Drug-Eluting Stents vs Intracoronary Brachytherapy for In-Stent Restenosis: A Meta-Analysis

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ABSTRACT

Background: It has been reported that drug-eluting stents (DES) were superior to intracoronary brachytherapy (ICBT) in patients with in-stent restenosis (ISR). However, it is unknown whether there might be differences between DES and ICBT in terms of efficacy and safety in large sample size and long-term follow-up.

Hypothesis: The aim of this study was to determine whether DES implantation remains favorable in large sample size and long-term follow-up when compared with ICBT among patients with ISR.

Methods: We conducted a search in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials without language restrictions. A meta-analysis of 1942 cases from 12 controlled trials of DES vs ICBT for ISR was performed.

Results: Drug-eluting stents were significantly more effective in reducing target-vessel revascularization (TVR) (odds ratio [OR]: 0.44, 95% confidence interval [CI]: 0.23–0.81, $P = 0.009$) and binary restenosis (OR: 0.34, 95% CI: 0.26–0.46, $P < 0.00001$) compared with ICBT at midterm follow-up. There were no significant differences between DES and ICBT in cardiac death, myocardial infarction (MI), and late stent thrombosis at midterm follow-up. A statistical significance has been found between the 2 groups in TVR (OR: 0.61, 95% CI: 0.43–0.86, $P = 0.005$) at long-term follow-up. There were no significant differences in cardiac death and MI between the 2 groups at long-term follow-up.

Conclusions: These findings provide evidence that DES is superior to ICBT for the treatment of ISR in TVR and binary restenosis reduction, but not in cardiac death, MI, and late stent thrombosis reduction.

Introduction

In-stent restenosis (ISR) occurs in 15%–50% of patients after bare-metal stent (BMS) implantation and continues to be one of the most common adverse events.¹ Although drug-eluting stents (DES) have significantly decreased the incidence of ISR, ISR remains a persistent, unresolved clinical issue, especially for patients with highly complex lesions.^{2,3}

Intracoronary brachytherapy (ICBT) has been considered a preferred treatment to reduce recurrent ISR compared with mechanical treatment.^{4,5} Several studies have proved that DES placement is superior to ICBT during follow-up periods of up to 9 months after treatment of ISR.^{6,7} A previous meta-analysis showed that DES reduced the rate of revascularization, major adverse cardiac events (MACE), and binary restenosis (BAR) compared with ICBT, but only 2 of the included studies compared DES with ICBT and follow-up was limited to 9 months.⁸ The potential long-term

effects after DES implantation for ISR, similar to those observed after ICBT, remain a concern. Moreover, in recent years a randomized controlled trial indicated that the incidences of overall cardiac mortality and myocardial infarction (MI) were higher in the DES group than in the ICBT group during follow-up periods of up to 3 years. Currently, treatment with DES for ISR is associated with high rate of late stent thrombosis and perhaps results in increased death and MI.^{9,10} Consequently, whether DES is superior to ICBT remains uncertain in large sample size and long-term follow-up, and there are 2 randomized controlled studies published in recent years.^{11,12}

We therefore conducted this meta-analysis to compare the clinical and angiographic outcomes of DES vs ICBT for ISR from all relative studies.

Methods

Identification of Studies

According to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses,¹³ we searched the electronic databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials without

Yong-Guang Lu, MD, and Yan-Mei Chen, MD, contributed equally to this work. The authors have no funding, financial relationships, or conflicts of interest to disclose.

language restrictions for articles dating from January 1966 to September 2010. The following free-text terms and their combinations were used to identify relevant studies: intracoronary brachytherapy, intracoronary radiation, intracoronary irradiation, coronary, coronary angiography, coronary disease, drug-eluting stents, sirolimus-eluting stents, paclitaxel-eluting stents, and restenosis. Additionally, the references lists of included articles, reviews, and editorials were screened manually. We consulted with the experts of studies for additional information and data. When duplicate reports or overlapping studies were present, the latest publication, the one with sufficient adjustment for confounding, or the larger study was included in the analysis, so that each report was unique.

Selection Criteria

Eligible studies were all published and ongoing clinical controlled trials comparing DES with ICBT for ISR lesions. The clinical and angiographic outcomes were followed up for ≥ 6 months. We excluded studies if they had a cross-sectional design, if they did not adjust for potential confounders, and if they did not provide a sufficient statistical analysis.

Quality Assessment

Two review authors (R.Z. and C.F.) independently assessed the risk of bias of each trial using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions.¹⁴ Any disagreement was resolved by discussion. The 6 domains for risk of bias were performed and included details of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other sources of bias." In the 6 domains, "Yes" means a low risk of bias, "Unclear" means there is an uncertain risk of bias, and "No" means there is a high risk of bias. The data were analyzed using Review Manager Software version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008).

Data Extraction

Data were extracted carefully from all included studies independently by 2 of the authors (Y.L. and Y.C.). Any discrepancies were resolved by discussion between the authors. If these 2 authors could not reach a consensus, discrepancies were resolved by the third author (L.L.). Data extraction included the first author, year of publication, number of participants, age and gender of participants, description of the intervention and control-group treatments, follow-up period, and data on relevant outcomes. Target-vessel revascularization was defined as the primary outcome. Other clinical outcomes of interest were BAR, late lumen loss, cardiac death, MI, and late stent thrombosis.

Data Analysis

Dichotomous data were expressed as odds ratio (OR) and 95% confidence intervals (CI). Weighted mean difference (WMD) with a 95% CI was used for continuous

outcomes. A P value < 0.05 was considered significant. A random-effects model was used if heterogeneity existed, whereas the fixed-effects model was applied in the absence of between-study heterogeneity. After data pooling, statistical heterogeneity was identified and evaluated by using the I^2 statistic, which represented the percentage of total variations across studies ($I^2 < 25\%$ represents trivial heterogeneity, $I^2 < 50\%$ suggests moderate heterogeneity, and $I^2 > 50\%$ suggests substantial and important heterogeneity).¹⁵ Analyses were performed using Review Manager Software version 5.0.

Results

Characteristics of the Studies

In total, 389 articles were reviewed, and 12 studies^{9,11,12,16–24} enrolling 1942 patients met the study criteria and were included in this meta-analysis. The demographic and clinical characteristics of patients are summarized in Table 1, and no significant differences were found in baseline characteristics between the 2 groups. The mean follow-up period ranged from 6 to 36 months.

A summary of the methodological quality of included studies was performed. Four of the 12 studies were randomized controlled trials, and 8 were nonrandomized controlled trials. The method of sequence generation and allocation concealment was well covered or adequately addressed in all included randomized controlled trials. Completeness of data was good in 8 included trials. Blinding was not clearly described in 8 trials. Selecting reports and other biases were not clearly recorded in 5 trials and 7 trials, respectively.

Target-Vessel Revascularization at Midterm Follow-Up

At a follow-up period of 6 to 12 months, the TVR data were available in 3 randomized trials^{9,11,16} and 5 nonrandomized studies.^{17,20–24} A significant heterogeneity was found between 2 groups ($I^2 = 59\%$, $P = 0.02$); then the random-effects model was used, and the pooled OR was 0.44 (95% CI: 0.23–0.81, $P = 0.009$), suggesting occurrence of TVR was significantly reduced by DES. Subgroup analysis revealed a difference in the result between randomized and nonrandomized studies. A benefit from DES implantation was found in randomized trials (OR: 0.45, 95% CI: 0.30–0.66, $P < 0.0001$), but not in nonrandomized studies (OR: 0.38, 95% CI: 0.10–1.45, $P = 0.16$) (Figure 1).

Binary Restenosis at Midterm Follow-Up

At a follow-up period of 6 to 12 months, DES was significantly more effective in the reduction of BAR. The incidence of BAR recorded in 3 randomized trials^{9,12,16} and 4 nonrandomized studies^{17–19,24} was 13.9% among patients treated with DES and 29.5% among those treated with ICBT. The pooled OR in favor of DES was 0.34 (95% CI: 0.26–0.46, $P < 0.00001$) by the fixed-effects model, with no significant study heterogeneity ($I^2 = 22\%$, $P = 0.26$). A statistically significant effect favoring DES was found for both randomized and nonrandomized studies (Figure 2).

Table 1. Main Clinical and Angiographic Baseline Characteristics of Included Trials

Study ID (Author, Year)	No. of Partici- pants		Treatment		Male, n (%)		DM, n (%)		Mean age, y		TLL, mm		Base RVD, mm		MLD, mm		Follow-Up, mo
	DES	ICBT	DES	ICBT	DES	ICBT	DES	ICBT	DES	ICBT	DES	ICBT	DES	ICBT	DES	ICBT	
Ellis 2008	195	201	PES	β	121 (62)	141 (70)	78 (40)	61 (30)	63	63	15.9	15	2.68	2.61	0.8	0.83	24
Feres 2005	25	25	SES	β	20 (80)	21 (84)	6 (24)	9 (36)	56 ± 12	58 ± 11	13.6 ± 7.6	18.6 ± 4.1	2.82 ± 0.35	2.72 ± 0.36	1.05 ± 0.31	1.06 ± 0.33	15
Holmes 2008	259	125	SES	β or γ	176 (68)	82 (66)	86 (33)	37 (30)	62.7 ± 10.7	63.5 ± 11.7	17.22 ± 7.97	16.76 ± 8.55	2.64 ± 0.44	2.62 ± 0.43	0.78 ± 0.37	0.86 ± 0.35	36
Lofina 2007	72	72	SES	β	49 (68)	48 (67)	14 (19)	12 (17)	62 ± 10	61 ± 11	12.01 ± 5.01	12.86 ± 6.60	2.60 ± 0.37	2.63 ± 0.38	0.69 ± 0.35	0.69 ± 0.33	30
Lee 2007	120	240	SES	β	91 (76)	172 (72)	40 (33)	72 (30)	59.9 ± 10.0	58.2 ± 9.48	25.1 ± 14.2	24.5 ± 10.4	2.98 ± 0.52	2.91 ± 0.42	0.74 ± 0.61	0.73 ± 0.40	36
Park 2008	65	64	SES	β	50 (77)	52 (81)	20 (31)	20 (31)	60.5 ± 9.3	59.1 ± 8.3	27.5 ± 14.0	27.8 ± 14.3	2.77 ± 0.57	2.67 ± 0.51	0.78 ± 0.39	0.81 ± 0.36	6
Pohl 2005	28	28	SES	β	18 (64)	25 (89)	5 (18)	5 (18)	65 ± 10	65 ± 11	11.9 ± 3.1	13.3 ± 5.4	2.8 ± 0.2	3.1 ± 0.3	0.5 ± 0.2	0.5 ± 0.3	9
Radke 2004	22	25	PES	β	15 (68)	22 (88)	5 (23)	5 (20)	61 ± 10	60 ± 13	13.3 ± 5.0	12.9 ± 4.8	2.78 ± 0.57	2.76 ± 0.44	0.91 ± 0.43	0.90 ± 0.28	12
Saia 2004	44	43	SES	β	32 (73)	31 (73)	11 (25)	11 (26)	63 ± 13	61 ± 10	17.5 ± 12.1	15.7 ± 10.4	2.64 ± 0.56	2.44 ± 0.45	0.90 ± 0.55	0.74 ± 0.52	9
Schukro 2007	20	17	PES	β	20 (54)		12 (32)		60.8 ± 12.3		15.1 ± 4.4	16.7 ± 9.4	2.25 ± 0.68	2.64 ± 0.74	1.04 ± 2.17	0.88 ± 0.56	12
Torguson 2006	50	61	SES or DES	β	32 (64)	39 (64)	22 (44)	26 (43)	62.0 ± 11.2	61.6 ± 13.5	NR	NR	NR	NR	NR	NR	8
Zavalloni 2006	73	68	SES or DES	β	54 (74)	54 (79)	25 (34)	19 (28)	66.5 ± 9.2	65.8 ± 8.12	16.7 ± 9.1	18.4 ± 8.2	2.63 ± 0.50	2.65 ± 0.63	0.64 ± 0.39	0.70 ± 0.37	9

Abbreviations: DES, drug-eluting stent; DM, diabetes mellitus; ICBT, intracoronary brachytherapy; MLD, minimal luminal diameter; NR, no report; PES, paclitaxel-eluting stent; RVD, reference vascular diameter; SES, sirolimus-eluting stent; TLL, target lesion length.

Figure 1. Forest plot of included trials comparing DES with ICBT in the incidence of TVR at a follow-up period of 6 to 12 months. Abbreviations: CI, confidence interval; DES, drug-eluting stents; ICBT, intracoronary brachytherapy; TVR, target-vessel revascularization.

Figure 2. Forest plot of included trials comparing DES with ICBT in the incidence of BAR at a follow-up period of 6 to 12 months. Abbreviations: BAR, binary restenosis; CI, confidence interval; DES, drug-eluting stents; ICBT, intracoronary brachytherapy.

Figure 3. Forest plot of included trials comparing DES with ICBT in the incidence of late lumen loss at a follow-up period of 6 to 12 months. Abbreviations: CI, confidence interval; DES, drug-eluting stents; ICBT, intracoronary brachytherapy.

Late Lumen Loss at Midterm Follow-Up

At a follow-up period of 6 to 12 months, the data on late lumen loss were recorded in 3 randomized trials^{9,11,12} and 4 nonrandomized studies.^{17–19,24} There was a statistical heterogeneity between 2 groups ($I^2 = 58\%$, $P = 0.03$); then the random-effects model was used, and the pooled WMD was -0.23 (95% CI: -0.35 to -0.11 , $P = 0.0002$), suggesting there was a statistical significance between the 2 groups. A subgroup analysis showed no significant effect of the use of DES on late lumen loss in randomized studies (WMD: -0.18 , 95% CI: -0.43 to 0.08 ; $P = 0.18$). On the other hand, DES implantation demonstrated a significant reduction in late lumen loss in nonrandomized trials (WMD: -0.26 , 95% CI: -0.38 to -0.14 , $P = 0.16$) (Figure 3).

Cardiac Death, MI, and Late Stent Thrombosis at Midterm Follow-Up

At a follow-up period of 6 to 12 months, there were no significant differences with respect to cardiac death, MI, and late stent thrombosis. The occurrence of cardiac death reported in 4 randomized trials^{9,11,12,16} and 6 nonrandomized studies^{17,20–24} was 0.6% with DES vs 0.9% with ICBT (OR: 0.91, 95% CI: 0.34–2.44, $P = 0.85$) and no significant heterogeneity between trials ($I^2 = 0\%$, $P = 0.44$). The MI adjusted percentage available in 4 randomized trials^{9,11,12,16} and 6 nonrandomized studies^{17,20–24} was 2.2% with DES vs 2.1% with ICBT (OR: 1.03, 95% CI: 0.52–2.06, $P = 0.92$) and no significant heterogeneity between trials ($I^2 = 0\%$, $P = 0.77$). The incidence of late stent thrombosis for DES (1.1%) vs ICBT (0.6%) was reported in 4 randomized trials^{9,11,12,16} and 3 nonrandomized studies.^{17,23,24} There was no statistical significance between the 2 groups, with the OR 1.45 (95% CI: 0.53–3.98, $P = 0.47$) and the P value of the heterogeneity test was 0.58 and I^2 was 0%. Prespecified subgroup analysis

for randomized and nonrandomized trials obtained similar outcomes (Table 2).

Target-Vessel Revascularization, Cardiac Death, and Myocardial Infarction at Long-Term Follow-Up

At a follow-up period of 24 to 36 months, TVR, cardiac death, and MI were recorded in 2 studies,^{16,19} 3 studies,^{9,16,19} and 3 studies,^{9,16,19} respectively. A statistical significance has been found between the 2 groups in TVR (OR: 0.61, 95% CI: 0.43–0.86, $P = 0.005$). There were no significant differences in cardiac death (OR: 1.33, 95% CI: 0.48–3.71, $P = 0.59$) and MI (OR: 1.16, 95% CI: 0.60–2.23, $P = 0.65$) between the 2 groups. The statistical analysis was not performed on the incidence of BAR and late lumen loss because sufficient data were not provided.

Discussion

In-stent restenosis has been a persistent challenge for interventional cardiology. It occurs in 15%–50% or more of all coronary BMS procedures.¹ Even in the era of DES, ISR is likely to remain a significant problem, especially in patients with high risk factors for restenosis, including diabetes mellitus, smaller vessel diameter, and longer and more complex lesions.^{2,3} In the present, there are a range of therapeutic approaches and options for ISR, most notably DES or BMS implantation, ICBT, cutting balloon angioplasty, and debulking approaches including rotational atherectomy and excimer laser atherectomy. However, the treatment modalities such as debulking approaches and cutting balloon angioplasty have not been shown to have a significant advantage over balloon angioplasty for ISR.^{25–27}

A meta-analysis including 5 randomized controlled trials comparing ICBT with placebo, involving a total of 1310 patients, demonstrated significant relative reductions in

Table 2. Quantitative Summary of Included Trials Comparing DES With ICBT in the Incidence of Cardiac Death, MI, and Late Stent Thrombosis at a Follow-Up Period of 6 to 12 Months

Endpoint	Subgroup	Studies	Incidence		OR (95% CI)	Overall Effects (P Value)	Heterogeneity	
			DES	ICBT			I ² (%)	P Value
Cardiac death	Overall	9, 11, 12, 16, 17, 20–24	5/781	6/657	0.91 (0.34–2.44)	0.85	0	0.44
	Randomized	9, 11, 12, 16	1/539	1/407	1.01 (0.14–7.25)	0.99	0	0.35
	Nonrandomized	17, 20–24	4/242	5/250	0.88 (0.28–2.75)	0.83	25	0.26
MI	Overall	9, 11, 12, 16, 17, 20–24	17/781	14/657	1.03 (0.52–2.06)	0.92	0	0.77
	Randomized	9, 11, 12, 16,	15/539	9/407	1.36 (0.59–3.12)	0.47	25	0.26
	Nonrandomized	17, 20–24	2/242	5/250	0.54 (0.15–2.020)	0.36	0	0.94
Late stent thrombosis	Overall	9, 11, 12, 16, 17, 23, 24	6/549	4/688	1.45 (0.53–23.98)	0.47	0	0.58
	Randomized	9, 11, 12, 16	6/401	2/534	2.5 (0.71–8.77)	0.15	0	0.64
	Nonrandomized	17, 23, 24	0/148	2/154	0.31 (0.03–3.08)	0.32	0	0.98

Abbreviations: CI, confidence interval; DES, drug-eluting stents; ICBT, intracoronary brachytherapy; MI, myocardial infarction; OR, odds ratio.

angiographic restenosis and TVR in the ICBT arm at midterm follow-up.²⁸ Drug-eluting stents tested against ICBT in a more recent meta-analysis including 2 randomized trials was found superior as evaluated by clinical and angiographic outcomes,⁸ but the superiority at longer follow-up is uncertain. The concern has arisen regarding the late adverse outcomes after both DES and ICBT placement.

The principal finding of this meta-analysis including 12 studies showed that DES placement for the treatment of ISR presented some advantages in reducing TVR, BAR, and late lumen loss compared with brachytherapy. Compared with ICBT, DES implantation for ISR demonstrated lower BAR at 6 to 12 months of follow-up, which was similar to the results that have been reported by Oliver et al.⁸ Despite the finding that the incidence of BAR was significantly reduced among patients treated with DES compared with ICBT, the absolute rate of 13.9% is higher than that seen with treatment of de novo lesions. Interestingly, a different trend was observed when comparing results from randomized and nonrandomized studies included in the meta-analysis. Randomized data showed significant benefits from DES implantation in TVR reduction, whereas nonrandomized studies did not confirm this result. A significant heterogeneity was found in the nonrandomized studies. The rate of TVR was higher in the DES group in the study by Torguson et al,²³ leading to a significant heterogeneity among the studies. The effect size was reduced considerably when the trial was excluded and heterogeneity was no longer present. In the study, more lesions were treated per patient in the DES group, which could favor recurrent restenosis and repeat revascularizations; thus, the results could be suspicious. Furthermore, a subgroup analysis of all the studies found a significant benefit from DES used in reduction of late lumen loss in nonrandomized studies. It found no significant difference between the 2 groups in late lumen loss in randomized studies. A striking heterogeneity in randomized studies was present. Several factors

may account for such lack of homogeneity. Various stents and irradiation were used in different studies, thus possibly implying different efficacy in ISR patients. Only 3 small randomized studies have been included, which are likely to include selected cohorts of patients and operators. Overall, the results suggest a possible favorable effect of the use of DES on late lumen loss reduction. More importantly, this study proved that DES implantation for ISR was more effective in decreasing recurrent restenosis and improving long-term outcomes. Finally, the study has a large sample size, 1942 patients, which provided stronger evidence than the previous studies.⁸

The second major concern were the indicators of safety, including cardiac death, MI, and late stent thrombosis after treatment of ISR. The results in the present study by data synthesis and quantitative analysis demonstrated no difference in the long-term rates of cardiac death, MI, and late stent thrombosis, which has not been shown in the previous meta-analysis because the included studies did not provide sufficient statistical data.⁸ However, the benefit of DES implantation was associated with a significant reduction of TVR and BAR, but not with reduction of clinical hard endpoints such as death or MI, which has been questioned because restenosis has no involvement with these more significant events in some trials.

In a previous randomized controlled trial, the overall cardiac mortality, Q-wave MI, and non-Q-wave MI were higher in the DES group than in the ICBT group at 3 years of follow-up, which was considerate to be associated with high rate of late stent thrombosis.^{9,10} Drug-eluting stent implantation and ICBT are both associated with delayed healing after percutaneous coronary intervention, which results in delayed stent thrombosis.²⁹ Although no significant difference has been found between DES implantation and ICBT, stent thrombosis remains relatively uncommon and significantly increased compared with that seen in patients treated with DES for de novo lesions. Thus,

it was particularly important to emphasize dual antiplatelet therapy with clopidogrel and aspirin for ≥ 12 months, which has been shown to effectively eliminate late stent thrombosis. Consequently, the results of this meta-analysis proved that DES was at least as safe as ICBT in the treatment of ISR during a midterm and long-term follow-up period.

In the era of DES, BMS and ICBT are rapidly substituted by DES due to their high restenosis rates after treatments. Although the current evidence has demonstrated the superiority of DES over ICBT for the treatment of ISR, ICBT remains an alternative treatment modality in patients not amenable to percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery. In the past, the studies comparing DES to ICBT for the treatment of ISR have paid more attention to BMS restenosis, but less to DES restenosis. A recent published paper showed that the incidences of late restenosis, ischemia-driven TLR, and MACE are higher after repeated SES implantation in ISR lesions treated with SES than in those treated with BMS.³⁰ Therefore, ICBT remains a proven method of restenosis prevention for the treatment of ISR, and its role in treating DES restenosis remains to be studied.

The current meta-analysis has several limitations worth noting. First, the most notable limitation is that only 4 randomized controlled trials were included in this study. Eight nonrandomized comparative studies were included to obtain as much comprehensive information as possible, but these are prone to selection, performance, attrition, and detection bias. Another limitation of the meta-analysis was that relevant data on the long-term follow-up period often was not available from each study, and this difficulty in retrieval results in missing data in the meta-analysis. Third, a limitation inherent to all meta-analyses is the potential heterogeneity among studies in terms of protocols, patients, and sample sizes, and the unavailability of patient-level data that might lead to inaccurate conclusions.

In conclusion, the findings of this meta-analysis suggest that DES implantation for ISR compared with ICBT appears to be associated with reduced occurrences of TVR and BAR. A possible benefit from DES implantation in late lumen loss reduction was found in the present study. Based on the current evidence, DES implantation was not superior to ICBT for the treatment of ISR in reducing the clinical endpoints of death and MI during midterm and long-term follow-up periods. Furthermore, a follow-up of up to 5 years is necessary to determine whether there are any differences in risk of adverse events, and large-scale randomized trials will be required to compare the clinical and angiographic outcomes of DES vs ICBT for ISR.

Acknowledgments

The authors would like to express their thanks to Shi-Xing Luo, PhD, and Xiao-Feng Li, PhD, for help in designing and conducting this study.

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