We have recently described a new clinical syndrome in patients receiving warfarin for anticoagulation therapy. First, we identified that warfarin therapy can result in acute kidney injury (AKI) by causing glomerular hemorrhage and renal tubular obstruction by red blood cell (RBC) casts in some patients. This syndrome has been named warfarin-related nephropathy (WRN), and patients with chronic kidney disease appear to be particularly susceptible. We defined WRN as an acute increase in international normalized ratio (INR) to >3.0, followed by evidence of AKI (defined as a sustained increase in serum creatinine of ≥0.3 mg/dl) within a week of the INR increase. We believe that anticoagulant-related kidney injury should be suspected in a patient on anticoagulation therapy, if there is a disproportion between the number of RBC tubular casts, acute tubular necrosis and the degree of underlying kidney lesion (such as glomerular immune complex depositions, glomerular basement membrane thickness abnormalities etc.) in kidney biopsy. Detailed evaluation of coagulation data and medications is recommended for all patients with RBC casts and AKI.

KEY WORDS: Drug, kidney, injury, nephropathy, toxicity
over-anticoagulation. Normal patients who develop WRN likely have undiagnosed CKD/glomerular injury

- When specifically analyzed, WRN is associated with progression of CKD and an increased risk of subacute mortality
- The true incidence of WRN is difficult to determine from the mainly retrospective studies published thus far, but it appears to be high. The only prospective study [1] suggests an incidence of 60%, at least in the elderly population examined
- Over 26 million people in the USA have CKD, and anticoagulation therapy is common in CKD patients [6, 7]. Furthermore, warfarin is difficult to titrate in CKD, and this difficulty in maintaining the target INR increases the risk of over-anticoagulation, which is the cause of WRN [8, 9]. It is interesting that WRN seen in patients without known CKD [3], may actually represent WRN in patients with sub-clinical CKD, which would put an even larger number of patients at risk. Adding to this public health problem is emerging evidence that WRN is only a subset of a broader syndrome we have named anticoagulant-related nephropathy, in which other, and possibly all currently used anticoagulants may cause AKI. Indeed, AKI associated with dabigatran (direct thrombin inhibitor) use has been reported [10-12] and recently demonstrated by us in experimental animals [13]. In addition, anticoagulants may aggravate an underlying kidney disease and induce hematuria and AKI [14].

There is a challenge for a renal pathologist to recognize WRN in kidney biopsy. Renal pathologists often do not recognize WRN because of an underlying kidney disease. Acute tubular injury and RBC casts are usually associated with those conditions.

In our first description of WRN, a variety of underlying kidney disease was found [Table 1] [1].

No guidelines are established yet to diagnose WRN. Here are several recent examples from our practice, when WRN was diagnosed:

**Case 1**

The first case is about a 61-year-old Caucasian female with recently diagnosed diabetes mellitus. Baseline SC was normal. She presented to the hospital after episodes of diarrhea with SC of 3.2 mg/dl. She developed deep vein thrombosis, and she was started on warfarin therapy. Her INR was as high as 5. SC increased up to 6.6 mg/dl within 2 weeks after initiation of warfarin therapy. Serologies showed positive ANA (1:640), but the complement levels were normal. Kidney biopsy findings by light microscopy included numerous RBC casts and acute tubular necrosis (ATN) [Figure 1a]. The glomeruli were unremarkable [Figure 1b]. Immunofluorescence showed mild smudgy staining for IgG [Figure 1c]. Electron microscopy showed scattered small electron-dense immune-type complex deposits [Figure 1d]. There was a disproportion between the number of RBC casts, the degree of ATN and relatively small immune complex deposits in the absence of proliferative glomerular lesions or cellular crescents.

**Case 2**

The second case we present here is a 41-year-old Caucasian female with a history of aortic bifurcation thrombosis, she underwent a graft placement and started on warfarin therapy. Her INR was as high as 27. Baseline SC was 1.0 mg/dl but

### Table 1: Demographics, laboratory data, and morphologic findings in patients with WRN

<table>
<thead>
<tr>
<th>Patient</th>
<th>Demographics and laboratory data</th>
<th>Morphological findings</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Gender</td>
<td>Race</td>
<td>Maximal SC change from baseline, mg/dl</td>
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<tr>
<td>---------</td>
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</tr>
<tr>
<td>1</td>
<td>27</td>
<td>F</td>
<td>AA 8.0</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>F</td>
<td>W 7.0</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
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<td>63</td>
<td>M</td>
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<td>F</td>
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<tr>
<td>8</td>
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<tr>
<td>9</td>
<td>55</td>
<td>M</td>
<td>W 3.8</td>
</tr>
</tbody>
</table>

*The mean GBM thickness established in our laboratory for males 373±56 nm and for females 351±40 nm; *Combined with frozen tissue. ATN: Acute tubular necrosis, GBM: Glomerular basement membrane, Gl: Glomeruli, RBC: Red blood cell, IntInf: Interstitial inflammation, IFTA: Interstitial fibrosis and tubular atrophy, WRN: Warfarin-related nephropathy, SC: Serum creatinine, M: Male, F: Female. Morphological findings were scored semiquantitatively using the following criteria: 0−: Absent, 1+: Mild, 2+: Moderate, 3+: Prominent. If changes were minimal but not absent, the score of ± was applied.
It is not clear whether other anticoagulants, including new oral drugs, can induce AKI. A case of dabigatran-induced AKI has been reported [10]. We had a kidney biopsy from a patient on heparin therapy, where we seen numerous RBC casts and ATN as well. We believe that anticoagulant-related kidney injury should be suspected in a patient on anticoagulation therapy, if there is a disproportion between the number of RBC tubular casts, ATN and the degree of underlying kidney lesion (such as glomerular immune complex depositions, GBM thickness abnormalities etc.) in kidney biopsy. Detailed evaluation of coagulation data and medications is recommended for all patients with RBC casts and AKI.

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