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Drug-eluting stents perform better than bare metal stents in small coronary vessels: A meta-analysis of randomised and observational clinical studies with mid-term follow up

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ABSTRACT

Background: We tested drug-eluting stent (DES) and bare metal stent (BMS) performance in small coronary vessels by means of meta-analysis of all available clinical studies.
Methods: The analysis included randomised controlled trials (RCT), subgroups of RCT and observational studies with a follow-up of at least six months comparing the use of DES and BMS during percutaneous interventions involving small coronary arteries (diameter<3 mm). The primary endpoint was target vessel failure (TVF); the others were pooled and isolated major adverse cardiovascular events (MACE), stent thrombosis (ST), binary restenosis and late lumen loss at the longest available follow-up. The effect of treatment was evaluated in terms of odds ratios (OR) and 95% confidence intervals (95% CI) for binary variables, and mean difference (MD) ± standard deviation (SD) for continuous variables. Fixed- or random-effect models were used depending on the statistical heterogeneity of studies. The analyses of major endpoints were stratified by study type, length of follow-up, and type of DES.
Results: We pooled 12 studies involving 3182 patients. Trial heterogeneity was a minor issue. TVF (OR: 0.35; CI: 0.24–0.51), MACE (OR: 0.36; CI: 0.29–0.45), binary restenosis (OR: 0.15; CI: 0.12–0.20) and late lumen loss (MD: −0.46; SD: −0.55 to −0.38) all significantly improved with DES treatment; ST (OR: 0.63; CI: 0.34–1.17) was not statistically different between studies.
Conclusions: DES are superior to BMS in terms of their efficacy in managing small coronary arteries (diameter<3 mm), and at least equivalent in terms of safety. The use of DES should be considered the treatment of choice in this setting.

1. Introduction

Percutaneous coronary interventions (PCI) involving small coronary vessels represent a true challenge in modern interventional cardiology because of the increased risk of restenosis and adverse outcomes [1]; furthermore, a small vessel does not always mean limited myocardial ischemia and so the percutaneous treatment of small coronary branches (i.e. those with a diameter of <3 mm) often has a considerable impact on future clinical events. Stents are currently the mainstay of such treatment, but the rate of adverse events is still high after the use of bare metal stents (BMS) [2–5] and, although drug eluting stents (DES) are now widely used to treat small coronary lesions, conflicting or inconclusive data have come from randomised clinical trials and registries because of the supposedly higher risk of stent thrombosis (ST) and even higher restenosis rate [6,7]. In the absence of a systematic overview of clinical and angiographic outcomes that would provide more robust evidence, we made this meta-analysis of the available trials and registries directly comparing the two types of stent.

2. Methods

2.1. Study selection strategy

The eligible studies included randomised controlled clinical trials (RCT) [8–10], subgroups from RCT and observational studies [11–20] of PCIs using a DES or BMS to treat small coronary artery disease, provided that they had a follow-up of at least six months. The target vessel had to have a diameter <3 mm with a clinical indication to

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Table 1
Studies included in the meta-analysis with main characteristics.

Study author	Study name	Design	Year	Drug of DES	Patients, n°	Median follow up, days
Schampaert, E	C-SIRIUS	RCT	2004	Sirolimus	100	270
Schofer, J	E-SIRIUS	RCT	2003	Sirolimus	352	270
Ardissino, D	SES-SMART	RCT	2004	Sirolimus	257	270
Pfisterer, M	BASKET	RCT subgroup	2009	Sirolimus, paclitaxel	268	1080
Moses, J	SIRIUS	RCT subgroup	2003	Sirolimus	673	240
Grube, E	TAXUS VI	RCT subgroup	2007	Paclitaxel	123	720
Jimenez-Quevedo, P	DIABETES I, II	Observational	2006	Sirolimus	85	360
Tsuchiya, Y	FUTURE I, II	Observational	2006	Everolimus	37	180
Stone, GW	TAXUS V	RCT subgroup	2005	Paclitaxel	203	270
Turco, MA	TAXUS ATLAS	RCT subgroup	2007	Paclitaxel	416	270
Meier, B	SVELTE	Observational	2006	Sirolimus	424	240
Umeda, H	–	Observational	2009	Sirolimus	244	360

DES = drug eluting stent; n° = number; RCT = randomised controlled trial.

PCI. All eligible studies had to contain both a DES and a BMS group. The main exclusion criteria were: 1) duplicate publications; 2) ongoing studies; 3) studies with a follow-up other than that specified in the study protocol; 4) studies with unretrievable or unclear data; and 5) studies lacking a control group.

Two trained investigators (B.C. and A.B.) used both sensitive and specific strategies to make independent searches of PubMed, Central, mRCT, BioMedCentral, clinicaltrials.gov, Cardiosource, ISI Web of Science, and the annual international meetings of the major cardiology associations (the European Society of Cardiology, the American Heart Association, the American College of Cardiology, the Cardiovascular Research Foundation, and the European Association of Percutaneous Cardiovascular Interventions), after which international experts were queried for additional trials results. All first authors of retrieved articles were sent an email to confirm the published data, and obtain further information regarding eventual longer follow-up.

The searches were updated to the end of January 2010, and the search key words were "small vessel", "PCI", "stent", "BMS", "DES", "randomized", and "randomised". Selected papers were screened at title and abstract level and then, if considered suitable, the complete manuscripts were checked for compliance with the inclusion criteria.

Study quality was evaluated using the established methods of the Cochrane Collaboration, with separate estimates of the risk of selection, performance, detection and attrition bias, or allocation concealment [21].

2.2. Study endpoints

The primary study endpoint was the occurrence of target vessel failure (TVF), defined target vessel revascularisation (TVR), or any death or myocardial infarction (MI) that could not be attributed to a vessel other than the target vessel by the end of the longest available study follow-up period.

The secondary endpoints were:

1) the occurrence of major adverse cardiovascular events (MACE), defined as the occurrence of any one of death, MI or TVR;
2) the occurrence of any of the above as single events;
3) the occurrence of definite or probable ST, following the ARC definition [22];
4) late lumen loss (LLL) at angiographic follow-up;
5) binary restenosis (defined as ≥50% in-stent restenosis) at angiographic follow-up.

MI was defined as any new chest pain associated with new ECG changes and an increase in the levels of the cardiac biomarkers of necrosis (depending on the criteria of each study).

2.3. Meta-analyses

The meta-analyses were based on cumulative data from the time of stent implantation. The between-group effect of treatment in each study was measured as the odds ratio (OR) with 95% confidence interval (95% CI) for binary variables, and as the mean difference (MD) with standard deviation (SD) for continuous variables. A single time point estimate for each study endpoint was chosen, assuming a constant absolute DES vs. BMS risk reduction throughout the follow-up period. Mantel–Haenszel (M–H) of inverse-variance weighted methods were applied to fixed-effect models, and DerSimonian and Laird methods to random-effect models [23,24]. Statistical heterogeneity was assessed using Cochrane Q via a χ^2 test, and was quantified using the I^2 test [25–27].

In the case of heterogeneity between studies, stratified analyses of the clinical and angiographic endpoints were made by grouping the studies on the basis of characteristics selected a priori as possible modifiers (type of study, length of follow-up, type of DES).

The studies with no events in either the intervention or control arms were excluded; if no events were recorded in only one of the arms, 0.5 was added to the cell counts.

Systematic bias was evaluated using Egger's funnel plot and correspondent asymmetry test [26].

All of the analyses were made using Stata, version 11.0 [28].

3. Results

A total of 72 citations were retrieved from the searches, a number of which were excluded at title/abstract level because they were not pertinent or provided insufficient clinical data on baseline characteristics or it was impossible to determine the study endpoints. The 12 finally selected studies (involving a total of 3182 patients) provided

Table 2
Clinical data of studies included in the meta-analysis.

Study author	Age, yrs	Male, %	Diabetes mellitus, %	Stable angina, %	Myocardial infarction, %	Suggested duration of dual antiplatelet treatment, months
Schampaert, E	60.5 ± 9.8	69	24	12	37	2
Schofer, J	62.3 ± 10.9	71	23	67	0	2
Ardissino, D	63.5 ± 11.4	73	23	45	45 (with UA)	2
Pfisterer, M	64 ± 11	79	19	42	21	6
Moses, J	N/A	N/A	N/A	N/A	N/A	3
Grube, E	62.7 ± 9.8	76	20	57	0	6
Jimenez-Quevedo, P	66.7 ± 9	59	100	N/A	N/A	2
Tsuchiya, Y	66.2	68	22	86	0	2
Stone, GW	N/A	N/A	41	N/A	N/A	6
Turco, MA	63.6 ± 11	59	37	N/A	N/A	6
Meier, B	62.5 ± 1.1	68	29	N/A	0	2
Umeda, H	66.6 ± 9.5	74	32	N/A	17	3

N/A = not available; UA = unstable angina; yrs = years.