ORIGINAL ARTICLE

Reduced Leaflet Motion after Transcatheter Aortic-Valve Replacement

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ABSTRACT

BACKGROUND

Subclinical leaflet thickening and reduced leaflet motion of bioprosthetic aortic valves have been documented by four-dimensional computed tomography (CT). Whether anticoagulation can reduce these phenomena after transcatheter aortic-valve replacement (TAVR) is not known.

METHODS

In a substudy of a large randomized trial, we randomly assigned patients who had undergone successful TAVR and who did not have an indication for long-term anticoagulation to a rivaroxaban-based antithrombotic strategy (rivaroxaban [10 mg] plus aspirin [75 to 100 mg] once daily) or an antiplatelet-based strategy (clopidogrel [75 mg] plus aspirin [75 to 100 mg] once daily). Patients underwent evaluation by four-dimensional CT at a mean (±SD) of 90±15 days after randomization. The primary end point was the percentage of patients with at least one prosthetic valve leaflet with grade 3 or higher motion reduction (i.e., involving >50% of the leaflet). Leaflet thickening was also assessed.

RESULTS

A total of 231 patients were enrolled. At least one prosthetic valve leaflet with grade 3 or higher motion reduction was found in 2 of 97 patients (2.1%) who had scans that could be evaluated in the rivaroxaban group, as compared with 11 of 101 (10.9%) in the antiplatelet group (difference, −8.8 percentage points; 95% confidence interval [CI], −16.5 to −1.9; P=0.01). Thickening of at least one leaflet was observed in 12 of 97 patients (12.4%) in the rivaroxaban group and in 33 of 102 (32.4%) in the antiplatelet group (difference, −20.0 percentage points; 95% CI, −30.9 to −8.5). In the main trial, the risk of death or thromboembolic events and the risk of life-threatening, disabling, or major bleeding were higher with rivaroxaban (hazard ratios of 1.35 and 1.50, respectively).

CONCLUSIONS

In a substudy of a trial involving patients without an indication for long-term anticoagulation who had undergone successful TAVR, a rivaroxaban-based antithrombotic strategy was more effective than an antiplatelet-based strategy in preventing subclinical leaflet-motion abnormalities. However, in the main trial, the rivaroxaban-based strategy was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than the antiplatelet-based strategy. (Funded by Bayer; GALILEO-4D ClinicalTrials.gov number, NCT02833948.)

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Transcatheter aortic-valve replacement (TAVR) for the treatment of severe aortic stenosis has become the standard of care for an increasing number of clinical indications on the basis of multiple large-scale randomized trials.[1-7] Hypoattenuated leaflet thickening and reduced leaflet motion, as detected by four-dimensional volume-rendered computed tomography (CT), have been reported in association with both transcatheter and surgical aortic bioprosthetic valves.[8,9] Several observational studies have alerted the medical community to these phenomena, have suggested a possible association with an increased risk of ischemic cerebrovascular events, and have hinted at the possible usefulness of oral anticoagulation.[8-17] However, data on this topic from randomized trials are lacking.

The oral direct factor Xa inhibitor rivaroxaban has been approved in several countries for the prevention of stroke in patients with atrial fibrillation and for the prevention and treatment of venous thromboembolism. The Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) was designed to investigate the effect of a treatment strategy that includes anticoagulation with rivaroxaban at a dose of 10 mg daily to reduce the risk of thromboembolic events after successful TAVR in patients who did not have an established indication for oral anticoagulation.[18] GALILEO-4D was a dedicated substudy of the main GALILEO trial that aimed to evaluate the effect of a rivaroxaban-based strategy as compared with an antiplatelet-based antithrombotic strategy on leaflet thickening and leaflet-motion abnormalities in patients with transcatheter aortic bioprostheses.

Methods

Trial Design

GALILEO-4D was designed as an investigator-initiated, international, randomized, open-label, imaging substudy of the main GALILEO trial. The main trial was sponsored by Bayer in collaboration with Janssen Pharmaceuticals. GALILEO-4D was separately sponsored by the European Cardiovascular Research Institute (ECRI) with funding provided by Bayer. Bayer did not have any role in the design, conduct, analysis, or reporting of the results from the substudy.

The substudy was designed and executed under the academic leadership of investigators at Rigshospitalet in Copenhagen, in collaboration with the ECRI. The substudy was conducted according to its own protocol, which is available with the full text of this article at NEJM.org. The protocol was approved by the ethics committees and corresponding health authorities for all participating sites. The substudy was conducted in compliance with the Declaration of Helsinki. Detailed information on roles and responsibilities is provided in the Supplementary Appendix, available at NEJM.org. The authors vouch for the accuracy and completeness of the data and for the fidelity of the substudy to the protocol.

Patient Eligibility and Randomization

Men and women 18 years of age or older were eligible for participation in the GALILEO trial if they had undergone successful TAVR for aortic stenosis; detailed inclusion and exclusion criteria are provided in the Supplementary Appendix. Eligible patients who provided written informed consent were randomly assigned in a 1:1 ratio to either a rivaroxaban-based strategy or an antiplatelet-based strategy.

The GALILEO-4D substudy enrolled patients at 12 sites that were involved in the main trial and that were able and willing to perform four-dimensional CT after TAVR. All patients eligible for inclusion in the main trial were also candidates for enrollment in the substudy, unless they had severe renal insufficiency (estimated glomerular filtration rate, <30 ml per minute per 1.73 m^2 of body-surface area), were undergoing dialysis, had post-TAVR unresolved acute kidney injury with renal dysfunction of stage 2 or higher, had iodine contrast allergy, or had another condition that prohibited CT imaging. Written informed consent, obtained at the same time as the consent for the main GALILEO trial, had to be obtained separately for participation in the substudy.

Treatment

Patients who were randomly assigned to the rivaroxaban-based strategy received rivaroxaban at a dose of 10 mg once daily plus aspirin at a dose of 75 to 100 mg once daily for 3 months, followed by monotherapy with rivaroxaban at a dose of 10 mg once daily. Patients who were randomly assigned to the antiplatelet-based strategy received aspirin at a dose of 75 to 100 mg

once daily and clopidogrel at a dose of 75 mg once daily for 3 months, followed by monotherapy with aspirin. More details regarding the treatment regimens are provided in the Supplementary Appendix.

IMAGING STUDIES

Patients included in GALILEO-4D were scheduled for a contrast-enhanced, electrocardiogram-gated cardiac CT scan with full cardiac-cycle coverage (four-dimensional CT) and a transthoracic echocardiogram at the time of the 3-month follow-up visit (mean [±SD], 90±15 days after randomization). The four-dimensional CT acquisition protocol is provided in the Supplementary Appendix. Depending on the scanner system and the institutional settings, the typical radiation exposure was 5 to 15 mSv. Leaflet thickening and motion were graded with the use of multiplanar reformats, with additional volume-rendered assessment as needed. Leaflet motion was classified in five grades (0 to 4, with higher grades indicating more restricted motion).[19] Four-dimensional CT core laboratory evaluations were independently performed at St. Paul's Hospital, Vancouver, British Columbia, and New York University Langone Health, New York, by investigators who were not aware of the patients' identities, the transthoracic echocardiographic data, or the random treatment assignment.

To limit crossovers in the main GALILEO trial, the results of the four-dimensional CT scan were concealed from the treating physician and patient until the end of the main trial. In the event of an overt ischemic stroke or systemic embolism, a clinically indicated cardiac four-dimensional CT scan could be performed. The result of this scan could be made available to the treating physician.

END POINTS

All end points for the GALILEO-4D substudy were assessed at 90 days — at the time of performance of the four-dimensional CT scan. The primary end point of the substudy was the percentage of patients with at least one prosthetic valve leaflet with reduced motion of grade 3 or higher (i.e., involving >50% of the leaflet). Secondary end points were the percentage of valve leaflets with reduced motion of grade 3 or higher, the percentage of patients with at least one thickened leaflet, the percentage of valve leaflets with thickening, the transprosthetic mean pressure gradient as determined by transthoracic echocardiography, and safety and efficacy end points identical to the primary end points of the main GALILEO trial. A full list of end points and definitions is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The main GALILEO trial was an event-driven trial with a target of 440 primary end-point events (the primary end point was a composite of death from any cause or thromboembolic events) and an originally anticipated enrollment of 1520 patients. In a separate power calculation for the GALILEO-4D substudy, we assumed that the primary end point of reduced motion of at least grade 3 at 90 days would occur in 20% of patients in the antiplatelet group. It was estimated that 246 patients would need to be enrolled to show a projected 65% lower percentage of patients with a primary end point in the rivaroxaban group, with a loss to follow-up of 5 to 10%.

The main GALILEO trial was terminated on August 13, 2018, at the recommendation of the data and safety monitoring board because of safety concerns. This did not affect the treatment or follow-up of patients enrolled in GALILEO-4D, since the last patient had been enrolled in the substudy on May 23, 2018.

The primary and secondary end points were evaluated in the intention-to-treat and per-protocol populations; these populations are defined in Figure S1 and Table S1 in the Supplementary Appendix. Unadjusted 95% confidence intervals for the differences in percentages between the two treatment groups are reported[20]; these unadjusted intervals cannot be used to infer effects. The Fisher's exact probability test was used to compare the percentages of patients with the primary end point between the treatment groups. Since no correction for multiple comparisons was used, the results of analyses other than that of the primary end point should be interpreted with caution. All statistical analyses were performed with SPSS software, version 24.0 (IBM).

RESULTS

PATIENT POPULATION

A sample of 246 patients was planned for the substudy on the basis of the power calculation. In May 2018, after 231 patients had been enrolled, the European Union General Data Protec-

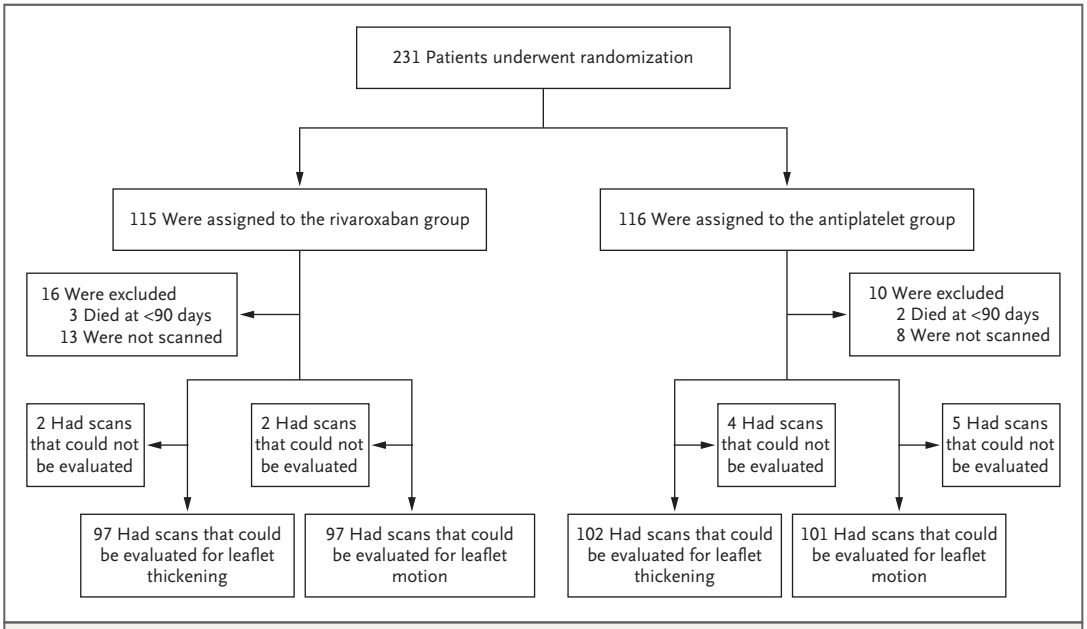

Figure 1. Population and Four-Dimensional CT Scans.

Shown are the numbers of four-dimensional computed tomographic (CT) scans that were available and of sufficient image quality to evaluate leaflet thickening and motion in each treatment group in the intention-to-treat population. One patient with a major clinical event (an episode of life-threatening bleeding) did not undergo scanning. The most common reasons for not undergoing scanning were logistic constraints, renal dysfunction, and patient preference. However, a systematic record of the reasons for 21 patients not undergoing scanning was not obtained in this substudy.

tion Regulation became effective, which would have required revision and reapproval of the consent forms that were then in use. Since recruitment was already close to the target number, the decision was made to close enrollment in the substudy.

Among the 231 patients enrolled, 115 were assigned to the rivaroxaban group and 116 to the antiplatelet group. Figure 1 shows the number of four-dimensional CT scans that were available and of sufficient image quality to allow assessment of both leaflet thickening and motion abnormalities in the intention-to-treat population; Figure S2 provides the same information for the per-protocol population. The characteristics of the patients in the substudy were well balanced between the treatment groups (Table 1 and Table S2A) and were similar to those in the main GALILEO population, except that only a few high-risk patients were enrolled in the substudy (Table S2B).

PRIMARY END POINT

In the intention-to-treat analysis, 2 of the 97 patients (2.1%) with scans that could be evaluated in the rivaroxaban group had at least one valve leaflet with reduced motion of grade 3 or higher, as compared with 11 of 101 (10.9%) in the antiplatelet group (between-group difference, −8.8 percentage points; 95% confidence interval [CI], −16.5 to −1.9; P=0.01) (Table 2 and Fig. 2). In the per-protocol analysis, the number of patients who had at least one valve leaflet with reduced motion of grade 3 or higher was 0 in the rivaroxaban group and 9 (9.6%) in the antiplatelet group (Table S3).

SECONDARY END POINTS OF FOUR-DIMENSIONAL CT IMAGING

In the intention-to-treat analysis, hypoattenuated thickening of at least one leaflet was found in 12 of 97 patients (12.4%) who were randomly assigned to the rivaroxaban group, as compared with 33 of 102 patients (32.4%) who were randomly assigned to the antiplatelet group (between-group difference, −20.0 percentage points; 95% CI, −30.9 to −8.5) (Table 2 and Fig. 2). Consistent results were obtained in the per-protocol analysis and in the analysis at the leaflet level, with the number of leaflets used

Table 1. Baseline Characteristics of the Patents in the Intention-to-Treat Population.*

Characteristic	Rivaroxaban (N=115)	Antiplatelet (N=116)
Clinical characteristics		
Age — yr	79.7±7.3	80.5±6.2
Male sex — no. (%)	74 (64.3)	74 (63.8)
Body-mass index†	27.7±6.5	27.8±5.1
Hypertension — no. (%)	98 (85.2)	95 (81.9)
Diabetes mellitus — no. (%)	21 (18.3)	27 (23.3)
STS risk score — %‡	2.8±1.5	3.0±2.1
STS risk category — no. (%)‡		
High	1 (0.9)	3 (2.6)
Intermediate	37 (32.2)	35 (30.2)
Low	77 (67.0)	78 (67.2)
Congestive heart failure — no. (%)	52 (45.2)	52 (44.8)
Coronary artery disease — no. (%)§	42 (36.5)	36 (31.0)
Previous stroke — no. (%)	11 (9.6)	6 (5.2)
Peripheral artery disease — no. (%)	10 (8.7)	10 (8.6)
Previous venous thromboembolism — no. (%)	1 (0.9)	1 (0.9)
Permanent pacemaker — no. (%)	14 (12.2)	14 (12.1)
Chronic obstructive pulmonary disease — no. (%)	19 (16.5)	16 (13.8)
Glomerular filtration rate — ml/min/1.73 m^2	73.6±19.2	76.6±19.4
Procedural characteristics		
Valve type — no. (%)		
Balloon-expandable	52 (45.2)	54 (46.6)
Self-expandable	63 (54.8)	62 (53.4)
Supra-annular leaflet position	37 (32.2)	46 (39.7)
Valve-in-valve — no. (%)	3 (2.6)	1 (0.9)
Post-TAVR echocardiographic characteristics before hospital discharge		
Aortic-valve area — cm^2	1.8±0.5	1.8±0.5
Mean aortic-valve gradient — mm Hg	11±5	11±4
Left ventricular ejection fraction — %	55±11	56±10
Paravalvular aortic regurgitation — no. (%)		
None or trace	94 (81.7)	96 (82.8)
Mild	19 (16.5)	19 (16.4)
Moderate or severe	2 (1.7)	1 (0.9)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. TAVR denotes transcatheter aortic-valve replacement.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The risk model of the Society of Thoracic Surgeons (STS) uses an algorithm that is based on the presence of coexisting illnesses to predict 30-day operative mortality. The STS score equals the predicted mortality expressed as a percentage. A score of greater than 8% indicates high risk, 3 to 8% intermediate risk, and less than 3% low risk.
§ Coronary artery disease is defined as previous myocardial infarction, percutaneous coronary intervention, or coronary-artery bypass grafting.

Table 2. Outcomes in the Intention-to-Treat Population.*

End Point	Rivaroxaban	Antiplatelet	Difference in Percentage (95% CI)
	no./total no. (%)		*percentage points*
Four-dimensional CT end points			
Reduced leaflet motion†			
Patient level			
At least one leaflet with grade ≥3 reduced motion‡	2/97 (2.1)	11/101 (10.9)	−8.8 (−16.5 to − 1.9)
At least one leaflet with grade ≥2 reduced motion	4/97 (4.1)	21/101 (20.8)	−16.7 (−25.9 to −7.6)
At least one leaflet with grade ≥1 reduced motion	12/97 (12.4)	32/101 (31.7)	−19.3 (−30.2 to −7.8)
Leaflet level			
Leaflets with grade ≥3 reduced motion	3/291 (1.0)	14/303 (4.6)	−3.6 (−6.7 to −0.9)
Leaflets with grade ≥2 reduced motion	6/291 (2.1)	26/303 (8.6)	−6.5 (−10.4 to −3.0)
Leaflets with grade ≥1 reduced motion	16/291 (5.5)	51/303 (16.8)	−11.3 (−16.4 to −6.3)
Severity of reduced leaflet motion			
Grade 1	10/291 (3.4)	25/303 (8.3)	−4.9 (−8.8 to −1.0)
Grade 2	3/291 (1.0)	12/303 (4.0)	−3.0 (−5.8 to −0.4)
Grade 3	3/291 (1.0)	12/303 (4.0)	−3.0 (−5.8 to −0.4)
Grade 4	0	2/303 (0.7)	−0.7 (−2.4 to 0.7)
Leaflet thickening			
Patient level			
At least one thickened leaflet	12/97 (12.4)	33/102 (32.4)	−20.0 (−30.9 to −8.5)
At least two thickened leaflets	3/97 (3.1)	16/102 (15.7)	−12.6 (−21.1 to −4.5)
At least three thickened leaflets	1/97 (1.0)	4/102 (3.9)	−2.9 (−8.7 to 2.3)
Leaflet level			
Leaflets with thickening	16/291 (5.5)	53/306 (17.3)	−11.8 (−16.9 to −6.8)
Clinical end points at time of four-dimensional CT scan§			
Major or life-threatening bleeding	4/115 (3.5)	1/116 (0.9)	—
Thromboembolic event	4/115 (3.5)	2/116 (1.7)	—
Nondisabling stroke	1/115 (0.9)	0	—
Disabling stroke	3/115 (2.6)	2/116 (1.7)	—
Death	3/115 (2.6)	2/116 (1.7)	—

* Analyses were not corrected for multiple comparisons.
† Leaflet motion was assigned a grade from 0 to 4: grade 0 denotes unrestricted, grade 1 minimally restricted (with restriction limited to the base), grade 2 mildly restricted (involving more than the base but <50% of the leaflet), grade 3 moderately restricted (involving >50% but <75% of the leaflet), and grade 4 largely immobile.
‡ This end point was the primary end point of the substudy. In case of discrepancies between the core laboratories (9 of 198 cases, 4.5%), a third independent expert was consulted to reach a consensus.
§ Clinical end points were adjudicated according to the Valve Academic Research Consortium–2 definitions.

as the denominator. All available four-dimensional CT data analyses are reported in Tables S3 and S4.

ECHOCARDIOGRAPHIC FINDINGS

There was no significant difference between the treatment groups with respect to the various

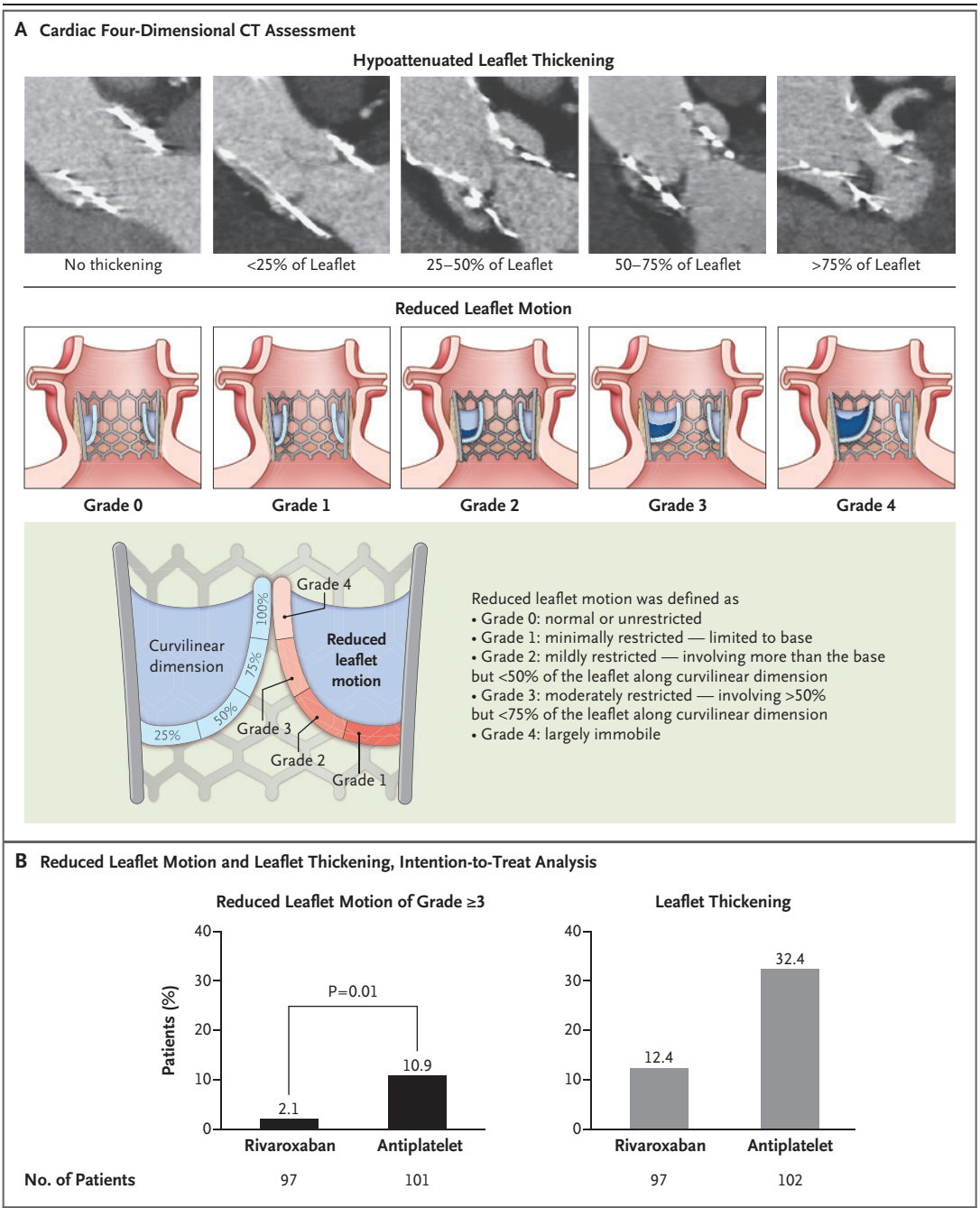

Figure 2. Four-Dimensional CT Imaging End Points.

Panel A shows the different degrees of hypoattenuated leaflet thickening and reduced leaflet motion used in classifying the findings on four-dimensional CT and provides definitions of the different degrees of reduced leaflet motion. Panel B shows the percentages of patients who had at least one prosthetic valve leaflet with reduced motion of grade 3 or higher and any degree of leaflet thickening in the rivaroxaban group and the antiplatelet group in the intention-to-treat analysis. The two-sided P value from the Fisher's exact probability test for the comparison of the primary end point between the two treatment groups is shown. Hypoattenuated leaflet thickening was defined as visually identifiable increased leaflet thickness on contrast-enhanced multiplanar reformats, carefully aligned with the long and short axes of the valve prosthesis.[19]

echocardiographic measures. An increase in the mean valve gradient of 5 mm Hg or more was found in 11 patients (7.3%) who did not have leaflet thickening and in 7 patients (15.9%) who did have leaflet thickening. A similar increase in the mean valve gradient was found in 14 patients (7.7%) who did not have reduced leaflet motion of grade 3 or higher and in 4 patients (30.8%) who did have reduced leaflet motion of grade 3 or higher (Tables S5 and S6).

Moderate hemodynamic structural valve deterioration[21] was reported in 4 of 207 patients (1.9%) at the time of the 3-month follow-up visit (Table S7). Two patients had an increase in the mean valve gradient of at least 10 mm Hg from baseline; one of these patients had clinical valve thrombosis with reduced leaflet motion of grade 3 or higher and heart failure symptoms.

CLINICAL EVENTS

The percentages of patients in the substudy who had major bleeding, thromboembolic events, or death at 90 days were each less than 3%, and only three patients with reported stroke underwent cardiac four-dimensional CT scanning; this did not allow for further statistical analysis (Tables S8 and S9).

DISCUSSION

In the GALILEO trial, a rivaroxaban-based strategy was compared with an antiplatelet-based strategy for the prevention of clinical thromboembolic events after TAVR. The GALILEO-4D substudy used four-dimensional CT imaging at 90 days after randomization to evaluate a subgroup of the bioprosthetic aortic valves that were implanted during the trial. The main findings were as follows: the overall percentages of patients with significantly reduced leaflet motion (grade 3 or higher) and leaflet thickening were 6.6% and 22.6%, respectively; both findings were less frequent with the rivaroxaban-based strategy than with the antiplatelet-based strategy, and echocardiography was not useful in identifying patients with these valvular abnormalities.

Subclinical leaflet thickening and reduced leaflet motion have been described with variable frequency in both transcatheter and surgical aortic bioprostheses.[8,9] Reports on the incidence of leaflet thickening mainly range between 7% and 15% but have reached 38% in some studies.[8-17,22,23] Our findings are not necessarily representative of an unselected population of patients who have undergone TAVR, since patients with known atrial fibrillation or an indication for oral anticoagulation (30 to 40% of all patients who undergo TAVR) were excluded from the substudy, half our patients were randomly assigned to rivaroxaban (10 mg daily), and patients were enrolled only after a successful TAVR procedure.

Previous observational studies indicated that oral anticoagulation reduces the risk of leaflet thickening more effectively than antiplatelet therapy.[8-17] In addition, there are registry data suggesting that dual antiplatelet therapy — which is the current standard of care after TAVR for patients without an established indication for oral anticoagulation[24,25] — is not superior to single-agent antiplatelet therapy for the prevention of this phenomenon.[9] However, in these registries, treatment was not randomly assigned, with resulting inherent patient selection bias, and the registries reported on a variety of different antithrombotic agents, dosages, and combinations.

In this randomized clinical trial, the percentages of patients with reduced leaflet motion and leaflet thickening were shown to be lower in the group assigned to a treatment strategy including anticoagulation with rivaroxaban at a dose of 10 mg once daily than in the group assigned to a treatment strategy involving antiplatelet therapy. Despite this beneficial effect of anticoagulation on the four-dimensional CT imaging findings, in the main GALILEO trial (also now published in the *Journal*) the rivaroxaban-based antithrombotic strategy was associated with a higher risk of death or thromboembolic complications (hazard ratio, 1.35) and a higher risk of life-threatening, disabling, or major bleeding (hazard ratio, 1.50) than the antiplatelet-based strategy.[26] There were too few clinical events in the imaging substudy to permit any assessment of the effect of reduced leaflet motion and leaflet thickening on clinical outcomes. The unsuitability of transthoracic echocardiography for the detection of subclinical leaflet thrombosis has previously been reported[8-15] and was reconfirmed here.

Limitations of this substudy include its sample size, which was too small to allow for ade-

quate correlation of imaging findings with clinical events; the fact that imaging was performed at only one time point (since these phenomena have been reported to be dynamic processes)[14,15]; the lack of valve imaging after cessation of anticoagulant therapy; and the lack of cerebrovascular imaging. Different antithrombotic agents or different doses would probably have different levels of risk and benefit; we selected a regimen without extensive previous data for guidance. Finally, we did not study the long-term effect on valve durability.

In conclusion, in patients without an established indication for long-term anticoagulation after successful TAVR, a treatment strategy that included anticoagulation with rivaroxaban at a dose of 10 mg once daily was more effective than an antiplatelet-based strategy in preventing subclinical reduced leaflet motion at 90 days. However, we cannot recommend routine imaging for the detection of reduced leaflet motion or the routine use of anticoagulation after TAVR with the aim of preventing leaflet-motion abnormalities, given the unfavorable clinical outcomes with rivaroxaban in the main GALILEO trial.

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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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