

Analysis of the Cost-effectiveness of Drug-Eluting and Bare-Metal Stents in Coronary Disease

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Abstract

Background: There is a scarcity of cost-effectiveness analyses in the national literature comparing drug-eluting stents (DES) with bare-metal stents (BMS), at late follow-up.

Objective: To estimate the Incremental Cost-Effectiveness Ratio (ICER) between DES and BMS in uniarterial coronariopathy.

Methods: 217 patients (130 DES and 87 BMS), with 48 months of follow-up (mean = 26 months) were assessed. **Primary outcome:** cost per prevented restenosis, with effectiveness being defined as the decrease in major events. The analytical model of decision was based on the study by Polanczyk et al. The direct costs were those used directly in the interventions.

Results: The sample was homogenous for age and sex. The DES was more used in diabetic patients: 59 (45.4%) vs. 16 (18.4%) ($p < 0.0001$) and with a history of coronary artery disease (CAD): 53 (40.7%) vs. 13 (14.9%) ($p < 0.0001$). The BMS was more used in simple lesions, but with worse ventricular function. The DES were implanted preferentially in proximal lesions: ($p = 0.0428$) and the BMS in the mid-third ($p = 0.0001$). Event-free survival: DES = 118 (90.8%) vs. BMS = 74 (85.0%) ($p = 0.19$); Angina: DES = 9 (6.9%) vs. BMS = 9 (10.3%) (NS); Clinical restenosis: DES = 3 (2.3%) vs. BMS = 10 (10.3%) ($p = 0.0253$). Cardiac deaths: 2 (1.5%) in DES and 3 (3.5%) in BMS (NS). Costs: the tree of decision was modeled based on restenosis. The net benefit for the DES needed an increment of R\$7,238.16. The ICER was R\$131,647.84 per prevented restenosis (above the WHO threshold).

Conclusions: The DES was used in more complex lesions. The clinical results were similar. The restenosis rate was higher in the BMS group. The DES was a non-cost-effective strategy. (Arq Bras Cardiol 2010; 94(3):286-292)

Key words: Drug-eluting stents; cost-benefit analysis; coronary artery disease.

Introduction

The cardiovascular diseases represent the main cause of morbimortality in Brazil as well as in the Western world and they have a significant impact on the costs of the public health system^{1,2}.

The treatment of coronary artery disease (CAD) has evolved a lot since the development of coronary angioplasty³ and, subsequently, with the inclusion of stents. Stents have become the standard procedure in percutaneous coronary intervention (PCI) and restenosis became the great challenge of interventional cardiology, with percentages varying from 15% and 30%, on average⁴⁻⁹.

The use of anti-proliferative drug-eluting stents (DES) has reduced stenosis¹⁰⁻¹⁸; however, the first studies that analyzed their cost-effectiveness showed that their elevated cost became the main limitation for their use in clinical practice^{19,20}.

Polanczyk et al²¹ carried out a cost-effectiveness analysis in our country, comparing the strategy of sirolimus-eluting stent implant versus a bare-metal stent implant in PCI, under the perspectives of the Brazilian Public Health System (SUS) and Supplementary Health System. The authors used an analytical model of decision to estimate the effectiveness and the costs related to the procedures, the complications and the outcomes. The main outcome analyzed in the model was "one-year event-free survival". The analysis was carried out with results of clinical trials and published reports. The researchers concluded that the cost-effectiveness associations for the use of sirolimus-eluting stents versus BMS are elevated in the Brazilian scenario, especially concerning the SUS.

The present analysis presents the results of a non-randomized, consecutive study, with patients treated at the

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Manuscript received April 02, 2009; revised manuscript received July 15, 2009; accepted August 07, 2009.

Supplementary Health System, with the primary objective of assessing the cost-effectiveness association between paclitaxel-eluting stents and BMS for the outcome “prevented restenosis during a one-year period”. The secondary objectives were to compare the clinical results of both groups for angina, target-lesion revascularization (TLR), restenosis and death.

Methods

This was a prospective study of 217 consecutive patients submitted to PCI, carried out in three private hospitals in Rio de Janeiro. The patients were divided in two groups: 130 patients received Taxus drug-eluting stents (DES) and 87 received Liberté bare-metal stents (BMS). The follow-up was carried out from September 2003 to December 2007, varying from 13 to 48 months, with a mean of 26 months.

The inclusion criteria included patients with stable angina and acute coronary syndromes, presenting obstructive lesions > 70% of the lumen, classified as types A, B or C²². All procedures were carried out by three surgeons from the participating institutions. The ventricular function was evaluated subjectively by the surgeons, at the moment of the examination. Five patients did not undergo the ventriculography, as they presented kidney failure or severe ventricular dysfunction.

Most of the BMS were used in patients with more favorable lesions (type A or B) and in those incapable of using the DES, either by economic reasons or due to the impossibility of using clopidogrel. The DES were preferentially used for complex lesions and/or diabetic patients.

The procedure was considered successful when the residual lesion was < 30% of the lumen, with absence of major events: death, myocardial infarction and subacute occlusion.

The exclusion criteria were: patients with myocardial infarction with ST-segment elevation and patients with cardiogenic shock.

During the hospital phase, the major cardiac events (infarction, death and TLR) and the direct costs were assessed. At the late phase, after the hospital discharge, information on the main cardiac events: restenosis, need for a new revascularization, were obtained from a consultation or telephone call.

The restenosis was clinically assessed and correlated with the presence of symptoms, as the asymptomatic patients were not submitted to control catheterism.

The adjuvant anti-platelet therapy, after the percutaneous intervention, established the use of clopidogrel and aspirin, during three months for the BMS and at least one year for the DES.

Statistical analysis

The continuous variables were expressed as means \pm SD and compared with Student's *t* or Mann-Whitney test, when applicable, whereas the categorical variables were compared using Fisher's exact test. The Kaplan-Meier method was used in the analysis of general and event-free survival and the comparison between the groups (BMS vs. DES) was carried

out using the log-rank test. The Cox method was used in the multivariate analysis.

Analysis of costs

The analytical model of decision was created with probabilistic data and costs extracted from the study by Polanczyk et al²¹. The effectiveness of the procedure was established as the restenosis-free survival for a minimum period of one-year clinical follow-up. The analytical model of decision was developed to estimate results, probabilities and costs in both groups. Direct costs were considered as the resources used directly in the interventions; the estimation of fees was homogenous and the medical procedures of the institutions were carried out through the Hierarchized Brazilian Classification of Medical Procedures (CBHPM), version 2005. Aiming at preventing the variability in the percentage of discount in the CBHPM list given to the hospitals, we chose to use the mean cost data of cardiovascular procedures previously published by Polanczyk et al²¹. In all the institutions, the unitary value of each device was the same, R\$4,200.00 for the BMS and R\$11,762.00 for the DES. Aiming at decreasing the selection bias for the indication of DES, the statistical adjustment was performed for both groups.

The costs of the resources were calculated in Reais (R\$), based on the exchange rates of the year 2005 (US\$1.00 was equivalent to R\$2.34). The effectiveness was related to the restenosis-free curve of survival for a one-year period (expressed in percentage).

The ICER (Incremental Cost-Effectiveness Ratio) was calculated by dividing the difference of direct costs between DES and BSM by the difference in effectiveness between them. The incremental value suggested by the World Health Organization (WHO) is up to three-fold the gross internal product per capita (US\$6,771.00), which, according to the Brazilian Institute of Geography and Statistics (IBGE) in 2005, corresponded to a total of US\$20,313.00²³.

Figure 1 shows the formula used to calculate the ICER between a paclitaxel-eluting stent vs. the BMS.

The statistical and analytical analysis of the model of decision was performed with the TreeAge Pro Health Care program (TreeAge Software, Inc, MA, USA - 2005 version).

Results

The clinical characteristics of the groups did not show any difference regarding sex and age. However, diabetes mellitus, sedentary life style and family history were more prevalent in the DES group ($p < 0.0001$ for these variables). Among the comorbidities, the patients with previous infarction tended to be more frequent ($p = 0.0512$) in the DES group, as well as those with previous surgical revascularization (0.0021) (Table 1).

There was no statistical difference between the two groups regarding the conditions of stable angina and acute coronary syndrome without ST-segment elevation. The DES group had more patients with normal or slightly impaired left ventricular function (Table 1).

There were more BMS implants in the anterior descending artery ($p=0.0239$) and more DES implants in the right coronary artery, ($p=0.0008$). The proximal segment of the vessels received more DES ($p=0.0428$) and the mid-segment received more BMS. The BMS was more used for type A lesions ($p=0.0229$) (Table 2).

The mean diameter of the stents in the DES group was 2.51 ± 0.35 mm (2.25 to 3.5mm) and in the BMS group, it was 2.91 ± 0.47 mm (2.25 to 4.0mm) ($p=0.006$).

The mean time of hospitalization was 2.2 days (1 to 29) in the DES group and 1.7 (1 to 10) in the BMS group ($p=NS$). The procedures were carried out successfully; there were no fatal complications or cardiac events in either of the two groups.

The mean clinical follow-up of 26 months (13 to 48 months) showed that after the procedure, 118 individuals (90.8%) in the DES group and 74 (85%) in the BMS group remained asymptomatic and event-free, with no difference between the groups ($p=0.19$). The angina symptoms were not different: DES=9 (6.9%) and BMS=9 (10.3%) ($p=NS$). There were 2 cardiac deaths (0.75%) in the DES group and 3 (1.2%) in the BMS group during the follow-up ($p=NS$). (Table 3).

In the DES group, one of the deaths (0.75%) was related to late thrombosis (6 months), associated to the withdrawal of clopidogrel. The other cardiac death was related to heart failure in an elderly patient (85 years). The three cardiac deaths in the BMS group were related to late restenosis.

Among the 9 patients with angina in the DES group, 5 occurred due to the disease progression in another segment (*de novo* lesion) and three by restenosis. All *de novo* lesions were treated by PCI. Among the three restenosis, one was treated clinically, one through surgery and the third one by percutaneous intervention with rapamycin stent.

The DES group presented a Kaplan-Meier curve for restenosis-free survival of 97.3% in six months and one year and 96.3% in two and three years. For the patients from the BMS group, the Kaplan-Meier curve for restenosis-free survival was 100% in six months, 96.8% in one year and 86.9% in two and three years ($p=0.062$) (Figure 2).

The symptoms of angina in the BMS group were related to restenosis, as there were no *de novo* lesions in this group (Table 3). None of the patients were submitted to another intervention.

The DES group presented a Kaplan-Meier curve of survival of 98.2% in up to 3 years. The patients from the BMS group presented a Kaplan-Meier survival curve of 98.4% in six months and one year and of 94.5% in two and three years ($p=0.28$), with no differences. (Figure 3).

The DES group presented a Kaplan-Meier curve for combined event, restenosis or death-free survival of 97.3% in six months and one year and 96.3% in two and three years. The patients from the BMS group presented a Kaplan-Meier curve for combined event-free survival of 98.4% in six months, 95.2% in one year and 82.2% in 2 and 3 years ($p=0.0067$) (Figure 4). There were no significant differences among the groups studied, even after the adjustment, for sub-groups to be created with different results.

$$ICER = \frac{\text{COST of Paclitaxel stent} - \text{COST of bare-metal stent}}{\text{EFFECTIVENESS of Paclitaxel stent} - \text{EFFECTIVENESS of bare-metal stent}}$$

Figure 1 – Incremental cost/effectiveness ratio (ICER) between the stent with paclitaxel and the bare-metal stent. Costs - hospital admission, complementary examinations, angioplasty procedure, professional fees and cost of stents with paclitaxel and bare-metal stents. Effectiveness - Restenosis-free survival of at least one year.

Table 1 – Clinical characteristics and comorbidities of the studied population (n=217)

Risk factors and comorbidities	Drug-eluting Stent (n=130)		Bare-metal Stent (n=87)		P
Age (mean)	42 to 85 yrs (m=64.1)		43 to 90 yrs (m=65.2)		NS
Other factors:	N	%	N	%	
Male sex	90	69.2	61	70.1	0.89
Hypertension	88	67.7	66	77.0	0.14
Dyslipidemia	74	56.9	37	42.5	0.0381
Obesity	25	19.2	18	20.7	0.79
Sedentary life style	77	59.2	30	34.5	0.0003
Smoking	23	17.7	19	21.8	0.45
Family history	53	40.7	13	14.9	<0.0001
Diabetes Mellitus	59 (*)	45.4	16 (**)	18.4	<0.0001
Stable angina	77	59.2	52	59.8	NS
Unstable angina	53	40.2	35	40.2	NS
Previous Infarction	51	39.2	23	26.4	0.0512
Previous revascularization	58	44.6	21	24.1	0.0021

m - mean; (*) 18 (30.5%) insulin-dependent; (**) 2 (12.5%) insulin-dependent

Result of the cost-effectiveness analysis

The tree of decision was modeled based on the frequency of restenosis detected in the DES group (2.3%) versus the BMS group (10.3%), during a 26-month follow-up period, with the due costs. The tree allows us to observe the frequencies of occurrence in the two groups and the respective costs and can establish the association between the cost and the effectiveness.

Using the net restenosis rate as a parameter, the difference in effectiveness is 7.7%. The final cost of the paclitaxel-stent implant, with an effectiveness of 97.7% was R\$13,098.60 versus R\$5,860.44 for the bare-metal implant, of which effectiveness was 89.7%. For the effectiveness of 7.7% of restenosis reduction, there was an increment in cost of R\$7,238.16. The ICER was R\$90,476.97 per prevented restenosis (Table 4).

Table 2 – Angiographic profile and ventricular function of the studied population (n= 217)

Angiographic Characteristics	Drug-eluting Stent (n=130)		Bare-metal Stent (n=87)		p
	N	%	N	%	
Ventricular function (*)					
Normal or slightly impaired	115	89.0	65	74.7	0.0005
Moderate/severe	10	7.7	22	25.3	0.0005
Not performed	5	3.3	-	-	-
Type of lesions:					
Type A	47	36.1	45	51.7	0.0229
Type B I	36	27.7	19	21.8	0.33
Type B II	33	25.4	14	16.1	0.10
Type C	14	10.7	9	10.3	NS
Arteries:					
Trunk	4	3.1	1	1.1	0.6421
Descending Anterior	65	50.0	57	65.5	0.0239
Right Coronary	27	20.7	4	4.6	0.0008
Circumflex	23	17.7	15	17.2	NS
Diagonal	4	3.1	6	6.9	0.3213
Saphenous vein graft	5	3.8	4	4.6	NS
Mammary artery anastomosis	2	1.5	0	0	NS

(*) The left ventriculography was not performed in 5 patients.

Table 3 – Follow-up of the studied population (n= 217).

Evolution	Drug-eluting Stent (n=130)		Bare-metal Stent (n=87)		p
	N	%	N	%	
Free of Events	118	90.8	74	85.0	0.191
Angina Pectoris	9	6.9	9	10.3	NS
Cardiac death	2	1.5	3	3.5	NS
Non-cardiac death	1	0.75	1	1.2	NS
Restenosis	3	2.3	10	10.3	0.025
“De novo” lesion	5	3.8	0	0	0.162

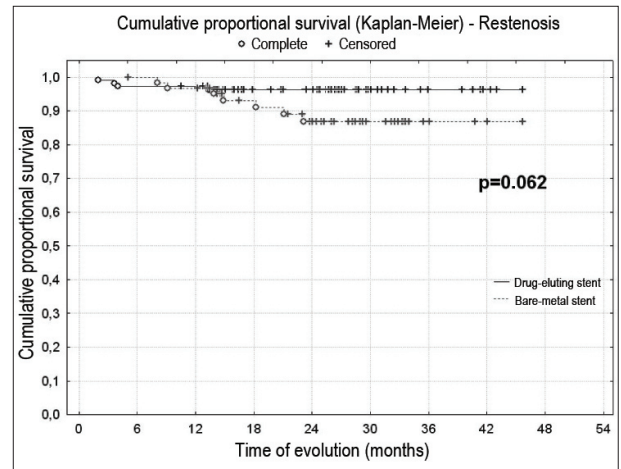


Figure 2 – General event-free (restenosis) Kaplan-Meier curve of survival for the studied population. Obs.: Conventional - Bare-metal Stent

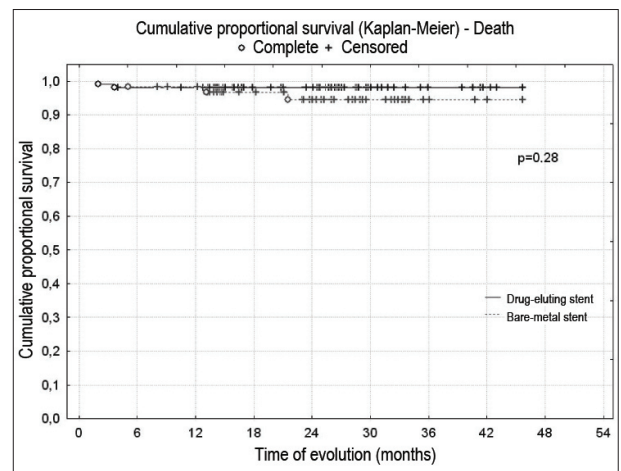


Figure 3 – General survival curve for the studied population. Obs.: Conventional = Bare-metal Stent

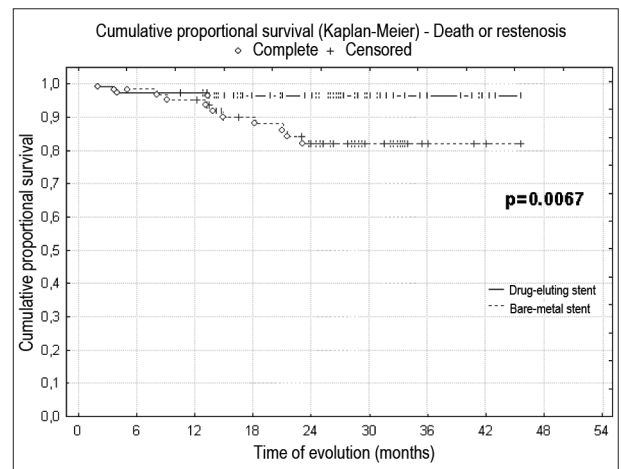


Figure 4 – General event-free (death and stenosis) Kaplan-Meier survival curve for the studied population. Obs.: Conventional = Bare-metal Stent.

Discussion

In this non-randomized study involving “real-world” patients, the DES were non-cost-effective when compared to the BMS. The clinical results during the hospitalization period and in the mid-term were similar between the two groups; however, the restenosis rate was higher in the BMS group. In spite of a higher rate of restenosis, the fact that the DES were considerably more expensive than the BMS does not allow us to establish the benefit of using such stents.

The cost-effectiveness ratio compares the relative value between the therapies. Its result can be expressed in YLS (“years of life saved”) or QALY (“quality adjusted life years”) units. It is usually admitted that therapies with a cost below US\$20,000/QALY are very favorable; between US\$20,000 and US\$40,000/QALY, they would be consistent with the usual interventions and above US\$40,000/QALY, they would be little favorable. Colombo et al²⁴, in 2004, demonstrated that, in the first year, the quality-adjusted life year depended on the restenosis. It is estimated that for the DES, the QALY value of U\$50,000 and the cost-effectiveness value of U\$10,000 per prevented restenosis are satisfactory. The additional costs can be counterbalanced by higher survival or better quality of life^{24,25}. The question to be answered is whether preventing the restenosis increases the quality or expectancy of life.

The SIRIUS²⁵ study, which involved 1,100 patients, comparing DES and conventional stents, demonstrated that the cost was U\$309 higher for patients treated with sirolimus. The ICER for each prevented revascularization was of US\$1,650²⁵. The patients with arteries of which caliber were < 2.5 mm presented additional costs of U\$1,256 with the use of BMS. The patients with arteries with length > 20 mm had additional costs of U\$1,055. The ICER per prevented target lesion revascularization (TLR) was of U\$1,650, with a QALY of U\$27,540. In 5 years, the RTL rate decreased by 60.4%, and the cost-effectiveness was below U\$10,000, per prevented repeat revascularization. The patients with arteries with a caliber < 2.5 mm presented additional costs of U\$1,256 with the use of BMS.

The randomization of the C-SIRIUS²⁶ compared the DES and the BMS in small vessels during one year. The DES decreased the TLR from 22% to 4% (p=0.015). Using 1.5 stent per lesions, with the cost of the DES at U\$2,700 and of the BMS at U\$700, the ICER was U\$11,275 per prevented restenosis. These values are considered borderline for the Canadian standards (U\$12,551).

The TAXUS IV study randomized 1,314 uniarterial patients, comparing DES with BMS. There was a decrease of 12.2 events for every 100 patients¹⁸. The difference in costs in 1 year was U\$572 per patient and the ICE was U\$4,678 per prevented TLR, with a QALY gain of U\$47,798. There was a decrease in events, with a moderate increase in costs.

Lacey et al²⁷ compared TaxusTM stents and BMS for one year and demonstrated costs of US\$20,170 for the DES and US\$19,327 for the BMS. The TLR rate was 5.36% for the DES and 16.43% for the BMS. The cost-effectiveness for each prevented TLR was US\$7,615. Even the diabetic patients, who presented more events, presented a cost-effectiveness of US\$1,585 per prevented restenosis.

Table 4 - Analysis of the Costs and Incremental Cost-Effectiveness Ratio of the DES versus BMS, during the 26-month period

Type of Stent	Effectiveness (26 months)	Effectiveness difference	Cost (R\$)*	Cost difference (R\$)	ICER**
Bare-metal Stent	89.7%	--	5,860.44	--	--
Drug-eluting Stent	97.7%	7.7 %	13,098.60	R\$ 7,238.16	R\$ 90,476.97

DES= drug-eluting stents; BMS=bare metal stents; *R\$ - cost in Reais; **ICER – Incremental Cost-Effectiveness Ratio

The Canadian Coordinating Office for Health Technology Assessment performed a meta-analysis comparing CypherTM and TaxusTM stents with BMS²⁸. The TaxusTM stents presented costs between US\$2,365 and US\$2,411 when compared to the BMS. The decrease in the TLR was 15% and 9% for Cypher and TaxusTM, resulting in an ICER of US\$10,751 and US\$22,794, respectively, per prevented restenosis²⁸. Although there is a trend in these results, one must consider the fact that this meta-analysis contemplated heterogeneous groups created to compare the two DES, resulting in a potential bias.

The RESEARCH study²⁹, a record comparing DES and BMS, showed that the TLR rate decreased 60.4% in 5 years. A total of 508 consecutive patients were assessed in the “real world”, with an event rate of 14.8% being observed in the BMS group and 9.7% in the DES group. The BMS group had a frequency of new revascularization of 10.9% and the DES, of 3.7% (p<0.001). The difference in the results between the two groups was non-cost-effective.

The BASKET study³⁰, which analyzed complex patients, did not show differences between population characteristics. The decrease in events in this study was 44%, in comparison with 34% of the RESEARCH study. However, the high cost of the stents did not compensate for the decrease in costs during the follow-up. These data must be interpreted with caution, due to the short period of follow-up.

In the present study, the tree of decision was modeled for restenosis, in both groups, with a mean time of follow-up of 26 months. The benefit of DES implantation in this series was a restenosis of 2.3%, but with an increase in costs of R\$7,238.16. The ICER was R\$90,476.97 for each prevented restenosis, which is above the threshold suggested by the World Health Organization (WHO), making its use non-cost-effective. The WHO suggests that the incremental value of the treatment presents a threshold that is three-fold the Gross Internal Product *per capita*. The GIP in 2005 was US\$ 6,771 (3x = US\$ 20,313 = R\$ 47,532.00), according to the data from the Brazilian Institute of Geography and Statistics (IBGE)²³.

In addition to the additional cost of DES, a low incidence of restenosis and TLR for the BMS contributed to a decrease in costs in these patients. The result of the BMS might be explained by a selective indication, with more favorable patients and lesions to the use of these stents.

The BASKET study³⁰ demonstrated that the DES were cost-effective in elderly individuals and patients at high risk. In our study, the DES was used in longer and lower-diameter lesions, as well as in a higher number of diabetic patients and those with more comorbidities. Still, the rate of restenosis was very low and comparatively lower than in the BMS group. However, due to the small sample size, it was not possible to detect specific sub-groups of patients, such as diabetics, the elderly, those with small vessels and long lesions, in whom the stent with paclitaxel could provide a good cost-effectiveness ratio. The good results of this study, in “real-world” patients, corroborate that a stringent indication of DES and BMS is crucial for patients’ good late evolution. The series presented by Ferreira et al³¹, in a comparative “real-world” population, including multiarterial patients, the stent size was the main factor concerning the restenosis, with an OR= 6.752 and RR= 4.366. The interpretation of these values is that patients from the BMS group had a 4.3-fold higher chance of restenosis than patients from the DES group. In our cohort, maybe due to sample size, the adjustment did not allow the demonstration of any clinical or angiographic characteristic that would interfere with the events.

The recent meta-analysis carried out by Kirtane et al³², clearly demonstrated, in more than 180,000 patients, in 52 trials, that the DES are safe, both at “on label” and “off label” indications, with a great superiority of DES regarding TLR. These data were confirmed in the randomized trials and in those that assessed the real world^{33,34}. The risk of a new intervention in the BMS varies from 5% to 14% in the records and it is much higher in the controlled studies (up to 30%). Thus, the absolute difference of repeat revascularization between BMS and DES is lower in the real life. Nevertheless, there is no increase in survival or decrease in AMI and thus, the difference of the economic impact decreases. The DES present a higher cost, but result in a decrease of repeat events²³.

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Study limitations

As this is an analysis of which decision of the treatment type depended, most of the times, on the indication of the assistant physician, it was not possible to perform an adequate randomization with a control-group. For the same reason, the study did not allow the angiographic control of all patients, mainly of the asymptomatic ones.

Thus, it becomes impossible to affirm that there was no late loss due to intrastent intimal hyperplasia. Although the sample size was limited, it allowed us to extrapolate the evolution of the patients during the analyzed period. Even when studying heterogeneous populations, it was possible, through the adjusted analysis, to show that there was no statistical difference between the stable angina and acute coronary syndrome pictures between the two groups.

Conclusions

Although drug-eluting stents present a higher cost when compared to the bare-metal stents, they show to be promising in the treatment of coronary artery disease, mainly for the more complex cases. The clinical results of the analyzed period were similar in both groups. Even though heterogeneous groups were assessed, we observed a lower rate of restenosis with the DES; however, this observation was not enough to demonstrate, in this cohort, that the use of DES is a cost-effective strategy.

Acknowledgements

This study is part of the author’s Doctorate Thesis at the University of Rio de Janeiro and the patients’ data were collected at the following institutions in Rio de Janeiro: Clínica Status Cor, Prontocor and Hospital Mario Lioni. The statistical analysis was performed at the National Institute of Cardiology. The authors are grateful to the excellence of the aforementioned institutions.

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