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DOACs in Chronic Kidney Disease and End-Stage Renal Disease: Is it DOAble?

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Objectives

- Review pharmacokinetic changes relevant for apixaban and rivaroxaban in chronic kidney disease and end stage renal disease.
- Discuss current recommendations for use and dosing of apixaban and rivaroxaban in patients with renal dysfunction.
- Summarize new evidence for the safety and efficacy of three pharmacologic oral anticoagulation options for atrial fibrillation and venous thromboembolism in patients with chronic kidney disease and end-stage renal disease.

Abbreviations

- CrCl: creatinine clearance
- GFR: glomerular filtration rate
- OAC: oral anticoagulation
- VTE: venous thromboembolism
- NVAF: nonvalvular atrial fibrillation

Definitions

- Direct Acting Oral Anticoagulants (DOAC): include apixaban, rivaroxaban, dabigatran, edoxaban
- Chronic kidney disease (CKD): Decreased GFR and kidney damage as defined by structural abnormalities or functional abnormalities for a duration >3 months
- End-stage renal disease (ESRD): medical condition in which a person's kidneys cease functioning on a permanent basis leading to the need for a regular course of long-term dialysis or a kidney transplant to maintain life

Kidney Int Suppl (2011). 2013 Jan; 3(1): 1–150.
Centers for Medicare and Medicaid Services. End-stage renal disease (ESRD). Available at: www.cms.gov

Criteria for Kidney Disease

Duration:

- Greater than 3 months or 90 days

Decreased GFR

- GFR <60 mL/min/1.73m^2

Markers for Kidney Damage

- Albuminuria
  - AER ≥30 mg/24 hours
  - ACR ≥30 mg/g
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Structural abnormalities detected by imaging
- Abnormalities detected by histology
- History of kidney transplantation

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AER: Albumin excretion rate
ACR: albumin-creatinine ration

Kidney Int Suppl (2011). 2013 Jan; 3(1): 1–150.

DOAC Metabolism and Elimination

Medication	Metabolism	Elimination
Apixaban	CYP3A4, with CYP 1A2, 2C8, 2C9, 2C19, 2J2	27% renal
Rivaroxaban	CYP3A4/5, CYP2J2, hydrolysis	36% renal

Eliquis. Package insert. Bristol-Myers Squibb Company; 2019
Xarelto. Package insert. Janssen Pharmaceutical Companies. 2011

Question 1

- Based only on pharmacokinetic data, which DOAC is more likely to be affected by renal dysfunction?
  A. Apixaban
  B. Rivaroxaban

Current Recommendations: **Apixaban**

- VTE Treatment: 10mg BID PO for 7 days then 5mg BID
  - No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis
- Nonvalvular atrial fibrillation: 2.5 mg PO twice daily if 2 criteria met

age ≥80 years
body weight ≤60 kg
serum creatinine ≥1.5 mg/dL

  - ESRD on dialysis: usual recommended dose

Eliquis. Package insert. Bristol-Myers Squibb Company; 2019.

ARISTOTLE Trial: Apixaban in NVAF

Creatinine clearance (mL/min)	Percent of patients
>80	41.2
>50-80	41.9
>30-50	15.0
≤30	1.5
<25 (or serum creatinine >2.5mg/dL)	Excluded

- Subgroup analysis:
  - Higher risk of cardiovascular events and bleeding in patient with worsening renal function

Hizaji Z, et al. *J Am Heart Assoc*. 2020;9(18)e07155

Amplify Trial: Apixaban in VTE

- Did not exclude patients with renal dysfunction

Creatinine Clearance (ml/min)	Percent of patients
>80	64.0
>50-80	20.4
>30-50	6.0
<30	0.5

- Subgroup analysis:
  - Both anticoagulants less effective in renally impaired patients
  - Safety data not significant

Agnelli G, et al.. NEJM. 2013. 369(9):799-808

Current recommendations: **Rivaroxaban**

Indication	Creatinine clearance (mL/min)	Dosage
NVAF	>50	20mg PO daily
	≤50	15mg PO daily
VTE treatment	≥15	15mg PO twice daily x21 days then 20mg PO daily
	<15	Avoid use

Xarelto. Package insert. Janssen Pharmaceutical Companies. 2011. .

ROCKET-AF Trial: Rivaroxaban in NVAF

- Excluded patients with CrCl <30 mL/min
- Mean CrCl: 67 mL/min
- Subgroup analysis:
  - No significant difference in the primary outcome

Patel MR, et al. NEJM. 2011. 365(10):883-891.

EINSTEIN PE/DVT: Rivaroxaban in VTE

Creatinine Clearance (mL/min)	Percent patients in EINSTEIN PE	Percent patients in EINSTEIN DVT
>80	64.3	68.5
50 - <80	26.3	23.0
30 - <50	8.6	6.8
<30	Excluded	

- Subgroup analysis:
  - No significant difference in VTE or bleeding outcomes

Büller HR, et al. N Engl J Med 2012; 366:1287-1297
Büller HR, et al. N Engl J Med 2010; 363:2499-2510

Question 2

- A female 75-year-old patient weighing 70kg, a serum creatinine 2.5mg/dL (CrCl 10ml/min) on hemodialysis three times weekly is going to be started on a DOAC for nonvalvular atrial fibrillation. Which of the following would you recommend?
  - A. Apixaban 5mg PO BID
  - B. Apixaban 2.5 mg PO BID
  - C. Rivaroxaban 20mg PO daily
  - D. Rivaroxaban 15mg PO daily

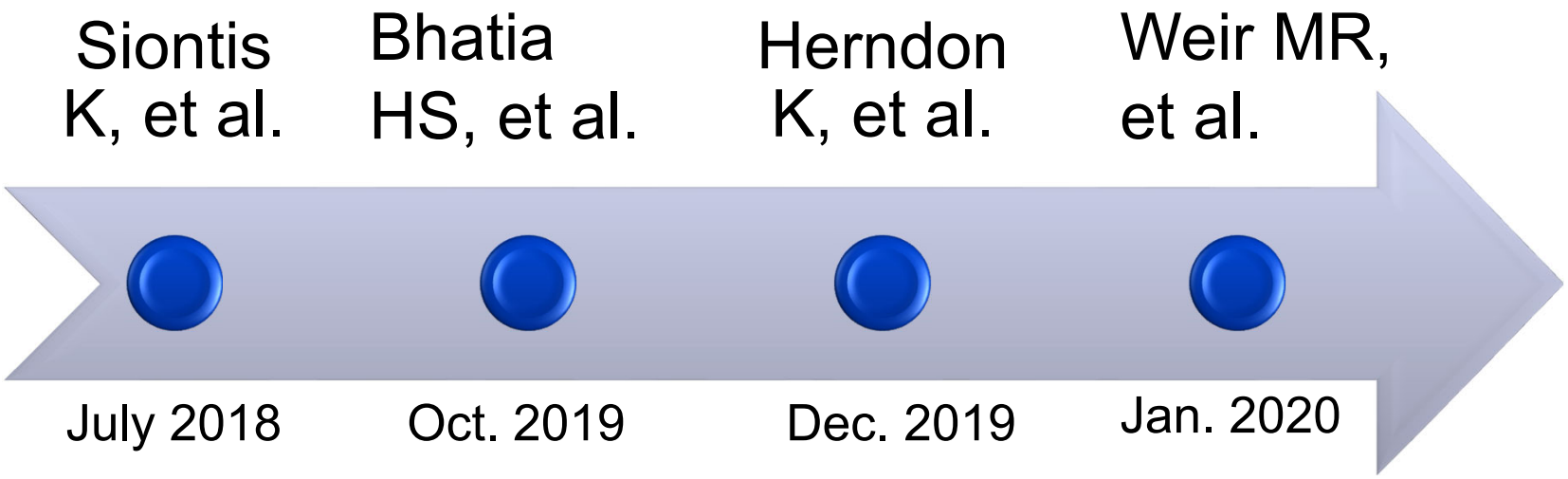
BID: twice daily

2019 Update to AHA Guidelines for NVAF

- For patients with NVAF moderate-to-severe CKD (SCr ≥1.5 mg/dL for apixaban, CrCl <50 mL/min in rivaroxaban), DOACs may be considered at reduced dosing
- For patients with NVAF and ESRD (CrCl <15 mL/min) or are on dialysis: warfarin (INR 2.0 to 3.0) or apixaban
  - Rivaroxaban not recommended

January CT, et al. Circulation. 2019 Jul 9;140(2):e125-e151.

Newer Studies



Siontis KC, et al.

Objective

- Determine patterns of apixaban use and its outcomes in dialysis-dependent patients with ESRD and NVAF

Inclusion

- ESRD undergoing dialysis
- NVAF
- Initiated treatment with an oral anticoagulant

Exclusion

- Mitral stenosis or heart valve replacement/repair procedure
- Anticoagulant prescription 1 year - 30 days before first NVAF diagnosis

Siontis KC, et al. Circulation. 2018;138(15):1519-1529.

Siontis KC, et al.

Outcome (Events per 100 person years)	Apixaban (n=2351)	Warfarin (n=23,172)	P value (<0.05)
ISSE	12.4	11.8	0.29
Major bleeding	19.7	22.9	<0.001
GI bleeding	3.4	3.1	0.32
Intracranial hemorrhage	3.1	3.5	0.32
Death	23.7	24.9	0.06

ISSE: ischemic stroke/systemic embolism

Siontis KC, et al. Circulation. 2018;138(15):1519-1529

Bhatia HS, et al.

Objective

- To evaluate the efficacy and safety of DOACs in patients with NVAF and CKD

Inclusion

- Adults with a history of NVAF or atrial flutter
- Use of DOAC for stroke prevention
- CKD III or above, or creatinine clearance <60 mL/min

Exclusion

- CrCl >60 mL/min
- History of valvular atrial fibrillation, mechanical heart valve
- Noncompliance with prescribed medical therapy or off-label dosing

Bhatia HS, et al. Pacing Clin Electrophysiol. 2019;42(11):1463-1470.

Bhatia HS, et al.

	Outcome	Incidence in DOACs	Incidence in Warfarin	P value (<0.05)
EGFR <30 or on dialysis	All-cause mortality	19.3	26.3	0.005
	Bleeding event	7.9	10.5	0.017
	Embolic stroke	2.1	2.9	0.92
	Hemorrhagic stroke	0.6	1.0	0.276
EGFR 30-60	All-cause mortality	8.4	12.3	<0.001
	Bleeding event	5.3	5.9	0.003
	Embolic stroke	2.4	2.5	0.117
	Hemorrhagic stroke	0.3	0.8	<0.001

Bhatia HS, et al. Pacing Clin Electrophysiol. 2019;42(11):1463-1470.

Herndon, K, et al.

Objective

- To compare major bleeding, secondary bleeding outcomes, stroke, and thromboembolism in veterans with CKD stage IV-V or on dialysis on apixaban or warfarin.

Inclusion

- 18 years or older
- SCr >2.5 with an estimated GFR <29 mL/min/1.73m², on hemodialysis, or on peritoneal dialysis
- Received either apixaban or warfarin

Exclusion

- Active bleeding from traumatic cause
- INR goal range other than 2-3, treatment of valvular atrial fibrillation, mechanical heart valve
- Pregnancy or lactation

Herndon, K, et al. The Ann Pharmacother. 2020:54(6);554-560

Herndon K, et al.

Outcome	Apixaban n=54 (%)	Warfarin n=57 (%)	P value (<0.05)
Major Bleeding	4 (7)	8 (14)	0.362
Clinically relevant non-major bleeding	4 (7)	3 (5)	0.712
Minor bleeding	3 (6)	15 (26)	0.004
VTE	0 (0)	2 (4)	0.496
Stroke	1 (2)	0 (0)	0.486

Herndon, K, et al. The Ann Pharmacother. 2020:54(6);554-560

Weir MR, et al.

Objective

- Compare the risks of ischemic stroke/systemic embolism (ISSE) and major bleeding in patients with NVAF and stage IV-V CKD treated with rivaroxaban or warfarin

Inclusion

- Adult patients with NVAF on rivaroxaban or warfarin
- Diagnosed with CKD or ESRD

Exclusion

- History of kidney transplant
- Evidence of other potential common indications for anticoagulation

Weir MR, et al. Am Heart J. 2020;223:3-11.

Weir MR, et al.

- Outcomes:

Outcome (events per 100 person years)	Rivaroxaban	Warfarin	Hazard Ratio	P-value (<0.05)
ISSE	1.8	1.96	0.93 (0.46-1.90)	0.85
Major Bleeding	8.44	9.39	0.91 (0.65-1.28)	0.60

ISSE: ischemic stroke/systemic embolism

Weir MR, et al. Am Heart J. 2020;223:3-11.

Study	Intervention	Demographics	Systemic embolism risk	Safety Risk
Siontis KC, et al.	apixaban vs warfarin	NVAF, ESRD on dialysis	No difference	Improved
Bhatia HS, et al.	DOAC vs warfarin	NVAF, CKD III-V, including dialysis	No difference	Improved
Herndon K, et al.	apixaban vs warfarin	CKD III-V, including dialysis	No difference	No difference
Weir MR, et al.	rivaroxaban vs warfarin	NVAF and stage IV-V CKD, including dialysis	No difference	No difference

Discussion

- None of these studies showed a significant increase in systemic embolic events or bleed risk in patients with CKD or ESRD on dialysis.
- Many of these studies were smaller in size and were retrospective chart reviews.
- Rivaroxaban and apixaban could be considered for treatment of VTE and prevention of stroke in atrial fibrillation in patients with CKD and ESRD, including those on dialysis.

Question 3

- True or False: Apixaban and rivaroxaban are associated with an increased risk of bleeding in patients with CKD when compared to warfarin.
  - True
  - False

Conclusion

- Both apixaban and rivaroxaban are excreted renally to some extent and can increase systemic exposure in renal dysfunction.
- Apixaban is approved in dialysis and does not need to be renally dosed, while rivaroxaban is not recommended in ESRD and have dosage adjustments at CrCl of 50 and 15ml/min.
- New studies show that there is no significant increase in systemic embolism or bleeding risk with apixaban or rivaroxaban compared to warfarin in CKD or ESRD.

Questions?

