European Review for Medical and Pharmacological Sciences 2015; 19: 1101-1116

Efficacy of drug-eluting stent for chronic total coronary occlusions at different follow-up duration: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: DESs have been proved to be beneficial for patients with chronic total coronary occlusions (CTO) in terms of cardiac function and other prognosis. We aim to compare the efficacy and safety of drug-eluting stent (DES) and bare-metal stent (BMS) in CTO recanalization at different follow-up duration.

METHODS: Articles comparing outcomes between DES and BMS implantation in patients with CTO was searched. A fixed-effect (inverse-variance weighted) and random-effect (DerSimonian and Laird) model were used to analyze the pooling results.

RESULTS: A total of 29 comparative studies including 24 cohort studies and 5 randomized controlled studies were identified with a total of 9140 patients (5008 received BMS and 4132 received DES). The risk of all cause death for DES was higher at 6 months and lower at 12 months than BMS, and no significant difference was shown at 24, 36 and 60 months. DES group had lower risk of MI after 12 months implantation, and no difference was shown at 6, 24, 36 and 60 months. Major adverse cardiovascular event (MACE)-free survival was clinically and significantly improved by 73%, 68%, 49%, 40% and 37% respectively in DES group at 6,12, 24, 36, and 60 months.

CONCLUSIONS: DES is superior to BMS in binary restenosis, reocclusion and MACE-free survival during long-term follow up. The occurrences of all-cause death and MI show that the risk rate of BMS is higher than that of DES at 12 months. The frequency of all-cause death of DES is higher than BMS at 6 months. DES has higher risk of in-stent thrombosis than BMS at 36 months of implantation.

Key Words:
Chronic total coronary occlusions, Drug-eluting stent, Bare metal stent, Systematic review.

Introduction

Recanalization in patients with chronic total coronary occlusions (CTO) is still considered as the biggest challenge due to disease complexity, difficulty in operation and postoperative comorbidity, although the success rate of the recanalization has been improved with the development of the technique intervention, equipment and the clinical practice. The long-term restenosis rates in CTO patients vary from 30% to 55%, and 10% to 20% with the treatment of bare metal stent (BMS) and drug-eluting stent (DES), respectively[1,2]. Success rate for recanalization of CTO continues to be improved with the help of new techniques.

DESs have been proved to be beneficial for patients with CTO in terms of cardiac function and other prognosis. DESs have considerably reduced in-stent restenosis and broadened the applications of percutaneous coronary interventions for the treatment of coronary artery disease[3]. The searches for improving the performance of DES various developments[4] and new technical[5] are in progress worldwide, Moreover, different types of DESs (such as sirolimus-eluting stent and paclitaxel-eluting stent) on the therapeutic effect of the disease also varies[6]. However, most of the studies related to the efficacy of different stents are not randomized clinical trials (RCTs) with different follow-up duration or small sample size. Different efficacy conclusions for DES are shown in these studies. The relative safety of DES and BMS continues to be debated, large sample sizes are needed to accurately estimate

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treatment differences between stents. As we know, although some meta-analyses have reported the results when considering different follow-up periods which may have an influence on the clinical outcomes, the further research on the efficacy of DES for CTO occlusions at different follow-up duration is necessary.

In this study, we performed a systematic review and meta-analysis of available RCTs and non-RCTs studies reporting outcomes after DES implantation in cases with CTO.

Methods

Search Strategy

Two independent reviewers (T.L. and Z.J.J) were conducted in online databases (Pubmed, Embase, Ovid, Cochrane Library and Chinese Biomedical Database) and cardiology society web sites (clinicaltrials.gov, tctmd.com, cardiosource.com, crtonline.org and escardio.org) from January 2004 to June 2011. The terms of CTO, total coronary occlusion (TCO), DES, BMS, sirolimus-eluting stents (SES), and paclitaxel-eluting stents (PES) were used. No language restrictions were used.

Study Selection Criteria

CTO was defined as a coronary obstruction with thrombolysis in myocardial infarction flow grade 0 or 1 (duration > 2 weeks). The studies that related to a direct comparison between DES and BMS in CTO recanalization with clinical or angiographic outcome follow-up period at least 6 months after stent implantation were retrieved. Ongoing studies, case reports, reviews, editorials and letters were excluded. All articles were identified by two independent reviewers (M.R. and T.L.) with discrepancies adjudicated by a third reviewer (Y.S.S).

Study Endpoints

The primary endpoint was major adverse cardiovascular events (MACEs) at 6, 12, 24, 36 and 60 months after stent implantation. The secondary endpoints were clinical outcomes (all-cause death, myocardial infarction (MI), in-stent thrombosis (IST), MACE-free survival and angiographic outcomes (binary restenosis and reocclusion). The MACEs included all-cause death, MI and target lesion revascularization (TLR) by either percutaneous or surgical method. Restenosis was defined as minimum lumen diameter in the recanalized artery of < 50% of the reference diameter both within the stent and in the adjacent segments 5 mm proximal and distal. Reocclusion was defined as 100% stenosis of the target vessel at follow-up angiography.

Quality Assessment and Data Extraction

Eligible studies were independently scored by two reviewers (T.L. and Z.J.J) according to the Cochrane Collaborations tool for assessing risk of bias for RCTs and Newcastle-Ottawa scale[7] for non randomized comparative studies (NRCS). Extracted data included first author, publication year, study design, patients in BMS and DES, stent type, period of follow-up, clinical and angiographic baseline characteristics, and outcomes of interest. Disagreements were resolved by discussion between them, or with a third reviewer (H.J.).

Statistical Analysis

Relative risk (RR) with their 95% confidence interval (CI) were calculated from abstracted dichotomous data of each study and pooled according to fixed-effects (inverse-variance weighted) and random-effects (DerSimonian and Laird) models.

When the events was rare (< 1%), the peto one-step odds ratio method was used in the analysis, which was found to be the least biased and most powerful method with the best confidence interval[8].

Statistical heterogeneity was assessed with Cochran's Q via a chi-square test and quantified with the I^2 test, $p < 0.10$ and $I^2 > 50\%$ suggesting significant heterogeneity, $I^2 \leq 25\%$ considering low heterogeneity. Binary meta-regressions were performed to assess the potential sources of heterogeneity. Publication bias was assessed by funnel plots and Begg test. Sensitivity analysis for included studies was performed. Analyses were performed using Stata 11.0 (Stata Corporation, Lakeway, TX, USA) and Comprehensive Meta Analysis 2.0 (Biostat, Englewood, NJ, USA).

Results

Literature Search and Quality Assessment

Twenty-nine studies (5RCTs and 24NRCs) were eligible and were assessed for quality ratings (Figure 1). Five RCTs were scored as moderate quality: two post-hoc subgroup analysis of a prospective randomized-controlled trials, the

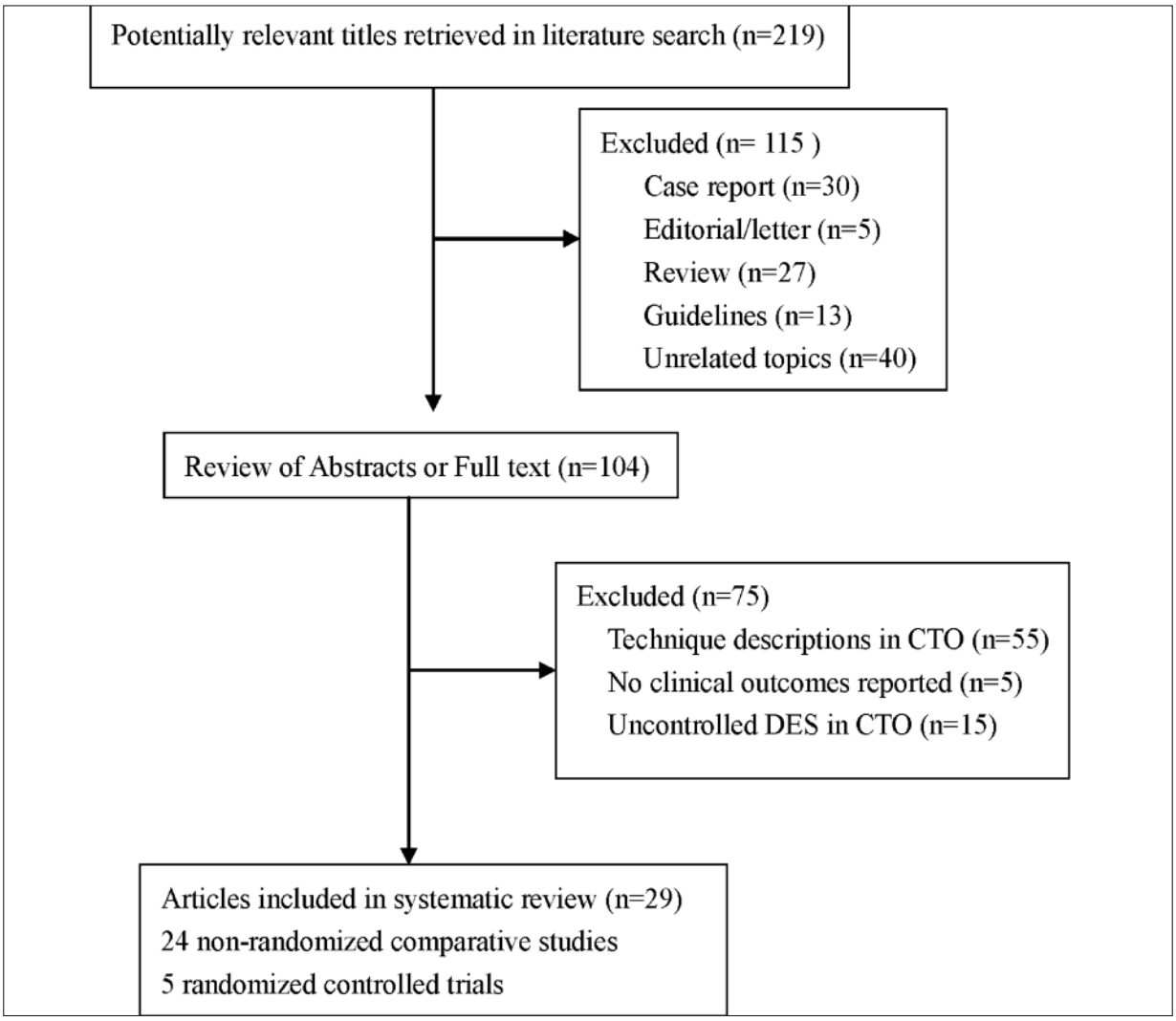

Figure 1. Flow diagram of the literature search.

Stenting Coronary Arteries in Non-Stress/Benestent Disease (SCANDSTENT) study; two prospective randomized, controlled single-blind trials, Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II); one prospective randomized, controlled unblind trial, Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche (GISSOC II). The quality for 24 NRCS were from moderate (4 of 8 stars) to good (7 of 8 stars).

Characteristics of Patients and Studies

A total of 5 RCTs and 24 NRCs with 9140 CTO patients (5008 received BMS and 4132received DES) enrolled from 2004 to 2011 were included in the comprehensive meta-analysis. The clinical follow-up duration for CTO patients were ranged from 6 to 60 months and the mean angiographic follow-up was 6 months. The characteristics of CTO patients were shown in Table I, II, and III[9-39], including sample size, age, gender, smoker, hypercholesterolaemia, hypertension, diabetes mellitus, prior coronary artery bypass graft (CABG) prior percutaneous coronary intervention (PCI), prior MI, ejection fraction, microvascular disease (MVD), left anterior descending artery (LAD), circumflex (Cx), right coronary artery (RCA), Lesion length, and stent length.

Angiographic Outcomes

Binary Restenosis

Data for this comparison were reported in 15 studies which included 1612 and 1581 patients in

Table I. Studies and their respective sample size rgouped by follow-up period.

Author	Publication year	Follow-up period	Sample size	Stent type	Study design
Kim K[5]	2004	6	194	DES/BMS	Cohort
Lei Ge[6]	2005	6	381	SES/BMS	Cohort
Maarten J. Suttorp[7]	2006	6	200	SES/BMS	RCT
Angela Migliorini[8]	2006	6	118	DES/BMS	Cohort
Aleksiadi ER[9]	2007	6	107	DES/BMS	Cohort
Kazuyuki O[10]	2008	6	112	SES/BMS	Cohort
Henning Kelbaek[11]	2006	7	127	SES/BMS	RCT
Angela Hoye[12]	2004	12	84	SES/BMS	Cohort
Gerald S. Werner[13]	2004	12	96	PES/BMS	Cohort
Sunao Nakamura[14]	2005	12	180	SES/BMS	Cohort
Gerald S. Werner[15]	2006	12	164	PES/BMS	Cohort
Abhiram Prasad[16]	2007	12	634	DES/BMS	Cohort
Francesco De Felice[17]	2009	12	99	DES/BMS	Cohort
Kandzari DE[18]	2009	12	402	SES/BMS	Cohort
Francesco De Felice[19]	2009	18	223	DES/BMS	Cohort
Paolo Rubartelli[20]	2010	24	152	SES/BMS	RCT
G. Godino[21]	2010	24	1147	DES/BMS	Cohort
Bimmer E. Claessen[22]	2010	24	1159	DES/BMS	Cohort
Carlo La Spina[23]	2009	26	111	DES/BMS	Cohort
Hector M. Garcia-Garcia[24]	2007	36	147	SES/BMS	Cohort
Gerald S. Werner[25]	2007	36	190	PES/BMS	Cohort
Kotaro Obunai[26]	2008	36	830	DES/BMS	Cohort
Kelbaek H[27]	2008	36	115	SES/BMS	RCT
Francesco De Felice[28]	2009	36	283	DES/BMS	Cohort
Rahel BM[29]	2009	36	200	SES/BMS	RCT
Han Ya-ling[30]	2009	60	1184	DES/BMS	Cohort
Shen ZJ[31]	2009	60	140	SES/BMS	Cohort
Zhang Jian[32]	2010	60	188	DES/BMS	Cohort
Bimmer E. Claessen[33]	2011	60	173	DES/BMS	Cohort

DES and BMS group respectively. Overall, 229 (14.21%) and 579 (36.62%) CTO patients in those two groups underwent binary restenosis until 6 months after operation. The pooled Random-effect relative risks (RRs) for binary restenosis was 0.30 (95% CI 0.18 to 0.49, $p < 0.001$, Figure 2). The heterogeneity was incorporated into the random-effects model (Q = 118.44, $p < 0.001$, $I^2 = 88.18\%$).

Reocclusion

Data for reocclusion were available for analysis from a total of 885 and 1144 CTO patients enrolled in 12 trials from DES and BMS group, respectively. There were 35 (3.95%) and 133 (11.63%) cases of reocclusion by the end of six months after implantation of the stents, indicating a peto OR of 0.34 (95% CI 0.18 to 0.72, $p = 0.004$ Figure 3). The heterogeneity was incorporated into the random-effects model (Q = 45.20, $p < 0.001$, $I^2 = 75.66\%$).

Clinical Follow-up Outcomes

MACEs

Data on MACEs were available for analysis of 29 studies in 4736 and 4071 CTO patients enrolled in DES and BMS groups. The incidence of MACE at 6, 12, 24, 36, and 60 months were 9.44%, 11.41%, 21.08%, 13.49%, and 18.76% respectively in DES group, and were 24.94%, 28.21%, 33.53%, 29.73%, and 28.79% respectively in BMS group. The MACE rates in DES group were significantly lower than those in BMS group. The pooled RRs were 0.43 (95% CI 0.20 to 0.93, $p = 0.03$, Q = 38.30 $p < 0.001$, $I^2 = 81.72\%$), 0.32 (95% CI 0.181 to 0.57, $p < 0.001$, Q = 27.42 $p < 0.001$, $I^2 = 78.12\%$), 0.63 (95% CI 0.55 to 0.71, $p < 0.001$, Q = 7.05 $p = 0.13$, $I^2 = 43.25\%$), 0.46 (95% CI 0.31 to 0.67, $p < 0.001$, Q = 15.06 $p = 0.01$, $I^2 = 66.80\%$), and 0.66 (95% CI 0.42 to 1.02, $p = 0.06$, Q = 6.22 $p = 0.045$, $I^2 = 67.86\%$) at those time points (Figure 4).

Table II. Study characteristics, by DES versus BMS of CTO recanalization.

Author	Sample size		Age		Male sex		Smoker		Hypercholesterolaemia		Hypertension		Diabetes	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
Kim K[5]	115	79	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Lei Ge[6]	122	259	61 ± 10	61 ± 10	107	226	62	95	77	111	61	111	34	49
Maarten J. Suttorp[7]	100	100	59.6 ± 10.6	59.3 ± 10.2	83	76	34	40	90	90	45	46	10	16
Angela Migliorini[8]	92	26	67 ± 11	64 ± 10	n/a	n/a	24	7	43	12	46	16	17	5
Aleksiadi ER[9]	47	60	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Kazuyuki O[10]	42	70	64.0 ± 9.0	62.0 ± 13.0	38	53	17	25	27	25	23	25	25	25
Henning Kelbaek[11]	64	63	63.56 ± 10.42	61.22 ± 8.94	49	51	25	20	54	60	31	21	12	13
Angela Hoye[12]	56	28	59.8 ± 11.1	60.2 ± 10.0	40	24	15	10	31	16	22	11	8	20
Gerald S. Werner[13]	48	48	63.1 ± 10.7	65.0 ± 7.9	38	36	14	11	38	35	39	36	16	14
Sunao Nakamura[14]	60	120	69.5± 8.8	68.6 ± 7.8	42	75	30	59	21	40	35	72	20	39
Gerald S. Werner[15]	82	82	62.4 ± 10.5	64.4 ± 9.8	68	59	26	18	69	63	68	57	29	25
Abhiram Prasad[16]	152	482	63.3 ± 12.0	64.0 ± 11.6	113	360	17	61	125	342	104	292	42	114
Francesco De Felice[17]	52	47	66.0 ± 9.0	63.0 ± 8.0	38	38	15	15	28	29	45	33	52	47
Kandzari DE[18]	200	202	60.3 (54.8,69.7)	57.7 (50.0,65.7)	160	169	35	36	n/a	n/a	139	70	49	30
Francesco De Felice[19]	111	112	62.9 ± 10.5	62.0 ±10.0	83	86	40	44	68	79	78	80	35	35
Paolo Rubartelli[20]	74	78	63.9 ± 9.6	63.9 ± 9.8	58	68	45	41	54	59	49	51	19	15
G.Godino[21]	750	397	n/a	n/a	n/a	n/a	n/a	n/a	518	210	n/a	n/a	183	62
Bimmer E. Claessen[22]	763	396	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Carlo La Spina[23]	88	23	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Hector M. Garcia-Garcia[24]	76	71	61.1 ± 10.6	60.9 ± 10.5	50	54	14	19	51	41	32	25	11	4
Gerald S. Werner[25]	95	95	63.0 ± 10.0	64.0 ± 10.0	67	70	n/a	n/a	n/a	n/a	79	72	29	27
Kotaro Obunai[26]	560	270	62.0 ± 11.0	62.0 ± 11.0	487	240	n/a	n/a	n/a	n/a	n/a	n/a	168	54
Kelbaek H[27]	59	56	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Francesco De Felice[28]	124	159	63.0 ± 10.0	61.0 ± 10.0	93	126	48	72	76	110	89	107	42	42
Rahel BM[29]	100	100	59.6 ± 10.6	59.3 ± 10.2	83	76	34	40	90	90	45	46	10	16
Han Ya-ling[30]	660	524	58.5 ±11.6	58.4 ± 11.8	540	433	n/a	n/a	n/a	n/a	336	281	151	108
Shen ZJ[31]	76	64	61.0 ± 10.6	60.3 ± 10.5	50	48	14	19	50	38	34	22	11	3
Zhang Jian[32]	118	70	58.3 ± 10.2	58.6 ± 10.4	99	58	47	34	29	10	86	44	32	14
Bimmer E. Claessen[33]	122	51	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Table III. Study characteristics, by DES versus BMS of CTO recanalization.

Author	Prior CABG		Prior PCI		Prior MI		EF (%SD)		MVD		LAD		Cx		RCA		Lesion length(mm)	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
Kim K[5]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	33.66 ± 19.65	25.76 ± 13.17
Lei Ge[6]	15	19	n/a	n/a	67	164	52.9 ± 10.4	53.4 ± 10.5	96	180	48	95	40	79	56	112	10.4 ±10.2	9.6 ± 6.9
Maarten J. Suttorp[7]	3	2	18	16	47	51	n/a	n/a	53	49	33	36	25	22	42	42	16.0 ± 9.3	16.3 ± 9.3
Angela Migliorini([8])	8	4	21	6	47	12	n/a	n/a	38	11	27	8	31	5	45	13	39 ± 22	33 ± 24
Aleksiadi ER[9]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Kazuyuki O[10]	n/a	n/a	n/a	n/a	18	41	56.0 ± 15.0	57.0 ± 13.0	34	45	17	37	13	8	16	29	41.0 ± 16.65	26.03 ± 14.10
Henning Kelbaek[11]	7	3	n/a	n/a	41	35	50 ± 11	51 ± 10	25	24	20	24	14	14	30	25	27.5 ± 15.0	22.8 ± 10.0
Angela Hoye[12]	0	0	7	6	31	13	n/a	n/a	26	17	29	8	14	8	13	13	12.7	11.3
Gerald S. Werner[13]	n/a	n/a	n/a	n/a	20	23	67 ± 16	68 ± 15	n/a	n/a	17	16	27	29	4	3	18 ± 13	16 ± 12
Sunao Nakamura[14]	7	10	n/a	n/a	22	42	51.8 ± 7.7	55.8 ± 6.8	47	100	31	65	17	32	17	40	24.8±5.5	23.6 ± 6.6
Gerald S. Werner[15]	9	5	n/a	n/a	31	42	65 ± 16	63 ± 18	n/a	n/a	27	22	8	6	47	54	n/a	n/a
Abhiram Prasad[16]	28	81	48	147	43	162	n/a	n/a	83	335	55	177	41	134	58	179	n/a	n/a
Francesco De Felice[17]	3	0	6	3	37	31	50 ± 14	51 ± 11	28	15	27	32	9	7	16	8	25 ± 14	17 ± 8
Kandzari DE[18]	17	3	65	25	67	136	n/a	n/a	n/a	n/a	59	78	43	29	98	95	n/a	n/a
Francesco De Felice[19]	3	3	8	8	68	82	52.0 ± 9.3	50.0 ± 10.0	57	53	61	61	18	24	32	27	23.7 ± 9.6	16.7 ± 6.9
Paolo Rubartelli[20]	5	4	11	15	24	24	55.1 ± 8.8	55.4 ± 11.3	48	53	24	20	15	21	35	37	n/a	n/a
G. Godino[21]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	354	140	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Bimmer E. Claessen[22]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Carlo La Spina[23]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Hector M. Garcia-Garcia[24]	3	0	n/a	n/a	39	36	n/a	n/a	n/a	n/a	35	20	15	20	28	32	n/a	n/a
Gerald S. Werner[25]	n/a	n/a	n/a	n/a	36	47	62.0 ± 17.0	64.0 ± 19.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	23.0 ± 16.0	22.0 ± 13.0
Kotaro Obunai[26]	n/a	n/a	269	170	409	208	52.0 ± 10.0	54.0 ± 10.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	25.9 ± 17.4	20.9 ± 15.6
Kelbaek H[27]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Francesco De Felice[28]	4	3	9	8	76	117	52.0 ± 9.0	52.0 ± 11.0	63	61	67	89	18	35	39	35	23.0 ± 10.0	16.0 ± 7.0
Rahel BM[29]	3	2	18	16	47	51	n/a	n/a	53	49	33	36	25	22	42	42	16.0 ± 9.3	16.3 ± 9.3
Han Ya-ling[30]	n/a	n/a	n/a	n/a	356	274	n/a	n/a	512	418	422	334	108	95	238	201	n/a	n/a
Shen ZJ[31]	2	0	n/a	n/a	37	34	n/a	n/a	39	37	33	18	15	18	28	29	n/a	n/a
Zhang Jian[32]	n/a	n/a	n/a	n/a	68	32	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Bimmer E. Claessen[33]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

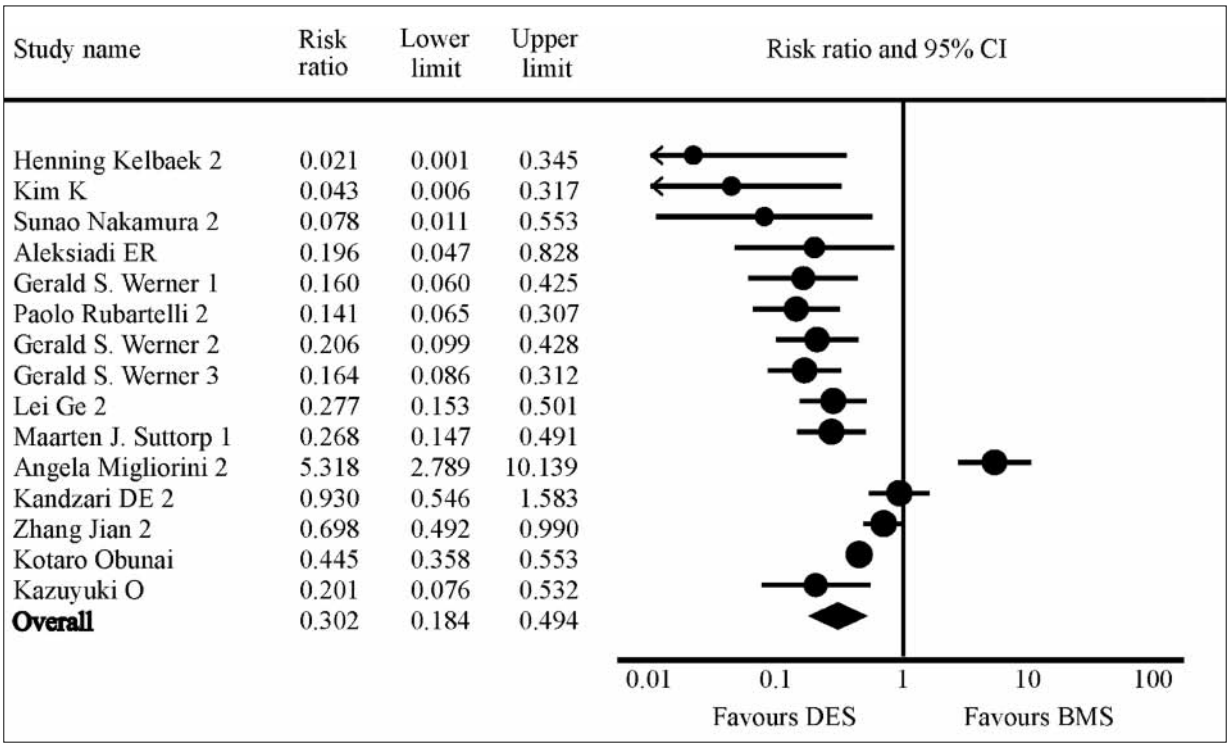

Figure 2. Forest plot of studies that compared the effect of chronic total occlusion recanalization with DES and BMS on binary restenosis during available follow-up.

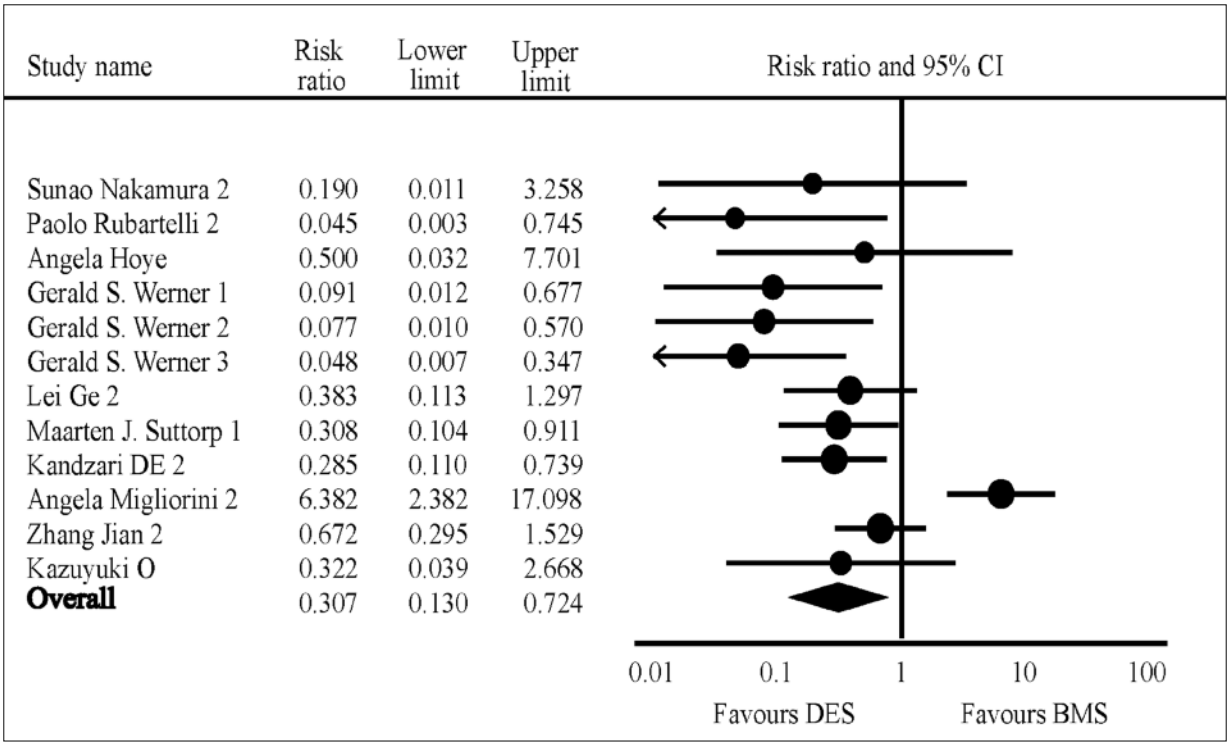

Figure 3. Forest plot of studies that compared the effect of chronic total occlusion recanalization with DES and BMS on reocclusion during available follow-up.

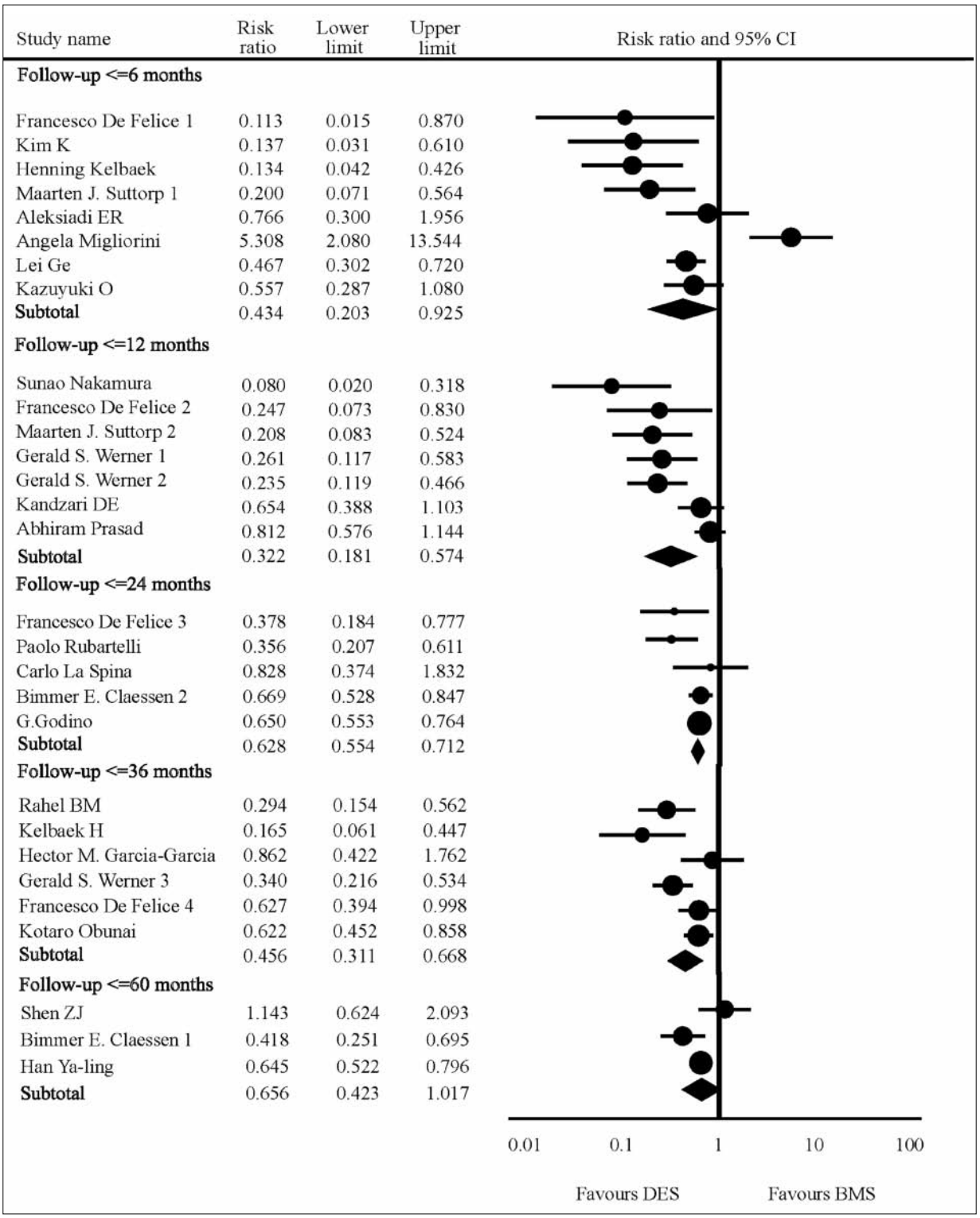

Figure 4. Forest plot of studies that compared the effect of chronic total occlusion recanalization with DES and BMS on MACEs during follow-up at 6, 12, 24, 36 and 60 months.

All-cause Death

All-cause death rate was available for analysis in 25 studies in 3,956 and 3,200 patients enrolled in DES and BMS groups. The incidence of all-cause death at 6, 12, 24, 36, and 60 months were 1.41%, 0.35%, 2.71%, 2.74%, and 9.63% respectively in DES group, and were 0.51%, 1.49%, 2.30%, 4.24%, and 11.28% respectively in BMS group. The pooled peto ORs are 5.09 (95% CI 1.22 to 21.34, $p = 0.03$, Q = 3.77 $p = 0.15$, $I^2 = 46.96\%$), 0.26 (95% CI 0.08 to 0.87, $p = 0.03$, Q = 0.79 $p = 0.94$, $I^2 = 0.00\%$), 1.12 (95% CI 0.58 to 2.14, $p = 0.74$, Q = 0.51 $p = 0.92$, $I^2 = 0.00\%$), 0.75 (95% CI 0.43 to 1.30, $p = 0.31$, Q = 7.69 $p = 0.10$, $I^2 = 47.95\%$), and 0.85 (95% CI 0.62 to 1.17, $p = 0.32$, Q = 5.85 $p = 0.12$, $I^2 = 48.74\%$) at those time points (Figure 5).

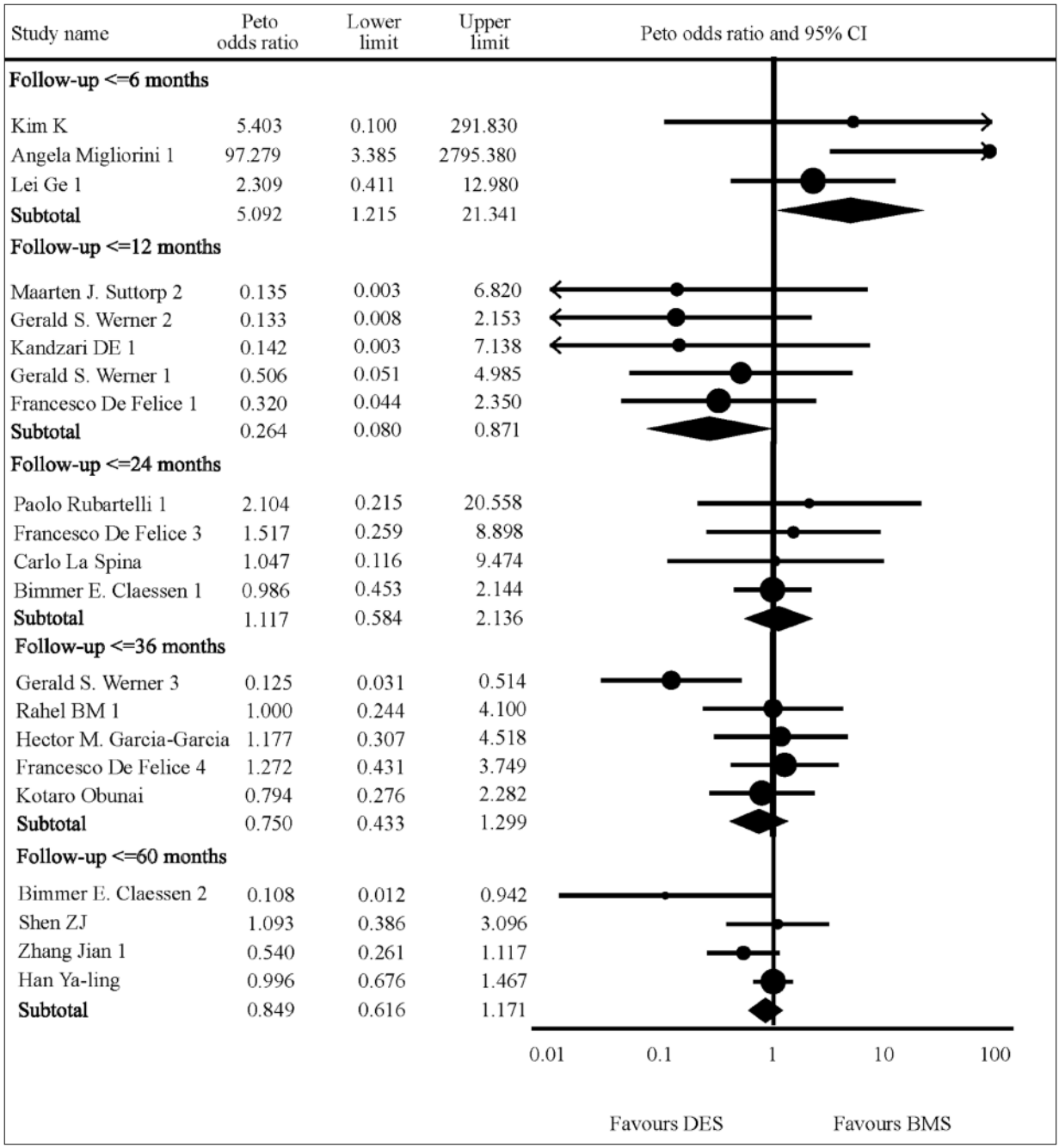

Figure 5. Forest plot of studies that compared the effect of chronic total occlusion recanalization with DES and BMS on all-cause death during follow-up at 6, 12, 24, 36 and 60 months.

Myocardial Infarction

Data on MI were available for analysis in 22 studies in 3,168 and 2,652 patients enrolled in DES and BMS groups. The incidence of MI at 6, 12, 24, 36, and 60 months were 2.54%, 0.78%, 2.03%, 1.09%, and 2.02% respectively in DES group, and were 3.60%, 5.71%, 1.81%, 2.63%, and 2.61% respectively in BMS group. The pooled peto ORs are 0.92 (95% CI 0.45 to 1.89, $p = 0.82$, Q = 1.20 $p = 0.55$, $I^2 = 0.00\%$), 0.21 (95% CI 0.11 to 0.40, $p < 0.001$, Q = 1.52 $p = 0.68$, $I^2 = 0.00\%$), 1.10 (95% CI 0.52 to 2.30, $p = 0.81$, Q = 1.03 $p = 0.79$, $I^2 = 0.00\%$), 0.85 (95% CI 0.43 to 1.66, $p = 0.63$, Q = 4.43 $p = 0.35$, $I^2 = 9.69\%$), 0.93 (95% CI 0.20 to 4.32, $p = 0.92$, Q = 0.47 $p = 0.50$, $I^2 = 0.00\%$) at those time points (Figure 6).

MACE-Free Survival

Eighteen studies were available with the comparison of MACE-free survival, which included 4,071 and 3,296 CTO patients in DES and BMS group. MACE-free survival was clinically and

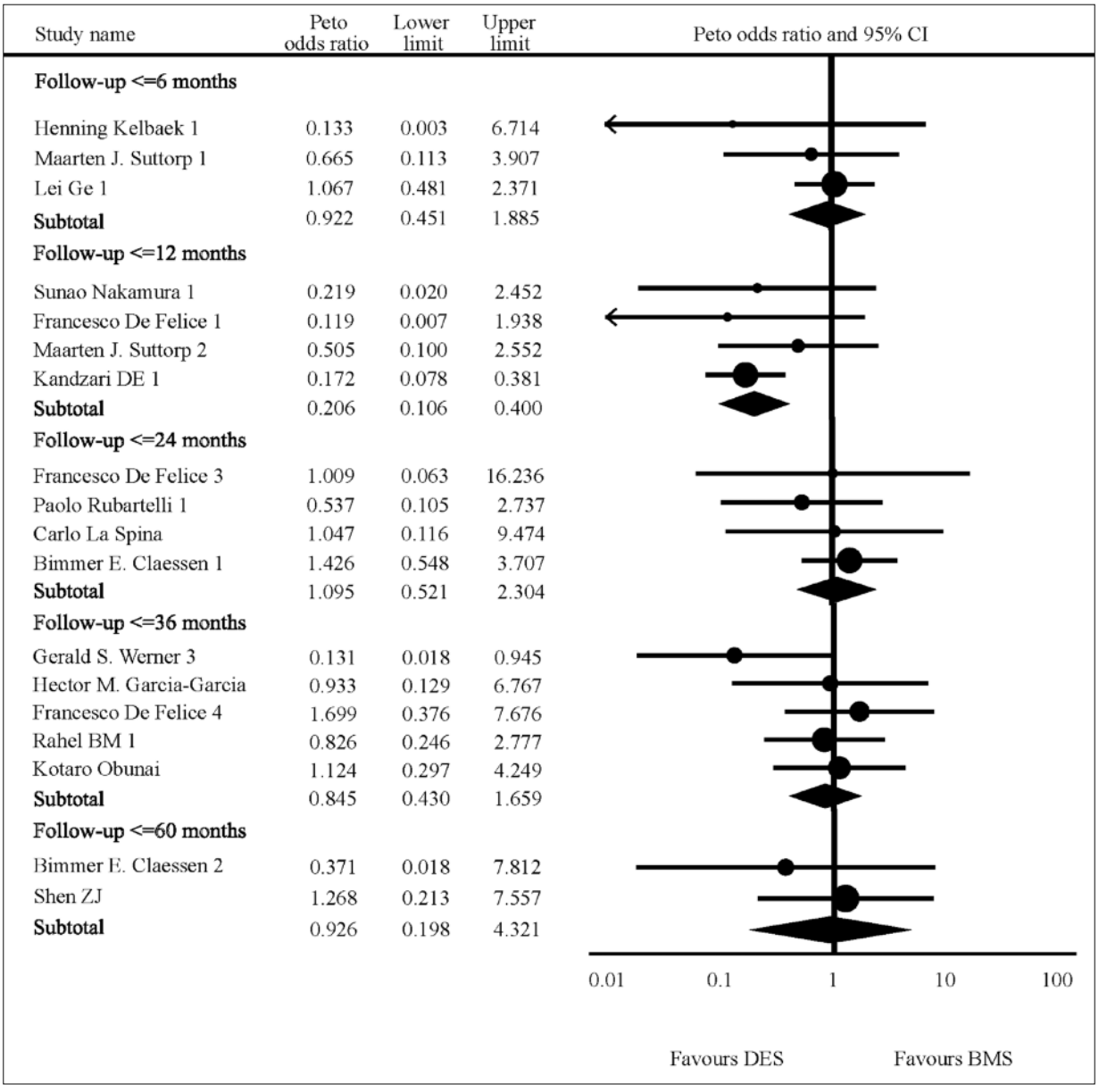

Figure 6. Forest plot of studies that compared the effect of chronic total occlusion recanalization with DES and BMS on myocardial infarction during follow-up at 6, 12, 24, 36 and 60 months.

significantly improved by 73%, 68%, 49%, 40% and 37% respectively in DES group at 6,12, 24, 36, and 60 months (HRs; 0.27 (95% CI 0.18 to 0.41, $p < 0.001$, Q = 2.94 $p = 0.23$, $I^2 = 32.08\%$), 0.32 (95% CI 0.23 to 0.43, $p < 0.001$, Q = 5.03 $p = 0.41$, $I^2 = 0.57\%$), 0.51 (95% CI 0.35 to 0.75, $p < 0.001$, Q = 7.20 $p = 0.03$, $I^2 = 72.22\%$), 0.58 (95% CI 0.45 to 0.75, $p < 0.001$, Q = 0.90 $p = 0.64$, $I^2 = 0.00\%$) and 0.63 (95% CI 0.51 to 0.77, $p < 0.001$, Q = 2.44 $p = 0.30$, $I^2 = 17.85\%$) respectively (Figure 7).

The effect of DES implantation on MACE-free survival at 6 months was significantly higher than those at 24, 36 or 60 months (Interaction $p = 0.04$, 0.005 and 0.003 for 6 months versus 24, 36 or 60 months). Furthermore, the effect of DES implantation on MACE-free survival at 12 months was also significantly higher than those at 36 or 60 months (Interaction $p = 0.003$ and 0.002 for 12 months versus 36 or 60 months). No statistical significance was shown when comparing the effect at other time points.

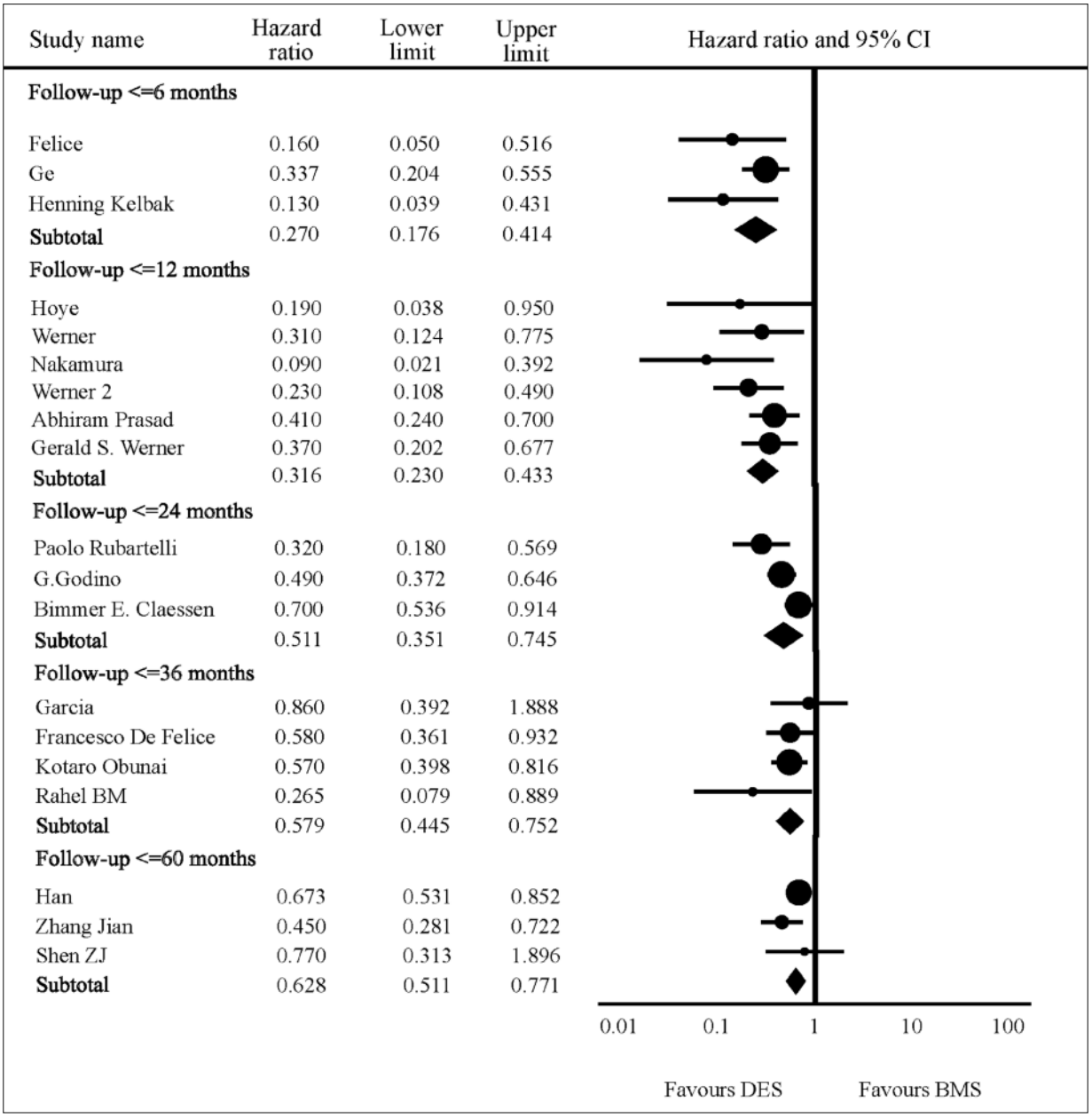

Figure 7. Forest plot of studies that compared the effect of chronic total occlusion recanalization with DES and BMS on MACE-Free survival during follow-up at 6, 12, 24, 36 and 60 months.

In-stent Thrombosis

Data on in-stent thrombosis were available for analysis in 17 studies in 3,373 and 2,333 patients enrolled in DES and BMS groups. The incidence of in-stent thrombosis at 6, 12, 24, 36, and 60 months were 0.70%, 1.35%, 1.08%, 2.11%, and 0.95% respectively in DES group, and were 0.47%, 0.00%, 0.67%, 1.02%, and 0.54% respectively in BMS group. The pooled peto ORs are 1.20 (95% CI 0.16 to 8.82, p = 0.86, Q = 3.47 p = 0.18, I^2 = 42.28%), 7.46 (95% CI 0.46 to 120.17, p = 0.16, Q = 0.00 p = 1.00, I^2 = 0.00%), 1.55 (95% CI 0.66 to 3.63, p = 0.32, Q = 3.09 p = 0.38, I^2 = 2.82%), 2.63 (95% CI 1.21 to 5.71, p = 0.01, Q = 2.99 p = 0.39, I^2 = 0.00%) and 1.84 (95% CI 0.24 to 13.86, p = 0.55, Q = 0.51 p = 0.47, I^2 = 0.00%) at those time points (Figure 8).

Discussion

CTO, which has a low success rate in recanalization, is the end stage of atherosclerosis. The high incidence of short term in-stent restenosis and reocclusion in BMS or balloon angioplasty throws doubt on long-term efficacy of percutaneous coronary interventions. The introduction of DES has been demonstrated to cause less restenosis and reocclusion than BMS in CTO pa-

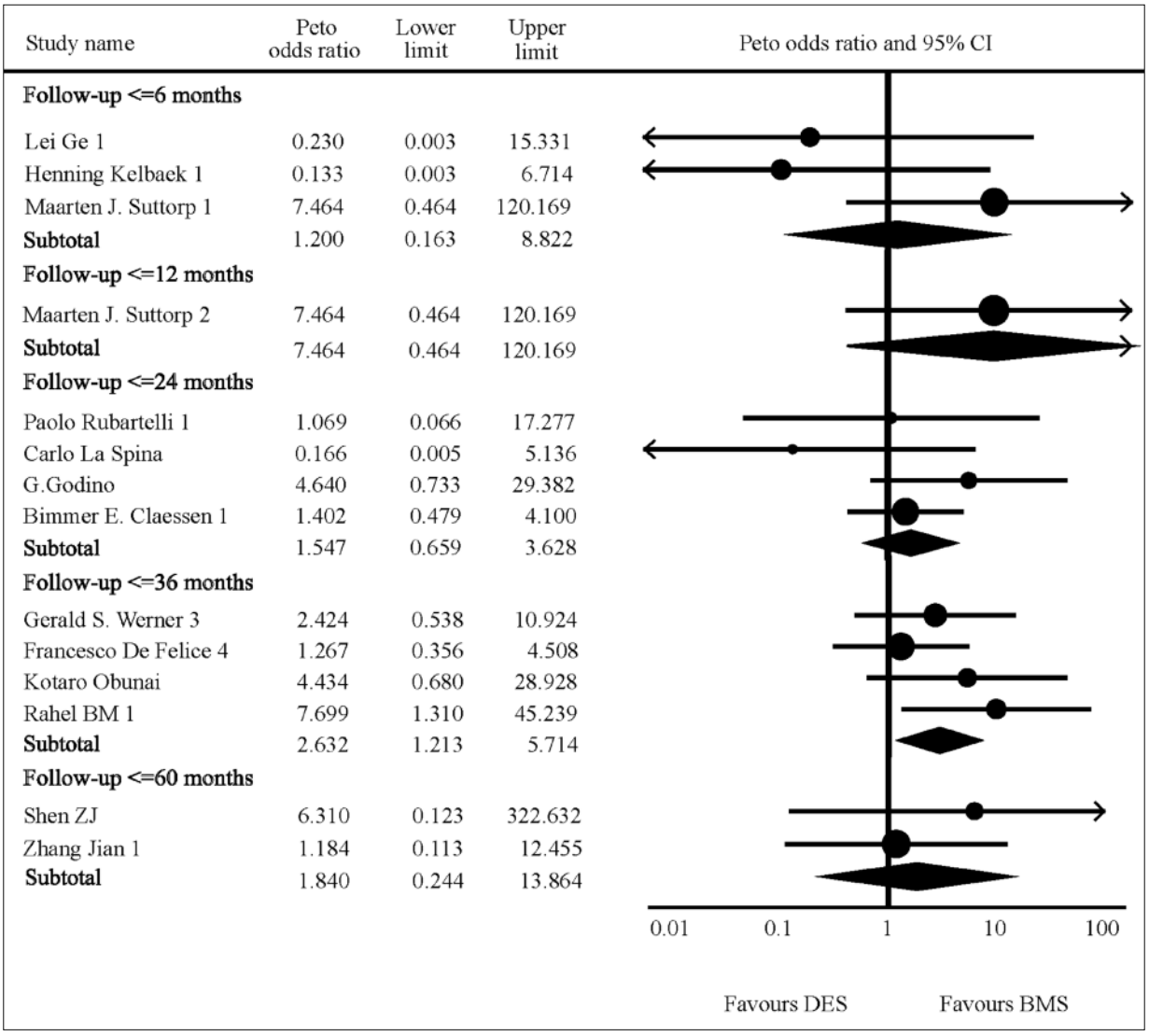

Figure 8. Forest plot of studies that compared the effect of chronic total occlusion recanalization with DES and BMS on in-stent thrombosis during follow-up at 6, 12, 24, 36 and 60 months.

tients. However, the long-term benefit and safety of DES in CTO remains unclear. Moreover, the influence of follow-up duration on the efficacy and safety profile of DES is not fully evaluated. There was no similar analysis in related published meta-analysis[38-40]. This systematic review and meta-analysis, which included 29 studies with 9106 CTO patients, focused on clinical and angiographic efficacy comparison between DES and BMS implantation for CTO lesions at different follow-up duration.

The results indicate that DES for CTO recanalization is superior to BMS in terms of restenosis, reocclusion during long-term periods. Published literatures show that the incidence of binary restenosis and reocclusion in DES group is reduced by 0.49%-59.07%, and 4.06%-21.05% respectively. The significant differences may be related to the different lost in follow-up rate, which varies from 0% to 43.22% and 0% to 28.57% in DES and BMS group respectively in published literatures. While this systematic review and meta-analysis indicated that, compared with BMS, DES reduced restenosis and reocclusion by 26.18% and 7.67% respectively after 6 months implantation in CTO recanalization ($p < 0.01$). The pooled analysis for published articles showed that the lost to follow-up rates were similar in both groups (5.29% and 6.84% in DES and BMS group, respectively). Sample size pooling for meta-analysis makes it possible to show the real effect of DES on binary restenosis and reocclusion. Moreover, the pooled results of binary restenosis and reocclusion for CTO patients in DES group were similar to those for non-CTO patients implanted with DES[41]. So DES plays an important role in the prevention of binary restenosis and reocclusion in the treatment of CTO lesions.

Compared with BMS group, DES group have a more significant MACE reduction in the previous studies, our analysis suggested that the incidence of MACE in DES group was lower than that in BMS group within 36 months after stent implantation, which is consistent with previous meta-analysis[38-40], but no difference was shown at 60 months ($p > 0.05$). DES may reduce death and MI by preventing binary restenosis and reocclusion resulted from inhibiting or delaying the growth of vascular endothelial cells within 36 months[42]. However, the role of DES and BMS might be equal when the effect of drug released from DES disappear completely within 60 months[43,44]. In addition, the influencing factors besides stent itself are more complicated during long term follow up.

Published independent studies show that the incidences of all cause death and MI are low after 6 months implantation both in BMS and DES group. Previous meta-analyses use randomized effect model for RR and OR without evaluating impact of low incidence factors on pooled parameters which lead to no difference between BMS and DES[38-40]. However, our meta-analysis applied peto OR, commonly used for low incidence events, for pooled effect evaluation and showed significant high death rate in DES group at 6 months ($p = 0.026$). The introduction of peto OR lead to the different results between present and previous study, so a larger sample size is needed for the confirmation of our conclusion. The peto OR of all cause death and MI showed significant difference between DES and BMS groups at 12 months ($p < 0.05$). We assumed that the much lower incidence of restenosis and reocclusion may have an influence on the lower MI and all-cause death rate in DES group. The reasons why no difference were shown at other time points could be (1) the sample size for death and MI evaluation is not large enough to identify the real difference between two groups. (2) All cause death also contained non-cardiac deaths during long term follow up which may be beyond the role of cardiac death. Further analysis should be done to fully evaluate the impact on long term death and MI.

Pooled effect of MACE-free survival from 17 articles in this meta-analysis showed that DES for CTO recanalization was superior to BMS in terms of prolonging the MACE-free survival at all time points, which indicates that DES may improve survival time for CTO patients compared with BMS. Moreover, HRs for DES and BMS comparison tended to increase at all 5 time points. HRs of MACE-free survival rate between two groups at 36 and 60 months were different from those at 6 and 12 months ($p < 0.05$), which indicates that the difference of HR for MACE-free survival are getting smaller with time going by. Usually, the high rate of censored data may affect the accuracy of data analysis. It is difficult to show statistical difference for survival rate when MACE-free morbidity is less than 50%. This meta-analysis did show significant difference even if MACE-free morbidity was less than 50%. But we still need to extend follow up duration to get less censored data with more valid conclusion.

In-stent thrombosis is one of the most serious complications of stent implantation, which could lead to acute MI, even death. The incidence of in-stent thrombosis is very low, but morbidity is up

to 20% to 25%[45,46]. Some studies suggest that delayed endothelialization at stented site and accumulation of platelets may increase the risk of late stage IST[47, 48]. But the difference of IST incidence between DES and BMS is still under debate. Our study revealed that the risk of in-stent thrombosis in DES group showed tendency to increase but no significant difference ($p = 0.067$) compared with BMS implantation regardless of follow up duration. The results are consistent with published meta-analysis[39]. After grouping by time, the IST incidence in DES group was twice that in BMS group at 36 months ($p < 0.05$). No significant heterogeneity was found by meta-regression for baseline diabetes, multivessls disease and long lesion length, It is indicated that all these baseline factors have no impact on the IST incidence of postoperative late stage. Further analysis found that antiplatelet therapy in DES group usually lasted for 6 to 12 months and in BMS group for 3 months[49], which may be a reason for the similar rate of in-stent thrombosis between BMS and DES. Nevertheless, the stent lesion may not be fully endothelialized because of sustained drug release even at 36 months after implantation[21], while at that time the antiplatelet therapy was stopped for nearly one year, which could increase the risk of in-stent thrombosis. Therefore, whether antiplatelet therapy should be maintained for longer time such as 36 months needs further investigation.

However, although risk of in-stent thrombosis was higher in DES group, there is no significant difference of the incidence of death and MI between two groups. Assumption could be like this: increased in-stent thrombosis in DES group may potentially increase the risk of death and MI for CTO patients, but decreased restenosis and reocclusion may have a contrary effect on death and MI, which is incomparable with that in BMS group.

Study limitation: there were only five RCTs available in this meta-analysis while the rest were cohort studies, which may lead to selection bias and become confounding factors for comparison. More RCTs should be done for valid conclusion for clinical practice.

Conclusions

In this study, we have obtained several conclusions. Firstly, DES in CTO recanalization leads to significant fewer major adverse cardiac events, restenosis, and reocclusion and improved MACE-free survival than BMS during long term follow up. Secondly, the incidence of death and MI shows significant difference at 6 and 12 months. Thirdly, the risk of in-stent thrombosis in DES is higher than that in BMS after 36 months of implantation. Finally, the change of MACE-free survival along with follow-up period indicates that the effect of drug-eluting stent fades away.

Acknowledgements

This study was supported by two grants from the National Nature Science Foundation of China (30872186, 81072388), one grant from the Leading Talents of Science in Shanghai 2010 (022) and the other grant was sponsored by Program of Shanghai Subject Chief Scientist (09XD1405500).

Conflict of Interest

The authors report no financial relationships or conflicts of interest regarding the content herein.

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