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Efficacy and safety of drug-eluting stents in elderly patients: A meta-analysis of randomized trials

Running title: DES vs. BMS in elderly patients

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Abstract

Background: Current guidelines recommend newer generation drug-eluting stents (DES) over bare-metal stents (BMS) in patients with ischemic heart disease. However, there is no age-specific recommendation in elderly patients.

Methods: Meta-analysis was performed of 6 randomized studies enrolling 5,042 elderly patients who underwent percutaneous coronary intervention (PCI) with stent implantation (DES, n = 2,579; BMS, n = 2,463).

Results: Combined data indicated a significant reduction in major adverse cardiovascular events (MACEs) with use of DES (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.44–0.71, p < 0.001). Moreover, use of DES was associated with a significantly lower incidence of myocardial infarction (OR 0.54, 95% CI 0.36–0.81, p = 0.003) and repeat

revascularization (OR 0.44, 95% CI 0.31–0.62, p < 0.001), was compared to that with the use of BMS. Stent thrombosis and bleeding complication rates were not significantly different between groups. In a subgroup meta-analysis, short duration (1 or 6 months) dual antiplatelet therapy (DAPT) was associated with a significantly lower MACE rate (OR 0.49, 95% CI 0.34–0.80; p = 0.003) in elderly patients who underwent PCI with everolimus-eluting stent (EES) implantation, compared with that using long duration DAPT.

Conclusions: This meta-analysis provides clinically relevant evidence that DES rather than BMS should be selected for elderly patients.

Key words: drug-eluting stent, bare-metal stent, elderly, clinical trials, clinical research

Introduction

The introduction of drug-eluting stents (DES) and advanced pharmacotherapy resulted in a significant reduction in restenosis rates [1–5]. This improvement, however, increased the prevalence of bleeding complications due to use of DES and longer duration of dual antiplatelet therapy (DAPT), compared to that using bare-metal stents (BMS) [6]. Long duration of DAPT after DES deployment was associated with higher risk of major bleeding complications despite the beneficial effects of novel platforms, especially in vulnerable populations such as patients over 75 years old [7].

Until recently, guidelines have not provided evidence-based recommendations for treatment of elderly patients [8]. Recently, the SYNERGY II Everolimus eluting stent in patients older than 75 years, undergoing coronary revascularization associated with a short dual antiplatelet therapy (SENIOR) trial demonstrated that use of DES rather than BMS in patients older than 75 years results in lower adverse clinical event rates at 1 year [9]. These observations were also previously seen in the Xience or Vision Stents for the Management of Angina in the Elderly (XIMA) trial, which demonstrated a reduction in myocardial infarction (MI) and in-stent restenosis in the DES group without an increase in bleeding [10]. The superiority of DES in the SENIOR trial was mainly due to a reduction of target lesion revascularization (TLR), but there were no significant differences between all-cause death, MI, and stroke. Therefore, it is unclear whether the clinical benefits of DES were overestimated [11]. Herein, a meta-analysis was performed of randomized studies aiming to assess the benefits and risks associated with DES versus BMS use for percutaneous coronary

intervention (PCI) in elderly patients.

Methods

This study was designed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [12]. A comprehensive MEDLINE, EMBASE, and Cochrane database search was conducted until September 6, 2018, using the following medical subject headings alone and in different combinations: "drug-eluting stent(s)", "DES", "bare-metal stent(s)", "BMS", "coronary artery disease" and "elderly patients". Randomized studies that evaluated elderly patients undergoing PCI and reported on clinical outcomes with follow-up time ≥ 12 months were included. Conventionally, "elderly" has been defined as a chronological age of ≥ 65 years. In the present study however, elderly patients were defined as > 70 years old. Only full articles in peer-reviewed journals were considered.

Two investigators (SAB, YK) extracted baseline study characteristics, clinical outcomes, and DAPT duration of interest from the retrieved studies. Any divergences were resolved by consensus. The number of events associated with clinical outcomes was tabulated for the longest follow-up available.

The primary endpoint was major adverse cardiovascular events (MACEs), defined as a composite of cardiac death, MI, and repeat revascularization, including TLR and target vessel revascularization (TVR). Secondary endpoints were individual components of MACE, definite/probable stent thrombosis, as defined by the Academic Research Consortium, and bleeding complications according to both Thrombolysis in Myocardial Infarction and Bleeding Academic Research Consortium classifications [13, 14]. Subgroup meta-analysis of DES implantation with short (1 or 6 months) versus long (> 12 months) DAPT duration was performed to determine MACE, stent thrombosis, and bleeding complication rates. Moreover, a meta-regression analysis was performed to identify moderators in a linear relationship among baseline characteristics according to the percentage of hypertension, diabetes mellitus, dyslipidemia, and acute coronary syndrome (ACS). The SENIOR trial was included in the short DAPT group, while the XIMA, Basel Stent Kosten Effektivitäts Trial-PROspective Validation Examination (BASKET-PROVE), and Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction (EXAMINATION) trials were included in the long DAPT group.

Quality assessment was performed for both study groups. The risk of bias was assessed of each study with the Cochrane tool and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool [15, 16] was used to assess quality as high, moderate, low, or very low. Most clinical trials showed low evidence of bias with the Cochrane tool. In addition, the level of evidence was strong for primary outcomes assessed with the GRADE tool.

Statistical analysis

The number of patients, events, means, standard deviations (SDs), and percentages were abstracted. Estimates were calculated with a random effects model and confirmed with a fixed effects model and was expressed as odds ratios (ORs). A p-value ≤ 0.05 (2-tailed) indicated statistical significance. The random effects model was prioritized over the fixed effects model and sensitivity analysis was conducted to identify sources of inconsistency. The I^2 statistic was used for evaluation of heterogeneity between studies with values of < 30%, 30% to 60%, and > 60%, corresponding to low, moderate, and high degrees of heterogeneity, respectively [17]. Publication bias was assessed using both the Egger and Begg's tests. A p-value < 0.05 indicated evidence of bias [18]. All data analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). This study was registered with PROSPERO, number CRD42019112969.

Results

The flow chart of the study selection process is shown in Figure 1. Six multi-center randomized controlled trials enrolling 5,042 elderly patients with coronary artery disease (CAD), who underwent PCI with either DES (n = 2,579) or BMS (n = 2,463) implantation were included [9, 10, 19–22]. The study design and characteristics of the trials involved are shown in Table 1. When studies reported results from both unmatched and matched populations, data regarding the matched subgroup were considered. The mean follow-up completion for all trials was relevant, with an overall rate of 98%. The recommended DAPT duration varied between trials (1–12 months), but was the same in both the DES and BMS groups, except in the XIMA trial (1 month of DAPT for patients receiving BMS and 12 months for patients receiving DES).

During long-term follow-up (range 1–2 years), combined data indicated a significant

reduction in MACE with DES use (OR 0.56, 95% confidence interval [CI] 0.44–0.71, p < 0.001, Fig. 2A). There was no significant difference in stent thrombosis between groups (OR 0.68, 95% CI 0.40–1.14, p = 0.142, Fig. 2B). Bleeding complication rates were similar for both groups (OR 0.96, 95% CI 0.78–1.18, p = 0.686, Fig. 2C). In addition, the risk of cardiac death did not differ between the groups (OR 0.81, 95% CI 0.65–1.02, p = 0.075, Fig. 3A). However, use of DES rather than BMS was associated with a significantly lower incidence of MI (OR 0.54, 95% CI 0.36–0.81, p = 0.003, Fig. 3B) and repeat revascularization (OR 0.44, 95% CI 0.31–0.62, p < 0.001, Fig. 3C). The funnel plots and the Egger and Begg tests did not suggest any significant publication bias (Fig. 4).

In elderly patients who underwent PCI with everolimus-eluting stent (EES) implantation, subgroup meta-analysis showed a significant decrease in MACE in the short DAPT (1 or 6 months) group (OR 0.49, 95% CI 0.34–0.80; p = 0.003), without statistical heterogeneity (I^2 = 23.7%; p = 0.08; Fig. 5A). However, there were no significant differences in stent thrombosis and bleeding complication rates according to DAPT duration (Fig. 5B, C). Subgroup analysis showed a significant decrease in MACE with all DES types, including EESs, biolimus-eluting stents, and zotarolimus-eluting stents (ZESs). Moreover, use of a ZES was associated with a significantly lower incidence of definite/probable stent thrombosis (OR 0.40, 95% CI 0.20–0.83; Fig. 6).

Discussion

The main findings of the present study were as follows: 1) DES deployment was associated with significant reduction in MACE, MI, and repeat revascularization in elderly patients; 2) DES implantation was associated with the risk of stent thrombosis and bleeding complications similar to that of BMS implantation; 3) In subgroup meta-analysis, clinical outcomes were similar for short and long DAPT duration in elderly patients who underwent PCI with EES implantation.

Current guidelines recommend stenting with the newer generation of DES rather than BMS in patients with ischemic heart disease including ST-segment elevation myocardial infarction (STEMI), because of better efficacy and safety profiles [23, 24]. Moreover, guidelines support DES as the preferred treatment option regardless of DAPT duration in patients with high bleeding risk [25]. Nevertheless, age-specific recommendations in elderly patients are not available; thus, BMS has been the preferred option in elderly patients due to shorter

DAPT duration [8].

As shown in Table 2, the results of 6 randomized trials , including 4 studies involving patients older than 80 years of age on average, can be seen as appropriate evidence to determine PCI strategy in elderly patients. However, differences in the definitions of primary and secondary outcomes make it difficult to comprehensively assess the benefits of DES in the treatment of elderly patients. The beneficial effects of DES on all-cause death have only been reported in a sub-study of the BASKET-PROVE trial [21]. Furthermore, the cardiac death rate was comparable to that in 6 of the studies included. In contrast to the other 4 randomized studies, the SENIOR trial and sub-study of the EXAMINATION trial did not show a difference in the risk of MI in both the DES and BMS groups [9, 22]. Particularly in the sub-study of the EXAMINATION trial for STEMI patients, DES use did not show any benefits over BMS use in patients over 75 years old [22]. In meta-analysis, DES use was associated with a significant reduction in redefined MACE, including cardiac death, MI, and repeat revascularization. Except for the sub-study of the EXAMINATION trial, the studies included showed benefits of DES use for MACE in elderly patients. Furthermore, our pooled analysis demonstrated that PCI with DES implantation was apparently superior to BMS use in terms of MI and repeat revascularization. The Norwegian Coronary Stent Trial (NORSTENT), a large randomized trial comparing long-term outcomes after DES (n = 4,504) versus BMS use (n = 4,509), reported results similar to those inthe present study, with a significantly lower rate of repeat revascularization at 6 years in the group receiving DES [26]. However, NORSTENT enrolled relatively younger patients, and did not show the benefits of DES use for MI compared with the findings in the present study. Although it is difficult to compare the outcomes of MI between the NORSTENT and the present study, the differences may reflect the significant benefit of DES for elderly patients who tend to have more extensive and complex lesions. The risk of stent thrombosis and bleeding complications with use of DES was comparable to that of BMS in the 6 trials included and the NORSTENT. This tendency was also observed in the meta-analysis. Therefore, when considering efficacy and safety, DES use should be considered in elderly patients, as described in the current guidelines.

The scoring systems used to determine DAPT duration include the DAPT score and PREdicting bleeding Complications in patients undergoing Stent implantation and subsequent Dual Anti Platelet Therapy (PRECISE-DAPT) [27, 28]. In both scoring models, age has been

used to assess bleeding and ischemic risk since post-PCI bleeding complications were associated with a significant increase in adverse clinical outcomes in patients older than 75 years of age [29]. However, the usefulness of these scores for improving outcomes remains unclear, due to the lack of evidence in the setting of randomized controlled trials. According to current guidelines, short DAPT duration should be considered in patients with high bleeding risk (PRECISE-DAPT score ≥ 25), with 3 months of DAPT for stable CAD and 6 months of DAPT for ACS [25]. The current subgroup meta-analysis in elderly patients who underwent PCI with EES implantation showed no significant differences between use of short DAPT duration and long DAPT duration in stent thrombosis and bleeding complications, as shown in Figure 5. Moreover, short DAPT duration was associated with a significantly lower incidence of MACE, compared with using long DAPT duration. Therefore, short DAPT duration is as safe as long DAPT duration in elderly patients who undergo PCI with EES implantation.

Limitations of the study

There were several limitations in this study. First, there was considerable heterogeneity between studies, which was particularly evident when comparing studies using different designs. Second, the definition of MACE was different in each study. Therefore, MACE was redefined to reduce confounders. Third, the definition of elderly varies from 65 to 75 years of age, but the present study defined elderly to be > 70 years of age, since there have been few randomized controlled trials in those aged ≥ 75 years. Fourth, differences in DAPT duration according to DES or BMS use were reported in only 1 of the 6 trials included (XIMA trial: 1 month of DAPT for patients receiving BMS and 12 months for those receiving DES), which could affect outcomes. Fifth, there are two types of EES, durable polymer EES (XIENCE™, Abbott Vascular, Santa Clara, CA, USA) and bioabsorbable polymer EES (SYNERGY™, Boston Scientific, Marlborough, MA, USA). Bioabsorbable polymer (BP)-DES implantation was reported to have better endothelial healing and conjugate protein expression than durable polymer-DES implantation [30]. Unique characteristics of BP-DES might affect the results of short and long DAPT duration on subgroup analysis. However, subgroup analysis included bioabsorbable or durable polymer EES. In addition, the proportion of ACS patients could not be assessed in the short and long DAPT duration groups and the comparison of DAPT duration was not randomly allocated between studies. Thus, a careful interpretation of

subgroup analysis of DAPT duration is necessary.

Conclusions

This meta-analysis builds upon recent evidence to support the efficacy and safety of DES use, and provides clinically relevant evidence that DES rather than BMS should be selected for treatment of elderly patients. Furthermore, short DAPT duration should be considered when PCI with EES implantation is performed in elderly patients.

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Conflict of interest: None declared

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Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for the trial selection process.

Figure 2. Forest plot for the risk of major adverse cardiovascular event (MACE; **A**), definite/probable stent thrombosis (**B**), and bleeding (**C**) in elderly patients treated with drug-eluting stents (DES) versus bare-metal stents (BMS); df — degree of freedom.

Figure 3. Forest plot for the risk of cardiac death (**A**), myocardial infarction (**B**), and repeat revascularization (**C**) in elderly patients treated with drug-eluting stents (DES) versus bare-metal stents (BMS); df — degree of freedom.

Figure 4. Funnel plot.

Figure 5. Subgroup meta-analysis of the effect of short (≤ 1 or 6 months) versus long (> 12 months) dual antiplatelet therapy (DAPT) duration in elderly patients who underwent percutaneous coronary intervention (PCI) with everolimus-eluting stent (EES) implantation.

Figure 6. Subgroup meta-analysis of the effect according to drug-eluting stents (DES) type.

Table 1. Randomized controlled trials design characteristics of included studies.

Study	Year	Design	DES device	Control device	Follow-up (months)	Total patients (DES/BMS)	Follow-up completion	Recommended duration of DAPT	Primary outcome
SENIOR trial [9]	2018	Multicenter randomized	Everolimus (synergy II)	BMS (Omega or Rebel)	12	596/604	98%	Stable: 1 month ACS: 6 months	All death, MI, TLR, or stroke
LEADERS FREE sub-study [19]	2017	Multicenter randomized	Biolimus (biofreedom)	BMS (Gazelle)	12	789/775	97%	1 month (all group)	Cardiac death, MI, TLR, stent thrombosis, or bleeding (BARC 3–5)
ZEUS sub-study [20]	2016	Multicenter randomized	Zotarolimus (endeavor)	BMS (Skylor, Vision, etc)	12	424/404	100%	1 month (all group)	All death, MI, or TVR
BASKET-PROVE sub-study [21]	2015	Multicenter randomized	Everolimus (Xiencce) + Sirolimus (Cypher)	BMS (Vision)	24	258/147	96%	12 months (all group)	Cardiac death or MI
EXAMINATION sub-study [22]	2015	Multicenter randomized	Everolimus (Xience)	BMS (Vision)	12	113/132	97%	12 months (all group)	All death, MI or repeat revascularization
XIMA trial [10]	2014	Multicenter randomized	Everolimus (Xience)	BMS (Vision)	12	399/401	100%	BMS: 1 month DES: 12 months	All death, MI, CVA, TVR, or bleeding (TIMI major)

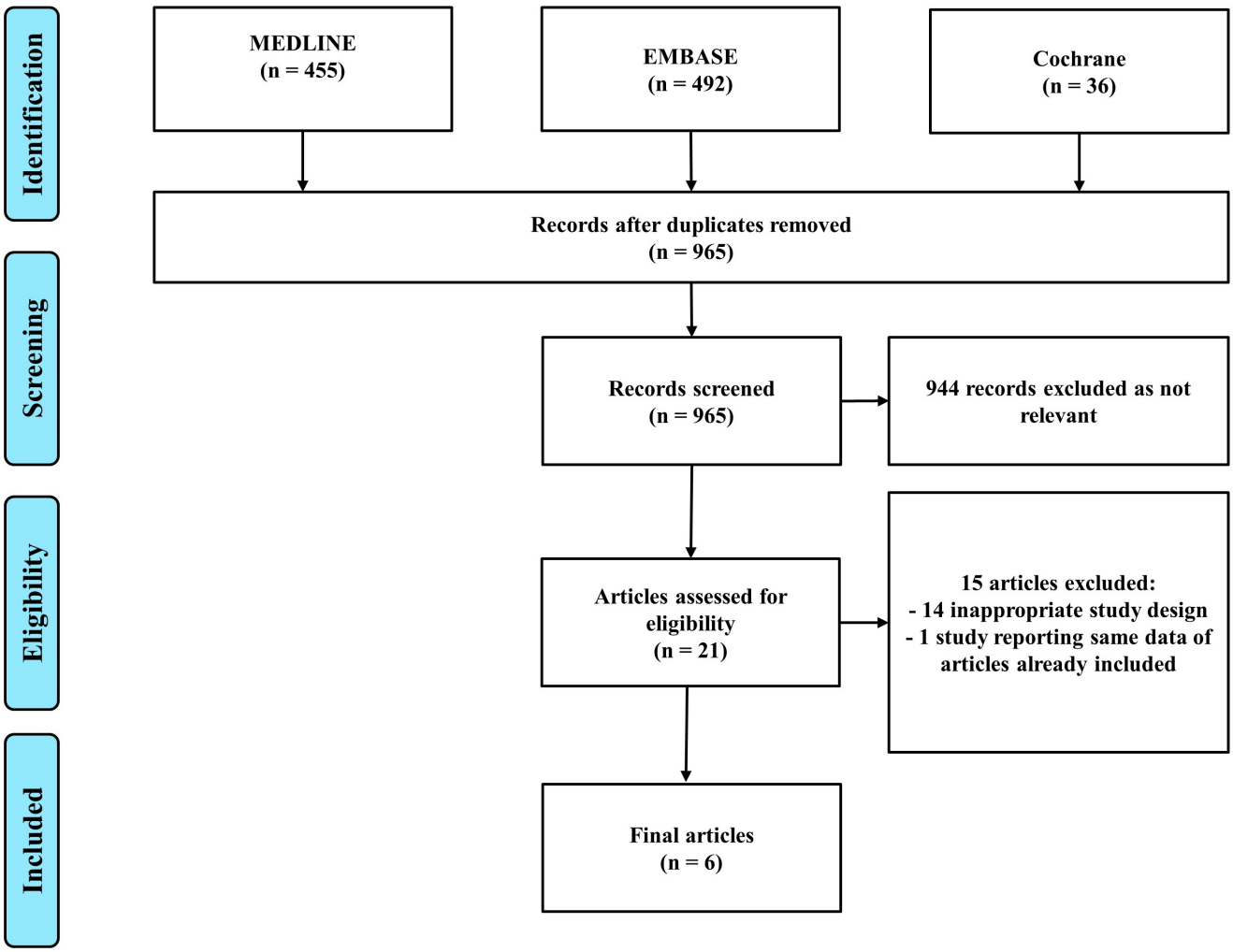
ACS — acute coronary syndrome; BARC — Bleeding Academic Research Consortium; BASKET-PROVE — Basel Stent Kosten Effektivitäts Trial–Prospective Validation Examination; BMS — bare metal stent; CVA — cerebrovascular accident; EXAMINATION — Everolimus-Eluting Stents vs Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction; LEADERS FREE — prospective, double-blind, randomized comparison of the Biofreedom Biolimus A9 Drug-Coated Stent vs the Gazelle Bare-Metal Stent in patients at high bleeding risk; MI — myocardial infarction; SENIOR — drug-eluting stents in elderly patients with coronary artery disease; TIMI — Thrombolysis In Myocardial Infarction; TLR — target lesion revascularization; TVR — target-vessel revascularization; XIMA — Xience or Vision Stents for the Management of Angina in the Elderly; ZEUS — Zotarolimus-Eluting vs Bare Metal Stents in Uncertain Drug-Eluting Stent Candidates

Table 2. Baseline characteristics of individuals enrolled in the clinical trials.

Variable	SENIOR trial [9]	LEADERS FREE sub-study [19]	ZEUS sub-study [20]	BASKET-PROVE sub-study [21]	EXAMINATION sub-study [22]	XIMA trial [10]

	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
Numbers of patients	**1,200 (596 vs 604)**		**1,564 (789 vs. 775)**		**828 (424 vs. 404)**		**405 (258 vs. 147)**		**245 (113 vs. 132)**		**800 (399 vs. 401)**	
Age (years)	81.4 ± 4.3	81.4 ± 4.2	81.3 ± 4.3	81.3 ± 4.3	80.4	80.5	79.1 ± 3.4	79.1 ± 3.6	≥ 75 years		83.6 ± 3.2	83.4 ± 3.1
Men	368 (62%)	379 (63%)	504 (63.9%)	492 (63.5%)	274 (61.6%)	259 (64.1%)	130 (50.4%)	93 (63.3%)	72 (63.7%)	87 (64.9%)	245 (61.1%)	237 (59.1%)
Body mass index	26.3 ± 4.3	25.9 ± 3.9	26.9 ± 4.3	26.5 ± 4.0	26 [24-29]	26 [24-29]	–	–	27.4 ± 3.77	27.6 ± 3.85	–	–
Diabetes mellitus	158 (27%)	157 (26%)	248 (31.4%)	214 (27.6%)	137 (32.3%)	117 (29%)	41 (15.9%)	21 (14.3%)	27 (23.6%)	33 (25%)	103 (25.6%)	97 (24.2%)
Hypertension	427 (72%)	488 (81%)	615 (77.9%)	618 (79.8%)	344 (81.1%)	336 (83.2%)	194 (75.2%)	102 (69.4%)	71 (62.8%)	94 (71.2%)	301 (75.1%)	311 (77.6%)
Dyslipidemia	311 (52%)	320 (53%)	474 (60.1%)	458 (59.1%)	191 (45%)	193 (47.8%)	145 (56.2%)	84 (57.1%)	38 (33.6%)	43 (32.6%)	231 (57.6%)	212 (52.9%)
Smoker	43 (7%)	38 (6%)	–	–	44 (10.4%)	45 (11.1%)	31 (12.2%)	21 (14.3%)	–	–	20 (5%)	16 (4%)
Previous stroke	39 (7%)	48 (8%)	80 (10.1%)	66 (8.5%)	32 (7.5%)	34 (8.4%)	15 (5.8%)	11 (7.5%)	5 (4.4%)	7 (5.3%)	31 (7.8%)	43 (10.7%)
Previous MI	109 (18%)	80 (13%)	155 (19.7%)	154 (19.9%)	117 (27.6%)	114 (28.2%)	45 (17.4%)	26 (17.0%)	5 (4.4%)	10 (7.6%)	119 (29.8%)	86 (21.5%)
Previous PCI	139 (23%)	143 (24%)	172 (21.8%)	164 (21.1%)	90 (21.2%)	83 (20.5%)	31 (12.0%)	19 (12.9%)	3 (2.7%)	6 (4.5%)	51 (12.8%)	41 (10.2%)
Previous CABG	36 (6%)	42 (7%)	69 (8.8%)	68 (8.8%)	39 (9.2%)	38 (9.4%)	10 (3.9%)	6 (4.1%)	5 (4.4%)	2 (5.3%)	28 (7%)	17 (4.2%)
Clinical indication												
Stable angina	201 (34%)	215 (36%)	556 (70.5%)	546 (70.5%)	147 (34.7%)	140 (34.7%)	89 (34.5%)	55 (37.4%)	–	–	256 (32%)	
UAP/NSTEMI	209 (37%)	208 (35%)	233 (29.5%)	229 (29.5%)	212 (50%)	199 (50.0%)	95 (36.8%)	50 (34.0%)	–	–	144 (18%)	
STEMI	65 (11%)	62 (10%)			65 (15.3%)	62 (15.3%)	74 (28.7%)	42 (28.6%)	113 (100%)	132 (100%)	400 (50%)	
Multivessel CAD	202 (34%)	183 (31%)	503 (63.7%)	494 (63.8%)	285 (67.2%)	176 (68.3%)	131 (50.8%)	78 (53.1%)	18 (15.9%)	19 (14.4%)	150 (37.4%)	158 (39.5%)
Treated coronary artery												
LAD	320 (54%)	313 (52%)	–	–	234 (55.2%)	196 (48.5%)	144 (55.8%)	82 (55.8%)	50 (44.2%)	50 (37.8%)	243 (60.7%)	253 (63%)
LCX	177 (30%)	159 (27%)	–	–	141 (33.3%)	155 (38.4%)	59 (22.9%)	41 (27.9%)	15 (13.2%)	16 (12.1%)	127 (31.7%)	120 (30%)
RCA	213 (36%)	227 (38%)	–	–	162 (38.2%)	161 (39.9%)	109 (42.3%)	58 (39.5%)	46 (40.7%)	64 (48.4%)	153 (38.1%)	142 (35.3%)
Left main	23 (4%)	8 (1%)	–	–	26 (6.1%)	27 (6.7%)	3 (1.2%)	3 (2.0%)	1 (0.01%)	1 (0.01%)	30 (7.6%)	33 (8.3%)

CABG — coronary artery bypass surgery; CAD — coronary artery disease; LAD — left anterior descending artery; LCX — left circumflex artery; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; RCA — right coronary artery; STEMI — ST-segment elevation myocardial infarction; UAP — unstable angina pectoris


Identification
Screening
Eligibility
Included
MEDLINE
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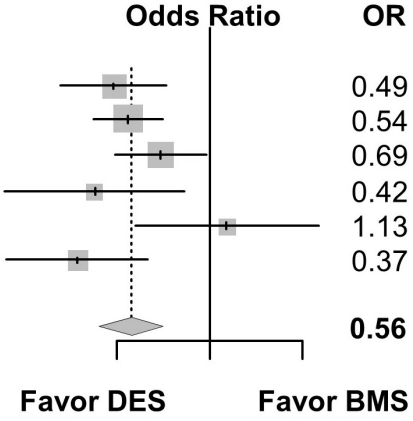
EMBASE
(n = 492)
Cochrane
(n = 36)
Records after duplicates removed
(n = 965)
Records screened
(n = 965)
944 records excluded as not relevant
Articles assessed for eligibility
(n = 21)
15 articles excluded:
- 14 inappropriate study design
- 1 study reporting same data of articles already included
Final articles
(n = 6)

A. MACE - cardiac death, MI, repeat revascularization

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
SENIOR trial	42	596	81	604	0.49	[0.33; 0.72]
LEADERS FREE trial	110	789	178	775	0.54	[0.42; 0.71]
ZEUS trial	76	424	97	404	0.69	[0.49; 0.97]
BASKET-PROVE trial	17	258	21	147	0.42	[0.22; 0.83]
EXAMINATION trial	19	113	20	132	1.13	[0.57; 2.25]
XIMA trial	21	399	52	401	0.37	[0.22; 0.63]
Overall		**2579**		**2463**	**0.56**	**[0.44; 0.71], $p<0.001$**

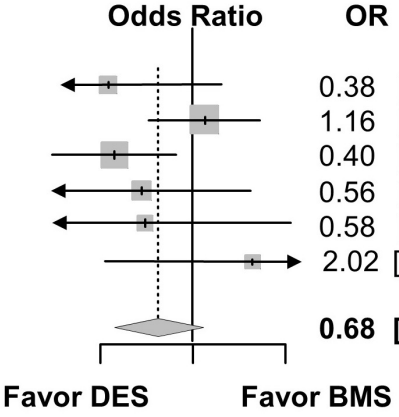
Heterogeneity: I^2 = 44%, τ^2 = 0.0366, p = 0.11



B. Definite/probable stent thrombosis

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
SENIOR trial	3	596	8	604	0.38	[0.10; 1.43]
LEADERS FREE trial	20	789	17	775	1.16	[0.60; 2.23]
ZEUS trial	11	424	25	404	0.40	[0.20; 0.83]
BASKET-PROVE trial	5	258	5	147	0.56	[0.16; 1.97]
EXAMINATION trial	2	113	4	132	0.58	[0.10; 3.21]
XIMA trial	4	399	2	401	2.02	[0.37; 11.09]
Overall		**2579**		**2463**	**0.68**	**[0.40; 1.14], $p=0.142$**

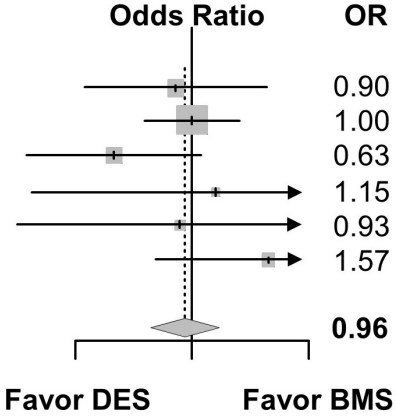
Heterogeneity: I^2 = 29%, τ^2 = 0.1160, p = 0.22



C. Major or minor bleeding

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
SENIOR trial	26	596	29	604	0.90	[0.53; 1.55]
LEADERS FREE trial	113	789	111	775	1.00	[0.75; 1.33]
ZEUS trial	26	424	38	404	0.63	[0.37; 1.06]
BASKET-PROVE trial	10	258	5	147	1.15	[0.38; 3.42]
EXAMINATION trial	8	113	10	132	0.93	[0.35; 2.44]
XIMA trial	23	399	15	401	1.57	[0.81; 3.06]
Overall		**2579**		**2463**	**0.96**	**[0.78; 1.18], $p=0.686$**

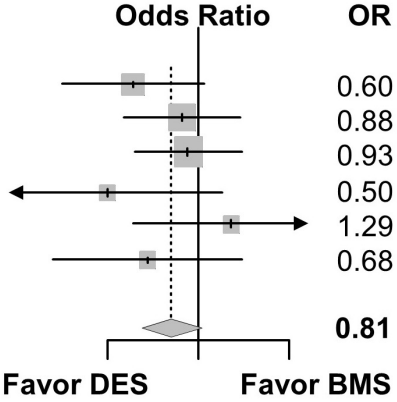
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.43



A. Cardiac death

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
SENIOR trial	22	596	36	604	0.60	[0.35; 1.04]
LEADERS FREE trial	38	789	42	775	0.88	[0.56; 1.39]
ZEUS trial	50	424	51	404	0.93	[0.61; 1.40]
BASKET-PROVE trial	10	258	11	147	0.50	[0.21; 1.20]
EXAMINATION trial	16	113	15	132	1.29	[0.61; 2.73]
XIMA trial	13	399	19	401	0.68	[0.33; 1.39]
Overall		**2579**		**2463**	**0.81**	**[0.65; 1.02], *p*=0.075**

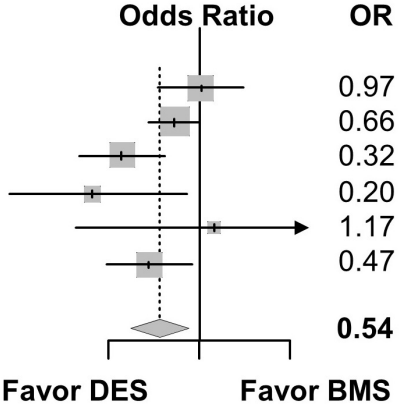
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.48



B. Myocardial infarction

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
SENIOR trial	21	596	22	604	0.97	[0.53; 1.78]
LEADERS FREE trial	56	789	80	775	0.66	[0.46; 0.95]
ZEUS trial	15	424	42	404	0.32	[0.17; 0.58]
BASKET-PROVE trial	3	258	8	147	0.20	[0.05; 0.78]
EXAMINATION trial	2	113	2	132	1.17	[0.16; 8.45]
XIMA trial	17	399	35	401	0.47	[0.26; 0.85]
Overall		**2579**		**2463**	**0.54**	**[0.36; 0.81], *p*=0.003**

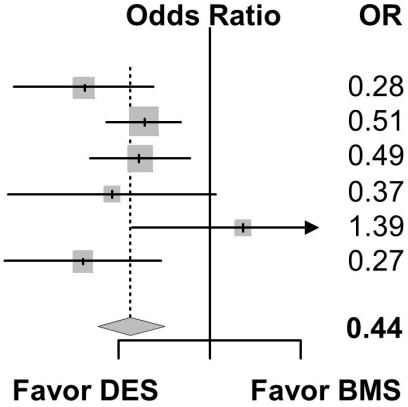
Heterogeneity: I^2 = 52%, τ^2 = 0.1189, p = 0.06



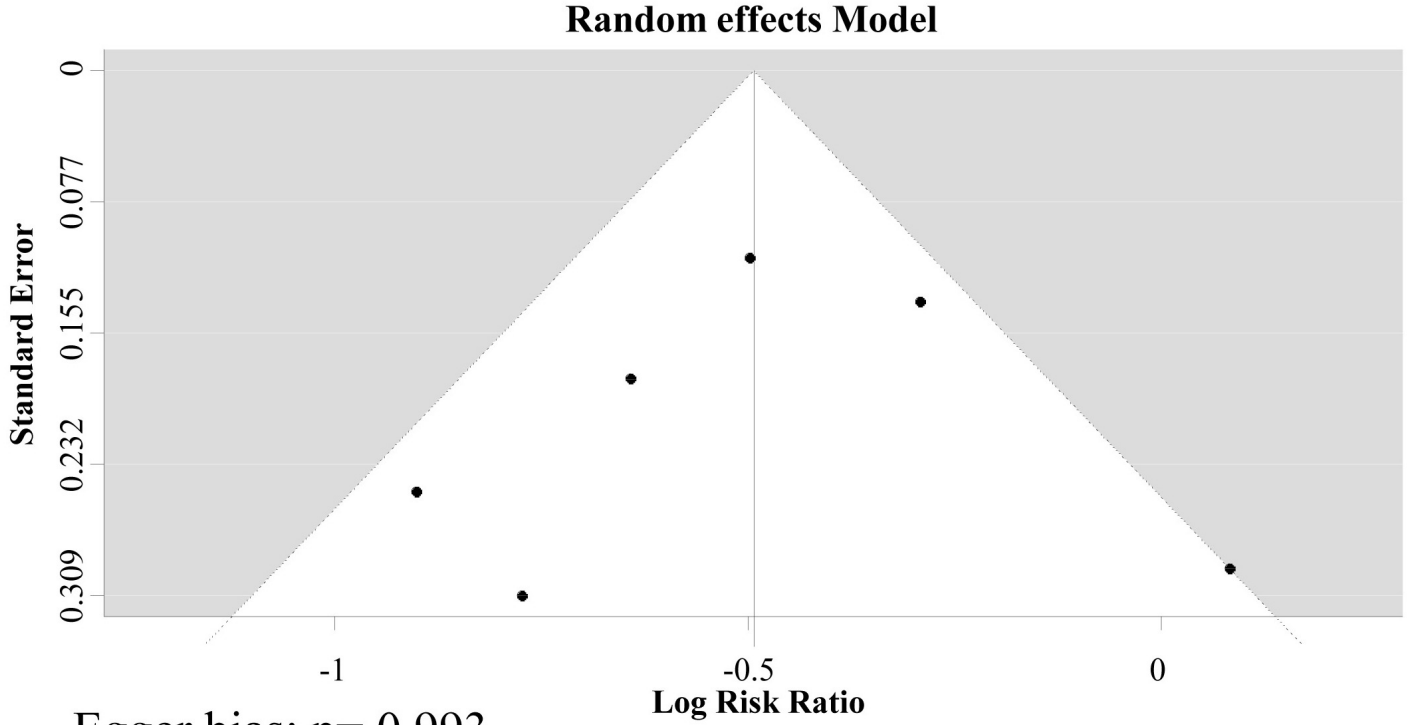
C. Repeat revascularization

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
SENIOR trial	10	596	35	604	0.28	[0.14; 0.57]
LEADERS FREE trial	46	789	84	775	0.51	[0.35; 0.74]
ZEUS trial	25	424	46	404	0.49	[0.29; 0.81]
BASKET-PROVE trial	6	258	9	147	0.37	[0.13; 1.05]
EXAMINATION trial	7	113	6	132	1.39	[0.45; 4.25]
XIMA trial	8	399	28	401	0.27	[0.12; 0.61]
Overall		**2579**		**2463**	**0.44**	**[0.31; 0.62], *p*<0.001**

Heterogeneity: I^2 = 36%, τ^2 = 0.0630, p = 0.17



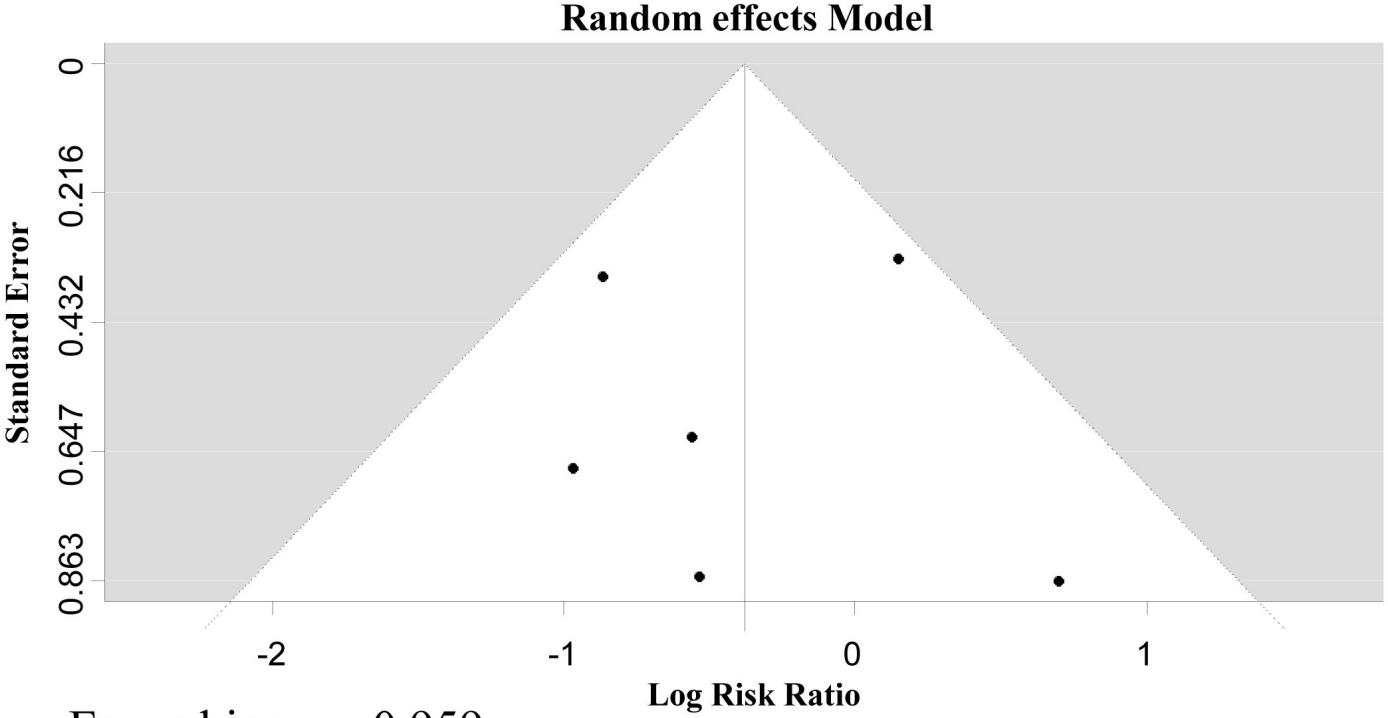
A. Funnel plot for MACE



Egger bias: p= 0.993

Begg's for funnel plot asymmetry: Kendall's tau= -0.292, p= 0.785

B. Funnel plot for definite/probable stent thrombosis



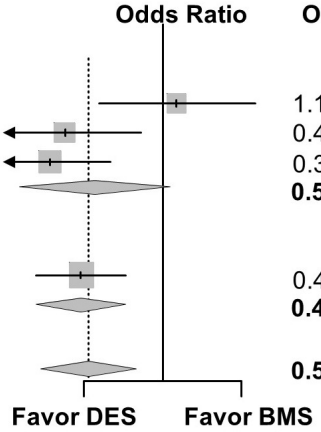
Egger bias: p= 0.959

Begg's for funnel plot asymmetry: Kendall's tau= -0.088, p= 0.934

A. MACE - cardiac death, MI or TVR

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
Long DAPT (> 12 months)						
EXAMINATION trial	19	113	20	132	1.13	[0.57; 2.25]
BASKET-PROVE trial	17	258	21	147	0.42	[0.22; 0.83]
XIMA trial	21	399	52	401	0.37	[0.22; 0.63]
Subtotal		**770**		**680**	**0.55**	**[0.28; 1.08], *p*=0.081**
Short DAPT (1 or 6 months)						
SENIOR trial	42	596	81	604	0.49	[0.33; 0.72]
Subtotal		**596**		**604**	**0.49**	**[0.33; 0.72], *p*<0.001**
Overall		**1366**		**1284**	**0.52**	**[0.34; 0.80], *p*=0.003**

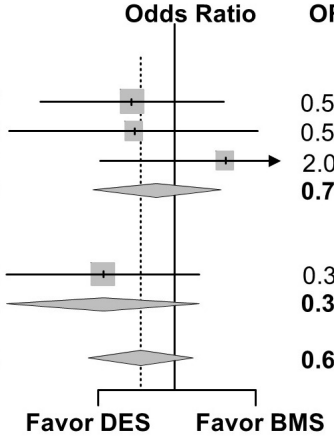
Heterogeneity: I^2 = 56%, τ^2 = 0.1017, p = 0.08
Test for subgroup difference: p = 0.764



B. Definite/probable stent thrombosis

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
Long DAPT (> 12 months)						
BASKET-PROVE trial	5	258	5	147	0.56	[0.16; 1.97]
EXAMINATION trial	2	113	4	132	0.58	[0.10; 3.21]
XIMA trial	4	399	2	401	2.02	[0.37; 11.09]
Subtotal		**770**		**680**	**0.79**	**[0.33; 1.89], *p*=0.596**
Short DAPT (1 or 6 months)						
SENIOR trial	3	596	8	604	0.38	[0.10; 1.43]
Subtotal		**596**		**604**	**0.38**	**[0.10; 1.43], *p*=0.151**
Overall		**1366**		**1284**	**0.63**	**[0.31; 1.31], *p*=0.219**

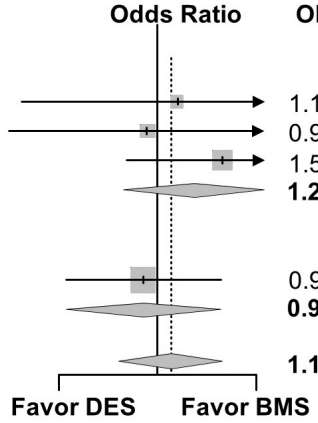
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.49
Test for subgroup difference: p = 0.362



C. Major or minor bleeding

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
Long DAPT (> 12 months)						
BASKET-PROVE trial	10	258	5	147	1.15	[0.38; 3.42]
EXAMINATION trial	8	113	10	132	0.93	[0.35; 2.44]
XIMA trial	23	399	15	401	1.57	[0.81; 3.06]
Subtotal		**770**		**680**	**1.29**	**[0.79; 2.10], *p*=0.309**
Short DAPT (1 or 6 months)						
SENIOR trial	26	596	29	604	0.90	[0.53; 1.55]
Subtotal		**596**		**604**	**0.90**	**[0.53; 1.55], *p*=0.716**
Overall		**1366**		**1284**	**1.10**	**[0.76; 1.58], *p*=0.610**

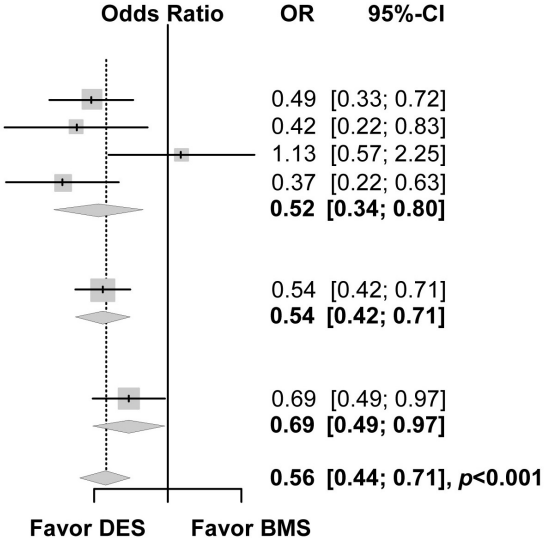
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.63
Test for subgroup difference: p = 0.341



A. MACE - cardiac death, MI or TVR

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
Everolimus-eluting stent						
SENIOR trial	42	596	81	604	0.49	[0.33; 0.72]
BASKET-PROVE trial	17	258	21	147	0.42	[0.22; 0.83]
EXAMINATION trial	19	113	20	132	1.13	[0.57; 2.25]
XIMA trial	21	399	52	401	0.37	[0.22; 0.63]
Subtotal		**1366**		**1284**	**0.52**	**[0.34; 0.80]**
Biolimus-eluting stent						
LEADERS FREE trial	110	789	178	775	0.54	[0.42; 0.71]
Subtotal		**789**		**775**	**0.54**	**[0.42; 0.71]**
Zotarolimus-eluting stent						
ZEUS trial	76	424	97	404	0.69	[0.49; 0.97]
Subtotal		**424**		**404**	**0.69**	**[0.49; 0.97]**
Overall		**2579**		**2463**	**0.56**	**[0.44; 0.71], p<0.001**

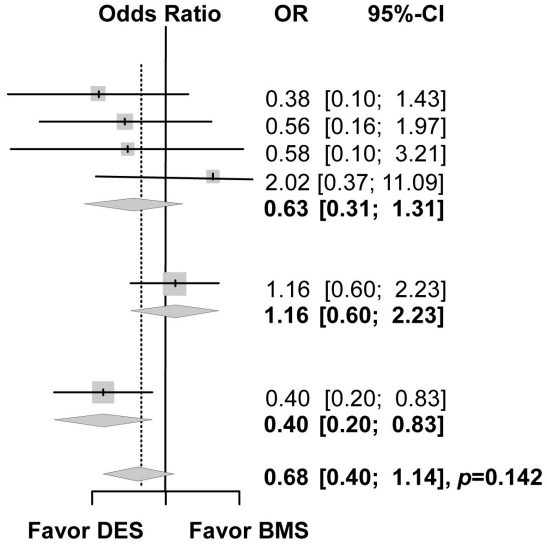
Heterogeneity: I^2 = 44%, τ^2 = 0.0366, p = 0.11
Test for subgroup difference: p = 0.473



B. Definite/probable stent thrombosis

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
Everolimus-eluting stent						
SENIOR trial	3	596	8	604	0.38	[0.10; 1.43]
BASKET-PROVE trial	5	258	5	147	0.56	[0.16; 1.97]
EXAMINATION trial	2	113	4	132	0.58	[0.10; 3.21]
XIMA trial	4	399	2	401	2.02	[0.37; 11.09]
Subtotal		**1366**		**1284**	**0.63**	**[0.31; 1.31]**
Biolimus-eluting stent						
LEADERS FREE trial	20	789	17	775	1.16	[0.60; 2.23]
Subtotal		**789**		**775**	**1.16**	**[0.60; 2.23]**
Zotarolimus-eluting stent						
ZEUS trial	11	424	25	404	0.40	[0.20; 0.83]
Subtotal		**424**		**404**	**0.40**	**[0.20; 0.83]**
Overall		**2579**		**2463**	**0.68**	**[0.40; 1.14], p=0.142**

Heterogeneity: I^2 = 29%, τ^2 = 0.1160, p = 0.22
Test for subgroup difference: p = 0.101



C. Major or minor bleeding

Study	DES Events	DES Total	BMS Events	BMS Total	OR	95%-CI
Everolimus-eluting stent						
SENIOR trial	26	596	29	604	0.90	[0.53; 1.55]
BASKET-PROVE trial	10	258	5	147	1.15	[0.38; 3.42]
EXAMINATION trial	8	113	10	132	0.93	[0.35; 2.44]
XIMA trial	23	399	15	401	1.57	[0.81; 3.06]
Subtotal		**1366**		**1284**	**1.10**	**[0.76; 1.58]**
Biolimus-eluting stent						
LEADERS FREE trial	113	789	111	775	1.00	[0.75; 1.33]
Subtotal		**789**		**775**	**1.00**	**[0.75; 1.33]**
Zotarolimus-eluting stent						
ZEUS trial	26	424	38	404	0.63	[0.37; 1.06]
Subtotal		**424**		**404**	**0.63**	**[0.37; 1.06]**
Random effects model		**2579**		**2463**	**0.96**	**[0.78; 1.18], p=0.686**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.43
Test for subgroup difference: p = 0.206