Management of Acute Coronary Syndrome in Chronic Kidney Disease

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Abstract
Few trials have addressed the management of acute coronary syndromes (ACS) in chronic kidney disease (CKD). Hence guidelines for the management of coronary heart disease (CHD) in CKD are based on meta-analysis, subgroup analyses, small prospective studies or retrospective analyses of controlled trials and registry data. The short-term as well as long-term prognosis of ACS patients with poor renal function is worse than those with normal renal function. The risk of cardiovascular (CV) events and mortality is inversely proportional to the estimated glomerular filtration rate (eGFR). Nevertheless, CV event rates increase even in early CKD. Contrast induced nephropathy (CIN) occurs in 15% of patients following diagnostic or therapeutic invasive procedures; less than 1% of these require dialysis. While treatment of CIN is not so effective, it is predictable and can be largely prevented. Despite a higher risk of adverse outcomes, patients with moderate-severe CKD are often treated less aggressively than patients with normal renal function due to safety concerns. Patients with CKD are less likely to receive aspirin, clopidogrel, or beta blockers and are less likely to undergo reperfusion or revascularization. Conservative treatment of ACS may partially account for worse outcome in CKD. Large registry data suggests that in-hospital revascularization is associated with improved survival, irrespective of eGFR. It is not clear whether coronary artery bypass grafting (CABG) surgery or percutaneous coronary intervention (PCI) leads to better outcomes in patients suitable for either procedure. While short-term risk of CABG in CKD is high, its long-term results have been better than medical treatment or PCI in registry data. Recent data suggest no differentials in outcomes with CABG or PCI. Randomized controlled trials involving patients with renal dysfunction are needed to confirm whether aggressive treatment of ACS will improve clinical outcomes.

Background
Death from cardiac causes is 10-20 times more common in chronic kidney disease (CKD) patients than in age- and gender-matched population.1 In end-stage renal disease (ESRD), cardiovascular (CV) mortality accounts for 45% of all-cause mortality.2 Sudden cardiac death (SCD) constitutes 62% of the CV mortality in ESRD and 25% of all-cause mortality.3,4 The annual rate of SCD in ESRD patients on dialysis is 7%.

Cardiovascular Outcomes Trials and CKD
Few trials have addressed the management of coronary heart disease (CHD) and acute coronary syndrome (ACS) in CKD. A meta-analysis of 153 randomized controlled trials (RCT) of CV interventions proven efficacious for CV disease (CVD) revealed that patients with renal disease were excluded in 86 (56%) trials. Only 5% of original articles reported the proportion of enrolled patients with renal disease, and only 10% reported baseline renal function. In 3% of the original articles, subgroup analyses of treatments stratified by renal function were performed. Hence guidelines for the management of CHD in CKD are mostly opinion based.

Mortality in CKD Patients after MI, PCI, and CABG
Patients with poor renal function carry worse prognosis than those with normal renal function after acute coronary syndromes (ACS), including myocardial infarction (MI), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) surgery.5 (Figure 1).

Estimated Glomerular Filtration Rate (eGFR) and CV Outcomes
Most studies have found that a threshold for development of accelerated atherosclerosis, plaque rupture and ACS, CHF, and CV death is eGFR below 60 ml/min/1.73 m² that corresponds roughly to a serum creatinine of 1.5 mg/dl.6 The risk of CV events and mortality increases as eGFR falls progressively.

Fig. 1 : Mortality in CKD vs. non- Patients after MI, PCI, and CABG Surgery

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Cystatin C may be a more sensitive marker of a fall in GFr.\(^{11}\) While patients with end-stage renal disease (ESRD) are at extreme risk, CV event rates increase even in early CKD. Therefore, CKD is considered to be CHD risk equivalent for risk factor management.

### CVD Treatment Outcomes in CKD Patients

As there is little evidence on which to base CVD treatment in CKD, current treatment strategies are based upon small prospective studies or retrospective analyses of controlled trials and registry data. It is thus uncertain whether CKD patients benefit similar to patients with normal renal function. Revascularization by CABG in CKD has been reported in registry data to provide better long-term results than medical treatment or PCI. Recent data however shows improvement in outcomes with PCI. Short-term risk of CABG in CKD remains high. It is not clear which revascularization technique has a better outcome in patients suitable for either procedure.

### Contrast-Induced Nephropathy

Wide use of diagnostic and therapeutic procedures utilizing iodinated contrast media in CV practice has led to an increase in the incidence of contrast-induced nephropathy (CIN) (overall incidence 15%, < 1% require dialysis).\(^{8}\) The most important risk factor for the development of CIN is baseline eGFR ≤ 60. Other risk factors include diabetes, proteinuria, volume depletion, CHF, and intraprocedural adverse events. For those who require dialysis for CIN, in-hospital mortality rate is 30% and with 80% 2-year mortality. Nevertheless, CIN is predictable and may be largely prevented. Since treatment of CIN is not so effective, prevention of renal injury is important.

A simple ‘Risk Score’ based on 8 independent predictors has been suggested to predict the risk of CIN (Figure 2).\(^{9}\) Rate of CIN increased exponentially with increasing risk score. The ability to diagnose CIN is limited by the lack of a sufficiently sensitive and specific marker of renal injury. Neutrophil gelatinase associated lipocalin, kidney injury molecule-1, interleukin-18 and others are under evaluation. Till such validation occurs, eGFR remains the most reliable single marker of CIN. In clinical practice, an increase in serum creatinine of ≥ 0.5 mg/dl or ≥25% occurring 48 to 72 hours after contrast exposure is often taken as an indication of CIN but changes in serum creatinine are not specific for a decrease in GFR. Furthermore, the time lag between a fall in GFR and a rise in creatinine may affect the sensitivity of the test.\(^{10}\) Cystatin C may be a more sensitive marker of a fall in GFR.\(^{11}\)

### Pharmaco-Prevention of CIN

Several approaches for preventing CIN e.g. systemically administered vasodilators (dopamine agonists, adenosine antagonists, prostaglandins, endothelin antagonists) and antioxidants (N-acetylcysteine, ascorbic acid), and bicarbonate have been tried and failed. A recent meta-analysis found that bicarbonate therapy did not reduce the need for dialysis or mortality when compared to normal saline.\(^{12}\) Bicarbonate was most effective in patients who had urgent or emergency contrast administration or in those receiving low osmolality contrast media.

### Under-treatment of ACS in CKD

Despite a higher risk of adverse outcomes, patients with moderate-severe CKD are treated less aggressively. In a study of 45,343 patients with non–ST-segment elevation (NSTEMI) ACS enrolled in the CRUSADE Quality Improvement Initiative, adherence to Class IA/Ib recommendations was lower in patients with moderate-severe CKD, who were significantly less likely to be treated with medications or undergo invasive cardiac procedures possibly because of safety concerns about adverse outcomes and absence of trial data.\(^{13}\)

Conservative treatment of ACS may partially account for worse outcome in CKD. Registry data suggests that in-hospital revascularization is associated with improved survival, irrespective of eGFR. In the prospective, multicentre, Canadian ACS I (n=3295; 1999–2001), ACS II (n=1956; 2002–03) registries and Global Registry of Acute Coronary Events (GRACE) (n=6491; 2004–07), patients with renal dysfunction were less likely to undergo invasive management. Unadjusted 1-year mortality was lower among patients receiving in-hospital coronary angiography within all eGFR categories.\(^{14}\) Revascularization is associated with improved survival, irrespective of eGFR. In the prospective, multicentre, Canadian ACS I (n=3295; 1999–2001), ACS II (n=1956; 2002–03) registries and Global Registry of Acute Coronary Events (GRACE) (n=6491; 2004–07), patients with renal dysfunction were less likely to undergo invasive management. Unadjusted 1-year mortality was lower among patients receiving in-hospital coronary angiography within all eGFR categories.

The Acute Coronary Treatment and Intervention Outcomes Network Registry suggests that patients admitted with acute MI and CKD also receive fewer evidence-based therapies and have substantially higher mortality rates.\(^{15}\) CKD was present in 30.5% of STEMI (n=19,029) and 42.9% of NSTEMI patients (n=30,462) respectively. Regardless of MI type, patients with progressively more severe CKD had higher rates of death. In addition, patients with progressively more severe CKD were less likely to receive aspirin, beta blockers, or clopidogrel, and were less likely to undergo any reperfusion (STEMI) or revascularization (NSTEMI). Recent increase in awareness about possible improvement in prognosis with standard management may be reducing under-treatment of ACS in CKD.\(^{16}\)

### Table 1: CV Events and Death Risk as a Function of eGFR\(^{12}\)

<table>
<thead>
<tr>
<th>Estimated GFR (eGFR)</th>
<th>Hazard Ratio for Cardiovascular Events</th>
<th>Hazard Ratio for Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥16</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>11-15</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>6-10</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>&lt;6</td>
<td>3.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

### Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>1</td>
</tr>
<tr>
<td>IABP</td>
<td>2</td>
</tr>
<tr>
<td>CHF</td>
<td>3</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6</td>
</tr>
<tr>
<td>Contrast media volume</td>
<td>7</td>
</tr>
<tr>
<td>Serum creatinine [mg/dL]</td>
<td>8</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>9</td>
</tr>
</tbody>
</table>

### Calculate Risk Score

- OR for 2-40: 2 for 20-40: 4 for 20-40: 6 for <20
- eGFR <60 mL/min/1.73 m² 1 for each 100 cc
- eGFR <60 mL/min/1.73 m²

### Fig. 2: Risk Score to Predict Contrast-induced Nephropathy (CIN) after PCI

The Acute Coronary Treatment and Intervention Outcomes Network Registry suggests that patients admitted with acute MI and CKD also receive fewer evidence-based therapies and have substantially higher mortality rates.\(^{15}\) CKD was present in 30.5% of STEMI (n=19,029) and 42.9% of NSTEMI patients (n=30,462) respectively. Regardless of MI type, patients with progressively more severe CKD had higher rates of death. In addition, patients with progressively more severe CKD were less likely to receive aspirin, beta blockers, or clopidogrel, and were less likely to undergo any reperfusion (STEMI) or revascularization (NSTEMI). Recent increase in awareness about possible improvement in prognosis with standard management may be reducing under-treatment of ACS in CKD.\(^{16}\)
Conservative vs. Early Invasive Strategy in CKD

An early invasive strategy is superior to conservative strategy in ACS but underutilized in patients with CKD partly due to concern about nephrotoxicity of radiocontrast agents. However, a recent meta-analysis of 5 randomized trials (n=1453 patients with CKD) concluded that an early invasive strategy was associated with a trend toward reductions in all-cause mortality, nonfatal MI, and a composite of death or nonfatal MI and a significant reduction in re-hospitalization. This is further reiterated by another recent meta-analysis of patients with unstable angina/NSTEMI (n=5467) that found that 5-year incidence of CV death or nonfatal MI in CKD patients was lower in routine invasive vs. selective invasive strategy (14.7% vs. 17.9%, hazard ratio-HR: 0.81, 95% confidence interval-CI: 0.71-0.93; p = 0.002).18

PCI in ACS with CKD

CKD is the most important factor in predicting adverse short- and long-term outcomes after PCI. The risks involved seem to be warranted, given comparative outcomes in conservatively treated patients. The presence of CKD should not preclude a potentially beneficial CV intervention like PCI. This is corroborated by the findings in a cohort of 4631 subjects with ACS, where cardiac catheterization with or without PCI was not associated with significant differences in long-term renal function when compared to medical therapy. Among CKD subjects, the risk of death greatly outweighed the risk of reduced eGFR or development of ESRD following ACS.20

Management of Acute MI in CKD and Dialysis Patients

CKD patients presenting with acute MI are also less likely to receive aggressive therapy and twice as likely to die in the hospital. The overall 1-year mortality rate of dialysis patients after MI is greater than 50%.21 To assess the impact of advanced CKD (stages 3-5) on the in-hospital mortality of PCI in acute MI, all patients who underwent PCI in New York State between 1997 and 1999 were evaluated (n=9,015). After adjusting for co-morbidity, cardiogenic shock or heart failure, advanced CKD remained an independent predictor of in-hospital mortality (odds ratio 2.4, 95% CI 1.002-5.804, p = 0.049).22 Notwithstanding higher mortality, primary PCI remains the preferred approach in ESRD due to unacceptably high complication and mortality rates with thrombolyis in ESRD.22

The long-term prognostic importance of CKD in patients undergoing primary PCI for STEMI was assessed from data from 1933 patients in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial (CADILLAC) in whom baseline serum creatinine values were available.23 Of these, 350 had an eGFR <60 in whom, procedural success rates were lower (87.2% vs. 92%, p = 0.01), and 9-fold greater mortality at 1 month and a 5-fold increase in mortality at 1 year. CKD was independently related to severe (≥70%) restenosis and late occlusion of coronary vessels and there was an inverse relationship between eGFR and mortality throughout the follow-up.

Drug-Eluting Stents in CKD

A recent analysis of observational studies published till January 2009 concluded that DES implantation in patients with various degrees of renal insufficiency was associated with less favourable outcomes than in those with normal renal function though DES implantation yielded better outcomes than did use of bare-metal stents.24

CABG Surgery vs. PCI in CKD

To compare long-term clinical outcomes after CABG or PCI with multivessel stenting in patients with CKD, the Arterial Revascularization Therapies Study (ARTS) randomly assigned participants with CKD to CABG (n=139) or multi-vessel PCI (n=151) and followed up for a mean of 3 years. No difference was observed in the primary endpoint of a composite of death, MI, or stroke with CABG or PCI among CKD participants (adjusted HR CABG vs. PCI: 0.93; 95% CI: 0.54-1.60; p = 0.97). However, CABG was associated with a reduced risk for repeat revascularization (HR = 0.28; 95% CI 0.14-0.54; P < 0.01).25

Coronary Revascularization in Patients on Maintenance Dialysis

Underutilization of medical and interventional therapies may be partially responsible for high risk of CV death with MI in patients on dialysis.26 Optimal method of coronary artery revascularization in patients on dialysis is controversial. In an exploratory meta-analysis, 30-days or in-hospital mortality was higher with CABG compared to PCI but there was no difference in mortality over subsequent 1-5 years.27

ACS and Anti-thrombotic Agents in CKD

Due to excessive risk of bleeding, anti-thrombotic agents should be used with caution in CKD. The dose of low molecular weight heparin should be reduced when eGFR is <30. Amongst GPIIb/IIa inhibitors, the infusion rate of tirofiban should be reduced to half when eGFR is <30. Both bolus dose and infusion rate of eptifibatide should be modified when serum creatinine is between 2 and 4 mg/dl.28 The direct thrombin inhibitor bivalirudin reduces ischemic and bleeding events after PCI. To assess whether this benefit is influenced by renal function, a meta-analysis of 3 randomized trials (n = 5,035) in different strata of eGFR concluded that the relative benefit of bivalirudin with respect to ischemic and bleeding events was maintained.29

In Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) substudy (n=13,819 moderate and high risk ACS, early invasive strategy), the safety and efficacy of bivalirudin monotherapy vs. bivalirudin plus a glycoprotein IIb/IIIa inhibitor (GPI) vs. heparin plus a GPI were compared.30 There were no significant differences between bivalirudin monotherapy and heparin plus a GPI in rates of 30-days composite ischemia or net clinical adverse outcomes as well as 1-year composite ischemia or mortality, the incidence of major bleeding at 30 days was remarkably less with bivalirudin alone (6.2% vs. 9.8%, p = 0.008).

Conclusions

Though routine invasive approach for ACS in renal dysfunction may increase the risk of short-term adverse outcomes, there is likely to be an improvement in long-term outlook. The fear of CIN continues to cause underutilization of routine invasive approach in this setting. Lack of randomized
controlled trial data is another major barrier to implementation of standard therapies for ACS in renal dysfunction.

References
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