

# Disorders of Hemostasis Associated with Chronic Kidney Disease

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## ABSTRACT

Chronic kidney disease (CKD) is a growing global health problem. CKD is typically associated with a prothrombotic tendency in the early stages of the disease, whereas in its more advanced stage, that is, end-stage renal disease, patients suffer from a prothrombotic tendency and, in many cases, a bleeding diathesis. The exact etiology behind the coexistence of these conflicting hemostatic disorders is poorly understood. This review critically appraises studies examining the abnormalities in the hemostasis pathway in patients with CKD, as well as the therapeutic options that are currently available to treat these individuals.

**KEYWORDS:** Chronic kidney disease, thrombosis, bleeding, hemostatic disorders

Hemostasis is the process that maintains the integrity of the circulatory system after vascular damage. It is a dynamic and tightly regulated process that we are just beginning to understand. Under normal circumstances, vessel wall injury rapidly initiates a series of coordinated events designed to seal the breach generated by the injury. These events lead to clot formation and require both platelet recruitment and activation as well as the generation of thrombin and fibrin.<sup>1</sup> In addition, this process is modulated by multiple mechanisms that contain it, thus preventing the otherwise imminent vascular inflammation and tissue damage.<sup>2</sup> Deficiencies of platelet function or of the coagulation cascade typically lead to bleeding disorders, whereas platelet hyperreactivity and abnormalities in the regulatory mechanisms may result in excessive thrombin formation and pathological thrombosis. Patients at various clinical stages of chronic kidney disease (CKD) display a wide range of derangements in all three aspects of hemostasis, and they experience a wide spectrum of clinical manifestations that lead to consid-

erable morbidity and mortality in this patient population, one that spans prothrombotic tendency leading to excessive cardiovascular events, as well as platelet dysfunction leading to increased bleeding tendency.<sup>3</sup>

This review summarizes the current knowledge on normal hemostasis, abnormalities in hemostatic pathways that have been described in CKD patients, and the different therapeutic options for these individuals as well as their effectiveness.

## NORMAL HEMOSTASIS

The success and normalcy of the clotting process depends on healthy communication between endothelial cells and platelets, and it also relies on a healthy balance between the pathways leading to thrombin-stimulated fibrin clot formation and those of plasmin-induced clot lysis.<sup>2</sup> Under normal conditions, once vascular injury ensues, the subendothelial elements of the vasculature such as collagen and laminin are exposed. Platelets

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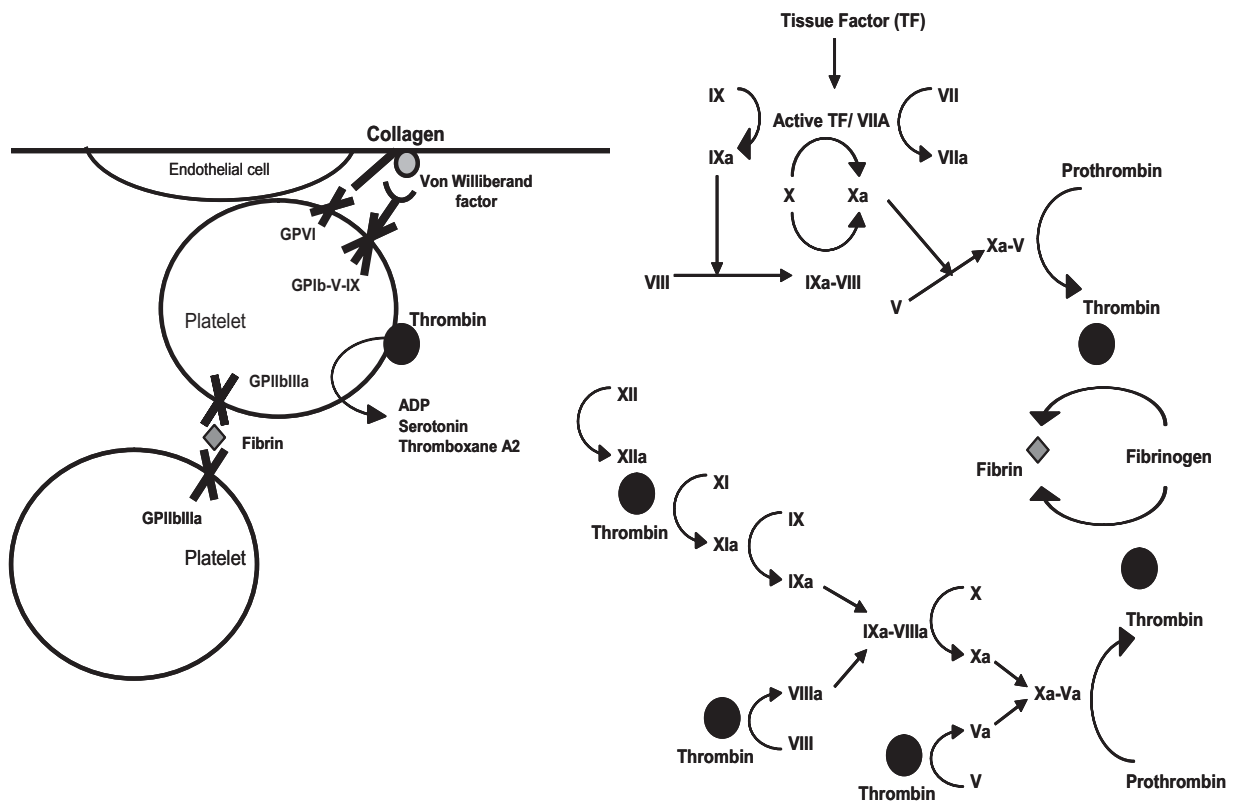
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possess several integrin glycoprotein (GP) receptors, including GP-VI that binds collagen and mediates both platelet adhesion and activation at the site of the injury,<sup>4</sup> and GP Ib-V-IX that interacts with collagen-bound von Willebrand factor (vWF) and is also required for platelet adhesion.<sup>5</sup> In addition to collagen-mediated platelet activation, tissue factor (TF) triggers another distinct and independent pathway for platelet activation where it complexes with the active factor VII (FVIIa), forming a TF/FVIIa complex and initiating a proteolytic cascade by activating factor X, interacting with several enzymes within the haemostasis pathways, and ultimately generating thrombin. Thrombin in its turn binds to its receptor, protease-activated receptor-1, on platelets and results in the release of adenosine diphosphate (ADP), serotonin, and thromboxane A<sub>2</sub>. These platelet agonists amplify the signal for thrombus formation by activating other platelets and recruiting them to the site of clot formation.<sup>1</sup> Thromboxane A<sub>2</sub> is synthesized in the platelets by way of cyclooxygenase (COX)-1 from the arachidonic acid released by the neighboring endothelial cells, and it functions as a platelet agonist and as a vasoconstrictor.<sup>6</sup> Platelet activation also involves a conformational change in GPIIb/IIIa that increases its affinity for fibrinogen and vWF, and as such it enhances platelet-platelet affinity.<sup>7</sup> Other substances released from platelets play important roles, such as fibronectin

that stabilizes platelet aggregates<sup>2</sup> and platelet-derived growth factor, that likely mediates tissue repair physiologically.<sup>8</sup> Fig. 1 shows the pathways involved in platelet aggregation.

Termination of the process of clot formation involves multiple factors including antithrombin (AT), tissue factor pathway inhibitor (TFPI), and the protein C/protein S system. In addition, prostacyclin and nitric oxide (NO) temper platelet reactivity.<sup>2</sup> AT neutralizes most of the enzymes in the coagulation cascade including factors Xa, IXa, XIIa, and thrombin.<sup>9</sup> TFPI forms a complex with factor Xa leading to its inhibition and that of TF/FVIIa. Protein C is activated by a thrombin/thrombomodulin complex that forms as the clot progresses, and once activated acts in concert with protein S to cleave and inactivate factors Va and VIIIa.<sup>10</sup> Prostacyclin is synthesized in the endothelium by COX-2 and antagonizes both platelet aggregation and thromboxane A<sub>2</sub>-mediated vasoconstriction.<sup>11</sup> NO is produced by the endothelium and acts locally to inhibit platelet adhesion and aggregation.<sup>12</sup>

Clot organization and removal is conducted by the proteolytic enzyme plasmin. Its precursor, plasminogen, binds fibrin and tissue plasminogen activator (tPA) and is converted to plasmin. Plasmin cleaves fibrin-releasing fibrin degradation products, including D-dimer. It also cleaves fibrinogen. Its activity is regulated by the



**Figure 1** Different pathways involved in platelet activation, including collagen-induced activation via glycoprotein (GP)VI and tissue factor-induced generation of thrombin. ADP, adenosine diphosphate.

endothelium, which secretes serine protease plasminogen activators (such as tissue-specific plasminogen activator) and plasminogen activator inhibitors (i.e., PAI-1 and PAI-2).<sup>13</sup>

### CHRONIC KIDNEY DISEASE AS A PROCOAGULANT STATE

CKD is a growing global health problem, and although end-stage renal disease (ESRD) is a prominent and much feared complication of the disease, the high mortality rate associated with CKD is mainly due to increased incidence of cardiovascular disease.<sup>14</sup> This is not surprising because CKD patients have a greater prevalence of traditional cardiovascular risk factors such as older age, smoking, hypertension, type 2 diabetes, and obesity (all considered prothrombotic conditions) than the general population.<sup>15</sup>

Several hemostatic abnormalities have been described in patients with even mild CKD in addition to platelet hyperactivity.<sup>16</sup> One report documented impaired release of tPA from the endothelium in patients with CKD despite intact endothelium-dependent vasodilatation.<sup>17</sup> Because acute release of tPA by the endothelium is important in modulating the thrombotic process, the impairment of its release likely affects timely thrombolysis in patients with CKD and may contribute to the hypofibrinolytic state and the increased risk of atherothrombotic events in this patient population. Elevated plasma fibrinogen concentrations are associated with increased cardiovascular risk in the general population<sup>18,19</sup> and may contribute to atherosclerotic plaque growth by increasing plasma viscosity, promoting platelet aggregation, and inducing regional fibrin deposition in the injured endothelium.<sup>20</sup> In CKD patients, plasma fibrinogen concentration is reportedly increased and correlates with systemic markers of inflammation such as C-reactive protein (CRP) and interleukin-6.<sup>21,22</sup> Increased plasma TF levels have also been reported in patients with CKD.<sup>23,24</sup> In addition to its role in platelet activation, TF has been proposed to be an inflammatory mediator because it ultimately activates protease-activated receptor-1 and induces intracellular inflammatory signaling cascades, such as those dependent on nuclear factor  $\kappa$  B, and thus may contribute to the development of atherosclerosis in CKD patients.<sup>25</sup>

Activation of the renin-angiotensin-aldosterone system (RAAS) has been linked to the procoagulant state in patients with hypertension<sup>26</sup> and is well documented in patients with CKD because its pharmacological inhibition has been associated with a reduced risk of cardiovascular morbidity and mortality<sup>27</sup> and with a slower progression of the underlying kidney disease<sup>28,29</sup> in these patients. In particular, activation of RAAS has been associated with increased plasma fibrinogen, D-dimer, and PAI-1 concentrations in hypertensive

**Table 1 Main Hemostatic Abnormalities in Patients with Chronic Kidney Disease**

1. Increased tissue factor
2. Increased von Willebrand factor
3. Increased factor XIIa
4. Increased factor VIIa
5. Increased activated protein C
6. Increased fibrinogen
7. Reduced tissue plasminogen activator
8. Increased plasminogen activator inhibitor 1

patients, and fibrinogen and PAI-1 specifically have been associated with evidence of end-organ damage including cardiac and renal disease.<sup>30</sup> Plasma PAI-1 levels are elevated in patients with diabetic kidney disease in association with endothelial dysfunction and inflammation.<sup>31</sup> Experimentally, PAI-1 inhibits plasmin-dependent extracellular matrix turnover, stimulates infiltration of macrophages and myofibroblasts, and regulates transforming growth factor  $\beta$ 1 expression, and hence may play a pathogenetic role in the progression of kidney disease<sup>32</sup> and atherosclerosis.<sup>33</sup>

Other reported hemostatic abnormalities may include elevated plasma levels of vWF and thrombomodulin<sup>34</sup> in the context of endothelial dysfunction, increased FXIIa and FVIIa activities,<sup>35</sup> and increased activated protein C complex levels,<sup>36</sup> as well as increased levels of thrombin-antithrombin complex levels and reduced antithrombin activity.<sup>37</sup> Table 1 summarizes the hemostatic abnormalities reported in patients with CKD.

Although patients with CKD express hemostatic abnormalities that suggest impaired fibrinolysis and enhanced prothrombosis, it remains unclear whether these markers of procoagulation such as increased fibrinogen, PAI-1, or TF may play a direct role in the development of atherothrombotic complications or whether they interplay with other traditional and non-traditional risk factors for cardiovascular disease in this set of patients. Similarly, their impact on the progression of underlying CKD is unknown.

### END-STAGE RENAL DISEASE AND INCREASED RISK OF BLEEDING

As CKD advances, the procoagulant abnormalities such as impaired release of tPA, increased PAI-1,<sup>33</sup> elevated fibrinogen and D-dimer,<sup>22</sup> and increased TF/FVIIa persist,<sup>35</sup> but in addition, patients start to exhibit platelet dysfunction that typically manifests with an increased risk of cutaneous, mucosal, or serosal bleeding. Several factors are thought to contribute to platelet dysfunction in patients with advanced CKD, such as impaired function of platelet glycoproteins like GPIIb/IIIa,<sup>38</sup> altered release of ADP and serotonin from platelet

granules,<sup>39</sup> and faulty arachidonic acid and prostaglandin metabolism,<sup>40</sup> which all lead to impaired platelet adhesion and aggregation. Certain uremic toxins such as guanidinosuccinic acid and methyl guanidine may contribute to platelet dysfunction by stimulating NO release.<sup>41</sup> Anemia may also play a pathogenetic role in the increased risk of bleeding in patients with advanced CKD because correcting it results in improved platelet function in this patient population.<sup>42</sup> The modern hemodialysis procedure itself may also directly activate tPA, but it is unknown whether this activation contributes to an increased bleeding tendency in patients receiving it.<sup>43</sup>

### **CLINICAL MANIFESTATIONS OF HEMOSTATIC ABNORMALITIES IN PATIENTS WITH CHRONIC KIDNEY DISEASE**

As mentioned previously, patients with CKD suffer considerably from major cardiovascular events such as myocardial infarction, stroke, and peripheral vascular disease. It remains unknown whether some of the abnormalities just cited, such as increased plasma TF, fibrinogen, or PAI-1 concentrations, are independent risk factors of cardiovascular events and mortality.

The clinical manifestations of platelet dysfunction in patients with ESRD are better described and primarily include mucocutaneous bleeding, such as epistaxis, and easy bruising of the skin. Patients with CKD also have a higher risk of gastrointestinal bleeding<sup>44</sup> and of intracranial bleeding that might be partially explained by the associated platelet dysfunction.<sup>45</sup>

### **DIAGNOSIS AND ASSESSMENT OF PROCOAGULANT STATUS IN CHRONIC KIDNEY DISEASE**

Currently, no specific laboratory tests are available that can help evaluate the procoagulant state in patients with CKD. Measurement of circulating levels of TF, PAI-1, or any of the other potential markers of a prothrombotic state is conducted in clinical studies; however, it is not recommended in clinical practice. Typically, patients with CKD have normal platelet counts and normal coagulation profiles (including partial thromboplastin time, and prothrombin time). Bleeding time is a universal test that is measured by making a small incision on the upper arm, earlobe, finger, or thigh and normally is between 1 and 7 minutes. However, it is known to have high variability and poor reproducibility because it depends on several factors involving primary hemostasis such as platelet function, fibrinogen concentration, and coagulation factors, in addition to factors independent of the hemostasis pathways such as skin quality and temperature.<sup>46</sup> Platelet function analyzer (PFA-100)

testing is another method that can be used to assess platelet function. It measures the time required for whole flowing blood to occlude a collagen and adenosine diphosphate or a collagen/epinephrine-coated membrane. Thus the process of platelet adhesion and activation is simulated in vitro. Zupan et al evaluated this PFA-100 in 34 dialysis patients and demonstrated better sensitivity and specificity for this test as compared with bleeding time.<sup>46</sup> Obtaining a quantitative assessment of platelet function in patients with CKD may be useful, and it is often the target of intervention aimed at lowering the risk of bleeding perioperatively. Elevations in blood urea nitrogen and creatinine do not significantly correlate with the risk of bleeding; neither does the degree of anemia.<sup>42</sup>

### **TREATMENT OF PROCOAGULANT STATE IN CHRONIC KIDNEY DISEASE**

There are no particular pharmacological agents that are recommended targeting any one element of the hemostasis pathway. The current recommendations<sup>47</sup> with regard to treatments are aimed at lowering the high risk of incident cardiovascular events in patients with CKD. Unfortunately, these recommendations are mainly based on clinical trials that have been conducted in the general population that have generally excluded patients with underlying CKD;<sup>48</sup> hence they are based on extrapolation rather than on hard evidence. Pertinent to our discussion in this review are the recommendations to treat patients with underlying CKD with RAAS blockers, antiplatelet and lipid-lowering agents such as statins and fibrates.

The value of RAAS blockers, as indicated earlier, is well documented in patients with CKD, where in addition to slowing down the progression of CKD,<sup>28</sup> their use lowers the risk of cardiovascular morbidity and mortality.<sup>27</sup> However, whether these agents mediate their beneficial effects partially by modulating the hypofibrinolytic state reported in patients with CKD is unknown. Although the use of aspirin is recommended in CKD patients, no randomized controlled trials have definitely addressed its clinical use in patients with CKD, and concerns remain that aspirin use may lead to an increased risk of bleeding in patients with advanced CKD.<sup>49</sup> It is tempting to assume that statins would favorably modulate the prothrombotic tendency in CKD patients because they lower plasma cholesterol concentration, and in addition they have many pleiotropic effects including reducing circulating levels of PAI-1,<sup>50</sup> TF,<sup>25</sup> and CRP. However, a recent randomized controlled study evaluating the chronic treatment with rosuvastatin in patients with ESRD did not find any significant difference in cardiovascular survival between the rosuvastatin-treated group and the control-treated group.<sup>51</sup> The Study of Heart and Renal Protection (SHARP) is currently on-



going and is evaluating the use of statins (simvastatin versus simvastatin plus ezetimibe) in a large cohort of patients with pre-ESRD CKD and in patients with ESRD.

## TREATMENT OF PLATELET DYSFUNCTION IN CHRONIC KIDNEY DISEASE

Several measures can be used to normalize bleeding time in patients with advanced CKD, including dialysis, correction of coexisting anemia, desmopressin (DDAVP), cryoprecipitate, and estrogen.<sup>42</sup>

Renal replacement therapy in the form of hemodialysis or peritoneal dialysis can help correct the bleeding time in uremic patients, and it has played an important role in lowering the risk of uremic bleeding in CKD patients since it was introduced. Its effects are likely mediated by the removal of uremic toxins.<sup>42</sup> The use of erythropoietin for the correction of the anemia associated with CKD has also contributed to the prevention of uremic bleeding. Erythropoietin may act through a variety of biological mechanisms, including increasing red blood cells in the vasculature and thus reducing platelet contact with the endothelium, enhancing platelet aggregation, and improving platelet adhesion.<sup>52</sup>

Rapid treatment of platelet dysfunction in patients with CKD is necessary if the patient is actively bleeding or will undergo a surgical procedure. DDAVP is the most frequently used drug to treat bleeding in uremic patients. It most likely acts by increasing plasma vWF and factor VIII levels immediately after its infusion and has a quick and short duration of action.<sup>53</sup> It can be administered either intravenously or subcutaneously at a dose of 0.3  $\mu\text{g}/\text{kg}$  in a single dose.<sup>42</sup> Cryoprecipitate is a blood product rich in factor VIII and VWF; it also has a rapid onset of action and its effect is short lived (4 to 12 hours). The major disadvantage to using it is that it is a blood product, and its transfusion carries the risk of transmitting blood-borne infections such as hepatitis C infection and human immunodeficiency virus infection.<sup>42</sup>

Estrogen administration also reduces bleeding time in patients with uremia. It can help achieve more prolonged control of bleeding.<sup>54</sup> It can either be administered intravenously at a dose of 0.6 mg/kg daily for 5 days, or it can be administered transdermally in the form of estradiol, 50 to 100  $\mu\text{g}$ , twice a week.<sup>42</sup>

## CONCLUSIONS

CKD patients exhibit many abnormalities in their hemostatic response that may account for their increased risk of both atherothrombotic events and bleeding. The early stages of CKD are mainly dominated by derangements that likely result in increased risk of major

cardiovascular events disease, a major source of morbidity and mortality in these individuals. In patients with advanced CKD, the procoagulant state persists, and in addition uremia is strongly associated with platelet dysfunction that gives these patients an increased risk of hemorrhagic events. Much of these pathways remain poorly characterized in patients with CKD. Although the current belief is that hemostatic abnormalities such as increased circulating TF and PAI-1 may contribute to the increased risk of cardiovascular disease, the exact role that any one abnormality may play is unknown. Therefore, identifying potential therapeutic targets is difficult. Furthermore, it is still unclear how these procoagulant tendencies in patients with CKD interact with other traditional and nontraditional cardiovascular risk factors. The current treatment recommendations in patients with CKD are based on clinical trials conducted in the general population, and these trials have generally excluded individuals with CKD. Thus further research is required to better understand the procoagulant state in patients with CKD, to explore the role it plays in increasing cardiovascular morbidity and mortality in this patient population, and to identify potential therapeutic interventions that could translate into improved cardiovascular and potentially renal outcomes in these patients.

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