PHARMACY VISION 2020

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Disneyland RESORT

Filtering Out the Evidence for the Use of NOACs in Advanced Kidney Disease

Samantha Yeung, PharmD, MS, BCCP

Clinical Translational Sciences Fellow in Cardiology

University of Southern California School of Pharmacy

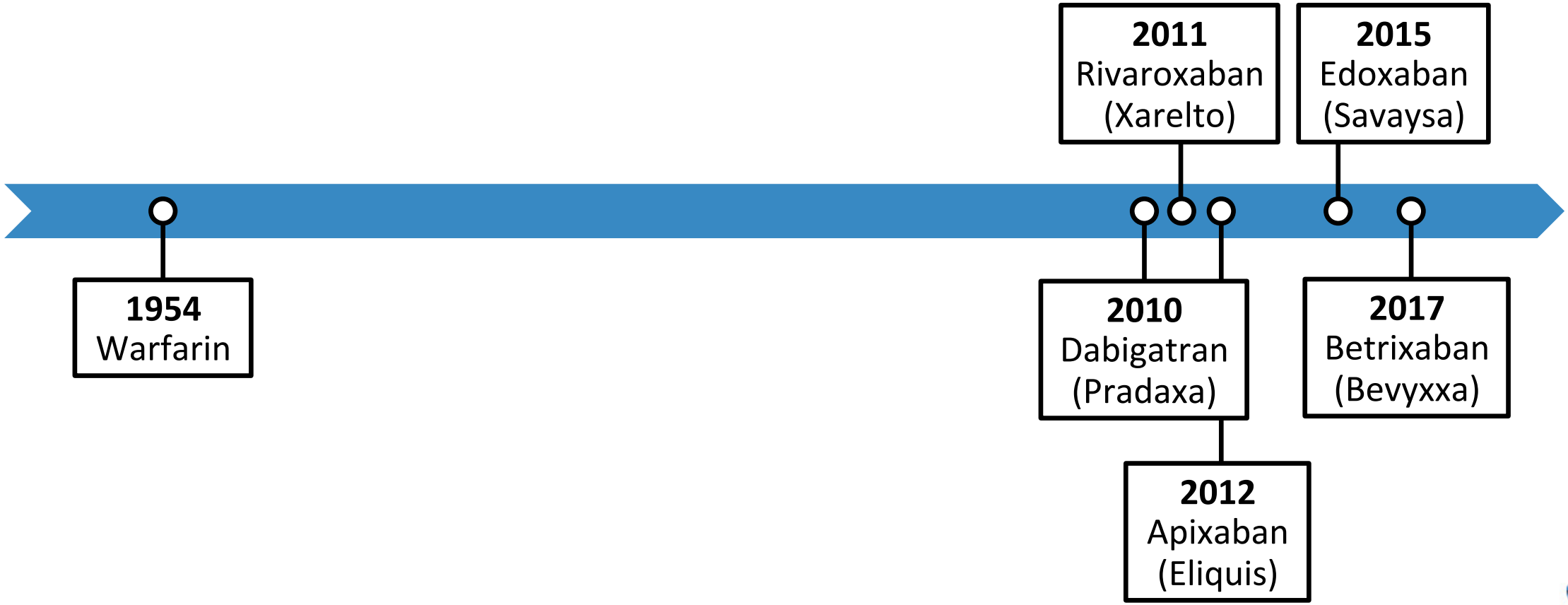
DISCLOSURE

I have no potential conflicts of interest to disclose.

Learning Objectives

- Review basic pharmacokinetic and pharmacodynamic properties of non-vitamin K oral anticoagulants (NOACs)
- Evaluate current literature regarding the evidence for use of NOACs in advanced kidney disease
- Design an anticoagulation regimen for a patient with advanced kidney disease using NOACs based on the evidence provided

Timeline of Oral Anticoagulant Approval



FDA Approved Indications

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Reduce risk of stroke and systemic embolism in NVAF	✔	✔	✔	✔	
Treatment of DVT/PE	✔*	✔	✔	✔*	
Reduce risk of recurrent DVT/ PE following initial therapy	✔	✔	✔		
Prophylaxis of DVT/PE in patients undergoing hip or knee replacement surgery	✔^	✔	✔		
Prophylaxis of VTE in acutely ill medical patients		✔			✔

*Patients should be treated with a parental anticoagulant for 5 to 10 days prior to treatment
^Hip replacement only

1. Pradaxa [package insert]. Boehringer Ingelheim Pharmaceuticals.
2. Xarelto [package insert]. Janssen Pharmaceuticals.
3. Eliquis [package insert]. Bristol-Myers Squibb and Pfizer.
4. Savaysa [package insert]. Daiichi Sankyo Co.
5. Bevyxxa [package insert]. Portola Pharmaceuticals.

PHARMACOKINETICS AND PHARMACODYNAMICS

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	IIa (thrombin)	Xa	Xa	Xa	Xa
Bioavailability, %	3 – 7	≤10 mg: 80 – 100 >10 mg: 66	50	62	34
Tmax, h	1 – 3	2 – 4	3 – 4	1 – 2	3 – 4
Half-life, h	12 – 17	5 – 9	12	10 – 14	19 – 27
Protein binding, %	35	92 – 95	87	55	60
Renal elimination, %	80	36	27	50	11
Dialyzable, %	50 – 60	Negligible	14	<7	Unknown

1. Pradaxa [package insert]. Boehringer Ingelheim Pharmaceuticals.
2. Xarelto [package insert]. Janssen Pharmaceuticals.
3. Eliquis [package insert]. Bristol-Myers Squibb and Pfizer.
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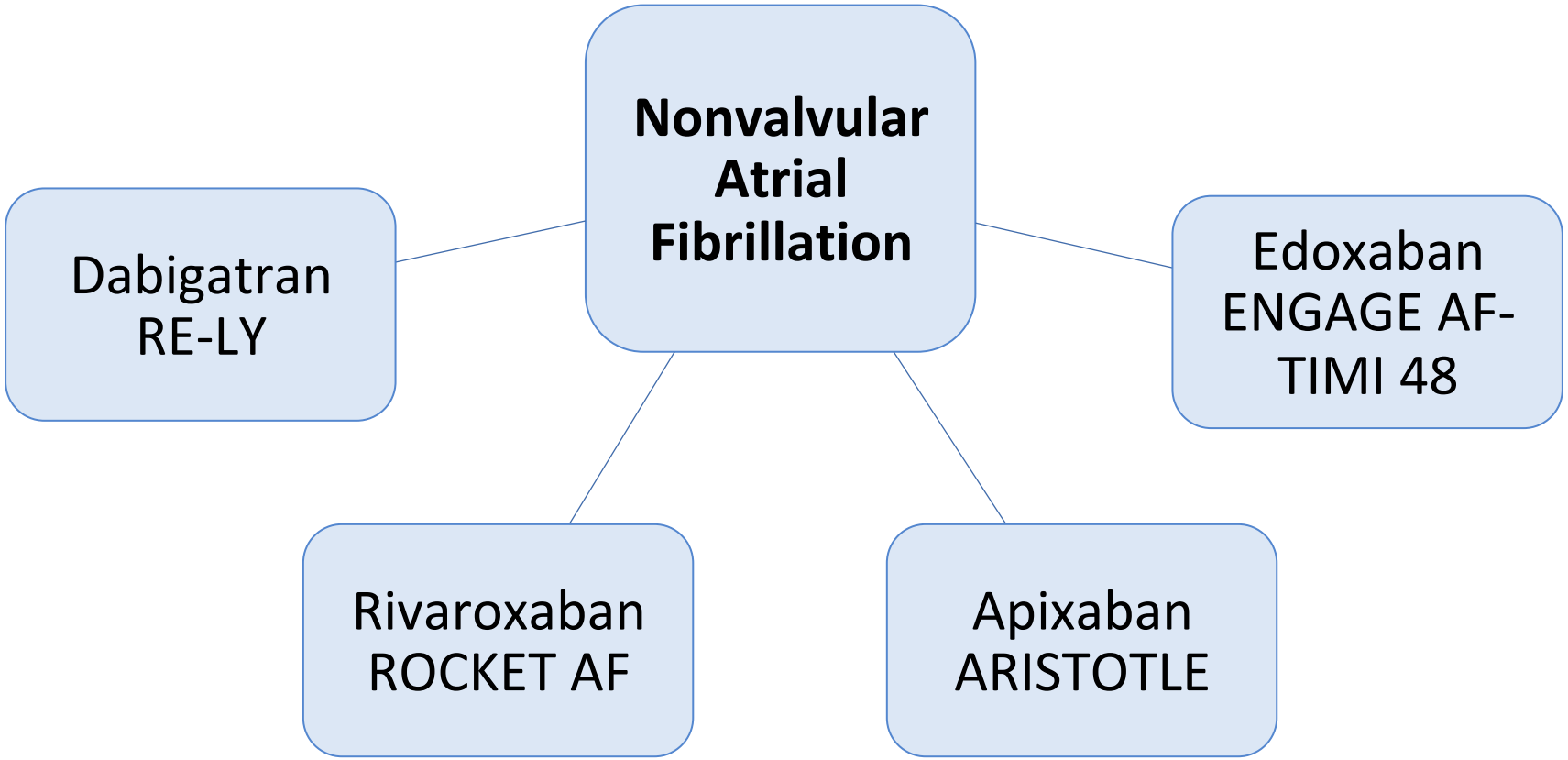
PHASE III TRIALS COMPARING NOACS VS. WARFARIN



PHASE III TRIALS: STUDY DESIGN

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Sample size	18,113	14,264	18,201	21,105
Study design	Open-label	Double-blind	Double-blind	Double-blind
Intervention	Dabigatran 110 mg Dabigatran 150 mg	Rivaroxaban 20 mg	Apixaban 5 mg	Edoxaban 30 mg Edoxaban 60 mg
Primary outcome	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Safety outcome	Major bleeding	Composite major & non-major bleeding	Major bleeding	Major bleeding
Median follow-up, y	2.0	1.9	1.8	2.8

6. Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-51.
7. Patel MR, et al. *N Engl J Med* 2011; 365:883-91.
8. Granger CB, et al. *N Engl J Med* 2011; 365:981-92.
9. Giugliano RP, et al. *N Engl J Med* 2013; 369:2093-2104.

PHASE III TRIALS: PATIENT POPULATION

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Age, y	71	73	70	72
Male, %	63.6	60.3	64.7	61.9
$CHADS_2$ score	2.1	3.5	2.1	2.8
Prior stroke or TIA, %	20.0	54.8*	19.4*	28.3
Previous VKA use, %	49.6	62.4	57.1	58.9
Time in therapeutic range (TTR), %	64.0	55.0	62.2	64.9

*Includes systemic embolism

6. Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-51.
7. Patel MR, et al. *N Engl J Med* 2011; 365:883-91.
8. Granger CB, et al. *N Engl J Med* 2011; 365:981-92.
9. Giugliano RP, et al. *N Engl J Med* 2013; 369:2093-2104.

Phase III Trials: Stroke or Systemic Embolism

	NOAC	HR (95% CI)
RE-LY	Dabigatran 110 mg Dabigatran 150 mg	0.91 (0.74–1.11) 0.66 (0.53–0.82)
ROCKET AF	Rivaroxaban 20 mg	0.79 (0.66–0.96)
ARISTOTLE	Apixaban 5 mg	0.79 (0.66–0.95)
ENGAGE AF-TIMI 48	Edoxaban 30 mg Edoxaban 60 mg	1.07 (0.87–1.31) 0.79 (0.63–0.99)

6. Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-51.
7. Patel MR, et al. *N Engl J Med* 2011; 365:883-91.
8. Granger CB, et al. *N Engl J Med* 2011; 365:981-92.
9. Giugliano RP, et al. *N Engl J Med* 2013; 369:2093-2104.

Phase III Trials: Major Bleeding

	NOAC	HR (95% CI)
RE-LY	Dabigatran 110 mg Dabigatran 150 mg	0.80 (0.69–0.93) 0.93 (0.81–1.07)
ROCKET AF	Rivaroxaban 20 mg	1.03 (0.96–1.11)
ARISTOTLE	Apixaban 5 mg	0.69 (0.60–0.80)
ENGAGE AF-TIMI 48	Edoxaban 30 mg Edoxaban 60 mg	0.47 (0.41–0.55) 0.80 (0.71–0.91)

6. Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-51.
7. Patel MR, et al. *N Engl J Med* 2011; 365:883-91.
8. Granger CB, et al. *N Engl J Med* 2011; 365:981-92.
9. Giugliano RP, et al. *N Engl J Med* 2013; 369:2093-2104.

Phase III Trials: All-Cause Mortality

	NOAC	HR (95% CI)
RE-LY	Dabigatran 110 mg Dabigatran 150 mg	0.91 (0.80–1.03) 0.88 (0.77–1.00)
ROCKET AF	Rivaroxaban 20 mg	0.85 (0.70–1.02)
ARISTOTLE	Apixaban 5 mg	0.89 (0.80–0.998)
ENGAGE AF-TIMI 48	Edoxaban 30 mg Edoxaban 60 mg	0.87 (0.79–0.96) 0.92 (0.83–1.01)

6. Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-51.
7. Patel MR, et al. *N Engl J Med* 2011; 365:883-91.
8. Granger CB, et al. *N Engl J Med* 2011; 365:981-92.
9. Giugliano RP, et al. *N Engl J Med* 2013; 369:2093-2104.

DOSING IN NVAF

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg BID	20 mg daily	5 mg BID	60 mg daily
Renal dose	75 mg BID	15 mg daily	2.5 mg BID	30 mg daily
Threshold for renal dose adjustment	CrCl 15 – 30 mL/min	CrCl ≤50 mL/min	If 2 of 3 criteria met: ≥80 years, ≤60 kg, SCr ≥1.5 mg/dL	CrCl 15 – 50 mL/min
Avoid use	CrCl <15 mL/min Dialysis			CrCl >95 mL/min CrCl <15 mL/min Dialysis

1. Pradaxa [package insert]. Boehringer Ingelheim Pharmaceuticals.
2. Xarelto [package insert]. Janssen Pharmaceuticals.
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Avoid use	CrCl <15 mL/min Dialysis			CrCl >95 mL/min CrCl <15 mL/min Dialysis
Exclusion criteria in clinical trials	**CrCl <30 mL/min**	**CrCl <30 mL/min**	**SCr >2.5 mg/dL or CrCl <25 mL/min**	**CrCl <30 mL/min**

1. Pradaxa [package insert]. Boehringer Ingelheim Pharmaceuticals.
2. Xarelto [package insert]. Janssen Pharmaceuticals.
3. Eliquis [package insert]. Bristol-Myers Squibb and Pfizer.
4. Savaysa [package insert]. Daiichi Sankyo Co.

CURRENT GUIDELINE RECOMMENDATIONS

2018 CHEST Guideline and Expert Panel Report	"In severe non-dialysis CKD (CrCl 15 – 30 mL/min), we suggest using VKAs and dose-reduced NOACs with caution. In ESRD (CrCl <15 mL/min or dialysis-dependent), we suggest using well-managed VKA with TTR >65-70% as NOACs should generally not be used."
2018 KDIGO Controversies Conference	"For patients with an estimated CrCl 15 – 30 mL/min, can consider VKAs or reduced dose NOACs. For patients with estimated CrCl <15 mL/min not on or on dialysis, reduced dose apixaban may be considered. There is insufficient evidence to recommend VKA in patients on dialysis."

10. Lip GYH, et al. *CHEST* 2018; 154:1121-1201.
11. Turakhia MP, et al. *Eur Heart J* 2018; 39:2314-25.

CURRENT GUIDELINE RECOMMENDATIONS

2018 EHRA Practical Guideline	"Use of either apixaban or edoxaban at reduced doses may be preferable in patients with severe CKD (CrCl of 15 – 29 mL/min). Routine use of NOACs in patient with ESRD (CrCl <15 mL/min) as well as in patients on dialysis is best avoided."
2019 AHA/ACC/HRS Focused Update	"For patients with moderate-to-severe CKD (SCr ≥1.5 mg/dL [apixaban], CrCl 15 – 30 mL/min [dabigatran], CrCl ≤50 mL/min [rivaroxaban], or CrCl 15 – 50 mL/min [edoxaban]), treatment with reduced doses of NOACs may be considered. For patients who have end-stage CKD (CrCl <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin or apixaban."

12. Steffel J, et al. *Eur Heart J* 2018; 39:1330-93.
13. January CT, et al. *Circulation* 2019; 140:e125-e151.

EVIDENCE FOR NOACS IN ADVANCED KIDNEY DISEASE

- There are no standard guideline recommendations for the use of NOACs in this patient population
- Randomized controlled trials generally excluded patients with Stage 4/5 CKD or on hemodialysis
- Literature and experience using NOACs in these patients are limited to small PK/PD studies, case reports, and observational studies

Dabigatran and Rivaroxaban Use in Atrial Fibrillation Patients on Hemodialysis

- Kevin E. Chan, Elazer R. Edelman, Julia B. Wenger, Ravi I. Thadhani, Franklin W. Maddux

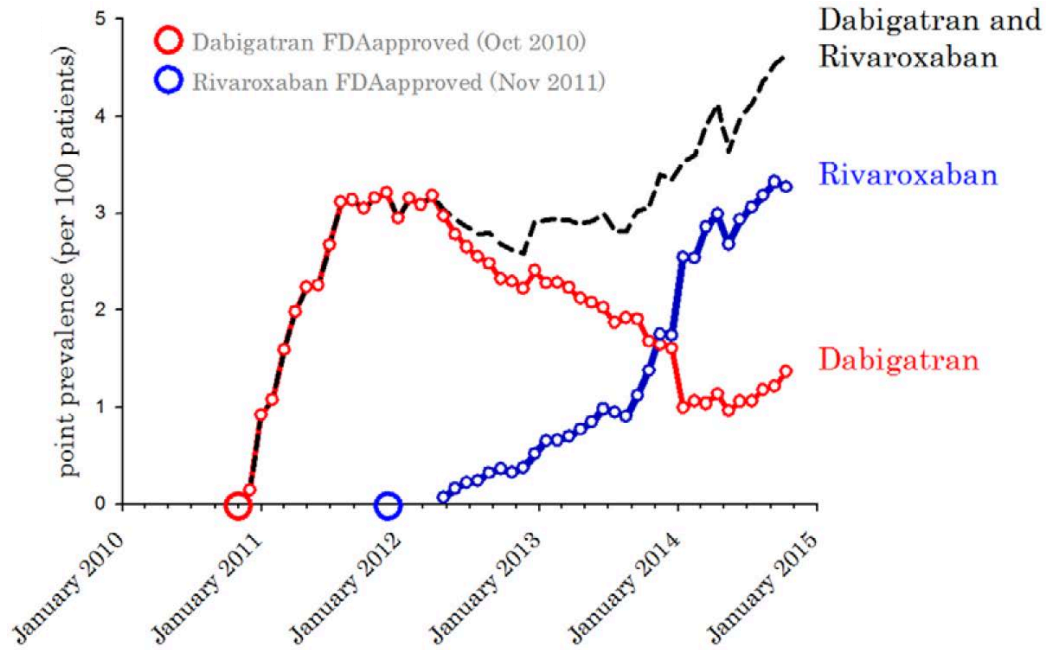
14. Chan KE, et al. *Circulation* 2015; 131:972-79.

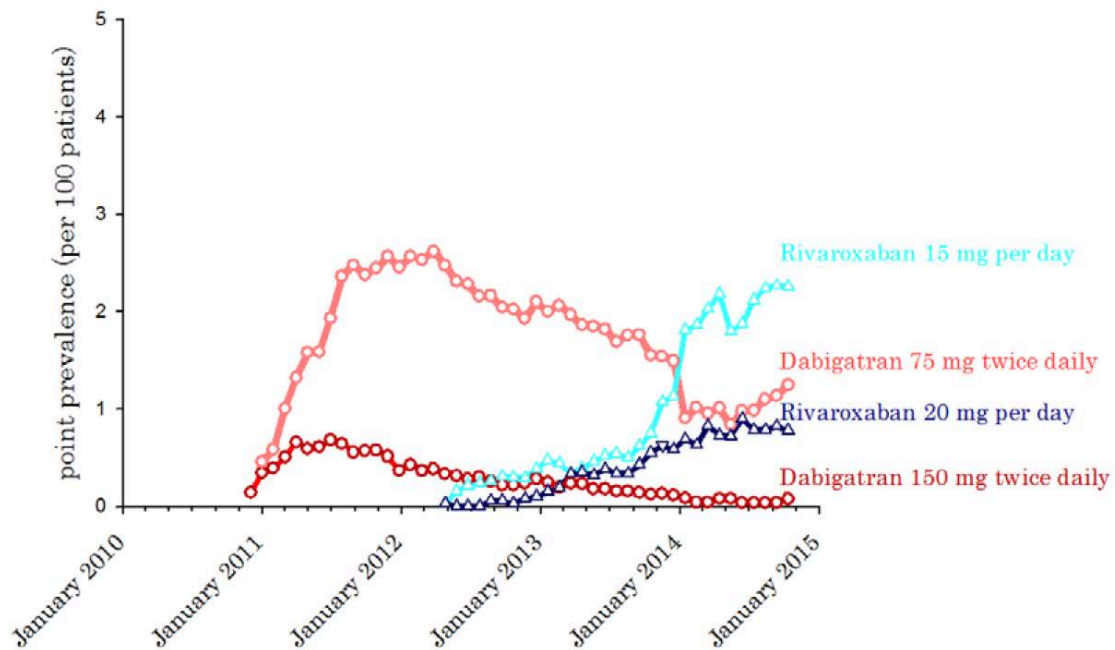
Study Overview

- Retrospective cohort study using data abstracted from the Fresenius Medical Care North America (FMCNA) ESRD database
- 14,607 patients on chronic hemodialysis with NVAF initiated de novo on either dabigatran, rivaroxaban, warfarin, or aspirin
  - Matching was performed on a 1:2 ratio (NOAC to warfarin)
- Patients were followed for up to 2 years for outcomes

14. Chan KE, et al. *Circulation* 2015; 131:972-79.

Prevalence of Dabigatran and Rivaroxaban Use





14. Chan KE, et al. *Circulation* 2015; 131:972-79.

BASELINE CHARACTERISTICS

	Dabigatran (n=281)	Rivaroxaban (n=244)	Warfarin (n=8064)
Age, y	68	67	71
Male	166 (59.2%)	148 (60.5%)	4935 (61.2%)
Time on HD, y	2.6	2.5	2.2
Comorbidities			
Embolic CVA	31 (11.2%)	36 (14.6%)	968 (12.0%)
Prior major bleed	12 (4.1%)	10 (4.2%)	266 (3.3%)
Prior GI bleed	21 (7.5%)	15 (6.0%)	427 (5.3%)
$CHADS_2$ score	2.3	2.2	2.4
Bleeding index score	1.9	1.8	1.9

14. Chan KE, et al. *Circulation* 2015; 131:972-79.

Overall Outcomes

Safety Endpoints		
	Dabigatran vs. Warfarin	**Rivaroxaban vs. Warfarin**
Major bleeding	1.48 (1.21–1.81)	1.38 (1.03–1.83)
Minor bleeding	1.17 (1.00–1.38)	1.35 (1.11–1.65)
Hemorrhagic death	1.78 (1.18–2.68)	1.71 (0.93–3.12)
Efficacy Endpoints		
	Dabigatran vs. Warfarin	**Rivaroxaban vs. Warfarin**
Stroke	* Too few events to detect any meaningful differences*	
Arterial embolism	* Too few events to detect any meaningful differences*	

*All endpoints reported as RR (95% CI)

14. Chan KE, et al. *Circulation* 2015; 131:972-79.

SUMMARY

- One of the first studies to evaluate the use of a NOAC in the dialysis patient population
- Compared to warfarin, patients taking dabigatran and rivaroxaban were at an increased risk for morbidity and mortality from bleeding
- Use of dabigatran and rivaroxaban is not recommended in patients undergoing dialysis

14. Chan KE, et al. *Circulation* 2015; 131:972-79.

Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

- Konstantinos C. Siontis, Xiaosong Zhang, Ashley Eckard, Nicole Bhave, Douglas E. Schaubel, Kevin He, Anca Tilea, Austin G. Stack, Rajesh Balkrishnan, Xiaoxi Yao, Peter A. Noseworthy, Nilay D. Shah, Rajiv Saran, Brahmajee K. Nallamothu

15. Siontis KC, et al. *Circulation* 2018; 138:1519-29.

Study Overview

- Retrospective matched cohort study of Medicare beneficiaries included in the United States Renal Data System

- 25,523 patients with NVAF and ESRD undergoing dialysis being treated with an oral anticoagulant
  - Analysis restricted to apixaban and warfarin given low number of prescriptions for dabigatran and rivaroxaban

- Primary outcomes identified through inpatient claims

15. Siontis KC, et al. *Circulation* 2018; 138:1519-29.

BASELINE CHARACTERISTICS

	Apixaban (n=2351)	Warfarin (n=23,172)
Age, y	69	68
Male	1280 (54.4%)	12,572 (54.3%)
HD	2216 (94.3%)	21,930 (94.6%)
Comorbidities		
Cerebrovascular event	778 (33.1%)	7683 (33.2%)
VTE	279 (11.9%)	4379 (18.9%)
Prior major bleed	217 (9.2%)	2319 (10.0%)
Prior GI bleed	249 (10.6%)	2717 (11.7%)
CHA_2DS_2-VASc score	5.3	5.2

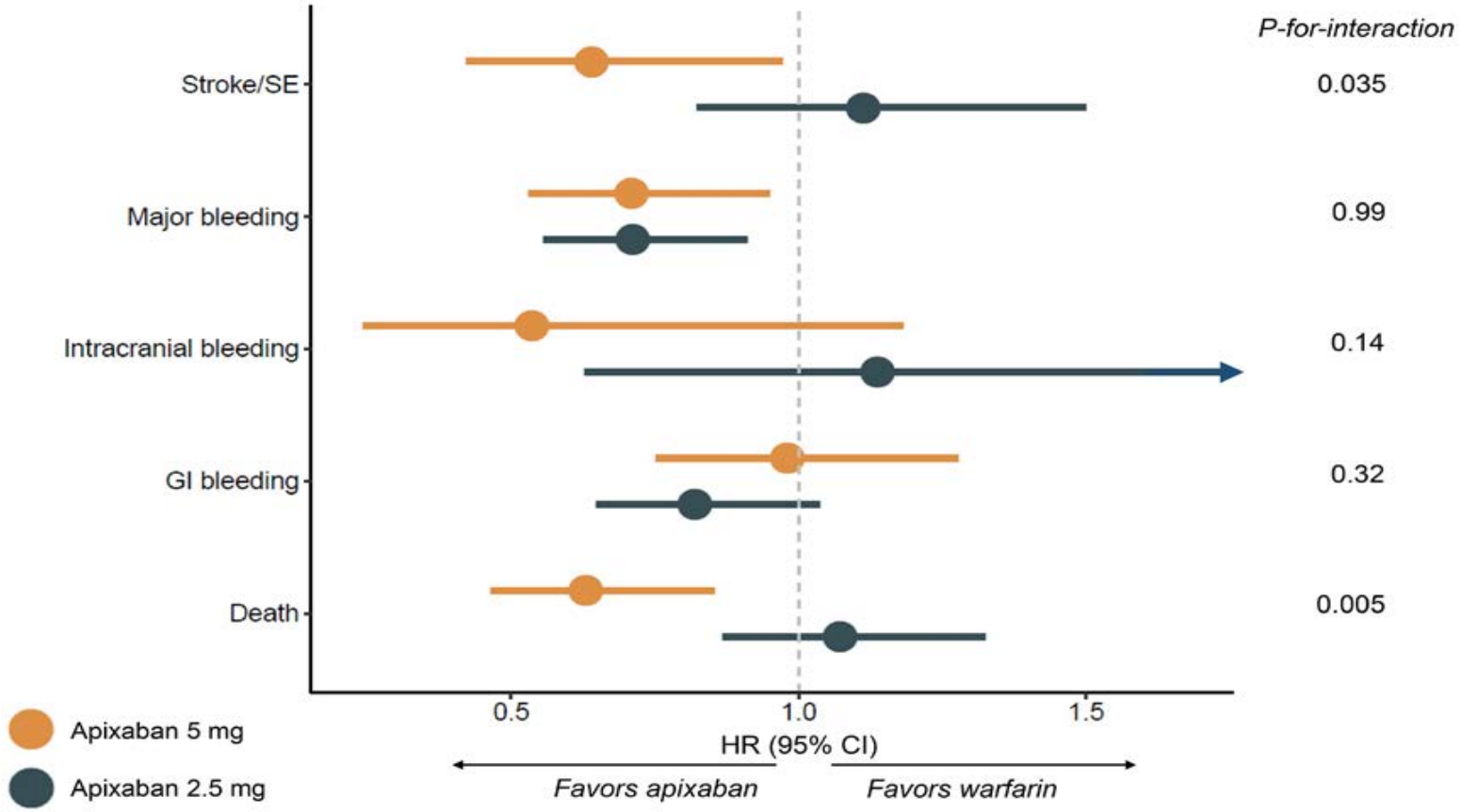
15. Siontis KC, et al. *Circulation* 2018; 138:1519-29.

Overall Outcomes

	Apixaban (n=2351)	Warfarin (n=7053)	HR (95% CI)
Stroke or systemic embolism	81 (3.4%)	373 (5.3%)	0.88 (0.69–1.12)
Major bleeding	129 (5.5%)	715 (10.1%)	0.72 (0.59–0.87)
GI bleeding	155 (6.6%)	710 (10.1%)	0.86 (0.72–1.02)
Intracranial bleeding	21 (0.9%)	111 (1.6%)	0.79 (0.49–1.26)
Death	159 (6.8%)	753 (10.7%)	0.85 (0.71–1.01)

15. Siontis KC, et al. *Circulation* 2018; 138:1519-29.

Impact of Dosing



15. Siontis KC, et al. *Circulation* 2018; 138:1519-29.

SUMMARY

- Patients taking apixaban were less likely to have major bleeding compared with warfarin
- The standard 5 mg dose of apixaban was associated with reduced thromboembolic and mortality risk
- Apixaban may be a reasonable choice for anticoagulation in patients receiving dialysis

15. Siontis KC, et al. *Circulation* 2018; 138:1519-29.

RIVAROXABAN VERSUS WARFARIN IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION AND SEVERE KIDNEY DISEASE OR UNDERGOING HEMODIALYSIS

- Craig I. Coleman, Reinhold Kreutz, Nitesh A. Sood, Thomas J. Bunz, Daniel Eriksson, Anna-Katharina Meinecke, William L. Baker

16. Coleman CI, et al. *Am J Med* 2019; 132:1078-83.

Study Overview

- Retrospective claims analysis using the United States (US) Truven MarketScan database

- 6,744 patients with NVAF and Stage 4/5 CKD or undergoing hemodialysis who are oral anticoagulant-naïve
  - Primary efficacy outcome of stroke or systemic embolism
  - Primary safety outcome of major bleeding as defined by the Cunningham algorithm

- 1.4 year median follow-up

16. Coleman CI, et al. *Am J Med* 2019; 132:1078-83.

BASELINE CHARACTERISTICS

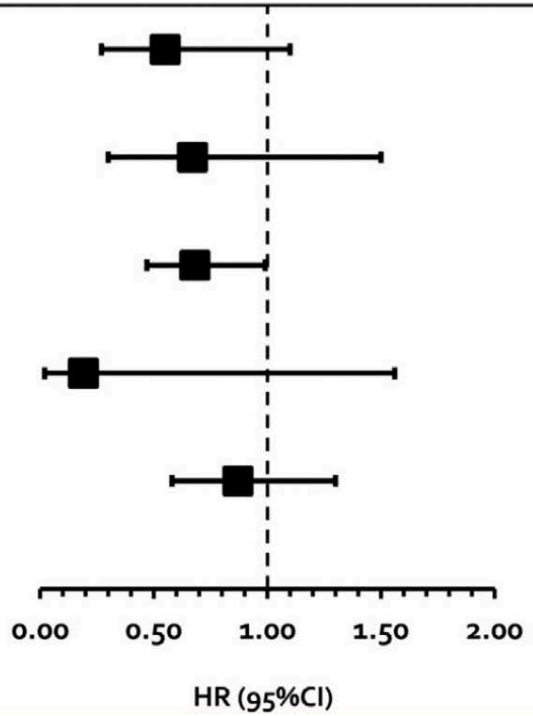
	Rivaroxaban (n=1896)	Warfarin (n=4848)
Age, y	72	72
Female	41.6%	38.4%
Stage 5 CKD or HD	88.6%	87.5%
Comorbidities		
Previous ischemic stroke	11.2%	12.1%
Prior ICH	0.4%	0.4%
Prior GI bleed	2.5%	3.1%

- Overall study population with a median CHA_2DS_2-VASc score of 4

16. Coleman CI, et al. *Am J Med* 2019; 132:1078-83.

OVERALL OUTCOMES

	Event Rate (per 100 Person-Years)		
	Rivaroxaban N=1896	Warfarin (n=4848)	HR (95%CI)
Stroke or Systemic Embolism	1.10	2.16	0.55 (0.27-1.10)
Ischemic Stroke	0.85	1.44	0.67 (0.30-1.50)
Major Bleeding	3.73	6.16	0.68 (0.47- 0.99)
Intracranial	0.08	0.28	0.19 (0.02-1.56)
Gastrointestinal	3.39	4.52	0.87 (0.58-1.30)



16. Coleman CI, et al. *Am J Med* 2019; 132:1078-83.

SUMMARY

- Patients taking rivaroxaban were marginally less likely to have major bleeding events compared with warfarin
- Rivaroxaban may be considered in patients with Stage 4/5 CKD or undergoing HD
- Further studies are needed to determine the optimal dosing of rivaroxaban in this patient population

16. Coleman CI, et al. *Am J Med* 2019; 132:1078-83.

Apixaban Versus Warfarin in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease

- John W. Stanifer, Sean D. Pokorney, Glenn M. Chertow, Stefan H. Hohnloser, Daniel M. Wojdyla, Samira Garonzik, Wonkyung Byon, Ziad Hijazi, Renato D. Lopes, John H. Alexander, Lars Wallentin, Christopher B. Granger

17. Stanifer JW, et al. *Circulation* 2020; 141:1384-92.

STUDY OVERVIEW

- Evaluated the safety and efficacy of apixaban vs. warfarin in 269 patients with NVAF and CrCl 25 – 30 mL/min enrolled in ARISTOTLE

- Highlights of the study design in ARISTOTLE:
  - Double-blind, randomized controlled trial
  - Primary safety outcome of major bleeding defined according to the ISTH; primary efficacy outcome of stroke or systemic embolism
  - 1.8 year median follow-up

17. Stanifer JW, et al. *Circulation* 2020; 141:1384-92.

BASELINE CHARACTERISTICS

	Apixaban (n=136)	Warfarin (n=133)
Age, y	81	81
Female	84 (61.8%)	79 (59.4%)
CrCl, mL/min	27.5	27.3
Previous stroke, TIA, or systemic embolism	40 (29.4%)	33 (24.8%)
CHA_2DS_2-VASc score	4.9	4.7
HAS-BLED score	2.3	2.3
Previous VKA use for >30 days	75 (55.1%)	63 (47.4%)

17. Stanifer JW, et al. *Circulation* 2020; 141:1384-92.

Overall Outcomes

Safety Endpoints			
	Apixaban (n=135)	**Warfarin (n=132)**	**HR (95% CI)**
Major bleeding	3.78 (7)	11.94 (19)	0.34 (0.14–0.80)
Major or CRNM bleeding	5.43 (10)	16.75 (26)	0.35 (0.17–0.72)
Intracranial bleeding	0.00 (0)	2.40 (4)	—
Efficacy Endpoints			
	Apixaban (n=136)	**Warfarin (n=133)**	**HR (95% CI)**
Stroke or systemic embolism	2.81 (6)	5.06 (10)	0.55 (0.20–1.51)
Death from any cause	15.2 (33)	15.3 (32)	1.02 (0.64–1.67)
Cardiovascular death	6.89 (15)	6.68 (14)	1.05 (0.51–2.18)

*All endpoints reported as event rates per 100 patient-years

17. Stanifer JW, et al. *Circulation* 2020; 141:1384-92.

Impact of Dosing

Apixaban 2.5 mg			
	Apixaban (n=87)	**Warfarin (n=85)**	**HR (95% CI)**
Major bleeding	3.42 (4)	11.1 (11)	0.34 (0.11–1.07)
Major or CRNM bleeding	4.28 (5)	17.9 (17)	0.27 (0.20–0.73)
Apixaban 5 mg			
	Apixaban (n=48)	**Warfarin (n=47)**	**HR (95% CI)**
Major bleeding	4.39 (3)	13.3 (8)	0.34 (0.09–1.29)
Major or CRNM bleeding	7.45 (5)	15.0 (9)	0.51 (0.17–1.53)

*All endpoints reported as event rates per 100 patient-years

17. Stanifer JW, et al. *Circulation* 2020; 141:1384-92.

SUMMARY

- First randomized controlled trial to assess the safety and efficacy of a NOAC compared to warfarin in patients with a CrCl <30 mL/min
- Patients taking apixaban experienced fewer major bleeding events but no significant reduction in stroke or systemic embolism
- Results of this study further supports the use of apixaban in this patient population

17. Stanifer JW, et al. *Circulation* 2020; 141:1384-92.

CONCLUSIONS

- The decision to use a NOAC in patients with advanced kidney disease should be made on an individual basis
- Apixaban has the most evidence to support its use in this high-risk patient population
- Further research is needed to confirm the efficacy and safety of NOACs in patients with advanced kidney disease via large randomized controlled trials

EMERGING DATA

	XARENO	SAFE-D	AXADIA
Study design	Prospective non-interventional observational registry	Open label randomized controlled trial	Open label randomized controlled trial
Comparators	Rivaroxaban vs. VKA vs. no oral anticoagulation	Apixaban vs. warfarin vs. no oral anticoagulation	Apixaban vs. phenprocoumon
Population	Patients with NVAF and CKD (eGFR 15 – 49 mL/min/1.73m^2)	Patients with NVAF receiving dialysis (HD or PD)	Patients with NVAF and ESRD on HD
Projected date of completion	December 2020	December 2021	July 2022

18. ClinicalTrials.gov Identifier: NCT02663076. https://clinicaltrials.gov/ct2/show/NCT02663076.
19. ClinicalTrials.gov Identifier: NCT03987711. https://clinicaltrials.gov/ct2/show/NCT03987711.
20. ClinicalTrials.gov Identifier: NCT02933697. https://clinicaltrials.gov/ct2/show/NCT02933697.

TEST QUESTION 1

Which of the following NOACs is dialyzable?

a) Apixaban
b) Betrixaban
c) Dabigatran
d) Edoxaban

TEST QUESTION 1

Which of the following NOACs is dialyzable?

a) Apixaban
b) Betrixaban
c) Dabigatran
d) Edoxaban

TEST QUESTION 2

Which of the following statements is most accurate based on the results of the Phase III NOAC trials in NVAF?

a) All NOACs are superior to warfarin in reducing stroke or systemic embolism
b) All NOACs significantly reduce major bleeding when compared to warfarin
c) Apixaban is the only NOAC that reduces all-cause mortality
d) The only NOAC to reduce rates of hemorrhagic stroke is rivaroxaban

TEST QUESTION 2

Which of the following statements is most accurate based on the results of the Phase III NOAC trials in NVAF?

a) All NOACs are superior to warfarin in reducing stroke or systemic embolism
b) All NOACs significantly reduce major bleeding when compared to warfarin
c) Apixaban is the only NOAC that reduces all-cause mortality
d) The only NOAC to reduce rates of hemorrhagic stroke is rivaroxaban

TEST QUESTION 3

Which of the following NOACs has been evaluated for use in patients with advanced kidney disease in a randomized controlled trial?

a) Apixaban
b) Dabigatran
c) Edoxaban
d) Rivaroxaban

TEST QUESTION 3

Which of the following NOACs has been evaluated for use in patients with advanced kidney disease in a randomized controlled trial?

a) **Apixaban**
b) Dabigatran
c) Edoxaban
d) Rivaroxaban

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