**Symposium: Review Article**

**Cardiovascular disease and renal insufficiency: special considerations with cardiac surgery**

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**Abstract:** Cardiovascular disease is an important cause of mortality in the chronic kidney disease (CKD) population. This review discusses cardiac surgery in the CKD population and considers postoperative acute renal failure (ARF). CKD patients have worse outcomes following coronary artery bypass grafting (CABG) and cardiac valvular surgery than the general population. However, surgical revascularization is an effective treatment for coronary artery disease (CAD) in this population and may be associated with improved survival over percutaneous intervention (PCI) in advanced CKD. Cardiac surgery in the CKD population requires careful preoperative planning and management. Acute renal failure (ARF) is a serious complication following cardiac surgery, occurring in 1 to 8% of cases. Management of postoperative ARF is largely supportive and emphasis is placed on preoperative risk stratification and prevention.

**Key Words** chronic kidney disease (CKD); cardiovascular disease; cardiac surgery; acute renal failure (ARF)

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**Introduction**

Cardiovascular disease is an important cause of mortality in the chronic kidney disease (CKD) population,¹,² and an independent association exists between severity of CKD and cardiovascular event rate.³,⁴ There is a high prevalence of traditional cardiovascular risk factors among CKD patients. Diabetes and hypertension are purported to be the causes of end stage renal disease (ESRD) in 35% and 23% of the US ESRD population.¹ CKD patients are also exposed to a variety of unique potential risk factors including abnormal calcium-phosphate metabolism,⁵ decreased nitric oxide levels,⁶ hyperhomocysteinemia,⁷ elevated CRP and raised IL-6 levels⁸ among other inflammatory markers. Advanced age is also an important predictor of both CKD and cardiovascular risk making this issue particularly relevant to the geriatric population.

In addition to being at higher risk of cardiovascular disease, CKD patients fare worse following acute cardiovascular events and interventional procedures. One year mortality among ESRD patients following MI is 59%.⁹ Also even mild CKD increases the risk of death or complications following AMI.²

CKD patients are more likely to be hospitalized because of valvular heart disease than the general population and CKD predicts poor outcomes in CHF.²,¹⁰ CKD patients undergoing invasive procedures such as PCI and CABG in general also have significantly inferior outcomes in unadjusted analyses.¹¹,¹² It is also apparent that despite such inferior outcomes CKD patients in general may still benefit from aggressive management.¹³,¹⁴ This review will discuss the role of cardiac surgery in the management of coronary artery disease and valvular heart disease among CKD patients. In addition, the problem of acute renal failure following cardiac surgery and perioperative management issues specific to CKD patients will be considered.

**Coronary artery bypass grafting and CKD**

Coronary artery bypass grafting (CABG) is an effective therapy for coronary artery disease in the general population.¹⁵ According to American Heart Association statistics, over 500,000 coronary artery bypass surgeries were performed in 2002. A significant proportion of patients undergoing CABG also have CKD. Estimates as to this prevalence vary according to how GFR is defined, data from the Society of Thoracic Surgeons National Database suggests that 4.6% of surgical candidates have preoperative renal impairment, using serum creatinine as a measure.¹⁶

There are many reports of inferior outcomes and increased mortality following CABG among CKD patients.¹⁷,¹⁸,¹⁹ Of 7419 dialysis patients who underwent CABG between 1978 and 1995 in-hospital and two-year mortality were 12.5% and 57% respectively.¹⁷ Liu et al.²⁰ demonstrated a threefold increase in in-hospital mortality following CABG among dialysis patients when compared to the general population. Dialysis patients are also more likely to have significant comorbidities such as diabetes, poor ejection fraction and advanced coronary artery...
Longer duration on dialysis, and advanced heart failure also increase the risk of adverse outcomes following surgery. Despite the increased risks of poor outcome and increased mortality it is also notable that dialysis patients gain good symptomatic relief and improvement in functional status following CABG. It has also been reported that dialysis dependent patients have better long-term outcomes following bypass than following PCI.

Non-dialysis CKD patients also have poor outcomes following CABG surgery, compared to patients without renal disease with 30-day and one-year survival failing as severity of preoperative renal impairment increases. CKD also increases risk of postoperative complications, with serious infections, bleeding, stroke, ventilatory complications and acute renal failure necessitating renal replacement therapy all seen more frequently, in addition to poor patient outcome. The increased morbidity seen with cardiac surgery in CKD patients has implications for resource use and length of hospital stay. Table 1 summarizes published comparisons of therapeutic options for CAD among CKD patients.

Unfortunately, there are no large randomised controlled trials comparing the outcome of different revascularisation strategies in the CKD population, therefore recommendations are based on retrospective data. Such papers are subject to a number of biases and must be interpreted with a certain amount of caution.

However, outcome following CABG appears to be consistently better than medical therapy across the spectrum of CKD. Although not as clear, CABG should probably be preferred over PCI in dialysis dependent patients based on available evidence. The data for non-dialysis dependent renal failure patients is less consistent but on balance favours CABG over PCI in patients with stage 3 CKD or greater.

In renal transplant recipients no long term survival difference between revascularisation strategies was found in a retrospective study comparing PCI and CABG, although CABG did offer an advantage over PCI for the combined endpoint of cardiac death and AMI. The economic consequences of more aggressive therapy for CAD in advanced CKD should also be considered. Cost-effectiveness of more aggressive care in this population has not yet been clearly assessed but such an assessment should be an important consideration in determining therapeutic decision making.

The use of arterial grafts in CABG surgery leads to improved graft patency and greater survival in the general population. Use of arterial grafts is safe in patients with renal failure, with no increase in operative complications when compared to surgery utilising venous grafts. One study comparing outcome of dialysis patients following CABG suggested reduced cardiac related death rate in patients with bilateral internal mammary grafts compared to venous grafts. However, little data exists regarding the influence of graft choice on survival in this population. In view of their benefit in the general population and operative safety in CKD patients arterial grafts should probably be used where possible, the only potential caveat being reports of intra-dialytic 'myocardial steal' occurring in patients with left internal mammary grafts and ipsilateral AV fistulas.

Cardiac valve surgery

Dialysis patients are more likely to be hospitalised because of valvular heart disease than the general population. In a study of French dialysis patients the annual incidence of severe VHD in the dialysis population was 15 to 19 cases per 100,000, with calcific valvular disease and endocarditis accounting for 69% and 19% of the cases respectively. There are a number of factors that potentially contribute to the

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>N</th>
<th>CABG vs. Medical therapy</th>
<th>CABG vs. PCI</th>
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<tr>
<td>Herzog 1999(17)</td>
<td>Dialysis patients</td>
<td>14306</td>
<td>N/S</td>
<td>Significant benefit</td>
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<tr>
<td>Herzog 2002(23)</td>
<td>Dialysis patients</td>
<td>15784</td>
<td>N/S</td>
<td>Significant benefit</td>
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<td>Szczek 2001(24)</td>
<td>Dialysis patients, Non-dialysis CKD patients</td>
<td>1247</td>
<td>N/S</td>
<td>Significant survival benefit in dialysis patients</td>
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<td>Reddan 2003(13)</td>
<td>Non-dialysis CKD patients</td>
<td>4584</td>
<td>Significant survival benefit across all groups</td>
<td>No survival difference in GFR 60ml/min patients</td>
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<tr>
<td>Hemmelgarn (25)2004</td>
<td>Dialysis patients, Non-dialysis CKD patients</td>
<td>1412</td>
<td>Significant survival benefit across all groups</td>
<td>No survival difference in Cr 2.3 patients</td>
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Cr = creatinine, N/S = not studied, GFR = glomerular filtration rate
accelerated calcific degeneration of cardiac valves seen in ESRD including abnormal calcium-phosphate balance, duration of dialysis and hypertension. The combination of degenerative valve disease and frequent access-associated bacteremia also puts this population at high risk of developing infective endocarditis. The incidence of confirmed bloodstream infections was 1.5 per 1000 dialysis sessions in one large study.

Outcomes following valve surgery are poor in dialysis patients. In a study of 5858 dialysis patients, there was a 19% in-hospital mortality and 40% 2-year survival following surgery.

Non-dialysis dependent CKD is also independently associated with adverse outcomes following valve surgery; one prospective study of 834 patients undergoing cardiac valve surgery demonstrated an association of high preoperative creatinine concentration with 30-day mortality (16% for CKD versus 6% for normal renal function, p=0.001) and complication rate.

The choice of valve replacement is a contentious issue in dialysis patients. The American College of Cardiology/American Heart Association Task Force Report advise against the use of bioprosthetic valves in renal failure. This stems from the perceived risk of accelerated calcific degeneration of bioprosthetic valves in the uraemic milieu.

However, a number of studies have taken issue with this, a large retrospective study of 5858 US dialysis patients compared the outcome following surgery with bioprosthetic (881 patients) and mechanical valve replacement (4944 patients) and showed similar survival in both groups. A small study comparing dialysis patients also showed that valve choice did not influence outcome and demonstrated that accelerated bioprosthetic valve degeneration did not play a significant role in valve failure. Additional studies of dialysis patients undergoing valve replacement have shown no difference in survival between valve type but an increased risk of stroke and bleeding in mechanical valve recipients.

In CKD, therefore, the choice of valve should probably be made on a case by case basis, in young fit patients with good life expectancy following surgery mechanical valve replacement is favoured because of its longer lifespan. However many dialysis patients have a relatively short survival following surgery and may benefit from the reduced stroke and bleeding risk of bioprosthetic valve replacements.

Acute renal failure

Acute renal failure (ARF) is a serious complication following cardiac surgery, occurring in 1 to 8% of the cases. In an analysis of over 43,000 patients undergoing cardiac surgery, dialysis was required in 1.1% of patients postoperatively.

Postoperative ARF requiring dialysis is a predictor of adverse outcome. In one study patients requiring renal replacement therapy (RRT) had a mortality rate of 63.7% compared to 4.3% in those without the complication.

The increased rate of adverse outcomes is not confined to patients requiring dialysis. A prospective study of 4118 patients undergoing cardiac surgery showed that even mild postoperative elevations in serum creatinine are associated with an increased 30-day mortality, additionally, postoperative renal deterioration, defined as postoperative rise in serum creatinine greater than 25%, is associated with significantly increased long term mortality irrespective of subsequent renal recovery.

Post-operative ARF occurs primarily as a result of renal hypoperfusion and ischaemia, and with its high metabolic demand and relatively poor blood supply the renal medulla is especially sensitive to reductions in tissue oxygenation. It is not surprising that cardiopulmonary bypass (CPB) particularly of longer duration, lower pressures and lower flow, and valve surgery, with its longer operative and aortic cross-clamp times are both associated with an increase risk of postoperative ARF.

However not all postoperative ARF is a result of ischaemic injury; atheroembolic disease and rhabdomyolysis are also reported causes. Despite the insults associated with surgery, renal failure occurs in only a small fraction of patients and it is likely that certain patients are more susceptible to the complication than others. A number of preoperative risk factors help to identify these patients. Analysis of a large cohort of patients with ARF requiring dialysis following cardiac surgery showed a graded association with preoperative renal dysfunction and risk of subsequent ARF. A number of other independent risk factors were identified including IABP use, prior heart surgery, New York Heart Association stage IV heart failure, peripheral vascular disease, ejection fraction <35%, pulmonary rales, COAD, hypotension in CABG patients and hypertension in cardiac valve replacement patients. These risk factors have been utilised in many preoperative scoring systems developed to quantify the risk of ARF.

The avoidance of CPB using 'off-pump' coronary artery bypass (OPCABG) surgery is now commonplace. OPCABG reduces the risk of subsequent ARF compared to its on-pump equivalent in the general population, while OPCABG with complete avoidance of aortic manipulation was associated with further reduction in complications in a South Korean study. OPCABG is an attractive option for patients identified preoperatively as being high risk for ARF. One recent study comparing outcomes following on-pump and off-pump bypass surgery in individuals with preoperative non-dialysis dependent CKD showed that acute renal failure and mortality rates were reduced in the off-pump group. However concern remains over long term outcome following OPCABG with reports of higher rates of incomplete revascularisation and use of fewer grafts in ‘off-pump’ compared to ‘on-pump’ CABG procedures.

A number of specific therapies have been used to prevent or treat post-operative ARF. The osmotic diuretic mannitol was part of surgical protocols for many years. One small prospective study in children undergoing cardiothoracic surgery demonstrated a reduction in post-operative creatinine with mannitol administration. However, in adults undergoing cardiac surgery there is no good evidence to support mannitol use.

The loop-diuretic frusemide is routinely used for perioperative renal protection in many centres. Loop diuretics
reduce renal tubular cell oxygen demand, producing a favourable oxygen supply-demand ratio. Increasing renal tubular flow may also help to reduce tubular obstruction and backflow. A number of experimental studies have shown administration of loop diuretics to be renoprotective. However, clinical studies have shown use of loop diuretic to have a detrimental effect on renal function and outcome following cardiac surgery, possibly as a result of volume depletion and their routine use is not recommended.

Dopamine infusion also has a number of theoretical benefits for renal function including increased renal blood flow, increased GFR and reduced renal oxygen demand. Little clinical evidence exists for its use in ARF, however low dose dopamine is still frequently used for ‘renoprotection’ perioperatively. A recent study looking at its role in the prevention of renal failure following cardiac surgery demonstrated no advantage over placebo.

Atrial natriuretic peptide (ANP) is an endogenous diuretic and naturetic substance which causes pre-glomerular vasodilatation and increases GFR in ischaemic ARF following cardiac surgery. A number of small trials suggest that ANP infusion reduces the incidence of acute renal failure complicating cardiac surgery and heart transplantation but further confirmatory evidence is awaited.

The treatment of ARF following cardiac surgery is largely supportive with removal of nephrotoxins, maintenance of adequate renal perfusion and renal replacement therapy where indicated. Timing of RRT is largely based on volume, electrolyte and metabolic parameters, although a number of studies looking at the timing of RRT in ARF following cardiac surgery suggests that early intervention with renal replacement therapy improves survival.

ARF is, therefore, a common and serious complication of cardiac surgery. Its development is related to a number of patient and surgical factors. ‘High-risk’ patients should be identified pre-operatively and special care should be taken to avoid nephrotoxins and maintain renal perfusion. Off-pump bypass should be offered to high-risk candidates with the understanding that long term and revascularisation outcomes may not be as good. Since specific therapies are largely unsuccessful or unproven, pre-operative risk stratification and prevention are paramount.

Perioperative Considerations

Nutrition

Dialysis patients are frequently malnourished and this contributes to poor postoperative wound healing. Nutritional status should be assessed prior to surgery. Guidelines exist regarding nutritional assessment in dialysis patients, useful clinical indicators include serum albumin and the calculated protein catabolic rate. Dietary advise, supplementation and adequate dialysis dose are important in optimising nutrition before elective surgery.

Perioperative dialysis management

Generally haemodialysis is performed the day prior to surgery; a longer hiatus puts the patient at risk of perioperative acidemia, hyperkalaemia and volume overload. If haemodialysis is to be performed on the same day as surgery, a break of at least four hours should be allowed for the APTT to normalise or alternatively heparin-free dialysis may be used. Postoperatively haemodialysis is usually deferred for at least 24 hours or until volume overload or hyperkalaemia develop. Heparin anticoagulation during dialysis should be avoided immediately postoperatively as it may contribute to bleeding complications and heparin free methods should be preferred.

In theory, intensive haemodialysis should result in more physiological volume and electrolyte control perioperatively. A small Japanese study involving 15 patients assessed the impact of intensive perioperative dialysis on outcome following cardiac surgery. The study patients underwent daily haemodialysis for three days before surgery, intraoperative haemodialysis and early continuous haemodiafiltration postoperatively. The outcome of the intensive dialysis group was excellent, similar to that of non-renal failure patients, however, the trial may have lacked external validity in that the patient population was relatively young.

Perioperative hyperkalaemia

Careful perioperative management of potassium homeostasis is required in CKD patients. Potassium has effects on myocardial excitability and hyperkalaemia may lead to ventricular fibrillation or asystole. Specific causes of perioperative hyperkalaemia include potassium-rich replacement fluids or cardioplegia, drugs such as beta-blockers and intraoperative transcellular potassium shifts. Potassium should be normalised preoperatively in CKD patients, despite anecdotal experience that CKD patients may safely tolerate chronic hyperkalaemia. Potassium-rich cardioplegia leads to improved myocardial preservation during CPB, however this is usually contraindicated in CKD patients. A recent study demonstrated that intraoperative haemodialysis permits safe use of potassium rich cardioplegia in these patients.

Anaesthetic measures in CKD

The pharmacokinetics of many drugs are altered in CKD primarily as a result of reduced renal excretion. Preoperative calculation of GFR is necessary for correct renal dosing of many common drugs. The formula suggested for calculating GFR is the modified MDRD formula (where estimated GFRMDRD=186.3 × Serum Creatinine[1.154] ×age[0.203] × [0.742 if male] × [1.212 if female]).

A number of drugs used perioperatively are noteworthy. Morphine-6-glucuronide, an active metabolite of morphine, is excreted renally and may accumulate in renal failure. Norpethidine, a metabolite of pethidine, accumulates in CKD and may lead to seizures. The preferred analgesia in the setting of CKD is fentanyl or methadone.

The half-lives of many neuromuscular blocking agents are increased in renal failure, however, atracurium is not affected and is the drug of choice. Succinylcholine, the depolarising muscle relaxant is associated with acute hyperkalaemia and should be avoided in renal failure.
Perioperatively, AV fistula limbs should be kept free from intravenous catheters and blood pressure measurements. Cannulation of subclavian veins should also be avoided as this is associated with late stenosis of the vessel leading to difficulty with ipsilateral AV fistula formation.101

**Bleeding**

CKD patients are at higher risk of bleeding complications following CABG surgery than the general population; the risk of bleeding increases with severity of renal dysfunction in a graded manner.102 In the laboratory, uremic diathesis manifests as a prolonged bleeding time103 although this test is rarely used in clinical practice. Bleeding tendency is partially reduced with haemodialysis.104 The increased bleeding tendency may also be related to reduced clearance of heparin (both fractionated and unfractionated) in this population and appropriate dose reductions are suggested.105, 106 Factor Xa monitoring is suggested in patients with CKD receiving low molecular weight heparin. With respect to unfractionated, heparin high peak levels and prolonged heparin activity have been reported in patients with impaired renal function undergoing aortic surgery resulting in an increase in the requirement for blood replacement.107 It is also notable that at higher doses of UFH, the proportion of drug that is renally cleared increases considerably.108 A number of other useful treatments are available for procoagulant prevention or management of haemorrhage in CKD patients including cryoprecipitate, DDAVP infusion and conjugated estrogens.109, 110 Preoperative treatment of anaemia with either transfusion or erythropoietin effectively reduces uremic bleeding.111-113 Erythropoietin also reduces transfusion requirements in the critical care setting.114 Careful preoperative planning and optimisation of haemocrit is therefore important in the CKD population.

**Conclusion**

Chronic kidney disease patients represent a population with a considerable cardiovascular risk. Although unadjusted outcomes following CABG are worse in CKD patients compared to the general population, the balance of available evidence suggests that surgical revascularisation may be preferable to PCI in patients with stage 3 CKD or greater. Available studies on CAD therapy in CKD predate the widespread use of technologies such as drug eluting stents and it remains to be seen whether these new developments shift the balance in favour of PCI in this population. Cardiac valve disease requiring operative intervention is also common in this population. CKD patients represent a significant portion of cardiac surgical candidates and demand careful perioperative management. Acute renal failure is a common complication following cardiac surgery. It is associated with poor short and long-term outcomes. Careful preoperative risk stratification and prevention of this complication are of utmost importance.

**References**
