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Late differences in outcomes of patients with stable angina and an isolated lesion in the proximal left anterior descending artery treated with new-generation drug-eluting stents☆

Konstantinos Toutouzas [a,*], Nikolaos Anousakis-Vlachochristou [a], Chrysoula Patsa [a], Ioannis L. Matsoukis [a,b], Maria Drakopoulou [a], Eleftherios Tsiamis [a], George Latsios [a], Andreas Synetos [a], Evmorfia Komatanou [a], Anastasios Spanos [c], Eleni Th. Petridou [b], Dimitris Tousoulis [a,1]

[a] 1st Cardiology Department, Athens Medical School, Hippokration General Hospital, Athens, Greece
[b] Department of Epidemiology and Medical Statistics, Athens Medical School, Athens, Greece
[c] Cardiology Clinic, Naval Hospital of Athens, Greece

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ABSTRACT

Background: New-generation drug-eluting stents have demonstrated the mid-term efficacy and safety, but possible differences between stents may emerge in a long-term period. We compared long-term outcomes of patients with chronic stable angina and an isolated de-novo lesion in the proximal left anterior descending artery that underwent percutaneous coronary intervention with Endeavor-zotarolimus eluting stents (E-ZES) and everolimus eluting stents (EES).

Methods: We prospectively enrolled 600 patients. Of these, 180 underwent E-ZES and 420 underwent EES implantation. Clinical follow-up was performed up to 7 years (median follow-up 61 months). The evaluated clinical outcomes were Target Lesion Failure (TLF), a composite of cardiac death, myocardial infarction and Target Lesion Revascularization (TLR), the Patient-Related Outcome (PRO) and stent thrombosis. Differences between groups evaluated with the Kaplan–Meier method and possible independent predictors with Cox proportional hazard regression.

Results: At 5 years, the cumulative probability for outcomes was: TLF: 13.8% versus 7.5%, p = 0.025, cardiac death: 3.1% versus 2.5%, p = 0.937, myocardial infarction: 1.2% versus 1.8%, p = 0.829, TLR: 10% versus 3.3%, p = 0.003, PRO: 19.6% versus 13.8%, p = 0.528, ST: 2.5% versus 2.7%, p = 0.965, for E-ZES and EES respectively. Differences between stents increased after 30 months. In multivariate analysis predictors of TLF adjusted for stent type were Diabetes mellitus and estimated Glomerular Filtration Rate (eGFR).

Conclusion: Both stents provided a favorable safety profile, with EES demonstrating better effectiveness. There was a late emergence in difference of endpoints after 30 months. Diabetes mellitus and eGFR predicted TLF.

1. Introduction

The proximal segment of left anterior descending coronary artery (pLAD) has drawn special attention in percutaneous coronary interventions (PCI), due to its great importance for blood supply to over 50% of the left ventricular myocardium. The ongoing improvement in stent material and design has increased their safety and efficacy compared to first generation drug-eluting or bare-metal stents [1,2]. Among them, zotarolimus-eluting and Everolimus-eluting stents are being used in large numbers in interventional practice. Although, several studies that compare these two types of stents exist, there are limited data regarding the long-term outcomes in patients with isolated pLAD stenoses. The aim of this study was to evaluate the safety and efficacy of Everolimus-eluting and zotarolimus-eluting stents in patients with stable angina and an isolated de-novo lesion in the pLAD artery.

Abbreviations: pLAD, proximal segment of left anterior descending artery; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; DES, drug-eluting stents; E-ZES, Endeavor zotarolimus-eluting stent; EES, everolimus-eluting stent; eGFR, estimated Glomerular Filtration Rate; MDRD, Modification of Diet in Renal Disease study equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration study equation; ACC/AHA, American Cardiology College/American Heart Association; MI, myocardial infarction; ST, stent thrombosis; ARC, Academic Research Consortium; TLF, Target Lesion Failure; TLR, Target Lesion Revascularization; PRO, Patient-Related Outcome.

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* Corresponding author at: Cardiology, Hippokration General Hospital, 114 Vas. Sofias ave, Athens, Greece.
E-mail address: ktoutouz@gmail.com (K. Toutouzas).

[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Baseline characteristics of the study population.

	Total (n = 600)	E-ZES (n = 180)	EES (n = 420)	p value
Age (years)	61.6 ± 11.0	60.9 ± 11.1	61.9 ± 10.9	0.280
Men	490 (81.6%)	153 (85.0%)	337 (80.2%)	0.205
BMI (km/m^2)	28.3 ± 3.9	28.0 ± 3.8	28.4 ± 3.9	0.306
EF (%)	53.5 ± 6.6	53.2 ± 6.3	53.6 ± 6.7	0.545
Diabetes mellitus	122 (20.3%)	43 (23.8%)	79 (18.8%)	0.184
Current smokers	267 (44.5%)	79 (43.9%)	188 (44.7%)	0.858
Arterial hypertension	343 (57.2%)	108 (60.0%)	235 (55.9%)	0.369
Family history of CAD	215 (35.8%)	64 (35.5%)	151 (35.9%)	0.926
Hypercholesterolemia	429 (71.5%)	130 (72.2%)	299 (71.2%)	0.844
eGFR	72.3 ± 18.5	71.8 ± 18.8	72.5 ± 18.4	0.687
CKD	155 (25.8%)	52 (28.9%)	103 (24.5%)	0.265
CHOL (mg/dl)	202.3 ± 43.1	199.6 ± 44.2	203.5 ± 42.6	0.279
LDL (mg/dl)	117.5 ± 34.3	114.2 ± 33.7	118.9 ± 34.4	0.133
HDL (mg/dl)	37.5 ± 10.9	38.2 ± 11.2	37.2 ± 10.8	0.285
TG (mg/dl)	145.7 ± 59.7	142.7 ± 62.0	147.0 ± 58.6	0.412
Ur (mg/dl)	41.4 ± 15.2	41.7 ± 15.2	41.2 ± 15.3	0.754
Cr (mg/dl)	1.1 ± 0.4	1.1 ± 0.5	1.1 ± 0.4	0.317

Values are mean ± standard deviation, n (%); BMI, Body Mass Index; CAD, coronary artery disease; CKD, Moderate or Severe Chronic Kidney Disease defined by eGFR levels; CHOL, Total Cholesterol; Cr, Serum Creatinine; EES, everolimus eluting stent(s); EF, Ejection Fraction; eGFR, estimated Glomerular Filtration Rate calculated by CKD-EPI equation; E-ZES, Endeavor-Zotarolimus eluting stent(s); HDL, High Density Lipoproteins; LDL, Low Density Lipoproteins; TG, Triglycerides; Ur, Urea; p value from t-test, Chi square or Fisher's exact test as appropriate.

2. Methods

Between 2006 and 2012, we prospectively enrolled 600 consecutive patients, with a single de-novo significant lesion (>75%) in the pLAD artery, which underwent PCI. All patients suffered from chronic stable angina and/or ischemia proven by stress tests. Exclusion criteria were acute coronary syndromes, lesion of the left main coronary artery, multivessel disease, prior myocardial infarction, prior PCI, contraindications for long-term antiplatelet therapy and the presence of serious comorbidities such as renal failure requiring hemodialysis, immunological diseases or cancer. The lesion was treated either with a zotarolimus-eluting stent [Endeavor, Medtronic Cardiovascular, Santa Rosa, California, USA, (E-ZES)] or an Everolimus-eluting stent [Xience V, Abbott Cardiovascular, Santa Clara, California, USA, (EES)]. The choice of stent was dictated by logistic reasons (availability of only one type of stent in the hospital at that time). The aim of the procedure was to obtain full lesion coverage with one or more stents. Interventions were performed via femoral or radial route according to standard techniques. Number and dimension of stents, lesion pre-dilation, direct stenting and/or post-dilation were left at the discretion of the operator. Cross-over between stent types was not permitted. After the intervention all patients were scheduled to receive dual anti-platelet therapy for at least 12 months, with daily acetylsalicylic acid (100 mg) and clopidogrel (75 mg). Acetylsalicylic acid was prescribed indefinitely. Lipid profile and renal function were assessed in all patients. Renal filtration rate was assessed by calculation of the estimated Glomerular Filtration Rate (eGFR) using both the Modification of Diet in Renal Disease (MDRD) study equation [3] and the newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)equation (2009 edition) [4], which has demonstrated improved accuracy for the estimation of GFR [5]. Written informed consent was obtained from every patient. The study protocol was approved by the hospital's Ethics Committee. After index PCI, clinical follow-up was performed at patients' visit to the cardiology department or by telephone interview using a pre-specified medical questionnaire, up to 7 years. In case of a clinical event all relevant medical records were retrieved. Patients were scheduled to undergo angiographic control in the case of a clinically-driven indication.

2.1. Definitions

Lesions were characterized according to the modified ACC/AHA classification [6]. Lesions were classified as calcified when excessive calcification was optically detected at the coronary angiographies and as long when its length exceeded 28 mm. All lesion classifications were made by the same investigator. The third universal definition of myocardial infarction (MI) was used [7], and classification of location of MIs was performed by evaluation of electrocardiographic and angiographic findings. Stent thrombosis (ST) was adjudicated to events according to ARC criteria [8], and was classified as acute, early, late, very late and as definite/probable, possible stent thrombosis. All deaths that could not be clearly attributed to another cause were considered cardiac deaths. Time of follow-up was considered as the time of retrieval of last follow-up or the time of the clinical event for the patients who suffered from an event eligible for one or more of the study's endpoints. Long-term follow-up was assumed when time exceeded 24 months.

The study's primary endpoint was Target Lesion Failure (TLF), defined by its composites in hierarchical order: cardiac death, non-fatal MI not clearly attributed to a non-target vessel and clinically-driven revascularization of the target lesion (Target Lesion Revascularization — TLR). Secondary endpoints were Patient-Related Outcome (PRO — a composite of all-cause mortality, any MI, any revascularization), ARC ST and the components of TLF (cardiac deaths, non-fatal MIs and TLR).

2.2. Statistical analysis

Categorical variables are reported as counts and percentages and continuous variables are expressed in mean ± standard deviation. Differences between groups were assessed using Chi square test or Fisher's exact test and continuous variables were compared using t-test as appropriate. Differences between the two groups regarding the time-to-endpoints were assessed using the method of Kaplan–Meier and the Log-rank test. Confidence Intervals (CIs) and p values were two-sided and a p value < 0.05 was considered statistically significant.

Multivariate analysis was performed with Cox proportional hazard regression. The procedure included a univariate analysis with an entry criterion of 0.2 and a model building with a step-by-step backward elimination approach based on Wald statistic criterion. Final models were built by adding variables that differed significantly between groups. Known variables from previous reports in bibliography that are relevant to endpoints were included in the univariate analysis [9–11]. Statistical analysis was performed using SPSS (version 20.0, SPSS, Chicago, Illinois).

Table 2
Baseline lesion and procedural characteristics.

	Total (n = 600)	E-ZES (n = 180)	EES (n = 420)	p value
ACC/AHA lesion class				
A	73 (12.2%)	23 (12.8%)	50 (11.9%)	0.786
B1	236 (39.3%)	68 (37.8%)	168 (40.0%)	0.649
B2	262 (43.7%)	81 (45.0%)	181 (43.1%)	0.719
C	29 (4.8%)	8 (4.4%)	21 (5.0%)	0.839
Long lesion	138 (23.0%)	53 (25.2%)	114 (24.9%)	0.833
Calcified	132 (22.0%)	29 (16.2%)	103 (24.6%)	**0.024**
Eccentric	374 (62.3%)	130 (72.6%)	244 (58.4%)	**0.001**
Stents implanted per patient	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.5	0.472
Total stent length (mm)	23.4 ± 10.4	23.4 ± 10.5	23.4 ± 10.4	0.975
Mean stent diameter (mm)	2.9 ± 0.3	2.9 ± 0.3	2.92 ± 0.3	0.055
Inflation pressure (mmHg)	15.3 ± 1.6	15.3 ± 1.8	15.3 ± 1.5	0.768
Pre-dilation	260 (43.7%)	81 (45.5%)	179 (42.9%)	0.589
Non-adherence to DAPT	29 (4.8%)	13 (7.2%)	16 (3.8%)	0.095

Values are mean ± standard deviation, n (%), ACC, American College of Cardiology; AHA, American Heart Association; Calcified, excessive calcification of lesion; EES, everolimus eluting stent(s); Eccentric, eccentric lesion; E-ZES, Endeavor-zotarolimus eluting stent(s); Long lesion, lesion's length > 28 mm; DAPT, Dual Anti-Platelet Therapy for 12 months; p value from t-test, Chi square and Fisher's Exact test as appropriate.