

Management of Coronary Artery Disease in Patients with Chronic Kidney Disease

Walter C. Coats, Sara Z. Baig, Martin A. Alpert, Kul Aggarwal

Patients with chronic kidney disease (CKD) are considered to belong to the highest risk group for the development of cardiovascular events. These patients should be subject to aggressive risk-factor modification. However, management of coronary artery disease in patients with CKD can be uniquely challenging. Many of the medications used in the treatment and prevention of coronary artery disease are metabolized or excreted by the kidney. Thus, patients with CKD are more likely to experience adverse effects from any attempt to aggressively modify risk factors for coronary artery disease.

Little is known regarding revascularization in patients with CKD. Patients with CKD may benefit from off-pump strategies during coronary artery bypass. Percutaneous coronary intervention in patients with CKD is associated with lower procedural success and increased peri-procedural myocardial infarction, ischemia, and target vessel revascularization.

In this review, we discuss the unique challenges of managing coronary artery disease in patients with CKD.

Key words

Chronic kidney disease, coronary artery disease, coronary revascularization, risk-factor modification

Introduction

Patients with chronic kidney disease (CKD) have a high prevalence of coronary artery disease (CAD). Patients with CKD tend to have more severe CAD and coronary calcification and a worse prognosis than do patients with other cardiovascular risk factors (1). In 1998, the U.S. National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease

recommended that patients with CKD be considered to belong to the highest risk group for the development of cardiovascular events (2). These patients present unique challenges to physicians attempting manage concomitant ischemic heart and CKD.

Discussion

Risk factor modification remains the cornerstone of management of both CKD and CAD. Many of the traditional risk factors for CAD—hypertension, diabetes mellitus, smoking, and so on—are common to CKD. However, decreased renal function limits the clinician's flexibility to manage both diseases simultaneously. Patients with decreased renal function are more likely to experience adverse reactions from medications used to treat CAD. In addition, patients with CKD are more likely to experience complications following left heart catheterization, percutaneous coronary interventions, and coronary artery bypass grafting.

Risk factors

HYPERTENSION

Hypertension is the most prevalent risk factor for both CKD and CAD. Renal dysfunction and hypertension are inextricably linked. Current guidelines from the U.S. National Kidney Foundation and the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommend a target blood pressure below 130/80 mmHg for prevention of cardiovascular events and progression of kidney disease in patients with a glomerular filtration rate below 60 mL/min for more than 3 months (3). However, many medications used to treat hypertension in CAD are renally excreted.

Interestingly, patients with end-stage renal disease who depend on hemodialysis do not benefit from aggressive blood pressure control. In this population, aggressive lowering of blood pressure results in increased mortality. This paradox has been termed "reverse epidemiology." Hypotension may be associated

From: Division of Cardiovascular Medicine, University of Missouri–Columbia, and Cardiology Section, Harry S. Truman Veterans Hospital, Columbia, Missouri, U.S.A.

with malnutrition, which is common in hemodialysis patients. In addition, hypotension predicts a poor prognosis in heart failure, which commonly affects many hemodialysis patients (4).

ADRENERGIC DRIVE

Patients with CKD experience higher rates of left ventricular hypertrophy, CAD, arrhythmias, sudden cardiac death, and heart failure. All of these processes are related to adrenergic drive. Therefore, beta blockers play an important role in the management of patients with CKD and CAD. However, patients with CKD are more likely to experience hypotension, hyperkalemia, impaired glucose control, and bradycardia when given beta blockers (5).

DYSLIPIDEMIA

Patients with CKD commonly experience dyslipidemia consisting of hypertriglyceridemia, elevated low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol. Current guidelines recommend aggressive lipid management in these patients, with a goal LDL below 100 mg/dL. Statins remain the drug of choice for the treatment of hyperlipidemia in CAD and CKD. Some authors have suggested that patients with end-stage renal disease may suffer increased adverse effects from statins (6). In 2005, Wanner *et al.* noted that patients with end-stage renal disease did not benefit from intensive lipid-lowering efforts in terms of cardiovascular death, myocardial infarction, and stroke (7). However, the bulk of the evidence suggests that statins are safe and effective in treating hyperlipidemia and preventing cardiac death in earlier stages of CKD (8).

Patients on peritoneal dialysis have higher triglyceride and LDL levels, accompanied by lower HDL levels. Despite this more atherogenic profile, peritoneal dialysis patients have cardiovascular mortality rates similar to those seen in patients on hemodialysis. This finding can be explained by the fact that peritoneal dialysis patients have fewer arrhythmias and hypotensive episodes than do patients on hemodialysis. The peritoneal dialysis patients derive the same metabolic benefits from statins (for example, LDL and triglyceride lowering and high sensitivity C-reactive protein lowering) that other CKD patients do (9).

Whether statins prevent all-cause mortality in CKD is unclear. Two large, long-term trials of aggressive lipid control in hemodialysis patients are currently

underway. SHARP (Study of Heart and Renal Protection) and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events) are designed to assess the effects of, respectively, simvastatin–ezetimibe (20 mg and 10 mg daily) and rosuvastatin (10 mg daily) on patients undergoing hemodialysis (10,11).

Acute coronary syndromes

ANTITHROMBOTIC THERAPY

Aspirin is arguably the most tested and widely supported medication in all of medicine. It is safe and effective in patients with CKD for primary prevention of ischemic events and management of acute coronary syndromes. Aspirin requires no dose modification when given to patients with renal insufficiency.

Evidence supporting clopidogrel in the management of acute coronary syndromes and CAD continues to grow. Clopidogrel is a thienopyridine that has largely supplanted ticlopidine because of a lower risk of thrombotic thrombocytopenic purpura and other less severe adverse reactions. Clopidogrel is metabolized in the liver and requires no dose adjustment in patients with CKD. Recently, a substudy of the CREDO (Clopidogrel for the Reduction of Events During Observation) trial revealed that clopidogrel may have decreased effectiveness in patients with mild-to-moderate CKD. That finding was not associated with increased bleeding in that particular subgroup (12).

Unfractionated heparin (UFH) is preferred over low molecular weight heparins in the treatment of acute coronary syndromes in patients with CKD. Dosing of UFH may be adjusted with follow-up measurements of activated partial thromboplastin time. Low molecular weight heparins such as enoxaparin are associated with increased bleeding in patients with CKD largely because of decreased renal excretion and difficulty in using factor Xa levels to monitor the effect of those agents (13).

SURGICAL INTERVENTIONS

Revascularization strategies in patients with CAD and CKD are not well studied. There is little consensus regarding the benefits of percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG) in this population. However, research seems to support a greater benefit from

CABG than from PCI for most individuals with multivessel CAD (14).

Cardiopulmonary bypass is an independent risk factor for development of acute renal failure. Off-pump bypass grafting reduces mortality and renal failure in patients with non-dialysis-dependent renal insufficiency (15). An off-pump strategy also lowers early operative mortality in patients with end-stage renal disease. However, long-term mortality may be increased in dialysis patients undergoing off-pump CABG (16).

Patients with CKD who undergo PCI are generally considered to be at high risk for complications. As compared with patients with normal renal function, patients with CKD experience an increased risk of death and major adverse cardiac events during and after PCI (17). This risk increases incrementally with the degree of renal impairment. Patients with CKD experience decreased procedural success and increased peri-procedural myocardial infarction. In addition, ischemia and target vessel revascularization are more common in patients with CKD (18). These patients also experience a greater risk of contrast-induced nephropathy following catheterization. A more detailed discussion of contrast-induced nephropathy is beyond the scope of this manuscript.

A recent substudy of the Global Registry of Acute Coronary Events confirmed higher mortality and lower reperfusion rates in patients with CKD undergoing primary PCI for ST-elevation myocardial infarction and left bundle branch block. Adverse outcomes increased incrementally with worsening renal function (19). Similarly, a report from the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) Registry demonstrated that, as a consequence of impaired renal function, patients with CKD experienced increased bleeding, ischemic events, and death after they received a drug-eluting stent. These findings persisted at 1 year. Interestingly, the authors also observed that the use of guideline-recommended medications (beta blockers, angiotensin converting-enzyme inhibitors, statins, aspirin, and clopidogrel) decreased with declining renal function (20).

ADJUNCT THERAPY

Data are emerging on the use of adjunct therapy during PCI in patients with CKD. The glycoprotein (Gp) IIb/IIIa inhibitors abciximab, tirofiban, and eptifibatide have proved very effective in the management of acute

coronary syndromes. Abciximab is the fragment antigen binding area of a chimeric human murine antibody that binds the Gp IIb/IIIa receptor on human platelets. Free abciximab is excreted in the urine, but platelet-bound abciximab is primarily eliminated by the spleen. No dose adjustment is therefore necessary in patients with CKD.

Tirofiban and eptifibatide are both excreted primarily by the kidney; these agents need dose adjustment in renal insufficiency. Although debated in the literature, use of Gp IIb/IIIa inhibitors in patients with CKD is generally associated with a greater risk of bleeding complications (13). However, a study at our own institution did not find an excess rate of bleeding with Gp IIb/IIIa inhibitors when used in patients with end-stage renal disease (21). Bivalirudin and argatroban are two direct thrombin inhibitors commonly used as adjunctive therapy during PCI. These drugs bind directly to thrombin and inhibit its interaction with substrate. Argatroban is metabolized primarily by the liver and does not require dose adjustment in patients with impaired renal function.

Summary

The management of CAD in patients with CKD is uniquely challenging. Patients with CKD are more likely to experience adverse effects from the drug therapies used for CAD. In addition, revascularization strategies in these patients are less effective. Future treatment modalities will perhaps improve outcomes in this patient population.

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- Corresponding author:*
 Kul Aggarwal, MD, MRCP (UK), FACC, Department of Internal Medicine, Division of Cardiology, University of Missouri–Columbia, and Harry S. Truman Veterans Hospital, CE306, DC 095.00, Five Hospital Drive, Columbia, Missouri 65212 U.S.A.
E-mail:
 AggarwalK@health.missouri.edu