GRAND ROUNDS CLINICI DEL MERCOLEDÌ
con il Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

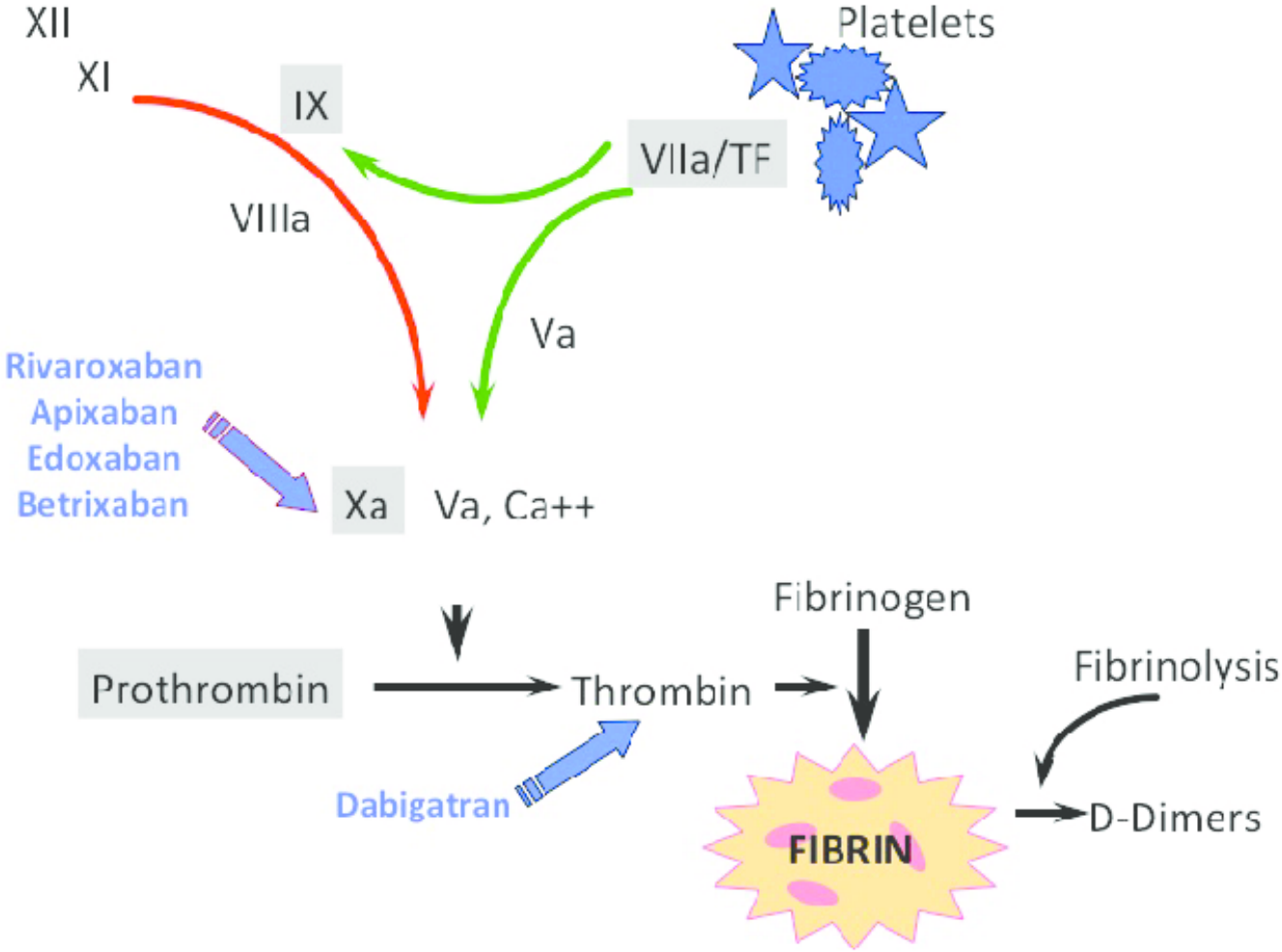
ATS Pavia

Aula Magna "C. Golgi"
& WEBINAR

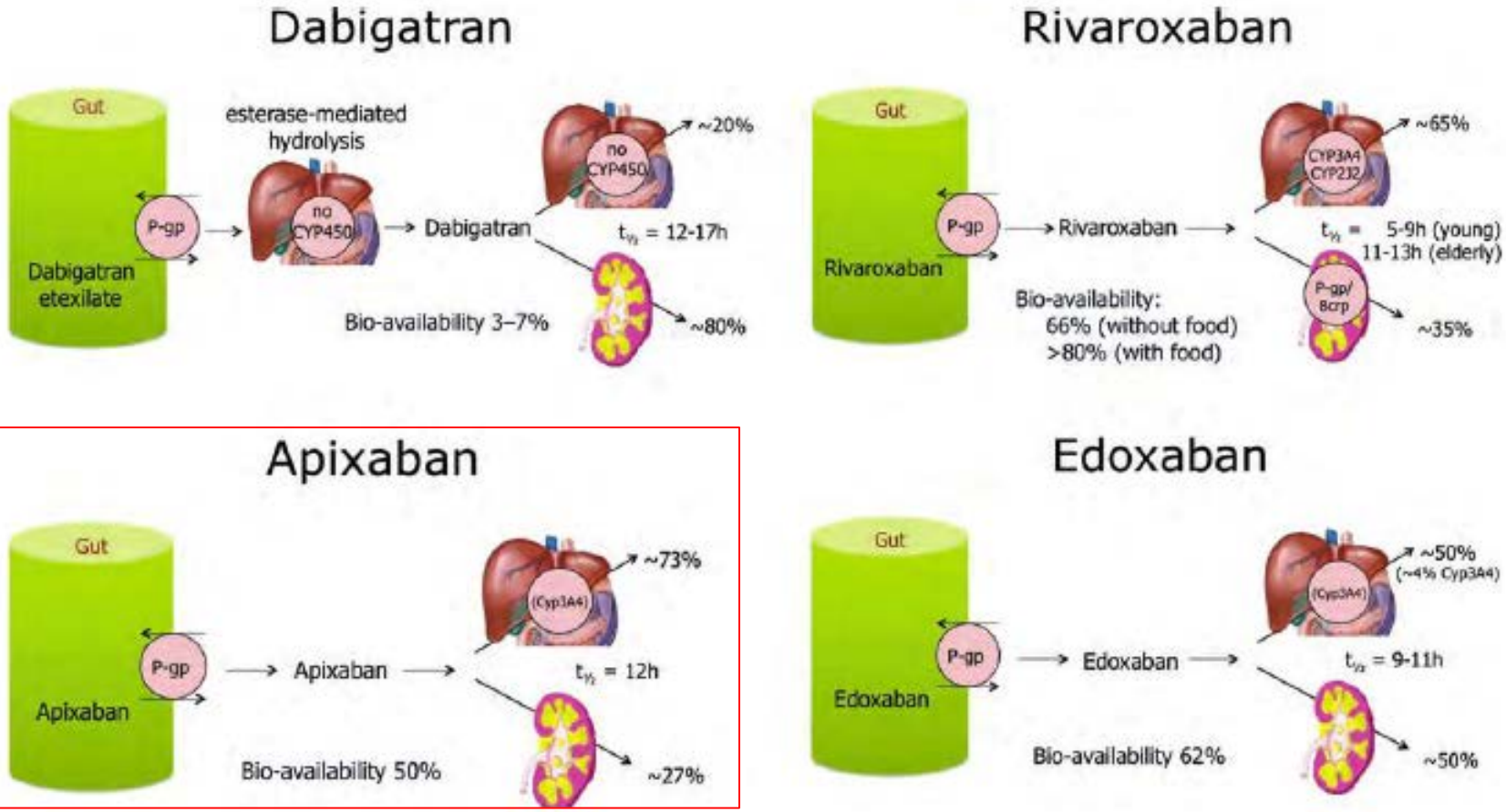
12 ottobre 2022

Marilena Gregorini
U.O.C. Nefrologia e Dialisi - Abilitazione al Trapianto

Nefropatia da anticoagulanti: una complicanza sottodiagnosticata


XII
XI
IX
VIIIa
VIIa/TF
Platelets
Va
Rivaroxaban
Apixaban
Edoxaban
Betrixaban
Xa
Va, Ca++
Fibrinogen
Prothrombin
Thrombin
Fibrinolysis
Dabigatran
FIBRIN
D-Dimers

Assorbimento e metabolismo di diversi NAO



Heidbuchel H, et al. *Europace* 2013;15:625-51

NOAC dosing for stroke prevention in patients with non-valvular atrial fibrillation according to renal function

★ Patients with ≥2 of the following should also receive 2.5mg BD dose of Apixaban:

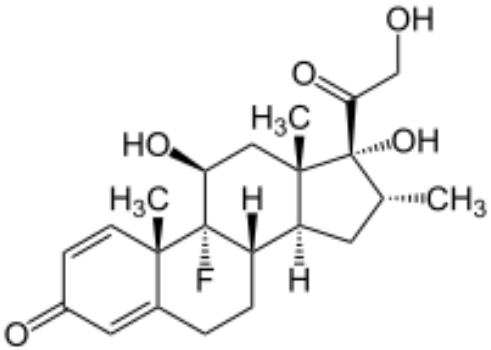
- Age ≥80
- Weight ≤60kg
- Serum Creatinine ≥133µmol/L (1.5mg/dl)

Clinical case

- **Age:** 31 years
- **Gender:** Male

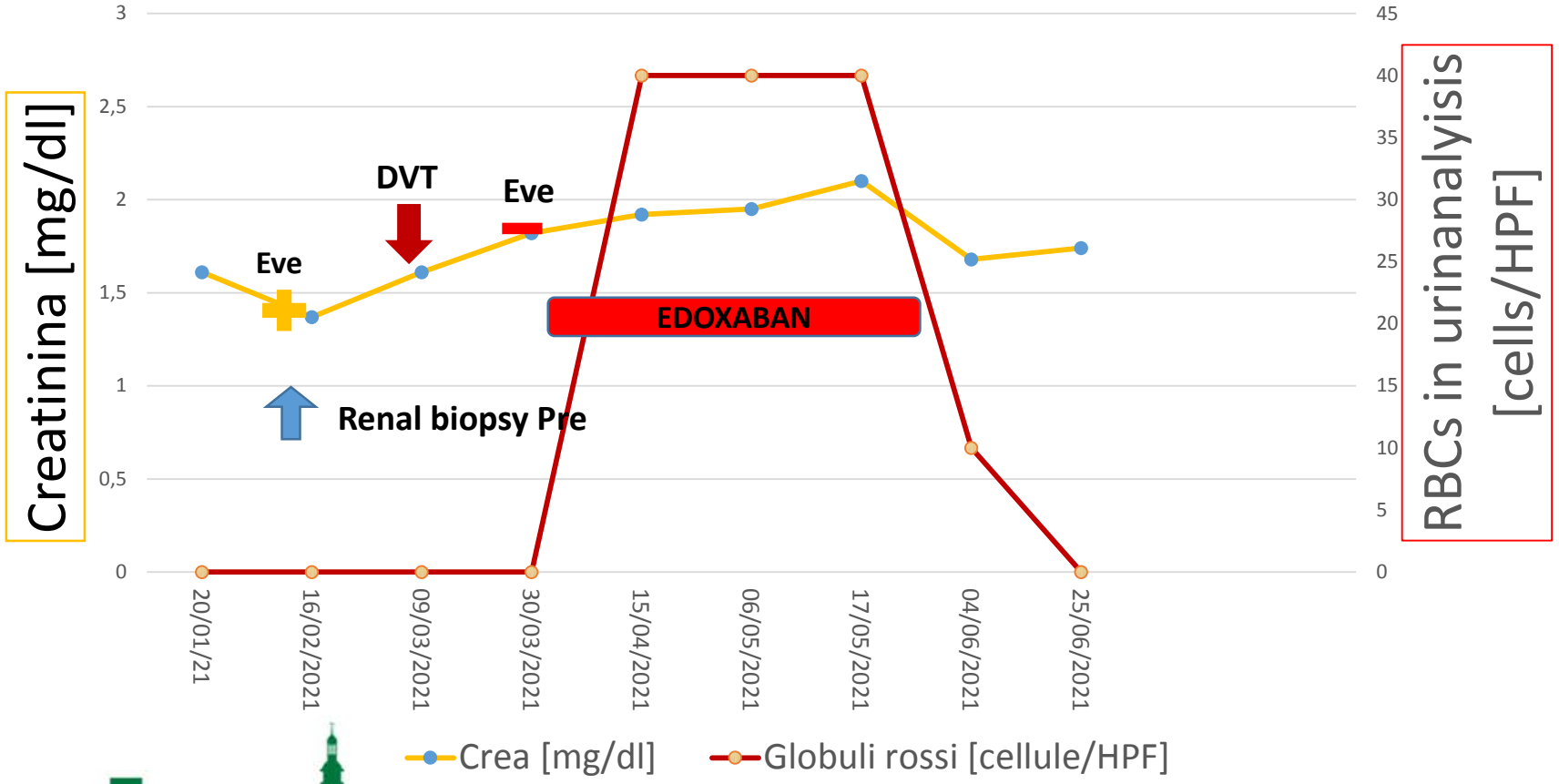
- **Nephropathy:** bilateral vesicoureteral reflux

- **Kindey transplant:** Aprile 2014 from a living donor
- **IS induction treatment:** BASILIXIMAB+MP
- **IS maintenance treatment:** FK+ MMF+MP
- **Comorbidities:** Hypertension complicated by hypertensive cardiopathy.

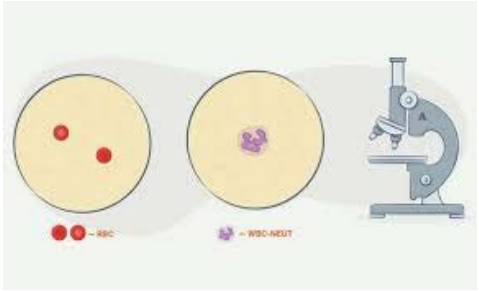


GFR

Timeline of events

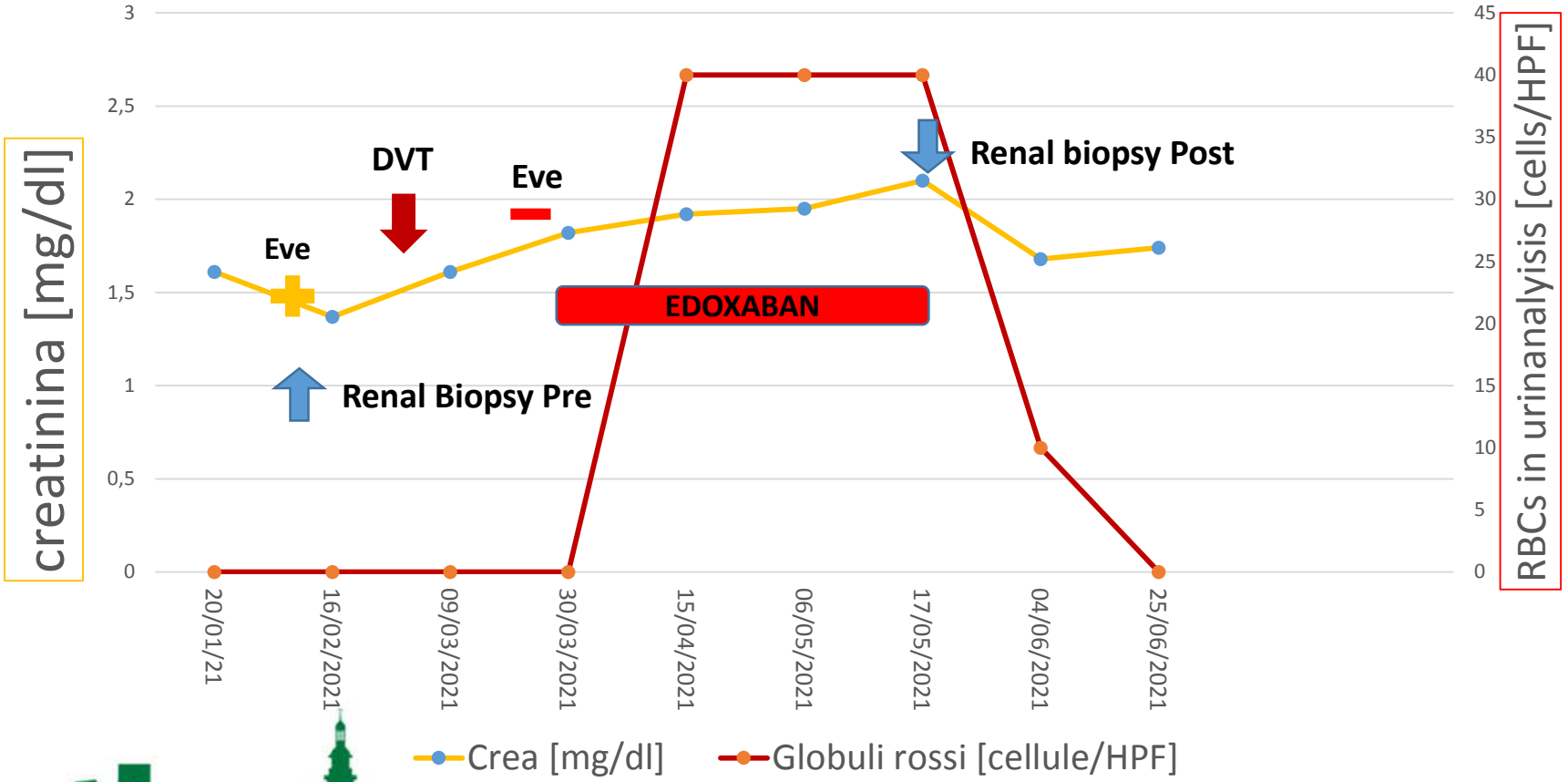


DIAGNOSTIC PATH



Urinary sediment analysis: evidence of RBCs cast and hematuria

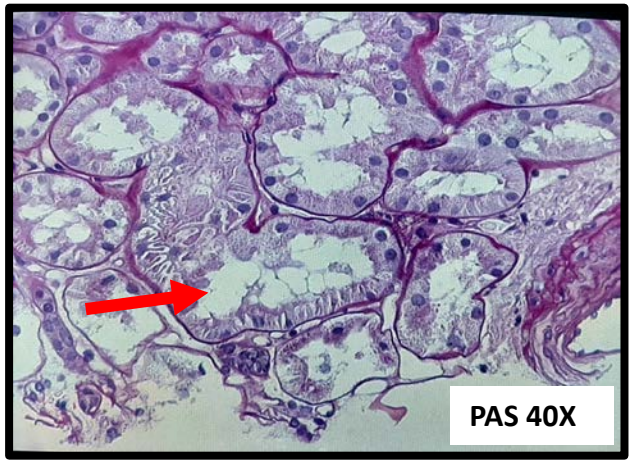
Timeline of events

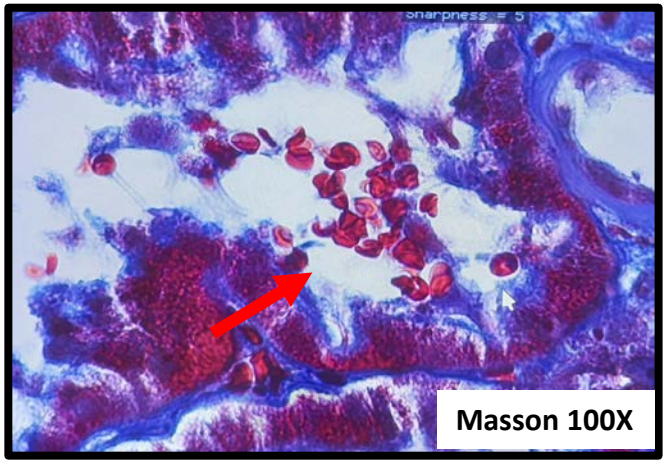


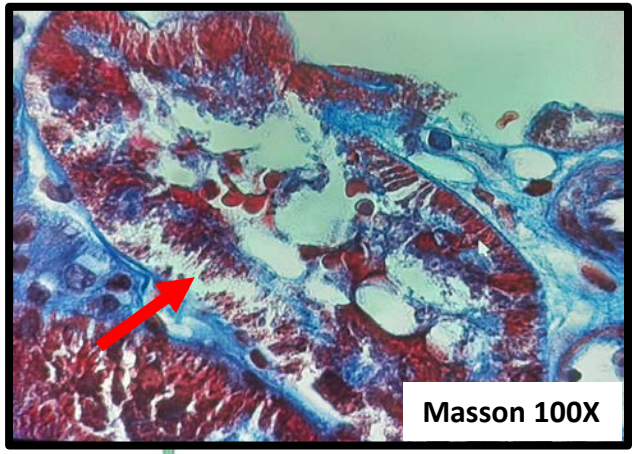
DIAGNOSTIC HYPOTHESIS

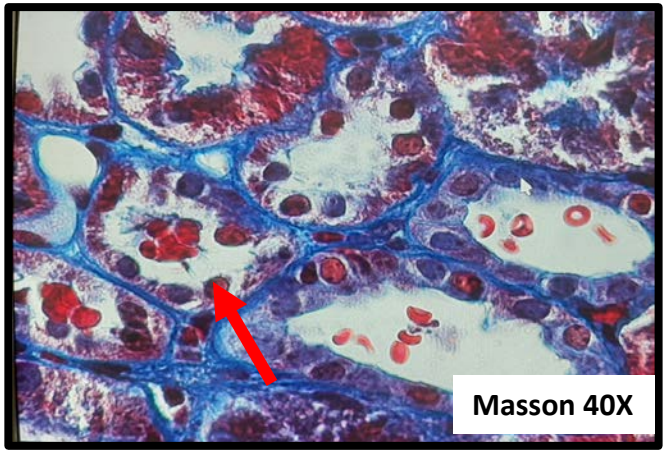
De novo IgAN
ARN
Acute rejection

Renal Biopsy Post









Anticoagulant related-nephropathy
ARN

Type of acute kidney injury related to anticoagulation or antiplatelet therapy

Case Reports > Am J Kidney Dis. 2009 Dec;54(6):1121-6. doi: 10.1053/j.ajkd.2009.04.024. Epub 2009 Jul 4.

Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases

Sergey V Brodsky [1], Anjali Satoskar, Jun Chen, Gyongyi Nadasdy, Jeremiah W Eagen, Mirza Hamirani, Lee Hebert, Edward Calomeni, Tibor Nadasdy

Anticoagulant-Related Nephropathy in a Renal Transplant Recipient

Check for upd

Hiranya D. Tennekoon[1], Andreas Kousios[2], Rebecca Gardiner[2], Linda Moran[1], Dawn Goodall[2], Jack Galliford[2], David Taube[2] and Candice Roufosse[1,3]

[1]Department of Cellular Pathology, North West London Pathology, Imperial College Healthcare NHS Trust, London, UK; [2]Renal and Transplant Centre, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; and [3]Centre for Inflammatory Disease, Imperial College London, London, UK

The incidence of ARN is difficult to determine

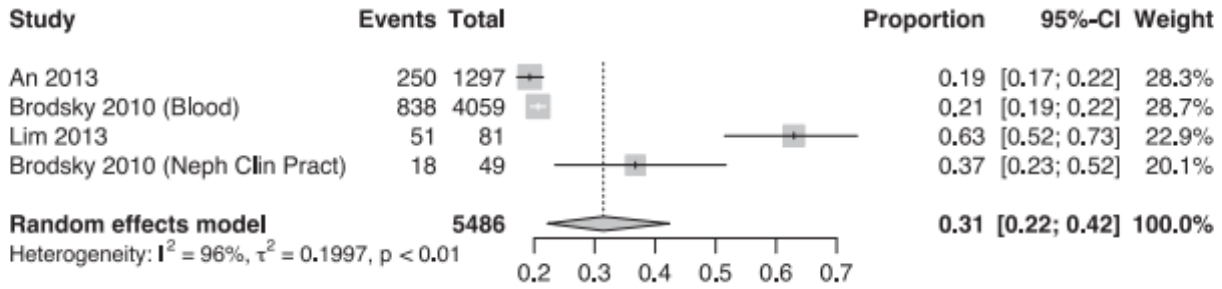


FIGURE 2: Meta-analysis of studies reporting prevalence of warfarin-related nephropathy. Random effects model (heterogeneity = I^2 = 96%).

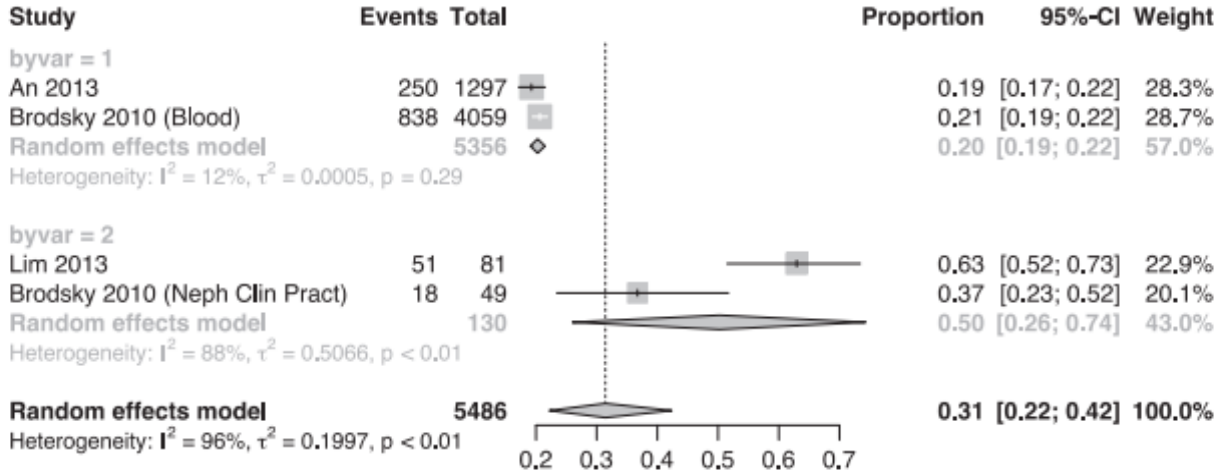
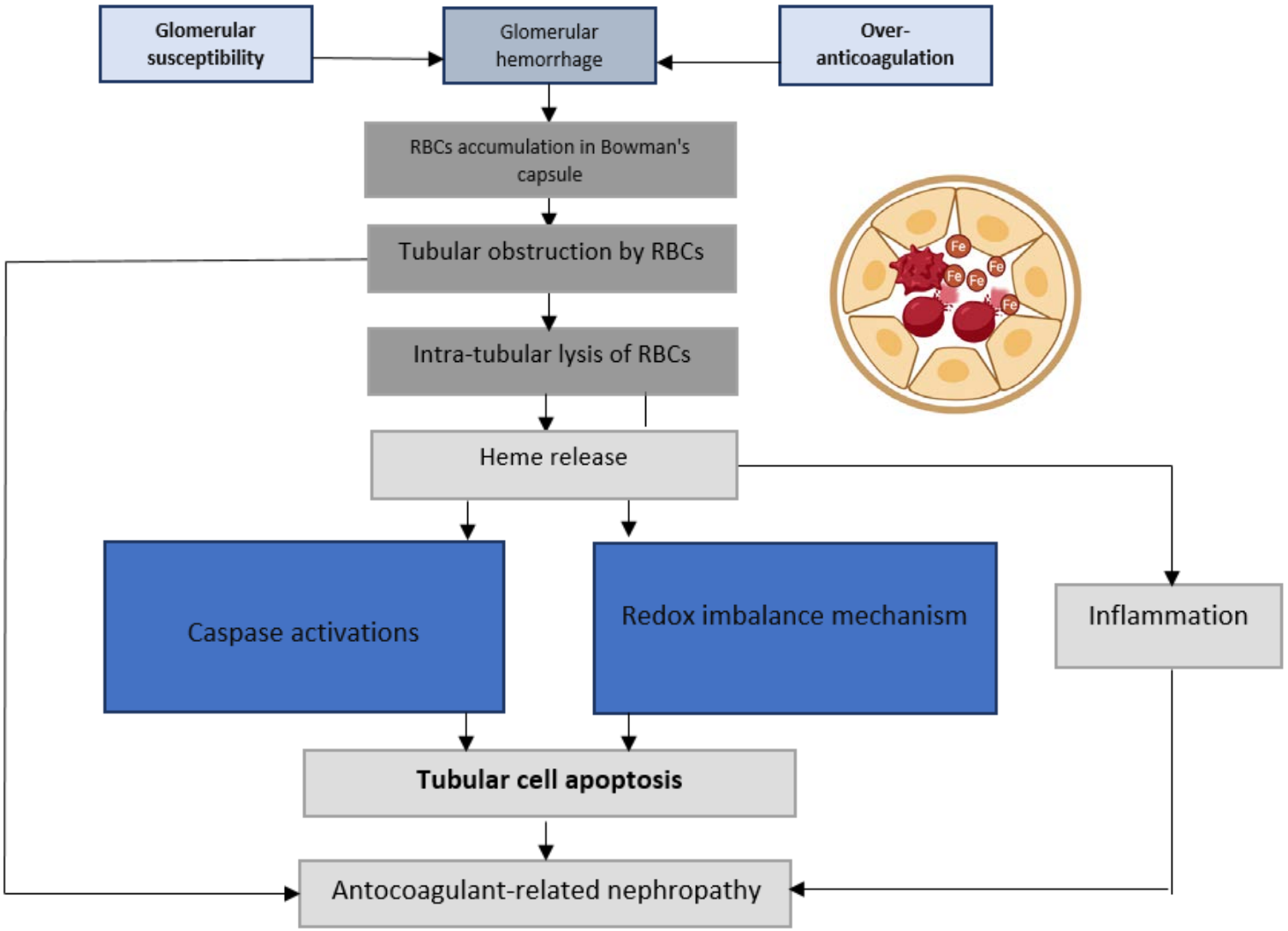


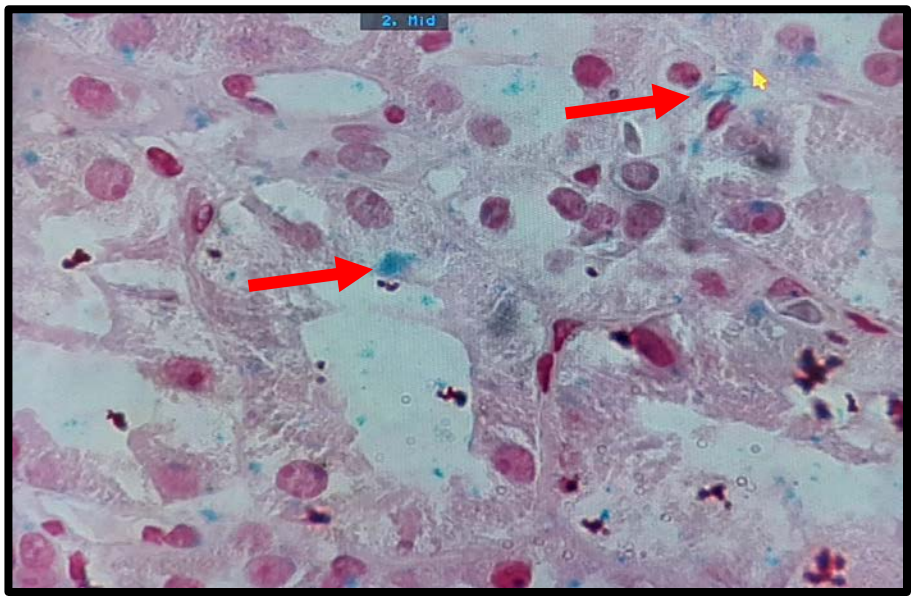
FIGURE 3: Meta-analysis of studies reporting prevalence of warfarin-related nephropathy by subgroup of type of patient included. Random effects model (within group heterogeneities of 12 and 88%).

K.B. de Aquino Moura et al.Clinical Kidney Journal, 2019, vol. 12, no. 3, 400–407

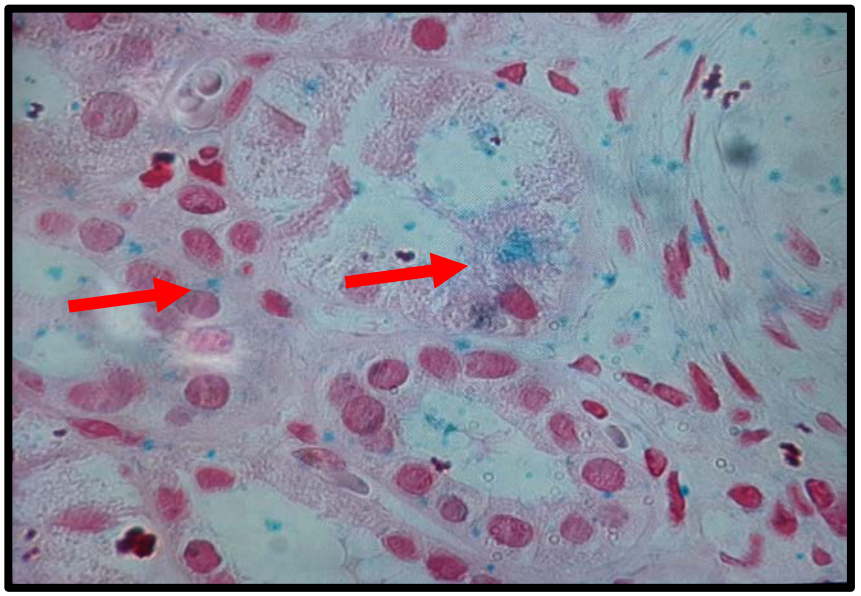
Pathogenesis of Anticoagulant-related nephropathy



Intra-cytoplasmatic tubular ferric iron/hemosiderin deposits Perl's Prussian Blue stain



Perls – Blu di Prussia 100X



Perls – Blu di Prussia 100X

Renal Biopsy Pre vs Renal Biopsy Post Anticoagulant therapy with Edoxaban

Renal biopsy Pre- Edoxaban	Renal biopsy Post- Edoxaban
• Non segni di rigetto acuto • Focale necrosi tubulare • Sclerosi glomerulare • Focale fibrosi • Minimo infiltrato flogistico • **Colorazione Perl's : Negativa**	• **Estesa necrosi tubulare** • **Cast eritrocitari tubulari** • **Emorragia glomerulare** • Flogosi interstiziale • Nefroangiosclerosi • **Colorazione Perl's : Positiva**
• C4d negativa • Anti-SV40 e Anti-CMV	• C4d negativa • Anti-SV40 e Anti-CMV negativi

Risk factors

- **Chronic Kidney disease (Reduced nephron mass)**
- **Preexisting GBM abnormalities**
- **Hypertension,** cardiovascular disease, heart failure
- **Drugs** (ACEi , Ca-Channel blockers…..)
- Diabetes mellitus
- **Other coagulopathies not related to therapy**
- Obesity

Physiol Rep. 2021 Jan;9(1):e14697. doi: 10.14814/phy2.14697.

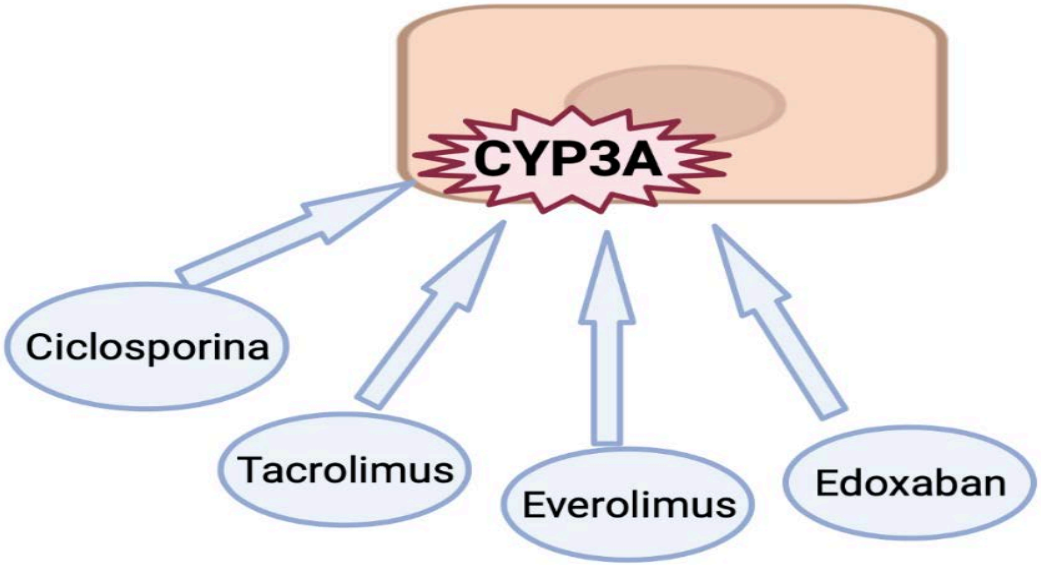
Role of glomerular filtration rate–modifying drugs in the development of anticoagulant–related nephropathy

Ajay K Medipally [1], Min Xiao [1], Brad H Rovin [2], Anjali A Satoskar [1], Iouri Ivano
Shahzeb Qaisar [1], Sergey V Brodsky [1]

Oral Warfarin and the Thrombin Inhibitor Dabigatran Increase Blood Pressure in Rats: Hidden Danger of Anticoagulants?

Kyle M. Ware,[1] Jay C. Vance,[2] Navin Muni,[1] Lee A. Hebert,[2] Anjali A. Satoskar,[1] Gyongyi Nadasdy,[1] Iouri Ivanov,[1] Tibor Nadasdy,[1] Brad H. Rovin,[2] and Sergey V. Brodsky[1]

Drugs Interaction



OVERANTICOAGULATION

Tabella 3 - Concentrazioni a valle e a picco ed influenza sui test coagulativi.

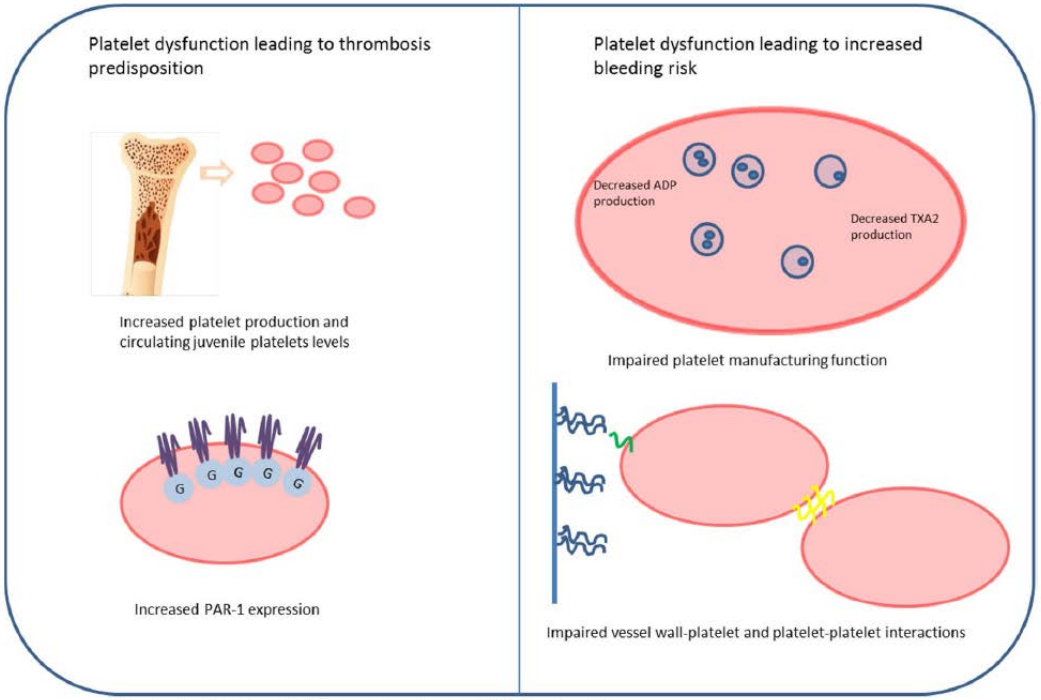
	Dabigatran	Rivaroxaban	Apixaban
Concentrazione plasmatica a valle (mediana e range, 25°-75° percentile)	91 ng/mL (61 - 143 ng/mL) 12-14 h dopo l'ingestione	32 ng/mL [6-239 ng/mL] 16-24 h dopo l'ingestione	103 ng/mL [41 – 230 ng/mL] 12-24 h dopo l'ingestione
Risposta del test	aPTT aumentato circa 1,5 volte limite superiore	–	Attività anti-FXa pari a circa 1,5 UI/ml
Concentrazione plasmatica a picco (mediana e range, 25°-75° percentile)	175 ng/mL [117-275 ng/mL] circa 2h dopo l'ingestione	215 ng/mL [22-535 ng/mL] 2-4 h dopo l'ingestione	171 ng/ml [91 – 321 ng/mL] 1-4 h dopo l'ingestione
Risposta del test	aPTT aumentato circa 2 volte limite superiore	PT aumentato circa 1,5 volte il limite superiore	Attività anti-FXa pari a circa 2,6 UI/ml

Over-anticoagulation

Bioptically Proven "Anticoagulation-Related Nephropathy" Induced by Dual Antiplatelet Therapy

Karolína Krátká[a] Martin Havrda[a] Eva Honsová[b] Ivan Rychlík[a]

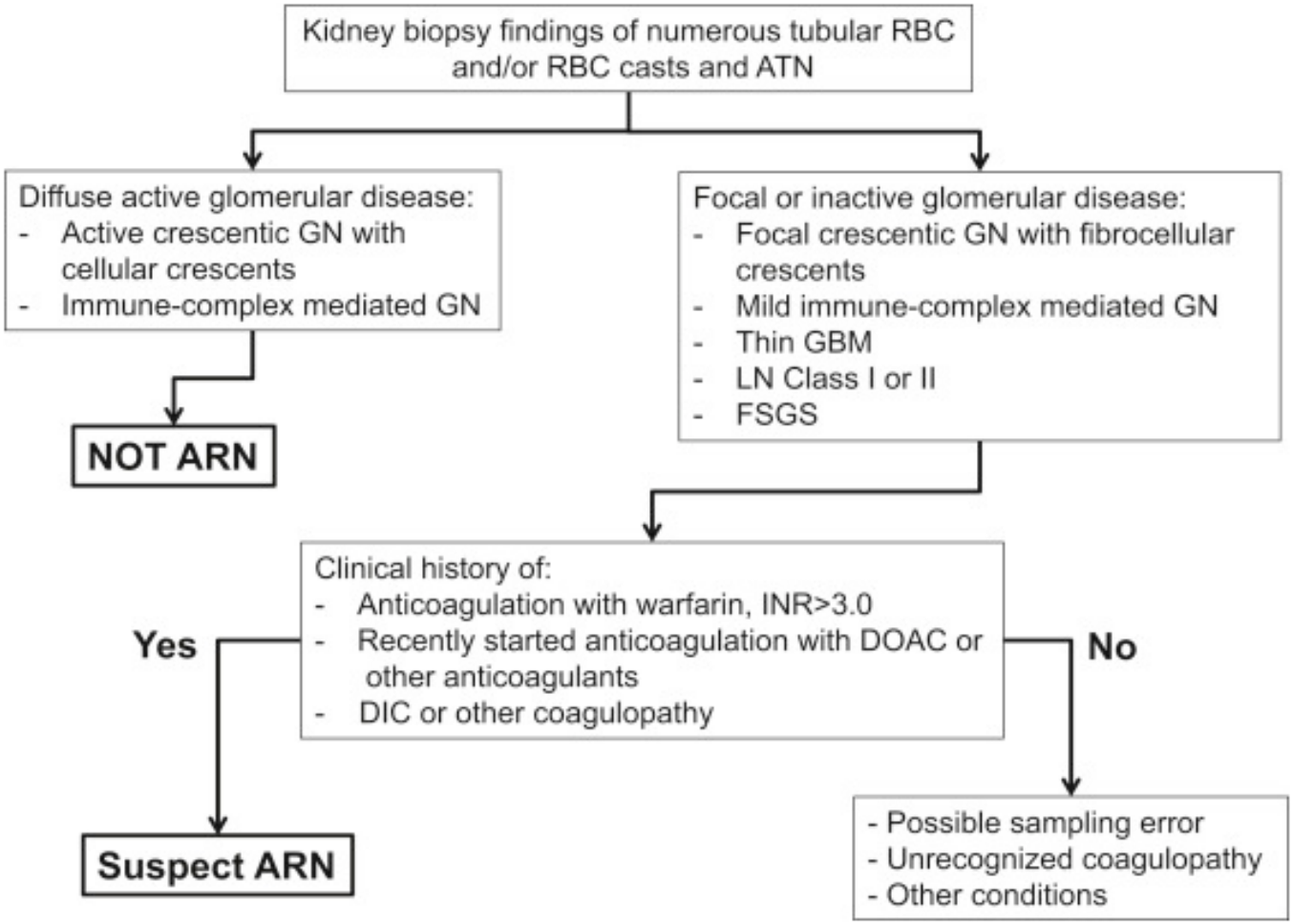
[a]1st Department of Medicine, Third Faculty of Medicine, Charles University, Prague, Czech Republic; [b]Clinical and Transplant Pathology Department, Institute for Clinical and Experimental Medicine, Prague, Czech Republic



ADP: adenosine diphosphate; PAR-1: Protease-activated receptor-1; TXA2: Thromboxan A2

H. Ibrahim, S. V. Rao,J Thromb Thrombolysis (2017) 43:519–527

Diagnosis of Anticoagulant-Related nephropathy



Therapeutic approach

- ARN optimal management remains unknown
- Reversal of anticoagulation using the appropriate antidote or, if unavailable, interruption of the offending agent
- Prenisolone, N-Acetylcysteine (?)

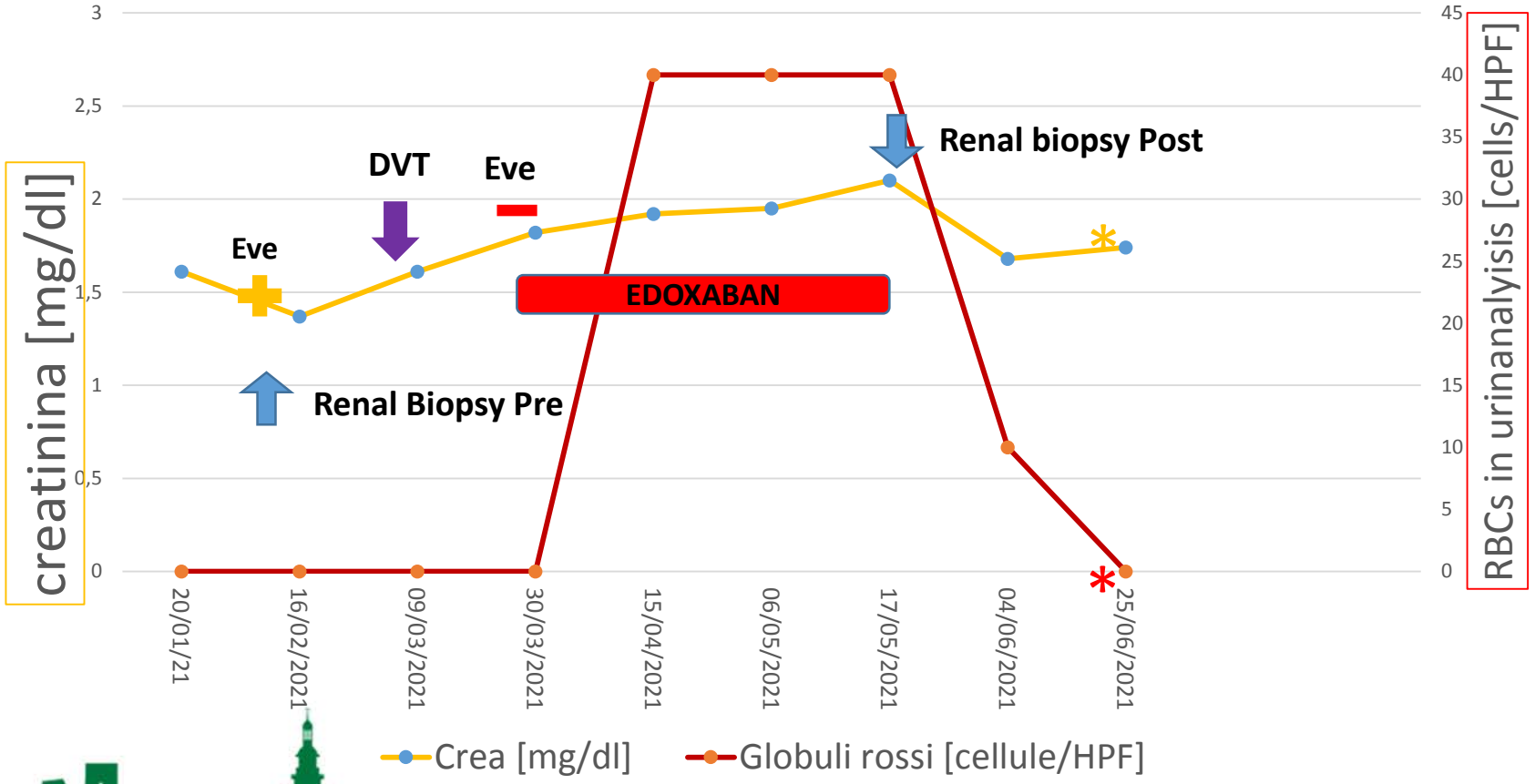
What is the best strategy for this form of kidney injury?

Prevention

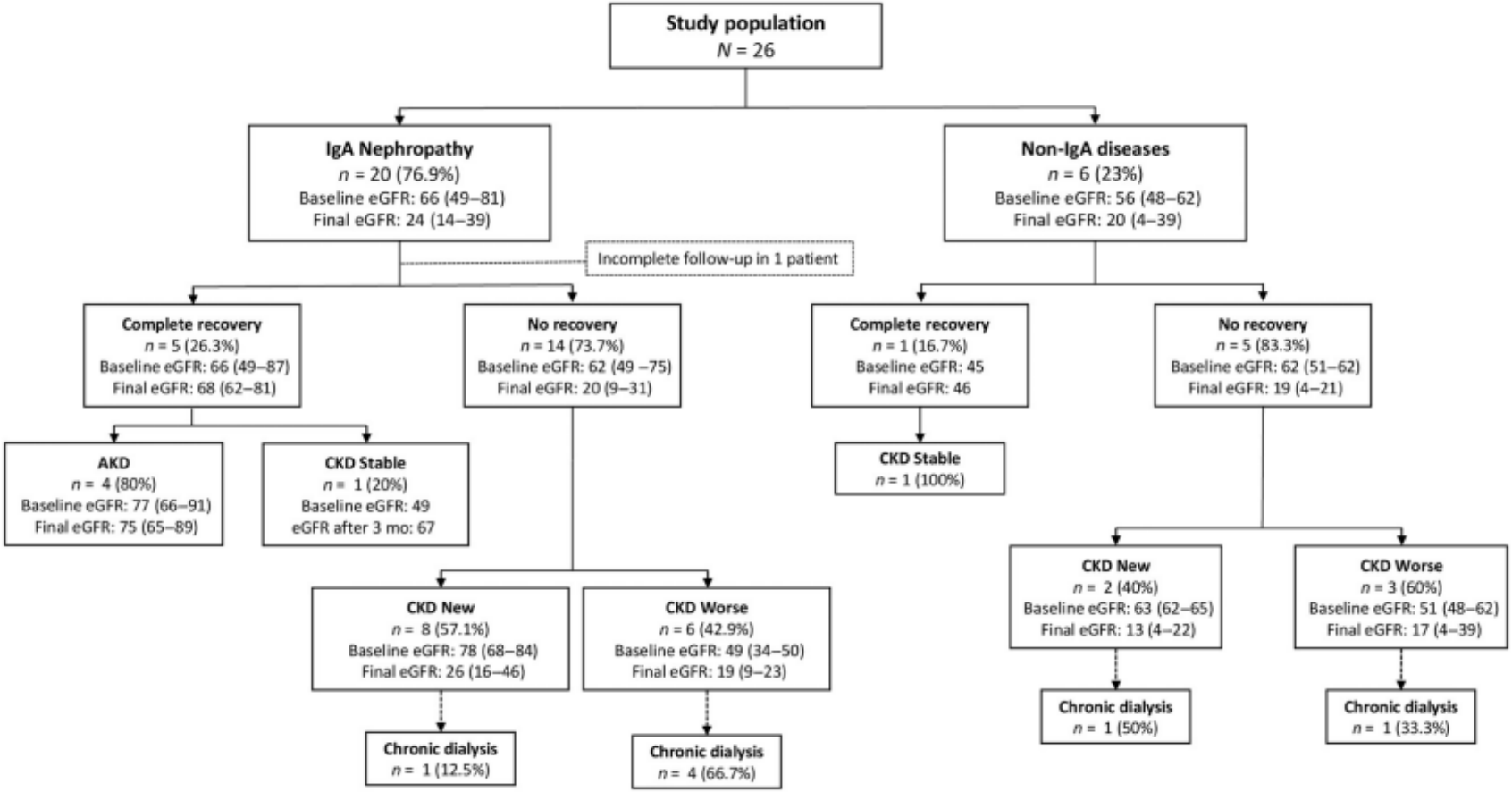
Drug withdraw

- Careful drug dosing and regular monitoring of coagulation parameter
- Correction of excess of anticoagulation (lowering dose, using antagonists, etc)
- Avoiding drugs interactions
- Optimize control of arterial hypertension and other predisposing factors

Timeline of events

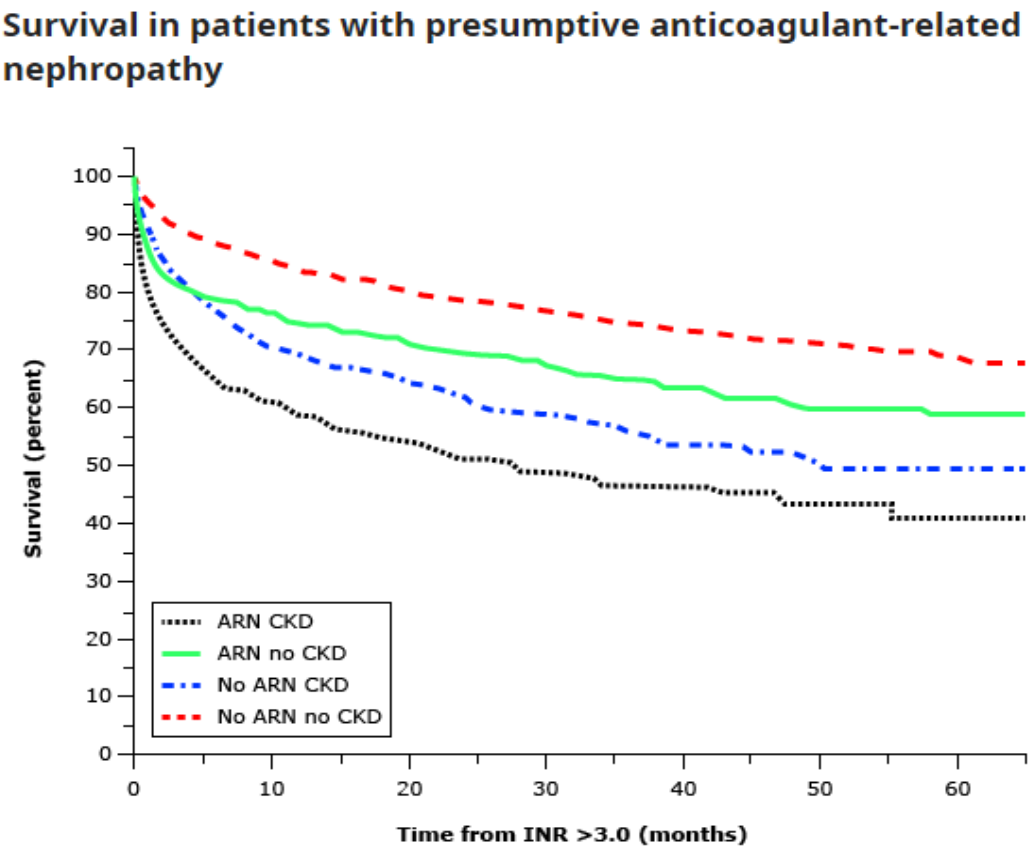


Renal Outcome



H Trujillo et al.: IgAN and Anticoagulant-Related Nephropathy

Renal Outcome



Kidney International. Brodsky SV, Nadasdy T, Rovin BH, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int 2011; 80:181.

Take home message

- Anticoagulation therapy along with pre-existing glomerular damage can lead to ARN
- Underdiagnosed disease with no viable treatment options
- Poor renal outcome - In the majority of reported cases, no recovery of renal function is observed.
- Close monitoring of renal function and urinary sediment after initiation of anticoagulant therapy is highly recommended.

Grazie per l'attenzione !