-in-valve — no. (%)	42 (5.1)	49 (6.0)

Table 1. (Continued.)

Characteristic	Rivaroxaban Group (N = 826)	Antiplatelet Group (N = 818)
Post-TAVR echocardiographic characteristics		
Aortic valve area — cm ²	1.8±0.6	1.9±0.5
Mean aortic valve gradient — mm Hg	10.0±4.7	10.1±4.6
Left ventricular ejection fraction — %	57.4±10.9	58.2±11.2
Paravalvular aortic regurgitation — no. (%)		
Mild	157 (19.0)	168 (20.5)
Moderate or severe	10 (1.2)	10 (1.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NYHA denotes New York Heart Association, and TAVR transcatheter aortic-valve replacement.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ 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 greater than 10% indicates high risk, 5 to 10% intermediate risk, and less than 5% low risk.

§ 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 greater than 8% indicates high risk, 3 to 8% intermediate risk, and less than 3% low risk.

¶ Coronary artery disease was defined as previous myocardial infarction, percutaneous coronary intervention, or coronary-artery bypass grafting.

RESULTS

TRIAL POPULATION

From December 2015 through May 2018, a total of 1644 patients underwent randomization after successful TAVR in 136 centers in 16 countries (Table S3); 826 patients were randomly assigned to the rivaroxaban group and 818 to the antiplatelet group. The median time from TAVR to randomization was 2.0 days (range, 0 to 8). Baseline characteristics are shown in Table 1. The mean (±SD) age was 80.6±6.6 years; 49.5% of the patients were female.

ADHERENCE AND FOLLOW-UP

Follow-up was complete for 96.8% of the patients, and vital status was available for 98.0% (Fig. 1); the median trial duration was 17 months (interquartile range, 13 to 21). Throughout the trial period, 307 patients in the rivaroxaban group prematurely discontinued the trial regimen, as compared with 194 in the antiplatelet group (Tables S4 and S5 and Fig. S1). In the rivaroxaban group, the median exposure to rivaroxaban was 428 days (interquartile range, 171 to 581), and the median exposure to aspirin was 90 days (interquartile range, 84 to 94). In the antiplatelet group, the median exposure to aspirin was 474 days (interquartile range, 298 to 603), and the

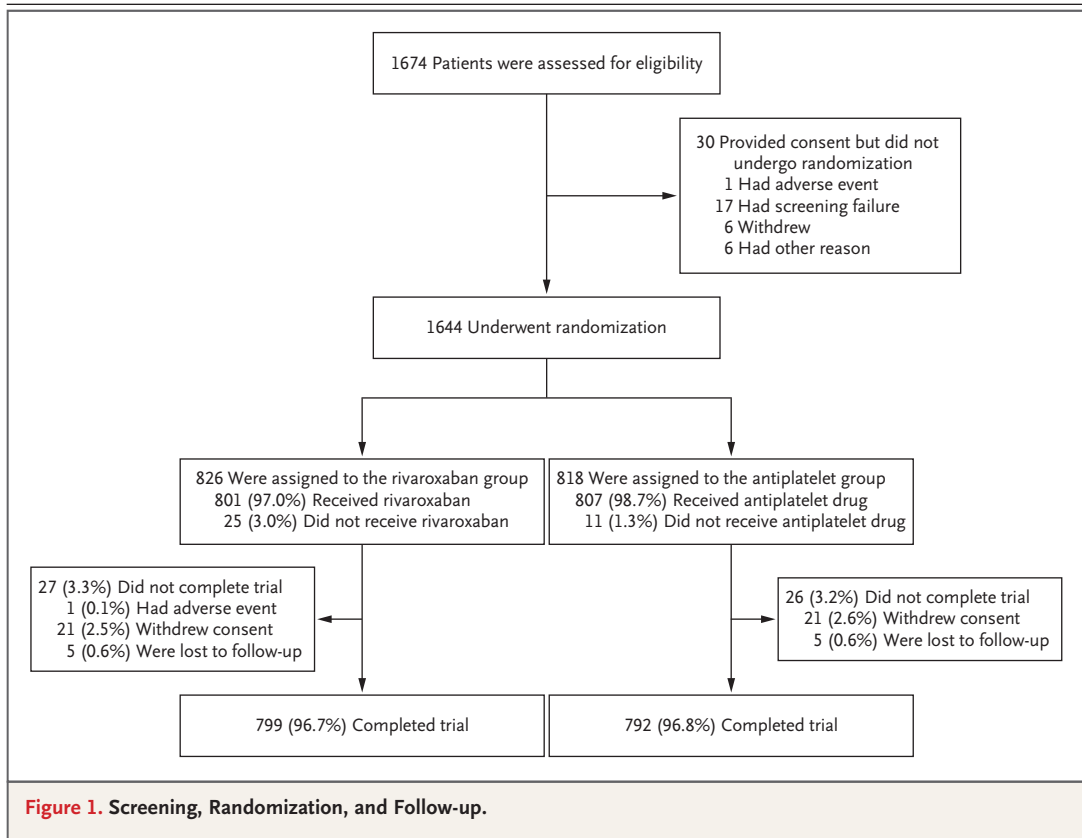
median exposure to clopidogrel was 90 days (interquartile range, 85 to 93). New-onset atrial fibrillation developed in 11.0% of the trial population (Table S6).

PRIMARY AND SECONDARY EFFICACY OUTCOMES

In the intention-to-treat analysis, death or first thromboembolic event (the primary efficacy outcome) occurred in 105 patients in the rivaroxaban group and in 78 patients in the antiplatelet group (incidence rates, 9.8 and 7.2 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.35; 95% confidence interval [CI], 1.01 to 1.81; P=0.04) (Fig. 2A and Table 2). This effect was consistent across prespecified subgroups (Fig. S2).

Death from cardiovascular causes or any thromboembolic event (the key secondary outcome) occurred in 83 patients in the rivaroxaban group and in 68 patients in the antiplatelet group (incidence rates, 7.8 and 6.3 per 100 person-years, respectively; hazard ratio, 1.22; 95% CI, 0.89 to 1.69). Symptomatic valve thrombosis occurred in 3 patients in the rivaroxaban group and in 7 patients in the antiplatelet group (incidence rates, 0.3 and 0.6 per 100 person-years, respectively; hazard ratio, 0.43; 95% CI, 0.11 to 1.66). Rates of stroke and myocardial infarction did not differ significantly between the two groups.

A total of 64 deaths occurred in the rivaroxaban



group, and 38 occurred in the antiplatelet group (incidence rates, 5.8 and 3.4 per 100 person-years, respectively; hazard ratio for rivaroxaban, 1.69; 95% CI, 1.13 to 2.53) (Fig. 2B and Table 2). Noncardiovascular mortality rates were 2.6 and 1.0 per 100 person-years, respectively (hazard ratio, 2.67; 95% CI, 1.33 to 5.35). Cardiovascular mortality rates were 3.2 and 2.4 per 100 person-years, respectively (hazard ratio, 1.30; 95% CI, 0.79 to 2.14). Adjudicated causes of death are presented in Tables S7 through S9.

PRIMARY SAFETY OUTCOME

In the intention-to-treat analysis, life-threatening, disabling, or major bleeding (the primary safety outcome) occurred in 46 patients in the rivaroxaban group and 31 patients in the antiplatelet group (incidence rates, 4.3 and 2.8 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.50; 95% CI, 0.95 to 2.37; $P=0.08$) (Fig. 2C). There was no significant between-group difference in the rate of life-threatening or disabling bleeding (1.6 and 1.5 per 100 person-years, respectively; hazard ratio, 1.06; 95% CI,

0.55 to 2.06). Bleeding rates according to other prespecified definitions occurred more frequently in the rivaroxaban group than in the antiplatelet group (Table 2). Subgroup analyses for the primary safety outcome are shown in Figure S3.

LANDMARK AND ON-TREATMENT ANALYSES

Landmark analyses for the primary efficacy and safety outcomes and for death from any cause are shown in Figures S4 through S6. In the on-treatment analyses, a primary efficacy outcome event occurred in 68 patients during use of rivaroxaban and in 63 patients during use of antiplatelet therapy (incidence rates, 8.1 and 6.6 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.21; 95% CI, 0.86 to 1.70). A primary safety outcome event occurred in 39 and 28 patients, respectively (incidence rates, 4.6 and 2.9 per 100 person-years; hazard ratio, 1.53; 95% CI, 0.94 to 2.49; $P=0.08$). There were 26 and 24 deaths during treatment, respectively (incidence rates, 3.0 and 2.5 per 100 person-years; hazard ratio, 1.23; 95% CI, 0.71 to 2.15) (Tables S10 and S11 and Figs. S7 through S9). Kaplan–Meier curves

Figure 2. Cumulative Risk of the Primary Efficacy and Primary Safety Outcomes and Death from Any Cause (Intention-to-Treat Analysis).

Shown are time-to-event Kaplan–Meier curves for the primary efficacy outcome, death from any cause, and the primary safety outcome. The primary efficacy outcome was defined as the composite of death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep-vein thrombosis, or systemic embolism. The primary safety outcome was defined as the composite of Valve Academic Research Consortium life-threatening, disabling, or major bleeding. The 95% confidence intervals (CIs) presented were not adjusted for multiple comparisons. Insets show the same data on an enlarged y axis.

for death from any cause after premature permanent trial drug discontinuation are provided in Figure S10.

DISCUSSION

GALILEO was a randomized, controlled trial to evaluate the efficacy and safety of rivaroxaban-based antithrombotic therapy as compared with antiplatelet-based therapy after successful TAVR in patients without an established indication for anticoagulation. A dose of rivaroxaban of 10 mg daily (lower than the approved dose for stroke prevention in patients with atrial fibrillation) was selected to provide a level of anticoagulation to prevent valve surface thromboembolism while mitigating bleeding complications.

We observed that the rivaroxaban group had higher rates of death or thromboembolic complications in the intention-to-treat analysis (rates that were attenuated in the on-treatment analysis) and higher rates of bleeding complications. These results underscore the challenge of antithrombotic therapy in the TAVR population, which includes patients who are generally elderly, potentially frail, or affected by multiple coexisting conditions associated with an increased risk of both bleeding and thromboembolic events. The lack of a clinical benefit of rivaroxaban in this context occurred despite evidence from an imaging substudy of GALILEO (also now published in the *Journal*)²¹ that rivaroxaban was associated with a lower incidence of subclinical valve-leaflet thickening and reduced leaflet motion than antiplatelet therapy.

The overall event rates in this trial were lower

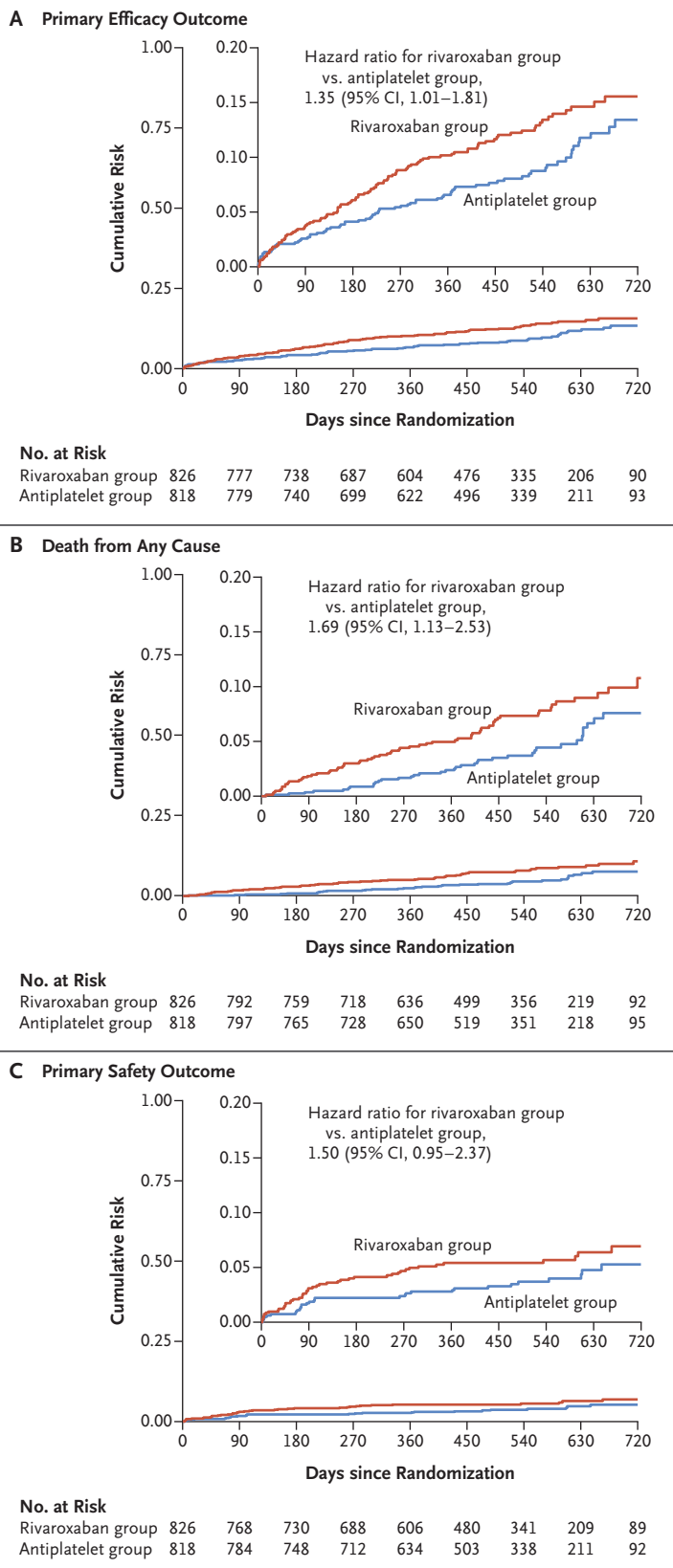


Table 2. Efficacy and Safety Outcomes (Intention-to-Treat Analysis).*

Outcome	Rivaroxaban Group (N=826)		Antiplatelet Group (N=818)		Difference (95% CI)	Hazard Ratio (95% CI)
	no. (%)	incidence rate/ 100 person-yr	no. (%)	incidence rate/ 100 person-yr		
Efficacy outcomes						
Primary efficacy outcome†	105 (12.7)	9.8	78 (9.5)	7.2	2.6 (0.1 to 5.1)	1.35 (1.01 to 1.81)
Death	64 (7.7)	5.8	38 (4.6)	3.4	2.4 (0.6 to 4.1)	1.69 (1.13 to 2.53)
From cardiovascular causes	35 (4.2)	3.2	27 (3.3)	2.4	0.7 (−0.7 to 2.1)	1.30 (0.79 to 2.14)
From noncardiovascular causes	29 (3.5)	2.6	11 (1.3)	1.0	1.6 (0.5 to 2.7)	2.67 (1.33 to 5.35)
Stroke	30 (3.6)	2.8	25 (3.1)	2.3	0.5 (−0.8 to 1.8)	1.20 (0.71 to 2.05)
Ischemic	28 (3.4)	2.6	22 (2.7)	2.0	0.6 (−0.7 to 1.8)	1.28 (0.73 to 2.23)
Hemorrhagic	2 (0.2)	0.2	3 (0.4)	0.3	−0.1 (−0.5 to 0.3)	0.67 (0.11 to 3.98)
Myocardial infarction	23 (2.8)	2.1	17 (2.1)	1.5	0.6 (−0.6 to 1.7)	1.37 (0.73 to 2.56)
Symptomatic valve thrombosis	3 (0.4)	0.3	7 (0.9)	0.6	−0.4 (−0.9 to 0.2)	0.43 (0.11 to 1.66)
Pulmonary embolism	3 (0.4)	0.3	2 (0.2)	0.2	0.1 (−0.3 to 0.5)	1.49 (0.25 to 8.93)
Deep-vein thrombosis	1 (0.1)	0.1	4 (0.5)	0.4	−0.3 (−0.7 to 0.1)	0.25 (0.03 to 2.23)
Systemic embolism	1 (0.1)	0.1	1 (0.1)	0.1	0.0 (−0.3 to 0.3)	0.98 (0.06 to 15.69)
Key secondary efficacy outcome‡	83 (10.0)	7.8	68 (8.3)	6.3	1.5 (−0.8 to 3.7)	1.22 (0.89 to 1.69)
Net clinical benefit§	137 (16.6)	13.2	100 (12.2)	9.4	3.8 (0.9 to 6.7)	1.39 (1.08 to 1.80)
Safety outcomes						
Primary safety outcome¶	46 (5.6)	4.3	31 (3.8)	2.8	1.5 (−0.1 to 3.1)	1.50 (0.95 to 2.37)
VARC life-threatening or disabling bleeding	18 (2.2)	1.6	17 (2.1)	1.5	0.1 (−1.0 to 1.2)	1.06 (0.55 to 2.06)
Fatal bleeding	2 (0.2)	0.2	1 (0.1)	0.1	0.1 (−0.2 to 0.4)	2.01 (0.18 to 22.19)
VARC major bleeding	30 (3.6)	2.8	15 (1.8)	1.4	1.4 (0.2 to 2.6)	2.02 (1.09 to 3.76)
TIMI major or minor bleeding	42 (5.1)	3.9	24 (2.9)	2.2	1.7 (0.3 to 3.2)	1.78 (1.08 to 2.94)
ISTH major bleeding	49 (5.9)	4.6	30 (3.7)	2.7	1.9 (0.2 to 3.5)	1.66 (1.05 to 2.62)
BARC type 2, 3, or 5 bleeding	148 (17.9)	15.4	85 (10.4)	8.2	7.2 (4.2 to 10.3)	1.84 (1.41 to 2.41)

* The 95% confidence intervals (CIs) were not adjusted for multiple comparisons. The proportionality assumption for the primary efficacy and safety outcomes was not violated. BARC denotes Bleeding Academic Research Consortium, ISTH International Society on Thrombosis and Hemostasis, TIMI Thrombolysis in Myocardial Infarction, and VARC Valve Academic Research Consortium.

† The primary efficacy outcome was defined as the composite of death, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep-vein thrombosis, or systemic embolism.

‡ The key secondary efficacy outcome was defined as the composite of death from cardiovascular causes, stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep-vein thrombosis, or systemic embolism.

§ Net clinical benefit was defined as the composite of the primary efficacy and primary safety outcomes.

¶ The primary safety outcome was defined as the composite of VARC life-threatening, disabling, or major bleeding.

than anticipated, probably reflecting the prerequisite of a successfully completed procedure and the overall declining risk profile among patients referred for TAVR (because of expanding indications). However, the rates are in line with those in the pivotal trials involving low-risk and intermediate-risk populations.^{6,7} Although the routine use of higher-dose rivaroxaban (15 to 20 mg daily) in this trial population would have been

expected to increase bleeding complications, we do not know whether a lower dose (e.g., 2.5 mg twice daily) might have afforded an improved risk–benefit profile as compared with the present results.

The higher number of deaths in the rivaroxaban group than in the antiplatelet group did not appear to be directly attributable to the higher risk of bleeding in the rivaroxaban group. Among

patients assigned to rivaroxaban who died, only a minority had a major bleeding event, myocardial infarction, or stroke within 30 days before death, and most deaths occurred long after discontinuation of the trial drug. Most of the adjudicated causes of death in the rivaroxaban group were sudden or from unknown reasons, as well as due to noncardiovascular causes. Hence, the mechanism underlying the higher mortality in the rivaroxaban group observed in the intention-to-treat analysis in this trial is unclear. The between-group differences in mortality were attenuated in the on-treatment analysis.

Since the inception of TAVR, postprocedural antithrombotic therapy has been based on expert consensus according to regimens used in the pivotal trials.^{14,15,22-24} Recent registry results have indicated an association between oral anticoagulation at hospital discharge and an increased risk of death but a decreased risk of bioprosthetic valve dysfunction in comparison to patients undergoing TAVR who did not receive anticoagulation therapy.²⁵ Whether a short-term course of anticoagulation monotherapy after TAVR is safe and effective warrants further investigation. The 90-day landmark analyses that we conducted did not suggest consistent differential effects over time.

GALILEO was an open-label trial and was potentially subject to reporting and ascertainment bias. However, trial outcomes were prespecified with the use of standardized definitions and adjudicated by a clinical-events committee whose members were unaware of the trial-group assignments. Patients undergoing TAVR with an

established indication for anticoagulation were not included in this trial, and treatment strategies for this patient population are being investigated in ongoing studies (ClinicalTrials.gov numbers, NCT02247128, NCT02664649, NCT02943785, and NCT02735902). On-treatment analyses are generally subject to misinterpretation since they effectively subvert the randomization, because patients who continue to receive treatment differ from those who do not, and thus their subsequent risk of an event is no longer comparable between the trial groups. In the present trial, in which there was a substantial imbalance in treatment discontinuation, the on-treatment analysis may be biased as described above. The P values in this article must be read with prudence, because these tests were not prespecified. Because we report multiple confidence intervals in the context of a trial that was prematurely terminated, all estimated treatment effects and their confidence intervals should be interpreted with caution. Finally, the early trial termination constitutes a limitation in its own right.

Among patients without an established indication for anticoagulation after successful TAVR, a treatment strategy including anticoagulation with rivaroxaban at a dose of 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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REFERENCES

- Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187-98.
- Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609-20.
- Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597-607.
- Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376:1321-31.
- Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790-8.
- Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695-705.
- Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706-15.
- Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. *J Am Coll Cardiol* 2016;68:2059-69.
- Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet* 2017;389:2383-92.
- Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med* 2015;373:2015-24.
- Puri R, Auffret V, Rodés-Cabau J. Bioprosthetic valve thrombosis. *J Am Coll Cardiol* 2017;69:2193-211.
- Dangas GD, Weitz JI, Giustino G, Makkar R, Mehran R. Prosthetic heart valve thrombosis. *J Am Coll Cardiol* 2016;68:2670-89.
- Jose J, Sulimov DS, El-Mawardy M, et al. Clinical bioprosthetic heart valve thrombosis after transcatheter aortic valve replacement: incidence, characteristics, and treatment outcomes. *JACC Cardiovasc Interv* 2017;10:686-97.
- Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739-91.
- Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63(22):e57-e185.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
- Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366:9-19.
- Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319-30.
- Windecker S, Tijssen J, Giustino G, et al. Trial design: rivaroxaban for the prevention of major cardiovascular events after transcatheter aortic valve replacement: rationale and design of the GALILEO study. *Am Heart J* 2017;184:81-7.
- Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;60:1438-54.
- De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med*. DOI: 10.1056/NEJMoa1911426.
- Van Belle E, Hengstenberg C, Lefèvre T, et al. Cerebral embolism during transcatheter aortic valve replacement: the BRAVO-3 MRI study. *J Am Coll Cardiol* 2016;68:589-99.
- Dangas GD, Lefèvre T, Kupatt C, et al. Bivalirudin versus heparin anticoagulation in transcatheter aortic valve replacement: the randomized BRAVO-3 trial. *J Am Coll Cardiol* 2015;66:2860-8.
- Dangas GD, Giustino G. Art and science of cerebrovascular event prevention after transcatheter aortic valve replacement. *Circ Cardiovasc Interv* 2016;9:9.
- Overtchouk P, Guedeney P, Rouanet S, et al. Long-term mortality and early valve dysfunction according to anticoagulation use: the FRANCE TAVI registry. *J Am Coll Cardiol* 2019;73:13-21.

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