EuroIntervention

Safety and efficacy of drug-eluting stents versus bare-metal stents in saphenous vein grafts lesions: a meta-analysis

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KEYWORDS
Saphenous vein graft, coronary artery bypass graft, drug-eluting stent, bare-metal stent

Abstract

Aims: Controversy exists about the safety and efficacy of drug-eluting stents (DES) in saphenous vein bypass grafts (SVGs). The aim of this study was to perform a meta-analysis of all published studies comparing DES and bare-metal stents (BMS) in patients with SVGs disease.

Methods and results: We included 22 studies comparing DES versus BMS in 5,543 patients with SVGs disease. The primary efficacy endpoint was target vessel revascularisation (TVR). The primary safety endpoint was mortality. Other outcomes of interest were cardiac mortality, myocardial infarction, target lesion revascularisation (TLR), stent thrombosis and a combined of major adverse cardiac events (MACE). DES significantly reduced the risk of TVR, OR=0.56 (95% CI, 0.41-0.76, p=0.0003) and TLR, OR=0.58 (95% CI, 0.41-0.81; p=0.001). Total mortality and cardiac mortality were significantly lower in DES versus BMS, OR=0.69 (95% CI, 0.49-0.98, p=0.04) and OR=0.71 (95% CI, 0.51-0.99; p=0.04), respectively. The overall risk of stent thrombosis, and myocardial infarction were not significantly different for patients receiving DES vs. BMS. Total MACE were significantly lower in patients receiving DES, OR=0.55 (95% CI, 0.42-0.71; p<0.00001).

Conclusions: This meta-analysis suggests that the use of DES in patients with SVG lesions is associated with a reduction of the need of reintervention and mortality compared with BMS.

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Introduction

Drug eluting stents (DES) have demonstrated to reduce restenosis, and the need for subsequent revascularisation procedures of the target vessel, by means of reducing the degree of neo-intimal hyperplasia when treating native coronary arteries[1]. However, controversy still remains regarding the safety and efficacy of DES in saphenous vein aortocoronary bypass grafts (SVGs). Unlike native coronary arteries, degenerated SVGs usually show diffuse and friable atherosclerotic plaques characterised by abundant lipid debris that tend to embolise during percutaneous coronary intervention (PCI)[2]. Also the mechanism of in-stent restenosis in SVGs may differ from that of native coronary arteries with delayed endothelialisation, accelerated atherosclerosis and profound inflammation and thrombotic tendency[3]. These factors could partially mitigate the beneficial effect of DES.

Several small observational studies and a very few randomised clinical trials evaluating DES outcomes in SVGs after up to one year follow-up showed a net beneficial effect compared with bare-metal stent (BMS), mainly reducing the risk of reintervention[4-12]. However, some concerns have been raised regarding to the safety of DES in patients with SVGs disease. Data from a recent small randomised clinical trial, DELAYED RRISC[13], a secondary *post hoc* analysis of the RRISC trial, have suggested that DES may be associated with an increased rate of mortality, and late stent thrombosis at an average of three years of follow-up. Also very recently, results of other observational studies have been reported with contradictory conclusions regarding the use of DES in SVGs[14-18].

All these observational studies and randomised clinical trials had insufficient power to assess the risk of rare complications, such as mortality. For this reason, we performed a meta-analysis from 22 studies comparing DES with BMS to evaluate the safety and efficacy of DES in patients with SVGs disease.

Methods

Selection of the studies

In order to identify the studies to be included, we conducted a computerised bibliographic search of the MEDLINE database (National Library of Medicine, Bethesda, MD, USA) until December 2009. We selected all the studies that compared DES and BMS in patients with SVGs stenosis and provided clinical follow-up data. Various combinations of the following keywords were used: saphenous, vein graft, coronary artery bypass graft, stent, drug-eluting stent, bare-metal stent, coronary surgery. All potentially relevant articles were independently reviewed according to the following inclusion criteria by two investigators (A.S-R and S. J-V) to establish eligibility for the meta-analysis: 1) study that had comparison between DES and BMS in patients with SVG disease; 2) mean duration of follow-up of at least six months; 3) reporting clinical events. Disagreements were resolved by discussion with a third reviewer (RM). When more than one article originated from the same centre, the study that reported more patients and more follow-up was included.

The flow chart of the strategy and selection of studies is depicted in Figure 1. A total of 23 studies were identified. One study was excluded because a study from the same institution was reported later with more patients and follow-up[19].

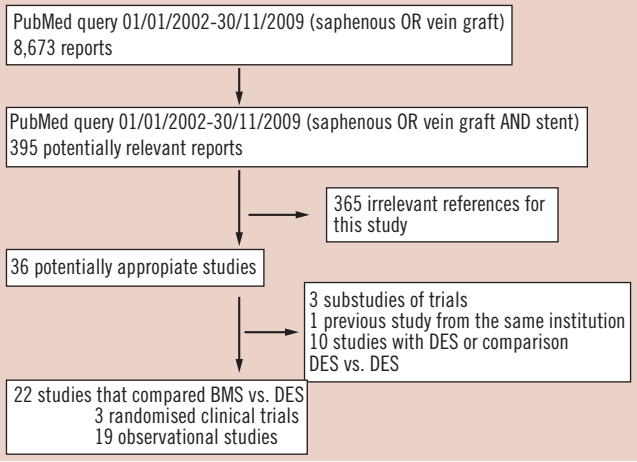

Figure 1. Flowchart of selected studies.

Study outcome

The primary efficacy endpoint of this meta-analysis was the need of reintervention of the target vessel (TVR). The primary safety endpoint was total mortality. Other outcomes of interest were cardiac death, myocardial infarction, target lesion revascularisation (TLR), stent thrombosis, and a combined endpoint of major adverse cardiac events (MACE). The event definitions used in individual studies are given in Table 1. Table 2 shows the number of patients included in each study, as well as the period of time, type of DES, primary outcome of the study, antiplatelet therapy duration, clinical and angiographic follow-up.

Statistical analysis

Review Manager 5.0 (The Cochrane Collaboration, The Nordic Cochrane Centre 2008, Copenhagen, Denmark) was used. Odds ratios (OR) for binary end-points and 95% confidence intervals (CI) were calculated by comparing DES with BMS rates using raw data for each study and for the pooled population. The review was conducted according to the meta-analysis of observational studies of observational studies in epidemiology (MOOSE) recommendations[20]. Heterogeneity among studies was assessed by the Q test and, as this test is not good enough when evaluating a small number of studies, the level of inconsistency was also assessed by I^2 test[21,22]. Although heterogeneity was not found for mortality, a number of sources of heterogeneity were anticipated *a priori*, therefore, Der Simonian and Laird random effects model was used to estimate summary measures and their 95% CI, making an adjustment to the study weights according to the extent of variation based on the inverse variance approach. The effect of each study was weighted for its number of patients. A sensitivity analysis was performed according the clinical follow-up (equal or shorter than one year of follow-up vs. longer than one year), population size (<200 vs. >200 patients) and study quality (randomised vs.

Table 1. Endpoints definitions in each study.

Author	Death (D)	Myocardial Infarction (MI)	Target vessel revascularisation (TVR)	Target lesion revascularisation (TLR)	Stent thrombosis (ST)	MACE
Lozano	NR	CK-MB elevation ≥2 or Troponin T ≥10 upper normal level	NR	NR	NR	NR
Twisk	Cause of D accordingly ICD-10 classification	CK-MB elevation ≥3 upper normal level	Clinically driven repeat revascularisation (percutaneous or surgical)	NR	Angiographically thrombus or TIMI 0-1 accompanied by acute symptoms	All-cause D, zMI and TVR
Minutello	Cardiac unless a clear non-cardiac cause was identified	Ischaemic symptoms or ECG changes in the setting of either CK>2 times normal or new Q-waves on ECG. Periprocedural MI if the CK was at least 3 times the upper limit of normal (295 IU/L) with elevated CK-MB	Clinically driven revascularisation of the target lesion or any segment of SVG or the epicardial coronary artery distal to the SVG anastomoses.	Any clinically driven repeat revascularisation of the original target lesion in the presence of a diameter stenosis >50% by quantitative angiography	According to the Academic Research Consortium definition of probable or definite ST	Cardiac D, MI, TVR
Okabe	NR	Q-wave MI : new pathologic Q-wave on ECG and CK-MB ≥2 times upper normal limit. Non-Q-wave MI: CK-MB ≥2 without Q-waves	Repeat revascularisation that was caused by any stenosis in the initially treated SVG	Repeat revascularisation either percutaneous or surgical, within the original stent segment or within 5 mm of the stent edges	Angiographically documented partial or total stent occlusion or ST-elevated or non-ST elevated MI in the territory of the treated vessel when ST could not be excluded definitely	D, Q-wave MI, TLR
Ellis	NR	Non-Q MI: CK-MB >3 x upper limit of normal	NR	NR	NR	NR
Goia	NR	STEMI required troponin or CK-MB elevation, ST elevation at least in 2 contiguous leads. Periprocedural MI were not counted in primary endpoint	Any intervention to the same graft during follow-up	Reintervention by of the target vessel for restenosis of the stent including 5 mm proximal or distal to it	NR	Cardiac D, STEMI, TLR
Applegate	Cardiac unless a clear non-cardiac cause was identified	Ischaemic symptoms and an elevation of CK-MB or troponin I above upper limit, with or without ST elevation or development of Q-waves	NR	NR	Presentation with ACS and angiographic or pathologic evidence of stent thrombosis, unexplained death within 30 days, or target vessel infarction in the absence of angiography	Cardiac D, MI
Hoffmann	NR	NR	NR	NR	NR	D, MI, ST, TLR, TVR
Ge	Cardiac unless a clear non-cardiac cause was identified	Non-Q-wave MI: CK-MB ≥3 upper limit of normal without Q waves. Q-wave MI: in addition were new pathological Q-waves	Repeat revascularisation within the treated vessel	Repeat revascularisation secondary to a stenosis ≥50% within the stent or the 5-mm borders	Angiographic intrastent filling defect or stent occlusion associated with a clinical event, unexplained sudden death, or MI after stent implantation and without concomitant demonstration of a patent stent	Cardiac D, MI, TLR, TVR,

Table 1. Endpoints definitions in each study. (Continued)

Author	Death (D)	Myocardial Infarction (MI)	Target vessel revascularisation (TVR)	Target lesion revascularisation (TLR)	Stent thrombosis (ST)	MACE
Vignali	NR	CK-MB elevation >2 upper normal level	Repeat intervention within the treated vessel, including the target lesion	Repeat revascularisation to treat a luminal stenosis ≥50% within stent or the 5-mm edges	NR	All-cause D, MI, TVR
Ramana	Cardiac unless a clear non-cardiac cause was identified	Periprocedural MI was defined as significant ECG ischaemic changes with elevated cardiac biomarkers.	NR	Repeat revascularisation procedure (PCI or CABG) as a result of restenosis in the stented segment.	According to the Academic Research Consortium definition of possible, probable or definite ST	All-cause D, MI, TVR, TLR
Lee	NR	Ischaemic symptoms with new pathologic Q-waves or CK elevation ≥3 upper limit of normal	Repeat revascularisation due to significant stenosis within the treated vessel with anginal symptoms or evidence of ischaemia	NR	NR	D, MI, TVR
Assali	NR	MI was confirmed by documentation of the referring physician	New revascularisation in the target vessel, also including TLR	Repeat revascularisation (PCI or CABG) as result of restenosis in stented segment	Definite ST: acute coronary event associated to angiographic or autopsy documentation of partial or total stent occlusion or thrombosis	D, MI, TVR, TLR
Bansal	All deaths were considered cardiac unless otherwise documented	Standard definitions were used to identify MI	Clinically driven revascularisation of target vessel associated with both ischaemic symptoms and stenosis ≥50%, or stenosis ≥70%	Clinically driven revascularisation of target lesion associated with both ischaemic symptoms and stenosis ≥50%, or stenosis ≥70%	Angiographic documentation of intrastent filling defect or stent occlusion associated with a clinical event	
Vermeersch	All deaths were considered cardiac unless a clear non-cardiac cause could be established	MI was defined as new ischaemic event with CK-MB > 2 times the upper limit of normal, or ECG presence of new pathologic Q-waves. Periprocedural MI: CK-MB > 3 times above upper limit of normal	New revascularisation procedure in the target vessel, also including TLR	Repeated revascularisation procedure (PCI or CABG), as the result of restenosis in the stented segment	According to the Academic Research Consortium definition of possible, probable or definite ST	
Kaplan	All deaths were considered cardiac unless otherwise documented	New pathologic Q-waves or elevation CK-MB >3 times the upper limit of normal (non-Q-wave MI)	Any repeat revascularisation on the vessel treated, involving the treated segment or other segments	Repeat revascularisation secondary to stenosis ≥50% in the stent or within 5 mm	According to the Academic Research Consortium definition of probable or definite ST	D, MI, TVR, TLR
Jeger	NR	Non-fatal MI: typical symptoms with CK-MB or troponin T elevation above the upper limit or typical ST changes in ECG at the time of symptoms	Clinical event since control angiography was not allowed without symptoms or signs of ischaemia.	NR	NR	D, MI, TVR
Whöhrle	NR	NR	NR	NR	NR	D, Q-MI,TVR

Table 1. Endpoints definitions in each study. (Continued)

Author	Death (D)	Myocardial Infarction (MI)	Target vessel revascularisation (TVR)	Target lesion revascularisation (TLR)	Stent thrombosis (ST)	MACE
Goswami	NR	Chest pain accompanied by new, typical ECG changes and biochemical evidence of myocardial necrosis		Reintervention of the stented segment for clinical manifestations: myocardial ischaemia or > 70% stenosis on follow-up angiogram	According to the Academic Research Consortium definition of probable or definite ST	CD, MI, TLR, definite or probable ST
Shishehbor	NR	Troponin elevation with ECG changes or angina	NR	NR	NR	D, MI, TLR
Brodie	NR	New elevation CK-MB >2 times normal and included both ST-segment elevation and non-ST-segment elevation.	Repeat procedure anywhere in the target vessel, including repeat PCI or CABG.	NR	According to the Academic Research Consortium definition of probable or definite ST	TVR
Brilakis	All deaths were considered to be cardiac unless an unequivocal non-cardiac cause could be established	MI: typical rise and fall of troponin or CK-MB above the upper limit of normal, with either ischaemic symptoms or ECG changes indicative of ischaemia. Post-PCI MI was defined as a postprocedural rise in CK-MB > 3 times the upper limit of normal	Repeat PCI or CABG performed in the target vessel in association with angina or objective evidence of myocardial ischaemia	Repeat PCI or CABG performed because of restenosis of the target lesion in association with angina or objective evidence of myocardial ischaemia	According to the Academic Research Consortium definition of probable or definite ST	D, MI, TVR, TLR and TVF

MACE: major adverse cardiac events; TVF: target vessel failure.

Table 2. Characteristics of studies included in the meta-analysis.

Author	Study design	N° patients	Setting	Period SES/PES (%)	Type of DES	Primary outcome (months)	Clopidogrel + Aspirin	FU months (%)	Angio FU
Lozano et al	Cohort	211	Multicentre	1999-2007	42/47	CD, TVR	NR	30	No routine
Van Twisk et al	Cohort	250	Single centre	2000-2005	NR/NR	MACE (D, MI, TVR)	DES (6) BMS (3) *	48	No routine
Minutello et al	Cohort	109	Single centre	2000-2005	100/0	MACE (D, MI, TVR)	DES (3) BMS (1) **	20	No routine
Okabe et al	Cohort	482	Single centre	2000-2006	64/36	MACE (D, Q-MI, TLR)	DES (≥6) MBS (1)	12	No routine
Ellis et al	Matched control	350	Multicentre	2000-2003	100/0	TVR BMS (26% 12 m)	DES (39% 12 m)	12	No routine
Gioia et al	Cohort	225	Multicentre	2002-2006	45/46	MACE (CD, STEMI, TLR)	DES (3-6) BMS (1)**	24	No routine
Applegate et al	Propensity score matching	148	Single centre	2002-2005	91/9	MACE (CD, MI)	DES (3-6) BMS (1)**	24	No routine
Hoffmann et al	Cohort	120	Multicentre	2002-2004	0/100	MACE (D, MI, TVR, TLR)	DES (6) BMS (1)**	6	DES: 79% BMS: 85%
Ge et al	Cohort	150	Single centre	2002-2004	57/43	MACE (D, MI, TVR, TLR)	DES (3-6) BMS (1)**	6	DES: 71% BMS: 69%
Vignali et al	Cohort	360	Multicentre	2003-2006	69/31	MACE (D, MI, TVR)	DES (≥6) BMS (1) **	12	No routine
Ramana et al	Cohort	311	Multicentre	2003-2007	100/0	All-cause D	DES (3) BMS (3) **	34	No routine
Lee et al	Cohort	223	Single centre	2003-	73/27	MACE (D, MI, TVR)	NR	9	DES: 30% BMS: 67%
Assali et al	Cohort	111	Single centre	2003-2005	89/11	MACE (D, MI, TVR, TLR)	DES (6) BMS (1)**	24	No routine
Bansal et al	Cohort	109	Single centre	2003-2005	95/-	MACE (CD, MI, TLR)	NR	33	No routine
Vermeersch et al	Randomised	75	Single centre	2003-2006	100/0	LLL at 6 month *Post hoc* analysis: All-cause D	DES (2) BMS (2)	36	DES: 94% BMS: 100%
Kaplan et al	Cohort	70	Single centre	2003-2006	NR	MACE (CD,MI,TLR,TVR)	DES (6-12) BMS (1)	12	DES: 24% BMS: 33%
Jeger et al	Randomised	47	Single centre	2003-2004	65/35	MACE (CD, MI, TVR)	DES (6) BMS (6)	18	No routine
Wöhrle et al	Matched control	39	Single centre	2003-2005	0/100	MACE (D, MI, TVR)	DES (6) BMS (6)	12	100% 6 months
Brodie	Propensity analysis	1128	Multicentre	2003-2006	59/38	TVR	NR	24	No routine
Shishehbor et al	Cohort	566	Multicentre	2000-2007	NR	MACE (D, MI,TLR)	NR	35	No routine
Goswami et al	Cohort	379	Single centre	2003-2007	84.4/15.5	All-cause D	DES (≥6) MBS (≥3)	36	No routine
Brilakis et al	Randomised	80	Multicentre	2005-2007	0/100	BR	DES (6-12) BMS (1)	12	DES: 75% BMS: 85%

DES: drug-eluting stents; SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent; FU: follow-up; Angio FU: angiographic follow-up; BMS: bare-metal stents; CD: cardiac death; TVR: target vessel revascularisation; MACE: major adverse cardiovascular events; D: death; MI: myocardial infarction; TLR: target lesion revascularisation; STEMI: ST elevation myocardial infarction; ST: stent thrombosis; BR: binary restenosis; LLL: late lumen loss; *Median time of dual antiplatelet treatment ** Minimum time of dual antiplatelet treatment

observational). Null hypothesis was rejected by a type I error minor than 0.05 (α<0.05). Also, we included an analysis for TVR, all-cause of death and MACE, using the adjusted hazard ratios for some co-variables considered in the observational studies themselves when this information was available.

Results

Characteristics of the trials included

A total of 22 studies were finally included, enrolling 5,543 patients (2,799 patients treated with DES and 2,744 patients treated with BMS)[4-8,11-18,23-30]. Table 3 shows the main angiographic and clinical baseline characteristics of the trials included. The proportion of diabetic patients ranged from 20% to 54%. Graft age ranged from nine years to 13 years. The use of distal embolic protection device varied from 4 to 84%, and glycoprotein IIb/IIIa inhibitors from 0 to 84%. Stent length ranged from 16 mm to 46 mm, and stent diameter from 3.1 mm to 3.8 mm.

Primary endpoints

EFFICACY ENDPOINT

Data on TVR were available in 4,476 patients (82%) out of 5,543 patients. Figure 2 shows the number of patients who experienced the primary efficacy endpoint of reintervention according to the treatment group, with the OR for each of the studies. Overall, the use of DES was associated with significant benefits in terms of TVR (15.2% vs. 19.2%; OR of 0.56 [95% CI, 0.41-0.76] p=0.0003), compared with the use of BMS. That means a relative risk decrease of 21% (95% CI 9.5 to 32.4). The number of patients needed to treat with DES to avoid 1 TVR is 25 (16-55). Sensitivity analysis (Table 4) showed that the results were not influenced by the follow-up, sample size or study quality. Adjusted hazard ratios for TVR were available in five studies, and also TVR was significantly lower in DES compared with BMS (Figure 3).

SAFETY ENDPOINT

Data on all-cause mortality were available in 4,339 (78%) out of the 5,543. Figure 4 shows the number of patients who experienced the primary safety endpoint of mortality according to the treatment group, with the OR for each of the studies. Overall, all-cause mortality was significantly lower in DES compared with BMS, (9.5% vs. 13.9%; OR=0.69 [95% CI, 0.49-0.98], p=0.04). That means a relative risk decrease of 31% (95% CI 18 to 45). The number of patients needed to treat with DES to avoid one death is 23[16-41]. Sensitivity analysis (Table 4) showed differences among subgroups: when studies with more than 200 patients were selected, mortality was significantly lower in the DES subgroup vs. BMS. Also mortality was lower in the subgroup of patients treated with DES vs. BMS when only observational studies were analysed. Adjusted hazard ratios for all-cause death were available in five studies, and also death was significantly lower in DES compared with BMS (Figure 5).

Table 3. Characteristics of studies included in the meta-analysis.

Study	Age (years)		Diabetes(%)		Graft age (years)		Distal device (%)		GP IIb/IIIa (%)		Direct stent (%)		Total stent length		Stent diameter	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
Lozano	71±9*	66±9*	38	49	10,1±6	9,0±5	9	4	16	27	39*	59*	22,4±131	16,0±5,51	3,3±0,5*	3,4±0,6*
Twisk	68	69	31	21	NR	NR	1,6	4,7	21*	41*	NR	NR	32	31,9	3,1*	3,5*
Minutello	71±13	69±11	47,5	44	12,9±6*	9,4±5*	71,2*	48*	49,2	64	NR	NR	26,1±16*	20,8±10*	3,1±0,4	3,4±0,5
Okabe	70±11	70±11	53	43	10,5±7	9,6±6	26	21	15*	48*	66	70	20,3±61	19,8±91	3,1±0,4*	3,8±2*
Ellis	70±9	68±10	38,9	38,9	10±6	9,8±6	35,1*	25,1*	52,3*	83,9*	NR	NR	20,6±8	21,6±11	NR	NR
Gioia	71±8	70±7	45	37	11±6	11±5	26	21	16	21	NR	NR	21±61	24±101	3,3±0,4*	3,9±0,5*
Applegate	69±11	69±10	23	28	NR	NR	53	47	NR	NR	NR	NR	26±111	25±41	NR	NR
Hoffmann	67±11	69±9	25	28	NR	NR	52	47	NR	NR	NR	NR	16,7±41	14,6±41	3,3±0,3	3,4±0,6
Ge	67±8	67±8	19,7	15,7	9,7±5,6	9,2±4,8	31,1	22,5	14,8	21,3	NR	NR	29,4±20*1	20,4±9*1	3,3±0,4*	3,8±0,6*
Vignali	72±8	71±9	28,6	24	9±2	10,6±3	NR	NR	NR	NR	NR	NR	19,7±61	18,7±61	3,0±0,4*	3,5±0,7*
Ramana	70	69	52	42	11,5	12,9	NR	NR	NR	NR	NR	NR	28,3	29,3	3,3*	4,2*
Lee	69±11	69,±11	23	24	7,6±3,8	7,7±2,8	15	19	8	12	NR	NR	NR	NR	NR	NR
Assali	70±8	71±9	54*	29*	10,8±5	11,4±4	38	48	52	33	NR	NR	30,3±18*	20,7±13*	3,3±0,4*	3,6±0,7*
Bansal	68±1,6	64,9±1	51	35	NR	NR	39	27	39	53	NR	NR	17,1±11	17,9±0,71	3,0±0,1*	3,8±0,1*
Vermeersch	73±7	72±8	16	14	12,4±5	12,6±6	78,7	83,7	2,6	0	NR	NR	36,9±17	33,4±18	3,4±0,2	3,4±0,2
Kaplan	72±9	70±8	16,2	24,2	7,5±1,3	7,6±1,3	27	33,3	21,6	30,3	51,4	51,5	18,9±7*1	15,6±4*1	3,4±0,5*	3,7±0,5*
Jeger	71±8	71±8	29	17	NR	NR	NR	NR	21	46	NR	NR	41±25	46±30	NR	NR
Whöhrle	71±4	70±6	23,1	30,8	11,4±7	9,1±5	NR	NR	15,4	19,2	NR	NR	23±12	23,6±14	3,2±0,8	3,4±0,4
Shishehbor	70	69	42	37	NR	NR	56	30	28	62	NR	NR	NR	NR	NR	NR
Goswami	71±10	69.5±10	43	41	NR	NR	NR	NR	57	75*	NR	NR	28±16	30±22	3,3±0,4	4,4±0,7
Brilakis	66±9	67±9	44	44	11±6	12±6	51	56	10	13	67	71	28±17	29±16	3,14±0,3	3,17±0,4
Brodie	67.5±10	69±10	38	37	NR	NR	37.3	33.7	46.5	48.1	NR	NR	18±13	16±101	NR	NR

DES: drug eluting stents; BMS: bare metal stents; GP IIb/IIIa: glycoprotein IIb/IIIa inhibitors; * p<0.05; 1. Mean stent length per lesion

Study or Subgroup	DES Events	DES Total	BMS Events	BMS Total	Weight	Odds Ratio IV, Random, 95% CI
Applegate	7	74	12	74	4.8%	0.54 (0.20, 1.46)
Assali	10	68	14	43	5.1%	0.36 (0.14, 0.90)
Bansal	13	37	30	72	5.6%	0.76 (0.33, 1.72)
Brilakis	6	41	12	39	4.3%	0.39 (0.13, 1.16)
Brodie	144	785	58	343	8.2%	1.10 (0.79, 1.54)
Ellis	11	161	19	161	5.8%	0.55 (0.25, 1.19)
Ge	3	61	21	89	3.7%	0.17 (0.05, 0.59)
Goia	15	106	17	119	6.0%	0.99 (0.47, 2.09)
Jeger	6	34	6	13	3.2%	0.25 (0.06, 1.02)
Kaplan	4	37	11	33	3.7%	0.24 (0.07, 0.86)
Lee	14	139	31	84	6.2%	0.19 (0.09, 0.39)
Lozano	16	107	19	130	6.1%	1.03 (0.50, 2.11)
Minutello	9	59	18	50	5.1%	0.32 (0.13, 0.80)
Okabe	27	138	46	344	7.2%	1.58 (0.93, 2.66)
Ramana	18	141	27	170	6.6%	0.78 (0.41, 1.47)
Twisk	17	122	36	128	6.6%	0.41 (0.22, 0.79)
Vermeersch	13	38	14	37	5.0%	0.85 (0.33, 2.20)
Vignali	6	72	32	288	5.1%	0.73 (0.29, 1.81)
Wöhrle	1	13	9	26	1.7%	0.16 (0.02, 1.41)
Total (95% CI)		**2233**		**2243**	**100.0%**	**0.56 (0.41, 0.76)**
Total events	340		432			

Heterogeneity: Tau²=0.29; Chi²=52.13, df=18 (P<0.0001); I²=65%
Test for overall effect: Z=3.64 (P=0.0003)

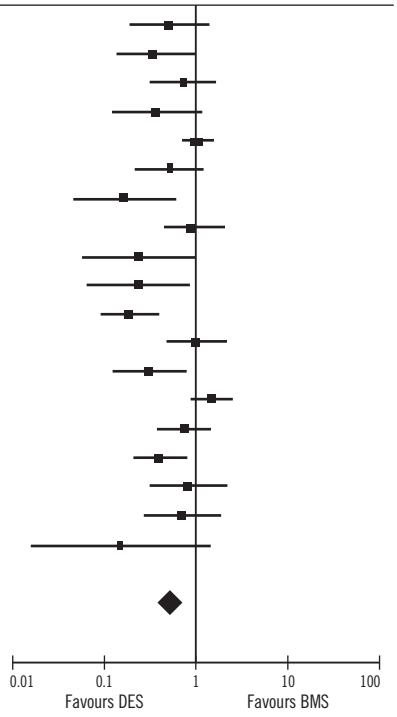

Figure 2. Odds ratios of target vessel revascularisation in patients treated with DES or BMS in each study and in overall patient population. DES: drug-eluting stent; BMS: bare-metal stent

Table 4.

A. Sensitivity analyses for TVR

Subgroup	N° of studies	N° of patients	DES	BMS	OR (CI 95%)	P-value	P-heterogeneity
Follow-up >1 year	11	2750	268/1571	251/1179	0.67 (0.50-0.91)	0.01	0.05
Follow-up ≤1 year	8	1726	72/662	181/1064	0.41 (0.20-0.82)	0.01	0.001
Large size (>200 patients)	9	3538	268/1771	285/1767	0.82 (0.67-0.99)	0.04	0.001
Small size (<200 patients)	10	938	72/462	147/476	0.40 (0.29-0.56)	0.0001	0.44
Randomised trials	3	202	25/113	32/89	0.51 (0.27-0.96)	0.04	0.30
Observational studies	16	4274	315/2120	400/2154	0.69 (0.59-0.82)	0.0001	0.001

B. Sensitivity analysis for mortality.

Subgroup	N° of studies	N° of patients	DES	BMS	OR (CI 95%)	P-value	P-heterogeneity
Follow-up > 1 year	7	2820	178/1655	226/1165	0.62 (0.38-0.99)	0.05	0.007
Follow-up ≤ 1 year	7	1519	31/531	74/988	0.90 (0.56-1.45)	0.01	0.001
Large size (> 200 patients)	8	3814	189/1928	292/1886	0.61 (0.44-0.85)	0.03	0.05
Small size (< 200 patients)	6	525	20/258	8/267	1.59 (0.54-4.67)	0.40	0.29
Randomised trials	2	155	16/79	2/76	6.79 (0.62-74.1)	0.12	0.14
Observational studies	12	4184	193/2107	298/2077	0.60 (0.46-0.78)	0.002	0.23

Secondary endpoints

Data on MACE were available in 4,844 patients (88%) out of 5,543 patients. The rate of MACE was also significantly lower in DES group than in BMS (17.6% vs. 29.2% respectively; OR 0.55, 95% CI 0.42 to 0.71, p<0.0001; Figure 6). Adjusted hazard ratios for MACE were available in eight studies, and also MACE was significantly lower in DES compared with BMS (Figure 7).

As shown in Figure 8, treatment with DES was associated with a lower cardiac mortality than BMS (6.5% vs. 8.8%; OR of 0.71 [0.51-0.99], p=0.04). That means a relative risk decrease of 25.6% (95% CI 1.2 to 50.1).

Figure 9 shows the absolute numbers of TLR in each treatment group, with the OR for each study. Data on TLR were available in 3,471 patients (79%) out of 4,415 patients. Overall, the use of DES was associated with

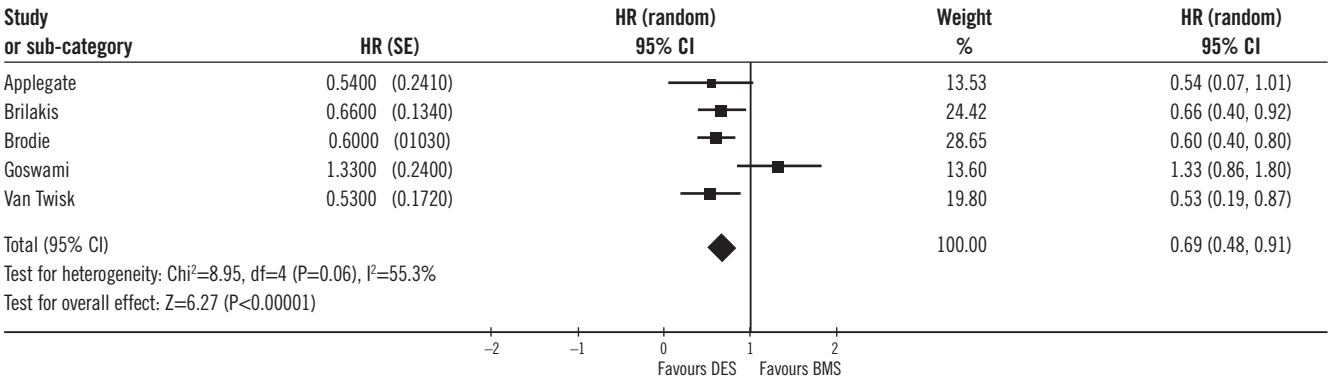

Figure 3. Adjusted hazard ratios of target vessel revascularisation in each study and in overall population. DES: drug-eluting stent; BMS: bare-metal stent

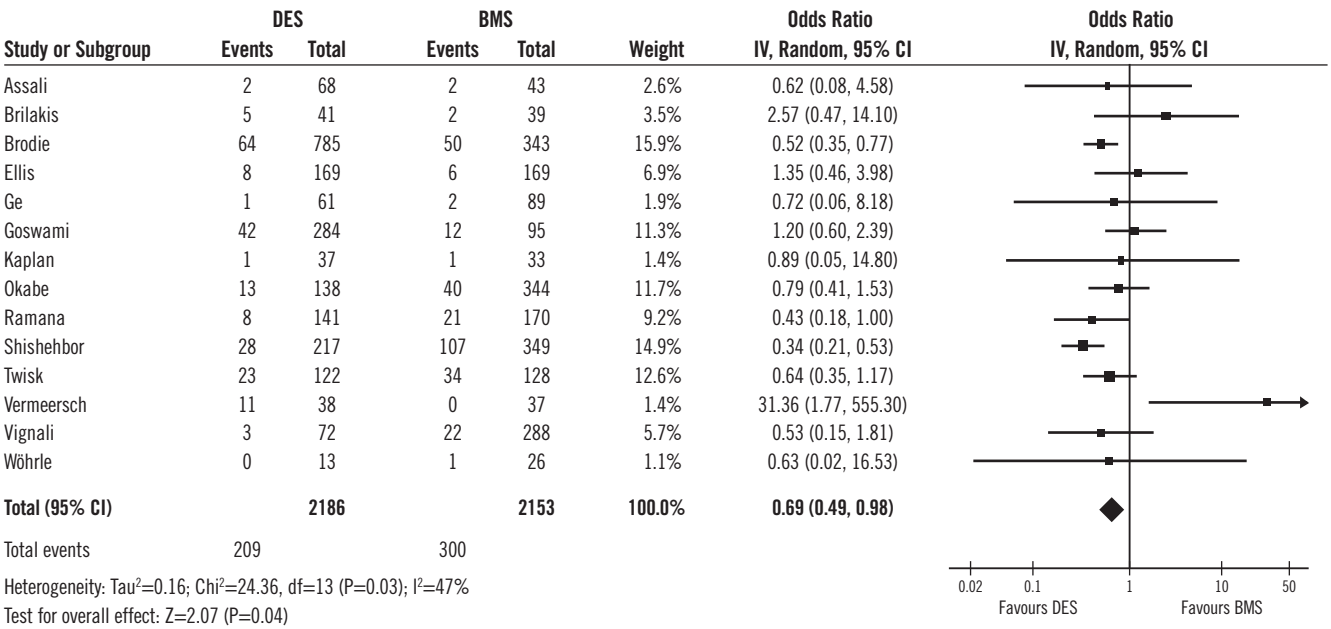

Figure 4. Odds ratios of total mortality in patients treated with DES or BMS in each study and in overall population. DES: drug-eluting stent; BMS: bare-metal stent

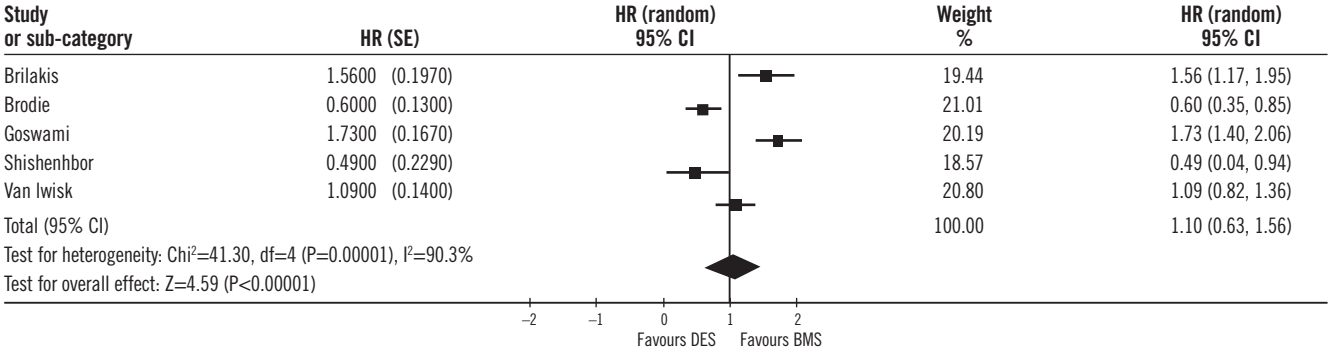

Figure 5. Adjusted hazard ratios of total mortality in each study and in overall population. DES: drug-eluting stent; BMS: bare-metal stent

significant benefits in terms of TLR (9.7% vs. 13.8%; OR of 0.58 [95% CI, 0.41-0.81] p=0.001), compared with the use of BMS.

No difference was observed in the rate of myocardial infarction between DES and BMS (8.3% vs. 7.4%, respectively; OR 0.89, [95% CI 0.60 to 1.32], p=0.57). Also, no difference was found in the rate of stent thrombosis between DES and BMS in the setting of SVGs disease (2.16% vs. 2.35%, respectively; OR of 0.82, [95% CI 0.43 to 1.59)], p=0.56).

Study or Subgroup	DES Events	DES Total	BMS Events	BMS Total	Weight	Odds Ratio IV, Random, 95% CI
Assali	14	68	18	43	4.8%	0.36 (0.15, 0.84)
Bansal	17	37	36	72	5.1%	0.85 (0.38, 1.88)
Brilakis	15	41	19	39	4.5%	0.61 (0.25, 1.48)
Brodie	64	785	50	343	7.8%	0.52 (0.35, 0.77)
Ge	7	61	25	89	4.4%	0.33 (0.13, 0.83)
Goia	20	106	22	129	5.9%	1.13 (0.58, 2.21)
Goswami	58	284	18	95	6.4%	1.10 (0.61, 1.98)
Hoffman	9	60	22	60	4.6%	0.30 (0.13, 0.74)
Jeger	7	34	8	13	2.6%	0.16 (0.04, 0.65)
Kaplan	4	37	12	33	3.0%	0.21 (0.06, 0.75)
Lee	14	139	31	84	5.6%	0.19 (0.09, 0.39)
Minutello	15	59	25	50	5.0%	0.34 (0.15, 0.76)
Okabe	26	138	63	344	7.0%	1.04 (0.62, 1.72)
Ramana	28	141	47	170	6.8%	0.65 (0.38, 1.11)
Shishehbor	58	217	154	349	8.0%	0.46 (0.32, 0.67)
Twisk	41	122	67	128	7.0%	0.46 (0.28, 0.77)
Vermeersch	22	38	15	37	4.4%	2.02 (0.80, 5.06)
Vignali	13	72	58	288	5.9%	0.87 (0.45, 1.70)
Wöhrle	1	13	10	26	1.3%	0.13 (0.01, 1.19)
Total (95% CI)		**2452**		**2392**	**100.0%**	**0.55 (0.42, 0.71)**
Total events	433		700			

Heterogeneity: Tau²=0.19; Chi²=48.60, df=18 (P<0.0001); I²=63%
Test for overall effect: Z=4.50 (P=0.00001)

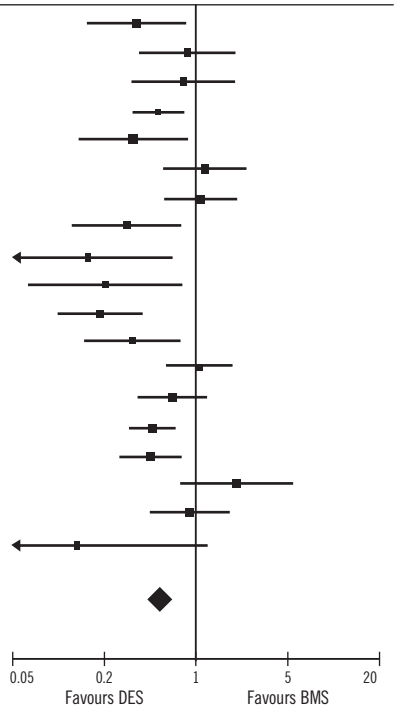

Figure 6. Odds ratios of major adverse cardiac events in patients treated with DES or BMS in each study and in overall patient population. DES: drug-eluting stent; BMS: bare-metal stent

Study or sub-category	HR (SE)	Weight %	HR (random) 95% CI
Brilakis	0.8000 (0.0860)	16.47	0.80 (0.63, 0.97)
Brodie	0.6800 (0.0730)	17.57	0.68 (0.54, 0.82)
Ge et al	0.4000 (0.2180)	7.43	0.40 (-0.03, 0.83)
Goswami	1.2900 (0.1450)	11.66	1.29 (1.01, 1.57)
Okabe	0.9000 (0.1500)	11.30	0.90 (0.61, 1.19)
Shishenhbor	0.6100 (0.1420)	11.87	0.61 (0.33, 0.89)
Van Twisk	0.7700 (0.1050)	14.84	0.77 (0.56, 0.98)
Vignal	0.8400 (0.1890)	8.86	0.84 (0.47, 1.21)
Total (95% CI)		100.00	0.79 (0.65, 0.94)

Test for heterogeneity: Chi²=19.52, df=7 (P=0.007), I²=64.1%
Test for overall effect: Z=10.77 (P<0.00001)

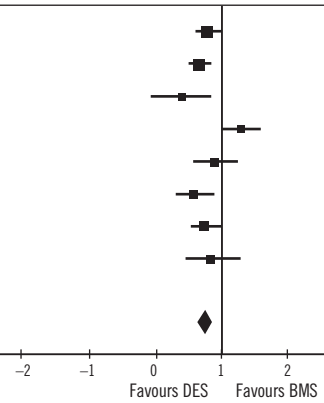

Figure 7. Adjusted hazard ratios of major adverse cardiac events in each study and in overall population. DES: drug-eluting stent; BMS: bare-metal stent

Discussion

The main finding of this meta-analysis is that DES implantation is associated with a significant reduction of the need of reintervention of the target vessel in diseased SVGs compared with BMS without an increase in mortality. Moreover, all-cause and cardiac mortality were significantly lower in patients treated with DES. There is also a significant decrease in the need of reinterventions with DES compared to BMS without increment in mortality when studies with follow-up longer than one year are selected.

The percutaneous treatment of degenerated SVGs has been challenging. Use of embolic protection devices and BMS has reduced the procedural complications as distal embolisation, and subsequently long-term cardiovascular events[31]. Use of DES has decreased the restenotic process caused by neo-intimal hyperplasia, and the rate of repeated revascularisation procedures when treating native coronary arteries. SVGs disease has been poorly represented if not completely excluded in pivotal randomised clinical trials that compared DES versus BMS. Currently, as it has been shown, the comparison of available data of DES versus BMS implantation in SVG disease is limited and based on few retrospective cohort studies, three matched control-case studies and three randomised clinical trials. These randomised clinical trials in the setting of SVGs lesions have several limitations. They included a limited number of patients: 80, 75 and 47[4,10,27]. Two out of the

Study or Subgroup	DES Events	DES Total	BMS Events	BMS Total	Weight	Odds Ratio IV, Random, 95% CI
Applegate	5	74	4	74	5.8%	1.27 (0.33, 4.92)
Bansal	7	37	16	72	10.8%	0.82 (0.30, 2.20)
Brilakis	1	41	2	39	1.8%	0.46 (0.04, 5.32)
Ge	0	61	2	89	1.1%	0.28 (0.01, 6.03)
Goia	6	106	7	119	8.5%	0.96 (0.31, 2.95)
Goswami	22	284	10	95	17.3%	0.71 (0.33, 1.57)
Jeger	1	34	2	13	1.7%	0.17 (0.01, 2.02)
Kaplan	1	37	1	33	1.4%	0.89 (0.05, 14.80)
Lee	1	139	3	84	2.1%	0.20 (0.02, 1.91)
Lozano	9	98	13	113	13.3%	0.78 (0.32, 1.91)
Minutello	4	59	6	50	6.1%	0.53 (0.14, 2.01)
Ramana	4	141	10	170	7.7%	0.47 (0.14, 1.52)
Twisk	15	122	22	128	21.3%	0.68 (0.33, 1.37)
Vermeersch	7	38	0	37	1.3%	17.86 (0.98, 325.07)
Total (95% CI)		**1271**		**1116**	**100.0%**	**0.71 (0.51, 0.99)**
Total events	83		98			

Heterogeneity: Tau^2=0.00; Chi^2=9.53, df=13 (P=0.73); I^2=0%
Test for overall effect: Z=2.04 (P=0.04)

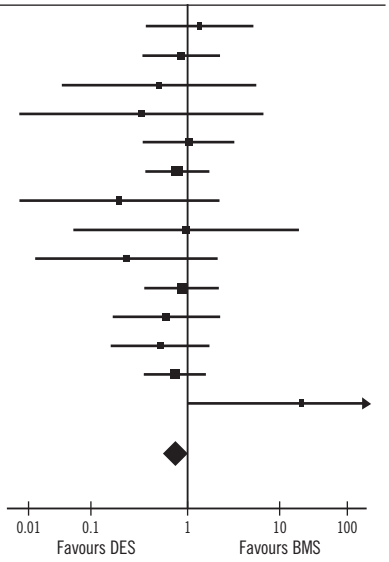

Figure 8. Odds ratios of cardiac mortality in patients treated with DES or BMS in each study and in overall population. DES: drug-eluting stent; BMS: bare-metal stent

Study or Subgroup	DES Events	DES Total	BMS Events	BMS Total	Weight	Odds Ratio IV, Random, 95% CI
Assali	7	68	12	43	6.3%	0.30 (0.11, 0.83)
Bansal	11	37	28	72	7.6%	0.66 (0.28, 1.55)
Brilakis	2	41	11	39	3.5%	0.13 (0.03, 0.64)
Ellis	11	162	16	162	8.1%	0.66 (0.30, 1.48)
Ge	2	61	18	89	3.8%	0.13 (0.03, 0.60)
Goia	14	106	15	119	8.3%	1.06 (0.48, 2.30)
Goswami	23	284	8	95	7.7%	0.96 (0.41, 2.22)
Hoffman	4	60	13	60	5.3%	0.26 (0.08, 0.85)
Kaplan	2	37	10	33	3.4%	0.13 (0.03, 0.66)
Minutello	8	59	11	50	6.4%	0.56 (0.20, 1.51)
Okabe	13	138	26	344	9.1%	1.27 (0.63, 2.55)
Ramana	10	141	24	170	8.3%	0.46 (0.21, 1.01)
Shishehbor	29	217	43	349	11.1%	1.10 (0.66, 1.82)
Vermeersch	9	38	11	37	6.2%	0.73 (0.26, 2.05)
Vignali	3	72	23	288	5.0%	0.50 (0.15, 1.72)
Total (95% CI)		**1521**		**1950**	**100.0%**	**0.58 (0.41, 0.81)**
Total events	148		269			

Heterogeneity: Tau^2=0.20; Chi^2=27.53, df=14 (P=0.02); I^2=49%
Test for overall effect: Z=3.18 (P=0.001)

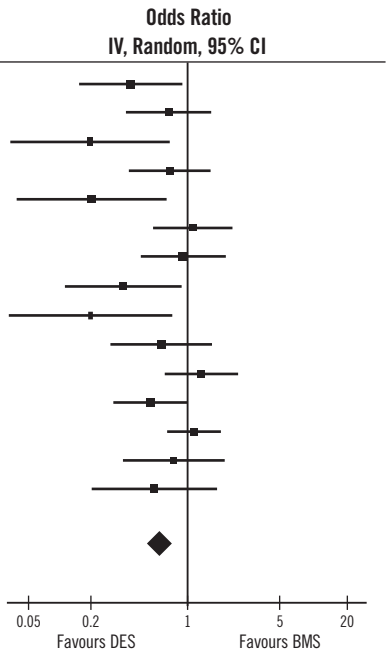

Figure 9. Odds ratios of target lesion revascularisation in patients treated with DES or BMS in each study and in overall patient population. DES: drug-eluting stent; BMS: bare-metal stent

three randomised clinical trials are single-centre and they are a secondary *post hoc* analysis of the RRISC and BASKET trials[10,27]. The primary endpoints of RRISC[10] and SOS[4] trials were angiographic endpoints (12-month binary in-segment restenosis and 6-month in-stent late lumen loss, in SOS and RRISC trials respectively), surrogate markers of the need of reintervention procedures. The primary endpoint in BASKET trial was the cost-effectiveness of DES versus BMS after six months mainly in patients with native coronary artery disease. Therefore, there are no randomised clinical trials designed to assess clinical endpoints at long-term follow-up.

The results of RRISC and SOS trials, the two dedicated randomised trials that evaluate only patients with SVGs lesions, are concordant regarding the primary endpoint. Both trials showed either sirolimus-eluting stents or paclitaxel-eluting stents reduce angiographic restenosis and the need for reintervention compared with bare-metal stents. But, concerns arose from the *post hoc* analysis of the first randomised clinical trial of sirolimus-eluting stents in the

treatment of SVGs, DELAYED RRISC trial[13]. This showed that the initial benefit of DES on the risk of reintervention was lost at three years suggesting a potential late "catch-up" phenomenon. Also sirolimus-eluting stents were associated with higher mortality at three years possibly related to late or very late stent thrombosis. There is no clear pathophysiological explanation for these findings especially when this phenomenon has not been seen in native coronary arteries and when 3-year mortality rate was surprisingly 0% in patients allocated to BMS and 28% in patients allocated to DES. Interestingly clopidogrel was mandated for only two months in both, DES and BMS. This could have influenced in the high rate of late stent thrombosis in patients allocated to sirolimus-eluting stents. The intravascular ultrasound substudy of RRISC trial[32] showed that sirolimus-eluting stents inhibit neointimal hyperplasia compared with BMS in diseased SVGs without evidence of increased incomplete apposition risk, similar to findings in native coronary artery disease.

This meta-analysis showed that DES implantation in diseased SVGs had a significant benefit in terms of reduction in repeated revascularisation procedures without an increase of mortality including all studies with a follow-up longer than one year. Moreover, if only observational studies with a follow-up longer than 30 months are included, DES implantation was associated with a significant decrease in TVR (15.6% vs. 23.2%, OR: 0.63 [95% CI 0.43-0.93; p=0.02]) and a trend toward lower cardiac death (8.3% vs. 12.3%, OR: 0.70 [95% CI 0.47-1.03; p=0.07]). Thus, the finding of late "catch-up" phenomenon was not suggested in observational studies with at least three years of follow-up.

Study limitations

First, the present meta-analysis was not performed on individual patient data. Some caution should be taken into account given the potential clinical heterogeneity among studies, due to definition of variables, study design, and inclusion criteria. Second, DES differ in their structural design, impregnated polymer, type of drug, and pharmacokinetic profile. Therefore, the clinical implication of using different DES in SVGs may be is different. In this meta-analysis, 11 studies included both sirolimus-eluting stents and paclitaxel-eluting stents. Third, most of the BMS used in the published SVG studies were thick-strut. The difference between DES and thin-strut BMS may be smaller than the difference between DES and thick-strut BMS. Forth, currently there is increasing information that prolonged dual antiplatelet regimen may prevent late stent thrombosis. The duration of clopidogrel administration was variable in these studies. Fifth, routine angiographic follow-up may influence the rate of TVR. Both randomised clinical trials, RRISC and SOS, have used routine angiographic follow-up, which may overestimate the need for repeat revascularisation procedures. Sixth, the clinical follow-up was variable among studies. For this reason, a sensitivity analysis was performed according to the clinical follow-up (equal or shorter than one year of follow-up vs. longer than one year). Seventh and the most important limitation is that most of data were derived from retrospective observational series rather than prospective randomised trials. Observational studies have several limitations because of inherent biases and differences in study designs.

Conclusion

In conclusion, this meta-analysis suggested that DES are associated with a significant reduction of the need of reinterventions and mortality at long-term follow-up in diseased SVGs compared with BMS. This is "hypothesis-generating" meta-analysis aimed at pushing funding sources to sponsor adequately sized, prospective, multicentre, and randomised clinical trials to conclusively assess the efficacy and safety of DES in the treatment of VSGs lesions.

References

1. Moreno R, Fernandez C, Sanchez-Recalde A, Galeote G, Calvo L, Alfonso F, Hernandez R, Sánchez-Aquino R, Angiolillo DJ, Villarreal S, Macaya C, Lopez-Sendon JL Clinical impact of in-stent late loss after drug-eluting coronary stent implantation. *Eur Heart J* 2007;28:1583-1591.

2. Kornowski R. Drug-eluting stent in saphenous vein graft lesions. *Catheter Cardiovasc Interv* 2008;71:894-895.

3. van Beusekom HM, van der Giessen WJ, van Suylen R, Bos E, Bosman FT, Serruys PW. Histology after stenting of human saphenous vein bypass grafts: observations from surgically excised grafts 3 to 320 days after stent implantation. *J Am Coll Cardiol* 1993;21:45-54.

4. Brilakis ES, Lichtenwalter C, de Lemos JA, Roesle M, Obel O, Haagen D, Saeed B, Gadiparthi C, Bissett JK, Sachdeva R, Voudris VV, Karyofillis P, Kar B, Rossen J, Fasseas P, Berger P, Banerjee S. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. *J Am Coll Cardiol* 2009;53:919-928.

5. Ellis SG, Kandzari D, Kereiakes DJ, Pichard A, Huber K, Resnic F, Yakubov S, Callahan K, Borgman M, Cohen SA. Utility of sirolimus-eluting Cypher stents to reduce 12-month target vessel revascularization in saphenous vein graft stenoses: results of a multicenter 350-patient case-control study. *J Invasive Cardiol* 2007;19:404-409.

6. Ge L, Iakovou I, Sangiorgi GM, Chieffo A, Melzi G, Cosgrave J, Montorfano M, Michev I, Airoldi F, Carlino M, Corvaja N, Colombo A. Treatment of saphenous vein graft lesions with drug-eluting stents: immediate and midterm outcome. *J Am Coll Cardiol* 2005;45:989-994.

7. Hoffmann R, Pohl T, Koster R, Blindt R, Boeckstegers P, Heitzer T. Implantation of paclitaxel-eluting stents in saphenous vein grafts: clinical and angiographic follow-up results from a multicentre study. *Heart* 2007;93:331-334.

8. Kaplan S, Barlis P, Kiris A, Dimopoulos K, Celik S, Di Mario C. Immediate procedural and long-term clinical outcomes following drug-eluting stent implantation to ostial saphenous vein graft lesions. *Acute Card Care* 2008;10:88-92.

9. Lee MS, Shah AP, Aragon J, Jamali A, Dohad S, Kar S, Makkar RR. Drug-eluting stenting is superior to bare metal stenting in saphenous vein grafts. *Catheter Cardiovasc Interv* 2005;66:507-511.

10. Vermeersch P, Agostoni P, Verheye S, Van den Heuvel P, Convens C, Bruining N, Van den Branden F, Van Langenhove G. Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC Trial. *J Am Coll Cardiol* 2006;48:2423-2431.

11. Vignali L, Saia F, Manari A, Santarelli A, Rubboli A, Varani E, Piovaccari G, Menozzi A, Percoco G, Benassi A, Rusticali G, Marzaroli P, Guastaroba P, Grilli R, Maresta A, Marzocchi A. Long-term outcomes with drug-eluting stents versus bare metal stents in the treatment of saphenous vein graft disease (results from the REgistro Regionale AngiopLastiche Emilia-Romagna registry). *Am J Cardiol* 2008;101:947-952.

12. Wohrle J, Nusser T, Kestler HA, Kochs M, Hombach V. Comparison of the slow-release polymer-based paclitaxel-eluting Taxus-Express stent with the bare-metal Express stent for saphenous vein graft interventions. *Clin Res Cardiol* 2007;96:70-76.

13. Vermeersch P, Agostoni P, Verheye S, Van den Heuvel P, Convens C, Van den Branden F, Van Langenhove G; DELAYED RRISC (Death and Events at Long-term follow-up AnalYsis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent) Investigators Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol* 2007;50:261-267.

14. Gioia G, Benassi A, Mohendra R, Chowdhury K, Masood I, Matthai W. Lack of clinical long-term benefit with the use of a drug eluting stent compared to use of a bare metal stent in saphenous vein grafts. *Catheter Cardiovasc Interv* 2008;72:13-20.

15. Goswami NJ, Gaffigan M, Berrio G, Plessa AL, Pfeiffer AM, Markwell SJ, Mishkel GJ. Long-term outcomes of drug-eluting stents versus bare-metal stents in saphenous vein graft disease: results From the Prairie "Real World" Stent Registry. *Catheter Cardiovasc Interv* 2010;75:93-100.

16. Lozano I, García-Camarero T, Carrillo P, Baz JA, de la Torre JM, López-Palop R, Pinar E, Salvatella N, Avanzas P, Valdés M. Comparison of drug-eluting and bare metal stents in saphenous vein grafts. Immediate and long-term results. *Rev Esp Cardiol* 2009;62:39-47.

17. Ramana RK, Ronan A, Cohoon K, Homan D, Sutherland J, Steen L, Liu J, Loeb H, Lewis BE. Long-term clinical outcomes of real-world experience using sirolimus-eluting stents in saphenous vein graft disease. *Catheter Cardiovasc Interv* 2008;71:886-893.

18. van Twisk PH, Daemen J, Kukreja N, van Domburg RT, Serruys PW. Four-year safety and efficacy of the unrestricted use of sirolimus- and paclitaxel-eluting stents in coronary artery bypass grafts. *EuroIntervention* 2008;4:311-317.

19. Chu WW, Rha SW, Kuchulakanti PK, Cheneau E, Torguson R, Pinnow E, Alexieva-Fournadjiev J, Pichard AD, Satler LF, Kent KM, Lindsay J, Waksman R. Efficacy of sirolimus-eluting stents compared with bare metal stents for saphenous vein graft intervention. *Am J Cardiol* 2006;97:34-37.

20. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-2012.

21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-1558.

22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.

23. Applegate RJ, Sacrinty M, Kutcher M, Santos R, Gandhi S, Little W. Late outcomes of drug-eluting versus bare metal stents in saphenous vein grafts: Propensity score analysis. *Catheter Cardiovasc Interv* 2008;72:7-12.

24. Assali A, Raz Y, Vaknin-Assa H, Ben-Dor I, Brosh D, Teplitsky I, Fuchs S, Kornowski R. Beneficial 2-years results of drug-eluting stents in saphenous vein graft lesions. *EuroIntervention* 2008;4:108-114.

25. Bansal D, Muppidi R, Singla S, Sukhija R, Zarich S, Mehta JL, Sachdeva R. Percutaneous intervention on the saphenous vein bypass grafts—long-term outcomes. *Catheter Cardiovasc Interv* 2008;71:58-61.

26. Brodie BR, Wilson H, Stuckey T, Nussbaum M, Laurent S, Bradshaw B, Humphrey A, Metzger C, Hermiller J, Krainin F, Juk S, Cheek B, Duffy P, Simonton CA; STENT Group. Outcomes with drug-eluting versus bare-metal stents in saphenous vein graft intervention results from the STENT (strategic transcatheter evaluation of new therapies) group. *JACC Cardiovasc Interv* 2009;2:1105-1112.

27. Jeger RV, Schneiter S, Kaiser C, Bonetti PO, Brunner-La Rocca H, Handke M, Osswald S, Buser PT, Pfisterer ME; BASKET Investigators. Drug-eluting stents compared with bare metal stents improve late outcome after saphenous vein graft but not after large native vessel interventions. *Cardiology* 2009;112:49-55.

28. Minutello RM, Bhagan S, Sharma A, Slotwiner AJ, Feldman DN, Cuomo LJ, Wong SC. Long-term clinical benefit of sirolimus-eluting stents compared to bare metal stents in the treatment of saphenous vein graft disease. *J Interv Cardiol* 2007;20:458-465.

29. Okabe T, Lindsay J, Buch AN, Steinberg DH, Roy P, Slottow TL, Smith K, Torguson R, Xue Z, Satler LF, Kent KM, Pichard AD, Weissman NJ, Waksman R. Drug-eluting stents versus bare metal stents for narrowing in saphenous vein grafts. *Am J Cardiol* 2008;102:530-534.

30. Shishehbor MH, Hawi R, Singh IM, Tuzcu EM, Bhatt DL, Ellis SG, Kapadia SR. Drug-eluting versus bare-metal stents for treating saphenous vein grafts. *Am Heart J* 2009;158:637-643.

31. Baim DS, Wahr D, George B, Leon MB, Greenberg J, Cutlip DE, Kaya U, Popma JJ, Ho KK, Kuntz RE; Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) Trial Investigators. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 2002;105:1285-1290.

32. Agostoni P, Vermeersch P, Semeraro O, Verheye S, Van Langenhove G, Van den Heuvel P, Convens C, Van den Branden F, Bruining N Intravascular ultrasound comparison of sirolimus-eluting stent versus bare metal stent implantation in diseased saphenous vein grafts (from the RRISC [Reduction of Restenosis In Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent] trial). *Am J Cardiol* 2007;100:52-58.