Pharmacological and Non Pharmacological Strategies in the Management of Coronary Artery Disease and Chronic Kidney Disease

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Abstract: Patients with advanced chronic kidney disease (CKD), including those treated with dialysis, are at high risk for the development of cardiovascular disease (CVD). CVD accounts for 45-50% of deaths among dialysis patients. Therapy of acute and chronic coronary heart disease (CHD) that is effective in the general population is frequently less effective in patients with advanced CKD. Drug therapy in such patients may require dose modification in some cases. Oral anti-platelet drugs are less effective in those with advanced CKD than in persons with normal or near normal renal function. The intravenous antiplatelet drugs eptifibatide and tirofiban both require dose reductions in patients with advanced CKD. Enoxaparin requires dose reduction in early stage CKD and is contraindicated in hemodialysis patients. Unfractionated heparin and warfarin maybe used without dose adjustment in CKD patients. Atenolol, acetbutolol and nadolol may require dose adjustments in CKD. Metoprolol and carvedilol do not. Calcium channel blockers and nitrates do not require dose adjustment, whereas ranolazine does. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers may safely be used in CKD patients with close observation for hyperkalemia. The safety of spironolactone in such patients is questionable. Statins are less effective in reducing cardiovascular complication in CKD patients and their initiation is not recommended in dialysis patients. Coronary artery bypass grafting is associated with higher short-term mortality, but better long-term morbidity and mortality than percutaneous coronary interventions in patients with advanced CKD with non-ST segment ACS and chronic CHD.

Keywords: Chronic kidney disease, end-stage renal disease, dialysis and hemodialysis, acute coronary syndrome, chronic coronary heart disease, pharmacotherapy, myocardial revascularization.

INTRODUCTION

Coronary heart disease (CHD) occurs commonly in patients with chronic kidney disease (CKD), particularly in those with end-stage renal disease (ESRD) treated with dialysis [1-20]. In the HEMO study nearly 40% of the 1,846 patients entered had ischemic heart disease on entering the study [9]. During the mean follow-up period of 2.8 years angina pectoris and acute myocardial infarction caused 43% of all cardiac hospitalizations. The United States Renal Data System (USRDS) surveys suggest that the annual rate of myocardial infarction and/or angina pectoris in dialysis patients is approximately 10% [10]. In a study by Parekh *et al.* the incidence of new onset atherosclerosis (predominantly CHD) was 147/1000 patient years in Caucasians and 119/1000 patient years in African-Americans in the United States [11]. Occult or silent-myocardial ischemia occurs commonly in dialysis patients. Ohtake and colleagues reported >50% stenosis of at least one coronary artery on coronary angiography in 16 of 30 asymptomatic patients receiving renal replacement therapy [12]. Charytan and co-workers reported $\geq 50\%$ stenosis of at least one coronary

artery in 28 of 67 asymptomatic patients receiving dialysis, 19 of whom had high-grade proximal stenosis [13]. Conlon *et al.* reported evidence of dynamic ST segment depression or ambulatory electrocardiographic monitoring in 16 of 67 asymptomatic dialysis patients suggesting silent myocardial ischemia [14]. In a Canadian multicenter study involving 432 patients beginning dialysis who were followed for a mean duration of 41 months, cardiac and vascular disease was common [15]. Myocardial infarction or unstable angina pectoris occurred in 15%, stable angina pectoris occurred in 19%, heart failure occurred in 31%, arrhythmias occurred in 7% and peripheral arterial disease occurred in 8% [15]. The USRDS Wave II Dialysis Morbidity and Mortality Study reported an incidence of acute coronary syndrome (ACS) of 2.9 % per year among 3329 incident dialysis patients followed for two years [16]. USRDS data from 1998-2000 demonstrated that among dialysis patients in the United States, the death rate was 23.6% per year with cardiac disease accounting for 45% of deaths [10]. Myocardial infarction accounted for 20% of cardiac deaths and sudden cardiac arrest accounted for 60% of cardiac deaths. Subsequent studies have shown a similar distribution of causes of death in dialysis patients [17-20]. Thus, cardiovascular disease (CVD) accounts for 45-50% of deaths in patients receiving dialysis. The mortality risk is 10-20 times higher in dialysis patients than in the patients from the general population

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matched for age, gender and race [17-20]. In younger patients receiving renal replacement therapy the risk of death from CVD approaches 100 times that at the age-matched population [20]. In a study of 34,198 HD patients cardiac mortality after acute myocardial infarction was 40.8% at one year, 51.8% at two years and 70.2% at five years [16]. Among patients with coronary artery disease detected on coronary angiography, the incidence of multi-vessel disease is significantly higher in hemodialysis (HD) patients than in non-HD patients (87% vs. 62%, $p < 0.05$) as is the incidence of calcified lesions (81% vs. 37%, $p < 0.05$) [20]. CHD may present acutely (ACS, sudden cardiac arrest) or chronically (stable angina pectoris, silent myocardial ischemia, ischemic cardiomyopathy). During the past 35 years numerous therapeutic modalities have been developed to treat acute and chronic CHD and have been successful in reducing morbidity and mortality in such patients in the general population [21, 22]. However, the pathophysiology and natural history of CHD in patients with advanced CKD (particularly treated with HD) differs in many respects from that in the general population [23-26]. Many therapeutic modalities that are effective in treating CHD in the general population are not as effective in patients with advanced CKD (stages 4-6) [23-27]. The purpose of this review is to discuss the efficacy and safety of pharmacologic and non-pharmacologic therapies used to treat acute and chronic CHD in patients with advanced CKD with special emphasis on those receiving HD, and to provide recommendations concerning the use of these modalities in such patients.

PHARMACOTHERAPY

Oral Anti-platelet Drugs

Oral anti-platelet drugs are employed routinely in patients with ACS and in those with chronic CHD [21, 22, 27]. Oral anti-platelet drugs used in CHD include aspirin, clopidogrel, prasugrel and ticagrelor [21, 22].

Aspirin has been shown to reduce short and long-term CV mortality and morbidity in patients with ACS and in those with chronic CHD in the general population [21, 22, 28-30]. Clinical trials specifically assessing the effect of aspirin on CV morbidity or mortality in HD patients are lacking; however, several studies have assessed the effect of aspirin on CV outcomes in patients with CKD and CVD [28-30]. In a post-hoc analysis of the Hypertension Optimal Treatment Trial by Gum *et al.* which included 18,597 patients with an estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73m² and who received aspirin 75 mg orally daily had significant reductions in major cardiac events (RR:0.66, 95% CI:0.33-0.83, $p=0.03$) and total mortality (RR: 0.49, 95% CI:0.06-0.73, $p=0.04$) compared to those with an eGFR ≥ 45 ml/min/1.73m² [2, 30]. There was a non-significant trend towards increased bleeding in the group receiving aspirin. In a meta-analysis of 50 studies comprising 27,139 patients with CKD of any stage (including 4820 dialysis patients) Palmer and colleagues showed that the risk of fatal and non-fatal myocardial infarction was significantly reduced in patients treated with oral anti-platelet drugs compared to those not treated with oral anti-platelet therapy (RR:0.66, 95% CI:0.51-0.87); however, there was no significant effect on total mortality [31]. A beneficial effect of oral

anti-platelet therapy was not observed in the HD subgroup which may be attributable to lack of statistical power (non-HD patients outnumbered HD patients by a factor of 3.8) [31]. Aspirin was the most common anti-platelet drug used in this study. No dose adjustments (Table 1) in aspirin are required in patients with CKD although close observation for gastrointestinal bleeding is advised.

Clopidogrel is a first generation thienopyridine that inhibits ADP-related platelet activation. It has been shown to be less effective in patients with than in those without CKD [31-34]. This may be attributable to reduced ADP-related glycoprotein IIb/IIIa receptor exposure leading to less platelet aggregation, increased platelet turnover, or impaired clopidogrel absorption. In a post-hoc analysis of the CREDO trial by Best and co-workers patients with mild to moderate CKD who received clopidogrel demonstrated no significant reduction in cardiovascular events at one year [34]. No dose adjustment is required in CKD patients receiving clopidogrel.

Prasugrel is a third generation oral thienopyridine P2Y₁₂ receptor antagonist [31, 35]. It has a more rapid time to peak effect than clopidogrel. In the TRITON-TIMI 38 trial prasugrel was more effective than clopidogrel in reducing cardiovascular events in patients with CKD [30, 35]. No information exists concerning the efficiency of prasugrel in HD patients. Prasugrel's active metabolite levels are reduced by 40% in ESRD, although the degree of platelet inhibition is similar to that of patients with normal renal function [30, 35]. For this reason no dose adjustment is required in patients with CKD receiving prasugrel. Bleeding risk is higher in patients receiving prasugrel than in those receiving clopidogrel in patients with and without CKD [30, 35].

Ticagrelor is a reversible P2Y₁₂ receptor antagonist. Like prasugrel, ticagrelor produces a more effective anti-platelet effect than clopidogrel [30, 36, 37]. In the PLATO trial ticagrelor significantly reduced the primary composite endpoint of CV death, myocardial infarction and stroke at 12 months compared to clopidogrel in patients with ACS [36]. In this study patients receiving ticagrelor did not have more major bleeding, but did have more procedure-related bleeding than those receiving clopidogrel [36]. Ticagrelor is cleared through the liver and doesn't require a dose adjustment in patients with CKD including those with ESRD [36].

Intravenous Anti-platelet Drugs

Multiple randomized clinical trials in the general population have shown a reduction in major adverse CV events with the addition of intravenous glycoprotein IIb/IIIa receptor antagonists to standard therapy of ACS, particularly in those receiving PCI [21, 22, 38-40]. Glycoprotein IIb/IIIa receptor antagonists used in these studies include abciximab, eptifibatide and tirofiban [21, 22, 38-40]. In a study of 889 patients with ACS, 312 were noted to have varying degrees of CKD. After adjustment for creatinine clearance intravenous glycoprotein IIb/IIIa receptor antagonist therapy was associated with reduced in-hospital mortality (adjusted OR:0.34, 95% CI:0.12-0.98, $p<0.04$) [40]. For patients with CKD undergoing PCI, abciximab does not require dose adjustment in patients with CKD as it is metabolized by the liver. Eptifibatide requires a 50% dose reduction in patients

Table 1. Dose adjustments for drugs used in CKD in patients with acute or chronic CHD.

Drug	Dose Adjustment In CKD/Dialysis
Aspirin	None
Clopidogrel	None
Prasugrel	None
Ticagrelor	None
Abciximab	None
Eptifibatide	50% dose reduction with a creatinine clearance <50 ml/min
Tirofiban	50% dose reduction with a creatinine clearance <30 ml/min
Unfractionated heparin	None
Enoxaparin	Reduce by 50% with CKD; contra-indicated in dialysis patients
Warfarin	None
Bivalrudin	No specific guidelines
Fondaparinux	No specific guidelines
Fibrinolytics	No specific guidelines
Beta-and alpha/beta-blockers	None required for metoprolol or carvedilol; possible dose reduction for atenolol, acetbutalol and nadolol
Calcium channel blockers	None required
Nitrates	None required
Ranolazine	Dose reduction required
ACE inhibitors	Initiate low dose and increase as tolerated; observe for deterioration of renal function and hyperkalemia
Angiotensin receptor blockers	Initiate low dose and increase as tolerated; observe for deterioration of renal functions and hyperkalemia
Aldosterone receptor blockers	Safety not well-established in advanced CKD
Statins	No dose adjustment required; efficiency not well-established in dialysis patients

Abbreviations: CKD = chronic kidney disease, CHD = chronic heart disease, qd = once per day, bid = twice per day, IV = intravenous, SQ = subcutaneous, ACE = angiotensin converting enzyme

with a creatinine clearance <50 ml/min [40]. Tirofiban requires a 50% dose reduction in those with a creatinine clearance <30 ml/min [38, 41, 42]. Neither eptifibatide nor tirofiban should be used in patients on HD as they are both associated with a greater risk of bleeding in such patients compared to abciximab [40, 41].

Anticoagulant Therapy

Anticoagulants are used most commonly to treat CHD in patients with or without CKD who have developed ACS [21, 22, 41-45]. In the general population intravenous infusion of unfractionated heparin and subcutaneous enoxaparin have received IA recommendations from the American Heart Association and American College of Cardiology as adjunctive therapy for STEMI, NSTEMI and unstable angina pectoris [21, 22]. Bivalrudin (a direct anti-thrombin drug) has received an IB recommendation [21, 22]. Unfractionated heparin may be used safely in all classes of CKD (including HD patients) without dose adjustment [21, 22, 41, 42, 44]. The dose of enoxaparin should be reduced by 50% in patients with CKD and is contra-indicated in HD patients as it is, to a

large extent, metabolized by the kidney [41, 43, 44]. No data are available concerning the safety and efficacy of bivalrudin in CKD patients with ACS. Bivalrudin is cleared by the kidney and is dialyzable. In the ACUTY trial which compared bivalrudin with other anti-coagulant/anti-platelet strategies, patients with non-ST segment ACS and a creatinine clearance <30 ml/min were excluded [45]. No data exists on the safety and efficacy of fondaparinux (a factor Xa inhibitor) in patients with advanced CKD and ACS. There are no formal criteria or dose modification guidelines for the use of fibrinolytic agents including streptokinase, alteplase, reteplase, lanetaplastase and tectaplastase in STEMI patients with advanced CKD including those receiving HD [21, 22].

At one time, warfarin was used as a substitute for aspirin following acute myocardial infarction in aspirin-intolerant or aspirin allergic patients. With the advent of multiple oral anti-platelet drugs, this is no longer necessary. Warfarin is used primarily for left ventricular thrombus or in patients with atrial fibrillation who develop ACS [21, 22]. Current guidelines suggest that if warfarin is to be used in patients receiving dual antiplatelet therapy that the target INR should be 2.0-2.5. Newer oral anticoagulant drugs including dabiga-

tran, rivaroxaban and apixaban are not currently approved for use in patients with ACS in the United States [46-48].

Anti-ischemic Drug Therapy

In the general population most, but not all studies assessing the effect of beta- and alpha/beta-adrenergic blocking agents (metoprolol, bisoprolol, carvedilol) in acute myocardial infarction have demonstrated improved survival, reduced risk for sudden cardiac death and a decrease in recurrence in patients who treated with these drugs [21, 22]. There are no studies specifically assessing the effect of beta-blockers or alpha/beta blockers on prognosis after acute myocardial infarction in patients with CKD. However, indirect evidence suggests that such agents may improve mortality in patients with advanced CKD. Among 11,142 patients in the 2012 USRDS registry, 8.5% received beta-blockers. Their use was associated a lower adjusted mortality rate (HR: 0.72, 95% CI: 0.66-0.79, $p < 0.0001$). The extent to which this occurred in patients with CHD or following myocardial infarction is uncertain. Both selective and non-selective beta-blockers have been shown to reduce CVD events in patients with CKD and heart failure [49-52]. Carvedilol is cleared by the liver and does not require dose adjustment in CKD. Atenolol, acetbutalol and nadolol undergo renal clearance and may require dose adjustment in patients receiving dialysis [49-52].

In the general population, first generation calcium channel blockers are commonly used to treat stable angina pectoris in the absence of moderate to severe left ventricular systolic dysfunction [51, 53]. Among second generation calcium channel blockers, amlodipine and nifedipine may be safely used for this purpose independent of left ventricular systolic function [51, 53]. First generation calcium channel blockers are generally avoided after ACS. Second generation calcium channel blockers may be safely used to treat hypertension in such patients [51, 53]. There are no studies assessing the role of calcium channel blockers in patients with CKD and ACS. Second generation dihydropyridine calcium channel blockers may be safely used to treat chronic stable angina pectoris in patients with CKD [51, 53]. Diltiazem and verapamil may be used in such patients in the absence of moderate to severe left ventricular systolic dysfunction.

Sublingual nitroglycerin and long-acting oral nitrates are hepatically-metabolized. They may be used safely in patients with CKD including those receiving HD.

Ranolazine blocks inward sodium channels and has been shown to reduce the frequency of stable angina pectoris in patients with chronic CHD with no effect on hemodynamics [54, 55]. The drug is 70% cleared by the kidney [54]. In the MERLIN TIMI-36 trial, it failed to reduce cardiovascular events in patients with NSTEMI [55]. It may be considered as a fourth line drug for chronic stable angina pectoris with dose modification in patients with CKD.

Renin-Angiotensin-Aldosterone System Blockers

Current guidelines recommend the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB's) in patients in the general population in patients who have suffered STEMI or NSTEMI and whose

left ventricular ejection fraction is $<40\%$ [21, 22]. These agents have been shown to reduce CV morbidity and mortality in such patients. The role of ACE inhibitors and ARB's in patients with chronic CHD and normal or near-normal left ventricular systolic function is less well-established, with some studies showing improved cardiovascular outcomes and others failing to do so [56-65]. ACE inhibitors and ARB's are generally well-tolerated in patients with CKD, but concern exists about their use in ESRD and particularly in HD patients [56-65]. Some trials have shown little or no hyperkalemia and hypotension, while others have demonstrated an increased incidence of hyperkalemia. A retrospective analysis of 126 HD patients showed that the use ACE inhibitors were associated a 52% improvement in survival (RR:0.482, CI:0.2-0.91) [60]. In the FOSDIAL trial 397 patients receiving HD were randomized to receive either fosinopril or placebo. There was a trend towards improved survival after two years (RR: 0.79, CI: 0.59-1.1, $p = 0.099$) [57]. In a trial of 366 HD patients randomly assigned to receive either an ARB or placebo, the use of an ARB reduced the composite endpoint CV death and specific CVD events (HR: 0.51, 95% CI: 0.33-0.79, $p < 0.002$). In a study of 80 HD patients randomized to receive either candesartan or placebo, candesartan significantly reduced non-fatal CV events (45.9% vs. 16.3%) and mortality (18.9% vs 0%) [63]. Data are sparse concerning the role of combined ACE inhibitor and ARB therapy in advanced CKD. In the VA NEPHRON D and ONTARGET trials combination therapy was associated with an increase in adverse events including acute kidney injury, hyperkalemia and death [64, 65].

The efficacy and safety of aldosterone receptor blockers and direct renin inhibitors has not been firmly established in patients with advanced CKD [66-69]. Several small studies have shown the aldosterone receptor blockers may be safe in HD patients with close monitoring of serum potassium levels. In a recent trial of 309 HD patients, 157 received spironolactone. There was a significant reduction in death and hospitalization for CV causes in this study (HR: 0.379, CI: 0.173-0.832, $p = 0.016$) [69].

The preponderance of evidence suggests that ACE inhibitors and ARB's may reduce CV morbidity and mortality in advanced CKD. There is insufficient evidence thus far concerning the effect of aldosterone receptor blockers and direct renin inhibitors on cardiovascular morbidity and mortality to recommend their routine use for this purpose in such patients.

Lipid Modification Therapy

Multiple randomized clinical trials have demonstrated that statins are capable of significantly reducing CV morbidity and mortality in the general populations. These observations apply to both primary prevention and secondary prevention populations. Such benefits have not been demonstrated in patients receiving HD [70-75].

Three large randomized clinical trials have studied the effects of various lipid modification drugs on CV outcomes in patients with CKD. The 4D (Deutsche Diabetes Dialysis) study randomized 1255 HD patients with diabetes mellitus to receive either atorvastatin 20 mg per day or placebo [72]. Patients were followed for a median of four years. The pri-

mary endpoint was CV death, non-fatal myocardial infarction or non-fatal stroke. The study showed no significant difference in the primary endpoint at six years. However, in patients whose LDL cholesterol was ≥ 145 mg/dl (highest LDL quartile) atorvastatin therapy was associated with a significantly lower cumulative incidence of the primary endpoint, death from cardiac causes, sudden death, non-fatal myocardial infarction and all cardiac events. The AURORA trial randomized 2,776 HD patients to receive either rosuvastatin 10 mg per day or placebo [73]. The primary composite endpoint was CV death, non-fatal myocardial infarction or non-fatal stroke. There was no significant difference in the cumulative incidence of the primary endpoint at five years between rosuvastatin and placebo-treated patients. However, patients on HD with diabetes mellitus in the AURORA trial appeared to benefit from rosuvastatin therapy HR: 0.08, 95% CI: 0.51-0.90). The SHARP trial randomized 9,000 patients with CKD (including 3,023 on maintenance dialysis) to receive either simvastatin 20 mg and ezetimibe 10 mg or placebo [74]. Patients were followed for a median of 4.9 years. There was a significant reduction of the cumulative incidence of first major atherosclerotic vascular event at five years (risk reduction: 17%, 95% CI: 0.06-0.26, $p = 0.0021$) favoring simvastatin/ezetimibe with the curves beginning to diverge at one year. A subgroup analysis of the SHARP trial demonstrated significant reductions non-hemorrhagic stroke, any revascularization and major atherosclerotic events, but not in major coronary events [74].

It is uncertain why statins are less effective in reducing CV events in HD patients than in the general population. Explanations include the possibility that greater inflammation exists in HD patients that cannot be overcome by statin therapy, no effect on electrolyte-related arrhythmias and reduced nitric oxide production which may interfere with the pleiotropic effects of statins. The 2013 KDIGO guidelines did not recommend beginning statin therapy in HD patients despite the high CV risk, but do suggest continuation of statin therapy of patients already receiving it prior to initiating of HD [76-78]. Guidelines for management of dyslipidemia in the general population may be applied to patients with CKD not receiving HD.

MYOCARDIAL REVASCULARIZATION

Myocardial revascularization may be achieved by surgical means or percutaneous coronary intervention (PCI). In the general population aortocoronary bypass, also known as coronary artery bypass grafting (CABG) is performed primarily in patients with multi-vessel coronary artery disease, particularly in those with high-grade proximal stenoses and/or severe left main stenosis. Prior studies have demonstrated that CABG is superior to medical therapy in patients with significant triple vessel coronary artery disease and moderate to severe left ventricular systolic dysfunction as well as in those with left main stenosis $\geq 50\%$. Advanced CKD is a major risk factor in patients undergoing CABG. PCI refers to catheter-based procedures that restore blood flow to ischemic segments of myocardium. Percutaneous transluminal coronary angioplasty, while still performed, has largely been replaced by primary stenting with either drug-eluting or bare metal stents. Rotational coronary atherectomy is rarely performed [21]. In patients with CKD, PCI engen-

ders a risk for contrast-induced acute kidney injury. This risk is heightened by the presence of diabetes mellitus and heart failure, two co-morbidities that are commonly present in patients undergoing PCI [21].

In the general population PCI is favored over medical therapy in the management of STEMI (if it can be provided within 90 minutes of the onset of chest pain) and in intermediate to high-risk patients with non-ST segment ACS [21, 22]. CABG in such circumstances is reserved for those with ongoing ischemia despite PCI, failed PCI and patients with severe triple vessel disease and/or left main stenosis. PCI is increasingly employed for myocardial revascularization in patients with chronic CHD in the general population, even in those with multi-vessel coronary artery disease.

CKD, particularly advanced CKD, appears to increase CV risk in patients with acute myocardial infarction [79]. Charytan *et al.* reported that patients with acute myocardial infarction and concomitant CKD had more proximal and longer culprit lesions [80]. In a substudy of the VALIANT trial Anakevar and colleagues reported that each ml/min/1.73m² decrease in eGFR below 81 ml/min/1.73m² was independently associated with increased risk of non-fatal cardiovascular events and death (HR:1.10, 95% CI: 1.08-1.12) [79]. Current guidelines recommend primary PCI in all patients with acute STEMI regardless of renal function if the intervention can be performed within 90 minutes of the onset of chest pain. PCI is also recommended in STEMI patients with CKD with evidence of ongoing myocardial ischemia <12 hours in duration [22]. Current guidelines suggest that there is insufficient evidence for or against an early invasive strategy for patients with advanced CKD in patients with non-ST segment ACS [21]. The SWEDEHEART registry of 23,262 consecutive patients with NSTEMI assessed the effect of early revascularization (within 14 days) by either PCI or CABG in patients with CKD [81]. In patients with stage 3 CKD one year mortality in the overall study population was 36% lower with early revascularization compared to those treated medically (HR:0.64; 95% CI: 0.56 to 0.73; $p < 0.001$). The benefit of an early invasive approach was not evident in patients receiving HD (44% versus 53%; HR: 1.61; 95% CI: 0.84 to 3.09; $p = 0.150$). One-year follow-up after PCI in a cohort of 27 HD patients and 250 non-HD patients showed that cardiac death was more frequent in dialysis patients. In a meta-analysis of seven studies enrolling 23,234 patients 6276 who received early revascularization were compared to 16,958 who received initial medical therapy [82]. Patients with ESRD, were observed to have a 40% reduction in the odds of one-year mortality; however the magnitude of the reduction in mortality with early revascularization diminished with greater severity of CKD.

More information is available concerning the effects of PCI and CABG on CV outcomes in patients with CKD and chronic CHD. In the APPROACH trial three categories of renal function were identified: dialysis-dependent kidney disease ($n = 662$), non-dialysis-dependent kidney disease ($n = 750$) and a reference group (serum creatinine < 2.3 mg/dl, ($n = 40,379$)) [83]. Survival was assessed in subgroups receiving CABG, PCI or no revascularization. The adjusted 8-year survival rates for CABG and PCI were significantly higher in the HD group for those receiving CABG (44.8%) or PCI

(41.2%) than for those receiving no revascularization (30.4%). A study utilizing the New York Department of Health database identified 407 patients with ESRD who underwent PCI or CABG. CABG was associated with reduced CV mortality compared to PCI (RR: 0.39, 95% CI: 0.22-0.67, $p=0.0006$) [84]. Two other studies of patients receiving HD reported decreased CV events in patients who underwent CABG rather than PCI [85, 86]. In a study of patients with ESRD on HD derived from the Duke database CABG was associated with significantly greater survival compared to medical therapy (adjusted HR: 0.45, 95% CI: 0.27-0.74) [87]. A study of 84 HD patients with chronic CHD who were randomized to receive CABG or PCI, showed that HD patients undergoing PCI had a higher risk of the combined endpoint of angina pectoris, myocardial infarction or CV death compared to those undergoing CABG [88]. Crawford and colleagues reported decreased saphenous vein graft patency in HD Patients [89]. Agirbusli and co-workers reported the results of a non-randomized study of 252 HD patients who received either CABG or PCI for chronic CHD [90]. There was no significant difference in mortality at one year (27% for PCI, 23% for CABG). A recent meta-analysis of 32,350 ESRD patients compared outcomes in patient receiving PCI or CABG for chronic CHD. CABG was associated with 10% relative risk reduction in mortality (95% CI: 0.87-0.93), a 36% relative risk reduction in myocardial infarction (95% CI: 0.61-0.68), a 78% relative risk reduction in repeat revascularization (95% CI: 0.16-0.31) and a 31% relative risk reduction in cumulative events (95% CI: 0.65-0.73) beyond one year compared to PCI, despite having a higher risk for early mortality (95% CI: 1.51-2.60) [91]. A retrospective study of 78 HD patients who underwent CABG had a 4.4 fold greater risk of in-hospital mortality and a 3.1 fold greater risk of stroke compared with patients undergoing CABG, but not receiving HD [92]. In a retrospective study of 10,076 consecutive patients who underwent PCI for CHD, 95(0.9%) were receiving on dialysis. One year mortality was significantly higher in dialysis patients at one year (48.8%) than in CKD patient not receiving dialysis (25.7%) or in patients without renal dysfunction (5.5%), $p<0.0001$ [93]. The high mortality rates in CKD patients occurred despite an angiographic success rate of 97%.

In patients undergoing PCI a decision must be made as to whether to deploy drug-eluting stents (DES) or bare metal stents (BMS). In the general population DES reduce the incidence of restenosis compared to BMS and particularly compared to percutaneous transluminal coronary angioplasty, both in patients with ACS and in those with chronic CHD [94]. Several studies have compared the effect of DES and BMS on CV outcomes in patients with chronic CKD including in those receiving HD. Kuchulakanti *et al.* studied 1,522 patients with CKD who received DES on BMS for chronic CHD [95]. Those receiving HD (40% those with CKD) showed a non-significant trend towards lower mortality rates, CVD events rates and risk of target lesion revascularization in patients receiving DES compared to those receiving BMS [96]. Using data derived from the American College of Cardiology National Cardiovascular Data Registry and Center for Medical Services Nation Claim Database Tsai and colleagues compared CV outcomes in 5000 HD patients receiving DES or BMS. DES use was associated

with a lower mortality rate at 30 months than BMS (48.9% vs. 56.4%, $p<0001$), but no significant difference in the incidence of myocardial infarction or target lesion revascularization. A study by Das and co-workers of 89 HD patients treated with PCI showed that the use of DES was associated with a significant reduction in target lesion revascularization (OR: 0.11, 95% CI: 0.006-0.844, $p=0.036$) and a significant reduction in the combined endpoint of death, myocardial infarction and target lesion revascularization (OR: 0.11, 95% CI: 0.002-0.513, $p=0.005$) [97]. Yachi *et al.* reported the results of a retrospective study of 123 HD patients treated with either a DES or BMS [98]. DES use was associated with a significantly lower incidence of major adverse cardiac events (MACE, 25.0% vs. 38.9%, $p=0.02$). In a retrospective observational analysis of 104 CKD patients one of whom one-third were receiving HD 104 patients received paclitaxel-eluting stents ($n=54$) or BMS ($n=50$), reported by Jeong *et al.*, there was no significant difference in mortality rates regardless of stent type [99]. In a study by Halkin and colleagues derived from the National Heart Lung and Blood Dynamic Registry, the use of DES and associates with a 75% reduction in MACE and a trend toward lower all-cause mortality at one year (HR: 0.40, 95% CI: 0.15-1.05, $p=0.06$) compared to BMS use [100]. Nakazawa and co-workers studied 304 patients who underwent sirolimus stent implantation including 31 HD patients [101]. Qualitative coronary angiography performed at eight months showed disproportionately greater neointimal growth in the HD group. Multivariate analysis showed that the severity of renal dysfunction was an independent predictor of late lumen loss. Additional studies of patients on HD receiving stents have called into question the efficacy of sirolimus eluting stents in preventing MACE [102-106]. In these studies, the high rates of MACE were driven by increased risk of target lesion revascularization. In a study of 6,320 patients with ESRD including HD patients reported by Rosenblum the use of DES did not significantly reduce target lesion revascularization rates compared to the use of BMS [106].

The preponderance of evidence suggests that CABG is associated with higher in-hospital mortality, but lower long-term risk for MACE compared to PCI in patients with advanced CKD, including those receiving HD. In most studies, DES use reduced the risk for MACE compared to BMS use with the possible exception of sirolimus-eluting stents. There are no studies involving the use of second and third generation DES in particular with advanced CKD.

CONCLUSION

Patients with CKD, particularly those with ESRD who receive dialysis are at high risk for CHD. Therapeutic options that are effective in patients with CHD in the general population may be less so in patients with advanced CKD. In some cases drugs used to treat ACS and chronic CHD may require dose adjustments due to reduced renal clearance. CABG is associated with higher in-hospital mortality than PCI, but better long-term CV outcomes. Because of variability in the severity of CHD and CKD, therapeutic decisions regarding patients with CKD and CHD must be individualized and guided by symptoms and long-term prognosis.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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