ORIGINAL ARTICLE

Aspirin with or without Clopidogrel after Transcatheter Aortic-Valve Implantation

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ABSTRACT

BACKGROUND

The effect of single as compared with dual antiplatelet treatment on bleeding and thromboembolic events after transcatheter aortic-valve implantation (TAVI) in patients who do not have an indication for long-term anticoagulation has not been well studied.

METHODS

In a randomized, controlled trial, we assigned a subgroup of patients who were undergoing TAVI and did not have an indication for long-term anticoagulation, in a 1:1 ratio, to receive aspirin alone or aspirin plus clopidogrel for 3 months. The two primary outcomes were all bleeding (including minor, major, and life-threatening or disabling bleeding) and non–procedure-related bleeding over a period of 12 months. Most bleeding at the TAVI 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 (secondary composite 1) and a composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction (secondary composite 2) at 1 year, with both outcomes tested sequentially for noninferiority (noninferiority margin, 7.5 percentage points) and superiority.

RESULTS

A total of 331 patients were assigned to receive aspirin alone and 334 were assigned to receive aspirin plus clopidogrel. A bleeding event occurred in 50 patients (15.1%) receiving aspirin alone and in 89 (26.6%) receiving aspirin plus clopidogrel (risk ratio, 0.57; 95% confidence interval [CI], 0.42 to 0.77; P=0.001). Non–procedure-related bleeding occurred in 50 patients (15.1%) and 83 patients (24.9%), respectively (risk ratio, 0.61; 95% CI, 0.44 to 0.83; P=0.005). A secondary composite 1 event occurred in 76 patients (23.0%) receiving aspirin alone and in 104 (31.1%) receiving aspirin plus clopidogrel (difference, −8.2 percentage points; 95% CI for noninferiority, −14.9 to −1.5; P<0.001; risk ratio, 0.74; 95% CI for superiority, 0.57 to 0.95; P=0.04). A secondary composite 2 event occurred in 32 patients (9.7%) and 33 patients (9.9%), respectively (difference, −0.2 percentage points; 95% CI for noninferiority, −4.7 to 4.3; P=0.004; risk ratio, 0.98; 95% CI for superiority, 0.62 to 1.55; P=0.93). A total of 44 patients (13.3%) and 32 (9.6%), respectively, received oral anticoagulation during the trial.

CONCLUSIONS

Among patients undergoing TAVI who did not have an indication for oral anticoagulation, the incidence of bleeding and the composite of bleeding or thromboembolic events at 1 year were significantly less frequent with aspirin than with aspirin plus clopidogrel administered for 3 months. (Funded by the Netherlands Organization for Health Research and Development; POPular TAVI EU Clinical Trials Register number, 2013-003125-28; ClinicalTrials.gov number, NCT02247128.)

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Transcatheter aortic-valve implantation (TAVI) is an established treatment in patients with symptomatic severe aortic stenosis.[1-7] Ischemic and bleeding complications that frequently occur after TAVI can be life-threatening.[4,6,7] Practice guidelines recommend clopidogrel in addition to aspirin for the first 3 to 6 months after TAVI in patients who do not have an indication for oral anticoagulation.[8,9] In trials that assessed the incidence of ischemic events after coronary-artery stenting, this form of dual antiplatelet therapy was shown to reduce the risk of thromboembolic complications.[10] Small and exploratory studies involving patients who have undergone TAVI have not shown a lower incidence of ischemic events with aspirin and clopidogrel than with aspirin alone[11-13]; however, dual antiplatelet therapy was associated with an increased incidence of bleeding in the ARTE (Aspirin Versus Aspirin + Clopidogrel following Transcatheter Aortic Valve Implantation) trial.[11]

In cohort B of the POPular TAVI trial (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic-Valve Implantation), clopidogrel in addition to oral anticoagulants was associated with a higher incidence of bleeding and no decrease in the incidence of ischemic events than anticoagulation alone.[14] Here, we describe the results in cohort A of the trial, which compared aspirin alone with aspirin plus clopidogrel in patients undergoing TAVI who did not have an established indication for long-term oral anticoagulation.

Methods

Trial Design and Oversight

The POPular TAVI trial comprised two investigator-initiated, randomized, open-label clinical trials performed at 17 European sites. Details of the design have been described previously,[14,15] and the trial protocol is available with the full text of this article at NEJM.org. The participating sites and investigators are listed in the Supplementary Appendix, available at NEJM.org. The trial was sponsored by the Netherlands Organization for Health Research and Development, which had no role in the design or execution of the trial or in the analysis of the data. There was no industry involvement in the trial.

The trial protocol was approved by the national authorities and ethics committees in each country and by an institutional review board at each participating site. The first two authors, the last author, and the steering committee supervised all aspects of the trial. An independent data and safety monitoring board periodically monitored all reported outcomes. The reported outcomes and their components were adjudicated by an independent clinical-events committee, whose members were unaware of the trial-group assignments. Trial monitoring was performed by an independent clinical research service organization (Research Drive, Norg, the Netherlands).

The first two authors and the last author prepared all drafts of the manuscript, and the analyses were performed by the first two authors and two other authors. All the authors reviewed and critiqued subsequent drafts of the manuscript and vouch for the accuracy and completeness of the data, the fidelity of the trial to the protocol, and the complete reporting of adverse events.

Patients

All patients who were scheduled to undergo TAVI and did not have an indication for long-term oral anticoagulation were eligible for enrollment in the trial. The main exclusion criteria were the implantation of a drug-eluting coronary-artery stent within 3 months or the implantation of a bare-metal stent within 1 month before TAVI. A list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. All the patients provided written informed consent before they underwent TAVI.

Randomization and Trial Procedures

Patients were randomly assigned at least 1 day and no more than 90 days before TAVI, in a 1:1 ratio, to receive either aspirin alone or aspirin plus clopidogrel for 3 months after TAVI. Randomization was performed by an electronic Web-response system, with stratification according to center.

Patients in the aspirin-alone group were assigned to receive aspirin at a dose of 80 to 100 mg daily for the duration of the trial and were advised to take aspirin on a lifelong basis. In patients who had not previously received aspirin, an initial loading dose of 300 mg of aspirin was administered within 1 day before TAVI. All other actively prescribed antiplatelet agents were discontinued at least 5 days before TAVI.

Patients in the aspirin–clopidogrel group were assigned to receive aspirin at a dose of 80 to

100 mg daily plus clopidogrel at a dose of 75 mg daily for 3 months, followed by aspirin alone (80 to 100 mg daily) for the entire duration of the trial and were advised to take aspirin on a lifelong basis. An initial loading dose of 300 mg of aspirin was administered within 1 day before TAVI in patients who were not already taking aspirin. An initial single loading dose of 300 mg of clopidogrel was administered 1 day before or on the day of TAVI, followed by 75 mg daily for 3 months after TAVI, with discretionary allowance of discontinuation of clopidogrel 1 month earlier or later than 3 months. In patients who were receiving clopidogrel for medical reasons (typically previous stroke or extensive arterial vascular disease) before enrollment, the treating physician was contacted about the possibility of switching to aspirin. If permission to switch to aspirin was denied, the patient continued to receive clopidogrel alone at a dose of 75 mg daily. If a stroke occurred during the trial, patients who had been assigned to aspirin could switch to clopidogrel at the discretion of the attending physician.

The TAVI procedures were performed according to the local protocol at each participating site. The trial protocol advised physicians to administer unfractionated heparin for anticoagulation during the procedure with a goal of an activated clotting time of more than 250 seconds. In patients in whom atrial fibrillation developed after TAVI, oral anticoagulation was initiated with a vitamin K antagonist or direct-acting oral anticoagulant, according to local practice. The trial coordinators and protocol recommended that an oral anticoagulant replace aspirin and, if applicable, that it be prescribed with clopidogrel.

Follow-up visits for routine care were scheduled at 1, 6, and 12 months and could be performed in either the treating or referring hospital (see the protocol). In addition, 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, their health status, and quality of life. At 6 months after TAVI, transthoracic echocardiography was performed. Follow-up data were collected and adjudicated by the research department of the coordinating center. The data were obtained from the questionnaires and the patients' electronic hospital records. If necessary, the patient, the patient's primary care physician (i.e., if death occurred at home), or the patient's pharmacist was contacted for additional data.

TRIAL OUTCOMES

The two primary outcomes were all bleeding (including minor, major, and life-threatening or disabling bleeding) and non–procedure-related bleeding over a period of 12 months. The first secondary outcome was a composite of bleeding or thromboembolic events and consisted of death from cardiovascular causes, non–procedure-related bleeding, stroke from any cause, or myocardial infarction (secondary composite 1). The other secondary outcome (secondary composite 2) was a composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction; this outcome differed from the first secondary outcome by excluding non–procedure-related bleeding.

The outcomes were primarily defined according to the Valve Academic Research Consortium (VARC) definitions.[16] Because the VARC definitions do not distinguish between procedure-related and non–procedure-related bleeding, procedure-related bleeding was classified as Bleeding Academic Research Consortium (BARC) type 4 severe bleeding,[17] which is characterized by any of the following: intracranial bleeding within 48 hours after a surgical procedure, reoperation after closure of sternotomy for the purpose of controlling bleeding, transfusion of at least 5 units of packed red cells within a 48-hour period, or chest-tube output of at least 2 liters within a 24-hour period. The outcome of non–procedure-related bleeding excluded BARC type 4 bleeding. Also, owing to the limitations of the definition of BARC type 4 bleeding, most bleeding at the TAVI puncture site was not classified as BARC type 4 but was counted separately and included in the outcome of non–procedure-related bleeding. All events in the non–procedure-related bleeding category are also counted in the category of all bleeding.

Bleeding events were also classified with the use of Thrombolysis in Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) definitions. The definitions of these outcomes are provided in Table S2.

STATISTICAL ANALYSIS

Our hypothesis was that aspirin alone would be superior to aspirin plus clopidogrel for 3 months

with respect to the incidence of bleeding (the primary outcomes) and would be noninferior with respect to the composite of bleeding or thromboembolic events and the composite of thromboembolic events (the two secondary outcomes). The trial was powered for both the primary outcomes and the first secondary outcome. On the basis of limited published data,[1,2,18-23] we estimated that a sample of 648 patients would provide the trial with at least 80% power to show superiority of aspirin alone over aspirin plus clopidogrel with respect to bleeding, assuming an incidence of all bleeding of 24% among patients in the aspirin-alone group and 36% among patients in the aspirin–clopidogrel group at 1 year and an incidence of non–procedure-related bleeding of 17% and 26%, respectively, at 1 year. We calculated that the trial would have at least 80% power to show noninferiority of aspirin alone as compared with aspirin plus clopidogrel with respect to the first secondary outcome of bleeding or thromboembolic events, assuming that the incidence would be 34% in the aspirin-alone group and 39% in the aspirin–clopidogrel group at 1 year. The noninferiority margin was set at 7.5 percentage points for the absolute between-group difference. If the requirement for noninferiority was met, each secondary outcome was subsequently tested for superiority ($P<0.05$). A sample of 684 patients was chosen to allow for withdrawals and loss to follow-up.

The primary analyses were performed in the modified intention-to-treat population, which included all the patients who had undergone randomization and subsequent TAVI. Sensitivity analyses of the primary and secondary outcomes were performed in the per-protocol population and are reported in the Supplementary Appendix. Patients who received clopidogrel before enrollment for medical reasons were included in their assigned treatment groups in the modified intention-to-treat analyses but excluded from the per-protocol analyses. In these patients, clopidogrel was administered for the entire duration of the study as monotherapy in the aspirin-alone group or with aspirin for 3 months in the aspirin–clopidogrel group. Patients who had a stroke during the trial and switched to clopidogrel were included in both the modified intention-to-treat analyses and per-protocol analyses. Kaplan–Meier curves were used to determine the incidence of outcomes over time at 1 year.

Because hazards were determined to be nonproportional for both the primary and secondary outcomes, post hoc risk ratios were calculated and compared with the use of the chi-square test. This analysis was added to the statistical analysis plan in an amendment on January 13, 2020, before the data were unlocked. A subgroup analysis was performed with Cox proportional-hazards or risk ratios, depending on whether the proportionality assumption was confirmed. We performed a Cox proportional-hazards model for the first 3 months. A two-sided P value of 0.05 or less was considered to indicate statistical significance.

Adjustment for multiple testing for the primary and secondary outcomes with the use of the Hochberg method was performed in order to control the family-wise error rate.[24] This analysis was also added to the statistical analysis plan in the above-mentioned amendment . In total, six tests were included in the Hochberg procedure (both primary outcomes for superiority and both secondary outcomes for noninferiority and superiority).

Imputation of missing data was to be performed as described in the statistical analysis plan (available with the trial protocol at NEJM.org), but there were no missing data for the primary or secondary outcomes. 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 March 2019, a total of 690 patients were randomly assigned before TAVI to receive aspirin alone or aspirin plus clopidogrel; 25 patients were excluded from the analysis as shown in Figure 1. The main reason for exclusion was that TAVI was not initiated, was aborted, or was converted to an open procedure. A total of 665 patients were included in the modified intention-to-treat analysis, of whom 331 were assigned to aspirin alone and 334 were assigned to aspirin plus clopidogrel (Fig. 1).

The baseline characteristics of the patients are listed in Table 1. The mean (±SD) age of the patients was 80.0±6.3 years, and 48.7% of the pa-

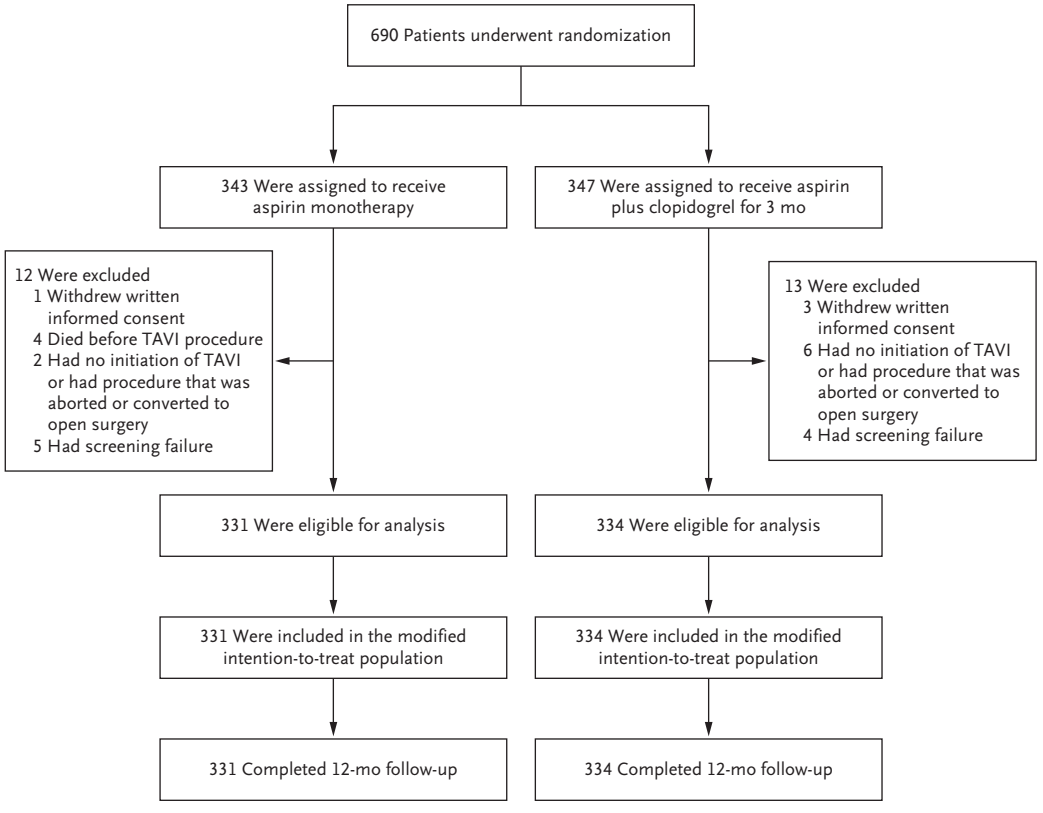

Figure 1. Randomization and Follow-up.
TAVI denotes transcatheter aortic-valve implantation.

tients were women. Procedure-related characteristics (including vascular complications), patient characteristics at discharge, and follow-up echocardiographic findings are provided in Tables S3 through S5. A total of 16 of the patients (4.8%) assigned to aspirin alone continued to receive clopidogrel alone throughout the trial for medical reasons, at the direction of their treating physician; 10 patients (3.0%) who had been receiving clopidogrel before enrollment were assigned to the dual antiplatelet group and received aspirin in addition to the previous clopidogrel. During the trial, 8 patients in the aspirin-alone group and 2 in the aspirin–clopidogrel group crossed over to the other group.

No patients were lost to follow-up, and data regarding the primary and secondary outcomes were complete for 100% of the patients. Among patients receiving clopidogrel, adherence to clopidogrel was 89.2% for the recommended period of 3 months. The median exposure to clopidogrel was 92 days (interquartile range, 90 to 92). Oral anticoagulation was initiated in 44 patients (13.3%) in the aspirin-alone group, and in 32 patients (9.6%) in the aspirin–clopidogrel group at a median of 12 days (interquartile range, 4 to 59) and 6 days (interquartile range, 3 to 66) after TAVI, respectively. The main reason for initiation of oral anticoagulation was new-onset atrial fibrillation. Details of the administration of the trial drugs, deviations from assigned drugs, and administration of oral anticoagulation are provided in Tables S6 and S7.

PRIMARY OUTCOMES

At 12 months, bleeding of any type had occurred in 50 patients (15.1%) receiving aspirin alone and in 89 patients (26.6%) receiving aspirin plus clopidogrel (risk ratio, 0.57; 95% confidence interval [CI], 0.42 to 0.77; P=0.001). Non–procedure-related bleeding occurred in 50 patients (15.1%) and 83 patients (24.9%), respectively (risk ratio,

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Aspirin (N=331)	Aspirin plus Clopidogrel (N=334)
Age — yr	80.4±6.2	79.5±6.4
Female sex — no. (%)	164 (49.5)	160 (47.9)
NYHA class III or IV — no. (%)	212 (64.0)	220 (65.9)
Body-mass index†	27.0±4.7	27.1±4.6
Society of Thoracic Surgeons risk score — %‡		
Median	2.6	2.4
IQR	1.6–3.7	1.7–3.7
Indication for TAVI — no. (%)		
Normal flow, high-gradient aortic stenosis	253 (76.4)	251 (75.1)
Low-flow, low-gradient aortic stenosis	64 (19.3)	58 (17.4)
Pure aortic regurgitation	8 (2.4)	7 (2.1)
Combination of above	6 (1.8)	18 (5.4)
Hypertension — no. (%)	243 (73.4)	255 (76.3)
Diabetes mellitus — no. (%)	78 (23.6)	85 (25.4)
Coronary artery disease — no. (%)	134 (40.5)	138 (41.3)
Previous myocardial infarction — no. (%)	28 (8.5)	31 (9.3)
Peripheral artery disease — no. (%)	47 (14.2)	68 (20.4)
Previous stroke — no. (%)	18 (5.4)	12 (3.6)
Estimated glomerular filtration rate — ml/min/1.73 m^2§	57.5±18.1	57.9±19.7
Chronic obstructive pulmonary disease — no. (%)	52 (15.7)	74 (22.2)
Previous coronary-artery bypass grafting — no. (%)	61 (18.4)	65 (19.5)
Previous aortic-valve surgery — no. (%)	23 (6.9)	20 (6.0)
Left ventricular ejection fraction — no. (%)		
>50%	244 (73.7)	245 (73.4)
31–50%	74 (22.4)	65 (19.5)
≤30%	13 (3.9)	24 (7.2)

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

0.61; 95% CI, 0.44 to 0.83; P=0.005) (Table 2 and Fig. 2, and Fig. S2). The TAVI access site was the location of bleeding in 29 of 50 patients (58.0%) receiving aspirin alone and in 48 of 89 patients (53.9%) receiving aspirin plus clopidogrel (Tables S8 and S9). Although most bleeding was related to the TAVI access site, these events did not qualify as procedure-related BARC type 4 bleeding and were classified as non–procedure-related. Severe procedure-related bleeding, defined as BARC type 4, was not observed in patients receiving aspirin alone and occurred in 6 patients (1.8%) receiving aspirin plus clopidogrel.

The results of the sensitivity analyses of the primary outcomes were generally in the same direction as in the primary analysis (Table S11). The results of a post hoc Cox proportional-hazards analysis of the primary outcomes over a pe-

Table 2. Primary and Secondary Outcomes.*

Outcome	Aspirin (N=331)	Aspirin plus Clopidogrel (N=334)	Risk Ratio (95% CI)	Absolute Difference (95% CI)	P Value
	number (percent)			*percentage points*	
Primary outcomes					
All bleeding	50 (15.1)	89 (26.6)	0.57 (0.42 to 0.77)		0.001
Non–procedure-related bleeding	50 (15.1)	83 (24.9)	0.61 (0.44 to 0.83)		0.005
Secondary outcomes					
First composite secondary outcome†					
Noninferiority analysis	76 (23.0)	104 (31.1)		−8.2 (−14.9 to −1.5)	<0.001
Superiority analysis	76 (23.0)	104 (31.1)	0.74 (0.57 to 0.95)		0.04
Second composite secondary outcome‡					
Noninferiority analysis	32 (9.7)	33 (9.9)		−0.2 (−4.7 to 4.3)	0.004
Superiority analysis	32 (9.7)	33 (9.9)	0.98 (0.62 to 1.55)		0.93
Death					
From any cause	21 (6.3)	19 (5.7)	1.12 (0.61 to 2.04)		
From cardiovascular cause	14 (4.2)	13 (3.9)	1.09 (0.52 to 2.28)		
Stroke	17 (5.1)	19 (5.7)	0.90 (0.48 to 1.71)		
Ischemic	17 (5.1)	18 (5.4)	0.95 (0.50 to 1.82)		
Hemorrhagic	0	1 (0.3)			
Nondisabling stroke	11 (3.3)	14 (4.2)	0.79 (0.37 to 1.72)		
Disabling stroke	6 (1.8)	5 (1.5)	1.21 (0.37 to 3.93)		
Myocardial infarction	4 (1.2)	6 (1.8)	0.67 (0.19 to 2.36)		
VARC bleeding					
Life-threatening or disabling bleeding	9 (2.7)	11 (3.3)	0.83 (0.35 to 1.97)		
Major bleeding	8 (2.4)	25 (7.5)	0.32 (0.15 to 0.71)		
Major, life-threatening, or disabling bleeding	17 (5.1)	36 (10.8)	0.48 (0.27 to 0.83)		
Minor bleeding	33 (10.0)	53 (15.9)	0.63 (0.42 to 0.94)		

* All outcomes were confirmed by an independent adjudication committee. The P values for the primary and secondary outcomes were adjusted for multiple comparisons with the use of the Hochberg method. The individual components of the secondary outcomes were analyzed post hoc, the 95% confidence intervals were not adjusted for multiple comparisons, and no clinical inferences can be made from these analyses. VARC denotes Valve Academic Research Consortium.

† A first composite secondary outcome was defined as a nonhierarchical composite of death from cardiovascular causes, non–procedure-related bleeding, stroke from any cause, or myocardial infarction.

‡ A second composite secondary outcome was defined as the nonhierarchical composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction.

riod of 3 months are shown in Table S12. Results of prespecified subgroup analyses of the primary outcomes are shown in Figures S3 and S4.

SECONDARY OUTCOMES

A secondary composite 1 event (bleeding, death from cardiovascular causes, non–procedure-related bleeding, stroke from any cause, or myocardial infarction) occurred in 76 patients (23.0%) receiving aspirin alone and in 104 patients (31.1%) receiving aspirin plus clopidogrel. These results showed that aspirin alone was noninferior to combined therapy by the prespecified margin of 7.5 percentage points, with an absolute differ-

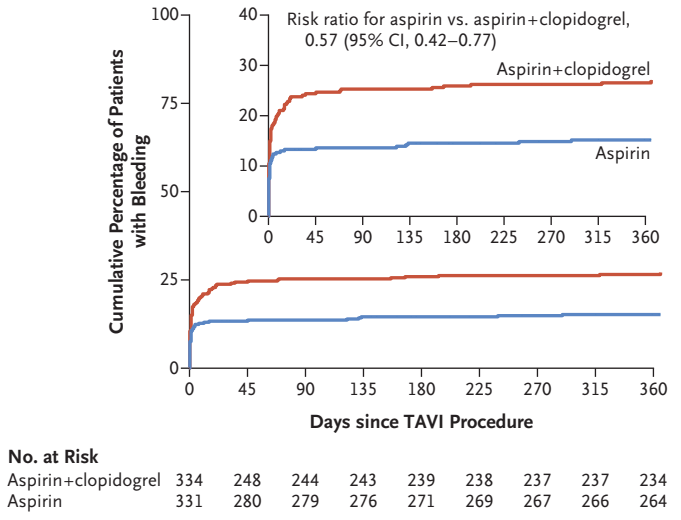

Figure 2. Primary Outcome of All Bleeding.

Shown are time-to-event Kaplan–Meier curves of one of the two primary outcomes (all bleeding, including minor, major, and life-threatening or disabling bleeding). The inset shows the same data on an enlarged y axis. Given the nonproportionality of the hazards during the follow-up period, a risk-ratio analysis with 95% confidence intervals was performed.

ence of −8.2 percentage points (95% CI, −14.9 to −1.5; P<0.001), and the criterion for the superiority of aspirin was met (risk ratio, 0.74; 95% CI, 0.57 to 0.95; P=0.04) (Table 2 and Fig. 3A).

A secondary composite 2 event (thromboembolic events, including death from cardiovascular causes, ischemic stroke, or myocardial infarction) occurred in 32 patients (9.7%) receiving aspirin alone and in 33 patients (9.9%) receiving aspirin plus clopidogrel. These results showed that aspirin alone was noninferior to combined therapy by the prespecified margin of 7.5 percentage points, with an absolute difference of −0.2 percentage points (95% CI, −4.7 to 4.3 for noninferiority; P=0.004), but it was not superior (risk ratio, 0.98; 95% CI, 0.62 to 1.55; P=0.93) (Table 2 and Fig. 3B). The results of the sensitivity analyses of the secondary outcomes were in the same direction as those of the primary analysis (Table S13). The results of a post hoc Cox proportional-hazards analysis of the secondary outcomes over a period of 3 months are shown in Table S14, and the results of post hoc analyses of the primary and secondary outcomes at 48 hours are shown in Table S15.

The incidences of the individual components of the secondary outcomes for each group were analyzed post hoc and are listed in Table 2, and post hoc time-to-event curves for death from cardiovascular causes and stroke from any cause are shown in Figures S5 and S6. Adjudicated causes of death are listed in Table S16. Stroke occurred in 17 patients (5.1%) receiving aspirin alone and in 19 patients (5.7%) receiving aspirin plus clopidogrel; these strokes were classified as disabling in 6 patients (1.8%) and 5 patients (1.5%), respectively. One cerebral hemorrhage occurred in a patient who was receiving aspirin plus clopidogrel, and no cerebral hemorrhages occurred in the aspirin-alone group. Symptomatic clinical aortic-valve thrombosis occurred in 3 patients (0.9%) in the aspirin-alone group and in 1 patient (0.3%) in the aspirin–clopidogrel group. In addition, an increased valve gradient (>10 mm Hg) was observed in 10 patients (3.0%) and 11 patients (3.3%), respectively. Secondary outcomes across prespecified subgroups are shown in Figures S7 and S8.

DISCUSSION

In this cohort of the POPular TAVI trial, we investigated antiplatelet therapy with aspirin alone as compared with aspirin plus clopidogrel for 3 months after TAVI in patients who did not have an indication for long-term oral anticoagulation. The incidences of the two primary outcome events of all bleeding and non–procedure-related bleeding at 1 year were lower among patients who received aspirin alone than among those who received aspirin plus clopidogrel for 3 months. This result was mainly driven by differences in the incidences of major bleeding. The incidence of severe procedure-related bleeding, defined as BARC type 4, was low (1.8%), but it was observed only in patients receiving aspirin plus clopidogrel. Aspirin alone was superior to aspirin plus clopidogrel with respect to the composite of bleeding or thromboembolic events (including death from cardiovascular causes, stroke, myocardial infarction, or non–procedure-related bleeding). Aspirin alone was noninferior, but not superior, to aspirin plus clopidogrel with respect to the composite of thromboembolic events including death from cardiovascular causes, ischemic stroke, or myocardial infarction.

The paucity of evidence with respect to antithrombotic and antiplatelet regimens in patients

undergoing TAVI has resulted in heterogeneity in the use of these drugs in clinical practice.[25,26] Guidelines recommend the use of clopidogrel in addition to aspirin for 3 to 6 months after TAVI in patients who do not have an indication for long-term use of oral anticoagulation.[8,9] A temporary intensified antiplatelet regimen with more than one drug is considered to mitigate the stent-mediated risk of thromboembolization before endothelialization of the valve has been completed. Endothelialization of the stent frame takes approximately 3 months, during which the observed risk of stroke is highest.[27] Thereafter, the incidence of stroke among these patients returns to that of the age-matched population.[28]

Intensifying the antiplatelet regimen comes at the cost of an increased bleeding risk. Major or life-threatening bleeding after TAVI occurred in up to 15% of patients at 1 year in several series.[4,6,7] This high bleeding risk might in part relate to characteristics of the typical population of elderly patients with aortic stenosis. Specific risk factors that may also contribute to bleeding risk include coexisting medical conditions, acquired von Willebrand factor deficiency, gastrointestinal angiodysplasia, and transient thrombocytopenia in the first days after TAVI.[29]

The ARTE trial showed a lower incidence of bleeding associated with aspirin alone than with aspirin plus clopidogrel at 3 months.[11] Our results were similar. The difference in bleeding events in our trial was driven by all three severity classifications including minor, major, and life-threatening bleeding, but it was most pronounced in major bleeding. Most bleeding occurred in the first month after TAVI, resulting in nonproportional hazards at 1 year, which led to the results of our trial being analyzed by relative risks rather than (as planned) by hazard ratios. Procedure-related bleeding occurred only in the aspirin–clopidogrel group. However, our definition of procedure-related bleeding was BARC type 4, indicating only severe bleeding and excluding most bleeding at the puncture site.

The incidences of thromboembolic events of stroke and myocardial infarction in the current trial were similar in the two groups at 12 months. These results are similar to data from smaller studies comparing aspirin alone with aspirin plus clopidogrel.[11-13] The incidence of symptomatic clinical aortic-valve thrombosis, a process reflecting a high thrombotic burden, was low and similar in the two groups. In addition, the incidence of increased valve gradients during follow-

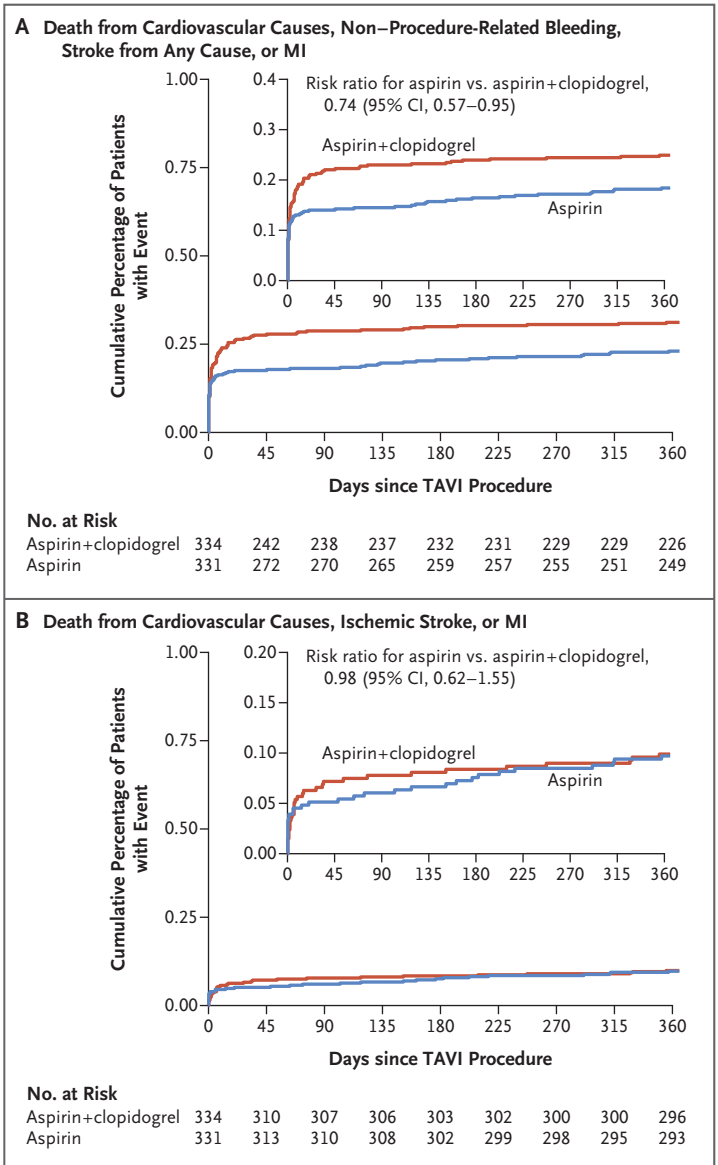

Figure 3. Secondary Outcomes.

Shown are time-to-event Kaplan–Meier curves for the secondary outcomes. One secondary outcome (Panel A) was a nonhierarchical composite of death from cardiovascular causes, all non–procedure-related bleeding, stroke from any cause, or myocardial infarction. The other secondary outcome (Panel B) was a nonhierarchical composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction. 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 risk-ratio analysis with 95% confidence intervals was performed. MI denotes myocardial infarction.

up, a finding that suggests valve hemodynamic deterioration, was similar in the two groups. One cerebral hemorrhage occurred in a patient who was receiving aspirin plus clopidogrel.

Our trial has several limitations. First, this was an open-label trial, and the patients and investigators were aware of the treatment assignments; however, the trial outcomes were adjudicated by a clinical-events committee, whose members were unaware of the trial-group assignments. Second, the trial was powered for the composite of bleeding or thromboembolic events rather than solitary thromboembolic events. Although there were no signs of a numerically higher incidence of thromboembolic events with aspirin alone than with aspirin plus clopidogrel, no clinical inferences should be drawn from these data. Third, the trial was designed to assess clinical outcomes and did not mandate computed tomographic imaging to detect subclinical valve thrombosis. Fourth, since VARC definitions do not distinguish between procedure-related bleeding and non–procedure-related bleeding, we used the BARC type 4 definition of procedure-related bleeding, with recognition that this definition was not designed for the TAVI population. Since most bleeding at the puncture site did not qualify as BARC type 4, these events were considered to be non–procedure-related bleeding and were counted separately.

Among patients who did not have indications for long-term use of oral anticoagulation and who were undergoing TAVI, aspirin alone was associated with a lower incidence of bleeding and a lower incidence of the composite of bleeding or thromboembolic events (including death from cardiovascular causes, stroke from any cause, myocardial infarction, or non–procedure-related bleeding) than was aspirin plus clopidogrel at 1 year of follow-up. Aspirin alone was noninferior, but not superior, to aspirin plus clopidogrel for the composite of thromboembolic events, including death from cardiovascular causes, ischemic stroke, or myocardial infarction.

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APPENDIX

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