Effect of Kidney Disease on Acute Coronary Syndrome

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Chronic kidney disease (CKD) is highly prevalent worldwide and is associated with an increased risk for adverse outcomes in patients hospitalized with acute coronary syndrome (ACS). In studies including thousands of patients admitted with myocardial infarction, CKD consistently determines a poorer prognosis for ACS patients. In contrast with CKD, information about the effect of acute kidney injury (AKI) on clinical outcomes after ACS is limited. Most data come from retrospective registry databank studies of nonconsecutive patients with a significant number of patients excluded from analyses. There are no prospective studies designed to determine whether AKI strictly diagnosed by the new the Acute Kidney Injury Network (AKIN) or RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria is a risk factor for death after ACS, and there are no data comparing the RIFLE and AKIN criteria for AKI diagnosis after myocardial infarction. This article reviews the most important data on CKD and ACS and the available data on AKI and ACS. The importance of obtaining an early serum creatinine level after admission for ACS and the importance of renal function monitoring during hospitalization are stressed.


The Independent Association between Renal Dysfunction and Mortality after ACS

Shlipak et al. (6) evaluated 130,099 elderly patients with acute myocardial infarction (AMI). Mild (admission serum creatinine [Scr] between 1.5 and 2.4 mg/d) or moderate (admission Scr between 2.5 and 3.9 mg/d) renal dysfunction were independent risk factors for death. At a 1-month follow-up, the adjusted hazard ratio (AHR) for death was 1.68 for mild and 2.35 for moderate renal dysfunction compared with patients without CKD. The 1-year mortality was higher for patients with moderate CKD compared with patients without renal dysfunction (66% versus 24%, P < 0.001).

Reddan et al. (7) evaluated 13,707 patients with ACS in two clinical trials: SYMPHONY and 2° SYMPHONY. Patients were categorized into four groups on the basis of hospital admission creatinine clearance (CrCL) calculated by MDRD (2): stage I (≥90 ml/min), stage II (60 to 89 ml/min), stage III (30 to 59 ml/min), and stage IV (<30 ml/min). The multivariate analysis showed that each 10-ml/min increase in CrCL was associated with a corresponding decrease in mortality (odds ratio [OR] = 0.897).

Suwaidi et al. (8) studied patients from a sample of four randomized clinical trials: Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb, GUSTO-III, Platelet Glycoprotein IIb/IIIa in Unstable Angina–Receptor Suppression Using Integrilin Therapy (PURSUIT), and Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON-A). They found renal dysfunction (defined as admission CrCL < 70 ml/min) in 18,621 patients (41%) with ST elevation myocardial
infarction (STEMI) and in 19,304 patients (42%) with non-STEMI. Patients with baseline renal dysfunction were older, more often female, and more likely to have prior comorbidities. Renal dysfunction was associated with higher early (30-day) and late (6-month) risk of death or nonfatal AMI regardless of ST elevation status compared with patients with normal renal function. At a 6-month follow-up, a higher CrCL was associated with lower mortality in non-STEMI (AHR 0.81) and STEMI patients (OR 0.79). In GUSTO-Iib, patients with STEMI and renal dysfunction at admission had a 6-fold higher 180-day mortality than the patients with normal CrCl (16.2\% versus 2.5\%, P < 0.001).

In non-ST elevation ACS, Gibson et al. (9) studied 13,307 patients from the Thrombolysis in Myocardial Infarction (TIMI) 11A, TIMI 11B, TIMI 12, Oral glycoprotein IIB/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16), and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TATICS)-TIMI 18 trials. GFR at admission was calculated by MDRD, and patients were classified into three groups: normal renal function (\(\geq 90\, \text{ml/min per 1.73 m}^2\)), mild decrease (60 to 89 ml/min per 1.73 m\(^2\)), and moderate to severe decrease (<60 ml/min per 1.73 m\(^2\)). Decreasing GFRs were independently associated with mortality within 30 days and 6 months. Impaired GFRs were also associated with a higher death rate compared with maintained GFRs, regardless of TIMI score status.

A prospective multicenter study, GRACE (Global Registry of Acute Coronary Events) (10), analyzed 11,774 patients with STEMI, non-STEMI, and unstable angina. Admission CrCL was calculated by the Cockcroft–Gault formula, and patients were divided into three groups: normal or mildly decreased renal function (CrCL >60 ml/min, moderate (CrCL 30 to 60 ml/min), and severe renal dysfunction (CrCL <30 ml/min). Compared with patients with normal or mildly impaired renal function, admission CrCL was independently associated with death, with an AHR of 3.71 for severe renal dysfunction and 2.09 for moderate renal dysfunction.

Mielniczuk et al. (11) studied 4178 patients with non-ST elevation ACS or STEMI from the A to Z trial. Impaired admission GFRs (CrCL < 60 ml/min) were associated with a higher mortality after adjusting for baseline levels of highly sensitive C-reactive protein.

The in-hospital mortality for patients with CKD after AMI may be higher for young individuals (<65 years) when compared with old (65 to 84 years) and very old (≥85 years) patients. Cardarelli et al. (12) studied 169,826 patients undergoing primary percutaneous coronary intervention (PCI) for AMI from the data registry collected by the American College of Cardiology National Cardiovascular Data Registry. They used a multivariate analysis and demonstrated that severe renal dysfunction (CrCL < 30 ml/min) was associated with higher rates of death compared with normal renal function (CrCL ≥ 60 ml/min). Young patients had the highest rate of death, with an OR of 7.58 compared with 4.75 for old patients and 3.5 for very old patients.

**Effects of Other Aspects of CKD on Outcomes after AMI**

Jurkowitz et al. (13) studied a prospective cohort of 13,329 middle-aged individuals without prior coronary heart disease. Subjects were followed for 9 years, and the authors demonstrated that patients with anemia (hemoglobin [Hgb] < 13 g/dl in men and Hgb < 12 g/dl in women) and elevated baseline SCr (≥12 mg/dl for women and ≥1.5 mg/dl for men) had a 2.7-fold greater risk of AMI or death due to coronary heart disease compared with patients with normal SCr. This association was NS in subjects with elevated baseline SCr and normal Hgb levels. Albuminuria is also a relevant marker to be considered. Hemmelgarn et al. (14) studied the progression of kidney dysfunction in a cohort of 10,184 community-dwelling elderly and demonstrated that subjects with diabetes experienced the greatest rate of decline in GFRs in the 2-year follow-up period. The authors suggested that high-risk patients can be identified by the presence of diabetes mellitus and proteinuria and that a substantial decline in GFR mainly occurs in subjects with a baseline GFR < 30 ml/min per 1.73 m\(^2\). However, it should be noted that the authors did not measure albuminuria in these patients.

**Therapeutic Differences in Treating ACS between Patients with and without CKD**

Shlipak et al. (6) related that patients with moderate CKD were less likely to receive proper treatment for ACS compared with those with normal renal function. Patients in the CKD group received less aspirin, β-blockers, thrombolitics, coronary angiography, and angioplasty than individuals with normal renal function during hospitalization for AMI.

Inrig et al. (15) demonstrated that patients with CKD were less likely to undergo a PCI during admission for ACS than patients with normal kidney function. They studied 4631 patients from the Blockade of the Glycoprotein Iib/IIIa Receptor to Avoid Vascular Occlusion trial. Time to death and to decrease of GFR >50% and progression to CKD stage 5 with dialysis were evaluated. A multivariate analysis found that each decrease of 10 ml/min per 1.73 m\(^2\) in the GFR was associated with a 15% increase in mortality (OR = 1.15, P = 0.01). Patients submitted to angiography or angioplasty had no significant long-term decrease in renal function. The authors suggested that the risk of cardiovascular death for patients with CKD outweighed the risk of renal function loss or development of chronic dialysis, and angiography or PCI should not be contraindicated in this group. Similarly, Reddan et al. (7) also demonstrated that CKD subjects were less likely to receive effective drug therapy to reduce cardiovascular risk.

**Diagnostic Challenges for ACS in Patients with CKD**

In CKD stage 5, patients with AMI on dialysis have a poorer outcome and are more likely to be underdiagnosed or have an atypical AMI presentation at admission than nondialysis patients. A retrospective cohort study (16) compared 3049 AMI patients on dialysis with 534,395 AMI patients who were not on
Why the Higher Mortality of CKD Patients after ACS?

Recently, the correlation between kidney and heart disease has been explored, and it was shown that the interaction between the kidney and the heart increases the burden for both organs if one becomes diseased. This phenomenon is named cardio-renal syndrome (CRS). Ronco et al. (17) described CRS as a primary disorder of one of these two organs, which may result in a secondary dysfunction or injury to the other organ. CRS was divided into five types, and CRS type four represents a situation in which CKD may increase the risk for adverse cardiovascular events and poor outcomes.

Various mechanisms have been proposed to explain the clinically unfavorable association between CKD and ACS.

- Residual confounding because of the high prevalence of traditional and nontraditional cardiovascular risk factors in patients with CKD, such as older age, diabetes, hypertension, dyslipidemia, left ventricular hypertrophy, hyperhomocysteinemia, oxidant stress, and elevated inflammatory markers (18).
- Complex interactions among anemia and erythropoietin resistance, malnutrition, calcium and phosphorus abnormalities, sodium and volume overload, endothelial dysfunction associated with the uremic environment, LDL oxidation and oxidative stress with monocyte stimulation leading to smooth muscle proliferation, accelerated atherosclerosis, coronary calcification, cardiac remodeling with left ventricular hypertrophy, and decreased coronary perfusion and left systolic and diastolic dysfunction (17).
- Suboptimal management of ACS in CKD patients (6,7,15) may be one of the causes of the worse prognosis described in this population. Nevertheless, it is important to mention that even CKD patients receiving optimal treatment have a poor outcome compared with non-CKD subjects.

Acute Renal Failure and Acute Kidney Injury as Risk Factors for Mortality in ACS

In contrast with CKD, there is little information about the role of acute renal failure (ARF) in clinical outcomes after ACS. ARF is defined as a complex, multicausal dysfunction with clinical features ranging from small changes in Scr to anuric renal failure. Diagnosis of ARF is often neglected or not recognized, especially if the increase in Scr is small. An additional difficulty for studying the outcomes of ARF is the lack of standardization of the diagnosis of ARF. There are more than 30 definitions of ARF in the medical literature. ARF has been defined using absolute values or percentile increases of Scr or different rates of reduction in urine output. Thus, the different definitions of ARF can cause confusion and can make comparisons more difficult (19).

Recently, two new definitions (19,20) have been proposed to standardize the diagnosis of ARF. Both definitions establish the new concept of acute kidney injury (AKI). There are subtle, important differences between the terms ARF and AKI. One important difference is that injury precedes failure. Several studies have shown that small increases in Scr during hospitalization are actually associated with a worse prognosis for the patient.

The classification system developed by the Acute Kidney Injury Network (AKIN) (20) applies the concept of small changes in Scr over a short period of time with the main purpose of allowing for early diagnosis and treatment of AKI. The AKIN group defined AKI as meeting one of the following criteria: an absolute increase in the Scr ≥ 0.3 mg/dl (≥26.4 μmol/L), an increase ≥50% (1.5 times) from baseline in a 48-hour time frame, or a reduction in urine output with documented oliguria of <0.5 ml/kg per hour for >6 hours. An important feature of this new definition is the concept of increasing stages of severity for AKI (Table 1).

RIFLE (19) (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria also represent a new system of diagnostic classification for AKI, which was developed by the Acute Dialysis Quality Initiative group and had the same aim as the AKIN group. The RIFLE criteria established the diagnosis of AKI as an increase in Scr of at least 1.5 times above the patient’s baseline value; additionally, this increase must be

<table>
<thead>
<tr>
<th>Stage</th>
<th>SCr Criteria</th>
<th>Urine Output Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Increase in Scr of ≥0.3 mg/dl (≥26.4 μmol/L) or increase of ≥150% to 200% (1.5- to 2-fold) above baseline</td>
<td>&lt;0.5 ml/kg per hour for &gt;6 hours</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Increase in Scr of &gt;200% to 300% (&gt;2- to 3-fold) above baseline</td>
<td>&lt;0.5 ml/kg per hour for &gt;12 hours</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Increase in Scr of &gt;300% (&gt;3-fold) above baseline or Scr of ≥4.0 mg/dl (≥354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L)</td>
<td>&lt;0.3 ml/kg per hour for 24 hours or anuria for 12 hours</td>
</tr>
</tbody>
</table>

<sup>a</sup>Modified from reference 20. Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage.

<sup>b</sup>200% to 300% increase = 2- to 3-fold increase.

<sup>c</sup>Individuals who receive renal replacement therapy (RRT) are considered stage 3 regardless of the stage they exhibit at the time of RRT.
Table 2. RIFLE criteria for diagnosing AKI

<table>
<thead>
<tr>
<th>Class</th>
<th>GFR Criteria</th>
<th>Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>SCr × 1.5 versus baseline</td>
<td>&lt;0.5 ml/kg per hour × 6 hours</td>
</tr>
<tr>
<td>Injury</td>
<td>SCr × 2 versus baseline</td>
<td>&lt;0.5 ml/kg per hour × 12 hours</td>
</tr>
<tr>
<td>Failure</td>
<td>SCr × 3 versus baseline or, when SCr ≥ 4 mg/dl, an acute increase of SCr &gt; 0.5 mg/dl</td>
<td>&lt;0.3 ml/kg per hour × 24 hours or anuria × 12 hours</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent ARF = complete loss of kidney function &gt; 4 weeks</td>
<td>End-stage kidney disease &gt; 3 months</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td></td>
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“Modified from references 19 and 21. RIFLE class is determined based on the worse of the two criteria (creatinine or urine output). Glomerular filtration criteria are calculated as an increase of SCr above the baseline SCr level. AKI should be abrupt (within 1 to 7 days) and sustained (> 24 hours). When the baseline SCr is elevated, an abrupt rise of at least 0.5 to > 4 mg/dl is all that is required to achieve “Failure.”

Abrupt (within 1 to 7 days) and sustained (>24 hours). A documented reduction in urine output with an oliguria rate of <0.5 ml/kg per hour for >6 hours is also a diagnostic criterion. This definition also includes a stage concept. Thus, patients are classified according to the maximum RIFLE class (risk, injury, or failure) reached during hospitalization (Table 2).

AKI has been associated with an increased risk of death in several clinical conditions (21,22). However, information about the prognostic effect of AKI in ACS and AMI is still relatively scarce. Goldberg et al. (23) studied a prospective databank of 1038 patients with STEMI, and the presence or absence of “worsening renal function” (WRF; defined as an arbitrary creatinine elevation ≥ 0.5 mg/dl at any point during the hospital stay) was determined. Overall, 9.6% of patients developed WRF during their hospital stay, which was associated with an adjusted OR of 11.4 for in-hospital death and 7.2 for 1-year mortality. The main shortcomings of this observational study were that neither the RIFLE nor the AKIN criteria were used for AKI diagnosis. Similarily, Parikh et al. (25) demonstrated that AKI was an independent risk factor for long-term mortality in elderly patients with myocardial infarction. The authors evaluated a retrospective cohort of 234,769 Medicare patients as part of the Cooperative Cardiovascular Project; 93,784 (40%) patients from the cohort were excluded from analysis. AKI was defined by absolute changes in SCr levels and classified as mild (0.3 to 0.4 mg/dl), moderate (0.5 to 0.9 mg/dl), or severe (≥ 1.0 mg/dl). AKI was found in 19.4% of the patients: 7.1% had mild AKI, 7.1% had moderate AKI, and 5.2% had severe AKI. The severe AKI group had the worst AHR for death after 10 years (1.33 compared with 1.15 for mild AKI). Long-term survival rate (10 years) in the severe AKI group was 6.5% compared with 31.7% for patients without AKI ($P < 0.001$). The validity of these results has been questioned (26) because the left ventricular ejection fraction was unavailable in 39.4% of the patients without AKI, and multivariate analysis has demonstrated that ventricular ejection fraction is a strong predictor of long-term survival after an AMI. However, considering the large size of the cohort, this criticism may be overstated. Another major point to be considered in this large retrospective study is that, again, neither RIFLE nor AKIN criteria were used for AKI diagnosis.

The effects of transient (resolved during hospital stay) and persistent AKI (elevations of SCr that persist at patient discharge) on the outcomes of STEMI patients have recently been assessed (27). Goldberg et al. evaluated 1957 patients who were divided into five groups according to absolute changes in SCr: transient mild AKI (0.3 to 0.49 mg/dl), persistent mild AKI, transient moderate/severe AKI (> 0.5 mg/dl), persistent moderate/severe AKI, and a control group that did not develop AKI. Patients with persistent moderate/severe AKI had the
highest rate of death, with an adjusted OR of 2.4, whereas patients with transient mild AKI had the lowest mortality, with an adjusted OR of 1.2, compared with patients without AKI. Interestingly, patients with transient moderate/severe AKI had mortality rates that were similar to those observed for persistent mild AKI when compared with the control group. The main limitation of this study was that retrospective analysis cannot establish a definitive etiological link between transient or persistent AKI and outcomes after STEMI. Additionally, RIFLE or AKIN classifications were not used.

Marenzi et al. (28) evaluated 97 consecutive STEMI patients with documented cardiogenic shock at admission who had undergone intra-aortic balloon pump support and primary PCI. AKI was arbitrarily defined as a 25% increase in baseline SCr. Overall, 55% of patients developed AKI during their intensive care unit stay, and AKI was independently associated with in-hospital mortality (OR 12.3; P < 0.001). The main limitations of this study were that the diagnosis of AKI was not established by RIFLE or AKIN criteria and the studied sample was small.

Biologic Plausibility of the Higher Mortality Rate of AKI Patients after ACS

This association between AMI and AKI, which leads to higher rates of morbidity and death, has been described as part of the CRS and is classified as CRS type 1. In this condition, acute heart disease with ischemic injury (e.g., AMI) may induce AKI through complex mechanisms, including hemodynamically mediated damage secondary to impaired cardiac output, exogenous factors such as the contrast media used in PCI, nephrotoxic effect of drugs, and humoral and immune-mediated damage to the kidney. These factors may contribute to decreased GFR with acute kidney hypoperfusion, reduced oxygen delivery, increased resistance to atrial natriuretic peptide and B-type natriuretic peptide, and increased cellular necrosis and apoptosis. It has also been suggested that AKI not only represents a marker of illness severity but also represents a causal factor for cardiovascular injury acceleration through the activation of neurohormonal, immunological, and inflammatory pathways (17).

Other mechanisms have been proposed to explain the association between outcomes related to AKI after ACS. Some authors call attention to the potential presence of a residual confounding factor due to the high prevalence of CKD in subjects with ACS developing AKI. Lo et al. (29) suggested that the association between AKI and adverse outcomes exists because patients who develop AKI have more severe pre-existing CKD than subjects who do not experience AKI. Confounding would thus be a major issue because CKD is a definitive risk factor for death; thus, CKD, and not AKI, would be the true reason for the observed higher rates of death. In a recent editorial about AKI in sepsis, Muntner et al. (30) stated that CKD increases the risk of developing AKI after an acute illness, whereas an absolute increase in SCr during the hospital stay is associated with short- and long-term mortality risks. In this regard, the current RIFLE and AKIN criteria for AKI can be criticized because both include absolute and relative changes in creatinine, which may be a significant source of confounding.

Conclusions

There is strong evidence to support the assertion that CKD is a powerful risk factor for death in ACS. Information about renal function and the presence and stage classification of CKD has been used to predict prognosis and may influence medical decisions. Recently, a validated model known as the GRACE (31) prediction score was used to calculate the 6-month mortality risk among 7638 patients, and the baseline SCr at admission was the fifth strongest risk factor for death.

There is also increasing information about the role of AKI in hospital outcomes after AMI. However, most of the available data come from retrospective multicentric databank studies of nonconsecutive patients (Table 3). Additionally, a significant number of patients were excluded from those analyses, and some studies performed the AMI diagnosis using only the International Classification of Diseases code. There have been no prospective studies that have controlled for all prognostic variables that may affect the rate of death after STEMI that have been designed to specifically determine whether AKI diagnosed by the AKIN or RIFLE criteria is a risk factor for mortality after STEMI. In fact, there are no data comparing the RIFLE and AKIN criteria for the diagnosis of AKI after AMI.

Table 3. AKI as a risk factor for mortality in AMI patients

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design (n)</th>
<th>AKI Criterion Used</th>
<th>AHR for Death</th>
</tr>
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<tbody>
<tr>
<td>Goldberg et al. (23), 2005</td>
<td>Prospective database (1038)</td>
<td>Increase in bSCr ≥0.5 mg/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.4 (in-hospital) 7.2 (1year)</td>
</tr>
<tr>
<td>Newsome et al. (24), 2008</td>
<td>Retrospective cohort study (87,094)</td>
<td>Increase in bSCr ≥0.1 mg/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.14 to 1.39 (4 years&lt;sup&gt;b&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Parikh et al. (25), 2008</td>
<td>Retrospective cohort study (147,007)</td>
<td>Increase in bSCr ≥0.3 mg/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.15 to 1.33 (10 years&lt;sup&gt;b&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Marenzi et al. (28), 2010</td>
<td>Prospective cohort study (97)</td>
<td>Increase in bSCr ≥25%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.3 (in-hospital)</td>
</tr>
</tbody>
</table>

<sup>a</sup>SCr, baseline SCr.
<sup>b</sup>The criteria used to diagnose AKI were not AKIN or RIFLE.
<sup>c</sup>Median follow-up.
There is also no information on whether AKI has a different effect on the outcomes in STEMI versus non-STEMI patients.

The available data indicate that a baseline SCr should be obtained early after admission for ACS and that renal function should be closely monitored during hospitalization. This approach will allow for the identification of a significant risk factor for death in this population and will permit the use of measures to prevent poorer outcomes and improve patient treatment.

Disclosures
None.

References


