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Review

Drug-eluting stents: an early systematic review to inform policy☆,☆☆

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Policy

Aims To provide systematic assessment of the clinical effectiveness of drug-eluting stents (DES) versus non-DES to inform national guidance.

Methods and results The review was conducted according to internationally recognised methods. The search strategy identified published (7) and unpublished (7) randomised controlled trials comparing the use of DES to non-DES. Outcomes included death, acute myocardial infarction (AMI), revascularisation, event rate (composite of adverse events), and binary restenosis. Data synthesis included descriptive statistics and meta-analysis. Fourteen randomised clinical trials comparing DES to non-DES and involving 5747 patients were identified.

There were reductions in event rates between DES and non-DES; odds ratio (OR) 0.63 (95% confidence interval [95% CI] 0.47, 0.84, $n = 1978$) for paclitaxel-eluting stents at 12 months, OR 0.30 (95% CI 0.22, 0.42, $n = 1296$) for sirolimus-eluting stents at 12 months. Combined event rates were inconsistently defined across trials and were primarily composed of revascularisations, possibly driven by protocol-required angiograms. DES reduced binary restenosis rates at angiogram compared to non-DES. No significant differences in rates of death or AMI were identified.

Conclusion The early data available indicate that DES reduce adverse cardiac events, mainly revascularisations. However, these data are limited in terms of patient numbers, length of follow-up, and method of outcome assessment. The evaluation of rapidly evolving technologies requires the inclusion of data not routinely considered for inclusion in systematic reviews of effectiveness.

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Introduction

Bare metal stents were introduced for use during percutaneous coronary interventions (PCI) to reduce the risk of restenosis. The role of stents has recently been reviewed,[1,2] and guidance in the UK[3] recommends their use. Registry data from Europe (in 1999) indicate the use of stents in more than 70% of percutaneous transluminal coronary angioplasty (PTCA) procedures in most countries[4] and more recent data from the UK indicate stent use in 85% of cases.[5]

Restenosis around and within stents due to neointimal proliferation causes a return of coronary symptoms and requires further procedures in 20—50% of cases, depending on the size and complexity of the lesion.[6] Current estimates in the UK indicate revascularisation rates to be in the range of 14—25%.[7] The rate of in-stent restenosis has been reduced with the use of intracoronary irradiation (brachytherapy),[8] but this is not widely available.[9] Drug-eluting stents (DES) that elute an antiproliferative agent reduce neointimal hyperplasia and the risk of restenosis without systemic toxicity.[9,10] This new technology comes at a considerable additional cost, typically 1800 to 2100 for DES compared to 800 to 1300 for non-drug-eluting stents (non-DES) in the UK.[11] Therefore health-care funding agencies require data on the clinical and cost effectiveness of this technology.

Rationale for the review

A number of comparative trials of DES have been completed and long-term follow-up continues while new trials are underway.[12] The technology is evolving rapidly and an American College of Cardiology Expert Consensus Panel[13] has stated: *"The rapid evolution of stent design, deployment approaches, and adjunctive therapy have led to changes in clinical practice patterns that precede rigidly controlled supporting scientific data."* Rapid changes in the technology make it difficult to evaluate the benefits and safety of DES compared to non-DES, but this is required before DES can be recommended as standard practise. As part of a wider health technology assessment of DES intended to inform policy in the UK, we conducted a systematic review and meta-analysis of available data from randomised controlled trials comparing DES to non-DES.

Methods

Searching

To identify relevant studies, we searched MEDLINE, EMBASE, Science Citation Index (Web of Science and ISI Proceedings) from January 1990 to December 2002, as well as The Cochrane Library (Issue 4, 2002). We also searched the reference lists of identified studies and hand-searched 14 cardiovascular journals (December 2001—December 2002) and abstracts from six cardiovascular conferences (January 2000—January 2003). Internet resources, including web pages supported by manufacturers, were investigated regularly during the review process. Submissions to the National Institute for Clinical Excellence (NICE) for England and Wales were examined for further studies and data.[14] Peer-reviewed journals, cardiovascular conferences, and Internet resources were monitored up to January 2004 for presentation of additional data or publications related to studies included in the review. Searching was limited to English-language papers. Full details of the search strategy and results are available from the authors.

Selection, validity assessment, and data abstraction

Studies were considered eligible for inclusion in the review only if they compared DES with non-DES within a randomised controlled trial. No limits were placed on the coronary artery disease state of the study participants (in terms of involvement of native or graft vessels; single or multiple vessels, or stable angina or acute coronary syndrome). In order for studies to be included in the review, data on at least one outcome of interest (composite event rate, mortality, acute myocardial infarction [AMI], or binary restenosis) had to be available in trial reports. Reports of unplanned interim or subgroup data were excluded.

Citations identified for inclusion were examined in two stages. Two reviewers independently scanned all titles and abstracts. Full-text copies of the selected papers were obtained and assessed independently by at least two reviewers for inclusion and study quality using internationally recognised guidelines.[15] Data were independently extracted by one reviewer using pretested data extraction forms and were checked by a second. Discrepancies were resolved through discussion.

Study characteristics

The review was limited to the inclusion of randomised controlled trials. Details of participant characteristics (age, gender, comorbidity, disease state) and study design (location, number of centres recruiting participants) were recorded. Trial outcomes of interest included composite event rate, mortality, AMI, and angiographic binary restenosis rates. The definitions of these outcomes are discussed in detail in the Results section.

Quantitative data synthesis

Meta-analysis was conducted for event rates, mortality, AMI, and angiographic binary restenosis rates. Data in the form of odds ratios (OR) and 95% confidence intervals (95% CI) were analysed using the Mantel—Haenszel method, fixed-effect model provided by the *RevMan Analyses 1.0* application contained in *RevMan 4.2*.[16] Heterogeneity was tested by the chi-square test in *RevMan Analyses 1.0*.

Results

Studies included

Fourteen studies, with data from multiple sources, met the inclusion criteria.[17–30] Of these, eight (ASPECT,[17] DELIVER,[18,31] ELUTES,[19] PATENCY,[20] TAXUS I[21,32,33] TAXUS II,[33,34] TAXUS IV,[23,35,36] and SCORE[24]) focused on stents eluting taxane compounds (paclitaxel, 7-hexanolytaxol), five (E-SIRIUS,[25,37] FUTURE,[28,38] FUTURE II,[29] RAVEL,[26,37,39] and SIRIUS,[37,40]) investigated sirolimus or everolimus-eluting stents, and one study involved actinomycin-dosed stents (ACTION[30]).

Table 1 Quality assessment

Study name[a]		Checklist items													
		Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		Intention to treat
		Truly random	Allocation concealment	Number stated	Presented	Achieved			Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
ASPECT[17]	Pub	√ ×	√	√	√	√	√	√	√	NS	√	×	√	√	√
DELIVER[18]	Abs/elec	NS	NS	√	√	√	√	√	NS	NS	NS	×	√	×	×
ELUTES[19]	Abs/elec	√	√	√	√	√	√	√	√	√	√	×	√	√	√
PATENCY[20]	elec	NS	NS	√	√	√	√	√	√	NS	NS	×	√	√	√
TAXUS I[21]	Pub	√	√	√	√	√	√	√	√	√	√	×	√	√	√
TAXUS II[34]	Pub	√	√	√	√	√	√	√	√	√	√	×	√	√	√
TAXUS IV[35]	Pub	√	√	√	√	√	√	√	√	√	√	×	√	√	√
SCORE[24]	Abs/elec	NS	×	√	√×	√×	√×	×	×	×	×	×	√	×	√
E-SIRIUS[25]	Pub	√	√	√	√	√	√	√	√	√	√	×	√	√	√
RAVEL[26]	Pub	√	√	√	√	√	√	√	√	√	√	×	√	√	√
SIRIUS[27]	Pub	√	√	√	√	√	√	√	√	√	√	×	√	√	√
FUTURE I[28]	Abs/elec	NS	NS	×	√	√×	√	×	NS	NS	NS	×	√	×	NS
FUTURE II[29]	elec	NS	NS	√	√	√×	√	×	NS	NS	NS	×	√	×	√
ACTION[30]	Abs/elec	×	×	√	×	×	√	√	×	×	×	×	√×	×	√

[a]*Data sources for quality assessment:* Abs: conference proceedings abstract; Pub: peer-reviewed journal publication; elec: electronic resource (not categorised under Abs. or Pub, such as manufacturer announcement, slide presentation). *Checklist scoring:* (√) yes (item adequately addressed); (×) no (item not adequately addressed); (√/×) partially (item partially addressed); (NA) not applicable or NS not stated.

Table 2 Study design and participants

Study name	Interventions	1^{ry} Endpoint study sites	Inclusion criteria	Co-therapies	Follow-up	Sex, male %		Diabetes %	
ASPECT[17]	Paclitaxel Supra G stent ($n = 58$) Supra G *non-polymeric* paclitaxel stent 3.1 and 1.3 μg/mm^2 ($n = 60$ and 58)	Angiographic Multicentre (3) Asia	Single vessel disease Diameter: 2.25–3.5 mm Length: <15 mm	Aspirin Ticlopidine (120), Clopidogrel (18) or Cilostazol (37) for 1–6 months	Clinical: 1 and 6 months Angiographic: 4–6 months	BMS DES 1.3 μg/mm^2 3.1 μg/mm^2	76 80 72	BMS DES 1.3 μg/mm^2 3.1 μg/mm^2	17 24 18
DELIVER[54]	Paclitaxel MULTI-LINK PENTA ($n = 519$) ACHIEVE MULTI-LINK PENTA *Non-polymeric* paclitaxel stent ($n = 524$)	TVF Multicentre (⩾ 16) USA	Multivessel disease Diameter: 2.5–4.0 mm	During procedure Heparin GP IIb/IIIa (652/1043 pt) Post procedure: Aspirin <365 days Clopidogrel 90 days	Clinical: 30 and 270 days Angiographic: 240 days	BMS DES	71 71	BMS DES	27 31
ELUTES[19]	Paclitaxel V-flex Plus ($n = 38$) V-flex Plus *non-polymeric* paclitaxel stent 0.2, 0.7, 1.4, 2.7 μg/mm^2 ($n = 37$, 39, 39, 37)	Angiographic/MACE Multicentre (10) Europe	Single and multiple vessel disease Diameter: 2.75–3.5 mm Length: <15 mm	Aspirin Clopidogrel 3 months	Clinical: 6 months Angiographic: 6 months	Overall	82	Overall	15.6
PATENCY[20]	Paclitaxel Logic stent ($n = 26$) Logic PTX paclitaxel-eluting 2.0 μg/mm^2 ($n = 24$)	– Multicentre (6) USA	Types of vessel disease included unclear Diameter: 2.7–4.0 mm	Clopidogrel 3 months	Clinical: 1, 9 and 18 months Angiographic: 6 months	BMS DES	62 67	BMS DES	23 25
TAXUS I[21,33]	Paclitaxel NIR ($n = 30$) NIRx Conformer coronary stent paclitaxel slow release ($n = 31$)	MACE Multicentre (3) Germany	Single vessel disease Diameter: 3.0–3.5 mm Length: ⩽ 12 mm	During procedure: Heparin Post procedure: Aspirin 12 months Clopidogrel 6 months	Clinical: 1, 6, 9 and 12 months Angiographic: 6 months	BMS DES	83 91	BMS DES	13 23
TAXUS II,[33,34]	Paclitaxel NIR ($n = 270$) NIRx paclitaxel slow and moderate release ($n = 266$)	Angiographic Multicentre (61) Europe	Single vessel disease Diameter: 3.0–3.5 mm Length: <12 mm	Post procedure: Aspirin 6 months Clopidogrel 6 months		BMS DES Slow Moderate	78 70 76	BMS DES Slow Moderate	15 11 17
TAXUS IV[23,35,36]	Paclitaxel Express 2 ($n = 652$) TAXUS (Express 2) paclitaxel slow release ($n = 662$)	TVF Multicentre (73) USA	Single vessel disease Diameter: 2.5–3.75 mm Length: 10–28 mm	Pre-randomisation: Aspirin Clopidogrel (recommended) Post procedure: Aspirin Clopidogrel 6 months	Clinical: 1, 4, 9 months and yearly for 5 years Angiographic: 9 months	BMS DES	72 72	BMS DES	25 23

Table 2 (*continued*)

Study name	Interventions	1^{ry} Endpoint study sites	Inclusion criteria	Co-therapies	Follow-up	Sex, male %		Diabetes %	
SCORE[24]	Taxane derivative: QP2 (7-hexanolytaxol) Bare stent (81% QueST stent) ($n = 138$) QUANAM QP2-eluted from external polymer 'sleeves' ($n = 128$)	Angiographic/MACE Multicentre (15) Europe	Single vessel disease Diameter: 3.0–3.5 mm Length: <20 mm	'Long-term' Plavix recommended	Clinical: 6 months Angiographic: 6 months	BMS DES	78 81	BMS DES	21 20
E-SIRIUS[25,37]	Sirolimus Bx Velocity stent ($n = 177$) CYPHER sirolimus-eluting stent ($n = 175$)	Angiographic Multicentre (35) Europe	Single vessel requiring intervention[A] Diameter: 2.5–3.0 mm Length: 15 mm and 32 mm	Before procedure: Aspirin Clopidogrel or Ticlopidine During procedure: Heparin GP IIb/IIIa (investigator discretion) Post-procedure: Aspirin Clopidogrel or Ticlopidine 2 months	Clinical: 1, 6, 9 and 12 months 2–5 years Angiographic: 8 months	BMS DES	71 70	BMS DES	27 19
RAVEL[26]	Sirolimus Bx Velocity stent ($n = 118$) Bx Velocity sirolimus-eluting stent ($n = 120$)	Angiographic Multicentre (19) International	Single vessel disease Diameter: 2.5–5.5 mm Length: covered with 18 mm stent	Aspirin Heparin Cloidogrel or Ticlopidine 2 months	Clinical: 1, 6, 12 and 24 months Angiographic: 6 months	BMS DES	81 70	BMS DES	21 16
SIRIUS[27,37,40]	Sirolimus Bx Velocity stent ($n = 525$) Bx Velocity sirolimus-eluting stent ($n = 533$)	TVF Multicentre (53) USA	Single vessel disease Diameter: 2.5–3.5 mm Length: 15–30 mm	During procedure: Heparin GP IIb/IIIa Post-procedure: Aspirin Clopidogrel Ticlopidine	Clinical: 1, 6, 9 and 12 months 2–5 years Angiographic: 8 months	BMS DES	70 73	BMS DES	28 25
FUTURE I[28,38]	Everolimus S-stent ($n = 15$) Challenge everolimus-eluting stent ($n = 27$)	MACE Single centre Germany	Single vessel disease Diameter: 2.75–4 mm Length: <18 mm		Clinical: 1 and 12 months Angiographic: 6 months	BMS DES	87 85	Excluded	
FUTURE II[29]	Everolimus S-stent ($n = 43$) Challenge everolimus-eluting stent ($n = 21$)	Angiographic Multicentre (3) Germany	Single vessel disease (Stents 2.5–4.0 diameter) Length: <18 mm		Clinical: 1, 6 and 12 months Angiographic: 6 months	BMS DES	70 71	BMS DES	28 24
ACTION[30]	Actinomycin MULTI-LINK TETRA ($n = 119$) MULTI-LINK TETRA-D Actinomycin-eluting stent 2.5 and 10 $\mu g/cm^2$ ($n = 120$ and 121)	Angiographic/ MACE Multicentre (28) Europe, Australia, New Zealand, Brazil	Single vessel disease Diameter: 3–4 mm Length: covered with 18 mm stent	GP IIb/IIIa	Clinical: 1, 6 and 12 months Angiographic: 6 months	BMS DES 2.5 $\mu g/cm^2$ 10 $\mu g/cm^2$	78 78 79	BMS DES 2.5 $\mu g/cm^2$ 10 $\mu g/cm^2$	5 15 21

DES: drug-eluting stent, BMS: bare metal, A: Patients with single or multiple vessel disease could be included, but only one lesion (>50%, but <100% stenosis) requiring interview[25] Angiographic: primary endpoint involving some form of in vessel measurement(s) (by angiography, Quantitative Coronary Analysis, Intravascular Ultrasound), reported as in stent net volume obstruction, minimal diameter, late loss, percent diameter stenosis.

The majority of the studies used polymer-coated DES. In the ASPECT,[17] DELIVER,[18,31] and ELUTES[19] trials, paclitaxel was applied directly to the stent surface, without the use of a polymer carrier. The SCORE[24] study utilised a DES with a set of polymer "sleeves" that ringed the outer surface of the stent and bore the active agent.

At the time of writing, ASPECT,[17] E-SIRIUS,[25] RAVEL,[26] SIRIUS,[27] TAXUS I,[21] TAXUS II,[34] and TAXUS IV[35] had been published in peer-reviewed journals, but with only 9–12-month data. Other data were largely obtained from conference abstracts, Internet-based sources (for example, conference reports or slide presentations), and documentation provided by manufacturers to the NICE.

Quality assessment of studies included

The limited information on trial methodology in abstracts affected our ability to assess the quality of some of the included studies. Study quality, as assessed using available reports, is presented in Table 1. The three studies investigating the CYPHER™ sirolimus-eluting stent,[25–27] three studies investigating the TAXUS™ paclitaxel-eluting stent,[21,34,35] and the ELUTES[19] study scored well on key aspects of quality assessment (randomisation, blinding, and follow-up).

Study characteristics

The characteristics of the studies and patient populations are provided in Table 2. Patient inclusion criteria are broadly comparable. Ten studies included patients with single-vessel disease only. Three studies included patients with smaller vessels and long lesions (E-SIRIUS,[41] SIRIUS,[42] and TAXUS IV[35]). Mean age ranged from 59 to 65 years and male patients predominated in all studies. Information on past or concurrent health factors was identified for all studies. The proportion of participants with diabetes mellitus varied from 14% (ACTION[30] and TAXUS II[34]) to 29% (DELIVER[18]). The FUTURE I[28] study excluded diabetic patients.

A total of 5747 participants were included (3633 evaluating taxanes, 1648 sirolimus, 360 actinomycin, and 106 everolimus). The numbers randomised to DES versus non-DES were not equal due to the nature of three trials (ACTION,[30] ASPECT,[17] and ELUTES[19]), which assessed various concentrations of drug elution, but used single control groups. The TAXUS II[34] trial explored two different DES "elution profiles" (one slow [SR], one moderate [MR] release) in two separate cohorts, each with its own control group. Trial size varied from 36 (FUTURE[28]) to more than 1000 patients (DELIVER,[18] SIRIUS,[42] and TAXUS IV[35]). All but one study (FUTURE I,[28] a single-centre study based in Germany) were multicentred. We have data on follow-up beyond 1 year from only two studies (RAVEL[26,37] and TAXUS I[21]).

Outcomes

Composite event rates (major adverse cardiac events [MACE], target vessel failure, or event-free survival) were the primary reported endpoints. The definition of "event rate" varied across studies: all included a hierarchy of death, AMI, and some measure of coronary revascularisation, usually either target vessel revascularisation or target lesion revascularisation (see Table 3). Given the varied definitions of revascularisation, it was not possible to directly compare results across trials. Revascularisation was included in the analysis event rate.

All studies included angiographic follow-up (9 months, PATENCY[20] and TAXUS IV;[35] 8 months, SIRIUS[42] and E-SIRIUS;[41] and 6 months for all others). Although a number of angiographic outcomes were reported, the most consistently reported was binary restenosis (percentage of lesions with greater than 50% of luminal narrowing compared to diameter at completion of the procedure).

Data synthesis

The review could not compare stents eluting different pharmaceutical agents since there are no studies that report head-to-head comparisons. In the analyses presented, however, the studies are grouped by eluted agent for convenience. Three studies (ACTION,[30] ASPECT,[17] and ELUTES[19]) evaluated the effects of differing doses of the same agent. The two cohorts of TAXUS II[34] are treated as two studies in the meta-analysis.

Event rate (Fig. 1)

Adverse events were less frequent with paclitaxel and sirolimus DES than non-DES at 6 and 12 months. In the RAVEL study, the benefit of DES is maintained at 2 years.[39] It is important to note that the event rates are made up primarily of revascularisations. For instance, in RAVEL, 27 of the 34 reported MACE (79%) at one year in the non-DES group were target vessel revascularisations.[26] In TAXUS I (the other study reporting up to 2 years), all reported MACE were revascularisations.[32]

Mortality (Fig. 2)

There is no difference in mortality up to 1 year between the DES and non-DES groups. The two-year data reported in RAVEL[39] showed one and two cardiac deaths and five and one noncardiac deaths in the DES and non-DES arms, respectively.

AMI (Fig. 3)

There was no difference in the incidence of AMI between DES and non-DES up to 12 months. The two-year RAVEL[39] data also show no difference between the groups in rate of AMI. One study, SCORE,[24] showed an advantage in the non-DES group at 1 year.

Binary restenosis (Fig. 4)

Binary restenosis is reported at 6 months for nine of the studies in the meta-analysis, at 8 months for SIRIUS[42] and

Table 3 Outcomes

Study name	Intervention		Event rate %		Comprising	Mortality %		Any MI %		Revascularization %		BRR %	
ASPECT[17]	BMS		1 month	1.7	MACE:	1 month	0.0	1 month	1.7	TLR		6 months	
	59 (58)		6 months	5	Death, MI, CABG,	6 months	0.0	6 months	1.7	6 months	3.4	($n = 55$)	27
			1 year ($n = 58$)	10.3	TLR and TLR for SAT	1 year ($n = 58$)	0.0	1 year ($n = 58$)	1.7				
	DES		1 month			1 month		1 month		6 months		6 months	
	118		1.3	3.4		1.3	1.7	1.3	1.7	1.3	1.7	1.3 ($n = 50$)	12
	1.3 μg/mm^2	58	3.1	6.6		3.1	0.0	3.1	3.3	3.1	1.7	3.1 ($n = 50$)	4
	3.1 μg/mm^2	60	6 months			6 months		6 months					
			1.3	8.6		1.3	1.7	1.3	1.7				
			3.1	11.7		3.1	0.0	3.1	3.3				
			1 year	25.4		1 year							
			1.3	12.1		1.3	1.7	1 year					
			3.1	16.7		3.1	0.0	1.3	1.7				
								3.1	3.3				
DELIVER[31]	BMS		MACE		TVF: Death, MI, TLR, TVR	Cardiac		30 days	0.2	TVR (non-TLR) *clinically driven*		9 months in-stent	
	519 (512)		30 days	0.4		30 days	0.2	9 months	1.0			($n = 214$)	20.6
			TVF *clinically driven*			9 months	0.8	1 year	1.0	9 months	0.0		
			9 months	8.6		1 year	0.8	($n = 512$)		1 year	0.0		
			1 year	9.4									
			($n = 512$)			Death as reported[55]				TLR *clinically driven*			
						9 months	1.2			30 days	0.0		
						($n = 512$)				9 months	6.8		
										1 year	7.6		
										($n = 512$)			
	DES		MACE			Cardiac		30 days	0.8	TVR (non-TLR) *clinically driven*		9 months in-stent	
	524 (517)		30 days	1.0		30 days	0.2	9 months	1.2			($n = 228$)	14.9
			TVF *clinically driven*			9 months	0.2	1 year	1.4	9 months	0.0		
			9 months	6.6		1 year	0.2	($n = 517$)		1 year	0.0		
			1 year	7.5									
			($n = 517$)			Death as reported[55]				TLR *clinically driven*			
						9 months	1.0			30 days	0.0		
						($n = 517$)				9 months	5.2		
										1 year	6.0		
										($n = 517$)			
ELUTES[19]	BMS		Event free survival		Death, MI, CABG, TLR,	1 month	0.0	1 month	0.0	TLR		6 months in-stent	
	38		1 month	97	SAT	6 months	0.0	6 months	0.0	6 months	7.9	($n = 34$)	20.6
			6 months	89		1 year	0.0	1 year	0.0	1 year	15.8		
			1 year	82									
	DES 152		Event free survival			1 month	0.7	1 month	0.7	6 months		6 months in-stent	
	0.2 μg/mm^2	37	30 days			6 months	0.7	6 months	1.3	combined	3.3	0.2	20
	0.7 μg/mm^2	39	0.2	100		1 year		1 year	1.3	0.2	2.7	0.7	11.8

Table 3 (*continued*)

Study name	Intervention		Event rate %		Comprising	Mortality %		Any MI %		Revascularization %		BRR %	
	1.4 μg/mm^2	39	0.7	100		0.2	0.7			0.7	2.6	1.4	13.5
	2.7 μg/mm^2	37	1.4	100		0.7	0.0			1.4	2.6	2.7	3.1
			2.7	92		1.4	0.0			2.7	5.4	($n = 139$ calculated)	
			6 months			2.7	0.0			1 year			
			0.2	95						combined	7.2		
			0.7	95						0.2	5.4		
			1.4	97						0.7	7.7		
			2.7	89						1.4	10.3		
			1 year							2.7	5.4		
			0.2	95									
			0.7	90									
			1.4	90									
			2.7	86									
PATENCY[20]	BMS		30 days	0.0	MACE: Death, MI,	30 days	0.0	30 days	0.0			9 months	
	26		270 days	23.1	CABG, TLR, SAT	270 days	3.8	270 days	0.0			($n = 17$)	35.3
	DES		30 days	0.0		30 days	0.0	30 days	0.0			9 months	
	2.0 μg/mm^2	24	270 days	12.5		270 days	0.0	270 days	0.0			($n = 21$)	38.1
TAXUS I[21,32,33]	BMS		30 days	0.0	MACE: Death, MI,	30 days	0.0	1 year	0.0	TLR:		6 months	
	30		6 months	6.6	TVR, stent thrombosis	1 year	0.0	2 years	0.0	30 days	0.0	($n = 29$)	10.3
			1 year	10.0		2 years	0.0			6 months	6.6		
			2 years	10.0						1 year	10.0		
										2 years	10.0		
										TVR—non-TLR			
										1 year	0.0		
										TVR			
										2 years	10.0		
	DES		30 days	0.0		30 days	0.0	1 year	0.0	TLR		6 months	
	31 (30)		6 months	0.0		1 year	0.0	2 years	0.0	30 days	0.0	$n = 30$	0.0
			1 year	3.0		Cardiac				6 months	0.0		
			2 years	3.3		2 years	0.0			1 year	0.0		
										2 years	0.0		
										TVR—non-TLR			
										1 year TVR	3.2		
										2 years	3.2		
TAXUS II[33,34]	BMS (270)		30 days ($n = 272$)	4.4	MACE: Death, MI, TVR, stent thrombosis	6 months		6 months		TVR (overall)		6 months stented segment	
	SR cohort 136		6 months			SR ($n = 133$)	0.7	SR ($n = 133$)	5.3	6 months		SR ($n = 134$)	17.9
	MR cohort 134		SR ($n = 133$)	19.5		MR	0.0	MR ($n = 130$)	5.4	SR ($n = 133$)	14.3	MR ($n = 129$)	20.1
			MR ($n = 130$)	20.0		1 year (33)		1 year		MR ($n = 130$)	17.7		
			1 year			SR ($n = 129$)	1.5	SR ($n = 132$)	5.3	1 year			
			SR ($n = 132$)	22.0		MR ($n = 131$)	1.5	MR ($n = 131$)	5.3	SR ($n = 132$)	15.9		
			MR ($n = 131$)	21.4						MR ($n = 131$)	19.1		
										TLR			

Table 3 (*continued*)

Study name	Intervention	Event rate %		Comprising	Mortality %		Any MI %		Revascularization %		BRR %	
									6 months			
									SR ($n = 133$)	12.0		
									MR ($n = 130$)	14.6		
									1 year			
									SR ($n = 132$)	12.9		
									MR ($n = 131$)	16.0		
	DES (262)	30 days	2.3		6 months		6 months		TVR (overall)		6 months stented segment	
	SR cohort 131	6 months			SR	0.0	SR ($n = 130$)	1.5	6 months		SR ($n = 128$)	2.3
	MR cohort 135	SR ($n = 130$)	8.5		MR	0.0	MR ($n = 129$)	2.3	SR ($n = 130$)	7.7	MR ($n = 128$)	4.7
		MR ($n = 129$)	7.7		1 year (33)		1 year		MR ($n = 129$)	6.2		
		1 year			SR ($n = 133$)	0.0	SR ($n = 129$)	2.3	1 year			
		SR ($n = 129$)	10.9		MR ($n = 131$)	0.8	MR ($n = 131$)	3.8	SR ($n = 129$)	10.1		
		MR ($n = 131$)	9.9						MR ($n = 131$)	6.9		
									TLR			
									6 months			
									SR ($n = 130$)	4.6		
									MR ($n = 129$)	3.1		
									1 year			
									SR ($n = 129$)	4.7		
									MR ($n = 131$)	3.8		
TAXUS IV[23,35,36]	BMS	MACE		MACE: Cardiac death,	Cardiac		30 days	2.3	TLR		9 months in stent	
	652	30 days	2.5	MI, TVR,	30 days	0.5	9 months	3.7	30 days	0.3	($n = 267$)	24.4
		9 months	15.0		9 months	1.1			9 months	11.3		
		TVF		TVF: Death, MI, TVR,					TVR			
		9 months	14.4						30 days	0.3		
									9 months	12.0		
	DES	MACE			Cardiac		30 days	2.6	TLR		9 months in stent	
	662	30 days	2.9		30 days	0.3	9 months	3.5	30 days	0.0	($n = 292$)	5.5
		9 months	8.5		9 months	1.4			9 months	3.0		
		TVF							TVR			
		9 months	7.6						30 days	0.0		
									9 months	4.7		
SCORE[24]	BMS	1 year		MACE: Death, MI, TVR	6 months	0.0	6 months	2.3	TLR		6 months in stent	
	138	Non-hierarchical			1 year	2.9	1 year	0.0	1 year	25.4	($n = 94$)	36.9
									TVR			
									1 year	5.1		
	DES	1 year			6 months	3.9	6 months	14.5	TLR		6 months in stent	
	128	Non-hierarchical			1 year	3.9	1 year	21.1	1 year	21.1	($n = 104$)	6.4
									TVR			
									1 year	11.7		

Table 3 (*continued*)

Study name	Intervention	Event rate %		Comprising	Mortality %		Any MI %		Revascularization %		BRR %	
E-SIRIUS[25,37]	BMS 177	9 months	22.6	MACE: Death, MI, emergency CABG, TLR	9 months	0.6	9 months	2.3	TLR (25) 9 months CABG 9 months TVR free 9 months TLR free 9 months	 20.9 1.7 76.9 78.3	8 months in stent[25] ($n = 156$) 8 months ($n = 154$)	 41.7 42.2
	DES 175	9 months	8.0		9 months	1.1	9 months	4.6	TLR (25) 9 months CABG 9 months TVR free 9 months TLR free 9 months	 4.0 0.0 76.9 95.9	8 months in stent[25] ($n = 152$) 8 months ($n = 151$)	 3.9 4.0
RAVEL[26,37,39]	BMS 118	1 year 2 years	28.8 19.5	MACE: Death, MI, TLR, SAT	In Hospital 1 year 2 years	0.0 1.7 2.5	In Hospital 1 year 2 years	2.5 4.2 5.1	TVR (non-TL) 1 year 2 years TLR (all) 1 year 2 years	 1.7 2.5 23.7 13.6	6 months in stent ($n = 107$)	 26.6
	DES 120	1 year 2 years	5.8 10.0		In Hospital 1 year 2 years	0.0 1.7 5.0	In Hospital 1 year 2 years	2.5 3.3 4.2	TVR (non-TL) 1 year 2 years TLR (all) 1 year 2 years	 0.8 0.8 0.8 2.5	6 months in stent ($n = 105$)	 0.0
SIRIUS[37,40]	BMS 525	In Hospital 9 months 1 year	1.5 18.9 22.3	MACE: Death, MI, TLR	In Hospital 9 months 1 year	0.0 0.6 0.8	In Hospital 9 months 1 year	1.5 3.2 3.4	TVR (non-TL) In Hospital 9 months 1 year TLR 30 days 9 months 1 year	 0.0 4.8 6.7 0.0 16.6 20.0	8 months in segment 8 months in stent ($n = 353$)	 36.3 35.4
	DES 533	In Hospital 9 months 1 year	2.4 7.1 8.3		In Hospital 9 months 1 year	0.2 0.9 1.3	In Hospital 9 months 1 year	2.3 2.8 3.0	TVR (non-TL) In Hospital 9 months 1 year TLR 30 days 9 months 1 year	 0.0 3.2 3.6 0.2 4.1 4.9	8 months in segment 8 months in stent ($n = 348$)	 8.9 3.2

Table 3 (*continued*)

Study name	Intervention	Event rate %	Comprising	Mortality %	Any MI %	Revascularization %	BRR %
FUTURE I[28,38]	BMS 15	30 days 0.0 6 months 8.3 ($n = 12$)	MACE: not defined	30 days 0.0 6 months 0.0 ($n = 12$)	30 days 0.0 6 months 0.0 ($n = 12$)	TLR 30 days 0.0 6 months 8.3 ($n = 12$)	6 months in stent ($n = 11$) 9.1
	DES 27	30 days 0.0 6 months 7.7 ($n = 26$)		30 days 0.0 6 months 3.8 ($n = 26$)	30 days 0.0 6 months 0.0 ($n = 26$)	TLR 30 days 0.0 6 months 3.8 ($n = 26$)	6 months in stent ($n = 25$) 0.0
FUTURE II[29]	BMS 43	30 days 2.3 6 months 17.5 ($n = 40$)	MACE: Death, MI, TLR	30 days 0.0 6 months 0.0 ($n = 40$)	30 days 2.3 6 months 2.5 ($n = 40$)	TLR 30 days 0.0 6 months 15.0 ($n = 40$)	6 months in stent ($n = 36$) 19.4
	DES 21	30 days 0.0 6 months 4.8		30 days 0.0 6 months 0.0	30 days 0.0 6 months 0.0	TLR 30 days 0.0 6 months 4.8	6 months in stent ($n = 21$) 0.0
ACTION[30]	BMS 119	30 days ($n = 119$) 0.8 6 months ($n = 88$) 10.2	MACE: Death, MI, TLR	30 days ($n = 119$) 0.0 6 months 0.0 ($n = 88$)	30 days ($n = 119$) 0.8 6 months 1.1 ($n = 88$)	TLR 30 days ($n = 119$) 0.0 6 months ($n = 88$) 9.1 TVR 30 days ($n = 119$) 0.0 6 months ($n = 88$) 0.0	6 months ($n = 64$) 11
	DES 241 2.5 μg/mm^2 120 10 μg/mm^2 121	30 days 2.5 0.8 10 2.5 6 months 2.5 ($n = 120$) 18.3 10 ($n = 121$) 28.1		30 days 2.5 ($n = 120$) 0.0 10 ($n = 121$) 0.0 6 months 2.5 ($n = 120$) 0.8 10 ($n = 121$) 0.0	30 days 2.5 ($n = 120$) 0.0 10 ($n = 121$) 2.5 6 months 2.5 ($n = 120$) 0.0 10 ($n = 121$) 3.3	TLR 30 days 2.5 ($n = 120$) 0.8 10 ($n = 121$) 0.0 TLR 6 months 2.5 ($n = 120$) 17.5 10 ($n = 121$) 23.1 TVR 30 days 0.0 2.5 ($n = 120$) 0.8 10 ($n = 121$) TVR 6 months 2.5 ($n = 120$) 0.0 10 ($n = 121$) 0.8	6 months 2.5 ($n = 113$) 25 10 ($n = 115$) 17

DES: drug-eluting stent; BMS: bare metal stents; MACE: major adverse cardiac event; MI: myocardial infarction; TVR: target vessel revascularisation; TLR: target lesion revascularisation; SAT: sub acute thrombosis.

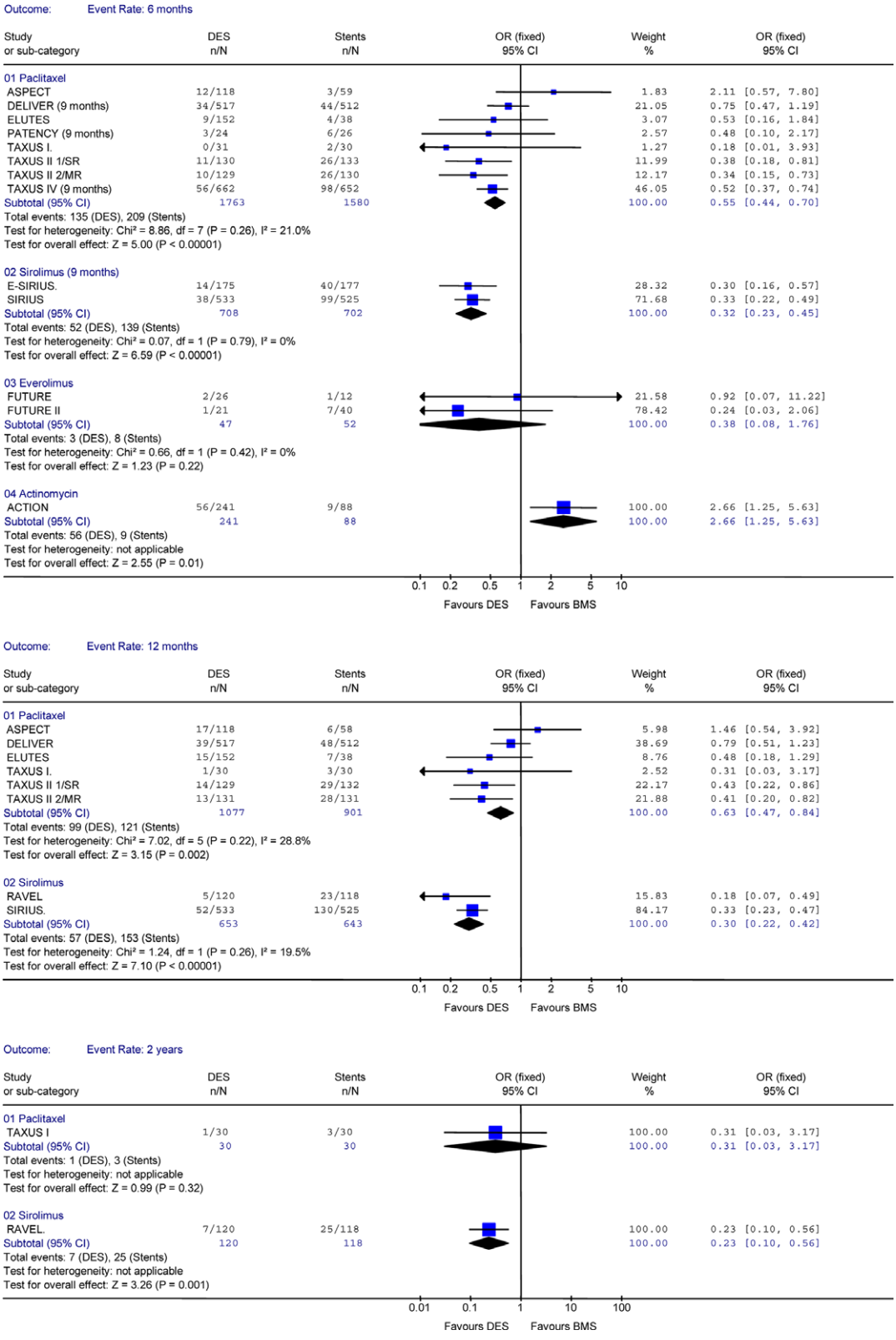

Fig. 1 Event rate.

E-SIRIUS, and at 9 months for PATENCY,[20] DELIVER,[18] and TAXUS IV.[35] Analysing these data suggests a benefit of DES over non-DES in the taxane and sirolimus groups and a marginally significant benefit in the relatively small-sized everolimus subgroup. This advantage is not evident in the evaluation of actinomycin-eluting stents.

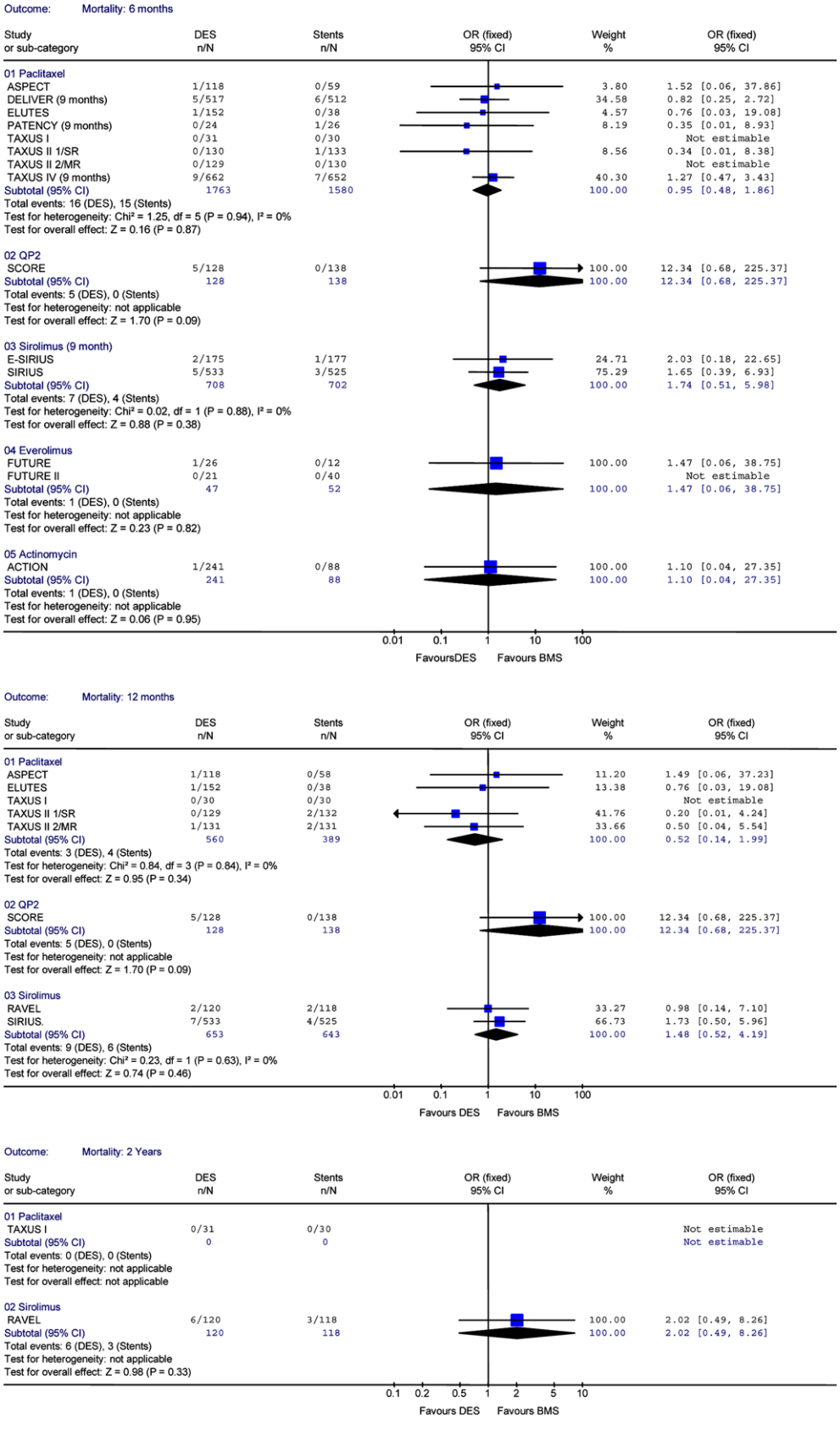

Fig. 2 Mortality.

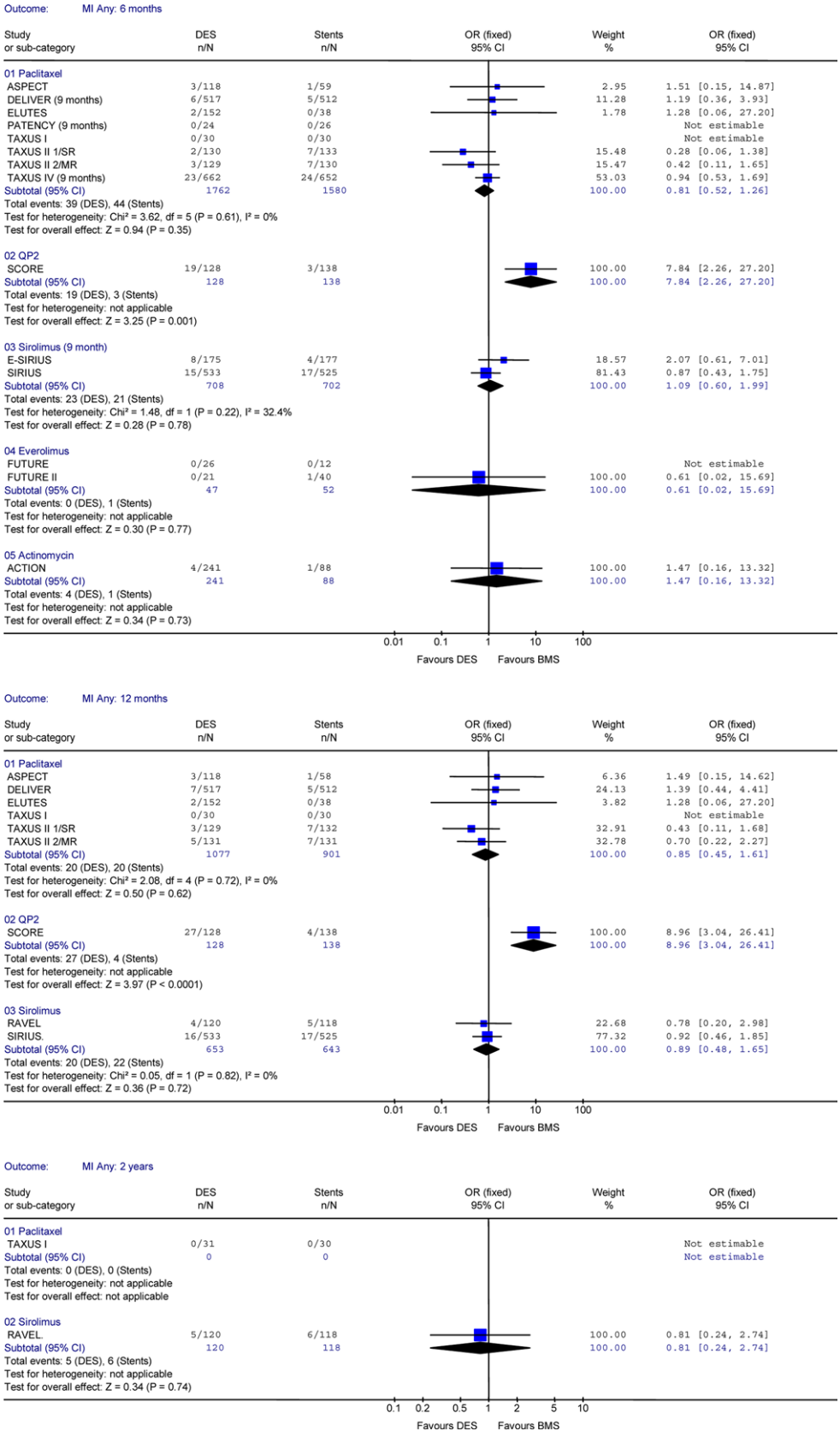

Fig. 3 Myocardial infarction.

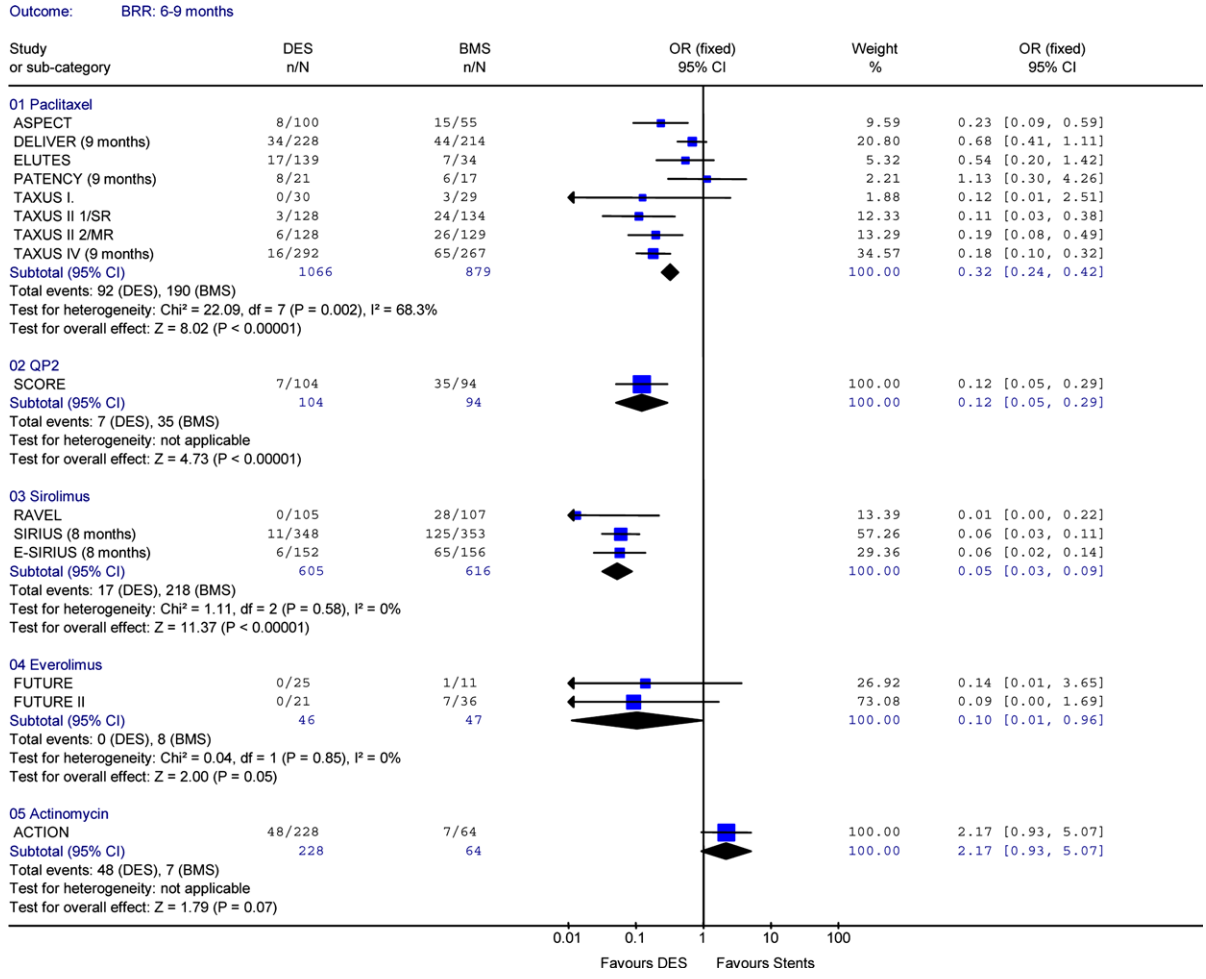

Fig. 4 Binary restenosis rate.

Discussion

The analysis indicates that DES can reduce event rates by 40—60% at 12 months. Event rate is heavily dependent on revascularisations and these, in turn, may be inflated by protocol-dictated angiography. This does not accurately reflect clinical practise and may bias studies in favour of the DES.[1,2] Clinicians faced with a narrowed lesion on angiogram may intervene even where not strictly necessary from a clinical point of view. This was well illustrated in BENESTENT II,[43] where a greater number of revascularisation procedures were reported in cohorts of patients with routine protocol angiography than in those who did not have angiographic evaluation (12.6% compared to 6%, respectively, $p = 0.003$).

To avoid this problem, trials report "clinically driven revascularisations". This is defined by the US Food and Drug Administration as cases where there was a positive exercise ECG or nuclear perfusion scan; ischaemic ECG changes at rest in a distribution consistent with the target vessel; ischaemic symptoms and an in-lesion diameter stenosis greater than 50%; or revascularisation of a target lesion with an in-lesion diameter stenosis greater than 70%, even without ischaemic signs or symptoms. This last point assumes that such patients would soon become symptomatic and require a repeat revascularisation but, in effect, allows protocol-driven revascularisation procedures. Trial sponsors report that the 70% stenosis criterion alone was rarely invoked in practise (S. Fearn, Cordis Corporation: personal communication, 2002). Nevertheless, Kaplan—Meier plots of events in many of the included trials indicate a major increase in events at the time of the protocol-dictated angiogram.

Trial reports confuse the issue further in their reporting of clinically-driven and non-clinically-driven events. For instance, in published data for RAVEL,[26] full MACE figures were reported in a table as 34/118 in the non-DES arm, but "clinically-driven" MACE were reported in the text of the article as only 23/118 (this latter figure is included in our meta-analysis). It is uncertain, therefore, how well even "clinically-driven" trial events as defined, reflect true clinical practise, and there is a clear need for randomised clinical trials with simple, truly clinical endpoints rather than the composite clinical and angiographic endpoints used in trials to date. A recent discussion of cost-effectiveness based on Medicare data in the USA indicates that the incidence of repeat revascularisation between 1 month and 1 year after initial PCI is 16.9%.[44]

Some patients may be at higher risk of restenosis (for example, those with diabetes). To date, no trial has been powered to evaluate the benefits within subgroups. A meta-analysis of individual patient data would help to address this limitation and guide the effective, targeted use of DES. Attempts from registry data or from limited trial data to define subsets at high risk[45–47] suggest that patients with smaller vessels and longer lesions and diabetic patients are at higher risk of restenosis.

The relative benefits of stenting are assumed to be similar for each type of lesion and the absolute benefits vary depending on the background risk of restenosis. Given that studies have not been powered to demonstrate effect on mortality or myocardial infarction, issues such as the improvement in quality of life brought about by DES and their cost-effectiveness in different subsets of patients will be critical in policy decisions about using DES. However, these data are not currently available.

A number of the included trials were stopped early because of lack of effect (ACTION,[30] actinomycin) or major adverse effects (SCORE,[24] with the taxol derivative 7-hexanolytaxol), or refer to devices that have not been approved for use. Including these studies in the review assumes compatibility of stents. In fact, each stent design and drug/polymer combination is unique and, without direct comparative studies, it is unclear if there are significant differences between them. The use of meta-analysis here should therefore not be taken to replace careful examination of each trial and consideration of each stent individually. As comparative data become available, appropriate analysis may prove possible.

This review reports results for all DES, but from the pragmatic view of the policy maker, the only DES of interest are those awarded the CE Mark (CYPHER™, TAXUS™, and the DEXAMET™ dexamethasone-eluting stent). If the report were confined to trials relating to these stents only, the odds ratio for reduction in events at 12 months of DES compared to non-DES would be 0.30 (95% CI 0.22, 0.42, $n = 1296$) for CYPHER™ sirolimus-eluting stent, and 0.41 (95% CI 0.25, 0.67, $n = 583$) for TAXUS™ paclitaxel-eluting stents. No data from randomised clinical trials evaluating the dexamethasone-eluting stents were identified for inclusion in this review.

Mortality and AMI

This analysis showed no improvement in mortality or AMI for DES compared to non-DES. However, none of the studies to date have been powered to detect changes in these endpoints. Recent reviews of stenting versus PTCA alone[2,11] involving almost 10,000 and 16,000 patients also show no benefit in mortality or AMI, and such a benefit for DES over non-DES seems unlikely with currently powered trails.

Limitations of the review

The review is constrained in its ability to draw conclusions by the trial evidence available. Some studies included small numbers of participants and, importantly, have limited long-term follow-up. Limiting the review to randomised controlled trials meant that the review failed to consider the DEXAMET stent, since the license for this DES was approved on the basis of registry data. Conversely, we included data from randomised controlled trials that had either been stopped due to lack of effect or had included DES that will not be available. This information, although interesting (and essential to include in a "gold standard" review of effectiveness), is of limited use in making policy decisions.

We included data from seven trials that have only been reported in conference presentations and abstracts and were therefore not subject to full peer review. The use of these data could be criticised. We found discrepancies in published papers as well as between published papers and data reported in conference presentations and abstracts and data provided through company submissions as a part of the NICE appraisal process. Although these differences are small, so are the study populations and a difference in reporting, for instance, one death, may significantly alter findings. Furthermore, it can be difficult to investigate the nature and clinical significance of such differences. Nevertheless, the evaluation of rapidly evolving technologies to inform policy decisions requires inclusion of data that would not be considered for "gold standard" systematic reviews of effectiveness. The decisions regarding inclusion, quality assessment, and weighting of evidence offer an ongoing challenge to research groups conducting systematic reviews designed to assess both clinical effectiveness and to inform health-policy decisions.

Standards exist that guide the conduct and reporting of reviews of clinical effectiveness.[48,49] However, when the purpose of the review is to inform health-policy decisions, the application of these strict standards often fails to provide data necessary to inform this decision-making process.[50,51]

Evidence, policy, and practise in new technologies

The potential for rapid uptake of a new technology has been demonstrated by the increase in the use of stents during PCI. By 2000, PCI included the use of stents in 80% of cases in the UK, before national guidance was issued. The use of DES is a simple adaptation of a current practise and is being adopted rapidly by enthusiastic interventional cardiologists. One survey of cardiologists in the USA[52] estimated that 77% of all stenting would be with DES within a year of licensing. This same survey identified device cost as the biggest barrier to uptake, rather than lack of clinical evidence. Therefore, clear and early policies are necessary, even if based on imperfect evidence and evaluations, both clinical and economic, before DES use becomes standard clinical practise and too late to reverse.

Based on an appraisal of the evidence presented here, a related economic evaluation based on limited individual patient data from one study, and evidence from manufacturers and cardiologists, the NICE for England

and Wales has recommended the use of DES in preference to non-DES for patients with lesions in small vessels (less than 3 mm), or long lesions (greater than 20 mm).[53] This policy is therefore inevitably based on small numbers of patients, trial "event rate" as an endpoint, short-term follow-up, and limited subgroup analysis, and will require re-examination as new data become available. Whether this is how DES are used in practise or will actually be used in the future remains to be seen.

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