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

Final Results of the ITALIC Trial (Is There a Life for DES After Discontinuation of Clopidogrel)

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ABSTRACT

OBJECTIVES The aim of this study was to test the hypothesis that 6-month dual antiplatelet therapy (DAPT) is non-inferior to 24-month DAPT in aspirin-sensitive patients.

BACKGROUND The ITALIC (Is There a Life for DES After Discontinuation of Clopidogrel) trial showed that rates of bleeding and thrombotic events at 1 year were much the same with 6 versus 12 months of DAPT after percutaneous coronary intervention with second-generation drug-eluting stents. In this report, 2-year follow-up is presented.

METHODS In a multicenter randomized study, patients with confirmed nonresistance to aspirin undergoing drug-eluting stent implantation were allocated to 6 or 24 months of DAPT. The primary endpoint was a composite of death, myocardial infarction, urgent target vessel revascularization, stroke, and major bleeding at 12 months post-percutaneous coronary intervention. The secondary endpoints comprised the same composite endpoint at 24 months and each individual component.

RESULTS Overall, 2,031 patients from 70 centers were screened; 926 were randomized to 6-month and 924 to 24-month DAPT. Noninferiority was demonstrated for 6- versus 12-month DAPT, with an absolute risk difference of 0.11% (95% confidence interval: −1.04% to 1.26%; $p = 0.0002$). At 2 years, the composite endpoint was unchanged, at 3.5% for 6 months and 3.7% for 24 months ($p = 0.79$), and rates of myocardial infarction (1.3% vs. 1.0%; $p = 0.51$), stroke (0.6% vs. 0.8%; $p = 0.77$), and target vessel revascularization (1.0% vs. 0.3%; $p = 0.09$) were likewise similar. There was a trend toward higher mortality with longer DAPT (2.2% vs. 1.2%; $p = 0.11$). Four patients (0.4%) in the 24-month group and none in the 6-month group had major bleeding.

CONCLUSIONS Two-year outcomes in the ITALIC trial confirmed the 1-year results and showed that patients receiving 6-month DAPT after percutaneous coronary intervention with second-generation drug-eluting stent have similar outcomes to those receiving 24-month DAPT. (J Am Coll Cardiol Intv 2017;10:1202–10) © 2017 by the American College of Cardiology Foundation.

Although the safety and efficacy of second-generation drug-eluting stents (DES) have substantially improved compared with the first generation, notably with a lower incidence of stent thrombosis (1), the corresponding optimal duration of dual antiplatelet therapy (DAPT) is controversial. The dilemma for physicians in daily practice is to weigh the risk for ischemic events with shorter DAPT against the risk for bleeding with longer therapy. Several randomized clinical trials, involving various clinical presentations, stent types, and $P2Y_{12}$ inhibitors (2–9), suggest that short DAPT is safe in terms of ischemic events, whereas higher rates of bleeding in the long-term groups have been reported, although not in all studies. In contrast, 2 recent randomized clinical trials, the DAPT study (10), and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) (11), reported that continuing DAPT beyond 1 year reduced the risk for ischemic events. However, the DAPT study reported not only an increase in hemorrhagic events, as expected, but also significantly higher mortality with extended DAPT. The PEGASUS-TIMI 54 trial recruited a specific population of patients with prior myocardial infarction (MI), so that results cannot be directly extrapolated to daily practice. Overall, continuing DAPT for 1 year after the implantation of a second-generation DES remains a subject of debate.

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The ITALIC (Is There a Life for DES After Discontinuation of Clopidogrel) trial showed that the rates of bleeding and thrombotic events at 1 year were much the same in 6- and 24-month DAPT groups in patients undergoing percutaneous coronary intervention (PCI) with second-generation DES implantation. We report in this paper the 2-year follow-up.

METHODS

STUDY DESIGN. Details and the flowchart of the trial were previously published (4). Briefly, the ITALIC trial was a prospective, open-label, randomized trial performed at 70 hospitals, designed to detect noninferiority between short 6-month DAPT and longer 24-month DAPT after second-generation DES implantation. Inclusions were performed from November 2008 to December 2010 at 48 French sites (ITALIC, conducted by the French Society of Cardiology) and, under the same protocol, from January 2012 to November 2013 at 7 European and Middle Eastern sites (ITALIC PLUS). The potential influence on the results of different health care systems between ITALIC and ITALIC PLUS was tested at the beginning of the analysis, and the study effect was nonsignificant. Patients were included following everolimus-eluting stent implantation (XIENCE V, Abbott Vascular Devices, Santa Clara, California). After aspirin resistance evaluation, nonresponders were excluded from randomization and followed separately. Six months after index PCI, in the absence of events, patients were centrally randomly allocated 1:1 to 6- or 24-month DAPT.

Inclusion criteria were eligibility for PCI with any clinical presentation except primary PCI for ST-segment elevation myocardial infarction (STEMI) or left main coronary artery PCI and implantation with at least 1 XIENCE V DES. Exclusion criteria were prior DES implantation in the previous year; platelet count <100,000/μl; hemorrhagic diathesis; anticoagulation therapy or abciximab treatment during hospital stay; contraindication to aspirin, clopidogrel, prasugrel, or ticagrelor; major surgery in the preceding 6 weeks; evidence of active gastrointestinal or urogenital bleeding; severe liver failure; any surgery scheduled during the year after enrollment; or severe

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
CI = confidence interval
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TVR = target vessel revascularization

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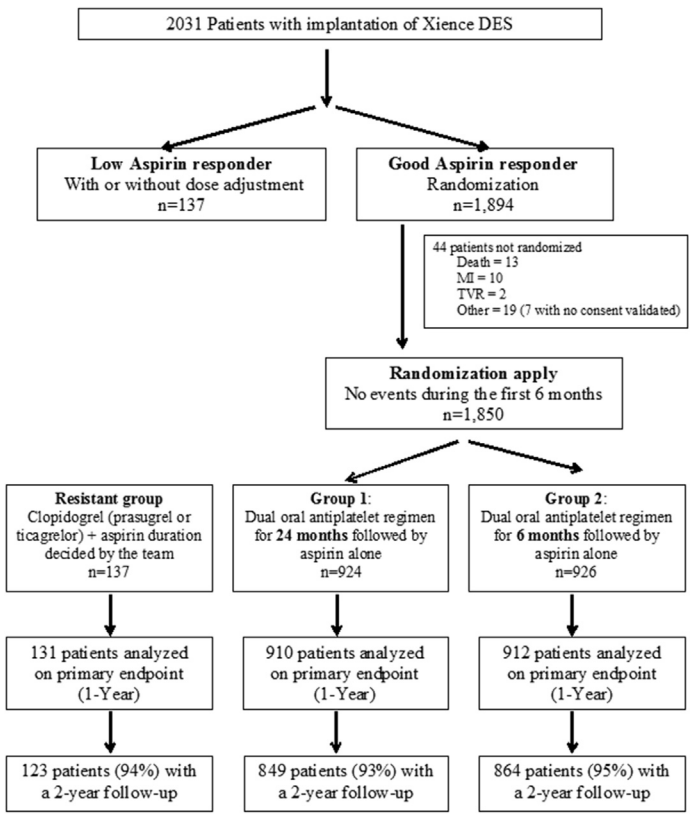
FIGURE 1 The ITALIC Trial: Flowchart



DES = drug-eluting stent(s); ITALIC = Is There a Life for DES After Discontinuation of Clopidogrel; MI = myocardial infarction; TVR = target vessel revascularization.

concomitant disease with <2 years' life expectancy. The trial was approved by the local Institutional Review Board, and written informed consent was obtained from all patients.

OUTCOMES AND DEFINITIONS. The pre-specified primary endpoint was a composite of all-cause mortality, MI, target vessel revascularization (TVR), stroke, or major bleeding according to the TIMI (Thrombolysis In Myocardial Infarction) criteria (12) at 1 year in the intention-to-treat population. Secondary endpoints were incidence of the same pre-specified composite outcomes, in addition to all individual efficacy endpoints (all-cause mortality, cardiac mortality, MI, stroke, TVR, and definite or probable stent thrombosis) and safety endpoints (minimal, minor, and major bleeding) at 24 and 36 months. The definitions of all clinical complications collected during 1- and 2-year follow-up were identical to those in the original trial and complied with the Academic Research Consortium criteria (13,14). An independent clinical events committee adjudicated all clinical outcomes.

STATISTICAL ANALYSIS. Sample size determination was previously described in the reference publication (4). Statistical analyses used SAS version 9.4 (SAS Institute, Cary, North Carolina). Two-year results are presented for the intention-to-treat population. Normally distributed continuous variables are presented as mean ± SD. Categorical variables are expressed as percentages. The Student *t* test or Wilcoxon rank sum test was used, as appropriate, to compare continuous variables and the chi-square test to compare categorical variables. All probabilities are 2-tailed; the significance threshold was set at $p < 0.05$. Kaplan-Meier curves were traced for the 2-year composite secondary endpoint for the overall population and for the subgroup of patients with histories of MI, with assessment of the differences between the curves by the log-rank test. In the post hoc subgroup analysis, an interaction term with DAPT group was tested in a Cox proportional hazards model, and in case of statistical significance, representation in curves was performed.

RESULTS

STUDY POPULATION. Overall, 2,031 patients were enrolled after DES implantation. One hundred thirty-seven were classified as aspirin resistant after aspirin monitoring and were not randomized but followed as a separate aspirin-resistant group. After the exclusion of 44 additional patients with exclusion criteria (13 deaths, 10 MIs, 2 TVRs, and 19 other reasons), 1,850 patients were randomized. Nine hundred twenty-four were allocated to the 24-month DAPT group (followed by aspirin alone) and 926 to the 6-month DAPT group (followed by aspirin alone) (Figure 1). Table 1 presents baseline patient characteristics; briefly, 36.9% had diabetes; the predominant clinical presentations were stable angina (41.3%) and acute coronary syndrome (ACS) (36.2%), with a minority of STEMI (7.2%).

One-year results were previously reported (4). There was no significant difference in the primary endpoint between 6- and 12-month DAPT (1.6% vs. 1.5%, respectively; $p = 0.85$), and 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%; $p = 0.0002$).

2-YEAR CLINICAL OUTCOMES. Two-year follow-up was performed in 94% of patients (Figure 1). In the 6-month DAPT group, 212 patients (23.2%) failed to respect treatment duration: 9 stopped before 6

months, 123 were on DAPT after 6 months but not at 24 months, and 80 remained on DAPT after 24 months. In the 24-month DAPT group, 170 patients (18.7%) discontinued treatment before 24 months.

At 2 years, the composite secondary endpoint did not differ significantly between the 2 groups (3.7% for 24-month vs. 3.5% for 6-month DAPT; p = 0.799) (Figure 2), nor did its individual components (Table 2). There was a trend toward higher all-cause mortality in the 24-month group compared with the 6-month group (2.2% vs. 1.2%, respectively; p = 0.110). Major bleeding was observed only in the 24-month group (0.4% vs. 0.0%).

Regarding efficacy criteria, incidence rates of cardiac death, MI, stroke, and stent thrombosis were the same in both treatment groups, except for TVR, which showed lower incidence in the 24-month group (0.3% vs. 1.0%; p = 0.099). In intention-to-treat analysis, noninferiority was maintained for 6- versus 24-month DAPT, with an absolute risk difference of 0.22% (95% confidence interval: −1.91% to 1.47%; p = 0.0197).

SUBGROUP ANALYSIS. In the specific high ACS risk population (unstable angina, non-ST-segment elevation MI, and STEMI), 2-year clinical outcomes showed no difference between groups for the composite secondary endpoint or its components (Table 3). Furthermore, subgroup analysis found no difference between 6- and 24-month DAPT in the subgroups with ACS, type 2 diabetes, multiple stents (≥2), previous MI, or age ≥75 years (Figure 3) and no difference as well with no ACS (hazard ratio [HR]: 1.04; 95% confidence interval [CI]: 0.54 to 2.02; p = 0.66 for interaction), no type 2 diabetes (HR: 1.24; 95% CI: 0.63 to 2.44; p = 0.26 for interaction), no multiple stents (HR: 0.66; 95% CI: 0.28 to 1.61; p = 0.39 for interaction), no prior MI (HR: 0.70; 95% CI: 0.40 to 1.23; p = 0.04 for interaction), and age <75 years (HR: 1.26; 95% CI: 0.72 to 2.20; p = 0.048 for interaction). However, patients with histories of MI showed a trend toward higher incidence of the composite secondary endpoint with 6-month than 24-month DAPT (p = 0.083) (Figure 4), whereas age ≥75 years was associated with a trend toward a higher incidence of events with 24-month DAPT (p = 0.057).

TABLE 1 Baseline Patient Characteristics

	Resistant Group (n = 137)	6-Month DAPT (n = 926)	24-Month DAPT (n = 924)	p Value*
Age (yrs)	62.5 ± 10.9	61.6 ± 10.9	61.5 ± 11.2	0.863
Male	111 (81.0%)	750 (81.0%)	733 (79.3%)	0.369
BMI (kg/m^2)	27.5 ± 4.3	27.0 ± 4.6	27.1 ± 4.7	0.581
Diabetes mellitus (any)	44 (32.1%)	336 (36.3%)	349 (37.8%)	0.508
Hypertension	79 (57.7%)	603 (65.1%)	594 (64.3%)	0.708
Dyslipidemia	88 (64.2%)	625 (67.5%)	618 (66.9%)	0.779
Tobacco smoker	74 (54.0%)	473 (51.1%)	487 (52.7%)	0.484
Heredity	51 (37.2%)	326 (35.2%)	328 (35.5%)	0.895
Previous MI	37 (27.0%)	144 (15.6%)	138 (14.9%)	0.713
Previous PCI	40 (29.2%)	226 (24.4%)	209 (22.6%)	0.365
Previous CABG	6 (4.4%)	61 (6.6%)	45 (4.9%)	0.111
Previous stroke	6 (4.4%)	28 (3.0%)	26 (2.8%)	0.789
Renal insufficiency	4 (2.9%)	29 (3.1%)	25 (2.7%)	0.586
Ejection fraction				
<31%	1 (0.7%)	29 (3.1%)	22 (2.4%)	0.554
31%–50%	22 (16.1%)	162 (17.5%)	154 (16.7%)	
>50%	67 (48.9%)	493 (53.2%)	518 (56.1%)	
Unknown	47 (34.3%)	242 (26.1%)	230 (24.9%)	
Clinical presentation				
Stable angina	54 (39.4%)	382 (41.3%)	383 (41.5%)	0.893
Silent ischemia	28 (20.4%)	143 (15.4%)	132 (14.3%)	
Unstable angina	20 (14.6%)	188 (20.3%)	186 (20.1%)	
NSTEMI	25 (18.2%)	145 (15.7%)	152 (16.5%)	
STEMI	10 (7.3%)	67 (7.2%)	68 (7.4%)	
Other	0 (0.0)	1 (0.1%)	3 (0.3%)	
Antiplatelet therapy associated				
Clopidogrel	135 (98.5%)	916 (98.9%)	909 (98.4%)	
Ticagrelor	2 (1.5%)	15 (1.6%)	16 (1.7%)	
Prasugrel	0 (0.0)	1 (0.1%)	0 (0.0)	

Values are mean ± SD or n (%). *Comparison between 24-month and 6-month DAPT groups.

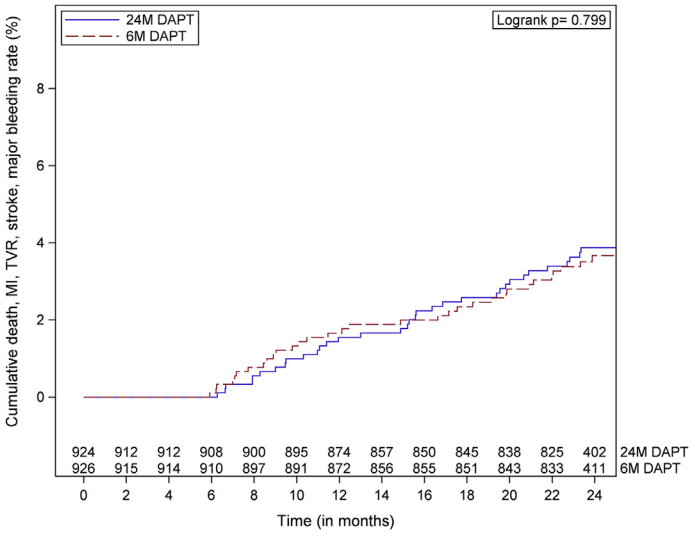
BMI = body mass index; CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

DISCUSSION

At 2 years following second-generation DES (XIENCE V) implantation in a non-aspirin-resistant population (excluding STEMI), this prospective randomized multicenter trial showed 3 main findings. First, in line with the 1-year results, the 2-year composite endpoint and the incidence of pre-specified cumulative events (all-cause mortality, MI, stroke, TVR, and major bleeding) did not differ between the 2 groups. Furthermore, although the study was not designed for 2-year noninferiority assessment, this hypothesis between 6- and 24-month DAPT was confirmed. Second, there was no relevant increase in bleeding events with longer DAPT but a nonsignificant trend toward higher mortality in the 24-month DAPT group. Third, in subgroup analysis, shorter or longer DAPT duration was not associated with better outcomes in patients with clinical presentations of ACS, type 2 diabetes, multiple stents, or total stent length >30 mm, while patients with histories of MI showed a nonsignificant trend toward higher cumulative all-cause mortality, MI, TVR, stroke, and major bleeding with shorter DAPT.

DURATION OF DAPT AFTER PCI. Recommendations for DAPT duration have continued to evolve over time,

FIGURE 2 Kaplan-Meier Survival Curve for Composite Endpoint at 2 Years



DAPT = dual antiplatelet therapy; MI = myocardial infarction; TVR = target vessel revascularization.

notably after reports of higher rates of late stent thrombosis with first-generation DES compared with bare-metal stents (15–17). Pfisterer et al. (18) reported that at 18 months, first-generation DES showed a lower incidence of TVR than BMS (4.5% vs. 6.7%, respectively), but twice as high a stent thrombosis rate (2.6% vs. 1.3%, respectively), and even more in case of early discontinuation of DAPT (4.9% vs. 1.3%, respectively). In light of this, the American (19) and European (20) guidelines initially recommended prolonging DAPT after DES implantation to 12 months for patients at high risk for ischemic events and to 6 to 12 months for other patients. However, with the new-generation DES, several randomized trials have demonstrated the safety of shorter DAPT duration in terms of ischemic events (2–9). In light of this, the most recent European (21) and updated American (22) guidelines reduced DAPT duration to 6 months after PCI in non-ACS patients and 3 months in patients with very high risk for bleeding. The finding of the ITALIC trial is in accordance with those previous randomized trials conducted on new-generation DES (2,3,5–9), except for the DAPT study (10), showing no advantage to extend beyond 1 year the duration of DAPT.

DURATION OF DAPT IN PATIENTS IN STABLE CONDITION. This all-comers trial highlighted a low rate of events (3.6%) at 2 years, in patients with a low risk profile (56.6% with stable angina or silent ischemia) undergoing PCI with a single type of second-generation DES. This low incidence of events is in line with other studies on the duration of DAPT, such as ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual

TABLE 2 2-Year Clinical Outcomes in the Intention-to-Treat Study Population

	Overall (N = 1,987)	Resistant Group (n = 137)	6-Month DAPT (n = 926)	24-Month DAPT (n = 924)	Hazard Ratio* (95% CI)	p Value
Composite secondary endpoint (all-cause mortality, MI, stroke, TVR, major bleeding)	69 (3.5%)	3 (2.2%)	32 (3.5%)	34 (3.7%)	0.939 (0.580–1.522)	0.799
Secondary safety endpoints						
Bleeding						
Minimal bleeding	18 (0.9%)	2 (1.5%)	8 (0.9%)	8 (0.9%)	0.998 (0.375–2.660)	0.997
Minor bleeding	12 (0.6%)	0 (0.0)	6 (0.6%)	6 (0.6%)	0.997 (0.322–3.093)	0.996
Major bleeding	4 (0.2%)	0 (0.0)	0 (0.0)	4 (0.4%)	NA	
Composite criterion						
Death, MI	51 (2.6%)	2 (1.5%)	22 (2.4%)	27 (2.9%)	0.816 (0.464–1.432)	0.478
Death, MI, stroke	61 (3.1%)	2 (1.5%)	28 (3.0%)	31 (3.4%)	0.902 (0.541–1.504)	0.693
Death						
All-cause	33 (1.7%)	2 (1.5%)	11 (1.2%)	20 (2.2%)	0.549 (0.263–1.146)	0.110
Cardiac	11 (0.6%)	1 (0.7%)	5 (0.5%)	5 (0.5%)	1.002 (0.290–3.460)	0.998
MI	21 (1.1%)	0 (0.0)	12 (1.3%)	9 (1.0%)	1.335 (0.562–3.167)	0.513
Stroke	13 (0.7%)	0 (0.0)	6 (0.6%)	7 (0.8%)	0.850 (0.285–2.528)	0.769
TVR	13 (0.7%)	1 (0.7%)	9 (1.0%)	3 (0.3%)	3.003 (0.813–11.092)	0.099
Definite or probable stent thrombosis	9 (0.5%)	0 (0.0)	6 (0.6%)	3 (0.3%)	1.995 (0.499–7.976)	0.329

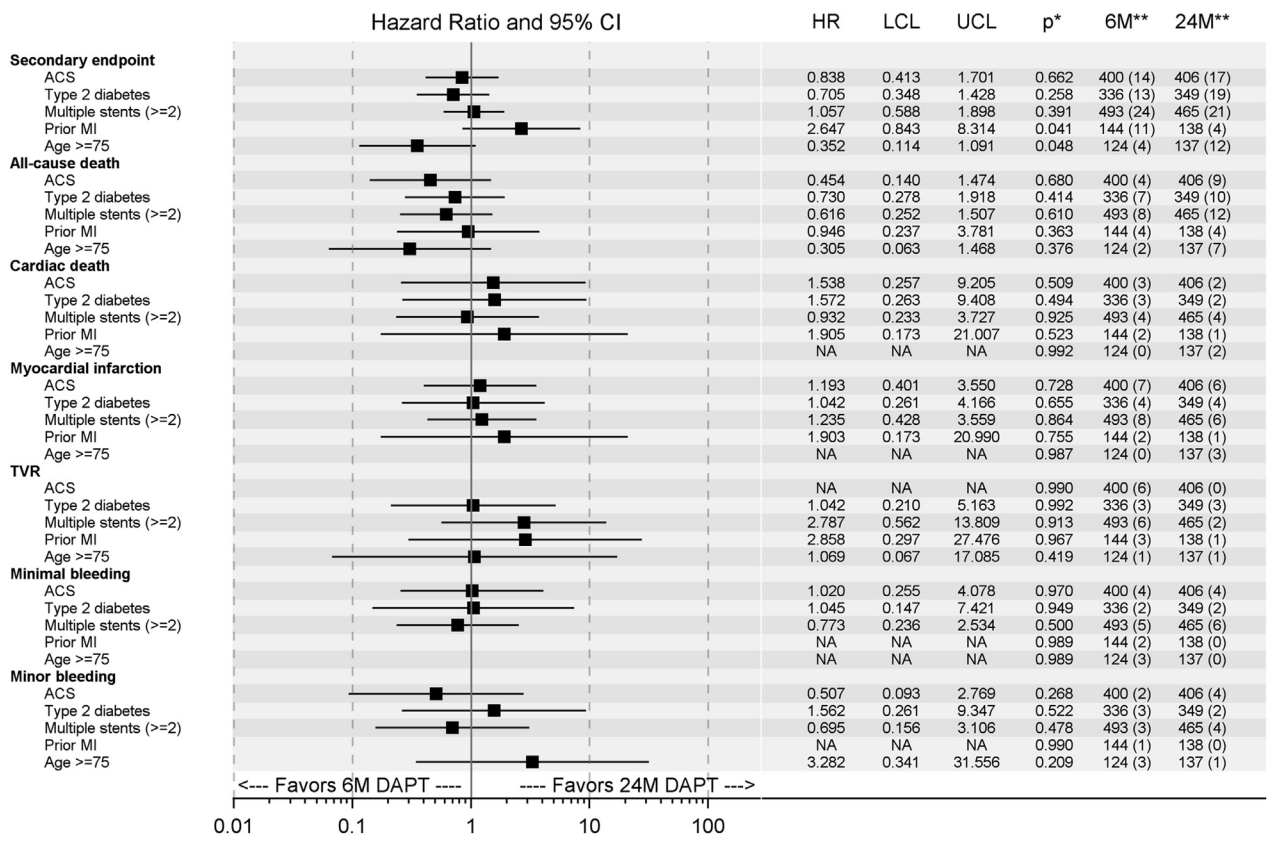
Values are n (%) or n unless otherwise indicated. *Hazard ratio calculated for 6-month DAPT vs. 24-month DAPT group.
NA = not applicable; TVR = target vessel revascularization; other abbreviations as in Table 1.

TABLE 3 2-Year Clinical Outcomes in the High-Risk Acute Coronary Syndrome Intention-to-Treat Study Population

	Resistant Group (n = 55)	6-Month DAPT (n = 400)	24-Month DAPT (n = 406)	Hazard Ratio* (95% CI)	p Value
Composite secondary endpoint (all-cause mortality, MI, stroke, TVR, major bleeding)	0 (0.0)	14 (3.5%)	17 (4.2%)	0.840 (0.414–1.704)	0.629
Secondary safety endpoints					
Bleeding					
Minimal bleeding	1 (1.8%)	4 (1.0%)	4 (1.0%)	1.020 (0.255–4.080)	0.977
Minor bleeding	0 (0.0)	2 (0.5%)	4 (1.0%)	0.507 (0.093–2.770)	0.433
Major bleeding	0 (0.0)	0 (0.0)	2 (0.5%)	NA	
Composite criterion					
Death, MI	0 (0.0)	11 (2.8%)	14 (3.4%)	0.804 (0.365–1.770)	0.587
Death, MI, stroke	0 (0.0)	12 (3.0%)	16 (3.9%)	0.766 (0.362–1.619)	0.485
Death					
All-cause	0 (0.0)	4 (1.0%)	9 (2.2%)	0.454 (0.140–1.473)	0.188
Cardiac	0 (0.0)	3 (0.8%)	2 (0.5%)	1.530 (0.256–9.156)	0.641
MI	0 (0.0)	7 (1.8%)	6 (1.5%)	1.193 (0.401–3.549)	0.751
Stroke	0 (0.0)	1 (0.3%)	3 (0.7%)	0.340 (0.035–3.267)	0.350
TVR	0 (0.0)	6 (1.5%)	0 (0.0)	NA	
Definite or probable stent thrombosis	0 (0.0)	5 (1.3%)	3 (0.7%)	1.700 (0.406–7.111)	0.468

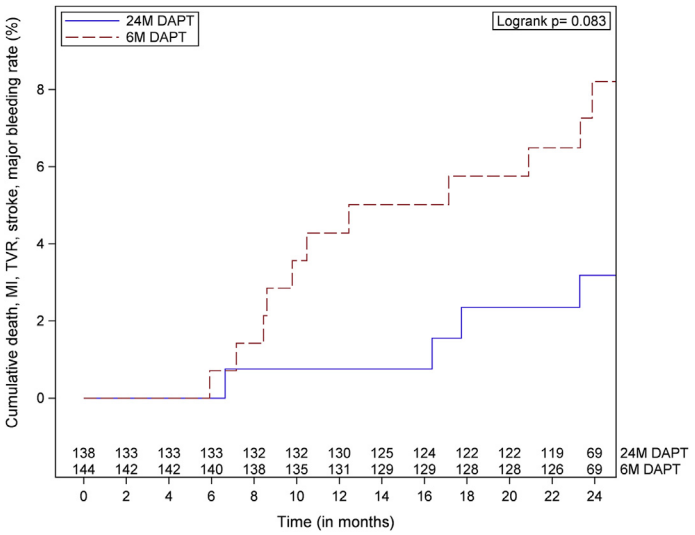
Values are n or n (%) unless otherwise indicated. *Hazard ratio calculated for 6-month DAPT vs. 24-month DAPT group.
Abbreviations as in Tables 1 and 2.

FIGURE 3 2-Year Clinical Outcomes per Subgroup



*The p value is from the test statistic for testing the interaction between dual antiplatelet therapy (DAPT) and any subgroup variable. **x(z), where x is the number of patients and z is the number of events in 6M DAPT and 24M DAPT populations for each subgroup. ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; LCL = lower confidence limit; MI = myocardial infarction; NA = not applicable; UCL = upper confidence limit.

FIGURE 4 Kaplan-Meier Survival Curve for Composite Endpoint at 2 Years in Patients With Previous Myocardial Infarction



DAPT = dual antiplatelet therapy; MI = myocardial infarction; TVR = target vessel revascularization.

Antiplatelet Therapy After Drug-Eluting Stenting) (23), that showed at 12 months a 1.5% rate of composite events (death, MI, stent thrombosis, stroke, and TIMI and major bleeding) compared with 1.5% in the ITALIC study. In addition to a lack of difference in the secondary composite endpoint between short and long DAPT, this study found no significant increase of bleeding in the long DAPT group at 2 years. This is consistent with the RESET (Real Safety and Efficacy of 3-Month Dual Anti-Platelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation) (7) and SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy) (5) randomized clinical trials in the same patient profile (45% stable angina in RESET, 62% in SECURITY). However, the 2-year results of the ITALIC trial showed a nonsignificant trend toward higher all-cause mortality in the 24-month DAPT group (2.2% for 24-month vs. 1.2% for 6-month DAPT; p = 0.11), as also reported in the Mauri et al. (10) study of 12- versus 30-month DAPT after DES implantation, in which all-cause mortality was 2.0% for extended DAPT versus 1.5% for placebo (HR: 1.36; 95% CI: 1.00 to 1.85; p = 0.05), mainly because of noncardiovascular causes.

The ITALIC subgroup analysis performed on type 2 diabetes, ACS, previous MI, and total stent length >30 mm did not show any difference between 6- and 24-month DAPT, in line with recent studies conducted in specific populations commonly considered at higher risk for ischemic events and requiring a potential longer duration of DAPT (24,25).

DURATION OF DAPT IN PATIENTS WITH ACS. Although the present study was not specifically designed to analyze the ACS population, no significant differences in terms of efficacy and safety were found. The PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study) trial (9), in all-comer patients with a majority of ACS clinical presentations (74%) and various type of stents, likewise reported no difference in a composite primary endpoint (10.1% vs. 10.0%, respectively; p = 0.91) or all-cause mortality (6.6% vs. 6.6%, respectively; p = 0.98) but, in contrast to the ITALIC trial, found a higher incidence of major bleeding with 24-month than 6-month DAPT (TIMI classification: 1.6% vs. 0.6%, respectively; p = 0.041). Moreover, in patients with prior MI, long antiplatelet therapy seemed to reduce the incidence of ischemic events (**Figure 4**), which is in line with the PEGASUS-TIMI 54 trial (11). PEGASUS was performed in a very high-risk population; the rate of bleeding was higher with extended DAPT than placebo (major TIMI, 2.30% vs. 1.06%; p < 0.001), whereas the incidence of cumulative cardiovascular death, MI, and stroke was much lower in the long DAPT group (7.77% for ticagrelor vs. 9.04% for placebo; p = 0.004). Likewise, Yeh et al. (26), in a subgroup analysis of DAPT, reported that extending DAPT beyond 1 year had no impact on all-cause mortality in patients with histories of MI (1.4% in DAPT group vs. 1.6% in placebo; p = 0.61), compared with increased overall mortality in patients without histories of MI (2.1% in the DAPT group vs. 1.5% in the placebo group; p = 0.04). It is possible to speculate that longer DAPT prevents thrombus formation in future plaque rupture in patients with histories of MI, who are at greater risk for ischemic events, mostly mediated by plaque destabilization (27), than those without histories of MI.

STUDY LIMITATIONS. Recruitment was stopped at 2,031 patients, rather than the 2,475 initially planned. However, the sample size was sufficient to confirm noninferiority at 2 years (4). Only DAPT with clopidogrel was tested, and no placebo was used in the 6-month group as a control. In addition, this trial was not designed to analyze the ACS subgroup and was underpowered to draw any conclusion in this population. In the subgroup analysis, major bleeding was not analyzed, because of a lack of events in the 6-month group.

CONCLUSIONS

Two-year outcomes in the ITALIC randomized controlled trial, performed in good aspirin responders with a low risk profile for ischemic events, confirmed that after the implantation of a single type of second-generation DES, 6-month DAPT is not inferior to 24-month DAPT in terms of all-cause mortality, MI, TVR, stroke, and major bleeding. In the specific subpopulation of patients with prior MI, longer compared with shorter DAPT duration was associated with a trend toward a lower rate of complications.

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PERSPECTIVES

WHAT IS KNOWN? Although the incidence of late stent thrombosis with second-generation of DES has been reduced compared with first-generation DES, the optimal duration of DAPT remains controversial.

WHAT IS NEW? Patients with a low risk profile for ischemic events receiving 6-month DAPT after PCI with second-generation DES have similar outcomes to those receiving 24-month DAPT.

WHAT IS NEXT? Further randomized clinical trials should pinpoint the population of patients who could benefit from longer duration of DAPT.

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