# Anticoagulant-Related Nephropathy
## It's the Real McCoy

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## Introduction

It is not uncommon for a description of a new clinicopathologic entity to be initially viewed with skepticism and/or ignored by the medical community as a whole, thus delaying its diffusion into the body of clinical knowledge. Such was the case for the seminal description by Brodsky *et al.* (1) a decade ago of what was soon to be designated as "warfarin-related nephropathy" (WRN) and later, by the broader appellation of "anticoagulant-related nephropathy" (ARN).

The original description of WRN or ARN arose from a retrospective analysis of kidney biopsies conducted at the Ohio State University Medical Center in patients having unexplained AKI and hematuria (visible or nonvisible) while receiving warfarin therapy (for a variety of clinical indications) (1). The interest in a possible causal connection between these disparate events arose from single patient experiences dating back to 2000 and 2004. After review of >2800 kidney biopsies, they were able to discover 11 biopsies from nine subjects in whom the AKI and hematuria could not be readily explained by active or acute GN. A detailed review of the microscopic pathology of these patients revealed a common morphologic picture of diffuse dysmorphic erythrocyte accumulation in kidney tubules, some of which were dilated and lined with a flattened epithelium (occupying about 6% of the tubular parenchyma), and in the absence of proliferative glomerular lesions, including crescents, in all patients. The dysmorphic erythrocytes were also commonly found in Bowman's space. Erythrocyte casts filling and occluding distal nephron segments were also common, and interestingly, these casts did not contain Tamm–Horsfall mucoprotein (Bowman's space also did not contain Tamm–Horsfall mucoprotein). On the basis of light, immunofluorescence, and electron microscopy, an underlying glomerular disease was found in six of the nine patients (mild lupus nephritis in one patient, IgA nephropathy in two patients, mesangial IgG/C3 deposits in one patient, FSGS in one patient, and diabetic nephropathy combined with IgA nephropathy in one patient). Nephrosclerosis, nephrocalcinosis, or chronic interstitial fibrosis was found in three patients. The patients exhibited a broad range of ages (27–82 years old), but six of nine were over 60 years of age. There was no sex or racial preference. Most, but not all, patients would be regarded as "overanticoagulated" (range of international normalized ratio [INR], 2.0–8.8; mean of 4.4±0.7 IU), with seven of nine patients having an INR of ≥3.0 IU. Many patients were taking concomitant medication, but warfarin only was prescribed in four of nine patients. Baseline eGFR (before the episode of AKI) was variable (23–154 ml/min), and it was <60 ml/min in three of nine subjects. The outcome of the episode of AKI was poor—four patients required dialysis, and only three patients eventually fully recovered kidney function. These observations led the authors to conclude that "warfarin therapy can result in AKI by causing glomerular hemorrhage and kidney tubular obstruction by red blood cell casts" (1). Thus, a causal inference was drawn between warfarin exposure (and excessive anticoagulation) and the AKI, the latter being attributed to intranephronal obstruction. Because this study was on the basis of a retrospective review of kidney biopsies, the prevalence of the disorder in the general warfarin-treated patient population could not be determined, but it is likely to be uncommon (WRN was found in <1% of the kidney biopsies reviewed). In addition, the design of the study precluded any conclusions concerning the specificity of the histopathologic lesions, because no group with AKI, hematuria, and absence of warfarin exposure was examined The main predisposing features seemed to be excessive anticoagulation, older age, and preexisting kidney disease (mild IgA nephropathy in one third of the patients).

## Follow-On Studies

After the initial observations of Brodsky *et al.* (1), numerous clinical studies affirmed the general thesis that excessive anticoagulation was associated with AKI (2–4). The phenomenon of ARN may be more common than generally suspected (4). This association of AKI and anticoagulation was also extended to newer anticoagulants, such as dabigatran, rivaroxaban, and apixaban, other forms of vitamin K antagonism, and even dual antiplatelet therapy (5). Thus, the term WRN was gradually replaced by the more inclusive term ARN.

In addition, experimental models of nephron ablation were used to ascertain the relationship of WRN and CKD progression (6). Epidemiologic studies of the risks and consequences of WRN were also pursued. In a patient-control study involving 15,258 patients who initiated warfarin therapy, AKI developed within 1 week of an INR>3.0 in 20.5% of the patients. Preexisting CKD

doubled the risk of AKI among these subjects (30.0% in patients with CKD and 16.5% in non-CKD controls) (7). Because this was not a biopsy study, the fraction of patients with true WRN could not be ascertained, and confounding by selection may have influenced the results. Nevertheless, it seemed from retrospective observational studies that excessive anticoagulation might be associated with more rapid progression of CKD. This latter finding needs confirmation in prospectively designed, propensity-adjusted studies. Systematic reviews and meta-analyses suggest that the development of AKI (possibly due to ARN) among patients who are anticoagulated almost doubles the mortality risk compared with those patients without AKI who are anticoagulated. Because AKI is undoubtedly multifactorial in origin in patients undergoing anticoagulation for prophylaxis or treatment of a thrombotic state, it is easy to see how such epidemiologic studies can be confounded by the occurrence of non-ARN causes of AKI in patients who are anticoagulated. These non-ARN causes of AKI could be congestive heart failure, recent initiation of renin-angiotensin system inhibitors, atheroembolic kidney disease (from a ruptured atherosclerotic plaque in the aorta or renal arteries), unrecognized endocapillary proliferative or crescentic GN, hypotension from gastrointestinal hemorrhage, or bladder clots causing ureteral obstruction.

Nevertheless, over time, the observations of Brodsky *et al.* (1) were confirmed and extended.

The best way to avoid WRN or ARN is to minimize the risk of excessive anticoagulation. Many risk factors for such an iatrogenic event have been characterized, particularly for vitamin K antagonists, such as warfarin, raising the important issue of prevention. Drug-drug interactions (particularly antibiotics) are potentially the most common. Genetic causes cannot be overlooked. The presence of a CYP2C9P*2/3 allele and the VKORC1–1639G>A genotype predicts excessive anticoagulation (with a slow appearance) using standard warfarin dosage (8). The treatment of an established biopsy-proven WRN or ARN is uncertain. The offending anticoagulant should be stopped, and its anticoagulant effects should reversed (by vitamin K for warfarin, idarucizumab for dabitgatran, or coagulation factor Xa [recombinant] for apixaban and rivaroxaban). Whether additional treatment with *N*-acetyl-cysteine or oral glucocorticoid is of value remains uncertain. A fraction of subjects with ARN will fail to recover kidney function and require maintenance dialysis or transplantation for ESKD.

## Mechanistic Considerations

Although the pathologic findings in WRN or ARN are quite distinctive, the mechanistic origins of the "occlusive" erythrocyte casts and the attendant tubular injury are not well understood. The normal kidney allows a miniscule number of circulating erythrocytes to migrate through the glomerular filter (about 1 erythrocyte per $10^9$ erythrocytes perfuses the glomeruli each 24 hours), and all of the erythrocytes in normal urine are dysmorphic, attesting to their glomerular source. Thus, hematuria originating in the glomerular filtrate augmented by anticoagulation is quite plausible. Indeed, in the original description (cited above), Bowman's space was filled with dysmorphic erythrocytes (but not with Tamm–Horsfall protein). Large numbers of erythrocytes trafficking through the nephron segments and undergoing lysis can release catalytic iron locally, resulting in localized excess production of hydroxyl radicals, which can damage the lipoprotein constituents of tubule cell membranes and lead to apoptosis/necrosis. Hemosiderin deposition in the tubules by Prussian blue staining is a biomarker of this process. A prominent feature of the histology of WRN or ARN is the formation of erythrocyte "casts" in the distal nephron. These casts might occlude the passage of urine and create a form of intranephronal "obstructive" nephropathy, causing a reduction of GFR in the obstructed nephron. A possible role for volume depletion and low urine flow velocity in the distal nephron is poorly understood. The absence of Tamm–Horsfall protein in the casts of WRN is interesting and might be explained by their distal location in the nephrons. The lack of Tamm–Horsfall protein in Bowman's space challenges the view that intranephronal obstruction is the main cause of AKI. A direct toxic effect on tubules without intranephronal

**SUSPECT when the following clinical findings are present:**

- Hematuria (without clots) combined with AKI or worsening of a known CKD
- Treatment with warfarin (or other novel oral anti-coagulants) started before the onset of hematuria and AKI
- Increase in prothrombin INR above 3.0 IU (warfarin-treated patients only)
- No record of acute haemorrhage
- Exclude other causes of AKI and hematuria (e.g. acute glomerulonephritis, vasculitis, athero-embolic disease, drug hypersensitivity)

**CONFIRM diagnosis by kidney biopsy (after normalization of INR) demonstrating:**

- Presence of dysmorphic erythrocytes in Bowman's space (by electron microscopy or other means)
- Extensive erythrocyte cast formation in distal nephron segments (not containing Tamm-Horsfall mucoprotein)
- Acute tubule cell injury with intra-cytoplasmic tubular ferric iron/hemosiderin deposits (Perl's Prussian Blue stain)
- Absence of endo-capillary or extra-capillary proliferative glomerulonephritis (mesangial deposition of IgA, IgG or IgM by IF may be present)
- Other causes of AKI and hematuria in an anti-coagulated patient (e.g. athero-embolic disease) have been excluded

**Figure 1. | A suggested approach to the recognition of Anti-Coagulant-related Nephropathy.** IF, immunofluorescence microscopy; INR, international normalized ratio. Modified from ref. 9, with permission.

obstruction is a tenable mechanistic explanation for the AKI seen in WRN or ARN (9). Animal models have also suggested possible roles for hypertension and protease-activating receptors in ARN (10). Patients with very mild (or even lanthanic) forms of IgA nephropathy or thin basement membrane nephropathy may be at increased risk for the development of WRN or ARN, and such an occurrence may adversely affect the prognosis of these patients.

## Synthesis

When the sum total of observations is considered, it seem inescapable that WRN and ARN are real and rather uncommon but likely underdiagnosed clinicopathologic entities. The development of AKI in a patient who is excessively anticoagulated exhibiting dysmorphic hematuria with or without known preceding CKD will not always have WRN or ARN—but this diagnosis should always be entertained in such patients. The diagnostic pathway toward identifying true WRN or ARN recently suggested by L'Imperio *et al.* (9) is a good one that should find broader use (Figure 1). In sum, iatrogenic kidney disease caused by excessive anticoagulation is the real McCoy.

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