Pharmacotherapy in Chronic Kidney Disease Patients Presenting With Acute Coronary Syndrome

A Scientific Statement From the American Heart Association

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Chronic kidney disease (CKD) is frequently encountered among patients presenting with acute coronary syndrome (ACS). Recent data from the National Cardiovascular Data Registry—Acute Coronary Treatment and Intervention Outcomes Network (NCDR-ACTION) reported CKD (defined as estimated creatinine clearance [CrCl] <60 mL·min⁻¹·1.73 m⁻²) prevalence rates of 30.5% among patients presenting with ST-segment–elevation myocardial infarction (STEMI) and 42.9% among patients presenting with non–ST-segment–elevation myocardial infarction (NSTEMI).¹ The presence of CKD among patients presenting with ACS has been associated with worse outcomes, including higher rates of mortality and bleeding.²⁻⁴ Despite the increased risk for adverse outcomes, CKD patients presenting with ACS are less likely to receive evidence-based therapies, including medications.¹ In addition, patients with CKD have been underrepresented in randomized controlled trials of ACS pharmacotherapy.⁵⁻⁶ Thus, the net effect is a relative lack of evidence and potential for uncertainty in selecting medications in this high-risk population. The purpose of this scientific statement is to provide a comprehensive review of the published literature and provide recommendations on the use of evidence-based pharmacotherapies in CKD patients presenting with ACS.

Background and CKD Staging

It has been appreciated now for more than a decade that CKD is a powerful independent predictor of cardiovascular morbidity, cardiovascular mortality, and all-cause mortality. The systematic classification of CKD in large part is based on the efforts of Andrew Levey and colleagues, who published the K/DOQI (Kidney Disease Outcomes Quality Initiative) clinical practice guidelines for CKD.⁷ The original schema somewhat arbitrarily defined stages 1 to 5 CKD on the basis of estimated glomerular filtration rate (eGFR) in the following manner: Stage 1, eGFR ≥90 mL·min⁻¹·1.73 m⁻² (with evidence of kidney damage present, such as albuminuria); stage 2, eGFR <90 but ≥60 (with evidence of kidney damage such as albuminuria); stage 3, eGFR <60 but ≥30; stage 4, eGFR <30 but ≥15; and stage 5, eGFR <15 or undergoing dialysis.⁷ An additional modification was made to create a stage 3a (eGFR 45–59 mL·min⁻¹·1.73 m⁻²) and stage 3b (eGFR 30–44 mL·min⁻¹·1.73 m⁻²). Most recently, based on the stepwise association of albuminuria with increased rates of CKD progression, cardiovascular mortality, and total mortality, the Kidney Disease: Improving Global Outcomes (KDIGO) group has recommended altering the classification scheme to include urinary albumin excretion (Figure 1).⁸

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As shown in Figure 2, there is a stepwise incremental age-standardized risk for all-cause mortality, cardiovascular events, and hospitalization associated with diminishing renal function.9 Compared with patients with eGFR ≥60 mL·min⁻¹·1.73 m⁻², the adjusted hazard for death among patients with eGFR 15 to 29 mL·min⁻¹·1.73 m⁻² is more than 3-fold higher, and nearly 6 times higher for patients with eGFR <15 mL·min⁻¹·1.73 m⁻².

It has been suggested that CKD should be regarded as a “coronary heart disease equivalent.” The publication by Tonelli and colleagues,10 using the Alberta Kidney Disease Network database and the National Health and Nutrition Examination Survey 2003 to 2006, estimated the risk of hospital admissions for myocardial infarction (MI) and all-cause death among individuals with previous MI, diabetes mellitus, or CKD. Among people without previous MI, the risk of death among patients with previous MI, diabetes mellitus or CKD was also less likely to have ST-segment elevation (15.9% versus 32.5%, respectively) but more likely to have NSTEMI and left bundle branch block among populations according to severity of CKD, with fewer STEMIs and more nonSTEMIs.

The clinical presentation of ACS among CKD patients is distinctly different from that of patients without CKD in the general population.11–15 First, the prevalence of chest pain among patients with ACS is inversely related to stage of CKD. As shown in Figure 3, there is a graded reduction in the frequency of chest pain as eGFR falls.15 For example, in a collaborative project of the United States Renal Data System (USRDS) and the National Registry of Myocardial Infarction (NRMI), the clinical characteristics were compared in a large population of MI patients that included 2390 dialysis patients, 29319 patients with advanced CKD (serum creatinine [SCr] >2.5 mg/dL), and 274777 non-CKD patients.14 Those with advanced CKD and dialysis were less likely to have chest pain on admission (40.4% and 41.1%, respectively) than those without CKD (61.6%). Similar observations were made in the SWEDHEART registry [Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies]; however, up to two thirds of patients with stage 4 and 5 CKD in that registry had chest pain at presentation.15 The USRDS-NRMI study also showed that MI patients with advanced CKD and those undergoing dialysis more often had a diagnosis at presentation other than ACS (44% and 47.7%, respectively) compared with patients without CKD (25.8%). Compared with patients without CKD, patients with advanced CKD were also less likely to have ST-segment elevation (15.9% versus 32.5%, respectively) but more likely to have heart failure on presentation (52.2% versus 27.2%, respectively) and a higher rate of in-hospital mortality (23% versus 12.6%, respectively).16 Similar differences existed between those with advanced CKD and those undergoing dialysis. The distribution of electrocardiographic presentations varies according to severity of CKD, with fewer STEMIs and more NSTEMIs and left bundle branch block among populations with increasingly worse renal function (Figure 3).11,15

An additional consideration in the diagnosis of ACS in patients with CKD is the interpretation of cardiac biomarkers. Chronic troponin elevations in clinically stable patients with renal failure have been observed and likely represent nonischemic myocardial injury.16 In spite of these chronic troponin elevations in a population of patients with CKD, the National Association of Clinical Biochemistry laboratory medicine practice guidelines recommend the use of troponins for the diagnosis of MI in patients with CKD presenting with symptoms or electrocardiographic changes suggestive of myocardial ischemia.17 These guidelines, along with other expert writing groups, advise the importance of a dynamic change in troponin values after presentation in the
identification of acute MI (AMI) in patients with end-stage renal disease (ESRD), who more frequently have chronically elevated troponin levels.16–18

This striking difference in clinical presentation and electrocardiographic findings has implications for correct diagnosis and subsequent treatment. It has been a subject of great attention that the use of evidence-based therapy is lower among patients with CKD.1–3,19–21 Not only are those with ACS and CKD less likely to receive evidence-based therapies, the atypical clinical presentation of these patients makes it less likely that they will be correctly identified as having ACS on presentation (and thus would not be considered for appropriate therapeutic interventions).

Methods of Estimating Renal Function for Drug Dosing
Whereas the Modification of Diet in Renal Disease (MDRD) equation is widely used for CKD diagnosis and staging, the Cockcroft-Gault (CG) equation has been the most commonly used equation to estimate renal function for dose adjustment of medications.22 Although these equations have limitations, both the CG and MDRD equations have been shown to correlate relatively well with measured glomerular filtration rate (GFR),23 but differences in medication dose recommendations have been reported depending on which equation is used.23–25

An analysis of the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry was conducted to compare the CG and MDRD equations with regard to the recommended doses of eptifibatide, tirofiban, and enoxaparin.23 Results of this analysis showed a 20% difference in CKD classification between the 2 equations. The proportion of patients classified as having normal/mild CKD (eGFR ≥60 mL/min), moderate CKD (eGFR 30–59 mL/min), and severe CKD (eGFR <30 mL/min) by the CG equation was 41.2%, 39.8%, and 19% compared with 58.9%, 31.5%, and 9.6%, respectively, by the MDRD equation. In addition, marked differences were seen in the proportion of patients for whom dose adjustment was recommended by the CG versus MDRD equation, respectively, for eptifibatide (45.7% versus 27.3%) and for enoxaparin or tirofiban (19.0% versus 9.6%). Over the past decade, the CG equation has been the preferred method used in assessing renal function for dose adjustment and to determine trial eligibility in randomized controlled trials of antithrombotic medications. Until further data validating the MDRD equation as a method for dose adjustment of cardiovascular medications become available, current data support the use of the CG equation for cardiovascular drug dosing (Table 1).

Pharmacotherapy for ACS Among Patients With CKD
Fibrinolytic Therapy
Current American College of Cardiology Foundation/American Heart Association guidelines give fibrinolytic therapy a Class I recommendation for STEMI patients presenting within 12 hours of the onset of ischemia symptoms and without contraindications, when it is anticipated primary percutaneous coronary intervention (PCI) cannot be performed within 120 minutes.26 Although primary PCI is the preferred reperfusion strategy for STEMI patients, recent data from the NCDR-ACTION Registry indicate that fibrinolytic therapy was the initial reperfusion strategy in ≈10% of patients in the United States.27 Because initial randomized controlled trials of fibrinolytic therapy did not assess the treatment effect of the fibrinolysis in the subgroup of patients with CKD, outcome data in this population are limited. Clinical trial and observational data on the outcomes of ACS patients with CKD receiving fibrinolytic therapy are summarized in Table 2.
A pooled analysis of 16710 patients enrolled in the Thrombolysis in Myocardial Infarction (TIMI)-10A, TIMI-10B, TIMI-14, and Intravenous NPA for the Treatment of Infarcting Myocardium Early (InTIME-II) trials was conducted to assess the impact of baseline renal function (SCr and CrCl) on outcomes in patients receiving fibrinolytic therapy.30 A stepwise increase in mortality was seen with worsening renal function, and rates of intracranial hemorrhage increased with worsening renal function (0.6%, 0.8%, 1.8%, and 3.0% for normal, mildly impaired, moderately impaired, and severely impaired CrCl, respectively; \( P < 0.0001 \) for trend).

Several observational analyses have evaluated the association of CKD with outcomes and the treatment effect of fibrinolytic therapy in STEMI patients with various results. Hobbach

### Table 1. Doses of Parenteral Antithrombotic Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Renal Elimination</th>
<th>Dose in Patients Without CKD</th>
<th>Dose Adjustment in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab26,27</td>
<td>NS</td>
<td>PO: 0.25-mg/kg bolus followed by infusion of 0.125 ( \mu )g·kg(^{-1})·min(^{-1}) (maximum 10 ( \mu )g/min) for 12 h after procedure</td>
<td>No adjustment</td>
</tr>
</tbody>
</table>
| Bivalirudin26 | 20% | PO: 0.75-mg/kg bolus followed by infusion of 1.75 mg·kg\(^{-1}\)·h\(^{-1}\) for duration of the procedure | CrCl <30 mL/min:  
- PO: 0.75-mg/kg bolus followed by infusion of 1 mg·kg\(^{-1}\)·h\(^{-1}\) for the duration of the procedure  
- Dialysis:  
- PO: 0.75-mg/kg bolus followed by infusion of 0.25 mg·kg\(^{-1}\)·h\(^{-1}\) |
| Enoxaparin26,27 | 40% |  
- UA/NSTEMI: 1 mg/kg SC every 12 h  
- STEMI patients \(<75\) y of age receiving fibrinolytic therapy: 30-mg single IV bolus plus a 1-mg/kg SC dose followed by 1 mg/kg SC every 12 h  
- STEMI patients \(\geq 75\) y of age receiving fibrinolytic therapy: No bolus, 0.75 mg/kg SC every 12 h | CrCl <30 mL/min:  
- UA/NSTEMI: 1 mg/kg SC once daily  
- STEMI patients \(<75\) y of age receiving fibrinolytic therapy: 30-mg single IV bolus plus a 1-mg/kg SC dose followed by 1 mg/kg administered SC once daily  
- STEMI patients \(\geq 75\) y of age receiving fibrinolytic therapy: No bolus, 1 mg/kg administered SC once daily  
- Not recommended in dialysis patients |
| Eptifibatide26,27 | 50% |  
- ACS: 180-\( \mu \)g bolus followed by an infusion of 2 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) for up to 72 h  
- PO: 180-\( \mu \)g bolus followed by continuous infusion of 2 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) for up to 18-24 h. A second 180-\( \mu \)g bolus given 10 min after the first bolus | CrCl <50 mL/min:  
- ACS: 180-\( \mu \)g bolus followed by infusion of 1 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) for up to 72 h  
- PO: 180-\( \mu \)g bolus followed by infusion of 1 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) for up to 18-24 h. A second 180-\( \mu \)g bolus given 10 min after the first bolus  
- Contraindicated in dialysis patients |
| Fondaparinux26,27 | 75% | STEMI patients receiving fibrinolytic therapy: 2.5 mg IV followed by 2.5 mg SC daily starting the following day; UA/NSTEMI: 2.5 mg SC daily | CrCl <30 mL/min:  
- Avoid use |

(Continued)
and colleagues conducted an observational analysis to assess the prognostic significance of baseline SCr in a study of 352 STEMI patients receiving fibrinolytic therapy. In this study, there was no association between baseline SCr and TIMI flow grade after fibrinolytic administration; however, there was a significant increase in mortality among patients with renal dysfunction (P < 0.001) but no difference in major bleeding (P = 0.363). In 5549 Canadian ACS patients without ESRD who survived to hospital discharge and were followed up for a mean of 5.6 years, moderate (eGFR 30–59 mL·min⁻¹·1.73 m⁻²) and severe (eGFR < 30 mL·min⁻¹·1.73 m⁻²) renal dysfunction were associated with increased mortality (P = 0.001 for trend) compared to normal renal function (eGFR > 60 mL·min⁻¹·1.73 m⁻²).

### Table 2. Summary of Fibrinolytic Studies in STEMI Patients With CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
<th>End Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibson et al²⁶</td>
<td>Subgroup analysis of pooled data from 4 trials</td>
<td>16,635 patients received fibrinolytic therapy in a clinical trial and were divided into 4 categories according to renal function: normal (CrCl ≥ 90 mL/min, n = 6,602), mildly impaired (CrCl 60–89 mL/min, n = 6,795), moderately impaired (CrCl 30–59 mL/min, n = 3,514), and severely impaired (CrCl &lt; 30 mL/min, n = 264)</td>
<td>Mortality (30 d) Angiographic outcomes (TIMI flow grade, corrected TIMI frame count)</td>
<td>A stepwise increase in 30-d mortality was seen in patients with normal, mildly, moderately, and severely impaired renal function with rates of 2.2%, 5.2%, 13.8%, and 30.7%, respectively (P = 0.0001). In patients who had angiographic assessment, the rates of TIMI flow grade 2 or 3 at 90 min were 80.7%, 80.2%, 85.5%, and 93.3% (P = 0.11 for trend) in the normal, mildly, moderately, and severely impaired groups, respectively.</td>
</tr>
<tr>
<td>Hobbach et al²⁶</td>
<td>Observational cohort</td>
<td>352 STEMI patients received fibrinolytic therapy. Patients were divided into groups based on SCR: normal (SCR &lt; 1.2 mg/dL, n = 256) and renal dysfunction (SCR 1.3–2.8 mg/dL, n = 87)</td>
<td>Mortality (30 d, 6 mo) Reinfarction (30 d, 6 mo) Major and minor bleeding</td>
<td>30-d mortality rates in patients in the normal and renal dysfunction groups were 3.4% and 16.1% (P = 0.001), respectively. 30-d rates of reinfarction in the normal and renal dysfunction groups were 3.4% and 3.6% (P = 0.001), respectively. Rates of major bleeding in the normal and renal dysfunction groups were 2.6% and 4.6% (P = 0.363), respectively, whereas rates of minor bleeding were 6.4% and 10.3% (P = 0.224), respectively.</td>
</tr>
<tr>
<td>Keough-Ryan et al²⁷</td>
<td>Observational cohort (ICONS registry)</td>
<td>5549 consecutive patients with ACS surviving to hospital discharge. Renal function classified into normal (n = 1430), mild CRI (60–80; n = 2018), moderate CRI (30–59; n = 1795), and severe CRI (&lt; 30; n = 306) mL·min⁻¹·1.73 m⁻². ESRD patients were excluded from this analysis.</td>
<td>Mortality (mean follow-up 5.6 y)</td>
<td>Moderate and severe CKD were found to be independent predictors of mortality. Patients with severe CKD were less likely to receive fibrinolytic therapy (OR, 0.55; 95% CI, 0.30–0.98). The adjusted HR (95% CI) for mortality was 0.885 (0.81–0.97) for the use of fibrinolytic therapy during hospitalization and 0.846 (0.79–0.91) for cardiac catheterization.</td>
</tr>
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</table>

(Continued)
severe (eGFR <30 mL·min⁻¹·1.73 m⁻²) CKD were independent predictors of mortality. Factors associated with lower mortality included thrombolysis (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.81–0.97) and cardiac catheterization (HR, 0.85; 95% CI, 0.79–0.91). Among 12,532 patients with ST-segment elevation or left bundle branch block, mortality increased with worsening renal function (P<0.001), and the use of reperfusion decreased with worsening renal function (P=0.001). Compared with no reperfusion, fibrinolytic therapy was not associated with in-hospital mortality for patients with normal or severe renal dysfunction, but it was associated with increased mortality among patients with moderate renal dysfunction (adjusted odds ratio [OR], 1.35; 95% CI, 1.01–1.80). A final observational analysis compared reperfusion strategies among 132 STEMI patients with renal failure (defined by history or SCr >1.5 mg/dL on admission) enrolled in the Acute Coronary Syndromes Israeli Survey (ACSIS). In this cohort, 24 patients (18.2%) received fibrinolytic therapy, 35 (26.5%) were treated by primary PCI, and 73 (55.3%) received no reperfusion. There was no significant difference in mortality among the fibrinolytic, primary PCI, and no reperfusion groups at 7 days; however, at 30 days, mortality was lower among patients who received the fibrinolytic strategy (8%) than among those with primary PCI (40%) or no reperfusion (30%; P=0.03).

In summary, although the above data suggest an increase in adverse outcomes with worsening renal function, assessment of the treatment effect of fibrinolytic therapy in the subgroup of patients with CKD is limited and variable. Data from a pooled analysis of early trials of fibrinolytic therapy in which all patients received a fibrinolytic agent show increasing rates of intracranial hemorrhage with worsening renal function. This observation is noteworthy because current models for estimating intracranial hemorrhage risk with fibrinolytic therapy do not include CKD as a risk factor. In spite of the limitations, taken collectively, the published data would support that fibrinolytic therapy be considered as a treatment strategy for CKD patients presenting with STEMI when primary PCI is not available. However, given the increased rates of intracranial hemorrhage observed with worsening renal function, careful consideration of the benefits and risk of fibrinolytic therapy in this population is required.

**Antiplatelet Therapy**

**Aspirin**

Current guidelines recommend aspirin should be initiated as soon as an ACS is suspected and should be continued indefinitely, unless a contraindication develops. Given that patients with renal insufficiency have an increased bleeding risk, there is some trepidation regarding the use of antiplatelet therapy in these patients. Although patients with CKD were excluded from most randomized trials of aspirin therapy in ACS, data on observational studies evaluating aspirin therapy in patients with renal impairment are shown in Table 3.

The Antiplatelet Trialist’s Collaboration performed a meta-analysis of 287 randomized trials that included 135,000 patients and compared various antiplatelet therapies versus control. Some of those trials included patients undergoing hemodialysis. Among those undergoing hemodialysis, antiplatelet therapy reduced the risk of serious
vascular events (nonfatal MI, nonfatal stroke, or vascular death) by 41% (standard error, 16%). There was no significant increase in extracranial bleeds, although the absolute number was small (2% in antiplatelet-treated patients versus 2.3% in control subjects).37

Most of the published observational data show similar benefits of aspirin therapy in ACS patients across the spectrum of renal function (Table 3). However, one study did find a significant interaction between discharge aspirin therapy and renal function, with an attenuated benefit with increasing degree of
renal dysfunction. Although not conducted in ACS patients per se, the United Kingdom Heart and Renal Protection Study and the Dialysis Outcomes and Practice Patterns Study both showed no increased bleeding risk with aspirin therapy among patients receiving hemodialysis, which provides further support for the safety of aspirin in patients with CKD. Collectively, the available data suggest that aspirin therapy is safe and effective in ACS patients with CKD and should be used in these patients to reduce the risk of death and vascular events.

**Clopidogrel, Prasugrel, and Ticagrelor**

Current guidelines recommend the use of a P2Y12 receptor inhibitor across the spectrum of ACS presentations. Data evaluating P2Y12 receptor inhibitors in patients with ESRD are limited, and such information is available predominantly for individuals with moderate or no CKD. Data on the use of P2Y12 receptor inhibitors in ACS patients with CKD are summarized in Table 4. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial randomized patients with an ACS without ST-segment elevation to either a 300-mg loading dose of clopidogrel followed by 75 mg per day or placebo. Based on tertiles of renal function, the relative risks (RR) and 95% CIs for the primary composite outcome associated with clopidogrel versus placebo were 0.74 (0.60–0.93) in the upper third, 0.68 (0.56–0.84) in the middle third, and 0.89 (0.76–1.05) in the lower third, with a Pinteraction of 0.11. In the Clopidogrel for the Reduction of Events During Observation (CREDO, a trial of patients undergoing planned PCI or coronary angiogram) and the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial (a trial of patients with STEMI), there was a qualitative decline in the efficacy of clopidogrel versus placebo as renal function worsened; the HRs (95% CIs) across renal function were 0.74 (0.60–0.93) in the upper third, 0.80 (0.51–1.25), and 1.42 (0.81–2.45) in CREDO and 0.6 (0.40–0.90), 0.6 (0.40–0.70), and 1.0 (0.70–1.6) in CLARITY-TIMI 28. In a substudy of the Clopidogrel for High Atherothrombotic Risk and Thrombolytic Stabilization, Management, and Avoidance (CHARISMA) trial, among patients with and without diabetic nephropathy, the HRs (95% CIs) for clopidogrel versus placebo were 0.9 (0.80–1.0) for those without diabetic nephropathy and 1.1 (0.80–1.6) for those with diabetic nephropathy.

In terms of safety, more bleeding occurred with clopidogrel than placebo overall; however, there was no significant interaction based on renal function in CURE, CREDO, or CHARISMA-TIMI 28. Within the CHARISMA analysis, the frequency of severe bleeding according to the Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO) definition among patients with diabetic nephropathy was nonsignificantly higher with clopidogrel than with placebo (2.6% versus 1.5%, P=0.075). In patients without diabetic nephropathy, there was no difference in GUSTO severe bleeding between patients randomized to clopidogrel versus placebo (1.5% versus 1.3%, P=0.28).

Prasugrel and ticagrelor are P2Y12 inhibitors that exhibit a more rapid onset, higher degrees of platelet inhibition, and less interpatient variability than clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38) randomized subjects who presented with moderate- to high-risk ACS with scheduled PCI to either prasugrel or clopidogrel. Within this study, the risk reduction associated with prasugrel versus clopidogrel was 20% among those with CrCl $\geq$ 60 mL/min and 14% among those with CrCl $\leq$ 60 mL/min. The Study of Platelet Inhibition and Patient Outcomes (PLATO) randomized patients admitted to the hospital with an ACS to treatment with ticagrelor or clopidogrel. The HRs (95% CIs) for ticagrelor versus clopidogrel for the primary composite outcome were 0.90 (0.79–1.02) among subjects with CrCl ≥ 60 mL/min and 0.77 (0.65–0.90) among those with CrCl < 60 mL/min. The HRs (95% CIs) for ticagrelor versus clopidogrel for major bleeding events were 1.08 (0.96–1.22) among patients with CrCl ≥ 60 mL/min and 1.07 (0.88–1.30) among those with CrCl < 60 mL/min. Thus, the efficacy associated with prasugrel and ticagrelor compared with clopidogrel was apparent among subjects with reduced and normal renal function. In summary, randomized placebo-controlled trial data on the use of clopidogrel in ACS patients with CKD have been derived primarily from patients not undergoing an early invasive strategy or primary PCI. The lack of a treatment–by–renal function interaction suggests clopidogrel should be considered as a treatment option in this population. In addition, although the observed rates of bleeding have been higher with clopidogrel than with placebo in CKD patients, the lack of a treatment interaction suggests no significant increase in risk with the use of clopidogrel in ACS patients with CKD. The efficacy associated with prasugrel compared with clopidogrel and the efficacy and safety associated with ticagrelor compared with clopidogrel were evident in patients with and without CKD, and the data suggest these agents should be considered in CKD patients who are not considered to be at high risk of bleeding. However, patients with ESRD have been excluded from the landmark trials of these newer agents.

**Glycoprotein IIb/IIIa Receptor Antagonists**

The glycoprotein (GP) IIb/IIIa receptor antagonists have been studied extensively in patients undergoing PCI and in patients presenting with ACS. In the setting of STEMI, recent guidelines give a Class IIa recommendation for the use of the GP IIb/IIIa receptor antagonists at the time of primary PCI in patients receiving unfractionated heparin (UFH). Among patients presenting with unstable angina (UA)/NSTEMI with medium- or high-risk features in whom an initial invasive strategy is selected, current recommendations for the use of GP IIb/IIIa receptor antagonists include the option for upstream initiation or initiation at the time of PCI. Additionally, the guidelines favor a selective strategy of upstream use of GP IIb/IIIa receptor antagonists, and the use of these agents as part of an upstream triple-antiplatelet therapy regimen may not be supported when there is a concern for increased bleeding risk. Of the 3 agents currently available in the United States, eptifibatide and tirofiban are dependent on renal clearance for elimination, and dose adjustment is required for the 2 agents in patients with CrCl $<$ 50 mL/min and CrCl $\leq$ 60 mL/min (Table 1),
respectively. In addition, eptifibatide is contraindicated in patients requiring dialysis.

Abciximab is cleared via the reticuloendothelial system, and no current recommendations exist for dose adjustment for patients with CKD. Data from randomized trials and observational studies on the clinical outcomes of ACS patients with CKD receiving a GP IIb/IIIa receptor antagonist are summarized in Table 5.

When used at the time of PCI in ACS patients with CKD, outcomes with the use of GP IIb/IIIa receptor antagonists have been variable. A subgroup analysis of the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrin Therapy (ESPRIT) trial showed the treatment effect of eptifibatide was maintained among those with CrCl <60 mL/min, and the presence of CKD was not associated with an increased risk of bleeding with eptifibatide therapy.
Observational cohorts of ACS patients receiving GP IIb/IIIa receptor antagonists at the time of PCI have provided additional insight into use in patients with CKD. Best et al\textsuperscript{57} assessed patients undergoing PCI in a large registry that divided patients into 3 categories according to creatinine clearance: >70, 50–69, or <50 mL/min. Among patients receiving abciximab, the interaction between CrCl and major bleeding was not statistically significant. Additionally, no interaction was seen between CrCl and abciximab for the frequency of death or MI (HR, 1.03; 95% CI, 0.97–1.08). A second observational study categorized patients undergoing PCI into 5 strata by CrCl (\(\geq 90\) mL/min, \(60–89\) mL/min, \(30–59\) mL/min, <30 mL/min, and requiring dialysis).\textsuperscript{59} After controlling for CrCl stratum, GP IIb/IIIa receptor antagonist use was associated with a lower risk of in-hospital mortality (OR, 0.34; 95% CI, 0.12–0.98) and an increased risk of a major bleeding event (OR, 2.13; 95% CI, 1.39–3.27). A final observational study reported the clinical outcomes of Table 5. Summary of GP IIb/IIIa Receptor Antagonist Studies in Patients With ACS and CKD

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<td>PRISM-PLUS\textsuperscript{56}</td>
<td>Post hoc analysis of an RCT</td>
<td>1537 UA/NSTEMI patients randomized to receive tirofiban or placebo. Renal function classified by CrCl*: &gt;75 mL/min (n=572), 60–75 mL/min (n=354), 30–60 mL/min (n=571), &lt;30 mL/min (n=40). Patients with SCr (\geq 2.5) mg/dL were excluded from the PRISM-PLUS trial.</td>
<td>7-d death/MI/refractory ischemia (primary composite)</td>
<td>Decreasing renal function was strongly associated with adverse outcomes, however, there was no evidence of treatment-by-CrCl interaction. The incidence of the composite end point in the tirofiban and placebo groups at 7 d was 35% vs 45% in patients with CrCl &lt;30 mL/min, 17.9% vs 23.8% in patients with CrCl 30–60 mL/min, 13.9% vs 15.5% in patients with CrCl 60–75 mL/min, and 6.8% vs 12.3% in patients with CrCl &gt;75 mL/min.</td>
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<tr>
<td>Best et al\textsuperscript{57}</td>
<td>Observational cohort</td>
<td>4158 patients undergoing PCI (indication for PCI was UA in 71% of patients in each group and MI in the previous 7 d in 26% of patients in the abciximab group and 15% of patients in the no abciximab group). Renal function classified based on CrCl*: &gt;70 mL/min (n=647 who received abciximab and n=1472 who did not), 50–69 mL/min (n=367 who received abciximab and 820 who did not), and &lt;50 mL/min (n=229 who received abciximab and 585 who did not).</td>
<td>Composite of death or MI</td>
<td>No interaction was seen between CrCl and abciximab for the frequency of death or MI (HR, 1.03; 95% CI, 0.97–1.08).</td>
</tr>
<tr>
<td>ESPRIT\textsuperscript{58}</td>
<td>Subgroup analysis of an RCT</td>
<td>Patients randomized to eptifibatide or placebo at the time of PCI. 2044 of 2064 patients had creatinine data available. A total of 1755 patients had CrCl* (\geq 60) mL/min, and 289 patients had CrCl &lt;60 mL/min. Patients with SCr &gt;4 mg/dL were excluded. Indication for PCI was UA in 44% of patients with CrCl (\geq 60) mL/min and 54% in those with CrCl &lt;60 mL/min.</td>
<td>Composite of death, MI, TVR, or thrombotic bailout assessed at 48 h</td>
<td>The adjusted ORs (95% CIs) for the effect of eptifibatide on the primary outcome remained for those with lower CrCl (60 mL/min) 0.52 (0.33–0.81) compared with those with higher CrCl (90 mL/min) 0.64 (0.46–0.89).</td>
</tr>
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</table>

(Continued)
### Table 5. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
<th>End Points</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Freeman et al</strong>&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Observational, cohort study</td>
<td>889 patients with ACS, including 310 patients with renal insufficiency defined as CrCl* &lt;60 mL/min (222 patients had CrCl of 30–59 mL/min, 63 had CrCl of &lt;30 mL/min, and 25 patients were dialysis dependent). 312 of the 889 patients enrolled received a GP IIb/IIIa antagonist.</td>
<td>In-hospital mortality</td>
<td>Although worsening CrCl stratum was a predictor of in-hospital mortality, a lower risk of in-hospital mortality was seen with the use of GP IIb/IIIa antagonist after controlling for CrCl (OR, 0.34; 95% CI, 0.12-0.98).</td>
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<tr>
<td><strong>Frilling et al</strong>&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Single-center registry</td>
<td>1040 patients including 44 with renal insufficiency (defined as Scr ≥1.3 mg/dL) undergoing PCI who received abciximab. The indication for PCI was ACS in 718 of 996 patients without renal insufficiency and 35 of 44 patients with renal insufficiency.</td>
<td>MACCE: death, MI, stroke, emergency aortocoronary bypass operation or PCI</td>
<td>Major bleeding events</td>
</tr>
<tr>
<td><strong>TARGET</strong>&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Subgroup analysis of an RCT</td>
<td>4623 patients undergoing PCI randomized to abciximab or tirofiban were grouped into CrCl quartiles (&gt;114, 90–114, 70–90, &lt;70 mL/min). Patients with Scr &gt;2.5 mg/dL were excluded from the TARGET trial. The indication for PCI was ACS in 63% of patients.</td>
<td>Composite of all-cause mortality, MI, and TVR at 30 d</td>
<td>Major and minor bleeding events</td>
</tr>
<tr>
<td><strong>EARLY ACS</strong>&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Subgroup analysis of an RCT</td>
<td>8708 patients with UA/NSTEMI were randomized to early eptifibatide or a strategy of delayed provision eptifibatide. A total of 1632 patients had a baseline CrCl* &lt;50 mL/min. Patients requiring dialysis within the past month were excluded.</td>
<td>Primary composite: death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 h Death or MI at 30 d</td>
<td>Rates of non-CABG related TIMI major bleeding and GUSTO severe/moderate bleeding</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; EARLY ACS, Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome; ESPRIT, Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy; GP, glycoprotein; GUSTO, Global Utilization of Streptokinase and Plasminogen Activator for Occluded Arteries; HR, hazard ratio; MACCE, major adverse cardiac or cerebrovascular event; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PRISM-PLUS, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; RCT, randomized controlled trial; Scr, serum creatinine; TARGET, Do Tirofiban and ReoPro Give Similar Efficacy Outcome; TIMI, Thrombolysis in Myocardial Infarction; TVR, target-vessel revascularization; and UA, unstable angina.

<sup>*Calculated via Cockcroft-Gault equation.</sup>
patients undergoing PCI who received abciximab. Of the 1040 patients included, 44 were classified as having renal insufficiency. The authors reported no significant differences in the rates of in-hospital mortality or nonfatal major adverse cardiac events among patients with renal insufficiency compared with those without, although major bleeding occurred more frequently among patients with renal insufficiency (4.5% versus 0.6%; \(P=0.003\)). Although limited data are available on the comparative safety and effectiveness of different GP IIb/IIIa receptor antagonists among patients with CKD, a subgroup analysis of the Do Tirofiban and ReoPro Give Similar Efficacy Outcome (TARGET) trial compared the outcomes of patients with renal insufficiency undergoing PCI who received either abciximab or tirofiban. The 4623 patients with a baseline SCr level available were divided into CrCl quartiles (<70, 70–90, 90–114, and >114 mL/min). Although the rates of both ischemic and bleeding events were higher among patients with lower creatinine clearances, there was no interaction between the assigned GP IIb/IIIa receptor antagonist, CrCl, and clinical outcome.

An analysis of the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial provided outcome data on the upstream use of GP IIb/IIIa receptor antagonists among patients presenting with ACS. This analysis showed tirofiban therapy to be effective in reducing ischemic events, with no evidence of treatment-by-CrCl interaction. Additionally, although decreasing renal function (\(P<0.001\)) and tirofiban \((P<0.001)\) were each associated with an increased risk for bleeding events, tirofiban therapy was not associated with an incremental increase in the risk for hemorrhage among those with CKD. A subgroup analysis of the Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial provided a comparative assessment of the early versus delayed provisional use of eptifibatide among patients with CKD presenting with non-ST-segment elevation ACS in whom coronary angiography was planned. This was the first large-scale randomized trial of eptifibatide that used the currently recommended dosing regimen \(1 
\frac{\mu g}{kg^{-1} \cdot min^{-1}}\) for patients with \(\text{CrCl} \geq 50 \text{ mL/min}\) and \(1 
\frac{\mu g}{kg^{-1} \cdot min^{-1}}\) for patients with \(\text{CrCl} < 50 \text{ mL/min}\), with patients requiring dialysis excluded from the trial. Among patients with \(\text{CrCl} < 50 \text{ mL/min}\), early eptifibatide compared with a delayed provisional eptifibatide strategy was not associated with a reduction in the composite ischemic end point(s) at 96 hours or at 30 days. Among patients with \(\text{CrCl} < 50 \text{ mL/min}\), rates of non–coronary artery bypass graft–related TIMI major bleeding and GUSTO severe/moderate bleeding were significantly higher with the early eptifibatide strategy.

In summary, data on the use of GP IIb/IIIa receptor antagonists in CKD patients with ACS indicate a reduction in ischemic events and a variable but overall increase in the risk of bleeding events. In addition, in a recent trial comparing a strategy of early versus delayed provisional GP IIb/IIIa receptor antagonist therapy in UA/NSTEMI patients, no reduction in ischemic events and an increase in bleeding events were seen with the early strategy in patients with CKD.

Although the existing data do not support a preferred GP IIb/IIIa receptor antagonist for use in patients with CKD, it is important that clinicians follow dosing recommendations for eptifibatide and tirofiban when either of these agents is used.

**Anticoagulants**

**Unfractionated Heparin**

UFH has been a mainstay in the treatment of ACS for several decades. Current guidelines recommend UFH as an anticoagulant option across the spectrum of ACS presentations. Once administered, the primary route of UFH elimination is via the reticuloendothelial system, with renal clearance being a minor route for elimination. Few data are available from early placebo-controlled trials on the treatment effect of UFH therapy in CKD patients presenting with ACS. In addition, given that UFH has often been the standard anticoagulant with which newer agents have been compared, the outcome data for UFH use in CKD patients will be discussed in the sections below.

**Low-Molecular-Weight Heparin**

**Enoxaparin**

Enoxaparin is the most widely studied low-molecular-weight heparin (LMWH) in the setting of ACS. Current guidelines recommend enoxaparin as an anticoagulant option in UA/NSTEMI patients being managed with either an early invasive (Class I recommendation) or initial conservative (Class I recommendation) strategy. For patients presenting with STEMI, current guidelines recommend enoxaparin as an adjunctive anticoagulant option in conjunction with fibrinolytic therapy (Class I recommendation). Enoxaparin elimination is largely dependent on renal function, with \(\approx40\%\) of a dose being eliminated by glomerular filtration. The current US Food and Drug Administration–approved dose for enoxaparin in ACS patients with CrCl \(<30 \text{ mL/min}\) is 1 mg/kg subcutaneously every 24 hours. However, patients with CrCl \(<30 \text{ mL/min}\) have been routinely excluded from randomized trials of enoxaparin in ACS; therefore, limited data are available from randomized controlled trials on the use of enoxaparin in this population. Data from randomized trials and observational studies on the use of enoxaparin in ACS patients with CKD are shown in Table 6.

A number of studies have shown increased anti-Xa activity in ACS patients with renal insufficiency receiving therapeutic doses of enoxaparin. In a substudy performed in 445 ACS patients enrolled in the TIMI 11A trial, the effect of renal function and other patient characteristics on the pharmacokinetics and pharmacodynamics of enoxaparin was examined. In this analysis, CrCl was the most influential factor on pharmacokinetic and pharmacodynamic parameters of enoxaparin. Patients with CrCl \(<40 \text{ mL/min}\) had higher peak and trough anti-Xa activity than patients with CrCl \(\geq 40 \text{ mL/min}\) and were more likely to have a major hemorrhagic event. Several clinical trials evaluating the use of enoxaparin in UA/NSTEMI patients have provided data on the outcomes of CKD patients receiving enoxaparin or UFH. A pooled analysis of CKD patients with severe renal impairment (defined as CrCl \(\leq 30 \text{ mL/min}\)) enrolled in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and TIMI 11B trials was performed to assess
Table 6. Summary of Enoxaparin Studies in Patients With ACS and CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
<th>End Points</th>
<th>Results</th>
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<tbody>
<tr>
<td>ESSENCE-TIMI 11B</td>
<td>Pooled subgroup analysis of 2 RCTs</td>
<td>7081 NSTE ACS patients enrolled in ESSENCE (n=3171) and TIMI 11B (n=3910) randomized to enoxaparin or UFH. CrCl &lt;30 mL/min was an exclusion in 1 trial (ESSENCE), whereas SCR &gt;2.0 mg/dL was an exclusion in the other (TIMI 11B). Severe renal impairment (CrCl* &lt;30 mL/min) was found in 74 UFH-treated patients and 69 patients receiving enoxaparin (2%). The enoxaparin dose was 1 mg/kg every 12 h.</td>
<td>All-cause death, recurrent MI, and urgent revascularization at 43 d</td>
<td>Major hemorrhage occurred in 5.9% of UFH patients and 7.5% of enoxaparin patients (OR, 1.53; 95% CI, 0.37–6.32).</td>
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<tr>
<td>Collet et al66</td>
<td>Observational cohort (GRACE registry)</td>
<td>11 881 patients presenting with UA/NSTEMI. Patients were divided into 3 groups based on CrCl*: &gt;60 mL/min (n=7194), 31–60 mL/min (n=3705), ≤30 mL/min (n=982). In the 3 renal function groups, LMWH was used in 30%, 31%, and 30%, respectively, whereas UFH was used in 22%, 24%, and 28%, respectively.</td>
<td>Mortality (30 d)</td>
<td>Worsening renal function was an independent predictor of 30-d mortality and in-hospital major bleeding. Rates of 30-d mortality were significantly lower with LMWH alone than with UFH alone in patients with CrCl &gt;60 mL/min and in those with CrCl 31–60 mL/min. No significant difference was seen in patients with CrCl &lt;30 mL/min (15.4% vs 18.6%, respectively).</td>
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<tr>
<td>ExTRACT-TIMI 25 Trial</td>
<td>Double blind RCT</td>
<td>20 479 patients with STEMI receiving fibrinolytic therapy randomized to UFH or enoxaparin. Patients with CrCl* &lt;30 mL/min received a maintenance enoxaparin dose of 1 mg/kg every 24 h. SCI &gt;2.5 mg/dL for men and &gt;2.0 mg/dL for women was an exclusion. Patients were divided into 4 groups based on CrCl*: &gt;90 (n=7462), ≥60 to 90 (n=7203), 30–60 (n=3671), and &lt;30 mL/min (n=212).</td>
<td>All-cause death or nonfatal recurrent MI within 30 d</td>
<td>Adjusted OR (95% CI) for enoxaparin vs UFH comparison: Primary end point: 0.69 (0.56–0.84) for CrCl* &gt;90 mL/min, 0.78 (0.66–0.92) for CrCl* &gt;60 to 90 mL/min, 0.94 (0.78–1.12) for CrCl* 30–60 mL/min, and 0.74 (0.58–1.14) for CrCl* &lt;30 mL/min</td>
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<tr>
<td>SYNERGY68</td>
<td>Open-label RCT</td>
<td>10 027 NSTE ACS patients randomized to enoxaparin or UFH. Maintenance dose of enoxaparin was 1 mg/kg every 12 h. Early angiography intended (median time, 22 h). Patients with CrCl &lt;30 mL/min were to be excluded. Patients were grouped according to CrCl*: &gt;60 mL/min (n=6950), 30–59 mL/min (n=2792), and &lt;30 mL/min (n=156)</td>
<td>All-cause death or nonfatal MI (30 d)</td>
<td>No significant treatment-by-CrCl interaction term was found for all treatment outcomes. 30-d death or MI in patients treated with UFH vs enoxaparin in patients was 12.9% vs 12.7% for CrCl* &gt;60 mL/min, 17.7% vs 17.0% for CrCl* 30–59 mL/min, and 23.3% vs 25.7% for CrCl* &lt;30 mL/min</td>
</tr>
<tr>
<td>OASIS-5</td>
<td>Double-blind RCT</td>
<td>20 078 patients randomized to fondaparinux or enoxaparin. SCR level &gt;3 mg/dL was an exclusion. Patients with CrCl* &lt;30 mL/min received an enoxaparin maintenance dose of 1 mg/kg every 12 h. Patients were grouped and analyzed in quartiles based on eGFR.†</td>
<td>Primary efficacy end point: Death, MI, or refractory ischemia at 9 d</td>
<td>HR (95% CI) for fondaparinux vs enoxaparin comparison: Efficacy end point at 30 d: 0.91 (0.74–1.12) for eGFR ≥86 mL/min·1.73 m−2, 0.95 (0.76–1.18) for eGFR 71 to &lt;86 mL/min·1.73 m−2, 1.10 (0.90–1.33) for eGFR 58 to &lt;71 mL/min·1.73 m−2, and 0.81 (0.69–0.96) for eGFR &lt;58 mL/min·1.73 m−2</td>
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ACS indicates acute coronary syndrome; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events; ExTRACT-TIMI 25, Enoxaparin and Thrombolysis Repurification for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction 25; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSTE, non–ST-segment elevation; NSTEMI, non–ST-segment–elevation myocardial infarction; OASIS-5, Organization for the Assessment of Strategies for Ischemic Syndromes 5; OR, odds ratio; RCT, randomized controlled trial; SCR, serum creatinine; STEMI, ST-segment–elevation myocardial infarction; SYNERGY, Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina; and UFH, unfractionated heparin.

* Cockcroft-Gault Formula.
† eGFR assessed by Modification of Diet in Renal Disease formula.
the treatment effects of enoxaparin and UFH.\textsuperscript{63} Severe renal impairment was identified in ≥2% of patients in this pooled analysis. There was no statistically significant difference between enoxaparin and UFH with regard to the rates of occurrence of the primary composite end point (18.8% versus 32.4%, respectively; \(P=0.12\)) or major hemorrhage (7.5% versus 5.8%, respectively; \(P=0.56\)) among patients with CrCl ≤30 mL/min. The association of CKD with outcomes among patients enrolled in the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial who received either enoxaparin or UFH was also assessed.\textsuperscript{64} Patients were placed into 3 groups based on CrCl: <30 mL/min (n=156), 30–59 mL/min (n=2732), and ≥60 mL/min (n=6950). No treatment-by-CrCl interaction was significant for the efficacy or safety outcomes, although the rates of TIMI major and GUSTO severe bleeding were numerically higher in patients with CrCl <30 mL/min and those with CrCl 30 to 59 mL/min. An analysis of GRACE evaluated the association of CKD with outcomes among patients with non–ST-segment–elevation ACS treated with either LMWH or UFH.\textsuperscript{65} Based on CrCl <30 mL/min (43 patients received UFH and 37 received LMWH), 30 to 59 mL/min (70 patients received UFH and 49 received LMWH), and ≥60 mL/min (50 patients received UFH and 45 received LMWH), results of this analysis showed that LMWH was associated with lower 30-day mortality (4.2% versus 6.2%; \(P<0.0001\)) and a lower rate of in-hospital major bleeds (2.1% versus 3.3%; \(P=0.006\)), but the mortality and in-hospital major bleeding benefit was not statistically significant in the group with CrCl <30 mL/min.

The association of renal function with outcomes among fibrinolytic agent–treated STEMI patients receiving enoxaparin or UFH was evaluated in an analysis of the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25 (ExTRACT-TIMI 25) trial.\textsuperscript{67} In this trial, patients with CrCl <30 mL/min received a dose of enoxaparin of 1 mg/kg once per day. On the basis of estimated CrCl <30 mL/min, 30 to 60 mL/min, >60 to 90 mL/min, and >90 mL/min, there was a statistically significant benefit of enoxaparin on the primary composite end point of death or nonfatal MI among patients with CrCl >60 mL/min that was not seen in patients with CrCl 30 to 60 mL/min or in those with CrCl <30 mL/min. In addition, there was an increase in the risk of major and minor bleeding events with enoxaparin treatment among patients with renal dysfunction (defined as CrCl ≤60 mL/min).\textsuperscript{67}

The randomized studies presented in this section have largely excluded patients with severe renal impairment. In aggregate, all demonstrate a stepwise increase in the incidence of death, MI, and bleeding with increasing levels of kidney dysfunction. However, the differential treatment effect of UFH versus LMWH on bleeding is more difficult to ascertain because of a lack of power caused by the small number of patients with severe renal impairment.\textsuperscript{65,66} Of the trials discussed in this section, only the ExTRACT-TIMI 25 trial demonstrated an association between treatment with enoxaparin and increased bleeding risk with worsening renal function.\textsuperscript{67} A meta-analysis of LMWH studies, including smaller randomized trials and observational studies in ACS and venous thromboembolism that exclusively examined patients with renal dysfunction, suggested that enoxaparin use was associated with a 2- to 3-fold increase in major bleeding events when CrCl was <30 mL/min.\textsuperscript{71} In clinical practice, the use of enoxaparin in ACS has been encumbered by challenges in correctly adjusting the dose of enoxaparin for creatinine clearance. In an analysis of the CRUSADE Quality Improvement Initiative, enoxaparin was used in 40% of 33094 patients with non–ST-segment–elevation ACS.\textsuperscript{72} Only 50% of patients treated with enoxaparin received the recommended dose according to their renal function, 18.7% received an excess dose, and 29.2% received a lower dose. An excess dose was associated with increased risk of major bleeding and in-hospital mortality. Major bleeding occurred in 14.2% and 7.3% of patients who received an excess and a recommended dose, respectively (adjusted OR, 1.43; 95% CI, 1.18–1.75). In-hospital death occurred in 5.6% and 2.4% of patients who received an excess and a recommended dose, respectively (OR, 1.35; 95% CI, 1.03–1.77).

**Factor Xa Inhibitors**

**Fondaparinux**

Fondaparinux is an indirect factor Xa inhibitor that has recently been evaluated in the management of patients presenting with ACS. Current guidelines for fondaparinux in ACS patients include a Class I recommendation for fondaparinux use as an adjunctive anticoagulant for STEMI patients receiving fibrinolytic therapy and a Class I recommendation for UA/NSTEMI patients being managed with either an invasive or conservative strategy.\textsuperscript{26,73} In addition, the guidelines recommend fondaparinux as the preferred anticoagulant in UA/NSTEMI patients being managed with a conservative strategy who have an increased risk of bleeding.\textsuperscript{73} Fondaparinux is primarily excreted unchanged through renal elimination, and is contraindicated in the United States for patients with severe CKD (CrCl <30 mL/min).\textsuperscript{74}

The Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS) 5 trial compared fondaparinux to enoxaparin in 20 078 patients with non–ST-segment–elevation ACS randomized to fondaparinux 2.5 mg subcutaneously once daily or enoxaparin 1 mg/kg subcutaneously twice daily (dose adjusted to 1 mg/kg once daily in patients with CrCl <30 mL/min).\textsuperscript{75} Although patients with SCr ≥3 mg/dL were excluded, a specific analysis was designed to examine efficacy and safety outcomes by quartiles of GFR (as estimated by the MDRD formula).\textsuperscript{69} This study showed a direct relationship between degree of renal impairment and the risk of death, MI, refractory ischemia, and bleeding. Among patients with a GFR ≥58 mL-min\(^{-1}\)·1.73 m\(^{-2}\), no significant difference was seen between treatment groups in the primary composite outcome of death, MI, or refractory ischemia at 9 days. However, at 30 days, the rate of the primary composite outcome was significantly lower among patients with a GFR <58 mL-min\(^{-1}\)·1.73 m\(^{-2}\) with fondaparinux (HR, 0.81; 95% CI, 0.69–0.96). Fondaparinux treatment was associated with lower rates of major bleeding events at 9 days among patients with a GFR <58 mL-min\(^{-1}\)·1.73 m\(^{-2}\) (HR, 0.42; 95% CI, 0.32–0.56). In addition, in the subgroup of patients with CrCl <30 mL/min, the rates of major bleeding at 9 days were
significant lower in the group receiving fondaparinux (2.4% versus 9.9%, \(P=0.001\)).\(^{25}\) Although the rates of major bleeding were lower with fondaparinux across all quartiles of estimated GFR, the difference was most marked among patients with a GFR <58 mL/min\(^{-1}\cdot 1.73\text{ m}^2\).\(^{49}\)

**Direct Thrombin Inhibitors**

**Bivalirudin**

Bivalirudin, a bivalent direct thrombin inhibitor, has been well studied in patients undergoing PCI, including patients presenting with ACS. Current guidelines recommend bivalirudin as an anticoagulant option in STEMI patients undergoing primary PCI (Class I)\(^{26-42}\) and in UA/NSTEMI patients in whom an invasive strategy is selected (Class I).\(^{26}\) Elimination of bivalirudin occurs through both proteolysis and renal clearance. In patients with normal renal function (CrCl > 90 mL/min) or mildly impaired renal function (CrCl > 60 mL/min), the pharmacokinetics of bivalirudin are linear, with an elimination half-life of 25 minutes. The elimination half-life is increased to 34 to 57 minutes in patients with moderate to severe renal impairment (CrCl between 10 and 59 mL/min) and \(\approx 3.5\) hours in patients with renal failure necessitating hemodialysis.\(^{76-78}\) For patients with renal insufficiency, the product labeling recommends no reduction in the bolus dose for any degree of renal impairment, although the infusion dose of bivalirudin may need to be reduced and anticoagulant status monitored in patients with renal impairment (Table 1).\(^{78}\) Data from randomized trials and observational studies on the use of bivalirudin in ACS patients with CKD are shown in Table 7.

A meta-analysis\(^{79}\) of 3 randomized trials comparing bivalirudin with UFH at the time of PCI (majority ACS) stratified by CrCl > 90 mL/min (n = 1578), CrCl 90 to 60 mL/min (n = 2163), CrCl 59 to 30 mL/min (n = 1255), and CrCl < 30 mL/min (n = 39) showed an increasing risk of ischemic and bleeding events with increasing degrees of renal impairment. The absolute benefit of bivalirudin on the ischemic and bleeding composite end point increased with decreasing CrCl strata (2.2%, 5.8%, 7.7%, and 14.4%, respectively; \(P_{\text{interaction}} = 0.044\)). Similarly, the association of CKD with adverse outcomes for patients undergoing PCI (43% ACS) randomized to bivalirudin and provisional GP IIb/IIIa inhibition or UFH and planned GP IIb/IIIa inhibition was examined in the Second Randomized Evaluation in PCI Linking Bivalirudin to Reduced Clinical Events (REPLACE-2) trial.\(^{80}\) Patients were grouped according to CrCl > 60 mL/min (n = 4824) and CrCl < 60 mL/min (n = 886). Among patients with CrCl < 60 mL/min, rates of 30-day ischemic events (death, MI, or urgent revascularization) were 9.7% and 9.4% (\(P = 0.870\)) in the bivalirudin and UFH and GP IIb/IIIa receptor antagonist groups, respectively, but there were significantly lower rates of TIMI major or minor hemorrhage (3.2% versus 7.1%; \(P = 0.009\)) with bivalirudin. There was no observed interaction between treatment, bleeding or ischemic events, and renal function. Although these bivalirudin studies excluded dialysis-dependent patients, a retrospective analysis comparing bivalirudin with UFH (GP IIb/IIIa receptor antagonists were excluded) in dialysis-dependent patients undergoing PCI showed no significant difference in the rates of in-hospital major bleeding (3.4% versus 3.1%, respectively; \(P = 0.9\))\(^{81}\) or in the rates of the primary composite ischemic end point of in-hospital death, Q-wave MI, and urgent target-vessel revascularization (1.8% versus 0.8%, respectively; \(P = 0.7\)).

Analyses from 2 randomized trials provide data on the association of CKD with outcomes among patients with ACS receiving bivalirudin. In a substudy of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, Mehran and colleagues\(^{82}\) showed that patients with CKD (defined as CrCl < 60 mL/min) had worse 30-day and 1-year clinical outcomes than those with normal renal function. Patients with CrCl < 30 mL/min were excluded from this trial. There were no significant differences between bivalirudin monotherapy and heparin plus a GP IIb/IIIa receptor antagonist in rates of 30-day composite ischemia (11.1% versus 9.4%; \(P = 0.27\)) and net clinical adverse outcomes (16.1% versus 16.9%; \(P = 0.65\)). There was significantly less major bleeding (6.2% versus 9.8%; \(P = 0.008\)) at 30 days but no significant difference in 1-year composite ischemia (22.0% versus 18.9%; \(P = 0.10\)) or mortality (7.1% versus 7.3%; \(P = 0.96\)). A substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial provided an assessment of the association of CKD with outcomes among patients undergoing primary PCI. Approximately 15% of patients enrolled had CrCl of 30 to 60 mL/min, whereas 1.4% had CrCl of < 30 mL/min. This analysis showed patients with CKD had higher rates of clinical events at 30 days, including death and major bleeding.\(^{83}\) Multivariable analysis identified baseline creatinine as an independent predictor of death at 3 years (HR, 1.51; 95% CI, 1.21–1.87; \(P < 0.001\)). Patients with CKD (defined as CrCl < 60 mL/min) randomized to bivalirudin monotherapy versus heparin plus GP IIb/IIIa receptor antagonist had no significant difference in major bleeding (12.3% versus 15.3%; HR, 0.79; 95% CI, 0.50–1.25) or death (8.4% versus 7.9%; HR, 1.09; 95% CI, 0.61–1.95) at 30 days.

Taken collectively, the randomized controlled trial data on anticoagulation therapy in CKD patients presenting with ACS are limited by the underrepresentation of patients with stage 4 and 5 CKD, which makes definitive conclusions about the treatment effect of anticoagulant agents challenging. Although a number of trials excluded patients with CrCl < 30 mL/min, the ExTRACT-TIMI-25, OASIS-5, and HORIZONS-AMI trials did not.\(^{75,84,85}\) The association of treatment with enoxaparin and increased bleeding risk with worsening renal function observed in the ExTRACT-TIMI-25 trial, as well as the increased rates of major bleeding in patients with CrCl < 30 mL/min with enoxaparin therapy observed in the OASIS-5 trial, suggests that caution is warranted when enoxaparin is used in this population.\(^{67,73}\)

**Anti-Ischemic Therapies**

**\(\beta\)-Blockers**

\(\beta\)-Blockers are recommended for all patients with ACS unless contraindicated.\(^{86,87}\) Metoprolol, atenolol, and propranolol have been studied in the setting of AMI, and carvedilol has been studied in the setting of AMI with left ventricular dysfunction.\(^{88-92}\) Atenolol is renally eliminated and requires dose adjustment in those with renal impairment. Dose adjustment is recommended...
**Table 7. Summary of Bivalirudin Studies in Patients With ACS and CKD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
<th>End Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chew et al</td>
<td>Meta-analysis of 3 trials: the Bivalirudin Angioplasty Study, CATCHET trial and REPLACE-1</td>
<td>The trials included patients undergoing PCI receiving bivalirudin or UFH during PCI. Patients were stratified by CrCl into groups: CrCl ≥90 mL/min (n=1578), CrCl 60–90 mL/min (n=2163), CrCl 30–59 mL/min (n=1255), and CrCl &lt;30 mL/min (n=39). Patients with SCr &gt;3 mg/dL were excluded from the trials. The indication for PCI was UA in ≈65% of patients in this analysis.</td>
<td>Primary efficacy end point: composite of death, MI, or urgent revascularization</td>
<td>Adverse ischemic and bleeding events increased with worsening renal function. The ORs (95% CIs) for reduction of the composite ischemic end point with bivalirudin in the 4 CrCl strata were 0.79 (0.52–1.18), 0.73 (0.53–0.99), 0.77 (0.55–1.07), and 0.81 (0.12–5.23), respectively.</td>
</tr>
<tr>
<td>REPLACE-2</td>
<td>Subgroup analysis of an RCT</td>
<td>Patients undergoing PCI randomized to bivalirudin and provisional GP IIb/IIIa inhibitor vs UFH and planned GP IIb/IIIa inhibitor. Exclusion criteria included SCr &gt;4 mg/dL. In this analysis, patients were grouped based on CrCl*: CrCl ≥60 mL/min (n=4824) and CrCl &lt;60 mL/min (n=886). The indication for PCI was ACS in ≈43% of patients enrolled in this trial.</td>
<td>Primary efficacy end point: 30-d composite of death, MI, or urgent revascularization</td>
<td>A significant increase in adverse events was noted in the group with renal insufficiency. In patients with CrCl &lt;60 mL/min, the rates of the composite ischemic outcome in the bivalirudin and UFH plus GP IIb/IIIa inhibitor groups were 7.4% and 6.7% (P=0.276), respectively.</td>
</tr>
<tr>
<td>Delhaye et al</td>
<td>Retrospective analysis of single-center registry</td>
<td>Chronic dialysis-dependent patients undergoing PCI receiving adjusted-dose bivalirudin (n=267) or UFH (n=129). Patients receiving GP IIb/IIIa inhibitor were excluded. ACS was the indication for PCI in 77% of patients receiving bivalirudin and 84% of those receiving UFH.</td>
<td>Primary ischemic end point: the composite of in-hospital death, Q-wave MI, or urgent TVR</td>
<td>The rates of the composite ischemic end point in the bivalirudin and UFH groups were 1.8% and 0.8% (P=0.7), respectively.</td>
</tr>
<tr>
<td>ACUITY</td>
<td>Subgroup analysis of an RCT</td>
<td>The ACUITY trial enrolled moderate- to high-risk ACS patients undergoing an early invasive management strategy. Patients were randomized to 1 of 3 groups: a heparin (UFH or enoxaparin) plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin plus provisional GP IIb/IIIa inhibitor use. Patients were grouped based on calculated CrCl*: CrCl ≥60 mL/min (n=10470) and CrCl &lt;60 mL/min (n=2469). Although CrCl &lt;30 mL/min was an exclusion criterion, 189 patients were enrolled.</td>
<td>Composite ischemic end point of death, MI, or unplanned revascularization</td>
<td>Patients with CKD had worse 30-d and 1-y outcomes. At 30 d, in patients with CKD (CrCl &lt;60 mL/min), the rates of the composite ischemic outcome in the bivalirudin alone vs heparin plus GP IIb/IIIa inhibitor groups were 11.1% vs 9.4%, respectively (RR, 1.18; 95% CI, 0.88–1.57). No significant difference was seen in the net clinical outcome at 30 d between treatment groups in those with CKD.</td>
</tr>
<tr>
<td>HORIZONS-AMI</td>
<td>Subgroup analysis of an RCT</td>
<td>Patients undergoing primary PCI for STEMI randomized to bivalirudin or UFH plus a GP IIb/IIIa inhibitor. Patients were grouped based on CrCl*: CrCl ≥60 mL/min (n=2783) and CrCl &lt;60 mL/min (n=554). There were 48 patients with CrCl &lt;30 mL/min</td>
<td>NACE (30 d); Major bleeding (non–CABG related), or a composite of MACE including death, MI, stroke, or TVR for ischemia</td>
<td>Patients with CKD (CrCl &lt;60 mL/min) had higher rates of NACE and major bleeding (non–CABG related) at 30 d, 1 y, and 3 y. In patients with CKD, 30-d event rates and HRs (95% CIs) for patients receiving bivalirudin vs UFH plus a GP IIb/IIIa inhibitor were as follows: MACE, 12.7% vs 10.6% (1.22; 0.75–1.99); NACE 21.1% vs 21.6% (0.98; 0.68–1.41).</td>
</tr>
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</table>

ACS indicates acute coronary syndrome; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; CABG, coronary artery bypass grafting; CATCHET, Comparison of Abciximab Complications With Hirulog for Ischemic Events Trial; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; GP, glycoprotein; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; NACE, net adverse clinical events; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; REPLACE, Randomized Evaluation in PCI Linking Bivalirudin to Reduced Clinical Events; RR, relative risk; SCr, serum creatinine; TIMI, Thrombolysis in Myocardial Infarction; TVR, target-vessel revascularization; UA, unstable angina; and UFH, unfractionated heparin.

*CrCl calculated by the Cockcroft-Gault formula.
with CrCl <35 mL/min (50 mg once daily for 15–35 mL/min and 25 mg once daily for CrCl <15 mL/min). Metoprolol, propranolol, and carvedilol are all extensively heptatically metabolized, with <5% of an oral dose excreted in the urine unchanged, so they do not require dose adjustments in renal impairment. Observational studies assessing CKD patients have analyzed all β-blockers together. Data on the use of β-blockers for ACS patients with CKD are summarized in Table 8.

Limited data are available from randomized trials on the use of β-blockers in ACS in patients with CKD. A post hoc analysis of pooled data from patients enrolled in the Carvedilol Postinfarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) and Carvedilol Prospective Randomized, Cumulative Survival (COPERNICUS) trials assessed carvedilol therapy in MI patients with left ventricular dysfunction (CAPRICORN) and in chronic systolic heart failure patients with CKD (COPERNICUS). In the group of patients with CKD (defined as eGFR ≤60 mL·min⁻¹·1.73 m⁻²), treatment with carvedilol was associated with a reduction in all-cause mortality (HR, 0.76; 95% CI, 0.63–0.93) and cardiovascular mortality (HR, 0.77; 95% CI, 0.62–0.94). However, a sensitivity analysis among the subgroup of patients with an eGFR <45 mL·min⁻¹·1.73 m⁻² (n=1116) failed to show a significant benefit for carvedilol therapy with regard to the primary or secondary outcomes. Several observational cohort studies have evaluated whether β-blockers were beneficial among patients with various degrees of renal impairment. These observational studies have found that the benefit of discharge β-blocker use was preserved across all degrees of renal dysfunction. One of the largest observational studies evaluated Medicare beneficiaries with AMI included in the ESRD program as part of the Cooperative Cardiovascular Project (CAPRICORN). This study identified a cohort of 145,765 patients with AMI, among whom 1025 had stage 5D CKD. They found that although β-blocker use did not reduce mortality to as great an extent among those receiving dialysis as among those without ESRD, the benefit was still significant. β-Blocker use was associated with a 40% relative reduction in mortality among those undergoing dialysis and a 56% relative reduction among those without ESRD (P<0.001 for both groups). Collectively, the data from randomized and observational studies support the routine use of β-blocker therapy in CKD patients presenting with ACS when no contraindications are present.

**Angiotensin Blockade**

For patients with ACS, angiotensin-converting enzyme (ACE) inhibitors are recommended by current guidelines to be initiated and continued indefinitely in all patients with a left ventricular ejection fraction <40% and for those with hypertension, diabetes mellitus, and CKD unless contraindicated. For patients who are considered intolerant to ACE inhibitors, angiotensin receptor blockers (ARBs) can be considered as an alternative. These Class I recommendations are based on data from several large randomized trials and meta-analyses documenting significant reductions in mortality among patients with ACS, in which the greatest benefit was demonstrated when angiotensin blockade was administered within the first 24 hours after an MI. Additionally, receipt of an ACE inhibitor or ARB after ACS for patients with left ventricular systolic dysfunction at the time of hospital discharge has become an important reportable quality performance measure via which many hospitals are compared. Unfortunately, among patients with renal dysfunction, these evidenced-based pharmacotherapies in the hospital and at discharge are often significantly underused, particularly for those with ESRD.

The most common concerns with ACE inhibitors or ARBs include perceived worsening renal function and hyperkalemia. There is no absolute level of SCr that precludes the use of these agents; however, if the SCr exceeds 2.5 mg/dL, caution is warranted. In a review of 12 randomized controlled trials of ACE inhibitor use in patients with renal dysfunction (SCr >1.4 mg/dL), acute increases in SCr of up to 30% that stabilized within the first 2 months of therapy initiation were associated with a 55% to 75% risk reduction in renal disease progression compared with those with normal renal function. Practically, the use of ACE inhibitors or ARBs can be considered in patients with CKD as long as the SCr does not increase beyond this point and the serum potassium remains <5.5 mEq/L. For patients with ESRD, the administration of these medications can be problematic. The use of ACE inhibitors or ARBs in patients undergoing chronic dialysis has been associated with an increased risk of hyperkalemia, although study results have been variable.

Most of the large randomized controlled trials evaluating the effectiveness of ACE inhibitors or ARBs in post-MI patients with left ventricular dysfunction have excluded patients with ESRD, with SCr cut offs ranging from 2 to 3.4 mg/dL. Nonetheless, the ability of these agents to prevent ventricular dilation and to significantly improve mortality for patients with compromised cardiac function should not be underestimated. Although randomized trials of ACE inhibitor therapy in ACS have systematically excluded patients with ESRD, the Fosinopril in Dialysis (FOSIDIAL) study was undertaken in chronic ESRD patients to assess the impact of fosinopril therapy on cardiovascular events. No significant benefit was seen with fosinopril in the intention-to-treat analysis for the composite of cardiovascular events (RR, 0.93; 95% CI, 0.68–1.26), although a per protocol analysis suggested a trend toward benefit for fosinopril (RR, 0.79; 95% CI, 0.59–1.1). Subgroup analyses from randomized trials and observational studies have suggested that among patients with ACS with reduced left ventricular ejection fraction, the use of ACE inhibitors or ARBs may be more beneficial when renal insufficiency coexists.

Data on the use of ACE inhibitors or ARBs in ACS patients with CKD are summarized in Table 9. In summary, the data on the use of ACE inhibitors in patients with post-MI left ventricular dysfunction and CKD consistently show improved outcomes with ACE inhibitor therapy. Caution is warranted at the time of initiation, and monitoring of serum creatinine and potassium is required.

**Aldosterone Receptor Antagonists**

According to the American College of Cardiology/American Heart Association guidelines, the use of aldosterone antagonists such as spironolactone and eplerenone have a Class I recommendation for post-MI patients who are receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a left ventricular dysfunction and a 56% relative reduction among those without ESRD.
Table 8. Summary of β-Blocker Studies in Patients With ACS and CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
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<tbody>
<tr>
<td>Wall et al⁵⁴</td>
<td>Post hoc analysis of pooled data from 2 RCTs (CAPRICORN and COPERNICUS)</td>
<td>4217 patients with either post-MI left ventricular dysfunction (CAPRICORN) or severe chronic HF (COPERNICUS) randomized to carvedilol or placebo; 46% of patients were from the CAPRICORN trial. Patients categorized based on eGFR: eGFR &gt;60 mL/min/1.73 m² (n=1,651), eGFR ≤60 (n=2,566). Among those with eGFR ≤60, 1,116 had an eGFR &lt;45 mL/min/1.73 m²</td>
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<tr>
<td>Yan et al⁵⁵</td>
<td>Observational, prospective cohort study</td>
<td>3510 patients hospitalized for ACS with normal renal function (CrCl ≥90 mL/min; n=1152), mild renal dysfunction (CrCl 60–89 mL/min; n=1253), moderate renal dysfunction (CrCl 30–59 mL/min; n=944), and severe renal dysfunction (CrCl &lt;30 mL/min; n=161)</td>
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<tr>
<td>Wright et al⁵⁶</td>
<td>Observational, retrospective cohort study</td>
<td>3106 patients with AMI with no renal disease (n=1320), mild chronic renal insufficiency (CrCl &gt;50 but ≤75 mL/min; n=860), moderate renal dysfunction (CrCl &gt;35 but ≤50 mL/min; n=491), severe renal insufficiency (CrCl &lt;35 mL/min; n=391), or ESRD (n=44)</td>
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<tr>
<td>Bae et al⁵⁷</td>
<td>Observational, retrospective analysis of KAMIR cohort</td>
<td>13901 consecutive patients with AMI divided into strata based on eGFR: ≥90 (n=3491; reference), ≥60 to &lt;90 (n=5791), ≥30 to &lt;60 (n=2609), ≥15 to &lt;30 (n=439, group 4), and &lt;15 (n=306, group 5) mL/min/1.73 m²</td>
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<tr>
<td>Keough-Ryan et al⁵⁸</td>
<td>Observational cohort</td>
<td>5549 consecutive patients with ACS. Renal function classified as ≥80 (n=14300), 60–80 (n=2018), 30–59 (n=1795), and &lt;30 (n=306) mL/min/1.73 m²</td>
</tr>
<tr>
<td>Berger et al⁵⁹</td>
<td>Observational, retrospective analysis of CCP and USRDS</td>
<td>AMI patients: 145 740 patients without ESRD and 10 252 patients with ESRD receiving dialysis</td>
</tr>
<tr>
<td>McCullough et al⁶⁰</td>
<td>Observational, prospective cohort study</td>
<td>1724 patients with STEMI. Renal function was classified by quartile corrected creatinine clearance: &gt;81.5 mL/min (n=524), 63.1 to ≤81.5 (n=421), 46.2 to ≤63.1 (n=421), ≤46.2 not undergoing dialysis (n=310), and chronic dialysis (n=47)</td>
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<tr>
<th>All-end Points (primary)</th>
<th>Cardiovascular mortality, HF mortality</th>
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<tr>
<td>No statistically significant interactions were observed between the randomized treatment and the study type for each clinical outcome. Adjusted HRs (95% CI) for carvedilol treatment were as follows: All-cause mortality: eGFR &gt;60: 0.59 (0.43–0.81); eGFR ≤60: 0.78 (0.64–0.95). In the subgroup with eGFR &lt;45, HR was 0.94 (95% CI, 0.72–1.23). Cardiovascular mortality: eGFR &gt;60: 0.59 (0.42–0.82); eGFR ≤60: 0.77 (0.62–0.94).</td>
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<tr>
<td>Short- and long-term survival stratified by CrCl</td>
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<td>β-Blockers were associated with improved 1-y survival to a similar extent among those with normal and impaired renal function. Discharge β-blocker use–adjusted OR, 0.76 (95% CI, 0.56–1.02), P=0.07; P=0.37 for heterogeneity across CrCl &lt;60 vs ≥60 mL/min.</td>
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<td>Short- and long-term MACE</td>
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<td>Use of β-blockers, ACE inhibitors, and statins (analyzed together) was associated with decreased risk of short- and long-term MACE. HRs (95% CIs) improved across the spectrum of renal impairment when discharge medication use was added to model that included age, Killip class &gt;1, diabetes mellitus and hypertension, hs-CRP, and PCI. Group 2: 0.93 (0.79–1.09) vs 0.97 (0.82–1.14); group 3: 1.58 (1.32–1.90) vs 1.73 (1.44–2.07); group 4: 2.12 (1.63–2.75) vs 2.26 (1.74–2.93); and group 5: 2.50 (1.89–3.29) vs 2.69 (2.04–3.56). Additionally, 1-mo and 1-y MACE were improved in a stepwise fashion with 3 medications vs 2 medications vs 1 medication vs no medications.</td>
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<tr>
<td>Death, secondary outcomes length of stay, surgical interventions</td>
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<tr>
<td>Discharge β-blockers were associated with significant reduction in mortality (HR, 0.91; 95% CI, 0.855–0.97), with no interaction with degree of renal impairment (P=0.10).</td>
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<tr>
<td>Mortality (30 d)</td>
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<td>β-Blocker therapy was associated with a 40% relative reduction in mortality in those receiving dialysis (P&lt;0.001) and a 56% relative reduction among those without ESRD (P&lt;0.001).</td>
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<tr>
<td>In-hospital mortality</td>
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<tr>
<td>Adjusted RR reduction for the combination of in-hospital aspirin and β-blocker was 80%, 74.9%, 69%, 64.3%, and 77.9% across the quartiles of corrected CrCl, respectively.</td>
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</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAPRICORN, Carvedilol Postinfarct Survival Control in Left Ventricular Dysfunction; CCP, Cooperative Cardiovascular Project; CI, confidence interval; CKD, chronic kidney disease; COPERNICUS, Carvedilol Prospective Randomized, Cumulative Survival; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; KAMIR, Korean Acute Myocardial Infarction Registry; MACE, major adverse cardiovascular events; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; STEMI, ST-segment–elevation myocardial infarction; and USRDS, United States Renal Data System.

*Glomerular filtration rate calculated by the modified Modification of Diet in Renal Disease equation.
†CrCl calculated via Cockcroft-Gault equation.
‡Corrected CrCl calculated as (140–age)/serum creatinine, multiplied by 0.85 if female.
ejection fraction <40%, and have either diabetes mellitus or heart failure.^37 These recommendations are primarily derived from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) trial, which demonstrated a 15% all-cause mortality risk reduction (P=0.008) and a 13% reduction in cardiovascular-related mortality or cardiovascular hospitalizations (P=0.002) among post-MI patients with a left ventricular ejection fraction ≤40% who received eplerenone 25 to 50 mg/d in addition to background heart failure therapy with an ACE inhibitor or ARB and β-blocker.123 However, important exclusion criteria for the EPHESUS trial were CrCl >2.5 mg/dL or a serum potassium >5.0 mEq/L. Serious hyperkalemia (≥6.0 mEq/L) occurred in 5.5% of patients receiving eplerenone compared with 3.9% in the placebo group (P=0.002). For patients with CrCl <50 mL/min, the incidence of serious hyperkalemia increased to 10.1% among those receiving eplerenone compared with 5.9% in the placebo group (P=0.006). Since the publication of the Randomized Aldactone Evaluation Study (RALES), concerns have been raised regarding the increased risk of life-threatening hyperkalemia attributable to aldosterone antagonists, particularly when combined with angiotensin blockade.124 Therefore, the American College of Cardiology/American Heart Association guidelines recommend against using aldosterone blockade if significant renal dysfunction (SCr >2.5 mg/dL in men and >2.0 mg/dL in women) or hyperkalemia (serum potassium >5.0 mEq/L) coexists.57

A post hoc analysis of the EPHESUS trial evaluated serial changes in eGFR related to eplerenone use in patients after ACS. In this analysis, Rossignol et al125 found that 5792 patients assigned to eplerenone 25 to 50 mg/d had a significant decline in their eGFR, with a mean adjusted difference of −1.4±0.3 mL/min·1.73 m−2 compared with placebo (P<0.0001). This effect occurred within the first month and persisted throughout the 24-month follow-up. Patients receiving eplerenone had

### Table 9. Summary of ACE Inhibitor Studies in Patients With ACS and CKD

<table>
<thead>
<tr>
<th>Study</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Frances et al, 2000118</td>
<td>Observational, retrospective cohort of the CCP database</td>
<td>20,902 Medicare beneficiaries admitted for MI with LVEF &lt;40%; 19,320 with SCR ≤3 mg/dL and 1582 with SCR &gt;3 mg/dL</td>
<td>All-cause mortality (1 y)</td>
<td>In the multivariate analysis, the HR (95% CI) for ACE inhibitor therapy at hospital on discharge on mortality at 1 y was 0.84 (0.77–0.92) in those with SCR ≤3 mg/dL and 0.63 (0.48–0.84) in those with SCR &gt;3 mg/dL.</td>
</tr>
<tr>
<td>Shlipak et al, 2001122</td>
<td>Observational, retrospective analysis of the CCP database</td>
<td>20,902 Medicare beneficiaries admitted for MI with LVEF &lt;40%. SCR ≥2 mg/dL was seen in 4133 patients.</td>
<td>All-cause mortality (1 y)</td>
<td>In the multivariate analysis, ACE inhibitor exposure was associated with a 23% increase in 1-y survival for patients with SCR ≥2 mg/dL (HR, 0.77; 95% CI, 0.66–0.90).</td>
</tr>
<tr>
<td>Berger et al, 200319</td>
<td>Observational, retrospective cohort using ESRD and CCP database</td>
<td>145,740 patients without ESRD and 1025 patients with ESRD admitted for MI using peritoneal dialysis or hemodialysis before admission</td>
<td>All-cause mortality (30 d)</td>
<td>Compared with ESRD patients not receiving an ACE inhibitor, those with ESRD receiving an ACE inhibitor exhibited a 48% lower 30-d mortality (P&lt;0.001).</td>
</tr>
<tr>
<td>CATS19</td>
<td>Post hoc analysis of an RCT</td>
<td>298 patients with a first anterior wall MI</td>
<td>Change in GFR* from baseline over a 12-mo period</td>
<td>Patients receiving captopril had an annual decline of only 0.5 mL/min in GFR vs 5.5 mL/min in the placebo group (P&lt;0.05). Patients with compromised renal function at baseline (&lt;81 mL/min) had the greatest improvement in GFR.</td>
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<tr>
<td>SAVE131</td>
<td>Post hoc analysis of an RCT</td>
<td>2183 patients with LVEF ≤40% post-MI with SCR &lt;2.5 mg/dL. Patients were grouped by eGFR*: eGFR &gt;60 (n=1464) and eGFR &lt;60 mL·min⁻¹·1.73 m⁻² (n=719).</td>
<td>All-cause and cardiovascular mortality and morbidity stratified by GFR* (4 y)</td>
<td>The relative risk reduction for all-cause cardiovascular mortality/morbidity, the relative risk reduction was higher for those treated with captopril with CKD than for those without CKD (31% vs 20%, respectively; P=0.29 for interaction).</td>
</tr>
<tr>
<td>Krause et al, 2004140</td>
<td>Observational, retrospective cohort of the CCP</td>
<td>1342 Medicare beneficiaries post-MI with mild (GFR 60–89), moderate (GFR 30–59), and severe (GFR 15–29 mL·min⁻¹·1.73 m⁻²) renal dysfunction†</td>
<td>300–400-d all-cause mortality</td>
<td>In the adjusted analysis, patients receiving aspirin, β-blocker, and ACE inhibitor exhibited the following reductions in mortality based on renal function: mild, HR 0.54 (95% CI, 0.26–1.12); moderate, HR 0.50 (95% CI, 0.28–0.88); and severe, HR 0.35 (95% CI, 0.09–1.42).</td>
</tr>
<tr>
<td>Reddan et al, 2005103</td>
<td>Post hoc analysis of the SYMPHONY trials</td>
<td>13,707 patients with CKD post-MI grouped based on CrCl: &gt;90 (n=6840), 60–89 (n=5909), and 30–59 mL/min (n=955)</td>
<td>Association between CrCl and 90-d all-cause mortality‡</td>
<td>The interaction between use of ACE inhibitors and CrCl was significantly associated with improved outcomes, with the greatest benefit seen in patients with CrCl of 30–59 mL·min⁻¹·1.73 m⁻² (P=0.0005 for interaction).</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; CATS, Captopril and Thrombolysis Study; CKD, chronic kidney disease; CCP, Cooperative Cardiovascular Project; CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RCT, randomized controlled trial; SAVE, Survival And Ventricular Enlargement study; SCR, serum creatinine; and SYMPHONY, Sibrafiban Versus Aspirin To Yield Maximum Protection From Ischemic Heart Events Post-Acute Coronary Syndromes.

*GFR calculated by the modified Modification of Diet in Renal Disease equation.†GFR calculated via Cockcroft-Gault equation.‡CrCl calculated by modified Modification of Diet in Renal Disease equation.

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a 1.15-fold increased odds of experiencing a >20% decline in eGFR within the first month compared with placebo ($P=0.017$). However, an eGFR $\leq 60$ mL·min$^{-1}$·1.73 m$^{-2}$ was not associated with early worsening renal function, and there was no interaction between worsening renal function and the favorable effects of eplerenone on cardiovascular death or hospitalization ($P=0.77$ for interaction) and hospitalization for heart failure ($P=0.82$ for interaction).125

**Statin therapy**

A large body of literature supports the use of statins after an ACS to reduce the risk of death or vascular events. Current guidelines recommend statins regardless of baseline low-density lipoprotein level in all ACS patients in the absence of contraindications.26,27 With regard to CKD patients, those receiving chronic dialysis in particular, the use of statins has been more controversial. No randomized controlled trials have assessed the safety and efficacy of statins in patients with ACS and CKD. Furthermore, patients with SCr $>2$ mg/dL were excluded from the original ACS randomized trials of early initiation of statins.126,127 However, in primary prevention, randomized trials of statin therapy in patients with CKD have yielded mixed results.128-131 Early studies found no benefit of statin therapy among patients with CKD (mostly dialysis dependent),129-131 which led to speculation that in ESRD, there may be a more advanced atherosclerotic state that leads to more sudden deaths caused by arrhythmias than among patients without ESRD. However, more recently, the largest of these studies, the Study of Heart and Renal Protection (SHARP), included patients with CKD both on dialysis and not on dialysis and showed a benefit of simvastatin plus ezetimibe therapy on the risk of the primary composite end point of first major atherosclerotic event (RR, 0.83; 95% CI, 0.74–0.94; $P=0.002$), although no statistically significant difference was observed for the risk of vascular death (RR, 0.93; 95% CI, 0.80–1.07).128

### Table 10. Summary of Statin Studies in Patients With ACS and CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population</th>
<th>End Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim et al122</td>
<td>Observational, retrospective analysis of KAMIR cohort</td>
<td>12,865 AMI patients; 3256 patients with AMI and renal insufficiency (eGFR $\leq 60$ mL·min$^{-1}$·1.73 m$^{-2}$) were included; 2218 were taking statins and 1038 were not</td>
<td>Death and complications during hospital course</td>
<td>Adjusted for covariates, HR (95% CI) 2.2 (1.696–2.881); $P&lt;0.001$ in renal dysfunction group with no statin therapy vs other groups. For eGFR $&lt;30$ but $\geq 15$ mL·min$^{-1}$ and no statin therapy: HR, 2.0; 95% CI, 1.2–3.5; $P=0.008$. For eGFR $&lt;15$ mL·min$^{-1}$: HR, 2.3; 95% CI, 1.1–4.8; $P=0.036$ compared with statin therapy.</td>
</tr>
<tr>
<td>CARE135</td>
<td>Post hoc analysis of an RCT</td>
<td>1711 participants with CrCl‡ $\leq 75$ mL·min$^{-1}$ with AMI 3–20 mo before randomization randomized to pravastatin or placebo</td>
<td>Death of coronary disease or symptomatic nonfatal MI confirmed by CK</td>
<td>Adjusted for covariates, HR (95% CI) 0.72 (0.55–0.95); $P=0.02$ compared with placebo.</td>
</tr>
<tr>
<td>Keough-Ryan et al127</td>
<td>Observational cohort</td>
<td>5549 consecutive patients with ACS. Renal function classified as $&gt;80$ (n=1430), 60–80 (n=2018), 30–59 (n=1795), or &lt;30 (n=306) mL·min$^{-1}$·1.73 m$^{-2}$‡</td>
<td>Death, secondary outcomes length of stay, surgical interventions</td>
<td>Discharge lipid-lowering therapy was associated with significant reduction in mortality (HR, 0.835; 95% CI, 0.783–0.890) with no significant interaction with degree of renal impairment ($P=0.01$).</td>
</tr>
<tr>
<td>Szummer et al133</td>
<td>Observational analysis of the SWEDEHEART registry</td>
<td>42,814 survivors of MI without statin therapy on admission classified into 5 renal function stages according to eGFR‡: $\geq 90$ (n=9935), 60–89 (n=20135), 30–59 (n=11103), 15–29 (n=1273), and &lt;15 mL·min$^{-1}$·1.73 m$^{-2}$ or undergoing dialysis (n=368)</td>
<td>Mortality at 1 y</td>
<td>Statin therapy was associated with a 37% reduction in risk of death (adjusted HR, 0.63; 95% CI, 0.58–0.69; $P&lt;0.001$). After adjustment, there was a significant interaction between statin therapy and renal function stage ($P&lt;0.001$). Benefit was significant in all groups except those with eGFR $&lt;15$ mL·min$^{-1}$·1.73 m$^{-2}$ or undergoing dialysis Adjusted HRs (95% CI) across the groups were as follows: 0.53 (0.41–0.67), 0.60 (0.52–0.68), 0.67 (0.60–0.76), 0.72 (0.66–0.94), and 1.13 (0.76–1.67) in ≥90, 60–89, 30–59, 15–29, and $&lt;15$ mL·min$^{-1}$·1.73 m$^{-2}$/dialysis, respectively.</td>
</tr>
<tr>
<td>Shibui et al134</td>
<td>Observational cohort</td>
<td>501 patients presenting with ACS who underwent successful PCI; 324 patients (64.7%) had CKD based on eGFR $&lt;60$ mL·min$^{-1}$·1.73 m$^{-2}$. Statin therapy was used in 34.3% of patients with CKD.</td>
<td>Composite end point of cardiac death or readmissions for ACS over a mean follow-up of 5.2 y</td>
<td>The composite end point occurred in 16.2% of CKD patients treated with statins compared with 26.3% of CKD patients not treated with statin therapy (HR, 0.58; 95% CI, 0.34–0.90; $P=0.039$).</td>
</tr>
</tbody>
</table>

*Glider filtration rate calculated via Cockcroft-Gault equation.
†CrCl calculated by modified Modification of Diet in Renal Disease equation.
‡Glider filtration rate calculated by the modified Modification of Diet in Renal Disease equation.

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; CARE, Cholesterol and Recurrent Events trial; CI, confidence interval; CK, creatine kinase; CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KAMIR, Korean Acute Myocardial Infarction Registry; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; and SWEDEHEART, Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.

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**CARE** et al

Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.

MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; and SWEDEHEART, Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.

Circulation 1142 March 24, 2015

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Summary/Future Directions

In patients presenting with ACS, declining renal function has been associated with increased risk for adverse clinical outcomes, including death, MI, and bleeding events. In spite of the high risk of adverse events in this population, CKD patients have largely been excluded from or underrepresented in randomized controlled trials in patients presenting with ACS. This presents a challenging situation for clinicians to make evidence-based medication choices, as well as for understanding the risk and benefits of different therapy combinations. Taken collectively, the available data suggest that patients with CKD benefit from the evidence-based medications routinely used in all patients presenting with ACS (Table 11); however, important considerations are necessary to provide the greatest benefit while limiting the chance for harm. These would include careful assessment of renal function, use of a validated equation for dose adjustment of medications, avoidance of medications that are contraindicated in patients with stage 4 and 5 CKD, and avoidance or limiting of the use of emerging medications that have not been formally studied in patients with CKD.

Currently, the US Food and Drug Administration provides guidance and recommendations for the pharmaceutical industry on the design and conduct of pharmacokinetic studies in patients with impaired renal function. However, moving forward, inclusion and better representation of patients with CKD in randomized clinical trials will be necessary to accurately assess the risks and benefits of medications in this population.
Disclosures

Writing Group Disclosures

<table>
<thead>
<tr>
<th>Writing Group Member</th>
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†Significant.
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**References**


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