Anticoagulation And Kidney Disease

Zahra Shafii, MD.
Assistant Professor of Nephrology
Rajaie Cardiovascular Medical and Research Center
IUMS

Outline

- Anticoagulation in CKD
- Anticoagulation in Nephrotic Syndrome
- Anticoagulation in Hemodialysis
- Anticoagulation in Kidney Transplantation
- Bleeding Management of Anticoagulants
- Anticoagulation Related Nephropathy

Anticoagulation in CKD

- Patients with chronic kidney disease are at increased risk for both arterial and venous thromboembolism
- The risk of AF and ACS is double in patients with eGFR <60 mL/min/1.73m
- Anticoagulants are cleared, with only a few exceptions, by kidneys and/or the liver

Vitamin K Antagonists

- *VKAs* are most widely used
- There is an Increased hemorrhagic risk in CKD particularly within the first 30 to 90 days
- Most major bleeding events are GI
- The guidelines for AF or VTE: no dose adjustment in CKD
- Start-low go-slow" rule to prevent the risk of hemorrhage reduce warfarin doses by 10% if eGFR: 30 and 59 and by 20% if eGFR < 30
- There is a relationship between warfarin-vascular calcifications and renal function decline.

Heparin

	Dose adjustment function of eGFR (mL/min)		
Anticoagulant	**59-30**	**29-15**	**<15**
Unfractionated heparin	Not necessary	Not necessary	Dose reduction by 33%: loading dose 60 IU/kg, maintenance 12 IU/kg/h, subsequent aPTT-adjusted dosing
Enoxaparin	Not necessary (1 mg/kg/12 hours) VTE 1.5 mg/kg once daily (The United States)	1 mg/kg once daily anti-Xa adjusted dosing (Anti-Xa:Iia ratio 3.9)	
Dalteparin	ACS (120 IU/kg/12 hours) VTE (100 IU/kg/12 hours or 200 IU/kg once daily 1 month, then 150 IU/kg once daily 5 months, then oral anticoagulants/LMWH)	-	
Tinzaparin	VTE (175 IU/kg once daily)	anti-Xa adjusted dosing to eGFR <20 (Anti-Xa:Iia ratio 2.8)	
Fondaparinux	VTE: 50% dose compared to the recommended dose per body weight ACS 2.5 mg once daily	VTE: not recommended for eGFR <30 ACS: not recommended for eGFR <20	

DOACs

- Dabigatran: FDA approval 2010
- Rivaroxaban: FDA approval in 2011
- Apixaban: FDA approval in late 2012
- Edoxaban: FDA approval in early 2015

Potential advantages and disadvantages of DOACs

Potential advantages	Potential disadvantages
Lower rates of intracranial bleed and hemorrhagic strokes than warfarin	Higher drug cost; may require prior insurance approval
No need for routine lab monitoring	Lack of availability of a reversal agent
Fewer drug or food interactions than warfarin	Increased risk of gastrointestinal bleeding
	Higher rebound rate of VTE events in patients with poor adherence
	No clear efficacy data in certain patient populations (e.g., patients with malignancy)

DOACs cont…

- Main issue :define kidney function
- 60% of the patients with mild-to-moderate CKD receive lower doses of DOACs, (increased thromboembolic events).
- Check renal function : initiation of treatment with DOACs, after 3 months, and then every year
- Check RF, in high-risk patients (elderly >75 years, women, patients with low body mass, frail or on dabigatran) : every 6 months
- Check RF in Any condition worsening RF :infections, acute heart failure, potentially nephrotoxic medication

Evidence for use of anticoagulant class according to renal function

eGFR (mL/min)	UFH	LMWHs	Warfarin	Direct oral anticoagulants
>90	Yes	Yes	Yes	Yes
60-89	Yes	Yes	Yes	Yes
30-59	Yes	Yes	Yes	Rivaroxaban dose adjustment
15-29	Yes	Dose adjustments may be needed; bioaccumulation possible Enoxaparin use with caution	Yes	Rivaroxaban and dabigatran contraindicated Apixaban use with caution
<15	Yes	Use contraindicated outside selected patients with appropriate monitoring	Yes	Rivaroxaban and dabigatran contraindicated; see text for discussion of apixaban

Yes indicates there is evidence for use without dose adjustment.

Pharmacokinetic properties of oral anticoagulants (adapted from Jain et al[13] and Lutz et al[14])

Oral anticoagulant	Mechanism of action	Prodrug	Pharmacokinetic properties		
			Metabolism	Dialyzable	Dose adjustment
Warfarin	Vitamin K antagonist	No	Predominantly via cytochrome P450 type 2C9 (CYP2C9)	No	No
Dabigatran	Direct inhibitor of free thrombin and fibrin-bound thrombin	Yes	Renal excretion 80%	Yes	Yes
Rivaroxaban	Free and clot-bound Xa factor inhibitor, prothrombinase activity inhibitor	No	Renal excretion 66%, 36% as unchanged drug	No	Yes
Apixaban	Free and clot-bound Xa factor inhibitor	No	Metabolized in liver via CYP3A4, renal excretion 27% and in feces	Partial	No
Edoxaban	Free Xa factor and tissue factor inhibitor	No	10% hydrolyzed by carboxylesterase 1, 50% unchanged upon renal excretion	No	Yes

	CrCl (mL/min) estimated using the Cockroft-Gault equation				
Recommended oral anticoagulant	**≥50**	**30–49**	**15–29**	**<15**	**End-stage renal disease on dialysis**
	DOACs	**DOACs**	**Warfarin/DOACs**	**Warfarin/DOACs (with caution)**	
Warfarin	Preferable to adjust the dose function of time in therapeutic range, optimal ≥70%				
Dabigatran	150 mg twice daily 110 mg twice daily ≥80 years, or associated with P-glycoprotein inhibitors, or high risk of hemorrhage	Idem	The United States (based only on FDA approval) - 75 mg twice daily Europe - NO	No	
Rivaroxaban	20 mg once daily	15 mg once daily (dose used by landmark trials recommended by small pharmacokinetic studies)		No	
Apixaban	5 mg twice daily 2.5 mg twice daily if any ≥2 of the following: age ≥ 80 years, body weight ≤ 60 kg and creatinine ≥1.5 mg/dL	Idem	2.5 mg twice daily	The United States – 2.5 mg twice daily Europe - NO	The United States (FDA) - 5 mg twice daily Europe - NO
Edoxaban	60 mg once daily 30 mg once daily when ≥2 of the following criteria are met: body weight ≤ 60 kg, CrCl 30-50 mL/min and therapy with Verapamil, Dronedarone or Quinidine is associated	30 mg once daily		No	

SAMe-TT2R$_2$ Score

Sex	Female gender		1
Age	Age < 60 years old		1
Medical history	Two or more co-morbidities: • Hypertension • Diabetes • Coronary disease • Peripheral artery disease • Heart failure • Prior stroke • Pulmonary disease • Renal disease • Liver disease		1
Treatment	Treatment with amiodarone		1
Tobacco		Tobacco use in the past 2 years	2
Race		Non-Caucasian race	2
Maximum points			8

Anticoagulation in Nephrotic Syndrome

- NS carry clinically significant risk of arterial and venous thromboembolic events especially in patients with membranous nephropathy.
- Anticoagulation should be considered in the setting of hypoalbuminemia.
- Must be balanced with the patient's risk of bleeding.
- It should be commenced as soon as it is safe as the risk of thrombosis is highest in the first 6 months of diagnosis.

- Etiology of NS
- Serum Albumin level
- Risk of bleeding
- Other VTE risk factors: immobility, obesity, malignancy, recent surgery, pregnancy, medications, central venous catheters, or genetic

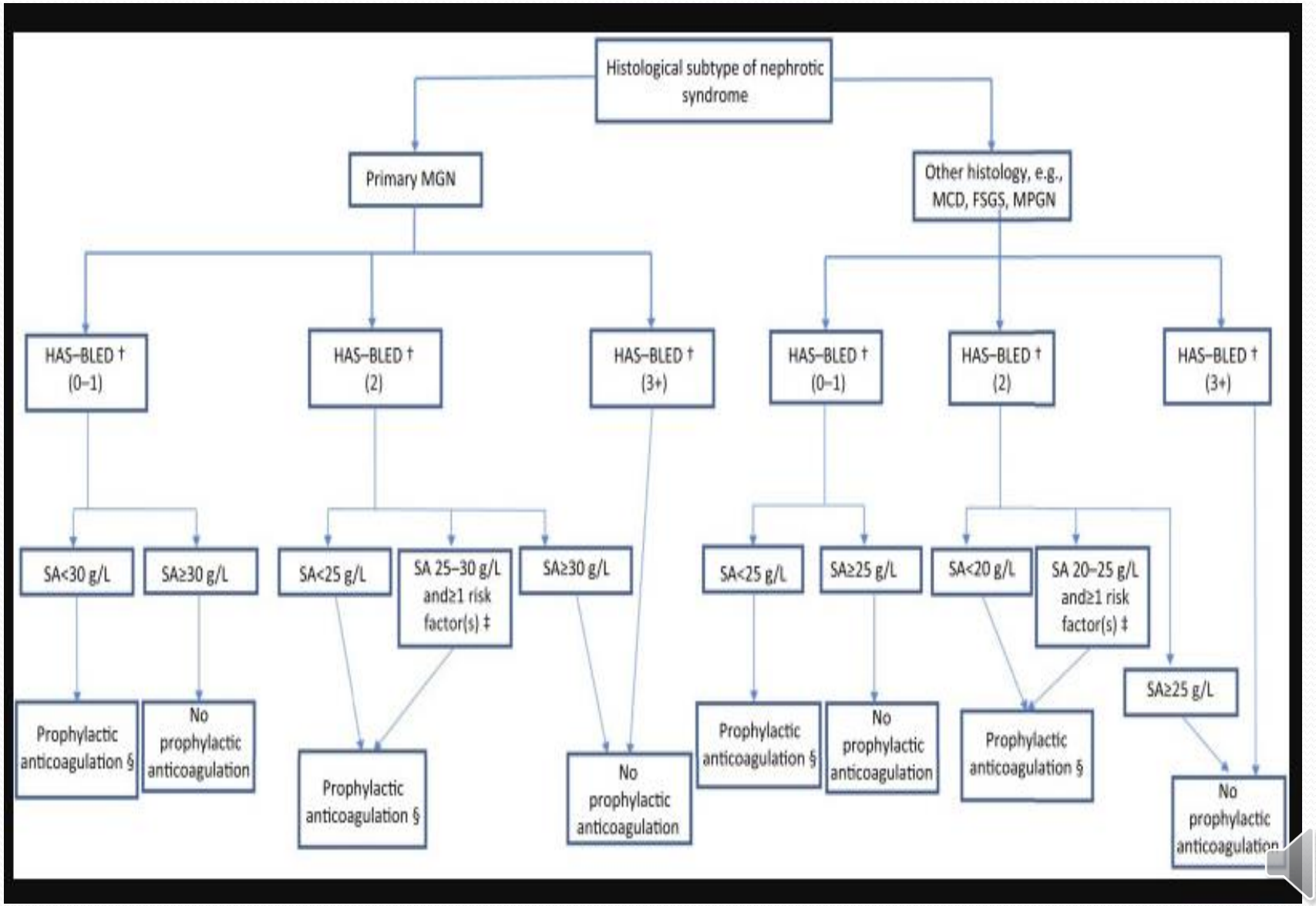
- Anticoagulation is not beneficial for patients with high bleeding risk scores, regardless of serum albumin.
- the HAS-BLED scoring may not be accurate, particularly in severe hypoalbuminemia

Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points
H	Hypertension (ie, uncontrolled blood pressure)	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding tendency or predisposition	1
L	Labile INRs (for patients taking warfarin)	1
E	Elderly (age greater than 65 years)	1
D	Drugs (concomitant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2
		Maximum 9 points

HAS-BLED score (total points)	Bleeds per 100 patient-years¶
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5 to 9	Insufficient data

The HAS-BLED bleeding risk score has only been validated in patients with atrial fibrillation receiving warfarin. Refer to UpToDate topics on anticoagulation in patients with atrial fibrillation


Histological subtype of nephrotic syndrome
Primary MGN
Other histology, e.g., MCD, FSGS, MPGN
HAS-BLED † (0–1)
HAS-BLED † (2)
HAS-BLED † (3+)
HAS-BLED † (0–1)
HAS-BLED † (2)
HAS-BLED † (3+)
SA<30 g/L
SA≥30 g/L
SA<25 g/L
SA 25–30 g/L and≥1 risk factor(s) ‡
SA≥30 g/L
SA<25 g/L
SA≥25 g/L
SA<20 g/L
SA 20–25 g/L and≥1 risk factor(s) ‡
SA≥25 g/L
Prophylactic anticoagulation §
No prophylactic anticoagulation
Prophylactic anticoagulation §
No prophylactic anticoagulation
Prophylactic anticoagulation §
No prophylactic anticoagulation
Prophylactic anticoagulation §
No prophylactic anticoagulation

- Choice of agent due to patient and clinical factors: ease of use and access, patient preference, and feasibility of monitoring requirements.
- DOACs: not first-line for prophylaxis and treatment of ATE/VTE in NS
- DOACs: reasonable alternatives to warfarin and LMWH in failure or intolerability of them
- Aspirin: higher albumin levels, high risk of ATE/VTE with high bleeding risk, Other (non MN) high-risk GNs

Duration of Treatment

- Optimal duration of treatment is poorly established.
- The KDIGO guidelines suggest continuation of prophylaxis while the patient remains nephrotic (serum albumin <30 g/l)

Anticoagulation in Hemodialysis

The risk of bleeding exceeds the risk of clotting in:

- Severe thrombocytopenia (platelet count of $<20{,}000 \times 10^9/L$)
- Evidence of active bleeding from the gastrointestinal tract, intra-abdominal bleeding, extensive bleeding from surgical wounds, or catheters at the time of dialysis
- Major surgery in the prior 72 hours
- Active intracranial or extradural hemorrhage
- Use of systemic anticoagulants
- Uremic pericarditis
- Factor VII or VIII deficiency

Use of antiplatelet agents alone is not bleeding risk factor

Standard-risk patients

- UFH**:** 1000 to 2000 units at beginning then infusion of 500 units per hour, turned off 60, if clotting develops 30 minutes before the end
- Enoxaparin: 20 mg for a four-hour dialysis session.
- If clotting detected: increase the UFH or LMWH bolus or UFH infusion and evaluate the dialysis access
- Bleeding from needle sites longer than 7 minutes: stop infusion earlier, lower the bolus dose for the following dialysis session, evaluation of HD access

High risk for bleeding patients

- No-heparin method
- Heparinized solution rinse
- Heparin-bonded dialyzer

Recurrent filter thrombosis

- Standard bleeding risk:
  - ✓ Dose adjustment of UFH or LMWH
- High bleeding risk:
  - ✓ Increase the blood flow rate and the needle gauge,
  - ✓ Converting to short daily HDF with a high volume of predilutional infusate
  - ✓ More frequent saline flushes
  - ✓ Citrate dialysate

Anticoagulation in Kidney Transplantation

Pre operation

- Warfarin:
  - Stopping 5 days before a planned or utilizing a reversal agent (FFP or PCCs)
- DOACs:
  - Discontinuation for two drug half-lives
  - Utilize with caution of in patients awaiting deceased-donor transplantation

Elimination half-life based on renal function

Renal insufficiency	Half-life (h)
Dabigatran[3,12,72]	
CLcr >80 mL/min	13.8
CLcr 50–79 mL/min	16.6
CLcr 30–49 mL/min	18.7
CLcr <30 mL/min	27.5
Hemodialysis	34.1
Rivaroxaban[3,23,24,72]	
CLcr >80 mL/min	8.3
CLcr 50–79 mL/min	8.7
CLcr 30–49 mL/min	9.0
CLcr <30 mL/min	9.5
Hemodialysis	12–13
Apixaban[3,33,34,72]	
CLcr >80 mL/min	15.1
CLcr 50–79 mL/min	14.6
CLcr 30–49 mL/min	17.6
CLcr <30 mL/min	17.3
Hemodialysis	12.5/12.7[a]
Edoxaban[37,38]	
CLcr >80 mL/min	8.6
CLcr 50–79 mL/min	8.6
CLcr 30–49 mL/min	9.4
Clcr <30 mL/min	16.9
Hemodialysis	10–14[b]

Original article

Safety and efficacy of direct-acting oral anticoagulants versus warfarin in kidney transplant recipients: a retrospective single-center cohort study

Alexandra L. Bixby ✉, Suhail A Shaikh, Abhijit S. Naik, Laura Cotiguala, Katie McMurry, Milagros D. Samaniego-Picota, Vincent D. Marshall, Jeong M. Park

First published: 27 February 2020 | https://doi.org/10.1111/tri.13599

Direct oral anticoagulant considerations in solid organ transplantation: A review

David M. Salerno,[1] Demetra Tsapepas,[1,2] Apostolos Papachristos,[3] Jae-Hyung Chang,[4] Spencer Martin,[5] Mark A. Hardy,[2] and Jaclyn McKeen[6]

‣ Author information ‣ Copyright and License information Disclaimer

After Transplantion

- DOACs should be started when hemostasis effectively achieved, with approval of the transplant surgeon.
- Avoid the use of DOACs in the immediate post-transplant period until a stable renal allograft function, especially in deceased-donor kidney transplants and in high-immunological risk kidney

DOACs in Renal Transplant

- Metabolism of the DOACs is dependent on the CYP 450 enzyme system and P-gp efflux pump
- Dabigatran is a substrate of P-gp efflux pump. With no contribution from CYP 450
- The choice of tacrolimus for immunosuppression may be favorable compared to CsA
- 50% dose decrease when coadministered with drugs that are strong dual-inhibitors including ketoconazole, itraconazole, ritonavir, or clarithromycin

Drug Interactions with Direct Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Increased concentration	Strong p-gp inhibitors: ketoconazole, ciclosporin, tacrolimus, ritonavir, dronedarone Caution with: amiodarone, verapamil, clarithromycin, quinidine, ticagrelor	Strong CYP3A4 and p-gp inhibitors: ketoconazole, ritonavir, dronedarone Caution with: ciclosporin, tacrolimus	Strong CYP3A4 and p-gp inhibitors: ketoconazole, ritonavir, dronedarone	Strong p-gp inhibitors: reduce dose with ketoconazole, ciclosporin, dronedarone Caution with: ritonavir
Reduced concentration	Strong p-gp inducers: rifampicin, St John's wort, carbamazepine, phenytoin, barbiturates, dexamethasone	Strong CYP3A4 and p-gp inducers: rifampicin, St John's wort, carbamazepine, phenytoin, barbiturates	Strong CYP3A4 and p-gp inducers: rifampicin, St John's wort, carbamazepine, phenytoin, barbiturates	Strong p-gp inducers: rifampicin, St John's wort, carbamazepine, phenytoin, barbiturates, dexamethasone

Bleeding Management of Anticoagulants

- Assess the severity of bleeding

  Minor bleeding

  Major bleeding
- Assess and the degree of anticoagulation drug dose, last dose

- Discontinue the drug
- Transfuse blood products if necessary
- Address the hemorrhage anatomically
- Administer pro-hemostatic therapies such as antifibrinolytic agents
- Use Antidote

Management of Patients in Cases of Bleeding

Patients with bleeding on novel oral anticoagulation agents

Mild bleeding

Delay next dose or discontinue treatment as appropriate

Moderate-severe bleeding

- Symptomatic treatment
- Mechanical compression
- Surgical intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion
- Oral charcoal application (if dabigatran etexilate is ingested <2h before)
- Hemodialysis†

Life-threatening bleeding

- Hemodynamic and hemostatic resuscitat
- Consideration of PCC,‡ activated PCC
- Charcoal filtration†
- rFVIIa

- **Dabigatran**:

  Idarucizumab, aPCC, antifibrinolytic agent, oral activated charcoal if the last anticoagulant dose was within the previous two hours, Hemodialysis

- **Rivaroxaban, apixaban, edoxaban, betrixaban**

  An antifibrinolytic agent, oral activated charcoal if the last dose of the anticoagulant was recent enough (rivaroxaban 8 hours; apixaban 6 hours; edoxaban 2 hours), andexanet alfa, unactivated 4-factor PCC

Anticoagulation Related Nephropathy

- A type of AKI by excessive anticoagulation with warfarin and other anticoagulants
- Can cause CKD and increase risk of mortality

Risk Factors

- moderate or severe anticoagulation induced anticoagulants:(INR >4) major risk factor
- Underlying chronic kidney disease
- Diabetes mellitus
- Heart failure
- Hypertension
- Glomerulonephritis particularly nephrotic syndrome

Clinical Presentation

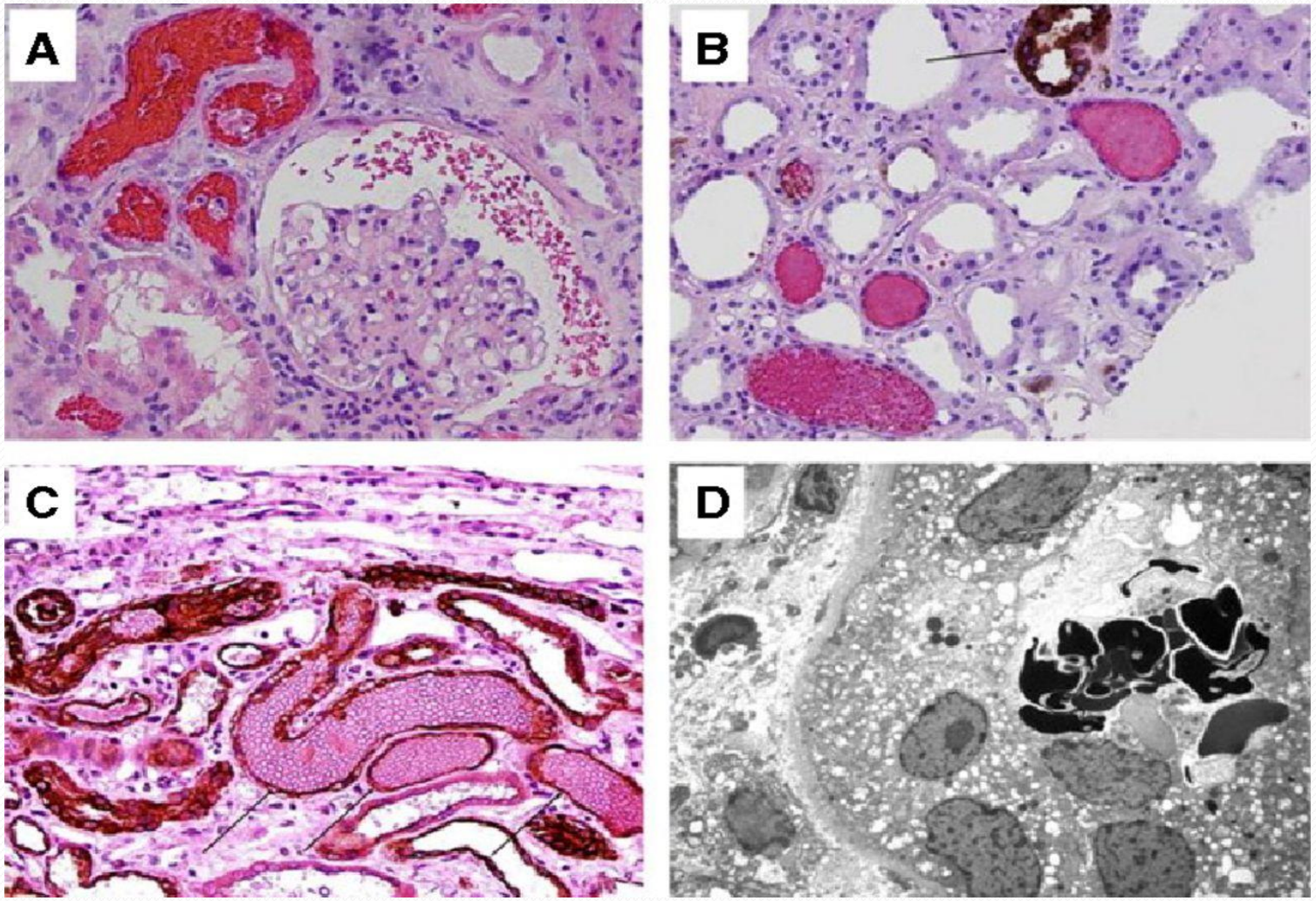
- AKI within several days of elevated INR.
- Microscopic or gross hematuria that may be transient
- No characteristic features on imaging

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


A
B
C
D

TREATMENT

- Prevent ARN: proper adjustment of the anticoagulant dose.
- In warfarin-treated Pt.: switch to dabigatran or rivaroxaban
- In Pt. receiving dabigatran ,rivaroxaban: reduce the dose
- In Pt. receiving apixaban: switch to rivaroxaban , dabigatran

Thank You