Update on Anticoagulation management of CKD patients with atrial fibrillation

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Declaration

- I have no disclosure.

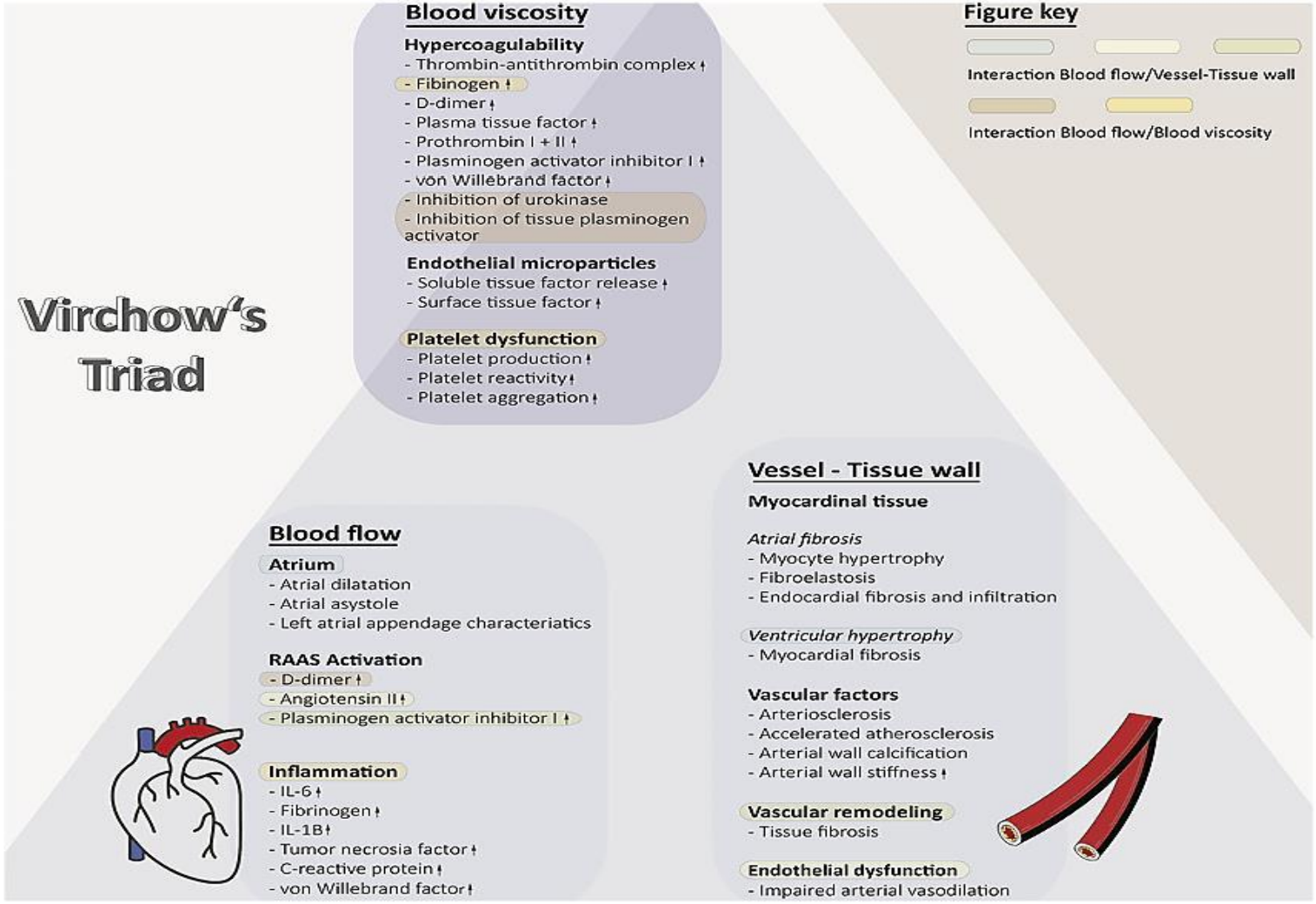
Outline

- Introduction
- Mechanisms of thromboembolism in CKD
- Mechanisms of bleeding in CKD
- Absorption and metabolism of different NOAC
- Pharmaco-dynamic and pharmacokinetic features of oral anticoagulants
- Available evidence
- Summary & conclusion

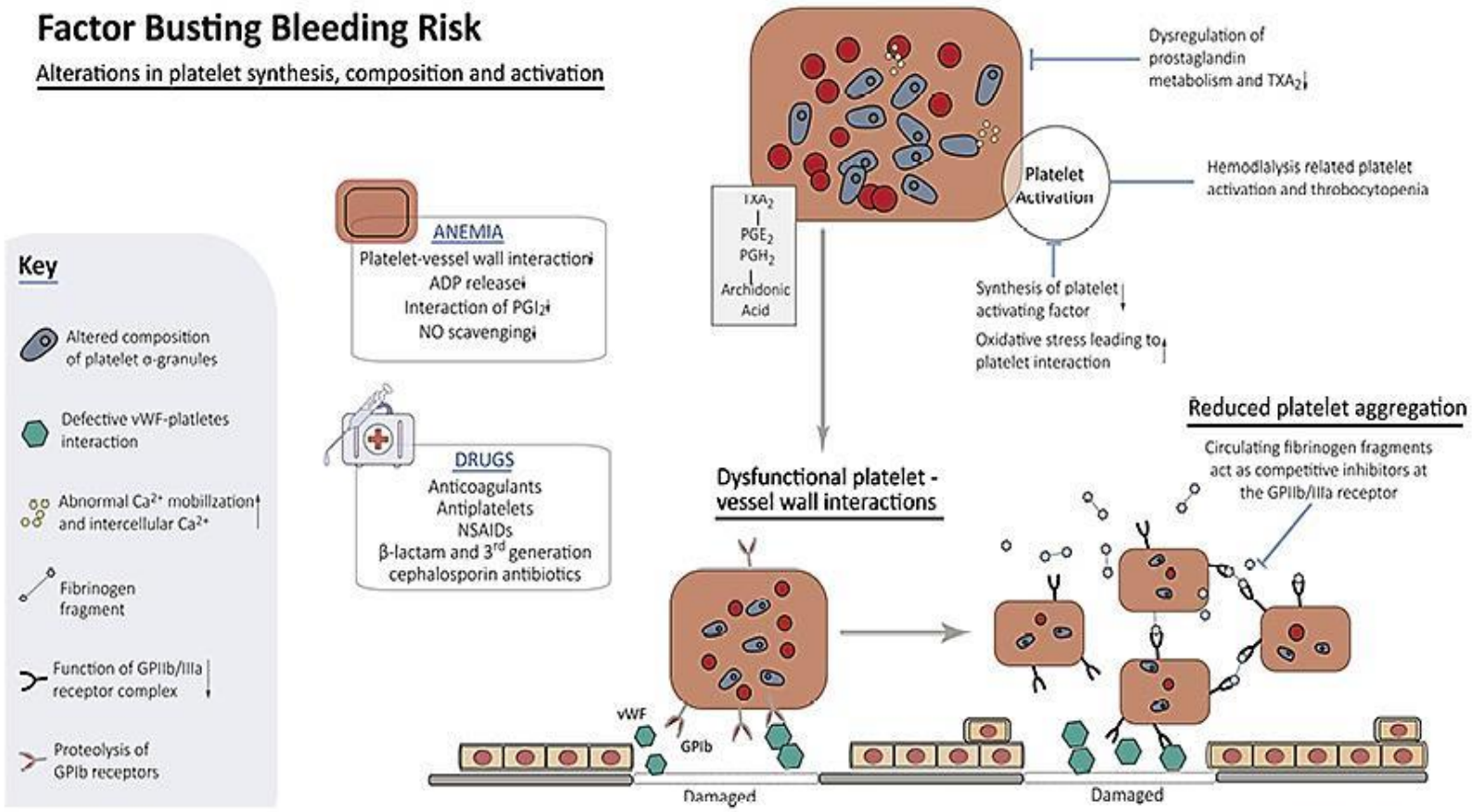
Introduction

- The prevalence of CKD is increasing due to aging and risk factor for CKD in population, such as systemic arterial hypertension.
- The prevalence and incidence of AF increase with decreasing renal function due to association with proinflammatory state, systemic arterial hypertension, endothelial dysfunction and left ventricular hypertrophy.
- Reduced eGFR and elevated urine albumin-to-creatinine ratio are significantly associated with higher risk of incidence of AF.
- AF and CKD frequently coexist: The relationship with AF and CKD is bi-directional
  - Up to 20 % of CKD patients present AF
  - 40 – 50 % of AF patients suffer from CKD

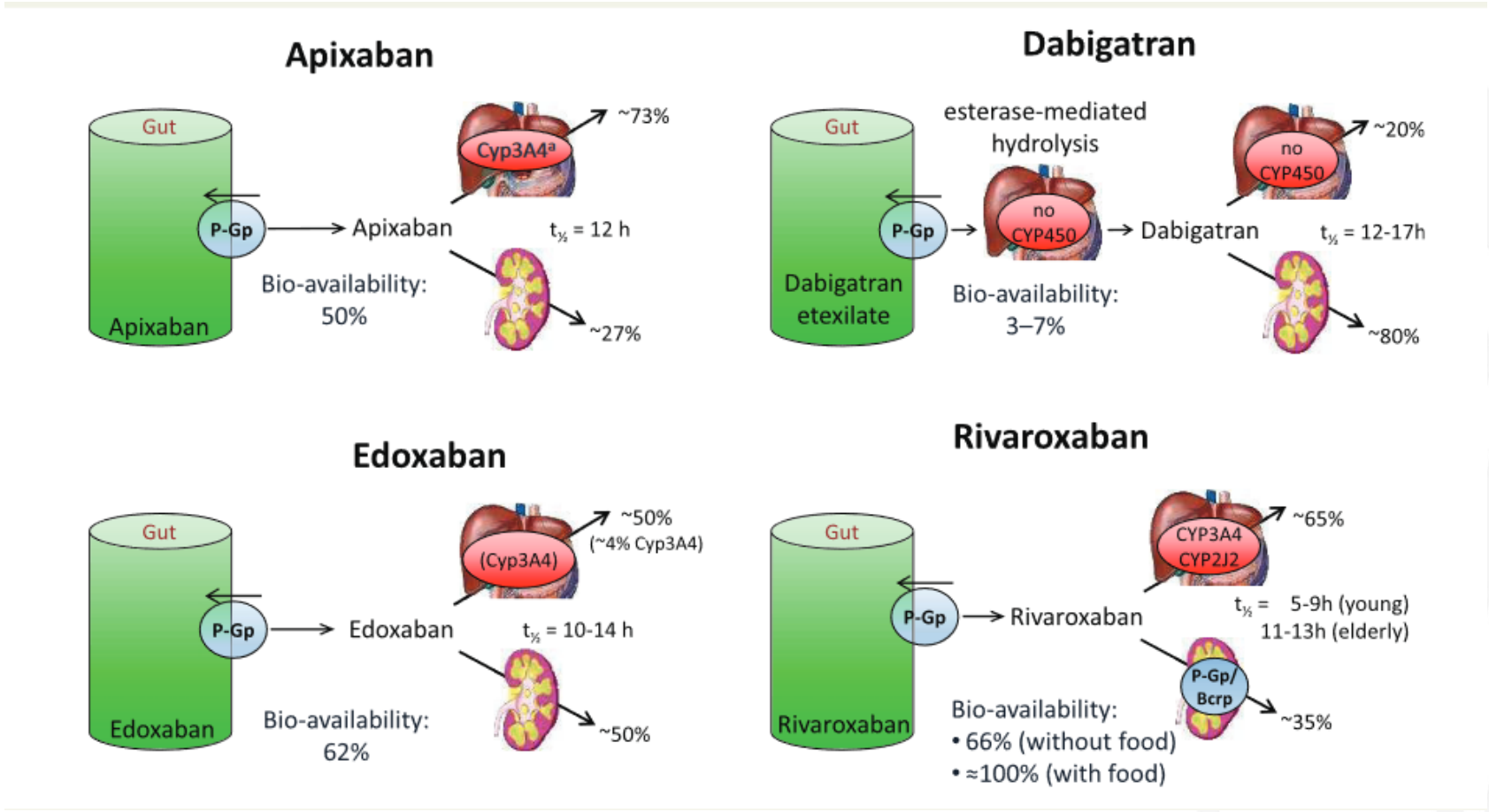
Main mechanisms of thromboembolism in patients with CKD



Main mechanisms of bleeding in patients with CKD



Absorption and metabolism of different NOAC



- **Both CKD and AF are strong risk factors for stroke or systemic embolism, congestive heart failure, myocardial infarction, and all-cause death**

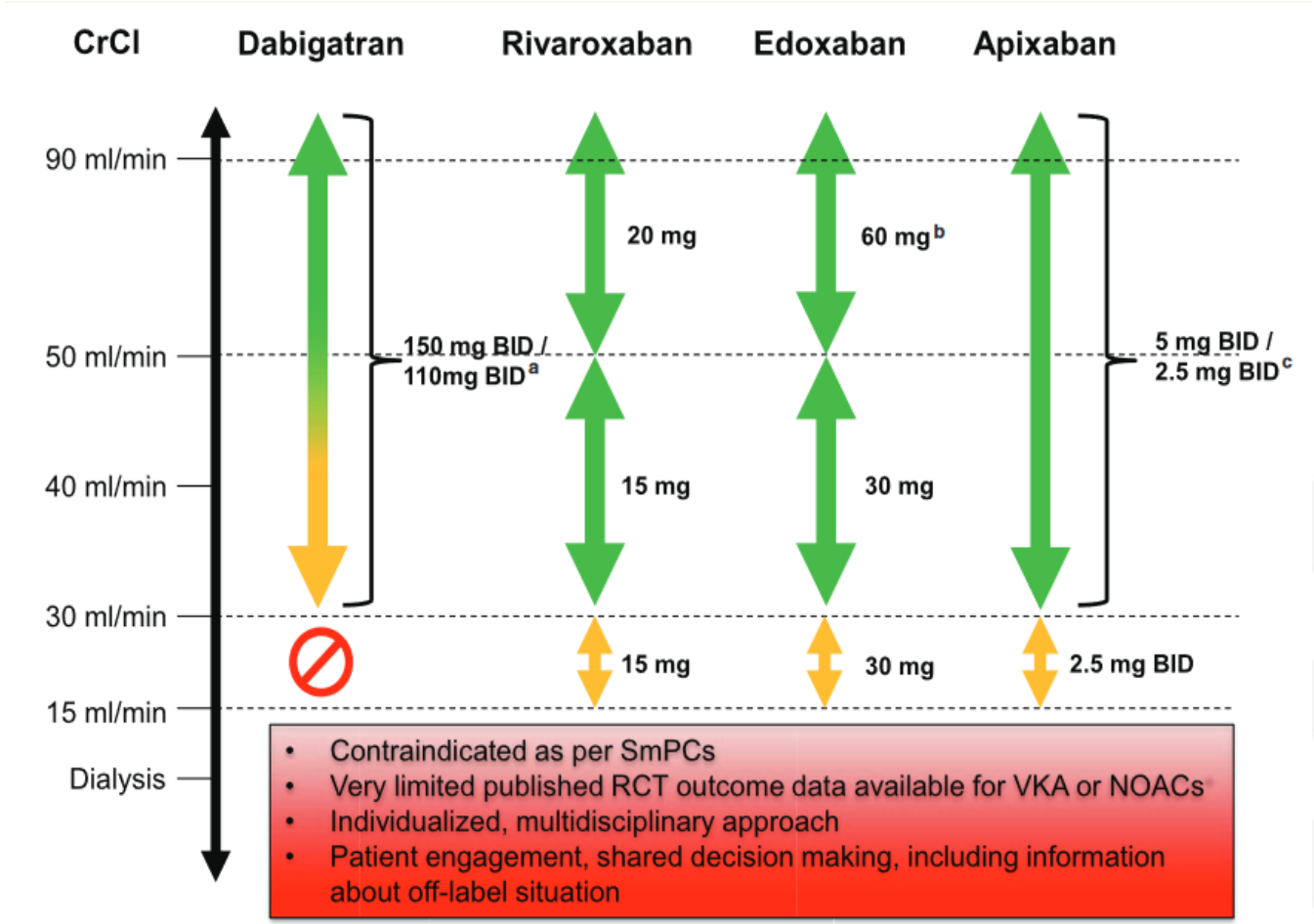
- **Since all direct oral anticoagulants (DOACs) are partly eliminated by the kidneys, the coexistence of CKD and AF represents unique challenge in clinical daily practice.**

- **Renal elimination of NOACs is 80% for dabigatran, 50% for endoxaban, 33% to 36% for rivaroxaban, and 25% to 27% for apixaban.**

CKD staging according to the 2021 EHRA practical guide on the use of DOACs

CKD stage	Description	GFR range, ml/min/1.73 m^2
G1	Normal or high	≥ 90
G2	Mildly decreased	60–89
G3a	Mildly to moderately decreased	45–59
G3b	Moderately to severely decreased	30–44
G4	Severely decreased	15–29
G5	Kidney failure	< 15

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation



Pharmacodynamic and pharmacokinetic features of oral anticoagulants

Characteristics	Warfarin	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Mechanism of action	Inhibition of vitamin K dependent clotting factors (II, VII, IX, X)	Factor Xa inhibition	Factor Xa inhibition	Factor Xa inhibition	Factor IIa (thrombin) inhibition
Dosing	Variable (INR monitoring) OD	Fixed 20/15 mg OD	Fixed 5/2.5 mg BID	Fixed 60/30 mg OD	Fixed 150/110 mg BID
Protein binding, %	99	90	87	40–59	35
Metabolism	Extensive metabolism by CYP2C9	Metabolized in the liver by CYP3A4/2J2 (65%)	Metabolized in the liver by CYP3A4 (75%)	Metabolized in the liver by CYP3A4 (50%)	Esterase mediated hydrolysis (no CYP450)
Interactions	Multiple food-drug and drug-drug	CYP3A4/2J2 P-gP	CYP3A4 P-gP	P-gP	P-gP
Renal excretion, %	<1	35	25	50	80–85
C_{max}, h	72–96	2–4	3–4	1–2	1–2
t1/2, h	40	6–13	12	10–14	12–14
Dialyzable	No	No	Small	No	Yes
Recommendation in severe renal impairment (eGFR = 15–29 mL/min/1.73 m^2)	Strict INR monitoring	Dose adjustment (15 mg QD)	No action until at least 2 criteria fulfilled (age ≥80 years; weight ≤60 kg; creatinine ≥1.5 mg/dL)	Dose adjustment (30 mg QD)	Contraindicated (EU)/ dose adjustment (75 mg BID [US])
Recommendation in ESRD or RRT (eGFR <15 mL/ min/1.73 m^2)	Strict INR monitoring	Dose adjustment (15 mg QD [US])/individualized multidisciplinary approach (EU)	No action until at least 2 criteria fulfilled (age ≥80 years; weight ≤60 kg; creatinine ≥1.5 mg/dL [US])/individualized multidisciplinary approach (EU)	Contraindicated (US)/ individualized multidisciplinary approach (EU)	Contraindicated

BID, twice a day; C_{max}, peak concentration; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; OD, once a day; P-gP, P glycoprotein transporter involved in absorption and renal clearance; t1/2, half-life.

Ref : Atrial Fibrillation and anticoagulation Treatment in ESRD, Cardiorenal Med 2022;12-131-140

Review > Mayo Clin Proc. 2023 May;98(5):750-770. doi: 10.1016/j.mayocp.2023.01.007.
Epub 2023 Apr 5.

Oral Anticoagulation in Patients With Advanced Chronic Kidney Disease and Atrial Fibrillation: Beyond Anticoagulation

Sofie A M Dhaese [1], An S De Vriese [2]

Summary of Mayo Clinic Proceedings 2023

- The DOACs
  - better protection against stroke
  - cause less major bleeding
  - associated with a slower decline of CKD
  - less acute kidney injury
  - associated with a lower incidence of cardiovascular events than VKAs

- The VKAs may be harmful in CKD patients, in particular in patients with a high bleeding risk and labile international normalized ratio.

Original Research

Kidney Medicine

Safety and Effectiveness of Rivaroxaban Versus Warfarin Across GFR Levels in Atrial Fibrillation: A Population-Based Study in Australia and Canada

Kidney Medicine. Published online May, 2023

Rivaroxaban vs Warfarin

- Large, multicenter cohort study of adults with AF
- to comprehensively assess
  - the effectiveness(risk of all-cause death, ischemic stroke, or TIA)
  - the safety (risk of hospitalization for major bleeding: either intracranial, upper or lower gastrointestinal, or other)
  - of rivaroxaban compared with warfarin across the range of kidney function (excluding patients receiving dialysis and kidney transplant recipient).

- In adults with AF, rivaroxaban compared with warfarin was associated with
  - lower or similar risk of all-cause death, ischemic stroke and transient ischemic attack
  - similar risk of bleeding across a broad range of kidney function

- The better safety and efficacy of NOACs as opposed to VKAs may be particularly evident in advanced CKD as a result of better on-target anticoagulation with DOACs, harmful off-target vascular effects of VKAs, and beneficial off-target vascular effects of DOACs.

- The intrinsic vasculo-protective effects of DOACs are supported by animal experimental evidence as well as by findings of large clinical trials and may result in use of DOACs beyond their anticoagulant properties.

Anticoagulation in hemodialysis patients

Nephrol Dial Transplant. 2022 Oct 19;37(11):2072-2079. doi: 10.1093/ndt/gfab060.

Anticoagulation management in haemodialysis patients with atrial fibrillation: evidence and opinion

An S De Vriese [1], Gunnar Heine [2]

- Recent evidence reveals that the superior benefit-risk profile of direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) observed in the general population and in moderate chronic kidney disease can be extended to the HD population.

- VKA may be especially harmful in dialysis patients and should therefore be avoided, in particular in patients with a high bleeding risk and labile INR.

- Dose-finding studies of DOACs suggest that rivaroxaban 10 mg daily and apixaban 2.5 mg twice daily are appropriate choices in dialysis patients

- Left atrial appendage occlusion is a potential attractive solution to reduce the risk of stroke without increasing bleeding propensity, but it has not been properly studied in dialysis patients.

REVIEW ARTICLES | JUNE 07 2022

Atrial Fibrillation and Anticoagulant Treatment in End-Stage Renal Disease Patients: Where Do We Stand?

Subject Area: Cardiovascular System , Endocrinology , Further Areas , Nephrology

Luca Di Lullo; Marco Valerio Mariani; Claudio Ronco ; Antonio Bellasi; Carlo Lavalle; Cristina Chimenti; Ernesto Paoletti; Maura Ravera; Monica Zanella

Cardiorenal Med (2022) 12 (4): 131–140.

- In patients with moderate to severely reduced renal function (GFR 15-49 ml/min/1.73 m^2), current guidelines recommend DOACs as preferred anticoagulant strategy over warfarin.

- DOACs are superior, compared to warfarin, in reducing AF-related thromboembolic complications and bleeding events.

- DOACs have mortality benefit and greater reno-protective effect.

- Also demonstrated that patients with moderate to severe CKD the use of rivaroxaban was associated with an improvement/stabilization in eGFR and cardiac valve calcifications as compared to warfarin.

- These results seem to be related to the significant reduction of cytokines levels observed in rivaroxaban arm: since higher cytokines levels were associated with reduction of eGFR and augmented severity of cardiac valve calcifications

- The anti-inflammatory effects of rivaroxaban may be responsible of the delay of kidney disease progression and of the decrease in cardiovascular calcifications

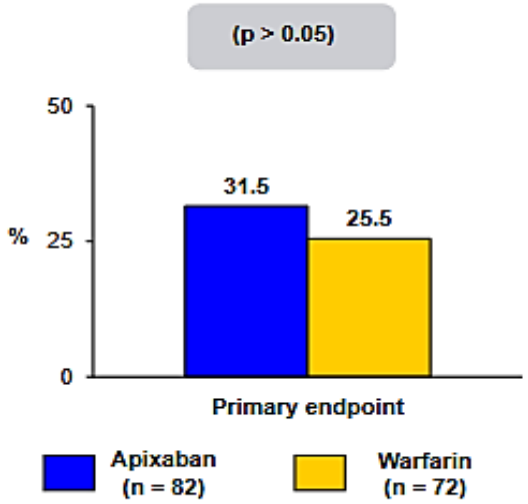
Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation - RENAL-AF

RENAL-AF

#AHA19

AMERICAN COLLEGE of CARDIOLOGY

Trial Description: Patients with AF and ESRD on hemodialysis were randomized in a 1:1 fashion to either apixaban 5 mg BID (29% on 2.5 mg BID) or warfarin with INR goal 2-3. Patients were followed for 1 year. Trial was stopped early due to loss of funding.



RESULTS

- Primary endpoint, clinically relevant nonmajor bleed: apixaban vs. warfarin: 31.5% vs. 25.5% (p > 0.05)
- Intracranial bleeding: 1.2% vs. 1.4%; GI bleeding: 2.4% vs. 8.3%
- ISTH major bleed: 8.5% vs. 9.7%; stroke: 2.4% vs. 2.8%; CV death: 11% vs. 5.6%

CONCLUSIONS

- Apixaban 5 mg BID results in similar rates of bleeding and strokes as warfarin among patients with ESRD on hemodialysis
- Time in therapeutic range with warfarin was only ~44%, with a large proportion of patients in the subtherapeutic range
- Remains unclear if lower apixaban dose (2.5 mg BID) and cessation of aspirin (used in ~40%) would have resulted in lower bleeding compared with warfarin

Presented by Dr. Sean D. Pokorney at AHA 2019

Apixaban Dosing in Patients With AF and Severe CKD

Xu Y, Chang AR, Inker LA, McAdams-DeMarco M, Grams ME, Shin JI.

- **This observational study reports a 1.6 times risk of bleeding with 5 mg apixaban (vs. 2.5 mg) twice daily in patients with AF and CKD stage 4/5, with no differences in stroke/systemic embolism or death.**

- **These findings suggest that 2.5 mg apixaban may be a better choice than 5 mg for patients with AF and severe CKD**

- **Given several limitations of the current analysis and the unclear benefits of anticoagulation in severe CKD and AF, prospective RCTs are required to provide guidance on the decision to initiate anticoagulation and which anticoagulant and what dose to use in this population at very high risk for death.**

A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study

Holger Reinecke, Christiane Engelbertz, Rupert Bauersachs, Günter Breithardt, Hans-Herbert Echterhoff, Joachim Gerß, Karl Georg Haeusler, Bernd Hewing, Joachim Hoyer, Sabine Juergensmeyer, Thomas Klingenheben, Guido Knapp, Lars Christian Rump, Hans Schmidt-Guertler, Christoph Wanner, Paulus Kirchhof and Dennis Goerlich **See fewer authors**

The AXADIA-AFNET 8 Study: Is Apixaban a Safe and Effective Alternative to Vitamin K Antagonists (VKA) for Patients with Atrial Fibrillation Undergoing Chronic Hemodialysis?

#NephJC

METHODS

- prospective randomized open label, blinded outcome assessment trial
- Germany, 39 sites
- 97 patients undergoing chronic hemodialysis with atrial fibrillation
- 30% women
  age 75 years
  CHA2DS2-VASc* = 4.5
- Median follow-up
  Apixaban 429 days
  VKA 506 days

* CHA2DS2-VASc- Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke or transient ischemic attack, Vascular disease, Age 65 to 74 years, female sex

RESULTS

48 APIXABAN 2.5mgx2/day

Adherence >80% (44/48 patients)

49 PHENPROCOUMON

Median time in therapeutic range on VKA was 50.7%

Primary composite outcomes

	Safety	Efficacy
	Major bleeding Clinically relevant Nonmajor bleeding or all-cause death	Ischemic stroke All-cause death Myocardial infarction Deep vein thrombosis or pulmonary embolism
Apixaban	45.8%	20.8%
HR / P	HR 0.93 0.53 –1.65	P = 0.51 log rank
VKA	51%	30.6%

Individual components

All cause death	Myocardial infarction	Major bleeding
18.8%	4.2%	10.4%
No significant difference		
24.5%	6.1%	12.2%

Conclusion: There were no significant differences in safety or efficacy between apixaban and VKA. Despite oral anticoagulation, patients with atrial fibrillation undergoing hemodialysis are still at a high risk of CV events. to identify the optimal anticoagulation approach larger randomized trials are needed.

Reinecke H, et al. A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study. Circulation. 2023

Visual abstract by Cristina Popa MD, @NephroSeeker

AXADIA–AFNET 8

- In this randomized trial, no differences in safety or efficacy were observed between apixaban 2.5 mg BID and vitamin K antagonists in patients with AF on chronic hemodialysis.
- Event rates in patients with AF on hemodialysis remain high on oral anticoagulation, including death or a clinically relevant bleeding event (45.8%) and stroke, myocardial infarction, systemic or pulmonary embolism, or death (20.8%).

What are the clinical implications?

- The data support consideration of apixaban for prevention of cardiovascular complications in patients with AF on chronic hemodialysis, but larger studies are needed.
- Additional interventions need to be developed to reduce the very high risk of thromboembolic and bleeding events in this population.

Summary

- DOACs have revolutionized treatment for AF in patients with CKD
  - Relative ease of use compared to warfarin
  - Steady pharmacokinetic parameters and predictable therapeutic effects- eliminate the need for continuous monitoring
  - Fewer drug and food interactions
  - Pleotropic effects of DOACs: anti-inflammatory and vascular protective properties, and slow the decline of kidney function

Conclusion

- Patients with CKD, especially ESRD on RRT, needing long-term anticoagulant therapy represent a challenging population
- Growing data suggest that DOACs may be better alternative to Warfarin in terms of reduction in thromboembolism & bleeding risk, preserving renal function
- LAAO has emerged as a promising alternative to life-long anticoagulation in patients with significant renal impairment

THANK YOU