# Six-month versus 24-month dual antiplatelet therapy after implantation of drug eluting stents in patients non-resistant to aspirin: ITALIC, a randomized multicenter trial

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# Six-month versus 24-month dual antiplatelet therapy after implantation of drug eluting stents in patients non-resistant to aspirin: ITALIC, a randomized multicenter trial

Running title: ITALIC: 6 versus 24 month DAPT

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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 acute coronary syndrome.

**Objectives:** It was hypothesized that antiplatelet treatment with DAPT for 6 versus may be non-inferior to DAPT for 24 months in aspirin-sensitive patients

**Methods.** A multicenter, randomized study assigned patients undergoing implantation of Xience V (Abbott vascular) to receive 6- or 24-month DAPT with confirmed non-resistance to aspirin. The primary endpoint was a composite of death, myocardial infarction, urgent target vessel revascularization, stroke and major bleeding at 12 months post-stenting.

**Results.** 2,031 patients were enrolled in 70 European and Middle East centers. The trial was prematurely terminated due to problems with recruitment. 941 patients were randomized to 24 month-DAPT and 953 to 6 month-DAPT; 137 patients were resistant to aspirin. The two treatment groups had similar baseline and procedural characteristics. There was no significant difference between the 2 treatment groups regarding the primary endpoint (1.5 vs. 1.6%, p=0.85), even in high-risk (ACS) patients. Non-inferiority was demonstrated for 6-month versus 24-month DAPT, with an absolute risk difference of 0.11% (95% CI: -1.04 to 1.26; p for non-inferiority = 0.0002). There were no significant differences in stent thrombosis and in bleeding complications. In the 792 (44%) high-risk patients with ACS, primary and secondary endpoints did not significantly differ 1.7% [95% CI: 0.519 to 6.057; p=0.361]. Interaction between DAPT duration and ACS was non significant (p=0.305).

**Conclusion:** The ITALIC trial showed that rates of bleeding and of thrombotic events were not significantly different according to 6- versus 24-month DAPT after PCI with new-generation DES in good aspirin responders.

Clinical trial info: ITALIC: Is There A LIfe for DES after discontinuation of Clopidogrel NCT01476020

**Key word:** percutaneous coronary angioplasty**,** double Antiplatelet duration, drug eluting stent

**Abbreviations**

DAPT: dual antiplatelet therapy
DES: drug eluting stent
BMS: bare metal stent
ACS: acute coronary syndrome
PCI: percutaneous coronary intervention
MI: myocardial infarction
TVR: target vessel revascularization

## Introduction

Randomized trials have demonstrated that drug eluting coronary 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 in first-generation DES compared with BMS (5-7).

New-generation DESs show improved efficacy and safety compared with first-generation DES and BMS. Several studies reported significant decreases in mortality and myocardial infarction (8-13). Compared with BMS and first-generation DES, the risk of definite or probable stent thrombosis is on average 50% lower with new-generation DES (10-13). Several randomized and observational trials of new-generation DES suggested that they allow a shorter duration of dual antiplatelet therapy (DAPT) (14-20). Current guidelines recommend 6 months' DAPT after DES in stable patients (21) and 1 year in acute coronary syndrome (ACS) patients (21-22). However, when the trial began, the guidelines (22) recommend 12 months' DAPT after DES implantation regardless the clinical situation. A randomized multicenter trial was therefore conducted to assess the effect of 6 versus 24 months' DAPT on medium-term clinical outcome after coronary intervention in a real-world clinical population receiving new-generation DES. To be sure that patients would be protected by their antiplatelet therapy in either situation, 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

trial) conduct by the French Society of Cardiology and in 7 European and Middle East sites from January 2012 to November 2013 under the same protocol (ITALIC PLUS trial). Complete lists and detailed information regarding the institutions involved are given in Appendix 1. 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 aged 18 years or over, eligible for percutaneous coronary intervention (PCI), with at least one Xience V DES (Abbott Vascular Devices, Santa Clara, California) implanted, in all clinical situations excluding primary PCI for acute myocardial infarction and treatment of the left main artery. Patients were required to be treated with Xience V only. All patients gave written informed and dated consent to the study. Patients were not pre-treated with abciximab during hospital stay. When the study was designed, resistance to aspirin was suspected to be associated with stent thrombosis after DAPT discontinuation. Consequently, non responders to aspirin were excluded from randomization.. Aspirin resistance was checked. In patient recieved tirofiban or eptifibatide, the aspirin resistance was checked at least 24 hours after the last injection. Patients were pre-treated with aspirin and clopidogrel (prasugrel or ticagrelor) before PCI. Exclusion criteria were: prior DES implantation within 1 year; known platelet level less than 100,000/µl 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 enrolment; or severe concomitant disease with less than 2 years' life expectancy.

**Randomization and aspirin resistance assessment**

PCI comprised implantation of at least one Xience V DES in patients under DAPT with clopidogrel (prasugrel or ticagrelor) and aspirin. The dose was 75 mg per day for clopidogrel,

60 mg per day for prasugrel and 90 mg twice per day for ticagrelor. Aspirin resistance was assessed after an initial dose of 75mg. In case of poor response to the first dose of aspirin, patients 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. In case of persistent poor response after increasing the aspirin dose, patients were included in the aspirin-resistant control group, with the same follow-up. During the PCI hospitalization, patients sensitive to aspirin were assigned to 6 versus 24 months' DAPT by centralized randomization using an interactive web-based system with a 1:1 ratio. If an endpoint (see below) 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 epinephrine-collagen cartridge closure time >165 seconds; multiplate electrical impedance aggregometry (Dynabyte, Munich, Germany), defining aspirin response as ≥30% reduction in platelet aggregation; or VerifyNow Aspirin (Accumetrics, San Diego, California), defining aspirin response as ≥ 550 aspirin reaction units (25). The type of test depended on the center. The same test, however, was systematically used in any given patient.

**Endpoints**

The primary endpoint was a composite criterion comprising death, myocardial infarction (MI), repeat emergency TVR, stroke or major bleeding according to the Thrombolysis in Myocardial Infarction criteria (26), from all causes, within 12 months of stenting. All clinical endpoints were defined according to the Academic Research Consortium criteria (27-28). Myocardial infarction 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 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 hours, diagnosed as stroke by a physician; stroke was classified as hemorrhagic (on computed tomography, magnetic resonance imaging or autopsy) or non-hemorrhagic. 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, 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-month, 12-month, 24-month 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 a 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**

*Sample size calculation.* In Spirit V (29), the composite rate of cardiac death, MI (per protocol), stent thrombosis (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 non-inferiority of short compared to long DAPT with 80% power. The expected rate of events was 3% and the non-inferiority margin was set at 2%, leading to inclusion of 900 patients per 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 consideting an alpha=5% but to be compliant with the most recent guidelines the non-inferiority confidence interval has been performed finally at 97.5%. Statistical comparison was performed between the 6 versus 24 months' 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 categoric variables. Kaplan-Meier survival curves were constructed (30), and differences between the curves were tested by log-rank test. Proportional hazard models (31) were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Survival analysis was performed in the intention-to-treat population, with primary endpoint as event. Sensitivity analysis was performed in the per-protocol population to assess robustness of results. Statistical analyses were performed and validated using SAS® software V9.4. Non-inferiority was tested on primary endpoint with a 1-tailed 97.5% confidence interval. Time to primary endpoint and all secondary endpoints were also assessed on survival analysis. The group of patients presenting acute coronary syndrome was analyzed post hoc.

**Results**

**Study population:** Figure 1 shows the trial flow-chart. 2,031 patients were enrolled. The trial

was prematurely terminated due to problems with recruitment. After aspirin monitoring, 131 patients were classified as aspirin resistant, and were not randomized but followed up in the aspirin-resistant group. 1,894 patients were eligible for randomization. Before 6 months, 44 patients were excluded from analysis as they experienced an endpoint-related event (13 deaths, 10 MIs, 2 TVRs). 1,850 patients were thus randomly allocated to 24-month (Group 1: 924 patients) versus 6-month DAPT (Group 2: 926 patients).

The two test groups had similar baseline (Table 1) and procedural characteristics (Table 2). One-third of patients had history of type-2 diabetes; a quarter had previous PCI or bypass surgery. Nearly half presented with ACS. In more than half of the patients, 2 or more lesions were stented, with a mean stent length of around 37 mm.

**Follow-up and clinical outcomes:** One-year follow-up information could be obtained for 98.5% of patients. In the short-DAPT arm, 221 patients (24.2%) did not respect the 6-month treatment duration, 83 (8.9%) continuing treatment longer and the others stopping earlier; in the long-DAPT arm, 49 patients (5.4%) discontinued treatment before 24 months.Table 3 shows endpoints during 1 year's follow-up. There was no significant difference between treatment groups regarding the primary endpoint (1.5 vs. 1.6%, p=0.85) (Fig 2) or its components (secondary endpoint). TVR rates were very low in both groups (2 (0.2%) vs. 5 patients (0.5%)); there were no stent thromboses in the 6-month DAPT group and only 3 in the 24-month group. There was no significant difference in bleeding complications. Major bleeding occurred only in 3 patients in the 24-month group. For the 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 and Fig 3).

Non-inferiority was established for 6-month versus 24-month DAPT, with an absolute risk difference of 0.11% (95% CI: -1.04 to 1.26; p for non-inferiority = 0.0002). The significance

of the test was confirmed by the lower limit of the 1-tailed 97.5% CI (-1.04%) being greater than the non-inferiority margin (-2%).

**Discussion**

This prospective randomized trial demonstrated that 6-month DAPT after new-generation DES implantation was non-inferior to 24-month DAPT for the composite primary endpoint of death, stroke, MI, emergency TVR and major bleeding and for the secondary endpoints. A single type of DES was implanted, so as to minimize variation in efficacy and safety, which may be expected to differ between types of stent.

The protocol was designed assuming a MACE rate of around 3% between 6 and 12 months in the control group; the observed rate was in fact close to 1.5% (respectively 1.5% and 1.6% in the 24-month and 6-month DAPT group), which was significantly lower than expected, although estimates of the expected event rate were based on data from previous studies (32-33) demonstrating the safety and efficacy of this generation of stent, even in a complex population (one-third diabetic, 44% ACS, and 43% multiple lesions). 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). The Xience V cobalt-chromium everolimus-eluting stent used in the present trial is probably one of the safest new-generation models: a recent large-scale network meta-analysis including more than 85,000 randomized patients showed it to be safe, with better outcome than BMS, first-generation DES or certain other new-generation DESs (34).

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

The present trial did not show an increase in bleeding in the long DAPT arm. Similar findings

were reported in the CREDO trial (35) where patients were randomized to 12 months' versus 1 month's DAPT after PCI with a bare metal stent (BMS); longer DAPT reduced the composite end point of death, stroke and MI, but there was no significant difference in the individual components of the end-point, and no significant risk of major or minor bleeding in contrast to the Prodigy Trial,which compared also 6 to 24 months of DAPT, and demonstrated an increased rate of bleeding in the long-duration treatment arm.

*New-generation DES and DAPT*

Regardless of DES type, several guidelines call for a minimum 12 months' DAPT after DES implantation, to prevent late stent thrombosis (22, 36). However, new-generation DESs have been shown to have a safety profile similar to or even better than BMS (4, 11-13, 37). No data support prolonging DAPT beyond 1 year after DES implantation. Indeed, the ZEST-LATE/REAL-LATE randomized trial (38) reported a non-significant trend for a higher rate of MI, stroke and death at a median 19 months' follow-up in patients continuing versus stopping clopidogrel 1 year after stenting. Several randomized trials comparing short (3-6 months) versus extended DAPT (12-24 months) consistently showed lack of benefit in terms of ischemic outcome but a higher risk of bleeding (14, 16-17). A recent meta-analysis comparing brief vs. prolonged DAPT (beyond 12 months) concluded that extending DAPT beyond 6 months increased the risk of bleeding without reducing the rate of ischemic events (15, 39). These findings explain the modifications 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 non-inferior safety for 6-months' versus 24-months' DAPT, without any specific advantage in terms of bleeding in the short DAPT group.

The 1-year duration of DAPT after ACS in the most recent guidelines was supported by 3 randomized trials. In the oldest, PCI-CURE (40), 15 years ago PCI was performed by stenting in only 80% of cases, using BMSs. The other trials, PLATO and TRITON TIMI 38

(41-42), used DESs in only 19% and 40% of cases, respectively; these were first-generation DESs, while new-generation DESs, with thin stent struts, advanced polymers and improved antiproliferation agents, have further improved efficacy and safety. Moreover, these 2 more recent trials compared efficacy between different DAPT associations, and not duration of DAPT following ACS. Randomized studies comparing longer versus shorter DAPT after ACS are lacking. The present trial showed a very low rate of thrombotic events with new-generation DES, even after ACS, in the 6-month DAPT group. However, in a setting of 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 stent thrombosis but also the risk of recurrent spontaneous ischemic events; in previous trials analyzing evolution after ACS (43), the majority of thrombotic events occurred within the 6 first months. Intra vascular ultrasound studies showed plaque healing with statin treatment after ACS (44-45). 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 the 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 greater than 50%, whereas in aspirin-resistant patients risk seems to noticeably increase (46). Several prospective studies demonstrated an association between biochemical aspirin resistance and clinical outcome (47-50). 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

ADP-induced LTA, PFA-100, and urinary thromboxane, is dose-related, indicating that aspirin non-response decreases with increasing dose, from 75 mg to 325 mg (25). The recent randomized ARCTIC trial of a bedside platelet function test was neutral in its findings (51); 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 a real opportunity to compare two strategies, aspirin-clopidogrel (prasugrel or ticagrelor) versus aspirin alone, in good aspirin responders. In ADAPT-DES trial, they reported that high platelet reactivity on aspirin was not significantly associated with stent thrombosis, myocardial infarction, or mortality after drug-eluting stent implantation, but was an independent predictor of freedom from clinically relevant bleeding. However, the trial was designed for the occurrence of stents thrombosis. They did not compare the duration of DAPT and the efficacy of aspirine alone (52).

Crossover from dual 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 over-treatment of patients known to be resistant to aspirin. The role of ASA resistance monitoring in clinical practice should be questioned.

*Study limitations and strengths*

Due to inclusion difficulties, recruitment stopped at 2,031 patients, rather than the 2,475 patients required in order to have 900 analyzable patients in each group; however, as we finally has a rate of events of 1.5% (compared to 3% expected), we might consider that the sample size would be enough to consider the conclusion as valid, also because we are far from the boundary. The study was open-label and not placebo-controlled in the 6-month arm.

However all clinical endpoints were assessed by members of independent clinical event adjudication committee and statistical analyses were performed by independent statisticians.

**Conclusion**

The present trial showed that rates of bleeding and thrombotic events were not significantly different between the 6- and 24-month DAPT groups after PCI with new-generation DES, and that 6-month DAPT was non-inferior to 24-month DAPT in good aspirin responders. Non-inferiority 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.

## PERSPECTIVES

### Clinical Competencies

The issue of post stenting dual antiplatelet treatment duration remains open to debate, especially in recipients of new-generation DES which have been developed to ensure increased safety.

The analysis reported here is one of many studies which have randomly compared variable short versus long DAPT durations.

The specificity of the ITALIC study design is that it includes aspirin resistance testing.

The results of the study suggest that reducing DAPT duration to 6 months is not associated with increased risks of thrombotic events and conversely that 24-month DAPT duration does not increase the risk of bleeding.

### Translational Outlook

Short DAPT durations comparable to those prescribed to bare metal stent recipients are currently being investigated in patients treated with the last DES generations.

Should the results be positive, one can expect that in the future, as a consequence of enhanced stent technology, DAPT duration will be prescribed according to the clinical status of the patients irrespective of the presence of an active stent.

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**Figure titles and legend**

**Figure 1 :** ITALIC Trial Flow Chart

**Figure 2:** Kaplan-Meier survival curve for primary endpoint

**Figure 3:** 1-Year clinical outcomes in the ACS (fig 3a) and non ACS patients (fig 3b)

**Table 1: Baseline patient data**

| | Resistant Group n=131 | 24-month DAPT n=910 | 6-Month DAPT n=912 | P |
|---|---|---|---|---|
| Age, yrs | 62.6 (10.8) | 61.5 (11.1) | 61.7 (10.9) | 0.792 |
| Male gender, n (%) | 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, n (%) | 42 (32.1%) | 344 (37.8%) | 331 (36.3%) | 0.505 |
| Hypertension, n (%) | 76 (58.0%) | 589 (64.7%) | 595 (65.2%) | 0.817 |
| Hyperlipidemia, n (%) | 84 (64.1%) | 611 (67.1%) | 612 (67.1%) | 0.986 |
| Smoker, n (%) | 69 (52.7%) | 480 (52.7%) | 464 (50.9%) | 0.424 |
| Family history, n (%) | 50 (38.2%) | 325 (35.7%) | 322 (35.3%) | 0.856 |
| Previous MI, n (%) | 36 (27.5%) | 134 (14.7%) | 142 (15.6%) | 0.615 |
| Previous PCI, n (%) | 39 (29.8%) | 205 (22.5%) | 220 (24.1%) | 0.421 |
| Previous CABG, n (%) | 6 (4.6%) | 45 (4.9%) | 61 (6.7%) | 0.111 |
| Previous stroke, n (%) | 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 to 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, n (%) | | | | 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%) | |

**Table 2 : Procedural characteristics**

| Characteristic | Resistant Group n=131 | 24-Month DAPT n=910 | 6-Month DAPT n=912 | p |
|---|---|---|---|---|
| Procedural success, n (%) | 130 (99.2%) | 901 (99.0%) | 895 (98.1%) | 0.112 |
| Target lesion coronary artery, n (%) | | | | |
| 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 no. of lesion treated/patient, n (%) | | | | 0.239 |
| 1 lesion treated | 77 (58.8%) | 494 (54.3%) | 459 (50.3%) | |
| 2 lesions treated | 38 (29.0%) | 252 (27.7%) | 275 (30.2%) | |
| 3 of more lesions treated | 16 (12.2%) | 164 (18.0%) | 178 (19.5%) | |
| Number of XienceV stent per patient,n(%) | 1.6 (0.8) | 1.7 (1.0) | 1.7 (1.0) | 0.497 |
| Total stent length, mean ± SD | 33.2 (22.7) | 37.8 (26.1) | 38.6 (25.6) | 0.533 |
| Stent diameter, mean ± SD | 3.0 (0.2) | 3.1 (0.3) | 3.1 (0.3) | 0.113 |
| Rotablator, n (%) | 4 (2.9%) | 12 (1.3%) | 15 (1.6%) | 0.553 |
| At least 1 restenotic lesion, n (%) | 5 (3.8%) | 51 (5.6%) | 54 (5.9%) | 0.772 |

**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** |
|---|---|---|---|---|---|
| Primary end point, n (%) | | | | | |
| Death from any cause, MI*, stroke, TVR†, major bleeding | 2 (1.5%) | 14 (1.5%) | 15 (1.6%) | 1.072 [0.517 ; 2.221] | 0.85 |
| Secondary end point, n (%) | | | | | |
| 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, n (%) | | | | | |
| 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, n (%) | 0 | 4 (0.4%) | 6 (0.7%) | 1.500 [0.423 ; 5.317) | 0.53 |
| Stroke, n (%) | 0 | 4 (0.4%) | 0 | N/A | |
| TVR, n (%) | 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, n (%) | 0 | 3 (0.3%) | 0 | N/A | |

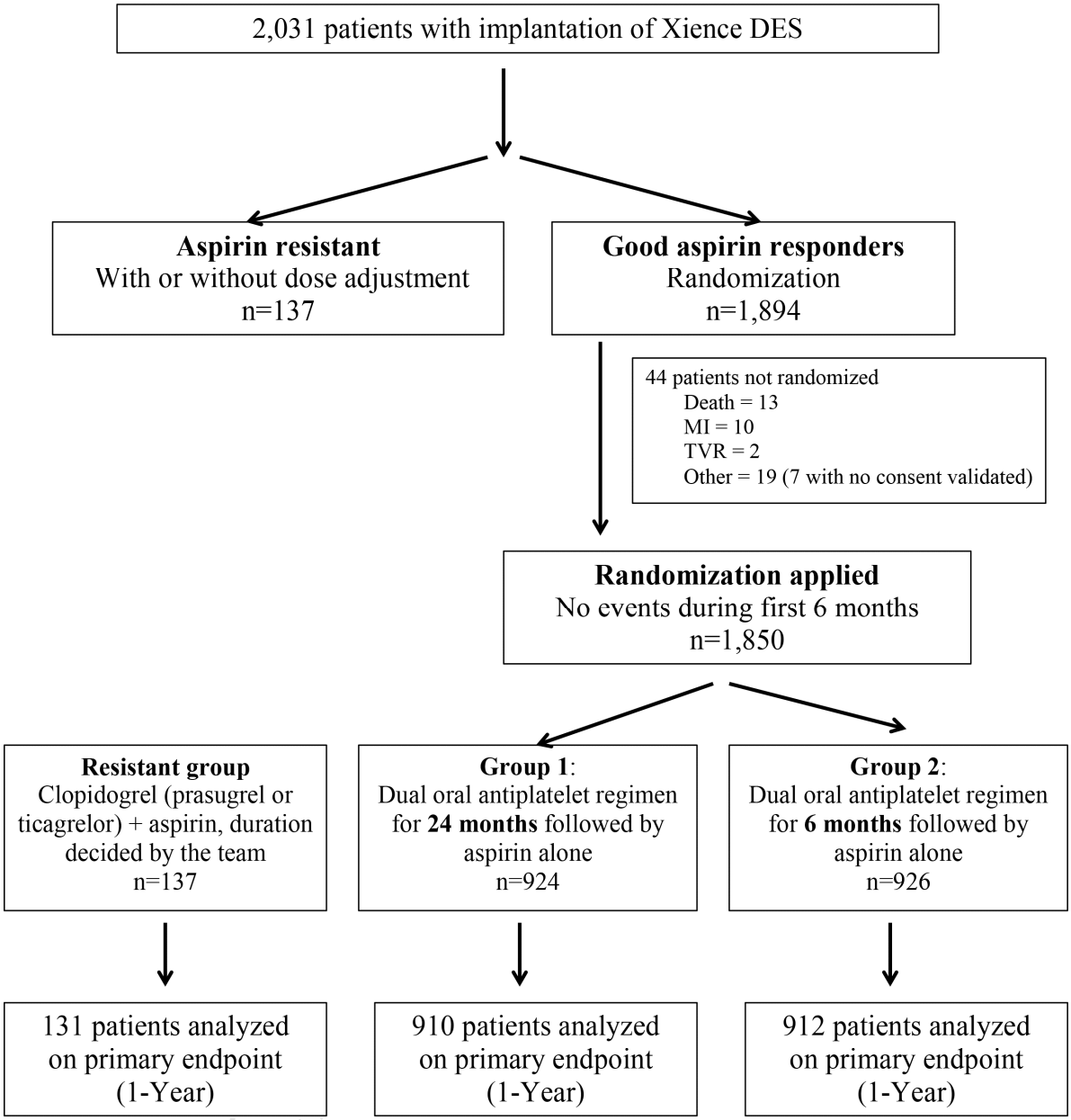
*MI: myocardial infarction; †TVR: urgent target vessel revascularization

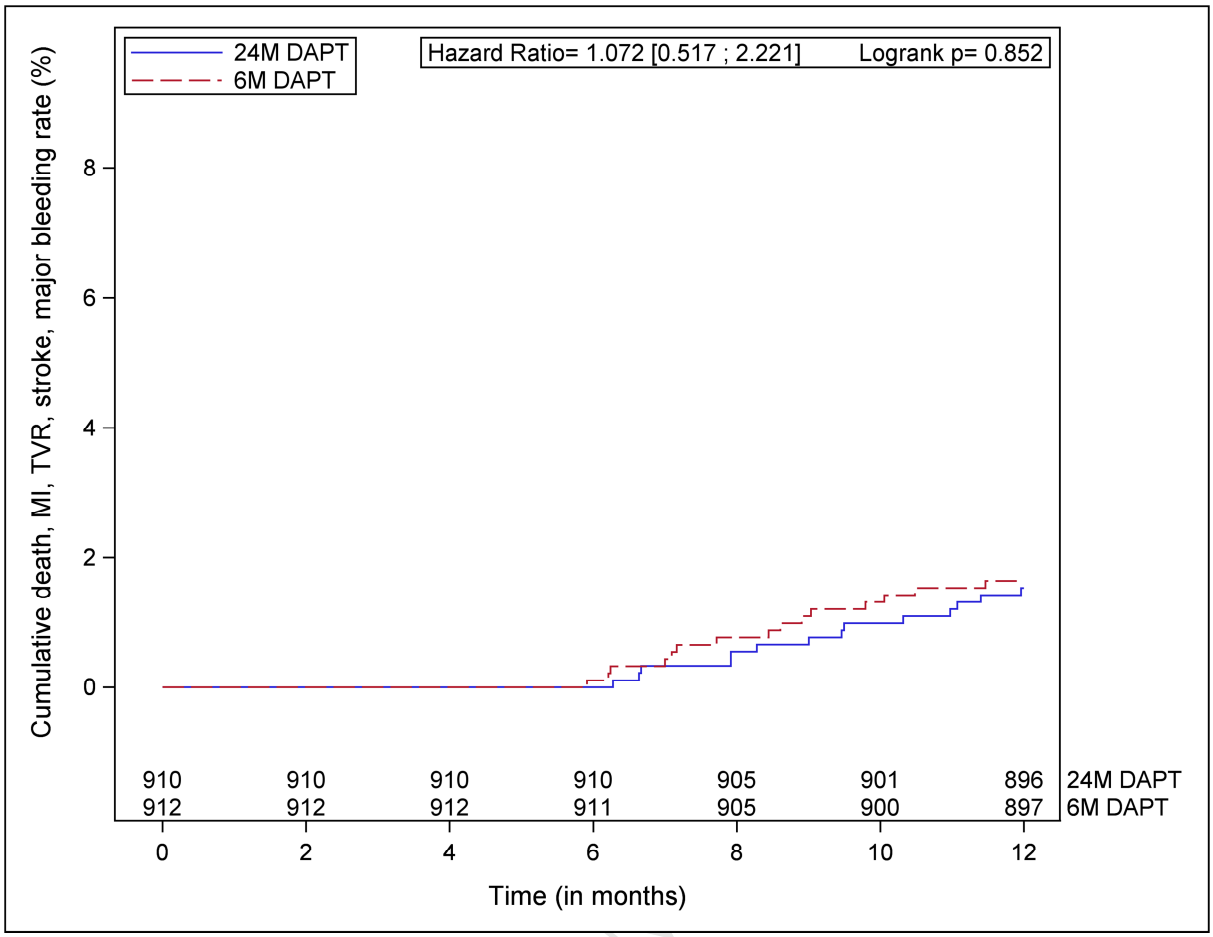
**Table 4: 1-year clinical outcomes in the high-risk intention-to-treat study population (acute coronary syndrome)**

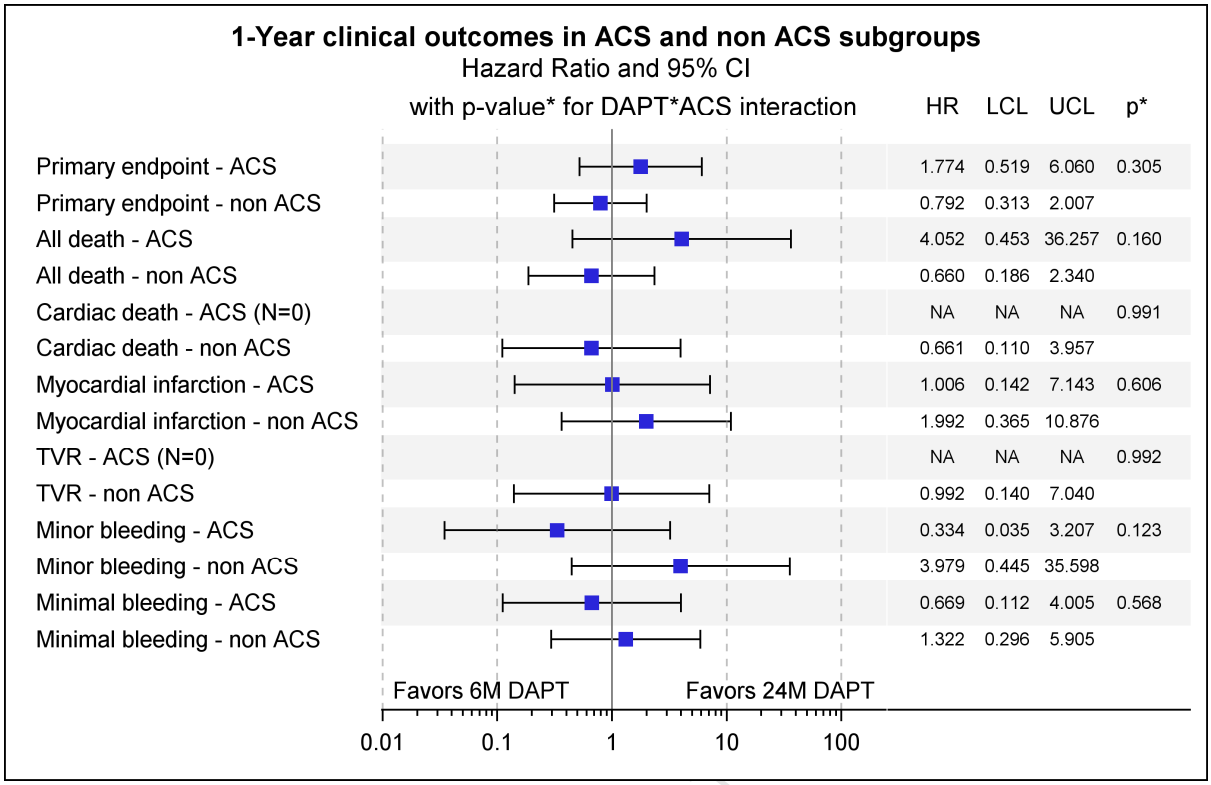
| | Resistant Group n=50 | 24-month DAPT n=397 | 6-Month DAPT n=395 | Hazard Ratio [95% CI] | **p** |
|---|---|---|---|---|---|
| Primary end point, n (%) | | | | | |
| Death from any cause, MI*, stroke, TVR†, major bleeding | 0 | 4 (1.0%) | 7 (1.8%) | 1.773 [0.519 ; 6.057] | 0.361 |
| Secondary end point, n (%) | | | | | |
| 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, n (%) | | | | | |
| 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 | |
| Myocardial infarction, n (%) | 0 | 2 (0.5%) | 2 (0.5%) | 1.006 [0.142 ; 7.144] | 0.99 |
| Stroke, n (%) | 0 | 1 (0.3%) | 0 | N/A | |
| TVR, n (%) | 0 | 0 | 3 (0.8%) | N/A | 0 |
| Stent thrombosis | 0 | 0 | 2 (0.5%) | N/A | |
| Major bleeding, n (%) | 0 | 1 (0.3%) | 0 | N/A | |

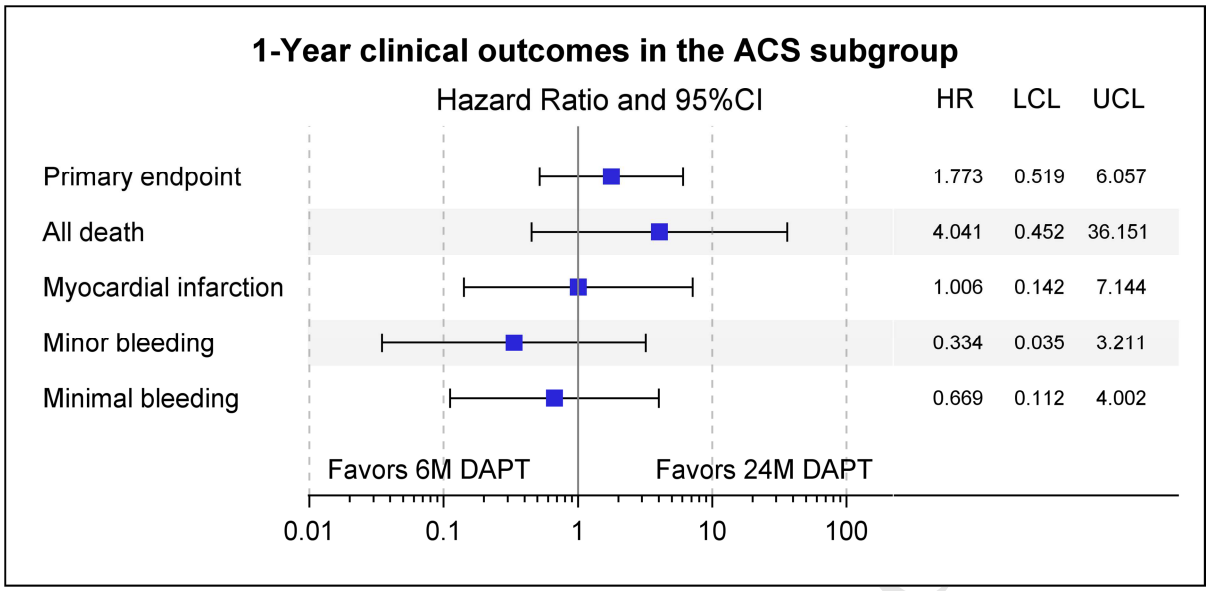
*MI: myocardial infarction; †TVR: urgent target vessel revascularization

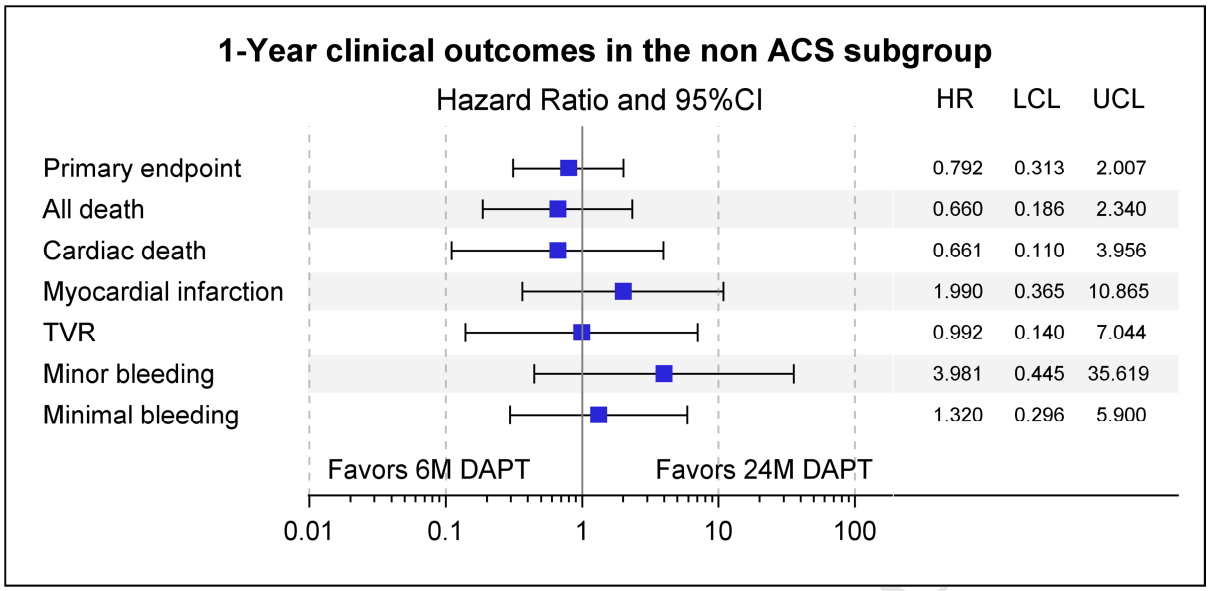
**The ITALIC Trial: FLOW CHART**











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