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SYSTEMATIC REVIEW AND META-ANALYSIS

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Is There Any Significant Difference in Stent Thrombosis Between Sirolimus and Paclitaxel Eluting Stents?

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: Several meta-analyses have shown no significant difference in stent thrombosis (ST) between sirolimus eluting stents (SES) and paclitaxel eluting stents (PES). However, other meta-analyses have found SES to be superior to PES. Therefore, to solve this issue, we aim to compare the clinical outcomes between SES and PES during a follow-up period of about 1 or more years.

We have searched Medline and EMBASE for randomized controlled trials (RCTs) comparing SES with PES. These RCTs have been carefully analyzed and then different types of ST including ST defined by the Academic Research Consortium (ARC), acute ST, late and very late ST have all been considered as the clinical endpoints in this study. A follow-up period of about 1 year, between 1 and 2 years as well as a longer follow-up period between 1 and 5 years have been considered. Data were retrieved and combined by means of a fixed-effect model because of a lower heterogeneity observed among the results. Odd ratios (OR) and 95% confidence intervals (CIs) were calculated and the pooled analyses were performed with RevMan 5.3 software.

Twenty-nine studies from 19 RCTs comprising of 16,724 patients (8115 patients in the SES group and 8609 patients in the PES group) satisfied the inclusion criteria and were included in this meta-analysis. No significant differences in ST have been observed between SES and PES. Results were as follow: definite ST with OR: 0.87; 95% CI: 0.64–1.18, $P = 0.36$; probable ST with OR:0.72; 95% CI: 0.42–1.21, $P = 0.21$; definite, probable and/or possible ST with OR: 0.94; 95% CI: 0.75–1.17, $P = 0.57$; acute ST with OR: 0.99; 95% CI: 0.38–2.56, $P = 0.98$; subacute ST with OR: 0.72; 95% CI: 0.41–1.25, $P = 0.25$; early ST with OR: 0.81; 95% CI: 0.53–1.25, $P = 0.34$; late ST with OR: 0.72; 95% CI: 0.39–1.34, $P = 0.30$; very late ST with OR: 1.02; 95% CI: 0.72–1.44, $P = 0.92$; and any ST with OR: 0.86; 95% CI: 0.69–1.07, $P = 0.18$. Long-term ST between 1 and 5 years with OR: 0.93; 95% CI: 0.71–1.22, $P = 0.60$ was also not significantly different.

No significant difference in ST has been observed between patients treated with either SES or PES. Hence SES and PES can both be considered almost equally effective.

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Abbreviations: CAD = coronary artery disease, DES = drug eluting stents, PES = paclitaxel eluting stents, SES = sirolimus eluting stents, ST = stent thrombosis.

INTRODUCTION

Stent thrombosis (ST) is a major concern for patients treated with drug eluting stents (DES). Sirolimus eluting stents (SES) and paclitaxel eluting stents (PES) have been the most commonly used first-generation DES.

Several meta-analyses comparing SES with PES showed no significant difference in ST between these 2 types of stents. For example, the meta-analysis conducted by Gurm et al[1] in 2008, including 7455 patients, found no significant difference in ST between SES and PES. A similar result was reported in another meta-analysis of 6 randomized controlled trials (RCTs) including 1183 patients with type 2 diabetes mellitus.[2] The result from the meta-analysis conducted by Zhang et al[3] in 2010 also showed no significant difference in ST among the 1173 patients analyzed. Moreover, the meta-analysis conducted by Kastrati et al[4] in 2005 including 3669 patients also showed a similar rate of ST between SES and PES in patients with coronary artery disease (CAD). Zhang et al's[5] study which included both RCTs and observational studies, also did not find any significant difference in ST between these 2 groups among the patients from RCTs.

However, ST was not always similar between SES and PES. The meta-analysis conducted by Schömig et al[6] in 2007 including 16 RCTs with 8695 patients surprisingly showed a significant reduction in ST with SES compared to PES. His study which included a large number of randomized patients could have had an effect on his results.

Therefore, in order to solve this issue, we aim to combine old studies comparing SES and PES with new ones and conduct a meta-analysis with an even larger number of randomized patients (a total of 16,724 patients) to confirm whether a significant difference in ST between the use of SES and PES really exists or not.

METHODS

Sources of Data and Search Strategy

We have searched Medline and EMBASE for RCTs by typing the words "drug eluting stents/DES and percutaneous coronary intervention/PCI," and also replacing the word "DES" by "PES and/or SES" or their full form "paclitaxel eluting stents and sirolimus eluting stents." PES and SES have also been replaced by Taxus and Cypher, respectively. All

reference lists of related studies were also reviewed for relevant articles. No language restriction was applied.

Inclusion and Exclusion Criteria

Studies were included if:

(1) They were RCTs.
(2) They compared sirolimus eluting stents (SES) with paclitaxel eluting stents (PES).
(3) ST was reported among the clinical endpoints.

Studies were excluded if:

(1) They were non-RCTs (observational studies, reports, meta-analyses, letter to editors).
(2) They did not compare SES with PES but instead, showed the effectiveness of SES and PES separately without comparison or compared SES or PES with another DES.
(3) ST was not reported among the clinical endpoints.

Defining the Different Types of Stent Thromboses, Outcomes, and Follow-Up

Definite ST, probable ST, possible ST, acute, subacute, late and very late ST with a follow-up of 1 month, short-term follow-up (1–12 months) and long-term follow-up (>1 year) including a follow-up between 1 and 2 years, and 1 and 5 years were analyzed in this study. The different types of ST have been defined in Table 1. Table 2 shows the types of ST reported in each of the included trials.

Data Collection and Analysis

Study Selection

All titles and abstracts were independently screened by 2 authors (PKB and ZW) and full papers of those studies which met the inclusion criteria were obtained for review. These studies were carefully checked. Disagreements were carefully discussed between these 2 authors, and if the authors could not reach a final decision, whether to include the study or not, disagreements were resolved by the help of the third author (MHC).

Data Extraction and Management

Data extraction was performed from full-text articles by the same 2 independent authors (PKB and ZW). Any disagreement was resolved through discussion and consensus between these 2 authors. The following data were extracted from each of the trials: author identification, year of patient enrollment, year of publication, language of publication, study design, study population, patient characteristics, intervention and outcomes reported as well as the follow-up periods.

Assessment of Risk of Bias

The bias risk of the included trials was assessed with the components recommended by the Cochrane Collaboration.[7]

Each of the included trials has been carefully assessed and a grade ranging from A to E has been allocated to specific trials depending on whether they satisfied all the components recommended by the Cochrane Collaboration. In other word, a grade between A to E was allocated to the trials depending on their risk of bias. Completely low risk of bias among all of these 6 components mentioned above corresponded to a grade A, whereas a grade E was given if this evaluation showed a high risk of bias among the data corresponding to these RCTs.

Except for 1 trial which have been allocated a grade C, all the other trials have been allocated a grade B even if a few were almost on a range between an A and a B.

Methodological Quality and Statistical Analysis

The selection of studies, collection and analysis of data, and reporting of the results obtained, followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The Cochrane Q-statistic and the *I2*-statistic tests were used to assess heterogeneity among the studies whereby $P \leq 0.05$ was considered statistically significant and $P > 0.05$ was considered statistically insignificant. *I2* described the total variation (due to heterogeneity rather than chance) across studies in terms of percentages whereby a value of 0% indicated no heterogeneity, and larger values especially from 50% and above indicated increasing heterogeneity. A fixed effect model was used if *I2* was <50% and a random effect model was used if *I2* was >50%. Funnel plots were assessed for publication bias. Odd

TABLE 1. Definitions of the Different Types of Stent Thrombosis Reported in This Study

Types of Stent Thrombosis	Definitions
Any stent thrombosis	Defined as any type of stent thrombosis mentioned below (definite, probable, early, late, very late)
Definite stent thrombosis	Defined as thrombosis within the stent at autopsy or thrombectomy or angiographic confirmation by TIMI flow 0 with thrombus in the stent or the 5 mm edges or TIMI flow 1, 2, or 3 with thrombus and at least one of these within 48 hours: new onset resting angina, new ECG ischemic changes or typical rise and fall in cardiac biomarkers
Probable stent thrombosis	Any unexplained death within the first 30 days postprocedure. Any MI in the territory of implanted stent without angiographic confirmation and in the absence of any other obvious cause
Possible stent thrombosis	Defined as any unexplained death from 30 days after intracoronary stenting until the end of follow-up
Acute stent thrombosis	Occurring between 0 and 24 hours after stent implantation
Subacute stent thrombosis	Occurring between 24 hours and 30 days
Early stent thrombosis	Acute or subacute stent thrombosis can also be replaced by the term early stent thrombosis
Late stent thrombosis	Occurring between 30 days and 1 year
Very sate stent thrombosis	Occurring after 1 year

ECG = electrocardiography, MI = myocardial infarction, TIMI = thrombolysis in myocardial Infarction.

TABLE 2. Types of Stent Thrombosis Reported Among the Trials

Trial Name	Outcome: Types of Stent Thromboses Reported
SIRTAX	Any stent thrombosis, early, late, definite, probable, possible stent thromboses
SORT OUT II	Early, late, acute, subacute, definite, probable, possible stent thromboses
CHINA	Subacute stent thrombosis
LIPSIA Yukon	Definite, probable, possible stent thromboses
TAXi	Any stent thrombosis
PROSIT	Any stent thrombosis, acute, subacute, late, very late stent thromboses
DiabeDES	Definite, probable, possible stent thromboses
ISRCTN90526229	Subacute and late stent thromboses
Long-DES	Any stent thrombosis
ISAR-DESIRE 2	Definite stent thrombosis
DES-DIABETES	Acute, subacute, late and very late stent thromboses
ZEST AMI	Acute, subacute and late stent thromboses
PASEO	Definite, early, late and very late stent thromboses
TAXUS	Definite, probable, early, late, and very late stent thromboses
ISAR-LEFT-MAIN	Definite and probable stent thromboses
REALITY	Acute, subacute and late stent thromboses
SINGLE KISS	Any stent thrombosis
J-DESsERT	Definite and probable stent thromboses
ZEST	Definite, probable, acute, subacute, and late stent thromboses

ratios (OR) and 95% confidence intervals (CIs) were calculated for categorical variables. RevMan 5.3 software was used for the statistical analysis. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written. Ethical approval was not required since this study is a systematic review and meta-analysis of RCTs.

RESULTS

Figure 1 shows the flowchart of study selection. We identified 42 studies comparing SES with PES in patients with CAD. Thirteen studies were excluded (6 of them were meta-analysis and 7 were observational studies). Finally, 29 studies from 19 RCTs that met the inclusion criteria comprising of 16,724 patients (8115 patients in the SES group and 8609

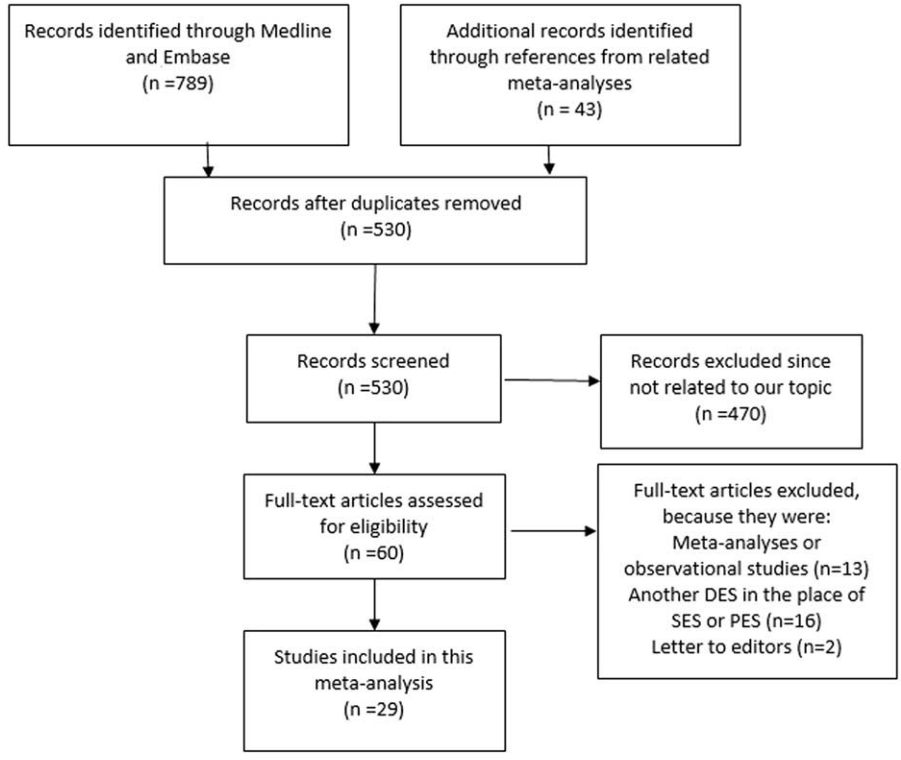

FIGURE 1. The flow diagram for study selection.

patients in the PES group) were included in this systematic review and meta-analysis.

General Characteristics of Included Trials

Table 3 reports the general features of all the 19 trials included in this meta-analysis. Features such as the number of participants involved in the SES group, number of participants involved in the PES group, the year of enrollment of patients for these trials, the follow-up periods as well as the Cochrane Bias Risk grade have been summarized in Table 3.

Baseline Characteristics of the Included Trials

Table 4 reports the baseline features of each of the included studies. Data from each study have been reported. The mean age of the patients, the percentage of male patients, the percentage of patients with hypertension, those patients who are current smokers and the percentage of patients who suffer from type 2 diabetes mellitus have been listed in Table 4.

No significant difference in age has been observed in patients from both groups. Almost all the studies reported similar number of male patients. Percentage of patients suffering from hypertension, smoking, and diabetes mellitus was almost similar in both groups. Overall, no significant differences have been observed in the baseline characteristics between these 2 groups.

Baseline features for the studies[14,19] have not been included since they were not made available by the authors in the original articles.

Main Results of This Meta-Analysis

The result for ST has been divided into several groups. Twelve thousand forty-five patients were analyzed for definite ST (5769 treated with SES and 6276 treated with PES), 11,415 patients were analyzed for probable ST (5454 treated with SES and 5961 treated with PES), 11,545 patients were analyzed for definite and probable/and or possible ST (5522 treated with SES and 6023 treated with PES), 6141 patients were analyzed for acute ST (3091 treated with SES and 3050 treated with PES), 6536 patients were analyzed for subacute ST (3289 treated with SES and 3247 treated with PES), 9931 patients were analyzed for early ST (4722 treated with SES and 5209 treated with PES), 8905 patients were analyzed for late ST (4204 treated with SES and 4696 treated with PES), 5788 patients were analyzed for very late ST (2646 treated with SES and 3142 treated with PES), and 16,724 patients were analyzed for any type of ST (8115 treated with SES and 8609 treated with PES).

The pooled analysis showed no significant difference between SES and PES in any category of ST. Since a lower heterogeneity has been observed, a fixed effect model has been used for the analysis. The results were as follow: definite ST with OR: 0.87; 95% CI: 0.64–1.18, $P = 0.36$; probable ST with OR:0.72; 95% CI: 0.42–1.21, $P = 0.21$; definite, probable and/or possible ST with OR: 0.94; 95% CI: 0.75–1.17, $P = 0.57$; acute ST with OR: 0.99; 95% CI: 0.38–2.56, $P = 0.98$; subacute ST with OR: 0.72; 95% CI: 0.41–1.25, $P = 0.25$; early ST with OR: 0.81; 95% CI: 0.53–1.25, $P = 0.34$; late ST with OR: 0.72; 95% CI: 0.39–1.34, $P = 0.30$; very late ST with OR: 1.02; 95% CI: 0.72–1.44, $P = 0.92$; and any ST with OR: 0.86; 95% CI: 0.69–1.07, $P = 0.18$. Table 5 summarizes the main result of this study and Figure 2A–C represents the detailed analysis of this meta-analysis.

Excluding the trials with a follow-up period of 1 year or less, another analysis was carried out considering trials with a follow-up period between 1 and 2 years, and between 1 and 5 years. However, even with these long-term follow-up periods, no significant differences in ST have been observed between SES and PES. Results were as follow: OR: 1.27; 95% CI: 0.83–1.94, $P = 0.27$ for a follow-up period between 1 and 2 years and OR: 0.93; 95% CI: 0.71–1.22, $P = 0.60$ for a follow-up period between 1 and 5 years. These results have been illustrated in Figure 3.

TABLE 3. General Features of the Included Trials

TRIAL Name	Year of Patient Enrollment	number of patients in SES group (n)	number of patients in PES group (n)	Follow-Up (Months)	Cochrane Bias Score
SIRTAX	2003–2004	503	509	1, 9, 12, 24, 60	B
SORT OUT II	2004–2006	1065	1033	18, 60	B
CHINA	2003–2004	202	196	19	C
LIPSIA Yukon	2006–2008	118	114	9, 60	B
TAXi	2003–2004	102	100	<1, 6	B
PROSIT	2004–2006	154	154	12, 36	B
DiabeDES	2005–2006	68	62	8	B
ISRCTN90526229	2005–2007	196	201	1, 9	B
Long-DES	2004–2005	250	250	1, 9	B
ISAR-DESIRE 2	2007–2009	225	225	12	B
DES-DIABETES	2005–2006	200	200	9, 48	B
ZEST AMI	2006–2007	110	110	12	B
PASEO	2003–2005	90	90	12, 24	B
TAXUS	2001–2004	878	1400	48	B
ISAR-LEFT-MAIN	2005–2007	305	302	1	B
REALITY	2003–2004	684	669	12	B
SINGLE KISS	2007–2008	380	391	12	B
J-DESsERT	2008–2010	1707	1719	12	B
ZEST	2006–2008	878	884	1, 12	B

PES = paclitaxel eluting stents, SES = sirolimus eluting stents.

TABLE 4. Baseline Features of the Included Studies

Trial Name	Associated Studies	Age (Years)	Males (%)	HT (%)	Cs (%)	DM (%)
SIRTAX		SES/PES	SES/PES	SES/PES	SES/PES	SES/PES
	Billinger et al[8]	—	73.6/75.9	67.2/70.2	31.8/28.5	21.5/18.3
	Räber et al[9]	62.0/62.0	76.0/78.0	60.0/57.0	37.0/36.0	22.0/18.0
	Togni et al[10]	—	53.2/79.2	63.6/63.2	35.7/35.6	24.4/18.5
	Windecker et al[11]	62.0/62.0	75.9/78.4	60.0/62.3	36.6/35.6	21.5/18.3
SORT OUT	Bligaard et al[12]	64.5/63.6	74.1/75.5	48.3/47.3	39.4/39.2	15.2/14.7
	Galløe et al[13]	64.5/63.6	74.1/75.5	48.3/47.3	39.4/39.2	15.2/14.7
CHINA	Ling[14]	—	—	—	—	—
LIPSIA Yukon	Desch et al[15]	67.0/67.3	69.0/68.0	98.0/97.0	23.0/27.0	100/100
	Stiermaier et al[16]	67.0/67.3	69.0/68.0	98.0/97.0	23.0/27.0	100/100
TAXi	Goy et al[17]	65.0/63.0	77.5/83.0	58.8/63.0	25.5/26.0	32.4/36.0
PROSIT	Lee et al[18]	60.0/60.0	76.0/76.6	45.5/40.9	61.7/55.8	22.1/28.6
	Kim et al[19]	—	—	—	—	—
DiabeDES	Jensen et al[20]	62.6/64.4	83.8/79.0	63.2/71.0	38.2/25.8	82.4/85.5
	Maeng et al[21]	66.0/65.0	84.0/74.0	63.0/75.0	38.0/23.0	83.0/87.0
ISRCTN90526229	Juwana et al[22]	61.0/61.0	69.0/74.0	27.0/33.0	50.0/55.0	10.7/6.5
Long-DES	Kim et al[23]	61.4/60.7	67.2/61.2	55.2/54.8	37.2/37.6	32.8/33.6
ISAR-DESIRE 2	Kufner et al[24]	66.6/66.8	79.0/73.5	73.5/72.0	10.5/12.0	38.2/33.8
	Mehilli et al[25]	66.4/67.1	79.2/74.3	72.4/72.4	11.6/12.4	38.2/33.8
DES-DIABETES	Lee et al[26]	61.1/60.7	61.0/55.0	57.0/62.0	27.0/28.5	100/100
	Lee et al[27]	61.1/60.7	61.0/55.0	57.0/62.0	27.0/28.5	100/100
ZEST AMI	Lee et al[28]	57.8/59.3	86.4/82.7	38.2/53.6	56.4/61.8	26.4/23.6
PASEO	Di Lorenzo et al[29]	62.0/63.0	71.1/68.9	27.8/26.7	24.4/24.4	27.8/23.3
TAXUS	Mauri et al[30]	61.9/62.8	71.6/71.5	63.8/72.1	21.2/23.8	22.2/25.4
	Stone et al[31]	61.9/62.4	71.6/72.4	63.8/69.3	21.2/23.7	22.2/23.2
ISAR-LEFT M	Mehilli et al[32]	69.3/68.8	80.0/75.0	69.0/70.0	10.0/10.0	28.0/30.0
REALITY	Morice et al[33]	62.6/62.6	74.1/72.0	65.5/67.6	20.2/22.0	27.3/28.7
SINGLE KISS	Nasu et al[34]	67.0/66.0	79.0/80.0	75.0/69.0	29.0/26.0	40.0/44.0
J-DESsERT	Otsuka et al[35]	70.1/70.1	72.7/72.0	80.2/83.1	18.0/18.3	48.8/49.3
ZEST	Park et al[36]	61.9/62.0	67.3/65.8	58.9/61.1	29.2/27.5	28.1/27.7

Cs = current smoker, DM = diabetes mellitus, HT = hypertension, PES = paclitaxel eluting stents, SES = sirolimus eluting stents.

For all of the above analyses, sensitivity analyses yielded consistent results. Based on a visual inspection of the funnel plots, there has been no evidence of publication bias for the included studies that assessed these ST. The funnel plots have been illustrated in Figure 4A and B.

DISCUSSION

Many recently published meta-analyses showed no differences in ST associated with SES and PES. However, the meta-analysis conducted by Schömig et al[6] in 2007 surprisingly showed a significant reduction in ST with the use of SES compared to PES. Compared to many previous studies, his study included a larger number of randomized patients. Therefore, to confirm the existence or absence of any significant difference in ST between SES and PES, old and new studies were combined to conduct this meta-analysis.

Among the 48.5% patients treated with SES, and the 51.5% patients treated with PES, no significant difference in ST has

TABLE 5. Summary of the Main Results of This Study

Outcomes	Events in SES Group	Events in PES Group	OR With 95% CI	*P*-Value	*I2* (%)
Definite ST	76/5769	93/6276	0.87 [0.64–1.18]	0.36	3
Probable ST	22/5454	33/5961	0.72 [0.42–1.21]	0.21	0
D/P or Po ST	167/5522	183/6023	0.94 [0.75–1.17]	0.57	14
Acute ST	6/3091	6/3050	0.99 [0.38–2.56]	0.98	0
Subacute ST	21/3289	29/3247	0.72 [0.41–1.25]	0.25	0
Early ST	36/4722	47/5209	0.81 [0.53–1.25]	0.34	0
Late ST	16/4204	24/4696	0.72 [0.39–1.34]	0.30	0
Very late ST	65/2646	67/3142	1.02 [0.72–1.44]	0.92	0
Any ST	151/8115	179/8609	0.86 [0.69–1.07]	0.18	0

CI = confidence interval, OR = odd ratio, PES = paclitaxel eluting stents, SES = sirolimus eluting stents, ST = stent thrombosis.

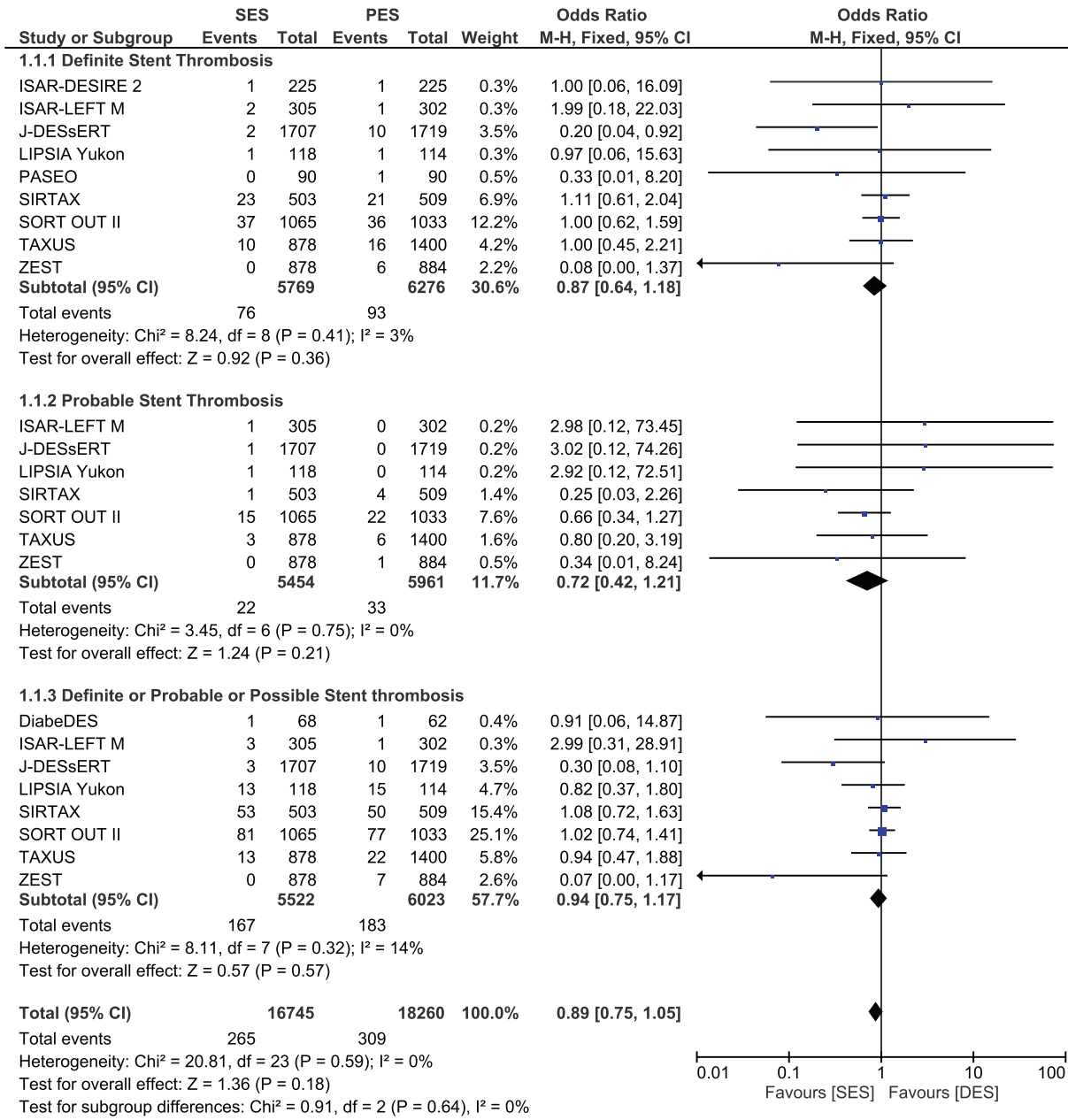

FIGURE 2. Forest plot comparing stent thrombosis between SES and PES.

been observed between these 2 groups. 1.9% of the patients in the SES group and 2.08% of the patients in the PES group suffered ''any'' ST (meaning any kind of ST). However, this result was not statistically significant. The result was still not statistically significant during a follow-up between 1 and 2 years as well as during a follow-up period between 1 and 5 years.

Despite of including a larger number of randomized patients in our study, our result was similar to the meta-analyses conducted by Gurm et al in 2008,[1] Zhang et al in 2010 and 2014, Kufner et al in 2011 and Kastrati et al in 2005.[2–5] These studies had a limited number of patients and 2 of these studies were conducted on patients with type 2 diabetes mellitus. Despite these differences, our study also showed similar results. Even many retrospective studies as well as the observational studies with a very large number of consecutive patients comparing SES with PES showed an equal rate of ST between these 2 groups.

In this current Era, which can be considered as a ''winning'' world for the DES, the use of bare-metal stents (BMS) is often only indicated when the use of DES is contraindicated. The use of DES clinically, has significantly lowered the incidence of several major adverse cardiovascular events as well as reduced the incidence of restenosis after PCI compared to the

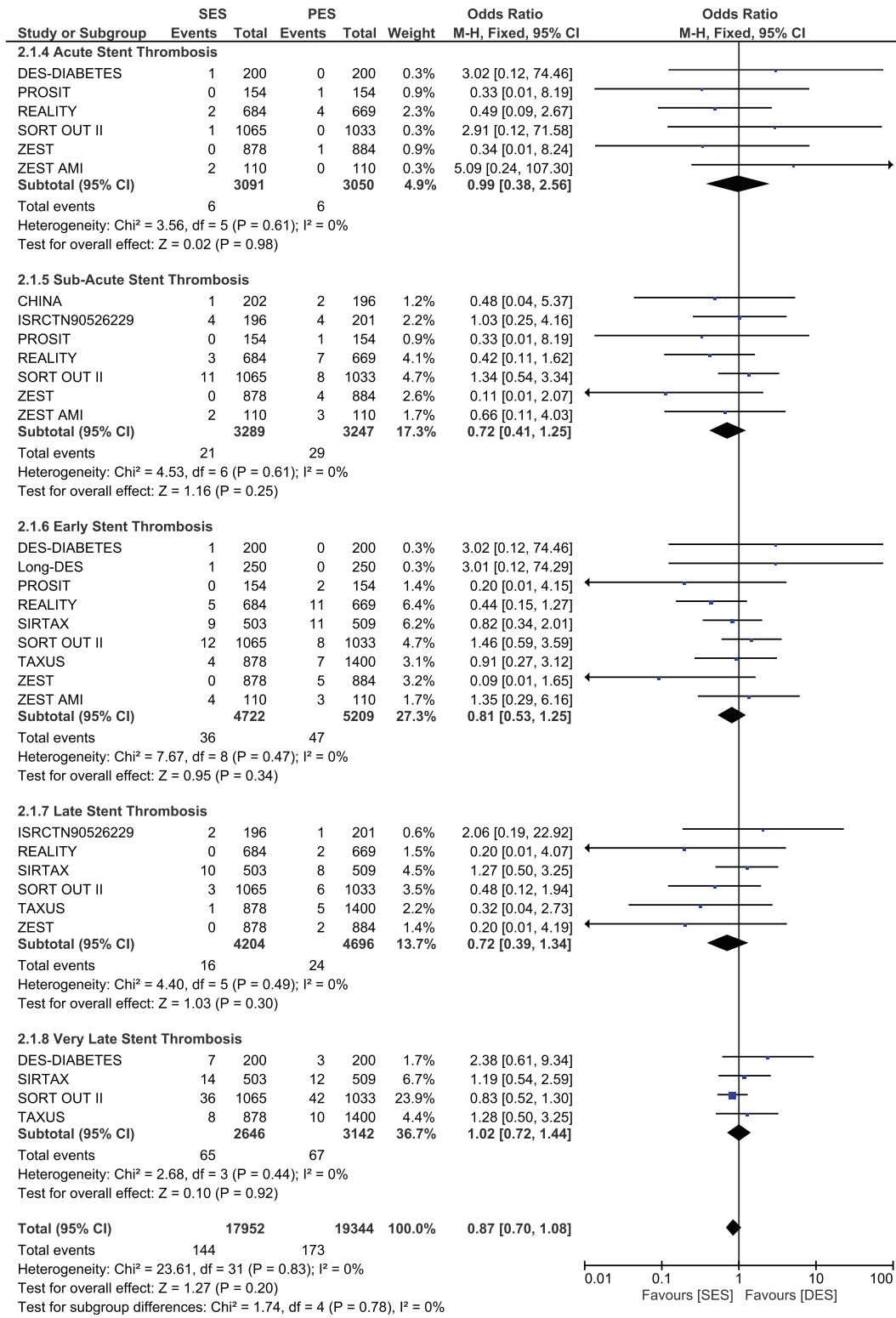

FIGURE 2. *Continued*

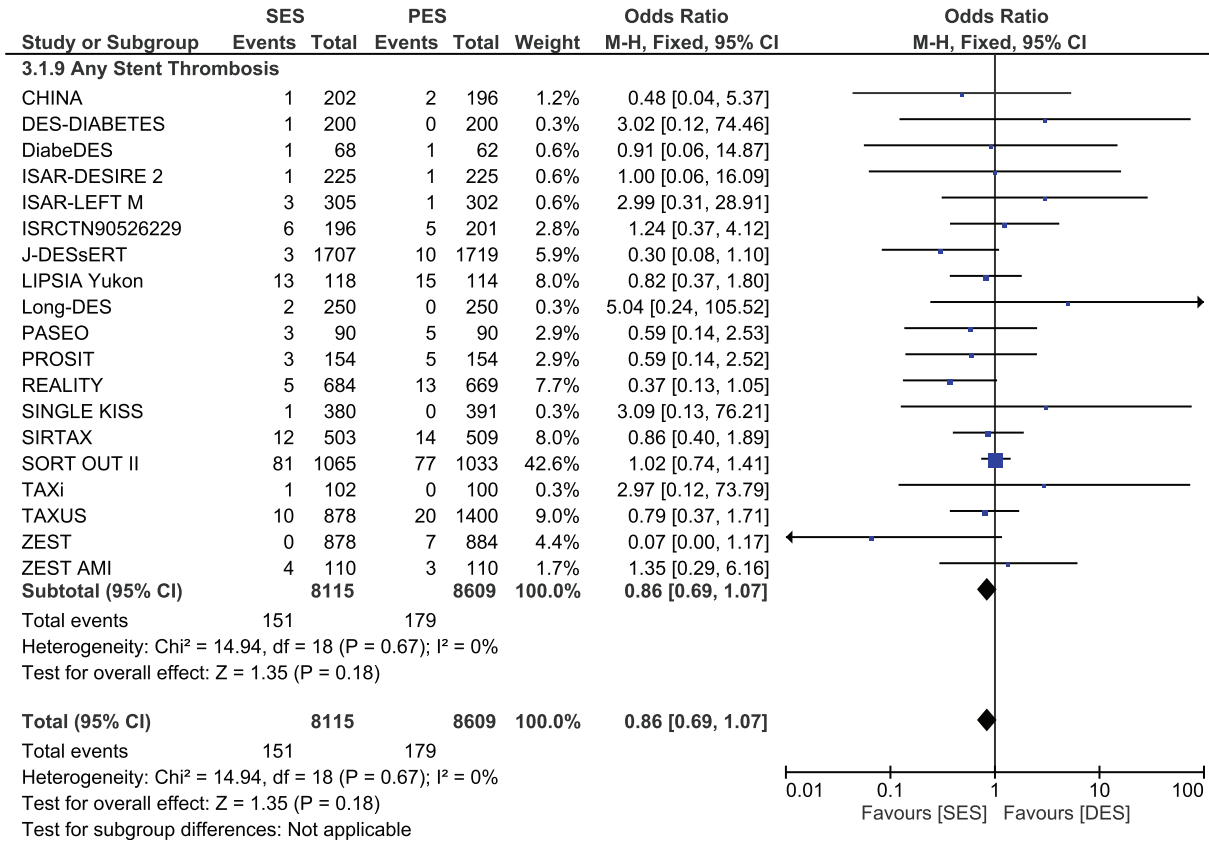

FIGURE 2. *Continued*

use of BMS. However, the use of DES is still associated with a higher rate of ST.

As shown in our results, and in the results of many other studies, the comparison of ST between the 2 first-generation DES has resulted in no significant difference in ST between SES and PES. However, it is a fact that most of the drugs which are currently approved to coat stents used in coronary angioplasty do not differentiate or simply do not recognize the difference between proliferative vascular smooth muscle cells (VSMCs) and endothelial cells (ECs).[37] The specification of these antiproliferative drugs which is normally very important, is often lacking and therefore, the proliferation and migration of VSMCs and ECs in the vessel are affected. These antiproliferative drugs also cause the inhibition of neointimal hyperplasia and they also severely affect the endothelial regeneration which is very important for the healing of these injured vessels and finally resulting in an incomplete reendothelialization. Because of this insufficient reendothelialization, late/long-term ST often manifests.[38–39]

Moreover, p27 is a component expressed by arteries. When arteries are injured, p27 is rapidly downregulated due to mechanisms initiated by activated VSMC triggering intimal hyperplasia which then results in arterial restenosis. Overexpression of exogenous p27 in VSMC results in mechanisms that led to the significant reduction in neointimal formation. Studies have shown sirolimus, which is the coating material of certain DES, would inhibit the breakdown of p27, as well as induce the increased production of p27 thus preventing the proliferation and migration of VSMC and could therefore inhibit reendothelialization of vessels by this way.[40–41] Also, overexpression of p27 without sparring ECs could prevent the normal physiological function of the injured blood vessels and this could further increase the risk of late ST among the several DES.

Even though the use of DES is associated with a higher rate of ST, our study showed a similar rate of ST between SES and PES. However, to further minimize ST in similar patients with CAD, other researches have introduce the microRNA-based strategy in coating stents.[42] MicroRNA has been described previously.[43] This microRNA-based strategy can strictly reduce restenosis by selectively inhibiting the proliferation and migration of VSMC without disturbing or inhibiting reendothelialization or causing impairment to the function of EC. Hence, incorporating the microRNA-based strategy in stents could increase the overexpression of p27 and at the same time protect ECs thus reducing ST in those patients treated with DES after PCI. Further studies should be conducted to confirm the effect of this microRNA-based strategy to make sure whether it truly protects ECs.[42] This will be a revolution in the field of Interventional Cardiology.

Our results showed SES and PES to have a similar rate of ST even during the long-term follow-up. However, a few studies also showed results which were different from our study. For example, the meta-analysis including 16 RCTs comparing SES with PES in patients with CAD published by Schömig et al[6] in 2007 showed a completely different result

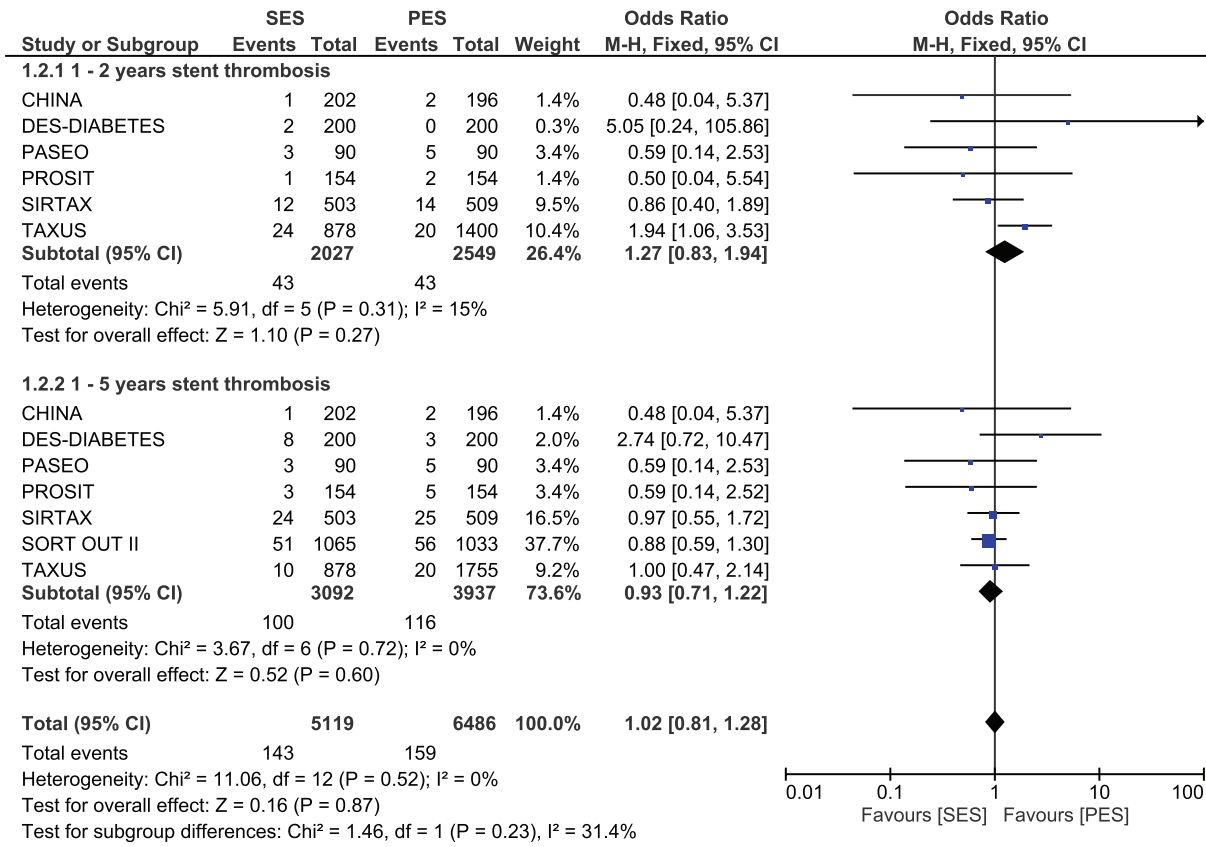

FIGURE 3. Forest plot comparing long-term (1–2 years and 1–5 years) stent thrombosis between SES and PES.

from ours. His study surprisingly showed ST to be significantly lower in the SES group compared to the PES group. However, in his study, ST was not reported according to the Academic Research Consortium (ARC) criteria which defined ST as definite and probable ST. Also, data which the author had used in his meta-analysis were completely different from that of our study because majority of his data were directly obtained from unpublished articles whose abstracts were represented and discussed in international meetings or from principal investigators. In our study, ST was reported according to ARC and we did not include data from unpublished articles.

The study by Bangalore et al[44] also showed different results from ours. His study which compared the effectiveness and safety between BMS and DES, performed a mixed treatment comparison meta-analysis (MTC meta-analysis) commonly known as a network meta-analysis. ''An MTC meta-analysis is slightly different in the way that it is an extension that allows data to be combined and compared directly and indirectly,'' which, are supposedly not considered as randomized data, but are ''observational findings across trials, which might result in more bias, for example due to confounding,'' even if they included high-quality RCTs.[7] However, in our study, all data were strictly obtained directly from RCTs.

Even if there is no novelty in our idea, our study satisfies all the requirements for a meta-analysis, in terms of low heterogeneity, absent publication bias, and sensitivity analysis, and provides robust scientific validity to our findings. Hence, it is believed to show better results.

LIMITATIONS

This study also has several limitations. First of all, as a general consideration, authors always consider their studies to have a limited number of patients. Hence, even if our study included more than 16,000 patients, it is always a fact that due to a small population of patients compared to other studies, this could have an effect on our results too. Most of the RCTs had a follow-up period of at least 1 year; however, several other RCTs had a follow-up period of less or more than 1 year. Therefore, combing different follow-up periods that are almost of the same length, but not exactly the same, could affect the results in one way or the other. Moreover, our study included patients from different categories of diseases. For example, a few studies were conducted on the general population suffering from CAD; however, other studies were conducted on patients with long coronary lesions, ST elevated myocardial infarction or on patients suffering from type 2 diabetes mellitus. These patients have other abnormalities, for example patients with type 2 diabetes mellitus have platelet dysfunction which expose them to a higher possibility of ST after PCI. So, this could also be a limitation in our study.

CONCLUSION

Similar to many meta-analyses and RCTs, no significant difference in ST has been observed between SES and PES. Hence, both SES and PES are expected to be equally effective.

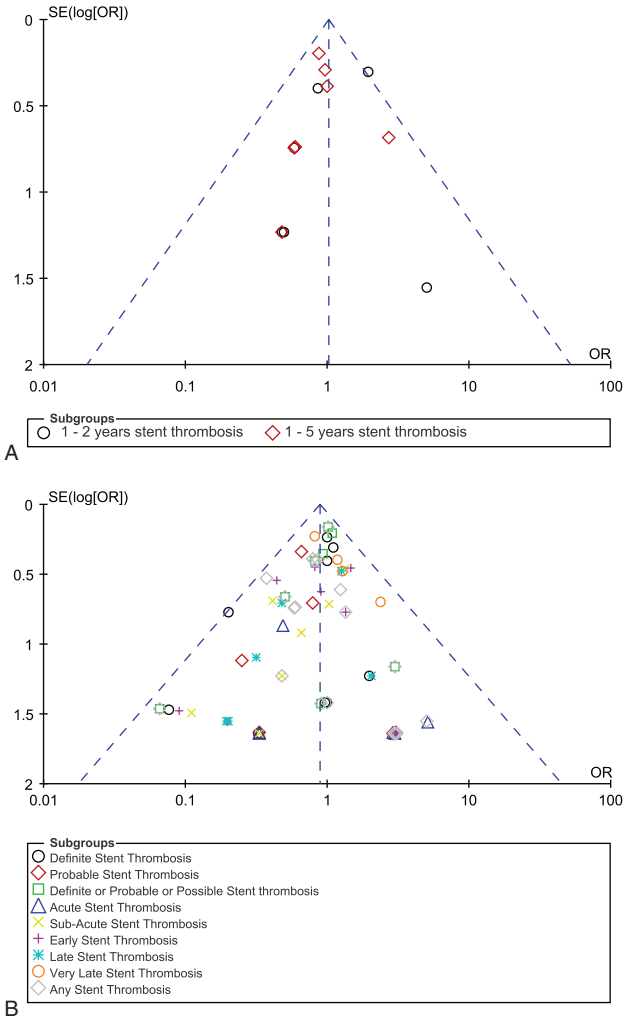

FIGURE 4. Funnel plots for sensitivity analyses.

REFERENCES

1. Gurm HS, Boyden T, Welch KB. Comparative safety and efficacy of a sirolimus-eluting versus paclitaxel-eluting stent: a meta-analysis. *Am Heart J.* 2008;155:630–639.
2. Kufner S, de Waha A, Tomai F, et al. A meta-analysis of specifically designed randomized trials of sirolimus-eluting versus paclitaxel-eluting stents in diabetic patients with coronary artery disease. *Am Heart J.* 2011;162:740–747.
3. Zhang F, Dong L, Ge J. Meta analysis of five randomized clinical trials comparing sirolimus- versus paclitaxel-eluting stents in patients with diabetes mellitus. *Am J Cardiol.* 2010;105:64–68.
4. Kastrati A, Dibra A, Eberle S, et al. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA.* 2005;294:819–825.
5. Zhang X, Xie J, Li G, et al. Head-to-head comparison of sirolimus-eluting stents versus paclitaxel-eluting stents in patients undergoing percutaneous coronary intervention: a meta-analysis of 76 studies. *PLoS ONE.* 2014;9:e97934.
6. Schömig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol.* 2007;50:1373–1380.
7. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Vol. 1.* Wiley; 2008:187–241.
8. Billinger M, Beutler J, Taghetchian KR, et al. Two-year clinical outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents in diabetic patients. *Eur Heart J.* 2008;29:718–725.
9. Räber L, Wohlwend L, Wigger M, et al. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. *Circulation.* 2011;123:2819–28286 p following 2828.
10. Togni M, Eber S, Widmer J, et al. Impact of vessel size on outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents: a subgroup analysis of the SIRTAX trial. *J Am Coll Cardiol.* 2007;50:1123–1131.
11. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel eluting stents for coronary revascularization. *N Engl J Med.* 2005;353:653–662.
12. Bligaard N, Thuesen L, Saunamäki K, et al. Similar five-year outcome with paclitaxel- and sirolimus-eluting coronary stents. *Scand Cardiovasc J.* 2014;48:148–155.
13. Galløe AM, Thuesen L, Kelbaek H, et al. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA.* 2008;299:409–416.
14. Han YL, Wang XZ, Jing QM, et al. Comparison of Rapamycin and Paclitaxel eluting stent in patients with multi-vessel coronary disease. *Zhonghua Xin Xue Guan Bing Za Zhi.* 2006;34:123–126.
15. Desch S, Schloma D, Möbius-Winkler S, et al. Randomized comparison of a polymer-free sirolimus-eluting stent versus a polymer-based paclitaxel-eluting stent in patients with diabetes mellitus: the LIPSIA Yukon trial. *JACC Cardiovasc Interv.* 2011;4:452–459.
16. Stiermaier T, Heinz A, Schloma D, et al. Five-year clinical follow-up of a randomised comparison of a polymer-free sirolimus-eluting stent versus apolymer-based paclitaxel-eluting stent in patients with diabetes mellitus (LIPSIA Yukon trial). *Catheter Cardiovasc Interv.* 2014;83:418–424.
17. Goy JJ, Stauffer JC, Siegenthaler M, et al. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXi trial. *J Am Coll Cardiol.* 2005;45:308–311.
18. Lee JH, Kim HS, Lee SW, et al. Prospective randomized comparison of sirolimus- versus paclitaxel-eluting stents for the treatment of acute ST-elevation myocardial infarction: pROSIT trial. *Catheter Cardiovasc Interv.* 2008;72:25–32.
19. Kim HS, Lee JH, Lee SW, et al. Long-term safety and efficacy of sirolimus- vs. paclitaxel-eluting stent implantation for acute ST-elevation myocardial infarction: 3-year follow-up of the PROSIT trial. *Int J Cardiol.* 2011;147:253–257.
20. Jensen LO, Maeng M, Thayssen P, et al. Neointimal hyperplasia after sirolimus-eluting and paclitaxel-eluting stent implantation in diabetic patients: the Randomized Diabetes and Drug-Eluting Stent (DiabeDES) Intravascular Ultrasound Trial. *Eur Heart J.* 2008;29:2733–2741.
21. Maeng M, Jensen LO, Galloe AM, et al. Comparison of the sirolimus-eluting versus paclitaxel-eluting coronary stent in patients with diabetes mellitus: the diabetes and drug-eluting stent (DiabeDES) randomized angiography trial. *Am J Cardiol.* 2009;103:345–349.
22. Juwana YB, Suryapranata H, Ottervanger JP, et al. Comparison of rapamycin- and paclitaxel-eluting stents in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Am J Cardiol.* 2009;104:205–209.

23. Kim YH, Park SW, Lee SW, et al. Sirolimus-eluting stent versus paclitaxel-eluting stent for patients with long coronary artery disease. *Circulation.* 2006;114:2148–2153.
24. Kufner S, Byrne RA, de Waha A, et al. Sirolimus-eluting versus paclitaxel-eluting stents in diabetic and non-diabetic patients within sirolimus-eluting stent restenosis: results from the ISAR-DESIRE 2 trial. *Cardiovasc Revasc Med.* 2014;15:69–75.
25. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol.* 2010;55:2710–2716.
26. Lee SW, Park SW, Kim YH, et al. A randomized comparison of sirolimus- versus Paclitaxel-eluting stent implantation in patients with diabetes mellitus. *J Am Coll Cardiol.* 2008;52:727–733.
27. Lee SW, Park SW, Kim YH, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus: 4-year clinical outcomes of DES-DIABETES (drug-eluting stent in patients with DIABETES mellitus) trial. *JACC Cardiovasc Interv.* 2011;4:310–316.
28. Lee SW, Park SW, Kim YH, et al. A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus 2-year clinical outcomes of the DES-DIABETES trial. *J Am Coll Cardiol.* 2009;53:812–813.
29. Di Lorenzo E, De Luca G, Sauro R, et al. The PASEO (PaclitAxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) Randomized Trial. *JACC Cardiovasc Interv.* 2009;2:515–523.
30. Mauri L, Hsieh WH, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med.* 2007;356:1020–1029.
31. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med.* 2007;356:998–1008.
32. Mehilli J, Kastrati A, Byrne RA, et al. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol.* 2009;53:1760–1768.
33. Morice MC, Colombo A, Meier B, et al. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. *JAMA.* 2006;295:895–904.
34. Nasu K, Oikawa Y, Yoshikawa R, et al. A randomized comparison of sirolimus- vs. paclitaxel-eluting stents for treatment of bifurcation lesions by single stent and kissing balloon: results of the SINGLE KISS trial. *Int J Cardiol.* 2013;166:187–192.
35. Otsuka M, Yokoi H, Matsuyama Y, et al. Comparison of sirolimus- and paclitaxel-eluting stents in patients with moderate renal insufficiency: results from the J-DESsERT trial. *Cardiovasc Revasc Med.* 2014;15:323–328.
36. Park DW, Kim YH, Yun SC, et al. Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. *J Am Coll Cardiol.* 2010;56:1187–1195.
37. Guagliumi G, Sirbu V, Musumeci G, et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. *JACC Cardiovasc Interv.* 2012;5:12–20.
38. Liu HT, Li F, Wang WY, et al. Rapamycin inhibits re-endothelialization after percutaneous coronary intervention by impeding the proliferation and migration of endothelial cells and inducing apoptosis of endothelial progenitor cells. *Tex Heart Inst J.* 2010;37:194–201.
39. Cassese S, Kastrati A. New-generation drug-eluting stents for patients with myocardial infarction. *JAMA.* 2012;308:814–815.
40. Marx SO, Totary-Jain H, Marks AR. Vascular smooth muscle cell proliferation in restenosis. *Circ Cardiovasc Interv.* 2011;4:104–111.
41. Sun J, Marx SO, Chen HJ, et al. Role for p27 (Kip1) in vascular smooth muscle cell migration. *Circulation.* 2001;103:2967–2972.
42. Santulli G, Wronska A, Uryu K, et al. A selective microRNA-based strategy inhibits restenosis while preserving endothelial function. *J Clin Invest.* 2014;124:4102–4114.
43. Santulli G, Totary-Jain H. Tailoring mTOR-based therapy: molecular evidence and clinical challenges. *Pharmacogenomics.* 2013;14:1517–1526.
44. Bangalore S, Kumar S, Fusaro M, et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation.* 2012;125:2873–2891.