Rev Bras Cardiol Invasiva.
2014;22(3):233-9

Original Article

OPTIMIZE Trial: Subanalysis of Patients Treated at Instituto Dante Pazzanese de Cardiologia

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ABSTRACT

Background: OPTIMIZE was a prospective study conducted in 33 Brazilian sites that randomized patients to receive dual antiplatelet therapy for 3 or 12 months after zotarolimus eluting stent implantation. Our objective was to evaluate the outcomes of patients treated at Instituto Dante Pazzanese de Cardiologia and compare them to the outcomes of patients from other participating study sites. **Methods**: Patients with stable angina or low risk acute coronary syndrome were included in the study. The primary outcome was the incidence of adverse clinical and cerebral events, a composite of all cause of death, myocardial infarction, stroke, or major bleeding at 12 months. **Results**: Between April/2010 and March/2012, we included 624 (20%) patients in the OPTIMIZE study. At 12 months, there was no significant difference between groups (3 vs. 12 months of dual antiplatelet therapy) for net adverse clinical and cerebral events (3.8% vs. 6.7%; $p = 0.15$), major adverse cardiac events (6.7% vs. 7.1; $p > 0.99$) or stent thrombosis (0 vs. 1.3%; $p = 0.12$). The heterogeneity test showed that the variability observed in the results of Instituto Dante Pazzanese de Cardiologia and in the remaining sites was not greater than the expected to occur by chance ($p = 0.064$). **Conclusions**: In patients treated at Instituto Dante Pazzanese de Cardiologia, 3 months of dual antiplatelet therapy was not inferior to 12 months of therapy for the occurrence of net adverse clinical and cerebral events or major adverse cardiac events. There was no significant increased risk of stent thrombosis. Our results did not differ from the remaining participating sites of OPTIMIZE.

DESCRIPTORS: Coronary artery disease. Drug-Eluting stents. Paclitaxel. Sirolimus. Hemorrhage. Coronary thrombosis.

RESUMO

Estudo OPTIMIZE: Subanálise dos Pacientes Tratados no Instituto Dante Pazzanese de Cardiologia

Introdução: O OPTIMIZE constituiu um estudo prospectivo conduzido em 33 centros no Brasil, que randomizou pacientes para receber terapia antiplaquetária dupla por 3 ou 12 meses, após o implante de stents com eluição de zotarolimus. Nosso propósito foi avaliar os resultados dos pacientes tratados no Instituto Dante Pazzanese de Cardiologia e, posteriormente, compará-los aos de outros centros envolvidos do estudo. **Métodos**: Foram incluídos pacientes com angina estável ou síndrome coronariana aguda de baixo risco. O objetivo primário foi avaliar a incidência de eventos clínicos e cerebrais adversos, uma combinação de morte por qualquer causa, infarto agudo do miocárdio, acidente vascular encefálico ou sangramento maior aos 12 meses. **Resultados**: Entre abril de 2010 e março de 2012, incluímos 624 (20%) pacientes no OPTIMIZE. Aos 12 meses, não houve diferença significativa entre os grupos (3 vs. 12 meses de terapia antiplaquetária dupla) quanto à incidência de eventos clínicos e cerebrais adversos (3,8% vs. 6,7%; $p = 0,15$), eventos cardíacos adversos maiores (6,7% vs. 7,1%; $p > 0,99$) e nem de trombose do stent (0 vs. 1,3%; $p = 0,12$). O teste de heterogeneidade mostrou que a variabilidade observada nos resultados do Instituto Dante Pazzanese e dos outros centros não foi maior que a esperada para ocorrer por acaso ($p = 0,064$). **Conclusões**: Nos pacientes tratados no Instituto Dante Pazzanese, o período de 3 meses de terapia antiplaquetária dupla não foi inferior a 12 meses quanto à ocorrência de eventos clínicos e cerebrais adversos ou eventos cardíacos adversos maiores. Não houve aumento significativo do risco de trombose do stent. Nossos resultados não diferiram dos demais centros participantes do OPTIMIZE.

DESCRITORES: Doença da artéria coronariana. Stents farmacológicos. Paclitaxel. Sirolimo. Hemorragia. Trombose coronária.

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Received on: 06/12/2014 • Accepted on: 08/31/2014

Rev Bras Cardiol Invasiva.
2014;22(3):233-9

The administration of the dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and a P2Y12 inhibitor is crucial to prevent coronary-stent thrombosis. This complication, considered to be severe, occurs in 1 to 2% of cases of patients submitted to percutaneous coronary intervention (PCI); it is associated with the occurrence of acute myocardial infarction (AMI) in approximately 70% of patients and with death in 30 to 40%.[1] The most important predisposing factor to thrombosis is early discontinuation of DAPT, either due to lack of patient adherence or to clinical indication, such as bleeding and need for non-scheduled surgeries.[2]

With the first generation of drug-eluting stents (DES), DAPT was originally recommended for a period ranging between three to 6 months.[3] However, limited data from studies and retrospective analyses demonstrated the occurrence of late and very late stent thrombosis, suggesting benefit from prolonged DAPT use (≥ 12 months).[4] Because of these controversies, in 2006, the Food and Drug Administration (FDA) recommended the use of this therapy for a period of 12 months for all patients treated with DES.

Recently, some questions have arisen regarding DAPT prescription for one year in patients receiving DES, as prolonged treatment might be unnecessary in many cases, in addition to several doubts regarding the decrease in the risk of late and very late thrombosis with longer therapy. Thus, randomized clinical trials were performed to test different periods of DAPT use (3 or 6 months *versus* 12 or 24 months) in patients treated with second-generation DES. Their results showed no benefit from prolonged use and some studies have even suggested that this time could be safely reduced to 6 months or less. It is important to stress that problems related to prolonged DAPT were identified, including bleeding complications, adherence, and costs related to the treatment.[5-7]

Although recent studies comparing first and second-generation DES demonstrated that the latter are safer,[8-12] the duration of DAPT remains uncertain. The Endeavor® (Medtronic Inc., Minneapolis, United States) is a second-generation zotarolimus-eluting stent (ZES), which demonstrated rates of stent thrombosis and clinical safety events at 5 years similar to those of bare-metal stents (BMS), using DAPT for a period of up to 6 months.[13] In order to prospectively assess the safety of short-term DAPT (three months) in contrast to the long-term use (12 months) in patients treated with ZES, the OPTIMIZE randomized trial was designed and conducted in 33 centers in Brazil.[14]

This analysis aimed, firstly, to evaluate the results of the patient population from one of the participating centers, the Instituto Dante Pazzanese de Cardiologia (IDPC), and secondly, to compare the results obtained in this center with those from other centers from the OPTIMIZE trial.

METHODS

Inclusion and exclusion criteria

The present study included only patients from IDPC randomized to the OPTIMIZE trial. Inclusion criteria were broad, as the aim was to characterize a population from everyday clinical practice. Patients had to have stable angina or low-risk acute coronary syndrome (unstable angina or acute myocardial infarction AMI < 30 days with negative myocardial necrosis markers) and at least one coronary lesion > 50% in a coronary artery > 2.5 mm.

Patients who had AMI with ST-segment elevation, candidates for primary or rescue PCI, lesions in saphenous vein grafts, previous treatment with DES, or elective surgery planned for the following 12 months were excluded.

Randomization

All patients included in the study signed an informed consent. Patients were randomized to use DAPT for a short (3 months) or long (12 months) period. Randomization was performed using groups of eight patients, with a ratio of 1:1 between the two study groups, stratified by the presence of diabetes mellitus.

Procedure and clinical follow-up

Stent implants were performed according to the technique established by the institution. ZES of varying sizes were used, according to vessel diameter and lesion extent.

All patients received ASA at a loading dose of 300 to 500 mg 24 hours before the procedure, and 100 to 200 mg a day were maintained indefinitely. Clopidogrel was administered at a loading dose of 300 mg, 24 hours prior to procedure (or 600 mg at least 2 hours before) with a maintenance dose of 75 mg daily for three or 12 months, according to randomization.

Patient return for clinical consultation or telephone contact was obligatory after 30 days and 3, 6, and 12 months. Patients were followed-up for one year, and all adverse events during this period were recorded. Clinical outcomes were validated by an independent committee of clinical events, blinded to the randomized groups.

Angiographic analysis

Angiographic analysis was performed by quantitative angiography at an independent central angiography laboratory. The protocol did not require angiographic follow-up, which was performed only in patients who

required new target-lesion revascularization, or stent thrombosis.

Clinical outcomes

The primary study outcome was the occurrence of net adverse clinical and cerebral events (NACCE), defined by a combination of death from any cause, AMI, stroke, or major bleeding. The criteria for major bleeding used in the study were major bleeding according to the modified REPLACE-2 and severe bleeding according to GUSTO. AMI was defined according to the World Health Organization criteria.

The secondary outcome included major adverse clinical events (MACE), defined as death from any cause, AMI, emergency coronary artery bypass graft surgery (CABG) and target-lesion revascularization; and definitive or probable stent thrombosis, according to the criteria of the Academic Research Consortium (ARC).

Statistical analysis

Categorical variables were presented as numbers and percentages and differences were evaluated by Fisher's exact test. Continuous variables were presented as mean ± standard deviation and analyzed by Student's *t*-test. The time until the primary outcome and its components were evaluated by the Kaplan Meier method, using the log-rank test to compare the differences.

Based on data obtained from the populations of IDPC and the other centers of the OPTIMIZE trial (other than IDPC), the odds ratio (OR) of NACCE in the 3 month group vs. the 12 month group was calculated. A test for heterogeneity was performed to verify whether the variability observed in the OR between the IDPC populations and then on IDPC populated was higher than that expected to occur by chance. A p-value < 0.05 was considered as significant.

RESULTS

Between April 2010 and January 2012, 3,119 patients were included in the OPTIMIZE trial, of whom 624 patients (20%) from the IDPC were submitted to PCI with ZES and randomized to DAPT for 3 months (312 patients) vs. 12 months (312 patients). One-year clinical follow-up was obtained in 99.8% of patients.

The rate of adherence to clopidogrel at 3 months was 99.7% for the short-term group and 99.4% for the long-term group. At the 1-year clinical consultation, clopidogrel use was 3.2% and 97.4% in the 3 month vs. 12 month group, respectively, and the use of ASA was 99.4% and 99%, respectively.

Table 1 presents the demographic and clinical characteristics of each group. Mean age was 60 ± 9 years, with a predominance of males (67%), and over one-third of the study population (38%) consisted of diabetic patients. The groups were homogeneous regarding all assessed demographic and clinical characteristics.

Table 2 illustrates the angiographic characteristics of the lesions treated in each group. Over one-third of patients in both groups had lesions in the left anterior descending artery, with rare cases of involvement of the left main coronary artery (less than 2% in each group). The groups were comparable regarding the mean reference vessel diameter and percentage of stenosis diameter.

TABLE 1
Demographic and clinical characteristics.

Variables	DAPT 3 months (n = 312)	DAPT 12 months (n = 312)	*p*-value
Age, years	61 ± 9	61 ± 10	0.12
Male gender, n (%)	211 (68)	209 (67)	0.33
Diabetes mellitus, n (%)	116 (37)	121 (39)	0.48
Using insulin	31 (10)	29 (9)	0.67
Arterial hypertension, n (%)	266 (85)	270 (87)	0.31
Dyslipidemia, n (%)	233 (75)	243 (78)	0.58
Smoking, n (%)	193 (62)	189 (61)	0.44
Current smoking	68 (22)	50 (16)	0.55
Family history of CAD, n (%)	71 (39)	71 (40)	0.79
Renal failure†, n (%)	22 (8)	10 (3)	0.52
Peripheral vascular disease, n (%)	8 (3)	9 (3)	0.51
Heart failure, n (%)	17 (5)	11 (4)	0.42
Ejection fraction < 50%, n (%)	105 (38)	92 (33)	0.62
Previous AMI, n (%)	150 (48)	160(51)	0.72
> 30 days	109 (35)	114 (37)	
≤ 30 days	41 (13)	46 (15)	
Previous PCI, n (%)	82 (26)	92 (29)	0.36
Previous CABG, n (%)	20 (6)	33 (11)	0.57
Previous stroke, n (%)	8 (2)	4 (1)	0.77
Previous bleeding episode, n (%)	1 (0.3)	1 (0.3)	0.65
Clinical presentation, n (%)			0,66
Silent ischemia	40 (13)	38 (12)	
Stable angina	188 (60)	185 (59)	
Unstable angina	20 (6)	22 (7)	
STEMI	5 (1)	1 (0.3)	
NSTEMI	7 (2)	7 (2)	
Asymptomatic post-AMI	52 (17)	59 (19)	

†Renal failure defined as basal serum creatinine ≥ 1.5 mg/dL. DAPT: dual antiplatelet therapy; CAD: coronary artery disease; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction.

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TABLE 2
Angiographic characteristics of the treated lesions.

Variables	DAPT 3 months (n = 312/ 413 lesions)	DAPT 12 months (n = 312/ 418 lesions)	*p*-value
Treated vessels, n (%)			
Left anterior descending artery	192 (46)	186 (44)	0.97
Left circumflex artery	93 (22)	111 (26)	0.63
Right coronary artery	121 (29)	113 (27)	0.58
Left main coronary artery	7 (1.7)	8 (2)	0.71
Bifurcation lesions, n (%)	59 (14)	62 (15)	0.88
Total occlusion, n (%)	15 (3.6)	14 (3.3)	0.79
Pre-TIMI flow < 3	41 (10)	37 (9)	0.82
Lesion length, mm	19 ± 11	19 ± 12	0.72
Reference diameter, mm	2.8 ± 0.5	2.7 ± 0.5	0.69
Minimum luminal diameter, mm	0.8 ± 0.4	0.8 ± 0.4	0.89
Stenosis diameter	71 ± 12	80 ± 13	0.61

DAPT: dual antiplatelet therapy; TIMI: Thrombolysis in Myocardial Infarction.

TABLE 3
Primary and secondary outcomes.

Outcomes	DAPT 3 months (n = 312)	DAPT 12 months (n = 312)	*p*-value
NACCE, n (%)	12 (3.8)	21 (6.7)	0.15
MACE, n (%)	21 (6.7)	22 (7.1)	> 0.99
All-cause mortality, n (%)	3 (1)	5 (1.6)	0.72
Cardiac death, n (%)	3 (1)	5 (1.6)	0.72
Stroke, n (%)	0 (0)	2 (0.6)	0.50
Acute myocardial infarction, n (%)	7 (2.2)	14 (4.5)	0.18
Major bleeding*, n (%)	2 (0.6)	4 (1.3)	0.68
Target-lesion revascularization, n (%)	11 (3.5)	11 (3.5)	> 0.99
Target-vessel revascularization, n (%)	12 (3.8)	13 (4.2)	> 0.99
Stent thrombosis, n (%)	0 (0)	4 (1.3)	0.12

*Three patients from the 12 month group presented stent thrombosis during the in-hospital phase, due to procedure-related complications. DAPT: dual antiplatelet therapy; NACCE: net adverse clinical and cerebral events; MACE: major adverse clinical events.

Primary outcomes

Table 3 shows the frequencies of the assessed outcomes in patients from IDPC. The primary outcome (NACCE) did not significantly differ between groups at the end of one year, occurring in 33 patients in total, with 12 in the DAPT group for 3 months (3.8%) and 21 (6.7%) in the DAPT group for 12 months ($p = 0.15$). Regarding each component of NACCE, there was no statistically significant difference between the two groups regarding death from all causes, AMI, stroke, and major bleeding.

Figure 1 presents the Kaplan-Meier curves of the primary study outcome (NACCE) comparing the two groups up to 12 months of clinical follow-up. Figure 2 shows the Kaplan-Meier curves for the isolated events that comprise NACCE.

Secondary outcomes

Regarding the secondary outcome (MACE), the incidence was almost the same between the short- and long-term DAPT groups: 6.7% vs. 7.1%, respectively ($p > 0.99$). Stent thrombosis did not occur in any patient from the 3 month DAPT group, but occurred in four patients from the 12 month DAPT group ($p = 0.12$) (Table 3). It is noteworthy that, of the four cases of stent thrombosis at the 12 month group, three occurred still during the hospitalization phase, due to procedure-related complications. Only one patient had definitive thrombosis at 10 months after implantation.

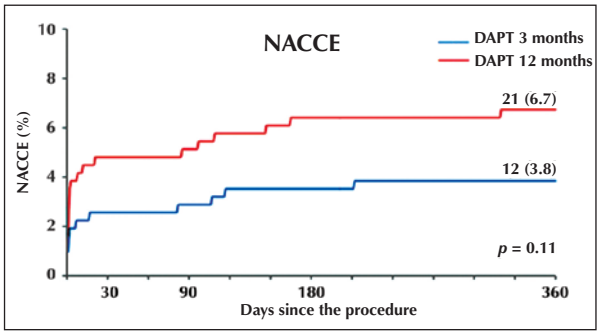


Figure 1 – Time until occurrence of the primary outcome (net adverse clinical and cerebral events – NACCE) in patients who received dual antiplatelet therapy for 3 or 12 months.

Figures 3 and 4 present the Kaplan-Meier curves for the secondary outcome (MACE) and stent thrombosis at 12 months.

Comparison of NACCE between the IDPC subgroup and other OPTIMIZE participating centers

Figure 5 shows the odds ratio of the primary outcome in IDPC subgroup and in other centers participating in the OPTIMIZE trial. The heterogeneity test showed that the observed result variability was not greater than that expected to occur by chance.

Figure 6 presents the cumulative incidence of the primary outcome (NACCE) according to the treatment center, between patients who received DAPT for 3 or 12 months.

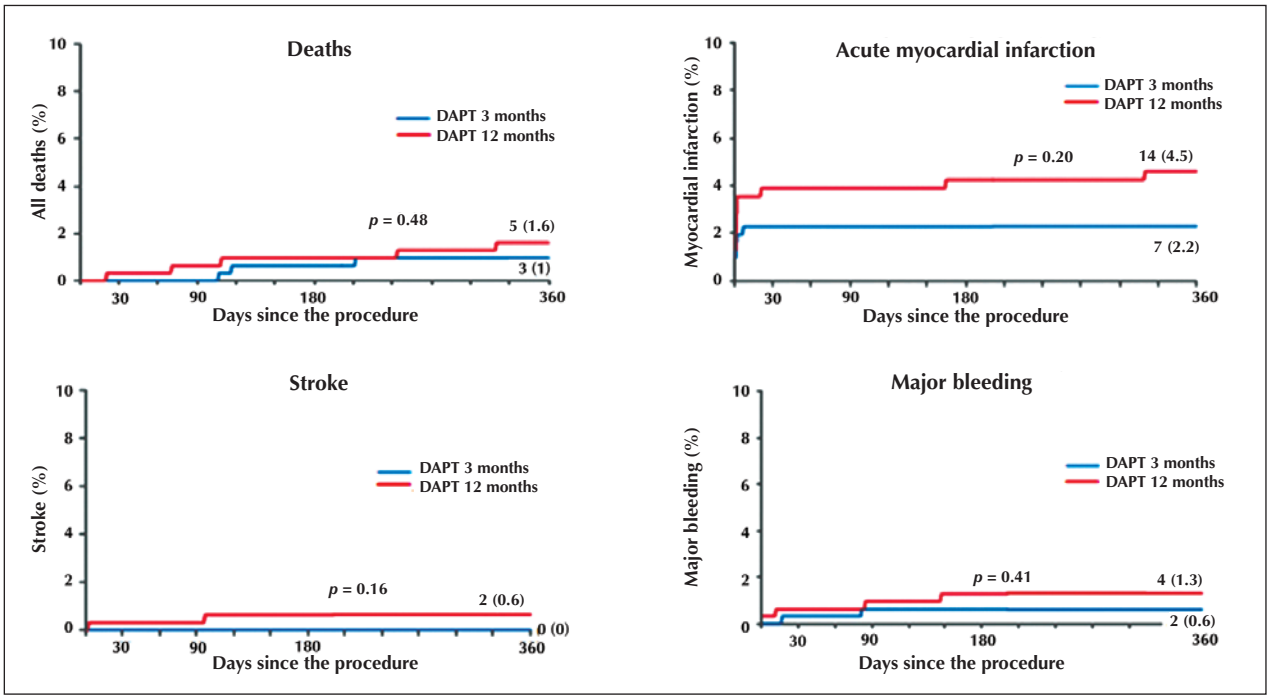


Figure 2 – Time until the occurrence of the individual components of the primary outcome (death, myocardial infarction, stroke, and major bleeding) in patients who received dual antiplatelet therapy (DAPT) for 3 or 12 months.

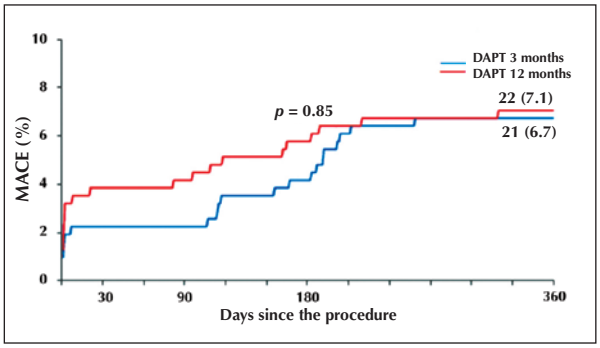


Figure 3 – Time untilthe occurrence of the secondary outcome (major adverse cardiac events – MACE) in patients receiving dual antiplatelet therapy (DAPT) for 3 or 12 months.

DISCUSSION

The combination of ASA with thienopyridines, such as clopidogrel, is mandatory after PCI, but DAPT duration is still a controversial topic. According to the guidelines of the American Heart Association/American College of Cardiology (AHA/ACC), DAPT must be maintained for 12 months after DES implantation, whereas the European Society of Cardiology (ESC) recommends its use for 6 to 12 months in the same clinical context.[15]

It is important to determine the most appropriate DAPT duration, considering that, despite its efficacy in reducing the incidence of stent thrombosis, the prolonged use of thienopyridines may be associated with higher bleeding rates, higher cost, and potential adherence impairment.

The Efficacy of Xience/promus versus Cypher in rEducing Late Loss after stENTing (EXCELLENT) trial observed no difference regarding the combined primary outcome (cardiac death, AMI, or target vessel revascularization guided by ischemia), when comparing DAPT for 6 months vs. 12 months after randomization of 1,443 patients submitted to PCI with first- or second-generation DES.[5]

The PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (PRODIGY) trial randomized 2,013 patients to receive BMS vs. ZES vs. paclitaxel-eluting stents vs. everolimus-eluting stents, followed by new randomization after 30 days of PCI to receive DAPT for 6 months vs. 24 months. At the end of the 24-month follow-up, the combined primary outcome (death from all causes, AMI, and stroke) was similar between groups, regardless of DAPT duration.[6]

After a 12-month follow-up, the REalSafety and Efficacy of 3 month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation (RESET) trial also observed no difference in the combined primary outcome (cardiac death, AMI, stent thrombosis, and

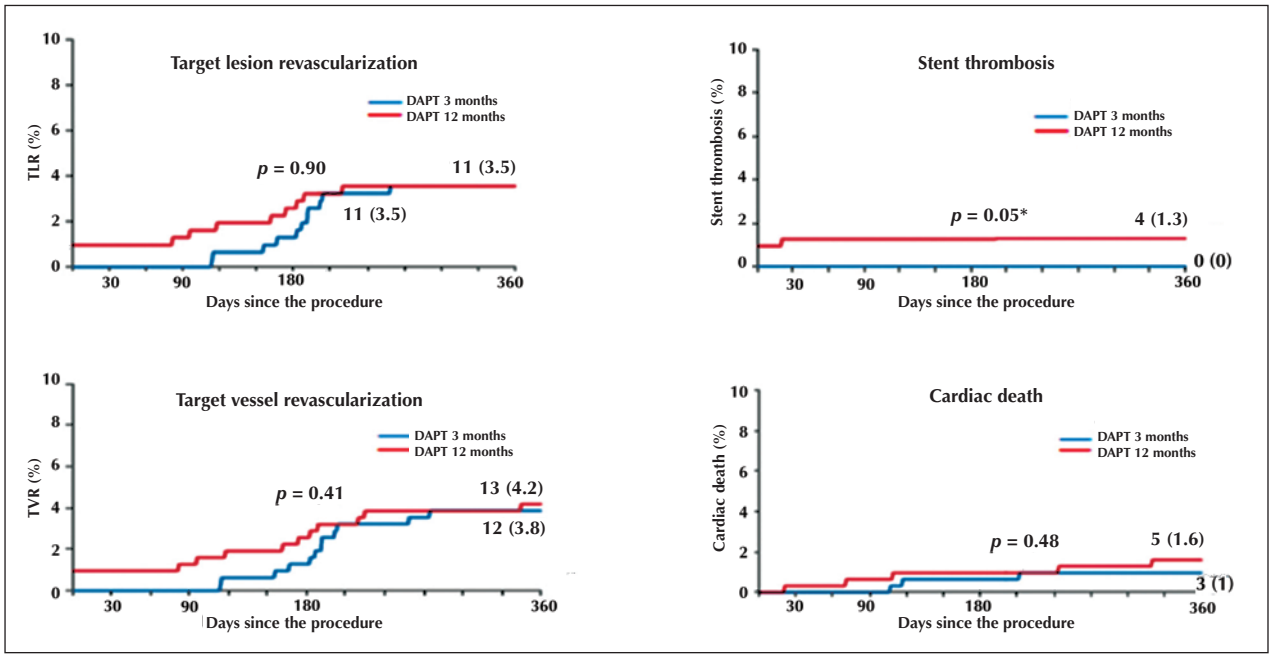
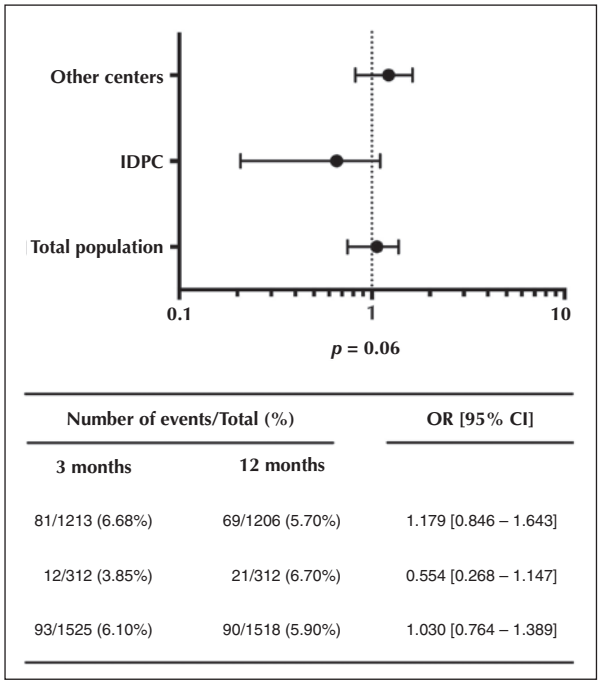


Figure 4 – Time until the occurrence of cardiac death, target-lesion and target-vessel revascularization (TLR and TVR, respectively), and stent thrombosis in patients who received dual antiplatelet therapy (DAPT) for 3 or 12 months.



Number of events/Total (%)		OR [95% CI]
3 months	12 months	
81/1213 (6.68%)	69/1206 (5.70%)	1.179 [0.846 – 1.643]
12/312 (3.85%)	21/312 (6.70%)	0.554 [0.268 – 1.147]
93/1525 (6.10%)	90/1518 (5.90%)	1.030 [0.764 – 1.389]

Figure 5 – Odds ratio (OR) of the primary outcome (NACCE) according to subgroups from Instituto Dante Pazzanese de Cardiologia (IDPC) and from other centers. Heterogeneity test (p = 0.06). 95% CI: 95% confidence interval.

target-vessel revascularization guided by ischemia) after randomizing 2,117 patients to ZES and three months of DAPT vs. first and second generation DES, with 12 months of DAPT.[7]

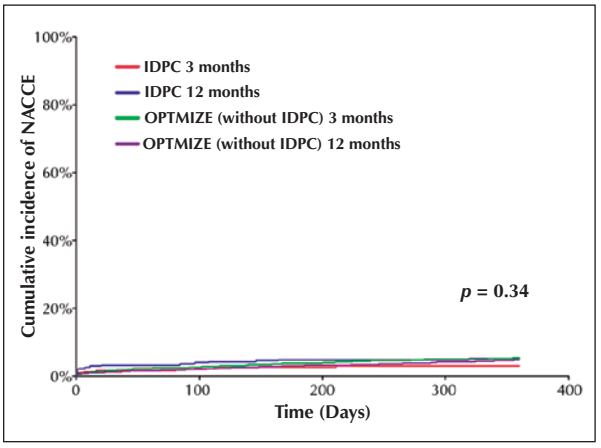


Figure 6 – Cumulative incidence of the primary outcome (net adverse cardiac and cerebral events – NACCE) according to the treatment center, in patients who received dual antiplatelet therapy for 3 or 12 months. IDPC: Instituto Dante Pazzanese de Cardiologia.

Scientific evidence suggests that the vascular response to different generations of DES is heterogeneous, and that lower rates of stent thrombosis are related to second-generation stents. Late-acquired incomplete stent strut apposition is a relatively common finding with sirolimus- and paclitaxel-eluting stents (8 to 12.1%)[16] and associated with thrombotic events. No thrombosis was observed with the use of ZES in the ENDEAVOR I and II trials,[17] or in the IDPC series;[18] the prevalence of thrombosis was only 0.5 and 1% in the ENDEAVOR III and IV subtrials, respectively.[19,20]

The polymeric component of first generation DES has been associated with more intense local inflammatory response, which could lead to greater positive remodeling in the treated segment. ZES allowed for a greater preservation of endothelial vasomotor function in the treated segment at 6, 9, and 12 months, when compared with the first generation DES.[21] Thus, it is unlikely that the ideal time of DAPT is the same for first and second generation DES.

Due to the peculiarities of the second-generation stents, this study was conducted with a specific DES (ZES), comparing different DAPT regimens, and thus the results cannot be safely extrapolated to other DES.

CONCLUSIONS

In patients treated at the IDPC, the 3-month period of DAPT was not inferior to the 12-month period for the occurrence of NACCE or MACE. The present results did not differ from those of the other centers participating in the OPTIMIZE trial.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING SOURCES

None declared.

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