Original Research Article

A COMPREHENSIVE META-ANALYSIS OF TRIALS COMPARING SAFETY AND EFFICACY OF DRUG-ELUTING STENTS WITH BARE METAL STENTS

Abstract

Background: Effects of drug-eluting stents (DESs) on clinical outcomes as well as stent thrombosis are still under debate.

Methods: Our meta-analysis included 26 randomized trials comparing DESs with bare metal stents (BMSs). The endpoints analyzed were all-cause mortality, cardiac death, myocardial infarction (MI), target lesion (TLR) and target vessel (TVR) revascularization, restenosis, and stent thrombosis.

Results: In-stent (Risk Ratio = 0.23 [95% confidence interval: 0.17 - 0.32]) and in-segment restenosis (RR = 0.31 [0.24 - 0.40]) significantly reduced in patients with DESs compared with BMSs. Nonetheless, the all-cause mortality (RR = 0.98 [0.79 - 1.21]) and cardiac death (RR = 0.93 [0.71 - 1.21]) were not significantly different for patients receiving DESs compared with BMSs. DESs versus BMSs resulted in a significant decrease in MI (RR = 0.79 [0.67 - 0.93]), TLR (RR = 0.33 [0.29 - 0.38]), and TVR (RR = 0.47 [0.42 - 0.52]). Stent thrombosis incidence that did not differ in DESs versus BMSs until the first year after implantation, showed an upward trend in DESs compared with BMSs from then on (RR = 3.09 [1.37 - 6.99]).

Conclusions: The use of DESs versus BMSs led to benefits in angiographic restenosis and clinical outcomes. However, higher incidence of long-term stent thrombosis warrants their cautious usage in patients at high-risk of stent thrombosis.

Keywords: drug-eluting stent; bare metal stent; safety; efficacy; meta-analysis.

Introduction

The use of stents during percutaneous coronary intervention (PCI) has substantially improved the outcomes of the management of ischemic heart diseases over the past decade**.** However, in-stent restenosis has been reported to be a potential complication of bare metal stents (BMSs) compared with drug-eluting stents (DESs) [1-7].

Progressive narrowing of in-stent lumen which is mainly due to neo-intimal hyperplasia,[8, 9] is associated with significant morbidity and even mortality.[10, 11] So as to decrease the in-stent restenosis rate following BMSs, two common DESs approved by US Food and Drug Administration, sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES), have found common application**.** Despite the advantages of DESs over BMSs with respect to in-stent restenosis[1-7], recent studies have reported a trend for more stent thrombosis (ST) among patients receiving DESs that has opened a debate on the long-term efficacy of DESs.[4, 6, 12-19]

On balance, with the aim of offsetting the bias and controversial results of single trials and comparing the DESs with BMSs in terms of the incidences of in-stent restenosis and stent thrombosis as well as their potential consequent influences on clinical outcomes such as death, myocardial infarction (MI), and revascularization, herein, we performed a comprehensive meta-analysis of randomized controlled trials (RCTs).

Methods

This meta-analysis was conducted in accordance with the Improving the Quality of Reports of Meta-analyses of Randomized Controlled Trials (the QUOROM statement).[20]

Search Strategy

Searching of PubMed database with the keywords “drug-eluting stents [MeSH]” and “bare metal stent” yielded 314 papers. With the same keywords, the Cochrane database was searched for clinical trials and systematic reviews yielding 95 clinical trials (31 Papers overlapped with PubMed papers) and 19 systematic reviews. References of the review articles were manually searched for potentially relevant studies. Overall, 420 papers were obtained for review.

Selection Process

Initially abstracts of the papers were reviewed for assessing the relevancy. Thereafter, aiming at exerting pre-specified inclusion and exclusion criteria, two independent reviewers (H.R. and S.C.), reviewed the full-texts of relevant papers and disagreements were reviewed and resolved by third reviewer (A.K.). Our pre-defined inclusion criteria were as follows:

1. Randomized controlled trial (RCT),
2. Comparison between BMSs and DESs,
3. Patients with IHD with or without co-morbidities, and
4. At least one of the desired outcomes was reported.

Papers were excluded if they met any of the following criteria:

1. Observational and non-randomized studies,
2. Socioeconomic system difference between two groups,
3. Inadequate information even with corresponding author contact,
4. Any additional intervention,
5. Duplication studies.

Validity Assessment

In order to assess validity of the included articles, we assessed the RCTs according to a critical appraisal framework which was written utilizing CONSORT statement and the Attia's report.[21, 22] We critically appraised the RCTs according to the following checklist:

1. Was the hypothesis of the study described clearly and thoroughly?
2. Was the Randomization described?
3. Are the baseline characteristics (Age, Sex, ethnicity, Comorbidities [CRF, DM, Smoking, CHF, HTN, HLP, Cancer, liver disease, MI, MI type, SES]) of the study groups similar (studies with ≥ 2 differences in above baseline characteristics were considered as invalid)?
4. Was the RCT free of any sources of bias (i.e. contamination, cross-over, compliance, co-intervention and major [> 10 %] loss to follow-up) in the follow-up period?
5. Was follow-up sufficiently long (> 6 months)?

Study Outcomes

Pre-specified end-points that were utilized for meta-analysis consisted of all-cause mortality, cardiac death, myocardial infarction (MI), target lesion revascularization (TLR), target vessel revascularization (TVR), major adverse cardiac events (MACE), in-stent restenosis, in-segment restenosis, and ST.

Cardiac death was defined as any death owing to a cardiac cause, sudden death, and perioperative death. MI was mainly defined as a new increase in MB fraction of creatine kinase enzyme. Although ischemic symptoms or electrocardiographic changes were mandatory for the diagnosis of a MI in some trials, however, they were not essential diagnostic criteria in others. Both fatal and non-fatal, Q-wave and non-Q-wave MI was included into the analysis. Target lesion revascularization (TLR) was surgical or percutaneous revascularization within 5 mm proximal and distal to the stent. Target vessel revascularization (TVR) included all surgical or percutaneous revascularization in the target vessel. Major adverse cardiac event (MACE) was

classified into the two categories: a composite of death (all-cause death or cardiac death), MI, and TLR (death/MI/TLR) and a composite of death (all-cause death or cardiac death), MI, and TVR (death/MI/TVR). Notably, in some studies the composite of cardiac death, MI, or TVR was named "target vessel failure" which was also analyzed as death/MI/TVR category of MACE. Studies that added stent thrombosis to MACE, were also included, however, those that added cerebrovascular diseases to MACE were not. Binary restenosis was defined as ≥ 50 % diameter stenosis at follow-up angiography; in-stent restenosis and in-segment restenosis were analyzed separately. Stent thrombosis (ST) was sub-classified into early (ST ≤ 1 month), late (1 month < ST ≤ 12 months), and very late (> 12 months). The sum of ST of all definitions (i.e. probable, possible, and definite) reported by Academic Research Consortium (ARC),[23] were included in the analysis.

Statistical methods

Risk ratios (RR) with 95 % confidence intervals (95 % CI) of all desired outcomes in the trials were calculated. Then, we utilized a fixed-effects model based on the Mantel-Haenszel method to combine RR from the included trials. To assess the validity of the pooled results from individual trials, the χ^2 test for heterogeneity was used. Also, we calculated I^2 statistic as a measure of heterogeneity proposed by Higgins et al.[24] An I^2 > 50% revealed a significant heterogeneity across pooled trials. All P values are two-sided and results were considered to be statistically significant at a P value of less than 0.05. All statistical analyses were performed with "Review Manager" version 5.0.20 (available at www.cochrane.org).

Results

Our search led to 420 papers and after screening their abstracts, 190 were found to be relevant. Exerting Inclusion/Exclusion criteria, 45 papers were included. Following critical appraisal of included papers for validity assessment according to the afore-mentioned checklist,

17 papers were excluded, [25-41] and 28 reports of 26 trials remained in the analysis for meta-analysis (Figure 1).[1, 2, 4, 6, 7, 12-19, 42-54 3, 45, 55] Characteristics of Included trials are summarized in Table 1. Publication bias was ruled out according to the symmetrical shape of funnel plot (Figure 2).

Mortality

Twenty six trials contributed to our analysis of all-cause mortality.[1, 2, 4, 6, 7, 12-19, 42-54] Figure 3 shows the absolute numbers of deaths in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 12654 patients included in the trials, 331 patients died during follow-up; 136 deaths occurred in 5368 patients with BMS and 65 of 2484 and 130 of 4802 patients died in SES and PES subgroups, respectively. Our pooled estimates did not find any difference in death incidence between the BMS and DES groups (RR = 0.98 [95% confidence interval: 0.79 - 1.21], P = 0.82). Likewise, subgroup analysis did not reveal any significant difference between mortality of SES (RR = 1.13 [95%: 0.80 - 1.60]) and PES (RR = 0.89 [95%: 0.67 - 1.17]) patients in comparison to BMS patients. No heterogeneity was observed across the trials ($\chi^2 = 15.80$, df = 23, P = 0.86; $I^2 = 0\%$).

Twenty three trials were pooled to estimate cardiac deaths difference between BMS- and DES-treated patients.[2, 4, 6, 12-19, 42-47, 49-54] Figure 4 shows the absolute numbers of cardiac deaths in each trial according to treatment group, with the RR (95% CI) and weight for each trial. A total of 12143 patients were randomized in the trials for cardiac deaths comparison between DES and BMS groups. Overall, 219 deaths were attributed to cardiac causes; 92 cardiac deaths occurred in 5183 patients with BMS and 35 of 2310 and 92 of 4650 patients died in SES and PES subgroups owing to the cardiac causes, respectively. No significant difference was found among BMS- and DES-treated patients in terms of cardiac-related deaths (RR = 0.93 [95% CI: 0.71 - 1.21], P = 0.58). Nor was there any difference in SES (RR = 1.17 [95% CI: 0.73 - 1.88]) and PES (RR = 0.83 [95%: 0.60 - 1.15]) compared to BMS in the subgroup analyses. There was

no statistical evidence of heterogeneity across the 23 trials (χ^2 = 7.76, df = 20, P = 0.99; I^2 = 0%).

Myocardial infarction

In 24 RCTs,[1, 2, 4, 6, 7, 12-19, 42, 43, 45, 47-54] DES versus BMS resulted in a significant reduction of MI in a fixed-effects model (RR = 0.79 [95% CI: 0.67 - 0.93], P = 0.006) without heterogeneity (χ^2 = 23.09, df = 24, P = 0.51; I^2 = 0%). Figure 5 demonstrates the absolute numbers of MIs in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 12113 patients included in the trials, 516 patients had MI during follow-up; 252 MI occurred in 5098 patients with BMS and 80 of 2218 and 184 of 4797 patients with SES and PES, respectively. Although restricting the analysis to the subgroup of patients with SES was in accord with overall results (RR = 0.70 [95% CI: 0.53 - 0.93], P = 0.01), however, patients with PES did not reveal a significant decrease of MI compared to those with BMS (RR = 0.84 [95% CI: 0.68, 1.05], P = 0.12).

Revascularization

Twenty three RCTs contributed to our pooled estimate of TLR.[1, 2, 4, 6, 7, 13-19, 42, 43, 45, 46, 48-54] Figure 6 shows the absolute numbers of TLRs in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 10609 patients randomized in trials, TLR occurred in 1119 of them; 787 TLR in 4478 patients with BMS and 93 of 1615 and 239 of 4516 patients with SES and PES, respectively. DES versus BMS led to a sharp decline in TLR rate in a fixed-effects model (RR = 0.33 [95% CI: 0.29 - 0.38], P < 0.00001), however, there was a noticeable heterogeneity across trials (χ^2 = 48.49, df = 23, P = 0.001; I^2 = 53%). Not only the benefit of DES versus BMS with respect to TLR, remained constant in subgroup analyses of trials restricted to SES (RR = 0.22 [95% CI: 0.18 - 0.28], P < 0.00001) and PES (RR = 0.44 [95% CI: 0.38 - 0.52], P < 0.00001), but also no significant heterogeneity remained across trials

in each subgroup (χ^2 = 8.65, df = 12, P = 0.73; I^2 = 0% and χ^2 = 16.91, df = 10, P = 0.08; I^2 = 41%, respectively).

Eighteen RCTs contributed to our pooled estimate of TVR.[1, 2, 4, 12, 13, 15, 17, 18, 42, 44, 45, 47, 49-54] Figure 7 shows the absolute numbers of TVRs in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 10724 patients randomized in trials, TVR occurred in 1304 of them; 824 TVR in 4459 patients with BMS and 156 of 1918 and 324 of 4347 patients with SES and PES, respectively. DES versus BMS led to a dramatic decrease in TVR rate in a fixed-effects model (RR = 0.47 [95% CI: 0.42 - 0.52], P < 0.00001), however, there was a considerable heterogeneity across trials (χ^2 = 33.27, df = 19, P = 0.02; I^2 = 43%). Not only the benefit of DES versus BMS with respect to TVR, remained constant in subgroup analyses of trials restricted to SES (RR = 0.36 [95% CI: 0.30 - 0.42], P <0.00001) and PES (RR = 0.58 [95% CI: 0.50 - 0.67], P < 0.00001), but also no significant heterogeneity remained across trials in each subgroup (χ^2 = 4.49, df = 9, P = 0.88; I^2 = 0% and χ^2 = 10.50, df = 9, P = 0.31; I^2 = 14%, respectively).

MACE

As mentioned earlier, MACE was analyzed in two categories: the composites of "death, MI, and TLR" and "death, MI, and TVR".

In 14 RCTs,[1, 2, 6, 7, 13-17, 19, 42, 48-50] DES versus BMS resulted in a significant decrease in the composite outcome of "death, MI, and TLR" (RR = 0.40 [95%CI: 0.34 - 0.46], P < 0.00001) without heterogeneity (χ^2 = 18.73, df = 13, P = 0.13; I^2 = 31%). Figure 8 demonstrates the absolute numbers of "death, MI, and TLR" in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 3783 patients randomized in the trials, "death, MI, and TLR" occurred in 711 patients, 499 of 1818 and 212 of 1965 patients with BMS and DES, respectively.

Likewise, in 14 RCTs,[1, 4, 12, 13, 18, 42, 44, 45, 47, 49, 50, 52-54] DES versus BMS resulted in a significant decline in the composite outcome of "death, MI, and TVR" (RR = 0.55 [95% CI: 0.50 - 0.62], P < 0.00001) without heterogeneity (χ^2 = 17.54, df = 14, P = 0.23; I^2 = 20%). Figure 8 demonstrates the absolute numbers of "death, MI, and TVR" in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 7129 patients randomized in the trials, "death, MI, and TVR" occurred in 1184 patients, 747 of 3417 and 437 of 3712 patients with BMS and DES, respectively.

Restenosis

In-stent restenosis and in-segment restenosis were analyzed separately. In 6 RCTs,[1, 3, 4, 45, 46, 54] DES versus BMS resulted in a sharp decline of in-stent restenosis in a fixed-effects model (RR = 0.23 [95% CI: 0.17 - 0.32], P < 0.00001) without heterogeneity (χ^2 = 3.19, df = 6, P = 0.78; I^2 = 0%). Figure 9 demonstrates the absolute numbers of in-stent restenosis in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 1256 patients included in the trials, in-stent restenosis occurred in 204 patients during follow-up; 163 of 613 patients with BMS and 41 of 643 patients with DES. Restricting the analyses to subgroups of SES and PES confirmed the overall results (data not shown).

Likewise, in 5 RCTs contributed to our analysis of in-segment restenosis,[1-4, 45] DES was associated with a dramatic decrease of in-segment restenosis compared to BMS in a fixed-effects model (RR = 0.31 [95% CI: 0.24 - 0.40], P < 0.00001) without heterogeneity (χ^2 = 3.54, df = 5, P = 0.62; I^2 = 0%). Figure 9 demonstrates the absolute numbers of in-segment restenosis in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Overall, 250 patients showed in-segment restenosis during angiographic follow-up, 187 of 605 patients with BMS and 63 of 637 patients with DES. Restricting the analyses to subgroups of SES and PES confirmed the overall results (data not shown).

Stent thrombosis

Twenty two RCTs contributed to our analysis of early ST.[1, 2, 4, 6, 7, 12-19, 42-44, 47, 49, 50, 52, 53, 55] Figure 10 demonstrates the absolute numbers of early ST in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 9322 patients randomized in trials, early ST occurred in 85 of them; 44 early ST in 4362 patients with BMS and 23 of 2348 and 18 of 2516 patients with SES and PES, respectively. DES versus BMS resulted in a slight yet not statistically significant decrease in early ST (RR = 0.86 [95% CI: 0.57, 1.30], P = 0.47) without heterogeneity (χ^2 = 8.83, df = 18, P = 0.96; I^2 = 0%).

Twenty two RCTs enrolled in the analysis of late ST.[1, 2, 4, 6, 7, 12-19, 42-44, 47, 49, 50, 52, 53, 55] Figure 10 demonstrates the absolute numbers of late ST in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 9322 patients randomized in trials, late ST occurred in 37 of them; 23 late ST in 4458 patients with BMS and 7 of 2348 and 7 of 2516 patients with SES and PES, respectively. DES versus BMS led to a non-significant decline in late ST (RR = 0.69 [95% CI: 0.39 - 1.21], P = 0.19) without heterogeneity (χ^2 = 10.54, df = 16, P = 0.84; I^2 = 0%).

Nine RCTs contributed to our analysis of very late ST.[13, 16-19, 43, 49, 50, 55] Figure 10 demonstrates the absolute numbers of very late ST in each trial according to treatment group, with the RR (95% CI) and weight for each trial. Of 3174 patients randomized in trials, very late ST occurred in 26 of them; 5 very late ST in 1581 patients with BMS and 17 of 1038 and 4 of 555 patients with SES and PES, respectively. DES versus BMS resulted in a significant increase in very late ST (RR = 3.09 [95% CI: 1.37 - 6.99], P = 0.007) without heterogeneity (χ^2 = 4.67, df = 7, P = 0.70; I^2 = 0%). Subgroup analysis of trials restricted to SES and PES revealed that the upward trend in the incidence of very late ST in DES, is mainly attributed to SES (RR = 4.06 [95% CI: 1.46 - 11.29]) rather than PES (1.65 [95% CI: 0.40 - 6.80]). Subgroup analyses are summarized in Table 2.

Discussion

The current meta-analysis of 26 trials enabled us to compare the safety and efficacy of DES compared with BMS. Our analysis showed that DES decreased angiographic restenosis and notwithstanding dramatic decline in incidences of MI, TLR, and TVR, no significant effect was found on overall mortality and cardiac death. In addition, although early and late ST seemed not to be different among DES and BMS, however, there was an upward trend in very late ST among patients with DES compared with BMS.

The application of DESs has put a substantial dent in restenosis which was a well-known and potentially hazardous complication of BMS[1-7]. On the basis of this finding, their implantation has become increasingly common over the recent years and a majority of > 2 million patients are taking at least one type of these novel stents.[56] Although new types of DESs have been developing[57], however, SESs and PESs have been implanted more than the others and most of the published RCTs have utilized the two thus far .[1, 2, 4, 6, 7, 12-19, 42-54] Notwithstanding the agreement of several studies with dramatic restenosis benefits of SESs[1, 43, 45, 46] and PESs[2-4, 7, 50, 51, 54] compared with BMSs, there are considerable discrepancies among RCTs,[1, 2, 4, 6, 7, 12-19, 42-54] as well as meta-analyses,[56, 58-60] with respect to their influences on clinical outcomes. On the other hand, some studies have debated the efficacy of DESs by reporting the increased incidence of stent thrombosis in comparison to BMSs. [4, 6, 12-19] To date, RCTs have been limited in power to precisely detect minor differences in stent thrombosis incidences between various types of stents and even attempts of recent meta-analyses have yet to resolve this uncertainty[58, 61, 62].

As mentioned earlier, in accord with previous studies, [1-7] restenosis benefit of DESs over BMSs was further corroborated in our analysis. Our data demonstrated that MACE following DES implantation decreased alike, contributed to lower incidences of MI and revascularization, while, death incidence did not differ between the two groups. The reasoning behind the finding

of death incidence equality in spite of discrepancy of MI incidence between the two groups might be related to clinical presentation of restenosis that mainly occurs as a result of progressive neointimal hyperplasia[8, 9]. Although restenosis might be associated with unstable angina and MI, its more common clinical manifestation is progressive angina.[63] Therefore, patients with restenosis are more likely to be diagnosed and treated by pre-MI revascularization rather than suffering a fatal MI when they become symptomatic. Moreover, in asymptomatic condition, patients enrolled in trials were more likely to be screened by follow-up angiography and consequently taking advantages of early revascularization rather than remaining undiagnosed and suffering from future consequences of silent restenosis; the fact explains the reasoning behind the finding of the smaller magnitude of difference among the two groups with respect to MI (i.e. $P < 0.01$) compared with restenosis, TLR, and TVR (i.e. $P < 0.00001$ for all). Therefore, patients randomized to BMS in the trials, were not at the higher risk for restenosis-related mortality, though restenosis had a significantly greater incidence among them. Notably, these data are collected form RCTs and they mostly had pre-specified follow-up angiography, however, in real-world practice, asymptomatic patients usually do not benefit from routine angiography; thus, in the latter case, the restenosis-related mortality in real-world is speculated to be more than that observed in the trials. Herein, the pivotal role of screening tests for diagnosing asymptomatic patients is clearly understood and they are highly recommended whereby early diagnosis and revascularization of restenosis and prevention of its adverse outcomes becomes possible.

On the other hand, ST which demonstrated similar incidences between BMSs and DESs in the first year after PCI, however, DESs associated with a significantly higher rate of very late ST. Contrary to restenosis, ST is usually associated with ST-segment elevation MI and high mortality.[64, 65] Nonetheless, clinical outcomes did not follow the pattern of stent thrombosis incidences. Considering the of our finding that restenosis has a higher incidence than ST and

since restenosis is more common among patients with BMSs whereas ST is more frequent in patients with DESs, therefore, restenosis-related adverse outcomes in BMSs outweigh those associated with ST in DESs. More interestingly, our analysis led to the finding that increased incidence of very late ST in DES compared with BMS, was mainly due to SES, and PES did not increase very late ST significantly (Table 2). Even though previous pooled analyses of randomized trials have attempted to find probable differences in risk of ST between DESs and BMSs, contributed to the wide CIs of these estimates, they have failed to find any significant difference between them. [58, 61]

Although there are several key predictors of ST including renal failure, bifurcation lesions, diabetes, low ejection fraction, and long stent length, however, premature cessation of antiplatelet therapy has been reported to be the crucial predictor of ST in patients with BMS or DES. [64, 66-70] With respect to duration of clopidogrel administration, both arms of the included randomized trials (i.e. BMS and DES) in our meta-analysis were the same except two in which patients with DESs had different duration of clopidogrel;[42, 50] however, the studies did not change the overall result of our meta-analysis. According to our finding in this analysis, it is strongly recommended that the clopidogrel should be administered for a longer period in patients receiving DESs at least those who are at higher risk; our study showed that SESs make patients more vulnerable to very late ST compared with PES. Also, it seems to be inadvisable to recommend DESs for patients with comorbidities who may need early cessation of antiplatelets due to nondefferable surgeries in the near future. Nevertheless, crucial risk factors for very late ST besides the optimal time period of clopidogrel usage should be investigated in future studies. Most of the included studies administered clopidogrel for 6 months, however, in some studies, it was taken for shorter and in others longer periods (Table 1). More interestingly, a new member of the thienopyridines class, prasugrel, has recently reported in TRITON-TIMI-38 to be more effective than clopidogrel in preventing MI and ST.[71] It is currently FDA-approved and

could be utilized for patients at-risk of ST;[72] however, available data confirms its efficacy in early and late periods and long-term studies should be performed to evaluate its efficacy for reduction of very late ST.[71, 72] In addition, a more recent study, PLATO trial, reported the superiority of ticagrelor over clopidogrel in reducing thrombosis-related events;[73] thus, its efficacy could also be considered for patients with DESs who are at-risk for ST.

To date, several meta-analyses have been performed attempting to compare angiographic and clinical effects of DESs with BMSs.[56, 58-60, 74] Nevertheless, they most had major drawbacks and several types of biases debated their results and made them unreliable to be utilized for a clinical guideline. The lack of a through and clearly-mentioned critical appraisal was frequently seen among previous meta-analysis,[58-60] and they have included some studies with major types of biases. Babapulle and colleagues,[59] used the RCT reported by Hong et al. (ASPECT),[30] in which more than 10 % loss to follow-up was reported. Cross-over bias was a crucial type of bias which was seen in MISSION[41] and SESAMI trials,[34] which were included in previous meta-analyses.[58, 60] In addition, publication bias, at least in part, affected the results of some previous analyses and made them less reliable to be considered for clinical decision making.[59, 74] More importantly, a major heterogeneity was seen across trials included in some previous meta-analyses and even limiting the trials in subgroups failed to remove the heterogeneity. On contrary, heterogeneity which was detected across trials included in our analyses of TLR and TVR outcomes was removed by limiting the data in subgroups of SES and PES.

In conclusion, this critically-appraised, comprehensive meta-analysis shed light on higher safety and efficacy of DES in decreasing angiographic restenosis as well as improving clinical outcomes including MI, TLR, and TVR compared with BMS. However, their increasing effect on very late ST, though it should be further confirmed in a future long-term, high-powered, randomized controlled trial, raises concern for its widespread usage. According to the current

evidence, we suggest cautious usage of DES, particularly SES, besides longer antiplatelet therapy in patients who are at higher risk for ST.

Figure Legend:

Figure 1. Search Strategy of meta-analysis.

Figure 2. Funnel plot of meta-analysis.

Figure 3. Meta-analysis of all-cause mortality.

Figure 4. Meta-analysis of cardiac death.

Figure 5. Meta-analysis of myocardial infarction.

Figure 6. Meta-analysis of target lesion revascularization.

Figure 7. Meta-analysis of target vessel revascularization.

Figure 8. Meta-analysis of major adverse cardiac event.

Figure 9. Meta-analysis of restenosis.

Figure 10. Meta-analysis of stent thrombosis.

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Table 1. Characteristics of Included Trials.

Trial / Author Name	Patients	Procedures (n)		Blinding	Duration of F/U (mo)		Follow-up (%)		Age (yr)	DM (%)	DES Type	Clopidogrel Time		Stent Length (mm)	
(Reference number)	(n)	Lesions	Stents		Clinical	Angiographic	Clinical	Angiographic				DES	BMS	DES	BMS
BASKET / Kaiser (12)	826	1281	1665	Single	6	-	99.7	-	64	18.5	PES	6	6	34.4±20	32±20
C-SIRIUS / Schampaert (6)	100	-	150	Double	9	8	100	88	60.5	24	SES	2	2	23.8±8.4	23.8±8.4
DECODE / Chan (1)	83	128	172	Single	12	6	98.7	92.7	60	100	SES	3	3	20.9±8.4	20.9±8.3
DESSERT / Maresta (42)	150	218	237	Single	12	8	92	76	70	100	SES	6	2	20.3±5	19.4±4.4
DIABETES / Jimenes-Quevedo (16)	160	221	-	Single	24	9	98.7	91.2	66.5	100	SES	12	12	14.6±8	15.3±8
E-SIRIUS / Schofer (14)	352	-	522	Double	9	8	100	87.5	62.3	23	SES	2	2	23±6.3	22.2±6.4
ELUTES / Gershlick (7)	190	190	190	Triple	12	6	100	92.1	59.9	15.7	PES	3	3	-	-
HORIZONS-AMI / Stone (51)	3006	3345	4434	Single	12	13	96.5	40	59.7	15.9	PES	6	6	30.8±17.8	27.3±14.9
PASSION / Dirksen (19)	619	-	802	Single	24	-	96.6	-	61	10.9	PES	6	6	19±5.6	19±5.5
PRISON II / Rahel (13)	200	-	280	Single	36	-	97	-	59.4	13.5	SES	6	6	31.9±15.3	28.9±13.7
RAVEL / van Hout (35)	238	238	238	Double	12	6	95.7	88.7	60.7	19	SES	2	2	18	18
RRISC / Vermeersch (45)	75	96	114	Double	6	6	100	96	72.5	14.6	SES	2	2	36.9±17.6	33.4±18.2
DELAYED RRISC / Vermeersch (55)	75	96	114	Single	36	6	100	96	72.5	14.6	SES	2	2	36.9±17.6	33.4±18.2

SCANDSTENT / Kelbaek (17)	319	-	431	Single	36	6	100	100	62.7	18	SES	12	12	26.1	22.6
SCORPIUS / Baumgart (15)	200	192	230	Single	12	8	95	72	66	100	SES	6	6	20.5±10.3	18.7±8.5
SELECTION / Chechi (2)	80	80	80	Single	7	7	100	95	60.7	12.5	PES	9	9	20.8±5.8	18.4±4.5
SES-SMART / Menozzi (43)	257	-	-	Single	24	8	98.8	-	63.6	24.9	SES	2	2	-	-
SIRIUS / Weisz (49)	1058	1058	1481	Double	24	8	91.9	66.4	62.3	26	SES	3	3	23	23
SOS / Brilakis (50)	80	112	124	Single	24	12	100	82.5	66	43.7	PES	12	1	18±6	18±6
TAXUS I / Grube (54)	61	61	61	Double	12	6	98.3	96.7	64.9	18	PES	6	6	15	15
TAXUS II / Colombo (4)	536	-	569	Double	12	6	97.3	97	60.1	14.5	PES	6	6	15	15
TAXUS IV / Stone (52)	1314	1314	1314	Double	12	9	96.8	42.5	62.4	24.2	PES	6	6	21.9±8.1	21.7±8.8
TAXUS V / Stone (53)	1156	-	1595	Double	9	9	97.4	85.6	62.8	30.7	PES	6	6	28.7±13.2	28.2±13
TAXUS VI / Dawkins (3)	446	-	570	Double	9	9	98.8	93.4	62.6	19.9	PES	6	6	33.7±10.7	33.2±10.1
TAXUS VI / Grube (18)	446	-	570	Double	24	9	97	93.4	62.6	19.9	PES	6	6	33.7±10.7	33.2±10.1
TYPHOON / Spaulding (47)	712	-	783	Single	12	8	100	23.8	59.2	16.2	SES	6	6	22.1±8.6	20.3±8.2
Pache (44)	500	-	600	None	12	6	97.4	81.8	67	30.8	SES	6	6	18	18
Sako (46)	32	32	32	Single	-	6	-	100	63.2	56.3	SES	-	-	21±3	20±5

F/U: follow-up; yr: year; DM: diabetes mellitus; DES: drug-eluting stent; BMS: bare metal stent; mm: millimeter; PES: paclitael-eluting stent; SES: sirolimus-eluting stent.

Table 2. Subgroup Analysis of Stent Thrombosis.

Subgroup	Trials, n	Patients		Fixed-Effects	P	Heterogeneity P	I^2, %
		DES (n/N)	BMS (n/N)	RR [95 % CI]			
Early							
SES	13	23/2348	23/2336	1.01 [0.59 - 1.74]	0.98	0.84	0
PES	10	18/2516	23/2403	0.74 [0.41 - 1.36]	0.33	0.94	0
Total	22	41/4864	44/4458	0.86 [0.57 - 1.30]	0.47	0.96	0
Late							
SES	14	7 2348	16/2336	0.54 [0.25 - 1.13]	0.1	0.88	0
PES	9	7 2516	7 2403	1.00 [0.41 - 2.43]	0.99	0.56	0
Total	22	14/4864	23/4458	0.69 [0.39 - 1.21]	0.19	0.84	0
Very late							
SES	6	17/1038	3/1026	4.06 [1.46 - 11.29]	0.007	0.6	0
PES	3	4/555	2/555	1.65 [0.40 - 6.80]	0.49	0.49	0
Total	9	21/1593	5/1581	3.09 [1.37 - 6.99]	0.007	0.7	0

DES: drug-eluting stent; BMS: bare metal stent; RR: risk ratio; SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent

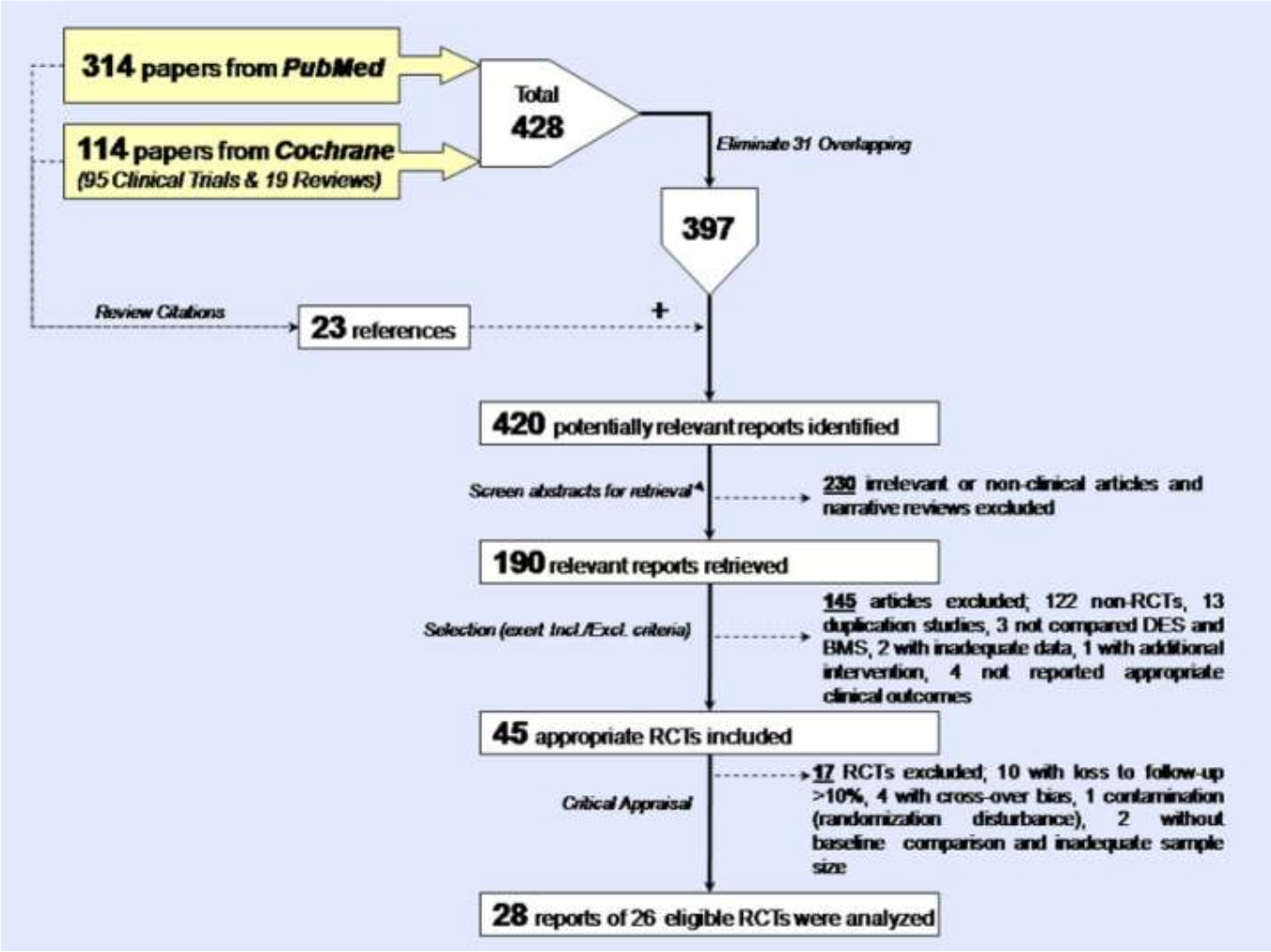

FIG. 1

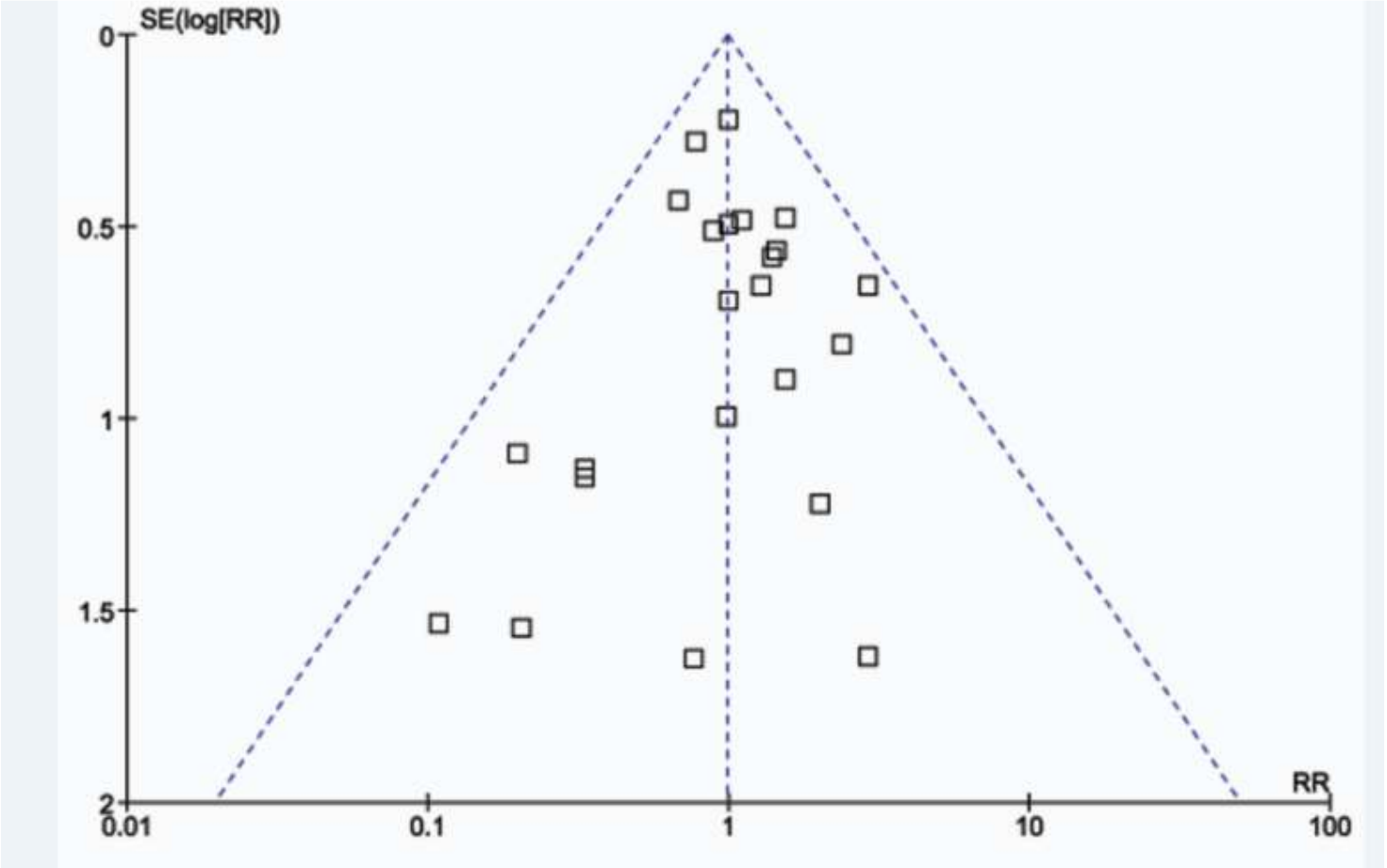

FIG. 2

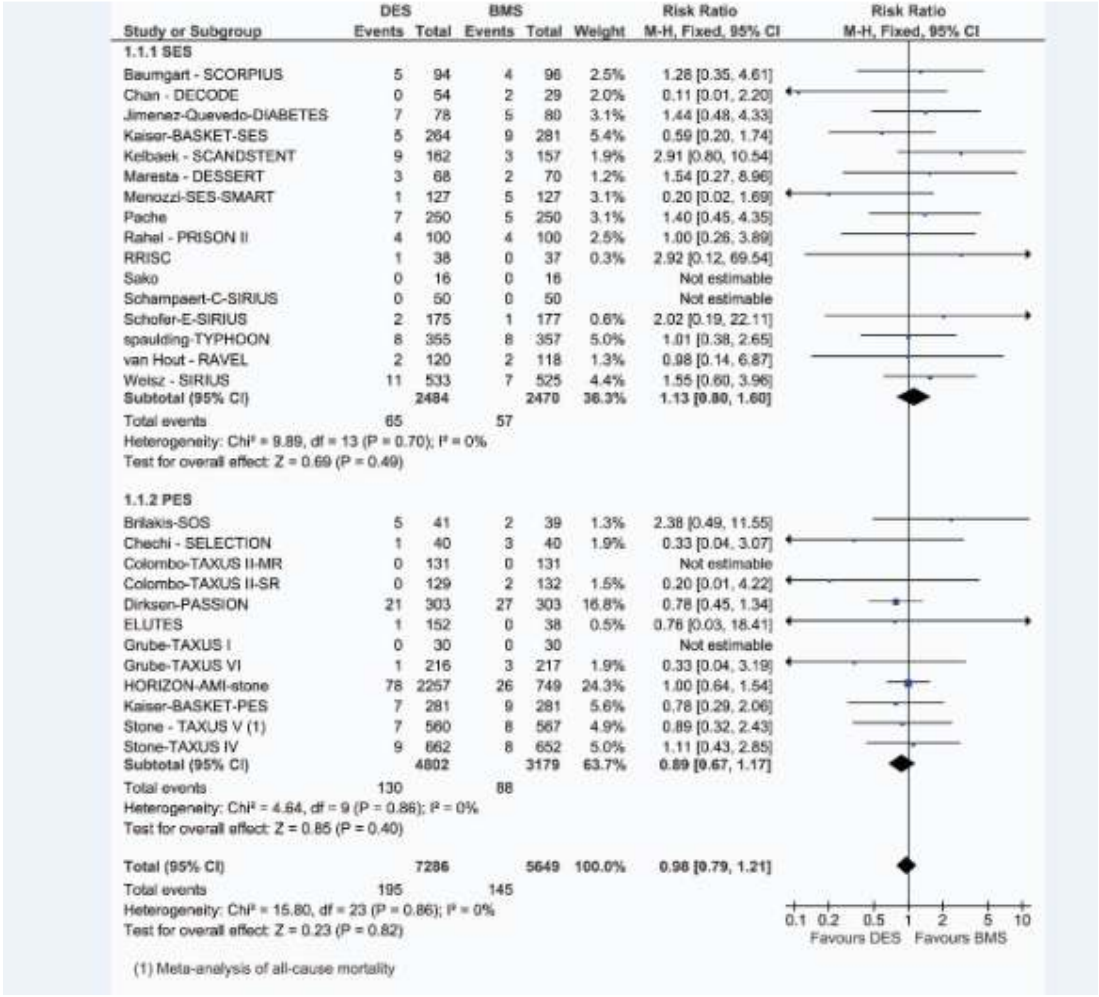

FIG. 3

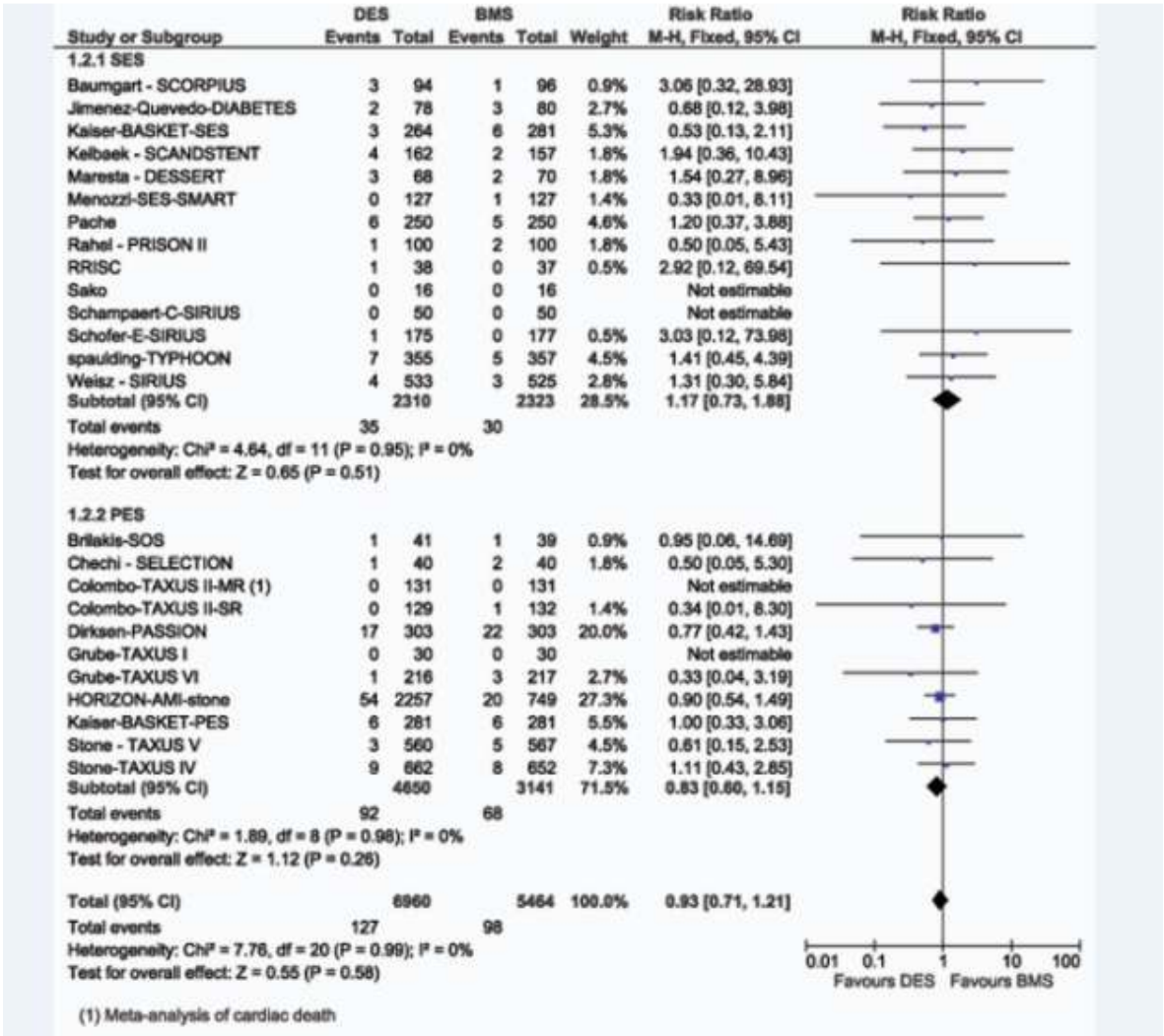

FIG. 4

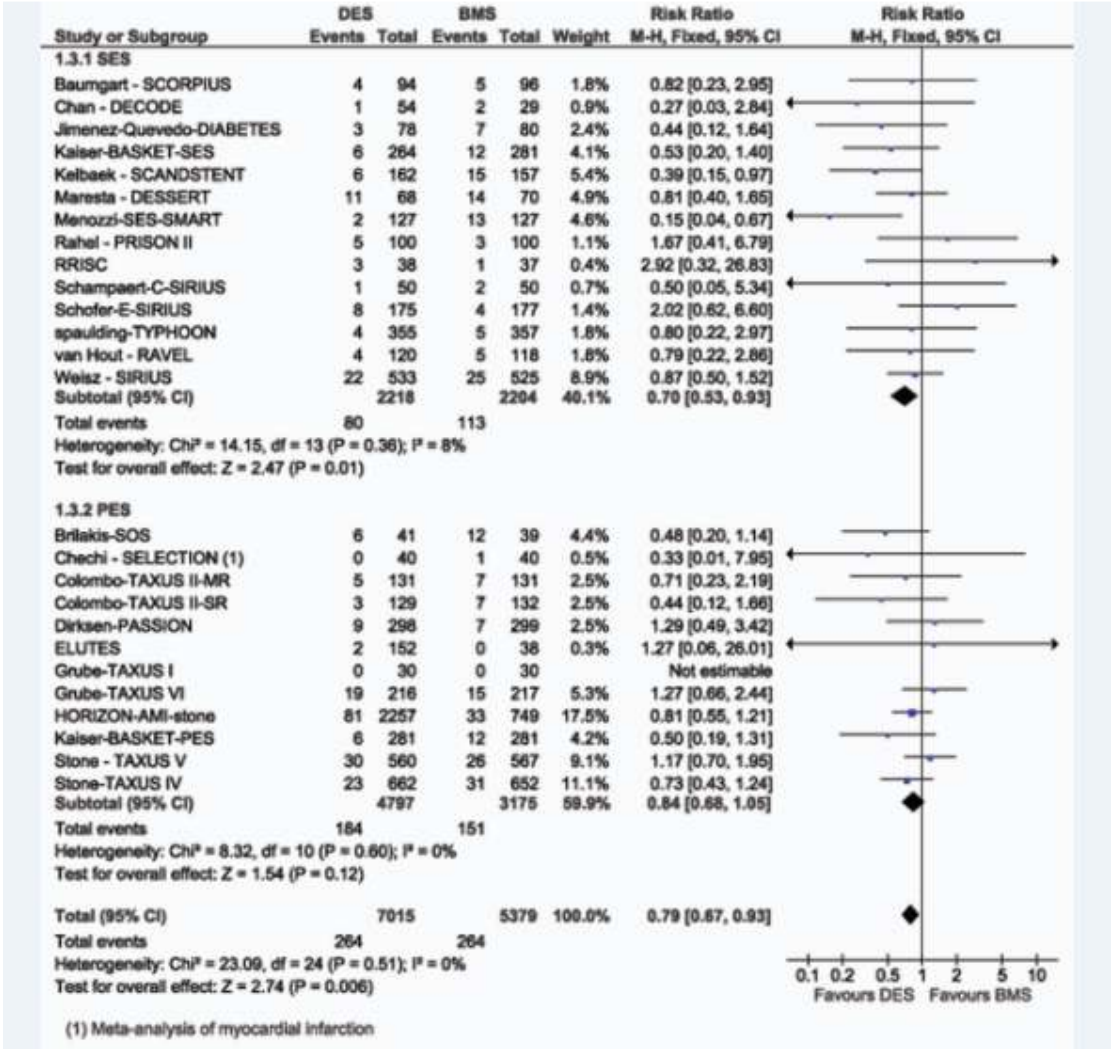

FIG. 5

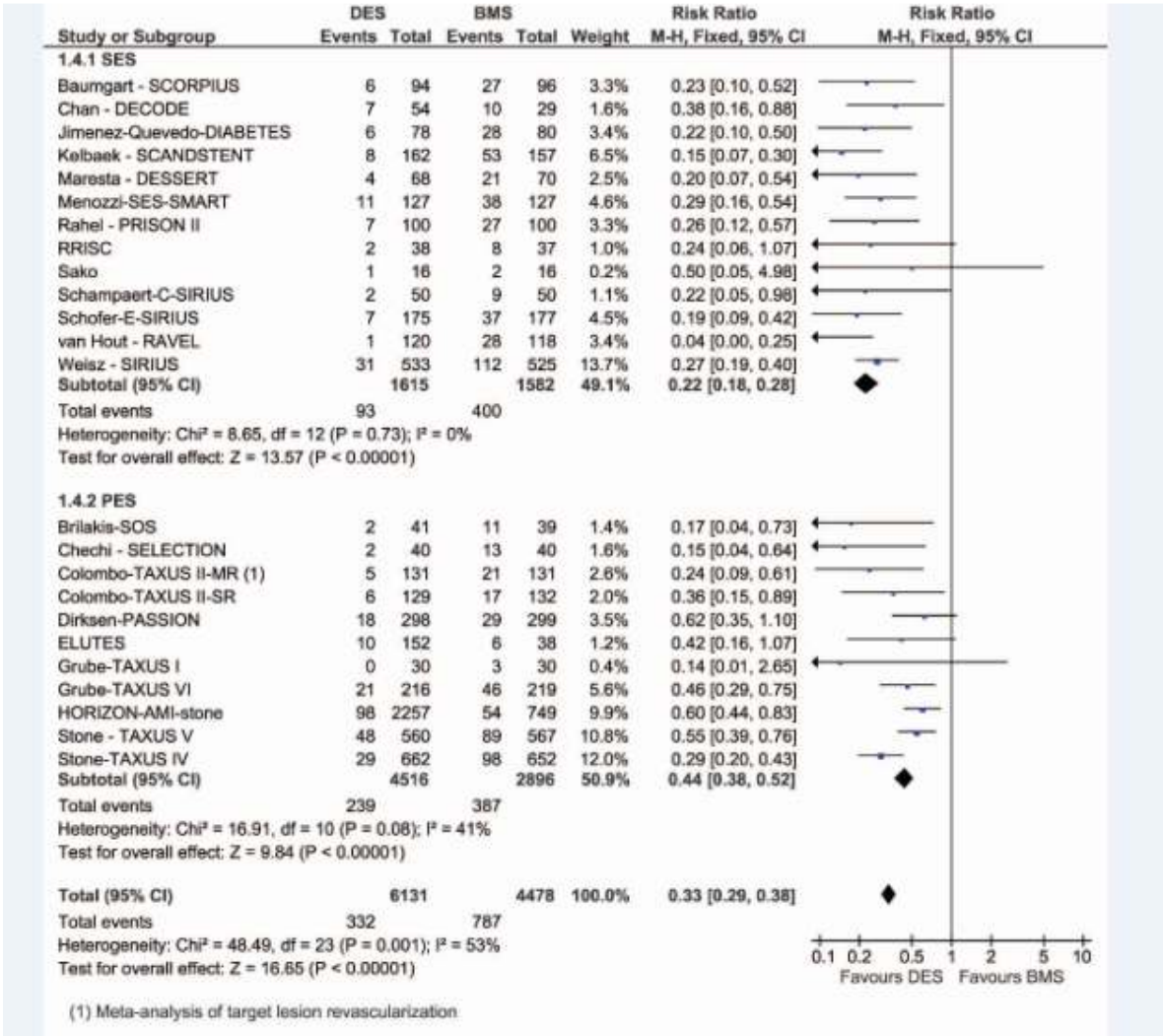

FIG. 6

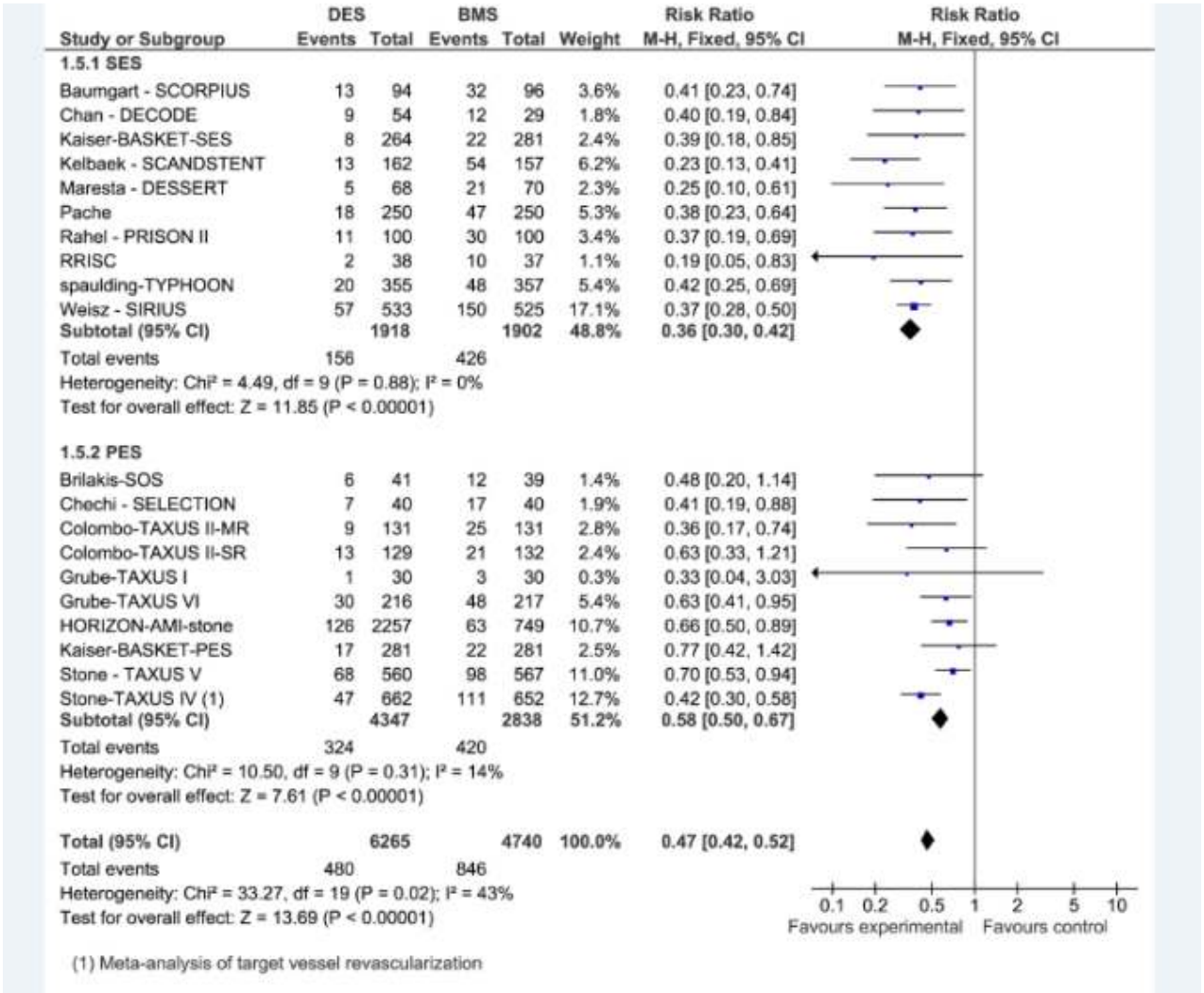

FIG. 7

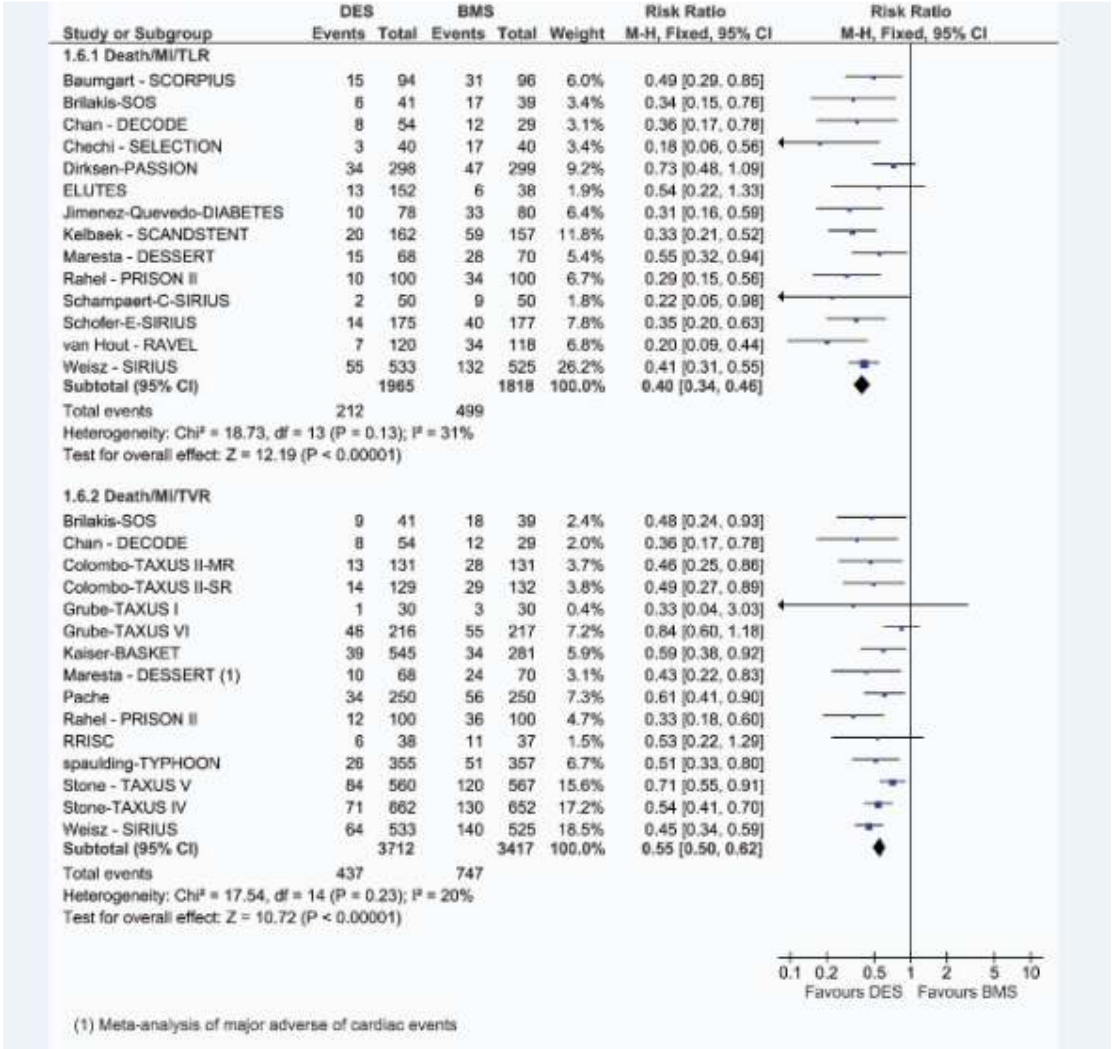

FIG. 8

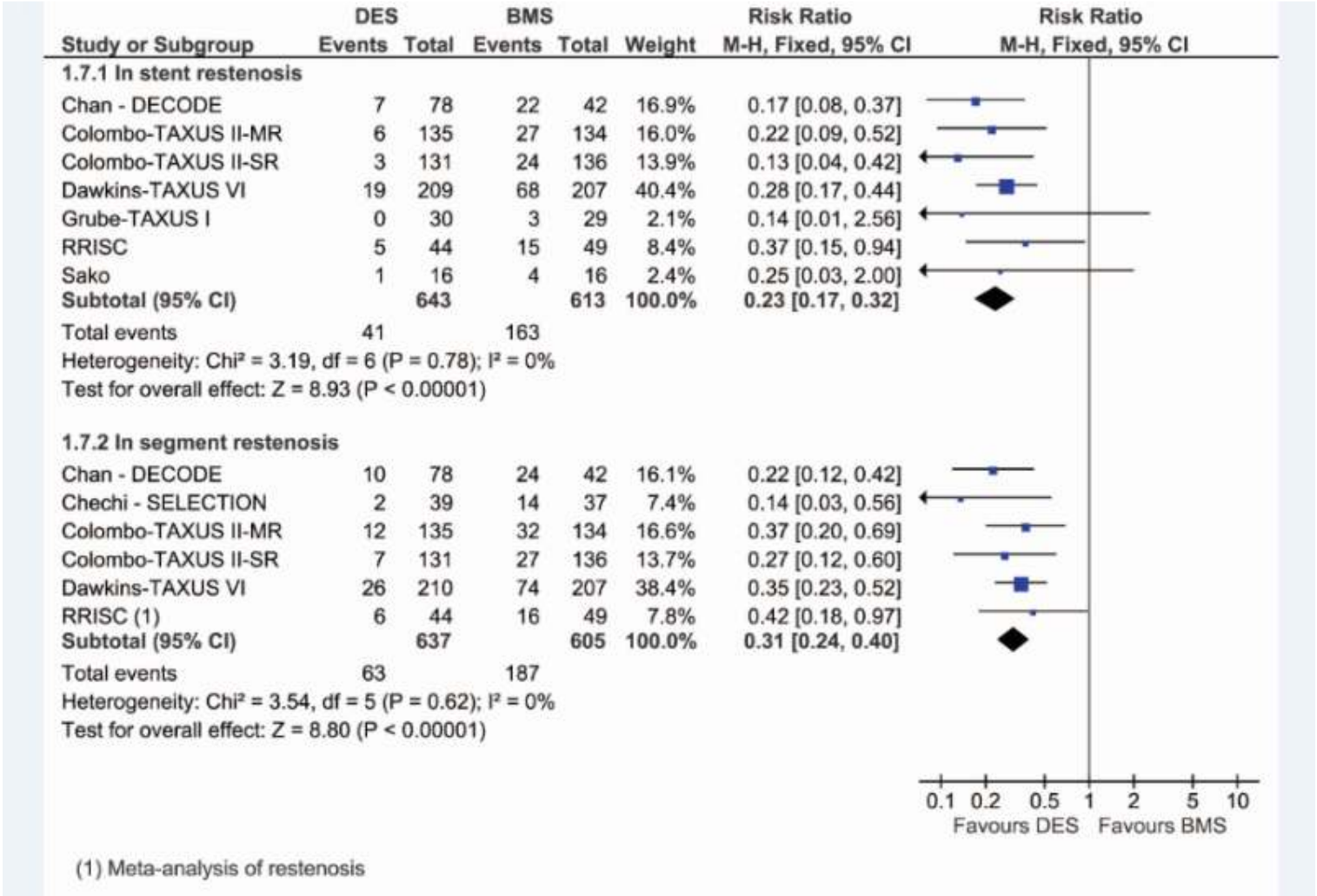

FIG. 9

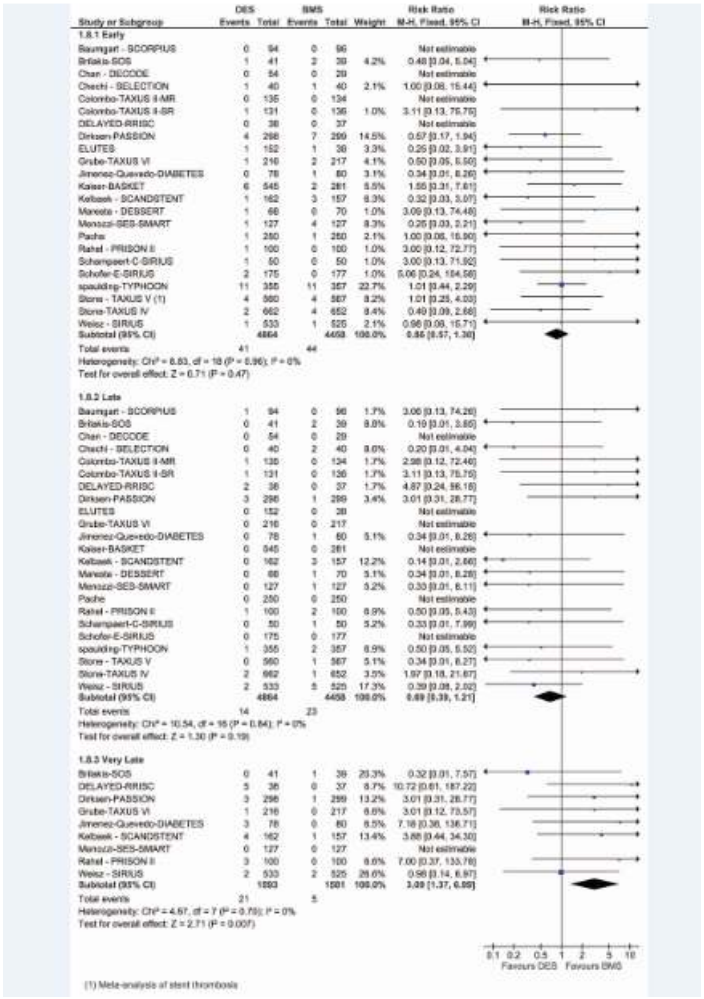

FIG. 10