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Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy

The SECURITY Randomized Clinical Trial

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ABSTRACT

BACKGROUND The optimal duration of dual antiplatelet therapy (DAPT) following second-generation drug-eluting stent (DES) implantation is still debated.

OBJECTIVES The aim of this study was to test the noninferiority of 6 versus 12 months of DAPT in patients undergoing percutaneous coronary intervention with second-generation DES.

METHODS The SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial was a 1:1 randomized, multicenter, international, investigator-driven, noninferiority study conducted from July 2009 to June 2014. Patients with a stable or unstable angina diagnosis or documented silent ischemia undergoing revascularization with at least 1 second-generation DES were eligible. The primary endpoint was a composite of cardiac death, myocardial infarction (MI), stroke, definite or probable stent thrombosis, or Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding at 12 months. The main secondary endpoint was a composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC type 2, 3, or 5 bleeding at 12 and 24 months.

RESULTS Overall, 1,399 patients were enrolled in the study and randomized to receive 6 months (n = 682) versus 12 months (n = 717) DAPT. The primary composite endpoint occurred, respectively, in 4.5% versus 3.7% (risk difference 0.8%; 95% confidence interval [CI]: −2.4% to 1.7%; p = 0.469) at 12 months. The upper 95% CI limit was lower than the pre-set margin of 2%, confirming the noninferiority hypothesis (p < 0.05). Moreover, no differences were observed in the occurrence of the secondary endpoint at 12 months (5.3% vs. 4.0%, difference: 1.2%; 95% CI: −1.0 to 3.4; p = 0.273) and between 12 and 24 months (1.5% vs. 2.2%, difference: −0.7%; 95% CI: −2.1 to 0.6; p = 0.289). Finally, no differences were observed in definite or probable stent thrombosis at 12 months (0.3% vs. 0.4%; difference: −0.1%; 95% CI: −0.7 to 0.4; p = 0.694) and between 12 and 24 months of follow-up (0.1% vs. 0%; difference: 0.1%; 95% CI: −0.1 to 0.4; p = 0.305).

CONCLUSIONS In a low-risk population, the noninferiority hypothesis of 6 vs. 12 months DAPT following second-generation DES implantation appears accepted for the incidence of cardiac death, MI, stroke, definite/probable stent thrombosis, and BARC type 3 or 5 bleeding at 12 months. (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy; NCT00944333) (J Am Coll Cardiol 2014;64:2086–97)
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Current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend administration of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation for a period of at least 12 months or for 6 to 12 months in patients not at high risk, respectively (1,2).

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However, randomized clinical trial (RCT) data supporting these recommendations are limited. RCTs comparing different durations of DAPT following DES implantation have not thus far demonstrated any benefit for prolonged DAPT (3,4). Park et al. (5) found no difference between extended DAPT (>12 months) versus aspirin monotherapy in reducing ischemic events or cardiac mortality after PCI with DES. The EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial demonstrated similar target vessel failure rates with 6-month versus 12-month DAPT following DES implantation (6). However, both studies were underpowered to draw any final conclusion regarding the safety of clopidogrel discontinuation after 12 months. The PRODIGY (PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY) trial demonstrated the noninferiority of 6 months versus 24 months of DAPT following the implantation of DES or bare-metal stents. Moreover, prolonged DAPT was associated with a higher incidence of bleeding events (3). Finally, the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice) trial, comparing 3 versus 12 months of DAPT following zotarolimus-eluting stent implantation in patients with stable coronary artery disease, reported that 3 months of DAPT was noninferior to 12 months in terms of the occurrence of major adverse cardiac events (7).

In the absence of appropriately powered RCTs evaluating new-generation DES in all-comer patients, the optimal duration of DAPT following new-generation DES is still debatable. Therefore, the aim of the SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial was to explore the clinical impact of 6-month versus 12-month DAPT in patients undergoing PCI using second-generation DES.

METHODS

STUDY DESIGN AND POPULATION. The SECURITY trial (NCT00944333) (8) was a prospective, randomized, noninferiority, investigator-driven, multicenter, international study. The study started in July 2009 (first patient enrolled). Because of logistic and economic constraints, in addition to evidence of slow enrollment and minimal differences in the rate of the primary endpoint between the 2 groups following an interim analysis, in December 2013, the study's steering committee, in agreement with the members of the data safety and monitoring board, decided to terminate patient inclusion and defined a common end date of June 15, 2014.

Inclusion criteria were symptoms of stable angina, as defined by Canadian Cardiovascular Society Classification, or unstable angina, as defined by Braunwald classification, or patients with documented silent ischemia, treated with at least 1 second-generation DES implanted in the target lesion in the past 24 h. Additional inclusion criteria were the presence of 1 or more de novo stenoses ≥70% in a native coronary artery, patient age over 18 years, no other DES implanted before the target procedure, and no bare-metal stent implanted in the 3 months before the target procedure. Exclusion criteria were patients treated for saphenous vein graft, in-stent restenosis, unprotected left main coronary artery, ST-segment elevation myocardial infarction (MI) in the 48 h before the procedure, or non-ST-segment elevation MI in the previous 6 months; left ventricular ejection fraction ≤30%; known hypersensitivity to aspirin, thienopyridines, heparin, limus analogs, cobalt, chromium, nickel, molybdenum, or contrast media; history of significant thrombocytopenia with aspirin or thienopyridines; chronic kidney disease (creatinine >2 mg/dl); women during pregnancy or during

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium
CI = confidence interval
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
RCT = randomized clinical trial
ST = stent thrombosis

Brescia, Italy; and the ##Policlinico Umberto I, Invasive Cardiology Department, Rome, Italy. Fondazione Evidence, a nonprofit organization based in Milan, Italy, supported this study, and received generous grants from Biosensors, Medtronic, and Terumo. Dr. Garbo is a consultant for Terumo and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Colombo and Chieffo are joint first authors.
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lactation; active bleeding or significant risk of bleeding; uncontrolled hypertension; life expectancy <24 months; and any medical condition that could preclude follow-up, as defined in the protocol. There was no limit to the number of lesions that could be treated.

TREATMENT PROTOCOL AND CLINICAL FOLLOW-UP. The trial protocol and informed consent forms were reviewed and approved by the ethical committee at each clinical site before initiating the investigation. All patients provided written informed consent. The study was conducted according to the principles of the Declaration of Helsinki, International Organization for Standardization Guidelines, and Good Clinical Practice Guidelines.

All patients in whom a target lesion met the eligibility criteria, who had at least 1 second-generation DES implanted, and who signed the informed consent were randomized to receive 6 versus 12 months DAPT. Randomization was performed by electronic case report, according to a 1:1 scheme, balanced within the center by blocks of 4. Second-generation DES used were the Endeavor Resolute (Medtronic, Minneapolis, Minnesota), Xience (Abbott Vascular, Abbott Park, Illinois), Promus (Boston Scientific, Natick, Massachusetts), Nobori (Terumo Corporation, Tokyo, Japan), and Biomatrix (Biosensors Europe, Morges, Switzerland).

Clopidogrel 75 mg per day for at least 3 days before the procedure or a pre-procedural loading dose of a minimum of 300 mg of clopidogrel was administered to patients not on chronic clopidogrel therapy. In the post-procedure period, 75 mg of clopidogrel for 6 or 12 months, according to randomization allocation, were administered. Conversely, post-procedure use of aspirin was prescribed indefinitely. Following

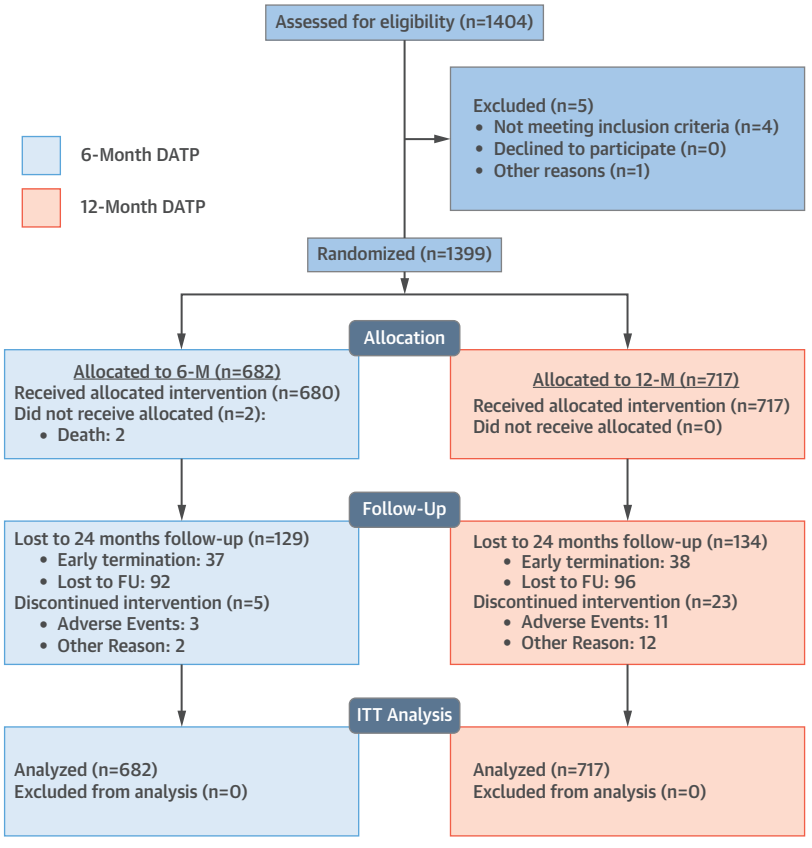


FIGURE 1 CONSORT Flow Diagram Showing the Study Design of the SECURITY Trial

6-M = 6 month; 12-M = 12 month; CONSORT = Consolidated Standards of Reporting Trials; DAPT = dual antiplatelet therapy; FU = follow-up; ITT = intention-to-treat; SECURITY = Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy.

their introduction to the market, the protocol was amended to allow the new antiplatelet compounds prasugrel and ticagrelor.

Follow-up assessments were done at 30 ± 5 days, at 180 ± 14 days (6 months), at 365 days (−14 days/+30 days), and at 730 days (−14 days/+30 days), by means of telephone call or outpatient clinical evaluation. No angiographic follow-up was mandatory in the protocol. The enrollment phase of the study was prematurely terminated for slow enrollment on December 10, 2013. All patients still in the study had a final visit/contact at a common end date (June 15, 2014). For this reason, the duration of follow-up depended on the study entry date. All investigators were strongly advised to rigorously follow each enrolled patient.

An independent clinical research organization (Mediolanum Cardio Research, Milan, Italy) performed data monitoring. Data collection was done using electronic case report forms, which were reviewed for accuracy and compared with source documents during onsite monitoring visits by Mediolanum Cardio Research. All centers were monitored, and source data verification was performed in 40% of patients. All events were evaluated and assigned by an independent clinical event committee composed of interventional cardiologists not participating in the study. For a list of the other principal site investigators, please refer to the Online Appendix of this article.

STUDY ENDPOINTS. The SECURITY trial's primary endpoint was a composite of cardiac death, MI, stroke, definite or probable stent thrombosis (ST), or Bleeding Academic Research Consortium (BARC) criteria type 3 or 5 bleeding at 12 months.

Cardiac death included any death without a noncardiac cause. Spontaneous MI was defined by the following criteria: cardiac enzyme elevation (troponin T/I or creatine kinase-myocardial band) above the upper normal limit associated with at least 1 ischemic symptom; development of Q waves on the electrocardiogram; electrocardiogram changes indicative of ischemia or coronary artery intervention.

Stroke was defined as any new neurological deficit lasting >24 h associated with neuroimaging evidence (computed tomography or magnetic resonance imaging).

TABLE 1 Baseline Clinical Characteristics of Patients Receiving 6 Months and 12 Months of DAPT

	6-Month DAPT (n = 682)	12-Month DAPT (n = 717)
Age, yrs	64.9 ± 10.2	65.5 ± 10.1
Female	153 (22.4)	166 (23.2)
Diabetes mellitus		
Oral therapy NIDDM	162 (23.9)	179 (25.2)
Insulin therapy IDDM	44 (6.5)	44 (6.2)
Hypertension	508 (74.5)	510 (71.1)
Dyslipidemia	446 (65.4)	436 (60.8)
Smoker status		
Never smoked	274 (40.5)	261 (37)
Previous smoker	239 (35.3)	238 (33.7)
Active smoker	139 (20.5)	172 (24.4)
Previous MI		
NSTEMI >48 h	65 (9.5)	71 (9.9)
STEMI >48 h	80 (11.7)	73 (10.2)
Previous PCI	132 (19.4)	116 (16.2)
Previous CABG	38 (5.6)	39 (5.4)
LVEF, %	56.3 ± 8.7	56.6 ± 8.2
Clinical presentation		
Stable angina	341 (61.6)	368 (61.6)
Unstable angina	213 (38.4)	229 (38.4)
Baseline medications		
Aspirin	616 (90.3)	621 (86.6)
Clopidogrel	301 (44.1)	305 (42.5)
Statin	489 (71.7)	494 (68.9)
Heparin	377 (55.3)	401 (55.9)
Glycoprotein IIb/IIIa inhibitors	25 (3.7)	30 (4.2)

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; IDDM = insulin-dependent diabetes mellitus; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NIDDM = non-insulin-dependent diabetes mellitus; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Baseline Lesion Characteristics of Patients Receiving 6 Months and 12 Months of DAPT

	6-Month DAPT (n = 682)	12-Month DAPT (n = 717)
Number of lesions		
1-vessel disease	383 (56.2)	424 (59.1)
2-vessel disease	221 (32.4)	210 (29.3)
3-vessel disease	77 (11.3)	82 (11.4)
4-vessel disease	1 (0.1)	1 (0.1)
Main branch lesion distribution		
Left anterior descending artery	402 (43)	423 (44)
Left circumflex artery	133 (14.3)	137 (14.2)
Diagonal artery	38 (4)	32 (3.3)
OM and RI arteries	106 (11.2)	118 (12.3)
Right coronary artery	206 (22)	207 (21.6)
Bifurcation	95 (13.9)	103 (14.4)
Baseline TIMI flow grade <3	140 (15.3)	145 (15.5)
AHA/ACC classification		
Class B	603 (64.5)	617 (64.3)
Class C	197 (21.1)	201 (21)
Baseline visual estimate		
Lesion length, mm	17.6 ± 9.8	18.1 ± 10.8
Reference vessel diameter, mm	2.9 ± 0.4	2.9 ± 0.4
Minimal lumen diameter, mm	0.6 ± 0.5	0.6 ± 0.6
Diameter stenosis	84 ± 10.1	84.4 ± 9.7

Values are n (%) or mean ± SD.

ACC = American College of Cardiology; AHA = American Heart Association; DAPT = dual antiplatelet therapy; OM = obtuse marginal; RI = ramus intermedius; TIMI = Thrombolysis In Myocardial Infarction.

Bleeding events and ST were classified according to BARC and Academic Research Consortium definitions, respectively (9,10).

Secondary endpoints were: 1) a composite of cardiac death, spontaneous MI, stroke, definite or probable ST, or BARC type 2, 3, or 5 bleeding at 12 and 24 months; 2) the cumulative incidence of the individual components of the primary endpoint at 12 and 24 months; 3) MI; 4) urgent target vessel revascularization (coronary artery bypass surgery or PCI because of acute cardiac ischemia); 5) bleeding events; and 6) all-cause mortality at 30 days and 6, 12, and 24 months.

TABLE 3 Procedural and In-Hospital Outcomes of Patients Receiving 6 Months and 12 Months of DAPT

	6-Month DAPT (n = 682)	12-Month DAPT (n = 717)
Femoral access	209 (30.6)	204 (28.5)
Radial access	465 (68.2)	502 (70)
Total number of treated vessels	825	844
Total number of treated lesions	934	960
Treated lesions		
1 lesion	484 (71)	519 (72.4)
>1 lesion	198 (29)	198 (27.6)
Average of treated lesions per patient	1.37 ± 0.65	1.34 ± 0.60
Total number of implanted stents	1117	1150
Stents implanted		
Per patient	1.64 ± 0.93	1.60 ± 0.91
Per lesion	1.19 ± 0.52	1.20 ± 0.50
Balloon pre-dilation (main branch)	512 (55.1)	537 (56.8)
Stent deployment pressure (main branch), atm	14.6 ± 2.8	14.7 ± 3.0
Balloon post-dilation (main branch)	484 (52)	499 (52.7)
IVUS-guided stent implantation	35 (3.7)	33 (3.4)
Mean stent length (main branch), mm	19.1 ± 7.2	19.0 ± 7.2
Mean stent size (main branch), mm	3.0 ± 1.7	2.9 ± 1.0
Total implanted drug-eluting stent type		
Endeavor Resolute stent	470 (42.1)	464 (40.3)
Nobori stent	283 (25.3)	314 (27.3)
Biomatrix stent	80 (7.2)	86 (7.5)
Promus stent	126 (11.3)	124 (10.8)
Xience stent	98 (8.8)	109 (9.5)
Total implanted bare-metal stent	16 (1.4)	11 (1)
Single stent success*	999 (93.5)	1,055 (95.6)
Stents in overlap	93 (9.9)	110 (11.5)
Final % stenosis = 0	834 (89.1)	852 (88.8)
Serious adverse events during hospitalization†	11 (1.6)	9 (1.3)
Therapy at discharge		
Aspirin	675 (99)	713 (99.4)
Clopidogrel	669 (98.1)	712 (99.3)
Prasugrel	2 (0.3)	1 (0.1)
Ticagrelor	4 (0.6)	2 (0.3)

Values are n (%) or mean ± SD. *Single stent success is defined as residual stenosis <30% and TIMI flow grade 3 by visual assessment. †Serious adverse events are defined as any untoward medical occurrences that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, or result in persistent or significant disability.

IVUS = intravascular ultrasounds; other abbreviations as in Table 2.

STATISTICAL ANALYSIS. The SECURITY trial was designed in 2009 and powered to test the noninferiority of the primary endpoint of 6 versus 12 months DAPT following second-generation DES implantation. The primary analysis was on the basis of the intention-to-treat population. In addition, a per-protocol population for primary analyses was considered by restricting the full analysis set to patients fulfilling all major inclusion criteria, treated according to the assigned group and completing the final assessment. If the sample size of the per-protocol population differed from that of the intention-to-treat population by more than 10%, the primary endpoint would have also been tested on the per-protocol patient subset.

The original protocol was sized to test the noninferiority of 6-month versus 12-month DAPT on the definite and/or probable ST rate and then amended to modify the primary endpoint into a combined efficacy and safety primary endpoint. To validate the estimated incidence of the primary endpoint, an independent statistician conducted a safety interim analysis when the first 1,000 randomized patients completed 12 months of follow-up. Results of the interim analysis were evaluated by the data monitoring committee. The incidence of the primary endpoint at 12 months after randomization was 4.5%. At the time of the blind interim analysis, the sample size was therefore recalculated, taking the actual proportion of the primary endpoint into account. Considering this low primary endpoint incidence and keeping the absolute noninferiority margin of 2.0% of the difference in the event proportions between the 6-month and the 12-month treatments, a power of 0.80 and a significance level of 0.05 (1-tailed), 1,370 patients were estimated to be needed in each group.

Descriptive statistics (arithmetic mean, median as indicated, minimum and maximum, and standard deviation) were calculated for continuous variables. Comparisons for continuous variables were performed by means of unpaired Student *t* tests for normal distributions or Mann-Whitney tests for nonnormal distributions. Absolute frequencies and percentages were obtained for qualitative variables. Qualitative variables were compared by Pearson chi-square tests for contingency tables with at least 5 expected cases per cell or by Fisher exact test for contingency tables with fewer than 5 expected cases per cell. For the main statistical analyses of primary and secondary endpoints, 95% confidence intervals (CIs) are reported. Survival curves were computed by the Kaplan-Meier method and compared using log-rank tests. A Cox proportional hazard multivariable regression analysis was also done. All variables with

statistically significant results from univariable analysis and those of clinical importance from previous reports were included in the multivariable model.

A 1-sided p value <0.05 was considered statistically significant. An independent statistician (B.M.C.) performed all analyses using Statistical Analysis System version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Because of enrollment difficulties, only 1,399 patients were randomized in the study and assigned to 6 (n = 682) versus 12 (n = 717) months of DAPT (Figure 1). Baseline clinical and angiographic characteristics were well balanced between the 2 study groups (Tables 1 and 2).

The mean age of the overall population was 65.2 ± 10.1 years; 31% of patients had diabetes mellitus, 5.5% had previous coronary artery bypass graft, 17.7% had previous PCI; 20.7% had a clinical history of previous MI; and 61.6% had a clinical presentation of stable angina.

Regarding baseline lesion and angiographic characteristics, 299 patients had more than 1-vessel disease (43.8%). Radial access was used in the majority of patients (n = 967; 69.1%). According to the American College of Cardiology/American Heart Association classification (11), 85% of patients had a class B or C lesion. The left anterior descending coronary artery was the target vessel for revascularization in 825 patients (43.6%). Bifurcation lesions were treated in 198 patients (14.2%). Among patients with a second-generation DES implanted, 934 (41.2%) received an Endeavor Resolute, 597 (26.3%) a Nobori, 250 (11%) a Promus, 207 (9.1%) a Xience, and 166 (7.3%) a Biomatrix stent. Procedural and hospital outcomes are reported in Table 3.

Follow-ups at 12 and 24 months were successfully performed in 1,260 (91%) and 1,136 (82.1%) patients, respectively. Because of early study termination, the average duration in the study was 643.17 ± 212.13 and 640.21 ± 202.18 days for the 6-month and 12-month groups, respectively.

Medications used during the trial are reported in Table 4. At the 12-month follow-up (primary endpoint), DAPT use was 33.8% in the 6-month group and 96.1% in the 12-month group. At 24 months, 96.5% of patients in the 6-month group and 97.9% in the 12-month group were on aspirin monotherapy.

PRIMARY AND SECONDARY ENDPOINTS. There was at least 1 occurrence of the primary composite endpoint by 12 months in 31 patients in the 6-month DAPT group (4.5%; 95% CI: 2.9 to 6.1) and 27 patients in the 12-month DAPT group (3.7%; 95% CI: 2.3 to 5.1; p = 0.469) (Table 5). There was a 0.8% (95% CI: −2.4 to 1.7) difference in occurrence of the primary endpoint between the 6-month and 12-month groups. The upper limit of the 95% CI was lower than the pre-set margin of 2%, confirming the noninferiority hypothesis (p < 0.05). The Central Illustration shows estimates of the probability of nonoccurrence of the primary endpoint in the study groups at 12 months and between 6 and 12 months (panels A and B, respectively).

No statistically significant difference in the secondary composite endpoints at 12 months and between 12 and 24 months was observed between the 2 study groups (5.3% vs. 4% difference, respectively: 1.2%, 95% CI: −1.0 to 3.4; p = 0.273; and 1.5% vs. 2.2%, difference: −0.7%, 95% CI: −2.1 to 0.6, p = 0.289). Figure 2 shows estimates of the probability of nonoccurrence of the secondary endpoint in the study groups.

Rates of occurrence of the individual components of the primary endpoint are reported in Table 5. No differences in MI were observed at 30 days (1.2% vs. 1.4%; difference: −0.6%; 95% CI: −1.9 to 0.6; p = 0.328), between 1 and 6 months (0.9% vs. 0.4%; difference: 0.4%; 95% CI: −0.3 to 1.3; p = 0.280), 6 and 12 months (0.3% vs. 0.3%; difference: 0.0%; 95% CI: −0.5 to 0.6 p = 0.960), and 12 and 24 months (0.9% vs. 0.7%; difference: 0.1%; 95% CI: −0.7 to 1.0; p = 0.681). Rates of urgent target vessel revascularization (coronary artery bypass surgery or repeat PCI) were also similar at the different time points (30 days, 0.2% vs. 0.1%, difference: 0.1%, 95% CI: −0.4 to 0.4, p = 0.971; 6 months, 0.5% vs. 0.1%, difference:

TABLE 4 Medication Use During Trial in Patients Receiving 6 Months and 12 Months of DAPT

	6-Month DAPT (n = 682)	12-Month DAPT (n = 717)
DAPT therapy at 6 months		
Clopidogrel only	2 (0.3)	6 (0.9)
ASA only	3 (0.5)	5 (0.7)
ASA + clopidogrel	618 (97.3)	655 (97.6)
ASA + prasugrel	8 (1.3)	2 (0.3)
ASA + ticagrelor	4 (0.6)	3 (0.4)
DAPT therapy at 12 months		
Clopidogrel only	11 (1.8)	8 (1.2)
ASA only	392 (63.6)	13 (2.0)
ASA + clopidogrel	208 (33.8)	622 (96.1)
ASA + prasugrel	0	1 (0.2)
ASA + ticagrelor	0	1 (0.2)
Drug therapy at 24 months		
Aspirin	525 (96.5)	563 (97.9)

Values are n (%).
ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy.

TABLE 5 Clinical Outcomes in Patients Receiving 6 Months and 12 Months of DAPT*

Outcome	6-Month DAPT (n = 682)	12-Month DAPT (n = 717)	Difference (95% CI)	p Value
Primary endpoint				
Primary efficacy composite endpoint†				
6–12 months	8 (1.2)	5 (0.7)	0.5% (−1.5 to 0.7)	0.356
12 months	31 (4.5)	27 (3.7)	0.8% (−2.4 to 1.7)	0.469
Secondary endpoints				
Secondary efficacy composite endpoint‡				
12 months	36 (5.3)	29 (4)	1.2% (−1.0 to 3.4)	0.273
12–24 months	10 (1.5)	16 (2.2)	−0.7% (−2.1 to 0.6)	0.289
Cardiac mortality				
30 days	4 (0.6)	0	0.6% (−0.0 to 1.2)	0.040
30 days–6 months	1 (0.2)	2 (0.3)	−0.1% (−0.6 to 0.3)	0.592
6–12 months	0	1 (0.2)	−0.1% (−0.4 to 0.1)	0.329
12 months	5 (0.7)	3 (0.4)	0.3% (−0.4 to 1.1)	0.435
12–24 months	1 (0.2)	3 (0.5)	−0.3 (−0.8 to 0.3)	0.341
24 months	6 (0.9)	6 (0.8)	−0.0% (−0.9 to 1.0)	0.931
MI				
30 days	8 (1.2)	10 (1.4)	−0.6% (−1.9 to 0.6)	0.328
30 days–6 months	6 (0.9)	3 (0.4)	0.4% (−0.3 to 1.3)	0.280
6–12 months	2 (0.3)	2 (0.3)	0% (−0.5 to 0.6)	0.960
12 months	16 (2.3)	15 (2.1)	0.2% (−1.2 to 1.7)	0.747
12–24 months	5 (0.9)	4 (0.7)	0.2% (−0.7 to 1)	0.681
24 months	21 (3.1)	19 (2.6)	0.4% (−1.3 to 2.1)	0.630
Stroke				
30 days	1 (0.2)	0	0.1% (−0.1 to 0.4)	0.305
30 days–6 months	2 (0.3)	2 (0.3)	0.0% (−0.5 to 0.6)	0.960
6–12 months	3 (0.5)	0	0.4% (−0.1 to 0.9)	0.075
12 months	6 (0.9)	2 (0.3)	0.6% (−0.2 to 1.3)	0.136
12–24 months	0	1 (0.2)	−0.1% (−0.4 to 0.1)	0.329
24 months	6 (0.9)	3 (0.4)	0.5% (−0.4 to 1.3)	0.280
Definite or probable stent thrombosis				
30 days	2 (0.3)	1 (0.1)	0.1% (−0.3 to 0.6)	0.534
30 days–6 months	0	2 (0.3)	−0.3 (−0.7 to 0.1)	0.167
6–12 months	0	0	–	–
12 months	2 (0.3)	3 (0.4)	−0.1% (−0.7 to 0.4)	0.694
12–24 months	1 (0.2)	0	0.1% (−0.1 to 0.4)	0.305
24 months	3 (0.4)	3 (0.4)	0.0% (−0.7 to 0.7)	0.951
Type 3 or 5 BARC bleeding				
30 days	2 (0.3)	2 (0.3)	0.0% (−0.5 to 0.5)	0.960
30 days–6 months	1 (0.2)	4 (0.6)	−0.4% (−1.0 to 0.2)	0.197
6–12 months	1 (0.2)	2 (0.3)	−0.1% (−0.6 to 0.3)	0.592
12 months	4 (0.6)	8 (1.1)	−0.5% (−1.4 to 0.4)	0.283
12–24 months	1 (0.2)	0	0.1% (−0.1 to 0.4)	0.305
24 months	5 (0.7)	8 (1.1)	−0.4% (−1.4 to 0.6)	0.455
Urgent TVR (PCI or CABG)				
30 days	1 (0.2)	1 (0.1)	0.1% (−0.4 to 0.4)	0.971
30 days–6 months	3 (0.5)	1 (0.1)	0.3% (−0.3 to 0.9)	0.292
6–12 months	0	1 (0.2)	−0.1% (−0.4 to 0.1)	0.329
12–24 months	0	1 (0.2)	−0.1% (−0.4 to 0.1)	0.329
Possible stent thrombosis				
6 months	0	0	–	–
24 months	0	0	–	–
All bleeding				
30 days	2 (0.3)	2 (0.3)	0.0% (−0.6 to 0.6)	0.958
30 days–6 months	2 (0.3)	4 (0.6)	−0.2% (−0.9 to 0.4)	0.450
6–12 months	1 (0.2)	2 (0.3)	−0.1% (−0.6 to 0.3)	0.593
12–24 months	1 (0.2)	2 (0.3)	−0.1% (−0.6 to 0.3)	0.593
All-cause mortality				
30 days	4 (0.6)	0	0.6% (−0.0 to 1.1)	0.040
30 days–6 months	4 (0.6)	6 (0.9)	−0.1% (−0.9 to 0.7)	0.795
6–12 months	0	2 (0.3)	−0.1% (−0.7 to 0.5)	0.695
12–24 months	6 (1.1)	7 (1.2)	−0.4% (−1.3 to 0.5)	0.409

Continued in the next column

Values are n (%). *Event rates based on Kaplan-Meier estimates. The p values were calculated by log-rank test. The confidence interval for differences in event rates has not been calculated in cases of no clinical events in either group. †Defined as a clinical composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC type 3 or 5 bleeding at 12 months (adjudicated events). ‡Defined as a clinical composite of cardiac death; MI; stroke; definite or probable stent thrombosis; or BARC type 2, 3, or 5 bleeding at 12 and 24 months (adjudicated events).

BARC = Bleeding Academic Research Consortium; CI = confidence interval; TVR = target vessel revascularization; other abbreviations as in Table 1.

0.3%, 95% CI: −0.3 to 0.9, p = 0.292; 12 months, 0% vs. 0.2%, difference: −0.1%, 95% CI: −0.4 to 0.1, p = 0.329; 24 months, 0% vs. 0.2%, difference: −0.1%, 95% CI: −0.4 to 0.1, p = 0.329). Two ST cases occurred in the 6-month group and 3 cases occurred in the 12-month group within 12 months of follow-up (0.3% [95% CI: 0.0 to 1.1] vs. 0.4% [95% CI: 0.1 to 1.2]; difference: −0.1%; 95% CI: −0.7 to 0.4; p = 0.694); all of these occurred within 6 months from the index procedure, while the patients were on DAPT. Conversely, 1 case occurred in the 6-month group between 12 and 24 months of follow-up (0.2% vs. 0%; difference: −0.1%; 95% CI: −0.1 to 0.4; p = 0.305): this patient had stopped all antiplatelet medications. Of note, no possible ST cases occurred during the clinical follow-up period. Finally, no differences in stroke incidence at 12 months and between 12 and 24 months were observed between the 2 groups (respectively, 0.9% vs. 0.3%, difference: 0.6%, 95% CI: −0.2 to 1.3, p = 0.136; and 0% vs. 0.1%, difference: −0.1%, 95% CI: −0.4 to 0.1, p = 0.329).

Only 6 cases of any bleeding occurred in the 6-month group and 10 cases in the 12-month group. No differences were noted at each specific time period between the 2 groups (30 days, 0.3% vs. 0.3%, difference: 0.0%, 95% CI: −0.6 to 0.6, p = 0.958; 30 days to 6 months, 0.3% vs. 0.6%, difference:

−0.2%, 95% CI: −0.9 to 0.4, p = 0.450; 6 to 12 months, 0.2% vs. 0.3%, difference: −0.1%, 95% CI: −0.6 to 0.3, p = 0.593; and 12 to 24 months, 0.2% vs. 0.3%, difference: −0.1%, 95% CI: −0.6 to 0.3, p = 0.593). BARC 3 or 5 bleeding occurred in 4 patients (0.6%) in the 6-month group and 8 patients in the 12-month group (1.1%) at 12 months of follow-up (difference: −0.5%; 95 CI: −1.4% to 0.4%; p = 0.283) and in 1 patient in the 6-month group between 12 and 24 months of follow-up.

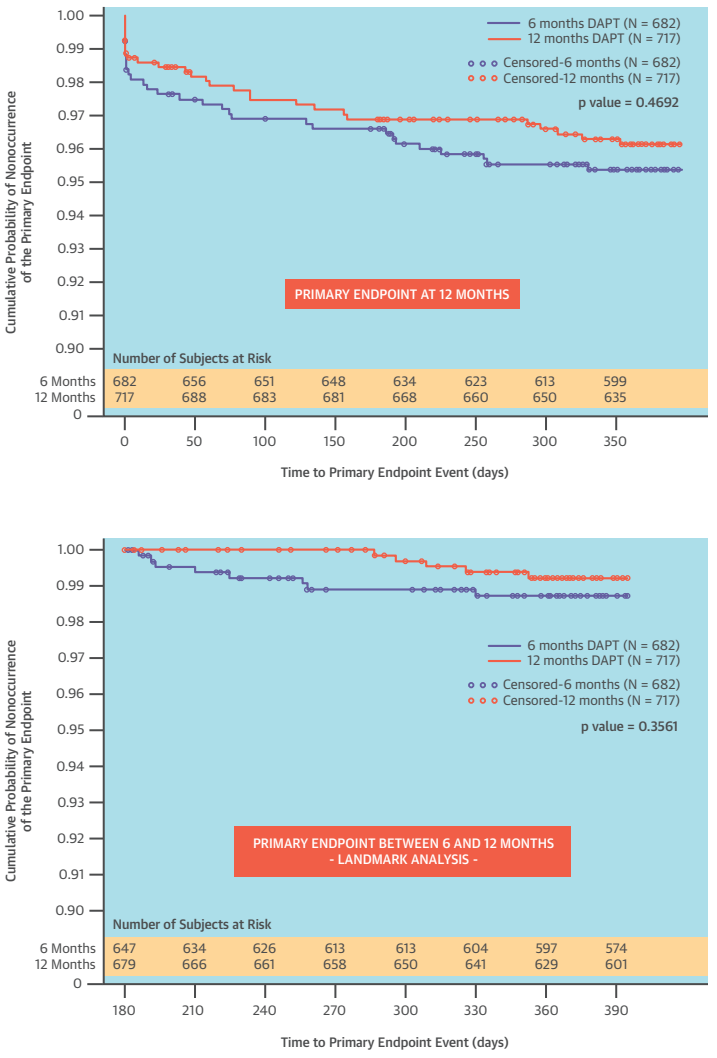
Finally, no significant differences in all-cause and cardiovascular mortality were observed at the different time points between the 6-month and 12-month DAPT regimens (Table 5).

PREDICTORS OF PRIMARY ENDPOINT AT MULTIVARIABLE ANALYSIS. By Cox regression multivariable analysis, predictors of the primary endpoint were (Table 6): age ≥75 years (hazard ratio [HR]: 2.211; 95% CI: 1.234 to 3.962; p < 0.007), stent type (Endeavor Resolute vs. Biomatrix/Xience/Promus, HR: 2.336; CI: 1.051 to 5.190; p = 0.019), mean number of stents (for each unit increase; HR: 1.410; 95% CI: 1.128 to 1.741; p = 0.002), mean stent length (for each 5-U increase, HR: 1.383; 95% CI: 1.135 to 1.685; p = 0.001), and mean stent size (for each 2.5-U increase; HR: 1.326; 95% CI: 1.106 to 1.590; p = 0.002). Finally, DAPT 6 versus 12 months was not a significant independent predictor of the primary endpoint (HR: 1.272; 95% CI: 0.754 to 2.145; p = 0.367).

DISCUSSION

The main results of the SECURITY trial are as follows:

1. In our study population undergoing PCI with second-generation DES, 6 months of DAPT appeared noninferior to a 12-month regimen with respect to the primary composite endpoint of cardiac death, MI, stroke, definite or probable ST, or BARC type 3 or 5 bleeding at 12 months of clinical follow-up.
2. Multivariable analysis found age ≥75 years, stent type used, mean number of stents implanted, mean stent length, and mean stent size as significant independent predictors of the primary endpoint. Of note, following multivariable adjustment, results for 6 versus 12 months of DAPT were not significant.
3. With respect to incidence of the secondary composite endpoints defined by the study protocol, 6 months DAPT appeared noninferior to 12 months.



Colombo, A. et al. J Am Coll Cardiol. 2014; 64(20):2086–97.

CENTRAL ILLUSTRATION Kaplan-Meier Estimates of the Probability of Nonoccurrence of the Primary Endpoint

There is no difference in the occurrence of the primary endpoint at 12 months **(upper panel)** and between 6 and 12 months **(lower panel)** for patients assigned to 6-month versus patients assigned to 12-month DAPT. **Blue line** = 6-month DAPT group; **salmon line** = 12-month DAPT group. DAPT = dual antiplatelet therapy.

Introduction of DES in clinical practice drastically changed the efficacy of PCI by reducing the need for repeated target lesion and target vessel revascularization (12,13). However, several retrospective analyses from real-world registries and clinical trials reported a higher incidence of late and very late ST with first-generation DES use compared with bare-metal stents (14–16). The pathological basis of late clinical events

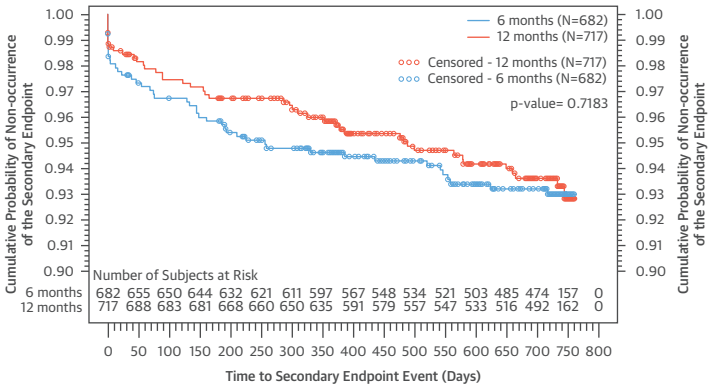


FIGURE 2 Kaplan-Meier Estimates of the Probability of Nonoccurrence of the Secondary Endpoint

Nonoccurrence of the secondary endpoint in the 6-month and 12-month DAPT groups is shown. There is no difference in freedom from occurrence of the primary and secondary endpoints for patients assigned to 6-month versus patients assigned to 12-month DAPT. **Blue line** = 6-month DAPT group; **salmon line** = 12-month DAPT group. DAPT = dual antiplatelet therapy.

with DES seems related mainly to delayed vascular healing and local stent strut hypersensitivity (17). Concerns regarding ST focused the scientific community's attention on the optimal DAPT duration following DES implantation. Several studies initially suggested potential benefits of long-term DAPT to prevent late thrombotic events (18). Moreover, several observational studies found a significant association between early DAPT discontinuation and occurrence of thrombotic complications following DES implantation (14,19–22). Current guideline recommendations for DAPT following PCI arose from these initial observations. The American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend, in patients who have undergone DES-PCI, a DAPT duration of 12 months or 6 to 12 months in patients not at high risk for acute coronary syndrome and not at high risk of bleeding, respectively (1,2). Although these initial observations were done in the first-generation DES era, guideline recommendations for DAPT were extended to newer-generation DES, notwithstanding the lack of supporting evidence from RCTs.

Before our study, several randomized trials demonstrated the safety and efficacy of reduced-term versus prolonged-term DAPT. The REAL-LATE (Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated With Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events) and the ZEST-LATE (Evaluation of the Long-Term Safety After Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions-Late Coronary Arterial Thrombotic Events) trials demonstrated no significant benefit in preventing major adverse cardiovascular events with clopidogrel continuation compared with clopidogrel discontinuation after 12 months in patients with DES implantation. Similarly, the DES-LATE (Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation) trial explored the use of DAPT for an additional 24 months in patients who were on 12-month DAPT without complications. Again, prolonged DAPT did not reduce major adverse cardiovascular events compared with aspirin alone (23). Moreover, the EXCELLENT trial reported the noninferiority of 6 months versus 12 months of DAPT in preventing major adverse cardiovascular events following everolimus-eluting or sirolimus-eluting stent implantation. However, the EXCELLENT study was designed to demonstrate the noninferiority of target vessel failure (cardiac death, MI, or ischemia-driven revascularization), the noninferiority margin was wide, and the study was underpowered for death or MI as the primary endpoint. Additionally, the PRODIGY trial demonstrated the noninferiority of 6 months of DAPT compared with 24 months, in terms of death, ST, MI, or cerebrovascular accident in patients who received a balanced mixture of DES or bare-metal stents.

Several reports suggested the association of second-generation DES with reduced rates of very late ST, compared with first-generation DES (24–26). However, the optimal DAPT duration following second-generation DES implantation is still debated. A pre-specified subanalysis from the PRODIGY trial reported reduced ST rates with paclitaxel-eluting stents and a prolonged (24-month) DAPT regimen

TABLE 6 Predictors of the Primary Endpoint at Multivariable Analysis

Variables in the Model*	HR	95% CI	p Value
Age ≥75 yrs	2.211	1.234–3.962	0.007
Endeavor Resolute vs. Biomatrix/Xience/Promus	2.336	1.051–5.190	0.019
Mean number of stents (for each unit increase)	1.410	1.128–1.741	0.002
Mean stent length (for each 5-U increase)	1.383	1.135–1.685	0.001
Mean stent size (for each 2.5-U increase)	1.326	1.106–1.590	0.002
Diabetes mellitus			0.069
NIDDM vs. none	0.895	0.464–1.729	
IDDM vs. none	2.349	1.080–5.106	
DAPT 6- vs. 12-month	1.272	0.754–2.145	0.367
Female	1.596	0.897–2.838	0.111

*Cox model fitted on 1,360 patients with 57 primary events because of missing values.
HR = hazard ratio; other abbreviations as in Tables 1 and 5.

(27). Conversely, no differences in ST between 24-month and 6-month DAPT were observed with the other stent types. In addition, the RESET trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following zotarolimus-eluting stent implantation) demonstrated noninferiority for the primary composite endpoint (cardiac death, MI, ST, target vessel revascularization, or bleeding) at 1 year with 3 months of DAPT following Endeavor zotarolimus-eluting stent implantation compared with 12 months of DAPT after other DES use (4). A substudy from the PROTECT (Patient Related OuTcomes with Endeavor vs. Cypher stenting Trial) study found a strong interaction among stent type used, DAPT duration, and ST events. Specifically, very late ST events (>1 year) with sirolimus-eluting stents were related to DAPT discontinuation, whereas no differences in very late ST events with Endeavor zotarolimus-eluting stents were observed in the presence of DAPT (28). Finally, the OPTIMIZE noninferiority trial, comparing 3 versus 12 months of DAPT in 3,119 patients with stable coronary artery disease undergoing PCI with zotarolimus-eluting stents, first demonstrated the noninferiority of 3 months versus 12 months of DAPT using 1 specific type of second-generation DES.

Our study, suggesting the noninferiority of 6 months versus 12 months of DAPT following implantation of different types of second-generation DES in the primary study endpoint, contributes to the evidence that reduced DAPT is safe and effective with currently used DES in patients with the characteristics of our study population.

One of the most evident results of our study, compared with previous studies, is the low rate of adverse cardiovascular events at clinical follow-up. This is consistent with improvements related to the introduction of second-generation DES in clinical practice and the low-risk clinical and lesion profiles of the patients in our study (**Tables 1 and 2**). Consequently, at 1-year clinical follow-up, the overall primary composite endpoint and definite or possible ST rates were 4.5% and 3.7%, respectively, in the 6-month versus the 12-month group. Definite or possible ST rates observed in our study compared favorably with reported rates in the OPTIMIZE trial (using zotarolimus-eluting stents) of 0.8% at 1 year in both the 3-month and 12-month DAPT groups. Our study also compared favorably in this respect to the PRODIGY and EXCELLENT trials, which reported ST incidences of 1.5% and 0.9%, respectively, in the 6-month DAPT group. However, almost 74% of patients in the PRODIGY trial and 50% of patients in the EXCELLENT trial presented with an acute coronary syndrome. Conversely, our results are very similar to those of the RESET trial, which reported a 1-year ST incidence of 0.2% using the Endeavor zotarolimus-eluting stent plus 3 months of DAPT, and 0.3% using sirolimus-eluting, everolimus-eluting, or Resolute zotarolimus-eluting stent plus 12 months of DAPT. Similar to our study, the majority of RESET trial patients (85%) presented with stable or unstable angina.

Following multivariable adjustment, DAPT duration did not independently predict the primary endpoint in our study, further demonstrating the safety of a 6-month regimen. By contrast, factors reflecting the burden of coronary artery stenting (mean stent length, size, and number of stents implanted) were strong independent primary endpoint predictors, even with second-generation DES. Independent of DAPT duration, patients in whom multiple smaller or longer stents are implanted may benefit from high-potency P2Y inhibitors. Finally, as expected, age ≥75 years was another independent predictor of mortality. Because of the low event rates and the implantation of an Endeavor Resolute DES in >40% of patients, we cannot draw conclusions regarding the correlation between primary endpoint occurrence and a specific stent type. The association of increased events with Resolute stent implantation should be interpreted cautiously, as the low event number, combined with the high Resolute implantation rate, increases the probability that this is due to chance.

Of note, our study did not find any difference in bleeding events between reduced and prolonged DAPT. The PRODIGY trial reported a significantly higher risk of hemorrhagic complications in patients allocated to the 24-month DAPT cohort. Most probably, our study population's low risk profile and the 12-month DAPT duration were both insufficient to increase the hazard of bleeding events.

STUDY LIMITATIONS. Our study has several important limitations to consider:

1. Considering the low event rates observed during the trial, our study was underpowered to demonstrate any difference in single outcomes such as cardiac death, MI, ST, bleeding, or stroke. Studies specifically designed to demonstrate differences in single outcomes are currently ongoing (NCT00977938 and NCT00661206).
2. Our study population included patients with reasonably low-risk clinical profiles; therefore, generalization of our results to patients at moderate or high risk cannot be made. Moreover, the lesion risk profile of our study population had

low prevalence of bifurcation lesions and complex lesions. Our conclusions are therefore applicable to a subset of patients at low risk and relatively simple coronary anatomy.

3. The primary endpoint rate was lower than expected at the interim analysis (4.5% vs. 6%). Therefore, keeping all the other assumptions of the study design unchanged, the sample size was reduced from 3,600 (originally expected) to 2,800. The actual number of 1,399 included patients allowed declaration of noninferiority, given the superimposable occurrence of the primary endpoint in the 2 groups. Because of the reduced number of enrolled patients, compared with the original sample size, and the small difference in primary endpoint occurrence between the 2 study groups, the power is lower than originally planned (around 60% following recalculation). Nevertheless, the upper limit of the CI is lower than the preset margin of 2%, confirming the noninferiority hypothesis.
4. As a practical approach, we randomized patients at the time of the index procedure, rather that at 6 months, which should be considered a debatable limitation.
5. Almost 34% of patients in the 6-month group continued DAPT after 6 months. As this could have affected our results, the per-protocol analysis excluding these patients (948 excluded patients with 32 primary events) confirmed the results of the intention-to-treat analysis.
6. Although stent type appeared to be a predictor of the primary endpoint, because several types were allowed by the study protocol, and because the majority of patients were treated with the Endeavor Resolute DES, we cannot determine the real association between the stent type used and occurrence of the primary endpoint.
7. We cannot exclude that the low incidence of major adverse cardiovascular events in our trial could have been due to under-reporting of adverse events by the participating centers, notwithstanding the continuous monitoring of the sites by an independent clinical research organization. However, source data verification was performed in 40% of patients.

CONCLUSIONS

In a low-risk population, as in this study, the noninferiority hypothesis for 6 versus 12 months of DAPT following second-generation DES implantation appears accepted regarding the incidence of cardiac death, MI, stroke, definite or probable ST, or BARC type 3 or 5 bleeding at 12 months.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The duration of DAPT following deployment of DES in patients not considered at high risk of stent thrombosis varies from 6 to >12 months according to American College of Cardiology/American Heart Association and European Society of Cardiology guidelines.

COMPETENCY IN PATIENT CARE: The results of the SECURITY trial support withdrawal of DAPT after 6 months in low-risk patients undergoing deployment of second-generation DES.

TRANSLATIONAL OUTLOOK: Additional studies are needed to define the optimum duration of DAPT in patients at higher risk of stent thrombosis.

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KEY WORDS coronary artery disease, percutaneous coronary intervention, platelet aggregation inhibitors, prospective studies, stents, thrombosis

APPENDIX For a list of the other principal site investigators, please see the online version of this article.