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Comparison of coronary DES and BMS in octogenarians: A systematic review and meta-analysis

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Abstract

Objective Uncertainty exists regarding the relative performance of drug-eluting stents (DES) versus bare-metal stents (BMS) in octogenarians undergoing percutaneous coronary intervention (PCI). We undertook a meta-analysis to assess outcomes for DES and BMS in octogenarians undergoing PCI. **Methods** Electronic data bases of PubMed, Cochrane, and EMBASE were searched. We included randomized, controlled clinical trials (RCT) and observational studies comparing DES and BMS in octogenarians receiving PCI. The methodological qualities of eligible trials were assessed using a "risk of bias" tool. The endpoints included all-cause death, major adverse cardiac events (MACE), myocardial infarction (MI), target vessel revascularization (TVR), major bleeding, and stent thrombosis (ST). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each endpoint. **Results** A total of one RCT and six observational studies were included and analyzed in this meta-analysis. All trials were of acceptable quality. At 30 days, compared with DES-treated patients, BMS-treated patients had a higher incidence of mortality (OR: 3.91, 95% CI: 1.10–13.91; $P = 0.03$). The OR for MACE (1.52, 95% CI: 0.56–4.17; $P = 0.13$), MI (0.81, 95% CI: 0.37–2.17; $P = 0.23$), TVR (0.75, 95% CI: 0.17–3.41; $P = 0.41$), major bleeding (0.77, 95% CI: 0.35–1.68; $P = 0.43$), and ST (1.44, 95% CI: 0.32–6.45; $P = 0.33$) did not reach statistical significance. At one year follow-up, the OR did not favor BMS over MACE (MACE, defined as the composite of death, myocardial infarction, and TVR) (1.87; 95% CI: 1.22–2.87; $P < 0.01$), MI (1.91, 95% CI: 1.22–2.99; $P < 0.01$), TVR (3.08, 95% CI: 1.80–5.26; $P < 0.01$) and ST (3.37, 95% CI: 1.12–10.13; $P < 0.01$). The OR for mortality (1.51; 95% CI: 0.92–2.47; $P = 0.10$) and major bleeding (0.85, 95% CI: 0.47–1.55; $P = 0.60$) did not reach statistical significance. At > 1 year follow-up, the OR for all endpoints, including mortality, MACE, MI, TVR, major bleeding, and ST, did not reach statistical significance. **Conclusions** Our meta-analysis suggests that DES is associated with favorable outcomes as compared with BMS in octogenarians receiving PCI.

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Keywords: Drug-eluting stents; Bare-metal stents; Percutaneous coronary intervention; Meta-analysis; Octogenarians

1 Introduction

Octogenarians constitute the fastest growing segment of the population in the Western world.[1,2] Octogenarians are characterized by a high prevalence of coronary artery disease with a growing number of octogenarians undergoing coronary revascularization.[3,4] Several randomized trials have shown that drug-eluting stents (DES) have significantly decreased the incidence of in-stent restenosis and the need for repeat revascularizations in the overall population with various clinical indications using DES.[5–8] However, there remains some clinical uncertainty over the ideal stent type for octogenarians receiving percutaneous coronary intervention (PCI). Firstly, very elderly patients were not adequately represented in these studies. There is a paucity of data on long-term safety and efficacy of DES pertaining specifically to octogenarians undergoing PCI. Additionally, the greater co-morbidity in octogenarians might make them more susceptible to complications due to the dual antiplatelet therapy required and the more frequent need for interruptions of this treatment. These concerns about safety may explain the reason why DES are used relatively less frequently in the very elderly population.[9] Given the limited evidence for these patients on the risks and benefits of coronary BMS and DES in octogenarians receiving PCI, we conducted a meta-analysis of all comparative studies available in the published data of this high-risk cohort.

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2 Methods

2.1 Literature search

We researched PubMed, Cochrane, and EMBASE for randomized, controlled trials and observational studies comparing coronary-BMS with DES in octogenarians (last update January 31, 2013). The terms used for searching, included "drug-eluting stents", "sirolimus", "everolimus", "zotarolimus", "paclitaxel", "bare metal stents", and "octogenarians". The references of the retrieved articles were also confirmed. Language restrictions were not imposed in our search. Studies included in this meta-analysis were based on the following inclusion criteria: (1) studies comparing the efficacy and safety of coronary DES to BMS in octogenarians, and (2) follow-up duration ≥ 12 months. The major reasons for exclusion from the study were: (1) Studies investigated either coronary DES or BMS (but not both) in octogenarians; (2) Data were duplicated; (3) Demographic background of the patients and preoperative conditions were not similar; and (4) No useful data on relevant clinical outcomes were reported. Inconsistencies were resolved by consensus among all authors.

2.2 Data extraction and main endpoints

The following information was extracted from each study: year of publication, study design, number of patients, stent type, average length of follow-up, all-cause death, myocardial infarction (MI), stent thrombosis (ST), target vessel revascularization (TVR), major bleeding, and major adverse cardiac events. These endpoints were extracted as outcomes at 30 days, 1 year follow-up, and > 1 year follow-up.

2.3 Risk of bias in individual studies

Included studies were assessed for the following characteristics: design (prospective or retrospective), randomization (yes or no), multi-center enrollment (yes or no), characteristics of participants and personnel (performance bias), outcome assessment (detection bias), incomplete outcome data addressed (attrition bias) and consideration of multivariate adjustment(s) for possible confounders. Two independent reviewers assessed the risk of bias. Agreement between the two reviewers was assessed using kappa statistics for full text screening, and rating of relevance and risk of bias. When there was disagreement concerning the risk of bias, a third reviewer (the first author) checked the data and determined the final decision on the differing (controversial) opinions.

2.4 Statistical analysis

For each trial, odds ratios (OR) with the 95% confidence intervals (95% CI) of death by any cause, MACE, MI, TVR, ST, and major bleeding were calculated, or were derived. For the meta-analysis, both the fixed-effects model and the random-effects model were considered. To assess the inter-study heterogeneity more precisely, both the chi-square based Q statistic test-to-test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation attributable to heterogeneity were calculated.[10] For each meta-analysis, the Q statistic of Cochrane was first calculated to assess the heterogeneity of the included trials. For *P* values less than 0.05, the assumption of homogeneity was deemed invalid, and the random-effects model was used; otherwise, data were assessed using the fixed-effects mode. Additionally, to validate the credibility of outcomes in this meta-analysis, a sensitivity analysis was performed by sequential omission of individual studies. Publication bias in this meta-analysis was assessed using funnel plot, and an asymmetric plot suggested the possiblility of publication bias. Consequently, funnel plot asymmetry was further assessed by linear regression test method of Egger. Statistical analyses were performed with the software program STATA (version 9.0, StataCorp LP, College Station, TX, USA). All *P* values were two-sided and a *P* value of less than 0.05 was deemed statistically significant.

3 Results

3.1 Search results and study characteristics

As shown in Figure 1, 236 potentially eligible studies were identified. A total of 216 of these records were excluded, leaving 20 potentially relevant studies. We then excluded seven duplicate articles and six studies for no (lacking) available data. Thus, seven studies (one random-

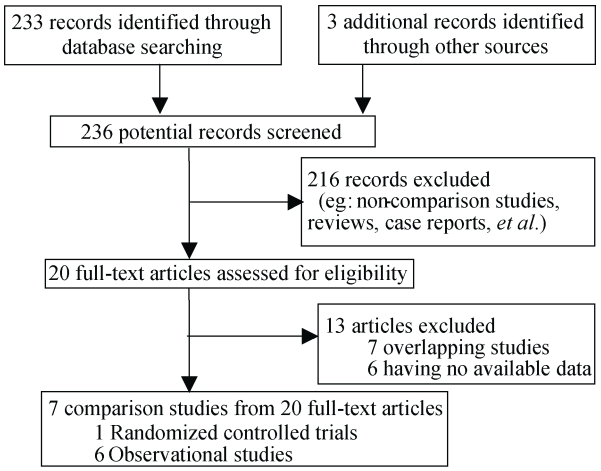

Figure 1. Flow chart demonstrating selection of studies for inclusion in the meta-analysis.

Table 1. Main characteristics of included studies.

Study	Year	Region	Patients (BMS/DES)	Study year	Study design	Age(yrs) (BMS/DES)	Outcome	Follow-up period(moth)
Ma, *et al*.[12]	2008	China	21/59	2004–2006	Observational	88/87	Cardiac death, TVR, MACE, MI, stroke, major bleeding	24 (12–36)
Ouldzein, *et al*.[11]	2009	France	293/167	2005	Observational	82/80	Death, cardiac death, MACE, MI, stroke, ST, major bleeding	12
López-Palop, *et al*.[13]	2009	Spain	86/90	2002–2006	Observational	83/83	Death, cardiac death, MACE, MI, stroke, ST, major bleeding, TVR	26.3
Maekawa, *et al*.[14]	2011	Japan	29/46	2005–2009	Observational	84/83	Death, MACE, MI, TVR	12
Marcolino, *et al*.[15]	2012	Netherlands	99/192	2000–2005	Observational	82/82	Death, MACE, MI, TVR, ST	48
Torre Hernandez, *et al*.[17]	2012	England/Spain	401/399	2011–2012	RCT	83/84	Death, cardiac death, MACE, MI, TVR, major bleeding	12
Matsumi, *et al*.[16]	2013	Japan	104/102	2004–2006	Observational	84/82	Death, cardiac death, MACE, MI, TVR, major bleeding, ST	39

BMS: bare-metal stent; DES: drug-eluting stent; MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularization; ST: stent thrombosis. RCT: randomized, controlled trials.

Table 2. Preoperative characteristics of patients.

Study	Patients (BMS/DES)	Age	Male Gender (%)	Hyperten-tion (%)	Diabetes (%)	Hyperlipi-demia (%)	Current Smokers (%)	Renal Fai-lure (%)	ACS (%)	Prior MI (%)	Prior PCI (%)	Prior CABG (%)
Ma, *et al*.[12]	21/59	88/87	57/52	62/68	10/12	33/49	0/5	NA/NA	100/100	33/32	14/36	29/20
Ouldzein, *et al*.[11]	293/167	82/80*	60/70	63/68	21/30*	46/53	26/30	16/18	68/65	20/20	18/27	8/10
López-Palop, *et al*.[13]	86/90	83/83	53/68	83/74	30/42	40/44	16/34*	11/13	90/93	21/20	6/4	8/6
Maekawa, *et al*.[14]	29/46	84/83	66/74	72/74	40/38	48/73	17/6	NA/NA	NA/NA	14/37*	7/37*	0/9
Marcolino, *et al*.[15]	99/192	82/82	51/53	33/43	15/14	23/41*	27/8*	2/6*	64/62	42/33	23/13*	24/14*
Torre Hernandez, *et al*.[17]	401/399	83/84	59/61	78/75	24/26	53/58	4/5	NA/NA	67/68	22/30*	10/13	4/7
Matsumi, *et al*.[16]	104/102	84/82*	53/74*	64/68	24/33	46/50	12/10	2/4	58/15*	16/25	26/43*	3/12*

Data are presented as number treated with bare metal stent/ number treated with drug-eluting stent. CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; BMS: bare-metal stents; DES: drug-eluting stents; MI: myocardial infarction; NA: not applicable; Other abbreviations as in Table 1. *$P < 0.05$.

ized, controlled trial (RCT) and six observational studies) from 20 full-text articles met our selection criteria and were included in this meta-analysis, involving a total of 2,088 octogenarians receiving coronary DES or BMS implantation.[11-17] The quality of the included RCT was assessed using the Jadad's scoring system, and considered high quality, randomized, controlled trials. Table 1 summarized the main characteristics of the analyzed studies. Patient demographics in the group undergoing BMS implantation were generally similar to those undergoing DES implants (Table 2). However, there was incomplete reporting of baseline demographics across studies. Medication profiles, including duration of antiplatelet drug therapy, were inconsistently reported.

3.2 Thirty days, one year, and over one year outcomes assessment

Estimates of rates for MACE, mortality, MI, TVR, major bleeding, and ST at each of the three recorded time points are displayed in Table 3. At 30 days, compared with DES-treated patients, BMS-treated patients had a higher incidence of mortality (OR: 3.91, 95% CI: 1.10–13.91; $P = 0.03$). The OR for MACE (1.52, 95% CI: 0.56–4.17; $P = 0.13$), MI (0.81, 95% CI: 0.37–2.17; $P = 0.23$), TVR (0.75, 95% CI: 0.17–3.41; $P = 0.41$), major bleeding (0.77, 95% CI: 0.35–1.68; $P = 0.43$), and ST (1.44, 95% CI: 0.32–6.45; $P = 0.33$) did not reach statistical significance. At 1 year follow-up, the OR did not favored BMS for MACE (1.87, 95% CI: 1.22–2.87; $P < 0.01$), MI (1.91; 95% CI: 1.22–2.99; $P < 0.01$), TVR (3.08, 95% CI: 1.80–5.26; $P < 0.01$) and ST (3.37, 95% CI: 1.12–10.13; $P < 0.01$). The OR for mortality (1.51, 95% CI: 0.92–2.47; $P = 0.10$) and major bleeding (0.85, 95%CI: 0.47–1.55; $P = 0.60$) did not reach statistical significance (Figure 2). At > 1 year follow-up, the OR for all endpoints, including mortality, MACE, MI, TVR, major bleeding, and ST, did not reach statistical significance (Table 3).

Table 3. Meta-analysis outcomes.

Outcome	Study	BMS		DES		OR	95% CI	*Q*	*P*	I^2 (%)
		Events	Non-events	Events	Non-events					
MACE										
30 d	4	45	459	29	389	1.524	0.557 – 4.172	8.86	0.031	66.2
1 yr	6	213	712	154	796	1.869	1.217 – 2.870	11.65	0.040	57.1
> 1 yr	4	116	190	144	296	1.271	0.933 – 1.734	4.24	0.237	29.3
Death										
30 d	5	48	485	15	449	3.910	1.099 – 13.914	11.05	0.026	63.8
1 yr	6	131	794	112	838	1.509	0.923 – 2.466	12.26	0.031	59.2
> 1 yr	4	87	219	109	331	1.223	0.873 – 1.713	0.10	0.992	0.00
MI										
30 d	5	10	895	11	806	0.81	0.366 – 2.166	0.63	0.959	0.00
1 yr	5	58	838	33	871	1.910	1.220 – 2.991	1.25	0.869	0.00
> 1 yr	4	20	286	21	419	1.486	0.766 – 2.880	2.86	0.414	0.00
Major bleeding										
30 d	4	13	892	14	803	0.768	0.352 – 1.677	2.33	0.508	0.00
1 yr	4	23	774	24	688	0.854	0.471 – 1.548	0.44	0.931	0.00
> 1 yr	1	0	19	4	53	0.305	0.016 – 5.926	0.00	.	.
TVR										
30 d	2	3	187	4	188	0.752	0.166 – 3.412	0.16	0.689	0.00
1 yr	4	47	566	21	705	3.081	1.804 – 5.263	3.92	0.270	23.4
> 1 yr	4	29	277	34	406	0.976	0.278 – 3.435	11.66	0.009	74.3
ST										
30 d	2	5	392	2	267	1.444	0.324 – 6.445	0.27	0.606	0.00
1 yr	2	17	375	4	355	3.373	1.123 – 10.131	0.79	0.374	0.00
> 1 yr	2	8	175	7	274	1.707	0.219 – 13.282	3.45	0.063	71.0

Data are presented as *n*, unless otherwise noted. BMS: bare-metal stent; DES: drug-eluting stent; I^2: index for degree of heterogeneity; MACE: major adverse cardiac events; MI: myocardial infarction; OR: odds ratio; Q: Cochran's Q-score for heterogeneity; ST: stent thrombosis; TVR: target vessel revascularization.

3.3 Sensitivity analysis and publication bias

To assess the impact of heterogeneity on the pooled effect estimates, we performed a sensitivity analysis. Eliminating the RCT study did not substantially change the pooled point estimate (Table 4). Assessment of publication bias using visual examination of the funnel plot (Figure 3) and Egger's weighted regression statistic (P = 0.26) indicated no significant publication bias.

4 Discussion

4.1 Main findings

The present study was designed to analyze the safety and efficacy of DES in an unselected population of octogenarian patients with an indication for revascularization. In the present meta-analysis of 2,088 octogenarians (≥ 75 yrs) with coronary artery disease receiving PCI, the main findings were as follows: (1) at one year follow-up, octogenarians undergoing PCI with DES had a significantly lower risk of MACE, MI, TVR and ST than those undergoing PCI with BMS; and (2) the accumulative incidence of major bleeding was similar between DES and BMS at 30 days, one year, and > 1 year follow-up.

4.2 Comparison with previous studies

There are limited data available concerning DES benefits specifically in octogenarians.[18] Several studies have observed the benefits of DES in reducing the risk of TVR in short- and long-term follow-up in the overall population, with no significant differences in the risk of death, MI and stent thrombosis.[6-8] The present meta analysis study suggests the benefits of DES in octogenarians with respect to a significant lower incidence of MACE, MI, TVR, and ST

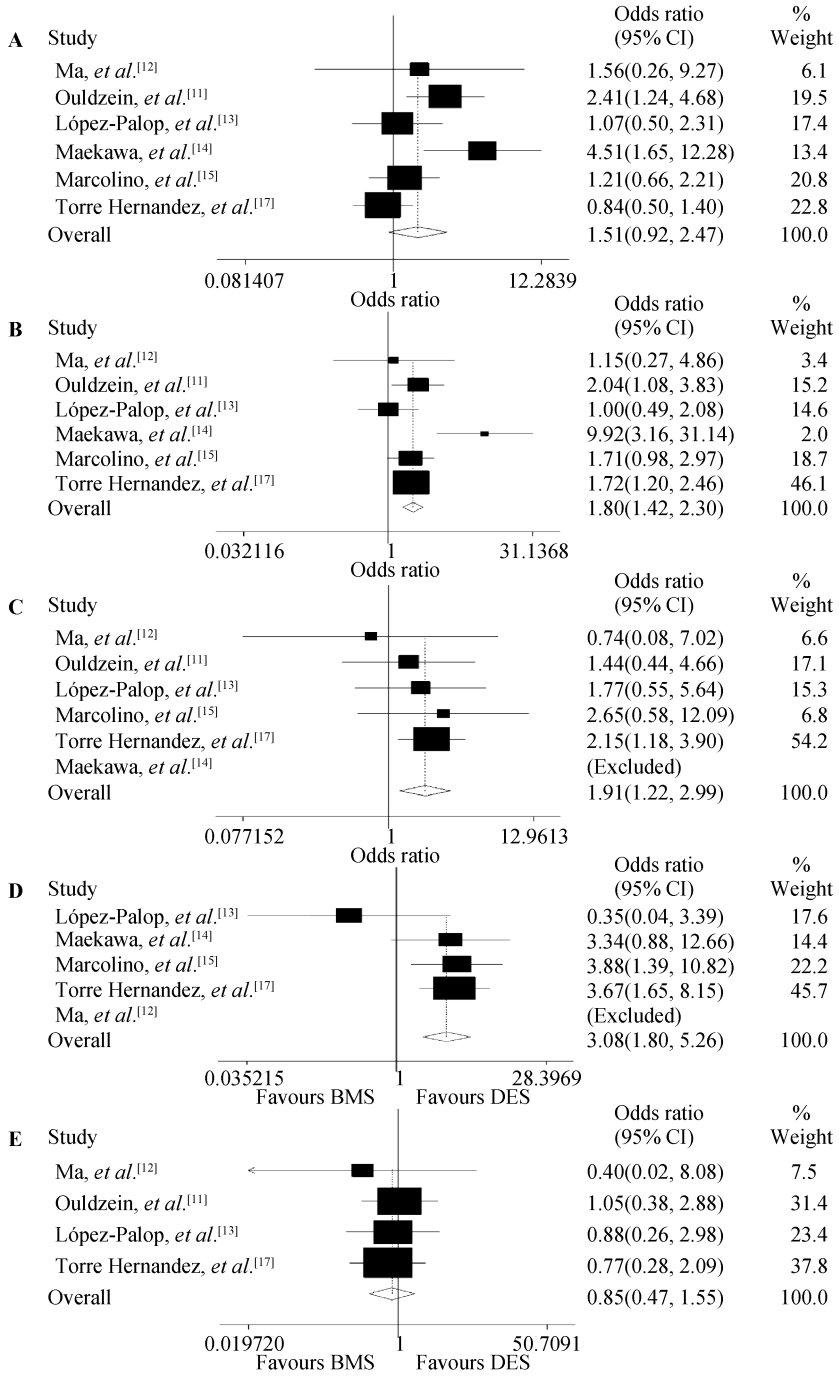

Figure 2. Forest plots showing clinical outcomes of (A) all-cause death, (B) MACE, (C) MI, (D) TVR, (E) major bleeding at 1 year of follow-up. AMI: acute myocardial infarction; BMS: bare-metal stents; DES: drug-eluting stents; ICH: intracranial hemorrhage; TLR: target lesion revascularization. MACE: major adverse cardiovascular events; MI: myocardial infarction; TVR: target vessel revascularization.

when compared to patients receiving a BMS at one year follow-up. However, there is no significant difference in the incidence of major bleeding between DES and BMS populations. Recently, Wang *et al*.[9] examined data from the National Cardiovascular Data Registry CathPCI Registry, which demonstrated that the adjusted hazard ratio (HR) for MI rehospitalization associated with DES use was significantly lower with increasing age: age ≥ 85 years, 9% *vs*. 12% (HR: 0.77, 95% CI: 0.71–0.83); age 75 to 84 years, 7% *vs*. 9% (HR: 0.81, 95% CI: 0.77–0.84). These results are consistent with findings in the meta-analysis in this (of our) study.

Improvement in main endpoints, including MACE, MI, TVR, and ST, observed in DES compared with BMS can be

Table 4. Meta-analysis outcomes after eliminating the RCT study.

Outcome	Study	BMS		DES		OR	95% CI	*Q*	*P*	I^2 (%)
		Events	Non-events	Events	Non-events					
MACE										
30 d	4	45	459	29	389	1.524	0.557 – 4.172	8.86	0.031	66.2
1 year	5	121	403	95	456	1.980	1.067 – 3.673	11.6	0.021	65.5
> 1 year	4	116	190	144	296	1.271	0.933 – 1.734	4.24	0.237	29.3
Death										
30 d	5	48	485	15	449	3.910	1.099 – 13.914	11.05	0.026	63.8
1 year	5	102	422	78	473	1.732	1.227 – 2.446	7.30	0.121	45.2
> 1 year	4	87	219	109	331	1.223	0.873 – 1.713	0.10	0.992	0.00
MI										
30 d	4	9	495	10	408	0.880	0.344 – 2.248	0.63	0.890	0.00
1 year	4	23	472	16	489	1.629	0.823 – 3.223	0.93	0.817	0.00
> 1 year	4	20	286	21	419	1.486	0.766 – 2.880	2.86	0.414	0.00
Major bleeding										
30 d	3	10	390	12	304	0.650	0.270 – 1.563	1.80	0.406	0.00
1 year	3	16	380	15	298	0.905	0.430 – 1.902	0.37	0.833	0.00
> 1 year	1	0	19	4	53	0.305	0.016 – 5.926	0.00	.	.
TVR										
30 d	2	3	187	4	188	0.752	0.166 – 3.412	0.16	0.689	0.00
1 year	3	19	193	13	314	2.586	1.250 – 5.349	3.73	0.155	46.3
> 1 year	4	29	277	34	406	0.976	0.278 – 3.435	11.66	0.009	74.3
ST										
30 d	2	5	392	2	267	1.444	0.324 – 6.445	0.27	0.606	0.00
1 year	2	17	375	4	355	3.373	1.123 – 10.131	0.79	0.374	0.00
> 1 year	2	8	175	7	274	1.707	0.219 – 13.282	3.45	0.063	71.0

Data are presented as *n*, unless otherwise noted. BMS: bare-metal stent; DES: drug-eluting stent; I^2: index for degree of heterogeneity; MACE: major adverse cardiac events; MI: myocardial infarction; OR: odds ratio; Q: Cochran's Q-score for heterogeneity; RCT: randomized controlled clinical trials; ST: stent thrombosis; TVR: target vessel revascularization.

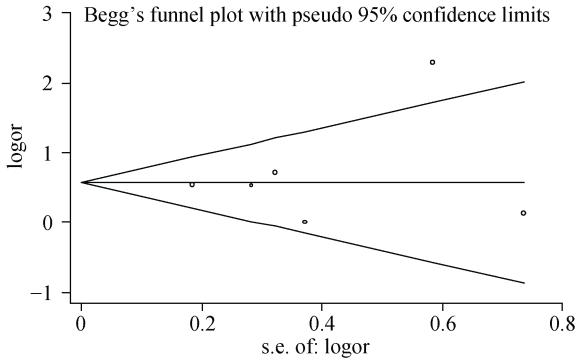

Figure 3. Funnel plot of primary outcome of MACE using 6 included studies showing a near symmetric distribution of effect sizes from the individual studies. MACE: major adverse cardiovascular events.

potentially explained by the fact that a large scale RCT (XIMA, xience or vision stent-management of angina in the elderly) was included in the meta-analysis. XIMA was a multicenter, randomized trial of everolimus-eluting stents (EES) and BMS in 800 octogenarians.[17] No differences in mortality, similar rates of major haemorrhage despite differing dual anti-platelet therapy regimes (1 month for BMS and 12 months for DES) and significantly lower rates of TVR and MI among DES-treated patients was found in the XIMA study. As the second-generation DES, EES is aimed to decrease the risk of TVR by thinning the strut thickness and by reducing the thrombogenicity of durable polymers compared to the first generation DES. In the small SPIRIT trial, the EES was shown to markedly reduce the extent of angiographic late loss at 6 and 12 months compared with the otherwise identical cobalt chromium Vision BMS.[19] To date, few studies directly compared the efficacy and safety between EES and BMS in high risk population,

however, recent published network meta-analysis demonstrated that cobalt-chromium EES was associated with significantly lower rates of cardiac death or MI and ST than BMS in patients with ST-segment elevation myocardial infarction.[20] Furthermore, in our meta-analysis, the absence of differences for major bleeding complications between the two groups might be due to the small number of events and a poor statistical power. Another reason might be the fact that antiplatelet aggregation treatment was continued for a fairly long time in the case of BMS stenting, nearly similar to the time for DES, because most patients in the study were presented as ACS when receiving PCI therapy.

4.3 Clinical implications

Our meta-analysis evaluated the outcomes of octogenarians treated with PCI using DES or BMS during the previous years. It is the largest report of its type describing the short- and intermediate-term clinical outcomes in this high-risk group of patients and includes comprehensive and robust meta-analyses of multiple clinical outcomes. Even though, only one RCT and six observational studies were included in this meta-analysis, they provide a real-world outlook of the comparative effectiveness of both DES and BMS strategies in octogenarians. In light of the benefits that can be obtained with the use of DES, and while waiting for data from additional randomized studies specifically involving octogenarians, DES use should not be limited in these patients solely because of their age.

4.4 Limitations

Clearly, our study has limitations. First, the limitations of the meta-analytical approach are well known and documented; the meta-analytical approach with observational data is even more subject to limitations. The inclusion of only published studies makes our analysis prone to publication bias.[21] Secondly, we did not have data for all studies at each time period, therefore, this limits the comparison of rates across time within a specific end point. Moreover until now, only one randomized, controlled trial has reported the results of coronary DES compared with BMS in octogenarians. Thus, further studies with larger sample sizes and longer term results are needed to verify the outcomes from this meta-analysis. Finally, we were unfortunaltely unable to control the specific type of DES or BMS implanted, as (since) some studies suggest heterogeneous outcomes within the stent types.

5 Conclusions

The results of this meta-analysis suggest that DES is associated with favorable outcomes as compared with BMS in octogenarians receiving PCI. Further studies with larger sample size and longer term results are needed to identify the outcomes from this meta-analysis.

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