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First Romanian registry of safety and effectiveness of drug eluting stent implantation in the real world scenario (RODESINO registry)

Claudiu STOICESCU, MD; Alexandru BURLACU, MD; Vlad VINTILA, MD; Cristian UDROIU, MD; Nicolae FLORESCU, MD, PhD; Octavian PARVU, MD; Mircea CINTEZA, MD, PhD; Dragos VINEREANU, MD, PhD

Cardiology Department, Emergency University Hospital, Bucharest, Romania

ABSTRACT

Background. *Medium-term outcome of patients with percutaneous coronary interventions (PCIs) is related to in-stent restenosis, which represents the main drawback for PCIs. Recent clinical studies have shown a decrease of restenosis rate from 25% to less than 10%, using sirolimus eluting stents (DES). However, "real-life" DES restenosis, by comparison with similar patients receiving BMS, has not been enough reported.*

Methods. *We performed a controlled registry study ("case control study") over a period of 44 months, including all patients who received ≥ 1 sirolimus eluting stent, comparing them to a control group of patients who received ≥ 1 bare metal stent (BMS). Primary end-point was the clinical restenosis (defined clinically and/or by ECG exercise test); when clinical restenosis was suspected, coronary angiography was repeated. Secondary end-points were major adverse cardiac events (MACE).*

Results. *448 patients were included into the controlled registry study: 224 DES patients (58±10 years, 75% males), compared to 224 age- and sex-matched BMS patients. 268 DES were used in 260 lesions, versus (vs.) 298 BMS used in 278 lesions. Major cardiovascular risk factors prevalence was: diabetes mellitus 26% vs. 11%, p=0.0001; arterial hypertension 79% vs. 72%, p=0.065; hypercholesterolemia 90% vs. 79%, p=0.001, in DES and BMS groups, respectively. 52% vs. 40% patients (p=0.005) associated at least 3 risk factors, and 16% vs. 3.5% patients had four major risk factors. 71% vs. 43% patients (p=0.0001) had previous myocardial infarction. 8% vs. 0.3% (p=0.001) stents were used for intrastent restenosis. Target vessel was LAD in 66% vs. 45% patients (p=0.003); left circumflex in 12% vs. 24% (p=0.012); and RCA in 20% vs. 31% (p=0.05). 71% vs. 41% (p= 0.0001) were lesions with RVD ≤ 3 mm, and 88% vs. 51% (p= 0.0001) were lesions longer than 15 mm. 3 cases of clinical restenosis were suspected in the DES group, confirmed by coronary angiography in 2 patients (0.9%), whereas 20 cases of clinical restenosis were suspected in the BMS group, confirmed by coronary angiography in 16 patients (7.0%) (p=0.001). 2.7% patients from the DES group had MACE, compared with 8.9% from the BMS group (p= 0.007). Myocardial infarction and total death did not differ significantly between the two groups.*

Conclusions. *By comparison with patients receiving BMS, patients who benefit from DES had more diabetes mellitus, more than 3 major cardiovascular risk factors, mainly LAD lesions, small and/or long vessel lesions. Clinically-driven in-stent restenosis was reduced from 7% to less than 1%, with a significant decrease of MACE.*

Address for correspondence:
Stoicescu Claudiu, MD, PhD, "Carol Davila" University of Medicine and Pharmacy, 8 Eroilor Sanitari Blvd., Bucharest, Romania
email address: claudius_md@yahoo.com

INTRODUCTION

Medium-term outcome of patients with percutaneous coronary interventions (PCIs) is related to in-stent restenosis, which represents the main drawback for PCIs. Following balloon angioplasty and stent implantation, the introduction of drug-eluting stents (DES) represents the third major step in interventional cardiology. Recent clinical studies have shown a decrease of restenosis rate from 25% to less than 10%, using sirolimus eluting stents. DES are used for a wide variety of clinical and anatomic situations, many of which have not been evaluated in randomized studies (1-3). However, in the "real-life" DES restenosis, by comparison with similar patients receiving bare metal stents (BMS), has not been enough reported. The policy to use DES for all lesions is difficult to apply because of the economic constraints we have to deal with. The aim of our registry was to evaluate the long-term outcome of the results of systematic implantation of DES in a large series of consecutive patients treated in a real-world scenario compared with similar patients who received BMS. ❑

METHODS

We performed a controlled registry study ("case control study") over a period of 44 months, including all patients who received ≥ 1 sirolimus eluting stent, comparing them to a control group of patients who received ≥ 1 bare metal stent (BMS). We identified 448 consecutive patients who underwent successful implantation with DES (224 patients, 260 lesions, 268 stents) or BMS (224 patients, 278 lesions, 298 stents) between March 2003 and January 2008. The study was designed as prospective, two-arms, one-center registry to evaluate clinical outcome after the implantation of DES or BMS. Patients were treated in an academic Romanian hospital. Clinical and demographical data, type of culprit lesion, procedural complications, and treatment were documented into standard case report files. There were no exclusion criteria, neither related to angiographic characteristics nor to clinical presentation (stable or unstable patients). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee.

All patients received a bolus of unfractionated heparin at a dose of 70 IU/kg before starting the procedure. The interventional strategy, the utilization of periprocedural glycoprotein IIb/IIIa inhibitors and antithrombotic medications, was entirely left to the discretion of the operators. A loading dose of 300 mg or 600 mg of clopidogrel was given to patients not previously taking the agent. After hospital discharge no attempt was made to standardize the therapy, apart from the anti-platelet regimen. All patients were evaluated at 1, 6, and 12 months after discharge. For those patients who did not return to the clinic at the designated time, follow-up information was collected by telephone interview. The study design was for the longest follow-up interval at 1 year. We decided to extend the follow-up period beyond one year due to increased published data showing late and very late stent thrombosis in patients with DES. Clopidogrel was recommended for at least nine month in both groups. Romania is in an unique situation in Europe because, based on the national clopidogrel program supported by the government, patients with at least one stent are entitled to receive free of charge combined anti-platelets treatment for at least 9 months.

For all patients we selected the femoral approach using 6 French (Fr) or 7 Fr guiding catheters. If necessary, the lesions were pre-dilated with an appropriate-sized balloon; the stent was delivered using pre-mounted systems. For the registry, DES lengths of 8, 13, 18, 23, 28, and 33 mm and diameters of 2.5 to 3.5 mm were available. The DES were implanted at high pressure (>12 atm). In case of suboptimal results judged by visual estimation or quantitative coronary angiography (QCA), the stent was post-dilated with a larger balloon. Depending on vessel diameter, tortuosity, lesion length, location, and operator preferences, a several kind of BMS were used. The arterial sheath was removed after 4 to 6 hours later, depending on the activated clotting time level achieved with manual compression. Baseline and post procedure anterograde flow were evaluated according to the Thrombolysis in Myocardial Infarction (TIMI) criteria 2. Coronary angiograms were analyzed by a semi automated edge

contour detection computer analysis system. For all the cases QCA was used to evaluate reference vessel diameter (RVD) and minimal lumen diameter (MLD). In a few cases, the manual editing of stenosis contours was considered mandatory. Acute gain, late loss, and loss index were calculated using standard morphologic criteria.

Primary end-point was the clinical restenosis (defined clinically and/or by electrocardiogram (ECG) exercise test); when clinical restenosis was suspected, coronary angiography was repeated. The target lesion revascularization (TLR) is define as a repeat intervention, surgical or percutaneous, driven by a new lesion located in the stented area treated at the index procedure, but no more than 5 mm pre and post stent. Secondary end-points were major adverse cardiac events (MACE), defined as cardiac death, myocardial infarction (MI), diagnosed by recurrent symptoms and/or new ECG changes in association with re-elevation of the creatine kinase (CK) and CK-MB levels of >1.5 times the previous value, if within 48 h, or >3 times the upper normal limit, if after 48 h from the index infarction (4).Thrombotic stent occlusion was angiographically documented as a complete occlusion (TIMI flow grade 0 or 1) or a flow-limiting thrombus (TIMI flow grade 1 or 2) of a previously successfully treated artery. ❑

STATISTICAL ANALYSIS

Continuous variables were presented as mean ± standard deviation, and were compared using the Student unpaired t test. Categorical variables were presented as counts and percentages, and compared with the Fisher exact test. Multivariate analyses were performed to identify independent predictors of long-term major adverse cardiac events and restenosis. Odds ratio (OR) and 95% confidence intervals (CIs) were reported with two-tailed probability value; p values of less than 0.05 were considered to indicate statistical significance. SPSS (Statistical Package for the Social Sciences) software, version 15.0 was used for statistical analyses. ❑

RESULTS

A total of 448 patients were included into the controlled registry study. The characteristics of patients chosen to receive a DES compared with a BMS, according to University Hospital of Bucharest selective funding policy for DES, are shown in Table 1 and Table 2. Patients chosen by their cardiologists to receive a DES were those with multiple risk factors for atherosclerosis, small vessels and long lesions, especially LAD lesions, and in-stent restenosis (ISR), showing that cardiologists did selectively implant drug-eluting stents in patients at increased risk for restenosis. Clinical follow-up was obtained in all patients at 12 months.

	DES	BMS	p value
Age	58±10 yrs	61±10 yrs	ns
Female	25%	28%	ns
Coexisting condition			
Smokers	82%	75%	0.05
Diabetes mellitus	26%	11%	0.0001
Hypertension	79%	72%	0.065
Hypercholesterolemia	90%	79%	0.001
Previous MI	71%	43%	0.0001
Previous stroke	1.8%	6.7%	0.017
At least 3 risk factors association	52%	40%	0.005
4 risk factors association	16%	3.5%	< 0.01

TABLE 1. Baseline clinical characteristics
MI = myocardial infarction

Index PCI	DES	BMS	p value
No. of stents	268	298	ns
No. of lesions	260	278	ns
LAD lesions	66%	45%	0.003
LCX lesions	12%	24%	0.012
RCA lesions	20%	31%	0.05
RVD < 3.0 mm	71%	41%	0.0001
Lesion length > 15 mm	88%	51%	0.0001
MLD pre-procedure	0.4±0.2 mm	0.5±0.2 mm	ns
MLD post-procedure	2.7±0.2 mm	2.8±0.3 mm	ns
Acute Gain	2.3±0.3 mm	2.2±0.2 mm	ns
Stents used for ISR	8%	0.3%	0.001
Complication during procedure			
Dissection require a second stent	5%	4%	ns
Acute stent thrombosis	3.5%	2.2%	ns

TABLE 2. Procedural and angiographic characteristics
PCI = percutaneous coronary intervention; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; RVD = reference vessel diameter; MLD = minimal lumen diameter; ISR = in-stent restenosis

The entire population baseline clinical characteristics are reported in Table 1. Patients from the DES group had more risk factors than patients from the compared group (52% vs. 40%, had at least 3 risk factors association, p=0.005). Significantly more patients for BMS group had more previous stroke (1.8% vs. 6.7%, p=0.017). The entire population angiographic and procedural characteristics are reported in Table 2. More DES were used in small vessel (71% vs. 41%, p<0.01) and long lesions (88% vs. 51%, p<0.01). All patients were discharge from the hospital with aspirin and thienopyridine to be continued for at least 9 months. ❑

RATES OF TARGET-LESION REVASCULARIZATION (TLR)

Overall, 7% of the patients receiving a BMS and 0.9% of those receiving a DES required TLR by first year of follow-up (p<0.01) (Table 3). The maximal reduction in the need for repeat revascularization from the use of drug-eluting stents was seen at 9 months. The most powerful predictors for in-stent restenosis were: diabetes mellitus, arterial hypertension, left anterior descendent arteries (LAD) lesions (R^2=0.39; p<0.05). None of the other subgroups had significant reductions in the rates of target-vessel revascularization. ❑

RATES OF MI AND DEATH

The rate of myocardial infarction after index PCI during the follow-up period was 1.4% in DES group vs. 3.6% in BMS group (p=ns). The rate of death after PCI in the matched cohort after the first year of follow-up was 0.8% among patients receiving a drug-eluting stent and 0.5% among those receiving a bare-metal stent (p=ns) (Table 3). All deaths in DES group were between 1 and second year after the index PCI, whereas in BMS group in the first 30 days. 2.7% patients from the DES group had MACE, compared with 8.9% from the BMS group (p<0.01), that means the composite outcome of death and MI favored DES. No MACE occurred during hospitalization. The diabetes mellitus, arterial hypertension, previously stroke and treatment of a complex lesion with stent thrombosis during index PCI significantly predicted an adverse outcome (R^2=0.46; p< 0.05). ❑

	DES	BMS	P value
TLR	0.9%	7%	< 0.01
MI	1.4%	3.6%	n.s.
Death	0.8%	0.5%	n.s.
composite MACE	2.7%	8.9%	< 0.01

TABLE 3. Cumulative In-Hospital and 15-Month Clinical Outcomes
TLR = target lesion revascularization; MI = myocardial infarction; MACE = major adverse cardiac events

DISCUSSION

To our knowledge this registry is the largest series of patients treated with DES compared with BMS in Romania. The stents implantation was successful in all patients, and an optimal angiographic result was possible in all of the target lesions.

This Registry has some unique features that distinguish it from other registry reports characterizing the outcomes of patients treated with DES versus BMS in routine clinical practice. It is the first Romanian registry where the elect of the DES must be careful done by the physician, because of no reimbursement for this kind of stents. Second, Romania is in a unique situation in Europe, probably in the world, offering 9 month, free of charge, dual anti-platelets therapy. Third, the registry enrolled patients treated with DES and BMS. The acceptance of BMS as preferred therapy in our country is reflected in the overwhelming proportion of stented lesions treated with BMS rather than DES. This is the opposite situation than it is finding in west and middle-west Europe where more than 70% of stented lesions are treated with DES. (1,4,5,6)

Baseline characteristics were similar between both study groups. Major cardiovascular risk factors prevalence were different (diabetes mellitus 26% vs. 11%, p=0.0001; hypercholesterolemia 90% vs. 79%, p=0.001, in DES and BMS groups). Procedural characteristics differed between both groups in terms of the target vessel (sirolimus: 66% vs. bare stents: 45%; p < 0.01 use of stent in LAD lesions) and also for the diameter and the length of the vessel (71% vs. 41%; p= 0.0001 were lesions with RVD ≤ 3 mm, and 88% vs. 51%; p= 0.0001 were lesions longer than 15 mm) (Table1 and Table 2).

Significant differences were reported for the selection of patients for DES compared with

BMS. Physicians favored DES for patients with multiple risk factors for atherosclerosis, LAD lesions, small vessels, and long lesions based on the proved that DES are more effective than BMS in reducing the need for target-vessel revascularization (2,3,7,8). BMS was used less often than DES for patients with a history of prior PCI, with stent implantation, probably based on the belief that the DES would be effective in the treatment of bare metal stent restenosis. The effectiveness of this strategy has now been validated by 2 randomized clinical trials and 1 observational report (9-11). The low rate of clinically driven target-lesion revascularization in the group of patients with BMS in our registry is in contrast to the rate of 15 to 20% or higher, in association with protocol-driven angiography and other factors, reported in clinical trials of DES (2,7,8). Differences in completeness of follow-up and possibly in the types of patients treated and interventional techniques used may explain the variation in these rates.

The first advantage of DES has been to reduce the need for revascularization. (4,12,13) In our study, the incidence TLR at one year with DES was significantly different from the results obtained with BMS (TABLE 3). A very recent meta-analysis has shown a TLR at 5 years for sirolimus eluting stent versus bare metal stent equal with 11.9 % vs. 31.9 % ($p < 0.0001$) (24,25) which is more consistent than data obtained after 1 year follow-up.

Observational registries from Europe have reported 1-year rates of death ranging from 1.4% to 5.3%, with combined death and MI rates ranging from 2.7% to 8.8%.4-6; the same values are reported in our Registry for the composite outcome. In a total cohort of patients, diabetes mellitus, arterial hypertension, previously stroke and treatment of a complex lesion with stent thrombosis during index PCI significantly predicted an adverse outcome. From this list, patients who possess these characteristics should undergo more regular clinical surveillance. In our registry, the presence of diabetes was an independent predictor of ischemia-driven TLR as well as clinical MACE. The higher rate of restenosis and clinical recurrence in patients with diabetes is reported in several studies with DES for de novo coronary lesions (4,14), and it has been related to an exaggerated intimal proliferative response to stent-related trauma proper of diabetic patients. A small percentage of patients with in-stent restenosis (8% vs. 0.3%) treated with SES were included in the present registry. Despite the excellent long-term results, the small number of patients stopped any definitive conclusions. However, new data have been shown that the in-stent restenosis is reasonable to be treat with DES. (22-23)

In the real world, recent registry reports (15-16) confirmed the benefit of drug-eluting stents in reducing the need for target-lesion or target-vessel revascularization but in the same time great concerns arise from a new debate: the risk of late stent thrombosis (17-20). In-stent thrombosis is a rare but extremely severe complication. Recent data suggest that use of DES may increase the risk of in-stent thrombosis, if combined anti-platelets treatment is stopped too early, as still recommended by many of the current guidelines. Because of the national clopidogrel program supported by the Romanian government, all patients received 9 months dual anti-platelet therapy. Because all deaths in DES group were sudden cardiac death, and those patients were not on clopidogrel treatment we cannot exclude very late stent thrombosis. Recent data show no significant difference for stent thrombosis (definite by Academic Research Consortium) between DES and BMS at 5 years follow-up (2.1% vs. 2.0%, $p = 0.99$), as well as for very late stent thrombosis (1.4% vs. 0.7%, $p = 0.22$) (24,25). ❑

STUDY LIMITATIONS

The rate of angiographic follow-up is insufficient for determination of the real binary restenosis rate for the entire lot. We consider that, the low angiographic follow-up rate does not affect the clinical relevance of the data because all subjects without angiographic follow-up were free from symptoms or induce ischemia. On the other hand, a higher angiographic follow-up rate would have allowed for more reliable information on restenosis rate. We assume the potential risk that we did not capture all adverse events, but we achieved high rates of follow-up. Initial, the study design says that the longest follow-up interval must be 1 year. These together with low rate of angiographic follow-up are the reason why we could not offer the Event-free Survival in a Propensity-Score using Kaplan–Meier curves. Because of the recent

awareness of very late DES thrombosis, the outcome beyond 1 year was quite desirable, so we extended it as long as possible, for a high number of subjects. Other important limitations of our study include the fact that our results may not be extended to countries with different health insurance program, especially reimbursement for anti-platelet treatment in the first 9 month. Because this study is not a randomized clinical trial designed to assess the efficacy of DES compared to BMS in patients with coronary artery disease, it contains all the disadvantages of such a comparative analysis. ❑

CONCLUSION

Systematic use of DES, compared with BMS, is safe and effective in patients treated in a real-world scenario providing a very low 12-month ischemia-driven TLR and MACE rate. These favorable results were obtained despite a higher risk factor profile (more diabetes mellitus, more than 3 major cardiovascular risk factors), or more complex lesion characteristics (longer lesions, smaller vessel, and mainly LAD lesions). ❑

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