Navigating the Debate: Anticoagulation Therapy in CKD in Patients with AF and VTE

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Disclosures

- *Speakers Bureau/Honoraria: Otsuka*
- *Consulting Fees: Otsuka, Bayer*

Learning Objectives

By the end of the presentation participants should be able to:

1. Discuss the pathophysiology of clotting and bleeding in patients with chronic kidney disease (CKD)/end-stage kidney disease (ESKD).
2. Assess the risk factors and clinical scenarios that warrant anticoagulation therapy in patients with CKD
3. Analyze the current evidence-based guidelines and recommendations for AF and VTE from various sources
4. Evaluate the benefits and risks of vitamin K antagonists and direct oral anticoagulants (DOACs) in patients with CKD and ESKD.
5. Develop a therapeutic bridging plan for patients with CKD/ESKD on anticoagulation undergoing invasive procedures.

Case 1

Mrs V. is a 55 year old lady on Home HD since 2007. She has ESKD from unknown origin.

- PMH:
  - CAD- MI and ischemic cardiomyopathy
  - AF- right occipital infarct in 2019
  - PVD
  - Hepatitis C (treated with interferon)
- Medications:
  - rosuvastatin, ramipril, metoprolol, ASA, **warfarin**, pantoprazole, replavite, cinacalcet, Aranesp, Venofer
- She is admitted with calciphylaxis of her left foot.

Question

How do we manage her anticoagulation for AF?

A) Continue warfarin
B) D/C warfarin and start a DOAC
C) D/C warfarin and start a LMWH
D) D/C warfarin

Question

What is the prevalence of AF in the general population?

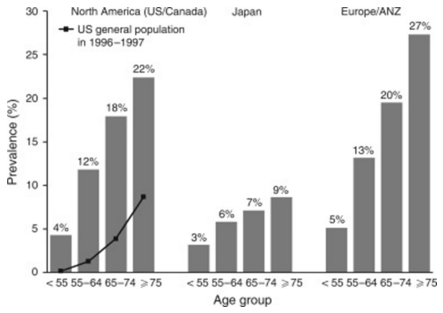
A) 2-3%
B) 6-7%
C) 9-10%
D) 18-20%

Question

What is the prevalence of AF in the HD population?

A) 2-3%
B) 6-7%
C) 9-10%
D)14-27%

Prevalence of AF in HD



Wizemann. KI 2010 (77): 1098-1106

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Question

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B) 6-7%
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Mortality Due to Bleeding and Stroke in Dialysis Patients

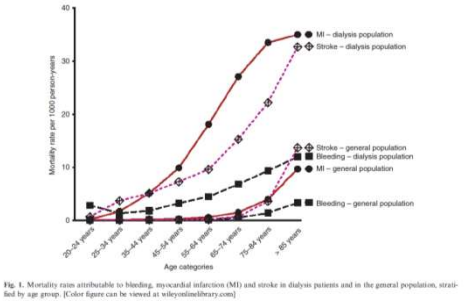
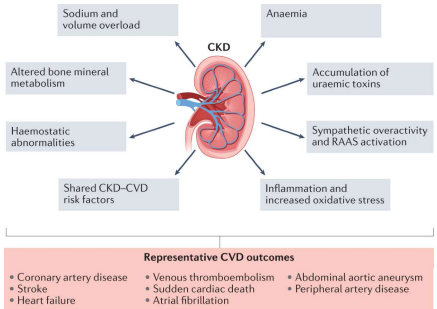


Fig. 1. Mortality rates attributable to bleeding, myocardial infarction (MI) and stroke in dialysis patients and in the general population, stratified by age group. [Color figure can be viewed at wileyonlinelibrary.com]

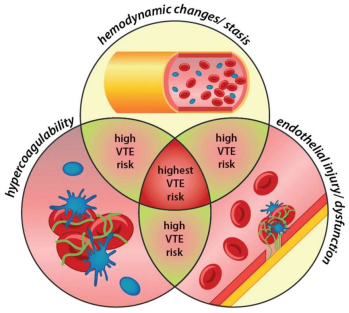
Ocak, JTH 2018;16:1953-1963

Pathophysiology of the Increased Risk of AF in CKD



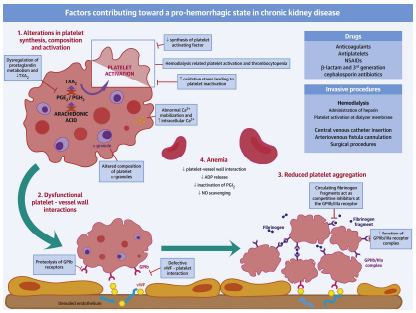
Matsushita, K.,*et al. Nat Rev Nephrol* 2022;**18**, 696–

Pathophysiology of the Increased Thrombotic Risk in CKD



Kumar, et al, JACC 2019; 74(17): 2204-2215.

The Pathophysiology of Bleeding in CKD



Kumar, et al, JACC 2019; 74(17): 2204-2215.

A few facts….

- High Prevalence of AF in CKD
- CKD/ESKD have greater risk of stroke, bleeding, mortality
- CHAD2DS2-VASc & HAS-BLED scores to determine management
- HAS-BLED in warfarin users (n/a to DOACs)
- ESKD excluded from validation studies
- ESKD excluded in warfarin & DOAC studies

Management of AF in HD patients

What do Guidelines Say?

CKD Stage[a]	AHA/ACCP/HRS	ESC	CCS	KDIGO
2–3 (30–89 mL/min/1.73 m²)	Warfarin or DOACs (dose according to label)	Warfarin or DOACs (dose according to label)	DOACs over warfarin (adjusted for INR 2–3)	Warfarin or DOACs (dose according to label)
4 (15–29 mL/min/1.73 m²)	Warfarin or DOACs (dose according to label)	Warfarin or DOACs (dose according to label)	Warfarin (very limited RCT data) Apixaban and edoxaban (very limited RCT data; dose adjust according to label)	Warfarin (adjusted to INR 2–3 can be considered) DOACs (per suggested dosing for all DOACs)[b]
5 (< 15 mL/min/1.73 m² or dialysis)	Warfarin or DOACs (dose according to label)	No specific recommendation given	Cannot recommend routine anticoagulation for dialysis patients because of lack of data	Equipoise for warfarin (based on observational data) DOACs (except for dabigatran)[c]

[a]CKD stage refers to eGFR
[b]Table 2 has dosing recommendations for all the DOACs in CKD/ESKD.
[c]Dabigatran is not recommended in ESKD dialysis.

Bhatia HS, et al. Clin Cardiol 2018;41:1395–1402; Jegatheswaran J et al. Can J Cardiol 2019;35:1241–55; Wanner C et al. Kidney Int 2018;94:231-4

What do Guidelines Say?

CKD Stage[a]	Guideline Recommendations	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
4 (15–29 mL/min/1.73 m²)	ACC/AHA/ACCP/ HRS	Dose adjust for INR 2–3	5 mg or 2.5 mg twice daily[b]	75 mg twice daily	30 mg once daily	15 mg once daily
	ESC/EHRA	Dose adjust for INR 2–3	2.5 mg twice daily (use with caution)	Do not use	30 mg once daily (use with caution)	15 mg once daily (use with caution)
	CCS/CHRS	Dose adjust for INR 2–3 (limited data on efficacy and safety)	5 mg or 2.5 mg twice daily (limited RCT data)[b]	Do not use	30 mg once daily (limited RCT data)	15 mg once daily (no RCT data)
	KDIGO	Dose adjust for INR 2–3	2.5 mg twice daily could be considered	Unknown (75 mg twice daily)[a]	30 mg once daily (could be considered)	15 mg once daily (could be considered)

[a]Dose adjustments with DOACs are based on CrCl using the Cockcroft-Gault equation
[b]Apixaban: Use 2.5 mg twice daily if at least 2 of the following are present: SCr ≥ 1.5 mg/dL, age ≥ 80 yr, body weight ≤ 60 kg.
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	ESC/EHRA	No recommendation	Do not use	Do not use	Do not use	Do not use
	CCS/CHRS	No RCT data[c]	Limited RCT data[d]	No RCT data[d]	Limited RCT data[d]	No RCT data[d]
	KDIGO	Equipoise	Unknown (2.5 mg twice daily could be considered)	Do not use	Do not use	Unknown (15 mg once daily could be considered)

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[d]Product monograph states the drug is contraindicated at Stage 5 CKD.

Bhatia HS, et al. Clin Cardiol 2018;41:1395–1402. Jegatheswaran J, et al. Can J Cardiol 2019;35:1241–55. Wanner C, et al. Kidney Int 2018;94:231-4.

Study (n=7)	Design	Risk of Stroke HR (95% CI)		Risk of Major Bleeding HR (95% CI)
		Ischemic	Hemorrhagic	
Chan et al. 2009	Retrospective cohort, n=1671	**1.81 (1.12-2.92)**	**2.22 (1.01-4.91)**	1.04 (0.73-1.46)
Winkelmayer et al. 2011	Prospective cohort, n=2313	0.92 (0.61-1.37)	**2.38 (1.15-4.96)**	0.96 (0.70-1.31) (GI bleed)
Garg et al 2016	Retrospective cohort, n=302	0.93 (0.49-1.82)	Not specified	1.53 (0.94-2.51)
Genovesi et al 2015	Prospective cohort,n=296	0.12 (0.00-3.59)	Not specified	**3.96 (1.15-13.68)**
Wakasugi et al	Prospective cohort, n=60	3.36 (0.67-16.66)	Not specified	0.85 (0.19-3.64)
Shah et al 2014	Retrospective cohort, n=1626	1.17(0.79-1.75)	Not specified	**1.41 (1.09-1.81)**
Yodagawa et al 2016	Retrospective cohort, n=84	1.07 (0.2-5.74)	Not specified	Not specified

Systematic Review Discussion

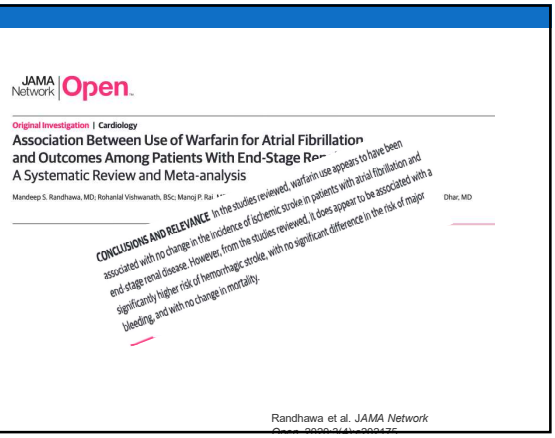
Conclusion

- Our review suggested a lack of association between warfarin use and reduced risk of stroke
- And an association between warfarin use and increased risk of bleeding in patients with AF on HD

Limitations

- Differences in definitions and reporting of outcomes make direct comparison difficult
- INR not recorded in studies

Battistella et al. CJKHD 2017


JAMA Network Open

Original Investigation | Cardiology

Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Re
A Systematic Review and Meta-analysis

Mandeep S. Randhawa, MD; Rohanlal Vishwanath, BSc; Manoj P. Rai

Dhar, MD

CONCLUSIONS AND RELEVANCE In the studies reviewed, warfarin use appears to have been associated with no change in the incidence of ischemic stroke in patients with atrial fibrillation and end-stage renal disease. However, from the studies reviewed, it does appear to be associated with a significantly higher risk of hemorrhagic stroke, with no significant difference in the risk of major bleeding, and with no change in mortality.

Randhawa et al. *JAMA Network*

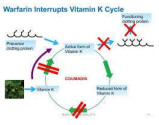
Calciphylaxis
Calcific Uremic Arteriolopathy (CUA)

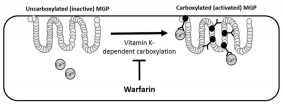
- Rare and serious disorder presenting with skin ischemia and necrosis
  - Reduced blood flow caused by calcification, fibrosis, and thrombus formation
- Most commonly occurs in ESKD and dialysis
  - CKD-mineral bone disorder
  - CKD-MBD treatment
  - Chronic inflammation
  - **Deficiencies in inhibitors of vascular calcifications**

Nigwekar SU, *N Engl J Med.* 2018;378:1704.

Warfarin and Vascular Calcification

- Matrix gamma-carboxyglutamate Gla protein (MGP)
  - Highly insoluble protein synthesized by vascular smooth muscle cells
  - Binds calcium phosphate, preventing calcification
  - MGP requires vitamin K to be converted to its active form
- Vitamin K antagonists (VKAs) such as Warfarin ↓MGP and then ↑ systemic calcification!!!





Poterucha TJ, *Am J Med.* 2016;129:635.e1–635.e4.

Warfarin Related Nephropathy (WRN)

- WRN associated with INR >3.0 causing AKI and micro/macrohematuria, and pathological changes on biopsy: ATN, glomerular hemorrhage, and tubular obstruction by RBC casts
- WRN associated with increased mortality and CKD progression

Wheeler DS, et al *J Thromb Haemost*. 2016;14:461–7.

What about the Direct Oral Anticoagulants (DOACS)?

DOACs

dabigatran

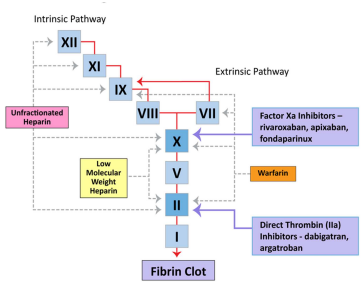
rivaroxaban

apixaban

edoxaban

Indications: DVT/PE, NVAF, post-op thromboprophylaxis **

Mechanism of Action of the DOACs



Dabigatran (Pradaxa)

Rivaroxaban (Xarelto)

Apixaban (Eliquis)

Edoxaban (Lixiana)

Drug Properties of the DOACs

	Warfarin	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
Renal clearance of parent drug	<1%	27%	36%	80%	50%
Removal with 4h of hemodialysis	<1%	7%	<1%	50-60%	9%
Volume of distribution (L)	8	21	50	50-70	107
Protein binding	99%	87%	92-95%	35%	55%
Metabolism	CYP2C9 Minor: CYP2C8, 2C18, 2C19, 1A2, 3A4	CYP3A4/5	CYP3A4/5, CYP2J2	Activated by esterases	Minimal: hydrolysis, CYP3A4

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[d]Product monograph states the drug is contraindicated at Stage 5 CKD.

Dosing of DOACS in CKD

- What is the evidence?

Edoxaban Dosing

Drug	Canada	US
Edoxaban	50-80ml/min: 60mg daily[1] 30-50ml/min: 30mg daily <30ml/min: Not recommended HD: Not recommended	51-95ml/min:60mg daily 15-50ml/min: 30mg daily <15ml/min: Not recommended HD: Not recommended

1. If ≤60kg or P-gp inhibitors except amiodarone and verapamil

The Impact of Renal Function on Outcomes with Edoxaban in the ENGAGE AF-TIMI 48 Trial

ORIGINAL ARTICLE

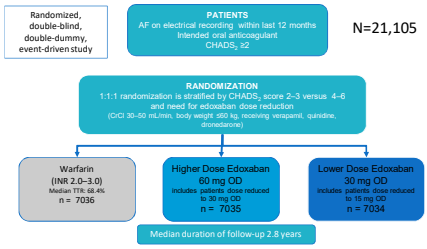
Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D.,

- in patients in the ENGAGE AF-TIMI 48 trial

Giugliano RP et al. N Engl J Med 2013;369:2093-2104

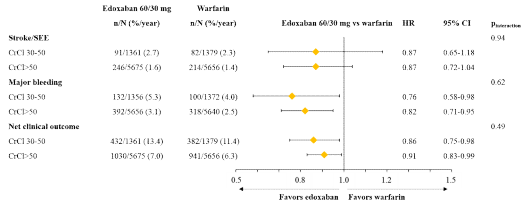
Study Design: ENGAGE AF-TIMI 48



To evaluate the efficacy, safety and net clinical outcomes with higher dose Edoxaban (60 mg/30 mg once-daily) compared with warfarin across the range of baseline kidney functions

Giugliano RP et al. N Engl J Med 2013;369:2093-2104

Rates of stroke, major bleeding & net clinical outcome endpoints by pre-specified CrCl subgroups from the ENGAGE AF-TIMI 48 study



Bohula EA, Giugliano R, Ruff C, et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. Circulation. 2016;134:24-36.

Post-hoc Analysis of ENGAGE AF TIMI 48 in Subjects with CrCL ≤ 30 mL/min Post-Baseline

Regimen Treatment received	Edoxaban 60/30 mg Edoxaban 30mg (N= 400)	Warfarin (Placebo Dose Reduced) (N = 407)
Stroke or SEE		
Number of events	6	5
Event rate (%/yr)	2.36	1.89
Major Bleeding		
Number of events	17	17
Event rate (%/yr)	6.83	6.49
Fatal Bleeding		
Number of events	0	3
Event rate (%/yr)	0.00	1.13
Life-threatening Bleeding		
Number of events	3	2
Event rate (%/yr)	1.17	0.76

https://wayback.archive-it.org/7993/20170405211245/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM420705.pdf

Regulatory approval for use in severe kidney impaired patients

Based on the results from the kidney impairment study and the population pharmacokinetics modelling with data from the **ENGAGE AF-TIMI 48 study**, both: the **European Medicines Agency** and **FDA**, granted edoxaban marketing authorization for patients with severe kidney impairment (CrCl 15–30 mL/min), with a recommended dose of 30 mg edoxaban once daily for patients with **CrCl 15-50 ml/min.**

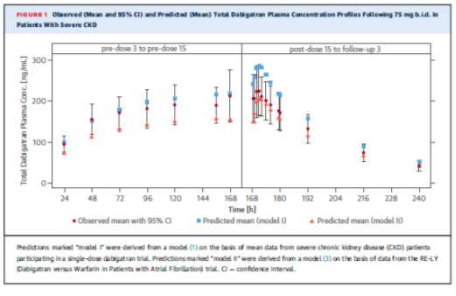
Lixiana® European Summary of Product Characteristics, current version.
Lixiana® European Public Assessment Report 2015. Available here: https://www.ema.europa.eu/en/documents/assessment-report/lixiana-epar-public-assessment-report_en.pdf. Last accessed on May 31st 2021
Savaysa FDA Advisory Committee Briefing Document 2014. available here: https://wayback.archive-it.org/7993/20170405211245/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM420705.pdf. Last accessed on May 31st 2021.

Dosing for Dabigatron

Drug	Canada	US
Dabigatran	>30ml/min: 150mg bid[1] or 110mg bid[3] <30ml/min: Avoid HD: Avoid	>50ml/min: 150mg bid 30-50ml/min:150mg bid[1] 15-30ml/min:75mg bid[2] <15ml/min: Avoid HD: Avoid

1. 75mg BID if concomitant dronedarone or ketoconazole
2. Avoid if concomitant P-gp inhibitor
3. Patients with high risk of bleeding including patients >75 years with 1 or more risk factors for bleeding

Dosing of Dabigatran



- 15 patients with eGFR 23 ml/min- 75mg bid for 7 days
- Observed compared to PK modeling

Kooiman et al. JACC 2016

Dosing for Rivaroxaban

Drug	Canada	US
Rivaroxaban*	>50ml/min: 20mg daily 15-50ml/min: 15mg daily < 15ml/min: Avoid HD: Avoid	>50ml/min: 20mg daily 15-50ml/min: 15mg daily <15ml/min: Avoid HD: Avoid

* Rivaroxaban updated monograph for VTE (15-50ml/min): 15mg bid x 3weeks then 20mg od; prevention: 10-20mg daily

Rivaroxaban Dosing

- Single Dose study-
- PK parameters calculated on unknown number of blood samples

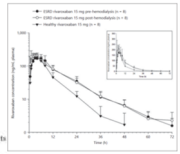


Table 2. Arithmetic mean (SD) plasma PK parameters following a single 15-mg dose of rivaroxaban in subjects with normal renal function and ESRD

Parameter	Normal renal function (CL_{CR} ≥80 ml/min; n = 8)	ESRD pre-dialysis[a] (n = 8)	ESRD post-dialysis[b] (n = 8)
C_{max}, ng/ml	210 (30.8)	194 (47.3)	247 (40.7)
t_{max}, h[c]	3.0 (0.5–6.0)	3.0 (1.0–6.0)	2.0 (1.0–4.0)
AUC_{inf}, ng·h/ml	1,848 (404)	2,740 (613)	2,857 (495)
$AUC_{τ}$, ng·h/ml	1,879 (432)[d]	2,770 (622)	2,907 (500)
$t_{1/2}$, h	6.3 (1.8)[d]	12.1 (3.8)	13.5 (5.7)
Vd/F, l	71.0 (8.9)[d]	101 (39)	101 (44)
CL/F, l/h	8.31 (1.70)[d]	5.69 (1.46)	5.34 (1.21)
Protein-bound rivaroxaban, %[e, f]	89 (87–93)	86 (80–94)	

[a] Pre-dialysis, subjects dosed 2 h before hemodialysis.
[b] Post-dialysis, subjects dosed 3 h after hemodialysis.
[c] Expressed as median (range).
[d] n = 7; healthy subject 220107 was excluded from $AUC_{(0-t)}$ PK parameter analysis due to variability in the terminal phase (r^2 adjustment <0.9000).
[e] Percentage of rivaroxaban that is protein-bound in pre-dose plasma.

Dias et al. AmJ Nephr 2016

Apixaban dosing for atrial fibrillation

Drug	Canada	US
Apixaban	>30 ml/min: 5mg BID[1] 15-29 ml/min: Use with caution <15 ml/min: Not recommended HD: Not recommended	> 15ml/min: 5 mg BID[1] HD: 5 mg BID[1]

1. 2.5mg BID if any 2 of following: ≥80 years, weight≤60kg or SrCr≥1.5mg/dL (133 umol/L)

Pharmacokinetics and Safety of Apixaban in Subjects on Hemodialysis

- Open-label, single dose study (5mg)
- Groups: HD (n=8) vs CrCl >80 ml/min(n=8)
  - Matched according to age (±5 years), weight (±20% post dialysis weight) and sex
- Results
  - ↑AUC by 36% higher in ESRD
  - Similar protein binding
  - 4-hr dialysis session: ↓exposure by 14%
  - No difference in INR, PT and aPTT

The Journal of Clinical Pharmacology 2016. 56(5) 628-636

Apixiban Pharmacokinetics in HD

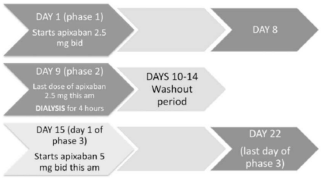
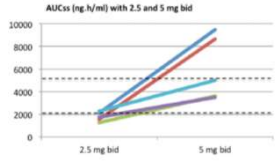


Figure 4. Schematic presentation of study interventions (phases 1–3). Phase 1: apixaban exposure after a 2.5 mg single dose and at steady state (day 8). Phase 2: effect of hemodialysis on apixaban concentration at steady state. Phase 3: apixaban exposure at steady state with a 5 mg bid dose. Bid, twice daily.

CJASN 2017; 28

Results



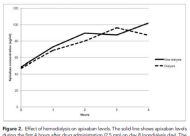


Figure 2. Effect of hemodialysis on apixaban levels. The solid line shows apixaban levels during the first 4 hours after drug administration (2.5 mg) on day 8 (nondialysis day). The dotted line shows apixaban levels during hemodialysis on day 9. The dialysis session started immediately after the drug administration (2.5 mg) and lasted for 4 hours.

Table 1. PK parameters during phase 1

Apixaban 2.5 mg Twice Daily	Day 1	Day 8	P Value	Reference Levels (for the 2.5 mg twice daily dose)
AUC_{0-12}, ng·h/ml	298.6 (38.0%)	1009.8 (30.7%)	<0.001	—
AUC_{0-24}, ng·h/ml	597.3 (38.0%)	2019.7 (30.7%)	<0.001	1661 (1120–2620)[19]
C_{max}, ng/ml	45.2 (69.9%)	131.5 (31.1%)	<0.001	123 (69–221)[19]
t_{max}, h	4.4 (62%)	3.6 (48%)	0.32	—
C_{min}, ng/ml	22.3 (41.2%)	58.0 (31.2%)	<0.001	56 (24–103)[19]
$t_{1/2}$, h	5.9 (15.8%)	7.5 (64.3%)	0.94	—
AI	N/A	3.6 (33.9%) [3.4]	N/A	[1.3–1.7][14,22]

Results are presented as mean (coefficient of variation), median (10th–90th percentile), or median (5th–95th percentile). The geometric mean (in brackets) is also provided for the AI. t_{max}, Time to peak apixaban concentration; AI, accumulation index; N/A, not applicable.
[a]Median (5th–95th percentile).

Table 2. PK parameters of apixaban after administration of 5 mg twice daily for a week and comparison with expected levels in the general population

Apixaban 5 mg Twice Daily	Day 22	P Value	Reference Levels (for the 5 mg twice daily dose)
AUC_{0-12}, ng·h/ml	3026.6 ± 46.6% [2770.4]	0.03	[1474–1717][19]
AUC_{0-24}, ng·h/ml	6053.2 ± 46.6% (3505.5–9469.7)	0.03	3370 (2070–5250)[19]
C_{max}, ng/ml	307.0 ± 39.4% (189.0–455.0)	0.02	171 (91–321)[19]
t_{max}, h	3.8 ± 35.6% (2.5–6.0)	0.89	—
C_{min}, ng/ml	217.5 ± 51.9% (91.0–337.4)	0.03	107 (56–203)[19]
$t_{1/2}$, h	17.4 ± 51.3% (7.1–29.8)	0.13	—

This table shows the PK parameters of apixaban 5 mg twice daily at steady state (day 8). Results are presented as mean ± coefficient of variation (range), median (10th–90th percentile), or median (5th–95th percentile). For AUC_{0-12}, the geometric mean (in brackets) is also depicted. P values are comparing apixaban 5 mg twice daily (day 22) with apixaban 2.5 mg twice daily at steady state (day 8; data depicted in Table 1, column 3). t_{max}, Time to peak apixaban concentration.
[a]Median (5th–95th percentile).

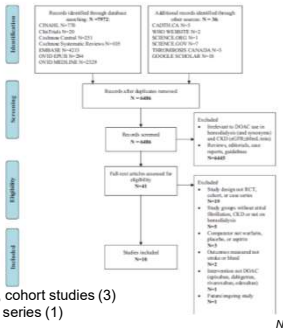
What is the clinical evidence with the DOACs in CKD Stage 4 or 5 or Dialysis?

DOAC use in CKD and Dialysis with AF Systematic Review

- **Background:** Lack of clear benefit and potential risk of bleeding with DOAC use in CKD and dialysis with AF
- **Aim:** Evaluate how treatment with DOACs affect stroke and bleeding outcomes compared with Warfarin or Aspirin in this population

Nephrol Dial Transplant. 2018:1–13.

Flow Diagram of Study Selection



RCTs (6), cohort studies (3) and case series (1)

Nephrol Dial Transplant. 2018:1–13.

DOACs vs. Warfarin in CKD with AF Systematic Review Results

DOAC	Stroke/Systemic Embolism	Major Bleeding
Apixaban 2.5–5mg BID	↓	↓
Dabigatran 110mg BID	↔	↔
Dabigatran 150mg BID	↓	↔
Rivaroxaban 10–20mg daily	↔	↔
Edoxaban 30–60mg daily	↔	↓

Nephrol Dial Transplant. 2018:1–13.

DOACs vs. Warfarin in Dialysis with AF Systematic Review Results

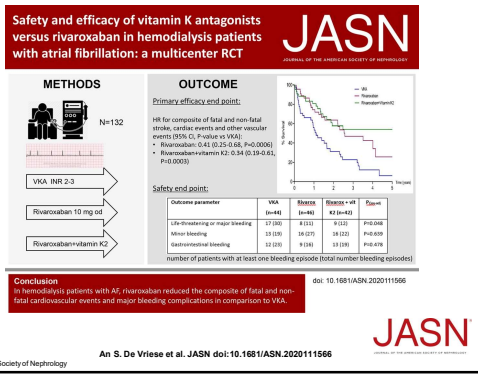
DOAC	Stroke/Systemic Embolism	Major Bleeding
Apixaban 2.5–5mg BID	↔	↔
Dabigatran 75–150mg BID	↔	↑
Rivaroxaban 15–20mg daily	↔	↑

Nephrol Dial Transplant. 2018:1–13.

Limitations

- Heterogeneity of the ten included studies.
  - the studies had varying definitions of major bleeding and stroke outcomes, and heterogeneous inclusion/exclusion criteria
- Each of the trials included had different definitions for kidney dysfunction and dose adjustments for the DOACs varied in the studies.
- Only two studies done comparing DOACs to warfarin for atrial fibrillation in HD patients
  - both were retrospective cohort studies.

Nephrol Dial Transplant. 2018:1–13.



Outcomes

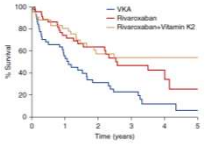


Table 3. Secondary efficacy outcomes

Outcome Parameter	VKA (n=44)	Rivaroxaban (n=46)	Rivaroxaban and Vitamin K2 (n=42)	P*
Death from any cause, n (%)	32 (72.7)	30 (65.2)	27 (64.3)	0.66
Sudden death, n	5	7	4	0.75
Stroke or systemic embolism, n				
Ischemic or uncertain type of stroke	7	4	2	0.20
Hemorrhagic stroke	2	0	0	0.21
Systemic embolism	0	0	0	—
Cardiac disease, n				
Acute coronary syndrome	6	9	2	0.12
Symptom-driven revascularization†	2	6	1	0.15
Hospitalization for heart failure	5	2	2	0.47
Symptomatic aortic-valve stenosis	2	0	0	0.21
Death from cardiac cause	5	4	2	0.58
Other vascular disease, n				
Symptomatic lower-limb ischemia	20	10	9	0.02
Calciphylaxis	4	2	0	0.14
Bowel ischemia	1	2	2	0.87

*According to Fisher exact test.
†Including acute coronary syndrome.

Outcomes

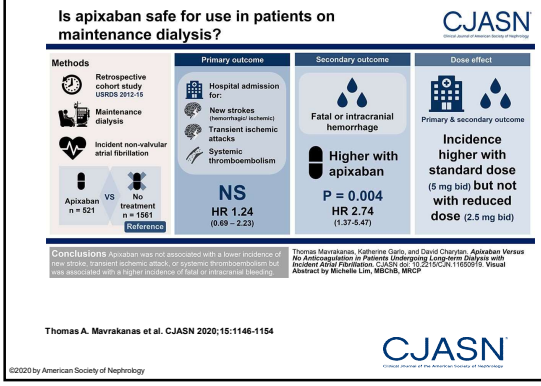
Table 4. Bleeding outcomes in the entire patient population

Outcome Parameter	VKA (n=44)	Rivaroxaban (n=46)	Rivaroxaban and Vitamin K2 (n=42)	P_{Gen}	$P_{Cox\ adj}$
Total bleeding	24 (49)	21 (38)	22 (34)	0.03	0.19
Life-threatening bleeding	11 (12)	3 (3)	6 (8)	0.05	0.08
Major bleeding	10 (18)	6 (8)	4 (4)	0.12	0.19
Life-threatening or major bleeding	17 (30)	8 (11)	9 (12)	0.04	0.05
Minor bleeding	13 (19)	16 (27)	16 (22)	0.85	0.64
Gastrointestinal bleeding	12 (23)	9 (14)	13 (19)	0.35	0.48

Cell entries are number of patients with at least one bleeding episode (total number of bleeding episodes). P_{Gen}, significance of differences in time to first bleeding episode according to Cox proportional hazard model analysis; $P_{Cox\ adj}$, P_{Gen} adjusted for competing risk of death.

Significance Statement

Direct oral anticoagulants (DOACs) have a superior risk-benefit profile compared with vitamin K antagonists (VKAs) in patients with normal renal function or early stage CKD, but whether this can be extended to the hemodialysis population is unknown. The authors report the first randomized controlled trial of thromboembolic and bleeding risk in patients on hemodialysis with atrial fibrillation on long-term treatment with a VKA or DOAC therapy. After a median follow-up of 1.88 years, the VKA and DOAC groups had a similar risk of stroke. However, the composite outcome of fatal and nonfatal cardiovascular events occurred more frequently with a VKA than with a DOAC, as did major bleeding complications. These findings support a superior risk-benefit profile of DOACs versus VKAs and suggest that VKAs should be avoided in patients on hemodialysis.



Thomas A. Mavrakanas et al. CJASN 2020;15:1146-1154

CJASN

Other Trials

- Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation (**RENAL-AF**)
- Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) (**AXADIA**)

Ongoing Trials

- **AVKDIAL**(Oral Anticoagulation in Haemdialysis Patients) in France
- **DAN-WARD** (The Danish Warfarin-Dialysis Study—Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis in Denmark

Ongoing Trials

- Stroke Prophylaxis with Apixaban in Chronic Kidney Disease Stage 5 Patients with Atrial Fibrillation (**SACK**)
- Strategies for the management of Atrial Fibrillation in patiEnts receiving HemoDialysis (**SAFE-HD**)

Case

Mrs V. is a 55 year old lady on HD since 2007. She has ESKD from unknown origin.

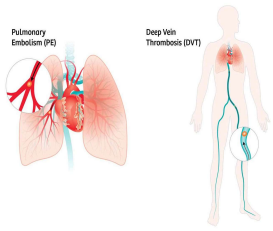
- PMH:
  - CAD- MI and ischemic cardiomyopathy
  - AF- right occipital infarct in 2015
  - PVD
  - Hepatitis C (treated with interferon)
- Medications:
  - rosuvastatin, ramipril, metoprolol, ASA, **warfarin**, pantoprazole, replavite, cinacalcet, Aranesp, Venofer
- She is admitted with calciphylaxis of her left foot

Question

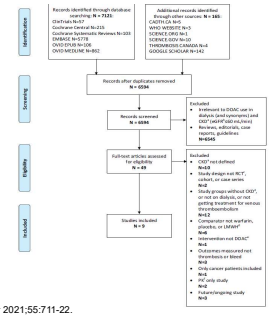
What do we do about her anticoagulation for AF?

A) Continue warfarin
B) D/C warfarin and start a DOAC
C) D/C warfarin and start a LMWH
D) D/C warfarin

DOACs for the management of VTE in CKD/ESKD



Systematic Review of DOACs for VTE in CKD/ESKD



2 RCTs, 7 cohort studies

Cheung CYS. Ann Pharmacother 2021;55:711-22.

Clinical Data Outcomes

1. There was no significant difference between DOACs and warfarin for reducing recurrent VTE events,
2. There was no significant difference between DOACs and warfarin in overall bleeding risk;
3. The risk of overall major bleeding from DOACs increased when the degree of kidney impairment increased, except with apixaban use;
4. In dialysis patients, apixaban had less overall bleeding when compared with warfarin.

Limitations:

- Various definitions for outcomes (ie bleeding)
- Small number of patients
- INRs TTR not reported

Cheung CYS. Ann Pharmacother 2021;55:711-22.

Dosing of DOACs for VTE in CKD/ESKD

CKD Stage[a]	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
4 (15–29 mL/min/1.73 m²)	Dose adjust for INR 2–3	LMWH for 7 days then apixaban 5 mg twice daily	Avoid (U.S. labeling suggests 75 mg twice daily	LMWH for 5–10 days then edoxaban 30 mg daily	Avoid (limited data for 15 mg daily)
5 (< 15 mL/min/1.73 m² or dialysis)	Dose adjust for INR 2–3	Avoid (limited data for 5 mg twice daily)[b]	Avoid	Avoid	Avoid

[a]Dose adjustments with DOACs are based on CrCl using the Cockcroft-Gault equation because the larger randomized controlled trials in the non-CKD population studies used CrCl as a measure of kidney function for dosing. This section will use CrCl as a measure of kidney function to reflect these trials' design.
[b]Apixaban: Use 2.5 mg twice daily if 2 of the following are present: SCr ≥ 1.5 mg/dL, age ≥ 80 yr, body weight ≤ 60 kg. Only the U.S. FDA suggests 5 mg twice daily for CrCl < 15 mL/min/1.73m² or ESKD.

Aursulesei V, Costache II. Clin Cardiol 2019;42:774-82.
Elenjickal EJ, et al. Am J Nephrol 2024;55:146-64. Cheung CYS. Ann Pharmacother 2021;55:711-22.

LMWH Dosing for Treatment of VTE in CKD/ESKD

CKD Stage	Unfractionated Heparin	Enoxaparin	Dalteparin	Nadroparin	Tinzaparin
4 (15–29 mL/min/1.73 m²)	80 units/kg IV bolus followed by 18–20 units/kg/hr infusion to achieve target PTT of 1–2 times normal Or 333 units/kg SC initial dose followed by 250 units/kg SC twice daily (no PTT monitoring)	1 mg/kg SC once daily	Not recommended (limited data)	Not recommended (limited data)	175 units/kg SC once daily
5 (< 15 mL/min/1.73 m² or dialysis)	Dose reduction by 33%; loading dose 60 units/kg, maintenance dose 12 units/kg/hr, subsequent aPTT-adjusted dosing	Not recommended (limited data)	Not recommended (limited data)	Not recommended (limited data)	175 units/kg SC once daily

Ortel TL, et al. Blood Adv 2020;4:4693–738; Kearon C, et al. Chest 2016;149:315-52; Mavrakanas TA. Clin J Am Soc Nephrol 2022;17:623-5; Aursulesei V. Clin Cardiol 2019;42:774-82.

Switching Between VKAs and DOACs

From Vitamin K Antagonists to DOACs		
Warfarin	Apixaban	Stop warfarin Start apixaban when INR < 2
	Dabigatran	Stop warfarin Start apixaban when INR < 2
	Edoxaban	Stop warfarin Start apixaban when INR < 2.5
	Rivaroxaban	Stop warfarin Start apixaban when INR < 3

Steffel J, Verhamme P, et al. Eur Heart J 2018;39:1330-93; Abdelnabi M, et al. Egypt Heart J 2022;74;18.

Switching Between VKAs and DOACs

From DOACs to Vitamin K Antagonists		
Apixaban	Warfarin	- Stop apixaban - Start warfarin and consider starting a bridging agent when next apixaban dose would be due - Start INR monitoring no sooner than 2 days after stopping apixaban[a] - Stop bridging agent when INR is at target
Dabigatran	Warfarin	- CrCl 50 mL/min/1.73m², start warfarin 3 days before stopping dabigatran - CrCl 30–49 mL/min/1.73m², start warfarin 2 days before stopping dabigatran - CrCl 15–29 mL/min/1.73m², start warfarin 1 day before stopping dabigatran - Start INR monitoring no sooner than 2 days after stopping dabigatran[a]
Edoxaban	Warfarin	- If taking 60 mg daily edoxaban, reduce dose to 30 mg daily and begin warfarin concomitantly; discontinue when INR is at goal - If taking 30 mg daily edoxaban, reduce dose to 15 mg daily and begin warfarin concomitantly; discontinue when INR is at goal - Start INR monitoring no sooner than 2 days after stopping edoxaban[a]
Rivaroxaban	Warfarin	- Stop rivaroxaban - Start warfarin and consider starting a bridging agent when next rivaroxaban dose would be due - Start INR monitoring no sooner than 2 days after stopping rivaroxaban[a] - Stop bridging agent when INR is at target

Steffel J, Verhamme P, et al. Eur Heart J 2018;39:1330-93; Abdelnabi M, et al. Egypt Heart J 2022;74;18.

[a]INR values drawn sooner may be falsely elevated by DOACs.

Perioperative Management of Anticoagulation Therapy

Thromboembolism Risk

High risk (bridging anticoagulation suggested):
- Any mechanical prosthetic mitral valve
- Older generation (cage-ball; tilting disc) mechanical aortic valve
- Recent (within 3 mo) arterial thromboembolism (stroke, systemic embolism, TIA)
- Recent (within 3 mo) venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Prior arterial or venous thromboembolism during interruption of warfarin
- Severe thrombophilia (e.g., deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies)

Intermediate risk (bridging anticoagulation optional and based on individual patient characteristics):
- Newer-generation (bileaflet) mechanical aortic valve
- Bioprosthetic aortic valve
- Chronic atrial fibrillation (valvular or nonvalvular) and at least 1 major stroke risk factor: prior stroke/TIA, left ventricular dysfunction, hypertension, diabetes, or age > 75 yr
- Prior venous thromboembolism within past 3–12 mo

Low risk (no bridging anticoagulation suggested):
- Chronic atrial fibrillation (valvular or nonvalvular) and no major stroke risk factors
- Prior venous thromboembolism over 12 mo ago

Spyropoulos AC, Douketis JD. Blood 2012;120:2954-62.
Thrombosis Canada. Clinical guides. Thrombosis Canada, 2023.

Bleeding Risk

Spyropoulos AC, Douketis JD. Blood 2012;120:2954-62.
Thrombosis Canada. Clinical guides. Thrombosis Canada, 2023.

High risk (2-day risk of major bleed 2%–4%):
- Neurosurgery (intracranial or spinal surgery)
- Cardiac surgery (coronary artery bypass or heart valve replacement)
- Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass)
- Major urologic surgery (prostatectomy, bladder tumor resection)
- Major lower limb orthopedic surgery (hip/knee joint replacement surgery)
- Permanent pacemaker insertion or internal defibrillator placement
- Selected invasive procedures (kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)
- Dental procedures (multiple tooth extractions > 2)

Intermediate risk (2-day risk of major bleed 0%–2%):
- Other intraabdominal surgery
- Other intrathoracic surgery
- Other orthopedic surgery
- Other vascular surgery

Low risk (2-day risk of major bleed 0%–2%):
- Laparoscopic cholecystectomy
- Laparoscopic inguinal hernia repair
- Dermatologic procedures
- Ophthalmologic procedures
- Coronary angiography
- Gastroscopy or colonoscopy
- Selected invasive procedures (bone marrow aspirate and biopsy, lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)

Very low risk (warfarin interruption not needed):
- Dental extractions (1 or 2 teeth) or teeth cleaning
- Skin biopsy or skin cancer removal
- Cataract removal

Timing of DOAC Therapy Perioperatively

DOAC	Procedure Bleeding Risk	Preprocedure DOAC Interruption			Procedure Day 0	Postprocedure
		> 50 mL/min/1.73m²	30–50 mL/min/1.73m²	< 30 mL/min/1.73m²		
Apixaban	High	Stop day −3	Stop day −4	Stop day −4	Keep holding	Restart day +2 or day +3
	Low/moderate	Stop day −2	Stop day −3	Stop day −3	Keep holding	Restart day +1
Dabigatran	High	Stop day −3	Stop day −4 or −5	N/A	Keep holding	Restart day +2 or day +3
	Low/moderate	Stop day −2	Stop day −3	N/A	Keep holding	Restart day +1
Edoxaban	High	Stop day −2	Stop day −3	Stop day −3	Keep holding	Restart day +2 or day +3
	Low/moderate	Stop day −1	Stop day −2	Stop day −2	Keep holding	Restart day +1
Rivaroxaban	High	Stop day −2	Stop day −3	Stop day −3	Keep holding	Restart day +2 or day +3
	Low/moderate	Stop day −1	Stop day −2	Stop day −2	Keep holding	Restart day +1

Sunkara T, et al. Health Serv Insights 2016;9(suppl 1):25-36.
Spyropoulos AC, Douketis JD. Blood 2012;120:2954-62

Case 2

R.J. is a 62-year-old, 69 kg woman with chronic kidney disease (CKD) stage 3b (estimated glomerular filtration rate [eGFR] 38 mL/min/1.73 m²). A doppler ultrasound confirmed deep vein thrombosis (DVT) involving the left popliteal vein. She was treated for acute phase DVT with rivaroxaban 15 mg twice daily for 21 days. She has no history of bleeding disorders or recent surgeries.

Two weeks after the initial diagnosis and initial treatment with rivaroxaban, the patient urgently needs a kidney biopsy because her kidney function has declined quickly since the diagnosis of the venous thromboembolism (VTE). Which one of the following is best to recommend for managing R.J.'s anticoagulation?

A. Continue rivaroxaban since kidney biopsy is low risk of bleeding.
B. Discontinue the rivaroxaban.
C. Stop rivaroxaban 3 days prior to the procedure and restart the rivaroxaban 2 days after the biopsy.
D. Switch rivaroxaban to warfarin and target INR 2-3.

Case 2

Answer: C
Guidelines for bridging recommend to stop the DOAC before a high risk of bleeding procedure such as a biopsy. Because R.J. is at high risk for thrombosis and the kidney biopsy confers a high risk of bleeding, the best recommendation would be to stop rivaroxaban 3 days before a high bleeding risk procedure and resume the rivaroxaban 2 days after the biopsy.
In general, the rapid offset and onset of action of DOACs obviates the need for "heparin bridging" as is done in selected warfarin-treated patients. Warfarin would also need to be stopped but bridging is necessary with warfarin.

Spyropoulos AC, Douketis JD. Blood 2012;120:2954-62.
Douketis JD. Blood 2011;117:5044-9.

Case 3

B.B. is a 62-year-old man who weighs 72 kg, with a medical history of hypertension, heart failure with reduced left ventricular ejection fraction (40%), and atrial fibrillation and no prior TIA or stroke. He has been on hemodialysis for the past 2 years. B.B. takes warfarin for his atrial fibrillation. His INR target range is 2-3.

Case 3

I) If B.B. undergoes dental cleaning, which one of the following is best to recommend for his anticoagulation plan?

A. Stop warfarin the day of dental cleaning and the restart the day after the cleaning procedure.
B. Stop warfarin 5 days before the dental cleaning and start LMWH and continue until the day of dental cleaning. Restart LMWH and warfarin the day after the procedure. Stop LMWH once INR reaches between 2 and 3.
C. Continue warfarin as per B.B.'s usual dose with keeping INR 2-3.
D. Patients taking warfarin should not have any dental cleaning or any dental work that is considered high risk of bleeding.

Case 3

I. Answer: C

Continue warfarin as per B.B.'s usual dose because dental cleaning does not have increased risk of bleeding. Dental cleaning does not have increased risk of bleeding and thus anticoagulation can be continued.

1. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-52. doi:10.1016/j.chest.2015.11.026
2. Thrombosis Canada. Clinical guides. Thrombosis Canada, 2023. Available at https://thrombosiscanada.ca/hcp/practice/clinical_guides.

Case 3

II) B.B. has been on warfarin for managing his AF with INR in target range 80% of the time. He is recently diagnosed with calciphylaxis. Which one of the following is best to recommend for managing anticoagulation for AF in B.B.?

A. Continue warfarin because B.B.'s INR is in target most of the time.

B. Stop warfarin.

C. Stop warfarin and start apixaban 5 mg twice daily for AF.

D. Stop warfarin and start tinzaparin 12600 units subcutaneous daily.

Case 3

II. Answer: C

Warfarin must be stopped because one of its potential adverse effects is calciphylaxis. Because this patient is young and has AF, it would be recommended to use oral anticoagulation such as a DOAC (Answer C is correct). DOACs are usually recommended over LMWH because the LMWH (such as tinzaparin) can worsen lesions in calciphylaxis.

1. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. N Engl J Med 2018;378:1704-14. 10.1056/NEJMra1505292

2. Jeong HS, Dominguez AR. Calciphylaxis: controversies in pathogenesis, diagnosis and treatment. Am J Med Sci 2016;351:21

Summary

- CKD increases the risk of thromboembolic events.
- CKD increases the risk of bleeding.
- DOACs should be used for CKD stages 1-4 with dose reductions accordingly.
- Limited data for DOACs and warfarin for treatment of AF and VTE in ESKD on dialysis – thus risks and benefits must be assessed on an individual basis.