A meta-analysis of trials comparing Cypher and Taxus stents in patients with obstructive coronary artery disease

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Aims

Drug-eluting stents have been shown to be superior to bare metal stents in reducing restenosis rates. Recently head-to-head trials comparing sirolimus-eluting stents and paclitaxel-eluting stents have been reported. An early combined analysis of these comparative trials is needed. The present meta-analysis was carried out to compare the effects of sirolimus-eluting stents with paclitaxel-eluting stents on the restenosis rate, major adverse cardiac events and late loss of arterial lumen diameter in patients with obstructive coronary artery disease.

Methods

Electronic (Medline, Cochrane and Embase) and manual search (Index Medicus and cross references of retrieved articles) were carried out for all the relevant articles up till March 2005. Only randomized trials with adequate data for calculation of odds ratio for restenosis rates and major adverse cardiac events using the method of DerSimonian & Laird and standardized mean difference for late loss of arterial lumen diameter were included.

Results

Four studies were found to be eligible for inclusion in the meta-analysis. Restenosis rate and late loss of arterial lumen diameter were significantly reduced by sirolimus-eluting stents as compared with paclitaxel-eluting stents (OR 0.598, 95% CI 0.400, 0.893, pooled mean difference -0.414 , 95% CI -0.492 , 0.336 , respectively). The incidence of major adverse cardiac events was less with sirolimus-eluting stents as compared with paclitaxel-eluting stents (OR 0.727, 95% CI 0.518–1.018) but the results were not statistically significant.

Conclusions

Sirolimus-eluting stents are superior to paclitaxel-eluting stents in decreasing restenosis rate and late loss of arterial lumen diameter. However, no statistically significant difference in major adverse cardiac events was noted between the two stents.

Introduction

Drug-eluting stents have been shown to reduce restenosis without increasing the risk of stent thrombosis in comparison with bare metal stents [1–9]. However, the trials were not adequately powered to address any potential effect on hard clinical endpoints such as death, and meta-analyses have not shown a definitive benefit of

drug-eluting stents over bare metal stents for these hard endpoints.

A large number of observational studies and clinical trials [10–27] have demonstrated safety and efficacy of drug-eluting stents in patients with obstructive coronary artery disease. Paclitaxel (Taxus) and sirolimus (Cypher) have been the most commonly used drug-eluting stents.

Both of these agents reduce the risk of restenosis through their inhibitory actions on vascular smooth muscle cell proliferation [28]. There is, however, some subtle difference between the mechanisms of the two. Sirolimus, which is a macrolide antibiotic, has been shown to act through its cytostatic and anti-inflammatory actions, whereas paclitaxel acts through its cytotoxic actions [29].

The degree of benefit provided by sirolimus- and paclitaxel-eluting stents has not been similar in various trials. Results of trials with head-to-head comparisons of these agents have recently been published [30–32] or reported in conference notes [33–36]. One of these studies [35] has recently been published [37].

In view of the differential effects on restenosis and major adverse cardiac events with Cypher and Taxus stents in the clinical trials, we conducted a meta-analysis to compare the effects of these two agents on cardiac outcomes, including major adverse cardiac events, restenosis rates and late loss of arterial lumen diameter.

Methods

Study selection

Two investigators independently searched Medline, the Cochrane database and Embase for all relevant articles until March 2005. Medical subjects heading (MeSH) terms with text words ‘obstructive coronary artery disease’ AND ‘acute coronary syndrome’ AND ‘stents’ were entered. Later ‘sirolimus eluting stents’ AND ‘paclitaxel eluting stents’ AND ‘comparison’ were entered. A repeat search was conducted using ‘Cypher’ AND ‘Taxus’ AND ‘comparisons’. All the searches were then combined. Hand search of articles listed in Index Medicus and those published in key cardiology journals was carried out. Additionally, the reference lists of the retrieved articles were cross-checked for any potentially relevant study. These articles were evaluated for eligibility and inclusion in the study.

Data extraction

Only randomized clinical trials in patients with coronary artery disease comparing sirolimus-eluting stents and paclitaxel-eluting stents were selected. Studies had to present data as relative risk (RR) or odds ratio (OR) or mean difference for one or more of the three endpoints. Otherwise, the study had to present enough data to allow them to be calculated. The endpoints analysed were major adverse cardiac events, restenosis rates and late loss of arterial lumen diameter.

Analysis

Quality assessment of all of the studies included in the meta-analysis was carried out using the method outlined

in the Center for Review and Dissemination guidance for carrying out or commissioning reviews [38]. Briefly, the quality of study was analysed taking into consideration various aspects such as presence or absence of randomization, baseline comparability, eligibility criteria, co-interventions, blinding, withdrawals, and intention-to-treat analysis.

Odds ratios (OR) with 95% confidence intervals were calculated for restenosis rate and major adverse cardiac events. The data were pooled using the random effects method of DerSimonian & Laird [39]. The results of late loss of arterial lumen diameter were expressed as mean difference between treatment groups for individual studies. The individual values were pooled to calculate the overall standardized mean difference with 95% CI [40].

Forest plots for each of the endpoints were plotted. In the forest plot the OR was represented as a box with 95% CI as whiskers on both sides of the box; the size of the box represents the weight of each trial. For heterogeneity testing the Q statistic was calculated. A *P* value of <0.01 was considered statistically significant.

Results

A total of 113 studies were obtained on the initial search. After using combined MeSH terms and manual search, eight studies were selected. Out of these, one was excluded as the study presented the results of a registry [31], one study was done exclusively in patients with restenosis [32], and another study had patients who had a high risk of restenosis or were restenosis cases [33]. Four trials [30, 34–36] with a total of 2704 patients were included in the meta-analysis (Figure 1). SIRTAX [34] and REALITY [36] were conference reports. The TAXI [30] and ISAR-DIABETES [37] trials were published as reports in medical journals. The salient features of the included studies are given in Table 1.

Pooled OR for restenosis rate and major adverse cardiac events were calculated using all four studies [30, 33, 35, 37]. For evaluation of late loss of arterial lumen diameter, overall standardized mean difference with 95% CI was calculated, including three studies [33, 35, 37] for which data on late loss were given. We contacted the authors of the study by Goy *et al.* [30] for the data on late loss. The authors informed us that they had such data for only 16% of the patients, as angiographic follow-up was not a part of this study.

Quality of studies

The quality assessment with respect to randomization, baseline comparability, eligibility criteria, co-interventions, blinding, withdrawals, and intention-to-treat analysis is outlined in Table 2.

Table 1

Characteristics of studies Included in the meta-analysis

Study	Study group	Duration of study	n	Restenosis rate (%)	Late loss (mm) (mean $\pm$ SD)	Major adverse cardiac events (%)	Concomitant medication
SIRTAX ³⁴	Cypher	9 months	693	3.2	0.13 $\pm$ 0.37	6.2	Pre-procedure: Aspirin, clopidogrel 300 mg, UF Heparin, GP IIb/IIIa inhibitors at physician's discretion Post-procedure: Aspirin 100 mg day ⁻¹ indefinitely, clopidogrel 75 mg day ⁻¹ for 12 months
	Taxus	9 months	708	6.7	0.25 $\pm$ 0.49	10.8	
ISAR-DIABETES ³⁷	Cypher	9 months	125	6.9	0.19	—	Oral hypoglycaemic agents
	Taxus	9 months	125	16.5	0.45	—	
REALITY ³⁶	Cypher	8 months	684	7.0	0.09 $\pm$ 0.43	9.2	Pre-procedure: Aspirin, thionopyridines During procedure: GP IIb/IIIa inhibitors Operator's discretion Post-procedure: Clopidogrel 75 mg once daily, ticlopidine 2 $\times$ 250 mg daily Following hospital discharge: Insulin > / = 2 months for Cypher, > / = 6 months for Taxus
	Taxus	8 months	699	8.3	0.31 $\pm$ 0.44	10.6	
TAXI ³⁰	Cypher	6 months	102	3		6	GP IIb/IIIa inhibitors
	Taxus	6 months	100	6		4	

n, number of patients. **Figure 1**

Flowchart of studies evaluated for inclusion in the meta-analysis

Figure 2

Plot of odds ratio of restenosis rates in four trials comparing Cypher and Taxus stents in patients with obstructive coronary artery disease

Major adverse cardiac events

The incidence of major adverse cardiac events was less with Cypher stents as compared with Taxus stents but was statistically not significant (OR 0.727, 95% CI 0.518, 1.018) (Figure 2).

Restenosis rates

Restenosis rate was significantly less with Cypher stents as compared with Taxus stents (OR 0.598, 95% CI 0.400, 0.893) (Figure 3).

Late loss of arterial lumen diameter

Pooled late loss was significantly less with sirolimus-eluting stents as compared with paclitaxel-eluting stents

Table 2
Quality assessment of included studies

Checklist items	Truly random	Randomization		Baseline comparability				Blinding		Participants assessed	Procedures assessed	> 80% in final analysis	Withdrawal	
		Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration				Reasons stated	Intention to treat analysis
1	2	3	4	5	6	7	8	9	10	11	12	13	14	
SIRTAX	v	v	v	v	v	v	v	x	v	v			v	
ISAR-DIABETES	v	v	v	v	v	v/x		x					v	
REALITY	v	v	v	v	v	v	x	x	x				v	
TAXI	v	v	v	v	x	v	x	x	x	x			v

Figure 3

Plot of odds ratio of major adverse cardiac events in four trials comparing Cypher and Taxus stents in patients with obstructive coronary artery disease

Figure 4

Plot of mean difference of late loss of arterial luminal diameter in three trials comparing Cypher and Taxus stents in patients with obstructive coronary artery disease

(pooled mean difference -0.414 , 95% CI -0.492 , 0.336) (Figure 4).

The heterogeneity test was not statistically significant, thereby implying an absence of remarkable difference between studies.

Discussion

The results of the present meta-analysis show that Cypher stents are significantly superior to Taxus stents for prevention of restenosis and late loss. The incidence of major adverse cardiac events, though lower with Cypher stents, did not reach statistical significance.

Results of two other meta-analyses have recently been reported [41, 42]. The first one of these is an indirect meta-analysis where data of trials of both of these stents compared with bare metal stents have been used for the analysis [43]. It has been pointed out earlier that conclusions about relative efficacy of two agents (here Cypher and Taxus stents) cannot be reliably obtained from cross-study comparisons, as the condi-

tions of the studies may have been quite different [43]. The authors have not analysed the incoherence among studies, which should be measured if indirect comparisons are made [43].

The second meta-analysis [42] was published when this manuscript was being revised. In addition to the studies included in our meta-analysis, the authors have included two other studies. As mentioned previously, these studies were excluded from our meta-analysis as they included patients with either high risk of restenosis or those with restenosis. The primary outcome was target vessel revascularization, which was found to be significantly less in Cypher stents as compared with Taxus stents (OR 0.64, 95% CI 0.49, 0.84). Angiographic restenosis (rates calculated as percentage of total lesions) was significantly less with Cypher stents as compared with Taxus stents (OR 0.68, 95% CI 0.55, 0.86). There was no significant difference observed for the outcomes of myocardial infarction or death. In our meta-analysis Cypher stents also showed a lesser rate of restenosis as compared with Taxus stents and the difference reached statistical significance. The results of our meta-analysis included major adverse cardiac events as an outcome, which did not show statistical difference between the two types of stents.

The study of Kastarati [32] was excluded from our analysis. This study was carried out to compare drug-eluting stents with balloon angioplasty in patients with in-stent restenosis. Additionally, the outcomes were compared between Taxus and Cypher stents. At 6 months Cypher stents were shown to reduce restenosis rates significantly more than Taxus stents (14.3% vs. 21.7%, respectively). In the other study that was excluded [33], the angiographic restenosis rates were less with Cypher stents as compared with Taxus stents although the results were not statistically significant (12% vs. 18%, respectively). It is known that in-stent restenosis has a negative impact on long-term survival of patients treated with coronary stents and hence patients with in-stent restenosis constitute a distinct group [44].

After having established the superiority of drug-eluting stents over bare metal stents, it was important to compare the different types of agents. The issue of head-to-head comparison of the two drug-eluting stents has been addressed recently. Though in SIRTAX, ISAR-DIABETES and REALITY the results were shown to favour sirolimus-eluting stents, in the TAXI trial, Taxus stents showed better efficacy outcomes, though this was not statistically significant. In view of such conflicting results, a meta-analysis is well justified. A possible reason for the difference in the performance of the two

stents could be that Taxus stents reduce restenosis in the short term and this may delay rather than prevent restenosis [45].

The patient population in ISAR-DIABETES was of exclusively diabetic patients. The inclusion of this study in the meta-analysis could be debated. However, diabetes is now considered a coronary equivalent [46] and in our opinion inclusion of this study is appropriate. Moreover, a considerable number of patients in the other studies were diabetics. Additionally, the Q statistic did not reveal any heterogeneity amongst the studies.

In the quality assessment of the studies, some of the parameters were not adequately mentioned. However, this by no means implies that the studies were compromised with respect to quality. Most of these studies were obtained as conference reports and, therefore, could be falling short of recommended standards of reporting. Analysis of published reports of these studies in medical journals will be able to better address the issue.

We have made an attempt to address the publication bias. A funnel plot (not shown) does reveal a possibility of publication bias. At least three trials with sufficient power demonstrating the superiority of paclitaxel over sirolimus will be required to change the result of meta-analysis in the opposite direction.

While sirolimus-eluting stents were clearly shown to be better than paclitaxel-eluting stents as far as restenosis is concerned, only a trend towards superiority was found for major adverse cardiac events. It is possible that had more trials been available for inclusion, major adverse cardiac events would also show a similar superiority. However, this remains a theoretical possibility only and as of now, the two stents can be considered similar in efficacy as far as major adverse cardiac events are considered.

The results of late loss of arterial lumen diameter show that Cypher stents are better than Taxus stents. As this analysis could be carried out for only three studies, such a conclusion may be rather premature. Moreover, endpoints such as restenosis and major adverse cardiac events have larger clinical significance compared with late loss.

An important limitation of the meta-analysis was that the number of studies was only four and the total evaluable sample was only 2704 patients. It is increasingly being realized that such a meta-analysis may reduce the need for additional trials by evaluating the results in a larger cohort of patients. Moreover, it provides an opportunity to recognize the areas that need to be evaluated further.

In conclusion, the present meta-analysis has shown that Cypher stents may be superior to Taxus stents, espe-

cially for reducing restenosis rates and late loss of lumen diameter.

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