Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials

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Summary

Background The safety and efficacy of drug-eluting stents (DES) in the treatment of coronary artery disease have been assessed in several randomised trials. However, none of these trials were powered to assess the safety and efficacy of DES in women because only a small proportion of recruited participants were women. We therefore investigated the safety and efficacy of DES in female patients during long-term follow-up.

Methods We pooled patient-level data for female participants from 26 randomised trials of DES and analysed outcomes according to stent type (bare-metal stents, early-generation DES, and newer-generation DES). The primary safety endpoint was a composite of death or myocardial infarction. The secondary safety endpoint was definite or probable stent thrombosis. The primary efficacy endpoint was target-lesion revascularisation. Analysis was by intention to treat.

Findings Of 43 904 patients recruited in 26 trials of DES, 11 557 (26·3%) were women (mean age 67·1 years [SD 10·6]). 1108 (9·6%) women received bare-metal stents, 4171 (36·1%) early-generation DES, and 6278 (54·3%) newer-generation DES. At 3 years, estimated cumulative incidence of the composite of death or myocardial infarction occurred in 132 (12·8%) women in the bare-metal stent group, 421 (10·9%) in the early-generation DES group, and 496 (9·2%) in the newer-generation DES group (p=0·001). Definite or probable stent thrombosis occurred in 13 (1·3%), 79 (2·1%), and 66 (1·1%) women in the bare-metal stent, early-generation DES, and newer-generation DES groups, respectively (p=0·01). The use of DES was associated with a significant reduction in the 3 year rates of target-lesion revascularisation (197 [18·6%] women in the bare-metal stent group, 294 [7·8%] in the early-generation DES group, and 330 [6·3%] in the newer-generation DES group, p<0·0001). Results did not change after adjustment for baseline characteristics in the multivariable analysis.

Interpretation The use of DES in women is more effective and safe than is use of bare-metal stents during long-term follow-up. Newer-generation DES are associated with an improved safety profile compared with early-generation DES, and should therefore be thought of as the standard of care for percutaneous coronary revascularisation in women.

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Introduction

Drug-eluting stents (DES) are a technological breakthrough for the percutaneous treatment of coronary artery disease.[1] In several randomised trials, improved clinical outcomes have been reported consistently with early-generation DES—releasing sirolimus and paclitaxel—compared with bare-metal stents, mainly attributable to the substantial reduction in the need for repeat revascularisation.[2] More recently, newer-generation DES were introduced with thinner stent struts, more biocompatible or biodegradable polymer coatings, and novel antiproliferative agents.[1] These devices improved safety and efficacy profiles compared with early-generation DES in several randomised trials and meta-analyses,[3–5] which has resulted in the widespread use of DES during the past decade. Although the safety and efficacy of DES are well established, only about 25% of patients enrolled in each trial were women. Indeed, percutaneous coronary interventions with DES implantation are the most common interventions in medicine,[1] with more than 500 000 patients receiving DES in the USA every year and a third of the procedures are done in women.[6] Data for safety and efficacy of DES in women are sparse because their inclusion in randomised clinical trials is restricted. In response to the US Food and Drug Administration (FDA) guidance for the assessment of sex differences in clinical studies of medical devices,[7] the Women in Innovation Initiative convened the Gender Data Forum to discuss the outcomes of DES in women.[8] This forum led to the request to investigate the efficacy and safety profiles of DES in women with an individual patient-level data pooled analysis from available randomised trials of DES. Here, we report the findings of this analysis.

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Methods

Study population

The rationale for the current analysis, list of trials, analytic strategies, and prespecified endpoints were generated during the Gender Data Forum (convened on Sept 24, 2012, in Washington, DC, USA). Subsequently, principal investigators and device manufacturers participating in the Gender Data Forum were contacted to obtain patient-level data for female participants from randomised trials of DES in patients with coronary artery disease. All of the contacted investigators agreed with the analysis plan and shared data in a preformatted extraction sheet. Overall, female participants from 26 randomised trials were pooled: RAVEL,[9] SIRIUS,[10] E-SIRIUS,[11] C-SIRIUS,[12] TAXUS I,[13] TAXUS II SR,[14] TAXUS IV,[15] TAXUS V,[16] SIRTAX,[17] ENDEAVOR II,[18] ENDEAVOR III,[19] ENDEAVOR IV,[20] SPIRIT II,[21] SPIRIT III,[22] SPIRIT IV,[23] BASKET-PROVE,[24] COMPARE I,[25] COMPARE II,[26] EXCELLENT,[27] RESET,[28] RESOLUTE AC,[29] TWENTE,[30] LEADERS,[31] ISAR-TEST 4,[32] PRODIGY,[33] and PROTECT.[34] There were no inclusion or exclusion criteria except willingness to provide data. Table 1 shows a summary of the characteristics of the trials included in this study. All trials were done between 2000 and 2013. Inclusion

	Year of publication	Patients	Women	Stents used	Key inclusion criteria	Key exclusion criteria	Minimum duration of dual antiplatelet treatment
RAVEL[9]	2002	238	58 (24%)	Cypher, bare-metal stent	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	2 months
SIRIUS[10]	2003	1058	305 (29%)	Cypher, bare-metal stent	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	3 months
E-SIRIUS[11]	2003	352	103 (29%)	Cypher, bare-metal stent	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	2 months
C-SIRIUS[12]	2004	100	31 (31%)	Cypher, bare-metal stent	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	3 months
TAXUS I[13]	2003	61	7 (11%)	Taxus, bare-metal stent	Stable coronary artery disease or unstable angina, single lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	6 months
TAXUS II SR[14]	2003	267	67 (25%)	Taxus, bare-metal stent	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	6 months
TAXUS IV[15]	2004	1314	367 (28%)	Taxus, bare-metal stent	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	6 months
TAXUS V[16]	2005	1156	353 (31%)	Taxus, bare-metal stent	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	6 months
SIRTAX[17]	2005	1012	231 (23%)	Cypher, Taxus	Stable coronary artery disease, unstable angina, or acute myocardial infarction	None	12 months
ENDEAVOR II[18]	2006	1197	283 (24%)	Endeavor, bare-metal stent	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	3 months
ENDEAVOR III[19]	2006	436	133 (31%)	Endeavor, Cypher	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	3 months
ENDEAVOR IV[20]	2010	1548	500 (32%)	Endeavor, Taxus	Stable coronary artery disease or unstable angina, single de-novo lesion	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	6 months
PROTECT[34]	2012	8709	2061 (24%)	Endeavor, Cypher	Stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction	None	12 months
RESOLUTE AC[29]	2010	2292	529 (23%)	Resolute, Xience	Stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction	None	6 months
TWENTE[30]	2012	1391	382 (27%)	Resolute, Xience	Stable coronary artery disease, unstable angina, or non-ST-elevation myocardial infarction	ST-elevation myocardial infarction	12 months
SPIRIT II[21]	2006	300	80 (27%)	Xience, Taxus	Stable coronary artery disease or unstable angina, maximum two de-novo lesions	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	6 months
SPIRIT III[22]	2008	1002	314 (31%)	Xience, Taxus	Stable coronary artery disease or unstable angina, maximum two de-novo lesions	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	6 months
SPIRIT IV[23]	2010	3687	1189 (32%)	Xience, Taxus	Stable coronary artery disease or unstable angina, maximum three de-novo lesions	Non-ST-elevation myocardial infarction or ST-elevation myocardial infarction	12 months
COMPARE I[25]	2010	1800	526 (29%)	Xience, Taxus	Stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction	None	12 months
BASKET-PROVE[24]	2010	2314	565 (24%)	Xience, Cypher, bare-metal stent	Stable coronary artery disease, unstable angina, or acute myocardial infarction, target vessel diameter ≥3·0 mm	None	12 months

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	Year of publication	Patients	Women	Stents used	Key inclusion criteria	Key exclusion criteria	Minimum duration of dual antiplatelet treatment
(Continued from previous page)							
EXCELLENT[27]	2011	1443	512 (35%)	Xience, Promus, Cypher	Stable coronary artery disease, unstable angina, or non-ST-elevation myocardial infarction	ST-elevation myocardial infarction	6 months
RESET[28]	2012	3197	742 (23%)	Xience, Cypher	Stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction	None	3 months
PRODIGY[33]	2012	2013	473 (23%)	Xience, Promus, Endeavor, Taxus, bare-metal stent	Stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction	None	6 months
LEADERS[31]	2008	1707	430 (25%)	Biomatrix, Cypher	Stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction	None	12 months
COMPARE II[26]	2013	2707	693 (26%)	Nobori, Xience, Promus	Stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction	None	12 months
ISAR-TEST 4[32]	2009	2603	623 (24%)	Yukon, Xience, Cypher	Stable coronary artery disease, unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction	None	6 months

Data are number or number (%), unless otherwise indicated.

Table 1: **Summary of included trials**

	Total (n=11 557)	Bare-metal stent (n=1108)	Early-generation DES (n=4171)	Newer-generation DES (n=6278)	p value
Age (years)	67·1 (10·6)	66·6 (10·5)	67·2 (10·7)	67·1 (10·5)	0·23
Body-mass index (kg/m²)	28·1 (5·8)	28·8 (6·2)	28·1 (5·9)	27·9 (5·6)	0·003
Risk factors					
Diabetes	31·2% (3602/11 556)	27·8% (308/1108)	32·0% (1338/4170)	31·1% (1956/6278)	0·02
Insulin-dependent diabetes	10·4% (1162/11 161)	9·8% (109/1108)	10·6% (423/3995)	10·3% (630/6098)	0·63
Hypertension	75·6% (8738/11 556)	77·4% (857/1107)	75·8% (3165/4171)	75·1% (4716/6278)	0·23
Hypercholesterolaemia	67·6% (7792/11 534)	67·8% (750/1107)	67·7% (2820/4164)	67·4% (4222/6263)	0·60
Smoking	26·7% (3074/11 523)	23·6% (262/1108)	26·7% (1109/4156)	27·2% (1703/6259)	0·047
Family history of coronary artery disease	39·5% (4165/10 547)	44·7% (362/810)	40·0% (1485/3718)	38·5% (2318/6019)	<0·0001
Clinical history					
Myocardial infarction	19·0% (2184/11 510)	24·3% (269/1108)	18·7% (777/4162)	18·2% (1138/6240)	<0·0001
Percutaneous coronary interventions	20·6% (2275/11 051)	16·2% (139/859)	20·9% (819/3917)	21·0% (1317/6275)	0·02
Coronary artery bypass surgery	5·0% (574/11 545)	4·7% (52/1103)	4·9% (206/4167)	5·0% (316/6275)	0·95
Multivessel disease	28·8% (2850/9908)	22·8% (196/860)	25·3% (891/3517)	31·9% (1763/5531)	<0·0001
Indication for percutaneous coronary interventions					<0·0001
Stable coronary artery disease	56·2% (6194/11 021)	52·6% (503/957)	59·2% (2329/3937)	54·9% (3362/6127)	
Acute coronary syndromes	43·8% (4827/11 021)	47·4% (454/957)	40·8% (1608/3937)	45·1% (2765/6127)	
Angiographic characteristics					
Lesions per patient*	1·3 (0·6)	1·2 (0·5)	1·2 (0·5)	1·3 (0·6)	<0·0001
Number stents per patient†	1·5 (0·9)	1·3 (0·8)	1·4 (0·7)	1·5 (0·9)	<0·0001
Mean stent diameter, mm‡	2·9 (0·4)	3·0 (0·4)	3·0 (0·3)	2·9 (0·3)	0·0002
Mean stent length, mm§	29·1 (18·7)	25·6 (15·7)	27·7 (16·9)	30·7 (20·1)	<0·0001
At least one type B2 or C lesion	63·4% (5687/8968)	67·0% (436/651)	63·0% (1962/3112)	63·2% (3289/5205)	0·14
At least one bifurcation lesion	18·7% (1052/5619)	12·8% (98/763)	19·9% (360/1807)	19·5% (594/3049)	<0·0001

Data are % (n/N) or mean (SD), unless otherwise indicated. DES=drug-eluting stents. *10 530 patients analysed (859 in the bare-metal stent group, 3673 in the early-generation DES group, and 5998 in the newer-generation DES group). †11 318 patients analysed (1108 in the bare-metal stent group, 4054 in the early-generation DES group, and 6156 in the newer-generation DES group). ‡7516 patients analysed (1103 in the bare-metal stent group, 2728 in the early-generation DES group, and 3685 in the newer-generation DES group). §10 117 patients analysed (1105 in the bare-metal stent group, 3602 in the early-generation DES group, and 5410 in the newer-generation DES group).

Table 2: **Baseline characteristics of women in the pooled analysis of 26 trials**

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criteria differed between trials, from including only patients with stable coronary artery disease to all comers. However, there were no randomised trials of the use of DES in specific subsets of patients and lesions.

All trials included in our analysis complied with the provisions of the Declaration of Helsinki, and the study protocols were approved by the institutional review board at each study centre. All patients provided written informed consent for participation in each study.

DES

The DES investigated in the trials that were included in our analysis were the sirolimus-eluting stents (Cypher and Cordis, Johnson & Johnson, Miami Lakes, FL, USA), paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, MA, USA), everolimus-eluting stents (Xience, Abbott Vascular, Santa Clara, CA, USA; Promus, Boston Scientific), zotarolimus-eluting stents (Endeavor, Medtronic, Santa Rosa, CA, USA; Resolute, Medtronic), biolimus (umirolimus)-eluting stents with biodegradable polymer coating (Biomatrix, Biosensors, Newport Beach, CA, USA; Nobori, Terumo, Tokyo, Japan), and sirolimus-eluting stents with biodegradable polymer coating (Yukon, Translumina, Hechingen, Germany). For the analysis, coronary stents were grouped as bare-metal stents, early-generation DES, and newer-generation DES. Early-generation DES were sirolimus-eluting Cypher stents and paclitaxel-eluting Taxus stents. Newer-generation DES were everolimus-eluting Xience and Promus stents, zotarolimus-eluting Endeavor and Resolute stents, biolimus-eluting Biomatrix and Nobori stents, and sirolimus-eluting Yukon stents.

Endpoints

The prespecified primary safety endpoint was the composite of death or myocardial infarction. The prespecified primary efficacy endpoint was target-lesion revascularisation. The secondary safety endpoint was definite or probable stent thrombosis. Other secondary endpoints were the individual components of the primary safety endpoint, definite stent thrombosis, and major cardiac adverse events (defined as the composite

	Total (n=11 557)	Bare-metal stent (n=1108)	Early-generation DES (n=4171)	Newer-generation DES (n=6278)	p value (overall)	p value (early *vs* newer DES)
Death or myocardial infarction						
0–3 years	1049 (10·3%)	132 (12·8%)	421 (10·9%)	496 (9·2%)	0·001	0·01
0–1 year	728 (6·3%)	92 (8·4%)	269 (6·5%)	367 (5·9%)	0·01	0·22
1–3 years	321 (4·2%)	40 (4·8%)	152 (4·8%)	129 (3·6%)	0·02	0·009
Death						
0–3 years	547 (5·7%)	62 (6·3%)	225 (6·0%)	260 (5·3%)	0·22	0·13
0–1 year	282 (2·5%)	27 (2·5%)	107 (2·6%)	148 (2·4%)	0·79	0·50
1–3 years	265 (3·3%)	35 (3·9%)	118 (3·5%)	112 (2·9%)	0·16	0·14
Myocardial infarction						
0–3 years	590 (5·5%)	81 (7·7%)	233 (6·0%)	276 (4·8%)	0·0003	0·03
0–1 year	497 (4·3%)	71 (6·5%)	181 (4·4%)	245 (3·9%)	0·001	0·28
1–3 years	93 (1·3%)	10 (1·3%)	52 (1·7%)	31 (0·9%)	0·01	0·003
Definite or probable stent thrombosis						
0–3 years	158 (1·6%)	13 (1·3%)	79 (2·1%)	66 (1·1%)	0·01	0·002
0–1 year	112 (0·9%)	10 (0·9%)	48 (1·2%)	54 (0·9%)	0·32	0·14
1–3 years	46 (0·6%)	3 (0·4%)	31 (0·9%)	12 (0·3%)	0·002	0·001
Definite stent thrombosis						
0–3 years	94 (0·9%)	8 (0·8%)	53 (1·4%)	33 (0·6%)	0·0005	0·0001
0–1 year	74 (0·7%)	6 (0·6%)	38 (0·9%)	30 (0·5%)	0·02	0·007
1–3 years	20 (0·3%)	2 (0·3%)	15 (0·5%)	3 (0·07%)	0·007	0·002
Target-lesion revascularisation						
0–3 years	821 (8·0%)	197 (18·6%)	294 (7·8%)	330 (6·3%)	<0·0001	0·005
0–1 year	615 (5·5%)	174 (16·0%)	205 (5·0%)	236 (3·9%)	<0·0001	0·004
1–3 years	206 (2·7%)	23 (2·9%)	89 (2·9%)	94 (2·6%)	0·59	0·49
Major adverse cardiac events†						
0–3 years	1682 (16·3%)	294 (27·7%)	636 (16·5%)	752 (14·1%)	<0·0001	0·002
0–1 year	1214 (10·6%)	240 (21·9%)	425 (10·3%)	549 (8·8%)	<0·0001	0·01
1–3 years	468 (6·4%)	54 (7·5%)	211 (6·9%)	203 (5·8%)	0·04	0·047

Data are number (%), unless otherwise indicated. DES=drug-eluting stents. *Cumulative incidences from Kaplan-Meier estimates of the time to first occurrence of the adverse event. †Composite of death, myocardial infarction, and target-lesion revascularisation.

Table 3: **Clinical outcomes during 3 years of follow-up***

of death, myocardial infarction, or target-lesion revascularisation). Definitions of clinical endpoints used in the trials included in this analysis are summarised in the appendix pp 1–3. Definitions of myocardial infarction differed between the 26 trials. Stent thrombosis was consistently defined in accordance with the Academic Research Consortium criteria in all the trials.[35] Definition of target-lesion revascularisation was also consistent. In the BASKET-PROVE and PRODIGY trials, target-lesion revascularisation was not available and target-vessel revascularisation was used as surrogate endpoint.

Statistical analysis

All patient-level data were aggregated and combined as one dataset on a prespecified extraction sheet. Baseline clinical, demographic, and procedural characteristics of the stent groups (ie, bare-metal stents, early-generation DES, and newer-generation DES) were compared with linear regression for continuous variables and χ^2 tests for categorical variables. Cumulative event rates in the stent groups were calculated with the Kaplan-Meier method and compared with the log-rank test. Because of the different follow-up times for the groups, event rates and comparisons were calculated for 0–3 years, 0–1 year, and 1–3 years. For these analyses, the total follow-up was defined as the time from index procedure until death, last follow-up date or 3 years, whichever came first. Separate comparisons were done for all stent groups and for early-generation versus newer-generation DES. The independent associations between stent group and outcomes were assessed with the Cox proportional hazards models that included a frailty term (γ) to assess random effects in the trials.[36,37] Frailties are the unmeasured factors that affect trial-specific baseline risk and are distributed as γ random variables with a mean of 1 and variance θ. The variance parameter is interpreted as a metric of heterogeneity in baseline risk between trials. The likelihood ratio test was used to test the significance of the variance parameter. The bare-metal stent group was the reference category for all analyses. Stent group, age, and baseline variables showing significant differences between groups were included as covariates in the multivariable model (body-mass index, diabetes, previous myocardial infarction, family history of coronary artery disease, previous percutaneous intervention for multivessel disease, smoking, presentation with an acute coronary syndrome, number of stents per patient, and type B2 or C lesions). We judged p values of less than 0·05 to be significant and all analyses were done with Stata (version 12.1).

Role of the funding source

There was no direct funding for the gathering of these data, statistical analyses, or drafting of this report. GGS, UB, and RM had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Of 43 904 patients recruited in 26 randomised trials of DES, 11 557 (26·3%) were women and therefore included in this analysis. Mean follow-up was 2·9 years (SD 1·4) for the overall cohort, and 3·3 years (1·5) in the bare-metal stent group, 3·2 years (1·4) in the early-generation DES group, and 2·6 years (1·4) in the newer-generation DES

See Online for appendix

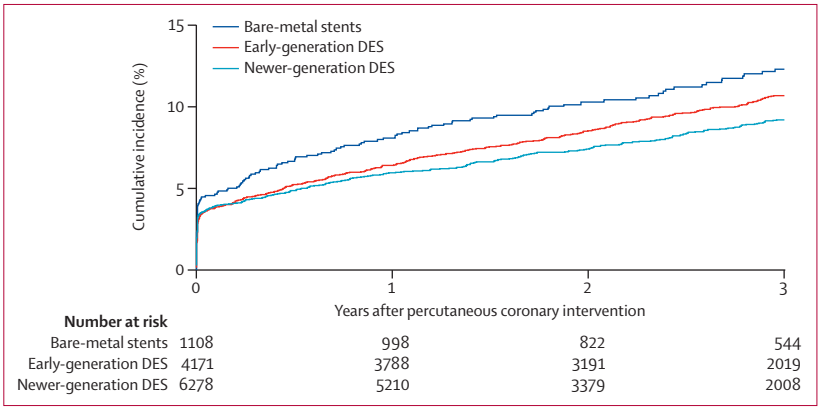

Figure 1: **Cumulative event rates of death or myocardial infarction during 3 years of follow-up**
DES=drug-eluting stents.

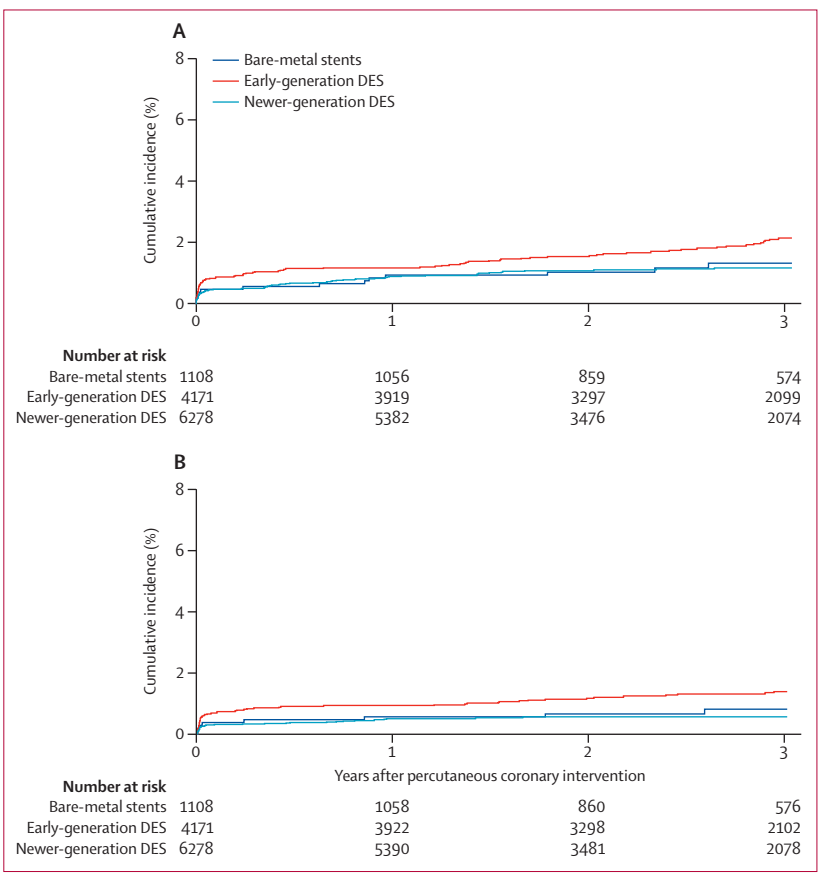

Figure 2: **Cumulative event rates of definite or probable stent thrombosis (A), and definite stent thrombosis (B) during 3 years of follow-up**
DES=drug-eluting stents.

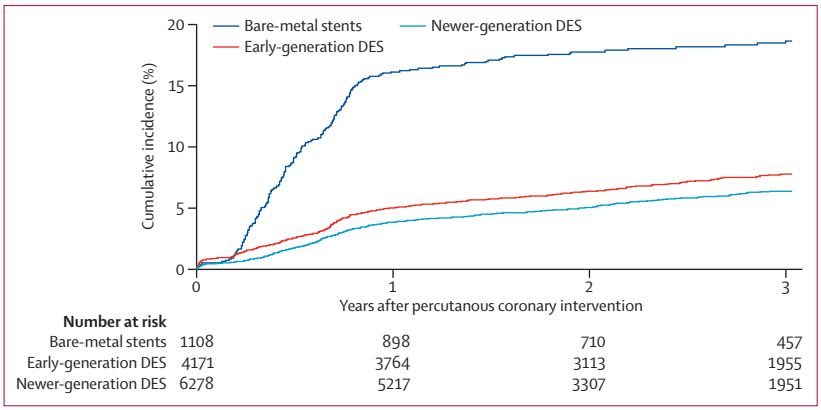

Figure 3: **Cumulative event rates of target-lesion revascularisation during 3 years of follow-up**
DES=drug-eluting stents.

group. Table 2 shows the baseline clinical characteristics of the overall female population and the women stratified according to stent type. The mean age of the study population was 67·1 years, and 31·2% had diabetes, 75·6% had hypertension, 67·6% had hypercholesterolaemia, 26·7% were smokers, and 28·8% had multivessel disease (table 2). Clinical indications for revascularisation were acute coronary syndromes in 43·8% of women (table 2).

1108 (9·6%) of 11557 women were allocated to bare-metal stents, 4171 (36·1%) to early-generation DES, and 6278 (54·3%) to newer-generation DES in the 26 trials (table 2). With respect to baseline clinical characteristics, significant differences were noted between patients allocated to bare-metal stents, early-generation DES, and newer-generation DES in body-mass index, smoking, family history of coronary artery disease, previous myocardial infarction, previous percutaneous coronary intervention, multivessel disease, and clinical presentation at the time of percutaneous coronary intervention (table 2). With respect to angiographic and procedural characteristics, we noted differences between groups in number of lesions treated, number of stents implanted, stent diameter, stent length, and treatment of bifurcation lesions (table 2).

Table 3 summarises the clinical outcomes. The composite of death or myocardial infarction occurred in 10·3% of 11557 women (table 3). 5·7% of the women died and 5·5% had myocardial infarction (table 3). 1·6% of the women had definite or probable stent thrombosis and 0·9% had definite stent thrombosis (table 3). Target-lesion revascularisation occurred in 8·0% of women (table 3).

At 3 years of follow-up, the cumulative incidence of death or myocardial infarction was higher in women in the bare-metal stent group (12·8%) than in those in the early-generation (10·9%) and newer-generation DES groups (9·2%; table 3). Figure 1 shows the cumulative event rates of death or myocardial infarction according to stent type during 3 years of follow-up. Death occurred with similar rates in the three groups (6·3% in bare-metal stent group, 6·0% in early-generation DES group, and 5·3% in newer-generation DES group; table 3). Myocardial infarction was significantly more frequent in women in the bare-metal stent group (7·7%) than in those in the early-generation DES group (6·0%) and newer-generation DES group (4·8%; table 3). Figure 2 shows cumulative event rates of definite or probable stent thrombosis and definite stent thrombosis according to stent type during 3 years of follow-up. At 3 years, the cumulative incidence of definite or probable stent thrombosis was lower in women in the bare-metal stent group (1·3%) than in those given early-generation DES (2·1%) but higher than in women given newer-generation DES (1·1%; figure 2A; table 3). Similar findings were noted for definite stent thrombosis (0·8%, 1·4%, and 0·6%; figure 2B; table 3). Differences in definite or probable stent thrombosis were mainly related to very late (≥1 year after stent implantation) stent thrombosis (table 3). The use of newer-generation DES was associated with significantly lower rates of death or myocardial infarction, definite or probable stent thrombosis, and definite stent thrombosis than was the use of early-generation DES (table 3).

Figure 3 shows cumulative event rates of the target-lesion revascularisation according to stent type during 3 years of follow-up. At 3 years, the cumulative incidence of target-lesion revascularisation (primary efficacy endpoint) was higher in women in the bare-metal stent group (18·6%) than in those in the early-generation DES (7·8%) and newer-generation DES groups (6·3%; table 3; figure 3). Moreover, women given newer-generation DES had significantly lower rates of target-lesion revascularisation than did those given early-generation DES at 3 years (table 3).

Table 4 shows the results of the multivariable analysis. The risks of death or myocardial infarction, definite or

	Bare-metal stent	Early-generation DES (HR, 95% CI)	p value	Newer-generation DES (HR, 95% CI)	p value	p value (early *vs* newer DES)
Death or myocardial infarction	1·00	0·94 (0·69–1·27)	0·67	0·70 (0·51–0·97)	0·03	0·002
Definite or probable stent thrombosis	1·00	0·95 (0·41–2·17)	0·91	0·55 (0·24–1·26)	0·16	0·02
Target-lesion revascularisation	1·00	0·46 (0·33–0·65)	<0·0001	0·44 (0·31–0·64)	<0·0001	0·68

HRs calculated for 3 year outcomes with random-effects Cox proportional hazards models with the trial included as a random effect. Models were adjusted for stent group, age, body-mass index, diabetes, myocardial infarction history, family history of coronary artery disease, history of percutaneous intervention, multivessel coronary artery disease, acute coronary syndromes, smoking, number of stents, and type B2 or C lesions. DES=drug-eluting stents. HR=hazard ratio.

Table 4: **Adjusted risk for outcomes associated with early-generation and newer-generation DES compared with bare-metal stents**

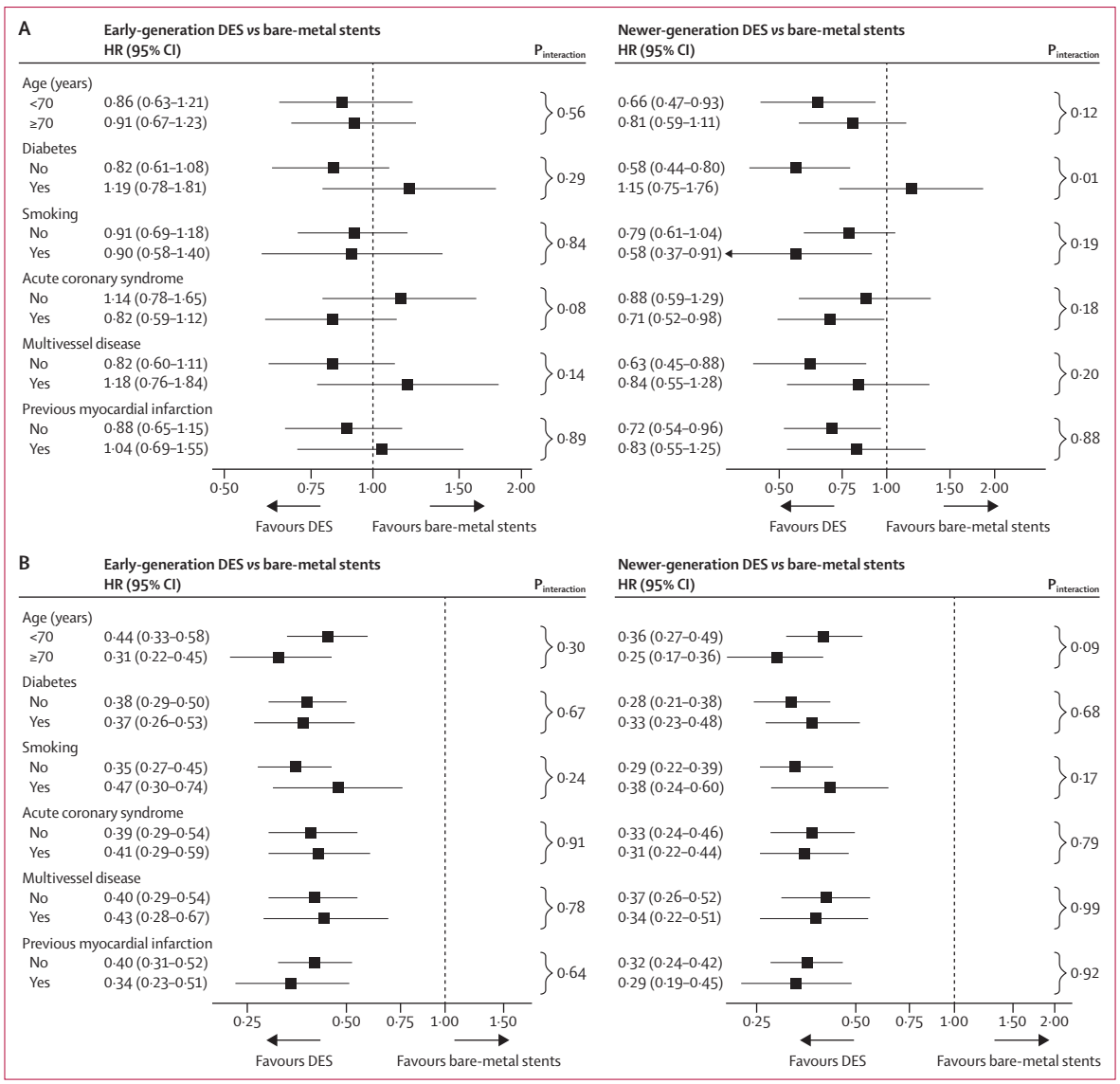

Figure 4: **Stratified analysis of death or myocardial infarction (A) and target lesion revacularisation (B)**
DES=drug-eluting stents. HR=hazard ratio.

probable stent thrombosis myocardial infarction, and target-lesion revascularisation myocardial infarction with early-generation DES and newer-generation DES compared with bare-metal stents remained similar before and after adjustment for baseline differences between groups (table 4). Values of the frailty parameter θ for heterogeneity were significant for the outcomes of death or myocardial infarction (θ=0·15; p<0·0001) and target-lesion revascularisation (θ=0·19; p<0·0001), whereas no heterogeneity was detected for definite or probable stent thrombosis (θ=0·09; p=0·16).

Figure 4 shows the stratified analyses of death or myocardial infarction and target-lesion revascularisation; the findings were similar for the main subgroups. Formal tests for interaction indicated a significant interaction between treatment effect and diabetes status for the comparison between newer-generation DES and bare-metal stents ($p_{interaction}$=0·01). No other significant interaction was noted.

Discussion

According to the results of our pooled analysis of 26 trials, roughly a quarter of the participants recruited in randomised clinical trials of DES are women. The use of DES is safe and effective in women compared with bare-metal stents. Newer-generation DES have further improved safety and efficacy profiles compared with the early-generation DES in women.

The use of DES has been shown to be effective and safe in patients with coronary artery disease in several

randomised trials in the previous decade. Accordingly, DES represent the standard of care in contemporary clinical practice and are used in more than 80% of patients undergoing percutaneous coronary interventions.[6] Although representing more than 30% of patients receiving these devices, only a small proportion of women are enrolled in randomised clinical trials of DES. The results of a few small-scale post-hoc analyses of randomised trials suggest a similar benefit of DES to bare-metal stents in women and men.[38–41] A similar effectiveness of DES with respect to angiographic restenosis was also noted in women and men in a pooled analysis of three randomised trials with angiographic surveillance.[41] Moreover, a large-scale analysis of the CathPCI registry showed favourable and similar risk reductions for major adverse cardiac events with DES compared with bare-metal stents in women and men, with no evidence of interaction between sex and stent type.[42] However, the size and observational nature of these reports precludes any definitive conclusions about the safety and efficacy of DES in women. An assessment of cardiovascular premarket approvals showed persistent under-representation of women in medical device studies.[43] In December 2011, the US Food and Drug Administration released a guidance document for the assessment of sex differences in medical device clinical studies, prompting reports of medical device outcomes in women to improve the quality and consistency of available data for the performance of medical devices in this patient population.[7] Subsequently, a Gender Data Forum to discuss the safety and efficacy of DES in women was organised by the Women in Innovation Initiative.[8]

As a result of the Gender Data Forum, we have provided a comprehensive summary of DES outcomes in women enrolled in the major randomised clinical trials of DES. Our findings support the use of DES in women by providing robust evidence of safety and efficacy of DES compared with bare-metal stents. Outcomes of DES in women are consistent with those in large all-comer patient populations including both sexes. The use of DES—including both early-generation and newer-generation devices—has no effect on overall mortality rate and greatly reduces the risk of repeat revascularisation compared with the use of bare-metal stents.[2,5] The use of early-generation DES has been associated with stent thrombosis during the very late follow-up (≥1 year) after stent implantation.[44] This limitation has been addressed by the development of newer-generation DES that have improved biocompatibility and are associated with a significant reduction in the risk of stent thrombosis compared with earlier platforms.[4,5,23,25] Findings from a network meta-analysis also suggest a lower risk of stent thrombosis with newer-generation DES than with bare-metal stents.[45] Concordant improvements in efficacy have also been noted with newer-generation versus earlier-generation DES.[4,5,23,25] The findings from our large pooled analysis were consistent with these results. Women treated with DES and bare-metal stents had similar risks of death. By contrast, both types of DES significantly reduced target-lesion revascularisation compared with bare-metal stents and benefits were increased with the use of newer-generation versus earlier-generation DES. Additionally, women treated with early-generation DES had a higher risk of stent thrombosis and very late stent thrombosis than did those treated with bare-metal stents. Conversely, the risks of stent thrombosis and very late stent thrombosis were significantly reduced in women treated with newer-generation DES. Notably, efficacy and safety outcomes improved with newer-generation DES despite the more complex clinical and angiographic characteristics.

Findings from subgroup analyses are concordant with our overall results. The interaction between treatment effect and diabetes status was significant with newer-generation DES compared with bare-metal stents. The findings of a pooled analysis comparison of newer-generation DES and early-generation DES in patients with and without diabetes were similar.[46] Indeed, patients with diabetes have increased risks of stent-related events and coronary artery disease progression.[47] However, because of the exploratory nature of this comparison and the interaction tests, this finding should be thought of as being hypothesis-generating and needs prospective confirmation.

The collaborative nature of the present investigation needs to be appraised. For the purpose of this pooled analysis, all of the contacted principal investigators and device manufacturers shared individual patient data for female participants in major randomised trials of DES. This collaborative effort shows the need for these types of analyses for minority groups (eg, based on sex or ethnic origin) that are under-represented in clinical trials.

To the best of our knowledge, this study is the first comprehensive large-scale analysis of the safety and efficacy of DES in women (panel). Our findings might be particularly robust because they are derived from

***Panel:* Research in context**

Systematic review

We searched PubMed for complete reports of randomised trials for the comparison of drug-eluting stents (DES) and bare-metal stents specifically in women, without language restrictions published up to Aug 1, 2013. No randomised trial was identified.

Interpretation

The findings of our patient-level pooled analysis of 11 557 women from 26 randomised trials indicate that use of DES is safe and effective compared with bare-metal stents in women during long-term follow-up (≤3 years). Additionally, the results show important changes in outcome of both safety and efficacy with device iteration. The risk of death or myocardial infarction was highest with bare-metal stents followed by early-generation DES and lowest with newer-generation DES. Similarly, target-lesion revascularisation was lowest with newer-generation DES. Therefore, this analysis shows for the first time, to the best of our knowledge, that the improved outcome in women in terms of safety with newer-generation DES did not compromise but rather improved efficacy.

individual patient-level data of prospective, randomised clinical trials, with data monitoring of adverse events and event adjudication by clinical event committees. Nevertheless this pooled analysis has several limitations. First, the trials included in the patient-level pooled analysis were done over one decade, during which clinical practice has changed. The changes in clinical practice other than the types of stents used might have affected the clinical outcomes. However, we accounted for differences between studies by including trial as a random effect in our adjusted analyses. Second, patient populations included in the 26 pooled trials had some heterogeneity. Early trials focused on patients with only stable coronary artery disease and single lesions, whereas later trials had broader criteria to include more patients with multivessel disease and acute coronary syndromes. Nevertheless, to reduce this heterogeneity, trials with focus on specific subsets of patients and lesions (eg, acute myocardial infarction, left main disease, chronic total occlusions, and bifurcation lesions) were not included in our analysis. Additionally, we included trial as a random effect in our analyses. Third, the inclusion and exclusion criteria for individual trials restricts the generalisability of our findings. Nevertheless, the analysed population included 44% of patients with an acute coronary syndrome at baseline, 31% with diabetes, and 29% with multivessel disease (table 2), similar to routine clinical practice. Fourth, the exclusion of data for male participants from this analysis precluded sex-specific analyses and is a limitation. Although sex-based differences after percutaneous coronary intervention have been assessed in several reports,[38–42] we are unable to comment on whether or not our findings in women are generalisable to men, nor can we establish whether there is a difference in outcomes between the sexes. Last, the 26 trials included in this patient-level pooled analysis were not primarily intended to investigate outcomes in women. Female patients represent a subgroup and our study therefore has intrinsic limitations for subgroup analyses.[48] Although we extracted data from randomised trials, the post-hoc nature of this subgroup analysis is likely to have the same biases that might arise in observational designs. To overcome these limitations, we adjusted for possible confounders and assessed associations in different intervals. As with any observational study, we cannot rule out the possibility of residual confounding on our point estimates. However, analysis of device safety and efficacy specifically in women is justified by their different biological risk profile.[48] Moreover, the credibility of our findings is supported by sex being a prespecified variable in all of the included trials, the prevalence of women was homogeneous across included trials, and our findings are consistent with available randomised trials and registries of the assessment of DES in patient populations comprising both women and men.

In conclusion, based on our findings, the use of DES in women is more effective and safe than is the use of bare-metal stents during long-term follow-up. Newer-generation DES are associated with an improved safety profile compared with early-generation DES, and should therefore be thought of as the standard of care for percutaneous coronary revascularisation in women.

Contributors

GGS, UB, and RM were responsible for conception and design of the study. GGS, UB, SS, and RM undertook and interpreted the analysis in collaboration with SW, GWS, MBL, GW, WW, EC, PGS, PCS, CVB, DK, SG, TK, GM, H-SK, MV, AK, PWS, DI, RO, LM, RJ, AC, and M-CM. GGS, UB, SW, and RM wrote the first draft of the report. All authors critically revised the report for important intellectual content and approved the final version.

Conflicts of interest

SW has received research contracts to the institution from Abbott, Boston Scientific, Biosensors, Cordis, and Medtronic. WW has received institutional research grants from Boston, Medtronic, Abbott, Terumo, Biosensors, and is an investigator for sponsored trials by Boston, Medtronic, Abbott, Terumo, and Biosensors. Fees or honoraria on behalf of WW from Boston, Medtronic, Abbott, Terumo, and Biosensors go to the Cardiovascular Center Aalst. CVB is a consultant to and has received lecture fees or travel expenses from Abbott Vascular, Biotronik, Boston Scientific, Medtronic, and Merck Sharp and Dohme. CVB's research department Thoraxcentrum Twente has received educational or research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. DK has received research or grant support from Medtronic, Abbott, Boston Scientific, and consulting honoraria from Medtronic and Boston Scientific. MV has received honoraria for lectures or advisory board and research grants from Merck, Iroko, Eli Lilly, and Medtronic; honoraria for advisory board and lectures from Medicines Company, Eli Lilly, Daiichi Sankyo, St Jude, and Abbott Vascular; and honoraria for lectures from Cordis, Carbostent and Implantable Devices, and Terumo. SG has received grant support from St Jude, Abbot, Terumo, and Biotronik, and advisory board honorarium from Eli Lilly and Servier. PGS received honorarium from Medtronic as a steering committee member in the PROTECT trial. RM has received institutional research grant support from the Medicines Company, Bristol-Myers Squibb and Sanofi-Aventis, and Lilly and Daiichi Sankyo, and consulting fees from Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, Janssen Pharmaceuticals, Maya Medical, Merck, Regado Biosciences, and Sanofi-Aventis, and serves on the advisory board of Covidien, Janssen Pharmaceuticals, and Sanofi-Aventis.

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