

6- Versus 24-Month Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stents in Patients Nonresistant to Aspirin



The Randomized, Multicenter ITALIC Trial

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ABSTRACT

BACKGROUND The currently recommended duration of dual antiplatelet therapy (DAPT) in drug-eluting stent (DES) recipients is 12 months to reduce the risk of late stent thrombosis, particularly in those with acute coronary syndrome (ACS).

OBJECTIVES This study hypothesized that antiplatelet treatment with DAPT for 6 months may be noninferior to 24-month DAPT in aspirin-sensitive patients.

METHODS A multicenter, randomized study assigned patients undergoing implantation of everolimus-eluting stents with confirmed nonresistance to aspirin to receive 6- or 24-month DAPT. The primary endpoint was a composite of death, myocardial infarction, urgent target vessel revascularization, stroke, and major bleeding at 12 months post-stenting.

RESULTS A total of 2,031 patients were enrolled in 70 European and Middle Eastern centers. The trial was prematurely terminated due to recruitment problems, leaving 941 patients randomized to 24-month DAPT and 953 to 6-month DAPT. The 2 treatment groups had similar baseline and procedural characteristics. There was no significant difference in the primary endpoint (24-month: 1.5% vs. 6-month: 1.6%; $p = 0.85$). Noninferiority was demonstrated for 6- versus 24-month DAPT, with an absolute risk difference of 0.11% (95% confidence interval: -1.04% to 1.26% ; p for noninferiority = 0.0002). There were no significant differences in stent thrombosis or bleeding complications. In the 792 (44%) high-risk patients with ACS, primary and secondary endpoints did not significantly differ (hazard ratio: 1.7 [95% confidence interval: 0.519 to 6.057; $p = 0.361$]).

CONCLUSIONS Rates of bleeding and thrombotic events were not significantly different according to 6- versus 24-month DAPT after PCI with new-generation DES in good aspirin responders. (Is There A Life for DES After Discontinuation of Clopidogrel [ITALICplus]; [NCT01476020](https://doi.org/10.1016/j.jacc.2014.11.008)) (J Am Coll Cardiol 2015;65:777-86) © 2015 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS****ACS** = acute
coronary syndrome(s)**BMS** = bare-metal stent(s)**DAPT** = dual
antiplatelet therapy**DES** = drug-eluting stent(s)**MI** = myocardial infarction**PCI** = percutaneous coronary
intervention**TVR** = target vessel
revascularization

Randomized trials have demonstrated that coronary drug-eluting stents (DES) reduce angiographic restenosis and emergency target vessel revascularization (TVR) compared with bare-metal stents (BMS) (1-4). However, concerns have been generated by trials showing an increased propensity for late and very late stent thrombosis (ST) in first-generation DES compared with BMS (5-7).

SEE PAGE 787

Second-generation DES show improved efficacy and safety, with several studies reporting significant decreases in mortality and myocardial infarction (MI) (8-13) compared with first-generation DES and BMS. Specifically, the risk of definite or probable ST is on average 50% lower with newer-generation DES versus first-generation stents (10-13).

Several randomized and observational trials of these newer DES suggest that they permit a shorter duration of dual antiplatelet therapy (DAPT) (14-20). Current guidelines recommend 6 months of DAPT post-DES in stable patients (21) and 1 year of DAPT in patients with acute coronary syndrome (ACS) (21,22). However, when our trial began, the guidelines (22) recommended 12 months of DAPT regardless of the clinical situation. A randomized, multicenter trial was, therefore, initiated to assess the effect of 6 versus 24 months of DAPT on medium-term clinical outcomes after coronary intervention in a real-world clinical population receiving second-generation DES. To be sure that patients would be protected by their antiplatelet therapy, patients resistant to aspirin were excluded (23,24).

METHODS

STUDY DESIGN AND PATIENTS. The ITALIC (Is There A Life for DES after Discontinuation of Clopidogrel) trial was a prospective, open-label randomized trial

conducted at 70 sites in Europe and the Middle East. Patients were included in 48 French sites from November 2008 to December 2010 (ITALIC, conducted by the French Society of Cardiology) and in 7 European and Middle East sites from January 2012 to November 2013 under the same protocol (ITALICPLUS). Complete lists and detailed information regarding the institutions involved are given in the [Online Appendix](#). The study was undertaken according to the Declaration of Helsinki, and the national review board of each participating center approved the trial protocol.

Inclusion criteria were: patients age 18 years or older; eligible for percutaneous coronary intervention (PCI); implanted with at least 1 Xience V DES (Abbott Vascular Devices, Santa Clara, California); and all clinical situations excluding primary PCI for acute MI and treatment of the left main artery. Only treatment with Xience V was permitted. All patients gave written informed and dated consent to the study. Patients were not pre-treated with abciximab during their hospital stay. When the study was designed, resistance to aspirin was suspected to be associated with ST after DAPT discontinuation. Aspirin resistance was checked, and nonresponders were excluded from randomization. In patients who received tirofiban or eptifibatid, aspirin resistance was checked at least 24 h after the last injection. Patients were pre-treated with aspirin and clopidogrel (or prasugrel or ticagrelor) pre-PCI. Exclusion criteria were: prior DES implantation within 1 year; known platelet level <100,000/ μ l or known hemorrhagic diathesis; oral anticoagulation therapy or abciximab treatment during hospital stay; contraindications to aspirin or clopidogrel (prasugrel or ticagrelor); major surgery within the preceding 6 weeks; evidence of active gastrointestinal or urogenital bleeding; severe liver failure; any surgery scheduled during the year after enrollment; or severe concomitant disease with <2 years' life expectancy.

RANDOMIZATION AND ASPIRIN RESISTANCE ASSESSMENT. PCI comprised implantation of at least 1 Xience V DES in patients on DAPT with aspirin plus

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clopidogrel 75 mg/day (or prasugrel 60 mg/day, or ticagrelor 90 mg twice per day). Aspirin resistance was assessed after an initial dose of 75 mg. Patients responding poorly to the first aspirin dose were either considered resistant or underwent a second check after 2 days of 160 mg oral aspirin; a third check was made after 2 days of 325 mg oral aspirin in case of poor response to 160 mg, and this dose was applied throughout the trial. If poor response persisted after increasing the aspirin dose, patients were included in the aspirin-resistant control group, with the same follow-up. During PCI hospitalization, patients sensitive to aspirin were assigned in a 1:1 ratio to 6 versus 24 months of DAPT by centralized randomization using an interactive web-based system. If an endpoint (see the following text) occurred during the first 6 months, the patient was withdrawn from analysis. It was a full analysis set.

Three aspirin resistance tests were used: PFA-100 (Dade-Behring, Deerfield, Illinois), defining aspirin response as an epinephrine-collagen cartridge closure time >165 s; multiplate electrical impedance aggregometry (Dynabyte, Munich, Germany), defining aspirin response as a $\geq 30\%$ reduction in platelet aggregation; or VerifyNow Aspirin (Accumetrics, San Diego, California), defining aspirin response as ≥ 550 aspirin reaction units (25). The test used depended on the center; however, the same test was systematically used in any given patient.

ENDPOINTS. The primary endpoint was a composite of death, MI, repeat emergency TVR, stroke, or major bleeding according to the Thrombolysis In Myocardial Infarction (TIMI) criteria (26), from all causes, within 12 months of stenting. All clinical endpoints were defined according to the Academic Research Consortium criteria (27,28).

MI was classified as Q-wave or non-Q-wave MI. Q-wave MI was defined by recurrence of symptoms and/or development of new pathological Q waves in 2 or more contiguous leads with elevated creatine kinase (CK), CK-MB, or troponin levels. Non-Q-wave MI was defined by >2-fold CK elevation with elevated CK-MB or troponin without new pathological Q waves. Emergency TVR was defined as emergency repeat coronary revascularization (PCI or surgery) of any segment of the treated coronary artery within 12 months of stenting. Stroke was defined as acute new neurological deficit ending in death or lasting longer than 24 h, diagnosed as stroke by a physician; stroke was classified as hemorrhagic (on computed tomography, cardiac magnetic resonance imaging, or autopsy) or nonhemorrhagic. Major bleeding was defined according to the TIMI classification as intracranial

hemorrhage, 5 g/dl decrease in hemoglobin concentration, or 15% absolute decrease in hematocrit.

Secondary endpoints were incidence of the same composite endpoint at 24 and 36 months as well as all individual endpoints used in the composite major adverse coronary event score (death, MI, or repeat emergency TVR and stroke requiring readmission). In addition, the incidence of minor and minimal bleeding complications at 12, 24, and 36 months was assessed according to the TIMI classification (26). All composite endpoints are presented with the individual components in hierarchical order.

DATA MANAGEMENT. In-hospital adverse events were recorded before discharge. Six-, 12-, 24-, and 36-month clinical follow-up data were obtained in outpatient consultation. Clinical data were processed by an independent external contract research organization (CERC, Massy, France). Adverse clinical events were independently adjudicated by an external clinical event committee. To ensure high data quality, all clinical sites were monitored at least once per year (all adverse events, endpoint-related events, and 15% random patient files); all source documents concerning events were provided to the clinical event committee, for accuracy and completeness. For the aspirin-resistant group, only patients with serious adverse events were fully monitored, with an additional 10% random spot-check of remaining data.

STATISTICAL ANALYSIS. In the SPIRIT V (A Clinical Evaluation of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Coronary Artery Lesions) study (29), the composite rate of cardiac death, MI (per protocol), ST (definite/probable), major bleeding (TIMI), and stroke between 6-month and 1-year follow-up was estimated to be less than but close to 2%. Sample size was calculated to detect noninferiority of short compared to long-term DAPT, with 80% power. The expected rate of events was 3%, and the noninferiority margin was set at 2%, leading to inclusion of 900 patients/arm, for a type I error of $\alpha = 5\%$. With a drop-out rate of 20% in the test group and 5% in the control group, and considering a 10% rate of aspirin resistance, a total of 2,475 patients needed to be included to enable a conclusion to be drawn. Sample size was calculated considering an $\alpha = 5\%$, but to be compliant with the most recent guidelines, the noninferiority confidence interval (CI) has been performed finally at 97.5%.

Statistical comparison was performed between the 6- and 24-month DAPT groups; the aspirin resistance group results were only descriptive. Baseline characteristics were compared between the 2 treatment groups by Student *t* test or Wilcoxon rank sum test as

appropriate for continuous variables, and chi-square test for categorical variables. Kaplan-Meier survival curves were constructed (30), and differences between the curves were tested by the log-rank test. Proportional hazard models (31) were used to estimate hazard ratios (HRs) and 95% CIs. Survival analysis was performed in the intention-to-treat population, with the primary endpoint as the event. Sensitivity analysis was performed in the per-protocol population to assess robustness of results. Statistical analyses were performed and validated using SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina). Noninferiority was tested on the primary endpoint with a 1-tailed 97.5% CI. Times to primary endpoint and all secondary endpoints were also assessed on survival analysis. The group of patients with ACS was analyzed post hoc.

RESULTS

STUDY POPULATION. Figure 1 shows the trial flow chart with 2,031 patients enrolled. The trial was prematurely terminated due to recruitment problems. After aspirin monitoring, 131 patients were classified as aspirin resistant, and were not randomized but were followed up as the aspirin-resistant group. A total of 1,894 patients were eligible for randomization. Before 6 months, 44 patients were excluded from analysis due to an endpoint-related event (13 deaths, 10 MIs, and 2 TVRs). Thus, 1,850 patients were randomized to 24-month DAPT (n = 924) versus 6-month DAPT (n = 926).

The 2 test groups had similar baseline (Table 1) and procedural (Table 2) characteristics. One-third of the patients had a history of type 2 diabetes; one-fourth

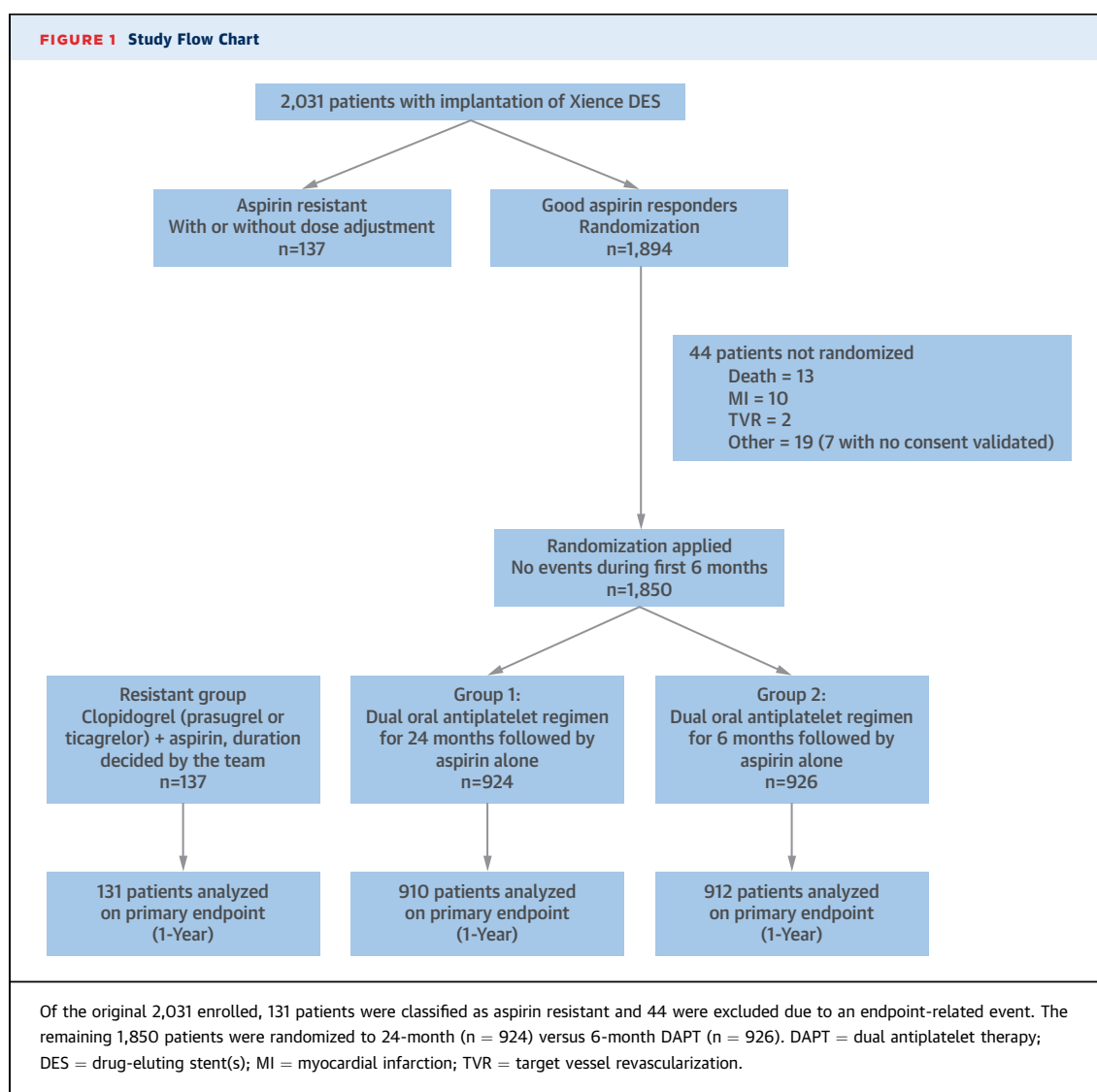


TABLE 1 Baseline Patient Characteristics

	Resistant Group (n = 131)	24-Month DAPT (n = 910)	6-Month DAPT (n = 912)	p Value
Age, yrs	62.6 ± 10.8	61.5 ± 11.1	61.7 ± 10.9	0.792
Male	106 (80.9)	721 (79.2)	737 (80.8)	0.399
Body mass index, kg/m ²	27.5 ± 4.2	27.1 ± 4.7	27.0 ± 4.6	0.549
Type 2 diabetes	42 (32.1)	344 (37.8)	331 (36.3)	0.505
Hypertension	76 (58.0)	589 (64.7)	595 (65.2)	0.817
Hyperlipidemia	84 (64.1)	611 (67.1)	612 (67.1)	0.986
Smoker	69 (52.7)	480 (52.7)	464 (50.9)	0.424
Heredity	50 (38.2)	325 (35.7)	322 (35.3)	0.856
Previous MI	36 (27.5)	134 (14.7)	142 (15.6)	0.615
Previous PCI	39 (29.8)	205 (22.5)	220 (24.1)	0.421
Previous CABG	6 (4.6)	45 (4.9)	61 (6.7)	0.111
Previous stroke	6 (4.6)	26 (2.9)	25 (2.7)	0.881
Renal insufficiency	4 (3.1)	25 (2.7)	28 (3.1)	0.682
Ejection fraction				0.321
<31%	1 (0.8)	20 (2.2)	29 (3.2)	
31%-50%	21 (16.0)	151 (16.6)	162 (17.8)	
>50%	65 (49.6)	514 (56.5)	482 (52.9)	
Unknown	44 (33.6)	225 (24.7)	239 (26.2)	
Clinical presentation				0.911
Stable angina	53 (40.5)	378 (41.5)	375 (41.1)	
Silent ischemia	18 (13.7)	183 (20.1)	185 (20.3)	
Unstable angina	23 (17.6)	149 (16.4)	143 (15.7)	
NSTEMI	9 (6.9)	65 (7.1)	67 (7.3)	
STEMI	0	3 (0.3)	1 (0.1)	
Antiplatelet therapy associated				
Clopidogrel	129 (98.5)	895 (98.4)	902 (98.9)	
Prasugrel	2 (1.5)	16 (1.8)	15 (1.6)	
Ticagrelor	0	0	1 (0.1)	

Values are mean ± SD or n (%).
CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

had previous PCI or bypass surgery; and nearly one-half presented with ACS. In more than one-half of the patients, 2 or more lesions were stented, with a mean stent length of approximately 37 mm.

FOLLOW-UP AND CLINICAL OUTCOMES. The 1-year follow-up information could be obtained for 98.5% of patients. In the 6-month DAPT arm, 221 patients (24.2%) did not follow the 6-month treatment duration: 83 (8.9%) continued treatment longer, and the others stopped earlier. In the 24-month DAPT arm, 49 patients (5.4%) discontinued treatment before 24 months. **Table 3** shows endpoints during 1-year follow-up. There was no significant difference between treatment groups regarding the primary endpoint (1.5% vs. 1.6%; p = 0.85) (**Figure 2**) or its components (secondary endpoint). The TVR rates were very low in both groups (n = 2 [0.2%] vs. n = 5 [0.5%]); there were no stent thromboses in the

TABLE 2 Procedural Characteristics

	Resistant Group (n = 131)	24-Month DAPT (n = 910)	6-Month DAPT (n = 912)	p Value
Procedural success	130 (99.2)	901 (99.0)	895 (98.1)	0.112
Target lesion coronary artery				
Left main	4 (3.1)	8 (0.9)	14 (1.5)	0.197
Left anterior descending	96 (73.3)	658 (72.3)	669 (73.4)	0.615
Left circumflex	59 (45.0)	436 (47.9)	456 (50.0)	0.373
Right coronary artery	62 (47.3)	474 (52.1)	489 (53.6)	0.513
Bypass graft	5 (3.8)	39 (4.3)	59 (6.5)	0.038
Total lesions treated/patient				0.239
1	77 (58.8)	494 (54.3)	459 (50.3)	
2	38 (29.0)	252 (27.7)	275 (30.2)	
≥3	16 (12.2)	164 (18.0)	178 (19.5)	
Number of Xience V stents per patient	1.6 ± 0.8	1.7 ± 1.0	1.7 ± 1.0	0.497
Total stent length, mm	33.2 ± 22.7	37.8 ± 26.1	38.6 ± 25.6	0.533
Stent diameter, mm	3.0 ± 0.2	3.1 ± 0.3	3.1 ± 0.3	0.113
Rotablator	4 (2.9)	12 (1.3)	15 ± 1.6)	0.553
At least 1 restenotic lesion	5 (3.8)	51 (5.6)	54 (5.9)	0.772

Values are n (%) or mean ± SD.
DAPT = dual antiplatelet therapy.

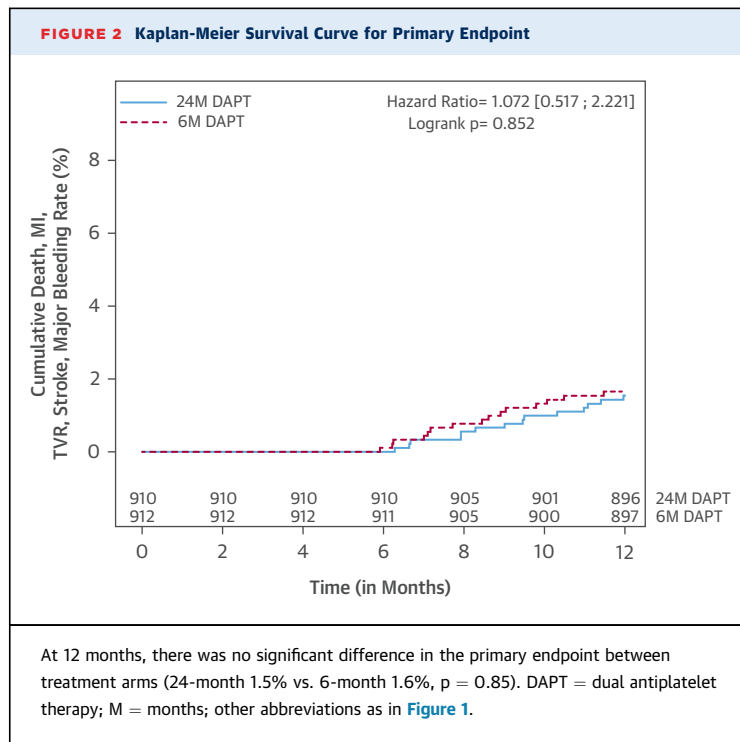
6-month DAPT group, and only 3 in the 24-month group. There was no significant difference in bleeding complications. Major bleeding occurred in only 3 patients in the 24-month group. For minor bleeding, the HR was 1.247 (95% CI: 0.335 to 4.643; p = 0.74). In the 792 (44%) high-risk patients with ACS, primary and secondary endpoints did not significantly differ from the global treatment population (**Table 4, Central Illustration**).

Noninferiority was established for 6- versus 24-month DAPT, with an absolute risk difference

TABLE 3 1-Year Clinical Outcomes in the Intention-to-Treat Study Population

	Resistant Group (n = 131)	24-Month DAPT (n = 910)	6-Month DAPT (n = 912)	Hazard Ratio (95% CI)	p Value
Primary endpoint: death from any cause, MI, stroke, TVR, or major bleeding	2 (1.5)	14 (1.5)	15 (1.6)	1.072 (0.517-2.221)	0.85
Secondary endpoints					
Minor bleeding	0	4 (0.4)	5 (0.5)	1.247 (0.335-4.643)	0.74
Minimal bleeding	1 (0.8)	6 (0.7)	6 (0.7)	0.997 (0.321-3.090)	0.99
Death					
All deaths	1 (0.8)	7 (0.8)	8 (0.9)	1.143 (0.414-3.152)	0.80
Cardiac death	0	3 (0.3)	5 (0.5)	1.667 (0.398-6.974)	0.48
Myocardial infarction	0	4 (0.4)	6 (0.7)	1.500 (0.423-5.317)	0.53
Stroke	0	4 (0.4)	0	N/A	
TVR	1 (0.8)	2 (0.2)	5 (0.5)	2.499 (0.485-12.882)	0.27
Stent thrombosis	0	0	3 (0.3)	N/A	
Major bleeding	0	3 (0.3)	0	N/A	

Values are n (%) unless otherwise indicated.
CI = confidence interval; TVR = urgent target vessel revascularization; other abbreviations as in **Table 1**.



of 0.11% (95% CI: -1.04% to 1.26% ; p for non-inferiority = 0.0002).

DISCUSSION

This prospective, randomized trial demonstrated that 6-month DAPT after second-generation DES implantation was noninferior to 24-month DAPT for the

composite primary endpoint of death, stroke, MI, emergency TVR, and major bleeding as well as for the secondary endpoints.

The protocol was designed assuming a major adverse cardiac event rate $\sim 3\%$ between 6 and 12 months in the control group; the observed rate was in fact 1.5% and 1.6% in the 24- and 6-month DAPT groups, respectively, which was significantly lower than expected. From a statistical point of view, this difference introduced no bias, as a lower expected endpoint rate would have led to a smaller sample. A low event rate was observed even in high-risk patients presenting with ACS, although primary PCI was an exclusion criterion (Table 4). A single type of DES was implanted to minimize potential variation in efficacy and safety; the Xience V cobalt-chromium everolimus-eluting stent used in the present trial is probably 1 of the safest new-generation models. A large-scale network meta-analysis including more than 85,000 randomized patients showed it to be safe, with better outcomes than BMS, first-generation DES, or certain other new-generation DES (32).

One-fourth of the patients (24.2%) allocated to the short-DAPT arm did not respect the 6-month treatment duration. However, only 83 (8.9%) of these patients continued treatment longer, whereas the vast majority stopped early.

The present trial did not show an increase in bleeding in the long-DAPT arm, in contrast to the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial, which also compared 6- to 24-month DAPT, but demonstrated an increased rate of bleeding in the long-duration arm (14).

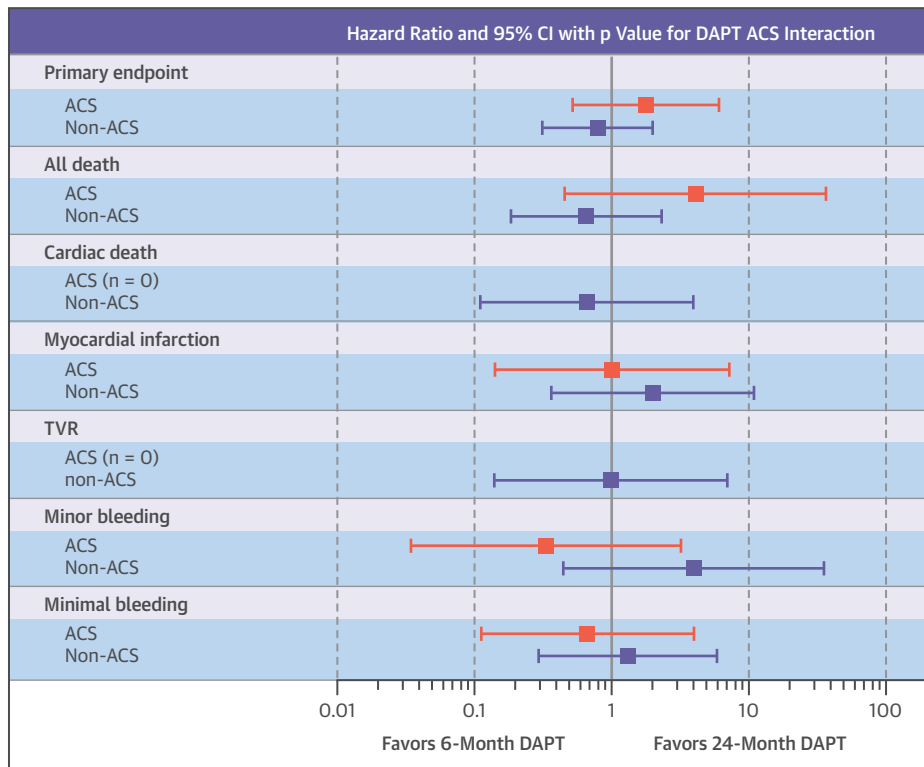
Regardless of the type of DES, several guidelines call for a minimum of 12 months of DAPT after DES implantation to prevent late ST (22,33). However, second-generation DES have been shown to have a safety profile similar to or even better than BMS (4,11-13,34). No data support prolonging DAPT beyond 1 year after DES implantation. Indeed, merged data from 2 randomized stenting trials ($n = 2,071$) showed a nonsignificant trend for a higher rate of MI, stroke, and death at a median of 19 months of follow-up in patients continuing versus stopping clopidogrel 1 year after stenting (35). Several randomized trials comparing short (3 to 6 months) versus extended (12 to 24 months) DAPT consistently showed a lack of benefit in terms of ischemic outcome but a higher risk of bleeding (14,16,17). A recent meta-analysis of brief versus prolonged DAPT (>12 months) concluded that extending DAPT beyond 6 months increased bleeding risk without reducing the rate of ischemic events (15,36). These findings explain the modifications

TABLE 4 1-Year Clinical Outcomes in the High-Risk ACS Intention-to-Treat Study Population

	Resistant Group (n = 50)	24-Month DAPT (n = 397)	6-Month DAPT (n = 395)	Hazard Ratio (95% CI)	p Value
Primary endpoint: death from any cause, MI, stroke, TVR, or major bleeding	0	4 (1.0)	7 (1.8)	1.773 (0.519-6.057)	0.361
Secondary endpoints					
Minor bleeding	0	3 (0.8)	1 (0.3)	0.334 (0.035-3.211)	0.34
Minimal bleeding	0	3 (0.8)	2 (0.5)	0.669 (0.112-4.002)	0.66
Death					
All deaths	0	1 (0.3)	4 (1.0)	4.041 (0.452-36.151)	0.21
Cardiac death	0	0	3 (0.8)	N/A	
MI	0	2 (0.5)	2 (0.5)	1.006 (0.142-7.144)	0.99
Stroke	0	1 (0.3)	0	N/A	
TVR	0	0	3 (0.8)	N/A	0
Stent thrombosis	0	0	2 (0.5)	N/A	
Major bleeding	0	1 (0.3)	0	N/A	

Values are n (%) unless otherwise indicated.
Abbreviations as in Tables 1 and 3.

CENTRAL ILLUSTRATION 1-Year Clinical Outcomes in ACS and Non-ACS Patients



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In the overall trial population, 6-month DAPT was noninferior to 24-month treatment (p for noninferiority = 0.0002), and there were no differences in stent thrombosis or bleeding complications. These endpoints did not differ significantly in the 792 (44%) high-risk patients with ACS (hazard ratio: 1.7%; 95% CI: 0.519 to 6.057; p = 0.361). ACS = acute coronary syndrome(s); CI = confidence interval; DAPT = dual antiplatelet therapy. HR = hazard ratio; TVR = target vessel revascularization; UCL = upper confidence limit.

to current guidelines, recommending that DAPT be administered for 6 months after new-generation DES in stable angina but for 1 year in ACS (21). The present trial demonstrated noninferior safety for 6- versus 24-month DAPT, without any specific safety advantage in terms of bleeding with short DAPT.

The 1-year duration of DAPT after ACS in the most recent guidelines was supported by 3 randomized trials. In the oldest trial (conducted 15 years ago), PCI-CURE (a substudy of the Clopidogrel in Unstable angina to prevent Recurrent Events trial) (37), PCI was performed with stenting in only 80% of cases, and that was with BMS. The other trials, PLATO (PLATElet inhibition and patient Outcomes) and TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) (38,39), used DES in only 19% and 40% of cases, respectively; these were first-generation DES,

whereas second-generation DES have thin stent struts, advanced polymers, and improved anti-proliferation agents that have further improved efficacy and safety. Moreover, these 2 more recent trials compared efficacy between different DAPT regimens (aspirin plus either ticagrelor in PLATO or prasugrel in TRITON-TIMI 38, both versus clopidogrel plus aspirin) and not the duration of DAPT following ACS.

Randomized studies comparing longer- versus shorter-term DAPT after ACS are lacking. The present trial showed a very low rate of thrombotic events with newer-generation DES, even after ACS, in the 6-month DAPT group. However, with ACS, it seems important to maintain an effective antiplatelet agent between 6 and 12 months in aspirin responders. The aim of long-term DAPT after ACS is to reduce not only the risk of late ST but also the risk of recurrent spontaneous ischemic events. In previous trials analyzing evolution after ACS (40), most thrombotic events

occurred within the first 6 months. In the present trial, there was no significant difference in thrombotic event rate in ACS patients according to DAPT duration.

ANTIPLATELET THERAPY MONITORING. There is no doubt that long-course aspirin attenuates the risk of MI, stroke, and vascular-related deaths in patients with cardiovascular disease (23). The major controversy about aspirin therapy is why certain patients do not show benefit with such therapy and how they might be identified. Reanalyzing data reported by the Aspirin Trialists' Collaboration (23), with an aspirin-resistance odds ratio factored in, the risk reduction in aspirin-sensitive patients is likely to be >50%, whereas in aspirin-resistant patients, risk seems to noticeably increase (41-43). Several prospective studies demonstrated an association between biochemical aspirin resistance and clinical outcome (42-45). In these trials, aspirin resistance was associated with increased risk of MI, stroke, or cardiac death, and this was confirmed by a large-scale meta-analysis (24). Platelet response to aspirin, as measured by collagen- and adenosine diphosphate-induced light transmittance aggregometry, PFA-100, and urinary thromboxane, is dose-related, indicating that aspirin nonresponse decreases with increasing dose from 75 to 325 mg (25). The recent randomized ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting) trial of a bedside platelet function test was neutral in its findings (46); however, only 27% of patients had ACS, and in stable patients, no data supported prolonged DAPT for new-generation DES.

Despite the variety of tests available, there is no consensus as to the standard for measuring platelet activation, and many definitions of aspirin resistance depend on which test is used (25). The possibility of using bedside assays to monitor aspirin offers an opportunity to compare 2 strategies in good aspirin responders: aspirin-clopidogrel (prasugrel or ticagrelor) versus aspirin alone. In the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) trial, investigators reported that high platelet reactivity on aspirin was not significantly associated with ST, MI, or mortality after DES implantation, but was an independent predictor of freedom from clinically-relevant bleeding. However, the trial was designed for ST occurrence; investigators did not compare DAPT duration and aspirin efficacy alone (47).

Crossover from DAPT to single antiplatelet therapy after 6 months is possible in good aspirin responders. However, in the present aspirin-resistant group, the rate of adverse events was also very low, probably due to overtreatment of patients with known aspirin resistance. The role of aspirin resistance monitoring in clinical practice should be questioned.

STUDY LIMITATIONS AND STRENGTHS. Due to enrollment difficulties, recruitment stopped at 2,031 patients, rather than the 2,475 patients required to have 900 analyzable patients in each group; however, as we finally had an event rate of 1.5% (compared to the 3% expected), and as we are far from the boundary, the sample size is enough for the conclusion to be valid. The study was open-label and not placebo-controlled in the 6-month arm. However, all clinical endpoints were assessed by members of an independent clinical event adjudication committee, and statistical analyses were performed by independent statisticians.

CONCLUSIONS

The ITALIC trial showed that bleeding and thrombotic event rates were not significantly different between 6- and 24-month DAPT groups after PCI with second-generation DES, and that 6-month DAPT was noninferior to 24-month DAPT in good aspirin responders. Noninferiority was also observed in the subgroup of unstable patients (one-half of patients). Larger trials are needed to assess the effect of antiplatelet duration in ACS patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Following deployment of new-generation DES, 6 and 24 months of DAPT are associated with similar rates of thrombotic and bleeding events in patients who are responsive to the platelet inhibitory effects of aspirin.

TRANSLATIONAL OUTLOOK: Future research should seek to identify the specific clinical characteristics associated with benefit or harm related to shorter or longer durations of DAPT following deployment of various types of coronary stents.

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KEY WORDS double antiplatelet duration, percutaneous coronary angioplasty

APPENDIX For a full list of ITALIC trial investigators, please see the online version of this article.