Antithrombotic Therapy in Patients With Chronic Kidney Disease

Davide Capodanno, MD, PhD; Dominick J. Angiolillo, MD, PhD

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Chronic kidney disease (CKD) is a pandemic public health problem, with >500 million people worldwide estimated to have some form of kidney injury. Survey data suggest that the prevalence of CKD in the United States has increased between 1988 to 1994 and 1999 to 2004 from 10% to 13%, reaching a rate of 14% in 2010. This underscores the importance of antithrombotic therapy. Unfortunately, dosing errors, which remain a challenge in patients with CKD treated with antithrombotic therapy. In particular, a description of thrombosis and hemostatic profiles that characterize CKD patients, considerations for use of antithrombotic agents, including antiplatelet and anticoagulant therapies, and a review of the safety and efficacy data in CKD patients in the settings of coronary artery disease manifestations and atrial fibrillation are provided. A discussion of antithrombotic therapy in patients with acute kidney injury and end-stage renal disease is beyond the scope of this article.

CKD: Definitions

The Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation defines CKD as either kidney damage or a decreased kidney glomerular filtration rate (GFR) of $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ for $\geq 3$ months. The different stages of CKD are listed in Table 1. While stages 3 through 5 are characterized by a gradient of GFR ranges, markers of structural or functional kidney damage other than GFR, including blood, urine, or imaging tests abnormalities, need to be present to establish a diagnosis of stage 1 and stage 2 CKD. Kidney failure is defined as either a GFR of $<15 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ or a need for initiation of kidney replacement therapy (dialysis or transplantation). End-stage renal disease is a US administrative definition that includes patients treated by dialysis or transplantation regardless of the GFR level. Many calculators are available to estimate the GFR. The National Kidney Foundation recommends using the Modification of Diet in Renal Disease equation.

Thrombosis and Hemostasis: Biological Considerations in Patients With CKD

Patients with CKD may present with platelet dysfunction and abnormalities in the enzymatic coagulation cascade. This may explain why patients with CKD may experience 2 opposite hemostatic complications: bleeding diathesis and thrombotic tendencies.

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Platelet dysfunction has been suggested to be the main factor responsible for hemorrhagic tendencies in advanced CKD and is likely to be multifactorial.\textsuperscript{11–13} First, a defective platelet adhesion to subendothelium caused by decreased membrane expression of glycoprotein (GP) Ib receptors leads to impaired platelet-vessel interactions.\textsuperscript{24–26} Second, platelets of patients with CKD reveal an aggregation defect at least partially attributable to decreased GPIIb/IIIa receptor expression with intrinsic dysfunction and the presence of a putative uremic toxin that inhibits fibrinogen binding to GPIIb/IIIa.\textsuperscript{27–29} Finally, several intrinsic platelet abnormalities have been described, including secretion defects related to impaired arachidonic acid release from platelet phospholipids and a storage pool defect.\textsuperscript{30} Lower mean content of adenosine diphosphate and \textbeta-thromboglobulin,\textsuperscript{31,32} reduced sensitivity to platelet agonists,\textsuperscript{33,34} and decreased thromboxane A\textsubscript{2} synthesis.\textsuperscript{35} Overall, the normal platelet response to vessel wall injury with platelet activation, recruitment, adhesion, and aggregation (primary hemostasis) is defective, likely as a consequence of uremic toxins present in the circulating blood.\textsuperscript{36}

On the other hand, uremic platelets may also display some features of procoagulant activity such as increased thrombin generation, phosphatidylserine exposure, and higher concentrations of von Willebrand factor\textsuperscript{11–13,37} and platelet-derived microparticles.\textsuperscript{38} These microparticles are small vesicles with procoagulant activity released by activated platelets that are enriched with membrane receptors for coagulation factor Va and provide a competent catalytic surface for the prothrombinase reaction, thereby contributing to the acceleration of thrombin generation.\textsuperscript{38} These abnormalities, although less characterized than functional defects contributing to the bleeding tendency observed in uremic patients, contribute to explain why patients with CKD may also present with a greater propensity to platelet aggregation. Importantly, patients with stage 3 to 4 CKD may present with significantly enhanced platelet activation and aggregation as assessed by multiple markers compared with those with stage 1 to 2 CKD, as well as a higher prevalence of high on-aspirin and on-clopidogrel platelet reactivity.\textsuperscript{39–43}

As far as the enzymatic coagulation cascade is concerned, hemostatic abnormalities consistent with a hypercoagulable state have been widely described in patients with end-stage renal disease on hemodialysis. These plasmatic abnormalities include increased fibrinogen, D-dimer, and prothrombin fragments.\textsuperscript{44–46} Likewise, plasma procoagulant activities of fac-

### Table 1. Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR, $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{m}^{-2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>$&gt;90$</td>
</tr>
<tr>
<td>2</td>
<td>Mild reduction in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduction in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduction in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>$&lt;15$</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate. Adapted from the National Kidney Federation\textsuperscript{21} with permission from the publisher. © 2002, Elsevier BV.

### Table 2. Pharmacokinetic Parameters Affected by Chronic Kidney Disease

- Increased bioavailability
- Increased distribution
- Prolonged time to reach maximum drug concentration
- Prolonged half-life
- Reduced excretion

**Pharmacological Issues and Dose Adjustment in Patients With CKD**

Guidelines and summaries of product characteristics drive guidance of dosing for patients with varying renal function.\textsuperscript{53–56} The summaries provide the medicolegal reference for the responsibility of the manufacturer when dosing errors are investigated. CKD may affect the pharmacokinetic parameters of antithrombotic drugs in several ways (Table 2). A reduced renal excretion up to 50%, in particular, leads to drug accumulation in almost two thirds of patients.\textsuperscript{57} In parallel, altered pharmacodynamic responses have also been described.\textsuperscript{58} In this section, the mechanism of action of the most commonly prescribed antithrombotic agents, including antiplatelet and anticoagulant therapies, and how they are affected by reduced renal function and dosing considerations are described. A summary of recommendations for dose adjustment of antithrombotic therapies in patients with CKD is provided in Tables I and II in the online-only Data Supplement.

**Antiplatelet Therapies**

**Aspirin**

Aspirin selectively and irreversibly acetylates cyclooxygenase-1, thereby blocking the formation of thromboxane $\text{A}_2$ in platelets.\textsuperscript{59} Aspirin is eliminated mainly by hepatic metabolism but is also excreted unchanged in the urine to an extent that depends on the dosage and urinary pH. Prostaglandin-induced vasodilatation is important in maintaining renal blood flow in subjects with CKD.\textsuperscript{60} By inhibiting the synthesis of renal prostaglandins, aspirin makes CKD patients vulnerable to further deterioration in renal function. For the above reasons, the package insert recommends that aspirin should be avoided in patients with severe renal impairment.\textsuperscript{61} However, although this recommendation is followed for primary prevention, in patients with coronary artery disease manifestations, low-dose aspirin (<100 mg) is still used in clinical practice even in the presence of severe renal impairment. Nonsteroidal anti-inflammatory drugs other than aspirin and paracetamol are associated with disease progression.
and should be avoided in patients with CKD owing to further decrease in volume of renal blood flow resulting from decreased prostaglandin synthesis and, less frequently, acute interstitial nephritis.62

**P2Y12 Receptor Antagonists**

Thienopyridines (ie, clopidogrel, prasugrel) and cyclopyren-triazolopyrimidines (ie, ticagrelor) are irreversible and reversible inhibitors, respectively, of the platelet adenosine diphosphate P2Y12 receptor, which is a key signaling pathway of platelet activation. Therapeutic experience with P2Y12 receptor antagonists is limited in patients with stage 4 to 5 CKD. The summary of product characteristics of clopidogrel recommends caution when using clopidogrel in the CKD population.63

The pharmacokinetics of the active metabolite of prasugrel is similar in patients with normal and in those with impaired renal function. In patients with stage 5 CKD, exposure to the active metabolite of prasugrel is about half that of healthy control subjects and patients with stage 3 CKD, but this issue does not translate into significant changes in platelet aggregation after ADP stimuli.64 As a result, the summary of product characteristics of prasugrel does not recommend dose adjustment based on renal function while warning that there is limited experience with prasugrel in patients affected by stage 5 CKD. The metabolism and excretion of ticagrelor depend minimally on the kidneys.65 Although the mechanism has not been elucidated, creatinine levels may increase during treatment with ticagrelor, especially in patients >75 years of age, those with stage 3 to 4 CKD at baseline, and those receiving concomitant treatment with angiotensin receptor blockers, warranting that creatinine levels be monitored 1 month after treatment initiation.65 The summary of product characteristics of ticagrelor does not recommend dose adjustment based on renal function, but like clopidogrel and prasugrel, use in patients with stage 5 CKD is not recommended because of the lack of data in this specific subpopulation. The pharmacokinetics of cangrelor, the first parenteral P2Y12 receptor antagonist not yet approved for use in the US, is similar in patients with normal and in those with impaired renal function. In patients with stage 5 CKD, exposure to the active metabolite of prasugrel and ticagrelor is limited experience with prasugrel in patients affected by stage 5 CKD.63

**Protease-Activated Receptor Type 1 Antagonists**

There were no significant changes in the results of laboratory tests, including kidney function, in preclinical testing of vorapaxar and atorapaxar, 2 thrombin receptor antagonists currently under more advanced clinical testing for the treatment and prevention of arterial thrombosis.66

**GPIIb/IIIa Inhibitors**

No dose adjustment based on renal function is required for abciximab because of the rapid removal of free drug from the circulation by the reticuloendothelial system.70 However, because the potential risk of bleeding is increased in patients with stage 4 CKD, the use of abciximab in CKD patients should be considered only after careful appraisal of the risks and benefits. In patients with stage 3 to 4 CKD, the clearance of eptifibatide is reduced by ~50%, and steady-state plasma levels are approximately doubled. The maintenance dose of eptifibatide should therefore be reduced from 2.0 to 1.0 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) in patients with creatinine clearance \( \geq 30 \) to <50 mL/min.71 Use in patients with more severe renal impairment is contraindicated. Renal excretion also contributes significantly to the elimination of tirofiban.72 As a result, in patients with stage 4 CKD, the infusion rate of tirofiban should be adjusted from 0.1 to 0.05 \( \mu g \cdot kg^{-1} \cdot min^{-1} \).73

**Anticoagulant Therapies**

**Indirect Thrombin Inhibitors**

Unfractionated heparin is metabolized primarily in the liver and endothelium, thereby not requiring dose adjustment in stage 4 to 5 CKD.73 Conversely, enoxaparin, the most extensively studied low-molecular-weight heparin, is eliminated predominantly via the renal pathway. Although monitoring of anticoagulation activity and dose adjustment of enoxaparin are not required in patients with stage 2 to 3 CKD, those with stage 4 CKD experience decreased clearance of enoxaparin and drug accumulation, leading to increased half-life, drug exposure, and bleeding risk.74 As a consequence, guidelines recommend extending the dosing interval of the maintenance dose of enoxaparin (1.0 mg/kg) from 12 to 24 hours in patients with stage 4 CKD presenting with an acute coronary syndrome (ACS).55 Given the concerns of overdosing, many clinicians in clinical practice consider this dose-adjusted regimen even in patients with stage 3 CKD.

**Direct Thrombin Inhibitors**

Bivalirudin is cleared from plasma by a combination of renal mechanisms and enzymatic cleavage. Because drug elimination is linearly related to GFR, the infusion dose of bivalirudin may need to be reduced in patients with advanced CKD. In particular, dose adjustment from 1.75 to 1.0 or 0.25 mg · kg\(^{-1} \) · h\(^{-1} \) should be considered in patients with stage 4 or 5 CKD, respectively.75

**Parenteral Anti–Factor Xa Inhibitors**

Fondaparinux is eliminated mainly as unchanged drug by the kidneys in subjects with normal kidney function.76 Conversely, the clearance of fondaparinux decreases with increased renal impairment.73,77 No dose reduction is required for patients with stage 2 to 3 CKD, whereas fondaparinux should be avoided in patients with stage 4 CKD.78 Otamixaban, another parenteral factor X inhibitor under advanced phase clinical testing, exhibits mixed renal and biliary excretion with constant renal clearance.79

**Oral Anticoagulants: Vitamin K Antagonists and Novel Anti–Factor II and Anti–Factor X Antagonists**

Warfarin and acenocoumarol (vitamin K antagonists) elimination is not governed primarily by the kidneys. Nonetheless, careful dosing and more frequent international normalized ratio monitoring have been recommended in patients with stage 3 CKD because of the higher baseline risk of bleeding complications.73 The respective summaries of product characteristics contraindicate vitamin K antagonists in patients with stages 4 to 5 CKD,80 although they are still often used...
judiciously in clinical practice to prevent thromboembolic recurrences.

Dabigatran is a direct thrombin inhibitor approved for clinical use in patients with atrial fibrillation but not ACS. Elimination of dabigatran is predominantly (85%) via the renal pathway, with \( \approx 80\% \) of the administered dose excreted unchanged in the urine (Figure 1). Limited data are available on dabigatran pharmacokinetics in patients with CKD. However, increased drug exposure, decreased clearance, and increased coagulation have been reported with decreased renal function. For patients with stage 4 CKD, whom exposure is increased by a factor of 6, dose adjustment to 75 mg twice daily is recommended by the Food and Drug Administration (FDA) on the basis of pharmacokinetic and pharmacodynamic considerations more than safety or efficacy data. However, other regulatory boards, including the European Medicine Agency, issued a recommendation on the 110 mg twice-daily dose for use on an individual basis and at the physician’s discretion in patients with low thromboembolic and high bleeding risks. Both the FDA and European Medicine Agency labels of dabigatran have recently been updated to advise physicians to assess renal function before starting therapy and to test it annually in patients >75 years of age and those with creatinine clearance <50 mL/min. In addition, the FDA label now states that physicians should consider using the 75 mg twice-daily dose in patients with creatinine clearance of 30 to 50 mL/min who are also taking dronedarone or systemic ketoconazole. The concomitant use of dabigatran and GPIIb/IIIa inhibitors should be avoided in patients with stage 4 CKD.

Different daily doses and regimens (once or twice daily) of rivaroxaban have been used in pivotal phase II and III trials of atrial fibrillation (20 mg daily) and ACS (2.5–10 mg twice daily). The approved dose of rivaroxaban for atrial fibrillation is 20 mg once daily. A dose modification from 20 to 15 mg once daily is required in atrial fibrillation patients with creatinine clearance <50 mL/min, whereas rivaroxaban is not recommended in patients with stage 5 CKD. Rivaroxaban is not yet approved for ACS. Other orally active direct factor Xa inhibitors at advanced stages of clinical development include apixaban and edoxaban, which have predominantly nonrenal clearance and thereby represent potentially interesting alternatives to warfarin and other selective coagulation factor antagonists in CKD patients (Figure 1). Similar to rivaroxaban, a range of different daily doses of apixaban has been used in pivotal trials of atrial fibrillation (5–10 mg daily) and ACS (2.5 mg twice daily, 10 mg daily, 10 mg twice daily, 20 mg daily). Apixaban has not yet received approval for clinical use in atrial fibrillation or ACS. Betrixaban, another factor Xa inhibitor in the early stages of development, could also be potentially of increased advantage in CKD patients because it is metabolized in the liver rather than being excreted by the kidney. The development of the oral anti-factor X inhibitor darexaban has recently been discontinued after completion of phase II clinical testing because of difficulty in finding a commercial partner for larger phase III testing and intensified competition in this product area.

**Impact of Antithrombotic Therapies in CKD Patients With Coronary Artery Disease**

**Antiplatelet Therapy**

**Aspirin**

Low-dose aspirin is as effective as higher doses in preventing ischemic events but is also associated with a lower rate of major bleeding and an improved net efficacy-to-safety balance. However, even low-dose aspirin may affect renal function in elderly patients. Few primary or secondary prevention trials specifically addressed the aspirin benefit-to-risk ratio in CKD patients. In the primary prevention Hyper-tension Optimal Treatment (HOT) study, low-dose aspirin therapy was associated with greater absolute reduction in major cardiovascular events and mortality in hypertensive patients with CKD than in those with normal kidney function. This finding can be explained in part by the high baseline risk of CKD patients, thereby translating a similar relative benefit into a greater absolute benefit. Importantly, an increased risk of major bleeding was outweighed by the substantial benefits, and aspirin therapy had no detrimental effect on renal function. Among 2539 patients with type 2 diabetes mellitus and coexisting renal dysfunction enrolled in the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (IPAD) trial, low-dose aspirin therapy did not reduce the primary ischemic end point in patients with stage 1 to 2 CKD compared with those with stage 3 to 4 CKD, suggesting the potential for a differential effect of low-dose aspirin therapy in diabetic patients with mild renal impairment. In an individual patient meta-analysis from the Antithrombotic Trialists’ Collaborative Group that included 105 cardiovascular events in 2704 patients with stage 5 CKD, a 41% odds reduction in the risk of vascular death, myocardial infarction (MI), and stroke with antiplatelet therapy among hemodialysis patients was found compared with a 22% odds reduction seen in the overall study population, although this difference was not statistically significant. Overall, these findings from subgroup analyses support the design of prospective randomized clinical trials of aspirin use for the primary prevention of cardiovascular events in patients with different stages of CKD.

**P2Y12 Receptor Antagonists**

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, the beneficial effect of adding clopidogrel to standard treatment was observed in all 3 tertiles of renal function (lower tertile, <64 mL/min; intermediate tertile, 64–81.2 mL/min; upper tertile, >81.2 mL/min), with a modest absolute and relative reduction in the primary ischemic end point with clopidogrel versus placebo among patients with renal dysfunction compared with those with normal renal function, although without any significant interaction (lower third: relative risk [RR], 0.89; 95% confidence interval [CI], 0.76–1.05); medium third: RR, 0.68; 95% CI, 0.56–0.84; upper third: RR, 0.74; 95% CI, 0.60–0.93; P for interaction = 0.11) (Figure 2). Clopidogrel treatment significantly increased the risk of minor bleeding in all tertiles of renal function. The risk of major or life-threatening bleeding increased moderately with the addition of clopidogrel to
standard treatment (lower third: RR, 1.12; 95% CI, 0.83–1.51; medium third: RR=1.4; 95% CI, 0.97–2.02; upper third: RR, 1.83; 95% CI, 1.23–2.73), but this did not appear to be greatest in those with the lowest renal function. In the Clopidogrel for Reduction of Events During Observation (CREDO) trial, clopidogrel versus placebo reduced the composite end point of death, MI, and stroke in patients with normal renal function, but a trend in the opposite direction was noted in patients with stage 2 to 4 CKD.96 Similarly, a post hoc analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial suggested that clopidogrel may even be harmful in patients with diabetic nephropathy.97 This finding could be attributable to a higher likelihood of clopidogrel resistance among patients with stage 3 to 4 CKD.38–42 Even in CKD patients, the presence of low platelet response to clopidogrel is associated with worse outcomes,98 thus emphasizing the need for novel antiplatelet strategies with a favorable risk-to-benefit profile.

Prasugrel is a new-generation thienopyridine that, because of higher bioavailability, achieves more potent antiplatelet effects than clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON) trial indicated that prasugrel was superior to clopidogrel in reducing the composite endpoint of cardiovascular death, myocardial infarction, or stroke in patients with non-ST-elevation acute coronary syndrome.99

### Table 1: Effect of P2Y<sub>12</sub> Receptor Antagonists on Platelet Function

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hazard Ratio for Efficacy (95% CI)</th>
<th>Total No. of Patients</th>
<th>Primary Endpoint Comparator-Ref (%)</th>
<th>Reduction in Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLOPIDOGREL</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;60 mL/min</td>
<td>999</td>
<td>17.8</td>
<td>13.1</td>
<td>+44</td>
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<tr>
<td>60-90 mL/min</td>
<td>672</td>
<td>10.3</td>
<td>12.8</td>
<td>-20</td>
</tr>
<tr>
<td>&gt;90 mL/min</td>
<td>331</td>
<td>4.4</td>
<td>10.4</td>
<td>-58*</td>
</tr>
<tr>
<td>&lt;64 mL/min</td>
<td>4087</td>
<td>13.4</td>
<td>14.9</td>
<td>-11</td>
</tr>
<tr>
<td>64-81.2 mL/min</td>
<td>4075</td>
<td>7.5</td>
<td>10.8</td>
<td>-32*</td>
</tr>
<tr>
<td>≥81.2 mL/min</td>
<td>4091</td>
<td>6.6</td>
<td>8.8</td>
<td>-26*</td>
</tr>
<tr>
<td><strong>PRASUGREL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 mL/min</td>
<td>1490</td>
<td>15.1</td>
<td>17.5</td>
<td>-14</td>
</tr>
<tr>
<td>≥60 mL/min</td>
<td>11,890</td>
<td>9.0</td>
<td>11.1</td>
<td>-20*</td>
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<tr>
<td><strong>TICAGRELOR</strong></td>
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<tr>
<td>&lt;60 mL/min</td>
<td>3237</td>
<td>17.3</td>
<td>22.0</td>
<td>-23*</td>
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<tr>
<td>≥60 mL/min</td>
<td>11,965</td>
<td>7.9</td>
<td>8.9</td>
<td>-10</td>
</tr>
<tr>
<td>&lt;60 mL/min†</td>
<td>2562</td>
<td>16.4</td>
<td>22.4</td>
<td>-29*</td>
</tr>
<tr>
<td>≥60 mL/min†</td>
<td>12,840</td>
<td>8.5</td>
<td>9.6</td>
<td>-10</td>
</tr>
</tbody>
</table>

*MDRD Estimation.

Figure 1. Pharmacokinetics of novel selective oral anticoagulants. Schematic overview of target, hours to C<sub>max</sub>, half-life, and metabolism for betrixaban, rivaroxaban, edoxaban, apixaban, and dabigatran.

Figure 2. Effect of P2Y<sub>12</sub> receptor antagonists stratified by creatinine clearance. Hazard ratio for efficacy (95% confidence interval [CI]) evaluated as the composite endpoint of cardiovascular death, myocardial infarction, or stroke in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), Clopidogrel for Reduction of Events During Observation (CREDO), Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON), and Platelet Inhibition and Patient Outcomes (PLATO) trials according to renal function calculated with the Cockcroft-Gault equation when not specified or the Modification of Diet in Renal Disease (MDRD) equation when indicated. *A significant relative risk reduction with the study criteria or a significant P value for interaction between subgroups. NA indicates not available. Adapted from Montalescot et al.95
(TRITON-TIMI 38) randomized study documented that, compared with clopidogrel, prasugrel results in a 19% reduction of ischemic events in moderate to high risk ACS patients undergoing percutaneous coronary intervention (PCI). Although in the TRITON-TIMI 38 trial this benefit was partially offset by the increased risk of bleeding, the net clinical benefit (defined as death resulting from any cause, nonfatal MI, nonfatal stroke, and TIMI major hemorrhages) remained in favor of prasugrel. In subjects with stage 3 to 4 CKD, prasugrel was associated with a higher absolute (2.4% versus 2.1%) and a lower relative (14% versus 20%) reduction of the primary end point compared with subjects with normal renal function or stage 1 to 2 CKD. However, in patients with stage 3 to 4 CKD (n = 1490), the incidence of ischemic events was not significantly different between those taking prasugrel and those taking clopidogrel (15.1% versus 17.5%), unlike patients with stage 1 to 2 CKD or normal renal function (n = 11 890; 9.0% versus 11.1%), which is likely a reflection of the smaller number of patients with stage 3 to 4 CKD enrolled in the trial (Figure 2).

Ticagrelor is a novel antiplatelet drug belonging to the family of cyclopentyltriazolopyrimidines that, unlike clopidogrel and prasugrel, requires a dual daily administration and reversibly binds to the P2Y12 receptor. In the Platelet Inhibitor and Patient Outcomes (PLATO) trial, conducted in patients with ACS, ticagrelor reduced the primary composite end point of cardiovascular death, MI, and stroke at 12 months compared with clopidogrel, with similar PLATO-defined major bleedings and higher non–coronary artery bypass grafting–related major bleedings. About 25% of the study population met the general definition of CKD. In subjects with stage 3 to 4 CKD (n = 3237), ticagrelor was associated with a higher absolute (4.7% versus 1.0%) and relative (23% versus 10%) reduction of the primary end point than clopidogrel compared with subjects with normal renal function or stage 1 to 2 CKD (n = 11 965). Consistently with the overall PLATO population, patients with CKD experienced a reduction in mortality (10.0% versus 14.0%; hazard ratio, 0.72; 95% CI, 0.58–0.89). Major bleeding rates, fatal bleedings, and non–coronary bypass–related major bleedings were not significantly relatively increased with ticagrelor compared with clopidogrel in patients with stage 3 to 4 CKD. Importantly, none of the above efficacy and safety outcomes were associated with significant interaction between CKD and treatment, which suggests that the size effect of ticagrelor remains of the same magnitude with or without renal insufficiency (Figure 2). However, when the more contemporary Modification of Diet in Renal Disease formula replaces the Cockcroft-Gault equation for the definition of CKD, a significant P value for interaction arises for the primary end point and mortality. If confirmed, these findings would target patients with stage 3 to 4 CKD as a preferred group for ticagrelor and conversely suggest limited added value of ticagrelor over clopidogrel in patients without stage 3 to 4 CKD. The reasons for a presumptive benefit in CKD are puzzling because they lack physiological explanation. In fact, the clearance of ticagrelor depends minimally on renal function; therefore, other factors (ie, play of chance, inhibition of adenosine reuptake by erythrocytes, differential benefits of intensified platelet inhibition in patients with different risk profiles) may have played a role. In view of the above-mentioned uncertainties, whether a causal and specific effect of ticagrelor exists in patients with stage 3 to 4 CKD needs to be further elucidated.

GPIIb/IIIa Inhibitors

CKD would seem to identify a population of high-risk patients undergoing PCI who could be considered candidates for selective use of GPIIb/IIIa receptor inhibitors. Although abciximab increases the risk of bleeding in all patients submitted to revascularization, there have been some inconsistencies among studies concerning whether the increase in relative risk is significantly greater in patients with CKD. If confirmed, these findings would target patients with stage 3 to 4 CKD as a preferred group for ticagrelor and conversely suggest limited added value of ticagrelor over clopidogrel in patients without stage 3 to 4 CKD. The reasons for a presumptive benefit in CKD are puzzling because they lack physiological explanation. In fact, the clearance of ticagrelor depends minimally on renal function; therefore, other factors (ie, play of chance, inhibition of adenosine reuptake by erythrocytes, differential benefits of intensified platelet inhibition in patients with different risk profiles) may have played a role. In view of the above-mentioned uncertainties, whether a causal and specific effect of ticagrelor exists in patients with stage 3 to 4 CKD needs to be further elucidated.

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In pooled data from abciximab trials, however, there was no difference in the rates of all major bleeding and the 30-day primary end point of death, MI, or urgent intervention in patients with CKD between the abciximab and placebo groups. With tirofiban, the pivotal trials evaluating efficacy and safety excluded patients with serum creatinine > 2.5 mg/dL. Among patients with stage 2 to 3 CKD in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS), tirofiban was well tolerated and effective in reducing ischemic ACS complications, with no evidence of treatment–by–creatinine-clearance interaction. With eptifibatide, no clinical data are available for patients with serum creatinine > 4.0 mg/dL. In the Enhanced Suppression of the Platelet Ib/IIa Receptor With Integrilin Therapy (ESPRIT) trial, a treatment effect of eptifibatide was noted regardless of renal function and trended toward being greater in patients with stage 2 CKD.

Anticoagulant Therapy

Currently approved anticoagulants for treatment of patients with coronary artery disease manifestations include unfractionated heparin, low-molecular-weight heparins, bivalirudin, and fondaparinux. Other agents in advanced stages of clinical development include oral (dabigatran, rivaroxaban and apixaban) and parenteral (otamixiban) anticoagulant agents. The kidneys eliminate most of these drugs. Therefore, assessment of renal function before administration in patients receiving anticoagulants is of primary importance.

A total of 11 881 patients with ACS from the Global Registry of Acute Coronary Events (GRACE) were divided into 3 groups according to creatinine clearance strata. Low-molecular-weight heparin alone was more beneficial than unfractionated heparin alone, regardless of renal status. Bleeding rates were significantly lower with low-molecular-weight heparin plus GPIIb/IIIa inhibitors than with unfractionated heparin plus GPIIb/IIIa inhibitors.

Bivalirudin provides comparable suppression of ischemic events with a decrease in bleeding events compared with heparin and GPIIb/IIIa inhibition. Among 5710 patients referred to PCI from the Second Randomized Evaluation in PCI Linking Bivalirudin to Reduced Clinical Events (REPLACE-2) study, stage 3 to 4 CKD was associated with increased ischemic events, bleeding complications, and 1-year mortality. There was no interaction between treat-
ment assignment, bleeding, or ischemic complications and stage 3 to 4 CKD. In a meta-analysis of 3 randomized trials (n = 5035) comparing bivalirudin with heparin during PCI, the relative benefit of bivalirudin with respect to ischemic and bleeding events was maintained regardless of renal function. The absolute benefit in terms of ischemic and bleeding complications increased with increasing CKD stage (normal renal function or stage 1 CKD, 2.2%; stage 2 CKD, 5.8%; stage 3 CKD, 7.7%; stage 4 CKD, 14.4%; P for trend < 0.001, P for interaction = 0.044).\textsuperscript{113} The authors concluded that bivalirudin provides greater absolute benefit in patients with impaired renal function. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, stage 3 to 4 CKD was present in 2469 of 12,939 randomized ACS patients (19.1%) with baseline creatinine clearance data.\textsuperscript{114} Similar to the overall population, the use of bivalirudin monotherapy in patients with stage 3 to 4 CKD resulted in nonstatistically different ischemic outcomes but significantly less 30-day major bleeding compared with heparin plus a GPIIb/IIa inhibitor. No significant interaction between treatment (bivalirudin or abciximab plus heparin) and renal function (GFR > 83 or \leq 83 mL/min) was found in another trial specifically focusing on patients with non–ST-segment-elevation MI undergoing PCI with regard to the primary net clinical outcome of death, large recurrent MI, urgent target vessel revascularization, or major bleeding at 30 days.\textsuperscript{111}

In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI), stage 3 to 4 CKD was present at baseline in 554 of 3397 patients (16.3%) undergoing primary PCI.\textsuperscript{115} Patients with stage 3 to 4 CKD randomized to bivalirudin monotherapy versus heparin plus GPIIb/IIa inhibitors had no significant difference in major bleeding or death compared with those without stage 3 to 4 CKD.

The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial showed similar efficacy of fondaparinux and enoxaparin in reducing the risk of ischemic events at 9 days. However, fondaparinux substantially reduced major bleeding (2.2% versus 4.1%; odds ratio, 0.52; \textit{P} < 0.001) and 30-day mortality (2.9% versus 3.5%; odds ratio, 0.83; \textit{P} = 0.02).\textsuperscript{116} A post hoc analysis focusing on patients with measured baseline creatinine showed that, in patients with stage 3 to 4 CKD, the benefit of fondaparinux compared with enoxaparin was more marked as a consequence of lower bleeding rates.\textsuperscript{117}

Novel anticoagulants are under clinical testing in the setting of ACS as an adjunct to dual antiplatelet therapy. In the phase II Study of Omacoxaban Versus Unfractionated Heparin and Eptifibatide in Non–ST Elevation Acute Coronary Syndrome (SEPIA-ACS-1), intermediate doses of the new intravenous direct factor Xa inhibitor omacoxaban showed a trend toward lower ischemic end points with a similar rate of bleeding complications compared with unfractionated heparin plus eptifibatide\textsuperscript{118}; however, patients with stage 4 to 5 CKD were excluded from this study. Further testing with omacoxaban (0.08-mg/kg bolus plus infusion at 0.10 or 0.14 mg \textcdot kg\textsuperscript{-1} \textcdot h\textsuperscript{-1}) in a phase III clinical trial is ongoing (NCT01076764). In the phase II Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome (RE-DEEM) trial, dabigatran was associated with a dose-dependent (ranging from 50 to 150 mg twice daily) increase in bleeding events and significantly reduced coagulation activity in patients with a recent MI.\textsuperscript{119} No significant interaction with subgroups based on creatinine clearance was noted, but patients with stage 4 to 5 CKD were not included in the trial. Phase III testing in the setting of ACS is not being pursued with dabigatran. In the phase II Apixaban for Prevention of Acute Ischemic Safety Events (APPRAISE-1) trial, apixaban (2.5 to 20 mg twice daily) resulted in a dose-dependent increase in bleeding compared with placebo in patients with a recent ACS, but a trend toward a reduction in clinically relevant ischemic events was also noted.\textsuperscript{120} However, the phase III Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial did not confirm these ischemic benefits using apixaban at a 5-mg twice-daily dose. In particular, the trial was stopped prematurely after recruiting 7392 of the planned 10,800 patients because an interim analysis showed that the increase in major bleeding with apixaban, including increases in events of fatal and intracranial bleeding, was not counterbalanced by the expected decrease in recurrent ischemic events compared with placebo.\textsuperscript{121} The safety and tolerability of rivaroxaban at total daily doses ranging from 5 to 20 mg in patients with a recent ACS have been the objective of the phase II Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes (ATLAS ACS-TIMI 46) trial.\textsuperscript{122} Clinically significant bleeding was increased in the rivaroxaban groups in a dose-dependent manner. The primary efficacy end point, a composite of death, MI, stroke, or severe recurrent ischemia requiring revascularization, was numerically, albeit nonsignificantly, lower in patients treated with rivaroxaban. Rivaroxaban doses of 2.5 and 5 mg twice daily reduced the risk of the composite end point of death resulting from cardiovascular causes, MI, or stroke in the ATLAS-2 trial with no significant interaction based on CKD stage but also increased the risk of major bleeding and intracranial hemorrhage.\textsuperscript{123} Unlike APPRAISE-2, in which apixaban was tested at the same dose used for atrial fibrillation, a lower dose of rivaroxaban than that used in atrial fibrillation patients was used in the ATLAS-2, with the best benefit, including reduced mortality, observed with a 2.5 mg dose.

**Impact of Antithrombotic Therapies in CKD Patients With Atrial Fibrillation**

CKD may be found in \textasciitilde 35% of patients with atrial fibrillation, with 3.3% of patients presenting with stage 4 to 5 CKD.\textsuperscript{124,125} Although the efficacy of vitamin K antagonists is well established for the prevention of stroke in patients with atrial fibrillation, warfarin is widely underused, at a cost of a greater number of unnecessary disabling strokes and systemic embolisms.\textsuperscript{126} This underuse is explained by a fear of causing fatal bleedings, but some shortcomings of warfarin use, including the need for international normalized ratio monitoring and multiple environmental and genetic factors,\textsuperscript{127} play another relevant role and warrant the development of novel alternatives to warfarin. Importantly, cost issues are going to
factor into the decision-making process with any new anticoagulant.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, patients were randomly assigned to receive 150 mg dabigatran twice daily, 110 mg dabigatran twice daily, or warfarin titrated to achieve an international normalized ratio of 2.0 to 3.0.129 Both dabigatran doses were shown to be noninferior to warfarin with respect to the primary combined end point of stroke or systemic embolisms, but the 150 mg regimen was significantly superior to warfarin and the 110 mg regimen. Bleeding episodes (defined as a reduction in hemoglobin of ≧2 g/dL, need for a transfusion of ≧2 U blood or packed cells, or symptomatic bleeding in a critical area or organ) were less common with dabigatran 110 mg than warfarin and were similar between dabigatran 150 mg and warfarin. Given these findings, in October 2010, only the higher 150 mg dose regimen of dabigatran was approved by the FDA for the reduction of the risk of stroke and systemic embolisms in patients with nonvalvular atrial fibrillation. This decision was affected by benefit-to-risk considerations in which disabling stroke and systemic embolisms are given more weight than nonfatal bleeding events.120 However, because dabigatran is cleared primarily by the kidneys (≏80%), leading to accumulation and hence potentially to more bleeding complications,130 patients with CKD could theoretically benefit from a lower dose. For this reason, the FDA approved a dose of 75 mg twice daily for patients with stage 4 CKD, whereas the European Medicine Agency currently recommends using the lower 110 mg dose used in the RE-LY trial in patients with low thromboembolic risk and high potential for bleeding. Analyses of the RE-LY trial restricted to patients (n=3343) with creatinine clearance ≧30 to <50 mL/min showed that dabigatran concentrations were 2 to 3 times as high as those in patients with normal renal function but the incidence of stroke or systemic embolism was approximately half with 150 mg dabigatran (1.3 per 100 patient-years) compared with 110 mg (2.4 per 100 patient-years) with no significant differences in bleeding (5.3 versus 5.7 major bleeding episodes per 100 patient-years).129 Therefore, even in a population exposed to higher dabigatran concentrations, the benefit-to-risk ratio is in favor of the 150 mg dose. Of note, although no relevant interaction was found between creatinine clearance and the relative risk of the primary outcome with both doses of dabigatran compared with warfarin in the RE-LY trial, patients with stage 4 to 5 CKD were excluded.128 However, patients with stage 4 to 5 CKD are known to be at increased risk for atrial fibrillation owing to structural and electric atrial remodeling.131,132

In the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), >14 000 patients with atrial fibrillation were randomized to 20 mg rivaroxaban once daily (or 15 mg in patients with moderate renal impairment at screening) or to dose-adjusted warfarin (titrated to an international normalized ratio of 2.5). Rivaroxaban was found to be noninferior to warfarin in terms of the combined primary end point of stroke and systemic embolisms and was superior to warfarin in the on-treatment but not in the stricter intention-to-treat analysis, raising concerns about potentially poor adherence with rivaroxaban in real-world practice. In terms of bleeding, the rates of the composite of major and nonmajor clinically relevant bleeding were comparable in the rivaroxaban and warfarin treatment groups, with less fatal bleeding and intracranial hemorrhage observed among patients treated with rivaroxaban. Compared with patients with creatinine clearance ≧50 mL/min, the 2950 patients (20.7%) with creatinine clearance ≧30 to <50 mL/min enrolled in the ROCKET-AF trial were older and had higher event rates regardless of study treatment.133 Among patients with creatinine clearance ≧30 to <50 mL/min, the annualized rates of the primary end point were 2.32% with rivaroxaban 15 mg once daily and 2.77% with warfarin (hazard ratio, 0.84; 95% CI, 0.57–1.23) in the per-protocol population. The intention-to-treat analysis yielded similar results (hazard ratio, 0.86; 95% CI, 0.63–1.17). Major and clinically relevant nonmajor bleeding occurred in 17.82% and 18.28% of patients in the rivaroxaban and warfarin groups (P=0.76). After the results from the ROCKET-AF trial became available, rivaroxaban was recently approved by the FDA for use in the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.134

In the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial, comparing apixaban 5 mg twice daily with warfarin in subjects with atrial fibrillation and risk factors for stroke, the oral direct factor Xa inhibitor apixaban was found to be superior to warfarin for the prevention of stroke and systemic embolism.135 Importantly, apixaban was also associated with less bleeding and lower mortality than warfarin. There was no interaction between treatment type and CKD stage for the primary efficacy outcome (P for interaction=0.72). However, a significant interaction (P=0.03) was found for the primary safety outcome. In particular, patients with stage 3 to 4 CKD appeared to gain a larger risk reduction in major bleeding with apixaban over warfarin compared with patients with stage 1 CKD or those with no renal impairment. Apixaban is currently pending approval by drug-regulating authorities for clinical use.

Recommendations for Clinical Practice
Patients receiving antithrombotic medications should be screened for CKD. General measures to prevent progression of CKD, including control of contributing risk factors (ie, hypertension, diabetes mellitus) and avoidance of potentially nephrotoxic medications, such as nonsteroidal anti-inflammatory drugs, should be considered. The choice and dose of antithrombotic drugs need to be carefully evaluated in patients with CKD. Therefore, patients requiring aspirin therapy should opt for low-dose regimens (<100 mg). Patients requiring a P2Y12 receptor antagonist have the option of choosing clopidogrel (ACS and non-ACS), ticagrelor (ACS), or prasugrel (only ACS undergoing PCI), none of which requires renal dosing adjustments. In addition to defining the clinical setting (ACS versus non-ACS; PCI versus coronary artery bypass graft surgery versus medically managed), patients requiring P2Y12-inhibiting therapy with a
high risk of bleeding should consider using clopidogrel since the more potent agents prasugrel and ticagrelor are both contraindicated in patients at high risk of bleeding. If bleeding risk is less of a concern and should patients require more potent P2Y<sub>12</sub> receptor blockade, then the choice between prasugrel and ticagrelor may depend on the individual patient. Prasugrel is contraindicated in patients with a prior transient ischemic attack/stroke, and should be used with caution in patients with low weight and the elderly, and considered only if patients underwent PCI in the setting of an ACS. Ticagrelor is contraindicated in patients with prior hemorrhagic stroke and severe hepatic impairment, and should be used with precaution in patients treated with potent inhibitors or inducers of CYP3A activity due to drug interactions. Although ticagrelor can be used across the spectrum of ACS, managed both medically and invasively, its use should be carefully considered in patients with poor compliance given its twice-daily administration. Also, aspirin at a maintenance dose >100 mg should be avoided as this has been associated with reduced effectiveness of ticagrelor.

Numerous antithrombotic agents available for parenteral use require dosage adjustments in patients with CKD, which clinicians should be aware of in order to avoid overdosing, and include eptifibatide, tirofiban, bivalirudin, enoxaparin, and fondaparinux. For ACS patients undergoing PCI in whom potent antithrombotic effects are warranted, recent trial data are strongly supportive of the use of bivalirudin, which, compared with GPIIb/IIIa inhibitors, has a similar impact on ischemic events but with significantly less bleeding, making bivalirudin a more desirable agent in this setting. However, if a GPIIb/IIIa inhibitor is chosen, it is important to ensure that dosage adjustments occur in CKD patients when small-molecule GPIIb/IIIa inhibitors (eptifibatide, tirofiban) are used. Long-term oral anticoagulation with warfarin requires careful dosing and more frequent international normalized ratio monitoring in CKD patients. The development of novel antithrombotic agents with a more favorable safety profile may have a promising role in this ever-growing population, but more clinical experience with these agents is warranted before we will be able to define which of them may have a better niche for patients with CKD.

Conclusions

CKD is a frequent consequence of diabetes mellitus, renal disease, or aging. Safety with antithrombotic therapy is a major concern, especially in patients with renal impairment, because of the potential for increased risk of bleeding events. Therefore, understanding strategies of antithrombotic management in patients with CKD is of key importance. The lack of studies performed specifically in patients with impaired renal function, particularly those with acute kidney injury or end-stage renal disease, who are generally excluded from many large-scale clinical trials, often leads to either no recommendation on their most appropriate antithrombotic treatment regimen or sometimes arbitrary assumptions. Overall, the choice and combination of antithrombotic drugs used should be balanced against the individual risk of thrombotic and bleeding complications. Clinical experience with newer agents is still limited, and more data from large-scale clinical trials or even dedicated studies in patients with CKD are warranted.

Disclosures

Dr Angiolillo reports receiving honoraria for lectures from Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly Co, Daiichi Sankyo, Inc, Abbott Vascular, and AstraZeneca; consulting fees from Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly Co, Daiichi Sankyo, Inc, The Medicines Company, Portola, Novartis, Medicure, Accutemetics, Arena Pharmaceuticals, Abbott Vascular, AstraZeneca, Merck, and Evolva; and research grants from Bristol Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Otsuka, Eli Lilly Co, Daiichi Sankyo, Inc, The Medicines Company, Portola, Accutemetics, Schering-Plough, AstraZeneca, and Eisai. Dr Capodanno has received honoraria for lectures from AstraZeneca and Eli Lilly Co.

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