Real-World Use of Drug-Eluting Stents: the Importance of Registries

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Summary

over the last decades the efficacy and safety of bare metal (BMS) and drug eluting stents (DES) have been demonstrated in many different clinical scenarios, leading to their use in more than 75% of the procedures worldwide. Compared to BMS, DES have shown lower rates of angiographic restenosis and target-vessel revascularization. This benefit was initially demonstrated in trials that excluded patients with more complex lesions, such as those with larger or smaller vessels, chronic total occlusions, bifurcation lesions, stent restenosis, long lesions and left main coronary artery disease. This real-world population has been recently evaluated in many registries and meta-analyses that are reviewed herein.

Introduction

The evolution of interventional cardiology has rapidly progressed over the last decades from percutaneous transluminal coronary angioplasty in the 1970s to the development of bare-metal stents (BMS) in the 1980s. The use of these endoprostheses has resulted in less residual restenosis and the elimination of dissection and acute recoil, as well as a reduced need for in-hospital coronary artery bypass graft surgery and a reduction in the incidence of myocardial infarction. The clear improvement in the outcomes of this technique has permitted the use of BMS in more than 90% of procedures for the treatment of more complex stenosis such as long lesions, small vessels, and multivessel disease[1-3].

Nonetheless, the treatment of more complex lesions and the more widespread use of BMS still require angiographic and clinical restenosis issues to be resolved. Accordingly, this has led to the development of drug-eluting stents (DES), a new marked revolution in interventional cardiology. These devices are able to inhibit neointimal hyperplasia by the local release of antiproliferative agents, with a consequent significant reduction in the incidence of angiographic and clinical restenosis, mainly attributable to the reduced need for target lesion revascularization.

Key words

Drug-eluting stents; meta-analysis; registries.

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For the approval of DES, well-designed multicenter studies involving various patients have been conducted at research hospitals, with the participation of physicians experienced in the field of interventional cardiology. These randomized studies represented the basis for the approval of DES by regulatory agencies. With respect to the Cypher™ (Cordis Corp, Miami Lakes, Fla) stent (sirolimus-eluting stent), the fundamental studies were the RAVEL trial and the SIRIUS, c-SIRIUS and e-SIRIUS studies. For the Taxus™ (Boston Scientific Corp, Natick, Mass) stent (paclitaxel-eluting stent), the TAXUS I, II, IV and V studies were the most significant ones.

However, these randomized studies had some limitations such as the participation itself of centers with vast experience in investigation, inclusion of selected lesions and patients, and compulsory angiographic assessment, a fact that may have increased the chance of target lesion reintervention by 50 to 100%. In addition, the selection of patients with favorable lesions for randomization corresponds to only approximately one-third of the real world population. The excellent outcomes of DES have led experienced professionals to use this novel technology in more complex clinical and angiographic situations than those initially evaluated in the randomized studies, extrapolating their efficacy and safety to a more real population that is currently being treated. The concepts of on-label and off-label indications arose from these practices, with DES becoming popular in so-called off-label situations, such as multivessel percutaneous coronary intervention, chronic total occlusions, bifurcation, saphenous vein graft, left main, small vessels, as well as ostial, restenotic and long lesions (> 30 mm).

The following situations are considered to be on-label indications: *de novo* lesion in a native coronary artery of patients with stable coronary disease. For the Cypher™ stent, the reference diameter of the treated vessel is 2.5 to 3.5 mm and lesion length is 30 mm or less. For the Taxus™ stent, the reference diameter of the treated vessel is 2.5 to 3.75 mm and lesion length is less than 28 mm.

Due to the increasing application of DES to on-label and also to off-label patients, and as far as there is a lack of adequately powered randomized clinical trials in the off-label patients, registry studies comprising all patients treated with DES have been utilized, in an attempt to better evaluate the device in this real-world population. These studies became more important after the publication of isolated cases of very late stent thrombosis (more than 1 year after the procedure), the release of the BASKE-LATE trial[4], and the 2006 European Society of Cardiology Congress, where 2 abstracts also highlighted the problem of very-late stent thrombosis. As a whole, these studies raised the question of whether DES increases the rate of late stent thrombosis and mortality, findings that would jeopardize the

long-term benefit of these devices. However, this fact was not confirmed in subsequent publications and important meta-analyses of the randomized studies[5-8].

With respect to the outcomes of DES for off-label indications, two questions remained to be addressed:

1. Is the benefit of DES in reducing the rate of target vessel revascularization as robust in the real world as it is in randomized clinical trials?
2. Are DES safe when used in off-label indications compared to BMS, which are also used in this situation?

DES and BMS meta-analyses comprising randomized trials and registries

In this article, we performed a sequential analysis of DES registries in an attempt to answer these questions, starting with the Swedish study[9]. In the original publication involving 19,771 patients treated in 2003 and 2004 and followed up over a period of 3 years, the authors observed that the use of DES was associated with an increased rate of death in patients treated with this device. Confirming the efficacy of these devices, the authors noticed a significant reduction in the reintervention rate in the group receiving DES. However, at the 2007 European Society of Cardiology Congress the same authors presented data extending the analysis to patients treated in 2005, totaling 35,266 patients. The overall analysis showed no increase in mortality, together with a reduction of approximately 50% in the need for reintervention**.** What had changed in the Swedish study to invert the results? Surely, the greater experience of the operators and the increased application of DES not only to very high-risk patients, such as the cases studied between 2003 and 2004. Furthermore, the use of DES was 22% in 2003, 36% in 2004 and 53% in 2005 in Sweden. Thus, how can one explain the increased use of a device that is not safe, although more effective in reducing restenosis[10]?

Other registries have subsequently been published, including the study by Tu et al[11] which showed a mortality rate at the end of 3 years of 5.5% *vs* 7.8% among 7,502 patients receiving DES and BMS, respectively (paired analysis, $p < 0.001$), a finding favoring DES. Likewise, a more recent publication by Marroquin et al[12] compared DES and BMS registries involving 6,551 patients. These registries were taken from the NHLBI Dynamic Registry, with patients being divided into phases over the last 10 years according to stent type (BMS or DES), and whether their use was on-label or off-label. The BMS group consisted of 3,858 patients (1,748 on-label *vs* 1,381 off-label) and the DES group consisted of 2,694 patients (2,110 on-label *vs* 1,312 off-label). The frequency of major adverse cardiac events in the on-label group was 2.8% *vs* 2.7% when comparing DES and BMS, respectively ($p = 0.88$), with a frequency of death or myocardial infarction of 5.8% *vs* 6.4% ($p = 0.42$). In the off-label group, mortality was 3.7% in the DES group *vs* 6.4% in the BMS group ($p < 0.001$). The combined frequency of death and myocardial infarction was 7.5% *vs* 11.6%, respectively, in the DES and BMS groups ($p < 0.001$). The need for repeat percutaneous or surgical revascularization was 7.7% *vs* 13.4% for DES and BMS patients, respectively, in the on-label group ($p < 0.001$), and 12.7% *vs* 17.5% in the off-label group ($p < 0.001$). The conclusions of that study are important in real-world clinical practice of interventional cardiology. Compared to BMS, the off-label use of DES reduces the chance of repeat revascularization at the end of 1 year and also significantly reduces the chances of death or infarction. These data support the use of DES in patients with off-label indications.

The most recent and complete combined analysis of randomized studies and registries, in which DES were used, was published recently by Kirtane et al[13]. A total of 22 randomized clinical trials that enrolled 9,470 patients and 34 observational studies comprising 182,901 patients were included in the comprehensive meta-analysis.

Concerning mortality, the authors evaluated 21 randomized studies involving 8,867 patients, for a mean follow-up of 2.9 years and observed a similar mortality rate (HR, 0.97; 95%CI, 0.81-1.15; $p = 0.72$) when comparing the results of patients receiving DES (Cypher™ or Taxus™) with those of patients receiving BMS. Additionally, there was no difference in mortality when the patients were divided according to on-label use (10 studies, 4,818 patients) (HR, 1.05; 95% CI, 0.84-1.30; $p = 0.69$) or off-label use (12 studies, 4,049 patients) (HR, 0.84; 95% CI, 0.62-1.13; $p = 0.24$). Thus, Cypher™ and Taxus™ DES were not associated with an increase in mortality over this follow-up period of 2.9 years. Regarding the registries, 169,595 patients were evaluated in 31 studies, with the population being closer to the real world of interventional cardiology and involving on-label and off-label patients. There was a 22% reduction in the mortality in a random-effects model of patients receiving DES when compared to those treated with BMS over a mean follow-up of 2.5 years (HR, 0.78; 95% CI, 0.71-0.86; $p < 0.001$). Despite the fact that there was a high level of heterogeneity ($I^2 = 71\%$; $p < 0.001$), the relative benefit of DES over BMS was consistent in most of the studies, including those with more than 1,000 patients, as well as those with longer follow-up periods (≥ 2 years).

With respect to the incidence of myocardial infarction in the same randomized studies, no differences were observed between the patients treated with DES or BMS, even when the patients were divided according to on-label and off-label indications. In 25 registries involving 130,191 treated patients, the incidence of myocardial infarction was reduced by 13% among those receiving DES in a random-effect (HR, 0.87; 95% CI, 0.78-0.97; $p = 0.014$). Again, there was a high level of heterogeneity ($I^2 = 60.3\%$; $p < 0.001$); nevertheless, the results were consistent in most of the studies, including those with more than 1,000 patients, as well as those with longer follow-up periods (≥ 2 years).

Finally, the need for target vessel revascularization in the randomized trials was reduced by 55% (HR, 0.45; 95% CI, 0.37-0.54; $p < 0.001$), favoring the use of DES over a mean follow-up of 3.2 years. The reduction in the reintervention rate was 47% in patients of the on-label group over a mean follow-up of 4.2 years (HR, 0.53; 95% CI, 0.43-0.65; $p < 0.01$), and 62% in the off-label group over a mean follow-up of 1.6 years (HR, 0.38; 95% CI, 0.27-0.52; $p < 0.001$). In registries that evaluated the need for reintervention, the

reduction reached 46% in 74,154 patients followed up for a mean period of 2.2 years, a finding that once more favored the use of DES (HR, 0.54; 95% CI, 0.48-0.61; p < 0.001). There was also a high level of heterogeneity (I^2 = 69.7%; p < 0.001); nevertheless, the results were consistent in most of the studies, including those with more than 1,000 patients, as well as those with longer follow-up periods (≥ 2 years).

In conclusion, as demonstrated in Tables 1 and 2, this important meta-analysis shows that in 22 randomized trials, involving 9,470 patients treated with DES or BMS, and followed up for more than 2 years, nonsignificant reductions of 3% in mortality and 6% in the incidence of myocardial infarction were observed in the former, whereas the reduction in the reintervention rate (55%) was highly significant in patients receiving DES. Among the registries involving 182,091 patients, significant reductions of 22% in mortality, 13% in myocardial infarction, and 46% in the target vessel revascularization rate were observed in patients receiving DES.

The brazilian experience

An important Brazilian registry is the so-called DESIRE registry, which represents the experience of the *Hospital do Coração*, São Paulo - Brazil[14]. This registry involved 2,084 patients predominantly treated with the Cypher™ stent (83.5%). Over a mean follow-up period of 2.6 years, the incidence of target lesion revascularization was 3.3%, stent thrombosis was 1.6%, and the rate of major cardiac events was 8.5% (cardiac death, nonfatal myocardial infarction, and target-lesion reintervention), thus resembling the outcomes reported in international studies.

At InCor we analyzed in our database 3,200 patients receiving a stent implant, between September 1998 and May 2002, including 2,250 receiving BMS, and between May 2002 and September 2006, including 910 receiving DES[15]. These patients were followed up with the primary objective to assess mortality. The population receiving DES was older and also comprised a higher proportion of diabetic individuals (33.6% *vs* 26.3%; p < 0.01). In addition, a history of revascularization surgery and coronary intervention was more prevalent among these patients, but DES were used less frequently in patients with acute myocardial infarction. Analysis of all patients showed that non-adjusted mortality at the end of 1.5 years was higher in the BMS group (HR, 0.66; 95% CI, 0.45-0.95; p = 0.025). Nonetheless, non-adjusted mortality was similar in the two groups (HR, 1.06; 95% CI, 0.73-1.55; p = 0.8), when patients treated for acute myocardial infarction were excluded from the analysis.

Conclusion

In summary, the efficacy and safety of DES have been demonstrated in both randomized studies and international registries, with these studies reporting progressively robust and solid data. These international data are in agreement with those observed at our institution, as well as with the Brazilian experience. Furthermore, the obvious message is that data from registry studies are complementary to those of randomized studies, with DES showing better angiographic and clinical outcomes than BMS across a broad range of coronary artery vessel and lesion characteristics, without an increase in eventual complications. Nevertheless, it is unquestionable that other issues, such as continuous long-

Table 1 - Main findings of the meta-analyses from randomized clinical trials[13]

		Studies, n	Patients, n	Median follow-up, y	Random effects	P
Mortality	Overall	21	8,867	2.9	0.97	0.72
	On-label trials	10	4,818	4.0	1.05	0.69
	Off-label trials	12	4,049	1.5	0.84	0.24
MI	Overall	20	8,850	2.9	0.94	0.54
	On-label trials	9	4,318	4.4	1.03	0.82
	Off-label trials	12	4,532	1.5	0.77	0.19
TVR	Overall	16	7,291	3.2	0.45	<0.001
	On-label trials	9	4,618	4.2	0.53	<0.01
	Off-label trials	8	2,673	1.6	0.38	<0.001

MI - myocardial infarction; TVR - target-vessel revascularization.

Table 2 - Main findings of the meta-analyses from observational studies[13]

		Studies, n	Patients, n	Median follow-up, y	Random effects	P
Mortality	Overall	31	169,595	2.5	0.78	<0.001
MI	Overall	25	130,191	2.5	0.87	0.014
TVR	Overall	18	74,154	2.2	0.54	<0.001

MI - myocardial infarction; TVR - target-vessel revascularization.

term (at least one year) dual antiplatelet therapy, anatomy and clinical scenarios should be taken into account in the decision of whether DES or BMS should be preferred.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

References

1. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med. 1994; 331: 496-501.
2. Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carrozza JP, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. J Am Coll Cardiol. 2002; 40: 2082-9.
3. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrick G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med. 1994; 331: 489-95.
4. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006; 48: 2584-91.
5. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med. 2007; 356: 1020-9.
6. Schomig A, Dibra A, Windecker S, Mehilli J, Suárez de Lezo J, Kaiser C, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol. 2007; 50: 1373-80.
7. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007; 356: 989-97.
8. Stone GW, Ellis SG, Colombo A, Dawkins KD, Grube E, Cutlip DE, et al. Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. Circulation. 2007; 115: 2842-7.
9. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med. 2007; 356: 1009-19.
10. Serruys PW, Daemen J. Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents. Circulation. 2007; 115: 1433-9.
11. Tu JV, Bowen J, Chiu M, Austin PC, He Y, Hopkins R, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med. 2007; 357: 1393-402.
12. Marroquin OC, Selzer F, Mulukutla SR, Williams DD, Vlachos HA, Wilensky RL. A comparison of bare-metal and drug-eluting stents for "off-label" indications. N Engl J Med. 2008; 358: 342-52.
13. Kirtane AJ, Gupta A, Iyengar S, Moses JW, Leon MB, Applegate R, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. Circulation. 2009; 119: 3198-206.
14. Sousa A, Costa Jr RC, Moreira AC, Cano MMG, Costa RA, Pavanello R, et al. Long-term clinical outcomes of the drug-eluting stents in the real world (DESIRE) registry. J Interv Cardiol. 2008; 21: 307-14.
15. Campos CAHMC, Ribeiro EE, Lemos PA, Falcão JL, Spadaro AG, Kajita L, et al. Perfil de segurança dos stents farmacológicos nas síndromes coronárias agudas: dados do registro INCOR. Rev Bras Cardiol Invas. 2008; 16: 289-94.