A focused review on optimal coronary revascularisation in patients with chronic kidney disease



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KEYWORDS

- atherectomy
- bare metal stent
- drug-eluting stent
- renal insufficiency stent thrombosis

Abstract

Concomitant chronic kidney disease (CKD) and coronary artery disease (CAD) is known to have poor outcomes. With a thorough literature review, we discuss the pathophysiological basis behind accelerated atherosclerosis in CKD, and the role of percutaneous coronary intervention (PCI) in these patients, focusing on drug-eluting stents, coronary artery bypass grafting, and adverse outcomes. We discuss factors contributing to poor outcomes in these patients, and the need for more work in this subgroup.

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Abbreviations

- BMS bare metal stent(s)CABG coronary artery bypass grafting
- **CAC** coronary artery calcification
- **CAD** coronary artery disease
- **CHF** congestive heart failure
- **CKD** chronic kidney disease **DAPT** dual antiplatelet therapy
- **DES** drug-eluting stent(s)
- **EES** everolimus-eluting stent(s)
- **eGFR** estimated glomerular filtration rate
- **ESRD** end-stage renal disease
- **LVD** left ventricular dysfunction
- MI myocardial infarction
- **OAS** orbital atherectomy system
- **PCI** percutaneous coronary intervention
- **RA** rotational atherectomy
- **SES** sirolimus-eluting stent(s)
- **ST** stent thrombosis
- TLR target lesion revascularisation
- **TVF** target vessel failure
- **TVR** target vessel revascularisation

Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage or reduced kidney function (eGFR <60 mL/min/1.73 m²) for \geq 3 months¹. Most studies concluded that an eGFR <60 mL/min/1.73 m² is associated with increased risk of restenosis, recurrent myocardial infarction (MI), congestive heart failure (CHF) and mortality².

The current recommendation for DES use in end-stage renal disease (ESRD) patients is deduced from extrapolation of information from patients with normal renal function³. Furthermore, CKD is sub-classified into stages 1-5¹, each associated with different mortality and revascularisation events with best pharmacological therapy, PCI, and coronary artery bypass grafting (CABG).

Unique vascular pathobiology in CKD

Inflammation drives atherosclerosis⁴. CKD patients have co-existing traditional cardiovascular risk factors propagating inflammation. Among non-traditional risk factors, contributors to inflammation include advanced glycated end products (AGEs), uraemia, peritoneal dialysis and haemodialysis⁵.

Retention of AGEs secondary to decreased renal function causes oxidative damage, recruitment of mononuclear cells and an inflammation, which is intensified by fluid retention via bacterial or endotoxin translocation from bowel oedema, producing pro-inflammatory cytokines (interleukin-6 [IL-6], high-sensitivity CRP [hsCRP]) (Figure 1). These are not adequately cleared secondary to uraemia. This is of clinical importance as IL-6 and hsCRP are independent predictors of mortality in CKD⁶.

Reduced renal function is associated with disruption of the balance between endothelin and nitric oxide, functional platelet abnormalities and coagulopathy⁷, predisposing to atherosclerosis.

Efficacy and safety of DES compared to BMS/ CABG

The bare metal stent (BMS) superseded balloon angioplasty as the treatment of choice following improved angiographic and clinical outcomes. However, BMS-related adverse events such as in-stent restenosis with rates of 20-30%⁸ led to the development of the drug-eluting stent (DES) which shares the same complications but at a delayed interval.

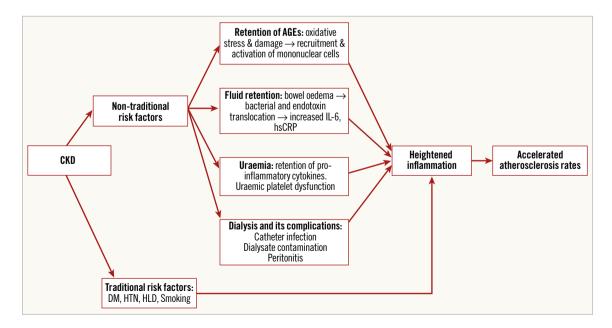


Figure 1. Pathophysiology of accelerated atherosclerosis in CKD. AGEs: advanced glycated end products; CKD: chronic kidney disease; DM: diabetes mellitus; HLD: hyperlipidaemia; hsCRP: high-sensitivity C-reactive protein; HTN: hypertension; IL-6: interleukin-6

New-generation DES with a reduced load of antiproliferative drugs, thinner metallic struts and improved biocompatibility of stent polymer are the new standard of care⁹. The NORSTENT trial¹⁰ failed to demonstrate benefits in mortality and non-fatal MI with the use of DES over BMS but revealed benefits in stent thrombosis and repeat revascularisation. Furthermore, NORSTENT did not target patients with CKD where the improved designs of new-generation DES might be less thrombogenic. Also, a recent meta-analysis comparing DES and BMS use in CKD patients concluded with observed benefits seen across mortality, MI, stent thrombosis (ST) and target vessel revascularisation (TVR). No difference was observed between first- and second-generation DES¹¹.

A meta-analysis comparing second-generation DES (everolimus-eluting stent [EES]) with CABG reported increased rates of MI and repeat revascularisation in patients receiving EES, despite comparable mortality rates¹². Hence, there might be a role for consideration of CABG in patients who are surgically fit to improve their quality of life.

Comparative outcomes of DES versus BMS in CKD

Mortality rates are inversely related to the degree of renal dysfunction, with tripling of mortality rates in patients with both CAD and severe CKD compared to patients with normal renal function¹³.

MORTALITY

Tsai et al¹⁴ (**Table 1**) reported benefits in all-cause mortality with DES compared to BMS both in patients with normal renal function and in those with CKD. This was echoed by similar findings in a *post hoc* analysis of the PRODIGY trial¹⁵ and in a study by Jeong et al¹⁶. However, Lemos et al¹⁷ reported insignificant differences in mortality despite improvements in clinical restenosis.

The benefits of second- over first-generation DES in the CKD population are unclear, with a retrospective analysis failing to demonstrate mortality benefits with the use of second-generation DES¹⁸, probably due to systemic factors which are recognised to worsen oxidative stress and systemic inflammation independently¹⁹. Other contributing factors include left ventricular dysfunction (LVD) which is associated with adverse outcomes post PCI²⁰.

STENT THROMBOSIS

An increased risk of stent thrombosis secondary to abnormal vascular pathobiology in CKD was demonstrated by a study which found that rates of ST were significantly raised in CKD compared to normal renal function at one-year follow-up post DES implantation⁷.

In PRODIGY, the number needed to treat to prevent one definite or probable ST at two-year follow-up was 20 in CKD patients versus 50 in patients with normal renal function, reinforcing the significant benefits of DES¹⁵.

The higher incidence of ST in CKD is related to increased severity of systemic atherosclerosis, and diffuse and calcified coronary artery disease which increases the risk of stent malapposition and underexpansion⁷. Restenosis rates following PCI range from 60-81% when assessed via repeat coronary angiography. In contrast to patients with normal kidneys, clinical restenosis is not raised in patients with CKD, suggesting silent progression of cardiac ischaemia, hence a high risk of adverse cardiac events²¹.

TARGET VESSEL/LESION REVASCULARISATION

The benefits of DES over BMS in relation to TVR/target lesion revascularisation (TLR) are unclear. While several studies have demonstrated a reduced incidence of repeat revascularisation with DES compared to BMS^{15,22}, Tsai et al's¹⁴ work on DES implantation demonstrated a significant reduction in repeat revascularisation only in patients with normal renal function. Besides inflammation, alternative explanations include antiplatelet resistance observed in chronic renal failure^{23,24}. Nevertheless, a lack of guideline-directed antiplatelet therapy in the CKD population might be contributory^{2,25,26}, which needs to be explored further.

NON-FATAL MI

The incidence of higher MI rates post PCI is universally increased in CKD patients compared to those with normal renal function^{7,27}. Despite an overall raised incidence of post-PCI MI in CKD patients, the use of DES over BMS is associated with reduced MI rates¹⁴. Increased MI rates in CKD patients despite DES use indicate that systemic inflammation and/or metabolic derangement have a greater impact on endpoints. This is insufficiently addressed by the local effects of antiproliferatives in current DES²⁷.

In summary, the current evidence suggests that CKD is an independent predictor of mortality, MI and stent thrombosis. Also, DES are superior to BMS in the CKD population, with the caveat that the requirement for dual antiplatelet therapy (DAPT) is unlikely to disrupt subsequent non-cardiac treatment.

Revascularisation in ESRD/haemodialysis DES VS. BMS

In line with contemporary guidelines advocating the use of DES in ESRD patients on dialysis²⁸, a meta-analysis has demonstrated mortality and adverse cardiac event benefits in ESRD patients who are treated with DES³.

Despite a lack of benefit at one-year follow-up, Ishii et al²⁹ **(Table 2)** reported reduced revascularisation rates in haemodialysis patients treated with DES over BMS on longer follow-up^{29,30}. This suggests the need for adequate endothelialisation of the deployed stent in the uraemic state, hence the need for extended follow-up.

FIRST- VS. SECOND-GENERATION DES

Despite a paucity of data on outcomes of second-generation DES in patients on maintenance haemodialysis, ESRD and haemodialysis are recognised as major predictors of adverse outcome following first-generation DES implantation, with approximately double the incidence of target vessel failure (TVF) in patients who received sirolimus-eluting stents (SES) compared to non-haemodialysis patients³¹.

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BES: biolimu: iltration rate SES: sirolimu	Cooper et al ³⁵	Wanha et al ¹⁸	et al ¹⁷	et al ⁵⁵	Tsai et al ¹⁴	Miao et al ⁷	crimi et al ¹¹⁵	
s-eluting stent; B ; ESRD: end-stag s-eluting stent; S	Retrospective	Retrospective	Retrospective	Single-centre prospective	Multicentre prospective	Single-centre prospective	Multicentre RCT	Study design
MS: bare m e renal dise 51: stent thro	483,914	1,908	1,080	4,687	283,593	2,862	1,981	Study size
etal stent; CABG: ase; HR: hazard r ombosis; TVR: tar	379,034 (78.3%)	331 (17.3%)	186 (17.2%)	1,543 (33%)	121,446 (42.8%)	445 (15.5%)	373 (18.8%)	CKD (eGFR <60 ml/ min/1.73 m ²)
coronary artery by atio; MACCE: maji get vessel revascu	CABG	DES-I (PES, SES) vs. DES-II (EES, ZES, BES)	DES vs. BMS	CABG vs. MM CABG vs. BMS CABG vs. DES	DES vs. BMS	DES-related ST in CKD vs. normal renal function	BMS vs. DES (PES/EES/ZES)	Comparison/ intervention
pass grafti or adverse (ularisation;	NA	1,908 (100%)	537 (49.7%)	1,278 (27%)	218,540 (77.1%)	2,862 (100%)	1,484 (75%)	DES stent use
BES: biolimus-eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; CKD: chronic kidney disease filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; MACCE: major adverse cardiac and cerebral events; M SES: sirolimus-eluting stent; SI: stent thrombosis; TVR: target vessel revascularisation; ZES: zotarolimus-eluting stent	All-cause mortality (within 30 days of CABG)	DES efficacy: MACCE (MI, TVR, death, stroke) DES safety: ST	All-cause mortality	All-cause mortality	All-cause mortality, Ml, repeat revascularisa- tion, bleeding	Definite/probable ST	Definite/probable ST	P rimary outcome
ney disease; DES: dru l events; MI: myocardi uting stent	Stroke, repeat CABG	NA	Repeat revascularisation	Composite of death, MI, revascularisation	NA	Composite of all-cause mortality, non-fatal MI, TVR	Composite of MI, stroke, death, and all-cause mortality	Secondary outcomes
BES: biolimus-eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; CKD: chronic kidney disease; DES: drug-eluting stent; DES-1: first-generation DES; DES-11: second-generation DES; EES: everolimus-eluting stent; eGFR: estimated glomenular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; MACCE: major adverse cardiac and cerebral events; MI: myocardial infarction; MM: medical management; NA: not applicable; PES: paclitaxel-eluting stent; RCT: randomised controlled trial; SES: sirolimus-eluting stent; ST: stent thrombosis; TVR: target vessel revascularisation; ZES: zotarolimus-eluting stent	Operative mortality rose inversely with decline in renal function.	No improvement with DES-II over DES-I irrespective of renal function.	All-cause mortality higher in CKD vs. normal renal function regardless of DES or BMS use. DES did not provide additional mortality benefit over BMS in CKD states.	CABG vs. MM: superior in CKO, excluding ESRD. CABG vs. BMS: superior in severe CKD CABG vs. DES: no significant differences. ESRD: no significant differences in CABG/BMS/ PCL/MM	Lower in DES-treated patients regardless of renal function.	CKD (10.6%) vs. normal renal function (4.1%); p<0.001.	Within CKD population: lowest in ZES (10.6%) compared to EES (14.9%), PES (25.5%), BMS (18.1%), p=0.040.	All-cause mortality
eneration DES; DES-II: secon nagement; NA: not applicab	NA	No difference between CKD vs. normal renal function.	A	A	Ą	Definite/probable ST: CKD (1.8%) vs. normal renal function (0.6%); p=0.014.	Within CKD population: lower in EES and ZES compared to BMS (HR 0.288 and 0.394; p=0.014 and 0.037, respectively)	Stent thrombosis
ld-generation DES; EES: ev le; PES: paclitaxel-eluting	Repeat CABG rose inversely with decline in renal function	No improvement with DES-II	Reduced with SES in both CKD and normal renal function.	Secondary endpoint lower with CABG vs. BMS/DES/MM except in dialysis patients.	Lower in DES-treated patients with normal renal function only.	Non-significant	Non-significant	Repeat revascularisation
verolimus-eluting stent; v stent; RCT: randomised	NA	No improvement with DES-II	NA	Secondary endpoint lower with CABG vs. BMS/DES/medical management except in dialysis patients.	Lower in DES-treated patients regardless of renal function, excluding haemodialysis patients.	CKD (7.4%) vs. non-CKD (4.3%); p=0.005	Non-significant	Non-fatal MI
eGFR: estimated controlled trial;	NA	1 year	1 year	5.1 years	2.5 years	1 year	2 years	Follow-up period
glomerular	2000-2003	2009-2010	2001-2002	2003-2010	2004-2007	2008-2009	2006-2008	Inclusion period

Table 1. Summary of studies comparing coronary revascularisation approaches in CKD (including ESRD).

Table 2. Summary of studies comparing coronary revascularisation approaches in ESRD (dialysis-dependent).

	Study design	Study size	ESRD	Com- parison/ inter- vention	DES stent use	Primary outcome	Second- ary out- comes	All-cause mortality	Stent thrombo- sis	Repeat revascu- larisation	Non-fatal MI	Addi- tional com- ments	Follow- up period	Inclusion period
Li et al ³	Meta- analysis	62,250	62,250 (100%)	DES vs. BMS	NR	All-cause mortality MI MACE TVR/TLR	NA	Favours DES	NR	Favours DES	Non- significant difference	NA	NR	2006-2016
Ishii et al ²⁹	Retrospec- tive	505	505	DES vs. BMS	SES, PES		Composite of cardiovas- cular death, non-fatal MI, ST, TLR	cant difference	Non- significant difference	Favours DES (beyond 1 year)	Non- significant difference	NA	42 months	1999-2009
Saka- kibara et al ³²	Single- centre prospec- tive	100	100	DES-I vs. DES-II	SES (50%), EES (50%)	Restenosis at 8-month follow-up	MACE (all-cause death, non-fatal MI, TLR)	Non-signifi- cant difference	Non- significant difference	Non- significant difference	Non- significant difference	EES reduced restenosis rates compared to SES	8 months	2010
Nevis et al ³⁸	Systematic review	32,388	32,388 (100%)	CABG vs. PCI	NR	Short-term (30 days) or long-term (>1 year) mortality	NA	Short-term: favours PCI Long-term: favours CABG	NA	Favours CABG	Favours CABG	NA	PCI: 28 months CABG: 31 months	

intervention; SES: sirolimus-eluting stent; ST: stent thrombosis; TLR: target lesion revascularisation; TVF: target vessel failure; TVR: target vessel revascularisation

When implemented on maintenance haemodialysis patients, EES significantly reduced the incidence of restenosis compared to SES with an equal safety profile³², with consistent results in improvements in diameter stenosis on follow-up compared with the OUCH-PRO registry³¹. Mechanisms for reduction in restenosis rates include reduced arterial injury and inflammation secondary to thinner struts and polymer of second-generation DES, respectively^{32,33}.

PCI VS. CABG

Despite increased early post-CABG mortality in ESRD^{34,35}, Zheng et al³⁰ demonstrated significant long-term benefits in mortality, MI, and repeat revascularisation compared to PCI. Supporting this is a systematic review reporting benefits in repeat revascularisation and major adverse cardiac events (MACE) with CABG, despite a higher early mortality risk³⁶. The proposed pathophysiology includes significant medial calcification in haemodialysis patients, predisposing to stent underexpansion, reduced efficacy of eluted drugs and suboptimal endothelialisation of stent struts, culminating in restenosis and stent thrombosis³⁷.

Nevertheless, there is an elevated baseline risk of long-term mortality in haemodialysis patients regardless of the choice of revascularisation technique³⁸.

Rotational atherectomy (RA) for the treatment of coronary artery calcification (CAC)

Severely calcified coronary lesions have lower PCI success rates, higher complication rates, and suboptimal long-term results. Contemporary PCI guidelines recommend RA as an option for heavily calcified lesions that might not be adequately traversed or dilated prior to stent implantation³⁹.

The ROTAXUS trial, comparing RA followed by stenting or stenting alone in complex native CAD, demonstrated higher success with use of RA and higher acute lumen gain post PCI. However, in-stent late lumen loss was significantly higher in the RA group compared to DES alone⁴⁰, indicating that rotablation alone failed to increase the efficacy of DES.

The Diamondback 360[®] coronary orbital atherectomy system (OAS; Cardiovascular Systems, Inc., St. Paul, MN, USA) presents an alternative in revascularisation of CACs. ORBIT I demonstrated 98% device success (\leq 50% residual stenosis post-OAS treatment) while ORBIT II exceeded primary safety (freedom from MACE at 30 days) and efficacy (residual stenosis <50% post stent without inhospital major cardiac events) endpoints, highlighting its suitability for implementation in CACs. Furthermore, subgroup analysis of DES use revealed a lower rate of TLR compared to BMS^{41,42}.

Besides technique, the approach to complex CACs should include accurate lesion assessment and characterisation which is poorly delineated by angiography alone^{41,43}. Optical coherence tomography might be the supplemental imaging modality of choice for the assessment of intraluminal calcium thickness⁴¹. Accurate assessment will facilitate optimal stent placement, reduce stent underexpansion, malapposition, damage to the DES polymer coating and subsequent drug delivery⁴². Compared to bail-out atherectomy, planned atherectomy is associated with a reduced procedural time, less use of contrast and reduced rates of complications⁴⁴. Overall, our review suggests that, while results regarding mortality benefit are mixed when DES are compared with BMS in both CKD and ESRD, DES are shown to improve rates of MI and repeat revascularisation^{3,14,15,29}. There is no significant benefit of second- over first-generation DES¹⁸. The benefits of rotational atherectomy warrant consideration for planned instead of bail-out use in appropriate lesions⁴⁴.

Choice and duration of DAPT in CKD

DAPT use post PCI is critical to minimise the rate of adverse cardiovascular events²⁵. Contemporary European and US guidelines recommend a DAPT duration of six to 12 months post DES deployment, followed by lifelong aspirin^{9,39}. However, no consensus for DAPT drugs and duration in patients with CKD/ESRD exists, owing to the lack of clinical trials²⁵. Though not targeted at CKD patients, the DAPT trial demonstrated that prolonged DAPT (30 months) significantly decreased rates of ST and the composite outcome of death, MI and stroke, at the expense of bleeding⁴⁵. However, the extrapolation of findings from a non-CKD/ESRD population into this high-risk population is probably inappropriate, due to an increased incidence of cardiovascular events or bleeding complications after PCI in haemodialysis patients^{46,47}.

Both CKD and prolonged DAPT independently predict elevated bleeding complications. However, it is uncertain whether prolonged DAPT worsens bleeding risk in CKD patients⁴⁸.

A pooled analysis comparing the safety and efficacy of shortterm (three to six months) versus long-term (\geq 12 months) DAPT post DES implantation in CKD patients found that the presence and degree of CKD have no effect on the rates of coronary thrombotic events, regardless of the duration of DAPT²⁵, which is in sync with a study by Baber et al⁴⁸, where severity of CKD has no effect on cardiovascular risk post DAPT cessation. Further, Chen et al's analysis⁴⁹ in the haemodialysis subgroup reported a six-month DAPT duration cut-off that reduces post-PCI death or MI, but shows no difference in long-term outcomes when compared to longer duration of DAPT (>6 months). However, these studies used clopidogrel instead of more potent P2Y₁₂ inhibitors such as prasugrel or ticagrelor, which may have had an impact on overall study outcome.

In summary, CKD and DAPT independently predict bleeding risk, while CKD contributes to an increased risk of ST. A lack of consensus regarding antiplatelet therapy in CKD/ESRD leads to a reduced use due to a perceived lack of benefit, coupled with fear of coagulopathy and antiplatelet resistance^{7,23,24}. Also, our review suggests that thrombotic complications post cessation of DAPT are independent of the severity of CKD. Future studies concerning DAPT and bleeding complications ought to have a uniform use of antiplatelets and duration to minimise possible confounding effects on stent choice and CKD severity.

Role of CABG in CKD

The 2014 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) Guidelines⁵⁰ on myocardial revascularisation recommend CABG over PCI in

patients with moderate to severe CKD and multivessel CAD, considering acceptable surgical risks and life expectancy beyond one year.

Given complex coronary lesions in CKD, findings from ASCERT reporting long-term mortality benefits with CABG over PCI in multivessel CAD could be applied. Though patients with CKD often have more complex coronary lesions with multivessel disease, increased coronary calcification, and the presence of thrombus in culprit coronary lesions, their SYNTAX score is comparable to patients with normal kidneys¹⁸. CABG should be considered since extensive coronary calcifications reduce PCI success rates and is also associated with significant improvements in symptoms and mortality⁵¹.

The FREEDOM trial⁵² comparing coronary revascularisation techniques in CKD concluded that CKD is an independent risk factor for adverse events regardless of revascularisation strategy, where there is no evidence of additional benefit in outcomes according to CKD severity. Being an independent risk factor for stent thrombosis, coronary revascularisation in CKD has shifted in favour of CABG especially on long-term follow-up^{52,53}. Nevertheless, CABG is superior to PCI with regard to reductions in rates of MI and repeat revascularisation regardless of renal function provided patients do not present with acute coronary syndrome^{52,54}.

Comparing rates of adverse events in CABG against BMS in CKD/ESRD, CABG is associated with reduced mortality rates though there was statistical significance only in severe CKD (eGFR <30 mL/min/1.73 m²)⁵⁵. A subsequent analysis comparing CABG against DES observed a trend towards mortality reduction for CABG without statistical significance. No mortality difference was observed in patients on dialysis, regardless of revascularisation strategy⁵⁵.

However, a five-year follow-up on the SYNTAX trial demonstrated that a statistically significant long-term benefit in mortality, MI and stroke is associated with revascularisation with CABG over DES. Differences in event rates were attributed to the higher rates of all-cause death and repeat revascularisation in the CKD population who received DES, secondary to diffuse atherosclerosis and reduced prevalence of guideline-directed antiplatelet therapy^{26,52}.

In conclusion, CKD and ESRD are independent risk factors for adverse events regardless of revascularisation strategy^{17,35}. CABG is associated with long-term benefits in both mortality and adverse cardiac events both in patients with CKD and in those with ESRD^{38,55}. However, physicians and patients ought to consider and accept higher risks of early complications such as mortality and stroke⁵³, stressing the importance of patient selection.

Conclusions

Despite an increasing prevalence of patients with CKD and CAD, there remain limited studies evaluating the optimum method of coronary revascularisation, and DAPT duration in this subgroup.

Our review highlights the following. 1) CKD is an independent predictor of mortality, MI and stent thrombosis. 2) DES is superior to BMS in a CKD population. 3) CKD and DAPT are independent predictors of bleeding complications post PCI, though the severity AsiaIntervention 2019;5:32-40

of CKD seems not to affect the rates of coronary thrombotic events. 4) CABG is the revascularisation modality of choice **(Table 3)** in CKD patients who are surgically fit due to mortality and symptomatic benefits, and the reduced need for repeat revascularisation compared to PCI. 5) It is also imperative for a consensus on DAPT choice and duration to be validated to maximise the benefits of high-risk, invasive procedures in this fragile subset of patients.

Table 3. Summ	ary of findings	and clinical i	implications.
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What is already known	Patients with CKD have an increased risk of post-PCI adverse events compared to the general population. DES is generally associated with improved outcomes compared to BMS in both the general population and CKD patients. DES implantation in the ESRD population on regular dialysis shows a reduced rate of revascularisation over longer follow-up (>1 year).			
What this review adds	No study focusing on DAPT duration post PCI in CKD/ESRD patients has yet been done. Results from available trials highlight that adverse events are higher in the CKD population. Among the CKD population, there is no observable benefit in extending DAPT duration beyond 12 months. In non-dialysis-dependent CKD patients, CABG improves mortality, repeat revascularisation and MI compared to PCI. There is no mortality difference when comparing first- and second-generation DES, while comparison of DES with BMS yields mixed results. In ESRD on regular haemodialysis, CABG provides long-term benefit despite short-term increased risk of adverse events. There is no significant mortality difference when first- and second-generation DES are compared, though there is a reduced repeat revascularisation rate with second-generation DES. Finally, DES provides mortality benefit over BMS.			
Clinical implications & future directions	CABG is still the intervention of choice for CKD/ ESRD patients requiring coronary revascularisation, provided fitness for surgery. CKD/ESRD patients will greatly benefit from RCTs/prospective studies focusing on DAPT choice and duration, especially in the advent of novel P2Y ₁₂ inhibitors and second-generation DES.			
BMS: bare metal stent; CABG: coronary artery bypass grafting; CKD: chronic kidney disease; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; ESRD: end-stage renal disease; PCI: percutaneous coronary intervention; RCT: randomised controlled trial; ST: stent thrombosis				

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. [No authors listed]. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011)*. 2013;3:19-62.

2. McCullough PA. Why is chronic kidney disease the "spoiler" for cardiovascular outcomes? *J Am Coll Cardiol*. 2003;41:725-8.

3. Li S, Ye D, Chen G, Xu W. Meta-Analysis of Comparison of Drug-Eluting Stents and Bare-Metal Stents in Patients on Dialysis. *Am J Cardiol.* 2017;119:1186-92.

4. Crea F, Libby P. Acute Coronary Syndromes: The Way Forward From Mechanisms to Precision Treatment. *Circulation*. 2017;136:1155-66.

5. Yao Q, Axelsson J, Stenvinkel P, Lindholm B. Chronic systemic inflammation in dialysis patients: an update on causes and consequences. *ASAIO J.* 2004;50:Iii-Ivii.

6. Dai L, Golembiewska E, Lindholm B, Stenvinkel P. End-Stage Renal Disease, Inflammation and Cardiovascular Outcomes. *Contrib Nephrol.* 2017;191:32-43.

7. Miao Y, Yu-Jie Z, Zhi-Jian W, Dong-Mei S, Yu-Yang L, Ying-Xin Z, Fei G, Shi-Wei Y, De-An J. Chronic kidney disease and the risk of stent thrombosis after percutaneous coronary intervention with drug-eluting stents. *Catheter Cardiovasc Interv.* 2012;80:361-7.

8. Buchanan K, Steinvil A, Waksman R. Does the new generation of drug-eluting stents render bare metal stents obsolete? *Cardiovasc Revasc Med.* 2017;18:456-61.

9. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head S, Jüni S, Kappetein A, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimgli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.

10. Bonaa KH, Mannsverk J, Wiseth R, Aaberge L, Myreng Y, Nygard O, Nilsen DW, Klow NE, Uchto M, Trovik T, Bendz B, Stavnes S, Bjornerheim R, Larsen AI, Slette M, Steigen T, Jakobsen OJ, Bleie O, Fossum E, Hanssen TA, Dahl-Eriksen O, Njolstad I, Rasmussen K, Wilsgaard T, Nordrehaug JE; NORSTENT Investigators. Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease. *N Engl J Med.* 2016;375:1242-52.

11. Volodarskiy A, Kumar S, Pracon R, Sidhu M, Kretov E, Mazurek T, Bockeria O, Kaul U, Bangalore S. Drug-Eluting vs Bare-Metal Stents in Patients With Chronic Kidney Disease and Coronary Artery Disease: Insights From a Systematic Review and Meta-Analysis. *J Invasive Cardiol.* 2018;30:10-17.

12. Bundhun PK, Pursun M, Teeluck AR, Bhurtu A, Soogund MZ, Huang WQ. Adverse Cardiovascular Outcomes associated with Coronary Artery Bypass Surgery and Percutaneous Coronary Intervention with Everolimus Eluting Stents: A Meta-Analysis. *Sci Rep.* 2016;6:35869.

13. van Domburg RT, Hoeks SE, Welten GM, Chonchol M, Elhendy A, Poldermans D. Renal insufficiency and mortality in patients with known or suspected coronary artery disease. *J Am Soc Nephrol.* 2008;19:158-63.

14. Tsai TT, Messenger JC, Brennan JM, Patel UD, Dai D, Piana RN, Anstrom KJ, Eisenstein EL, Dokholyan RS, Peterson ED, Douglas PS. Safety and efficacy of drug-eluting stents in older patients with chronic kidney disease: a report from the linked CathPCI Registry-CMS claims database. *J Am Coll Cardiol.* 2011;58:1859-69.

15. Crimi G, Leonardi S, Costa F, Adamo M, Ariotti S, Valgimigli M. Role of stent type and of duration of dual antiplatelet therapy in patients with chronic kidney disease undergoing

percutaneous coronary interventions. Is bare metal stent implantation still a justifiable choice? A post-hoc analysis of the all comer PRODIGY trial. *Int J Cardiol.* 2016;212:110-7.

16. Jeong YH, Hong MK, Lee CW, Park DW, Kim YH, Kim JJ, Park SW, Park SJ. Impact of significant chronic kidney disease on long-term clinical outcomes after drug-eluting stent versus bare metal stent implantation. *Int J Cardiol.* 2008;125:36-40.

17. Lemos PA, Arampatzis CA, Hoye A, Daemen J, Ong AT, Saia F, van der Giessen WJ, McFadden EP, Sianos G, Smits PC, de Feyter P, Hofma SH, van Domburg RT, Serruys PW. Impact of baseline renal function on mortality after percutaneous coronary intervention with sirolimus-eluting stents or bare metal stents. *Am J Cardiol.* 2005;95:167-72.

18. Wanha W, Kawecki D, Roleder T, Pluta A, Marcinkiewicz K, Morawiec B, Dola J, Gladysz S, Pawlowski T, Smolka G, Ochala A, Nowalany-Kozielska E, Wojakowski W. Long-Term Percutaneous Coronary Intervention Outcomes of Patients with Chronic Kidney Disease in the Era of Second-Generation Drug-Eluting Stents. *Cardiorenal Med.* 2017;7:85-95.

19. Landes U, Kornowski R, Assali A, Vaknin-Assa H, Greenberg G, Lev EI, Bental T. Predictors of long term outcomes in 11,441 consecutive patients following percutaneous coronary interventions. *Am J Cardiol.* 2015;115:855-9.

20. De Silva K, Webb I, Sicard P, Lockie T, Pattinson S, Redwood S, Perera D. Does left ventricular function continue to influence mortality following contemporary percutaneous coronary intervention? *Coron Artery Dis.* 2012;23:155-61.

21. Best PJ, Lennon R, Ting HH, Bell MR, Rihal CS, Holmes DR, Berger PB. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol.* 2002;39:1113-9.

22. Halkin A, Mehran R, Casey CW, Gordon P, Matthews R, Wilson BH, Leon MB, Russell ME, Ellis SG, Stone GW. Impact of moderate renal insufficiency on restenosis and adverse clinical events after paclitaxel-eluting and bare metal stent implantation: results from the TAXUS-IV Trial. *Am Heart J.* 2005;150:1163-70.

23. Lee K, Lee S, Lee JW, Kim SY, Youn YJ, Ahn MS, Kim JY, Yoo BS, Yoon J, Choe KH. The significance of clopidogrel low-responsiveness on stent thrombosis and cardiac death assessed by the verifynow p(2)y(12) assay in patients with acute coronary syndrome within 6 months after drug-eluting stent implantation. *Korean Circ J.* 2009;39:512-8.

24. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, Costa MA. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol.* 2007;49:1505-16.

25. Hwang D, Park KW, Lee JM, Rhee TM, Hong MK, Jang Y, Valgimigli M, Colombo A, Gilard M, Palmerini T, Stone GW, Kim HS. Efficacy and safety of dual antiplatelet therapy after coronary stenting in patients with chronic kidney disease. *Am Heart J.* 2018;197:103-12.

26. Milojevic M, Head SJ, Mack MJ, Mohr FW, Morice MC, Dawkins KD, Holmes DR Jr, Serruys PW, Kappetein AP. The

impact of chronic kidney disease on outcomes following percutaneous coronary intervention versus coronary artery bypass grafting in patients with complex coronary artery disease: five-year follow-up of the SYNTAX trial. *EuroIntervention*. 2018;14:102-11.

27. Choi DH, Park KW, Yang HM, Lee HY, Park JS, Kang HJ, Kim YJ, Koo BK, Oh BH, Park YB, Kim HS. Renal dysfunction and high levels of hsCRP are additively associated with hard endpoints after percutaneous coronary intervention with drug eluting stents. *Int J Cardiol.* 2011;149:174-81.

28. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis.* 2005;45:S31-153.

29. Ishii H, Toriyama T, Aoyama T, Takahashi H, Tanaka M, Yoshikawa D, Hayashi M, Yasuda Y, Maruyama S, Matsuo S, Matsubara T, Murohara T. Percutaneous coronary intervention with bare metal stent vs. drug-eluting stent in hemodialysis patients. *Circ J.* 2012;76:1609-15.

30. Zheng H, Xue S, Lian F, Huang RT, Hu ZL, Wang YY. Metaanalysis of clinical studies comparing coronary artery bypass grafting with percutaneous coronary intervention in patients with end-stage renal disease. *Eur J Cardiothorac Surg.* 2013;43:459-67.

31. Ikari Y, Kyono H, Isshiki T, Ishizuka S, Nasu K, Sano K, Okada H, Sugano T, Uehara Y. Usefulness of Everolimus-Eluting Coronary Stent Implantation in Patients on Maintenance Hemodialysis. *Am J Cardiol.* 2015;116:872-6.

32. Sakakibara T, Ishii H, Toriyama T, Aoyama T, Takahashi H, Kamoi D, Kawamura Y, Kawashima K, Yoneda K, Amano T, Tanaka M, Yoshikawa D, Hayashi M, Matsubara T, Murohara T. Sirolimus-eluting stent vs. everolimus-eluting stent for coronary intervention in patients on chronic hemodialysis. *Circ J.* 2012;76:351-5.

33. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schühlen H, Neumann FJ, Fleckenstein M, Pfafferott C, Seyfarth M, Schömig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation*. 2001;103:2816-21.

34. Liu JY, Birkmeyer NJ, Sanders JH, Morton JR, Henriques HF, Lahey SJ, Dow RW, Maloney C, DiScipio AW, Clough R, Leavitt BJ, O'Connor GT. Risks of morbidity and mortality in dialysis patients undergoing coronary artery bypass surgery. Northern New England Cardiovascular Disease Study Group. *Circulation*. 2000;102:2973-7.

35. Cooper WA, O'Brien SM, Thourani VH, Guyton RA, Bridges CR, Szczech LA, Petersen R, Peterson ED. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation.* 2006;113:1063-70.

36. Deo SV, Shah IK, Dunlay SM, Erwin PJ, Dillon JM, Park SJ. Myocardial revascularisation in renal dysfunction: a systematic review and meta-analysis. *Heart Lung Circ.* 2013;22:827-35.

37. Madhavan MV, Tarigopula M, Mintz GS, Maehara A, Stone GW, Généreux P. Coronary artery calcification: pathogenesis and prognostic implications. *J Am Coll Cardiol*. 2014;63:1703-14.

38. Nevis IF, Mathew A, Novick RJ, Parikh CR, Devereaux PJ, Natarajan MK, Iansavichus AV, Cuerden MS, Garg AX. Optimal method of coronary revascularization in patients receiving dialysis: systematic review. *Clin J Am Soc Nephrol.* 2009;4:369-78.

39. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH; American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011;58:e44-122.

40. Abdel-Wahab M, Richardt G, Joachim Büttner H, Toelg R, Geist V, Meinertz T, Schofer J, King L, Neumann FJ, Khattab AA. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. *JACC Cardiovasc Interv.* 2013;6:10-9.

41. Shlofmitz E, Martinsen BJ, Lee M, Rao SV, Généreux P, Higgins J, Chambers JW, Kirtane AJ, Brilakis ES, Kandzari DE, Sharma SK, Shlofmitz R. Orbital atherectomy for the treatment of severely calcified coronary lesions: evidence, technique, and best practices. *Expert Rev Med Devices*. 2017;14:867-79.

42. Chambers JW, Feldman RL, Himmelstein SI, Bhatheja R, Villa AE, Strickman NE, Shlofmitz RA, Dulas DD, Arab D, Khanna PK, Lee AC, Ghali MG, Shah RR, Davis TP, Kim CY, Tai Z, Patel KC, Puma JA, Makam P, Bertolet BD, Nseir GY. Pivotal Trial to Evaluate the Safety and Efficacy of the Orbital Atherectomy System in Treating De Novo, Severely Calcified Coronary Lesions (ORBIT II). *JACC Cardiovasc Interv.* 2014;7:510-8.

43. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, Ditrano CJ, Leon MB. Patterns of calcification in coronary artery disease. A statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. *Circulation*. 1995;91:1959-65.

44. Allali A, Abdel-Wahab M, Sulimov DS, Jose J, Geist V, Kassner G, Richardt G, Toelg R. Comparison of Bailout and Planned Rotational Atherectomy for Heavily Calcified Coronary Lesions: A Single-Center Experience. *J Interv Cardiol.* 2017;30: 124-33.

45. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med.* 2014;371:2155-66.

46. Mulukutla SR, Marroquin OC, Vlachos HA, Selzer F, Toma C, Kip KE, Abbott JD, Holper E, Lee JS, Khandhar S, Kutcher M, Kelsey S, Smith C, Faxon D, Williams DO. Benefit of long-term dual anti-platelet therapy in patients treated with drugeluting stents: from the NHLBI dynamic registry. *Am J Cardiol.* 2013;111:486-92.

47. Hiremath S, Holden RM, Fergusson D, Zimmerman DL. Antiplatelet medications in hemodialysis patients: a systematic review of bleeding rates. *Clin J Am Soc Nephrol.* 2009;4:1347-55.

48. Baber U, Li SX, Pinnelas R, Pocock SJ, Krucoff MW, Ariti C, Gibson CM, Steg PG, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Iakovou I, Dangas G, Aquino MB, Sartori S, Chieffo A, Moliterno DJ, Colombo A, Mehran R. Incidence, Patterns, and Impact of Dual Antiplatelet Therapy Cessation Among Patients With and Without Chronic Kidney Disease Undergoing Percutaneous Coronary Intervention: Results From the PARIS Registry (Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients). *Circ Cardiovasc Interv.* 2018;11:e006144.

49. Chen YT, Chen HT, Hsu CY, Chao PW, Kuo SC, Ou SM, Shih CJ. Dual Antiplatelet Therapy and Clinical Outcomes after Coronary Drug-Eluting Stent Implantation in Patients on Hemodialysis. *Clin J Am Soc Nephrol.* 2017;12:262-71.

50. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention*. 2015;10:1024-94.

51. Hemmelgarn BR, Southern D, Culleton BF, Mitchell LB, Knudtson ML, Ghali WA; Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) Investigators. Survival after coronary revascularization among patients with kidney disease. *Circulation.* 2004;110:1890-5.

52. Baber U, Farkouh ME, Arbel Y, Muntner P, Dangas G, Mack MJ, Hamza TH, Mehran R, Fuster V. Comparative efficacy of coronary artery bypass surgery vs. percutaneous coronary intervention in patients with diabetes and multivessel coronary artery disease with or without chronic kidney disease. *Eur Heart J.* 2016; 37:3440-7.

53. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Revascularization in Patients With Multivessel Coronary Artery Disease and Chronic Kidney Disease: Everolimus-Eluting Stents Versus Coronary Artery Bypass Graft Surgery. *J Am Coll Cardiol.* 2015;66:1209-20.

54. Zhang X, Hu L, Zheng W. Percutaneous Coronary Intervention versus Coronary Artery Bypass Graft in Acute Coronary Syndrome patients with Renal Dysfunction. *Sci Rep.* 2018;8:2283.

55. Roberts JK, Rao SV, Shaw LK, Gallup DS, Marroquin OC, Patel UD. Comparative Efficacy of Coronary Revascularization Procedures for Multivessel Coronary Artery Disease in Patients With Chronic Kidney Disease. *Am J Cardiol.* 2017;119:1344-51.