A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents

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Summary

Background Drug-eluting stents (DES) are associated with lower restenosis rates than bare-metal stents (BMS), but the benefits and safety of the new devices have not been systematically quantified across different trials. We undertook a meta-analysis of randomised trials comparing BMS and stents eluting sirolimus or paclitaxel.

Methods A systematic literature search aimed to identify all randomised clinical trials with 6–12 months of clinical follow-up. Results were pooled by a hierarchical Bayesian random-effects model with prespecified stratification for drug and the presence of carrier polymer. The primary outcomes examined were rates of death, myocardial infarction, target-lesion revascularisation, major adverse cardiac events (death, myocardial infarction, and target-vessel revascularisation), and angiographic restenosis.

Findings We identified 11 eligible trials involving 5103 patients. The pooled mortality rates were low for both DES and BMS with no evidence of any difference between them (odds ratio 1·11 [95% credible interval 0·61–2·06]). Pooled rates of myocardial infarction showed no between-group difference (0·92 [0·65–1·25]). The rate of major adverse cardiac events was 7·8% with DES and 16·4% with BMS (0·42 [0·32–0·53]), and the angiographic restenosis rates were also lower for DES (8·9% *vs* 29·3%; 0·18 [0·06–0·40]). The pooled rates of major adverse cardiac events for each DES type and the respective BMS were: for sirolimus, 6·8% versus 21·0% (0·28 [0·17–0·41]); for polymer-based paclitaxel 8·7% versus 16·7% (0·47 [0·25–0·71]); and for non-polymer-based paclitaxel 7·7% versus 9·5% (0·64 [0·42–1·00]). We did not observe higher rates of edge restenosis, stent thrombosis, or late incomplete stent apposition with DES, although the credible intervals were wide.

Interpretation Sirolimus-eluting and polymeric paclitaxel-eluting stents are effective at decreasing rates of angiographic restenosis and major adverse cardiac events compared with BMS. However, there is no evidence that they affect mortality or myocardial-infarction rates. They also appear to be safe in the short to medium term, although definitive conclusions are not possible. Larger studies with longer follow-up are needed to define better the role of these new devices.

Introduction

During the past decade, the use of stents has become common practice during percutaneous coronary intervention both to treat acute complications of balloon angioplasty and to decrease rates of angiographic restenosis.[1,2] However, rates of angiographic restenosis even in patients who receive stents are 15–40% at 6 months.[3] Restenosis after percutaneous coronary intervention with stenting occurs primarily within the stent (in-stent restenosis) and is almost entirely due to neointimal hyperplasia.[4,5] Studies evaluating stents coated with antimitotic drugs have shown promise at reducing restenosis rates.[6] These drugs are commonly released in a controlled way from biocompatible polymer coatings that act as drug reservoirs.[7] Medium-term results from several randomised clinical trials suggest that drug-eluting stents (DES) substantially lower rates of angiographic restenosis and the subsequent need for repeat revascularisation procedures compared with bare-metal stents (BMS). However, there have been concerns about the safety of DES, because rare but clinically important complications may become apparent only in larger or combined studies.[8,9] We therefore undertook a meta-analysis of all randomised

clinical trials examining DES to quantify more accurately their effect on clinical events and restenosis rates.

Methods

Search strategy

We carried out this meta-analysis in accordance with the standard protocol recommended by the Quality of Reporting of Meta-analyses group.[10] We searched the PubMed database (Dec 16, 1998, to April 18, 2004) with the keywords "drug*" and "restenosis". 1137 papers were discovered. The titles were screened so that antimitotic drugs currently under investigation for the treatment of restenosis could be identified. We defined antimitotic drugs as agents that directly inhibit the cell cycle. We then limited our search results to studies in adult patients reported in English, resulting in 209 papers. We read the abstracts of these papers and identified papers presenting original results from randomised clinical trials that compared stents eluting antimitotic drugs (DES) with BMS (six papers). A second literature search was done with the names of the previously identified antimitotic drugs as keywords. After limiting the results to studies in adult patients,

reported in English, and adding a second keyword ("stent"), we identified the following numbers of papers: sirolimus or rapamycin (44 papers), paclitaxel or taxol (18 papers), QP2 (7-hexanoyltaxol; five papers), tacrolimus or FK506 (two papers), and mycophenolate or mycophenolic acid (one paper); we found no papers reporting on everolimus, dactinomycin, or cytochalasin. Papers presenting the primary results of clinical trials examining DES were identified (three additional papers). Trials had to report at least 6 months of clinical follow-up to be eligible for our analysis, and we included only those papers presenting medium-term follow-up results (6–12 months after index percutaneous coronary intervention). Long-term (>12 months) follow-up results from these randomised clinical trials were excluded because their inclusion would have added heterogeneity to the data. If the primary report of each randomised clinical trial did not give data on all outcomes of interest, we also included data from secondary publications that examined these outcomes, such as intravascular ultrasonographic findings.

We also searched the internet with the above keywords, including three websites dedicated to dissemination of results from cardiovascular trials (www.tctmd.com, www.theheart.org, www.clinicaltrialresults.org) and included trials published only in abstract form, to limit the influence of possible publication bias. We identified an additional six clinical trials that reported follow-up data in abstract form. References from identified studies and from recent review articles on DES were also searched for relevant papers, although no further studies were identified. Data were abstracted from the identified randomised clinical trials by one author (MNB) and independently verified by two others (JMB and MJE). Disagreements were resolved by consensus. Although we were able to extract overall study data from the identified clinical trials, we did not have access to individual data of patients enrolled in the trials so we could not analyse results according to specific clinical characteristics.

Classification of trials, outcomes, and definitions

We classified the identified DES trials on the basis of antimitotic drug used and the use of a polymer coating. The prespecified subgroups were: sirolimus, polymeric paclitaxel, non-polymeric paclitaxel, and others. All stents eluting sirolimus and "other" drugs were polymer coated.

The clinical outcomes investigated were rates of all-cause mortality, myocardial infarction, target-lesion revascularisation, and major adverse cardiac events. Myocardial infarction was most commonly defined in the trials as a new increase in serum creatine kinase of at least twice the upper limit of the normal reference range, with a concomitant rise in the MB fraction of the enzyme. In many trials, symptoms or diagnostic electrocardiographic changes were not mandatory for the diagnosis of a myocardial infarction. Rates of non-fatal
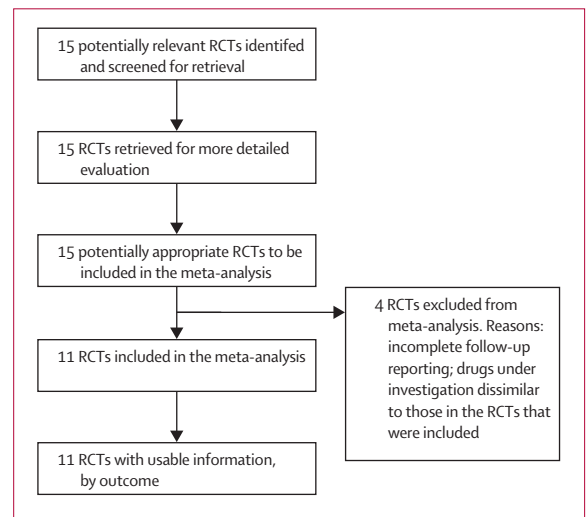

Figure 1: Flow diagram of trials in analysis
RCTs=randomised controlled trials.

myocardial infarction were not given separately in many reports, so our reported rates of myocardial infarction probably include a small number of fatal cases. Target-lesion revascularisation was defined as percutaneous or surgical revascularisation of the stented lesion and 5 mm segments immediately proximal and distal to the stent. We included revascularisations for stent thrombosis in the rate of target-lesion revascularisation if these were reported. The outcome "major adverse cardiac events" was defined as a composite of death, myocardial infarction, and target-vessel revascularisation. If the rates of revascularisation of the target vessel were not reported, we defined major adverse cardiac events as the composite of death, myocardial infarction, and revascularisation of the target lesion.

The angiographic outcome of interest was the in-lesion restenosis rate, which was defined as at least 50% restenosis by quantitative coronary angiography involving the stented vessel segment or the segments 5 mm proximal and distal to the stent edges. If rates of in-lesion restenosis were not reported, we analysed the rates of in-stent angiographic restenosis (at least 50% restenosis within the stent) for both the DES and the BMS groups of the trials. If the number of patients undergoing repeat angiography was not specified, we assumed it to be all of those enrolled. We also examined the rate of edge restenosis—ie, restenosis occurring exclusively within 5 mm of the proximal and distal edges of the stents. This outcome was defined as the rate of in-lesion angiographic restenosis minus the rate of in-stent angiographic restenosis. Edge restenosis has been frequently observed in patients treated with radioactive stents and could possibly be an issue with DES.

To assess safety, we examined rates of stent thrombosis and late incomplete stent apposition. We considered all cases of acute, subacute, and late

Trial	Design	Restenosis risk*	Number of patients			Follow-up, months		% QCA follow-up
			DES	BMS	Total	QCA	Clinical	
Sirolimus								
RAVEL[15]	R, DB, MC	Low	120	118	238	6	12	89
SIRIUS[16]	R, DB, MC	Low	533	525	1058	8	9	66
C-SIRIUS[17]	R, DB, MC	Low to intermediate	50	50	100	8	9	86
E-SIRIUS[18]	R, DB, MC	Low to intermediate	175	177	352	8	9	88
Paclitaxel, polymeric								
TAXUS I[19]	R, DB, MC	Low	31	30	61	6	12	97
TAXUS II[20]	R, DB, MC	Low	266†	270‡	536	6	12	97
TAXUS IV[21]	R, DB, MC	Low	662	652	1314	9	9	43
Paclitaxel, non-polymeric								
ASPECT[22]	R, DB, MC	Low	117†	58	175	6	6	89
ELUTES[23]	R, SB, MC	Low	152§	38	190	6	12	90
DELIVER[24,25]¶	R, SB, MC	Low	517	512	1029	8	9	43
PATENCY[26]¶	R, UB, MC	Low	24	26	50	9	9	76
Others								
SCORE (QP2)[27]¶	R, UB, MC	Low	128	138	266	6	12	76
ACTION (dactinomycin)[28]¶	R, SB, MC	Low	241†	119	360	6	6	81
FUTURE I (everolimus)[29]	R, SB, SC	Low	27	15	42	6	12	86
FUTURE II (everolimus)[30]¶	R, DB, MC	Low	21	43	64	6	6	86

QCA=quantitative coronary angiography; R=randomised; DB=double-blind; MC=multicentre; SB=single-blind; UB=unblinded; SC=single centre. *Based on independent clinical and angiographic predictors of restenosis (see text). †Combined number of patients in two DES groups examining two doses of drug. ‡Combined number of patients in two separate BMS groups. §Combined number of patients in the DES group examining four doses of drug. ¶Trials with results published only in abstract form.

Table 1: **Randomised clinical trials investigating DES**

thrombotic complications involving the study stent (or stents) inserted at the index percutaneous coronary intervention as being stent thrombosis. Late incomplete stent apposition (stent malapposition) was defined as new evidence of blood flow between the stent struts and the vessel wall on intravascular ultrasonography that was present at follow-up but was not observed immediately after the index percutaneous coronary intervention. This outcome is thought to reflect positive remodelling of the vessel wall and may be an early marker of aneurysmal dilatation of the vessel.[11,12] To date, there does not appear to be an increase in adverse events clearly attributable to late incomplete stent apposition after DES implantation.[9,13] However, the number of cases examined has been limited and long-term follow-up data are not available.

Statistical methods

Differences in trial methods, patients' characteristics, and investigators' practice patterns mean that the effects of DES within each of these trials are unlikely to be identical, as would be implied by the use of a fixed-effects meta-analysis model. We therefore used a Bayesian hierarchical model to synthesise the results; this approach accounts for between-trial variations in odds ratios.[3,14] In this model, the probability (p) of an event within each group of each trial is allowed to vary both between the treatment (DES) and control (BMS) groups within each study and between each study included in the meta-analysis. To model the between-study variability, the logarithms of the odds ratios of each outcome variable are assumed to have a normal distribution. The mean of the normal distribution of log

odds ratios across studies therefore represents the average effect in the studies, and the variance represents the variability among the studies. Bayesian analysis allows for the combination of existing knowledge with new information according to established rules of probability. Substantive prior knowledge can thereby be included into any Bayesian analysis by choice of initial (pre-data) distribution. However, because we incorporated all relevant past studies, we wanted our final (posterior) distribution to reflect the information in our dataset only and not to be influenced by our choice of

Trial	Clinical characteristics			Mean (SD) lesion characteristics	
	Mean age, years	% male	% with diabetes	Lesion length, mm	RVD, mm
Sirolimus					
RAVEL[15]	61·8	70	16	9·6 (3·3)	2·60 (0·54)
SIRIUS[16]	62·1	73	25	14·4 (5·8)	2·79 (0·45)
C-SIRIUS[17]	60·3	70	24	14·5 (6·3)	2·65 (0·30)
E-SIRIUS[18]	62·0	70	19	14·9 (5·4)	2·60 (0·37)
Paclitaxel, polymeric					
TAXUS I[19]	66·0	94	23	10·7 (3·3)	2·99 (0·46)
TAXUS II[20]*	61·5	70	11	10·6 (3·9)	2·8 (0·40)
TAXUS IV[21]	62·8	72	23	13·4 (6·2)	2·75 (0·47)
Paclitaxel, non-polymeric					
ASPECT[22]†	58·0	80	18	10·9 (3·6)	2·94 (0·39)
ELUTES[23]‡	56·0	81	11	11·1 (3·1)	2·95 (0·43)
DELIVER[24,25,31]	61·8	71	31	11·7 (5·0)	2·85 (0·54)
PATENCY[26]	NR	67	25	NR	2·77 (0·45)

RVD=reference-vessel diameter; NR=not reported. The data given are those for patients assigned DES in the trials; randomisation ensured that those assigned BMS had similar baseline characteristics. *Data are for the paclitaxel-slow-release group. †Data are for the higher-dose paclitaxel group (3·1 μg per mm² stent). ‡Data are for the highest-dose paclitaxel group (2·7 μg per mm² stent).

Table 2: **Baseline characteristics of patients in clinical trials investigating DES**

Trial	Death, %		Myocardial infarction, %*		TLR, %†		MACE, %		Angiographic restenosis, %	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
Sirolimus										
RAVEL[15]	1·7	1·7	3·3	4·2	0	22·9	5·8	29·7	0	26·3
SIRIUS[16]	0·9	0·6	2·8	3·2	4·1	16·6	7·1	18·9	8·9	36·3
C-SIRIUS[17]	0	0	2·0	4·0	4·0	18·0	4·0	18·0	2·3	51·1
E-SIRIUS[18]	1·1	0·6	4·6	2·3	4·0	20·9	8·0	22·6	5·9	42·3
Pooled	1·0	0·7	3·2	3·2	3·5	18·5	6·8	21·0	6·2	36·9
Paclitaxel, polymeric										
TAXUS I[19]	0	0	0	0	0	10·0	3·2	10·0	0	10·3
TAXUS II[20]	0‡	0·8‡	3·1	5·3	4·2	14·4	10·4	21·7	7·1	21·9
TAXUS IV[21]	1·4‡	1·1‡	3·5	3·7	3·0	11·3	8·5§	15·0§	7·9	26·6
Pooled	0·9	1·0	3·3	4·0	3·3	12·2	8·7	16·7	7·1	23·5
Paclitaxel, non-polymeric										
ASPECT[22]	0·9	0	2·6	1·7	6·8	3·4	8·5	5·2	8·0	27·3
ELUTES[23]	0·7	0	1·3	0	7·2	15·8	9·9	18·4	13·1	21·6
DELIVER[24, 25, 31]	1·0	1·0	1·4	1·0	5·2	6·8	6·6¶	8·6¶	16·7	22·4
PATENCY[26]	0	3·8	0	0	12·5	19·2	12·5	23·1	38·1	35·3
Pooled	0·9	0·9	1·5	0·9	6·0	7·6	7·7	9·5	14·8	23·8
Sirolimus and paclitaxel pooled	0·9	0·9	2·7	2·9	4·2	13·2	7·8	16·4	8·9	29·3

TLR=target-lesion revascularisation; MACE=major adverse cardiac events. *Both Q-wave and non-Q-wave. †Revascularisation by repeat percutaneous coronary intervention or coronary-artery bypass surgery of the index lesion, including for stent thrombosis. ‡Cardiac deaths only. §These are the correct rates; there was an error in the origial paper. ¶The MACE rate in this study included only cardiac deaths.

Table 3: Clinical events and restenosis rates in randomised clinical trials investigating DES

initial (prior) distribution. Therefore, low-information prior distributions were used throughout, so that the data from the trials dominated the final inferences. In particular, we used normal (mean=0, variance=100) prior distributions for all means and gamma (0·0001, 0·0001) prior distributions for all precisions (which is defined as the reciprocal of the variance). Sensitivity analyses with different choices of low-information prior distributions showed robustness to this choice. In particular, a wide range of low-information values used for our gamma distributions did not change any of our posterior

inferences. Therefore, our estimates of odds ratios and their associated 95% credible intervals (which are the Bayesian equivalent of standard confidence intervals) were not unduly affected by our choice of prior distribution. Inferences were calculated with the Gibbs sampler programmed in WinBUGS software (version 1.4, MRC Biostatistics Unit, Cambridge, UK). Finally, we also include forest plots for all major outcomes, which display the odds ratios and 95% credible intervals for both the individual trials and for the pooled results from our meta-analysis.
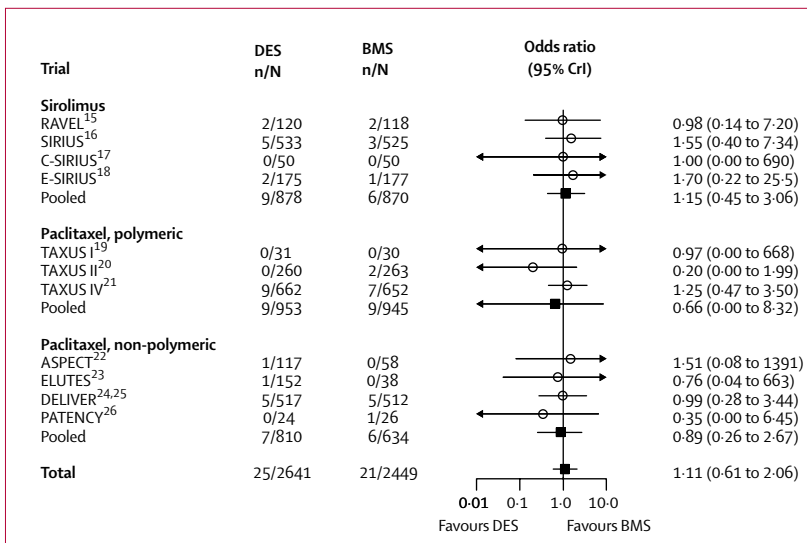
Role of the funding source
The statistical analyses for this project were funded by the Fonds de la recherche en santé du Québec (Quebec Foundation for Health Research). The funding source did not have any role in the study design, data analyses, or writing of the report.

Results
Our literature search identified 15 randomised clinical trials (figure 1), involving 5835 patients, that investigated DES, including four with sirolimus, seven with paclitaxel, and four with other drugs (table 1).[15–30] Two trials examining stents eluting QP2 and dactinomycin were terminated prematurely owing to adverse events and had incomplete follow-up reporting.[27,28] In view of the heterogeneity of the antimitotic drugs and polymer coatings in this "other" group, we restricted our primary analyses to those trials examining stents eluting sirolimus or paclitaxel. Secondary analyses that included results from the excluded trials showed that their exclusion did not have an important effect on any of the outcomes of interest.

Trial	DES n/N	BMS n/N	Odds ratio (95% CrI)	
Sirolimus				
RAVEL[15]	2/120	2/118		0·98 (0·14 to 7·20)
SIRIUS[16]	5/533	3/525		1·55 (0·40 to 7·34)
C-SIRIUS[17]	0/50	0/50		1·00 (0·00 to 690)
E-SIRIUS[18]	2/175	1/177		1·70 (0·22 to 25·5)
Pooled	9/878	6/870		1·15 (0·45 to 3·06)
Paclitaxel, polymeric				
TAXUS I[19]	0/31	0/30		0·97 (0·00 to 668)
TAXUS II[20]	0/260	2/263		0·20 (0·00 to 1·99)
TAXUS IV[21]	9/662	7/652		1·25 (0·47 to 3·50)
Pooled	9/953	9/945		0·66 (0·00 to 8·32)
Paclitaxel, non-polymeric				
ASPECT[22]	1/117	0/58		1·51 (0·08 to 1391)
ELUTES[23]	1/152	0/38		0·76 (0·04 to 663)
DELIVER[24,25]	5/517	5/512		0·99 (0·28 to 3·44)
PATENCY[26]	0/24	1/26		0·35 (0·00 to 6·45)
Pooled	7/810	6/634		0·89 (0·26 to 2·67)
Total	25/2641	21/2449		1·11 (0·61 to 2·06)

0·01   0·1   1·0   10·0
Favours DES — Favours BMS

Figure 2: Forest plot comparing all-cause mortality rates for DES and for BMS
White circles represent the odds ratios for individual trials, and black squares the meta-analytic odds ratios for the indicated subgroups and for the overall (total) results. Horizontal lines represent the 95% credible intervals (CrI) for the data. The TAXUS-II and TAXUS-IV trials reported only cardiac mortality.

In general, the patients enrolled in the trials of DES with sirolimus or paclitaxel were young and were mostly male. The trials were well conducted, with random allocation of treatment, masking of treatment assignment, and clinical follow-up rates of more than 90% (table 1). Follow-up quantitative coronary angiography was done in 43–97% of enrolled patients 6–9 months after the index percutaneous coronary intervention (table 1). Most trials were designed to assess the medium-term (6–12 months after index percutaneous coronary intervention) efficacy of DES at decreasing angiographic restenosis or clinical events. The inclusion criteria of all the trials specified that enrolled patients had de-novo (not restenotic) lesions in a native coronary artery. Multilesion percutaneous coronary intervention with DES was not permitted in any trial. Patients with a recent myocardial infarction or a low ejection fraction were also excluded. Lesion lengths and reference-vessel diameters of the treated vessels varied between the trials, although in general the stented lesions were intermediate in length in medium-calibre vessels (table 2). Depending on the study protocol, antiplatelet therapy with clopidogrel, ticlopidine, or cilostazol was recommended for at least 2–6 months after percutaneous coronary intervention.

Several clinical and procedural characteristics are known to be independent predictors of angiographic restenosis. Of these characteristics, the strongest predictors include prior restenosis (neointimal hyperplasia), multi-vessel percutaneous coronary intervention, small vessel diameter, long lesion length, and diabetes.[32] On the basis of these variables, the patients enrolled in the DES trials had a low risk of angiographic restenosis in general. However, in two trials the implanted stent length exceeded the lesion length on average by 80% and 70%, respectively, thereby possibly exaggerating the risk of restenosis.[17,18]

Two trials reported only cardiac mortality, not total mortality.[20,21] The pooled mortality rate was low for both DES and BMS groups, and there was no evidence of a difference in mortality between the groups before or after stratification by the type of DES (table 3, figure 2). The pooled rates of myocardial infarction were also similar for the two groups (table 3, figure 3). However, wide credible intervals precluded definitive statements of equivalence for these two outcomes.

Repeat revascularisation of the target lesion was in many cases "protocol-driven" by the mandatory follow-up angiograms, although some trials did report clinically driven revascularisations.[16–18,21,25] Clinical follow-up occurred at the time of or after routine follow-up angiography in all trials. The pooled rates of target-lesion revascularisation and major adverse cardiac events are given in table 3. Both sirolimus-eluting and polymeric paclitaxel-eluting stents were associated with substantially lower rates of target-lesion revascularisation and major adverse cardiac events than BMS (figures 4 and 5).
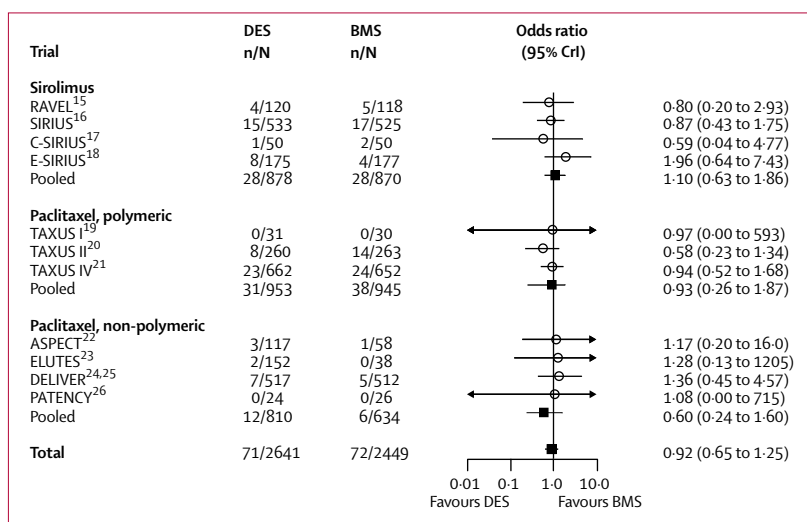

Figure 3: **Forest plot comparing myocardial-infarction rates for DES and for BMS**
See figure 2 for key.

The effect on these outcomes for non-polymeric paclitaxel-eluting stents was less striking, possibly owing to a lower rate of restenosis in the trials investigating these stents. Since there was no evidence of reductions in rates of death and myocardial infarction, the reduction in major adverse cardiac events in the DES trials was explained entirely by reductions in target-lesion revascularisations.

Most trials had more than 80% routine angiographic follow-up, although there were exceptions (table 1). The rates of repeat angiography were roughly the same in both treatment groups of each of the trials. The rate of in-lesion angiographic restenosis was substantially lower with both sirolimus-eluting stents and polymeric paclitaxel-eluting stents than with BMS (table 3, figure 6). Wide credible intervals for this outcome made the results
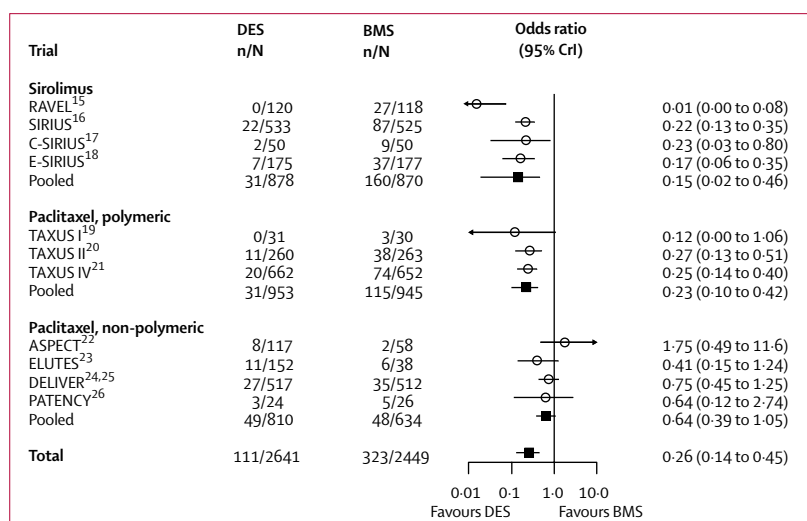

Figure 4: **Forest plot comparing rates of target-lesion revascularisation for DES and for BMS**
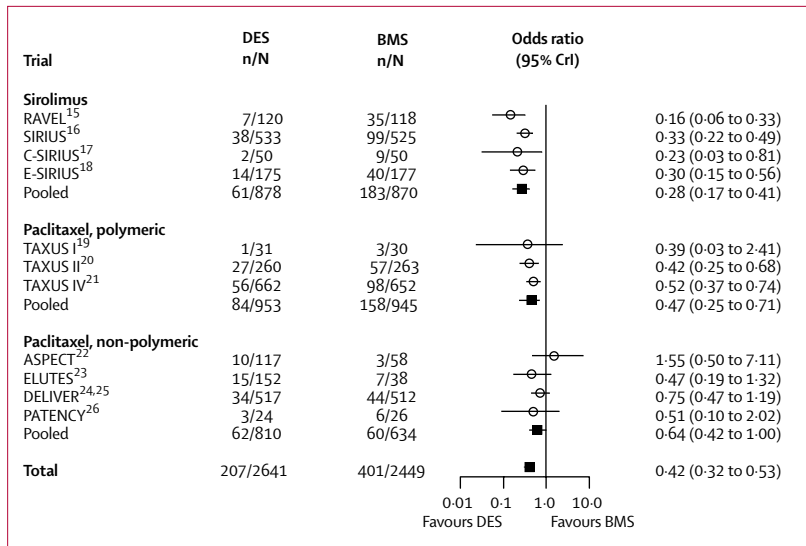See figure 2 for key.

Figure 5: Forest plot comparing rates of major adverse cardiac events for DES and for BMS
See figure 2 for key.

less clear-cut for non-polymeric paclitaxel-eluting stents. We observed a higher rate of edge restenosis (restenosis at the proximal or distal edges of the stent) with DES than with BMS in the SIRIUS trial (odds ratio 6·21 [95% credible interval 2·37–27·15]). However, the overall pooled data did not suggest a higher rate of edge restenosis with DES (1·41 [0·47–2·86]).

Our pooled estimates did not demonstrate a difference in stent-thrombosis rates between the DES and BMS groups (1·08 [0·53–2·20]). Nor was there an increased risk of late incomplete stent apposition with DES than with BMS (2·12 [0·64–7·72]), although the number of patients undergoing routine intravascular ultrasonographic examinations to detect this potential

complication was small. Overall, the credible intervals for complication rates of DES were wide because the outcomes were rare (table 4).

Discussion

The objective of our meta-analysis was to quantify the treatment effect and safety of DES. We found no evidence that DES have any effect on medium-term mortality or rates of myocardial infarction, although further data are needed before definitive conclusions can be drawn. However, the restenosis rate on routine follow-up angiography was substantially lower with DES than with BMS, with consequent reductions in rates of target-lesion revascularisation and major adverse cardiac events. These effects were observed with sirolimus-eluting stents and polymeric paclitaxel-eluting stents. Effects on rates of angiographic restenosis and revascularisation with non-polymeric paclitaxel-eluting stents were less apparent, and any treatment effect with these stents might be less substantial than those of sirolimus-eluting and polymeric paclitaxel-eluting stents. We did not observe a higher rate of complications, including stent thrombosis or late incomplete stent apposition, with DES during medium-term follow-up, although definitive conclusions could not be drawn because the outcomes were rare.

The findings of our meta-analysis accord with current understanding of the pathophysiological basis of restenosis.[6] Angiographic restenosis after percutaneous coronary intervention with stenting is due mainly to neointimal hyperplasia within the stent (in-stent restenosis).[4,5] The reduction in angiographic restenosis observed in the DES trials probably reflects inhibition of neointimal hyperplasia by the controlled elution of the antimitotic drug. However, restenosis after percutaneous coronary intervention does not appear to be causally linked to an increase in mortality or myocardial infarction.[3,36] Similarly, we found that although DES substantially lower the risk of restenosis after percutaneous coronary intervention, there was no evidence of any effect on mortality or myocardial infarction. Consequently, the substantial reduction in the rate of major adverse cardiac events that we observed with DES is entirely driven by differences in rates of the target-lesion revascularisation between DES and BMS. The clinical significance of these additional revascularisation procedures is unclear because angiography was done routinely as mandated by the study protocols 6–9 months after index percutaneous coronary intervention. Although some trials attempted to count only clinically driven revascularisations, lesions of borderline haemodynamic and prognostic significance might have undergone repeat revascularisation as a result of this protocol-mandated angiography—the so-called oculo-stenotic reflex.[37,38]

The risk of any individual patient developing restenosis is largely unpredictable, although several
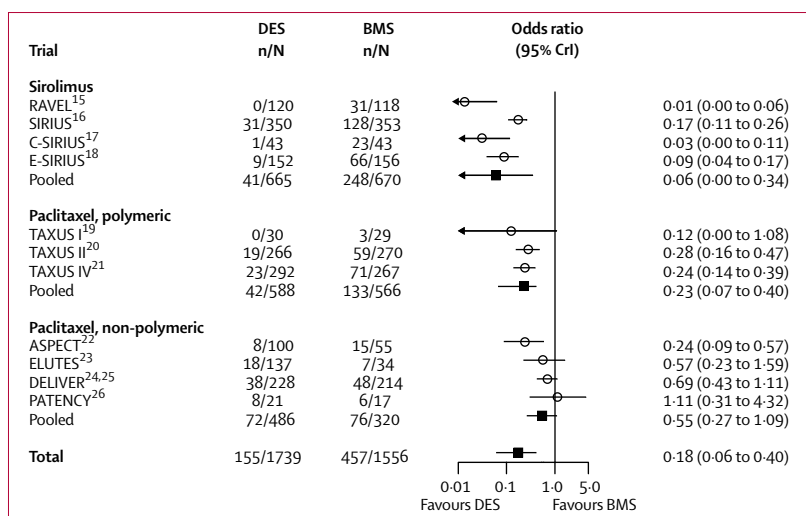

Figure 6: Forest plot comparing rates of angiographic restenosis for DES and for BMS
See figure 2 for key. The proportion of patients who underwent repeat angiography in each group was not specified in the RAVEL trial, and was assumed to be 100%.

Trial	Edge restenosis, %*		Stent thrombosis, %†		Late incomplete stent apposition, %‡	
	DES	BMS	DES	BMS	DES	BMS
Sirolimus						
RAVEL[13,15]	0	0	0	0	20·8	4·3
SIRIUS[16,33]	5·7	0·8	0·4	0·8	8·8	0
C-SIRIUS[17]	2·3	11·6	2·0	2·0	NR	NR
E-SIRIUS[18]	2·0	0·6	1·1	0	NR	NR
Pooled	3·6	1·3	0·6	0·6	13·3	1·9
Paclitaxel, polymeric						
TAXUS I[19]	0	0	0	0	NR	NR
TAXUS II[20]	3·8	3·0	1·1	0	11·3	8·5
TAXUS IV[21,34]	2·4	2·2	0·6	0·8	1·1	2·2
Pooled	2·9	2·5	0·7	0·5	8·6	6·9
Paclitaxel, non-polymeric						
ASPECT[22,35]	NR	NR	3·4	0	1·8	0
ELUTES[23]	NR	NR	0·7	2·6	NR	NR
DELIVER[24,25,31]	1·8	1·8	0·4	0·4	0	0
PATENCY[26]	NR	NR	0	0	NR	NR
Pooled	1·8	1·9	0·9	0·5	1·1	0
Sirolimus and paclitaxel pooled	3·0	1·9	0·7	0·5	8·5	5·1

NR=not reported. *Patients with restenosis only at the stent edges (in-lesion binary restenosis rate minus the in-stent binary restenosis rate). †Cases of acute, subacute, and late stent thrombosis documented by angiography. ‡Evidence of blood flow between stent strut (or struts) and vessel wall by intravascular ultrasonography at follow-up not observed immediately after the index percutaneous coronary intervention.

Table 4: Edge restenosis and potential complications of DES

clinical and lesion characteristics appear to be associated with subsequent restenosis. However, the patients enrolled in the DES trials in general had a low risk of angiographic restenosis. Whether DES will show similar efficacy at inhibiting restenosis in patients at a higher risk of restenosis is unclear, although preliminary data from two non-randomised studies are promising.[39,40]

Paclitaxel elution from a metal stent without a polymer coating initially seemed to be an attractive choice because some polymers were associated with an exaggerated inflammatory response and increased neointimal hyperplasia in animal studies.[6] Although our meta-analysis suggested a reduction in rates of restenosis and target-lesion revascularisation with these non-polymeric paclitaxel-eluting stents compared with BMS, the magnitude of the reduction was smaller than those with other DES (figures 4 and 5). The implication of this finding is that controlled elution of antimitotic drugs from drug carriers (reservoirs) could have an important role in inhibiting neointimal hyperplasia. However, the baseline restenosis risk and event rates in the trials of non-polymeric paclitaxel-eluting stents were lower than those in the trials of sirolimus-eluting and polymeric paclitaxel-eluting stents (table 3), which might at least partly explain these results.

Edge restenosis, also called the candy-wrapper effect, has commonly been observed after implantation of radioactive stents.[41,42] This effect involves accelerated neointimal hyperplasia at the areas of vessel trauma after percutaneous coronary intervention, and it has been suggested as a possible limitation of DES.[13,43] In our

analysis, there was a higher rate of edge restenosis with DES than with BMS in the SIRIUS trial.[16] However, we did not observe a higher rate of this outcome with DES after pooling of trials on sirolimus-eluting stents or all DES trials. Definitive conclusions about this outcome could not be drawn because the credible intervals were wide, and further evidence is needed to clarify this issue.

We found no evidence that sirolimus-eluting and paclitaxel-eluting stents have different safety profiles from BMS, at least in the short to medium term. Stent thrombosis, especially delayed cases due to incomplete endothelialisation of the stent struts, has been described with DES.[8,44] We did not observe a higher propensity for stent thrombosis with DES than with BMS in our meta-analysis. However, stent thrombosis is a rare event (0·5% in the pooled BMS group), so even our meta-analysis has less than 50% power to exclude a two times higher risk of stent thrombosis with DES. Continued surveillance of all patients with DES for this complication therefore appears appropriate, especially after discontinuation of dual antiplatelet therapy.[45]

We did not observe a higher rate of late incomplete stent apposition in the DES group. This intravascular ultrasonographic finding may be an early sign of vascular remodelling and aneurysm formation, although medium-term follow-up data so far do not suggest that this process is related to adverse clinical events.[9,13] The number of patients who underwent routine follow-up intravascular ultrasonography in the DES trials was small, and the data were inconclusive owing to the large between-study variances.

The clinical and angiographic follow-up periods in the DES trials included in our analysis extend only for 6–12 months, and this period may be too short for delayed progression of neointimal hyperplasia to become apparent.[46,47] Although long-term follow-up data from observational studies of sirolimus-eluting stents do not suggest a late "catch-up" in neointimal hyperplasia,[48,49] experience with radioactive stents should prompt caution in interpretation of the promising short-term to medium-term results of DES.[50]

The substantial effect of DES on rates of restenosis and repeat revascularisation after percutaneous coronary intervention has been received with much enthusiasm by the cardiovascular community.[51] However, the individual trials examining DES have been underpowered to examine outcomes such as mortality, myocardial infarction, and other potential complications of DES. Although our study had a significantly higher statistical power to examine rare events than any one clinical trial, we had inconclusive evidence on whether DES have any effects on these rare outcomes. Further data are needed before definitive conclusions can be drawn about these clinically important outcomes.

Several potential limitations of our study should be noted. First, we found a possible publication bias involving DES trials that did not demonstrate efficacy

(table 1). Several of these trials with "negative" results have been published in abstract form only, with incomplete follow-up and reporting of results in some cases. We made every effort to complete a comprehensive literature search, including searching the internet and abstracts, to keep this publication bias to a minimum. Second, the baseline risk of restenosis of the patients and the treatment protocols in each trial varied and these differences could have affected our quantification of the outcomes and the generalisability of our results. Finally, we did not have access to individual patients' data to analyse results according to specific clinical characteristics. The principal investigators of the major DES trials should consider such a collaborative, patient-based meta-analysis so that the treatment effect can be further quantified in specific subgroups of patients who are at a higher risk of restenosis.

In conclusion, DES have a substantial effect on angiographic restenosis and the need for repeat revascularisation procedures when implanted in patients who are at low risk of subsequent restenosis. However, as with BMS, there is no evidence that DES have any effect on medium-term mortality or rates of myocardial infarction. DES appear to be safe over the short and medium term, although the data are currently too sparse for firm conclusions to be drawn. Long-term follow-up and results from larger studies investigating DES are needed.

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