Symposium: Review Article

Outcomes after percutaneous coronary interventions in patients with chronic kidney disease

Tan Huay Cheem

Cardiac Department, Level 3, Main Building, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074, Singapore

Introduction

Chronic kidney disease (CKD) is a significant contributor to cardiovascular morbidity and mortality. Patients with CKD are known to have a greater prevalence of cardiovascular disease than the general population,1 and patients with concurrent CKD and coronary artery disease (CAD) have greater mortality than patients without CKD.2,3 The rate of cardiovascular mortality is approximately 50%, five to 10 times higher than the general population.

Percutaneous coronary intervention (PCI) is a proven effective treatment for reducing myocardial ischemia and clinical symptoms in patients with coronary artery disease. It enjoys a high primary success rate of between 90% and 95% in the general population. However, in patients with CKD, there is an increased risk of procedural complications, an adverse long-term clinical outcome, and a high rate of clinical and angiographic restenosis. This paper reviews the current literature of PCI in patients with CKD and examines the acute and long-term clinical outcomes in elective and emergency settings, the comparative efficacy of the different revascularisation strategies and the impact of drug-eluting stents.

Choice of revascularisation in patients with CKD

Patients with CKD are making up an increasing percentage of population undergoing PCI. They are generally older with more associated comorbidities such as diabetes, hypertension, lower left ventricular ejection fraction, chronic obstructive pulmonary disease, vascular disease, congestive heart failure, cardiogenic shock, multi-vascular disease, history of prior coronary artery bypass grafting (CABG), and history of previous myocardial infarction.4 Irrespective of coronary artery disease severity or choice of revascularisation strategies, the presence of CKD was associated with increased risk of mortality.

Previous surgical and angioplasty studies have shown that coronary revascularisation improves prognosis in patients with end-stage renal failure.5,6 In the only randomised trial in which dialysis patients were randomised to be treated with an invasive revascularisation approach (both PCI and CABG) or medical therapy, the invasive approach had a clear survival benefit.7 However, coronary artery revascularisation has inferior outcomes among patients with CKD compared to those without.8 Even so, revascularisation strategy (either percutaneous or surgical) has been consistently shown to be superior to medically treated patients. Keeley et al.9 showed improved long-term survival in patients with severe CKD (eGFR < 60 ml/min/1.73 m2) who underwent revascularization compared with medical therapy alone, having adjusted for the types of acute coronary syndrome, medical therapy received, and other significant baseline variables (Fig. 1). Reddan et al also showed that PCI was associated with a survival benefit compared with medical management among patients with normal to moderately impaired renal function.7 The APPROACH study showed that PTCA have a survival benefit over medical therapy in patients with CKD (80.4% vs 72.3%, p<0.001). The difference was particularly pronounced in the dialysis group (41.2% vs 30.4%, p=0.03).9

Fig. 1. Long-term survival in patients with severe CKD by different management strategies

There appears to be a gradient of survival probabilities that exist among patients with CAD and CKD that is a function of the severity of renal insufficiency. CABG was associated with greater mortality reduction than PCI in severe CKD.7,9 Reddan et al showed that CABG had a greater survival benefit when compared with medical management (HR 0.42; 95% CI

Corresponding author: Tan Huay Cheem, M.D., Cardiac Department, Level 3, Main Building, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074, Singapore.
had a beneficial association with survival among patients with moderate and severe renal insufficiency not demonstrated among patients with normal renal function and mild renal insufficiency. This was corroborated by other studies which also suggested that a differential treatment benefit from PCI and CABG exists among patients with end stage renal disease (ESRD). Hemmelgarn et al reported a survival benefit for CABG over PTCA or medical therapy in patients with all categories of renal function. Szczek et al published an analysis of survival outcome in dialysis patients after PTCA and CABG surgery in New York State by using a clinical database, and revealed a survival advantage of CABG surgery compared with PTCA in dialysis patients. Herzog et al also reported a more favourable survival outcome for dialysis patients who underwent CABG than balloon angioplasty or stenting (56% vs 48% 2-year all cause survival). In particular, diabetic patients receiving CABG surgery fared better than those receiving stents or PTCA. In non-diabetic ESRD patients, patients who received stents were found to do better than PCI, with a 10% and 13% lower risk of all-cause death and cardiac death respectively.

Percutaneous coronary intervention in patients with CKD

Patients with CKD have an accelerated rate of atherogenesis with typical extensive coronary calcification, abnormal platelet function, anemia, chronic inflammation and multiple comorbidities (higher incidence of diabetes mellitus, hypertension and dyslipidemia). They also have a higher incidence of complex coronary lesion morphology with poor distal target vessels and may therefore be less amenable to conventional balloon angioplasty. CKD significantly impacts clinical outcomes following coronary revascularisation procedures. Adverse clinical events have been shown to increase exponentially with declines in glomerular filtration rate (GFR).

PCI in patients with CKD is definitely feasible but is associated with a doubling of in-hospital mortality even with mild renal insufficiency. Best et al from Mayo Clinic reported an increasing one-year mortality rate when stratified according to worsening renal function: 1.5% (GFR 370ml/min), 3.6% (GFR 50-60ml/min), 7.8% (GFR 30-49 ml/min) and 18.3% (GFR <30ml/min). In the BARI trial, patients with CKD experienced a doubling of mortality compared with patients without CKD during a 7-year follow-up period after revascularisation treatment for coronary atherosclerosis. The in-hospital mortality for patients undergoing PTCA was much higher for patients with than without renal insufficiency (6.7% vs 0.7% respectively, p<0.05). The incidence of the combined endpoint of death or Q-wave MI was much higher as well. The risk of death among patients with mild renal insufficiency without diabetes mellitus was similar to that of patients with diabetes mellitus without CKD. When both mild CKD and diabetes were present, the mortality risk was additive at 70% at 7 years. Among patients who underwent PTCA, patients with CKD had a significantly higher frequency of inhospital death (p<0.05), cardiogenic shock (p=0.01), rehospitalisation (p=0.003), shorter time to CABG (p=0.01) and a trend towards a greater likelihood experiencing angina at 5 years (p=0.079).

Despite the complex lesion morphology and the multitude of comorbidities associated with CKD, such patients continue to enjoy a high rate of procedural success in the current era of percutaneous coronary revascularisation. The utilization of stenting and debulking techniques further improves the immediate and long-term outcomes in this complicated patient population. In a study that saw an increasing rate of stent placement from 9% to 56% over a 4-year period for patients with CKD, the procedural success rate increased from 84% to 95%. Regression analysis showed that conventional balloon angioplasty strategy is an independent predictor of in-hospital major adverse cardiac events (MACE) rates in the renal failure group. Thus coronary stenting and debulking techniques have largely supplanted balloon angioplasty treatment alone in present times.

BARI trial was conducted in an era when stents were not available for use and one wonders about the effect of coronary stenting on the clinical outcomes of PCI in patients with CKD. Recent observational study showed that patients with CKD are still associated with a 2.2 fold increased need for repeat revascularisation (35% vs 16% for CKD patients vs controls) despite the use of coronary stents. In patients with ESRD, a high rate of angiographic and clinical restenosis following coronary angioplasty has been reported. However these studies were biased towards a high rate of angiographic restenosis, as only patients with recurrent anginal symptoms were included for angiographic follow-up. In a retrospective case-control study by Schoebel et al, the rate of angiographic restenosis in ESRD patients was found to be 60% compared with 35% in controls. Interestingly, clinically apparent restenosis is not increased in patients with CKD compared with patients with normal renal function. It is likely that increased restenosis after PCI procedures in patients with CKD may account for part of the increased mortality rate after PCI in this population, and restenosis leading to severe silent myocardial ischemia has been hypothesised to account for the high risk of subsequent cardiac events among patients with renal failure undergoing PCI.

PCI in patients with CKD and acute coronary syndromes

In multiple epidemiologic studies, renal dysfunction has been shown to be an independent predictor of survival in patients with acute coronary syndromes and acute myocardial infarction (AMI). In fact, the mortality rate for patients with ESRD rises to more than 60% during the first year after AMI. Primary PCI for AMI has demonstrated a superior reperfusion rate compared with fibrinolytic therapy and is generally the preferred strategy for acute reperfusion.

Sadeghi et al reported that patients with CKD and AMI undergoing primary PCI had a markedly higher risk of mortality, as well as bleeding and restenosis, than those without
CKD. The mortality at 30 days was significantly increased in those with CKD compared to those without (7.5% vs 0.8%, p<0.0001) and at 1 year (12.7% vs 2.4%, p<0.0001) (Fig. 2). Hemorrhagic complications and transfusion requirements were increased more than 2-fold in patients with CKD, and restenosis was also higher (diameter stenosis 370%; 20.6% vs 11.8%, p=0.024).

In another study conducted in Japan, Yamaguchi et al reported higher in-hospital mortality in patients with CKD who underwent successful primary PCI. There was a gradient of mortality associated with more severe renal dysfunction. The in-hospital mortality of patient with mild (1.27 creatinine <2.0mg/dl) and severe (creatinine 32.0mg/dl) renal dysfunction was greater (17.1% and 34.5%, respectively) than that of patients without renal dysfunction (3.9%) (RR 1.72, 95% CI 0.94 to 3.14, p=0.08; and RR 4.26, 95% CI 1.48 to 12.27, p<0.001, respectively). The in-hospital mortality of patients with mild renal dysfunction was greater (17.1% and 34.5%, respectively) than that of patients without renal dysfunction (3.9%) (RR 1.72, 95% CI 0.94 to 3.14, p=0.08; and RR 4.26, 95% CI 1.48 to 12.27, p<0.001, respectively).

Baseline renal function as a strong independent predictor of in-hospital and long term mortality is further confirmed in a large study of 1400 patients with unstable angina (UA)/non ST-segment elevation MI (NSTEMI). Treated uniformly and early with PCI, patients whose GFR were 3130ml/min/1.73m² had 0% in-hospital mortality whereas those with GFR <60ml/ min/1.73m² had 5.1% mortality rate. The cumulative 3-year survival rates were 92.6% and 76.8% respectively. The explanation for why CKD is such a potent risk factor for adverse outcomes in UA/NSTEMI patients include excess co-morbidity, less use of beneficial treatments, excess toxicity from conventional treatments used and the unique pathobiology of CKD.

Drug-eluting stents in patients with CKD

Coronary stenting has been shown to have significantly improved the procedural success rates and long term outcomes for patients with CKD. Drug-eluting stents (DES) have been shown to be effective in reducing neointimal growth and in-stent restenosis compared with conventional stents, leading to an impressive reduction in the rate of target vessel revascularization. The evidence regarding the impact of drug-eluting stents in patients with CKD has been limited.

Table 1 PCI complications in patients with CKD

<table>
<thead>
<tr>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy calcification</td>
</tr>
<tr>
<td>Higher dissection</td>
</tr>
<tr>
<td>Higher risk of balloon rupture from high pressure balloon inflation</td>
</tr>
<tr>
<td>Higher perforation</td>
</tr>
<tr>
<td>Higher incidence of balloon entrapment</td>
</tr>
<tr>
<td>Higher major adverse cardiac events (MACE)</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Q or non-Q wave myocardial infarction</td>
</tr>
<tr>
<td>Contrast induced nephropathy</td>
</tr>
<tr>
<td>Higher restenosis</td>
</tr>
<tr>
<td>Higher target vessel revascularisation</td>
</tr>
</tbody>
</table>

Lemos et al reported in a case-control study showing that patients with renal impairment who received sirolimus-eluting stents (SES) had no mortality benefits over patients who received bare stents (hazard ratio 0.91, 95% CI 0.49-1.68, p=0.8). However the incidence of target vessel revascularisation (TVR) decreased significantly in the SES group compared with the bare metal stent group (hazard ratio 0.37, 95% CI 0.15 to 0.90, p=0.03), with a consequent decrease in clinical restenosis rate. As this benefit was not paralleled by a decrease in the risk of death, it seems unlikely that restenosis could be a contributing factor that influenced the increased mortality of patients who had impaired renal function.

The data of DES on dialysis patients is even more lacking. Daemen J et al showed that the strategy of implanting SES in these high-risk subsets appeared to be safe and associated with a low incidence of MACE at 1-year follow-up. In his small series of 10 consecutive patients on hemodialysis and peritoneal dialysis, there were no cases of death, MI or TVR at mean follow-up of 403 days. However, 4 patients went on to receive renal transplantation at least 3 months after SES implantation with no clinical evidence of any interaction between local administration of sirolimus and the systemic immunosuppression therapy that was given.

Contrast-induced nephropathy after PCI

Acute deterioration in renal function is a recognised complication after coronary angiography and intervention. Contrast-induced nephropathy (CIN) is typically defined as an increase in serum creatinine >0.5mg/dl (44umol/L) or >25% of the baseline level 48 hrs after contrast exposure. It is rare in patients with normal renal function in the absence of diabetes mellitus. Rihal et al found a 2% incidence of CIN in nondiabetic patients with a baseline creatinine >1.1mg/dl. On the other hand, 50% of patients with diabetic nephropathy and a mean serum creatinine of 5.9mg/dl had a >25% increase in serum creatinine after coronary angiography, and 12% required dialysis within a week. Significant predictors of CIN in patients with CKD include decreased GFRs, periprocedural hypotension, higher contrast media volumes, lower baseline hemocrit, diabetes mellitus, pulmonary edema at presentation and left ventricular ejection fraction <40%.
For patients with pre-existing CKD, renal function deterioration after coronary intervention is a marker for poor outcomes, especially for patients who require dialysis. Gruber et al reported an in-hospital mortality of 14.9% for patients with further renal function deterioration versus 4.9% for patients with no creatinine increase (p=0.001).32 For those patients who require dialysis, the in-hospital mortality rose to 22.6%. The cumulative one-year mortality was 45.2% for those who required dialysis, 35.4% for those who did not require dialysis and 19.4% for patients with no serum creatinine increase (p=0.001). Levy et al reported 183 patients who developed CIN and compared those index patients against controls matched for age and baseline serum creatinine. The in-hospital mortality was 34% in the patients who developed CIN versus 7% in the control population.33

Intravenous hydration (saline 0.45%, if tolerated 0.9% at a rate of 1ml/kg/h) 12 hour before and after contrast exposure and the use of low or iso-osmolality contrast agents are used to prevent CIN. The benefit of low-dose dopamine, fentanyl and theophylline is unproven. N-acetylcysteine (NAC) has been evaluated in several trials with inconsistent results. Newer data suggest a benefit of high dose NAC (1200mg twice daily) for patients receiving high doses (>140ml) of contrast agent, or those with advanced renal insufficiency (serum creatinine >2.5 mg/dl).34

Secondary prevention

Besides coronary revascularisation, patients with CKD and CAD need to be managed aggressively insofar as modification of risk factors is concerned. Hypertension should be treated to a target of <130/80mmHg which will often require two or three antihypertensive agents. Patients with persistent proteinuria, usually the first indicator of kidney damage, are preferentially treated with moderate-to-high doses of either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB). ARBs have been shown to confer significant benefits in retarding the progression of diabetic nephropathy, and delay the need for dialysis or transplantation.35 All patients should also be prescribed a diuretic in order to treat volume-mediated hypertension.

While the benefits of lipid-lowering have not yet been established specifically in patient with severe CKD, post hoc analysis of patients with mild CKD in the CARE study demonstrated that HMG CoA reductase therapy resulted in a reduced rate of major adverse cardiovascular effects.36 It may even slow down the progressive decline in renal function in these patients.37 The purported anti-inflammatory effect of statins may perhaps be even more beneficial in this group of patients because of the increased inflammatory state associated with renal failure.

Conclusions

The etiology of cardiovascular disease in CKD is complex and may result from an increased prevalence of classic cardiovascular risk factors and factors unique to uremia. Patients with CKD undergoing coronary revascularisation have an increased mortality rate, and greater degrees of renal dysfunction are associated with a higher mortality rate. Percutaneous coronary intervention involving coronary stenting is feasible, safe and effective in patients with CKD but the full impact of DES awaits to be established. CABG appears to be superior to PCI or medical therapy in patients with ESRD.

Reference


