

Review Article

Cardiovascular Disease in Patients with End-Stage Renal Disease on Hemodialysis

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Cardiovascular disease is a major concern for patients with end-stage renal disease (ESRD), especially those on hemodialysis. ESRD patients with coronary artery disease often do not have symptoms or present with atypical symptoms. Coronary lesions in ESRD patients are characterized by increased media thickness, infiltration and activation of macrophages, and marked calcification. Several studies showed worsened clinical outcomes after coronary revascularization, which were dependent on the severity of renal dysfunction. ESRD patients on hemodialysis have the most severe renal dysfunction; thus, the clinical outcomes are worse in these patients than in those with other types of renal dysfunction. Medications for primary or secondary cardiovascular prevention are also insufficient in ESRD patients. Efficacy of drug-eluting stents is inferior in ESRD patients, compared to the excellent outcomes observed in patients with normal renal function. Unsatisfactory outcomes with trials targeting cardiovascular disease in patients with ESRD emphasize a large potential to improve outcomes. Thus, optimal strategies for diagnosis, prevention, and management of cardiovascular disease should be modified in ESRD patients.

Keywords: cardiovascular disease, coronary, hemodialysis, stent, bypass

Epidemiology

Cardiovascular disease is a frequent cause of death in patients with hemodialysis, with the ratio reported as 10–20 times higher than that observed in populations with normal kidney function.¹ One reason for this discrepancy is suggested to be the increased frequency of coronary artery disease in these patients.² The United States Renal Data System (USRDS) reported that approxi-

mately 50% of death was attributed to cardiovascular disease in dialysis patients,³ and acute coronary syndrome (ACS) was reported as a complication in 2.9% of dialysis patients per year. The Hemodialysis (HEMO) study in the United States reported that 40% of dialysis patients had cardiovascular disease at entry and that the cause of 63% of admission to hospitals due to cardiovascular reasons was coronary artery disease.⁴ Rostand et al. reported that 73% of hemodialysis patients had significant coronary stenosis of more than 50%.⁵ The Japanese Renal Data Registry by the Japanese Society for Dialysis Therapy reported that the most frequent cause of death was cardiac death (32.7%), including heart failure (23.9%), acute myocardial infarction (AMI) (4.1%), and sudden death (4.7%).

Dialysis patients with coronary artery disease frequently do not experience symptoms or present with atypical symptom. Joki et al. performed coronary angiography for asymptomatic patients who started maintenance hemodialysis within the past month and observed significant coronary stenosis in more than 50% of the patients.⁶ Ohtake et al. also observed significant coronary stenosis in 53% of asymptomatic hemodialysis patients at the time of maintenance hemodialysis initiation.⁷ Charytan et al. reported that 42% of asymptomatic dialysis patients had significant coronary stenosis and that 29% of the lesions were in proximal sites of coronary arteries.⁸

These observations suggest that coronary artery disease are more frequent in dialysis patients than in those with normal kidney function. Significant coronary stenosis can frequently exist at the time of hemodialysis induction and may result in cardiovascular death. Mortality rate following AMI in dialysis patients are extremely high (41%, 52%, and 70% at 1, 2 and 3 years, respectively).⁹ Another study reported that annual mortality rate was 53% following AMI.¹⁰ Dialysis is one of the risk factors for coronary artery disease; therefore, screening of coronary artery disease is suggested for patients with hemodialysis.

Diagnosis

Given that hemodialysis patients with coronary artery disease are asymptomatic, diagnosis is difficult in these

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patients. Furthermore, ACS diagnosis is challenging. Pain in chest, neck, and shoulder was less frequent in patients on dialysis, compared to those with normal kidney function.¹¹⁾ Symptoms sometimes include shortness of breath. The USRDS database revealed that 44.8% of the dialysis patients were diagnosed as not having ACS on admission for treating coronary artery disease compared with 21.2% of the non-dialysis patients. Additionally, 44.4% of the dialysis patients presented with chest pain compared with 68.3% of the non-dialysis patients, and the percentages of those with ST elevation were 19.1% and 35.9% among dialysis and non-dialysis patients, respectively. Cardiac arrest and in-hospital death rates were approximately twice as frequent among dialysis patients than those among non-dialysis patients (11.0% versus 5.0% and 21.3% versus 11.7%, respectively). In a logistic regression model, the odds ratio (OR) for in-hospital death for dialysis versus non-dialysis patients was 1.498 (95% confidence interval [CI], 1.340–1.674).¹²⁾ Dialysis patients hospitalized for AMI are strikingly different in clinical presentation from non-dialysis patients. Therefore, intensive efforts for early, accurate recognition of AMI in dialysis patients are warranted.

Pathophysiology

Coronary plaques in end-stage renal disease (ESRD) patients are characterized by increased media thickness, infiltration and activation of macrophages, and marked calcification.¹³⁾ Inflammation, oxidative stress, endothelial dysfunction, protein-energy wasting, sympathetic activation, coagulation/fibrinolysis disorders, insulin resistance, vascular calcification, uremic toxin accumulation, volume overload, subclinical hypothyroidism, and anemia contribute to an accelerated atherosclerosis process in dialysis patients.¹⁴⁾ The most marked difference observed in ESRD patients compared with normal controls concerns not the size but the composition of plaques: the heavily calcified and inflamed plaques contribute to the excessive cardiovascular risk in ESRD patients. Intimal calcification is associated with plaque vulnerability, and medial calcification is associated with vascular stiffness. In an autopsy study, renal function and traditional coronary risks were linked to intimal calcification in coronary arteries; however, medial calcification occurred only in patients with chronic kidney dysfunction (CKD).¹⁵⁾ PO₄, calcium, potassium, parathyroid hormone, fetuin-A, osteoprotegerin, and osteopontin are novel biomarkers that were shown to be associated with coronary calcification that increases cardiovascular risk in CKD patients.^{14,16–18)}

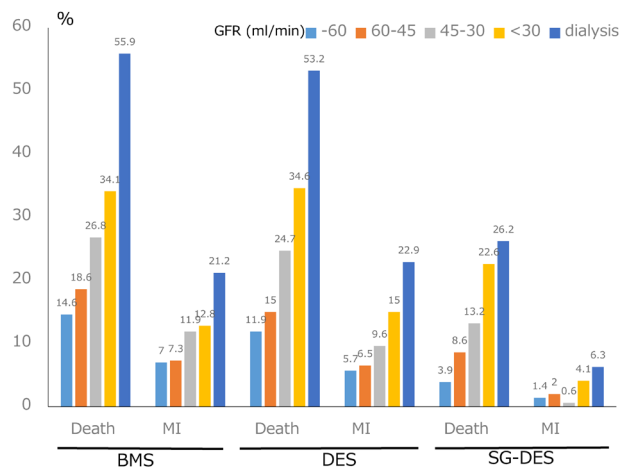


Fig. 1 Three-year mortality and myocardial infarction (MI) rates following coronary stents implantation according to the severity of renal dysfunction.^{20,21)}

Percutaneous Coronary Intervention

Impact of the severity of renal dysfunction on clinical outcomes following coronary stents implantation

The association between CKD and cardiovascular events following coronary intervention has been a main focus of many studies over the past decade.¹⁹⁾ Several studies showed worsened clinical outcomes after coronary revascularization, which were dependent on the severity of renal dysfunction^{20,21)} (Fig. 1). ESRD patients on hemodialysis comprise the most severe category of renal dysfunction; thus, clinical outcomes in these patients are the worst compared to those with other types of dysfunction. Patients on hemodialysis tend to have multivessel, diffuse, and calcified coronary artery disease.¹³⁾ Rigid calcified vessels impede the delivery of coronary stents and are associated with stent under-expansion, which is one of the main risk factors for stent restenosis and stent thrombosis.^{22,23)} In addition, severe endothelial dysfunction, enhanced platelet activation, and poor response to antiplatelet drugs contribute to the poor outcomes after coronary stent implantation in hemodialysis patients.^{24,25)}

Drug-eluting stents versus bare metal stents in hemodialysis patients

Drug-eluting stents (DESs) were developed to reduce in-stent restenosis, the Achilles heel of coronary stents. Restenosis rate is dramatically reduced with DES implantation compare to bare metal stents (BMSs) in patients with complex clinical presentation including renal dysfunction.^{20,26)} However, not many studies have investigated whether the efficacy of DES implantation in reducing restenosis is sustained in hemodialysis patients. Furthermore, hemodialysis patients are at a high risk for serious bleeding

events due to uremia-induced platelet dysfunction and chronic anticoagulant use during hemodialysis. Therefore, hemodialysis patients are more likely to discontinue dual antiplatelet therapy, which exacerbates the risk of stent thrombosis, a major limitation of DESs, especially the first-generation models.²⁷⁾ The safety and efficacy of DESs in comparison with BMSs in hemodialysis patients were evaluated in several observational registries but not randomized trials (Table 1). Although some of these studies did not find significant differences due to the small sample sizes, vast majority of the studies found that the number of clinical events was lower with DESs than with BMSs. In 2010, Abdel-Latif et al. conducted a meta-analysis to examine the clinical outcomes after DES and BMS implantation in hemodialysis patients²⁸⁾ and found that major adverse cardiac events ((MACE), cardiac death, myocardial infarction (MI), and target lesion revascularization) were significantly lower (OR, 0.54; 95%CI, 0.40–0.73) and mortality tended to be lower (OR, 0.68; 95%CI, 0.45–1.01) with DESs compared to BMSs. However, the total number of hemodialysis patients was only 389 in this meta-analysis, and the sample size was too small for sufficient statistic power. The only large database with available data on outcomes after coronary intervention in hemodialysis patients is the USRDS, the US national registry of patients with hemodialysis. From 2003 to 2010, 36,117 hemodialysis patients who underwent coronary

stenting were identified in the USRDS.²⁹⁾ DESs were associated with 18% lower risk of death; 16% lower risk of death or MI; and 13% lower risk of death, MI, or repeat revascularization compared to BMSs. These differences in risks, which were significant for all comparisons, were sustained in ACS patients. Among 9,563 hemodialysis patients with ACS, the use of BMSs was a significant predictor of mortality compared to DESs (hazard ratio [HR], 1.20; 95%CI, 1.13–1.26).³⁰⁾ Thus, current evidence supports the use of DESs over BMSs in hemodialysis patients.

Second-generation DESs

Second-generation DESs are associated with significantly lower in-stent restenosis rate and lower late stent thrombosis rate, compared with the first-generation DESs.³¹⁾ First-generation DESs have been almost completely discontinued. Even in the era of second-generation DESs, hemodialysis remains a significant predictor of MACE. In a post-marketing surveillance study of cobalt-chromium everolimus-eluting stents (EESs) in Japan, hemodialysis was the strongest predictor of MACE (HR, 5.42; 95%CI, 3.46–8.49).³²⁾ In the Korean multicenter DES registry, hemodialysis was found to be a significant predictor of target lesion failure (HR, 5.46; 95%CI, 4.13–7.21).²¹⁾ However, second-generation DESs appear to be associated with better angiographic outcomes compared to the first-generation DESs. In a cohort of 100 consecutive

Table 1 DES versus BMS in hemodialysis patients

Authors	Year	Country	Sample size (DES/BMS)	Follow-up (Months)	Clinical outcomes		
					Definition	Event rates (DES versus BMS)	
Halkin et al. ⁷⁸⁾	2006	USA	33/41	12	Death/MI/TVR	25.2% versus 57.3%	p=0.01
Das et al. ⁷⁹⁾	2006	USA	24/65	9	Death/MI/TVR	33% versus 60%	p=0.03
Ishio et al. ⁸⁰⁾	2007	Japan	54/54	9	Death/MI/TLR	14% versus 21%	p=0.4
Okada et al. ⁸¹⁾	2008	Japan	80/124	12	CD/MI/ST/TLR	25.2% versus 38.2%	p=0.048
Aoyama et al. ⁸²⁾	2008	Japan	88/78	12	TLR	17.0% versus 20.5%	p=0.57
Yachi et al. ⁸³⁾	2009	Japan	56/67	9	Death/MI/TLR	25.0% versus 38.9%	p=0.02
Kim et al. ⁸⁴⁾	2009	Korea	54/51	36	Death/MI/TLR	37% versus 43%	p=0.33
Ichimoto et al. ⁸⁵⁾	2010	Japan	63/45	36	Death/MI/TLR	24.7% versus 31%	p=0.61
Ishii et al. ⁸⁶⁾	2012	Japan	301/204	72	CD/MI/ST/TLR	42.5% versus 58.0%	p=0.036
Shroff et al. ⁶²⁾	2013	USA	11844/5011	60	Death	76% versus 81%	p=N.A.
Meliga et al. ⁸⁷⁾	2013	Italy	92/77	50	Death/MI/stroke/all revascularization	49.1% versus 42.4%	p=0.11
Fujita et al. ⁸⁸⁾	2014	Japan	58/36	12	Death/MI/TLR	53% versus 21%	p=0.0037
Shroff et al. ³⁰⁾	2016	USA	ACS	24	Death	52% versus 57%	p=N.A.
			6566/2997 Non-ACS 5278/2014	24	Death	41% versus 48%	p=N.A.
Lee et al. ⁸⁹⁾	2016	Taiwan	738/2097	12	Death/MI/stroke/all revascularization	32.5% versus 40.2%	p=0.0012
Chang et al. ²⁹⁾	2016	USA	24915/11202	12	Death/MI/all revascularization	67.0% versus 81.3%	p=N.A.
Chen et al. ⁹⁰⁾	2016	Taiwan	492/492	14.4	CD/MI/revascularization	41.7% versus 47.6%	p=0.005
Asami et al. ⁷⁷⁾	2016	Japan	64/59	84	CD/MI/ST/TVR	66.0% versus 70.0%	p=0.42

ACS: acute coronary syndrome; BMS: bare metal stent; CD: cardiovascular death; DES: drug-eluting stent; MI: myocardial infarction; ST: stent thrombosis; TLR: target lesion revascularization; TVR: target vessel revascularization

hemodialysis patients, EESs were associated with significantly lower rates of late loss (0.26 mm versus 0.53 mm, $p=0.03$) and binary restenosis (8.7% versus 21.2%, $p=0.04$) after stenting, compared to sirolimus-eluting stents (SES) at one year.³³ This significant effect on inhibition of neointimal growth was consistent with the findings of a study of the multicenter registry in Japan (OUCH-PRO registry), which revealed that the average rate of late loss was 0.37 mm and that the binary restenosis rate was 16%.³⁴ Clinical outcomes were also acceptable in this subset of patients with worst and complex disease presentation. They also reported that the incidence of target lesion failure was 18% and that no stent thrombosis was recorded at one year among a cohort of 123 hemodialysis patients. However, few reports investigated whether second-generation DESs significantly improved clinical outcomes compared to first-generation DESs. Otsuka et al. compared clinical outcomes between EESs ($n=102$) and paclitaxel-eluting stents (PESs) ($n=107$) in hemodialysis patients. The incidence of 3-year MACE was 13.2% in the EES group and 17.4% in the PES group ($p=0.25$).³⁵ Currently, several uncertainties regarding second-generation DESs in hemodialysis patients remain to be answered, including the best DES type among those currently available and the efficacy of bioresorbable polymer-based DESs in improving angiographic and clinical outcomes compared to durable polymer-based DESs. Further assessment of these unsettled issues are warranted in future studies.

Rotational atherectomy

Severely calcified lesions are a specific characteristic of coronary artery disease in hemodialysis patients. Stent implantation for severely calcified lesions may result in stent under-expansion, incomplete stent apposition, and damage to the polymer on DES struts. Rotablator is a rotational atherectomy device that uses a high-speed, rotating, diamond-coated elliptical burr and is enabled to modify superficial calcifications in plaques.^{36,37} Rotablator can theoretically facilitate stent delivery and stent expansion as well as avoidance of polymer damage. Several studies evaluated clinical outcomes after rotational atherectomy and SES implantation between hemodialysis and non-hemodialysis patients with severely calcified lesions; they found that clinical outcomes were significantly worse in hemodialysis patients than in non-hemodialysis patients³⁸⁻⁴⁰ (Fig. 2). Although the underlying causes for the worse clinical outcomes in hemodialysis patients were unclear, there are several potential explanations. First, the degree of the calcium arc and thickness were more severe in hemodialysis patients than in non-hemodialysis patients. Rotational atherectomy may not be sufficient to remove calcification while avoiding stent under-expansion, incomplete apposition, and polymer damage in

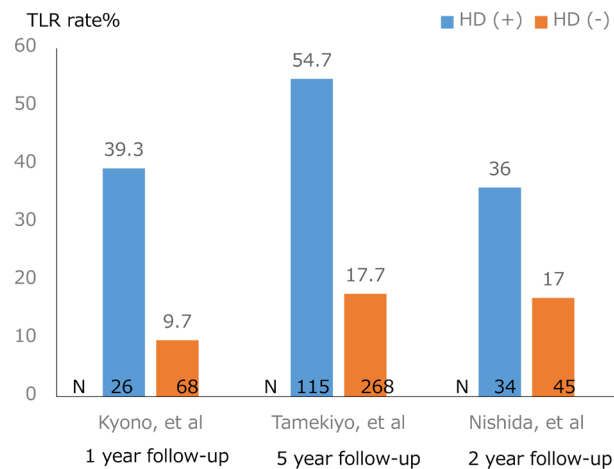


Fig. 2 Target lesion revascularization rate (TLR) after rotational atherectomy and SES implantation in severe calcified lesion with and without dialysis.³⁸⁻⁴⁰

hemodialysis patients. Second, the eluted drug may not be able to penetrate the thick calcified plaque in hemodialysis patients. Third, severe endothelial dysfunction, enhanced platelet activation, and poor response to antiplatelet drugs in hemodialysis patients tend to augment thrombosis formation on the stent strut, which is the etiology of stent restenosis and thrombosis. Although the outcomes of rotational atherectomy are suboptimal in hemodialysis patients, there are no other interventional treatment options for the severe complexed coronary disease observed in hemodialysis patients.

Drug-coated balloons

Drug-coated balloons (DCBs) are an alternative option for the treatment of coronary artery disease. Paclitaxel-coated balloons, which are available only in Japan, are used for in-stent restenosis (ISR) and small vessel lesions.^{41,42} The efficacy of DCBs in arteriovenous hemodialysis access in hemodialysis patients has been reported, which found that DCBs significantly improved patency compared to balloon therapy.⁴³ However, arteriovenous access disease does not generally include severely calcified lesions such as those observed with coronary artery disease in hemodialysis patients. Application of DCBs for coronary artery disease has not been reported in hemodialysis patients. Therefore, the safety and efficacy of DCBs for calcified lesions in hemodialysis patients is largely unknown.

Bioresorbable scaffolds

Everolimus-eluting bioresorbable scaffolds (BRSs) based on poly-L-lactic acid (Abosrb GT1™) are the only FDA-approved BRSs. The scaffold is ultimately converted into carbon dioxide and water at approximately four years after BRS implantation.⁴⁴ BRSs have several advantages over metallic stents. The removal of rigid struts facilitates

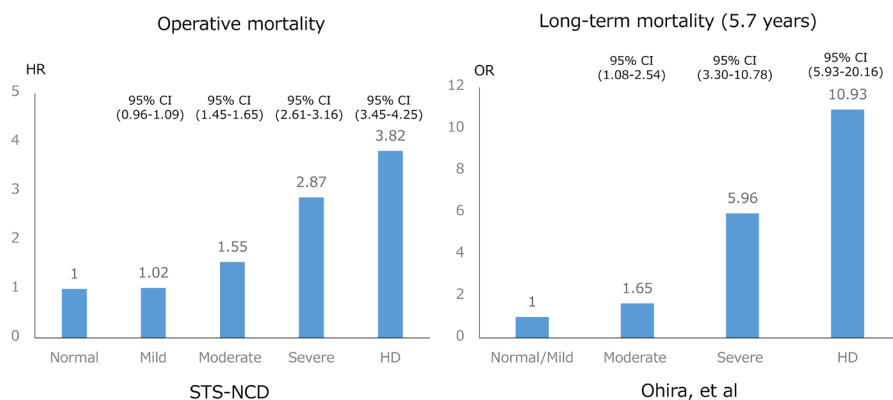


Fig. 3 Impact of the severity of renal dysfunction on clinical outcomes following coronary artery bypass grafting (CABG).^{57,58)}

the return of vessel vasomotion, adaptive shear stress, late luminal enlargement, and late expansive vessel remodeling. However, recent trials alert the safety of BRSS. In the AIDA trial, the rate of definite device thrombosis was significantly higher in the scaffold group than the metal stent group at two years (3.1% versus 0.6%, $p < 0.001$).⁴⁵⁾ This tendency for increased thrombosis rate was confirmed in several meta-analysis.^{46–48)} Late scaffold discontinuity may cause dislocation of the strut remnants into the lumen, leading to disturbed hemodynamic flow and activation of the thrombotic cascade.⁴⁹⁾ To avoid the risk of device thrombosis, sufficient strut embedment and scaffold dilatation (with a final residual stenosis of less than 10%) are recommended.^{50–52)} As severely rigid calcified plaques are one of the specific characteristics in hemodialysis patients, sufficient scaffold dilatation and embedment is difficult especially in hemodialysis patients. Furthermore, extent of the resorption of the bioresorbable material is not clear in hemodialysis patients. Therefore, BRSS are currently not recommended in hemodialysis patients.

Coronary Artery Bypass Grafting

Impact of the severity of renal dysfunction on clinical outcomes after coronary artery bypass graft

Renal dysfunction is a well-known risk factor for mortality and perioperative complications after coronary artery bypass graft (CABG).^{53–56)} Operative risk and mortality increases with increasing severity of renal dysfunction^{57,58)} (Fig. 3). Hemodialysis in ESRD patients is associated with the worst clinical outcomes compared with that in those with other types of renal dysfunction. In the Society of Thoracic Surgeons National Adult Cardiac Database, perioperative mortality was very high in hemodialysis patients compared to those with normal renal function (OR, 3.82; 95%CI, 3.45–4.25).⁵⁷⁾ A study from Japan reported that the long-term mortality was also very high in hemo-

dialysis patients compared to those with normal and mild renal dysfunction (HR, 10.93; 95%CI, 5.93–20.16).⁵⁸⁾ Furthermore, hemodialysis duration affects clinical outcomes. In the Taiwan national database, hemodialysis for more than three years was associated with significantly worse mortality than that was less than three years (HR, 1.56; 95%CI, 1.35–1.80).⁵⁹⁾

Use of internal mammary artery or off-pump CABG

CABG on a beating heart (off-pump CABG, OFP-CABG) was developed to decrease the risk of perioperative complications and improve long-term outcomes.⁶⁰⁾ Some complications associated with on-pump CABG (ONP-CABG) may be related to the use of cardiopulmonary bypass and to cross-clamping of the aorta. However, OFP-CABG did not improve clinical outcomes in hemodialysis patients. In a meta-analysis evaluating clinical outcomes in hemodialysis patients treated with OFP-CABG ($n = 2762$) or ONP-CABG ($n = 11310$), mortality and perioperative complications were similar between the OFP-CABG and ONP-CABG groups.⁶¹⁾ Conversely, several studies demonstrated the significant effect of internal mammary artery (IMA) grafts. In the USRDS, use of IMA grafts was independently associated with a reduced hazard of long-term mortality (HR, 0.83; 95%CI, 0.77–0.90).⁶²⁾ Thus, current evidence strongly supports the use of IMA grafts in hemodialysis patients undergoing CABG.

CABG versus percutaneous coronary intervention

Hemodialysis patients have a high burden of coronary artery disease, which includes multivessel and diffuse disease. Although there were several randomized trials comparing CABG and percutaneous coronary intervention (PCI) in multivessel coronary disease, none of the trials included hemodialysis patients. Evidence from several observational registries comparing CABG with PCI in

hemodialysis patients is inconclusive. Heterogeneity of the study populations, treatment strategies (e.g., DES or BMS, use of IMA), and small sample sizes from single-center studies hinder substantial results. To overcome these limitations, several meta-analyses compared CABG with PCI in hemodialysis patients (Table 2), which revealed consistent clinical findings. Compared to PCI, early mortality was significantly higher and long-term clinical events including mortality were significantly lower after CABG; these outcomes were reconfirm in the USRDS. From 1997 to 2009, 14,316 and 7,665 hemodialysis patients underwent CABG and PCI, respectively. In this cohort, relative risk of short-term mortality (six months) was 1.08 (95%CI, 1.01–1.06) and long-term mortality (five years) was 0.88 (95%CI, 0.85–0.92) after CABG, compared to PCI.⁶³ Even in the second-generation DES era, a similar trend was observed. In the New York State database, PCI using EESs was associated with significantly higher 4-year mortality than CABG in hemodialysis patients (HR, 2.02; 95%CI, 1.40–2.93).⁶⁴ However, these studies have several limitations, and the results should not be generalized. First, patient and procedural characteristics such as the presence of diabetes, left ventricular function, hemodialysis duration, and use of IMA and stent type were heterogeneous. Second, coronary lesion complexity was not assessed. Syntax score is useful for prediction of clinical outcomes after coronary revascularization in patients with multivessel and left main coronary artery disease.⁶⁵ Although the outcomes with DES and CABG were not significantly different in patients with low syntax scores in several studies,⁶⁶ there are currently no evidence on whether these findings extend to hemodialysis patients. Considering the current evidence, clinical decision-making on coronary revascularization should be individualized. Status of patients and coronary lesion morphology are important factors to determine the optimal strategy for

coronary revascularization.

Medications

Statins

Lowering low-density lipoprotein (LDL) cholesterol with statins reduces the risk of cardiovascular events and is essential for primary and secondary cardiovascular prevention in patients without renal dysfunction. Several studies evaluated the efficacy of statins in patients with renal dysfunction. The largest of these studies is SHARP (the Study of Heart and Renal Protection).⁶⁷ More than 9,000 patients with CKD, including 3,000 hemodialysis patients, were randomly assigned to simvastatin and ezetimibe, with a matching placebo group. Most of the patients were evaluated for primary prevention but not secondary prevention. Reduction of cholesterol with statins significantly reduced cardiovascular events. However, this effect was weaker in hemodialysis patients (Fig. 4). In the CREDO-Kyoto PCI/CABG registry, the efficacy of statins was evaluated for secondary prevention,⁶⁸ which found that statin therapy was associated with significantly lower risk for cardiovascular events in patients with non-CKD and mild CKD undergoing coronary revascularization. However, therapeutic benefits of statins were not apparent in patients with severe CKD on hemodialysis (Fig. 4). The 4D and AURORA randomized trials evaluated the safety and efficacy of atorvastatin and rosuvastatin, respectively, for primary or secondary cardiovascular prevention in hemodialysis patients.^{69,70} Both trials showed that statin therapy had no significant effect on major atherosclerotic events in hemodialysis patients. The efficacy of statins was attenuated in patients with severe CKD or those on hemodialysis. Patients with advanced CKD generally have advanced atherosclerosis, typically characterized by heavily calcification, and statins might no longer be able

Table 2 Meta-analyses for CABG versus PCI in hemodialysis patients

Authors	Years	Number of studies	Early mortality	Late mortality	MI	Repeat revascularization
			Relative risk (95%CI)	Relative risk (95%CI)	Relative risk (95%CI)	Relative risk (95%CI)
Nevis et al. ⁹¹⁾	2009	17	RR 1.82 (1.07–3.09) CABG versus PCI	RR 0.42 (0.26–0.66) CABG versus PCI	—	—
Zheng et al. ⁹²⁾	2013	16	RR 1.98 (1.51–2.60) CABG versus PCI	RR 0.90 (0.87–0.93) CABG versus PCI	RR 0.64 (0.87–0.93) CABG versus PCI	RR 0.22 (0.16–0.31) CABG versus PCI
Deo et al. ⁹³⁾	2013	16	RR 0.51 (0.40–0.64) PCI versus CABG	RR 2.26 PCI versus CABG	RR 1.48 (0.93–2.36) PCI versus CABG	RR 2.70 (1.83–3.99) PCI versus CABG
Krishnaswami et al. ⁹⁴⁾	2016	23	—	RR 0.92 (0.89–0.96) CABG versus PCI	—	—
Bundhun et al. ⁹⁵⁾	2016	18	—	RR 0.81 (0.69–0.96) CABG versus PCI	RR 0.37 (0.18–0.74) CABG versus PCI	RR 0.20 (0.14–0.30) CABG versus PCI

CABG: coronary artery bypass graft; CI: confidence interval; PCI: percutaneous coronary intervention; RR: relative risk

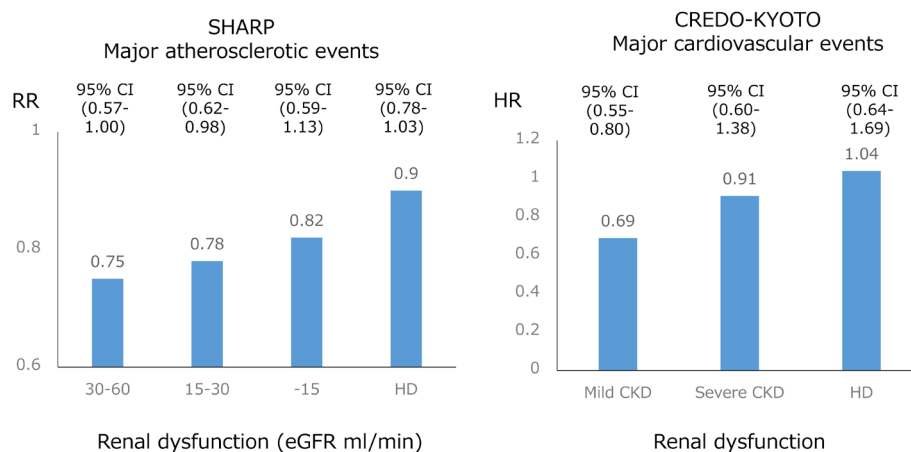


Fig. 4 Impact of the severity of renal dysfunction on clinical outcomes after statin therapy.^{67,68)}

to provide significant benefit in these high-risk patients. Currently, there is no evidence to support for treatment of hemodialysis patients with statins. However, statins are relatively safe, and the evidence on the benefits of lowering cholesterol to reduce cardiovascular disease is overwhelmingly strong in patients without severe renal dysfunction; therefore, it might be reasonable to continue using statins in hemodialysis patients without side effects.⁷¹⁾

Antiplatelet drugs

Patients with CKD have a high risk of cardiovascular disease and are predisposed to bleeding complications. Defining the fine balance between safety and efficacy remains a challenge in patients with ESRD. The efficacy and safety of aspirin for patients with CKD presenting with ACS is established. In a meta-analysis by the Antithrombotic Trialists' Collaboration, low-dose aspirin was found to be efficacious for secondary cardiovascular prevention in patients with CKD on hemodialysis.⁷²⁾ The UK HARP-1 trial and the DOPPS showed that low-dose aspirin in CKD patients was not associated with increased major bleeding events or progression of CKD.⁷³⁾ Similar to aspirin, the current American College of Cardiology/American Heart Association guidelines recommend the use of clopidogrel in patients with ACS. However, few sub-analysis studies investigated the safety and efficacy of thienopyridines such as clopidogrel, prasugrel, and ticagrelor in CKD patients with ACS. Impaired renal function is associated with reduced clopidogrel-induced antiplatelet effects and a greater prevalence of high post-treatment platelet reactivity.⁷⁴⁾ There is a clear dearth of studies evaluating the safety and efficacy of these drugs for treating CKD patients with ACS. The optimal duration of dual antiplatelet therapy (DAPT) after DES placement remains uncertain. Although treatment with DAPT beyond one year after DES implantation reduces MI risk and stent thrombosis, it is also associated with increased mortality

and severe bleeding.⁷⁵⁾ Morel et al. reported that the presence of low platelet response to clopidogrel was associated with worse outcomes in CKD patients following coronary intervention.⁷⁶⁾ Only one study compared short- and long-term DAPT in hemodialysis patients following DES implantation. The cumulative incidence of MACE beyond one year was significantly higher in the DAPT-on group (beyond one year) than in the DAPT-off group (less than one year).⁷⁷⁾ Furthermore, bleeding events were 5.1 times more frequent in the DAPT-on group than in the DAPT-off group. An individualized approach, wherein the specific benefit-risk profile of each patient is carefully considered, should be practiced, especially in patients with severe CKD including hemodialysis.

Conclusion

Cardiovascular disease is a major issue for patients with ESRD, especially those on hemodialysis. Nonetheless, most cardiovascular outcome trials have thus far excluded patients with ESRD including those on hemodialysis. Moreover, major cardiovascular outcome trials that have been conducted in patients with ESRD, particularly those on hemodialysis, have not demonstrated treatment benefits. Current revascularization therapies and medications for both primary and secondary presentations are insufficient. Optimal strategies for diagnosis, prevention, and management should be modified in ESRD patients. Trials targeting cardiovascular disease in patients with ESRD have a significant potential to improve outcomes, and there is a big opportunity to improve cardiovascular outcomes in this patient population that is overlooked/excluded in cardiovascular disease trials.

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