

# DIRECT ORAL ANTICOAGULANTS IN STAGE 5 OR END-STAGE KIDNEY DISEASE

**Jessica Starr, PharmD, FCCP, BCPS**  
**Associate Clinical Professor**  
**Harrison School of Pharmacy**



HARRISON  
SCHOOL OF PHARMACY

# FACULTY DISCLOSURE/CONFLICT OF INTEREST

**I, Jessica Starr, have no  
actual or potential conflict of  
interest in relation to this  
program.**



# ABBREVIATIONS

HARRISON  
SCHOOL OF PHARMACY

- ▶ AF: atrial fibrillation
- ▶ CKD: chronic kidney disease
- ▶ CVD: cardiovascular disease
- ▶ CrCl: creatinine clearance
- ▶ CVD: cardiovascular disease
- ▶ DOAC: direct oral anticoagulant
- ▶ ESKD: end-stage kidney disease
- ▶ HD: hemodialysis
- ▶ OAC: Oral anticoagulant
- ▶ PK: pharmacokinetic
- ▶ PE: pulmonary embolism
- ▶ RCR: retrospective chart review
- ▶ SCr: serum creatinine
- ▶ TTR: time in therapeutic range
- ▶ VTE: venous thromboembolism



HARRISON  
SCHOOL OF PHARMACY

# OBJECTIVES

- ▶ Discusses the role of oral anticoagulation in patients with stage 5 or end-stage kidney disease
- ▶ Review consensus recommendations for oral anticoagulation in patients with stage 5 or end-stage kidney disease
- ▶ Determine an effective and safe treatment regimen for patients with atrial fibrillation or venous thromboembolism and stage 5 or end-stage kidney disease

# CVD + CKD/ESKD

- ▶ Cardiovascular disease (CVD) is the leading cause of death in patients with end-stage kidney disease (ESKD)
- ▶ Increased incidence of atrial fibrillation (AF) and venous thromboembolism (VTE)
- ▶ Therapeutic interventions with well established efficacy and safety profiles have varying benefit
  - ▶ Direct Oral Anticoagulants (DOAC)
  - ▶ Warfarin
- ▶ Data for oral anticoagulation (OAC) is significantly lacking

# PK REVIEW: ELIMINATION

	Warfarin	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Renal clearance	Minimal unchanged drug; primarily metabolites	27% of total clearance	66% (36% unchanged; 30% active)	50% (primarily unchanged)	80%
Renal dose adjustment for NVAf	No adjustment	If two of the following: <ul style="list-style-type: none"> <li>• Scr <math>\geq</math> 1.5 mg/dL</li> <li>• Age <math>\geq</math> 80 years</li> <li>• <math>\leq</math> 60 kg</li> </ul>	CrCl < 50 mL/min	CrCl < 15 mL/min: Avoid use	CrCl < 15 mL/min: No recommendation provided
Renal dose adjustment for VTE	No adjustment	No adjustment	CrCl < 15 mL/min: Avoid use	CrCl < 15 mL/min: Avoid use	CrCl < 30 mL/min: No recommendation provided

Savaysa. Package Insert. Daiichi Sankyo, Inc. 1/2015.

Xarelto. Package Insert. Janssen Pharmaceuticals. 5/2016.

Pradaxa. Package Insert. Boehringer Ingelheim Pharmaceuticals, Inc. 11/2011.

Eliquis. Package Insert. Bristol-Myers Squibb. 8/2014.

Coumadin. Package Insert. Bristol-Myers Squibb. 10/2011.



# DOACs USE IN CKD & NVAF

HARRISON  
SCHOOL OF PHARMACY

- ▶ Overall use of OAC increased from 56.8% in 2009 to 66.3% in 2018
- ▶ 2013
  - ▶ DOACs use was 10.7%
  - ▶ Warfarin use was 45.1%
- ▶ 2018
  - ▶ Increase in DOAC use (38.7%)
  - ▶ Decrease in warfarin use (24.5%)
  - ▶ Stage 4 or 5 CKD
    - ▶ DOAC (33.3%) and warfarin (27.1%)



ANTICOAGULATION FOR  
NON-VALVULAR AF  
IN PATIENTS WITH ESKD





# MEET EK

HARRISON  
SCHOOL OF PHARMACY

- ▶ EK is a 63-year-old white female who was diagnosed with atrial fibrillation during this hospitalization. She has been adequately rate controlled. EK weighs 68 kg.
- ▶ PMH:
  - ▶ ESKD on HD MWF
  - ▶ HTN
  - ▶ Type 2 Diabetes Mellitus
  - ▶ Hyperlipidemia
  - ▶ Peripheral neuropathy
- ▶ The medical team wants to start apixaban for long-term stroke prevention and asks the pharmacist to recommend an appropriate dose.



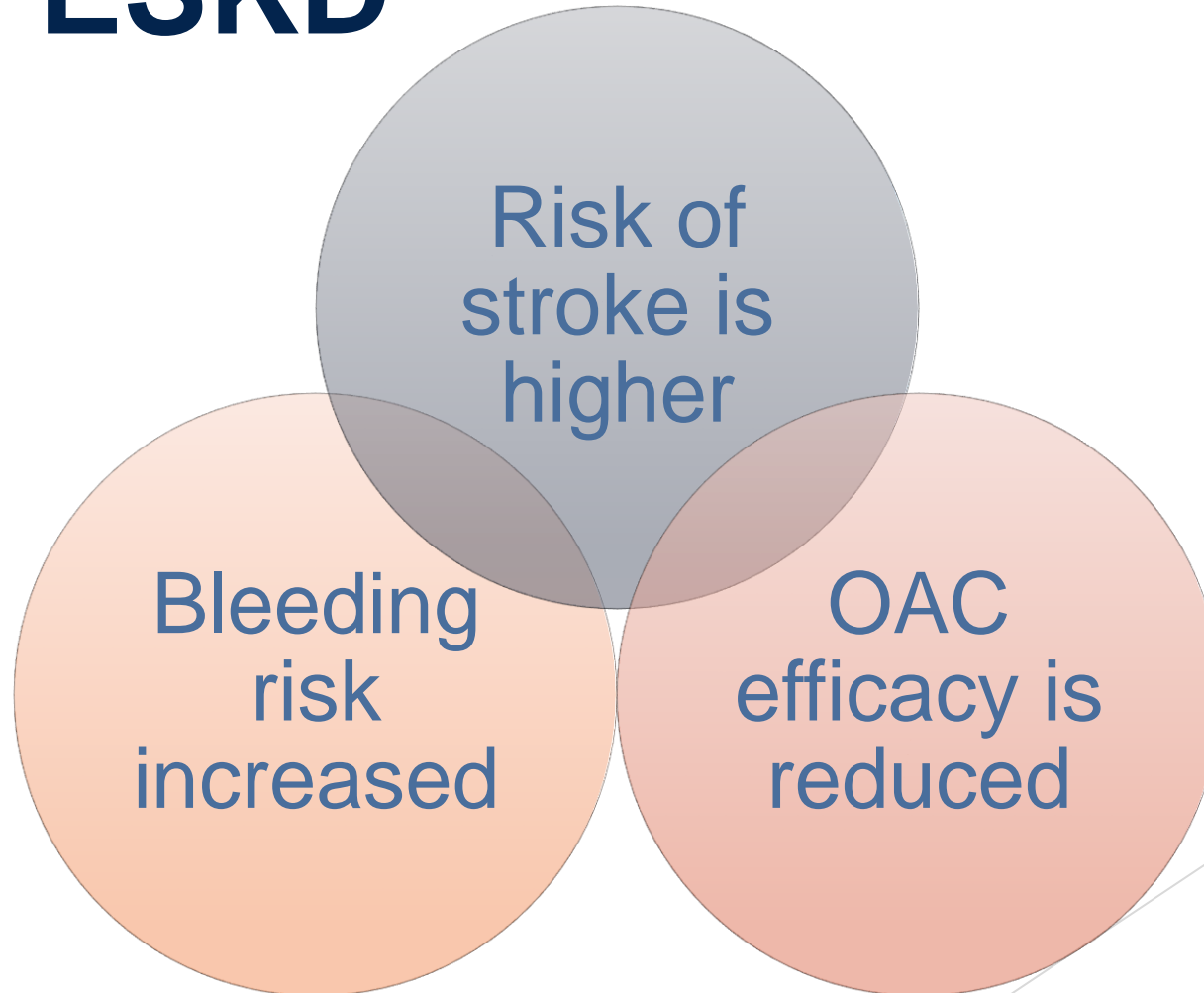
HARRISON  
SCHOOL OF PHARMACY

# ATRIAL FIBRILLATION AND CKD

- ▶ Prevalence of AF is higher in patients with CKD
- ▶ CKD is independent risk factor for stroke
- ▶ Increased risk of major and intracranial bleeding
- ▶ Increased bleeding risk with anticoagulation
- ▶ CHA<sub>2</sub>DS<sub>2</sub>VASc
- ▶ Significant controversy for the net clinical benefit of oral anticoagulation (OAC)

Nephrol Dial Transplant 2015;30:1162-9.  
Am J Kidney Dis 2009; 53:417-425.  
Europace. 2015;17(8):1169-1196.

# OAC USE IN AF IN PATIENTS WITH ESKD



Guideline	Recommendations
<p>2019 AHA/ACC/HRS JACC 2019;7(1):104-32.</p>	<p>Patients with ESKD (CrCl &lt;15 mL/min or on dialysis)</p> <ul style="list-style-type: none"> <li>• <b>It might be reasonable to prescribe warfarin or apixaban</b> for oral anticoagulation (IIb, B-NR)</li> <li>• Further studies are warranted</li> </ul>
<p>2018 CHEST CHEST 2018;154(5):1121-1201.</p>	<p>Patients with ESKD (CrCl &lt;15 mL/min or dialysis-dependent)</p> <ul style="list-style-type: none"> <li>• We suggest that individualized decision-making is appropriate</li> <li>• We <b>suggest using well-managed VKA</b> with TTR &gt; 65-70%</li> </ul>
<p>2018 KDIGO Kidney International 2018;94(2):231-234.</p>	<p>Patients with eCrCl &lt;15 mL/min +/- dialysis</p> <ul style="list-style-type: none"> <li>• <b>Warfarin: Equipoise</b> based on observational data and meta-analysis</li> <li>• <b>Apixaban: Unknown</b></li> <li>• <b>Rivaroxaban: Unknown</b></li> </ul>
<p>2018 EHRA European Heart Journal 2018;39(16):1330–1393.</p>	<p>Patients with a CrCl of 15 mL/min or dialysis</p> <ul style="list-style-type: none"> <li>• <b>Warfarin: Observational studies yield conflicting results</b></li> <li>• <b>DOACs: Routine use is best avoided</b></li> <li>• Decision to anticoagulate remains a very individualized one</li> </ul>
<p>2016 ESC European Heart Journal 2016;37(38):2893–2962.</p>	<p>Patients on dialysis</p> <ul style="list-style-type: none"> <li>• <b>Controlled studies</b> of both warfarin and DOACs are <b>needed</b></li> </ul>

# Warfarin - Standard of Care?

Proportion of time in target INR range is lower

Labile INR

Enhanced vascular calcification

Study	Observational Study Design	Patient Population	Efficacy	Major Bleeding
Tan J, et al. Nephrology. 2019;24:234–44.	Retrospective cohort • US Renal Data System	Dialysis patients with AF • Warfarin (1649), nonusers (4116)	0.88 (0.70–1.11)	1.50 (1.33–1.68)
Yoon CY, et al. Stroke. 2017;48:2472–9.	Retrospective cohort • Korean Health Ins Service	Dialysis patients with AF • Warfarin (2921), nonusers (7053)	1.09 (0.93–1.28)	1.44 (1.10–1.88)
Genovesi S, et al. J Nephrol. 2017;30:573–81.	Prospective cohort • 10 Italian dialysis centers	ESKD patients with AF • OAC (134), no OAC (156)	0.60 (0.26–1.36)	1.57 (0.91–2.72)
Yodogawa K, et al. Heart Vessels. 2016;31:1676–80.	Retrospective cohort • Single center	ESKD patients with AF • Warfarin (30), nonusers (54)	1.07 (0.2-5.74)	No Difference
Wang TK, et al. Heart Lung Circ. 2016; 25:243-9.	Retrospective cohort • Single center	ESKD patients with AF • Warfarin (59), nonusers (82)	1.01 (0.5-2.04)	1.44 (0.71-2.92)
Garg L, et al. Int J Cardiol. 2016;222:47-50.	Retrospective cohort • Single health system	ESKD patients with AF • Warfarin (119), nonuser (183)	0.93 (0.49–1.82)	1.53 (0.94–2.51)
Shen JI, et al. Am J Kidney Dis. 2015;66:677–88.	Retrospective cohort • US Renal Data System	Dialysis patients with AF • Warfarin (1838), nonusers (10446)	0.68 (0.47-0.99)	0.82 (0.37-1.81) HS
Shah M, et al. Circulation. 2014;129:1196–203.	Retrospective cohort • Single center	Patients with AF (dialysis cohort) • Warfarin (756), nonusers (870)	1.14 (0.78-1.67)	1.44 (1.13-1.85)
Bonde, et al. JACC. 2014;64:2471-82.	Retrospective cohort • Danish national registry	Patients with AF (dialysis cohort) • N = 1142 (0.7% of study sample)	0.85 (0.72-0.99) (mortality)	Not reported
Wakasugi M, et al. Clin Ex Nephrol. 2014;18:662–9.	Prospective cohort • Multicenter	Dialysis patients with AF • Warfarin (28), nonusers (32)	1.94 (0.63–5.93)	0.85 (0.19–3.64)
Olesen, et al. NEJM. 2012;367:625-635.	Retrospective cohort • Danish national registry	Patients with AF (dialysis cohort) • N = 901 (0.7% of study sample)	0.44 (0.26-0.74)	1.27 (0.91-1.77)
Winkelmayer WC, et al. Clin J Am Soc Nephrol. 2011;6:2662–8.	Retrospective cohort • Medicare claims data (3 states)	Dialysis patients with AF • Warfarin (237), nonusers (948)	0.92 (0.61-1.37)	2.38 (1.15 - 4.96) (HS)
Chan KE, et al. J Am Soc Nephrol. 2009;20:2223–33.	Retrospective cohort • Single center	Dialysis patients with AF • Warfarin (747), nonusers (924)	1.81 (1.12 – 2.92)	2.22 (1.01-4.91) (HS)
Lai, et al. Int J Nephrol Renovasc Dis. 2009;2:33-37.	Retrospective cohort • Single center	CKD patients with AF (23% HD) • Warfarin (232), nonusers (167)	HD patients: 10%(W) vs 38% P = < 0.005	All patients: 14%(W) vs 9% P= NS



# WARFARIN USE IN AF IN PATIENTS WITH ESKD: META-ANALYSES

Meta-Analysis	Patient Population	Stroke or Thromboembolism	Mortality	Bleeding
Kuno, et al. JACC. 2020;75:237-85.	Dialysis patients with AF on OAC • Warfarin vs no OAC <u>subset</u>	0.91 (0.72-1.16)	0.94 (0.82-1.09)	1.31 (1.15-1.5)
Van Der Meersch, et al. Am Heart J. 2017;184:37-46.	Dialysis patients with AF • Warfarin vs non-users	0.74 (0.51-1.06) I <sup>2</sup> = 70%; n = 12	1.00 (0.92-1.09) I <sup>2</sup> = 14%; n = 7	1.21 (1.03-1.43) I <sup>2</sup> = 34%; n = 11
Harel, et al. Can J Card. 2017;33:37-46.	Dialysis patients with AF • Warfarin vs non-users	0.85 (0.62-1.15) P=0.29; I <sup>2</sup> = 69%; n = 14	0.89 (0.72-1.11) P=0.29; I <sup>2</sup> = 79%; n = 7	1.93 (0.93-4) HS P=0.08; I <sup>2</sup> = 58%; n = 4
Nochaiwong S, et al. Open Heart. 2016;3:e000441.	Dialysis patients with AF • Warfarin vs non-users	1.06 (0.82-1.36) P=0.467; I <sup>2</sup> = 60%; n = 11	0.99 (0.89-1.1) P=0.162; I <sup>2</sup> = 35%; n = 7	1.6 (0.91-2.81) HS P=0.1; I <sup>2</sup> = 64%; n = 5
				1.35 (1.11-1.64) P=0.003; I <sup>2</sup> = 59%; n = 7
Dahal, et al. Chest. 2016;149:951-9.	CKD patients with AF • Warfarin vs non-users • ESKD on RRT subset	1.12 (0.69-1.82) P=0.65; I <sup>2</sup> = 76%; n = 7	0.96 (0.81-1.13) P=0.6; I <sup>2</sup> = 57%; n = 6	1.3 (1.08-1.56) P=0.005; I <sup>2</sup> = 24%; n = 5



HARRISON  
SCHOOL OF PHARMACY

# WARFARIN – STANDARD OF CARE?

- ▶ Observational studies
- ▶ Mainly retrospective data
- ▶ Time in therapeutic range
- ▶ Concomitant antiplatelet therapy
- ▶ Significant heterogeneity seen in outcomes



# DOAC USE IN AF IN PATIENTS WITH ESKD

Dabigatran  
(RE-LY 2009)

- Excluded: CrCl <30 mL/min

Rivaroxaban  
(ROCKET AF 2011)

- Excluded: CrCl <30 mL/min

Apixaban  
(ARISTOTLE 2011)

- Excluded: CrCl <25 mL/min

Edoxaban  
(ENGAGE 2013)

- Excluded: CrCl <30 mL/min

# DOAC DOSING IN AF

	Apixaban	Rivaroxaban
Normal Dosing	<b>5 mg PO BID</b>	<b>20 mg PO daily</b>
Renal Dose Adjustment	If two of the following: Scr $\geq$ 1.5 mg/dL Age $\geq$ 80 years $\leq$ 60 kg  <b>2.5 mg PO BID</b>	CrCl < 50 mL/min: <b>15 mg PO daily</b>

Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
De Vriese, 2021	Prospective randomized • Multicenter with 18 month extension	Dialysis patients with AF prescribed OAC • Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)	0.41 (0.25–0.68)	65% R vs 73% W P=0.66	13% R vs 23% W P=0.12
			4.3% R vs 11.4% W P=0.22	32.6% R vs 43.2% W P=0.46	13% R vs 16% W P=0.16
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563)	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
See, 2020	Retrospective cohort • Taiwan Insurance claims	Dialysis patients with AF prescribed OAC • DOAC (448), warfarin (448 matched cohort)	1.2 (0.76-1.92)	Not reported	0.98 0.64-1.51
Miao, 2020	Retrospective cohort • MarketScan Claims	Dialysis patients with AF prescribed OAC • Rivaroxaban (787), apixaban (1836)	1.18 (0.53-2.63)	Not reported	1.00 (0.63-1.58)
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57)	Not reported	Not reported	15% A vs 17% W P=0.338
Siontis, 2018	Retrospective cohort using prognostic score matching • Medicare patients	Dialysis patients with AF prescribed OAC • Apixaban (2351), warfarin (7053 matched cohort)	0.88 (0.69–1.12)	0.85 (0.71–1.01)	0.72 (0.59-0.87)
					0.79 (0.49-1.26)
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50)	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120)	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338
					12.5% A vs 5.8% W (Nonmajor) P=0.16

# DE VRIESE, ET AL.

Characteristics	Rivaroxaban 10mg (n=46)	Warfarin (n=44)	
Indication: AF	100%		
Indication: VTE	--		
Follow-up	1.88 years	1.88 years	
Outcomes	Rivaroxaban 10mg	Warfarin	HR (95% CI)
CV and thrombotic events	50%	80%	0.41 (0.25-0.68)
Major Bleeding	13%	23%	0.12

Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
De Vriese, 2021	Prospective randomized • Multicenter with 18 month extension	Dialysis patients with AF prescribed OAC • Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)	0.41 (0.25–0.68)	65% R vs 73% W P=0.66	13% R vs 23% W P=0.12
			4.3% R vs 11.4% W P=0.22	32.6% R vs 43.2% W P=0.46	13% R vs 16% W P=0.16
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563)	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
See, 2020	Retrospective cohort • Taiwan Insurance claims	Dialysis patients with AF prescribed OAC • DOAC (448), warfarin (448 matched cohort)	1.2 (0.76-1.92)	Not reported	0.98 0.64-1.51
Miao, 2020	Retrospective cohort • MarketScan Claims	Dialysis patients with AF prescribed OAC • Rivaroxaban (787), apixaban (1836)	1.18 (0.53-2.63)	Not reported	1.00 (0.63-1.58)
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57)	Not reported	Not reported	15% A vs 17% W P=0.338
Siontis, 2018	Retrospective cohort using prognostic score matching • Medicare patients	Dialysis patients with AF prescribed OAC • Apixaban (2351), warfarin (7053 matched cohort)	0.88 (0.69–1.12)	0.85 (0.71–1.01)	0.72 (0.59-0.87)
					0.79 (0.49-1.26)
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50)	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120)	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338  12.5% A vs 5.8% W (Nonmajor) P=0.16

# IONESCU, ET AL.

Characteristics	Apixaban (n=144)	Warfarin (n=563)	
Indication: AF	61.7%		
Indication: VTE	38.3%		
Apixaban 5mg BID	64%	--	
Apixaban 2.5mg BID	36%	--	
Time on Therapy	5.2 months	6.3 months	
Outcomes	Apixaban	Warfarin	P Value
Thrombotic events*	4.9%	6.6%	0.448
Bleeding**	16.7%	30.1%	<0.01

\*All events occurred in 2.5mg group

\*\* No difference between 5mg and 2.5mg

Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
De Vriese, 2021	Prospective randomized • Multicenter with 18 month extension	Dialysis patients with AF prescribed OAC • Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)	0.41 (0.25–0.68)	65% R vs 73% W P=0.66	13% R vs 23% W P=0.12
			4.3% R vs 11.4% W P=0.22	32.6% R vs 43.2% W P=0.46	13% R vs 16% W P=0.16
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563)	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
See, 2020	Retrospective cohort • Taiwan Insurance claims	Dialysis patients with AF prescribed OAC • DOAC (448), warfarin (448) • Matched cohort	1.2 (0.76-1.92)	Not reported	0.98 0.64-1.51
Miao, 2020	Retrospective cohort • MarketScan Claims	Dialysis patients with AF prescribed OAC • Rivaroxaban (787), apixaban (1836)	1.18 (0.53-2.63)	Not reported	1.00 (0.63-1.58)
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57)	Not reported	Not reported	15% A vs 17% W P=0.338
Siontis, 2018	Retrospective cohort using prognostic score matching • Medicare patients	Dialysis patients with AF prescribed OAC • Apixaban (2351), warfarin (7053 matched cohort)	0.88 (0.69–1.12)	0.85 (0.71–1.01)	0.72 (0.59-0.87)
					0.79 (0.49-1.26)
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50)	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120)	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338
					12.5% A vs 5.8% W (Nonmajor) P=0.16

# SEE, ET AL.

Characteristics	DOAC (n=448)	Warfarin (n=448)	
Indication: AF	100%		
Indication: VTE	--		
Apixaban	18%	--	
Dabigatran	30.6%	--	
Edoxaban	3.8%		
Rivaroxaban	47.6%	--	
Time on Therapy	5 years	5 years	
Outcomes	DOAC	Warfarin	P Value
Thrombotic events	6.67 events/ 100 person-yrs	5.3 events/100 person-yrs	0.4183
Bleeding	7.07 events/ 100 person-yrs	7.15 events/ 100 person-yrs	<0.9373



Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
De Vriese, 2021	Prospective randomized • Multicenter with 18 month extension	Dialysis patients with AF prescribed OAC • Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)	0.41 (0.25–0.68)	65% R vs 73% W P=0.66	13% R vs 23% W P=0.12
			4.3% R vs 11.4% W P=0.22	32.6% R vs 43.2% W P=0.46	13% R vs 16% W P=0.16
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563)	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
See, 2020	Retrospective cohort • Taiwan Insurance claims	Dialysis patients with AF prescribed OAC • DOAC (448), warfarin (448) • Matched cohort	1.2 (0.76-1.92)	Not reported	0.98 0.64-1.51
Miao, 2020	Retrospective cohort • MarketScan Claims	Dialysis patients with AF prescribed OAC • Rivaroxaban (787), apixaban (1836)	1.18 (0.53-2.63)	Not reported	1.00 (0.63-1.58)
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57)	Not reported	Not reported	15% A vs 17% W P=0.338
Siontis, 2018	Retrospective cohort using prognostic score matching • Medicare patients	Dialysis patients with AF prescribed OAC • Apixaban (2351), warfarin (7053 matched cohort)	0.88 (0.69–1.12)	0.85 (0.71–1.01)	0.72 (0.59-0.87)
					0.79 (0.49-1.26)
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50)	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120)	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338
					12.5% A vs 5.8% W (Nonmajor) P=0.16

# MIAO, ET AL.

Characteristics	Rivaroxaban (n=787)	Apixaban (n=1836)	
Indication: AF	100%		
Indication: VTE	--		
Apixaban 2.5mg BID	--	28.9%	
Rivaroxaban < 20 mg	28.8%	--	
Time on Therapy	0.87 years	0.87 years	
Outcomes	Rivaroxaban	Apixaban	HR (95% CI)
Thrombotic events	1.27 events/ 100 person-yrs	1.26 events/100 person-yrs	1.18 (0.53-2.63)
Major Bleeding	3.73 events/ 100 person-yrs	3.49 events/ 100 person-yrs	1.00 (0.63-1.58)

Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
De Vriese, 2021	Prospective randomized • Multicenter with 18 month extension	Dialysis patients with AF prescribed OAC • Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)	0.41 (0.25–0.68)	65% R vs 73% W P=0.66	13% R vs 23% W P=0.12
			4.3% R vs 11.4% W P=0.22	32.6% R vs 43.2% W P=0.46	13% R vs 16% W P=0.16
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563)	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
See, 2020	Retrospective cohort • Taiwan Insurance claims	Dialysis patients with AF prescribed OAC • DOAC (448), warfarin (448) • Matched cohort	1.2 (0.76-1.92)	Not reported	0.98 0.64-1.51
Miao, 2020	Retrospective cohort • MarketScan Claims	Dialysis patients with AF prescribed OAC • Rivaroxaban (787), apixaban (1836)	1.18 (0.53-2.63)	Not reported	1.00 (0.63-1.58)
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57)	Not reported	Not reported	15% A vs 17% W P=0.338
Siontis, 2018	Retrospective cohort using prognostic score matching • Medicare patients	Dialysis patients with AF prescribed OAC • Apixaban (2351), warfarin (7053 matched cohort)	0.88 (0.69–1.12)	0.85 (0.71–1.01)	0.72 (0.59-0.87)
					0.79 (0.49-1.26)
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50)	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120)	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338
					12.5% A vs 5.8% W (Nonmajor) P=0.16

# HERNDON, ET AL.

Characteristics	Apixaban (n=54)	Warfarin (n=57)	
Indication: AF	77.4%		
Indication: VTE	22.5%		
CKD 5	n=54		
Hemodialysis	n=49		
Apixaban 5mg BID	46%	--	
Apixaban 2.5mg BID	54%	--	
Outcomes	Apixaban	Warfarin	P Value
Major Bleeding	14%	17%	0.338

Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
De Vriese, 2021	Prospective randomized • Multicenter with 18 month extension	Dialysis patients with AF prescribed OAC • Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)	0.41 (0.25–0.68)	65% R vs 73% W P=0.66	13% R vs 23% W P=0.12
			4.3% R vs 11.4% W P=0.22	32.6% R vs 43.2% W P=0.46	13% R vs 16% W P=0.16
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563)	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
See, 2020	Retrospective cohort • Taiwan Insurance claims	Dialysis patients with AF prescribed OAC • DOAC (448), warfarin (448) • Matched cohort	1.2 (0.76-1.92)	Not reported	0.98 0.64-1.51
Miao, 2020	Retrospective cohort • MarketScan Claims	Dialysis patients with AF prescribed OAC • Rivaroxaban (787), apixaban (1836)	1.18 (0.53-2.63)	Not reported	1.00 (0.63-1.58)
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57)	Not reported	Not reported	15% A vs 17% W P=0.338
Siontis, 2018	Retrospective cohort using prognostic score matching • Medicare patients	Dialysis patients with AF prescribed OAC • Apixaban (2351), warfarin (7053 matched cohort)	0.88 (0.69–1.12)	0.85 (0.71–1.01)	0.72 (0.59-0.87)
					0.79 (0.49-1.26)
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50)	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120)	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338  12.5% A vs 5.8% W (Nonmajor) P=0.16

# SIONTIS, ET AL.

Characteristics	Apixaban (n=2351)	Warfarin (n=23172)		
Indication: AF	100%			
Indication: VTE	--			
Apixaban 5mg BID	44%	--		
Apixaban 2.5mg BID	56%	--		
Time on Therapy	105 days	157 days		
Outcomes	Apixaban (n=2351)	Warfarin (n=7053)	HR (95% CI)	P Value
Stroke/systemic embolism	3.4%	5.3%	0.88 (0.69–1.12)	0.29
Major bleeding	5.5%	10.1%	0.72 (0.59–0.87)	<0.001

Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
De Vriese, 2021	Prospective randomized • Multicenter with 18 month extension	Dialysis patients with AF prescribed OAC • Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)	0.41 (0.25–0.68)	65% R vs 73% W P=0.66	13% R vs 23% W P=0.12
			4.3% R vs 11.4% W P=0.22	32.6% R vs 43.2% W P=0.46	13% R vs 16% W P=0.16
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563)	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
See, 2020	Retrospective cohort • Taiwan Insurance claims	Dialysis patients with AF prescribed OAC • DOAC (448), warfarin (448) • Matched cohort	1.2 (0.76-1.92)	Not reported	0.98 0.64-1.51
Miao, 2020	Retrospective cohort • MarketScan Claims	Dialysis patients with AF prescribed OAC • Rivaroxaban (787), apixaban (1836)	1.18 (0.53-2.63)	Not reported	1.00 (0.63-1.58)
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57)	Not reported	Not reported	15% A vs 17% W P=0.338
Siontis, 2018	Retrospective cohort using prognostic score matching • Medicare patients	Dialysis patients with AF prescribed OAC • Apixaban (2351), warfarin (7053 matched cohort)	0.88 (0.69–1.12)	0.85 (0.71–1.01)	0.72 (0.59-0.87)
					0.79 (0.49-1.26)
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50)	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120)	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338
					12.5% A vs 5.8% W (Nonmajor) P=0.16

# REED, ET AL

Characteristics	Apixaban (n=74)	Warfarin (n=50)	
Indication: AF	47%		
Indication: VTE	53%		
Apixaban 5mg BID	80%	--	
Apixaban 2.5mg BID	20%	--	
Time on Therapy	7.9 months	10 months	
Outcomes	Apixaban	Warfarin	P Value
Recurrent VTE	4.4%	28.6%	0.99
Major bleeding	5.4%	22%	0.01



Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
De Vriese, 2021	Prospective randomized • Multicenter with 18 month extension	Dialysis patients with AF prescribed OAC • Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)	0.41 (0.25–0.68)	65% R vs 73% W P=0.66	13% R vs 23% W P=0.12
			4.3% R vs 11.4% W P=0.22	32.6% R vs 43.2% W P=0.46	13% R vs 16% W P=0.16
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563)	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
See, 2020	Retrospective cohort • Taiwan Insurance claims	Dialysis patients with AF prescribed OAC • DOAC (448), warfarin (448) • Matched cohort	1.2 (0.76-1.92)	Not reported	0.98 0.64-1.51
Miao, 2020	Retrospective cohort • MarketScan Claims	Dialysis patients with AF prescribed OAC • Rivaroxaban (787), apixaban (1836)	1.18 (0.53-2.63)	Not reported	1.00 (0.63-1.58)
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57)	Not reported	Not reported	15% A vs 17% W P=0.338
Siontis, 2018	Retrospective cohort using prognostic score matching • Medicare patients	Dialysis patients with AF prescribed OAC • Apixaban (2351), warfarin (7053 matched cohort)	0.88 (0.69–1.12)	0.85 (0.71–1.01)	0.72 (0.59-0.87)
					0.79 (0.49-1.26)
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50)	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120)	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338  12.5% A vs 5.8% W (Nonmajor) P=0.16

# SARRATT, ET AL

Baseline Characteristics	Apixaban (n=40)	Warfarin (n=140)	
Indication: AF	70.6%		
Indication: VTE	29.4%		
Apixaban 5mg BID	42.5%	--	
Apixaban 2.5mg BID	57.5%	--	
Length of Stay	9 days	9 days	
Outcomes	Apixaban (n=40)	Warfarin (n=140)	P Value
Major bleeding	0	5.8%	0.338
Clinically relevant nonmajor bleeding	12.5%	5.8%	0.166
Any bleeding	15%	14.2%	0.438



# SUMMARY

HARRISON  
SCHOOL OF PHARMACY

- ▶ No study has reported greater rates of bleeding with DOACs compared to warfarin
- ▶ No single DOAC has been established as safer than any other in CKD-5 or ESKD
- ▶ Retrospective nature yields significant limitations
  - ▶ Variations in DOAC dosing
  - ▶ Time in the therapeutic range for warfarin
  - ▶ Lack of control for concomitant antiplatelet therapy
  - ▶ Overall short duration of therapy
- ▶ None of these studies analyzed patients NOT receiving OAC therapy



HARRISON  
SCHOOL OF PHARMACY

# NOT TO BEAT A DEAD HORSE....

- ▶ Data from non-ESKD or dialysis population cannot be reliably and safely extrapolated
- ▶ Retrospective observational studies provide conflicting data
  - ▶ Overall lack of efficacy
  - ▶ Apixaban may decrease the incidence of bleeding compared to warfarin
- ▶ Randomized controlled trials are needed
- ▶ Decision of **WHETHER AND HOW** to initiate OAC in patients with ESKD requires an individualized approach

Guideline	Recommendations
<p>2019 AHA/ACC/HRS JACC 2019;7(1):104-32.</p>	<p>Patients with ESKD (CrCl &lt;15 mL/min or on dialysis)</p> <ul style="list-style-type: none"> <li>• <b>It might be reasonable to prescribe warfarin or apixaban</b> for oral anticoagulation (IIb, B-NR)</li> <li>• Further studies are warranted</li> </ul>
<p>2018 CHEST CHEST 2018;154(5):1121-1201.</p>	<p>Patients with ESKD (CrCl &lt;15 mL/min or dialysis-dependent)</p> <ul style="list-style-type: none"> <li>• We suggest that individualized decision-making is appropriate</li> <li>• We <b>suggest using well-managed VKA</b> with TTR &gt; 65-70%</li> </ul>
<p>2018 KDIGO Kidney International 2018;94(2):231-234.</p>	<p>Patients with eCrCl &lt;15 mL/min +/- dialysis</p> <ul style="list-style-type: none"> <li>• <b>Warfarin: Equipoise</b> based on observational data and meta-analysis</li> <li>• <b>Apixaban: Unknown</b></li> <li>• <b>Rivaroxaban: Unknown</b></li> </ul>
<p>2018 EHRA European Heart Journal 2018;39(16):1330–1393.</p>	<p>Patients with a CrCl of 15 mL/min or dialysis</p> <ul style="list-style-type: none"> <li>• <b>Warfarin: Observational studies yield conflicting results</b></li> <li>• <b>DOACs: Routine use is best avoided</b></li> <li>• Decision to anticoagulate remains a very individualized one</li> </ul>
<p>2016 ESC European Heart Journal 2016;37(38):2893–2962.</p>	<p>Patients on dialysis</p> <ul style="list-style-type: none"> <li>• <b>Controlled studies</b> of both warfarin and DOACs are <b>needed</b></li> </ul>



# MEET EK

HARRISON  
SCHOOL OF PHARMACY

- ▶ EK is a 63 year old white female who was diagnosed with atrial fibrillation during this hospitalization. She has been adequately rate controlled.
- ▶ PMH:
  - ▶ ESKD on HD MWF
  - ▶ HTN
  - ▶ Type 2 Diabetes Mellitus
  - ▶ Hyperlipidemia
  - ▶ Peripheral neuropathy
- ▶ The medical team wants to start apixaban for long-term stroke prevention and asks the pharmacist to recommend an appropriate dose.

DECISION OF WHETHER  
AND HOW TO INITIATE OAC  
IN PATIENTS WITH ESKD  
REQUIRES AN INDIVIDUALIZED  
APPROACH

# SIONTIS, ET AL

## APIXABAN DOSING IN NVAF

Outcomes	Apixaban 5mg (n= 1034)	P-Value	Apixaban 2.5mg (n= 1317)	P-Value
Stroke/systemic embolism	0.64 (0.42–0.97)	0.04	1.11 (0.82–1.50)	0.49
Death	0.63 (0.46–0.85)	0.003	1.07 (0.87–1.33)	0.52
Major bleeding	0.71 (0.53–0.95)	0.02	0.71 (0.56–0.91)	0.007

Apixaban 5 mg BID SUPERIOR to warfarin in terms of stroke, death and risk of major bleeding

Apixaban 2.5 mg BID SUPERIOR to warfarin in risk of major bleeding only



# APIXABAN DOSING IN NVAF

Characteristics	Apixaban (n=144)	Warfarin (n=563)	
Indication: AF	61.7%		
Indication: VTE	38.3%		
Apixaban 5mg BID	64%	--	
Apixaban 2.5mg BID	36%	--	
Time on Therapy	5.2 months	6.3 months	
Outcomes	Apixaban	Warfarin	P Value
Thrombotic events*	4.9%	6.6%	0.448
Bleeding**	16.7%	30.1%	<0.01

\*All events occurred in 2.5mg group

\*\* No difference between 5mg and 2.5mg



HARRISON  
SCHOOL OF PHARMACY

# RIVAROXABAN DOSING IN NVAF

Study	Observational Study Design	Patient Population
De Vriese, 2021	Prospective randomized <ul style="list-style-type: none"><li>• Multicenter with 18 month extension</li></ul>	Dialysis patients with AF prescribed OAC <ul style="list-style-type: none"><li>• Rivaroxaban (46), rivaroxaban + Vitk2 (42), warfarin (44)</li></ul>
See, 2020	Retrospective cohort <ul style="list-style-type: none"><li>• Taiwan Insurance claims</li></ul>	Dialysis patients with AF prescribed OAC <ul style="list-style-type: none"><li>• DOAC (448), warfarin (448)</li><li>• Matched cohort</li></ul>
Miao, 2020	Retrospective cohort <ul style="list-style-type: none"><li>• MarketScan Claims</li></ul>	Dialysis patients with AF prescribed OAC <ul style="list-style-type: none"><li>• Rivaroxaban (787), apixaban (1836)</li></ul>



# MEET EK

HARRISON  
SCHOOL OF PHARMACY

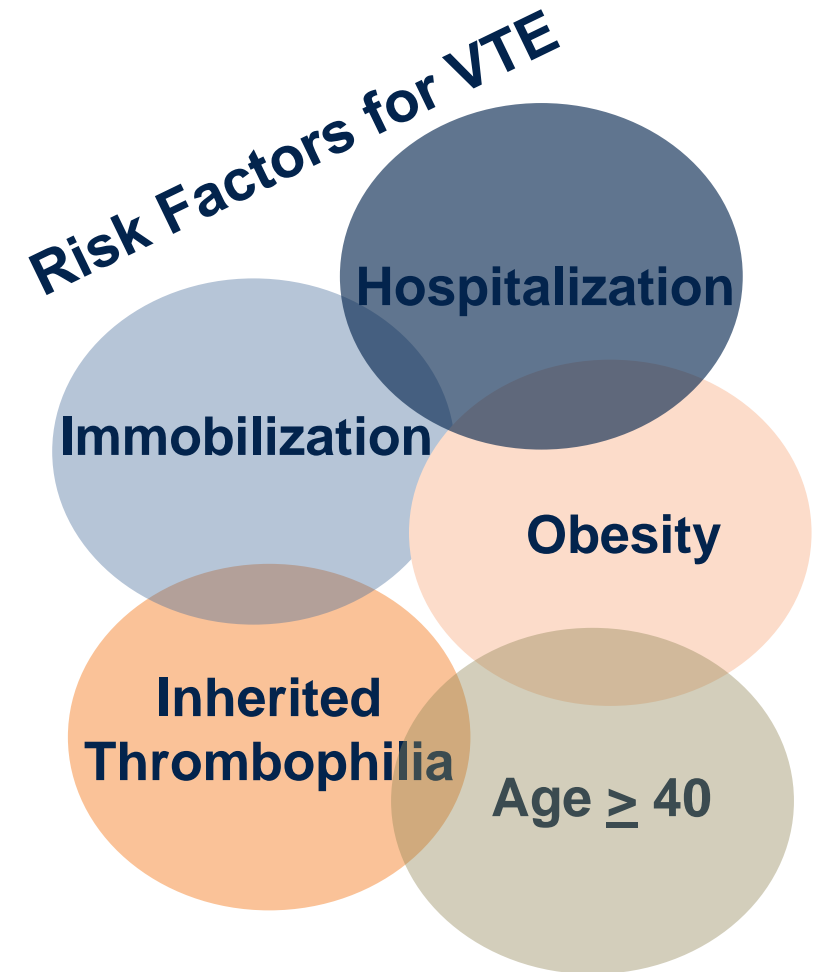
- ▶ EK is a 63 year old white female who was diagnosed with atrial fibrillation during this hospitalization. She has been adequately rate controlled.
- ▶ PMH:
  - ▶ ESKD on HD MWF
  - ▶ HTN
  - ▶ Type 2 Diabetes Mellitus
  - ▶ Hyperlipidemia
  - ▶ Peripheral neuropathy
- ▶ The medical team wants to start apixaban for long-term stroke prevention and asks the pharmacist to recommend an appropriate dose.



# OAC FOR VTE IN PATIENTS WITH ESKD

# VTE IN CKD/ESKD

- ▶ Patients with CKD/ESKD often have concomitant risk factors for VTE
- ▶ Increased risk of PE with worsening renal function
  - ▶ 66 (per 100,000 persons) with normal kidney function
  - ▶ 204 with CKD
  - ▶ 527 with ESKD
- ▶ Increased length of stay and in-hospital mortality
- ▶ **2016 CHEST guidelines recommend warfarin over DOAC in CrCl < 30 mL/min**



Anderson FA. *Circulation*. 2003;107(23 Suppl 1):I9-I16

Kumar G. *Clin J Am Soc Nephrol*. 2012;7(10):1584-1590

Kearon C. *Chest*. 2016;149(2):315-52

# DOAC DOSING IN VTE

	Apixaban	Rivaroxaban
Normal Dosing	10 mg PO BID x 7 days, then 5 mg PO BID	15 mg PO BID x 21 days, then 20 mg PO daily
Renal Dose Adjustment	No adjustment	CrCl < 15 mL/min: Avoid use

# DOAC USE IN VTE IN PATIENTS WITH ESKD

Study	Observational Study Design	Patient Population	Efficacy	Mortality	Safety
Ionescu, 2021	Retrospective cohort • Healthcare system	Dialysis patients with indication for OAC • Apixaban (144), warfarin (563) • <b>271 with VTE</b>	4.9% A vs 6.6% W P=0.448	Not reported	16.7% A vs 30.1% W P=0.01
Herndon, 2020	Retrospective cohort • Single center	Stage 4 or 5 CKD +/- dialysis with an indication for OAC • Apixaban (54), warfarin (57) • <b>25 with VTE</b> • <b>9 received apixaban</b>	Not reported	Not reported	15% A vs 17% W P=0.338
Reed, 2018	Retrospective cohort • Single center	Dialysis patients with indication for OAC • Apixaban (74), warfarin (50) • <b>66 with VTE</b> • <b>45 received apixaban</b>	4.4% A vs 28.6% W (VTE) P=0.99	Not reported	0.15 (0.05-0.46) 5.4% A vs 22% W (major) P=0.01
Sarratt, 2017	Retrospective cohort • Single inpatient center	Dialysis patients with indication for OAC admitted to inpatient medical center • Apixaban (40), warfarin (120) • <b>47 with VTE</b> • <b>8 received apixaban</b>	Not reported	Not reported	0% A vs 5.8% W (Major) P=0.338 12.5% A vs 5.8% W (Nonmajor) P=0.16

# KEY TAKEAWAYS

- Data for OAC in the setting ESKD is limited
  - Limited efficacy data for any OAC
  - DOACs may have better bleeding profile
- Risk vs benefit must be assessed for each individual patient
- There is NOT a one size fits all approach

Medication	Recommendation CrCl < 15 mL/min or hemodialysis	
	Atrial Fibrillation	VTE
Warfarin	Unknown benefit Recommend target INR 2-3	Unknown benefit Recommend target INR 2-3
Apixaban	Unknown benefit Consider 5 mg PO BID	Not recommended
Rivaroxaban	Unknown benefit Dosing TBD	Not recommended
Dabigatran	Not recommended	Not recommended
Edoxaban	Not recommended	Not recommended



A 62 YO M with ESKD on HD has NVAF with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 5. What is the most appropriate OAC to prevent stroke and minimize the risk of bleed?

- A** Apixaban 5 mg PO BID
- B** Warfarin dose adjusted to target INR 2-3
- C** Rivaroxaban 15 mg PO daily
- D** Assess risk vs benefit for OAC use

# DIRECT ORAL ANTICOAGULANTS IN STAGE 5 OR END-STAGE KIDNEY DISEASE

**Jessica Starr, PharmD, FCCP, BCPS**  
**Associate Clinical Professor**  
**Harrison School of Pharmacy**