Anticoagulant Use In Patients With Renal Disease

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Thrombotic complications: special considerations in patients with renal disease

- Nephrotic syndrome. (primary and secondary)
- SLE with or without antiphospholipid syndrome
- pauci-immune antineutrophil cytoplasmic antibody vasculitis,
- CKD,ESKD

CKD

- CKD is a global health problem affecting up to 14% of the adult population in developed countries.
- VTE is two to three times greater in patients with CKD and ESKD, than the general population.
- The risk for (AF) is also 10 to 20 times greater in patients with CKD and ESKD.
- patients with both CKD and AF have a higher stroke risk and mortality than patients with either isolated AF or CKD.

CKD

- The mechanisms of hypercoagulability in CKD/ESRD are multiple and the underlying pathophysiology is essentially attributable to all three components of Virchow's triad:

  - endothelial injury/dysfunction
  - venous stasis
  - abnormal blood constituents.

ESKD

- the conventional thrombotic sites, AVF and AVG as well as dialysis lines .
- Central venous stenosis and thrombosis are associated with catheterisation resulting in excessive vessel wall shear stress, endothelial damage, and neointimal hyperplasia.
- primary renal or inherited or acquired disease perhaps such as nephrotic syn, DM, vasculitis
- hyperhomocysteinemia
- may relate to elevated levels of factor VIII and von Willebrand factor in this population??????

CKD

- The presence of CKD/ESKD is associated with an increased haemorrhage risk.

- The pathophysiological mechanisms of the increased bleeding risk associated with uremia

1. increased vascular prostaglandin I_2
2. decreased von Willebrand factor,
3. hyperparathyroidism,
4. chronic inflammation,
5. decreased NO bioavailability,
6. anemia
7. platelet abnormalities leading to abnormal adhesion and aggregation.

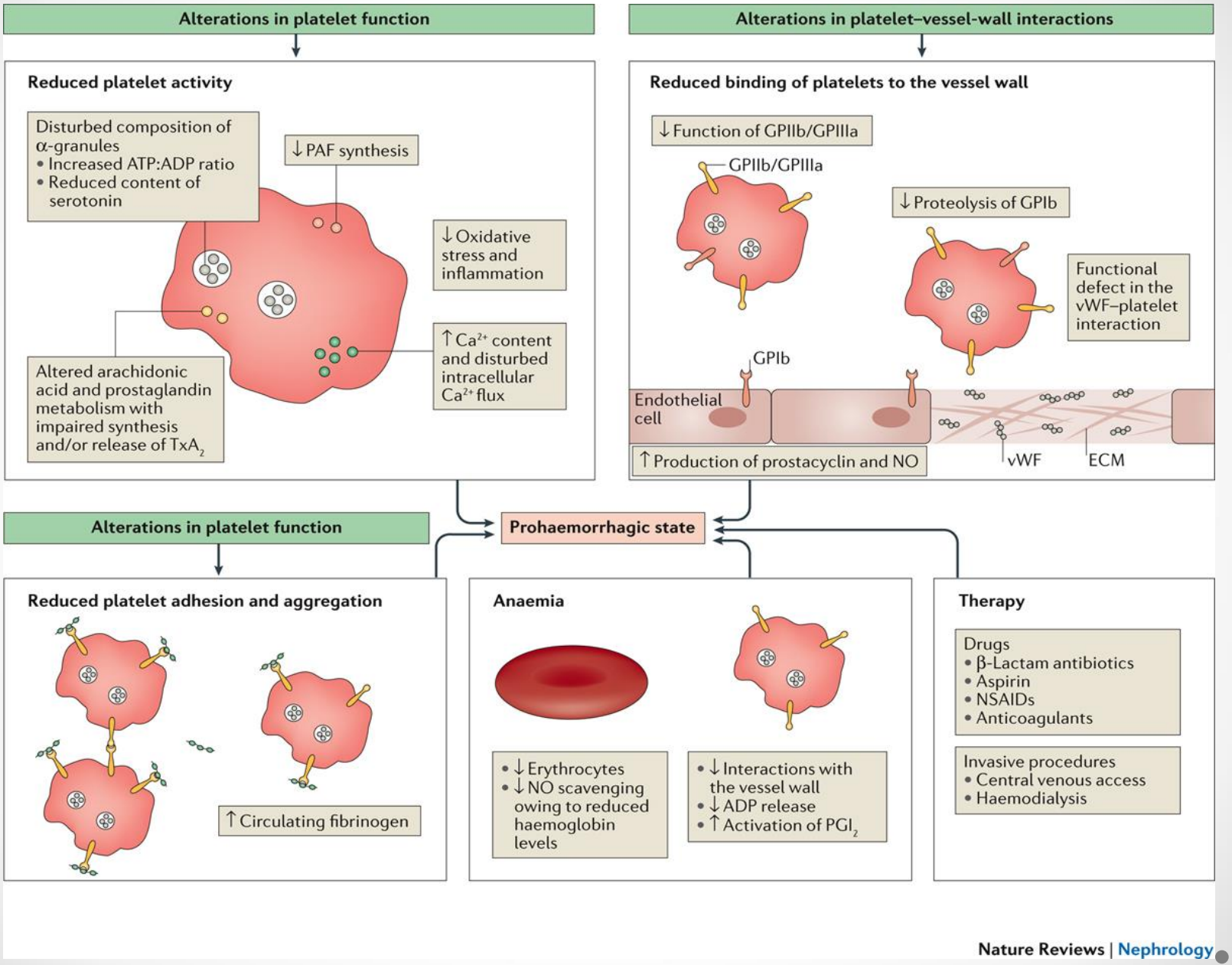
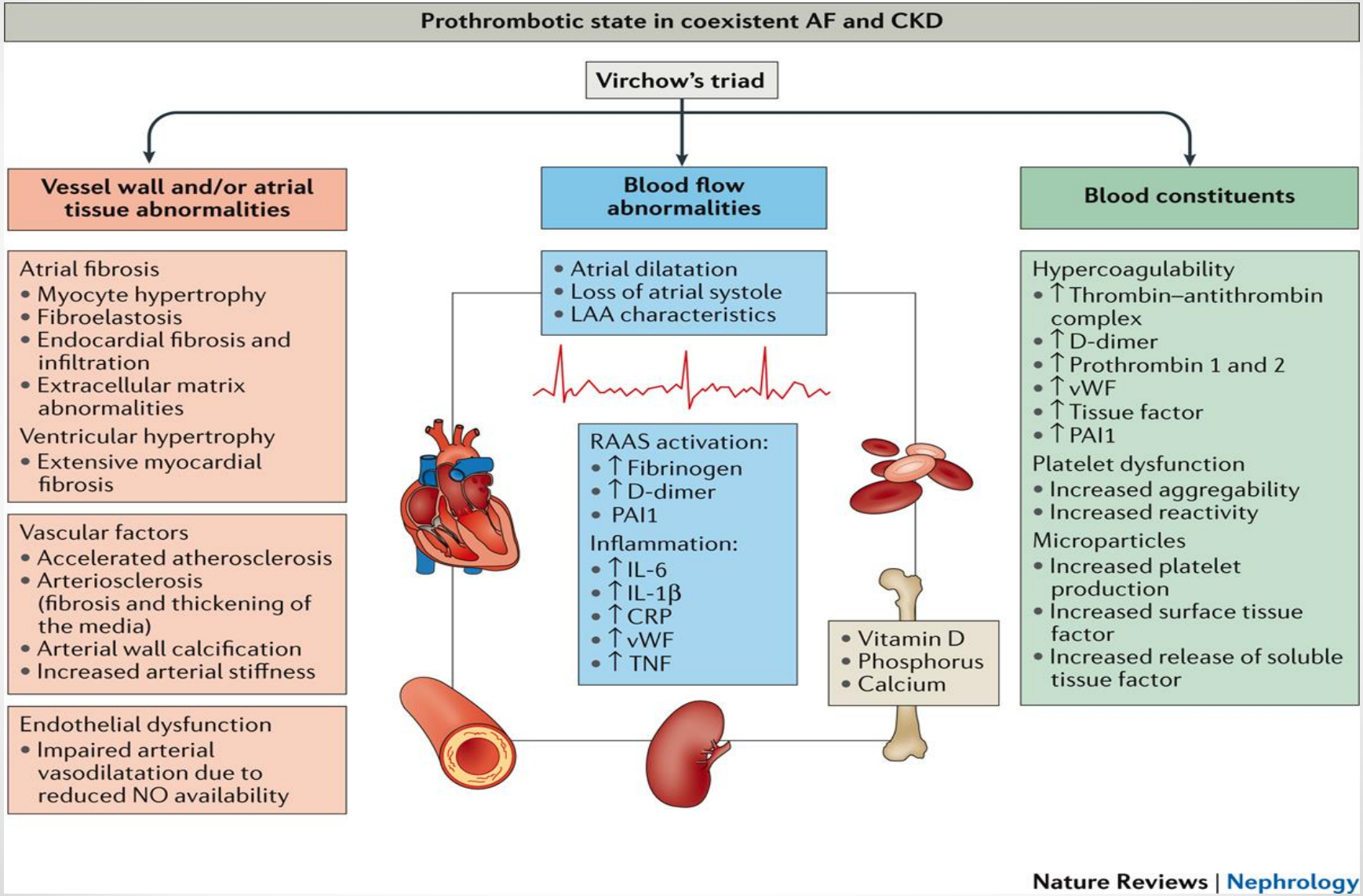
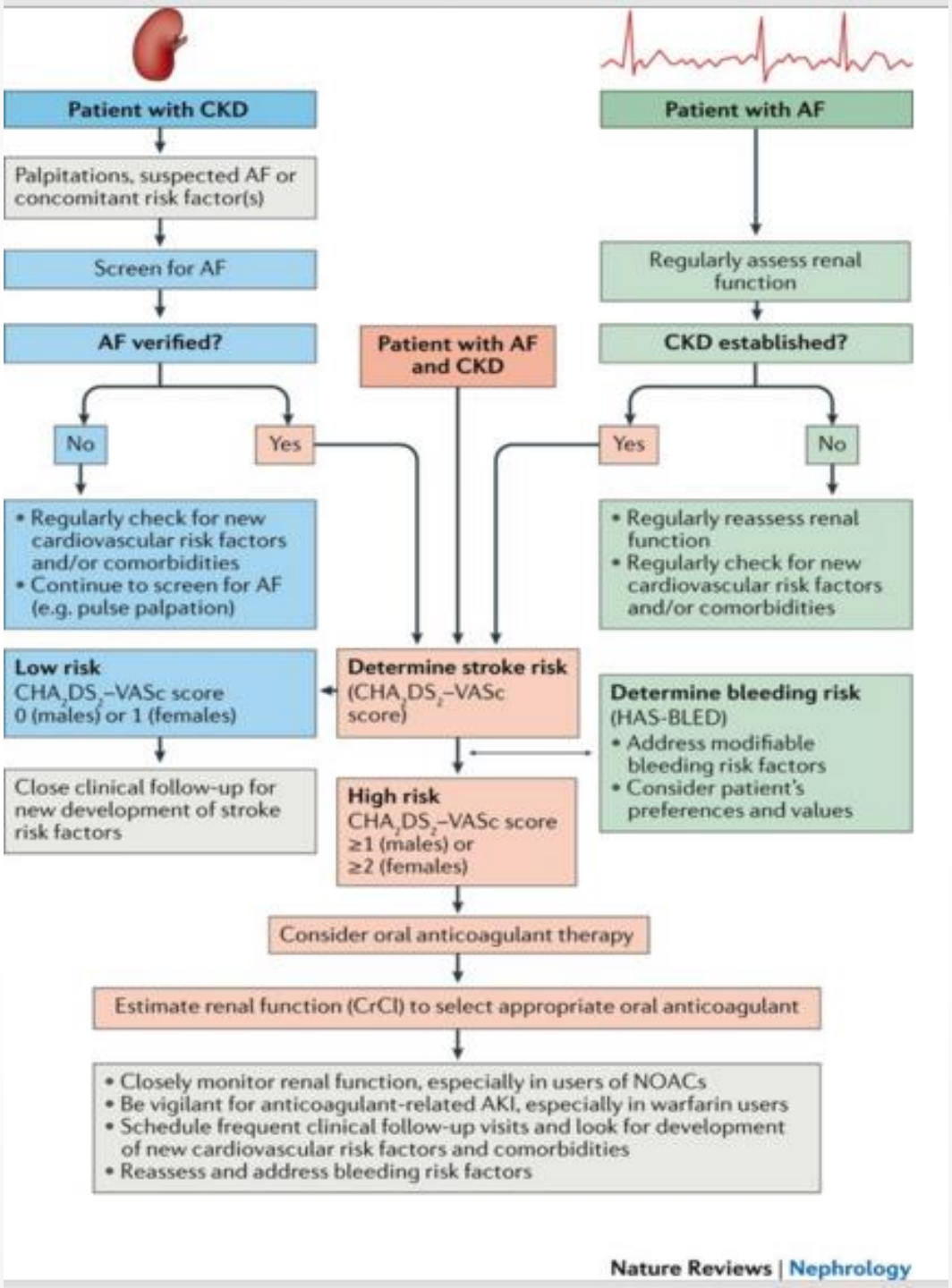

Alterations in platelet function
Alterations in platelet–vessel-wall interactions
Reduced platelet activity
Disturbed composition of α-granules
• Increased ATP:ADP ratio
• Reduced content of serotonin
↓PAF synthesis
↓Oxidative stress and inflammation
↑Ca^{2+} content and disturbed intracellular Ca^{2+} flux
Altered arachidonic acid and prostaglandin metabolism with impaired synthesis and/or release of TxA_2
Reduced binding of platelets to the vessel wall
↓Function of GPIIb/GPIIIa
GPIIb/GPIIIa
↓Proteolysis of GPIb
Functional defect in the vWF–platelet interaction
GPIb
Endothelial cell
↑Production of prostacyclin and NO
vWF
ECM
Alterations in platelet function
Prohaemorrhagic state
Reduced platelet adhesion and aggregation
↑Circulating fibrinogen
Anaemia
• ↓Erythrocytes
• ↓NO scavenging owing to reduced haemoglobin levels
• ↓Interactions with the vessel wall
• ↓ADP release
• ↑Activation of PGI_2
Therapy
Drugs
• β-Lactam antibiotics
• Aspirin
• NSAIDs
• Anticoagulants
Invasive procedures
• Central venous access
• Haemodialysis

Figure 2 The pathophysiology of prothrombotic conditions in patients with AF and CKD




Patient with CKD
Palpitations, suspected AF or concomitant risk factor(s)
Screen for AF
AF verified?
No
Yes
• Regularly check for new cardiovascular risk factors and/or comorbidities
• Continue to screen for AF (e.g. pulse palpation)
Low risk
CHA2DS2–VASc score
0 (males) or 1 (females)
Close clinical follow-up for new development of stroke risk factors
Patient with AF
Regularly assess renal function
CKD established?
Yes
No
• Regularly reassess renal function
• Regularly check for new cardiovascular risk factors and/or comorbidities
Patient with AF and CKD
Determine stroke risk
(CHA2DS2–VASc score)
High risk
CHA2DS2–VASc score
≥1 (males) or
≥2 (females)
Determine bleeding risk
(HAS-BLED)
• Address modifiable bleeding risk factors
• Consider patient's preferences and values
Consider oral anticoagulant therapy
Estimate renal function (CrCl) to select appropriate oral anticoagulant
• Closely monitor renal function, especially in users of NOACs
• Be vigilant for anticoagulant-related AKI, especially in warfarin users
• Schedule frequent clinical follow-up visits and look for development of new cardiovascular risk factors and comorbidities
• Reassess and address bleeding risk factors
Nature Reviews | Nephrology

bjh review

The use of direct oral anticoagulants in chronic kidney disease

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Summary

Increasing use of direct oral anticoagulants (DOACs) has made management of non-valvular atrial fibrillation and venous thromboembolism easier in most patients. But the

Patients with chronic kidney disease (CKD) are at an increased of developing AF and VTE (Wattanakit *et al*, 2008; Albertsen *et al*, 2013). These patients are also at increased risk of bleeding events compared to those with normal renal function. Bleeding risk is increased in CKD due to reduced

The field would benefit from carefully designed trials that consider renal function, intravascular volume, plasma protein drug binding, and interactions with commonly used medications in each type of kidney disease where anticoagulation is frequently indicated.

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doi: 10.1093/ndt/gfy031

ndt
Nephrology Dialysis Transplantation

A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation

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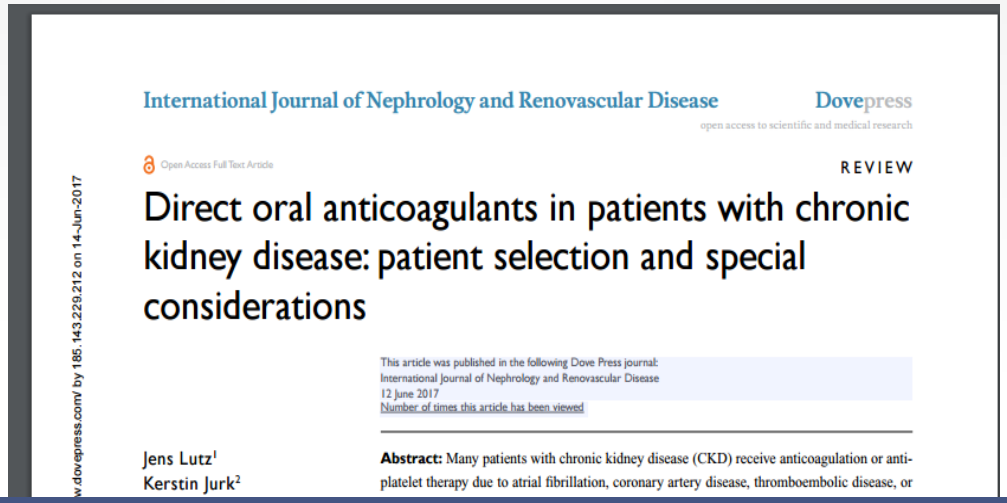
ORIGINAL ARTICLE

DOACs are preferred in stages 1 to 3. In stage 4, the choice between DOACs vs warfarin will consider the pharmacokinetics of the drugs and patient characteristics. Warfarin remains the first-line treatment in ESRD.Anticoagulation with heparin is safe in nondialysis-dependent CKD if optimal monitoring is ensured, but remains a challenge in the hemodialysis patients

DOACs should be avoided in severe forms of CKD.



International Journal of Nephrology and Renovascular Disease

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REVIEW

Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations

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International Journal of Nephrology and Renovascular Disease
12 June 2017
Number of times this article has been viewed

Jens Lutz[1]
Kerstin Jurk[2]

Abstract: Many patients with chronic kidney disease (CKD) receive anticoagulation or anti-platelet therapy due to atrial fibrillation, coronary artery disease, thromboembolic disease, or

Apixaban may be used cautiously as an alternative in acute VTE treatment in severe CKD patients. Insufficient evidence is available to suggest the use of dabigatran and rivaroxaban in this patient population. The benefit of using DOACs in this population for VTE treatment should be weighed against the potential bleeding risk in patients with CKD

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CLINICAL RESEARCH

A Systematic Review of Prophylactic Anticoagulation in Nephrotic Syndrome

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Introduction: Nephrotic syndrome is associated with an increased risk of venous and arterial thromboembolism, which can be as high as 40% depending on the severity and underlying cause of nephrotic syndrome. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend prophylactic anticoagulation only in idiopathic membranous nephropathy but acknowledge that existing data are limited and of low quality. There is a need for better identification of vulnerable patients in order to

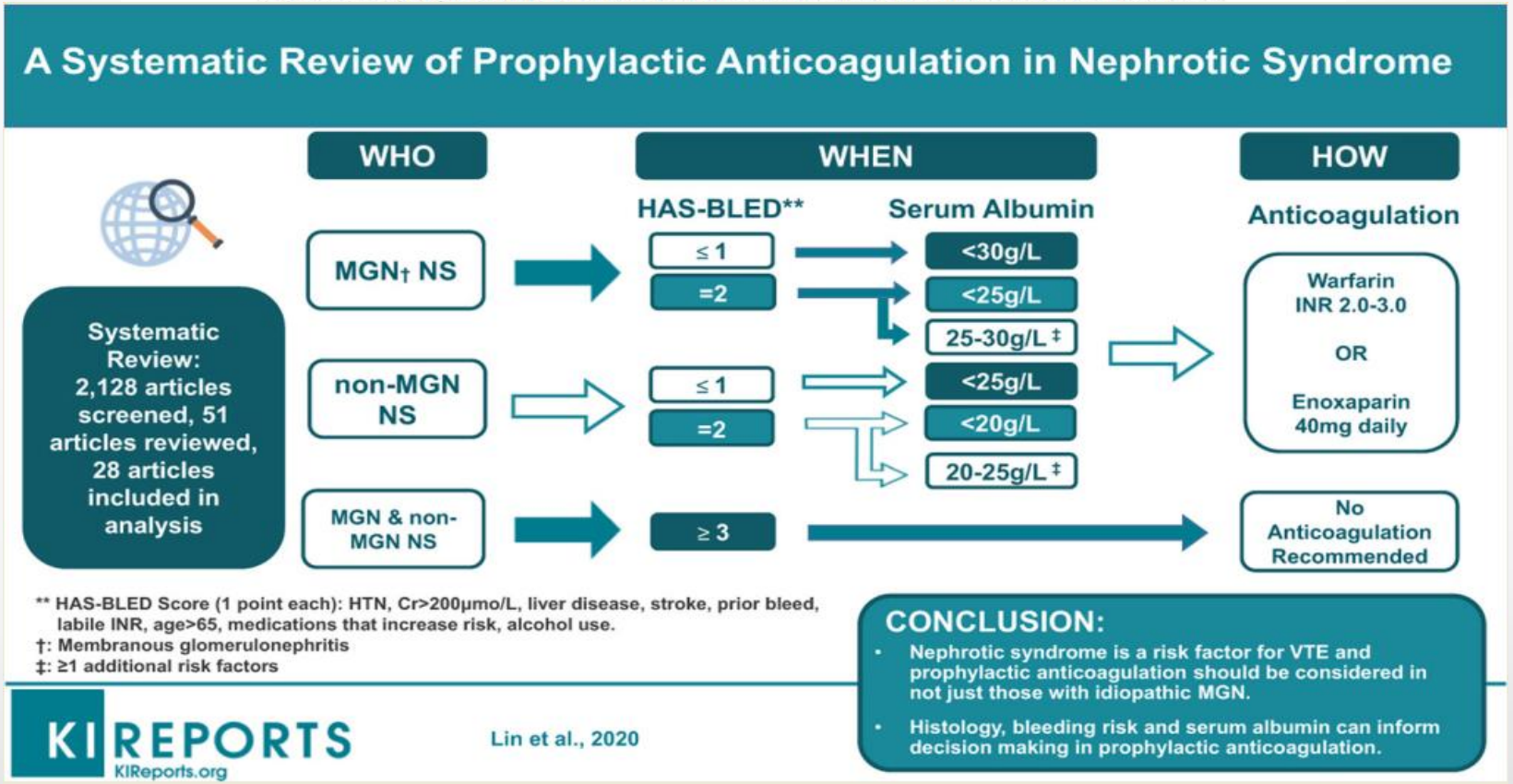
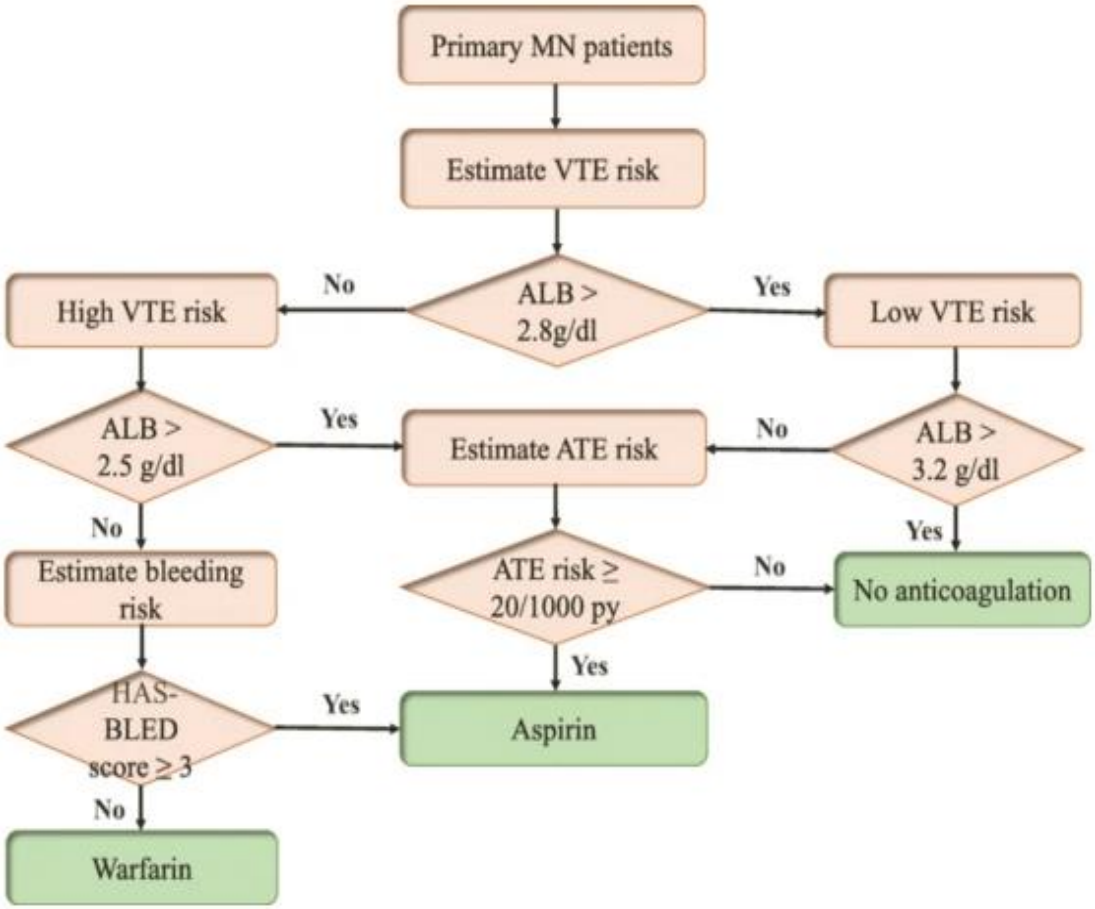
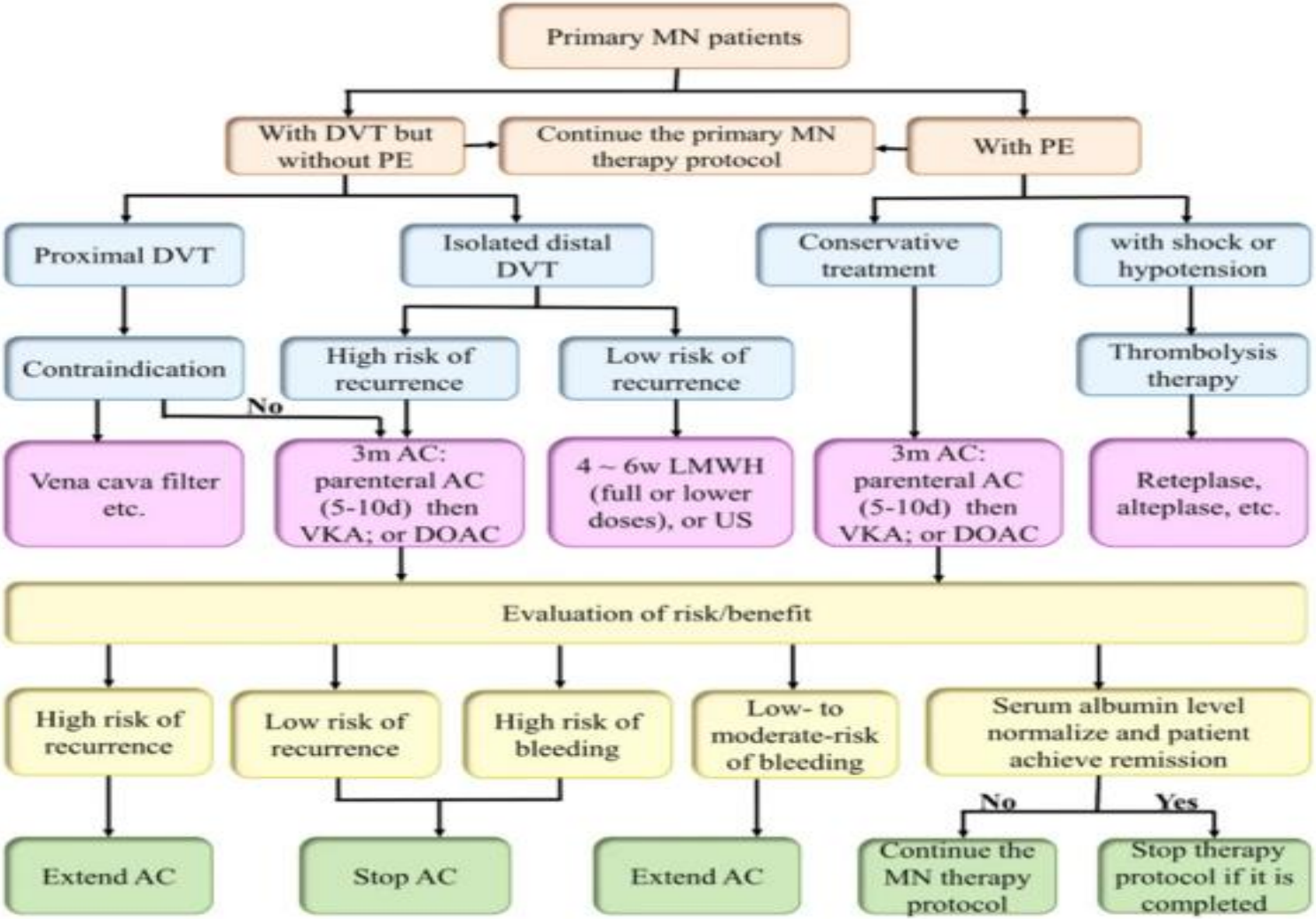


Fig. 1

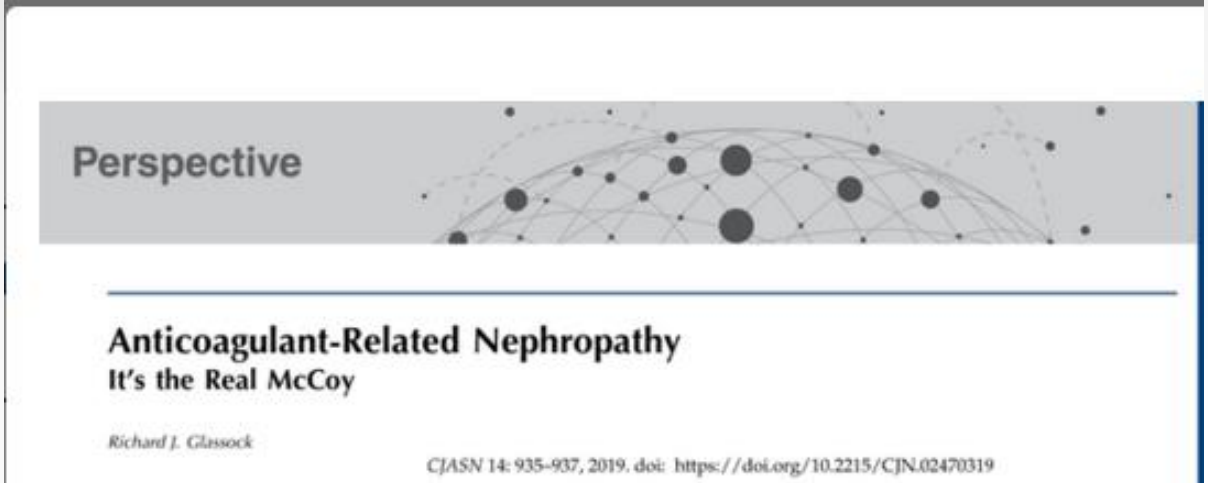


Decision approach for the primary prevention of VTEs and ATEs in primary MN patients. MN: membranous nephropathy; VTE: venous thromboembolic event; ALB: serum albumin; ATE: arterial thromboembolic event; HAS-BLED: hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol;

Fig. 2



Proposed algorithm to guide the decision on anticoagulant management in primary MN patients with VTE. MN: membranous nephropathy; VTE:

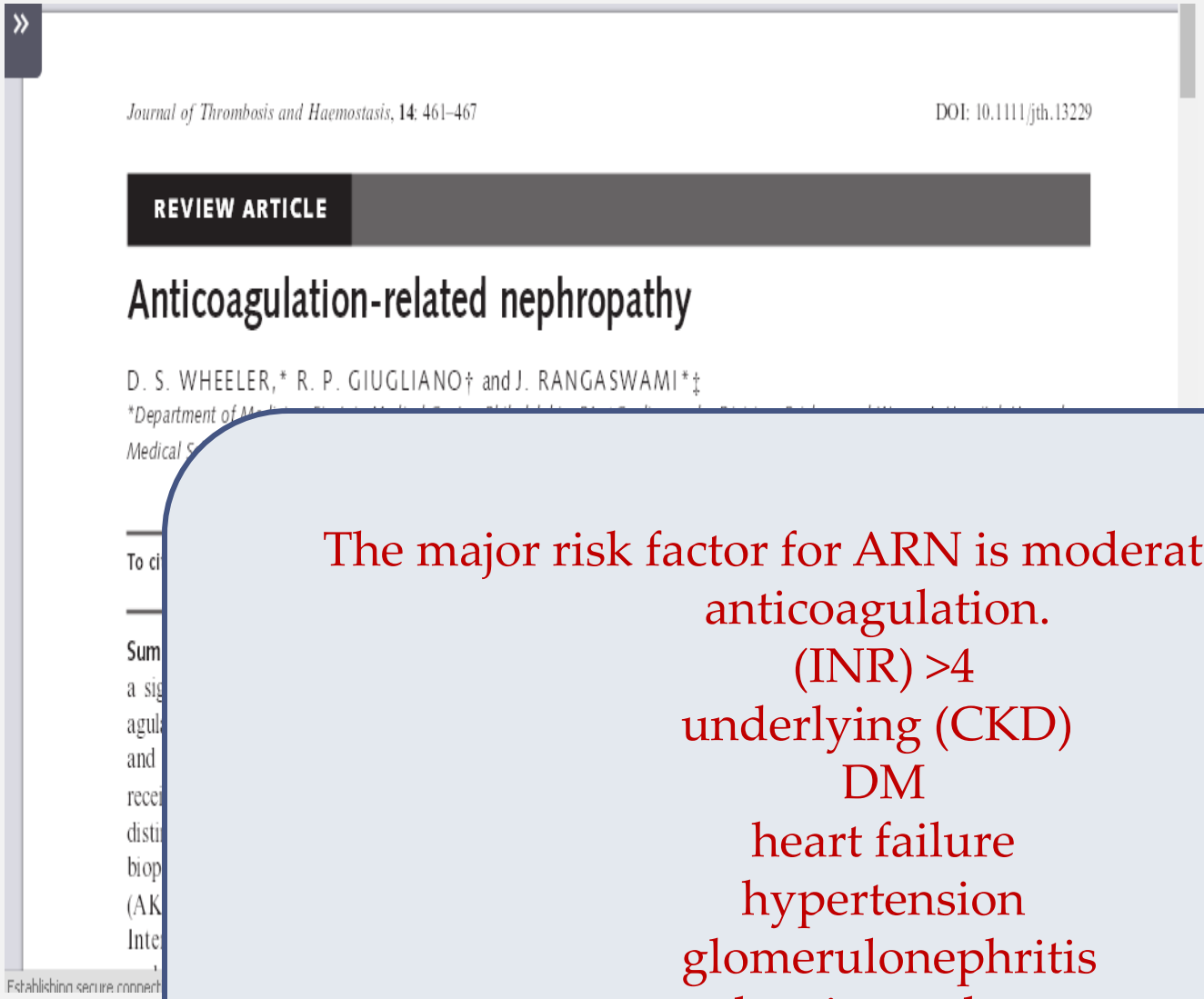


SUSPECT when the following clinical findings are present:

- 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



Journal of Thrombosis and Haemostasis, **14**: 461–467 DOI: 10.1111/jth.13229

REVIEW ARTICLE

Anticoagulation-related nephropathy

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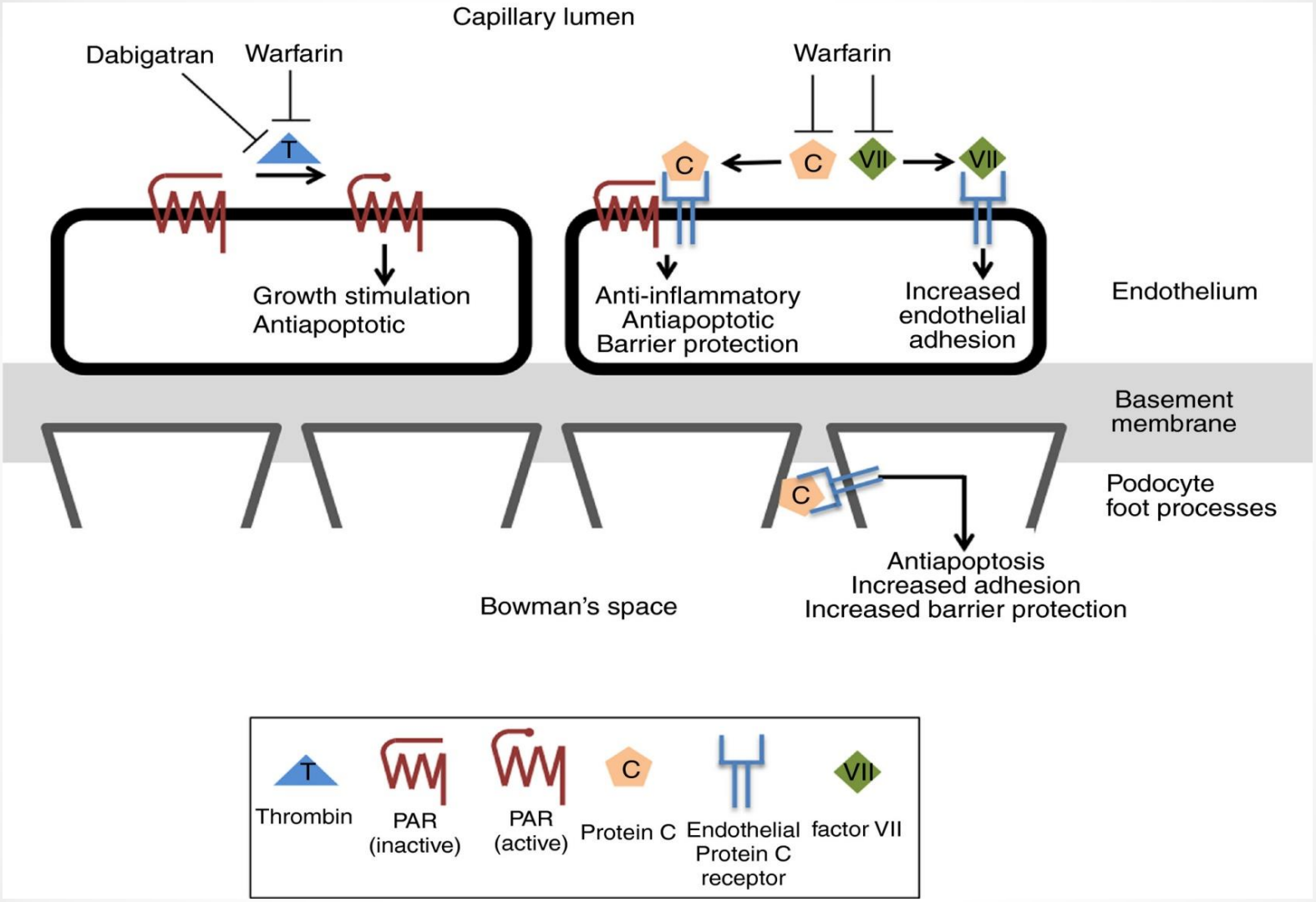
*Department of

The major risk factor for ARN is moderate or severe anticoagulation.
(INR) >4
underlying (CKD)
DM
heart failure
hypertension
glomerulonephritis
nephrotic syndrome.

Anticoagulation-related nephropathy



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Original Research

Kidney Medicine

Anticoagulant-Related Nephropathy in Kidney Biopsy: A Single-Center Report of 41 Cases

Sergey V. Brodsky, Anjali Satoskar, Jessica Hemminger, Brad Rovin, Lee Hebert, Margaret S. Ryan, and Tibor Nadasdy

Rationale & Objective: In 2009, the first case of acute kidney injury and occlusive red blood cell (RBC) tubular casts associated with a high international normalized ratio in a patient receiving warfarin was identified. This entity, named warfarin-related nephropathy, was later renamed anticoagulant-related nephropathy (ARN) after similar cases with other anticoagulants were described. We provide our 10-year experience with ARN based on a single-center kidney biopsy laboratory.

Study Design: The kidney pathology database at the Ohio State University Wexner Medical Center (OSUWMC) was searched for native kidney biopsy cases consistent with ARN. Clinical data were obtained from patient medical records.

Setting & Participants: Native kidney biopsies evaluated between January 1, 2009, and December 31, 2017 at OSUWMC.

Results: Among 8,636 native kidney biopsies reviewed at the OSUWMC, there were 41 (0.5%) patients for whom deterioration in kidney function could not be explained by kidney biopsy findings alone if anticoagulation was not considered. There were 63% men and 95% were white; average age was 62 ± 14 years. Most were on warfarin therapy (N = 28), although cases were also attributed to direct-acting anticoagulants (N = 2), antiplatelet medications (N = 1), heparin or enoxaparin (N = 4), and disseminated intravascular coagulopathy (N = 6). Morphologically, there was acute tubular necrosis and RBC casts. The majority of biopsies had an underlying glomerular disease and many patients had positive serologic test results. In all these cases, the severity of kidney failure, RBC tubular casts, and hematuria were disproportionate to glomerular morphologic changes.

Limitations: Selection bias in the decision to perform a kidney biopsy.

Conclusions: ARN is an uncommon diagnosis in kidney pathology practice, but it should be considered when the number of RBC tubular casts is disproportionate to the severity of glomerular changes in a kidney biopsy in patients either receiving anticoagulation therapy or who presented with acute coagulopathy. Our data suggest that anticoagulation aggravates underlying glomerular diseases rather than directly affecting the glomerular filtration barrier.

Complete author and article information provided before references.

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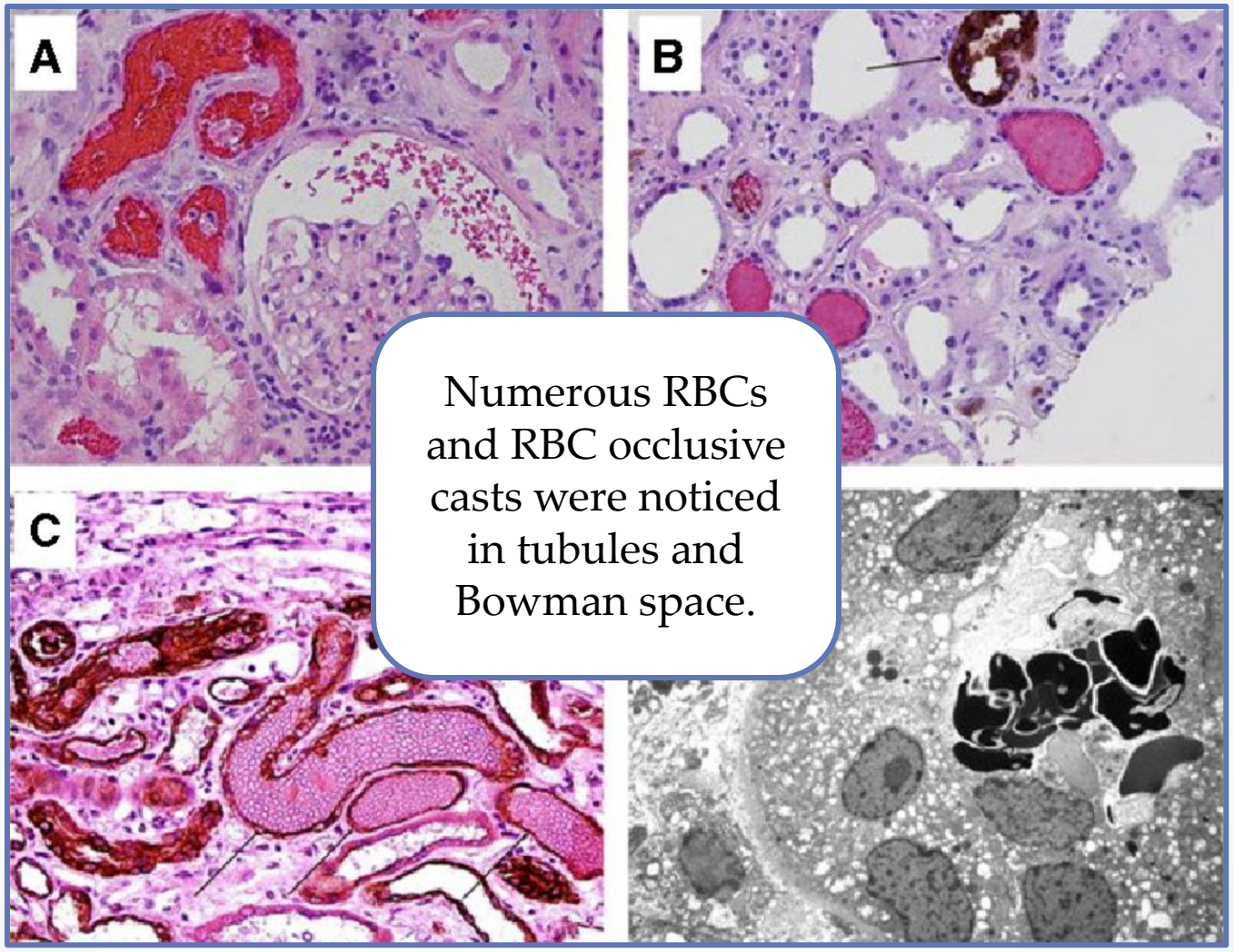
In 2009, we described the first patient who presented with acute kidney injury (AKI) while being treated with warfarin. The patient had a supratherapeutic international normalized ratio (INR) before the AKI. Kidney biopsy showed acute tubular necrosis (ATN) with occlusive red blood cell (RBC) tubular casts.[1] The glomerular changes alone could not explain this severe glomerular hematuria. After searching our renal pathology database, 8 other patients with similar clinical presentation were identified. These patients also were receiving warfarin therapy with high INRs (>3.0) and had ATN and glomerular hematuria (defined by RBCs in Bowman space and RBC tubular casts and acanthocytes in urine sediment) that were unexplained by other morphology findings.[1] This AKI associated with a high INR initially was named warfarin-related nephropathy similar to human disease, including ATN and glomerular hemorrhage.[4,5]

Later it was demonstrated that morphologic features similar to warfarin-related nephropathy may also be seen in 5/6 nephrectomy rats treated with the direct thrombin inhibitor dabigatran.[6] This observation and clinical data suggested that such AKI may be associated not only with vitamin K antagonists, but other anticoagulants as well. Accordingly, the term "anticoagulant-related nephropathy" (ARN) is preferred. Since the seminal report of pathologic features of warfarin-related nephropathy,[1] several investigators published case reports and retrospective studies showing AKI in association with different anticoagulants, including multiple case reports and case series that describe warfarin-related nephropathy,[7-12] case reports of dabigatran-associated AKI,[13-17] a case report of

Typical renal biopsy findings in warfarin-related nephropathy.



Sergey Brodsky et al. JASN 2018;29:2787-2793

Clin Kidney J (2013) 6: 507–509
doi: 10.1093/ckj/sft076
Advance Access publication 10 September 2013

Clinical Report

CKJ

Warfarin-related nephropathy in a patient with mild IgA nephropathy on dabigatran and aspirin

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Abstract
Dabigatran is a direct thrombin inhibitor used as an alternative to warfarin for long-term anticoagulation. We describe a patient who developed acute kidney injury (AKI) in the setting of warfarin conversion to dabigatran, and a renal biopsy demonstrating acute tubular injury. Although the patient had undiagnosed IgA nephropathy that may have predisposed him to bleeding, AKI was due to heme-associated tubular injury. We propose that severe hematuria in patients with underlying glomerular pathology treated with either dabigatran or warfarin may lead to toxic tubular injury through the accumulation of heme-proteins.

Keywords: acute kidney injury; acute tubular necrosis; dabigatran

Background

Dabigatran (Pradaxa, Boehringer-Ingelheim) is a direct thrombin inhibitor that is often substituted for warfarin

was unremarkable. SCr was 5.5 mg/dL (420 μmol/L) with no evidence for systemic hemolysis. The international normalized ratio (INR) was 1.6 with a prothromboplastin time of 62 s. He was initially managed with i.v. fluids, and anticoagulants were held. A serological workup, including anti-

REVIEW ARTICLE

Anticoagulation-related nephropathy

Recommended frequency of renal monitoring for patients receiving anticoagulation

		Maintenance		
	Initiation (3 months)	GFR > 60 mL min^{-1}	GFR 30–60 mL min^{-1}	GFR < 30 mL min^{-1}
Warfarin	3–4 weeks	6 months	2–3 months	2–3 months
DOAC	3–4 weeks	12 months	6 months	3 months

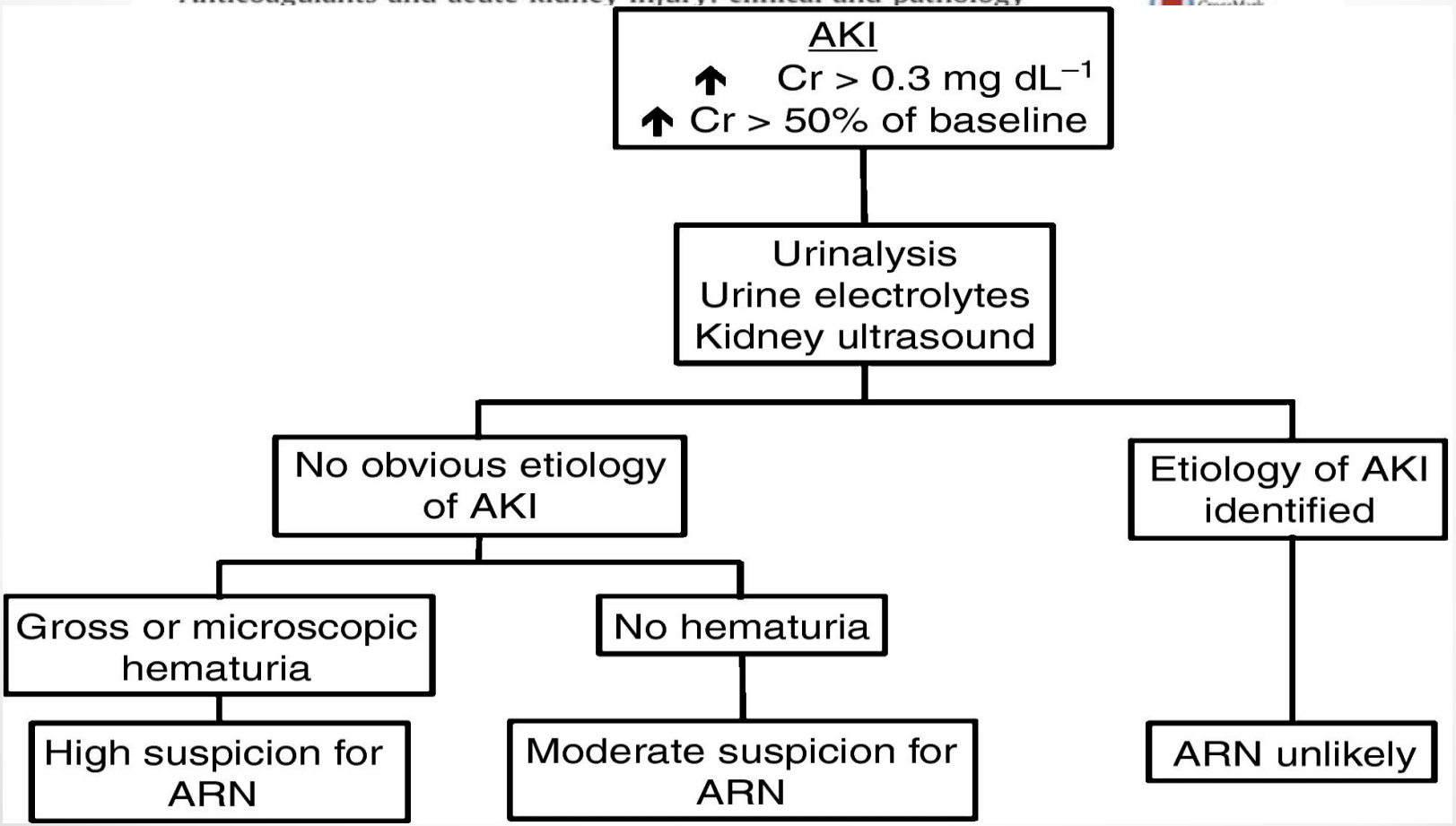
Kidney Res Clin Pract 33 (2014) 174–180

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Review Article

Anticoagulants and acute kidney injury: clinical and pathology

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