Determining clinical benefits of drug-eluting coronary stents according to the population risk profile: A meta-regression from 31 randomized trials

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ABSTRACT

Background: The use of drug-eluting stents (DES) in unfavourable patients has been associated with higher rates of clinical complications and stent thrombosis, and because of that concerns about the use of DES in high-risk settings have been raised.
Objective: This study sought to demonstrate that the clinical benefit of DES increases as the risk profile of the patients increases.
Methods: A meta-regression analysis from 31 randomized trials that compared DES and bare-metal stents, including overall 12,035 patients, was performed. The relationship between the clinical benefit of using DES (number of patients to treat [NNT] to prevent one episode of target lesion revascularization [TLR]), and the risk profile of the population (rate of TLR in patients allocated to bare-metal stents) in each trial was evaluated.
Results: The clinical benefit of DES increased as the risk profile of each study population increased: NNT for TLR $= 31.1–1.2$ (TLR for bare-metal stents); $p < 0.001$. The use of DES was safe regardless of the risk profile of each study population, since the effect of DES in mortality, myocardial infarction, and stent thrombosis, was not adversely affected by the risk profile of each study population (95% confidence interval for β value 0.09 to 0.11, -0.12 to 0.19, and -0.03 to -0.15 for mortality, myocardial infarction, and stent thrombosis, respectively).
Conclusions: The clinical benefit of DES increases as the risk profile of the patients increases, without affecting safety.

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1. Introduction

In most countries, drug-eluting stents (DES) are approved only for use in *de novo* lesions of up to 30 mm in length occurring in native coronary arteries with diameters of between 2.5 and 3.5–3.75 mm (depending on the type of stent). Yet studies from the USA have shown that nearly 50% of procedures involves off-label or untested indications [1] and that such off-label use is associated with higher rates of complications including stent thrombosis, myocardial infarction and death [1,2]. This may lead to the conclusion that clinicians should be cautious about extrapolating the benefits of DES over bare-metal stents (BMS) observed in randomized clinical trials to higher-risk clinical settings that have not been assessed [2]. Furthermore, the US Food & Drug Administration (FDA) has stated that, until more data are available, DES labelling should indicate that when devices are used off-label, patient outcomes may not be the same as those observed in clinical trials.

However, the untested or not fully tested indications of DES include situations associated with a high risk of restenosis, such as chronic total occlusions, saphenous vein graft disease, in-stent restenosis, very small (<2.5 mm) vessels, and complex lesions. Theoretically, therefore, the clinical benefits of using DES over BMS may actually be greater in such patients than in the more straightforward cases.

We therefore decided to assess the relationship between the clinical benefit of using DES and the patient risk profile. For this purpose we performed a meta-regression analysis based on the findings of 31 randomized trials comparing DES and BMS in very different clinical and angiographic scenarios.

2. Methods

2.1. Trials included

We included randomized trials that compared commercially available DES and BMS [3–26]. In order to identify the trials to be included in the study, a systematic review of the literature was carried out in electronic databases (DARE, Cochrane Database, Medline, Embase, Pascal Biomed and Cinahl). Search was performed using the Medical Subjects Heading terms "Angioplasty, Transluminal, Percutaneous, Coronary", "Stents", "Drug-eluting", "Paclitaxel", "Sirolimus", "Everolimus", "Zotarolimus",

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"Tacrolimus". Abstract supplements of major scientific meetings (American College of Cardiology, American Heart Association, European Society of Cardiology and Transcatheter Cardiovascular Therapeutics) were also reviewed. The review was conducted according to the Quality of Reports of Meta-Analysis of Randomized Clinical Trials (QUOROM) recommendations.

Trial characteristics are shown in Table 1. There were 15 trials with sirolimus-eluting stents (Cypher™, Cordis Corporation) involving 5168 patients; 10 trials with paclitaxel-eluting stents (Taxus™, Boston Scientific) involving 5065 patients, and six trials with other types of DES involving 1802 patients. Overall, 12,035 patients were included in these trial. Trials evaluating Cypher stents included: RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, DIABETES, SCANDSTENT, SES-SMART, STRATEGY, PRISON-II, BASKET (Cypher arm), RRISC, TYPHOON, SESAMI, BASKET-AMI (Cypher arm), and the study by Pache et al. Trials evaluating the Taxus stent included: TAXUS-I, TAXUS-II (slow release, and moderate release arms), TAXUS-IV, TAXUS-V, TAXUS-VI, BASKET (Taxus arm), PASSION, HAAMU-STENT, and BASKET-AMI (Taxus arm). Other trials evaluated the zotarolimus-eluting Endeavor stent (ENDEAVOR-II), the everolimus stent (FUTURE-I, FUTURE-II, SPIRIT-I), the tacrolimus-eluting Janus stent (JUPITER-II), and the biolimus-eluting Bio-Matrixx stent (STEALTH).

2.2. Definitions

The clinical benefit of DES in each trial was defined as the reduction in target lesion revascularization (TLR) expressed as the Number of patients Needed to Treat (NNT) to prevent one case of TLR, where NNT is the inverse of the Absolute Risk Reduction. The patient risk profile was defined as the underlying risk of clinical restenosis in each trial, taken as the rate of TLR occurring in the BMS arm. It is important to clarify that the risk for clinical restenosis is not necessarily related with the risk of death in each trial. For example, patients with ST-segment elevation acute myocardial infarction may have higher mortality but a lower risk of clinical restenosis in comparison with patients with more stable coronary artery disease [27]. Although some of the trials included have available data at long-term follow-up (3–5 years), data for up to one year post-procedure (6–12 months) were included in the present analysis, in order to include similar periods of follow-up for all the trials included. Trials with long-term follow-up have shown that the clinical benefit of DES is maintained beyond 1 year after stent implantation.

2.3. Statistical analysis

Quantitative variables are summarized with mean and standard deviation (SD) or 95% confidence interval (95% CI) and qualitative variables with percentages and 95% CI. Correlations between quantitative variables were evaluated with the Spearman *rho* coefficient.

To evaluate the association between population risk profile and the clinical benefit of using DES, meta-regression analyses were conducted, weighting for the number of patients included in each study. The estimated β coefficients and their 95% CI were also calculated as well as the R^2 coefficient in order to assess the percentage of ST variability explained by each model. Statistical significance was considered when p value was less than 0.05 (alpha error probability = 0.05). Both SPSS 14.0 and CIA statistical packages were used to perform the analysis.

3. Results

3.1. Clinical benefit of DES

Data were available from 31 randomized trials comparing DES and BMS (Table 1). Trial outcomes (major adverse events, death, TLR, angiographic restenosis and stent thrombosis), as well as the clinical benefit of DES over BMS (expressed as NNT for TLR) for each trial are shown in Table 2. The relationship between the clinical benefit of using DES (expressed as the NNT for TLR) and the patient risk profile (expressed as the underlying rate of TLR) is shown in Fig. 1. The regression analysis shows that the clinical benefit of DES is greater in the patients at highest risk of TLR. The NNT for DES falls by 12 for every 10% increase in the risk of TLR. The NNT for TLR = 31.1–1.2 (TLR for BMS); 95% CI for β − 1.7, − 0.6, $p < 0.001$. Thus, the absolute clinical benefit of using DES (in terms of ARR in the need for TLR) increases as the risk of clinical restenosis increases. This relationship was observed with both sirolimus- and paclitaxel-eluting stents (Fig. 2). When only trials without routine angiographic follow-up were included, the relationship between risk profile and the clinical benefit of using DES was also statistically significant (NNT for TLR = 49.9–2.4 (TLR for BMS); $p = 0.035$).

3.2. Effect of DES on death, myocardial infarction, and stent thrombosis

The relationship between patient risk profile and mortality or the incidence of acute myocardial infarction with DES versus BMS is

Table 1
Main clinical and angiographic baseline characteristics of participants in included trials.

Trial name	N (DES/BMS)	Stent type	Mean age (y)	Female (%)	DM (%)	RVD (mm)	MLD (mm)	Length (mm)
RAVEL	238 (120/118)	Cypher	61	24	19	2.62	0.94	9.6
SIRIUS	1058 (533/525)	Cypher	62	29	26	2.80	0.98	14.4
E-SIRIUS	352 (175/177)	Cypher	62	29	23	2.55	0.88	15.0
C-SIRIUS	100 (50/50)	Cypher	61	29	24	2.63	0.80	13.6
DIABETES	160 (80/80)	Cypher	66	37	100	2.34	0.90	15.0
SCANDSTENT	322 (163/159)	Cypher	63	24	18	2.86	0.65	18.0
SES-SMART	257 (129/128)	Cypher	64	28	25	2.20	0.72	11.8
STRATEGY	175 (87/88)	Cypher	63	36	13	2.30	0.0	13.1
PRISON-II	200 (100/100)	Cypher	59	20	13	3.32	0.0	16.2
BASKET-Cy	545 (264/281)	Cypher	64	21	19	–	–	–
Pache et al.	500 (250/250)	Cypher	67	22	31	2.70	–	12.6
RRISC	75 (38/37)	Cypher	73	15	15	3.31	1.09	17.4
TYPHOON	712 (355/357)	Cypher	59	22	16	2.81	0.20	–
SESAMI	320 (160/160)	Cypher	62	19	21	–	–	–
BASKET-MI-Cy	150 (76/74)	Cypher	62	21	15	–	–	–
TAXUS-I	61 (31/30)	Taxus	65	12	18	2.97	1.27	11.3
TAXUS-II-SR	267 (131/136)	Taxus	61	26	14	2.80	0.93	10.6
TAXUS-II-MR	269 (135/134)	Taxus	59	24	16	2.70	2.73	10.5
TAXUS-IV	1314 (662/652)	Taxus	62	28	24	2.75	0.94	13.4
TAXUS-V	1172 (586/586)	Taxus	63	31	31	2.69	0.86	17.3
TAXUS-VI	446 (219/227)	Taxus	63	24	30	2.79	0.86	20.6
BASKET-Tx	562 (281/281)	Taxus	64	21	20	–	–	–
PASSION	619 (310/309)	Taxus	61	24	11	3.22	–	–
HAAMU-Stent	164 (82/82)	Taxus	63	28	15	–	0.70	–
BASKET-MI-Tx	141 (67/74)	Taxus	62	21	15	–	–	–
ENDEAVOR-II	1197 (598/599)	Endeavor	62	24	20	2.75	0.83	14.2
JUPITER-II	332 (166/166)	Janus	64	24	19	–	1.03	12.1
FUTURE-I	36 (25/11)	EES	65	14	2	3.05	1.12	8.9
FUTURE-II	57 (21/36)	EES	63	30	27	2.95	1.04	11.4
SPIRIT-I	60 (28/32)	EES	63	27	11	2.66	–	10.5
STEALTH	120 (80/40)	BioMatrix	62	33	25	2.96	–	14.8

DM: Diabetes Mellitus. RVD: Reference Vessel Diameter. MLD: Minimum Lumen Diameter.