Contemporary Management of Coronary Artery Disease and Acute Coronary Syndrome in Patients with Chronic Kidney Disease and End-Stage Renal Disease

Chin-Chou Huang and Jaw-Wen Chen

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) have emerged as a worldwide public health problem. Due to the remarkably higher incidence and prevalence of this chronic disease in Taiwan than in other countries, CKD/ESRD has contributed to a significant health burden in Taiwan. Patients with CKD/ESRD have an increased risk of coronary artery disease (CAD) and acute coronary syndrome (ACS) compared to the normal population. Patients with ACS alone can present differently than patients with ACS and CKD/ESRD. Also, due to the lower prevalence of chest pain and ST-segment elevation, CKD/ESRD patients were more difficult to diagnose than other patients. Furthermore, whether advances in ACS management with medical therapy and an early invasive approach could improve patient outcomes with CKD/ESRD is not known. The use of antiplatelets such as aspirin and other antithrombotic agents might reduce the incidence of ACS or stroke in CKD patients. However, such use could also increase bleeding risk and even increase the likelihood of mortality, especially in dialysis patients. While recent clinical data suggest the potential benefit of aggressive management with coronary intervention for CAD and ACS in this category of patients, further clinical studies are still indicated for the proper medical strategy and revascularization therapy to improve the outcomes of CAD and ACS in CKD/ESRD patients, both in Taiwan and worldwide.

Key Words: Acute coronary syndrome • Chronic kidney disease • Coronary artery disease • Diagnosis • End-stage renal disease • Management

INTRODUCTION

Chronic kidney disease (CKD) has emerged as a worldwide public health problem.1-3 The size of the global population suffering from CKD and end-stage renal disease (ESRD) continues to increase because of epidemic levels of diabetes mellitus and obesity, as well as the rapidly aging population.3,4 It causes a huge economic burden worldwide. Health costs of treating people with CKD are nearly 3-fold higher than those for people without CKD, and the cost of treating ESRD is 10-fold higher.5 There is an increased risk of coronary artery disease (CAD) and acute coronary syndrome (ACS) in these patients. Due to the poor clinical outcomes, the diagnosis and management of CAD and ACS are particularly important for patients with CKD/ESRD.

EPIDEMIOLOGY DATA OF CKD AND ESRD IN TAIWAN

Abundant clinical evidence indicates that there is a
remarkably higher incidence and prevalence of CKD and ESRD in Taiwan than in other countries. Hsu et al. reported a prevalence rate of 6.9% of CKD stage 3-5 in subjects over 20 years of age in the Taiwanese Survey on Blood Sugar, Blood Lipids and Blood Pressure (TW3H). Kuo et al. reported that the prevalence of CKD increased from 1.99% in 1996 to 9.83% in 2007 by using disease code analysis from the dataset of National Health Insurance (NHI). Wen et al. later reported an overall prevalence of 11.93% of CKD stage 1-5 in a cohort consisting of 462,293 individuals who participated in a standard medical screening program in Taiwan.

**THE RISK OF ACS IN PATIENTS WITH CKD AND ESRD**

CKD is closely associated with a higher risk of cardiovascular disease (CVD). Even in early-stage CKD, the risk for premature CVD is increased by 25% to 30%, and is more than 30- to 50-fold higher in patients with ESRD. Wen et al. have reported that patients with CKD in Taiwan may have 83% higher mortality for all-cause and 100% higher for CVD. Chien et al. reported that the deterioration of renal function could be related to cardiovascular and all-cause death mortality based on the data from healthy adults in Taiwan. Furthermore, the effect was additive with the presence of metabolic syndrome components. Hwang et al. also reported that late-stage CKD is a significant risk factor for mortality in elderly Taiwanese, especially due to cardiovascular and renal diseases, which is according to the data in the Elderly Health Examination Program (EHEP), an observational cohort study in Kaohsiung City, Taiwan. Compared with a reference group with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m$^2$, adjusted HR for all-cause mortality was 1.5, 2.1 and 2.6 for groups with eGFR of 30-44, 15-29 and less than 15 mL/min per 1.73 m$^2$, respectively. Recently, Chou et al. reported that the incidence of ACS in the Taiwanese Chinese population under dialysis was 1.780/100-person-years. Another nationwide analysis of ACS patients in Taiwan showed that peak incidence was up to 9/1000 in males and 8/1000 in females. In the United States Renal Data System Wave 2 study, the incidence of ACS over 2.2 years was 10.2%. Dialysis patients in Taiwan had a higher rate of ACS when compared with the general population, but lower than that of similar cohorts in the United States. The increased prevalence of prior cardiovascular disease and coexisting conditions with ESRD may interact to increase the risk of ACS in dialysis patients.

**THE PRESENTATION OF ACS IN PATIENTS WITH CKD AND ESRD**

Many earlier studies have demonstrated the atypical presentation of ACS in patients with renal disease. Sosnov et al. reported that patients with renal disease experiencing acute myocardial infarction (AMI) were significantly less likely to report chest pain. Shroff et al. reported that only 40% of advanced CKD patients with AMI complained of chest pain as the presenting symptom. In contrast, shortness of breath was the index symptom for most of these patients, which was likely not recognized by clinicians as an “anginal equivalent.” Similar findings have also been reported in the dialysis population. The possible explanations would be that kidney disease may alter the clinical presentation of AMI. Furthermore, the higher prevalence of diabetes in this population may also mask the “typical” symptoms of AMI. Therefore, a routine survey of those CKD patients with the presentation of shortness of breath may be needed to most effectively identify the possibility of ACS.

There was also a noteworthy difference in electrocardiographic findings for patients with and without significant renal disease. ST-segment elevation was present in only 15.9% of advanced CKD patients presenting with AMI, compared with 32.5% of non-CKD patients. Using a combination of ST-segment elevation and left bundle branch block (LBBB), 25.8% of advanced CKD patients met the criteria for STEMI compared with 37.9% of non-CKD patients. The proportions of advanced CKD and dialysis patients with ST-segment elevation/LBBB on initial ECG were identical. According to the ACTION registry, Fox et al. estimated that nearly 30% of patients with ST-segment elevation myocardial infarction (STEMI) and 43% with non-STEMI had CKD stage 3 or higher (eGFR < 60 mL/min/1.73 m$^2$). Similarly, Szummer et al. reported moderate or higher incidence of CKD (eGFR < 60 mL/min/1.73 m$^2$) in approximately 24% of
non-ST-segment elevation myocardial infarction (NSTEMI) patients from the SWEDHEART registry. In the GRACE study, Gurm et al. reported that dialysis patients presented less typically and were most likely to manifest with a NSTEMI when compared to nondialysis patients. Due to the lower prevalence of chest pain and ST-segment elevation, the diagnosis of ACS is difficult in CKD/ESRD patients, which may likely contribute to the poor outcomes of this population. However, the related data is insufficient, and future prospective investigation is indicated to clarify the above issue in Taiwan.

In addition to the symptom of chest pain and electrocardiographic findings, detection of a rise and/or fall of cardiac biomarkers is essential to the diagnosis of AMI. The preferred biomarker is cardiac troponin (I or T), which has high myocardial tissue specificity as well as high clinical sensitivity. In the third universal definition of myocardial infarction by the ESC/ACCF/AHA/WHF task force, an increased cardiac troponin concentration is defined as a value exceeding the 99th percentile of a normal reference population [upper reference limit (URL)]. For patients with ESRD, the National Academy of Clinical Biochemistry guidelines have recommended a change in the cardiac troponin concentration of ≥ 20% for the diagnosis of AMI in those who present with elevated cardiac troponin, 6-9 h after presentation, as indicative of a relevant concentration change. Recently, in a cohort of asymptomatic patients with ESRD, a troponin concentration exceeding the 99th percentile value using the new highly sensitive cardiac troponin T assay was found in 100% of patients.

**THE PROGNOSIS OF ACS IN CKD AND ESRD PATIENTS**

Patients with CKD, particularly those on maintenance dialysis, have poor outcomes after the occurrence of ACS. Herzog et al. reported that mortality rates for AMI in dialysis patients were 26% in 1998 and 21.6% in 2007. Fox et al. reported a higher mortality rate for those with STEMI compared with those NSTEMI (31.8% vs.12.4%) in ESRD patients. Wright et al. reported that AMI in patients with non-dialysis-dependent advanced CKD was also associated with poor long-term cardiovascular outcomes and survival. Anavekar et al. reported that minor reductions in eGFR in CKD patients with AMI and left ventricular dysfunction were associated with escalating hazards of future cardiovascular events and death. Best et al. reported CKD as a powerful predictor of adverse outcomes after percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG).

The occurrence of ACS increases the risk of in-hospital heart failure and sudden cardiac death in patients with CKD/ESRD. Shroff et al. reported that in-hospital heart failure rates were significantly higher in advanced CKD patients (41% vs. 25.8% in dialysis and 21.1% in non-CKD patients). Fox et al. reported about a 3-fold higher likelihood of developing in-hospital heart failure in stage 4 CKD patients than in non-CKD patients. Pun et al. reported a progressive increase in the rate of sudden cardiac death associated with worsening eGFR values in a cohort of 19,440 patients undergoing cardiac catheterization.

There are also some reports about the poor prognosis of patients with CKD/ESRD in Taiwan. Chien et al. reported that poor renal function was a poor prognostic factor for patients after ACS events in Taiwan. Chen et al. reported that metabolic syndrome was associated with a higher probability of CAD, cardiac death, and major cardiac events in Taiwanese patients with ESRD complicated by ACS. Recently, Hsieh et al. reported that CKD increased the risk of in-hospital mortality [odds ratio, 2.0; 95% confidence interval (CI), 1.8-2.1] in a total of 97,220 patients with ACS during 2004 to 2008 from the national health insurance database in Taiwan. From the same database, Chou et al. reported the overall in-hospital mortality rate in dialysis patients with ACS was 9.7%. Male gender, age of ≥ 65 years, and associated comorbidities were independent risk factors for ACS.

**POSSIBLE MECHANISMS RELATED TO THE POOR PROGNOSIS IN CKD/ESRD PATIENTS**

There are several potential factors associated with poor outcomes after ACS in patients with CKD/ESRD. First, these patients usually have excess comorbidities such as hypertension, diabetes, and so on. Second, the presence of impaired renal function can lead to activation of the renin-angiotensin system, oxidative stress, elevated asymmetric dimethylarginine, low-grade inflammation with increased circulating cytokines and...
dyslipidemia, which may promote the development and progression of clinical atherosclerosis diseases.\textsuperscript{43} Third, structural and functional abnormalities of the heart in these patients may also contribute to excess cardiovascular risk.\textsuperscript{42,46,47} Fourth, while platelet dysfunction is frequently associated with the presence of CKD, the use of antiplatelet and antithrombotic agents can increase the risk of bleeding contributing to the increased mortality in CKD patients.\textsuperscript{48} Finally, it is reported that the use of evidence-based pharmacologic and interventional therapies could be reduced in this population.\textsuperscript{24,25,37,42,49-52}

**THE MANAGEMENT OF CAD AND ACS IN PATIENTS WITH CKD/ESRD**

Accumulated data indicated that patients with CKD/ESRD could be less likely to receive traditional evidence-based inpatient and outpatient treatment, including medical therapy and revascularization.\textsuperscript{24,25,37,42,49-52} Furthermore, it is also not known whether advances in ACS management such as aggressive medical therapy and an early invasive approach may improve the prognosis of patients with CKD/ESRD. Patients with CKD were excluded from 75% of the published CAD trials.\textsuperscript{53} Despite optimal contemporary medical therapy and revascularization, the prognosis of patients with CKD and, in particular, of patients undergoing dialysis, remains poor.\textsuperscript{51} There have been serial studies about the management of CKD and ESRD patients with CAD or ACS (Table 1).

### Table 1. Findings from the studies about managing chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients with coronary artery disease (CAD) or acute coronary syndrome (ACS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patient size</th>
<th>Patient characteristics</th>
<th>Renal status</th>
<th>Major findings</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy</td>
<td>Berger et al.</td>
<td>Retrospective study</td>
<td>N = 1,025 AMI</td>
<td>ESRD</td>
<td>There are benefits on 30-day mortality among ESRD patients (aspirin: RR 0.64; 95% CI 0.50 to 0.80; beta-blocker: RR 0.78; 95% CI 0.60 to 0.99; ACE inhibitor: RR 0.58; 95% CI 0.42 to 0.77).</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Scialbasi et al.</td>
<td>Retrospective study</td>
<td>N = 595 AMI</td>
<td>Whole spectrum of renal dysfunction</td>
<td>Chronic aspirin and statin therapy has a cardioprotective role that is evident also in patients with CKD</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>DOPPS study</td>
<td>Retrospective study</td>
<td>N = 28,320 Patients with or without CAD</td>
<td>ESRD</td>
<td>Aspirin was associated with decreased risk of stroke (RR, 0.82; p &lt; 0.01) and increased risk of myocardial infarction (RR, 1.21; p = 0.01) and cardiac event (RR, 1.08; p &lt; 0.01) in all patients, with similar results for patients with CAD.</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>OASIS 5 trial</td>
<td>Sub-analysis</td>
<td>N = 19,979 NSTE-ACS</td>
<td>Whole spectrum of renal dysfunction</td>
<td>Lower rates of the composite end point (death, myocardial infarction, refractory ischemia, and major bleeding) in patients with fondaparinux than with enoxaparin among patients with a GFR less than 58 mL/min per 1.73 m\textsuperscript{2}.</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>HOT study</td>
<td>Sub-analysis</td>
<td>N = 18,597 Diastolic hypertension</td>
<td>Whole spectrum of renal dysfunction</td>
<td>Aspirin therapy produces greater absolute reduction in major cardiovascular events and mortality in hypertensive patients with CKD than with normal kidney function. Clopidogrel was beneficial and safe in patients with and without CKD.</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>CURE trial</td>
<td>Sub-analysis</td>
<td>N = 12,253 NSTE-ACS</td>
<td>Whole spectrum of renal dysfunction</td>
<td></td>
<td>66</td>
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</tbody>
</table>
### Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Population</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PLATO trial</strong></td>
<td>Sub-analysis</td>
<td>15,202</td>
<td>ACS</td>
<td>Whole spectrum of renal dysfunction</td>
<td>67</td>
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<td></td>
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<td></td>
<td><strong>Continued</strong></td>
<td>In ACS patients with CKD, ticagrelor compared with clopidogrel significantly reduces ischemic end points and mortality without a significant increase in major bleeding but with numerically more non-procedure-related bleeding.</td>
<td></td>
</tr>
<tr>
<td><strong>Antithrombotic</strong></td>
<td>Meta-analysis</td>
<td>212,000</td>
<td>Patients at high annual risk of vascular events</td>
<td>Whole spectrum of renal dysfunction</td>
<td>55</td>
</tr>
<tr>
<td><strong>Trialists’</strong></td>
<td></td>
<td></td>
<td><strong>Collaboration</strong></td>
<td>Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an AMI or ischemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischaemia, peripheral arterial disease, or atrial fibrillation.</td>
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<tr>
<td><strong>Palmer et al.</strong></td>
<td>Meta-analysis</td>
<td>21,670</td>
<td>ACS or were undergoing PCI (N = 9,969) and stable or no cardiovascular disease (N = 11,701)</td>
<td>CKD</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Continued</strong></td>
<td>Benefits for antiplatelet therapy among persons with CKD are uncertain and are potentially outweighed by bleeding hazards.</td>
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</tr>
<tr>
<td><strong>Coronary</strong></td>
<td>Retrospective</td>
<td>19,974</td>
<td>Patients with or without CAD ESRD</td>
<td>Whole spectrum of renal dysfunction</td>
<td>19</td>
</tr>
<tr>
<td><strong>intervention</strong></td>
<td>study</td>
<td></td>
<td><strong>therapy</strong></td>
<td>Dialysis patients with PCI for ACS may have a reduced risk of mortality than those with medical treatment only.</td>
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<td></td>
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<td></td>
<td>Dialysis patients had better long-term survival after CABG surgery than after PCI.</td>
<td>36</td>
</tr>
<tr>
<td><strong>Chou et al.</strong></td>
<td>Retrospective</td>
<td>15,784</td>
<td>Patients undergoing coronary revascularization procedures</td>
<td>NSTEMI</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>study</td>
<td></td>
<td><strong>Continued</strong></td>
<td>Early invasive therapy is associated with greater 1-year survival in patients with NSTEMI and mild-to-moderate renal insufficiency, but the benefit declines with lower renal function, and is less certain in those with renal failure or on dialysis.</td>
<td></td>
</tr>
<tr>
<td><strong>Herzog et al.</strong></td>
<td>Retrospective</td>
<td>23,262</td>
<td>Patients undergoing CABG or PCI ESRD</td>
<td>Whole spectrum of renal dysfunction</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>study</td>
<td></td>
<td><strong>Continued</strong></td>
<td>There was a survival benefit among patients with ESRD undergoing CABG surgery as compared with PCI.</td>
<td></td>
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<tr>
<td><strong>Szummer et al.</strong></td>
<td>Retrospective</td>
<td>59,576</td>
<td>Patients undergoing CABG or PCI ESRD</td>
<td>Whole spectrum of renal dysfunction</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>study</td>
<td></td>
<td><strong>Continued</strong></td>
<td>CABG surgery in chronic renal dialysis patients can be accomplished with a better short- and long-term outcome than coronary angioplasty.</td>
<td></td>
</tr>
<tr>
<td><strong>Szczekel et al.</strong></td>
<td>Retrospective</td>
<td>43</td>
<td>Patients undergoing CABG or PCI ESRD</td>
<td>Whole spectrum of renal dysfunction</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>study</td>
<td></td>
<td><strong>Continued</strong></td>
<td>In-hospital revascularization was independently associated with improved survival, irrespective of eGFR.</td>
<td></td>
</tr>
<tr>
<td><strong>Koyanagi et al.</strong></td>
<td>Retrospective</td>
<td>11,377</td>
<td>Patients undergoing CABG or PCI ESRD</td>
<td>Whole spectrum of renal dysfunction</td>
<td></td>
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<tr>
<td></td>
<td>study</td>
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<td><strong>Continued</strong></td>
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</table>

ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RR, relative risk.
(ACC) and American Heart Association (AHA) guidelines for management of ACS clearly acknowledge the lack of sufficient studies so as to make specific recommendations for patients with CKD.54

Medical therapy for stable CAD in CKD patients

Antiplatelet agents are widely used to prevent cardiovascular events by inhibiting intravascular thrombosis. It has been shown that antiplatelet drugs reduce vascular deaths by 15% and serious cardiovascular events by 20% in persons at high risk for a vascular event.55 However, extrapolating these benefits of antiplatelet therapy to persons with CKD/ESRD is problematic because nonatherosclerotic conditions (cardiac failure, sudden cardiac death, and arrhythmia) are more common causes of CVD in persons with CKD than in the general population.55,56 On the other hand, uremia is associated with prolongation of bleeding time and abnormal platelet aggregation and adhesion due to intrinsic and extrinsic factors.57 Therefore, the bleeding risk of antiplatelet agents may be elevated.24,49,58-62 Previous studies showed that low eGFR values are associated with an increased risk of bleeding.60,61 Holden et al.62 reported the substantially higher baseline risk for bleeding in persons with CKD (approximately 2.5% per year compared with 1% in other at-risk populations),55 suggesting that absolute bleeding risks with antiplatelet therapy might be at least doubled in patients with CKD than in those patients without CKD.

Berger et al.52 reported that there were benefits of medical therapy on 30-day mortality among ESRD patients [aspirin: relative risk (RR) 0.64; 95% CI 0.50 to 0.80; beta-blocker: RR 0.78; 95% CI 0.60 to 0.99; ACE inhibitor: RR 0.58; 95% CI 0.42 to 0.77]. In a post-hoc subgroup analysis of HOT study,56 aspirin therapy produced a greater absolute reduction in major cardiovascular events and mortality in hypertensive patients with CKD than in those patients with normal kidney function. Sciahsasi et al.63 reported that the chronic use of aspirin or statins was independently associated with the decreased probability of STEMI (odds ratio, 0.5; 95% CI, 0.2-1.0, p = 0.05) in patients with CKD. In the DOPPS study,64 however, aspirin was associated with a decreased risk of stroke (RR, 0.82; p < 0.01) but increased risk of myocardial infarction (RR, 1.21; p = 0.01) and cardiac event (RR, 1.08; p < 0.01) in patients with hemodialysis. On the other hand, although ß-blockers and ACE inhibitors are commonly used in this population, randomized data of these drugs in dialysis patients are also absent.65 Accordingly, medical treatment seems helpful in stable CKD patients. An antiplatelet such as aspirin may reduce the incidence of AMI, ACS, or stroke but also increase the bleeding risk in patients with CKD. It may even be harmful and should be carefully used, particularly in dialysis patients.

Medical therapy for ACS in CKD patients

In the sub-analysis of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial,58 the beneficial effect of adding clopidogrel to standard treatment in non-ST-segment elevation ACS was observed in all three tertiles of renal function [lower third RR = 0.89 (95% CI 0.76-1.05); medium third RR = 0.68 (95% CI 0.56-0.84); upper third RR = 0.74 (95% CI 0.60-0.93)] in spite of the significantly increased risk of minor bleeding in all tertiles of renal function. Furthermore, recent subgroup data from the PLATO (Platelet Inhibition and Patient Outcomes) trial67 indicated that ticagrelor, an oral purinergic receptor inhibitor cleared by extrarenal mechanisms, reduced mortality and major cardiovascular events better than clopidogrel among persons with CKD and ACS. Finally, a recent meta-analysis68 indicated that antiplatelet agents reduced myocardial infarction in persons with CKD but had uncertain effects on stroke and mortality, and may increase bleeding hazards. However, glycoprotein IIb/IIIa inhibitors or clopidogrel given in addition to standard care had little or no effect on death, myocardial infarction, or coronary revascularization, and may increase major bleeding in persons with CKD and ACS or those having high-risk coronary artery intervention. Taken together, aspirin is still essential in CKD patients with ACS. However, it is not known whether other antiplatelets might be helpful in this particular group of patients.

Statins use in CKD patients

Recently, the efficacy of statin therapy in patients with CKD has drawn much attention. Strippoli et al.69 reported that statins decreased the risk of cardiovascular events and cardiovascular mortality in CKD patients, irrespective of the stage of disease (pre-dialysis, dialysis, and transplant). Another systematic review and meta-analysis70 showed that lipid-lowering therapy decreased
cardiac death and atherosclerosis-mediated cardiovascular events in persons with CKD. However, Slinin et al. reported that statin therapy was not effective for reducing all-cause mortality or stroke in individuals with type 2 diabetes and CKD.

When focusing on the patients with ESRD, the data was still controversial and not of sufficient power. In the Dialysis Outcomes and Practice Patterns Study, statins were shown to reduce mortality in HD patients. In the Die Deutsche Diabetes Dialyse Studies (the 4D study), atorvastatin did not reduce the composite primary end point (including cardiovascular death, nonfatal myocardial infarction, and stroke) in diabetic patients undergoing HD. In the post hoc analysis of the 4D study, however, treatment with atorvastatin in diabetic patients undergoing HD significantly reduced the risk of fatal and nonfatal cardiac events and death from any cause if pretreatment LDL-cholesterol was > 145 mg/dL (3.76 mmol/L). In the AURORA trial, rosuvastatin didn’t reduce the combined end point of myocardial infarction, stroke, or death from cardiovascular causes in patients undergoing HD. In the post hoc analysis of the AURORA trial, however, treatment with rosuvastatin in diabetic patients undergoing HD reduced atherosclerotic coronary events by 32%. In the SHARP (Study of Heart and Renal Protection) trial, treatment with simvastatin and ezetimibe could reduce major atherosclerotic events in a wide range of patients with advanced CKD. However, the study didn’t have sufficient power to assess the effects on major atherosclerotic events separately in HD and non-HD patients. Further study is still needed to clarify the impacts of statins in patients with CKD and ESRD, especially those with ACS.

Coronary revascularization therapy

Coronary revascularization therapy including PCI and CABG is being applied to a widening spectrum of patients, including those with CKD. A more recent multicenter observational study demonstrated an independent association between in-hospital coronary revascularization and improved one-year survival in patients with ACS, irrespective of eGFR. Chou et al. also reported that in Taiwan, dialysis patients with PCI for ACS may have a reduced risk of mortality than those with medical treatment only. When comparing different strategies of coronary revascularization, patients with CKD or ESRD had better long-term survival after CABG surgery than after PCI. However, most of these studies were retrospective designed. Future prospective randomized study may be indicated to clarify if aggressive strategy with PCI or CABG should be routinely applied to the management of ACS in patients with CKD/ESRD.

On the other hand, patients with CKD/ESRD continue to be treated more conservatively, with an associated worse outcome. Fox et al. noted that non-STEMI patients with stage 4 CKD were least likely to undergo coronary revascularization (40% less likely than non-CKD patients), followed by patients with stage 5 CKD or on dialysis (20% less likely). Among dialysis patients treated with an invasive approach, there may be concerns about excess bleeding related in part to the use of antiplatelet and antithrombotic agents. The long-term safety and efficacy of antiplatelet and antithrombotic agents and the technical challenge of intervening in heavily calcified coronary vessels may potentially influence physicians’ choices with respect to coronary revascularization in this particular patient cohort.

CONCLUSIONS

There is a remarkably high incidence and prevalence of CKD/ESRD in Taiwan. The CKD/ESRD patients may be at higher risk of ACS when compared to the normal population. Due to the lower prevalence of chest pain and ST-segment elevation, the diagnosis of ACS could be difficult in these patients. They are less likely to receive traditional evidence-based treatment. Until now, there was still lack of sufficient evidence for the proper treatment of CAD/ACS in these patients. While recent clinical data suggest the potential benefit of aggressive management with coronary intervention for CAD and ACS in this category of patients, further prospective randomized clinical studies are still indicated for the proper medical strategy and revascularization therapy to improve the outcomes of CAD and ACS in CKD/ESRD patients in Taiwan as well as worldwide.

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