

# openheart First-generation versus second-generation drug-eluting stents in current clinical practice: updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients

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## ABSTRACT

**Background:** First-generation drug-eluting stents (DES) have become the most widely used devices worldwide for management of coronary artery disease. As remote follow-up data were becoming available, concerns emerged in regard to their long-term safety. Second-generation DES were designed to overcome safety issues, but the results of randomised clinical trials remain conflicting.

**Methods:** We compared the safety and efficacy of first-generation versus second-generation Food and Drug Administration approved DES; the following devices were included: first-generation sirolimus-eluting stent (SES) and paclitaxel-eluting stents (PES); second-generation everolimus-eluting stent (EES), zotarolimus-eluting stent Endeavor and ZES-Resolute (ZES-R). Prespecified safety end points comprised  $\leq 1$  and  $>1$  year: overall and cardiac mortality, myocardial infarction (MI), definite/definite or probable ST; efficacy end points were target lesion revascularisation and target vessel revascularisation. Composite end points were analysed as well.

**Results:** 33 randomised controlled trials involving 31 379 patients with stable coronary artery disease or acute coronary syndrome undergoing DES implantation were retrieved. No differences in mortality among devices were found. In the overall class comparison, second-generation DES were associated with a 22% reduction of odds of MI at short-term OR 0.77 (95% CI 0.68 to 0.89)  $p=0.0002$ ; EES reduced the odds of definite-probable ST compared with PES: OR 0.33 (95% CI 0.15 to 0.73)  $p=0.006$ ; First-generation SES along with second-generation EES and ZES-R showed similar efficacy in decreasing the odds of repeat revascularisation.

**Conclusions:** Second-generation EES and ZES-R offer similar levels of efficacy compared with first-generation SES, but are more effective than PES; however, only

## KEY MESSAGES

### What is already known about this subject?

- Second generation DES are similarly effective as first generation DES.

### What does this study add?

- Everolimus eluting stent was found to significantly reduce the odds of myocardial infarction and stent thrombosis.

### How might this impact on clinical practice?

- No differences in mortality was found between these devices.

second-generation EES significantly reduced the incidence of MI and ST, and therefore should be perceived as the safest DES to date.

## INTRODUCTION

Over the past 10 years, first-generation drug-eluting stents (DES), especially sirolimus-eluting stent (SES) and paclitaxel-eluting stents (PES), have become the most widely used devices worldwide for management of coronary artery disease. However, despite their clear superiority in preventing restenosis and the need for repeat revascularisation due to eluted antiproliferative drugs is certainly proven,<sup>1</sup> as remote follow-up data were becoming available, concerns emerged in regard to their long-term safety, strictly late and very late thrombotic events, in turn associated with a high rate of death and

Table 1 Characteristics of included studies

Study	Journal	Year	Number of patients	First generation	Second generation	Short-term follow-up (≤12 months)	Long-term follow-up (>12 months)	Primary end point	MACE/TVF definition	Clinical setting	Minimal DAPT duration (ADP receptor/P2Y12 inhibitor)	Protocol defined follow-up angiography
APPENDIX-AMI <sup>13 14</sup>	<i>PLoS ONE</i>	2013	977	SES Cypher	EES Xience V	12 months*	24 months	MACE	Cardiac mortality, MI, TVR	Stable/ACS	12 months	No
BASKET-PROVE <sup>15</sup>	<i>NEJM</i>	2010	1549	SES Cypher	EES Xience V	n.r.	24 months	MACE	Mortality, MI, TVR	Stable/ACS	12 months	No
CATOS <sup>16</sup>	<i>Circulation Journal</i>	2012	160	SES Cypher	ZES Endeavor	12 months	n.r.	In-segment binary restenosis rate at 9 months angiographic follow-up	Cardiac mortality, MI, TVR	CTO	12 months	Yes
CIBELES <sup>17</sup>	<i>Circulation Cardiovascular Interventions</i>	2013	207	SES Cypher	EES Xience V	12 months	n.r.	In-stent late loss at 9 months angiographic follow-up	Mortality, MI, TVR	TCO	12 months	Yes
COMPARE <sup>18–20</sup>	<i>Lancet JACC</i>	2010	1800	PES Taxus Liberte	EES Xience V	12 months	24, 36 months	MACE	Mortality, MI, TVR	Stable/ACS	12 months	No
ENDEAVOR III <sup>21 22</sup>	<i>JACC Cardiovascular Interventions</i>	2006 2011	436	SES Cypher	ZES Endeavor	9 months	60 months	In-segment late lumen loss at 8 months angiographic follow-up	Mortality, MI, TLR	Stable/ACS	3 months	Yes
ENDEAVOR IV <sup>23 24</sup>	<i>JACC Cardiovascular Interventions</i>	2010 2013	1548	PES Taxus Express	ZES Endeavor	12 months	60 months	TVF at 9 months	Mortality, MI, TLR	Stable/ACS	6 months	Yes
ESSENCE-Diabetes <sup>25</sup>	<i>Circulation</i>	2011	300	SES Cypher	EES Xience V	12 months	n.r.	In-segment late lumen loss at 8 months angiographic follow-up	Mortality, MI, TLR	Stable/ACS	12 months	Yes
EXCELLENT <sup>26</sup>	<i>JACC</i>	2011	1428	SES Cypher	EES Xience V or Promus	12 months	n.r.	In-segment late lumen loss at 9 months angiographic follow-up	Cardiac mortality, MI, TLR	Stable/ACS	6 months	Yes
EXECUTIVE <sup>27</sup>	<i>JACC Cardiovascular Interventions</i>	2013	200	PES Taxus Liberte	EES Xience V	12 months	n.r.	In-segment late lumen loss at 9 months angiographic follow-up	Mortality, MI, TVR	Stable/ACS	6 months	Yes
ISAR-TEST-2 <sup>28 29</sup>	<i>EHJ JACC</i>	2009 2010	674	SES Cypher	ZES Endeavor	12 months	24 months	binary angiographic restenosis at 6–8-month follow-up angiography	Mortality, MI, TLR	Stable/ACS	12 months	Yes
KOMER <sup>30</sup>	<i>EuroIntervention</i>	2011	611	SES Cypher and PES Taxus Express	ZES Endeavor	12 months	18 months	MACE	Cardiac mortality, MI, TLR	STEMI	12 months	Yes

Continued

Table 1 Continued

Study	Journal	Year	Number of patients	First generation	Second generation	Short-term follow-up (≤12 months)	Long-term follow-up (>12 months)	Primary end point	MACE/TVF definition	Clinical setting	Minimal DAPT duration (ADP receptor/P2Y12 inhibitor)	Protocol defined follow-up angiography
LONG-DES III <sup>31</sup>	<i>JACC</i>	2011	450	SES Cypher	EES Xience V or Promus	12 months	n.r.	In-segment late lumen loss at 9 months angiographic follow-up	Mortality, MI, TVR	Stable/ACS	12 months	Yes
LONG-DES IV <sup>32</sup>	<i>Circulation Cardiovascular Interventions</i>	2012	500	SES Cypher	ZES Resolute	12 months	n.r.	In-segment late lumen loss at 9 months angiographic follow-up	Mortality, MI, TVR	Stable/ACS	12 months	Yes
Naples-Diabetes <sup>33</sup>	<i>Circulation Cardiovascular Interventions</i>	2011	226	SES Cypher and PES Taxus Liberte	ZES Endeavor	In-hospital; 12 months	36 months	MACE	Mortality, MI, TVR	Stable/ACS	6 months	No
PRISON III <sup>34</sup>	<i>EuroIntervention</i>	2013	304	SES Cypher	ZES Resolute or ZES Endeavor	12 months	n.r.	In-segment late lumen loss at 8 months angiographic follow-up	Mortality, MI, TLR	TCO	12 months	Yes
R-CHINA RCT <sup>35</sup>	<i>JACC Cardiovascular Interventions</i>	2013	400	PES Taxus Liberte	ZES Resolute	12 months	n.r.	In-stent late lumen loss at 9 months angiographic follow-up	Mortality, MI, TLR	Stable/ACS	6 months	Yes
RESET <sup>36</sup>	<i>Circulation</i>	2012	3197	SES Cypher	EES Xience V	12 months	n.r.	TLR at 12 months; composite of all-cause death and MI at 36 months	Cardiac mortality, MI, TLR	Stable/ACS	3 months	No
Sakakibara et al <sup>37</sup>	<i>Circulation Journal</i>	2012	100	SES Cypher	EES Xience V	12 months	n.r.	binary angiographic restenosis at 8 month follow-up angiography	Mortality, MI, TLR	Stable	12 months	Yes
Sawada et al <sup>38</sup>	<i>International Journal of Cardiology</i>	2012	35	SES Cypher	EES Xience V or Promus	7 months	n.r.	Neointimal thickness and ST	n.a.	STEMI	7 months	Yes
SEA-SIDE <sup>39</sup>	<i>JACC Cardiovascular Interventions</i>	2011	150	SES Cypher	EES Xience V	n.r.	18 months	Occurrence of any trouble in the side-branch (SB) management	Mortality, MI, TVR	Stable/ACS	12 months	No
SEZE <sup>40</sup>	<i>Chinese Medical Journal</i>	2012	122	SES Cypher	ZES Endeavor	12 months	n.r.	In-stent late lumen loss at 9 months angiographic follow-up	Cardiac mortality, MI, TVR	STEMI	12 months	Yes
Song et al <sup>41</sup>	<i>JACC</i>	2012	1114	SES Cypher	EES Xience V	12 months	n.r.	In-segment late lumen loss at 9 months angiographic follow-up	Mortality, MI, TVR	Stable/ACS	6 months	Yes

Continued

Table 1 Continued

Study	Journal	Year	Number of patients	First generation	Second generation	Short-term follow-up (≤12 months)	Long-term follow-up (>12 months)	Primary end point	MACE/TVF definition	Clinical setting	Minimal DAPT duration (ADP receptor/P2Y12 inhibitor)	Protocol defined follow-up angiography
SORT OUT III <sup>42 43</sup>	<i>Lancet JACC Cardiovascular Interventions</i>	2010 2013	2332	SES Cypher	ZES Endeavor	9 months	36 months	MACE	Cardiac mortality, MI, TVR	Stable/ACS	12 months	No
SORT OUT IV <sup>44 45</sup>	<i>Circulation JACC</i>	2012 2012	2774	SES Cypher	EES Xience V or Promus	9 months	24, 36 [ref-tctmd] months	MACE	Cardiac mortality, MI, TVR, def. ST	Stable/ACS	12 months	No
SPIRIT II <sup>46 47</sup>	<i>EuroIntervention EuroIntervention</i>	2007 2012	300	PES Taxus Liberte or PES Taxus Express	EES Xience V	12 months	60 months	In-stent late lumen loss at 6 months angiographic follow-up	Cardiac mortality, MI, TLR	Stable/ACS	12 months	Yes
SPIRIT III <sup>48 49</sup>	<i>JAMA The American Journal of Cardiology</i>	2008 2011	1001	PES Taxus Express	EES Xience V	12 months	36, 60 [ref stone ppt] months	In-stent late lumen loss at 8 months angiographic follow-up	Cardiac mortality, MI, TLR	Stable/ACS	6 months	Yes
SPIRIT IV <sup>50 51</sup>	<i>NEJM JACC</i>	2010 2011	3687	PES Taxus Express	EES Xience V	12 months	24 months	Composite of cardiac death, target vessel MI and TLR	Cardiac mortality, MI, TLR	Stable/ACS	12 months	No
SPIRIT V Diabetic Study <sup>52</sup>	<i>American Heart Journal</i>	2012	324	PES Taxus Liberte	EES Xience V	12 months	n.r.	In-stent late lumen loss at 9 months angiographic follow-up	Mortality, MI, TVR	Stable/ACS	6 months	Yes
Wang <i>et al</i> <sup>53</sup>	<i>JACC abstracts</i>	2011	875	SES Cypher	ZES Endeavor	6 months	n.r.	MACE	Cardiac mortality, MI, TLR	STEMI	n.r.	No
XAMI <sup>54</sup>	<i>JACC</i>	2012	625	SES Cypher	EES Xience V	12 months	n.r.	MACE	Cardiac mortality, MI, TVR	STEMI	12 months	No
ZEST <sup>55</sup>	<i>JACC</i>	2010	2645	SES Cypher or PES Taxus Liberte	ZES Endeavor	12 months	n.r.	MACE	Mortality, MI, TVR	Stable/ACS	12 months	Yes
ZEST-AMI <sup>56 57</sup>	<i>The American Journal of Cardiology</i>	2009	328	SES Cypher or PES Taxus Liberte	ZES Endeavor	12 months	n.r.	MACE	Mortality, MI, TVR	STEMI	12 months	Yes

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; EES, everolimus-eluting stent; MACE, major adverse cardiovascular events; MI, myocardial infarction; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; STEMI, ST elevation myocardial infarction; TLR, target lesion revascularisation; TVR, target vessel revascularisation; ZES, zotarolimus-eluting stent.

myocardial infarction (MI).<sup>2 3</sup> Such events have been attributed to the incomplete re-endothelialisation caused by the drug-induced inhibition of endothelial cell proliferation, stent malapposition, accelerated neoatherosclerosis and, importantly, polymer-induced prolonged vessel wall inflammation.<sup>4</sup> Second-generation DES were designed to overcome safety issues in the long term, employing new biocompatible polymer coatings, less toxic antiproliferative drugs and eventually state-of-the-art thin strut Co-Cr metal alloys, and extensively tested in randomised clinical trials (RCTs). The everolimus-eluting stent (EES) has been found to be safer than first-generation and biodegradable DES;<sup>5</sup> on the other hand, zotarolimus-eluting stent (ZES) was inferior to SES in terms of major adverse cardiac events (MACE) and superior to PES in terms of MI in independent recent meta-analyses of RCTs.<sup>6 7</sup>

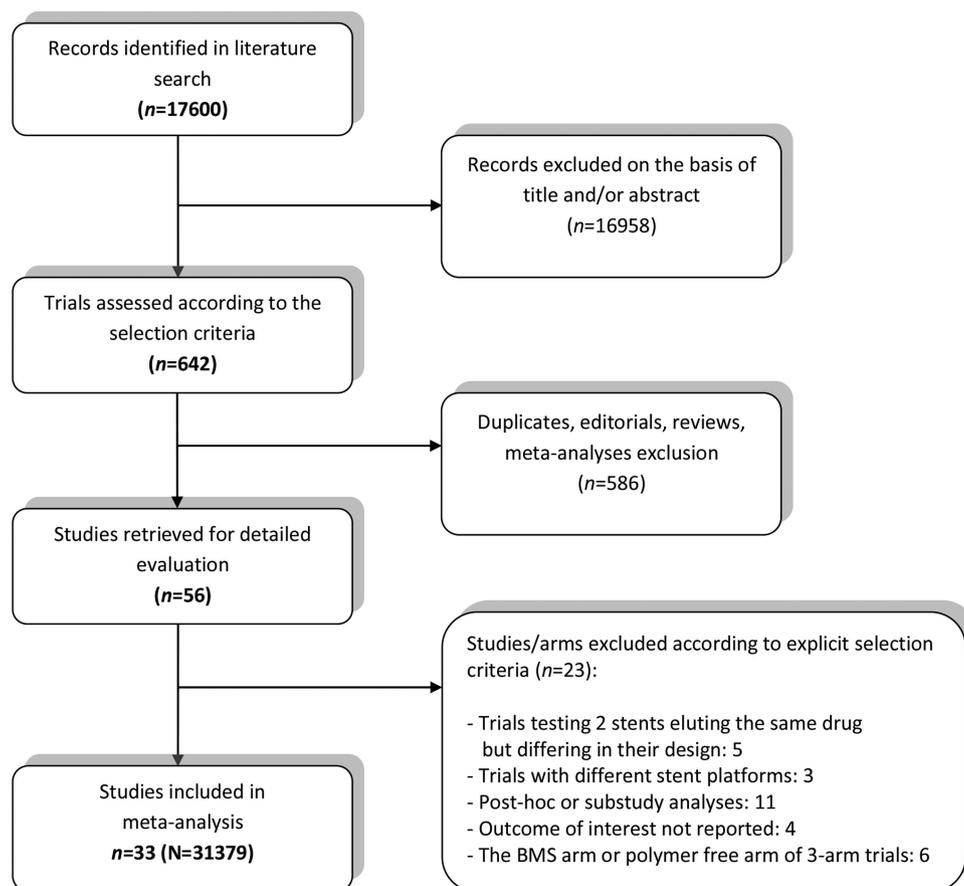
Driven by conflicting evidence on first-generation versus second-generation DES performance in regard to efficacy and safety along with another recent meta-analysis<sup>8</sup> showing significant outcomes in one comparison only (ST rates reduction with second-generation EES vs first-generation PES, we performed a comprehensive and updated meta-analysis of all relevant DES data published to date comparing first-generation and second-generation DES in clinical practice.

## METHODS

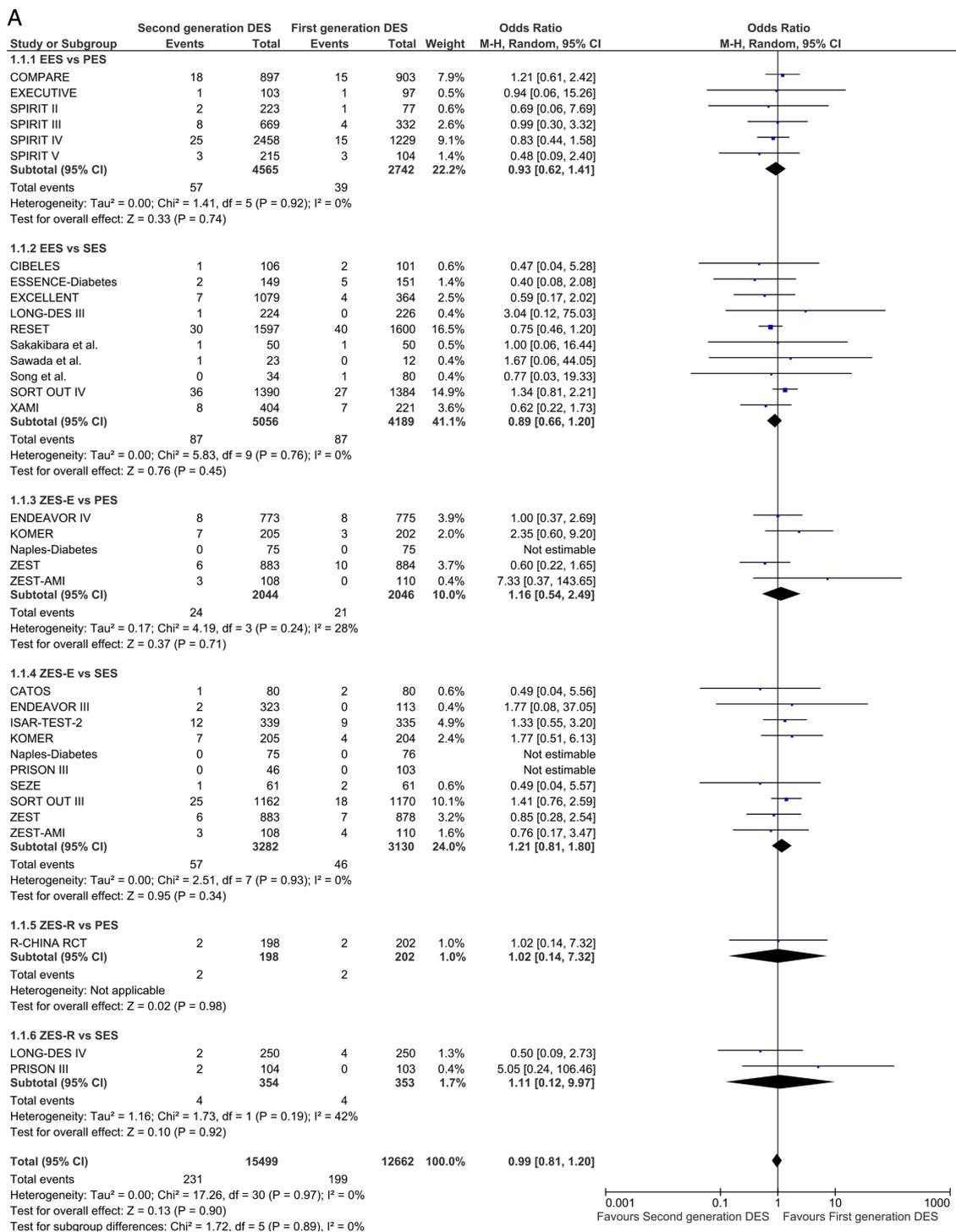
We compared the safety and efficacy of first-generation vs second-generation Food and Drug Administration (FDA) approved DES; the following devices were included: first-generation SES and PES, 2) second-generation EES, ZES-Endeavor (ZES-E) and ZES-Resolute (ZES-R).

Established methods were used in adherence to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses in healthcare interventions.<sup>9</sup> Relevant RCTs were searched until September 2013 through MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar and EMBASE databases and through <http://www.tctmd.com>, <http://www.clinicaltrials.gov>, <http://www.clinicaltrialresults.org> and <http://www.cardiosource.com> websites; documents accessible through the FDA website were scrutinised as well. The following keywords were used: “randomized trials”, “drug-eluting stent”, “durable polymer stent”, “sirolimus stent”, “paclitaxel stent”, “everolimus stent”, “zotarolimus stent”, “Endeavor zotarolimus-stent”, “Resolute zotarolimus-stent”. No language, date or publication status restrictions were imposed. For each RCT, the most updated or most inclusive data were used.

Citations were screened at the title/abstract level and retrieved as full reports. Inclusion criteria were: (1)



**Figure 1** Flow diagram of the review process according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.



**Figure 2** Analysis of all-cause mortality at short-term (A) and long-term (B) follow-up. ORs and 95% CIs. Size of squares is proportional to the statistical weight of each trial.

human studies; (2) RCTs; (3) studies comparing safety AND/OR efficacy of first-generation versus second-generation durable polymer DES; (4) additional data from retrieved studies available at a longer follow-up. Exclusion criteria were: (1) non-RCTs; (2) a substudy of RCTs; (3) a bare metal stent (BMS), biodegradable/bioabsorbable stent or polymer-free stent as the control group, (4) RCTs comparing DES within their class.

Internal validity was appraised according to the proper allocation sequence/concealment, patient blinding, investigator blinding and complete outcome data/full reporting.

Prespecified safety end points comprised  $\leq 1$  year: overall and cardiac mortality, MI and definite/definite or probable ST according to the definition criteria of the Academic Research Consortium (ARC).<sup>10</sup> Efficacy

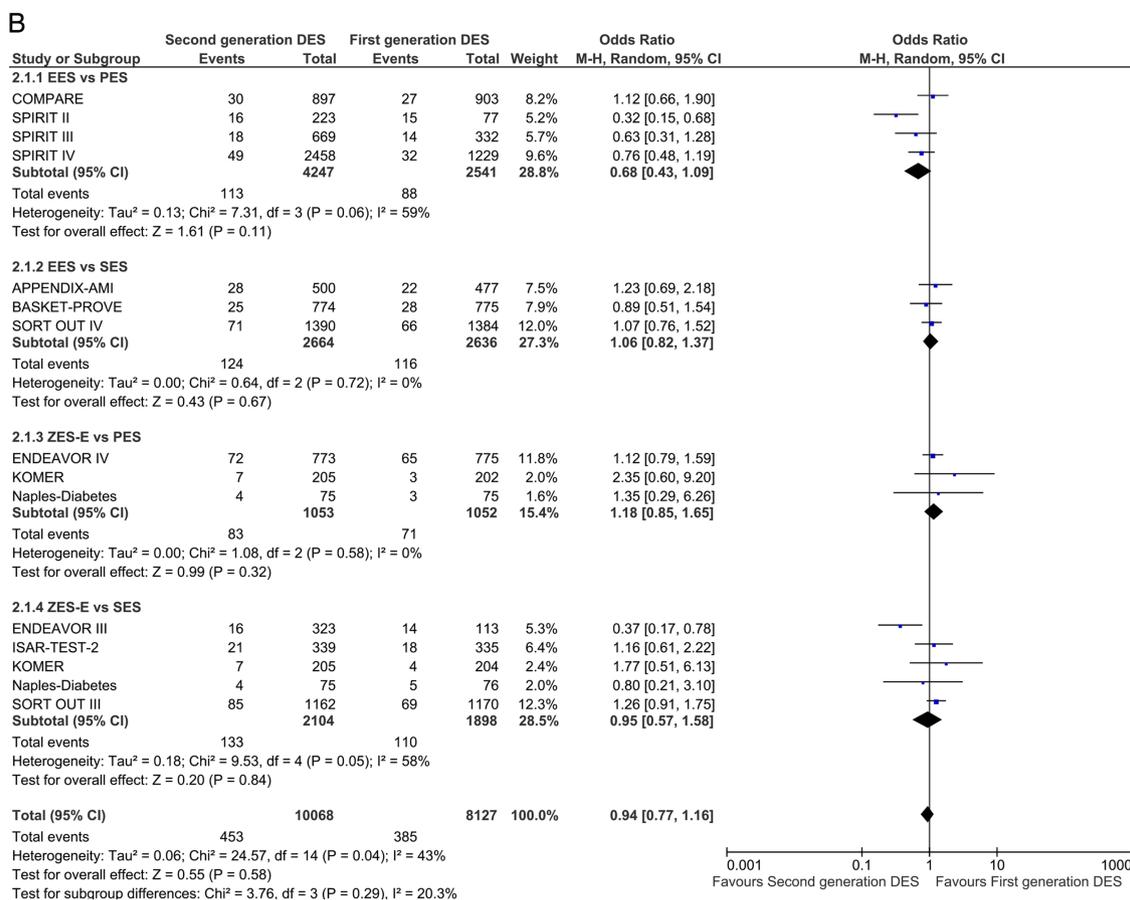


Figure 2 Continued

end points were target lesion revascularisation (TLR) and target vessel revascularisation (TVR). We also analysed the composite end point of MACE to appreciate the cumulative effect of combining non-frequent safety and efficacy adverse events; the MACE definition of each individual study was accepted, although it varied across studies (table 1). To account for over time changes in both the DES properties and eluted drug release kinetics, analyses of each clinical outcome were repeated at longest available, beyond 1 year follow-up.

**Statistical analysis**

Data were analysed according to the intention-to-treat principle. ORs and 95% CIs were used as summary statistics. Heterogeneity was assessed by the Cochran Q test. Statistical heterogeneity was summarised by the I<sup>2</sup> statistic, which quantifies the percentage of variation in study results that is due to heterogeneity rather than chance.<sup>11</sup> Pooled ORs were calculated using a fixed effect model with the Mantel-Haenszel method. The random effects model was applied in case of significant heterogeneity and/or moderate or significant inconsistency (heterogeneity >50%; inconsistency p≤0.05) across studies.<sup>12</sup> Results were considered statistically significant at two-sided p≤0.05. All pooling analyses were conducted using Review Manager 5.1 (Cochrane Collaboration, Copenhagen, Denmark).

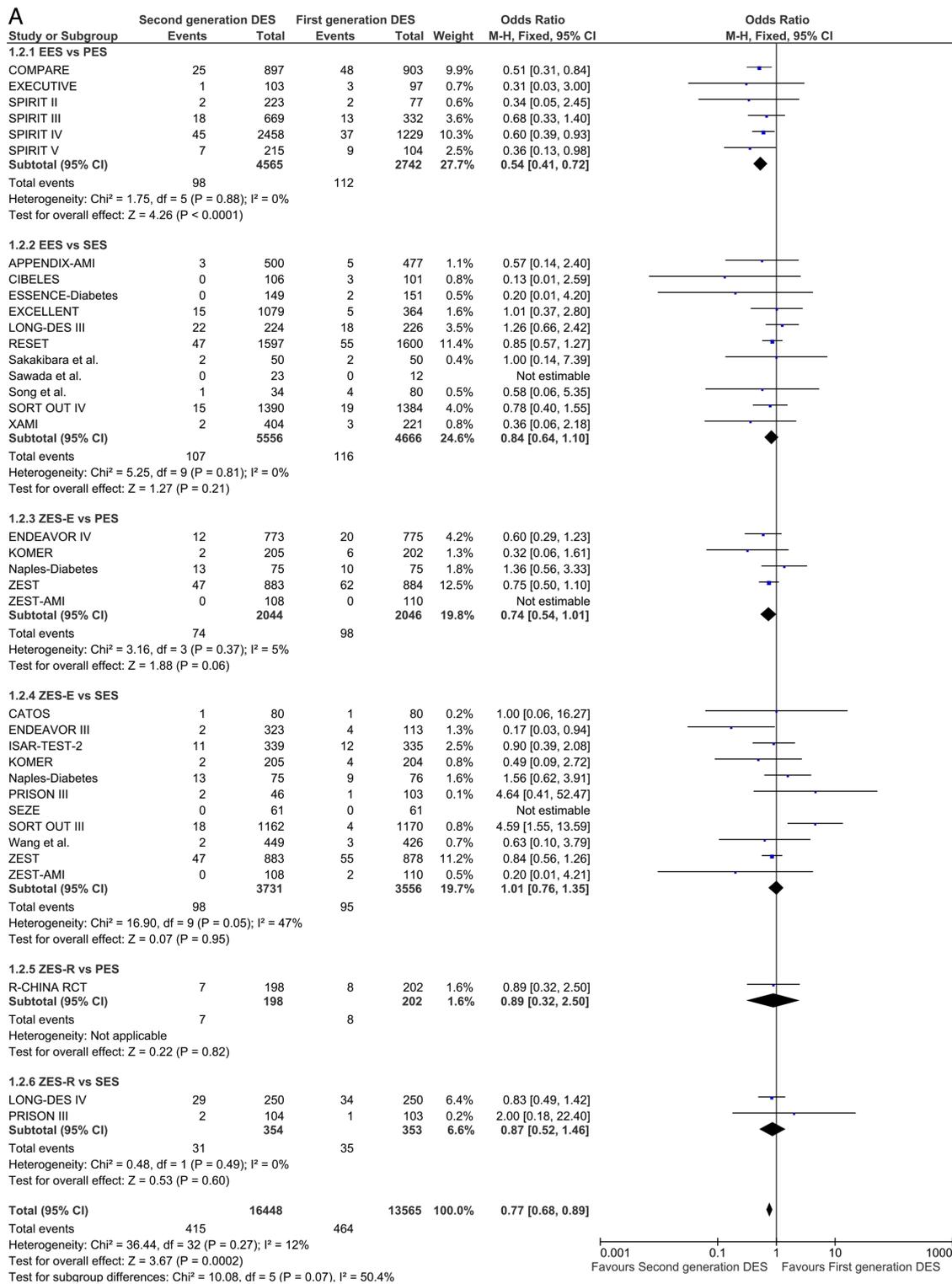
**RESULTS**

**Studies and patient population**

The PRISMA flow diagram of the studies selection is presented in figure 1. The full electronic MEDLINE database search process along with inclusion/exclusion criteria and risk of bias analysis of included studies is shown in the online supplementary material. Thirty-three<sup>13–57</sup> trials comprising a total of 31 379 patients met the inclusion criteria and entered the analysis. Information on stent comparators, clinical setting, minimal DAPT duration and primary end points is delineated in table 1. Most trials enrolled high-risk patients with stable coronary artery disease and acute coronary syndrome presentations, with six trials restricting their inclusion criteria to STEMI patients only<sup>30 38 40 53 54 56</sup>; clopidogrel was administered across all studies; the composite end point of MACE was similar throughout the studies and included cardiac death, MI and repeat revascularisation; detailed definitions are listed in table 1. Funnel plots did not reveal publication bias or small study effect and are included in the online supplementary material (see online supplementary figure S1A, B).

**Mortality, cardiac death**

Twenty-nine studies contributed to the analysis of ≤1 year mortality. Second-generation DES were associated with results that did not differ significantly from



**Figure 3** Analysis of MI at short-term (A) and long-term (B) follow-up. ORs and 95% CIs. Size of squares is proportional to the statistical weight of each trial. MI, myocardial infarction.

those of the first-generation in either comparison group: OR 0.99 (95% CI 0.81 to 1.20) p=0.90. Results in the long term (13 studies included) were consistent with the short-term analysis: OR 0.94 (95% CI 0.77 to 1.16) p=0.58 (figure 2A). A non-significant trend favouring EES was shown in comparison with PES in the long term: OR 0.68 (95% CI 0.43 to 1.09) p=0.06 (figure 2B).

The cardiac mortality analysis did not diverge from the findings from all-cause death calculations with OR 1.03 (95% CI 0.81 to 1.31) p=0.79 and OR 1.02 (95% CI 0.79 to 1.31) p=0.89, for short-term and long-term follow-up, respectively, for overall first-generation versus second-generation stents comparison (see online supplementary figure S2A,B).

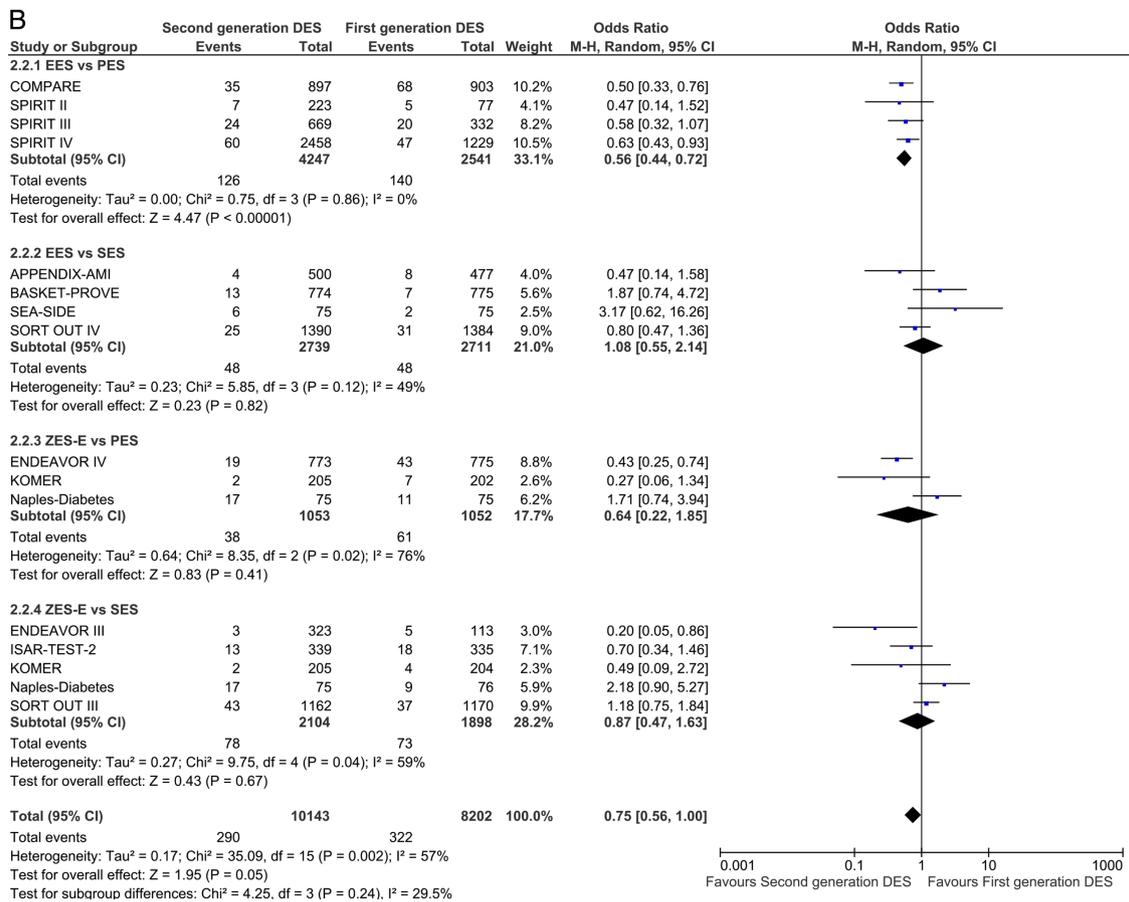


Figure 3 Continued

**Myocardial infarction**

Thirty-one studies were included in the MI analysis in the short term. EES significantly reduced the odds of MI compared with PES: OR 0.54 (95% CI 0.41 to 0.72) p<0.0001 (figure 3A). In the overall class comparison, second-generation DES were associated with a 23% reduction of odds of MI OR 0.77 (95% CI 0.68 to 0.89) p=0.0002 in the short term. A significant class effect favouring second-generation DES was sustained in the long-term analysis: OR 0.75 (95% CI 0.56 to 1.00) p=0.05, with the odds of MI halved in comparison with EES versus PES: OR 0.56 (95% CI 0.44 to 0.72) p<0.001 (figure 3B).

**Stent thrombosis**

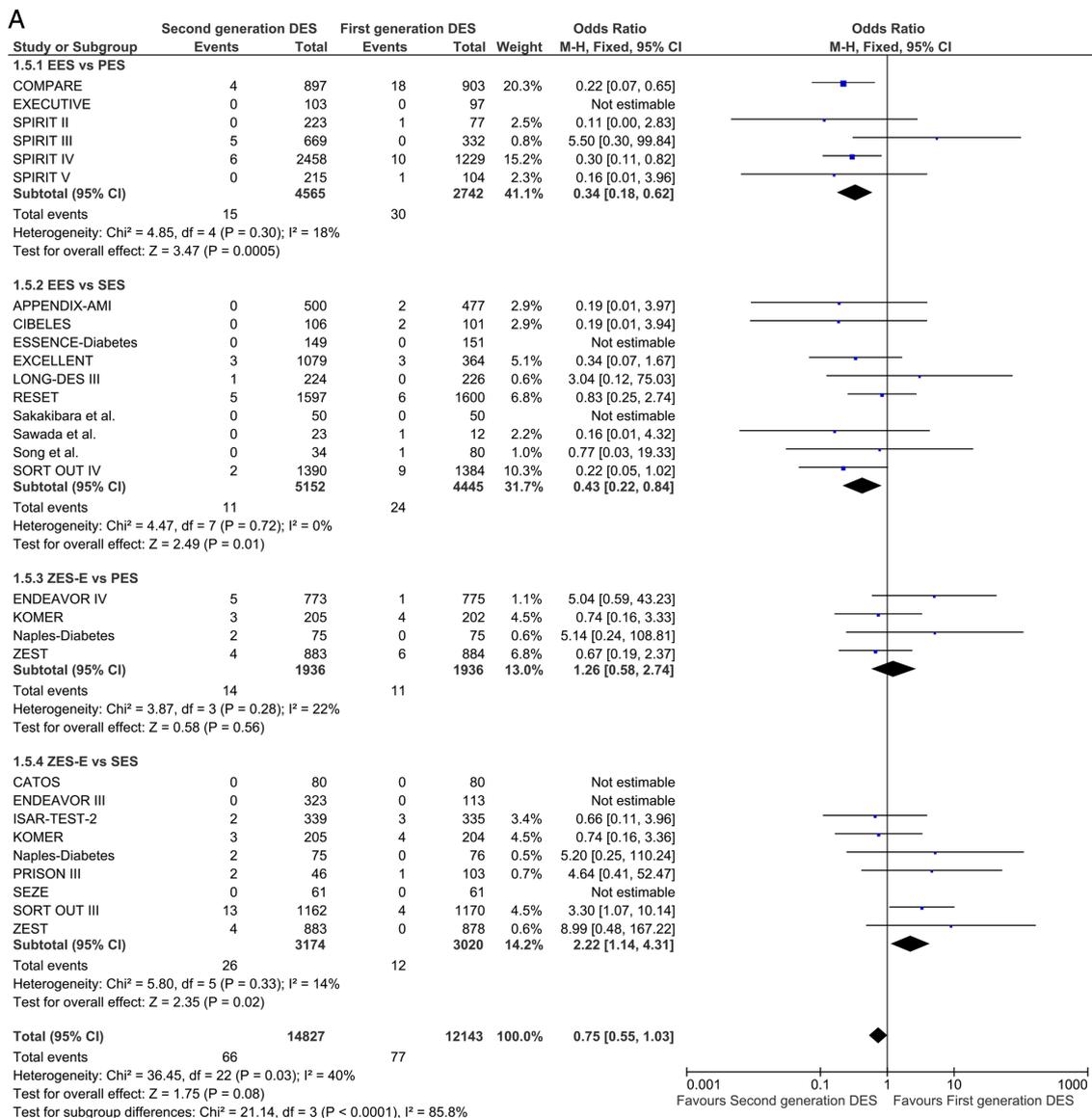
For the analysis of definite ST, 26 studies were included. In the short term, EES was associated with significant reduction of odds of ST compared with PES and SES: OR 0.34 (95% CI 0.18 to 0.62) p=0.0005 and OR 0.43 (95% CI 0.22 to 0.84) p=0.01, respectively (figure 4A). Second-generation ZES-E increased the odds of ST by 122% compared with first-generation SES: OR 2.22 (95% CI 1.14 to 4.31) p=0.02. Results in the long term confirmed short follow-up findings; EES was associated with a more pronounced and significant reduction of odds of ST over time as compared with PES and SES:

OR 0.26 (95% CI 0.14 to 0.49) p<0.0001 and OR 0.30 (95% CI 0.11 to 0.78) p=0.01, respectively (figure 4B).

Analysis of definite-probable ST reflected the direction of the definite ST estimates. EES reduced the odds of definite-probable ST compared with PES and SES: OR 0.33 (95% CI 0.15 to 0.73) p=0.006 and OR 0.61 (95% CI 0.37 to 1.01) p=0.05 (see online supplementary figure 3A). Also, at long-term follow-up, a significant reduction of definite-probable ST odds was observed with EES versus PES (OR 0.32 (95% CI 0.17 to 0.59) p=0.0002) and versus SES (OR 0.50 (95% CI 0.28 to 0.88) p=0.02; see online supplementary figure 3B). The overall class comparison of definite-probable ST favoured second-generation DES over SES at both short-term (OR 0.67 (95% CI 0.47 to 0.94) p=0.02) and long-term (OR 0.54 (95% CI 0.37 to 0.80) p=0.002) follow-up.

**Repeat revascularisation TLR/TVR**

Twenty-nine studies reported TLR incidence at short-term follow-up. First-generation SES along with second-generation EES and ZES-R showed a similar degree of efficacy in decreasing the odds of TLR. EES reduced the odds of TLR by 43% compared with PES (OR 0.57 (95% CI 0.36 to 0.91) p=0.02) and ZES-E markedly increased the odds in comparison to SES (OR 2.61 (95% CI 1.97 to 3.46) p<0.00001; figure 5A), with direction and significance of the estimates being sustained



**Figure 4** Analysis of definite ST at short-term (A) and long-term (B) follow-up. ORs and 95% CIs. Size of squares is proportional to the statistical weight of each trial. ST, stent thrombosis.

over long-term follow-up (12 studies; EES vs PES: OR 0.57 (95% CI 0.46 to 0.72)  $p < 0.00001$ ; and ZES-E vs SES: OR 1.85 (95% CI 1.18 to 2.89)  $p = 0.007$ ; figure 5B).

TVR calculations were in line with those of TLR, confirming a similar high efficacy of EES, SES and ZES-R but not ZES-E or PES at both short-term and long-term follow-up (see online supplementary figure S4A,B).

### Major adverse cardiac events

The analysis of composite end point of MACE included 31 studies at short-term and 13 at long-term follow-up. EES and ZES-R were found to be significantly superior to PES (OR 0.63 (95% CI 0.52 to 0.76)  $p < 0.00001$  and OR 0.44 (95% CI 0.21 to 0.92)  $p = 0.03$ ) and ZES-E performed significantly worse than SES (OR 1.41 (95% CI 1.13 to 1.76)  $p = 0.002$ ) in reducing the odds of MACE at  $\leq 1$  year (figure 6A). Long-term follow-up confirmed the direction and magnitude of the estimates with

EES reducing the odds of MACE by 37% compared with PES (OR 0.63 (95% CI 0.54 to 0.73)  $p < 0.00001$ ; figure 6B)

### Sensitivity analyses

Prespecified sensitivity analyses after exclusion of studies which did not mandate 12-month DAPT for the outcomes of MI and ST did not change the magnitude or direction of the estimates.

### Myocardial infarction

Twenty-one studies were included in MI analysis in the short term. EES significantly reduced the odds of MI compared with PES: OR 0.55 (95% CI 0.40 to 0.76)  $p = 0.0003$ . In the overall class comparison, second-generation DES were associated with a 23% reduction of odds of MI OR 0.77 (95% CI 0.65 to 0.91)  $p = 0.002$  in the short term. A borderline significant class effect favouring

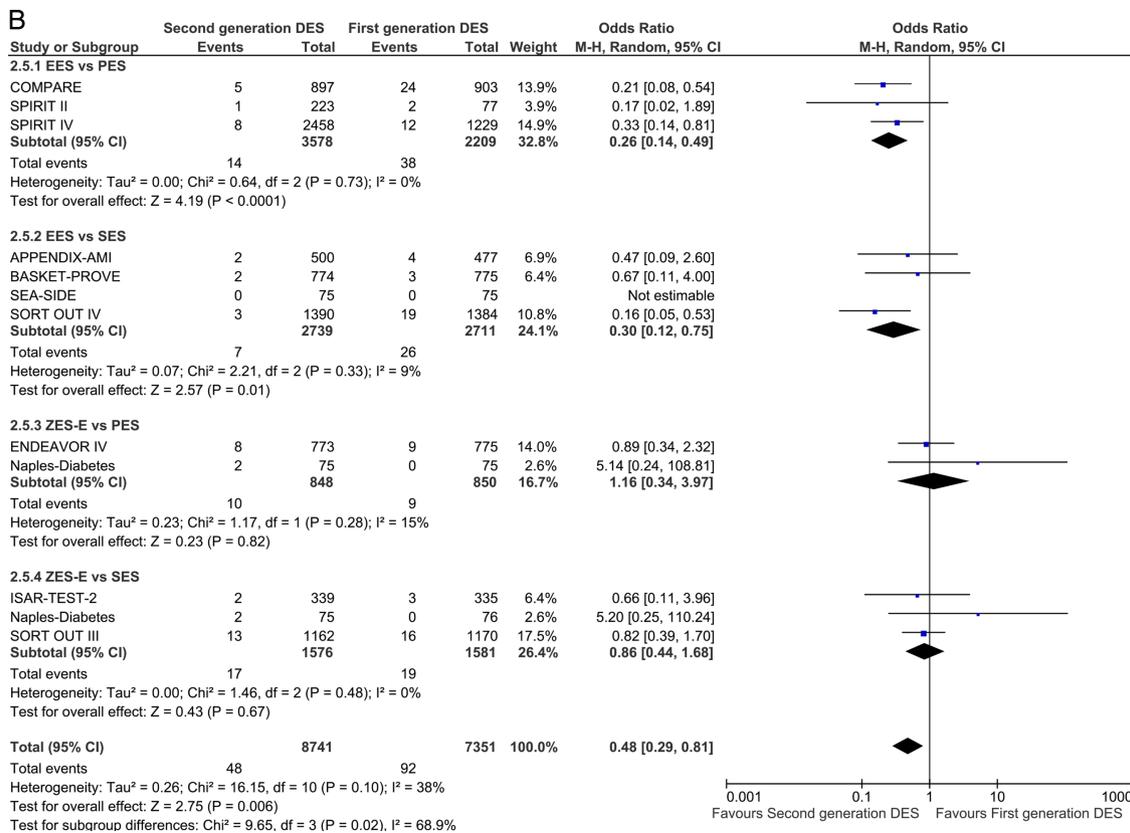


Figure 4 Continued

second-generation DES was sustained in the long-term analysis: OR 0.75 (95% CI 0.55 to 1.01) p=0.06, with odds of MI roughly halved in comparison with EES versus PES: OR 0.56 (95% CI 0.42 to 0.74) p<0.0001.

**Stent thrombosis**

For the analysis of definite ST, 17 studies were included. In the short term, EES was associated with a significant reduction of odds of ST compared with PES and SES: OR 0.24 (95% CI 0.12 to 0.50) p=0.0001 and OR 0.46 (95% CI 0.21 to 0.99) p=0.05, respectively. Second-generation ZES-E increased the odds of ST by 122% compared with first-generation SES: OR 2.10 (95% CI 1.06 to 4.16) p=0.03. Results in the long term confirmed the short-term follow-up findings; EES was associated with a more pronounced and significant reduction of odds of ST over time as compared with PES and SES: OR 0.20 (95% CI 0.08 to 0.49) p=0.0004 and OR 0.30 (95% CI 0.12 to 0.75) p=0.01, respectively.

**DISCUSSION**

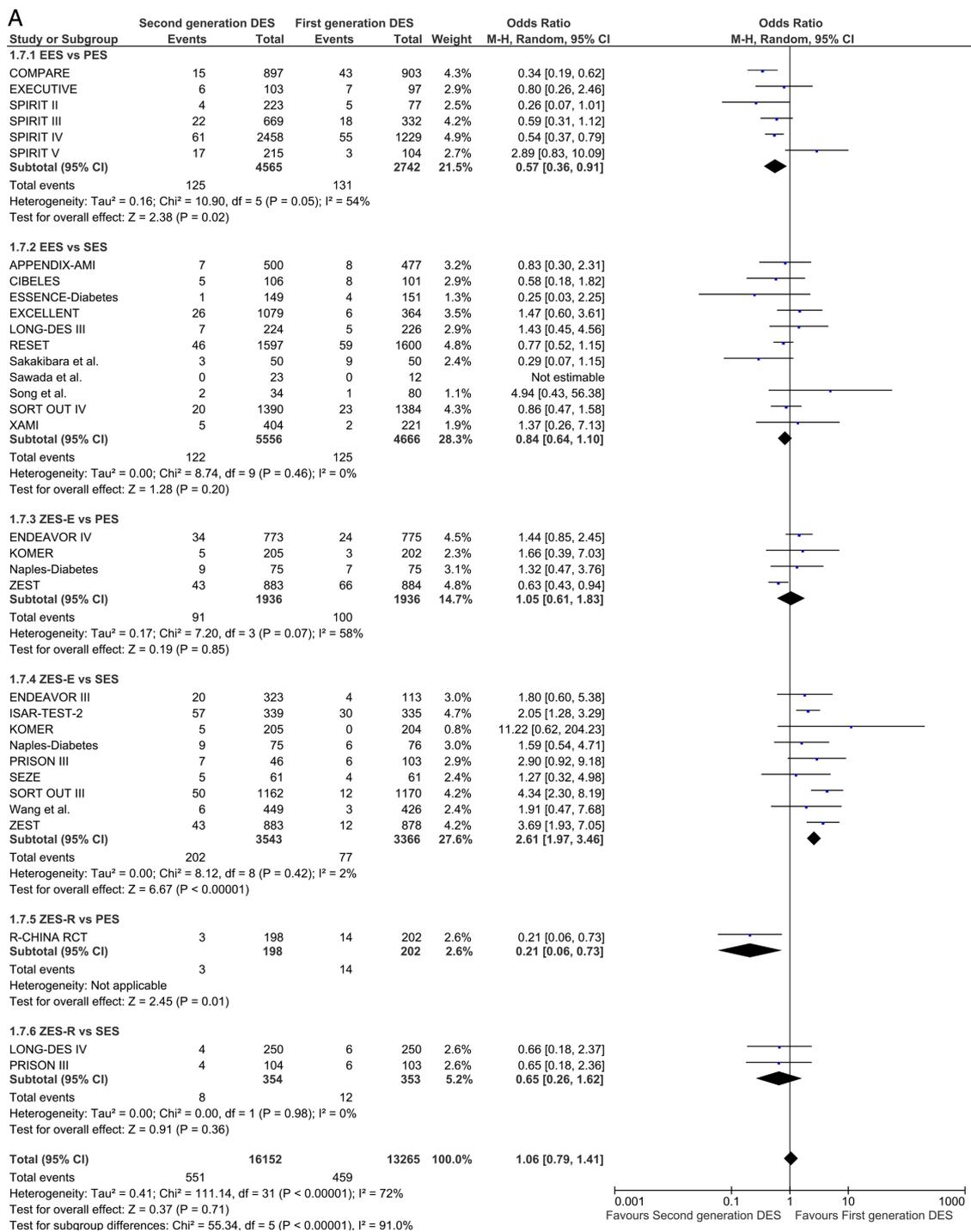
The present study is the largest report so far comparing first-generation versus second-generation DES. With 31 379 patients included, it provides the most comprehensive overview on the safety and efficacy outcomes of different first-generation and second-generation stents. The main findings of this meta-analysis are as follows:

(1) second-generation EES and ZES significantly reduced the incidence of MI compared with first-generation PES; (2) only second-generation EES significantly reduced the odds of definite and definite/probable ST compared with first-generation DES (3) second-generation EES and ZES-R, and the first-generation SES, are similar to each other with regard to their efficacy and significantly better than ZES-E and PES with regard to repeat coronary revascularisations.

In the present large-scale study analysis, single and composite safety end points did not differ in direction or magnitude of the effect favouring durable polymer EES.

**Safety**

First-generation DES have been found to be superior to BMS in reducing restenosis and the need for repeat revascularisation. Their performance in terms of safety, and strictly, increased propensity for late and very late thrombotic events, however, was questioned as long follow-up data were becoming available; further studies showed that late and very late stent thrombosis could be attributed to numerous complex mechanisms with device design-related factors being of paramount importance.<sup>4</sup> The inflammation induced by the durable polymers of first-generation DES may result in delayed healing and incomplete covering of stent struts by new and functional endothelium, with uncovered stent struts serving as a source



**Figure 5** Analysis of TLR at short-term (A) and long-term (B) follow-up. ORs and 95% CIs. Size of squares is proportional to the statistical weight of each trial. TLR, target lesion revascularisation.

for future episodes of ST; second, other factors such as stent malapposition, mechanical tissue injury caused by stent struts during implantation and finally, polymer hypersensitivity or even toxicity, as is the case for PES,<sup>58</sup> in turn associated with persistent fibrin deposition, might also play a potential role. Second-generation DES were introduced to address the concerns raised by first generation DES by either optimising their metallic stent

platform or polymer and eluted drug; that is, second-generation EES uses thin struts coated with durable, fluorinated polymer, which has been shown to have thromboresistant properties in experimental studies; similarly, ZES-R combined more rapid elution kinetics than sirolimus (SES) in the same time offering thinner, more biocompatible phosphorylcholine polymer placed on a cobalt alloy stent platform.<sup>7</sup>

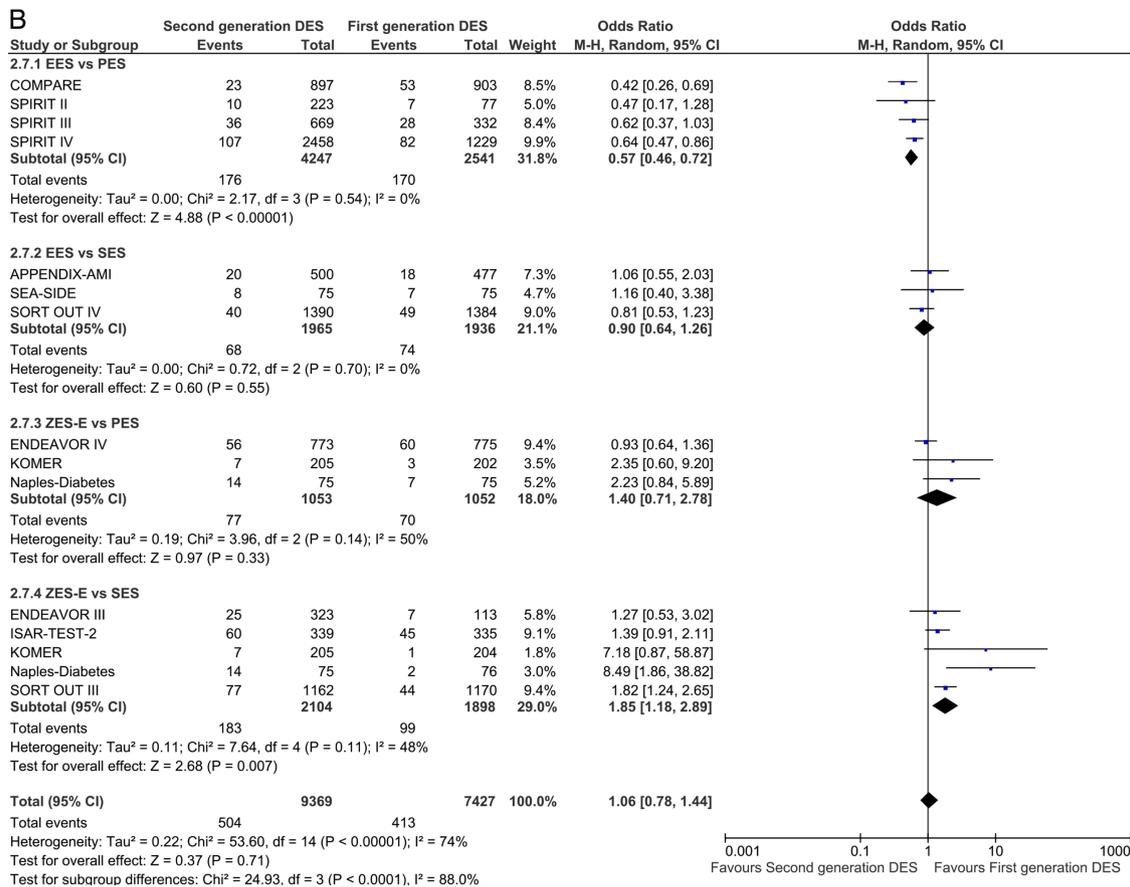


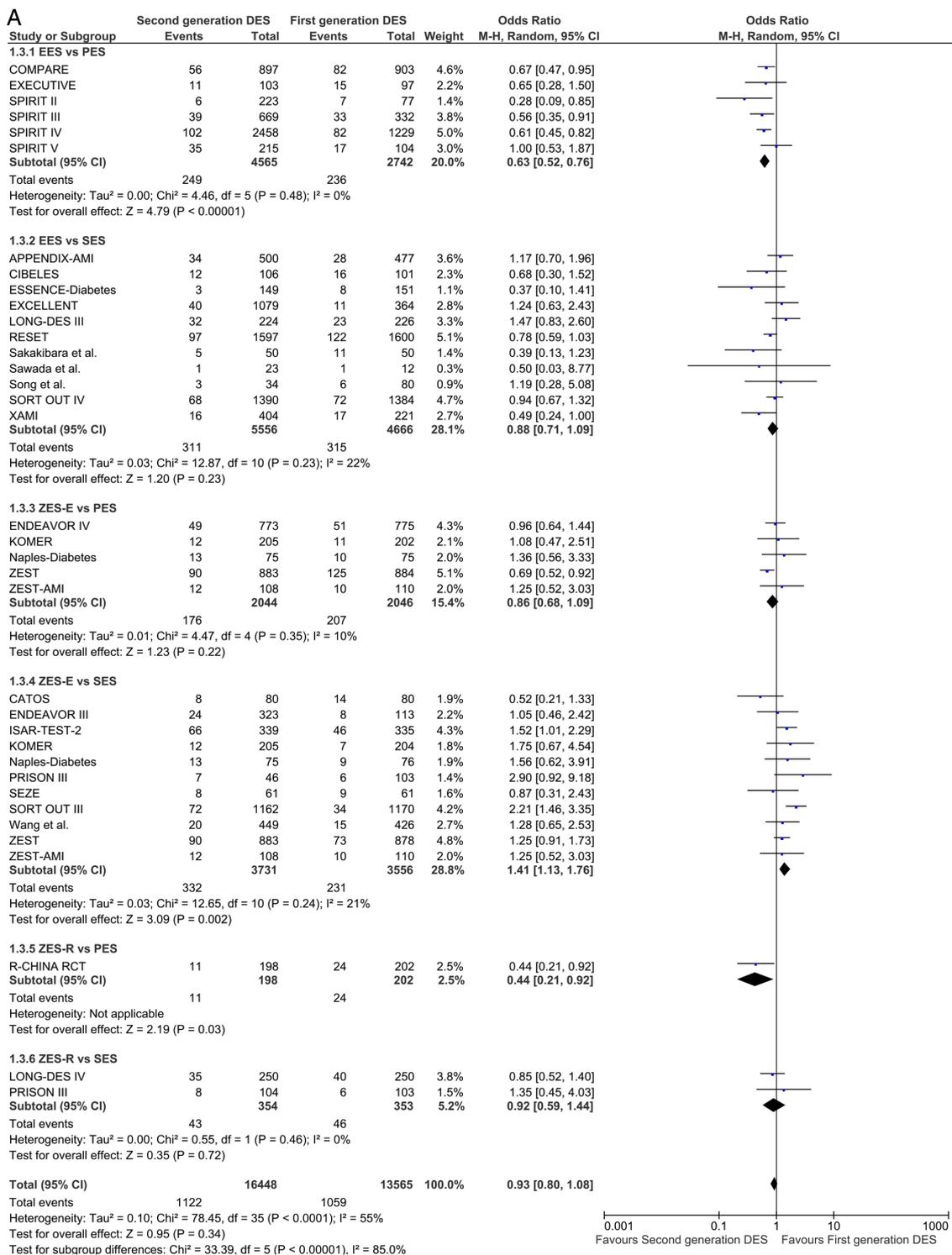
Figure 5 Continued

In the present meta-analysis, which compared most robust evidence of first-generation versus second-generation DES data, second-generation EES was found to be superior in regard to safety end points as compared with first-generation PES but not SES; this might be attributed to the proven overdose and/or accumulation of paclitaxel in the arterial wall due to a coronary uptake, in turn leading to toxicity, inflammation and late in-stent stenosis, which is not the case with SES.<sup>59</sup> The superiority of thin strut EES and ZES in reducing the incidence of MI in the short clinical follow-up might also come from mechanistic reasons; indeed, this might be related to the more frequent side branch jailing with thick strut devices (SES Cypher 140 μm and PES Taxus Express 134 μm vs ZES Endeavor/Resolute 91 μm and Abbott Xience V 81 μm), resulting in turn in higher rates of periprocedural MI.<sup>60–62</sup> Although ST should be considered a surrogate safety end point, which must be interpreted in perspective of MI and mortality, it remains a devastating complication and is often associated with high rates of mortality and morbidity. Second-generation EES was associated with significantly lower rates of definite and definite or probable ST in short-term analysis compared with first-generation DES; this finding is in line with a meta-analysis by Palmerini,<sup>5</sup> which for the first time demonstrated the superiority of EES over BMS and first-generation and second-generation DES in reducing early (0–30 days) and late

(31 days–12 months) ST. This analysis integrates the most updated data and enriches the previous findings of longer follow-up clinical data for particular devices, demonstrating for the first time that EES reduces definite and definite or probable ST also beyond these time frames (very late ST) compared with first-generation DES. Notably, data on EES do not reflect the performance of second-generation ZES-E in terms of stent thrombosis; indeed, Endeavor was found to even increase the incidence of definite ST as compared with SES at ≤1 year, mainly driven by the results of the SORT OUT III<sup>42</sup> and ZEST<sup>55</sup> trials. As zotarolimus is a synthetic analogue of sirolimus, the disparities between stents are attributed to different kinetics of drug release from the polymers used for drug elution (1 week with ZES and 3 months with SES); postulated quick zotarolimus release and high initial concentrations not only affect the healing of the plaque and arterial wall, but may also allow for exposure of the atheromatous debris to the bloodstream, thus increasing the risk of early ST, which is of particular importance in high-risk patients with acute coronary syndrome or multivessel disease.

**Efficacy and MACE**

Design-related factors such as strut thickness, type of anti-proliferative agent, drug elution kinetics, elution time and type of polymer are all factors that may as well impact



**Figure 6** Analysis of MACE at short-term (A) and long-term (B) follow-up. ORs and 95% CIs. Size of squares is proportional to the statistical weight of each trial. MACE, major adverse cardiovascular events.

efficacy outcomes<sup>63</sup>; although not a new finding, in this analysis all limus-eluting DES, with the exception of ZES-E, were associated with significantly lower rates of TLR/TVR than the first-generation PES. Taken together, inflammation causing properties of paclitaxel along with the short release curve of ZES-E preclude optimal suppression of procedure related injury responses, in turn resulting in subsequent intimal hyperplasia and increased

need for repeat revascularisation.<sup>64</sup> Unlike ZES-E, the more recently introduced ZES-R, which has a much longer (up to 180 days) release curve of the same antiproliferative agent, zotarolimus, is associated with a significant reduction in TVR/TLR compared with ZES-E.<sup>65</sup>

In the present paper, we additionally analysed the incidence of MACE, which to the best of our knowledge is the most proper measure of device performance, as it

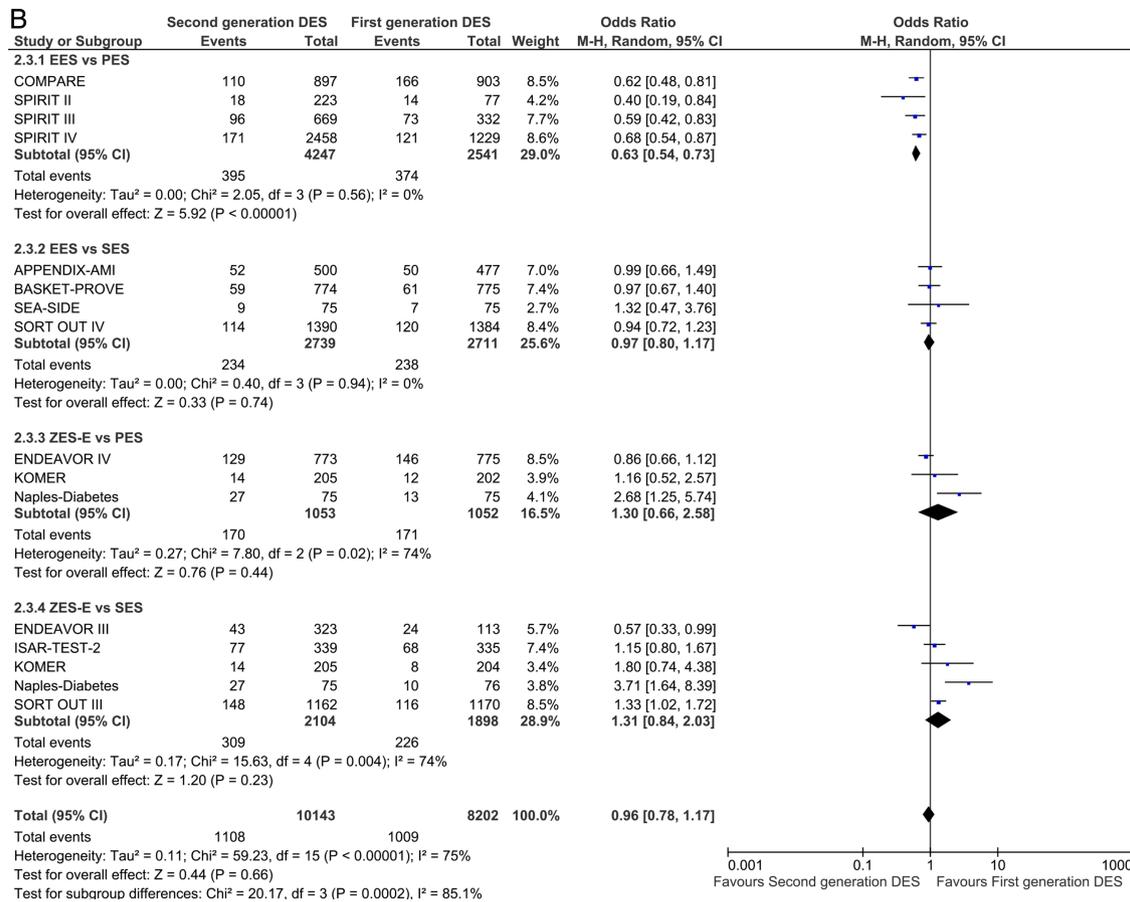


Figure 6 Continued

takes into account both safety and efficacy outcomes, providing statistical power given the low numbers of single outcome events. Not surprisingly, MACE analysis confirmed the single-outcome findings, with second-generation EES outperforming first-generation PES at ≤1 year and beyond. Remarkably, the initial short-term benefit of SES over ZES-E, attributable mainly to higher rates of repeat revascularisation with the latter, becomes less pronounced at long-term follow-up when drug elution is over.

**Limitations**

As with any meta-analysis, our study shares the limitations of the original studies. Results were analysed on trial level data, and therefore we could not assess whether all baseline characteristics were balanced among groups (although for the most part they were balanced within each RCT). Data for follow-ups longer than 1 year are limited but appear to confirm the direction of the estimates at ≤1-year. The patient inclusion criteria of this meta-analysis are broad, more closely reflecting current practice, comprising stable and unstable high-risk patients. Potentially heterogeneous definitions of MI used across the trials may represent another limitation.

Another aspect is the duration of dual antiplatelet therapy (DAPT), that is, the combination of aspirin and

a P2Y12 receptor blocker, which varied among the different trials. The variability of DAPT may, however, be less important in the context of the present meta-analysis given that BMS were excluded and most trials employed at least 6 months DAPT duration. Owing to the limited number of trials comparing ZES-R to first-generation DES, the findings with this device should be viewed as exploratory but certainly deserve further attention. Despite these limitations, this meta-analysis provides the largest-scale comparative information on the efficacy and safety profiles of different DES in current clinical practice.

**CONCLUSIONS**

Second-generation EES and ZES-R offer a similar level of efficacy compared with first-generation SES, but are more effective than PES; however, only second-generation EES significantly reduced the incidence of both MI and ST and therefore should be perceived as the safest DES to date.

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**Contributors** All authors contributed to the present article. MK, BG and LK were responsible for data search and abstraction and critical analysis of eligibility. EPN and MK drafted the manuscript. DK, AL, RW, SB, GM, UL, RJvS, JK, and HS critically revised the manuscript.

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