Management of Chronic Coronary Disease and Acute Coronary Syndromes in Patients with Chronic Kidney Disease

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Abstract

Abstract coronary atherosclerosis is accelerated and highly prevalent among patients with chronic kidney disease (CKD). Acute coronary syndromes (ACS) are common in CKD and are a major source of morbidity and mortality in this population. The management of chronic coronary disease and ACS includes anti-ischemic agents, antiplatelet medications, anticoagulants, and medications that modify the natural history of myocardial remodeling after injury. In addition, revascularization, primarily with catheter-based techniques, is critical for optimal outcomes in moderate- and higher-risk patients. This article will review the array of treatments used in combination for stable coronary disease and ACS and will provide critical guidance concerning benefits, risks, and dose adjustments required for patients with baseline CKD.

Keywords

Acute coronary syndromes, treatment, chronic stable angina, chronic kidney disease, angiography, glomerular filtration rate, mortality, creatinine, hemodialysis, cardiovascular disease, renal insufficiency, antiplatelet agent, anticoagulation

Disclosure: The authors have no conflicts of interest to declare.
Received: July 3, 2011 **Accepted:** August 12, 2011 **Citation:** *US Cardiology*, 2011;8(2):123–31
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Chronic kidney disease (CKD) affects approximately 26 million people in the US.[1] CKD is considered a coronary risk equivalent and also a risk factor for progression of cardiovascular disease (CVD).[2] Cardiovascular death rates are 10–30 times higher in dialysis patients than in the general population.[3] This increase in CKD patients is multifactorial and is now mainly considered via two pathways: pump failure and arrhythmias.[4] The uremia-related non-traditional cardiac risk modifiers include cardiomyocyte dysfunction, defective iron re-utilization and erythropoietin deficient anemia, abnormal calcium–phosphate homeostasis with phosphate retention and hyperparathyroidism, inflammation, hyperhomocysteinemia, and hypervolemia; these all contribute to the increased risks observed in CKD patients.[5] In addition, the dialysis procedure (peritoneal or hemodialysis) itself likely contributes to CVD morbidity. Due to the under-representation of CKD patients in controlled trials of CVD[6], there is a limited body of evidence for treatment modalities specific to this population. Most of the current evidence suggests that with appropriate monitoring, cardiovascular medications and interventional strategies can be applied safely and provide a benefit in patients with renal impairment.[7]

To increase awareness of CKD, an American Heart Association (AHA) science advisory for the detection of CKD in patients with, or at increased risk for, CVD was recently developed in collaboration with the National Kidney Foundation. The advisory recommends that all patients with CVD be screened for evidence of kidney disease by estimating glomerular filtration rate (GFR) and testing for microalbuminuria by measuring the albumin:creatinine ratio (Class IIa, Level of Evidence: C).[8] A GFR less than 60 ml/min/1.73 m^2 of body surface area should be regarded as abnormal (Class I, Level of Evidence: B). Furthermore, the albumin:creatinine ratio should be used to screen for the presence of kidney damage in adult patients with CVD, with values greater than 30 mg albumin per 1 g creatinine regarded as abnormal (Class IIa, Level of Evidence: B). It has been shown that urine microalbuminuria will detect CKD in younger populations while estimated GFR (eGFR) is the major identifier in older age groups.[9]

The Kidney Early Evaluation Program (KEEP) is a free community-based health screening program that targets populations 18 years and older at high risk of kidney disease.[10] For screening patients for CKD, KEEP now employs the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation instead of the Modification of Diet in Renal Disease (MDRD) equation.[11] The use of the CKD-EPI equation results in a higher eGFR for a given creatinine level compared with the MDRD study equation for most people younger than 75 years. Therefore, the use of the CKD-EPI equation led to a lower estimated prevalence of CKD in the National Health and Nutrition Examination Survey (NHANES) at 11.1 %, compared with 13.2 % using the MDRD study equation. When analyzed with respect to CVD risk factors, researchers found that net

reclassification showed a 15.9 % improvement (p<0.001) in the association of eGFR with mortality. Therefore, the CKD-EPI equation is now considered the preferred eGFR equation when providing prognostic information concerning CVD and mortality.

Cardiovascular Disease in Patients with Chronic Kidney Disease

A history of CKD should be considered more than a coronary risk equivalent, and patients should receive equally intensive risk factor intervention as those with clinically apparent coronary heart disease (Level of Evidence: A).[3] The risk of cardiovascular mortality in patients with moderate CKD was as high as that in patients with a history of myocardial infarction (MI) or diabetes mellitus (DM).[12]

The most common initial manifestation of ischemic heart disease is chronic stable angina, occurring in almost half of patients.[13,14] Even patients with mild anginal symptoms may have severe coronary artery disease (CAD).[15–17] Initial evaluation in all patients suspected of symptomatic CVD, including those with CKD, includes a thorough history and physical examination, as well as a baseline electrocardiogram (ECG). Further risk stratification for CVD in patients with a higher index of suspicion should be done with exercise or pharmacologic stress echocardiography or nuclear scintigraphy.

Coronary Artery Calcification in Chronic Kidney Disease

Coronary artery calcification (CAC), a marker for atherosclerosis, is more common in CKD than in the general population. Although elevated CAC can occur without significant obstructive atherosclerosis, evidence suggests a predictive trend, even in CKD, of elevated CAC with obstructive atherosclerosis.[18] Coronary computed tomography angiography (CCTA) is useful especially due to its negative predictive ability to exclude obstructive CAD.[19,20] Historically, patients with CKD and those on dialysis have largely been excluded from trials involving CCTA due to the high coronary artery calcium burden, which may interfere with CCTA evaluation, as well as the high contrast volume load, which raises safety concerns for contrast-induced acute kidney injury. The change on coronary calcium scoring on serial CCTA should not be considered a valid endpoint in clinical trials or a measure of response to anti-atherosclerotic therapies, since osteoblastic transformation of vascular smooth muscle cells is a late-stage, stabilizing feature of fibrous plaques.[21–24]

Importance of Optimal Blood Pressure Control

The Joint National Committee VII (JNC VII) guidelines recommend a tighter control of blood pressure in the CKD patient, with a goal of less than 130/80 mmHg.[25] The risk of cardiovascular events and cardiovascular deaths could be reduced by almost one-third among dialysis patients if they all received blood pressure-lowering agents.[26] Optimal management of CKD requires coordination of antihypertensive therapy with other therapies, such as smoking cessation, lipid-lowering therapy, management of diabetes, and other dietary and lifestyle modifications.[27] The most important lifestyle change is to restrict sodium to <2 g/day, which will result in lower blood pressure, less soft tissue edema, and greater responsiveness to oral antihypertensive therapy. For hypertensive patients with well-established CAD, it is useful to add blood pressure medication as tolerated, treating initially with beta-blockers and/or angiotensin-converting enzyme (ACE) inhibitors, with the addition of other drugs as needed to achieve target blood pressure (Class IC recommendation).[27] The cardiovascular protective benefit of ACE inhibitors has been demonstrated by the Heart outcomes prevention evaluation (HOPE) trial as well as several smaller studies.[28] Therefore, in CKD patients, ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction less than or equal to 40 %, as well as those with hypertension or diabetes (Class IA recommendation).[27] Despite the benefits of blood pressure control, compliance still remains a barrier; one-third of CKD patients have low adherence to antihypertensive medication, contributing to poor blood pressure control.[29]

Pharmacologic Interventions Recommended for Chronic Coronary Disease

Pharmacologic treatment of patients with chronic stable angina in the presence of CKD includes aspirin, beta-blockers, ACE inhibitors, nitrates, and statin therapy, with ranolazine used as adjunctive therapy (see *Table 1*). Aspirin reduces mortality in patients with stable known or suspected coronary heart disease.[30] Aspirin should be started and continued indefinitely at a dose of 75–100 mg/day in all patients unless contraindicated.[27] There are no particular recommendations for the change in dosing of aspirin in CKD patients; however, they are recognized to be at increased risk of bleeding with all antiplatelet agents, given uremic platelet dysfunction. Beta-blockers have been shown to reduce mortality in all patients, and have similar benefits in CKD patients. Selective beta-1 adrenergic blockers such as metoprolol and combination alpha- and beta-blockers such as carvedilol should be generally favored because of studies demonstrating cardiovascular protection with these agents, particularly in patients with heart failure.[31,32] Metoprolol and atenolol are dialyzable agents, and require supplementation after dialysis.[33] Metoprolol, primarily excreted by the liver, does not need dosage adjustment in dialysis patients.[33] Atenolol, acebutolol, and nadolol, however, are renally excreted and may require dosage adjustment in dialysis patients.[34] There is weak evidence that some beta-blockers may hinder peritoneal transport in patients on peritoneal dialysis (PD)[35] but this evidence is not sufficient to warrant withholding the use of beta-blockers in dialysis patients when they are clearly indicated. In patients with previous MI or with well-established CAD, beta-blockers should be the preferred antihypertensive agent.

Angiotensin receptor blockers (ARBs) should be initiated in those patients that are intolerant to ACE inhibitors.[27] ARBs are also recommended for use in post-MI patients without significant renal dysfunction (creatinine <2.5 mg/dl in men and <2.0 mg/dl in women) or hyperkalemia (potassium <5.0 mEq/l) who are already receiving therapeutic doses of an ACE inhibitor and a beta-blocker, and have a left ventricular ejection fraction less than or equal to 40 % (Class IA Recommendation).[27]

Nitrates have commonly been shown to decrease anginal symptoms in patients. The use of nitrates results in a relaxation of vascular smooth muscle, and a decrease in systemic arterial blood pressure.[36] Therefore, caution should be exercised when using nitrates in dialysis patients. Hemodialysis creates a transient low-preload state (i.e. hypovolemia at

Table 1: Oral Agents Used for Chronic Coronary Disease and Acute Coronary Syndrome

Class	Medication	Normal Dose	CKD Patient Population	Notes
Antiplatelet	Aspirin	Acute MI: 162–325 mg PO as soon as possible MI prophylaxis: 81–325 mg PO qDay PTCA: 325 mg PO two hours pre-surgery, then 160–325 mg PO maintenance Unstable angina: 75–162 mg PO qDay	All dialysis patients with CAD not allergic to aspirin should receive aspirin Withholding aspirin before surgery is usually unnecessary There are no data on use of aspirin in primary prevention of CVD in dialysis patients	Metabolism: Liver, microsomal enzyme system Renal clearance: 80–100 % 24–72 hr Excretion: Principally in urine (80–100 %), sweat, saliva, feces
Antiplatelet (ADP receptor antagonists)	Clopidogrel (Plavix)	Unstable angina, non-ST-segment elevation myocardial infarction: 300–600 mg initial loading dose, follow by 75 mg PO qDay in combination with aspirin ST-segment elevation myocardial infarction: 75 mg PO qDay in combination with aspirin 75–162 mg/day Recent MI: 75 mg PO qDay	No specific dosing adjustments in CKD patients	Metabolism: CYP3A4, CYP2C19 (predominantly) and others to generate active metabolite; also by esterase to an inactive metabolite Excretion: Urine and feces
	Prasugrel (Effient)	Acute coronary syndrome: Loading dose: 60 mg PO once Maintenance dose: 10 mg PO qDay with aspirin 75–325 mg/day; bleeding risk may increase if weight <60 kg, consider 5 mg PO qDay (efficacy/safety not established)	No specific dose adjustments Increased risk of bleeding, monitor closely	Metabolism: Liver; CYP450: 2B6, 2C9/19 (minor), 3A4 substrate; 2B6 (weak) inhibitor Excretion: Urine (68 %) and feces (27 %)
ACE inhibitors	(Class)		The dosing schedules may need to be individualized for each dialysis session in order to avoid intradialytic hypotension	
ARBs	(Class)		As a first line of treatment in the majority of patients, we propose the use of ACE inhibitors or ARBs. The latter also reduce LVH in hemodialysis patients, and may be more potent than ACE inhibitors[89,90] Levels of ARBs do not change significantly during hemodialysis	
Beta-blockers	(Class)		Hemodialysis reduces blood levels of atenolol, acebutolol, and nadolol; by contrast, levels of carvedilol and labetalol do not change significantly	
	Metoprolol (Lopressor)	Acute MI: Metoprolol tartrate: 2.5–5 mg rapid i.v. q2–5min, up to 15 mg over 10–15 minutes, then 15 min after last i.v. and receiving 15 mg i.v. or 50 mg PO q6 hr x 48 hours, then 50–100 mg PO b.i.d Angina: Metoprolol tartrate: initially 50 mg PO b.i.d. then titrated to 200mg PO b.i.d. Metoprolol succinate (Toprol XL) 100 mg PO qDay, no more than 400 mg/day	No specific dose adjustments Recommend close monitoring for side effects Consider avoiding extended release preparationin renal insufficiency	Dialyzable: Yes. Metabolism: Hepatic CYP2D6 Metabolites: Inactive Excretion: Urine 95 %
	Esmolol (Brevibloc)	1. Immediate Control: For intraoperative treatment give an 80 mg (approximately 1 mg/kg) bolus dose over 30 seconds followed by a 150 mcg/kg/min infusion, if needed. Max infusion rate: 300 mcg/kg/min. 2. Gradual Control: For postoperative treatment, give loading dosage infusion of 500 mcg/kg/min over 1 minute followed by a 4 min infusion of 50 mcg/kg/min. If no effect within 5 min, repeat loading dose and follow with infusion increased to 100 mcg/kg/min.	Note elevated metabolite levels in ESRD	Metabolism: Extensively metabolized by esterase in cytosol of red blood cells Metabolites: Major acid metabolite (ASL-8123), methanol (inactive) Excretion: urine <1–2 %
	Carvedilol	Hypertension: 6.25–25 mg PO b.i.d	No specific dose adjustments	

Table 1: Continued

		start at 6.25 mg b.i.d., then increase q1–2 wk to 12.5 mg b.i.d., then 25 mg b.i.d. Post-MIprotection: Start 6.25 mg p.o. b.i.d., increase q3–10 days to 12.5 mg b.i.d., then 25 mg b.i.d	In a small study of dialysis patients with dilated cardiomyopathies, carvedilol was found to improve LV function and decrease hospitalization, cardiovascular deaths and total mortality[31]	
CCBs	(Class)	In UA/NSTEMI patients where beta-blockers are contraindicated, a non-dihydropyridine calcium channel blocker should be given as initial therapy in the absence of clinically significant LV dysfunction or other contraindications (Level of Evidence: B)[74]	No specific dose adjustments The medical management of chronic CAD in dialysis patients should follow that of the general population and use of CCBs as indicated The hemodynamic and electrophysiological effects of CCBs are markedly different from each other, and these differences should be evaluated when selecting a suitable therapy	
HMG-CoA reductase inhibitors	Simvastatin	Cardiovascular event protection: 20 mg combined with 10 mg ezetimibe Maximum dose: 40 mg PO qPM	With the Study of heart and renal protection (SHARP), lipid lowering with statin + ezetimibe is beneficial in patients with kidney (Statins) insufficiency[42] Severe impairment, consider starting dose at 5 mg qPM	Metabolism: Liver, CYP450 Excretion: Bile primarily urine <2 %
	Atorvastatin	Cardiovascular event protection: 10 mg p.o. daily	No specific dose adjustments Atorvastatin 10 mg in patients with kidney dysfunction revealed a significantly lower risk of the primary endpoint (non-fatal MI or cardiacdeath) in the atorvastatin group when compared with placebo	Metabolism: Liver, CYP450 Excretion: Bile primarily, urine <2 %
	Fluvastatin	Cardiovascular event protection: 40 mg p.o. b.i.d. Extended Release: 80 mg p.o. daily	No specific dose adjustments. Caution for increased risk of rhabdomyolysis. A multicenter, randomized, double-blind, placebo-controlled trial of 40–80 mg fluvastatin was conducted in kidney transplant recipients.[91] Fluvastatin reduced low-density lipoprotein cholesterol concentrations by 32 %. The fluvastatin group experienced a third fewer cardiac death and non-fatal myocardial infarctions than the placebo group. Coronary intervention procedures and other secondary endpoints were not significantly different between the two groups	Excretion: Feces 90 %, urine 5 %
	Pravastatin	Cardiovascular event protection: Start 40 mg p.o. daily, may adjust dose q4wk, 80 mg max	Start at 10 mg p.o. daily in patients with renal dysfunction. A randomized trial of pravastatin versus placebo in with patients with previous MI and chronic renal insufficiency.[39] The incidence of coronary death or non-fatal MI was lower in patients receiving pravastatin, suggesting that pravastatin is effective for secondary prevention of cardiovascular events in persons with mild chronic kidney insufficiency	Excretion: Feces 70 %, urine 20 %
Nitrates	Nitroglycerin	2% ointment: Angina: 0.5–2 inches applied in a.m. and 6 hours later to truncal skin Heart Failure: 1.5 inches, increase by 0.5–1 inch up to 4 inches, q4hr Sublingual: 0.4 mg for relief of chest pain in ACS Sublingual: 0.3-0.6 mg SL q5min. Maximum: 3 doses within 15 minutues	No specific dose adjustments Care must be used to avoid hypotension in low volume states such as dialysis sessions	Metabolism: Mainly in liver, extrahepatic sites: vascular wall, red blood cells Excretion: Urine
Antianginal	Ranolazine (Ranexa)	Start 500 mg PO bid. Maximum: 2,000 mg/day.	No specific dose adjustments. Prolongs QTc. Recommend close monitoring, particularly in those with renal insufficiency	Excretion: Urine 73–75 %, feces 25 %

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; ADP = adenosine diphosphate; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCB = calcium channel blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; HMG-CoA = hydroxymethylglutaryl coenzyme A; LV = left ventricle; LVH = left ventricular hypertrophy; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; UA/NSTEMI = unstable angina/non-ST-elevated myocardial infarction.

the end of a hemodialysis session), and this may potentiate the hypotensive effect of the drug.[37]

A history of CKD also confers an increased risk of dyslipidemia characterized by impaired reverse cholesterol transport and reduced lipolysis. In NHANES III, participants with CKD (GFR <60 ml/min/1.73 m^2) had higher levels of apolipoprotein B and lower levels of apolipoprotein A than those with normal renal function (p=0.003 and 0.021, respectively).[38] Multiple trials in CKD subgroups have demonstrated that lipid-lowering therapy with pravastatin and atorvastatin reduces cardiovascular events.[39–41] The Study of heart and renal protection (SHARP) demonstrated a 17 % reduction in the rate of atherosclerotic events in CKD patients using simvastatin and ezetimibe when compared with placebo.[42] Therefore, we recommend the administration of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and ezetimibe as lipid-lowering agents in CKD patients, but note that the benefits may not translate into reductions in mortality.[43]

Ranolazine, a piperazine derivative that exerts anti-ischemic actions without a clinically significant effect on heart rate or blood pressure, is an adjunctive therapy for chronic stable angina.[44,45] The Monotherapy assessment of ranolazine in stable angina (MARISA) trial demonstrated a dose-dependent benefit of ranolazine compared with placebo in improving exercise duration.[45] However, due to an association with a modest prolongation of the QT interval, certain patients could be more prone to torsades de pointes.[44] Ranolazine in non-ST-elevation (non-STE) acute coronary syndrome (ACS) does not show a clear mortality benefit, but has been shown to have an adequate safety profile.[46] Pharmacokinetically, ranolazine has a 73 % excretion through urine.[47] Reduced glomerular filtration has been shown to increase, up to twofold, the area under the concentration time curve (AUC) between 0 and 12 hours after the dosing of ranolazine.[48] Despite the higher serum levels of ranolazine in CKD patients, no serious adverse events have been observed. In the light of these findings, dose reduction of ranolazine may be needed depending on the severity of renal dysfunction.

Risk Assessment in Acute Coronary Syndromes

Among patients presenting with chest discomfort to the emergency department, patients with CKD have an approximate 40 % chance of MI, heart failure, or death.[49] Across the spectrum of confirmed ACS, patients with chronic renal insufficiency have more extensive CAD, a worse risk profile, more atypical and delayed presentations, and are less likely to receive evidence-based therapy.[50] Of the eight variables used in the Global Registry of Acute Coronary Events (GRACE) risk model, which predicts in-hospital mortality in patients with unstable angina (UA), non-ST-segment MI (NSTEMI), or ST-segment MI (STEMI), serum creatinine level demonstrated a 1.2-fold greater risk of mortality per 1 mg/dl increase.[51,52] The severity of renal dysfunction is associated in a graded fashion with short- and long-term mortality.[53,54] Patients with renal dysfunction experience increased bleeding risk, have higher rates of heart failure and arrhythmias, have been under-represented in cardiovascular trials, and may not enjoy the same magnitude of benefit with therapies compared with patients with normal renal function.[6] The medical history, physical examination, ECG, assessment of renal function, and cardiac biomarker measurements in patients with symptoms suggestive of ACS at the time of initial presentation are essential in estimating the risk of death and non-fatal cardiac ischemic events which, as indicated above, are clearly higher than in those without CKD.[3,55–58]

When evaluating a patient with suspected ACS, the diagnostic role of cardiac troponins, consisting of Troponin I (cTnI), Troponin T (cTnT), and Troponin C (cTnC) subunits, is complicated by renal insufficiency. Although troponins accurately identify myocardial necrosis, they do not inform as to the causes of necrosis; these can be multiple,[59] including renal insufficiency.[60] In patients with renal dysfunction, cTnI assessment appears to have a specific role.[61] Among patients with end-stage renal disease and no clinical evidence of acute myocardial necrosis, 15–53 % show increased cTnT, but fewer than 10 % have increased cTnI; dialysis generally increases cTnT and, to a lesser extent, cTnI. The exact reasons for the high rates of elevation of cardiac troponins, especially cTnT, in renal failure are not clear; they can be related to myocardial damage, differential clearance, or to other biochemical or metabolic abnormalities.[61] It is plausible that the elevation in serum cardiac troponins in asymptomatic dialysis patients is a reflection of silent ischemic heart disease or non-ischemic cardiomyopathy; troponin levels have also been shown to be related to left ventricular (LV) mass.[62] In almost 7,000 patients enrolled in the Global use of strategies to open occluded coronary arteries (GUSTO IV) trial with suspected ACS, TnT level was an independent predictor of risk across the entire spectrum of renal function.[63] A sequential change in cardiac troponin levels in the first 24 hours of observation for a suspected ACS supports new myocardial injury, whereas unchanging levels are more consistent with a chronic disease state without ACS.[3]

Treatment of Acute Coronary Syndromes

Patients presenting with STEMI should be taken to a percutaneous coronary intervention (PCI) center and undergo primary PCI with stenting within 90 minutes. In addition, thrombolysis may be an initial reperfusion strategy for patients presenting outside of a 90 minute door-to-balloon time for percutaneous intervention in the setting of STEMI. Patients with STEMI and kidney disease do not receive thrombolytic therapy as quickly as those without kidney disease.[64] Newsome et al. found that of 109,169 Medicare patients with MI (mean age 77), fewer patients with kidney disease received thrombolytic therapy, and patients with the worst kidney disease waited the longest for therapy. The disparity may arise from the concern about thrombolytic-associated bleeding in patients with kidney disease, yet Newsome et al. demonstrated the adjusted odds ratio (OR) for bleeding events was lower in patients on dialysis versus patients with normal kidney function (OR 1.84 versus 2.28). There are no formal dose adjustment recommendations for the use of streptokinase, alteplase, reteplase, or tenecteplase in patients with CKD. The post-reperfusion care of STEMI patients largely follows a similar set of guidance to that of NSTEMI patients. Once a patient with suspected non-STE ACS is admitted to the hospital, standard medical therapy should be initiated, consisting of aspirin, beta-blocker, anticoagulant therapy, possibly a glycoprotein (GP) IIb/IIIa antagonist or abciximab, and a thienopyridine, unless there is a specific contraindication.[3] In the untreated state, patients with CKD have greater tendencies to blood clotting given excessive generation of thrombin and potential losses of protein C in the urine. However, in the setting of anticoagulants, given the presence of a greater number of circulating thrombin–antithrombin complexes, all forms of indirect thrombin and factor Xa inhibitors

Table 2: Intravenous Antiplatelet Agents for Unstable Angina/Non-ST-elevated Myocardial Infarction and ST-elevated Myocardial Infarction

Class	Medication	Normal Dose	CKD Patient Population	Notes
Glycoprotein IIb/IIIa inhibitors	(Class)		When a glycoprotein IIb/IIIa antagonist is used, abciximab and tirofiban should be considered preferred agents, since no dosing changes are required for abciximab, and dialysis-specific dosing recommendations are available for tirofiban	
			Increased bleeding but reduced in-hospital mortality in CKD patients with ACS treated with IIb/IIIa antagonists has also been shown[78]	
	Abciximab (ReoPro)	Adjunct to PCI 0.25 mg/kg i.v. bolus over at least 1 min, 10–60 min before start of PCI, then 0.125 mcg/kg/min (not to exceed 10 mcg/min) continuous i.v. infusion x 12 hr Unstable angina with PCI planned within 24 hr 0.25 mg/kg i.v. bolus over at least 1 minute, then 0.125 mcg/kg/min (not to exceed 10 mcg/min) i.v. infusion x 18–24 hours concluding 1 hour post-PCI	No specific dose adjustments Abciximab should also be considered as adjunctive therapy in ACS in dialysis patients In CKD, safety of abciximab was shown for creatinine >2.0 mg/dl[92] Although increased bleeding with abciximab in renal failure has been reported,[93] other studies have shown no increase in bleeding for renal failure versus no renal failure for abciximab in PCI[94]	Metabolism: Other, CYP450: unknown Excretion: Urine
	Eptifibatide (Integrilin)	ACS 180 mcg/kg i.v. bolus, then 2 mcg/kg/min i.v. for up to 72 hours PCI 180 mcg/kg i.v., then continuous infusion 2 mcg/kg/min with another 180 mcg/kg i.v. bolus 10 minutes after first bolus Continue infusion for at least 12 hours	Creatinine clearance <50 ml/min. ACS: 180 mcg/kg i.v., then continuous infusion 1 mcg/kg/min Hemodialysis: Safety and use during hemodialysis not established	Metabolism: Other, minimal; CYP450: unknown Excretion: Urine 50 %
	Tirofiban (Aggrastat)	In patients undergoing PCI, tirofiban not recommended as an alternative to abciximab.[79] ACS: 0.4 mcg/kg/min i.v. for 30 minutes, then 0.1 mcg/kg/min i.v. for 48–108 hours PCI: Continue 0.1 mcg/kg/min i.v. through procedure and for 12–24 hours after	Creatinine clearance <30 ml/min: reduce dose to 50 % of normal rate	Excretion: Urine 65 % (primarily unchanged), feces 25 % (primarily unchanged)

ACS = acute coronary syndromes; CKD = chronic kidney disease; PCI = percutaneous coronary intervention.

(heparin, low molecular weight heparin [LMWH], fondaparinux) have a more potent effect on the coagulation system, and hence have greater rates of major bleeding complications. Intravenous bivalirudin, a direct thrombin inhibitor, has been associated with the lowest bleeding risk and best cardiovascular endpoint outcomes in patients with CKD.[65]

The American College of Cardiology (ACC)/AHA guidelines for ACS give additional detail on the issue of PCI in non-STE ACS.[3] Mild to moderate kidney disease is considered high-risk in UA/NSTEMI, and an invasive strategy is preferred to conservative medical management.[66] However, for patients undergoing dialysis or those with end-stage renal disease, the data are not sufficient to recommend catheterization, and may even suggest harm.[66] Although CKD patients are less likely to be offered coronary angiography in ACS, they still benefit from revascularization and have a reduction in six-month mortality.[67,68] The choice for primary PCI in CKD has been questioned in recent studies.[69] The Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART) showed that in 23,262 consecutive cases of non-STE MI, as eGFR declined there was a lesser use of coronary angiography and revascularization.[70] In patients with eGFR <30 ml/min/1.73 m^2, fewer than one-third are selected for an early invasive management approach for ACS. This group, however, had a 33.7 % relative risk reduction in mortality compared with those managed conservatively (41.5 % all-cause mortality).[71] Patients with CKD with or without diabetes who undergo angiography are at higher risk of contrast-induced acute kidney injury. This risk, however, is not compounded by the choice of the contrast agent used for angiography. The 2009 ACC/AHA guidelines for PCI recommend that for patients with CKD undergoing angiography who are not undergoing chronic dialysis, either an iso-osmolar contrast medium (Level of Evidence: A) or a low molecular weight contrast medium other than ioxaglate or iohexol is indicated (Level of Evidence: B).[72,73] The 2011 ACC/AHA guidelines denote less emphasis on specific types of contrast agents, and more emphasis on the volume of contrast used during

Table 3: Anticoagulants for Unstable Angina/Non-ST-elevated Myocardial Infarction and ST-elevated Myocardial Infarction

Class	Medication	Normal Dose	CKD Patient Population	Notes
Indirect factor Xa inhibitors	UFH	Recommended dosage and desired aPTT values per institutional protocol PCI: 60–100 units/kg IV x 1 Target ACT 250–350s; in patients receiving glycoprotein IIb/IIIa inhibitor, give 50–70 units/kg IV x 1 to target ACT 200s STEMI, adjunct treatment, streptokinase use: Dose: <80 kg: 800 units/h >80 kg: 1000 units/h Start: 5000 units IV x 1 Adjust dose to target aPTT 50–75s. NSTEMI: 12-15 units/kg/h i.v Start: 60–70 units/kg IV x 1; Max 5000 units bolus, max rate 1000 units/h Adjust dose to target aPTT 50–75s	Suggested starting dose heparin 50 IU/kg bolus, then 18 IU/kg/hr. Monitor aPTT values and adjust accordingly per local protocol	Metabolism: Liver (partial) Metabolites: None Excretion: Urine
	Low molecular weight heparin Enoxaparin (Lovenox)	Unstable angina, non-Q-wave MI: 1 mg/kg s.c. b.i.d STEMI: <75 years old: 30 mg IV bolus x 1 plus 1 mg/kg s.c. x 1, then 1 mg/kg s.c. q12hr PCI patients: Additional 0.3 mg/kg IV bolus if last s.c. given >8 hours before balloon inflation >75 years old: 0.75 mg/kg s.c. q12hr (no IV bolus)	STEMI, <75 years old, CrCl <30: 30 mg IV bolus x 1 plus 1 mg/kg s.c. x 1, then 1 mg/kg s.c. qDay STEMI, >75 years old, Unstable Angina, CrCl <30 mL/min: 1 mg/kg SC qDay	Excretion: Urine 40 %
Direct factor Xa inhibitor	Fondaparinux (Arixtra)	UA/NSTEMI Conservative strategy: 2.5 mg subcutaneously once daily During PCI: Add UFH 50–60 units/kg IV bolus for prophylaxis of catheter thrombosis[85]	CrCl 30-50 ml/min: Use with caution CrCl <30 ml/min: Not indicated	Excretion: Urine (primarily unchanged)
Direct thrombin inhibitors	Bivalirudin (Angiomax)	Intended for use with aspirin 300–325 mg/day 0.75 mg/kg IV bolus initially, followed by continuous infusion at rate of 1.75 mg/kg/hr for duration of procedure Perform ACT 5 minutes after bolus dose May administer additional 0.3 mg/kg bolus if necessary May continue infusion following PCI beyond 4 hours (optional post-PCI, at discretion of treating healthcare provider) initiated at rate of 0.2 mg/kg/hr for up to 20 hours p.r.n.	CrCl 10–29: usual bolus dose, then initial infusion of 1 mg/kg/h i.v up to 4h Hemodialysis: usual bolus dose, then initial infusion 0.25 mg/kg/h i.v., up to 4h Bivalirudin is a direct thrombin inhibitor specifically studied in dialysis patients with dosing recommendations and should be preferentially considered	Excretion: Urine Dialyzable: Yes, with 25 % reduction in levels
	Dabigatran (Pradaxa)	Indicated for prevention of stroke and thromboembolism associated with non-valvular atrial fibrillation CrCl >30ml/min: 150 mg PO b.i.d.	CrCl 15–30 ml/min: 75 mg PO b.i.d. CrCl <15 ml/min or hemodialysis: Not indicated For patients currently taking dabigatran, wait 12 hours (CrCl ≥30 ml/min) or 24 hours (CrCl <30 ml/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant. If possible, discontinue dabigatran 1–2 days (CrCl ≥50 ml/min) or 3–5 days (CrCl <50 ml/min) before invasive or surgical procedures because of the increased risk of bleeding	Excretion: Urine 7 %, feces 86 %

ACT = activated clotting time; aPTT = activated partial thromboplastin time; CKD = chronic kidney disease; CrCl = creatinine clearance; IV = intravenous; MI = myocardial infarction; NSTEMI = non-ST-elevated myocardial infarction; PCI = percutaneous coronary intervention; PO = per os*; STEMI = ST-elevated myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.*

PCI.[66] In addition, it is recommended that patients should be adequately hydrated prior to undergoing angiography.

As mentioned previously, all patients, including those with CKD, should receive aspirin and beta-blockers unless otherwise contraindicated. In UA/NSTEMI patients where beta-blockers are contraindicated, a non-dihydropyridine calcium channel blocker should be given as initial therapy in the absence of clinically significant LV dysfunction or other contraindications (Level of Evidence: B).[74] Thienopyridines are indicated in the setting of ACS, and can be used in CKD patients. Clopidogrel is approved in the general population for the secondary prevention of atherosclerotic CVD events, including CAD. Most dialysis patients would theoretically be candidates for long-term clopidogrel therapy. The 2011 ACC/AHA guidelines add prasugrel to the list.[66] Prasugrel is recommended

at the time of decision for PCI (Class IA Recommendation). However, the guidelines note that it is not recommended for patients undergoing conservative, non-invasive management. In patients managed non-invasively, clopidogrel, administered as an initial loading dose followed by a maintenance dose, should be started as soon as possible after admission and given for at least one month. Prasugrel may also be used in this clinical scenario, with a class IIB recommendation. Following PCI, both clopidogrel and prasugrel should be given for at least 12 months. The 2011 ACC/AHA guidelines recommend the use of GP IIb/IIIa inhibitors in high-risk UA/NSTEMI patients already taking aspirin and a thienopyridine and who are selected for an invasive strategy.[66] However, they note that in UA/NSTEMI patients at low risk of ischemic events, such as those with a thrombolysis in MI (TIMI) risk score <2 or those at high risk of bleeding, who are already treated with aspirin and clopidogrel, the upstream use of GP IIb/IIIa inhibitors is not recommended (see *Table 2*). In addition, those with elevated cardiac troponins also benefit from GP IIb/IIIa inhibitors. Abciximab and tirofiban have both been shown to reduce death or non-fatal MI in patients with cTnT elevation[75,76] and should also be considered as adjunctive therapy in ACS in dialysis patients. Abciximab is the preferred agent for PCI, and the clearance of the drug is not altered in dialysis patients. Tirofiban requires a 50 % dose reduction for eGFR <30 ml/min. Eptifibatide, also a platelet GP IIb/IIIa inhibitor, is renally cleared and requires a 50 % dose reduction for eGFR <50 ml/min. Its use is not recommended in dialysis patients because of increased bleeding risk.[77] Despite increased bleeding events, reduced in-hospital mortality in CKD patients with ACS treated with IIb/IIIa antagonists has been shown.[78] The 2008 American College of Chest Physicians (ACCP) non-STE ACS guidelines recommend anticoagulation in all patients with unfractionated heparin (UFH), LMWH, bivalirudin, or fondaparinux over no anticoagulation (see Table 3).[79] In patients selected for an invasive strategy, both UFH and an LMWH, such as enoxaparin, are Class IA recommendations in the 2011 ACC/AHA UA/NSTEMI guidelines.[66] Whether managed invasively or conservatively, fondaparinux, a direct Factor Xa inhibitor, is also an option with a Class IB recommendation, and is preferred in those with an increased risk of bleeding. Bivalirudin, a direct thrombin inhibitor, is a Class IB recommendation only in patients selected for an invasive strategy. When choosing these agents in patients with renal dysfunction, it should be noted that UFH is not renally cleared, and can be used in CKD and dialysis patients.[80] LMWH has long shown clear benefits in patients with elevated cardiac troponins suspected of UA and NSTEMI.[81,82] However, enoxaparin, a renally cleared LMWH, should be used with caution in patients with renal insufficiency, due to the increased risk of bleeding complications. It is not recommended in dialysis patients for this reason.[83,84] Fondaparinux is also cleared renally, and is contraindicated in patients with a creatinine clearance <30 ml/min. Bivalirudin, cleared with partial renal excretion, is currently only recommended for use in patients selected for an invasive strategy, and requires dosage adjustment in patients with renal dysfunction.[85] Of note, bivalirudin is also dialyzable.

Atrial fibrillation is a common comorbidity in patients with ACS and CKD.[86] Dabigatran, an oral direct thrombin inhibitor, was recently approved by the Food and Drug Administration for anticoagulation in patients with non-valvular atrial fibrillation.[87] For patients with renal dysfunction, the 75 mg twice daily dose was approved for a creatinine clearance of 15-30 ml/min. In dialysis patients or those with a creatinine clearance <15 ml/min, it is contraindicated at this time.[88] Currently, dabigatran is being studied for the secondary prevention of cardiac events in patients with prior coronary events, and we await the results to help define its role. Another newly available agent is rivaroxaban, an oral factor Xa inhibitor. It is currently being studied in the setting of ACS, via the ongoing Anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with ACS (ATLAS ACS) 2-TIMI 51 trial, the results of which will help determine its benefit in this setting.

Conclusions

CKD is a high-risk condition in the evaluation and treatment of patients with coronary atherosclerosis. Treatment in this patient population should consist of therapies proven to improve symptoms and reduce morbidity and mortality. Certain medications require dosing adjustment based on renal clearance. In the setting of ACS, pre-dialysis CKD patients should preferentially undergo an early invasive strategy, consisting of coronary angiography for further risk assessment and classification. This recommendation does not include patients undergoing hemodialysis or PD, where additional research is needed. ■

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