Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis

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Summary

Background **Whether the two drug-eluting stents approved by the US Food and Drug Administration—a sirolimus-eluting stent and a paclitaxel-eluting stent—are associated with increased risks of death, myocardial infarction, or stent thrombosis compared with bare-metal stents is uncertain. Our aim was to compare the safety and effectiveness of these stents.**

Methods **We searched relevant sources from inception to March, 2007, and contacted investigators and manufacturers to identify randomised controlled trials in patients with coronary artery disease that compared drug-eluting with bare-metal stents, or that compared sirolimus-eluting stents head-to-head with paclitaxel-eluting stents. Safety outcomes included mortality, myocardial infarction, and definite stent thrombosis; the effectiveness outcome was target lesion revascularisation. We included 38 trials (18 023 patients) with a follow-up of up to 4 years. Trialists and manufacturers provided additional data on clinical outcomes for 29 trials. We did a network meta-analysis with a mixed-treatment comparison method to combine direct within-trial comparisons between stents with indirect evidence from other trials while maintaining randomisation.**

Findings **Mortality was similar in the three groups: hazard ratios (HR) were 1·00 (95% credibility interval 0·82–1·25) for sirolimus-eluting versus bare-metal stents, 1·03 (0·84–1·22) for paclitaxel-eluting versus bare-metal stents, and 0·96 (0·83–1·24) for sirolimus-eluting versus paclitaxel-eluting stents. Sirolimus-eluting stents were associated with the lowest risk of myocardial infarction (HR 0·81, 95% credibility interval 0·66–0·97, p=0·030 *vs* bare-metal stents; 0·83, 0·71–1·00, p=0·045 *vs* paclitaxel-eluting stents). There were no significant differences in the risk of definite stent thrombosis (0 days to 4 years). However, the risk of late definite stent thrombosis (>30 days) was increased with paclitaxel-eluting stents (HR 2·11, 95% credibility interval 1·19–4·23, p=0·017 *vs* bare-metal stents; 1·85, 1·02–3·85, p=0·041 *vs* sirolimus-eluting stents). The reduction in target lesion revascularisation seen with drug-eluting stents compared with bare-metal stents was more pronounced with sirolimus-eluting stents than with paclitaxel-eluting stents (0·70, 0·56–0·84; p=0·0021).**

Interpretation **The risks of mortality associated with drug-eluting and bare-metal stents are similar. Sirolimus-eluting stents seem to be clinically better than bare-metal and paclitaxel-eluting stents.**

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Introduction

The long-term safety of the two polymer-based drug-eluting stents approved by the US Food and Drug Administration (FDA)—a sirolimus-eluting stent and a paclitaxel-eluting stent—was questioned by recent studies, which reported increased rates of death, myocardial infarction, or late stent thrombosis compared with bare-metal stents.[1–5] These studies were hampered by few patients, limited durations of follow-up, or an observational study design.

Network meta-analyses[6,7] or mixed treatment comparisons[8–10] would allow us to do a unified, coherent analysis of all randomised controlled trials that compared either of the two drug-eluting stents with bare-metal stents or the two drug-eluting stents head-to-head, while fully respecting randomisation. We established a collaborative group of investigators who provided trial data based on standardised definitions of outcomes,[11,12] and did a network meta-analysis.

Methods

Search strategy and selection criteria

We searched Medline, EmBase, the Cochrane Central Register of Controlled Trials (CENTRAL), and relevant websites (www.acc.org, www.tctmd.com, www.theheart.org, www.clinicaltrialresults.org) for studies in any language (from the inception of each database to March, 2007), searched reference lists and conference abstracts by hand, checked relevant reviews, book chapters, and the proceedings of the relevant FDA advisory panels, and contacted manufacturers and trialists. Two investigators (CSt, SA) independently assessed reports for eligibility. To be included, studies had to be randomised controlled trials in individuals with symptoms or signs of myocardial ischaemia due to coronary artery disease, comparing the paclitaxel-eluting Taxus stent (Boston Scientific, Natick, MA, USA) or the sirolimus-eluting Cypher stent (Cordis, Miami Lakes, FL, USA) with each other, or with bare-metal stents.

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Trials had to have a clinical follow-up duration of at least 6 months.

Data collection

Two investigators (CSt and SA) independently extracted all data, with disagreements resolved in consultation with a third investigator (PJ). Trialists and manufacturers of drug-eluting stents were required to check the extracted information and provide outcome data on an electronic form according to standardised definitions. We prespecified the following primary safety outcomes:[12] (1) overall mortality; (2) cardiac death, defined as any death due to cardiac cause (eg, myocardial infarction, low-output failure, fatal arrhythmia), procedure-related deaths, and deaths related to concomitant treatment and death of unknown cause; (3) myocardial infarction, including fatal and non-fatal non-Q-wave or Q-wave myocardial infarction; (4) a composite of death or myocardial infarction; (5) definite stent thrombosis within the stented segment, confirmed by angiography or post-mortem examination in accordance with the Academic Research Consortium (ARC) criteria.[11,12] We ensured that secondary stent thromboses, occurring after a patient had undergone a target lesion revascularisation, were included. Target lesion revascularisation was the secondary effectiveness outcome, defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel done for restenosis or other complications of the target lesion (ranging from 5 mm proximal to 5 mm distal to the stent). Rates of target lesion revascularisation were unavailable in three trials[13–15] and we used rates of target vessel revascularisation[12] as a proxy measure. The number of patients experiencing an event and the overall number of patients at risk were recorded separately for years 1 to 4. We assessed three key domains of internal validity:[16] concealment of allocation, blinding of research staff adjudicating clinical outcomes, and the inclusion of all randomised individuals in the analysis according to the intention-to-treat principle.

Statistical analysis

We used an extension of multivariable Bayesian hierarchical random effects models[17] for mixed multiple treatment comparisons,[8] which fully preserves the within-trial randomised treatment comparison of each trial.[8,18] To account for varying follow-up times, we used a random-walk model based on piece-wise constant hazards (webappendix 1).[19] The model included random effects at the levels of trials, adjacent time periods, and comparisons, and was fitted to the four prespecified time periods (years 1 to 4). Time periods with zero events in either group were excluded from the analyses.

See Online for webappendix 1

For stent thrombosis, we also did separate analyses for early (0–30 days after stent implantation) and late events (>30 days after implantation) and an analysis with per-protocol definitions of stent thrombosis from individual trials. In post-hoc analyses, we distinguished between stent thromboses occurring between more than 30 days to 1 year and those occurring after more than 1 year to 4 years.

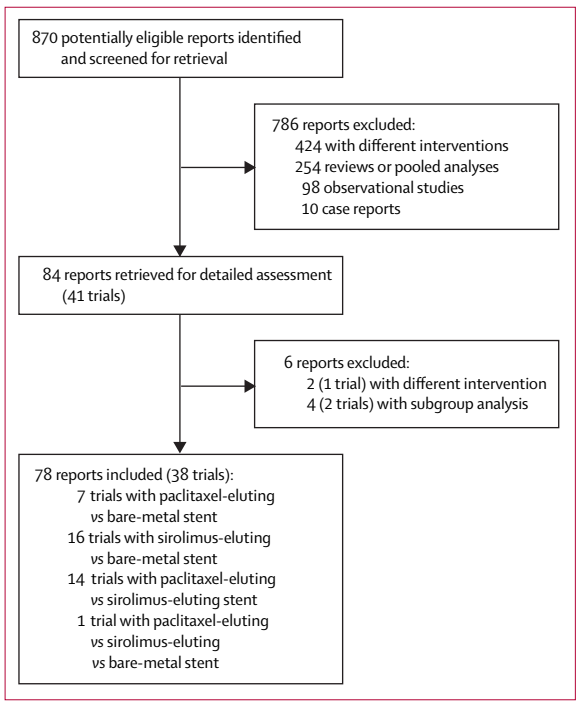

Figure 1: **Study selection**

In sensitivity analyses, we restricted the network to trials with adequate concealment of allocation, blind adjudication of clinical outcomes, and intention-to-treat analyses, and high quality trials satisfying all three methodological criteria.[16] Since strut thickness or type of stent platform might affect clinical outcomes,[20] we did sensitivity analyses adjusted for strut thickness and for type of stent platform. Finally, we derived pooled estimates from standard random-effects meta-analyses[21] of direct within-trial comparisons. In addition to the primary network meta-analyses in all patients, we stratified analyses of mortality and the composite of death or myocardial infarction according to the presence or absence of diabetes and did a test for interaction between estimated hazard ratios (HR) and diabetes.

HR and cumulative incidences were estimated from the median of the posterior distribution. HR below one indicate a benefit of the experimental intervention. We estimated 95% credibility intervals from the 2·5th and 97·5th percentiles of the posterior distribution, also calculating two-sided p values from the posterior distribution. 95% credibility intervals and p values from posterior distributions can be interpreted in the same way as conventional 95% CI and p values. Finally, we derived numbers-needed-to-treat (NNT) and numbers-needed-to-harm (NNH) using the cumulative incidences and HR estimated in the network meta-analysis.[22] The heterogeneity between trials was estimated from the median between-trial variance (τ^2) observed in the posterior

distribution.[23] The consistency of the network was determined by use of inconsistency factors;[24] goodness of fit was assessed by use of the residual deviance (webappendix 1).[10,19,24] All analyses were done with WinBUGS version 1.4 and Stata version 9.2.

Role of the funding source

The study sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

We screened the titles and abstracts of 870 potentially eligible reports, examined the full text of 84 articles reporting on 41 different trials, and identified 38 trials[13–15,20,25–58] that met our inclusion criteria (figure 1).

	Number of patients	Primary endpoint	Inclusion criteria			Diabetes mellitus (%)	Mean age (years)	Sex (% female)	Number of centres	Source of funding
			Indication for PCI	Lesion length (mm)	Lesion diameter (mm)					
Paclitaxel-eluting *vs* bare-metal stents										
TAXUS I[25]	61	Combination of death, AMI, TVR, stent thrombosis	Stable or unstable AP, silent ischaemia	≤12	3·0–3·5	18%	66	10%	3	MF
TAXUS II[26]	536	Neointimal proliferation	Stable or unstable AP, silent ischaemia	≤12	3·0–3·5	15%	62	24%	38	MF
TAXUS IV[27]	1314	TVR	Stable or unstable AP, provokable ischaemia	10–28	2·5–3·75	32%	63	28%	73	MF
TAXUS V[28]	1172	TVR	Stable or unstable AP, silent ischaemia	10–46	2·25–4·0	32%	63	31%	66	MF
TAXUS VI[29]	446	TVR	Stable or unstable AP, silent ischaemia	18–40	2·5–3·75	20%	62	24%	44	MF
PASSION[30]	619	Combination of cardiac death, AMI, TLR	AMI	No restrictions	>2·5	11%	61	24%	2	NA
HAAMU-STENT[15]	164	NA	AMI	NA	NA	15%	63	28%	1	NA
Sirolimus-eluting *vs* bare-metal stents										
RAVEL[31]	238	Late lumen loss	Stable or unstable AP, silent ischaemia	≤18	2·5–3·5	19%	62	37%	19	MF
SIRIUS[32]	1058	Combination of cardiac death, AMI, TVR	Stable or unstable AP, signs of myocardial ischaemia	15–30	2·5–3·5	26%	62	28%	53	MF
E-SIRIUS[33]	352	Minimal lumen diameter	Stable or unstable AP, silent ischaemia	15–32	2·5–3·0	23%	62	29%	35	MF
C-SIRIUS[34]	100	Minimal lumen diameter	Stable or unstable AP, silent ischaemia	15–32	2·5–3·0	24%	60	31%	8	MF
SES-SMART[35]	257	Binary restenosis	Stable AP, ACS, silent myocardial ischaemia as shown by exercise stress test	≤33	<2·75	25%	64	28%	20	MF
DIABETES[36]	160	Late lumen loss	Symptoms or objective evidence of ischaemia	No restrictions	<4·0	100%	67	38%	4	NP
Pache et al[20]	500	Binary restenosis	Symptomatic coronary heart disease	No restrictions	No restrictions	31%	67	22%	2	NP
PRISON II[37]	200	Binary restenosis	Chronic total occlusion, positive exercise stress test	No restrictions	No restrictions	13%	60	20%	2	NP
SCANDSTENT[38]	322	Minimal lumen diameter	Stable or unstable AP, recent AMI (non ST-elevation)	≥15*	2·25–4·50	18%	63	23%	4	NP
TYPHOON[39]	715	Combination of vessel-related death, AMI, TVR	AMI	≤30	2·25–3·50	16%	59	22%	48	MF
SESAMI[40]	320	Binary restenosis	AMI	No restrictions	No restrictions	21%	62	20%	1	NP
DECODE[41]	83	Late lumen loss	Stable or unstable angina	NA	NA	100%	60	33%	NA	NA
SCORPIUS[42]	200	Late lumen loss	Stable or unstable angina	≤42	2·5–3·5	100%	60	66%	16	MF
RRISC[43]	75	Late lumen loss	Stable or unstable AP, previous coronary artery bypass surgery	≤66	2·5–4·0	15%	73	15%	1	NP
MISSION[44]	308	Late lumen loss	AMI	NA	NA	NA	NA	NA	1	NA
Ortolani et al[45]	104	Late lumen loss	Critical coronary artery stenosis	≤28	NA	16%	66	24%	1	NA

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Sirolimus *vs* pacilitaxel-eluting stents										
TAXi[46]	202	Combination of death, AMI, TLR, stent thrombosis	No restrictions	No restrictions	No restrictions	34%	64	20%	1	NP
ISAR-DESIRE[47]	200	Binary restenosis	AP and/or positive stress test, previously stented, no AMI	No restrictions	No restrictions	29%	64	22%	2	NP
ISAR-DIABETES[48]	250	Late lumen loss	AP or positive stress test, no AMI	No restrictions	No restrictions	100%	68	27%	2	NP
SIRTAX[49]	1012	Combination of cardiac death, AMI, TLR	Stable AP, ACS, including AMI	No restrictions	2·25–4·00	20%	62	23%	2	NP
CORPAL[50]	652	Binary restenosis	Documented myocardial ischaemia, no AMI	<20	<2·5	31%	61	23%	2	NP
REALITY[51]	1353	Binary restenosis	Stable or unstable AP, documented silent ischaemia, no AMI	>15	2·25–3·00	28%	63	28%	90	MF
ISAR-SMART 3[52]	360	Late lumen loss	AP or positive stress test, no AMI	No restrictions	<2·8	0%	67	28%	2	NP
Zhang et al[14]	449	Combination of death, AMI, TVR	Stable or unstable AP, ACS	NA	2·5–3·5	26%	64	31%	1	NA
LONG DES II[53]	500	Binary restenosis	AP or positive stress test, no AMI	≥25	≥2·5	33%	61	36%	5	NP
PROSIT[54]	231	Late lumen loss	AMI or persistent ischaemia 12-24 h	NA	NA	26%	61	26%	NA	NA
SORT OUT II[55]	2098	Combination of cardiac death, AMI, TLR, TVR, TVF	Unstable AP, AMI	NA	NA	15%	64	25%	5	NP
Cervinka et al[56]	70	Neointimal hyperplasia	Signs and/or symptoms of myocardial ischaemia, including AMI	>20	<2·5	25%	56	27%	1	NP
Petronio et al[57]	100	Neointimal hyperplasia	Stable AP or documented ischaemia, no AMI	≥16	2·5–3·7	25%	63	18%	1	NP
Han et al[58]	416	NA	Stable or unstable AP, no AMI	NA	NA	NA	NA	NA	NA	NA
Sirolimus *vs* paclitaxel-eluting *vs* bare-metal stents										
BASKET[13]	826	Combination of cardiac death, AMI, TVR	Stable or unstable AP, AMI	No restrictions	≥4	19%	64	21%	1	NP

ACS=acute coronary syndrome. AMI=acute myocardial infarction. AP=angina pectoris. MF=funding by manufacturer of the stent. NA=data not available. NP=funding by non-profit organisations. PCI=percutaneous coronary intervention. TLR=target lesion revascularisation. TVF=target vessel failure. TVR=target vessel revascularisation. *Or bifurcation, ostial location, or angulation.

Table 1: **Characteristics of included trials**

Investigators or manufacturers provided data for 29 trials.[13,14,20,25–34,36–40,43,46–53,56,57] 18 023 patients were randomised in the 38 included trials (table 1). Nine trials reported data up to 4 years,[20,25–27,31–34,57] eight trials up to 3 years,[29,36,46–48,50–52] eight trials up to 2 years,[13,28,37,40,43,49,53,56] and 13 trials up to 1 year.[14,15,30,35,38,39,41,42,44,45,54,55,58] 29 trials described appropriate methods of allocation concealment.[13,20,27–40,42,43,45–53,56,57] 28 trials reported blind adjudication of clinical outcomes.[13,20,25–40,43,45,47–49,51–53,55,56] We were able to include all randomised patients in the analyses according to the intention-to-treat principle for 31 trials.[13,15,20,25,27,29–38,40,41,43–56]

See Online for webtable

All 38 trials contributed to our analysis of overall mortality. The webtable presents the numbers of events separately for years 1 to 4 for each included trial. 768 patients died during the entire follow-up: 232 of the 4921 patients with bare-metal stents, 263 of the 6331 patients with paclitaxel-eluting stents, and 273 of the 6771 patients with sirolimus-eluting stents. The incidence of death was similar in the three groups (figure 2).

36 trials, with 17 705 enrolled patients, contributed to our analysis of cardiac deaths (webtable).[13–15,20,26–34,36–58] 447 patients died from cardiac causes: 130 of 4763 patients with bare-metal stents, 154 of 6300 with paclitaxel-eluting stents, and 163 of 6642 patients with sirolimus-eluting stents. The incidence of cardiac death was much the same in all three groups (figure 2).

37 trials, with 17 962 enrolled patients, contributed to our analysis of myocardial infarction (webtable).[13–15,20,26–58] 850 myocardial infarctions occurred: 256 in 4891 patients with bare-metal stents, 319 in 6300 patients with paclitaxel-eluting stents, and 275 in 6771 patients with sirolimus-eluting stents. Sirolimus-eluting stents were associated with the lowest incidence of myocardial infarction; the incidence of myocardial infarction was much the same with paclitaxel-eluting and with bare-metal stents (figure 2).

All 38 trials contributed to our analysis of the composite endpoint of death or myocardial infarction (webtable). 1524 patients experienced a myocardial infarction or died: 454 of 4921 patients with bare-metal stents, 556 of 6331 patients with paclitaxel-eluting stents, and 514 of 6771 patients with sirolimus-eluting stents. There was no significant difference in the incidence of the composite endpoint between the different types of stent (figure 2).

27 trials[13,20,25–28,30–34,36–40,43,46–53,56,57] provided data on definite stent thrombosis according to ARC criteria,[11,12] but no events had occurred in three of these trials.[25,36,57]

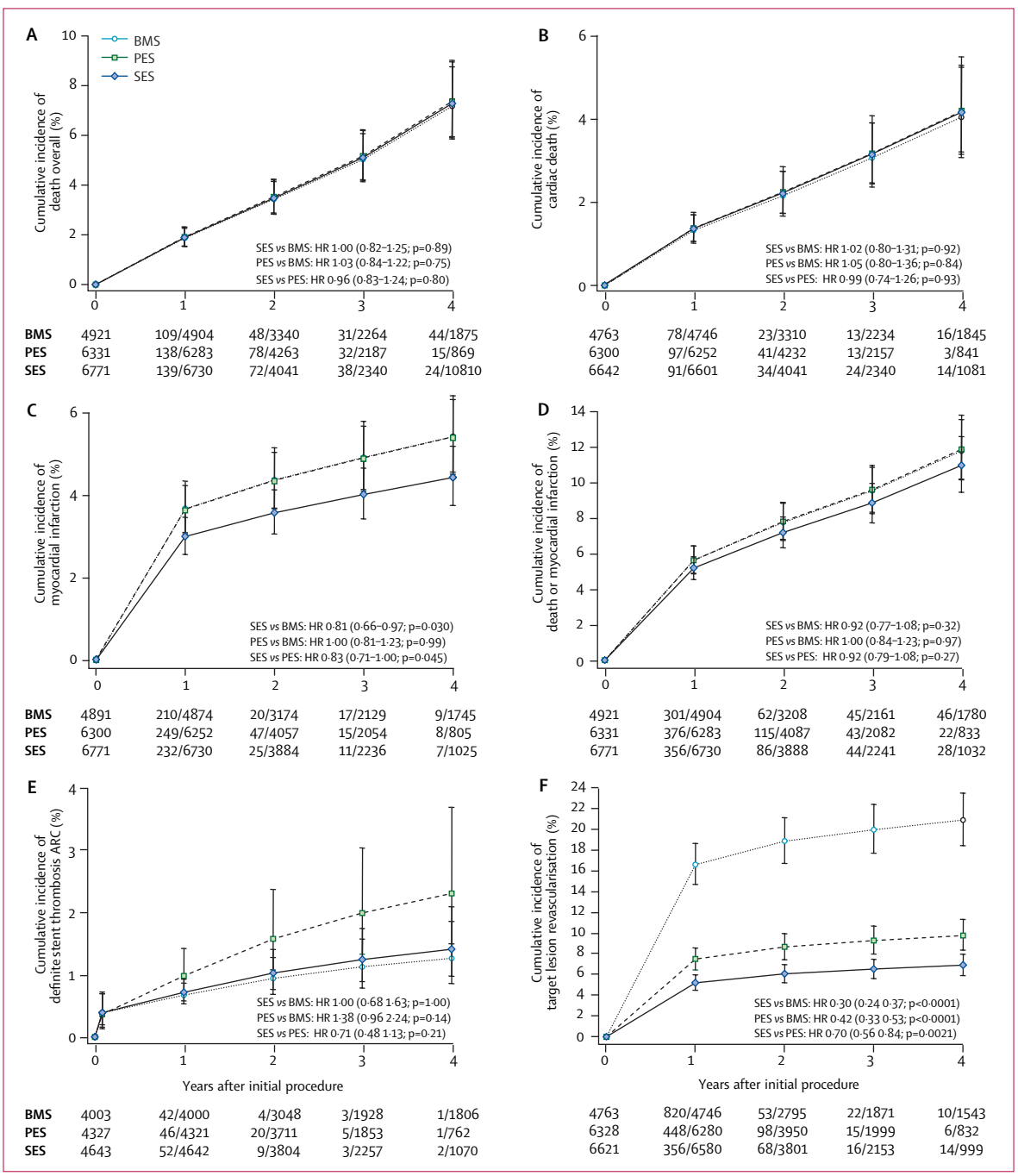

Figure 2: **Cumulative incidences estimated from the network meta-analysis for the three stent types**
(A) Overall mortality, (B) cardiac death, (C) myocardial infarction, (D) composite of death or myocardial infarction, (E) definite stent thrombosis according to ARC definitions, and (F) target lesion revasularisation. Error bars are 95% credibility intervals. Hazard ratios, 95% credibility intervals, and p values estimated from the network meta-analysis for pair-wise comparisons on primary safety outcomes and the secondary effectiveness outcome. Data under each panel are number of events/number of patients. BMS=bare-metal stent. PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent.

	Events				Comparison		
	BMS	PES	SES	Total	SES *vs* BMS	PES *vs* BMS	SES *vs* PES
ARC definition of definite stent thrombosis							
n	4003	4327	4643	12 973			
0 days to 4 years	50	72	66	188	1·00 (0·68–1·63; 1·00)	1·38 (0·96–2·24; 0·14)	0·71 (0·48–1·13; 0·21)
0 to 30 days	28	30	36	94	1·02 (0·46–2·67; 0·96)	0·95 (0·38–2·53; 0·90)	1·05 (0·46–3·17; 0·90)
>30 days to 4 years	22	42	30	94	1·14 (0·62–2·26; 0·71)	2·11 (1·19–4·23; 0·017)	0·54 (0·26–0·98; 0·041)
>30 days to 1 year	14	16	16	46	1·14 (0·45–2·88; 0·78)	1·61 (0·65–4·04; 0·23)	0·68 (0·26–1·64; 0·43)
>1 to 4 years	8	26	14	48	1·43 (0·27–6·24; 0·64)	3·57 (0·86–16·85; 0·071)	0·39 (0·09–1·32; 0·10)
Per-protocol definition of stent thrombosis*							
n	4822	5178	5673	15 673			
0 days to 4 years	57	96	85	238	1·03 (0·59–1·67; 0·92)	1·56 (0·84–2·58; 0·13)	0·65 (0·41–1·06; 0·08)
0 to 30 days	35	35	38	108	0·86 (0·47–1·70; 0·59)	1·01 (0·48–2·07; 0·98)	0·84 (0·42–1·89; 0·63)
>30 days to 4 years	22	47	35	104	1·13 (0·66–2·81; 0·57)	2·36 (1·23–7·00; 0·011)	0·45 (0·25–0·79; 0·011)
>30 days to 1 year	20	20	23	63	0·92 (0·37–1·69; 0·80)	1·32 (0·66–3·07; 0·62)	0·74 (0·32–1·35; 0·32)
>1 to 4 years	2	27	12	41	5·82 (0·88–76·89; 0·07)	20·02 (3·92–221·7; 0·001)	0·30 (0·05–0·98; 0·046)

Comparison data are hazard ratio (95% credibility interval; p value). *Note that we were unable to distinguish between early (day 0 to day 30) and late (day 31 onwards) events for SORT-OUT II,[55] therefore the sum of early and late events according to per-protocol definitions is not equal to the total number of stent thromboses for paclitaxel-eluting and sirolimus-eluting stents. p values for effect by time interaction (0–30 days *vs* >30 days) were 0·84, 0·17, and 0·27 for ARC definitions and 0·58, 0·14, and 0·20 for per-protocol definitions for sirolimus-eluting *vs* bare-metal stents, paclitaxel-eluting *vs* bare-metal stents, and sirolimus-eluting *vs* paclitaxel-eluting stents, respectively. BMS=bare-metal stent. PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent.

Table 2: **Stent thromboses according to ARC criteria for definite stent thrombosis and according to per-protocol definitions used in individual trials**

Therefore, 24 trials, with 12 973 enrolled patients, contributed to our analysis of this endpoint (webtable).[13,20,26–28,30–34,37–40,43,46–53,56] 188 definite stent thromboses were recorded; 94 occurred within 30 days of stent implantation and 94 thereafter (table 2). There was no significant difference in the cumulative incidence of definite stent thrombosis between the three types of stent (figure 2). There was no evidence for any difference in the incidence of early stent thromboses, up to 30 days, between the three types of stent (table 2). However, the risk of late stent thromboses, after 30 days, seemed to be roughly doubled with paclitaxel-eluting stents compared with bare-metal stents and compared with sirolimus-eluting stents (table 2). There was no significant difference in the incidence of late stent thromboses between individuals with sirolimus-eluting and those with bare-metal stents (table 2).

37 trials[13,14,20,25–58] had data available for a secondary analysis of per-protocol defined stent thromboses, but in four of these trials no events had occurred.[25,31,41,57] Therefore, 33 trials, with 15 673 enrolled patients, contributed to the analysis (table 2).[13,14,20,26–30,32–40,42–56,58] In general, differences between paclitaxel-eluting stents and the other two stent types became more pronounced.

37 trials, with 17 712 enrolled patients, contributed to our analysis of target lesion revascularisations (webtable).[13–15,20,25–43,45–58] 1926 target lesion revascularisations were done during the entire follow-up period: 905 in the 4763 patients with bare-metal stents, 567 in the 6328 patients with paclitaxel-eluting stents, and 454 in the 6621 patients with sirolimus-eluting stents. Compared with bare-metal stents, the incidence of target lesion revascularisations was significantly reduced with both drug-eluting stents; the reduction was more

	SES *vs* BMS	PES *vs* BMS	SES *vs* PES
Overall mortality	NNT ∞ (NNT 77 to NNH 56)	NNH 463 (NNT 87 to NNH 63)	NNT 338 (NNT 79 to NNH 56)
Cardiac mortality	NNH 1220 (NNT 122 to NNH 79)	NNH 488 (NNT 122 to NNH 68)	NNT 2381 (NNT 92 to NNH 92)
Myocardial infarction	NNT 99 (NNT 54 to NNT 686)	NNT 6173 (NNT 97 to NNH 80)	NNT 106 (NNT 64 to NNT 4630)
Death or myocardial infarction	NNT 106 (NNT 37 to NNH 106)	NNT ∞ (NNT 53 to NNH 37)	NNT 105 (NNT 40 to NNH 105)
Definite stent thrombosis	NNT ∞ (NNT 256 to NNH 130)	NNH 216 (NNT 2049 to NNH 66)	NNT 155 (NNT 86 to NNH 345)
Late definite stent thrombosis	NNH 805 (NNT 292 to NNH 88)	NNH 100 (NNH 573 to NNH 34)	NNT 113 (NNT 71 to NNT 2105)
Target lesion revascularisation	NNT 7 (NNT 6 to NNT 8)	NNT 8 (NNT 7 to NNT 10)	NNT 35 (NNT 23 to NNT 65)

Data are NNH or NNT (95% credibility interval). BMS=bare-metal stent. NNT=number needed to treat to avoid one event over 4 years. NNH=number needed to harm to cause one event over four years. PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent.

Table 3: **Estimated numbers-needed-to-treat and numbers-needed-to-harm for different outcomes**

	Network meta-analysis							Conventional meta-analysis
	All trials	Allocation concealed	Adjudication blinded	Intention-to-treat analysis	High quality trials	Adjusted for type of stent platform	Adjusted for strut thickness	
Death overall								
SES *vs* BMS	1·00 (0·82–1·25)	1·10 (0·84–1·40)	1·14 (0·91–1·43)	1·05 (0·84–1·40)	1·16 (0·84–1·52)	1·17 (0·91–1·47)	1·00 (0·79–1·25)	1·12 (0·88–1·44)
PES *vs* BMS	1·03 (0·84–1·22)	0·93 (0·77–1·27)	1·06 (0·84–1·36)	0·99 (0·82–1·38)	1·02 (0·72–1·37)	1·15 (0·97–1·53)	0·93 (0·76–1·18)	0·91 (0·72–1·17)
SES *vs* PES	0·96 (0·83–1·24)	1·15 (0·91–1·50)	1·06 (0·85–1·33)	1·02 (0·84–1·26)	1·11 (0·88–1·38)	0·99 (0·80–1·18)	1·05 (0·83–1·26)	0·94 (0·75–1·17)
Cardiac death								
SES *vs* BMS	1·02 (0·80–1·31)	1·08 (0·79–1·53)	1·16 (0·81–1·68)	0·97 (0·66–1·37)	1·06 (0·70–1·54)	1·37 (0·96–1·81)	0·99 (0·67–1·32)	1·21 (0·86–1·69)
PES *vs* BMS	1·05 (0·80–1·36)	1·01 (0·76–1·35)	1·16 (0·80–1·76)	0·96 (0·67–1·29)	1·03 (0·64–1·63)	1·32 (0·91–1·70)	1·06 (0·77–1·25)	0·90 (0·65–1·26)
SES *vs* PES	0·99 (0·74–1·26)	1·10 (0·76–1·44)	0·99 (0·69–1·40)	1·02 (0·76–1·41)	1·02 (0·73–1·57)	1·04 (0·74–1·38)	0·91 (0·71–1·34)	0·88 (0·66–1·17)
Myocardial infarction								
SES *vs* BMS	0·81 (0·66–0·97)	0·84 (0·65–1·04)	0·88 (0·65–1·07)	0·86 (0·72–0·98)	0·85 (0·65–1·07)	0·81 (0·63–1·02)	0·84 (0·68–1·05)	0·86 (0·67–1·09)
PES *vs* BMS	1·00 (0·81–1·23)	1·04 (0·81–1·33)	1·02 (0·76–1·28)	1·03 (0·68–1·18)	1·04 (0·80–1·45)	0·94 (0·72–1·21)	1·03 (0·85–1·23)	1·06 (0·83–1·34)
SES *vs* PES	0·83 (0·71–1·00)	0·80 (0·66–1·01)	0·85 (0·71–1·11)	0·83 (0·70–0·95)	0·82 (0·62–1·00)	0·86 (0·70–1·04)	0·83 (0·69–0·96)	0·84 (0·69–1·02)
Death or myocardial infarction								
SES *vs* BMS	0·92 (0·77–1·08)	0·92 (0·78–1·14)	0·98 (0·82–1·14)	0·91 (0·78–1·09)	0·98 (0·79–1·24)	0·96 (0·78–1·22)	0·85 (0·78–0·98)	0·98 (0·82–1·16)
PES *vs* BMS	1·00 (0·84–1·23)	0·99 (0·84–1·21)	1·05 (0·87–1·24)	0·99 (0·85–1·19)	1·09 (0·89–1·37)	1·07 (0·84–1·31)	1·00 (0·91–1·05)	1·01 (0·85–1·20)
SES *vs* PES	0·92 (0·79–1·08)	0·94 (0·78–1·12)	0·94 (0·79–1·12)	0·93 (0·78–1·06)	0·89 (0·73–1·10)	0·91 (0·77–1·07)	0·85 (0·78–0·99)	0·87 (0·75–1·01)
Definite stent thrombosis								
SES *vs* BMS	1·00 (0·68–1·63)	0·99 (0·55–1·66)	1·11 (0·62–2·09)	1·17 (0·65–2·38)	1·30 (0·65–2·91)	1·31 (0·77–2·30)	1·04 (0·68–1·81)	1·29 (0·80–2·07)
PES *vs* BMS	1·38 (0·96–2·24)	1·24 (0·66–2·12)	1·42 (0·80–2·78)	1·51 (0·81–3·07)	1·85 (0·84–4·12)	2·36 (1·12–4·51)	1·47 (0·94–2·59)	1·20 (0·68–2·11)
SES *vs* PES	0·71 (0·48–1·13)	0·80 (0·49–1·36)	0·77 (0·42–1·51)	0·78 (0·44–1·36)	0·68 (0·40–1·40)	0·61 (0·33–1·04)	0·70 (0·43–1·17)	0·69 (0·45–1·06)
Target lesion revascularisation								
SES *vs* BMS	0·30 (0·24–0·37)	0·28 (0·22–0·37)	0·29 (0·22–0·37)	0·28 (0·21–0·36)	0·27 (0·20–0·36)	0·34 (0·26–0·43)	0·27 (0·22–0·35)	0·40 (0·32–0·51)
PES *vs* BMS	0·42 (0·33–0·53)	0·46 (0·34–0·60)	0·41 (0·31–0·54)	0·41 (0·30–0·55)	0·43 (0·29–0·59)	0·47 (0·38–0·60)	0·43 (0·33–0·54)	0·58 (0·46–0·72)
SES *vs* PES	0·70 (0·56–0·84)	0·62 (0·47–0·80)	0·70 (0·52–0·92)	0·68 (0·50–0·85)	0·64 (0·47–0·89)	0·71 (0·58–0·88)	0·64 (0·52–0·78)	0·76 (0·66–0·88)

Data are hazard ratio (95% credibility interval) for network meta-analyses and risk ratio (95% CI) for standard meta-analyses of direct within-trial comparisons. BMS=bare-metal stent. PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent.

Table 4: **Sensitivity analyses**

pronounced with sirolimus-eluting stents than with paclitaxel-eluting stents (figure 2).

Table 3 presents the estimated NNTs to prevent one event and NNHs to cause one event over 4 years for different outcomes. For the comparison of sirolimus-eluting with bare-metal stents on overall mortality, for example, the NNT was infinity and 95% credibility intervals indicated that results were compatible with both a beneficial effect of sirolimus-eluting compared with bare-metal stents, resulting in an NNT to prevent one event of 77 or more, and with a harmful effect of sirolimus-eluting stents, resulting in an NNH to cause one event of 56 or more.

Table 4 presents results from sensitivity analyses. 29 trials[13,20,27–40,42,43,45–53,56,57] (13 677 patients) contributed to the analyses restricted to trials with adequate concealment, 28 trials[13,20,25–40,43,45,47–49,51–53,55,56] (15 218 patients) to the analyses restricted to trials with blind adjudication of clinical outcomes, 31 trials[13,15,20,25,27,29–38,40,41,43–56] (14 435 patients) to the analyses restricted to trials with an intention-to-treat analysis, and 22 trials[13,20,27,29,31–38,40,43,45,47–49,51–53,56] (10 017 patients) to the analyses restricted to high quality trials satisfying all three criteria.[16] 37 trials[13,14,20,25–58] (17 859 patients) contributed to the analyses adjusted for type of stent platform and adjusted for strut thickness. Results were generally robust to the different analytical approaches used in the sensitivity analyses. When adjusting for the type of stent platform, however, differences in stent thromboses between paclitaxel-eluting stents and the other two stent types tended to become more pronounced. Table 4 also shows risk ratios and 95% CI from conventional random-effects meta-analyses of direct within-trials comparisons. 17 trials[13,20,31–45] (5537 patients) contributed to the comparison of sirolimus-eluting with bare-metal stents, eight trials[13,15,25–30] (4874 patients) to the comparison of paclitaxel-eluting with bare-metal stents, and 15 trials[13,14,46–58] (8438 patients) to the comparison of sirolimus-eluting with paclitaxel-eluting stents. Although CI were wider for these conventional meta-analyses than the credibility intervals in the combined network meta-analyses, point estimates were much the same.

Estimates of statistical heterogeneity between trials were low and criteria for an adequate fit of the model were all satisfied for all outcomes, except target lesion

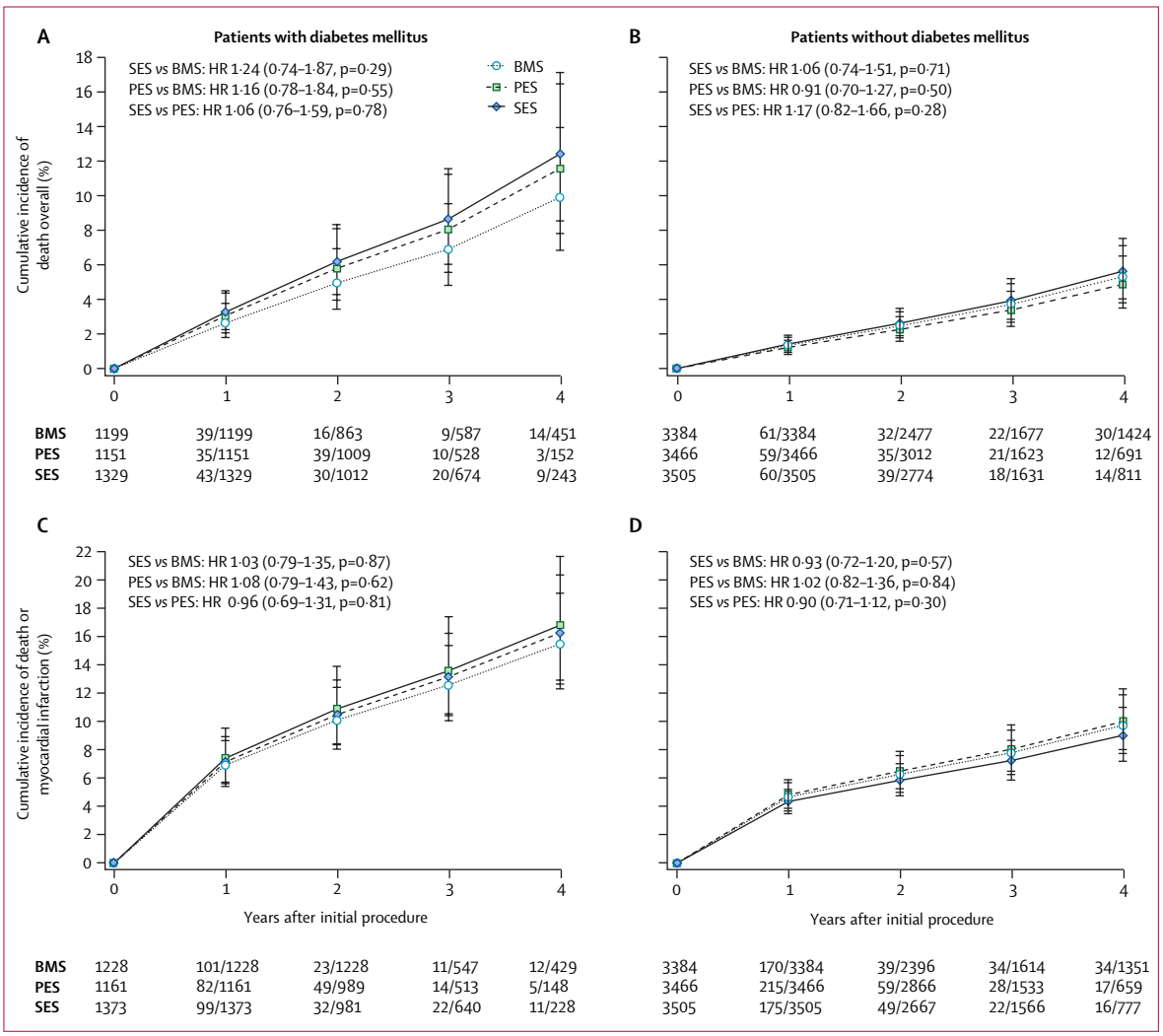

Figure 3: **Stratified analysis according to presence (A, C) or absence (B, D) of diabetes mellitus**
BMS=bare-metal stent. PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent. Error bars are 95% credibility intervals. Hazard ratios are presented with 95% credibility intervals and p values.

See Online for webappendix 2

revascularisation (webappendix 2). Criteria for consistency of the network were all satisfied for all outcomes, except stent thrombosis and target lesion revascularisation (webappendix 2). In conventional meta-analyses, all estimates of statistical heterogeneity between trials were low, except for comparisons of sirolimus-eluting versus bare-metal stents and paclitaxel-eluting versus bare-metal stents on target lesion revascularisation (webappendix 2).

Figure 3 shows analyses for overall mortality and the composite of death or myocardial infarction stratified by the presence or absence of diabetes mellitus. For eight trials[14,15,44,45,54,55,57,58] (3870 patients), we were unable to obtain data separately for diabetic and non-diabetic patients; the remaining 30 trials[13,20,25–43,46–53,56] (14153 patients) contributed to the stratified analyses. 29 trials[13,20,25–43,46–51,53,56] (3762 patients) contributed to the analyses of diabetic patients and 26 trials[13,20,25–35,37–40,43,46,47,49–53,56] (10 355 patients) to the analysis of non-diabetic patients. The presence or absence of diabetes did not alter the effect of any stent on the incidence of death (for interaction, p=0·59 for sirolimus-eluting *vs* bare-metal stents, p=0·38 for paclitaxel-eluting *vs* bare-metal stents, and p=0·70 for sirolimus-eluting *vs* paclitaxel-eluting stents) or on the incidence of the combined outcome of myocardial infarction or death (for interaction, p=0·61 for sirolimus-eluting *vs* bare-metal stents, p=0·79 for paclitaxel-eluting *vs* bare-metal stents, and p=0·74 for sirolimus-eluting *vs* paclitaxel-eluting stents).

Discussion

Our collaborative network meta-analysis indicates that drug-eluting stents and bare-metal stents are associated with similar rates of overall and cardiac mortality, and that use of sirolimus-eluting stents is associated with a reduction in the risk of myocardial infarction compared

with use of bare-metal and paclitaxel-eluting stents. About 100 patients will have to receive sirolimus-eluting stents, rather than bare-metal or paclitaxel-eluting stents, to prevent one myocardial infarction over 4 years.

Although there was little evidence of an overall increase in definite stent thrombosis associated with drug-eluting stents, we found paclitaxel-eluting stents to be associated with an increased incidence of late stent thrombosis compared with bare-metal and sirolimus-eluting stents. Wide credibility intervals precluded definite conclusions about a potential increase of late stent thrombosis with sirolimus-eluting stents compared with bare-metal stents. A secondary analysis showed a marked reduction in target lesion revascularisation with both drug-eluting stents, which was more pronounced for sirolimus-eluting stents than for paclitaxel-eluting stents. About six patients will have to receive a sirolimus-eluting stent rather than a bare-metal stent to prevent one target lesion revascularisation over 4 years; 35 would need to receive a sirolimus-eluting rather than a paclitaxel-eluting stent to prevent one such event. Lastly, we found little evidence of an increased risk of mortality associated with either drug-eluting stent in diabetic patients, but wide credibility intervals precluded definite conclusions.

A recent series of pooled analyses of randomised trials comparing drug-eluting stents with bare-metal stents found little evidence for an increase in mortality or myocardial infarction associated with either drug-eluting stent, and preliminary evidence for an increased risk of late stent thrombosis associated with both drug-eluting stents compared with bare-metal stents.[11,59–61] These analyses included between four[59,60] and 14[61] trials, and between 1748[59,60] and 4958[61] patients. The paucity of trials, patients, and events included in these analyses resulted in imprecise estimates and CI that were compatible with both clinically relevant harms or benefits of drug-eluting stents. In view of their wide CI, results of these previous analyses[5,11,59–62] are all compatible with our study. We included a similar number of patients as a recently published observational study by Lagerqvist and colleagues,[63] which suggested an increased risk of death associated with drug-eluting stents compared with bare-metal stents. Observational studies cannot reliably determine whether there are small to moderate risks or benefits of an intervention.[64] Factors associated with the selected stent type are difficult to control and confounding by indication or other systematic errors have to be considered to be plausible explanations of observed results. Using more reliable evidence from randomised trials, we found similar rates of overall and cardiac mortality associated with drug-eluting and bare-metal stents. A pooled analysis of four trials including 428 diabetic patients by Spaulding and colleagues[59] found a significant increase in mortality with sirolimus-eluting stents compared with bare-metal stents. These results are difficult to interpret: the number of patients was small and the mortality rate of diabetic patients was surprisingly low among those with bare-metal stents.[59] Chance could therefore have contributed to Spaulding and colleagues' results, despite their statistical significance. Our analysis of 3762 diabetic patients reduced the play of chance and provided little evidence for an increased mortality associated with sirolimus-eluting stents, even though wide credibility intervals indicate that our results are compatible with both clinically relevant benefits or harms.

The increase in the risk of ARC-defined definite late stent thrombosis that we found for paclitaxel-eluting stents compared with bare-metal stents was lower—but more precise—than the increase reported in a pooled analysis by Stone and colleagues.[60] The use of per-protocol definitions for stent thrombosis by Stone and colleagues[60] could have resulted in an overestimation of the risk increase associated with paclitaxel-eluting stents. Our results suggest that late stent thrombosis occurs less frequently with sirolimus-eluting stents than with paclitaxel-eluting stents, which is concordant with a recent observational study by Daemen and colleagues.[1] With regard to target lesion revascularisation, our results are compatible with those from the two largest trials—REALITY[51] and SORT OUT II[55]—which failed to show a significant difference in target lesion revascularisation between the two drug-eluting stents. CI were wide for both trials[51,55] and overlap with those from our analysis. The HR of the largest study, SORT OUT II,[55] tended to be closer to one than the HR in our study. SORT OUT II[55] did not include scheduled, protocol driven clinical follow-ups. Instead, data were ascertained from death and hospital registries, which could have resulted in diagnostic misclassification and biased estimates of differences between the two drug-eluting stents.[65]

Our network meta-analysis integrated evidence from direct and indirect comparisons while fully preserving randomisation. The considerably higher number of patients and events of our study, compared with previous analyses,[11,59–61] resulted in a relevant gain in statistical precision, particularly for the HR of death, myocardial infarction, and stent thrombosis. As with conventional meta-analyses,[3,5,59–62,66–72] some will argue that we have not compared like with like. However, our model was based on relative treatment effects (log HR) and variations in patient or lesion characteristics between trials are fully accounted for in the analysis by maintaining randomised comparisons within each trial. Network meta-analysis makes similar assumptions to standard meta-analysis of direct within-trial comparisons, but requires that these assumptions hold over the entire set of trials in the network,[9] including the assumption that relative treatment effects comparing two interventions in different trials are from the same common distribution.[21] The smaller the heterogeneity between trials, the more likely relative treatment effects originate from the same

distribution. Additional assumptions are that the model fits the data and that the network of trials is consistent.

We carefully monitored heterogeneity between trials, goodness of fit of the model, and consistency of the network and found all assumptions satisfied for all outcomes, except for stent thrombosis and target lesion revascularisation. Some will argue that our results are therefore less reliable for these two outcomes. However, for stent thrombosis the goodness of fit of the model was excellent and estimates of between-trial heterogeneity were low. In addition, a p value for inconsistency of 0·69 suggested that the observed inconsistency could have been due to chance alone. Conversely, the goodness of fit of the model was not optimal for target lesion revascularisation and there was some evidence for heterogeneity between trials and inconsistency of the network. However, the differences between stent types in target lesion revascularisation rates were large, and results from conventional random-effects meta-analyses of direct within-trial comparisons were concordant with results from the network meta-analysis (table 4). Furthermore, there was no heterogeneity between trials for the comparison of sirolimus-eluting versus paclitaxel-eluting stents on target lesion revascularisation, neither in network meta-analysis nor in conventional meta-analysis (webappendix 2). Results were also robust in sensitivity analyses restricted to trials of high methodological quality and after adjusting for the strut thickness or the type of stent platform used. We believe, therefore, that our estimates are reliable also for stent thrombosis and target lesion revascularisation.

One of the strengths of our study is the standardised definition of outcomes. Most importantly, we used ARC definitions of definite stent thrombosis,[11,12] which avoids the exclusion of secondary stent thromboses occurring after a patient had undergone a target lesion revascularisation. Excluding secondary stent thromboses violates the intention-to-treat principle and favours stents that are associated with high rates of target lesion revascularisation. 11 trials[14,15,29,35,41,42,44,45,54,55,58] were excluded from the analysis because we were unable to obtain data in accordance with ARC definitions of definite stent thrombosis. Data for per-protocol definitions of stent thromboses were available for 37 trials.[13,14,20,25–58] These definitions resulted in the exclusion of secondary stent thromboses occurring 2–4 years after the initial procedure, especially in those with bare-metal stents (at least six events were excluded, compared with the main analysis of ARC-defined definite stent thromboses); therefore, our HR of stent thromboses according to per-protocol definitions comparing drug-eluting with bare-metal stents were biased toward higher estimates (table 2). We did not obtain data for the composite of probable and definite stent thrombosis. Therefore, our estimates of the cumulative incidence of stent thrombosis could be too conservative.[11,12] We were unable to obtain data for target lesion revascularisation in three trials,[13–15] and used data for target vessel revascularisation as a proxy measure. When these three trials were excluded from the analysis, we found similar results for target lesion revascularisation (data not shown).

Our estimates of NNT and NNH were based on the cumulative incidences estimated in the network meta-analysis. Incidences seen in routine populations could be higher, resulting in lower NNT and NNH. However, estimates from the SIRTAX trial,[49] which enrolled unselected patients, were much the same as those seen here. Finally, we could include only 30 trials in the stratified analyses according to presence or absence of diabetes. These trials yielded imprecise mortality estimates, precluding definite conclusions for the subgroup of patients with diabetes.

This collaborative network meta-analysis of randomised controlled trials indicates that overall and cardiac mortality associated with drug-eluting stents and bare-metal stents are similar. Relevant harms associated with sirolimus-eluting stents compared with bare-metal stents are unlikely, while rates of target lesion revascularisation and myocardial infarction are lower with sirolimus-eluting stents than with paclitaxel-eluting and bare-metal stents. We conclude, therefore, that sirolimus-eluting stents seem to be clinically better than bare-metal and paclitaxel-eluting stents.

Contributors

PJ and CSt conceived the study. PJ, CSt, SWa, SA, and SWi were responsible for conception and design of the study. SWa, PJ, CSt, SA, MZ, SR, and ST did the analysis and interpreted the analysis in collaboration with PD, BM and SWi. CSt, SA, AK, MCM, AS, MEP, GWS, MBL, JSdL, JJG, SJP, MS, MJS, HK, CSp, MM, PV, MTD, PC, ASP, AJN, PD, BM, SWi, and PJ were responsible for the acquisition of data. PJ, CSt, SWa, SA, ST, and SWi wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript. CSt, SR, and PJ obtained public funding. Administrative, technical, and logistical support were provided by PJ, CSt, PD, BM, MZ, and SWi.

Conflict of interest statement

CSt, SR, and PJ have received unrestricted grants from the Swiss National Science Foundation. AK has received lecture fees from Bristol-Myers Squibb, Cordis, GlaxoSmithKline, Lilly, Medtronic, Novartis, and Sanofi-Aventis. AS has received unrestricted grant support for the Department of Cardiology he chairs from Amersham/General Electric, Bayerische Forschungsstiftung, Bristol-Myers Squibb, Cordis, Cryocath, Guidant, Medtronic, Nycomed, and Schering. MEP has received lecture fees from Medtronic. GWS has received consulting fees from Boston Scientific, Abbott, Guidant, Xtent, and BMS Imaging, and has received lecture fees from Boston Scientific, Abbott, and Medtronic, has equity interests in Devax and Xtent, and is a member of the board of directors of Devax. MBL has received consulting fees from Cordis, Medtronic, Boston Scientific, and OrbusNeich and has equity interests in Conor, Medinol, and OrbusNeich. JJG is in the advisory board of Boston Scientific and has received research grant support from Cordis. SJP has received research grant support from Cordis. HK has received unrestricted grant support from Cordis. CSp has received consulting and lecture fees from Cordis, Boston Scientific, Abbot, Lilly and Pfizer. MTD has received lecture fees from Boston Scientific. BM has received research grant support of various stent companies, including Cordis and Boston Scientific, and has taken part in the speaker bureaux of various stent companies, including Cordis and Boston Scientific. SWi has received lecture and consulting fees from Abbot, Biotronic, Biosensors, Boston Scientific, Cordis, and Medtronic. GWS and MBL are directors of the Cardiovascular Research Foundation, a public charity affiliated with Columbia University Medical Center, from which they receive no compensation; the Cardiovascular Research

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