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REVIEW ARTICLE

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Drug eluting stents are superior to bare metal stents to reduce clinical outcome and stent-related complications in CKD patients, a systematic review, meta-analysis and network meta-analysis

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Aims: To compare clinical outcome in Chronic kidney disease (CKD) patients receiving coronary stents according to stent type BMS versus DES and 1st generation versus 2nd generation DES.

Methods and Results: PubMed, Cinhal, Cochrane, Embase, and Web of Science were searched for studies including CKD patients. CKD was defined as eGFR < 60 mL/min. We selected *n* = 35 articles leading to 376 169 patients, of which 76 557 CKD patients receiving BMS *n* = 35,807, 1st generation DES *n* = 37,650, or 2nd generation DES *n* = 3100. Patient receiving DES, compared to BMS, had a 18% lower all-cause mortality (RR 0.82, 95%CI 0.71-0.94). The composite of death or myocardial infarction (MI) was lower in DES patients (RR 0.78, 95%CI 0.67-0.91), as was stent thrombosis (ST) (RR 0.57, 95%CI 0.34-0.95), target vessel/lesion revascularization (TVR/TLR) (RR 0.69, 95%CI 0.57-0.84) and death for cardiovascular cause (RR 0.43, 95%CI 0.25-0.74). We also found a gradient between 1st and 2nd generation DES, through BMS. Second, compared to 1st generation DES, were associated with further relative risk (RR) reduction of −18% in of all-cause death, and lower incidence of stent-related clinical events: −39% RR of ST risk; −27 RR of TVR/TLR risk.

Conclusions: DES in CKD patients undergoing PCI were superior to BMS in reducing major adverse clinical events. This was possibly explained, by a lower risk of stent-related events as ST and TVR or TLR. Second, compared to 1st generation DES may furtherly reduce clinical events.

KEYWORDS
chronic kidney disease, coronary stents, network meta-analysis, randomized trial, thrombosis

1 | INTRODUCTION

Chronic kidney disease (CKD) is a prevalent risk factor for cardiovascular disease (CVD). Of note, CKD patients are more likely to die from CVD complications than to develop end-stage kidney failure.[1,2] In addition, CKD patients have increased risk of stent-related complications when treated with percutaneous coronary interventions (PCI) such as stent thrombosis (ST) and target lesion/vessel revascularization (TLR/TVR). In facts, ST

occurs more likely in CKD patient as compared with non-CKD patients, with consistent hazard ratios, up to 6.5.[3] With this background, in the 1st generation drug eluting stents (DES) era, following the general ST warning with DES, the European Society of Cardiology (ESC) Guidelines for myocardial revascularization (2010), discouraged the systematic use of DES CKD patients.[4] This statement was then mitigated by the following release of ESC Guidelines in 2014,[5] when the use of 2nd generation took over 1st generation DES. However, the evidence to support this shift of recommendation, was coming mostly from retrospective registries[6,7] and by a confident generalization in CKD patients of data which favor of 2nd generation DES in the overall population. No specific recommendations in this subset of patients are provided by American Heart/College guidelines.

Importantly, CKD patients, are systematically excluded or under-included by randomized controlled trials (RCT), therefore the evidence to guide stent type implantation in these specific population is scarce, albeit needed.

We reported, in a cohort of CKD patients out of the PRODIGY study, that 2nd generation, limus-based DES, should be favored over 1st generation paclitaxel-based DES or bare-metal stents (BMS) to reduce ST and improve outcome.[8] The objective of this manuscript is to perform a systematic review of all the evidence available in CKD patients undergoing PCI and to meta-analyze clinical outcome according to stent type (BMS vs DES). For this purpose, primary outcome was all-cause mortality. We also collected the following secondary outcome: composite of all-cause mortality and recurrent myocardial infarction (MI); cardiovascular mortality; stent-related complications such as ST and TVR/TLR; we also include direct and indirect comparisons of clinical outcome between 1st generation DES, 2nd generation DES and BMS in a network meta-analysis design.

2 | METHODS

2.1 | Study outcome and eligibility criteria

We searched articles including both stent-related outcome and long term clinical events in patients with CKD, defined by eGFR < 60 mL/min (either Cockroft-Gault or MDRD formula), studies including *only* patients on permanent haemodialysis were excluded. Eligibility criteria are summarized in Table 1. Randomized clinical trials (RCT), post-hoc analysis and observational longitudinal studies were considered. 1st generation DES were defined as eluting sirolimus (Cypher) or paclitaxel based (Taxus), 2nd generation DES were defined as eluting everolimus, zotarolimus or other DES with resorbable polymer.

2.2 | Search strategies and article classification

PubMed, Cinhal, Cochrane, Embase, and Web of Science were searched for eligible articles on May 30th, 2017, supplementary Table S1. Research strategies and keywords are outlined in supplementary Table S2. Also, additional articles were retrieved from the reference lists and a citation analysis was performed to identify newer studies that had cited older ones. The librarian (VS) examined titles and abstracts and classified them as "to be included," "to be excluded," and "to be decided upon," based on the eligibility criteria and the keywords used. Two junior interventional Cardiologists (VG and VG) reviewed full text articles independently to check eligibility criteria. Final decision to include was made by consensus between an experienced Interventional Cardiologist (GC) and a Biostatisticians (CK).

2.3 | Systematic review

Articles full text were retrieved. Reasons for non-inclusion were reported. The quality of the studies was rated based upon adherence to the CONSORT (for controlled clinical trials) and STROBE (for observational studies) statements as well as the GRADE and AHRQ guidelines. The biostatistician and cardiologists retrieved separately the quantitative information for outcomes and patient's characteristics (clinical and angiographic) from the selected articles. Whenever discrepancy was noted, it was reconciled by consensus between them.

TABLE 1 Clinical and procedural variables of studies included

Variable	BMS *n* = 35,807	DES overall[a] *n* = 40 750
Follow-up time (months)	24 [12-36]	
Age (years)	73 [70-76]	71 [70-74]
Male gender (% of pts)	60 [48-77]	56 [50-73]
Diabetes (% of pts)	40 [33-43]	41 [33-49]
Left ventricular ejection fraction (%)	51 [49-53]	51 [50-52]
Estimated glomerular filtration rate (ml/min)	46 [44-48]	45 [43-47]
Haemodialysis (% of pts)	9 [0-10]	16 [0-27]
Acute coronary syndrome (% of pts)	66 [51-86]	67 [55-79]
ST-elevation myocardial infarction (% of pts)	23 [17-61]	20 [14-70]
Multivessel disease (% of pts)	59 [46-70]	58 [43-72]
Total stent length (mm)	22 [21-28]	25 [23-29]

Data are displayed as median of percentage [interquartile range].
[a]Follow-up time is the same for both group.

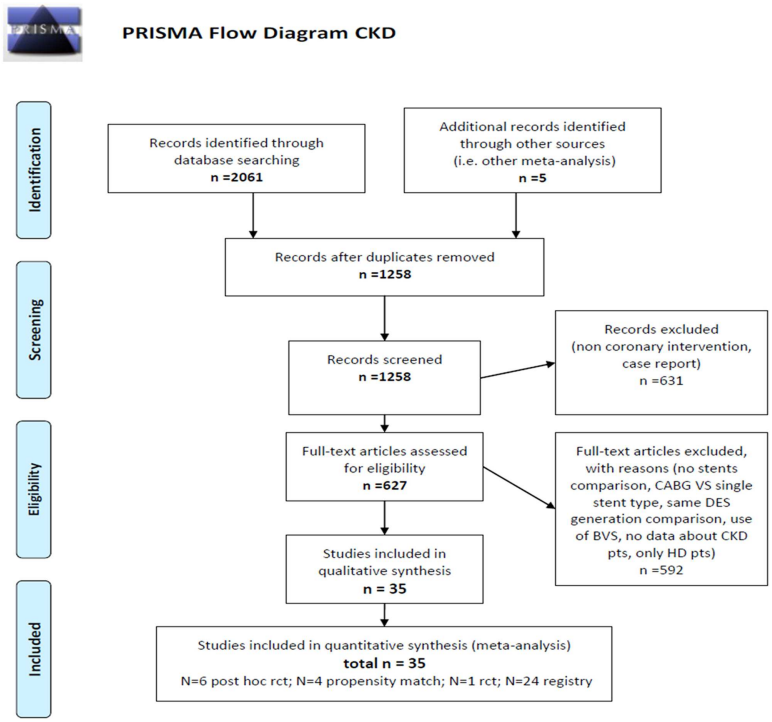

FIGURE 1 PRISMA flow diagram

2.4 | Statistical analysis

The PRISMA and MOOSE guidelines for meta-analysis, as well as the Cochrane manual, were used. The review included retrospective studies with unadjusted estimates of the relative risk (RR), adjusted by multivariable regression or propensity score analysis, and RCTs. Primary outcome was the incidence of all-cause death; among secondary outcome, we included: the composite endpoint of death and MI, MI alone, ST, TLR, or TVR and death for cardiovascular cause. Outcome of interest were compared using a person-year approach between patients receiving BMS or DES in the meta-analysis and between patients receiving 1st generation DES, 2nd generation DES and BMS in the network meta-analysis. Patient characteristics were summarized over studies with the median and 25th-75th percentiles. Within each study, the adjusted relative risk (RR) with its 95%CI for each categorical outcome, was retrieved from the articles. For the analysis of the secondary populations the RR was either retrieved from the articles or calculated from the available data. Finally, study RRs were then pooled according to the DerSimonian and Laird random effects models. Statistical heterogeneity was evaluated by the Cochran Q test and measured by the I-squared statistic. The meta-analytic estimates were computed both by design and overall. The following study designs were considered: registries, cohort studies with propensity score matching, post-hoc RCT and RCT. Two sensitivity analyses on outcome of interest were performed: a "leave-one-out" meta-analysis to confirm that no study had a major influence on the overall estimate and a meta-regression to confirm that no study/patient characteristic had a major influence on the overall estimate. The following potential confounders were assessed: prevalence of patients on dialysis, gender, age, diabetes, eGFR, acute coronary syndrome and, total stent length.

Finally, an exploratory network meta-analysis was performed to make use of the indirect comparisons of 1st generation DES and 2nd generation DES through BMS. A consistency test between direct and indirect estimates was performed. Stata 14 (StataCorp, College Station, TX) was used for computation.

3 | RESULTS

3.1 | Bibliographic search and identification of articles

We retrieved 2066 articles from online databases between 2005 and May 2017. After excluding 808 records which were included in more than one database, we screened 1258 abstracts and 627 full-text for eligibility. We included in the review and meta-analysis 35 articles, of which 1 RCT, 6 post-hoc analysis of RCT, 4 propensity matched analysis and 24 retrospective registries (Figure 1).

3.2 | Study design and population

The final population included 376 169 patients of which 76 557 patients with CKD who received BMS (35 807) or DES (37 650 1st generation and 3100 2nd generation DES). Patients characteristics were well matched between the groups as it is shown in Table 2, we only found a higher prevalence of patients in permanent haemodialysis in the DES group as compared to patients receiving BMS. Median

TABLE 2 Clinical outcome

Study	BMS vs DES 1	BMS vs DES 2	DES 1 vs DES 2	All-cause death	Death or MI	MI	ST	TVR or TLR	Death cardiovascular cause
Studies including 1st generation DES									
Appleby[40]	X			X					
FRIST[19]	X			X	X	X	X	X	X
Kim[20]	X							X	
Resmini[21]	X			X	X	X	X	X	
Rodriguez-Capitain[22]	X			X	X	X		X	
Simsek[23]	X			X	X		X	X	
Tsai[7]	X			X	X	X			
Bhatt[24]	X			X				X	
Charytan[25]	X			X	X	X		X	
Green[26]	X			X	X	X			
HORIZONS_AMI 2011[27]	X			X	X	X	X	X	
KAMIR[28]	X			X				X	
Shenoy[6]	X			X		X	X		
SIRIUS[29]	X			X	X	X	X	X	X
Na[30]	X			X	X	X		X	X
Rosenblum[31]	X							X	
Jeong[32]	X			X	X	X		X	X
Shaw[33]	X			X					
Kuchulakanti[34]	X			X	X	X		X	
Zhang[35]	X			X	X	X		X	X
Lemos[36]	X							X	
TAXUS IV 2005[37]	X			X	X	X		X	X
Studies including 1st and 2nd generation DES									
Wang[38]	X	X						X	
Wanha[39]			X	X					
Barthelemy[41]	X	X					X	X	X
Baber[11]			X	X	X	X	X	X	X
Naito[12]	X	X		X		X			
PRODIGY post-hoc 2016[8]	X	X	X	X	X	X	X	X	
Kitasato[13]			X			X		X	X
Siddiqi[15]	X			X	X				
Chan[16]			X	X					
BASKET PROVE 2013[17]	X	X		X	X	X	X	X	X
Ahmed[18]	X	X	X	X	X	X	X	X	X
Studies including 2nd generation DES									
LEADERS FREE 2015[11]		X			X		X	X	
RENAL DES 2014[14]		X		X			X	X	

TABLE 3 Network meta-analysis consistency table (direct and indirect effects and comparison with the test of consistency)

		Direct		Indirect		Difference		Test of consistency
Endpoint	Side^	RR	SE	RR	SE	RR	SE	P>z
All-cause Death	BMS vs 1st DES	0.83	1.10	0.66	1.79	1.25	1.80	0.982
	BMS vs 2nd DES	0.57	1.36	0.77	1.31	0.74	1.51	0.716
	1st DES vs 2nd DES	0.82	1.24	0.81	1.58	1.02	1.66	0.841
Death OR	BMS vs 1st DES	0.81	1.12	0.73	1.93	1.09	1.95	0.892
Myocardial	BMS vs 2nd DES	0.59	1.34	0.75	1.48	0.79	1.63	0.635
Infarction	1st DES vs 2nd DES	0.86	1.32	0.68	1.52	1.26	1.65	0.650
Stent thrombosis	BMS vs 1st DES	0.68	1.31	0.80	2.20	0.85	2.32	0.852
	BMS vs 2nd DES	0.13	1.45	0.77	1.77	0.45	1.99	0.249
	1st DES vs 2nd DES	0.61	1.48	0.63	1.92	0.96	2.05	0.953
Target Vessel	BMS vs 1st DES	0.74	1.13	0.81	1.70	0.91	0.00	0.868
OR Lesion	BMS vs 2nd DES	0.67	1.31	0.50	1.46	1.35	1.60	0.519
Revascularization	1st DES vs 2nd DES	0.73	1.32	0.97	1.43	0.74	1.58	0.511

Legend: direct and indirect effects and comparison with the test of consistency; coefficient from the regression model are exponentiated to provide RR, BMS was used as reference.
*Warning: all the evidence about these contrasts comes from the trials which directly compare them.

follow-up time across the studies was 24[12–36] months. The clinical outcome of interest were outlined in Table 3 and shown in Figure 2. A detailed report of different MI definitions as reported by each study is provided in supplementary Table S4.

3.3 | Primary outcome

Patient receiving DES had a significant 18% lower incidence of all-cause mortality (95% confidence interval 6% to 29% lower in DES) compared to patients receiving BMS as it is shown in Figure 3.

3.4 | Secondary outcome

The composite of death or MI was significantly reduced in DES patients (random effect, RR 0.78, 95%CI 0.67-0.91), as it is shown in Figure 4. Stent related outcome as ST was significantly lower in DES group (random effect, RR 0.57, 95%CI 0.34–0.95), (Figure 5), as it was TVR/TLR (random effect, RR 0.69, 95%CI 0.57-0.84) (Figure 6). When we explored death for cardiovascular cause we found a significant reduction in DES receiving patients (random effect, RR 0.43, 95%CI 0.25-0.74) (Figure 7). MI alone was not significantly reduced in DES patients as compared with BMS patients (random effect, RR 0.92, 95% CI 0.74-1.15) (Figure 8).

Importantly, we did not find any evidence of publication bias (data not shown).

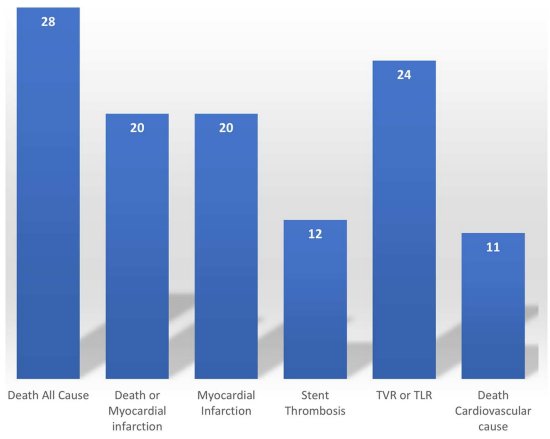

FIGURE 2 Collected outcomes

3.5 | Outcome and network meta-analysis

Results from the network meta-analysis design are summarized in Table 3. These results confirmed a lower incidence of all cause death, death or MI, TVR or TLR and ST when 1st generation or 2nd generation DES are separately compared to BMS. Interestingly, we found a gradient of effect between 1st and 2nd generation DES on clinical outcome. Second generation as compared with 1st generation DES are associated with further relative risk (RR) reduction of −18% (−19% indirect estimate) in of all-cause death, and lower incidence of stent-related clinical events: −39% RR (−37% indirect estimate) of ST risk; −27% RR (−3% indirect estimate) of TVR/TLR risk. The estimate of direct and indirect effects did not differ substantially, showing consistency of estimates. This also suggested a low impact of time-bias, since indirect estimate include patients enrolled in different time-points.

3.6 | Sensitivity analyses

The "leave-one-out" analysis confirmed that no study had a major influence on the overall estimate of clinical outcome. Similarly, the meta-regression

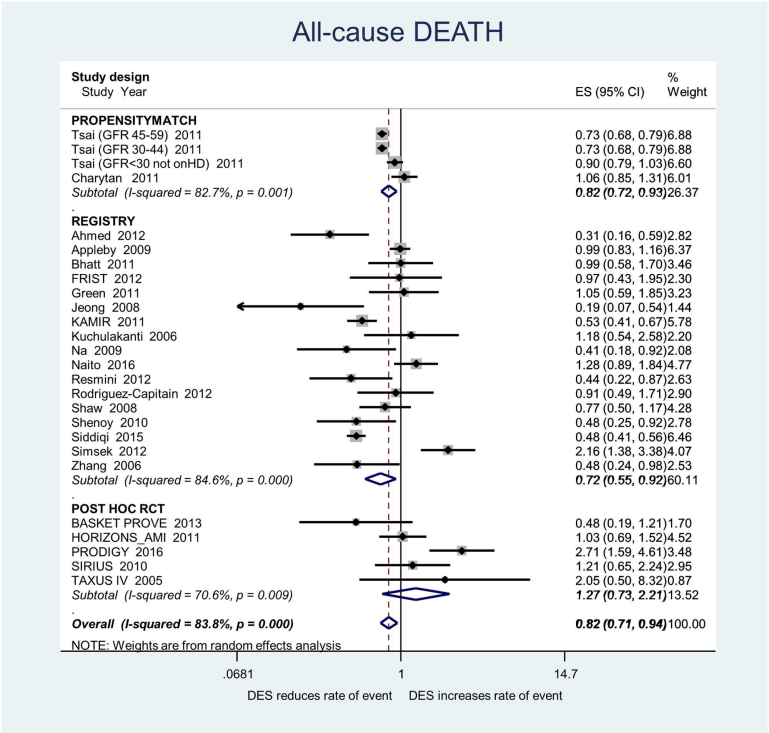

FIGURE 3 Primary outcome, all cause death

including study design as potential confounder. Among baseline characteristics and risk factors, the prevalence of haemodialysis, diabetes, acute coronary syndrome, median eGFR, stent length and age, did not have significant influence on any clinical outcome explored. However, we found that prevalence of male and acute coronary syndrome patients were potential confounders of the composite endpoint of all cause death or MI. We found no effect of male or acute coronary syndrome prevalence on all-cause death as on other explore outcomes.

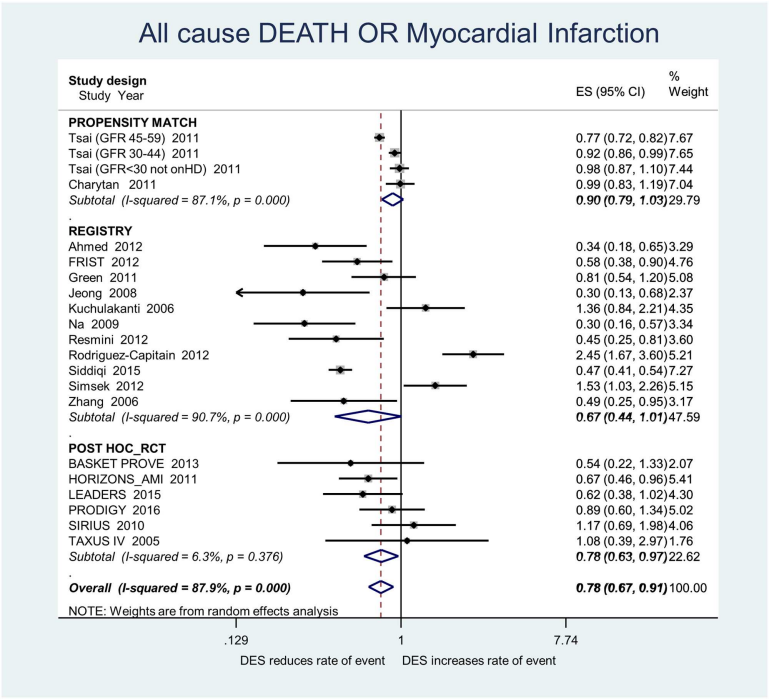

FIGURE 4 Secondary outcome, death or myocardial infarction

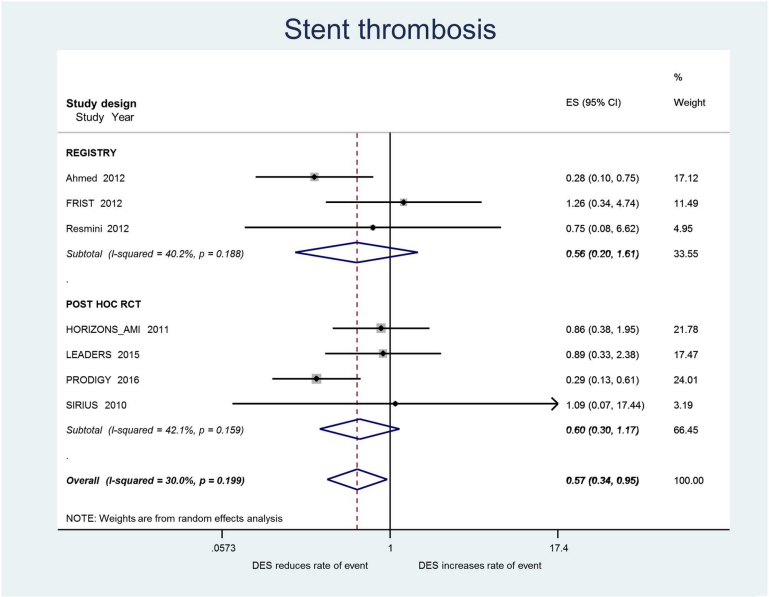

FIGURE 5 Secondary outcome, Stent thrombosis

4 | DISCUSSION

The main findings of the present meta-analysis, including 35 studies and 76 557 CKD patients receiving stent implantation, may be summarized as follows: (1) the use of DES is superior to BMS in reducing clinical events with 18% lower all-cause mortality and 22% lower risk of the composite of death OR MI; (2) this is supported, possibly explained, by a lower RR of stent-related events as ST (−43%), TVR/TLR (−31%) and death for cardiovascular cause (−57). (3) In the network design, we found that 2nd generation as compared with 1st generation DES, are associated with a further reduction in clinical events: −18% RR for all-cause mortality and −39% RR for ST. This finding extends that reported by Palmerini et al,[9] to the specific subset of CKD patients. In facts, Palmerini's meta-analyses included RCT

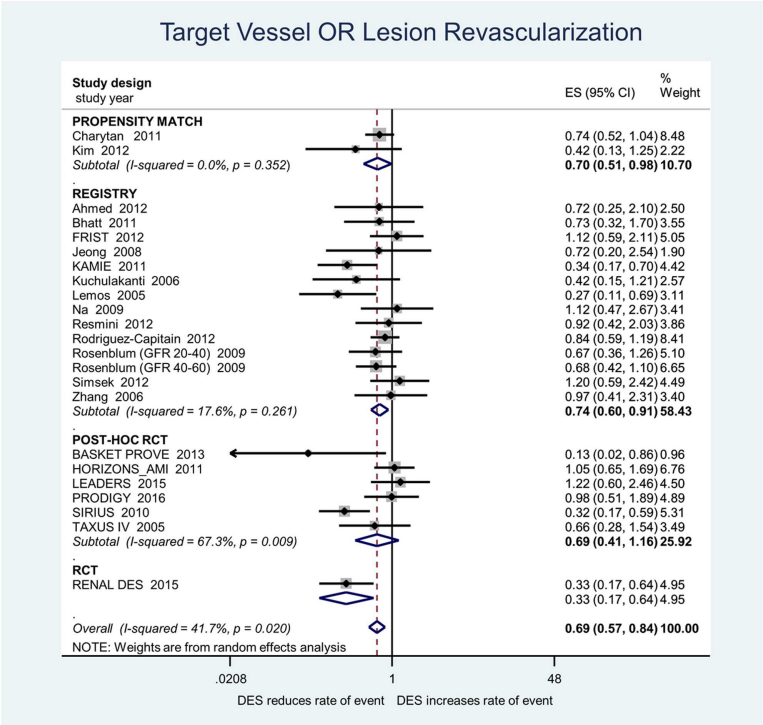

FIGURE 6 Secondary outcome, target lesion revascularization or target vessel revascularization

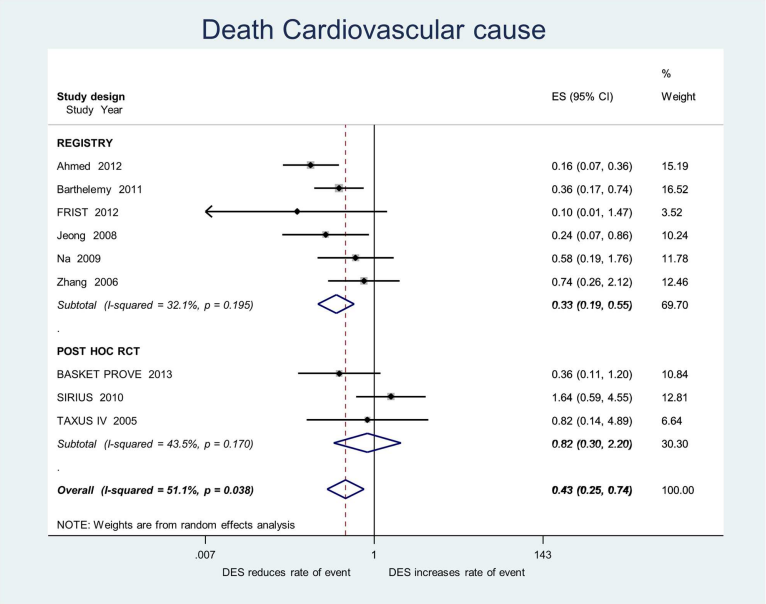

FIGURE 7 Secondary outcome, death for cardiovascular cause

comparing DES vs BMS. Importantly, RCT systematically excluded or rather under-included CKD patients, thus, our meta-analysis may cover the evidence gap to guide stent choice in CKD patients undergoing PCI. Of note, the network meta-analysis, support ESC guidelines shift of recommendation in CKD patients, from the 2010 version[4] in which it was suggested: ". . .there is only weak evidence that DES are superior to BMS .." to the 2014 version[5]: ". . . newer generation DES should be preferred over BMS.". DES superiority over BMS in stent-related events is even more important in CKD patients than non-CKD patients, since they are higher risk population with up to six times higher risk to develop a ST in their follow-up.[3] Thus, a relative risk reduction of 43% with DES in this subset, possibly even lower with newer DES, may translate into a sizeable survival improvement in CKD patients with lower number needed to treat than the overall population.[8]

There are two main reasons to explain why DES are superior to BMS in CKD patients: (1) a direct effect of stent design, which include polymer and drug; (2) an indirect effect of prolonged double

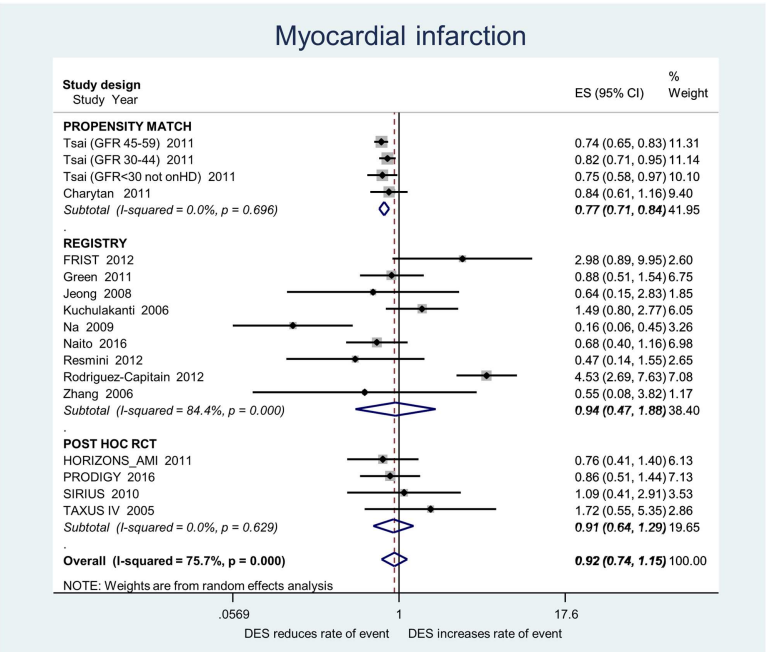

FIGURE 8 Secondary outcome, myocardial infarction

antiplatelet therapy (DAPT) usually indicated in stable patients receiving DES; both may act synergistically to reduce clinical events.

CKD patients associated with higher atherosclerotic burden, diffuse coronary disease, and calcification which may also be associated to sub-optimal mechanical stent result as malaposition, under-expansion, or fracture. In such difficult PCI candidates, DES versus BMS may reduce neo-intimal hyperplasia which is linked to major adverse clinical events and ST. In addition, 2nd generation DES with thinner struts, lower metal to vessel ratio, more biocompatible polymers, less polymer mass, and limus-based antiproliferative drugs may further reduce local inflammation, delayed endothelization, and explain the lower incidence of stent-related complications as ST, TVR/TLR and major cardiovascular events as compared to 1st generation DES, Table 3.

Interestingly, we found that acute coronary syndrome prevalence, by meta-regression, is a potential confounder on death OR MI endpoints. This may be also explained by the use of prolonged DAPT in acute coronary syndrome, which is not guided by stent type and may blunt the effect of DES versus BMS on clinical outcome. Renal impairment in CKD is *per se* associated with systemic persistent inflammation and endothelial dysfunction; furthermore, CKD patients are often affected by multiple risk factors such as diabetes. Indeed, median prevalence of diabetes was 40% which is consistently higher than that usually reported in RCT. In this respect, CKD represent a subset of patients that may benefit of prolonged DAPT after PCI, regardless of stent type. Although this issue was not directly addressed by our meta-analysis, prolonged DAPT is usually more likely prescribed in patients receiving DES as compared to BMS implantation. In a recent publication from the SWEDEHEART registry, Carrero et al demonstrated that prolonged, as compared to 3 months DAPT, was associated with lower risk of death, stroke, or reinfarction, regardless of underlying CKD.[10] On the contrary, Valgimigli et al[2] in a post-hoc analysis of the PRODIGY trial, showed that prolonged DAPT did not reduce major adverse cardiovascular events, but this finding was again consistent between CKD and non-CKD patients. While optimization of DAPT duration to harmonize thrombotic and bleeding risk in CKD patients is still a matter of controversy, the present meta-analysis support, in indicated CKD PCI candidates, systematic use of newer generation DES.

5 | LIMITATIONS

Studied including CKD patients in permanent haemodialysis and after kidney transplantation are excluded from our meta-analysis. Specifically, haemodialysis define end-stage CKD patients with severe metabolic impairment and altered drug kinetics which may also impact outcome, therefore the reason to exclude these patients, is to focus on the most homogeneous and prevalent CKD population.

The studies included used different MI definitions, this may partly explain heterogeneity across the studies and should be considered for generalizations, a detailed outline of MI defintions is shown in supplementary Table S4.

We may not exclude a time bias to explain superiority of 2nd gen DES over 1st gen DES, especially on indirect comparisons, as trials comparing 2nd gen DES are more contemporary, with improved medical facilities, medical treatments, use of new antiplatelet agents, and interventional strategies. However direct and indirect effect are consistent as reported in Table 3.

CKD patients with stable or acute coronary syndrome often present with multivessel disease, in this clinical setting, international guidelines recommend to consider myocardial revascularization with coronary artery bypass grafting rather than PCI. We acknowledge that CABG treated CKD patient are not included for comparison in the present meta-analysis.

6 | CONCLUSIONS

The use of DES in CKD patients undergoing PCI is superior to BMS in reducing major adverse clinical events such as all-cause mortality and the composite of death or MI. This is supported and possibly explained, by a lower risk of stent-related events such as ST and TVR/TLR. Second generation DES may further reduce clinical events as compared to 1st generation DES and should be considered the first choice in CKD patients with indication to PCI.

CONFLICTS OF INTEREST

All authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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