ORIGINAL ARTICLE

Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation

V.J. Nijenhuis, J. Brouwer, R. Delewi, R.S. Hermanides, W. Holvoet, C.L.F. Dubois, P. Frambach, B. De Bruyne, G.K. van Houwelingen, J.A.S. Van Der Heyden, P. Toušek, F. van der Kley, I. Buysschaert, C.E. Schotborgh, B. Ferdinande, P. van der Harst, J. Roosen, J. Peper, F.W.F. Thielen, L. Veenstra, D.R.P.P. Chan Pin Yin, M.J. Swaans, B.J.W.M. Rensing, A.W.J. van 't Hof, L. Timmers, J.C. Kelder, P.R. Stella, J. Baan, and J.M. ten Berg

ABSTRACT

BACKGROUND

The roles of anticoagulation alone or with an antiplatelet agent after transcatheter aortic-valve implantation (TAVI) have not been well studied.

METHODS

We performed a randomized trial of clopidogrel in patients undergoing TAVI who were receiving oral anticoagulation for appropriate indications. Patients were assigned before TAVI in a 1:1 ratio not to receive clopidogrel or to receive clopidogrel for 3 months. The two primary outcomes were all bleeding and non–procedure-related bleeding over a period of 12 months. Procedure-related bleeding was defined as Bleeding Academic Research Consortium type 4 severe bleeding, and therefore most bleeding at the puncture site was counted as non–procedure-related. The two secondary outcomes were a composite of death from cardiovascular causes, non–procedure-related bleeding, stroke, or myocardial infarction at 12 months (secondary composite 1) and a composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction (secondary composite 2), both tested for noninferiority (noninferiority margin, 7.5 percentage points) and superiority.

RESULTS

Bleeding occurred in 34 of the 157 patients (21.7%) receiving oral anticoagulation alone and in 54 of the 156 (34.6%) receiving oral anticoagulation plus clopidogrel (risk ratio, 0.63; 95% confidence interval [CI], 0.43 to 0.90; P=0.01); most bleeding events were at the TAVI access site. Non–procedure-related bleeding occurred in 34 patients (21.7%) and in 53 (34.0%), respectively (risk ratio, 0.64; 95% CI, 0.44 to 0.92; P=0.02). Most bleeding occurred in the first month and was minor. A secondary composite 1 event occurred in 49 patients (31.2%) receiving oral anticoagulation alone and in 71 (45.5%) receiving oral anticoagulation plus clopidogrel (difference, –14.3 percentage points; 95% CI for noninferiority, –25.0 to –3.6; risk ratio, 0.69; 95% CI for superiority, 0.51 to 0.92). A secondary composite 2 event occurred in 21 patients (13.4%) and in 27 (17.3%), respectively (difference, –3.9 percentage points; 95% CI for noninferiority, –11.9 to 4.0; risk ratio, 0.77; 95% CI for superiority, 0.46 to 1.31).

CONCLUSIONS

In patients undergoing TAVI who were receiving oral anticoagulation, the incidence of serious bleeding over a period of 1 month or 1 year was lower with oral anticoagulation alone than with oral anticoagulation plus clopidogrel. (Funded by the Netherlands Organization for Health Research and Development; POPular TAVI EU Clinical Trials Register number, 2013-003125-28; ClinicalTrials.gov number, NCT02247128.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. ten Berg at St. Antonius Hospital, Koekoekslaan 1, 3435CM, Nieuwegein, the Netherlands, or at jurtenberg@gmail.com.

Drs. Nijenhuis and Brouwer contributed equally to this article.

This article was published on March 29, 2020, at NEJM.org.

N Engl J Med 2020;382:1696-707.
DOI: 10.1056/NEJMoa1915152

Transcatheter aortic-valve implantation (TAVI) is used in patients with symptomatic severe aortic stenosis.[1-8] The procedure is complicated by major and life-threatening bleeding in 3 to 13% of patients, and strokes occur in 1 to 12% at 1 year after TAVI.[7-16] Atrial fibrillation is common in patients undergoing TAVI and constitutes an indication for long-term oral anticoagulation therapy with a vitamin K antagonist or direct-acting oral anticoagulant.[17,18] Current practice guidelines on antithrombotic treatment in patients who have an indication for anticoagulation after TAVI are based on expert opinion and suggest a vitamin K antagonist either alone[19] or in combination with aspirin or clopidogrel.[20] The rationale for additional antiplatelet therapy after TAVI is to reduce the risk of thromboembolic complications, but the trade-off of the risk of bleeding has not been well studied.[14,21]

The current trial (POPular TAVI) of antithrombotic therapy after TAVI involves two cohorts. This report describes the results in cohort B, which included patients who had an established indication for long-term oral anticoagulation. Our investigation of cohort A, which includes patients who did not have an indication for long-term anticoagulation, has not been completed.

Methods

Trial Design and Oversight

The POPular TAVI trial is an investigator-initiated, parallel-group, randomized, open-label trial performed at 17 European sites (9 in the Netherlands, 6 in Belgium, 1 in the Czech Republic, and 1 in Luxembourg). Details of the design have been described previously,[22] and the trial protocol is available with the full text of this article at NEJM.org. The trial is sponsored by the Netherlands Organization for Health Research and Development, which has had no role in the design or execution of the trial or in the analysis of the data. There is no industry involvement in the trial.

The trial protocol was approved by the national authorities and ethics committees in each country and by institutional research boards at each participating site. An independent data and safety monitoring board provided oversight by periodically reviewing all reported outcomes. Adjudication of all reported outcomes was executed by an independent clinical-event committee, whose members were unaware of the trial-group assignments. Trial monitoring was performed by an independent and external clinical research organization (Research Drive, Norg, the Netherlands).

The first two authors and the last author prepared all drafts of the manuscript. All the authors reviewed the manuscript and attest to the accuracy and completeness of the data, the fidelity of the trial to the protocol, and the accurate reporting of adverse events.

Patients

All patients suitable for TAVI, as determined by a dedicated heart team at each institution consisting of at least one interventional cardiologist and one cardiothoracic surgeon, were eligible for enrollment in the trial. Before randomization, patients were divided into two cohorts: those who had no indication for long-term oral anticoagulation (cohort A), and those, whose data are reported here, who had an established indication for long-term oral anticoagulation (cohort B). The main exclusion criteria were drug-eluting stent implantation within 3 months or bare-metal stent implantation within 1 month before the TAVI procedure and allergy to or unacceptable side effects from clopidogrel. Details regarding inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. Before the TAVI procedure was performed, all the patients provided written informed consent to participate in the trial.

Randomization and Trial Procedures

All the patients were receiving oral anticoagulation before randomization. Patients continued oral anticoagulation, which could be with a vitamin K antagonist or with a direct-acting oral anticoagulant, depending on the drug that the patient was using before randomization. Patients were randomly assigned before TAVI, in a 1:1 ratio, to receive either clopidogrel or no clopidogrel for 3 months. Randomization was executed by an electronic Web-response randomization system, with stratification according to center.

The TAVI procedures were performed according to the local protocol at each participating site. The trial protocol advised physicians to continue oral anticoagulation during admission for the TAVI procedure with a goal of an international normalized ratio of 2.0 for vitamin K antagonists, but the choice to either continue or interrupt oral anticoagulation periprocedurally was left to the discretion of the attending physician.

During the procedure, the use of unfractionated heparin was recommended with the goal of an activated clotting time of more than 250 seconds, or more than 200 seconds in patients with continuation of oral anticoagulation therapy. In patients assigned to oral anticoagulation plus clopidogrel, an initial loading dose of 300 mg of clopidogrel was administered either 1 day before or on the day of TAVI, followed by 75 mg once a day for 3 months, with discretionary allowance of cessation of clopidogrel 1 month earlier or later than 3 months.

Follow-up visits for routine care were scheduled at 30 days, 6 months, and 12 months, which could be performed in either the treating or referring hospital. Transthoracic echocardiography was performed 6 months after TAVI. All the patients were asked to complete a questionnaire at 3, 6, and 12 months after TAVI regarding the occurrence of primary and secondary outcomes, the prescribed medication, health status, and quality of life. Follow-up data were collected and adjudicated centrally by the research department of the coordinating center and assessed by persons unaware of the trial-group assignments. Data were obtained from hospital electronic patient records and the questionnaires and, if necessary, the patient, the patient's primary care physician (i.e., when death occurred at home), or the patient's pharmacist.

OUTCOMES

All the patients were followed for at least 1 year after TAVI. The two primary outcomes were all bleeding and non–procedure-related bleeding. Bleeding events and vascular complications were classified according to the Valve Academic Research Consortium-2 (VARC-2) definitions (Table S2).[23] Because the VARC-2 classification does not distinguish between procedure-related and non–procedure-related bleeding events, procedure-related events were defined as Bleeding Academic Research Consortium (BARC) type 4 severe bleeding.[24] This category is defined by any of the following: perioperative intracranial bleeding within 48 hours, reoperation after closure of sternotomy for the purpose of controlling bleeding, transfusion of 5 or more units of whole blood or packed red cells within a 48-hour period, or chest-tube output of 2 or more liters within a 24-hour period. Non–procedure-related bleeding consisted of all VARC-2 bleeding, excluding BARC type 4 severe bleeding; therefore, most bleeding at the puncture site was counted as non–procedure-related. Minor procedure-related bleeding events, not classified as BARC type 4, were counted separately and included in the non–procedure-related bleeding outcome. Bleeding events were also classified with the use of BARC, Thrombolysis in Myocardial Infarction (TIMI), and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) definitions (Table S2). Definitions of these outcomes are provided in the Supplementary Appendix.

There were two secondary outcomes: one was a composite of death from cardiovascular causes, non–procedure-related bleeding, stroke from any cause, or myocardial infarction (secondary composite 1); the other was a composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction (excluding bleeding) (secondary composite 2). We used these two composite outcomes to infer net clinical benefit and efficacy, respectively. The plan was to test noninferiority for secondary outcomes and, if this was shown, to test superiority.

STATISTICAL ANALYSIS

The hypothesis was that oral anticoagulation alone would be superior to oral anticoagulation plus 3 months of clopidogrel with respect to the incidence of bleeding (the primary outcome), while being noninferior with respect to the secondary outcomes. The primary and secondary outcomes were powered separately. The primary outcome was powered both for all bleeding and non–procedure-related bleeding. We estimated the incidence of all bleeding to be 18% among patients receiving oral anticoagulation alone and 36% among those receiving oral anticoagulation plus clopidogrel. We estimated the incidence of non–procedure-related bleeding to be 13% and 26%, respectively. These estimates were based on limited published data.[25,26] Accordingly, we calculated that 284 patients would be needed for the trial to show superiority with 80% power and a two-sided alpha of 0.05 for the primary outcomes.

For secondary composite 1, we estimated the incidence to be 31% among patients receiving oral anticoagulation alone and 39% among those receiving oral anticoagulation plus clopidogrel. Accordingly, we calculated that 296 patients

would be needed for the trial to show noninferiority with a noninferiority margin of 7.5 percentage points for the absolute difference with 80% power and a one-sided alpha of 0.025. If the requirement for noninferiority was met, secondary outcomes were tested for superiority. With accounting for withdrawals and loss to follow-up, the sample size was set at 316. Because there was no plan for adjustment for multiple comparisons of secondary outcomes, point estimates and unadjusted 95% confidence intervals are reported, and no clinical inferences can be made from these results.

The main analyses were performed in the modified intention-to-treat population, which included all the patients who underwent randomization and TAVI. Secondary analyses of the primary and secondary outcomes were performed in the per-protocol population.

For time-to-event analyses of the primary and secondary outcomes, hazard ratios and 95% confidence intervals were planned to be generated with Cox proportional-hazards models and tested by the log-rank test. Kaplan–Meier curves were used to show the incidence of outcomes over time. However, for both the primary and secondary outcomes, the underlying assumption of proportional hazards from randomization through 1 year was not met. We therefore performed a post hoc risk-ratio analysis for 12 months and a Cox proportional-hazards model for the first month. A two-sided P value of 0.05 or less was considered to indicate statistical significance. Analyses for the prespecified subgroups were performed for the primary and secondary outcomes with time to first event with the use of the Cox proportional-hazards model to evaluate treatment-by-subgroup interactions, but the trial was not powered to allow conclusions drawn from these subgroups. Data for patients who were lost to follow-up were planned to be treated as censored at the time of their last known vital status. Statistical analyses were performed with the use of R software, version 3.6.1 (R Foundation for Statistical Computing).

RESULTS

TRIAL POPULATION

From December 2013 through August 2018, a total of 326 patients who were receiving oral anticoagulation were randomly assigned in a 1:1 ratio to receive either clopidogrel or no clopidogrel for 3 months (Fig. 1). After randomization, 13 patients were excluded from analysis for the following reasons: TAVI was not initiated, was aborted, or was converted to an open procedure (5 patients); patients withdrew consent (5); or patients did not meet inclusion criteria (3). Therefore, 157 patients receiving oral anticoagulation alone and 156 receiving oral anticoagulation plus clopidogrel were included in the modified intention-to-treat primary analyses.

Baseline characteristics were similar in the two groups (Table 1). The mean (±SD) age of the patients was 81.0±5.9 years, and 45.4% of the patients were women. Procedural characteristics (including vascular complications), patient characteristics at discharge, and echocardiographic findings at discharge and during follow-up are shown in Tables S3 through S5. No patients were lost to follow-up at 12 months; data on primary and secondary outcomes were complete for 100% of the patients. Among patients receiving oral anticoagulation plus clopidogrel, adherence to clopidogrel was 95.5% for the recommended period of 3 months. Oral anticoagulation was discontinued by 2 patients receiving oral anticoagulation alone and by none receiving oral anticoagulation plus clopidogrel.

PRIMARY OUTCOMES

At 12 months, bleeding of any type had occurred in 34 patients (21.7%) receiving oral anticoagulation alone and in 54 patients (34.6%) receiving oral anticoagulation plus clopidogrel (risk ratio, 0.63; 95% confidence interval [CI], 0.43 to 0.90; P=0.01), and non–procedure-related bleeding had occurred in 34 patients (21.7%) and in 53 patients (34.0%), respectively (risk ratio, 0.64; 95% CI, 0.44 to 0.92; P=0.02) (Table 2, Fig. 2, and Fig. S2). The TAVI access site was the most common location of bleeding in both groups (15 of 34 patients [44%] receiving oral anticoagulation alone and 27 of 54 patients [50%] receiving oral anticoagulation plus clopidogrel) and was classified as non–procedure-related because it was not BARC type 4 (Tables S6 and S7). Severe procedure-related bleeding, defined as BARC type 4, was observed in 1 patient receiving oral anticoagulation plus clopidogrel and in none receiving oral anticoagulation alone, and this single event was the difference between the two primary outcomes.

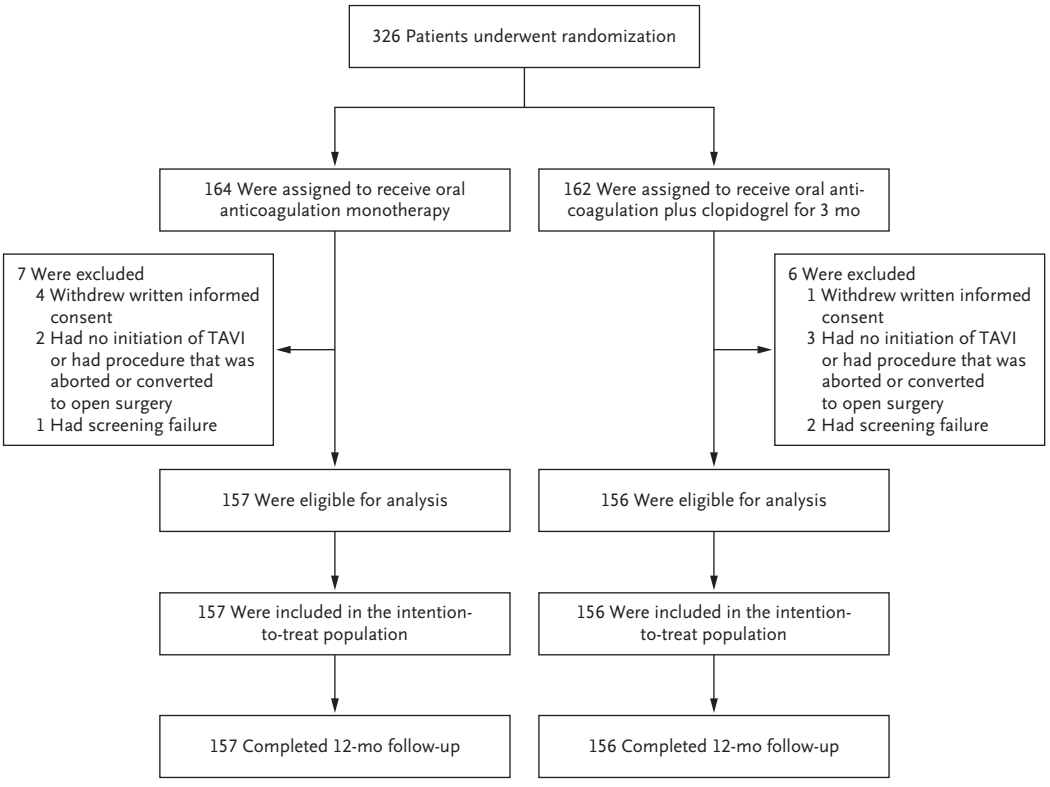


Figure 1. Randomization and Follow-up.
TAVI denotes transcatheter aortic-valve implantation.

Post hoc Cox proportional-hazards analysis of the primary outcomes during the first month, the period during which most bleeding occurred, is shown in Table S10, with hazard ratios of 0.60 (95% CI, 0.38 to 0.97) for all bleeding and 0.62 (95% CI, 0.39 to 1.00) for non–procedure-related bleeding. Sensitivity analyses of the primary outcomes and the secondary outcomes are shown in Tables S8 and S9, respectively, and are in the same direction as the primary analysis. Prespecified subgroup analyses of the primary outcomes are shown in Figures S3 and S4.

SECONDARY OUTCOMES

A secondary composite 1 event (death from cardiovascular causes, non–procedure-related bleeding, stroke from any cause, or myocardial infarction) occurred in 49 patients (31.2%) receiving oral anticoagulation alone and in 71 patients (45.5%) receiving oral anticoagulation plus clopidogrel (difference, –14.3 percentage points; 95% CI for noninferiority, –25.0 to –3.6; risk ratio, 0.69; 95% CI for superiority, 0.51 to 0.92) (Table 2 and Fig. 3A). A secondary composite 2 event (death from cardiovascular causes, ischemic stroke, or myocardial infarction) occurred in 21 patients (13.4%) receiving oral anticoagulation alone and in 27 patients (17.3%) receiving oral anticoagulation plus clopidogrel (difference, –3.9 percentage points; 95% CI for noninferiority, –11.9 to 4.0; risk ratio, 0.77; 95% CI for superiority, 0.46 to 1.31) (Table 2 and Fig. 3B). These results showed that no receipt of clopidogrel was noninferior to receipt of clopidogrel for both secondary outcomes by the prespecified margin of 7.5 percentage points, superior for the secondary outcome that included bleeding (secondary composite 1), and not superior for the secondary outcome that excluded bleeding (secondary composite 2). No clinical inferences can be drawn for these sec-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Oral Anticoagulation (N=157)	Oral Anticoagulation plus Clopidogrel (N=156)
Age — yr	80.9±6.2	81.0±5.5
Female sex — no. (%)	69 (43.9)	73 (46.8)
NYHA class III or IV — no. (%)	119 (75.8)	110 (70.5)
Body-mass index†	27.4±5.3	27.5±5.1
Logistic EuroSCORE — %‡		
Median	15.6	14.1
IQR	9.2–23.8	10.6–22.8
Society of Thoracic Surgeons risk score — %§		
Median	3.2	3.1
IQR	2.2–4.8	2.3–4.5
Indication for TAVI — no. (%)		
Normal-flow, high-gradient aortic stenosis	98 (62.4)	98 (62.8)
Low-flow, low-gradient aortic stenosis	51 (32.5)	50 (32.1)
Pure aortic regurgitation	6 (3.8)	4 (2.6)
Combination of above	2 (1.3)	4 (2.6)
Atrial fibrillation — no. (%)¶	150 (95.5)	147 (94.2)
Hypertension — no. (%)	115 (73.2)	105 (67.3)
Diabetes mellitus — no. (%)	43 (27.4)	46 (29.5)
Coronary artery disease — no. (%)	65 (41.4)	69 (44.2)
Previous myocardial infarction — no. (%)	14 (8.9)	20 (12.8)
Peripheral artery disease — no. (%)	30 (19.1)	28 (17.9)
Previous stroke — no. (%)	15 (9.6)	15 (9.6)
Estimated glomerular filtration rate — ml/min/1.73 m^2‖	53.4±17.7	55.6±17.1
Chronic obstructive pulmonary disease — no. (%)	33 (21.0)	30 (19.2)
Previous coronary-artery bypass grafting — no. (%)	30 (19.1)	30 (19.2)
Previous aortic-valve surgery — no. (%)	7 (4.5)	9 (5.8)
Left ventricular ejection fraction — no. (%)		
>50%	91 (58.0)	97 (62.2)
31–50%	54 (34.4)	46 (29.5)
≤30%	12 (7.6)	13 (8.3)

* Plus–minus values are means ±SD. There were no significant differences between the two groups. Percentages may not total 100 because of rounding. IQR denotes interquartile range, NYHA New York Heart Association, and TAVI transcatheter aortic-valve implantation.

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

‡ Values for the logistic-regression version of European System for Cardiac Operative Risk Evaluation (EuroSCORE) range from 0 to 100%, with higher values indicating a higher risk of death after cardiac surgery.

§ Society of Thoracic Surgeons risk scores range from 0 to 100%, with higher scores indicating a higher risk of death after cardiac surgery.

¶ Shown are patients with a history of atrial fibrillation and those with atrial fibrillation newly diagnosed on admission. Other indications for oral anticoagulation therapy included lung embolism, deep-vein thrombosis, poor left ventricular ejection fraction (including left ventricle aneurysms), and extensive arterial vascular disease.

‖ In the calculation of the estimated glomerular filtration rate, the creatinine clearance was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 2. Primary and Secondary Outcomes.*

Outcome	Oral Anticoagulation (N=157)	Oral Anticoagulation plus Clopidogrel (N=156)	Risk Ratio (95% CI)	Absolute Difference (95% CI)	P Value
	number (percent)			*percentage points*	
Primary outcomes					
All bleeding	34 (21.7)	54 (34.6)	0.63 (0.43 to 0.90)		0.01
Non–procedure-related bleeding	34 (21.7)	53 (34.0)	0.64 (0.44 to 0.92)		0.02
Secondary outcomes					
Secondary composite 1†					
Noninferiority analysis	49 (31.2)	71 (45.5)		−14.3 (−25.0 to −3.6)	
Superiority analysis	49 (31.2)	71 (45.5)	0.69 (0.51 to 0.92)		
Secondary composite 2‡					
Noninferiority analysis	21 (13.4)	27 (17.3)		−3.9 (−11.9 to 4.0)	
Superiority analysis	21 (13.4)	27 (17.3)	0.77 (0.46 to 1.31)		
Death from any cause	21 (13.4)	24 (15.4)	0.87 (0.51 to 1.50)		
Death from cardiovascular causes	13 (8.3)	20 (12.8)	0.65 (0.33 to 1.25)		
Stroke	9 (5.7)	9 (5.8)	0.99 (0.41 to 2.44)		
Ischemic	8 (5.1)	9 (5.8)	0.88 (0.35 to 2.23)		
Hemorrhagic	1 (0.6)	0			
Myocardial infarction	1 (0.6)	1 (0.6)	0.99 (0.06 to 15.75)		
VARC-2 bleeding					
Life-threatening or disabling bleeding	6 (3.8)	13 (8.3)	0.46 (0.18 to 1.18)		
Major bleeding	8 (5.1)	13 (8.3)	0.61 (0.26 to 1.43)		
Major, life-threatening, or disabling bleeding	14 (8.9)	26 (16.7)	0.54 (0.29 to 0.99)		
Minor bleeding	20 (12.7)	28 (17.9)	0.71 (0.42 to 1.21)		

* All outcomes were confirmed by an independent adjudication committee. The 95% confidence intervals for the secondary outcomes were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses. Individual elements of the primary and secondary outcomes were analyzed post hoc, and the 95% confidence intervals were not adjusted for multiple comparisons. VARC-2 denotes Valve Academic Research Consortium-2.

† A secondary composite 1 event was death from cardiovascular causes, non–procedure-related bleeding, stroke from any cause, or myocardial infarction.

‡ A secondary composite 2 event was death from cardiovascular causes, ischemic stroke, or myocardial infarction.

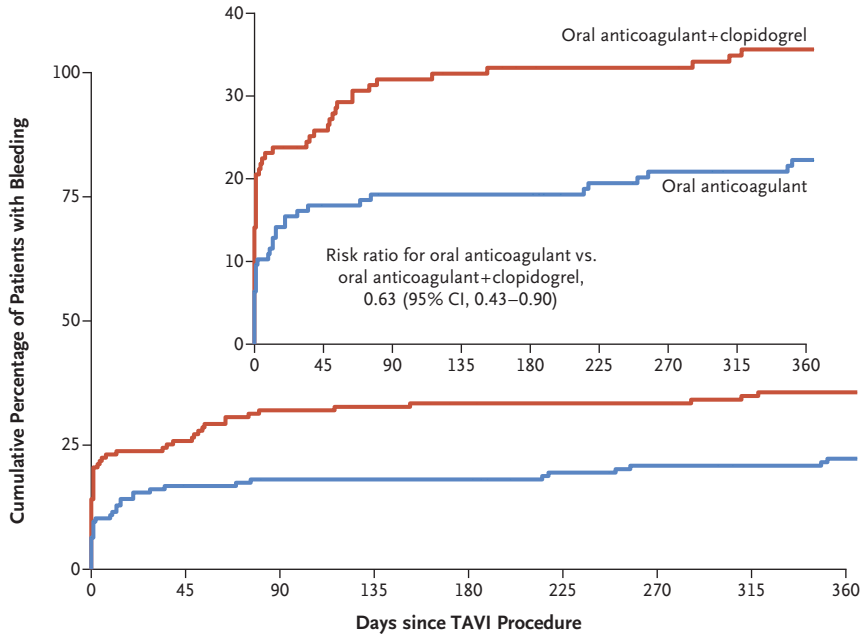
ondary outcome results because of the lack of a plan for correction for multiple comparisons.

In post hoc analyses, the individual components of the secondary outcomes were similar in the two groups (Table 2). Secondary outcomes across prespecified subgroups are shown in Figures S5 and S6. Post hoc Cox proportional-hazards analysis over a period of 3 months for the secondary outcomes is shown in Table S11.

Stroke occurred in nine patients (5.7%) receiving oral anticoagulation alone and in nine patients (5.8%) receiving oral anticoagulation plus clopidogrel. There was one hemorrhagic stroke (intraparenchymal) in a patient receiving oral anticoagulation alone and none in those receiving oral anticoagulation plus clopidogrel. Fatal stroke was observed in one patient receiving oral anticoagulation alone and in two patients receiving oral anticoagulation plus clopidogrel.

DISCUSSION

In this cohort of the POPular TAVI trial, we investigated antithrombotic treatment with oral anticoagulation alone as compared with oral anticoagulation plus clopidogrel for 3 months after



No. at Risk

Oral anticoagulant+clopidogrel	156	108	98	96	92	91	91	88	87
Oral anticoagulant	157	126	123	123	123	117	114	112	110

Figure 2. Primary Outcome of All Bleeding.

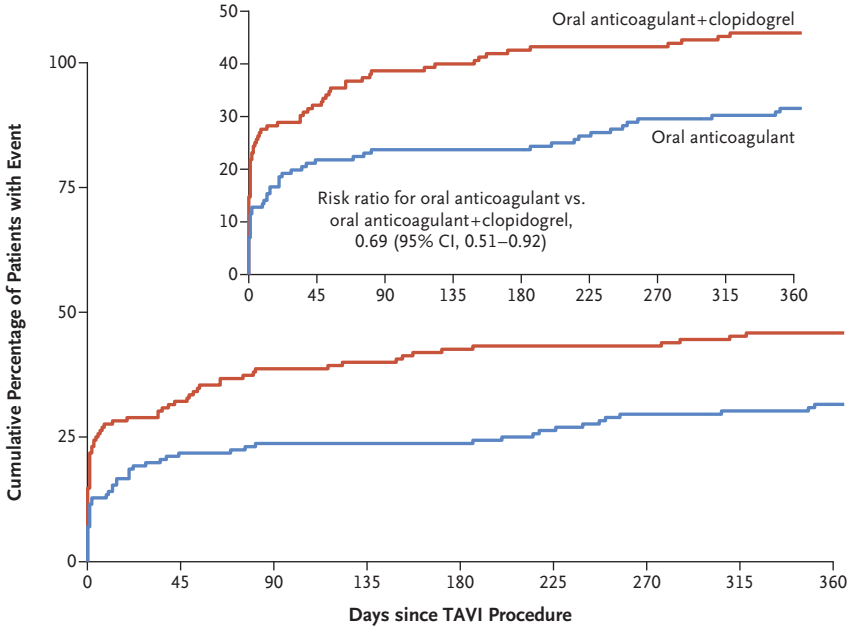
Shown are time-to-event Kaplan–Meier curves of the primary outcome of all bleeding. The inset shows the same data on an enlarged y axis. Given the nonproportionality of the hazards during the follow-up period, a post hoc risk-ratio analysis with 95% confidence intervals was performed. Results of a post hoc Cox proportional-hazards analysis over a period of 1 month for the primary outcome are shown in Table S10.

TAVI, in patients who were receiving indicated long-term oral anticoagulation. Antithrombotic treatment with oral anticoagulation alone was associated with a lower incidence of serious bleeding events than oral anticoagulation plus clopidogrel with regard to the primary outcomes of all bleeding and of non–procedure-related bleeding at 12 months. Our definition of procedural bleeding was BARC type 4, indicating severe bleeding and excluding most bleeding at the puncture site. The planned 1-year analysis showed nonproportional hazards, but post hoc risk ratios with respect to all bleeding and non–procedure-related bleeding also favored monotherapy at 1 month and at 1 year. Most bleeding occurred in the first few weeks after the procedure, as shown by post hoc landmark analysis at 1 month and is evident from visual inspection of the Kaplan–Meier curves. Minor bleeding rather than major bleeding, as defined by several classifications, contributed to this difference. The difference in bleeding events occurred mainly in the first month after TAVI, during which clopidogrel was administered, resulting in nonproportional hazards and requiring analysis by risk ratios.

As for the secondary outcomes, between-group differences that were not adjusted for multiple comparisons were in the same directions as the primary outcomes for noninferiority with regard to secondary composite 1 and secondary composite 2. The former, but not the latter, secondary outcome was in the same direction as the primary outcomes for superiority. The lack of a plan for multiple comparisons of secondary outcomes did not allow clinical inferences from these secondary outcome data.

Current guidelines recommend the use of a vitamin K antagonist with or without antiplatelet therapy for 3 to 6 months after TAVI in patients with a long-term indication for oral anticoagulation.[19,20] The rationale for additional antiplatelet therapy is to prevent thromboem-

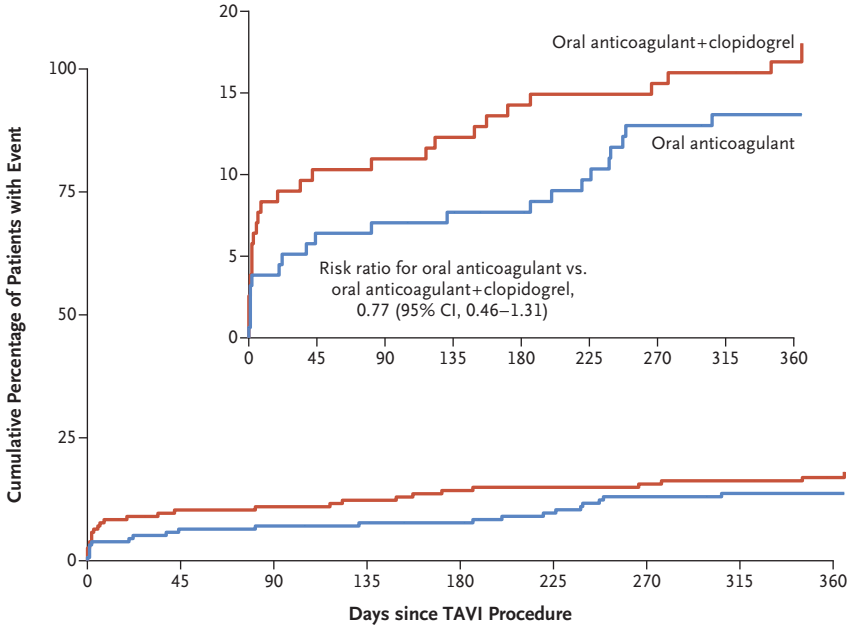
A **Death from Cardiovascular Causes, Non–Procedure-Related Bleeding, Stroke, or MI (Secondary Composite 1)**



No. at Risk

Oral anticoagulant+clopidogrel	156	104	94	92	88	87	87	84	83
Oral anticoagulant	157	122	119	119	119	113	108	106	104

B **Death from Cardiovascular Causes, Ischemic Stroke, or MI (Secondary Composite 2)**



No. at Risk

Oral anticoagulant+clopidogrel	156	136	135	133	130	129	128	127	124
Oral anticoagulant	157	146	145	143	141	136	131	129	129

Figure 3 (facing page). Secondary Outcomes.
Shown are time-to-event Kaplan–Meier curves for secondary composite 1 (Panel A) and secondary composite 2 (Panel B). The inset in each panel shows the same data on an enlarged y axis. Given the nonproportionality of the hazards during the follow-up period, a post hoc risk-ratio analysis with 95% confidence intervals was performed. Results of a post hoc Cox proportional-hazards analysis over a period of 3 months for the secondary outcomes are shown in Table S11. The 95% confidence intervals for the secondary outcomes were not adjusted for multiple comparisons, and therefore no clinical inferences can be made. MI denotes myocardial infarction.

bolic complications before endothelialization of the valve is completed.[14,21] However, observational data from patients with atrial fibrillation undergoing TAVI have shown a higher incidence of bleeding with a vitamin K antagonist plus a single antiplatelet therapy than with vitamin K antagonist monotherapy, with a similar incidence of thromboembolic events in the two groups.[14,15,21]

Reported incidences of stroke among patients with atrial fibrillation range from 3 to 12% in the first year after TAVI, of which approximately one fourth occurred within the first 24 hours and half within 30 days after TAVI.[14-16] Whereas periprocedural stroke is considered to be caused by embolization of calcified native valve or aortic tissue, stroke at later times is more often related to valve thrombosis (i.e., native or prosthetic valve thrombosis or atherothrombotic disease) and is therefore more amenable to antithrombotic therapy.[27] The incidences of all types of stroke and of ischemic stroke in cohort B of the POPular TAVI trial were similar in the trial groups at 12 months and were similar to published observational data.[14-16] There was one hemorrhagic stroke in a patient receiving oral anticoagulation alone. Fatal stroke occurred in one patient receiving oral anticoagulation alone and in two patients receiving oral anticoagulation plus clopidogrel.

The current trial included patients receiving either a vitamin K antagonist or a direct-acting oral anticoagulant. Prespecified subgroup analyses showed a possible benefit of direct-acting oral anticoagulants over vitamin K antagonists with regard to the primary outcomes (Figs. S3 and S4); however, no conclusions can be drawn from these analyses because this trial was neither designed nor powered to assess differences between subgroups. A trial involving patients without an established indication for oral anticoagulation after undergoing TAVI showed that rivaroxaban (10 mg daily) with aspirin was associated with a higher risk of bleeding and a higher risk of death or thromboembolic complications than was aspirin with clopidogrel.[28]

Our trial has several limitations. First, the trial was an open-label trial and 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 trial was powered to detect a difference in bleeding and secondary composite 1. However, the underlying assumption of proportionality for hazards for 12 months was not met, and an alternative plan was not prespecified in the statistical analysis plan. We therefore calculated post hoc risk ratios, and these were in the same direction as the primary analysis. Third, comparisons between trial groups for the secondary outcomes were not adjusted for multiple comparisons, and no clinical inferences can be made from these results. Fourth, the results of this report do not apply to patients undergoing TAVI who do not have an indication for long-term oral anticoagulation. This population is currently under investigation in cohort A of the POPular TAVI trial. Fifth, the most important limitation is the unconventional definition of procedural bleeding as BARC type 4, which represents severe bleeding and would exclude most bleeding at the puncture site.

Among patients with long-term indications for oral anticoagulation undergoing TAVI, oral anticoagulation alone was associated with a lower incidence of serious bleeding over a period of either 1 month or 1 year than was anticoagulation plus clopidogrel. Composite outcomes with and without bleeding were in the same direction as the primary outcomes for noninferiority; superiority of oral anticoagulation alone was shown for the composite outcome that included bleeding but not for the outcome that excluded bleeding.

Supported by the Netherlands Organization for Health Research and Development.

Dr. Delewi reports receiving lecture fees from Bayer; Dr. De Bruyne, receiving grant support, paid to his institution, from

Abbott Vascular and Biotronik, receiving grant support and consulting fees, paid to his institution, from Boston Scientific, receiving consulting fees, paid to his institution, from Opsens, and being a shareholder in Siemens, GE, Bayer, Philips Healthcare, HeartFlow, Edwards Lifesciences, and Ceylad; Dr. Swaans, receiving consulting fees and lecture fees from Abbott Vascular, Boston Scientific, Philips Healthcare, and BioVentrix; Dr. van 't Hof, receiving grant support from Medtronic and Abbott Vascular and grant support and lecture fees from AstraZeneca; and Dr. Baan, receiving grant support from Edwards Lifesciences. No other potential conflict of interest relevant to this article was reported.

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

The authors' full names and academic degrees are as follows: Vincent J. Nijenhuis, M.D., Jorn Brouwer, M.D., Ronak Delewi, M.D., Ph.D., Renicus S. Hermanides, M.D., Ph.D., Wouter Holvoet, M.D., Christophe L.F. Dubois, M.D., Ph.D., Peter Frambach, M.D., Bernard De Bruyne, M.D., Ph.D., Gert K. van Houwelingen, M.D., Jan A.S. Van Der Heyden, M.D., Ph.D., Petr Toušek, M.D., Ph.D., Frank van der Kley, M.D., Ian Buysschaert, M.D., Ph.D., Carl E. Schotborgh, M.D., Bert Ferdinande, M.D., Pim van der Harst, M.D., Ph.D., John Roosen, M.D., Joyce Peper, M.Sc., Frederick W.F. Thielen, M.Sc., Leo Veenstra, M.D., Dean R.P.P. Chan Pin Yin, M.D., Martin J. Swaans, M.D., Ph.D., Benno J.W.M. Rensing, M.D., Ph.D., Arnoud W.J. van 't Hof, M.D., Ph.D., Leo Timmers, M.D., Ph.D., Johannes C. Kelder, M.D., Ph.D., Pieter R. Stella, M.D., Ph.D., Jan Baan, M.D., Ph.D., and Jurriën M. ten Berg, M.D., Ph.D.

The authors' affiliations are as follows: the Department of Cardiology, St. Antonius Hospital, Nieuwegein (V.J.N., J. Brouwer, J.P., D.R.P.P.C.P.Y., M.J.S., B.J.W.M.R., L.T., J.C.K., J.M.B.), the Department of Cardiology, Amsterdam University Medical Centers, Location AMC, Amsterdam (R.D., J. Baan), the Department of Cardiology, Isala Hospital, Zwolle (R.S.H.), the Department of Cardiology, Maastricht University Medical Center and Cardiovascular Research Institute, Maastricht (W.H., L.V., A.W.J.H.), the Department of Cardiology, Medisch Spectrum Twente, Enschede (G.K.H.), the Department of Cardiology, Leiden University Medical Center, Leiden (F.K.), the Department of Cardiology, Haga Hospital, The Hague (C.E.S.), the Department of Cardiology, University Medical Center Groningen, Groningen (P.H.), Erasmus School of Health Policy and Management, Erasmus University, Rotterdam (F.W.F.T.), the Department of Cardiology, Zuyderland Medical Center, Heerlen (A.W.J.H.), and the Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht University, Utrecht (P.R.S.) — all in the Netherlands; the Department of Cardiology, University Hospital Leuven, Leuven (C.L.F.D.), the Department of Cardiology, Onze Lieve Vrouwe Hospital (B.D.B.), and the Department of Cardiology, Algemeen Stedelijk Hospital Aalst (I.B.), Aalst, the Department of Cardiology, Sint-Jan Hospital, Brugge (J.A.S.V.D.H.), the Department of Cardiology, Hospital Oost-Limburg, Genk (B.F.), and the Department of Cardiology, Imelda Hospital, Bonheiden (J.R.) — all in Belgium; the Department of Cardiology, Institut National de Chirurgie Cardiaque et de Cardiologie Interventionnelle, Luxembourg, Luxembourg (P.F.); and the Department of Cardiology, University Hospital Královské Vinohrady and Third Medical Faculty, Charles University, Prague, Czech Republic (P.T.).

REFERENCES

1. 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.
2. 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.
3. 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.
4. 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.
5. Reardon MJ, Van Mieghem NM, Popma JJ. Surgical or transcatheter aortic-valve replacement. N Engl J Med 2017;377:197-8.
6. 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.
7. 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.
8. 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.
9. Gilard M, Eltchaninoff H, Donzeau-Gouge P, et al. Late outcomes of transcatheter aortic valve replacement in high-risk patients: the FRANCE-2 Registry. J Am Coll Cardiol 2016;68:1637-47.
10. Hira RS, Vemulapalli S, Li Z, et al. Trends and outcomes of off-label use of transcatheter aortic valve replacement: insights from the NCDR STS/ACC TVT Registry. JAMA Cardiol 2017;2:846-54.
11. Wendler O, Schymik G, Treede H, et al. SOURCE 3: 1-year outcomes post-transcatheter aortic valve implantation using the latest generation of the balloon-expandable transcatheter heart valve. Eur Heart J 2017;38:2717-26.
12. Chieffo A, Petronio AS, Mehilli J, et al. 1-Year clinical outcomes in women after transcatheter aortic valve replacement: results from the first WIN-TAVI Registry. JACC Cardiovasc Interv 2018;11:1-12.
13. Manoharan G, Van Mieghem NM, Windecker S, et al. 1-Year outcomes with the Evolut R self-expanding transcatheter aortic valve: from the international FORWARD Study. JACC Cardiovasc Interv 2018;11:2326-34.
14. Abdul-Jawad Altisent O, Durand E, Muñoz-García AJ, et al. Warfarin and antiplatelet therapy versus warfarin alone for treating patients with atrial fibrillation undergoing transcatheter aortic valve replacement. JACC Cardiovasc Interv 2016;9:1706-17.
15. D'Ascenzo F, Benedetto U, Bianco M, et al. Which is the best antiaggregant or anticoagulant therapy after TAVI? A propensity-matched analysis from the ITER Registry: the management of DAPT after TAVI. EuroIntervention 2017;13(12):e1392-e1400.
16. Jochheim D, Zadrozny M, Ricard I, et al. Predictors of cerebrovascular events at mid-term after transcatheter aortic valve implantation — results from EVERY-TAVI Registry. Int J Cardiol 2017;244:106-11.
17. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962.
18. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Tho-

racic Surgeons. Circulation 2019;140(2):e125-e151.
19. 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.
20. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 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 Clinical Practice Guidelines. Circulation 2017;135(25):e1159-e1195.
21. Geis NA, Kiriakou C, Chorianopoulos E, Pleger ST, Katus HA, Bekeredjian R. Feasibility and safety of vitamin K antagonist monotherapy in atrial fibrillation patients undergoing transcatheter aortic valve implantation. EuroIntervention 2017;12:2058-66.
22. Nijenhuis VJ, Bennaghmouch N, Hassell M, et al. Rationale and design of POPular-TAVI: antiPlatelet therapy fOr Patients Undergoing Transcatheter Aortic Valve Implantation. Am Heart J 2016;173:77-85.
23. 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. EuroIntervention 2012;8:782-95.
24. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.
25. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 2010;170:1433-41.
26. Figini F, Latib A, Maisano F, et al. Managing patients with an indication for anticoagulant therapy after transcatheter aortic valve implantation. Am J Cardiol 2013;111:237-42.
27. Van Mieghem NM, El Faquir N, Rahhab Z, et al. Incidence and predictors of debris embolizing to the brain during transcatheter aortic valve implantation. JACC Cardiovasc Interv 2015;8:718-24.
28. Dangas GD, Tijssen JGP, Wöhrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. N Engl J Med 2020;382:120-9.