ORIGINAL RESEARCH

Comparison of Drug-Eluting and Bare Metal Stents in Patients With Chronic Kidney Disease: An Updated Systematic Review and Meta-Analysis

Renjie Lu, MS; Fenglei Tang, BS; Yan Zhang, MS; Xishan Zhu, BS; Shanmei Zhu, BS; Ganlin Wang, BS; Yinfeng Jiang, MS; Zhengda Fan, BS

***Background*—**Drug-eluting stents (DESs) and bare metal stents (BMSs) are both recommended to improve coronary revascularization and to treat coronary artery disease in patients with chronic kidney disease (CKD). However, the potential superiority of DESs over BMSs for reducing the incidence of long-term major adverse cardiovascular events and mortality in CKD patients has not been established, and the results remain controversial. We aimed to systematically assess and quantify the total weight of evidence regarding the use of DESs versus BMSs in CKD patients.

***Methods and Results*—**In this systematic review and conventional meta-analysis, electronic studies published in any language until May 20, 2016, were systematically searched through PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. We included randomized controlled trials and observational studies comparing outcomes in CKD patients with DESs versus BMSs and extracted data in a standard form. Pooled odd ratios and 95% CIs were calculated using random- and fixed-effects models. Finally, 38 studies involving 123 396 patients were included. The use of DESs versus BMSs was associated with significant reductions in major adverse cardiovascular events (pooled odds ratio 0.75; 95% CI, 0.64–0.88; $P<0.001$), all-cause mortality (odds ratio 0.81; 95% CI, 0.73–0.90; $P<0.001$), myocardial infarction, target-lesion revascularization, and target-vessel revascularization. The superiority of DESs over BMSs for improving clinical outcomes was attenuated in randomized controlled trials.

***Conclusions*—**The use of DESs significantly improves the above outcomes in CKD patients. Nevertheless, large-sized randomized controlled trials are necessary to determine the real effect on CKD patients and whether efficacy differs by type of DES. **(*J Am Heart Assoc*. 2016;5:e003990 doi: 10.1161/JAHA.116.003990)**

Key Words: bare metal stent • cardiac • cardiac biomarkers • chronic kidney disease • coronary disease • dialysis • drug-eluting stent • outcomes

Chronic kidney disease (CKD) is a worldwide public health concern[1,2] and is frequently accompanied by cardiovascular diseases, including coronary artery disease.[3,4] Cardiovascular diseases are the leading cause of morbidity and mortality in CKD patients. CKD is a well-recognized risk factor of premature atherosclerosis.[5,6] This disease promotes hypertension and dyslipidemia, which—together with diabetes mellitus (a major cause of renal failure)—are important risk factors of endothelial dysfunction and atherosclerosis progression.[7] In addition to these common risk factors, the accelerated atherosclerosis in CKD patients is also associated with several uremia-related risk factors, such as inflammation, oxidative stress, hyperhomocysteinemia, and immunosuppressant use. Finally, the increase in calcification promoters and the reduction in calcification inhibitors favor metastatic vascular calcification, another important risk factor of vascular injury in CKD patients.[8] CKD patients frequently require coronary revascularization, which poses technical challenges due to the extensiveness and calcifiability of coronary artery disease. Accordingly, percutaneous coronary intervention is expected to reduce procedural success.[9] CKD is an independent predictor of worse outcomes following percutaneous coronary intervention compared with preserved kidney function.[10–13] Conflicting

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Accompanying Table S1 and Figures S1 through S3 are available athttp://jaha.ahajournals.org/content/5/11/e003990/DC1/embed/inline-supplementary-material-1.pdf

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results of efficacy and safety between drug-eluting stents (DESs) and bare metal stents (BMSs) have been reported. Several post hoc analyses and registries have compared the efficacy of DESs and BMSs in this high-risk population. Recent randomized controlled trials (RCTs) and observational studies (OSs) suggest that the introduction of DESs versus BMSs may provide favorable outcomes.[14–17] The benefit of DESs, however, is limited to short-term outcomes because of extremely late stent thrombosis in DESs, especially in first-generation DESs in populations with CKD[18] or high bleeding risk.[19] In addition, no significant difference in long-term outcomes among first-generation DESs, second-generation DESs, and BMSs[20] was found. Moreover, these studies included small population sizes and presented conflicting findings. A broad range of kidney function should be included because CKD patients are susceptible to both bleeding incidents and in-stent thrombosis.[13] The potential superiority of DESs over BMSs for reducing the incidence of long-term major adverse cardiovascular events (MACE) and mortality in CKD patients has not been established.

To assess the clinical outcomes of DESs versus BMSs in CKD patients, we performed a meta-analysis of the existing and up-to-date studies.

Methods

Search Strategy and Selection Criteria

In this systematic review and conventional meta-analysis, the search strategy was developed and the search performed by 2 experienced medical investigators (R.L. and Y.Z.). They searched for RCTs and OSs published until May 20, 2016 (date of the last search) in PubMed, Ovid Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. Keywords included *coronary artery disease, chronic kidney disease, end-stage renal disease, dialysis, drug-eluting stents, bare metal stents*, and *stents*. Subsequently, another investigator (F.T.) manually searched the references cited by relevant published reviews. We attempted to contact the authors to clarify published data if necessary.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) RCT, cohort study, or OS and (2) comparison of clinical outcomes between DESs and BMSs in CKD patients (regardless of CKD stage or dialysis type). Exclusion criteria were comparison of different types of DESs; kidney transplantation; and case report, review, comment,

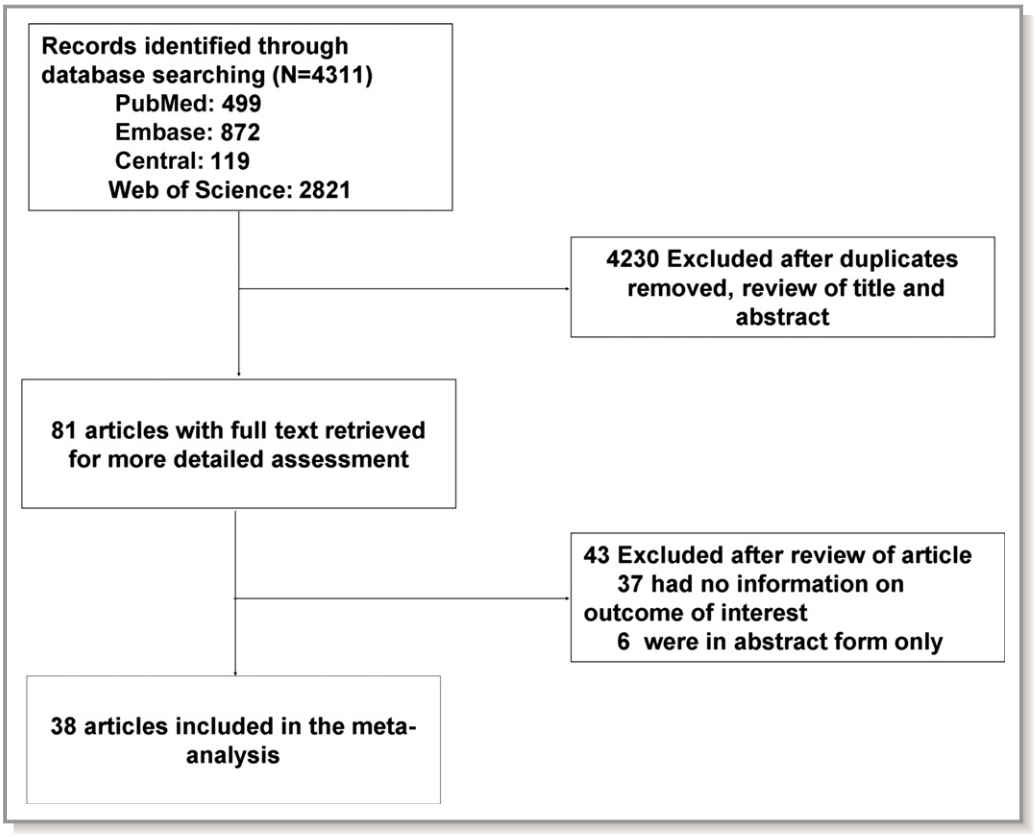

Figure 1. Flow diagram of study selection. Central indicates Cochrane Central Register of Controlled Trials.

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Table. Detailed Characteristics of Studies Included in the Meta-Analysis

Study	Country	Ethnicity	Study Design	Sample Size (DES/BMS)	Mean Age, y	Sex (%Male)	Dialysis Status (Yes or No)	Duration of Follow-up (Months)	Diabetes Mellitus (%)	Type of DES	Adjusted Covariates or Propensity Score Matching (Yes or No)	MACE (Reported and Definition)
Halkin et al (2005)[25]	USA	White	Post hoc analysis of RCT	123/100	74.0	47.1	No	12	22.4	PES	NR	Death from cardiac causes, MI, or TVR
Zhang et al (2006)[29]	China	Asian	RCS	264/146	72.0	61.5	No	17	19.8	DES	No	Cardiac death, infarction, restenosis, TVR
Kuchulakanti et al (2006)[30]	USA	White	RCS	68/120	68.7	58.9	Yes or no	6	57.2	SES	No	Death, Q wave, MI, or repeat revascularizations
Halkin et al (2006)[47]	USA, Canada	White	PCS	33/41	63.9	NR	Yes	12	NR	SES	Yes	Death, MI or any repeat revascularization
Das et al (2006)[31]	USA	White	RCS	24/65	62.4	75.0	Yes	9	79.8	DES	Yes	Death, MI and TVR
Ishio et al (2007)[32]	Japan	Asian	RCS	54/54	63.0	72.2	Yes	9	63.0	DES	No	NR
Okada et al (2008)[33]	Japan	Asian	RCS	80/124	67.0	64.7	Yes	12	65.7	SES	Yes	Cardiac death, nonfatal MI, stent thrombosis, or TLR
Aoyama et al (2008)[34]	Japan	Asian	RCS	88/78	64.5	66.9	Yes	12	59.0	SES	Yes	Cardiac death, nonfatal acute MI, CABG, and repeated PCI
Jeong et al (2008)[35]	Korea	Asian	RCS	104/50	65.0	66.2	No	12	60.4	SES or PES	No	Cardiac death, nonfatal MI or TVR
Appleby et al (2009)[11]	Canada	White	RCS	749/2321	73.0	54.9	No	48	31.8	DES	Yes	Death, repeat revascularization by PCI or CABG, or MI
Yachi et al (2009)[36]	Japan	Asian	RCS	56/67	65.6	69.1	Yes	9	50.4	SES	Yes	All-cause death, MI, and TLR
Rosenblum et al (2009)[37]	USA	White	RCS	1291/682	73.5	53.6	No	12	43.7	DES	No	NR
Na et al (2009)[38]	Korea	Asian	RCS	312/60	NR	NR	Yes or no	11	NR	DES	Yes	Restenosis, MI, or TVR
Kim et al (2009)[48]	Korea	Asian	PCS	54/51	61.0	63.8	Yes	30.6	66.7	SES	Yes	Death, MI, TVR
Shenoy et al (2010)[49]	USA	White	PCS	222/214	71.0	20.0	No	40.7	21.0	SES	Yes	Death, MI or TVR

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Table. Continued

Study	Country	Ethnicity	Study Design	Sample Size (DES/BMS)	Mean Age, y	Sex (%Male)	Dialysis Status (Yes or No)	Duration of Follow-up (Months)	Diabetes Mellitus (%)	Type of DES	Adjusted Covariates or Propensity Score Matching (Yes or No)	MACE (Reported and Definition)
Garg et al (2010)[24]	USA, Germany, Canada	White	Pooled analysis of RCTs	109/119	73.6	42.1	No	60	29.8	SES	NR	NR
Ichimoto et al (2010)[39]	Japan	Asian	RCS	63/45	64.8	77.8	Yes	26.2	63.0	SES	No	Death, MI or TLR
Green et al (2011)[10]	USA	White	RCS	763/345	70.8	52.7	No	12	45.7	DES	Yes	No definition
Barthelemy et al (2011)[50]	France	White	PCS	126/224	73.9	67.1	No	12	27.7	DES	No	Cardiovascular death, MI, stroke, and TLR
Bae et al (2011)[40]	Korea	Asian	RCS	1967/208	70.0	55.4	No	12	41.3	DES	Yes	Mortality, nonfatal MI, and TLR
Saltzman et al (2011)[26]	USA, Germany, Italy, Israel, Poland	White	Post hoc analysis of RCT	418/136	75.4	55.2	No	36	19.3	DES	NR	Death, reinfarction, TVR, or stroke
Charytan et al (2011)[51]	USA	White	PCS	431/431	NR	NR	Yes or no	24	NR	DES	Yes	NR
Tsai et al (2011)[18]	USA	White	RCS	27 567/27 567	NR	NR	Yes or no	30	38.0	DES	Yes	NR
Simsek et al (2012)[52]	The Netherlands	White	PCS	175/72	72.2	51.0	No	72	21.9	SES or PES	Yes	A composite of all-cause mortality, MI, and TVR
Ishii et al (2012)[41]	Japan	Asian	RCS	301/204	66.0	69.5	Yes	72	58.4	DES	No	Cardiovascular death, nonfatal MI, stent thrombosis, and TLR
Kersting et al (2012)[17]	Germany	White	RCS	117/63	72.2	72.2	No	33.6	40.0	SES or PES	Yes	All-cause mortality, MI, repeat revascularization, duration of dual antiplatelet therapy, and the development of complications such as stroke, sepsis, tumor, or bleeding complications
Resmini et al (2012)[42]	Italy	White	RCS	55/164	72.9	76.7	No	48.1	44.3	DES	No	Death, MI and repeat revascularization

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Table. Continued

Study	Country	Ethnicity	Study Design	Sample Size (DES/BMS)	Mean Age, y	Sex (%Male)	Dialysis Status (Yes or No)	Duration of Follow-up (Months)	Diabetes Mellitus (%)	Type of DES	Adjusted Covariates or Propensity Score Matching (Yes or No)	MACE (Reported and Definition)
Wanitschek et al (2013)[27]	Austria, Switzerland Denmark, Italy	White	Post hoc analysis of RCT	123/66	74.4	56.1	No	24	26.5	DES	NR	Cardiac death, MI, TVR
Shroff et al (2013)[43]	USA	White	RCS	11 844/5011	NR	55.4	Yes	17	57.0	DES	Yes	NR
Meliga et al (2013)[12]	Italy	White	RCS	92/77	68.1	78.7	Yes	26.3	36.7	DES	No	Cardiac death, MI, cerebrovascular accidents, and any revascularization
Fujita et al (2014)[14]	Japan	Asian	RCS	58/36	64.4	72.3	Yes	12	55.3	SES	No	Death, Q and non–Q wave MI, and TLR
Tomai et al (2014)[15]	Italy	White	RCT	257/255	73.0	72.6	Yes or no	12	43.7	EES	NR	NR
Shroff et al (2015)[16]	USA	White	RCS	6566/2997	68.0	53.6	Yes	24	74.6	DES	Yes	NR
Crimi et al (2016)[28]	Italy, the Netherlands, Switzerland	White	Post hoc analysis of RCT	279/94	75.0	81.5	No	24	35.4	ZES-S or PES or EES	NR	MI, stroke, or death
Naito et al (2016)[44]	Japan	White	RCS	550/405	68.7	80.0	Yes	36	42.8	DES	No	All-cause mortality, nonfatal ACS, nonfatal stroke, repeat revascularization
Lee et al (2016)[45]	Taiwan	Asian	RCS	738/2097	64.5	58.3	Yes	12	80.3	DES	Yes	All-cause mortality, hospitalization and MI, repeat revascularization hospitalization and stroke
Chang et al (2016)[13]	USA	White	RCS	10 751/10 751	64.5	58.1	Yes	12	77.5	DES	Yes	NR
Chen et al (2016)[46]	Taiwan	Asian	RCS	492/492	68.5	60.6	Yes	14.4	73.4	DES	Yes	NR

ACS indicates acute coronary syndrome; BMS, bare-metal stents; CABG, coronary artery bypass grafting; DES, drug-eluting stent; EES, everolimus-eluting stent; MACE, major adverse cardiovascular events; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; PCS, prospective cohort study; PES, paclitaxel-eluting stent; RCS, retrospective cohort study; RCT, randomized controlled trial; SES, sirolimus-eluting stents; TLR, target-lesion revascularization; TVR, target-vessel revascularization; ZES-S, zotarolimus-eluting Endeavor Sprint stent.

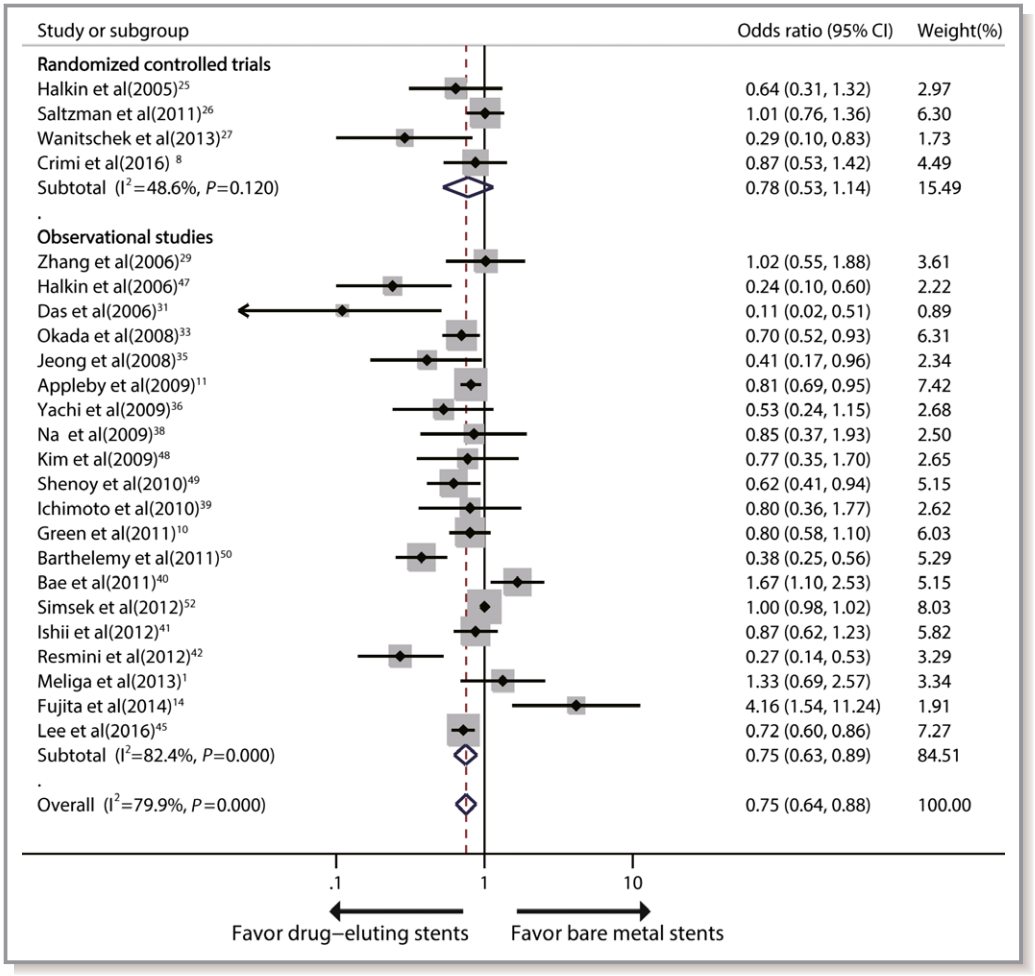

Figure 2. Forest plot for major adverse cardiovascular events.

editorial, letter, quasiexperiment, or unpublished study. When >1 study from the same team or institution met the inclusion criteria, only the study with the largest sample size or the latest publication was included.

Data Extraction

We selected studies and extracted data according to a standard Cochrane protocol.[21] All investigators independently reviewed the abstracts and identified potential articles for retrieval. Following the inclusion criteria, 2 investigators (R.L. and Y.Z.) independently reviewed eligible articles for study characteristics and clinical relevance and, if appropriate, extracted data. Any disagreement between the investigators was resolved through consensus or discussion with the third investigator (F.T.), if necessary. Demographic characteristics (age, sex, ethnicity), stage and duration of CKD, presence of diabetes mellitus, and follow-up duration were extracted using standardized forms. We also extracted data on trial characteristics (inclusion and exclusion criteria), type of study, trial intervention, and clinical outcomes (MACE, all-cause mortality, myocardial infarction [MI], target-lesion revascularization [TLR], and target-vessel revascularization [TVR]).

Quality Assessment

The quality of each study was independently assessed by 2 investigators (R.L. and Y.Z.). The risk of bias of each RCT was evaluated with the Cochrane Collaboration's risk of bias tool containing 6 domains (sequence generation; allocation concealment; blindness of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; other sources of bias), with 3 levels for each domain (low, unclear, or high bias). The summary risk of bias was determined to be high if at least 1 domain was assessed as high risk of bias and low only if all domains were judged as low risk of bias.[22] The Newcastle-Ottawa Scale (NOS) consists of 3 quality parameters for cohort studies, namely, selection, comparability, and outcome, which were assigned a maximum of 4, 2, and 3 stars, respectively; therefore, 9 stars reflected the highest quality. A study with >6 stars was considered high quality.[23] Any discrepancy was resolved through a joint

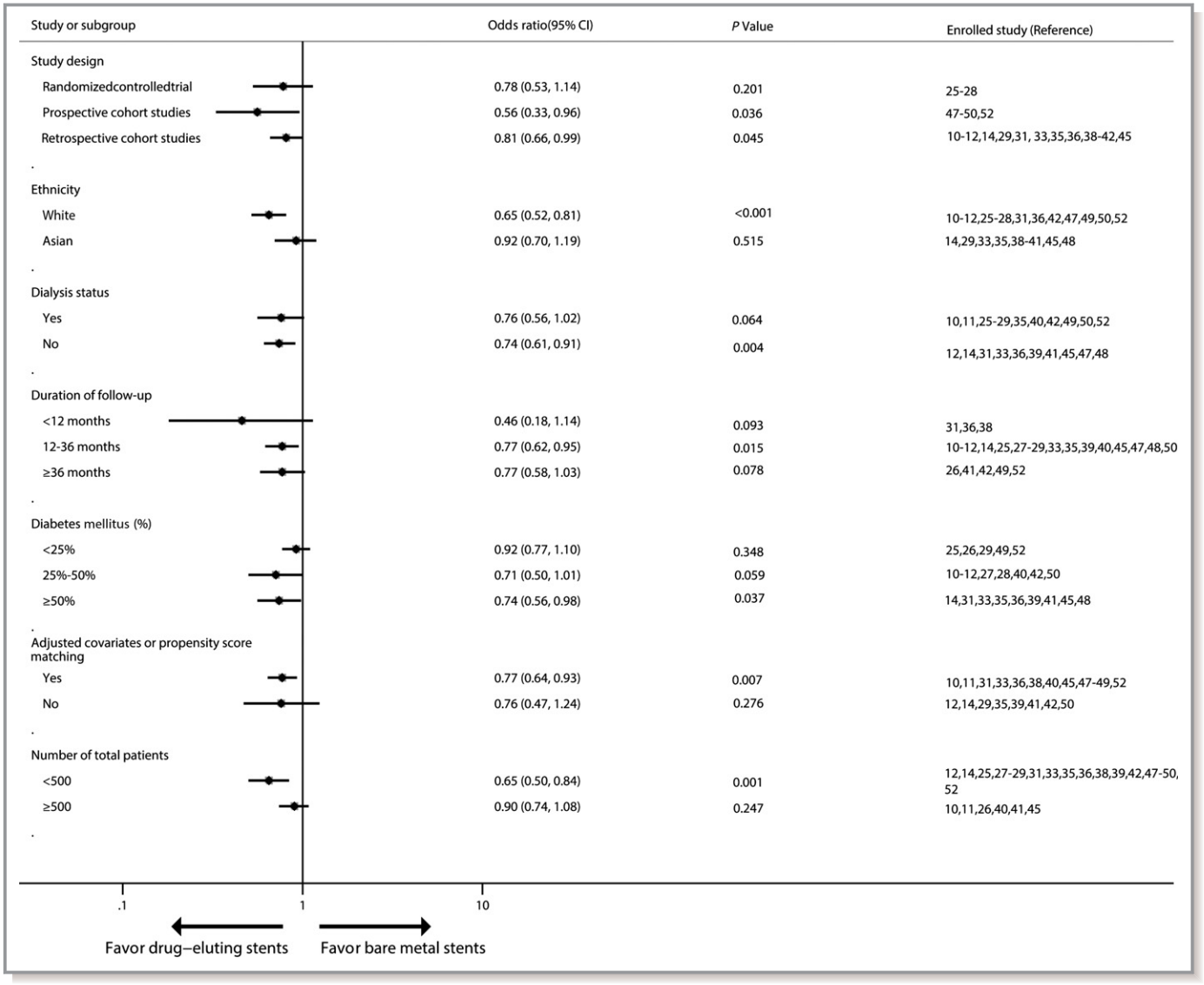

Figure 3. Forest plot for major adverse cardiovascular events according to some clinically important variables.

revaluation of the original article with the third investigator (F.T.).

Data Synthesis

Dichotomous outcomes were pooled using odd ratios (ORs) with 95% CIs. Heterogeneity among studies was assessed using the I^2 statistic, with I^2<25% as minimal, I^2<50% as moderate, and I^2≥50% as substantial. All analyses were performed using the random-effects model regardless of heterogeneity testing. Publication bias was examined through (1) visual interpretation of funnel plot asymmetry, with the estimated effects plotted against standard errors; (2) Begg's adjusted rank correlation test; and (3) Egger's regression asymmetry test. If publication bias was found, Duval and Tweedie's trim-and-fill method was performed.

Sensitivity and meta-regression analyses were conducted to assess whether heterogeneity could be attributed to any measurable source. Subgroup analyses for MACE and all-cause mortality against several variables were performed to identify possible causes of heterogeneity and to assess the robustness of the relationships. These variables included study design (RCT, prospective cohort study, and retrospective cohort study), number of patients (<500 or ≥500 total patients), ethnicity (white and Asian), CKD stage (dialysis and nondialysis), mean duration of follow-up (<12, 12–36, and ≥36 months), percentage of patients with diabetes mellitus (<25%, 25–50%, and ≥50%), and adjusted or propensity score matching (yes and no). All analyses were performed using Stata 12.0 (StataCorp) and Review Manager 5.3.5 (Cochrane Collaboration). P<0.05 was considered statistically significant, except for the publication bias test (P<0.10).

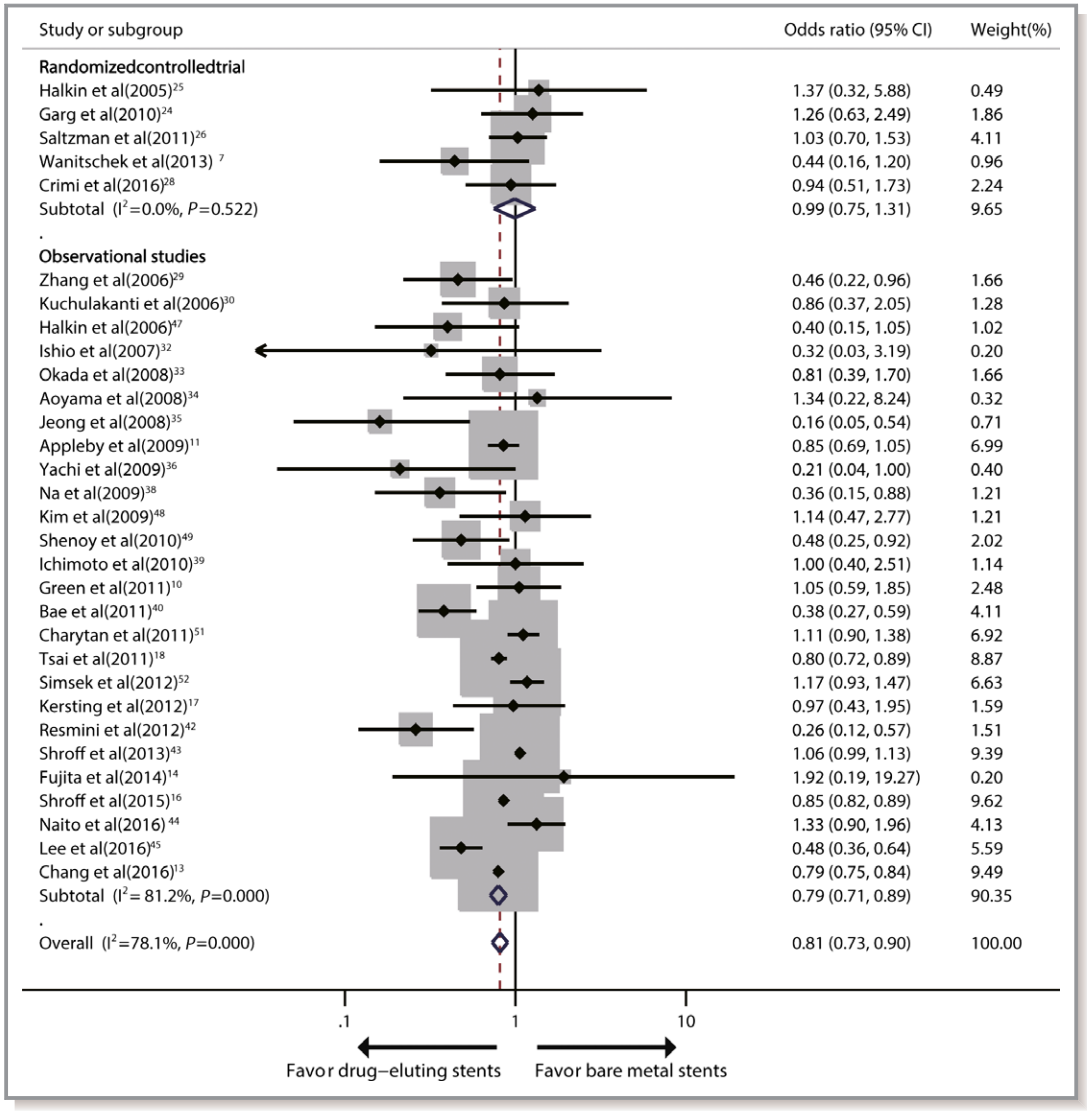

Figure 4. Forest plot for all-cause mortality.

Results

Selection and Characteristics of Studies

A total of 4311 potentially relevant articles were initially identified and screened. Among these articles, 81 were retrieved for detailed evaluation. In total, 38 articles met the inclusion criteria (Figure 1), including 6 RCTs (1 real RCT,[15] 1 pooled analysis of RCTs,[24] and 4 post hoc analyses of an RCT[25–28]) and 32 OSs (26 retrospective cohort studies[10–14,16–18,29–46] and 6 prospective cohort studies[47–52]).

Table lists the key characteristics of the 38 studies. In many OSs, a wide variety of potential confounders were adjusted to investigate the associations between DESs or BMSs and clinical outcomes, including age, sex, body mass index, presence of diabetes mellitus, duration of dialysis, and dialysis modality. The 38 articles presented data about MACE (n=24),* all-cause mortality (n=31),† MI (n=19),‡ TLR (n=14),§ and TVR (n=18).‖

Quality Assessment

Methodological quality assessments showed that the 32 OSs had an average NOS score of 8.125 and were all of high quality (NOS score ≥7) except 1 (Table S1).[30]

*References 10–12, 14, 25–29, 31, 33, 35, 36, 38–42, 45, 47–50, 52.
†References 10, 11, 13, 14, 16–18, 24–30, 32–36, 38–40, 42–45, 47–49, 51, 52.
‡References 10, 12, 17, 18, 24–26, 28, 30, 34, 35, 38, 39, 42, 45, 46, 48, 51.
§References 12, 14, 25, 28, 30, 32–34, 36, 37, 39, 41, 48, 50.
‖References 12, 15, 17, 24–31, 35, 38, 42, 48, 49, 51, 52.

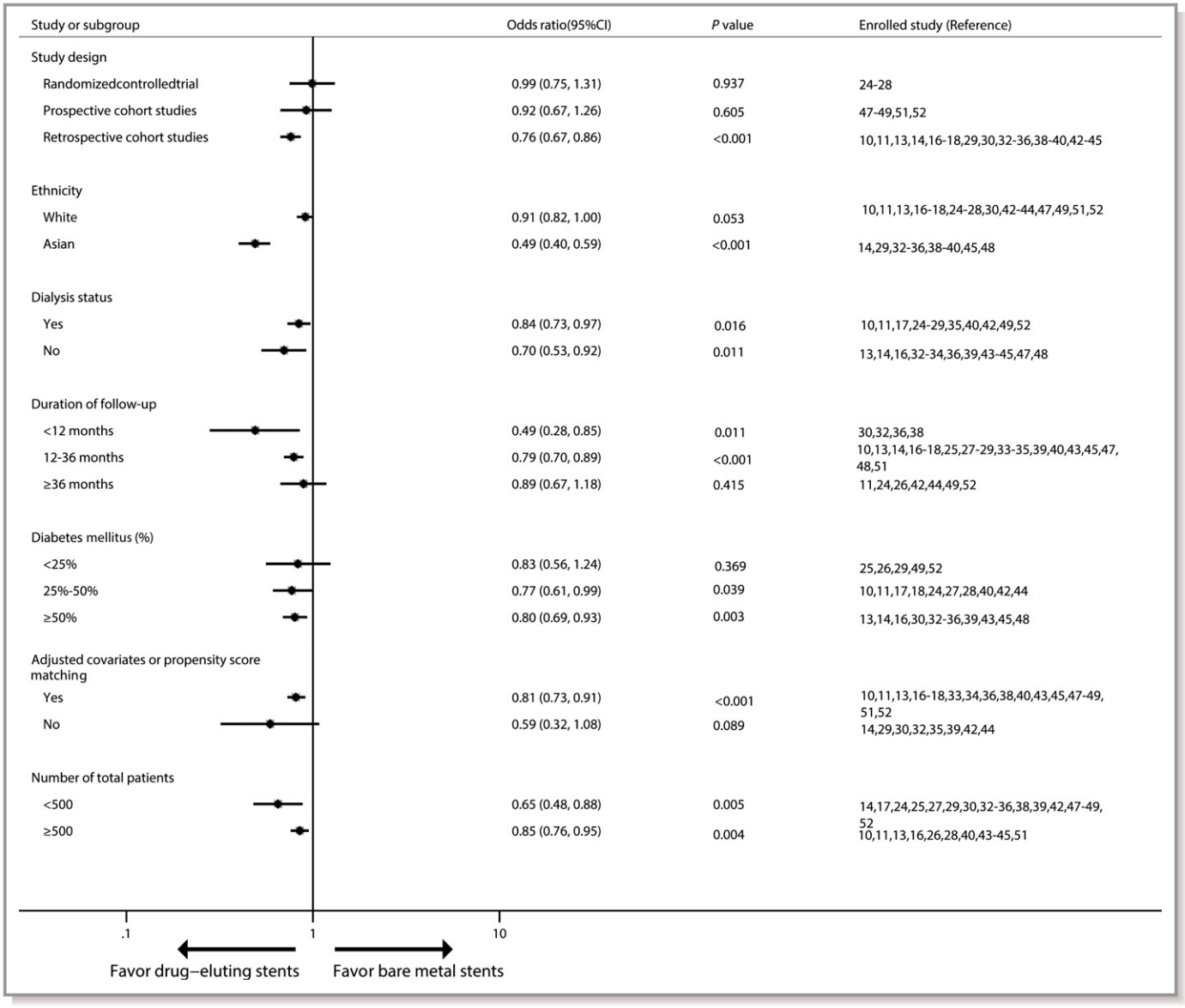

Figure 5. Forest plot for all-cause mortality according to some clinically important variables.

Effect of DESs Versus BMSs on MACE and All-Cause Mortality

In 4 RCTs (including analysis of RCT),[25–28] the association between the use of DESs or BMSs and the incidence of MACE was insignificant (pooled OR 0.78; 95% CI 0.53–1.14; P=0.201) in the random-effects model without heterogeneity (Figure 2). In 20 OSs,[¶] the association was significant (a 25% reduction in the incidence of MACE; pooled OR 0.75; 95% CI 0.63–0.89; P=0.001) in the random-effects model with substantial heterogeneity (I^2=82.4%; P<0.001) (Figure 2). In 5 prospective cohort studies,[39,47,49,50,52] the association was significant with a reduced incidence of MACE (pooled OR, 0.56; 95% CI, 0.33–0.96; P=0.036) in the random-effects model with substantial heterogeneity (I^2=89.5%; P<0.001) (Figure 3). In 15 retrospective cohort studies,[#] the association was also significant (pooled OR 0.81; 95% CI, 0.66–0.99; P=0.045) with substantial heterogeneity (I^2=70.6%; P<0.001) (Figure 3).

Subanalyses showed that the association between DESs or BMSs and MACE was significant for small sample sizes, white ethnicity, nondialysis status, moderate duration of follow-up, high percentage of patients with diabetes mellitus, and adjusted or propensity score matching (Figure 3).

[¶]References 10–12, 14, 29, 31, 33, 35, 36, 38–42, 45, 47–50, 52.

[#]References 10–12, 14, 29, 31, 33, 35, 36, 38, 40–42, 45, 48.

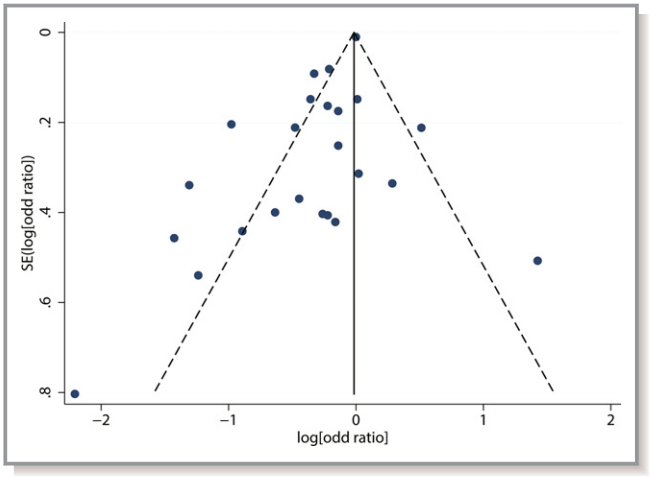

Figure 6. Funnel plot for major adverse cardiovascular events.

Metaregressions were conducted to determine whether the inconsistency could be explained by any of the heterogeneity sources; however, no significant factor that contributed to heterogeneity was found (all $P>0.1$), indicating that the between-study heterogeneity was not well explained by any of the characteristics tested.

The association between DESs or BMSs and all-cause mortality was significant (pooled OR 0.81, 95% CI 0.73–0.90; $P<0.001$) (Figure 4) in the random-effects model with substantial heterogeneity in the magnitude of effect across all included studies ($I^2=78.1\%$; $P<0.001$). The subsequent subgroup analysis (Figure 5) revealed greater effects for retrospective cohort studies, Asian ethnicity, moderate duration of follow-up, moderate and high percentages of patients with diabetes mellitus, and adjusted or propensity score matching, which was attenuated to some extent in RCTs and prospective cohort studies.

The funnel plots showed no apparent systematic bias (Figure 6) (Begg's test, $P=0.941$), but Egger's tests revealed significant publication bias ($P=0.004$) in the analysis of MACE. When the influence of potential publication bias was investigated using the trim-and-fill method, the potential missing data were not replaced, and the findings were generally similar with a decreased risk of MACE in the patients with percutaneous coronary intervention (pooled OR 0.62; 95% CI 0.52–0.72; $P<0.001$). No substantial systematic bias was found from the funnel plots (Figure 7) in the analysis of all-cause mortality (Begg's test, $P=0.61$; Egger's test, $P=0.271$).

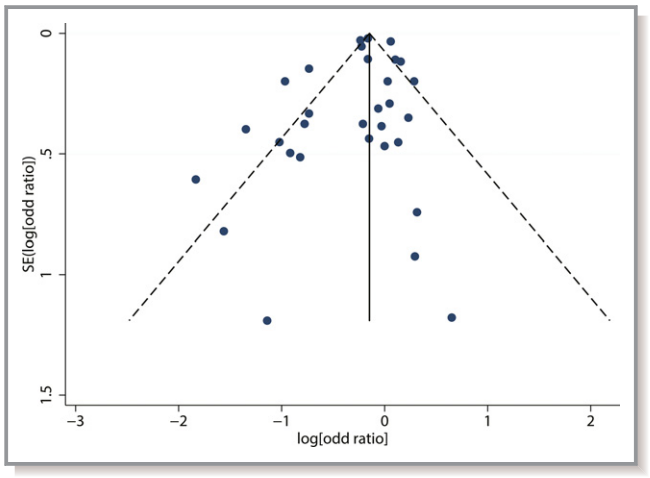

Figure 7. Funnel plot for all-cause mortality.

Effect of DESs Versus BMSs on MI, TLR, and TVR

The use of DESs versus BMSs produced a 20% significant reduction in MI (OR 0.80; 95% CI 0.67–0.95; $P<0.001$) (Figure S1), with no substantial heterogeneity ($I^2=32.9\%$; $P=0.082$). It had a significant effect on TLR (OR 0.69; 95% CI 0.52–0.92; $P=0.014$) (Figure S2) and TVR (OR 0.55; 95% CI 0.42–0.73; $P<0.001$) (Figure S3). Substantial heterogeneity existed in the results of TLR ($I^2=58.0\%$, $P=0.003$) and TVR ($I^2=64.1\%$, $P<0.001$). Metaregressions were also used to explore whether the inconsistency could be explained by any of the heterogeneity sources; however, no significant factor that contributed to heterogeneity was found (all $P>0.1$).

Discussion

The meta-analysis demonstrated that the use of DESs versus BMSs in CKD patients was significantly associated with reductions in the incidence of MACE, all-cause mortality, MI, TLR, and TVR. The use of DESs versus BMSs showed superior efficacy in reducing the rate of MACE in the CKD population primarily by reducing TLR.

Our survival result is similar to that of a present meta-analysis that shows use of DESs versus BMSs significantly reduces mortality rate in OSs but not in RCTs.[53] Several possible explanations may exist as to why the mortality rate was significantly reduced with the use of DESs compared with BMSs in the OSs, with an attenuated effect in the RCTs. Proponents of observational data cite added generalizability and the fact that more patients have been studied in the observational registries compared with the RCTs, providing much more power to detect differences in low-frequency safety events. Conversely, observational analyses are subject to confounding with regard to the nonrandomized choice of either DESs or BMSs. Multivariable adjustment can be used to mitigate the effect of measured confounders on the effect estimate for DESs versus BMSs within individual studies. As such, the observed attenuation of the overall summary estimate of mortality favoring DESs compared with BMSs in the adjusted versus unadjusted analyses was notable. Consequently, this survival benefit of DESs versus BMSs should be interpreted with caution because of the nonrandomized nature of the data sources and the

heterogeneity across studies. The mortality benefit of DESs versus BMSs should be verified in large RCTs.

Significant differences were found in the incidence rates of MI, TLR, and TVR between DES- and BMS-treated patients. Real-world patients with CKD, particularly those with end-stage renal disease on dialysis, are at high risk of serious bleeding events due to chronic heparin exposure, uremia-induced platelet dysfunction, and concomitant use of anticoagulants.[54–56] Such patients are also more likely to discontinue clopidogrel or other antiplatelet agents prematurely.[57] The discontinuation of these agents leads to in-stent thrombosis and subsequent MI.[58] Moreover, data regarding medication, especially antiplatelet regimens, are limited, but the use of DESs typically follows a dual antiplatelet regimen that can increase the mortality rate in patients with coronary artery disease.[59] Meanwhile, the difference in MI definitions may change the end point measurement and curative effect comparison. MI is defined as hospitalization with a principal diagnosis of MI[45] or as an elevation of cardiac enzymes and/or the development of new pathological Q wave on electrocardiogram.[22,30] The benefit of decreased TLR and TVR from the use of DESs is not clearly elucidated and may be affected by multiple factors, such as longer use of antiplatelet agents (eg, clopidogrel) and differences in follow-up care.

As expected, our systematic review and meta-analysis showed the heterogeneity in ORs among OSs. This heterogeneity may be attributed to the differences in study designs, demographics, and statistical approaches. Despite the strict criteria used, the included studies represented a comprehensive attempt to cull published and unpublished literature reports in this field; therefore, we used the summary-level estimates of individual study effects. Meanwhile, conventional statistical approaches used in OSs were not sufficiently powerful to address the effects of unmeasured confounders on the overall effect estimate. We attempted to investigate the heterogeneity sources through various sensitivity analyses and metaregressions but did not find any simple explanation or way that accounted for the heterogeneity.

This review and meta-analysis has several strengths, including the broad search strategy (standard Cochrane protocol) and large sample size. It also has several shortcomings. First, only 1 real RCT was included, but the patient cohort in this trial was excessively selected. Its 1-year death rate of only 3.7% was much lower than the annual death rates for patients with CKD and coronary heart disease overall. Second, we could not identify unpublished reports, and that might bias our results. Significant heterogeneity was noted among OSs. Meanwhile, the forms of DESs differed substantially across trials because second-generation DESs showed survival superiority over first-generation DESs.[60] Moreover, Egger's tests showed a potential publication bias for MACE that is difficult to ascertain. Our findings might have overestimated the true effect if we missed some insignificant studies.

In summary, this meta-analysis provides substantial evidence that DESs significantly decreased the occurrence of MACE, all-cause mortality, MI, TLR, and TVR in CKD patients. DESs, particularly second-generation DESs for percutaneous coronary intervention, appeared to be safe and efficient in CKD patients. Nevertheless, the true effect of DESs versus BMSs should be confirmed by further RCTs.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Quality assessment of the observational studies included in the meta-analysis by NOS[#]

NOS scale	Zhang et al(2006)[1]	Kuchulakanti et al(2006)[2]	Halkin et al(2006)[3]	Das et al(2006)[4]	Ishio et al (2007)[5]	Okada et al(2008)[6]	Aoyama et al(2008)[7]	Jeong et al(2008)[8]	Appleby et al(2009)[9]	Yachi et al(2009)[10]	Rosenblum et al(2009)[11]
A-Selection (maximum 4*)											
1.Representativeness of general community population	*	*	*	*	*	*	*	*	*	*	*
2.The reference group was drawn from the same community	*	*	*	*	*	*	*	*	*	*	*
3.Ascertainment the exposure of PCI	*	*	*	*	*	*	*	*	*	*	*
4.Clinical outcomes was not present at baseline	*	*	*	*	*	*	*	*	*	*	*
B-Comparability (maximum 2*)											
5.Controlled for age and sex	0	0	*	*	*	0	*	0	*	*	0
6.Controlled for 2 or more variables besides age and sex	0	0	*	*	*	*	*	0	*	*	0
C-Outcome (maximum 3*)											
7. Clinical outcomes was certificated by hospital or local municipal registration	*	*	*	*	*	*	*	*	*	*	*
8. Adequate duration of follow-up (≥12 months)	*	0	*	0	*	*	*	*	*	0	*
9. Adequacy of follow-up rate (>90%) of cohorts	*	*	*	*	*	*	*	*	*	*	*
Total scores (maximum 9*)	7	6	9	8	9	8	9	7	8	8	7

[#] "NOS" represented the Newcastle-Ottawa Scale

"*" meant the study corresponded to the NOS criteria," 0" meant the study did not correspond to the NOS criteria

Table S1-continued

NOS scale	Na et al(2009)[12]	Kim et al(2009)[13]	Shenoy et al(2010)[14]	Ichimoto et al(2010)[15]	Green et al(2011)[16]	Barthelemy et al(2011)[17]	Bae et al(2011)[18]	Charytan et al(2011)[19]	Tsai et al(2011)[20]	Simsek et al(2012)[21]	Ishii et al(2012)[22]
A-Selection (maximum 4*)											
1.Representativeness of general community population	*	*	*	*	*	*	*	*	*	*	*
2.The reference group was drawn from the same community	*	*	*	*	*	*	*	*	*	*	*
3.Ascertainment the exposure of vitamin D	*	*	*	*	*	*	*	*	*	*	*
4. Clinical outcomes was not present at baseline	*	*	*	*	*	*	*	*	*	*	*
B-Comparability (maximum 2*)											
5.Controlled for age and sex	*	*	*	0	*	0	*	*	*	*	0
6.Controlled for 2 or more besides age and sex	*	*	*	0	*	0	*	*	*	*	0
C-Outcome (maximum 3*)											
7. Clinical outcomes was certificated by hospital or local municipal registration	*	*	*	*	*	*	*	*	*	*	*
8. Adequate duration of follow-up (≥12 months)	0	*	*	*	*	*	*	*	*	*	*
9. Adequacy of follow-up rate (>90%) of cohorts	*	*	*	*	*	*	*	*	*	*	*
Total scores (maximum 9*)	8	9	9	7	9	7	9	9	9	9	7

[#] "NOS" represented the Newcastle-Ottawa Scale

"*" meant the study corresponded to the NOS criteria," 0" meant the study did not correspond to the NOS criteria

Table S1-continued

NOS scale	Kersting et al(2012)[23]	Resmini et al(2012)[24]	Shroff et al(2013)[25]	Meliga et al(2013)[26]	Fujita et al(2014)[27]	Shroff et al(2015)[28]	Naito et al(2016)[29]	Lee et al(2016)[30]	Chang et al(2016)[31]	Chen et al(2016)[32]
A-Selection (maximum 4*)										
1.Representativeness of general community population	*	*	*	*	*	*	*	*	*	*
2.The reference group was drawn from the same community	*	*	*	*	*	*	*	*	*	*
3.Ascertainment the exposure of vitamin D	*	*	*	*	*	*	*	*	*	*
4. Clinical outcomes was not present at baseline	*	*	*	*	*	*	*	*	*	*
B-Comparability (maximum 2*)										
5.Controlled for age and sex	*	0	*	0	0	*	0	*	*	*
6.Controlled for 2 or more variables besides age and sex	*	0	*	0	0	*	0	*	*	*
C-Outcome (maximum 3*)										
7. Clinical outcomes was certificated by hospital or local municipal registration	*	*	*	*	*	*	*	*	*	*
8. Adequate duration of follow-up (≥12 months)	*	*	*	*	*	*	*	*	*	*
9. Adequacy of follow-up rate (>90%) of cohorts	*	*	*	*	*	*	*	*	*	*
Total scores (maximum 9*)	9	7	9	7	7	9	7	9	9	9

[#] "NOS" represented the Newcastle-Ottawa Scale

"*" meant the study corresponded to the NOS criteria," 0" meant the study did not correspond to the NOS criteria

Figure S1. Forest plot for myocardial infarction.

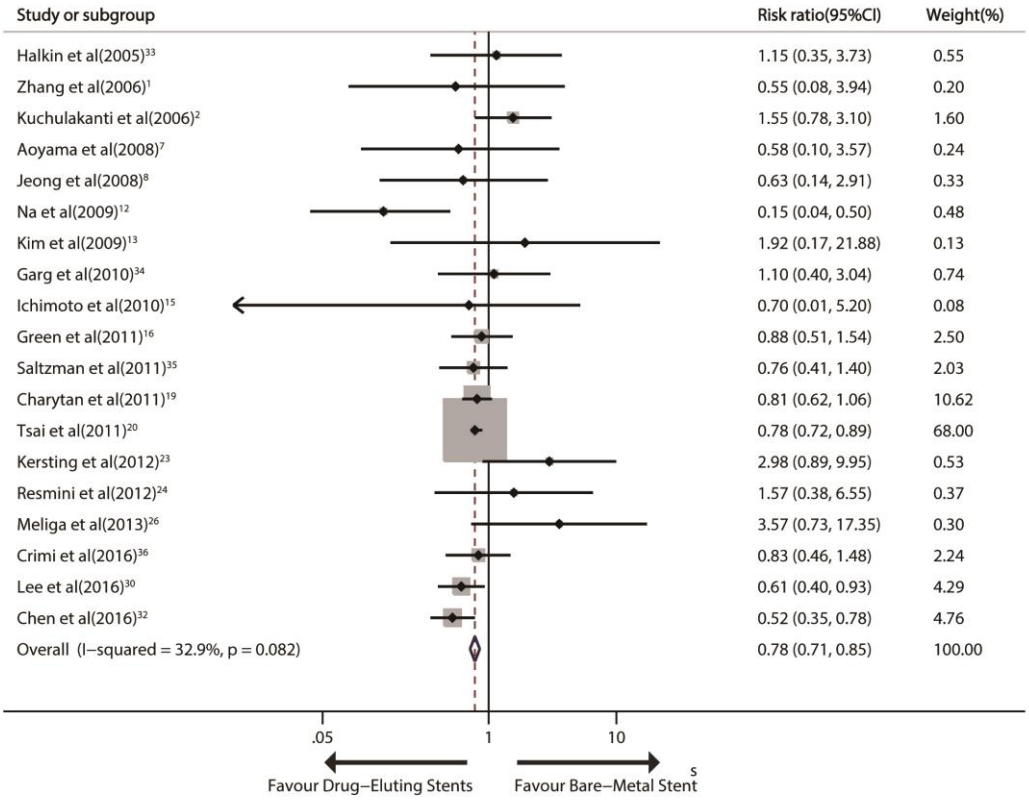


Figure S2. Forest plot for target-lesion revascularization.

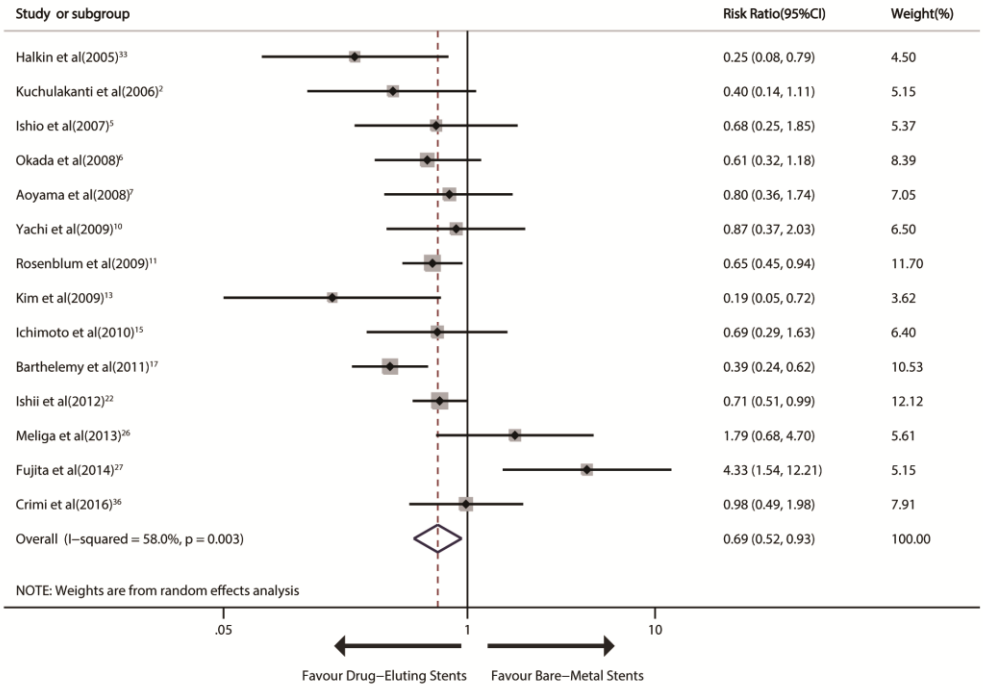
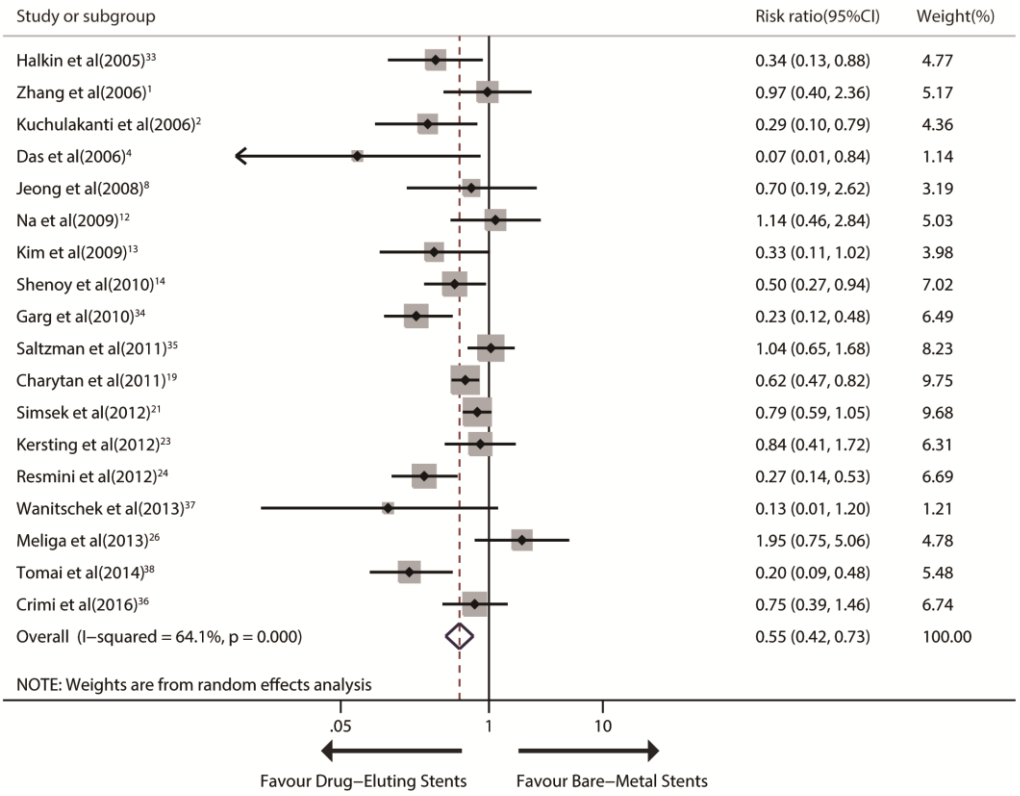


Figure S3. Forest plot for target-vessel revascularization.



Supplemental References:

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