ATRIUM CARDIOLOGY COLLABORATIVE

@atriumrx

Direct Oral Anticoagulants vs Warfarin in Atrial Fibrillation and End Stage Renal Disease – Whose side are you on?

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Disclosure

- The speakers have no actual or potential conflicts of interest to disclose.

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Objectives

- Explain the pharmacokinetic differences between direct oral anticoagulants (DOACs) and compare the dosing for stroke prevention in atrial fibrillation (SPAF) in patients with end stage renal disease (ESRD).
- Describe the risk of stroke and bleeding in patients with AF and ESRD.
- Given a patient with AF and ESRD, develop a therapeutic plan for anticoagulation and discuss advantages and disadvantages of using a DOAC or warfarin.

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Housekeeping

CVD = cardiovascular disease

CKD = chronic kidney disease

ESRD = end stage renal disease

IHD = intermittent hemodialysis

PD = peritoneal dialysis

DOAC = direct oral anticoagulant

SPAF = stroke prevention in atrial fibrillation

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Case Scenario

A 79-year-old man is admitted to the hospital after a routine visit with his primary care physician revealed worsening renal disease. He was in usual state of health until two weeks ago when he describes starting to feel more fatigued than usual.

PMH: hypertension, type II diabetes, atrial fibrillation, benign prostatic hyperplasia, and chronic kidney disease (baseline SCr 3.5 mg/dL, CrCl 15 mL/min)

PMH, past medical history; SCr, serum creatinine; CrCl, creatinine clearance

Case Scenario

- Medications:
  - Amlodipine 10 mg PO daily
  - Lisinopril 20 mg PO daily
  - Atorvastatin 20 mg PO daily
  - Insulin glargine 20 units subcut daily
  - Dabigatran 150 mg PO BID
  - Tamsulosin 0.4 mg PO daily
- Vital Signs: HR 90 bpm, BP 147/89 mm Hg, O_2 Sat 99% (room air)
- Laboratory Data:
  - SCr 5.3 mg/dL (CrCl 11.2 mL/min)
  - BUN 105 mg/dL
  - Potassium 7.0 mmol/L
  - Hgb 10.5 g/dL
- Electrocardiogram: AF with controlled heart rate and peaked T-waves

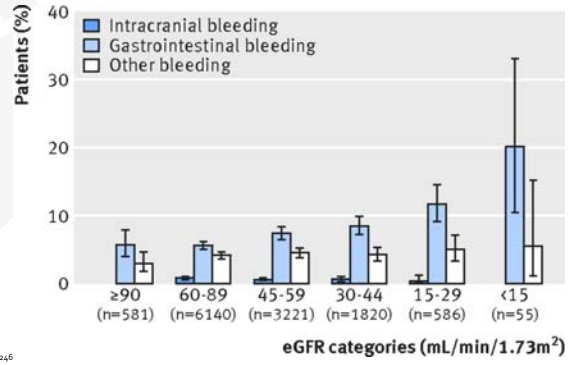
HR, heart rate; bpm, beats per minute; SCr, serum creatinine; CrCl, creatinine clearance; BUN, blood urea nitrogen

Epidemiology: AF in ESRD

- 10-25% in ESRD on dialysis

Alonso A, et al. Circulation 2011; 123:2946-2953
Simonetta G, et al. Am J Kidney Dis 2008; 51:255-262
Zimmerman D, et al. Nephrol Dialysis Transplant 2012; 27:3816-3822

Bleeding Risk for AF with ESRD



Jun M, et al. BMJ 2015; 350:h246

Anticoagulation in AF and ESRD: Is Less More?

Favors Anticoagulation

- Endothelial dysfunction
- Atrial fibrosis
- Arteriosclerosis
- Increased thrombin, vWF, tissue factor
- RAAS activation

Favors No Anticoagulation

- Uremia-induced platelet dysfunction
- Decreased GPIIb/IIIa
- Altered alpha-granule composition and secretion
- Impaired synthesis of TxA2

Ghadban R, et al. Hemodialysis International 2017; 21:S47-S56
Bansal V, et al. Am J Kidney Dis 2017;70(6):859-868.

Guideline Recommendations for Anticoagulation in AF and ESRD

Guideline	Year	Recommendation
KDIGO CVD in CKD clinical update	2011	Routine anticoagulation not indicated until further evidence becomes available

KDIGO, Kidney Disease: Improving Global Outcomes; AHA, American Heart Association; ACC, American College of Cardiology; HRS, Heart Rhythm Society

Macle L, et al. Can J Cardiol. 2016;32(10):1170-1185.
January CT, et al. J AM Coll Cardiol. 2014;64(21):e1-e76.
Herzog CA, et al. Kidney Int. 2011;80(6):572-586.

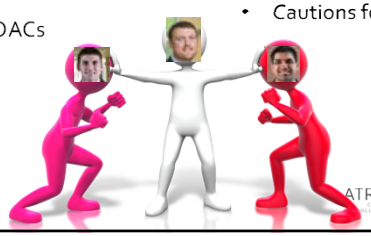
DOAC vs Warfarin in AF and ESRD on IHD

DOAC

- Diminished efficacy of warfarin
- Risks of warfarin
- Available data for DOACs

Warfarin

- More data and experience with warfarin
- Cautions for DOACs



Warfarin for SPAF: An Anomaly in ESRD Patients

Study	Design	Outcomes
Nochaiwong S, et al (2016)	Systematic review and meta-analysis	No difference in mortality or ischemic stroke in those receiving warfarin Risk of major bleeding greater with warfarin (HR=1.35; 95% CI 1.11-1.64)
Wang T, et al (2016)	Single center retrospective review	No difference in ischemic stroke (13.4% v 13.6%) Warfarin associated with increased intracranial hemorrhage (0 v 6.8%; p-value 0.029)
Winkelmayer, et al (2011)	Retrospective review of Medicare registry	No difference in ischemic stroke Warfarin associated with increased intracranial hemorrhage (HR=2.38; 95% CI 1.15-4.96)

Nochaiwong S, et al. Open Heart. 2016;3: e000441.
Wang T, et al. Heart Lung Circ. 2016 Mar;25(3):243-9.
Wenkelmayer, et al. Clin J Am Soc Nephrol. 2011 Nov;6(11):2662-8

Reasons to Avoid Warfarin in AF and ESRD

- Calciphylaxis
  - Warfarin associated with 10-fold greater risk of developing calciphylaxis in ESRD
- Vitamin K deficiency
  - Overall nutritional deficiency, including vitamin K
  - Labile INR

Parker K, et al. British Journal of Haematology. 2018. doi: 10.1111/bjh.15144

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Positive Outcomes with Warfarin in AF and ESRD

Study	Design	Outcomes
Brancaccio, et al (2016) n = 3248	Retrospective, observational cohort	Increase in overall survival with warfarin: • 3 months: HR 0.47 (p-value < 0.001) • 1 year: HR 0.69 (p-value < 0.001) • 6 years: HR 0.76 (p-value < 0.001)
Shen, et al (2015) n = 12,284	Retrospective, observational cohort	Risk of ischemic stroke lower for warfarin (HR 0.68, 95% CI 0.47-0.99) Lower all-cause mortality (HR 0.84, 95% CI 0.73-0.97)
Kai, et al (2017) n = 4286	Retrospective, observational cohort	Lower risk of all-cause death (HR 0.76, 95% CI 0.69-0.84) and ischemic stroke (HR 0.68, 95% CI 0.52-0.91) Similar risk of hemorrhagic stroke (HR 1.2, 95% CI 0.6-2.2) or GI bleeding (HR 0.97, 95% CI 0.77-1.2)

HR, hazard ratio; CI, confidence interval
Brancaccio D, et al. Am J Nephrol 2016; 44:258-267
Shen JI, et al. Am J Kidney Dis 2015; 66:677-688
Kai, et al. Heart Rhythm 2017; 14:645-651

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Interpreting Existing Warfarin Data

- Observational study limitations
  - Biases: indication, administrative
  - Lacking data on time in therapeutic range
  - Concomitant therapy (e.g., aspirin)
  - Risk assessment scores not validated in ESRD

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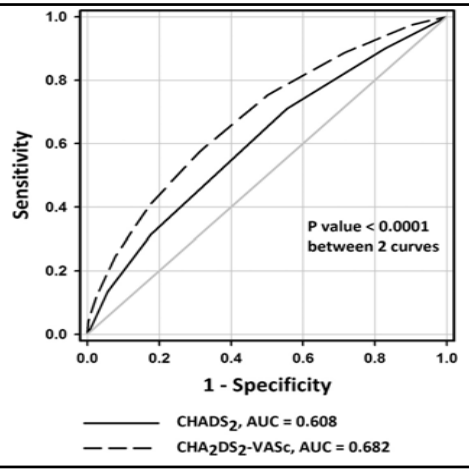
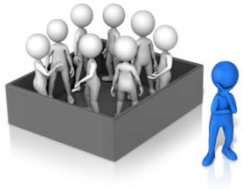
Extrapolating Risk Assessment Tools in ESRD



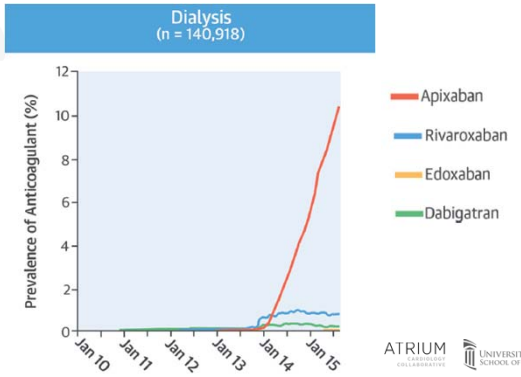
Chao TF, et al. Heart Rhythm 2014; 11:1752-1759

We Suffer From…

Xenophobia



An Appealing Alternative?



Chan K, et al. JACC. 2016.
http://dx.doi.org/10.1016/j.jacc.2016.02.082

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Metabolism and Elimination of DOACs

Medication	Renal Elimination (%)	Protein Bound (%)	Dialyzability (%)*
Dabigatran	80%	35%	50-60%
Rivaroxaban	33%	95%	5%
Apixaban	25%	87%	6%
Edoxaban	50%	55%	9%

*Variable depending on filter, dialysis modality, and duration of dialysis session

Chan K, et al. JACC. 2016. http://dx.doi.org/10.1016/j.jacc.2016.02.082
Dias C, et al. Am J Nephrol. 2016;43:229–236

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Apixaban

- FDA update to package label includes patients with ESRD on IHD

"Patients with ESRD with or without hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendation is **based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data** in subjects with ESRD maintained on dialysis. **The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily.** For ESRD patients maintained with hemodialysis with one of the following patient characteristics, age ≥ 80 years or body weight ≤ 60 kg, reduce dose to 2.5 mg twice daily *[see Dosage and Administration (2.7), Clinical Pharmacology (12.2, 12.3)]*."

Package Insert. Eliquis. 2016

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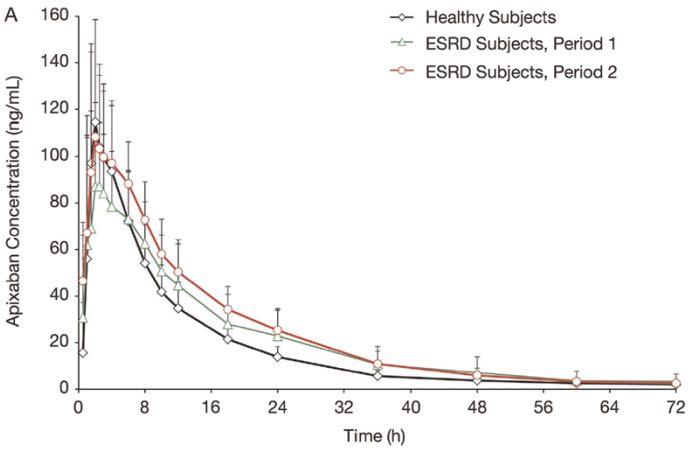
Apixaban – Single Dose Pharmacokinetic Data

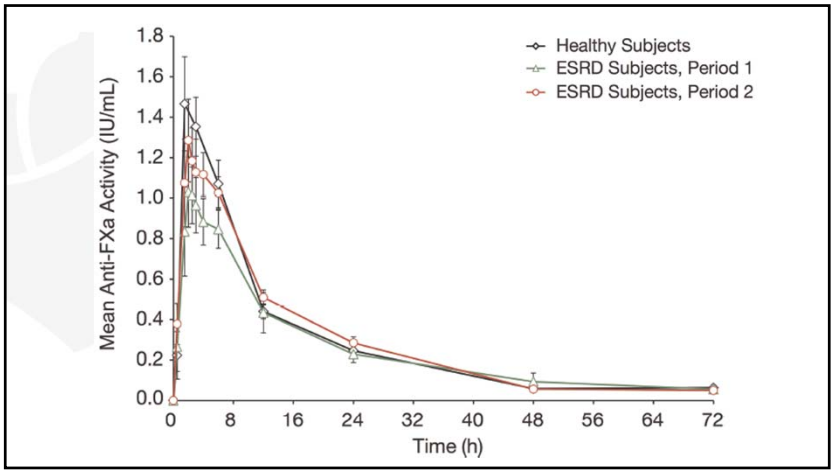
- Single dose study of apixaban 5 mg in 8 patients with ESRD on stable IHD and without significant comorbidities
  - Group 1: single dose before dialysis
  - Group 2: single dose after dialysis
- Comparator group: 8 healthy adults with normal renal function

Group	Cmax (ng/ml)‡	AUC (ng*h/mL)‡	Tmax (h)◊	T1/2 (h)†
Healthy	126 (29%)	**1265 (30%)**	2 (1,4)	20 (14.45)
Group 1	98.9 (29%)	**1474 (44%)**	2 (1,6)	12.5 (3.14)
Group 2	114 (31%)	**1717 (24%)**	2 (2,6)	12.7 (3.4)

‡ coefficient of variation in parentheses; ◊ min, max in parentheses; † standard deviation in parenthese

Wang, et al. J Clin Pharmacology. 2016, 56(5) 628-636.





Apixaban – Steady State Pharmacokinetic Data

- **Day 1**
  - Start apixaban 2.5 mg bid (N = 7)
  - Single dose levels obtained
- **Day 9**
  - Steady state levels before and after dialysis obtained
  - 10-14 day washout
- **Day 15**
  - Start apixaban 5 mg bid (N = 5)
  - Steady state apixaban levels obtained

Mavrakanas T, et al. J Am Soc Nephrol 28: 2241–2248, 2017.

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Apixaban 2.5 mg – Steady State Pharmacokinetic Data

Apixaban 2.5 mg twice daily	Day 1‡	Day 8‡	P Value	Reference for 2.5 mg twice daily dose†
AUC_{0-24} (ng*h/mL)	597 (38%)	2019 (30.7%)	<0.001	1661 (1120-2620)
C_{max} (ng/mL)	45.2 (49.9%)	131.5 (131.5%)	<0.001	123 (69-221)
$t_{1/2}$ (h)	5.9 (16%)	7.5 (64%)	<0.001	-

‡ coefficient of variation in parentheses; † 10-90th percentile in parentheses

Mavrakanas T, et al. J Am Soc Nephrol 28: 2241–2248, 2017.

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Apixaban 5 mg – Steady State Pharmacokinetic Data

Apixaban 5 mg twice daily	Day 8‡	P Value	Reference for 5 mg twice daily†
AUC_{0-24} (ng*h/mL)	6053 (46%)	0.03	3370 (2070-5250)
C_{max} (ng/mL)	307 (39.4%)	0.02	171 (91-321)
$t_{1/2}$ (h)	17 (51%)	0.13	---

‡ coefficient of variation in parentheses; † 10-90th percentile in parentheses

Mavrakanas T, et al. J Am Soc Nephrol 28: 2241–2248, 2017.

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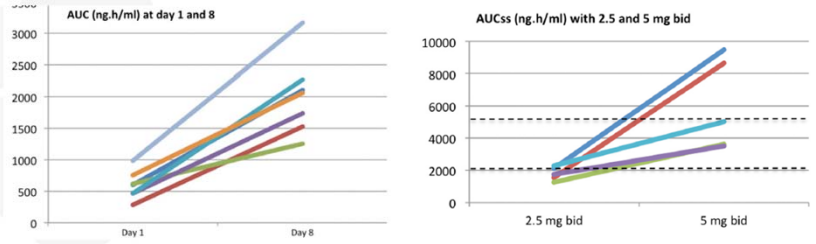

Mavrakanas T, et al. J Am Soc Nephrol 28: 2241–2248, 2017.

Apixaban v Warfarin – Real World Data

- Meta-analysis of 5 studies comparing warfarin and apixaban in chronic kidney disease (3 of which were exclusively ESRD patients)
  - Similar risk of thromboembolic events with apixaban compared to warfarin (OR 0.56; 95% CI 0.23-1.39)
  - Lower risk of major bleeding with apixaban compared to warfarin (OR 0.27; 95% CI 0.28-0.61)

Chokesuwattanaskul R, et al. PACE. 2018. https://doi.org/10.1111/pace.13331

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Other DOACs in ESRD on IHD

- Rivaroxaban
  - 2 pharmacokinetic studies evaluating 10 and 15 mg doses
  - 10 mg dose resulted in roughly equal exposure to 20 mg dose in patients with normal renal function
- Edoxaban
  - 1 pharmacokinetic study evaluating 15 mg pre- and post-dialysis
  - No comparator group

Dias C, et al. Am J Nephrol 2016;43:229–236
De Vriese An, et al. Am J Kidney Dis. 66(1):91-98.
Sankyo D, et al. Thromb Haemost 2015; 113: 719–727

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DOACs in AF and ESRD: Caution Advised

- Extrapolation of data to ESRD
- Renal function assessment
  - Regular reassessment during follow-up
  - Unclear drug accumulation
- Reversal in setting of bleed

Heidbuchel H, et al. Europace 2015; 17:1467-1507
Yao X, et al. Circulation 2017; 131:972-979
Pathak R, et al. Am J Cardiol 2015; 115:323-327

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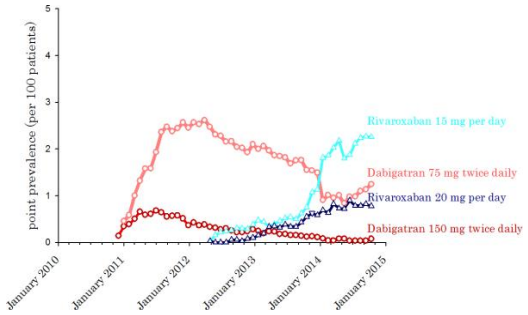
Erroneous Use of DOACs in ESRD

- 5.9% of ESRD started on rivaroxaban or dabigatran
- Increased risk of hospitalization due to bleeding
  - Dabigatran (rate ratio 1.48; 95% CI, 1.21-1.81, p- value = 0.0001)
  - Rivaroxaban (rate ratio 1.38; 95% CI, 1.03-1.83; p-value = 0.04)



Chan KE, et al. Circulation 2015; 131:972-979

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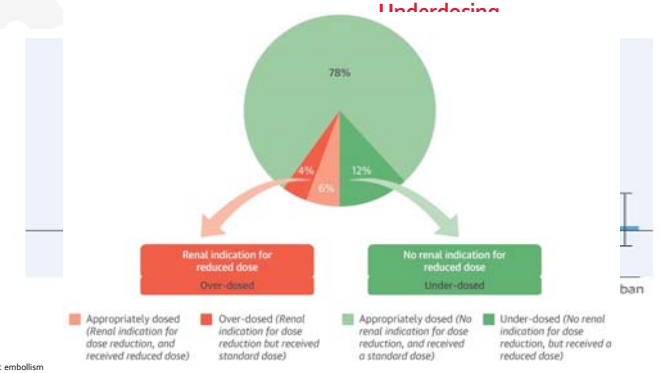
Inappropriate DOAC Dosing

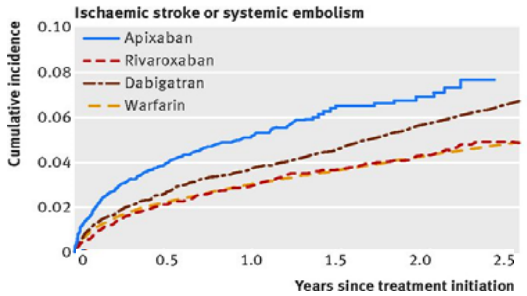


S/SE, stroke/systemic embollism

Yao X, et al. J Am Coll Cardiol 2017; 69:2779-2790

Apixaban Dosing in ESRD

- Based on a small pharmacokinetic study
- No proven clinical efficacy and safety

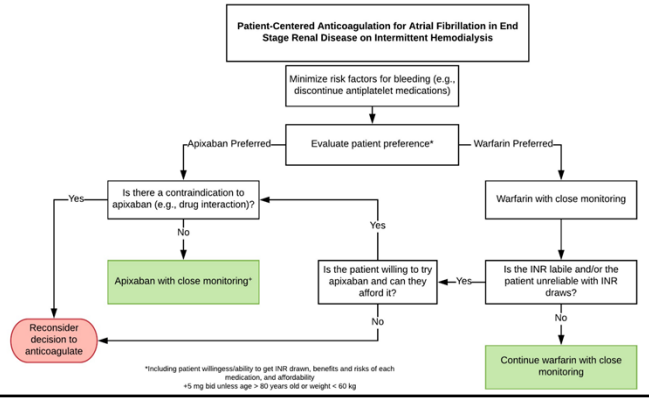


Nielson, et al. BMJ 2017; 356:j510

Ongoing Studies

- 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)

Anticoagulation Algorithm in ESRD



Back to Case Scenario

- A 79-year-old man with history of HTN, T2DM, AF, and stage 5 CKD is admitted to the hospital for worsening renal disease. Team has made the decision to initiate intermittent hemodialysis during admission.
- Prior to admission, patient was taking dabigatran 150 mg PO twice daily for SPAF.
- On day of discharge, vital signs and laboratory data are stable.

HTN, hypertension; T2DM, type 2 diabetes mellitus

Closing Remarks – Who's Side Are You On?

DOAC

Warfarin

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Questions?

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