

Review Article

Anticoagulation-related nephropathy for the internist: a concise review

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Abstract: Anticoagulation-related nephropathy (ARN) is a clinical entity that has significant morbidity and mortality consequences/burden but has not been well described. Consequently, ARN has been underdiagnosed and sub-optimally managed. ARN has been reported with warfarin use especially in the setting of supratherapeutic international normalized ratio (INR) but the association is far less established with the use of direct-acting oral anticoagulants (DOAC). Accelerated progression to CKD and ultimately ESRD has been reported in patients with ARN. With the expanding indications for DOAC use, there is growing concern about ARN in the setting of DOAC use and its attendant clinical and socioeconomic burden. In this review, we highlight precautionary measures to aid prompt diagnosis of ARN and suggest possible therapeutic strategies.

Keywords: Anticoagulation, nephropathy, DOAC

Introduction

Anticoagulation-related nephropathy (ARN) is an understudied renal complication of anticoagulant therapy. It is characterized by acute kidney injury (AKI,) defined as an increase in baseline serum creatinine ≥ 0.3 mg/d, without any alternate etiology, in the setting of a supra-therapeutic International Normalized Ratio (INR) greater than 3.0 [1-5]. ARN usually occurs in the first two months of starting anticoagulant therapy. The true incidence of ARN is not known as there are no prospective studies on this unique form of renal injury, however retrospective studies have estimated the prevalence to range from 16% to 37% of patients on anticoagulation in the setting of usage of warfarin [4, 5].

The pathophysiologic mechanism of ARN is complex and involves multiple factors that include excessive glomerular proliferation, glomerular hypertension causing hematuria, and a complex interaction of heme molecules that

result in oxidative stress and activation of inflammatory cascade in the renal tubular epithelium and surrounding stroma [1-5].

The use of anticoagulation is ubiquitous in medicine for various indications including atrial fibrillation and the prophylaxis and treatment of venous thromboembolism. It is estimated that more than two million patients are treated with oral anticoagulants annually in the United States [6]. The burden of renal disease on the American health system in terms of morbidity, mortality and health costs is profound. A recent analysis found that end stage renal disease treatment alone costs the Medicare program \$35 billion per year [7]. An awareness of ARN is thus important to the internist as both anticoagulation and renal damage co-exist in ways that were previously unrecognized and underdiagnosed, and it is likely that the accompanying morbidity and mortality could have been prevented with early diagnosis. The expanding indications for the usage of direct-acting oral

Table 1. Risk factors for Anticoagulation-Related Nephropathy (ARN)

Risk Factors for ARN
Pre-existing Chronic Kidney Disease
Hypertension
Diabetes Mellitus
Age > 65 years
Supra-therapeutic INR on coumadin therapy

anticoagulants has also prompted consideration of ARN as a complication of DOAC use.

Pathophysiology

ARN has mainly been studied retrospectively in relation to warfarin [1-5]. Kidney biopsy findings indicate that the kidney injury may be the result of severe glomerular hematuria leading to extensive tubular obstruction by red cell casts [2, 3]. The underlying molecular mechanism is theorized to be due to warfarin-induced thrombin depletion which may also lead to increases in endothelial pressure that leads to renal damage [8-10]. Some recent studies have also suggested alternate pathways involving a reduction in protein C and abnormal endothelial protein C receptor signaling [11, 12].

The strongest risk factor for ARN is pre-existing chronic kidney disease (CKD) [1-5]. Other risk factors include supratherapeutic INR in coumadin therapy, older age, diabetes mellitus and hypertension as shown in **Table 1** [1-5]. Patients with ARN have an accelerated progression of CKD and a retrospective study of more than 15,000 patients on warfarin showed a 65% increase in mortality in patients with ARN [2].

Direct-acting oral anticoagulants (DOACs) such as dabigatran, rivaroxaban and apixaban are gradually replacing warfarin in the clinical setting. A few animal models and sporadic case reports have shown that these DOACs can lead to deterioration of kidney function, but this has not been studied epidemiologically [13-16]. The clinical trials that compared the DOACs to warfarin did not specifically study ARN and did not repeat creatinine and urinalysis testing in the first two to three months of therapy to establish possible ARN diagnosis and hence the condition was underdiagnosed in those trials [17-24]. A recent study of a retrospective cohort in Taiwan suggests a lower rate of ARN in patients

on Dabigatran compared to coumadin [25]. The safety data from patients randomized to apixaban in ARISTOTLE trial showed that the observed worsening of glomerular filtration rate was more than 20% in 16,869 patients [26]. This observation adds to the growing evidence that DOACs may cause clinically significant renal injury. Considering the increasing number of patients requiring anticoagulation and specifically DOACs, the incidence of ARN is expected to increase and may result to a worsened morbidity burden and survival decline in affected patients. If undiagnosed, ARN may also accelerate progression to end stage renal disease, especially in patients with pre-existing renal disease, and pose huge economic consequences. We suggest an age-matched prospective study stratified across different GFR categories to establish a strong association between DOACs and ARN. However, achieving an ideal study design may be challenging due to the confounding variables. Also, because certain DOACs are contra-indicated when GFR drops below 30 ml/min the chances of a perfectly stratified data/analysis are low.

Diagnosis

The clinical diagnosis of ARN is usually one of exclusion [1]. ARN should be suspected when a patient develops an AKI in the first few months of starting anticoagulation therapy, and a urinalysis with hematuria. It is important that other causes of AKI be excluded beginning with a well taken history (to exclude dehydration, hypotension or recent use of nephrotoxic agents) and a physical examination (ie. signs of volume contraction) and imaging (such as a renal ultrasound to exclude obstruction). A definitive diagnosis can be established with a kidney biopsy, however bleeding risks make this an unlikely choice. Wheeler, et al, suggest a clinical diagnostic algorithm that can help internists in early recognition of ARN (**Figure 1**). They also recommend a monthly monitoring of INR and kidney function in the first three months of commencement of anticoagulation, with regular quarterly or biannual monitoring after the first three months for those with and without CKD respectively [1].

Management

The cornerstone of management of ARN is early detection of the AKI, hence monitoring kidney

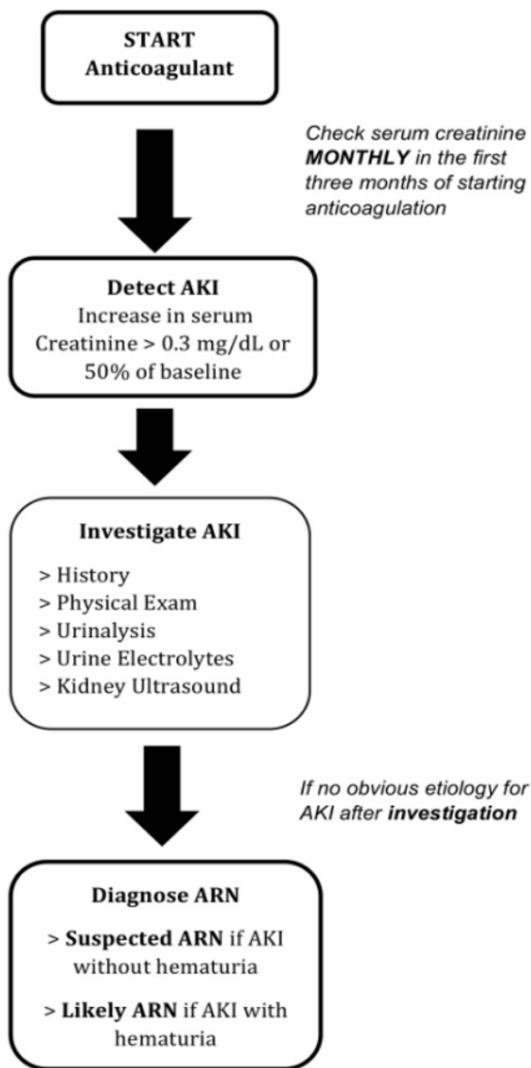


Figure 1. Clinical Diagnostic Algorithm for Suspected ARN (adapted from Wheeler et al [1]).

function is vital. Treatment should involve correcting suprathreshold INR for patients on coumadin, switching anticoagulation and precautionary measures such as adequate hydration and avoiding nephrotoxic agents such as non-steroidal anti-inflammatory drugs and contrast agents. Revisiting the need for continued anticoagulation is crucial when considering discontinuation of anticoagulation therapy to avoid further renal deterioration.

Prognosis

In most patients with ARN, the kidney function recovers spontaneously, however it should be noted that in the seminal study of nine patients of biopsy proven ARN, five patients did not

regain previous kidney function [3]. Patients with ARN have an accelerated progression of CKD and increase in mortality which is evident even after the first year [2, 5]. In a cohort of 4006 patients, Brodsky et al showed that the 5 year Kaplan-Meier survival rate was significantly lower in patients with ARN than those without ARN (58% vs. 73%, $P < 0.001$), with 1-year survival of 68.9% in ARN vs. 81.1% in no-ARN group, $P=0.049$ [5].

Conclusion

Anticoagulant-related nephropathy (ARN) is a relatively new and underdiagnosed complication of anticoagulant therapy with the potential to accelerate chronic kidney disease and lead to increased morbidity and mortality. Carefully monitoring kidney function in the first few months of starting anticoagulation holds the key to early diagnosis and potentially averting irreversible kidney injury.

Disclosure of conflict of interest

None.

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