

Drug-eluting compared to bare metal stents in patients with end-stage renal disease on dialysis: a meta-analysis

Vincenzo Alessandro Galiffa^{a,b}, Gabriele Crimi^a, Valeria Gritti^a, Valeria Scotti^c, Maurizio Ferrario^a, Alessandra Repetto^a, Marco Ferlini^a, Barbara Marinoni^a, Gaetano Maria De Ferrari^d, Stefano De Servi^e, Angelo Sante Bongo^b, Luigi Oltrona Visconti^a and Catherine Klersy^f

Aims To systematically review literature comparing bare metal stent (BMS) to drug-eluting stent (DES) in end-stage renal disease (ESRD) patients on dialysis. ESRD patients on dialysis often suffer from accelerated atherosclerosis and higher rate of stent-related complications including major adverse cardiovascular events. Because dialysis usually qualifies ineligibility for randomized clinical trials, an evidenced-based stent choice for these patients is scarce.

Methods PUBMED, CINHAL, COCHRANE, EMBASE and WEB OF SCIENCE were searched for studies comparing BMS vs. DES outcome in ESRD patients on dialysis.

Results Twenty studies including 64 232 patients were considered. The use of DES was significantly associated with a reduction in all-cause mortality [odds ratio (OR) 0.83, 95% confidence interval (CI) 0.76-0.89], death from a cardiovascular cause (OR 0.80, 95% CI 0.76-0.84) and target lesion revascularization/target vessel revascularization (OR 0.73, 95% CI 0.53-1.00). No significant difference was found in stent thrombosis (OR 1.08, 95% CI 0.50-2.33) and myocardial infarction incidence (OR 0.91, 95% CI 0.69-1.20).

Conclusions Our meta-analysis shows a significant reduction in all-cause and cardiovascular mortality with the use of DES over BMS in dialyzed patients. Despite the lack of randomized studies, systematic use of DES in these highrisk patients should thus reasonably be considered as a first option in percutaneous coronary intervention candidates.

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Keywords: Stents, DES, dialysis, renal failure

^aDivision of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, ^bCoronary Care Unit and Catheterization Laboratory, A.O.U. Maggiore della Carità, Novara, ^cCenter for Scientific Documentation, ^dCoronary Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, ^eIRCCS Multimedica, UO Cardiologia, Sesto San Giovanni, Milan and ^fService of Clinical Epidemiology and Biostatistic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Correspondence to Gabriele Crimi, MD, S.C. Cardiologia – Fondazione IRCCS Policilinico San Matteo, Viale Golgi 19, 27100 Pavia, Italy Tel: +39 0382 50 1598; fax: +39 0382 50 3159; e-mail: qabrielecrimi@qmail.com

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Introduction

About 50% of patients with an end-stage renal disease (ESRD) present asymptomatic coronary artery disease (CAD) at the beginning of a renal replacement therapy¹; furthermore, dialysis itself is associated with atherosclerosis progression and cardiovascular complications. Several factors may contribute to this condition: coprevalence of other cardiovascular risk factors, including diabetes mellitus, impaired calcium/phosphate metabolism, endothelial dysfunction caused by chronic inflammation and chronic oxidative stress given by renal replacement therapy. As a result, ESRD patients on dialysis often present multivessel atherosclerosis, small diffused obstructive disease and severe calcification, which challenge percutaneous coronary intervention (PCI) management,² leading to increased risk of stentrelated complications, 3,4 including restenosis and stent thrombosis.⁵ Finally, ESRD patients have an impaired and unpredictable antithrombotic drugs metabolism, which can lead both to ischemic or bleeding complications. In this setting, prolonged double antiplatelet therapy required after drug-eluting stent (DES) implantation could be a matter of concern. As a matter of fact, after an initial enthusiasm in DES use to reduce restenosis, some safety issues were raised for this highrisk population. Considering the increased risk of stent thrombosis as potentially outweighing the reduced risk of restenosis, in the 2010 European Society of Cardiology guidelines, routine use of DES over bare metal stents (BMS) was discouraged in patients with ESRD receiving dialysis. This recommendation was reformulated when second-generation DES took over, although based on poor specific evidence. It is also noteworthy the fact that no recommendations in this subset of patients are provided by American Heart/College guidelines.

Because patients on dialysis have been under-included or rather excluded from large randomized clinical trials, there is no randomized trial validating stent-type choice in these patients.¹⁰

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The main aim of this study is to systematically review the evidence in ESRD patients on dialysis undergoing PCI and to perform a meta-analysis of clinical events focused on all-cause mortality and stent-related complications according to stent type (BMS vs. DES).

Methods

Study endpoints and eligibility criteria

The PRISMA (Providing Innovative Service Models and Assessment) and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines for meta-analysis, and also the Cochrane manual, were used to design this study. The main focus of our analysis was both stent-related events and mid- to long-term clinical events in patients with ESRD on dialysis. The primary endpoint of the study was the rate of all-cause death; the secondary endpoints were death from a cardiovascular cause, myocardial infarction (MI), and stent-related outcomes such as stent thrombosis, target lesion revascularization (TLR) or target vessel revascularization (TVR). For the endpoint TLR/TVR: when both were available, we included TLR as more specific for stent failure; if no data were reported about TLR, we included TVR.

Eligibility criteria for study inclusion were: randomized controlled trial (RCT), post-hoc analysis of RCT or cohort studies; use of BMS, first-generation and second-generation DES in ischemic patients with coronary obstructive disease undergoing PCI. Both patients on hemodialysis and on peritoneal dialysis were considered (see Supplementary Table 1, http://links.lww.com/JCM/A153). Furthermore, we systematically reviewed and included registries of patients with chronic kidney disease^{8,13} in which authors provided separate outcomes of patients on dialysis.

Search strategies and article classification

PUBMED, CINHAL, COCHRANE, EMBASE and WEB OF SCIENCE were searched for eligible articles on 30 May 2017. Research strategies and keywords are outlined in Supplementary Table 2 (http://links.lww.com/JCM/A153). Furthermore, additional articles were retrieved from the reference lists of eligible studies and relevant review articles; finally, a citation analysis was performed to identify newer studies that had cited older ones. A librarian (V.S.) examined all the titles and abstracts, and classified them into the following three categories: 'to be included,' 'to be excluded' and 'to be decided upon,' based on the eligibility criteria and the keywords used. A junior interventional cardiologist (V.A.G.) and a clinical fellow (V.G.) independently reviewed full-text articles to check eligibility criteria and worked in duplicate using a standardized form to abstract data from each study. Our final decision to include the articles in the review was made by consensus with an experienced interventional cardiologist (G.C.).

Systematic review

Article full texts were further examined by a biostatistician (C.K.), who classified them as eligible or not eligible for meta-analysis. Reasons for noninclusion were reported. The quality of the studies was rated upon adherence to the STROBE (for observational studies) statements, and also the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) and AHRQ (Agency for Healthcare Research and Quality) guidelines. The biostatistician and the cardiologists separately retrieved the quantitative amount of information for outcomes and patient characteristics (clinical and angiographic) from the articles selected. Whenever discrepancy was noted, it was reconciled by consensus.

Statistical analysis

The review included retrospective studies with unadjusted estimates of the relative risk (RR), adjusted by propensity score analysis, and RCTs. Study endpoints were compared between patients receiving BMS or DES, and a person-year approach was used to address different follow-up time. Patient characteristics were summarized over studies with median and 25th-75th percentiles. Within each study, the adjusted RR with its 95% confidence interval (CI) for each categorical outcome, and standardized mean difference (SMD) with its 95% CI for continuous variables, was retrieved from the articles. Finally, study RRs were pooled according to the Der-Simonian 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 study design and overall. The following study designs were considered: registry, cohort with propensity score matching, post-hoc randomized clinical trials and clinical trials. Two sensitivity analyses of the primary endpoint were performed: a 'leave-one-out' meta-analysis to confirm that no study had a major influence on the overall estimate and a metaregression to confirm that no study/patient characteristic had a major influence on the overall estimate. The following potential confounders were assessed: design, prevalence of patients on dialysis, sex, age, diabetes, acute coronary syndrome (ACS), and total stent length. Funnel plots and test for small sample bias were performed. The analysis was performed using Stata 14 (StataCorp, College Station, Texas, USA); P < 0.05 was considered statistically significant.

Results

Bibliographic search and identification of articles

We identified 2061 potentially relevant articles in different online databases and 5 additional articles from references of reviews and meta-analysis uploaded between 2005 and 2017. After removing duplicates, we screened 1258 abstracts and 627 full texts for eligibility. Twenty articles meeting criteria were included in the review and meta-analysis, made up of 1 post-hoc analysis of RCT,

Clinical and procedural variables of studies included

Variable	BMS (n = 20 757)	DES (n = 26 370)
Age (years)	64 [63-66]	65 [64-66]
Male sex (%)	67 [59-72]	66 [60-74]
Diabetes (%)	63 [57-69]	64 [58-74]
Left ventricular ejection fraction (%)	52[49-57]	53 [49-56]
Time from beginning of dialysis (months)	80 [67-82]	80[69-126]
Acute coronary syndrome (%)	56 [31-69]	54 [29-64]
ST-elevation myocardial infarction (%)	7 [2-9]	6 [4-7]
Multivessel disease (%)	67 [44-75]	80 [34-86]
Total stent length (mm)	20 [19-22]	28 [22-29]

Data are displayed as median [interquartile range]. BMS, bare metal stent; DES, drug-eluting stent.

3 propensity-matched analysis and 16 retrospective registries (Supplementary Fig. 1, http://links.lww.com/JCM/ A153).

Study design and population

Final population included a total of 64232 patients on dialysis, 20757 receiving BMS and 26370 receiving DES. The characteristics of patients were well matched between the groups (see Table 1), except for prevalence of multivessel CAD [67% BMS patients vs. 80% DES patients; P = 0.03 and stent length in DES group (28 vs. 20 mm; P < 0.01)]. Median follow-up time [interquartile range] across the studies was of 12 [12–27] months.

Outcome and meta-analysis

The primary endpoint of all-cause mortality was reported in 18 of the included studies (see Supplementary Table 3, http://links.lww.com/JCM/A153). Definitions of MI and stent thrombosis across the studies are included in Table 2.

Drug-eluting stent-treated patients had a significant 17% lower incidence of all-cause mortality as compared with patients receiving BMS (random effect: OR 0.83, 95% CI 0.76-0.89; Fig. 1). Moreover, they had a significant reduction in cardiovascular death (OR 0.80, 95% CI 0.76-0.84; Fig. 2) and TLR/TVR incidence (OR 0.73, 95% CI 0.53–1.00; Fig. 3). No significant difference was found in stent thrombosis (OR 1.08, 95% CI 0.50-2.33; Supplementary Fig. 2, http://links.lww.com/JCM/A153) and MI incidence (OR 0.91, 95% CI 0.69-1.20; Supplementary Fig. 3, http://links.lww.com/JCM/A153).

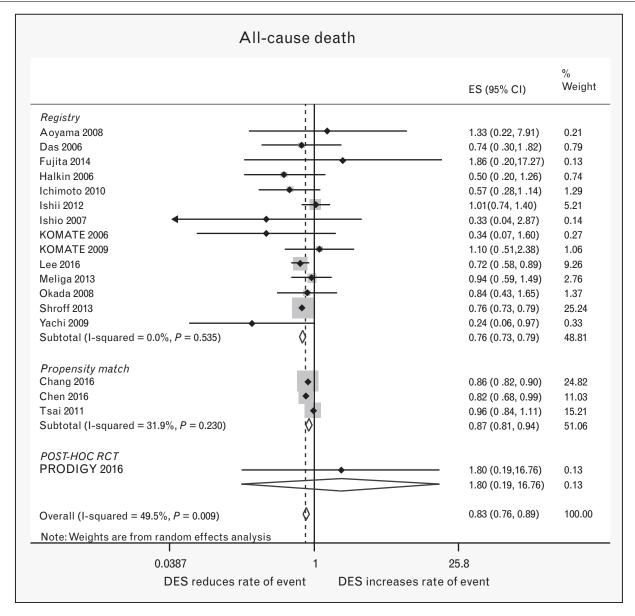
Sensitivity analyses

No study had a major influence on the overall estimate of clinical outcome when performing the 'leave-one-out' meta-analysis. Among baseline characteristics and risk factors the meta-regression showed a significant role of type 2 diabetes on MI and TLR/TVR as potential confounders, but no effect on the other explored outcomes. Moreover, the prevalence of male, ACS, ST-elevation myocardial infarction (STEMI), multivessel disease, age, left ventricular ejection fraction (LVEF) and time from dialysis beginning has not significantly influenced any of the clinical outcomes explored. Funnel plots to assess publication bias are reported in the supplemental material together with the corresponding test for small samples (Supplementary Figs. 4 and 5, http://links.lww.com/JCM/ A153).

Table 2 Outcome definitions across the studies

Study	Year	Patients	MI definition	ST definition
Aoyama et al.16	2008	166	Not reported	Not reported
Chang et al.17	2016	36 117	Primary diagnosis for hospital admission (ICD-9-CM)	· _
Chen et al.18	2016	984	Primary diagnosis for hospital admission (ICD-9-CM)	_
Das et al.19	2006	69	I Universal Definition of MI	_
Fujita <i>et al.</i> ²⁰	2014	94	ST-segment changes in two contiguous ECG leads; $2\times$ upper limit CK-MB elevation	-
Halkin et al.21	2006	74	I Universal Definition of MI	_
Ichimoto et al.22	2010	108	New pathological Q wave or $3\times$ upper limit CK-MB elevation	ACS with angiography or autopsy evidence of thrombus or occlusion
Ishii et al. ²³	2012	505	ST-segment changes in two contiguous ECG leads; $2\times$ upper limit CK-MB elevation	ARC definite or probable ST
Ishio et al. ²⁴	2007	108	New pathological Q wave or 3× upper limit CK-MB elevation	Not reported
Kim et al. ²⁵	2016	2835	ICD-9-CM diagnostic code	· _
KOMATE ²⁶	2006	92	Not reported	_
KOMATE ²⁷	2009	105	New pathological Q wave or 3× upper limit CK-MB elevation post-PCI or chest pain with CK-MB elevation	ARC definite or probable ST
Meliga et al.28	2013	169	New pathological Q wave or 3x upper limit CK-MB elevation	ARC definite or probable ST
Okada <i>et al.</i> ²⁹	2008	204	3× upper limit CK-MB elevation	ACS with angiographic evidence of thrombus or occlusion
PRODIGY ³⁰	2016	24	II Universal Definition of MI	ARC definite or probable ST
Rosenblum et al.13	2009	294	_	· <u>-</u>
Shroff et al.31	2013	16 855	_	_
Suzuki <i>et al.</i> ³²	2007	124	_	_
Tsai et al.8	2011	5182	ICD-9-CM	_
Yachi et al.33	2009	123	ST-segment changes in two contiguous ECG leads; $2\times$ upper limit CK-MB elevation	ARC definite or probable ST

ACS, acute coronary syndrome; ARC, Academic Research Consortium; CK-MB, Creatinine Kinase Myocardian Band; KOMATE, Korean Multicenter Angioplasty Team; MI, myoicardial infarction; PCI, percutaneous coronary intervention; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia study; ST, stent thrombosis; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.



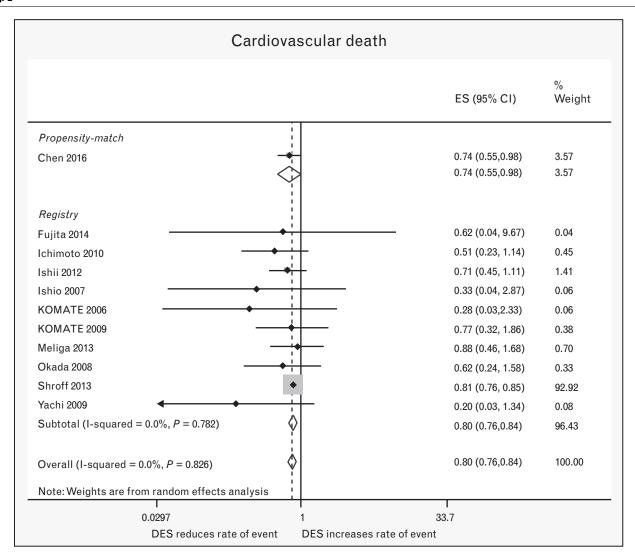
All-cause death.

Discussion

End-stage renal disease patients on dialysis are ineligible for most RCTs, thus resulting in a lack of evidence in stent type choice for this population. In this setting, our meta-analysis gathered data from 20 observational studies and more than 64 000 real-life patients, showing that the use of DES over BMS was associated with a reduction in all-cause mortality by 17%, death for cardiovascular cause by 20% and in-stent restenosis TLR/TVR by 27%. No differences were found in incidence of stent thrombosis and MI.

We suppose that mortality reduction, in particular cardiovascular death, in patients receiving DES, could be related to a lower incidence of stent failure. Although stent failure and restenosis are not usually lethal events, in these complex patients with high prevalence of multivessel disease and narrow vessels, restenosis may be linked to major adverse cardiovascular events and mortality.

In fact, patients on dialysis are no longer able to regulate their hydro-electrolytic, acid-base and hemodynamic



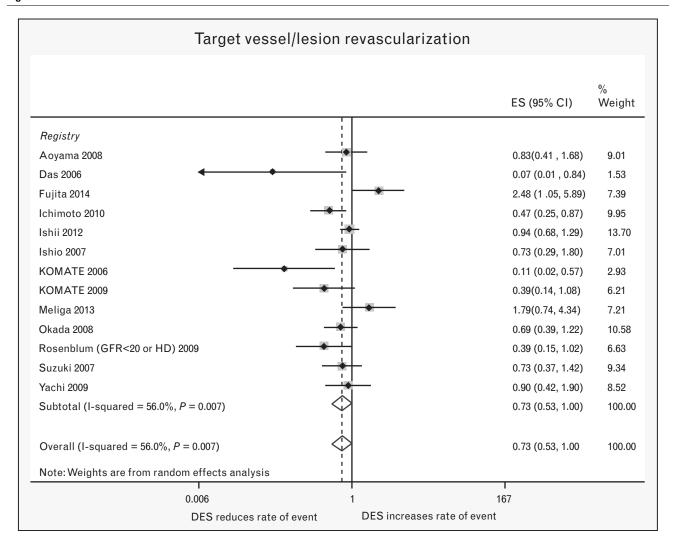
Cardiovascular death.

balance, and often suffer from resistant hypertension and hyperkalemia in the phase of fluid overload; on the contrary, during dialysis treatment, they are exposed to transient hypotension, low-calcium and low-potassium dialysate baths and metabolic alkalosis due to a high bicarbonate concentration; all these factors have been associated with hypokalemia, hemodynamic instability and QT-interval prolongation.34

Because of the co-presence of risk factors, metabolic impairment and chronic inflammatory, ESRD patients have also high prevalence of complex (type C) coronary lesions in combination with a small coronary diameter, which easily lead to suboptimal deployment, malaposition, under-expansion or stent fracture during stent implantation.

In this setting, the presence of a substrate of ischemic myocardium with a trigger of electrolytic imbalance, hypertension or sudden hypotension could be linked to lethal arrhythmias with sudden cardiac death – one of the most frequent causes of death in dialyzed patients.³⁴

The use of DES with antiproliferative drug reduces neointimal hyperplasia and smooth muscle cell proliferation effectively reducing TVR/TLR with a lower amount of vulnerable ischemic myocardium during oscillation in blood pressure and electrolytic levels. Furthermore, the introduction of second-generation DES with thinner struts, lower metal-to-vessel ratio, more biocompatible polymers, less polymer mass and limus-based antiproliferative drugs may improve TLR/TVR outcome. In 2011, Sakakibara et al. conducted a randomized study including



Target lesion revascularization (TLR) or target vessel revascularization (TVR).

only 100 patients on dialysis treatment comparing the first-generation sirolimus-eluting stent (SES) and the second-generation everolimus-eluting stent (EES). The study had not enough power to draw conclusion on hard endpoint, but showed a nonsignificant trend in reduction in Major Adverse CLinical Events (MACE) with secondgeneration EES.³⁵ A recent network meta-analysis about chronic kidney disease (CKD) patients not on dialysis showed that DES were superior to BMS in reducing major adverse clinical events and that second-generation DES as compared with first further reduces clinical events.³⁶ Another meta-analysis by Volodarskiy *et al.* including both patients with CKD and on dialysis showed a benefit with DES in terms of all-cause mortality, cardiovascular mortality and TVR when compared with BMS, with a better outcome with second-generation DES; nevertheless, they collected only 11 of 31 studies

with dialyzed patients and did not differentiate outcome according to the dialysis treatment.³⁷ We tried to compare outcome according to first- or second-generation DES; however, most of the 21 studies with only dialyzed patients included in our meta-analysis did not report the type of DES used, which did not allow a reliable analysis first vs. second-generation DES.

Then this meta-analysis is mainly based on nonrandomized studies, so another explanation for cardiovascular mortality reduction in this population could be found in unmeasured confounders in the stent choice for these patients. In the past, DES use was preferred in diabetic patients, in long lesion with small diameter, in left main disease and in bifurcations, whereas BMS were preferred if there were concerns or contraindications for prolonged Double Anti-Platelet Therapy (DAPT). We found no

difference in the prevalence of diabetes between groups, whereas DES patients were treated with longer stent, probably because of longer coronary lesion. Then, despite the prognostic importance of the location and type of the lesions, most of the studies did not collect data on left main disease and bifurcations. In this setting, a restenosis of unprotected left main or other lesions with a large myocardium at jeopardy may represent another link between stent failure and mortality.³⁸ Finally, ESRD patients have both increased thrombotic and hemorrhagic risk, and probably both risks coexist in the same individual considering the alternate drug metabolism of dialysis and the periodic fluctuations in the hydro-electrolytic imbalance described above. It is possible that, at least in the past, frailest patients on dialysis received BMS due to the perceived bleeding risk and with the goal of shorter DAPT, whereas the introduction of last-generation DES has helped to overcome these concerns.

Finally, our study supports a reduction of cardiovascular death with DES, but not a reduction of MI or stent thrombosis, events that may cause cardiovascular death. This could be the result of a definition bias. In fact, studies included in our analysis covered a period of 15 years (2002–16) in which different MI and stent thrombosis definitions were validated (see Table 2). Stent thrombosis is a rare event, and only 8 out of 20 studies collected this outcome with very few events, with a resulting CI very wide, so no easy conclusion can be drawn. Moreover, most of the registries in which the outcome MI was collected used the definition 'primary diagnosis for hospital admission according to ICD-9-CM'; using these definitions a considerable number of non-STelevation acute coronary syndromes (NSTE-ACS) may not have been reported. NSTE-ACS contributes to cardiovascular death and sometimes are related to in-stent restenosis. The effect of DES in reducing cardiovascular death and TLR/TVR could also be translated into a reduction of new NSTE-ACS, even though NSTE-ACS was not an endpoint of our study.

Our results are in line with and expand the meta-analysis published by Li et al. 39 Noteworthy was also the fact that we substantially gathered more patients and events by including 20 studies as compared with 14 studies. In addition, the authors only reported MACE events, which is an important limitation, because all-cause death is increased in ESRD patients, regardless of stent-type implantation. We reported a comprehensive set of clinical events which include cardiovascular death and stentrelated complications, which are more reliable to explore the hypothesis, especially in a non-RCT setting. Finally, as compared with Li et al., we used a person-year approach to correctly compare studies with different follow-up time.

Although our meta-analysis could be considered the most comprehensive up-to-date available data about use of

DES in the dialysis population, it has limitations too. We have already discussed the nature of the included studies, thus selection and allocation bias cannot be excluded; moreover, we hypothesized a cause-effect association linking TLR/TVR and cardiovascular death in this particular population, even though we cannot rule out unmeasured confounders and an effect due to play of chance.

Anyway, the lack of randomized evidence is also a point of strength to support the need for the present metaanalysis. Limits on definition of and cut-off for MI and stent thrombosis are mentioned above. Finally, ESRD patients often present with multivessel disease, and if indicated, surgical revascularization is a valid therapeutics option, even though with an elevated risk of perioperative complications and higher short- and long-term mortality. We acknowledge that Coronary Artery Bypass Grafting-treated CKD patients are not included for comparison in the present meta-analysis.

Conclusion

The use of DES instead of BMS in ESRD patients requiring dialysis is associated with reduction of all-cause death, cardiovascular death and TLR/TVR. Although we found no difference in terms of stent thrombosis and MI. our results support the safety of DES compared to BMS in this setting. These results provide important clinical implications to guide stent-type implantation when coronary intervention is indicated in this high-risk population.

Acknowledgements

Conflicts of interest

V.A.G., C.G., V.G., V.S., M.F., R.A., M.F., B.M., G.M.D.F., S.D.S., A.S.B., L.O.V.: nothing to disclose. C.K.: received statistical consulting for Livanova.

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