Best available evidence regarding the DOAC use in patients with *End-Stage Renal Disease*

Parham Sadeghipour, MD

Rajaie Cardiovascular Medical and Research Center

Disclosures

- Consultancy for Abidi, Actover, Arena, Bayer and Boehringer Ingelheim
- Research funding from Abidi, Actover, Arena, Bayer and Boehringer Ingelheim
- Advisory committee or board of ELAQUIT (Abidi), XARELTO (Bayer)

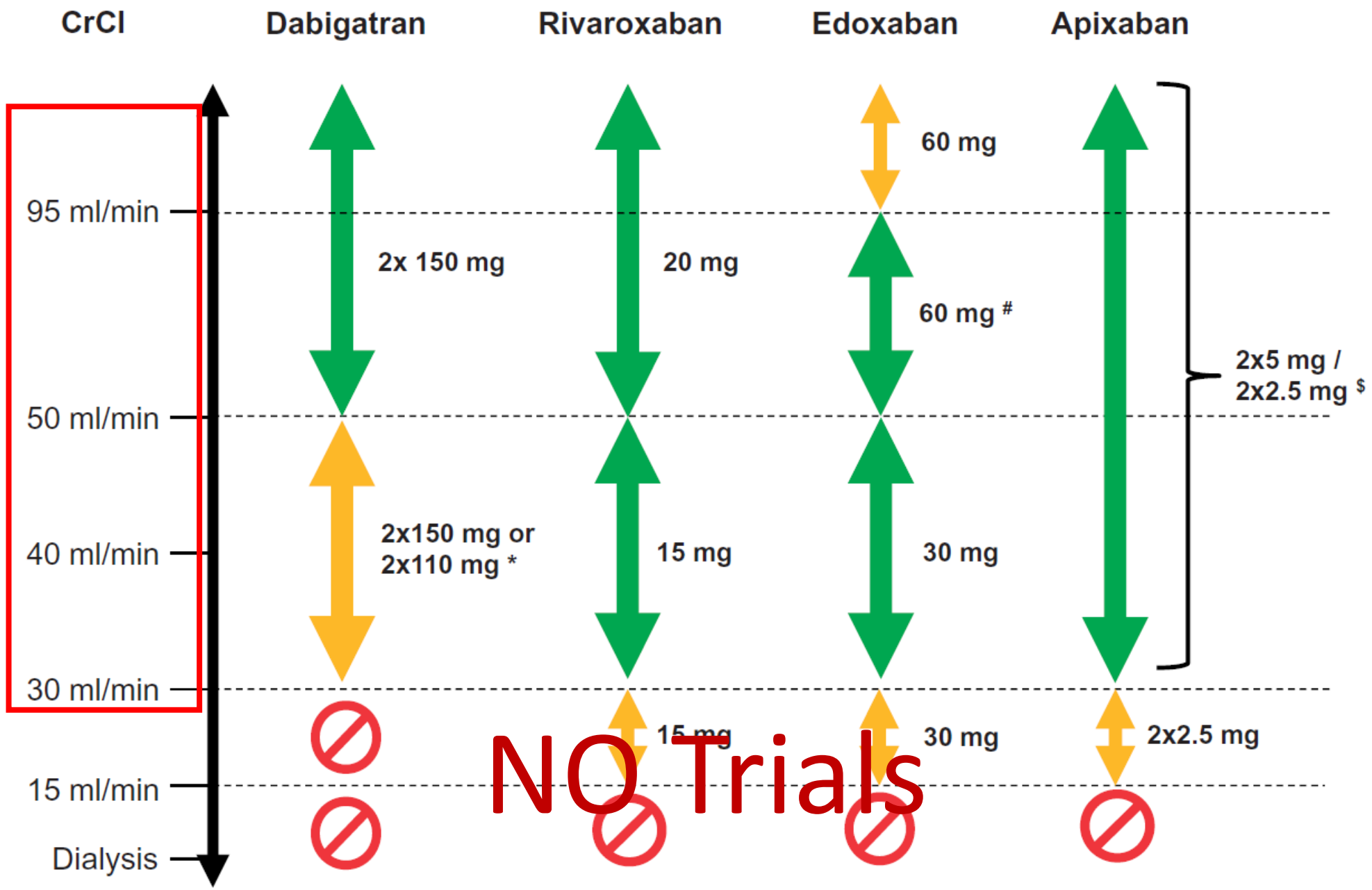
	Stroke/Systemic Embolism HR (95% CI)	Bleeding HR (95% CI)
Off-Label UNDER-dose	↑ **22%** **1.22 (1.05-1.42)**	No difference 0.95 (0.82-1.11)
Off-Label OVER-dose	↑ **26%** **1.26 (1.11-1.43)**	↑ **30%** **1.30 (1.04-1.62)**

DOAC trough RCT

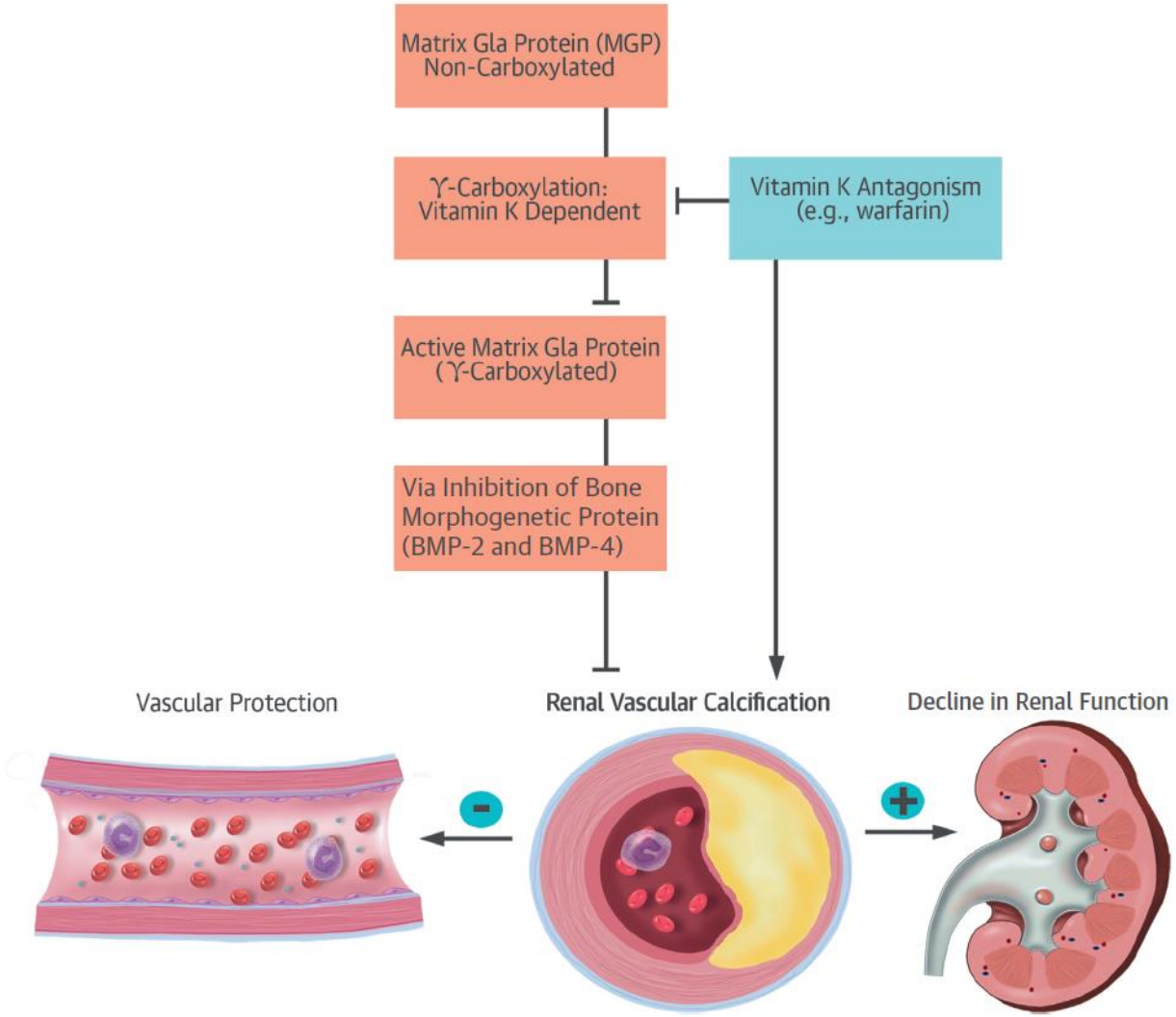
	Dabigatran (RE-LY[1–3]) 150 mg BID	Dabigatran (RE-LY[1–3]) 110 mg BID	Apixaban (ARISTOTLE[4,5]) 5/2.5 mg BID	Rivaroxaban (ROCKET AF[6]) 20/15 mg OD	Edoxaban (ENGAGE AF-TIMI 48[7]) 60/30 mg OD
Stroke/SE	↓ 35%	Similar	↓ 21%	Similar	Similar
Ischemic stroke	↓ 24%	Similar	Similar	Similar	Similar
CV mortality	↓ 15%	Similar	Similar	Similar	↓ 14%
Major bleeding	Similar	↓ 20%	↓ 31%	Similar	↓ 20%
ICH	↓ 70%	↓ 59%	↓ 58%	↓ 33%	↓ 53%

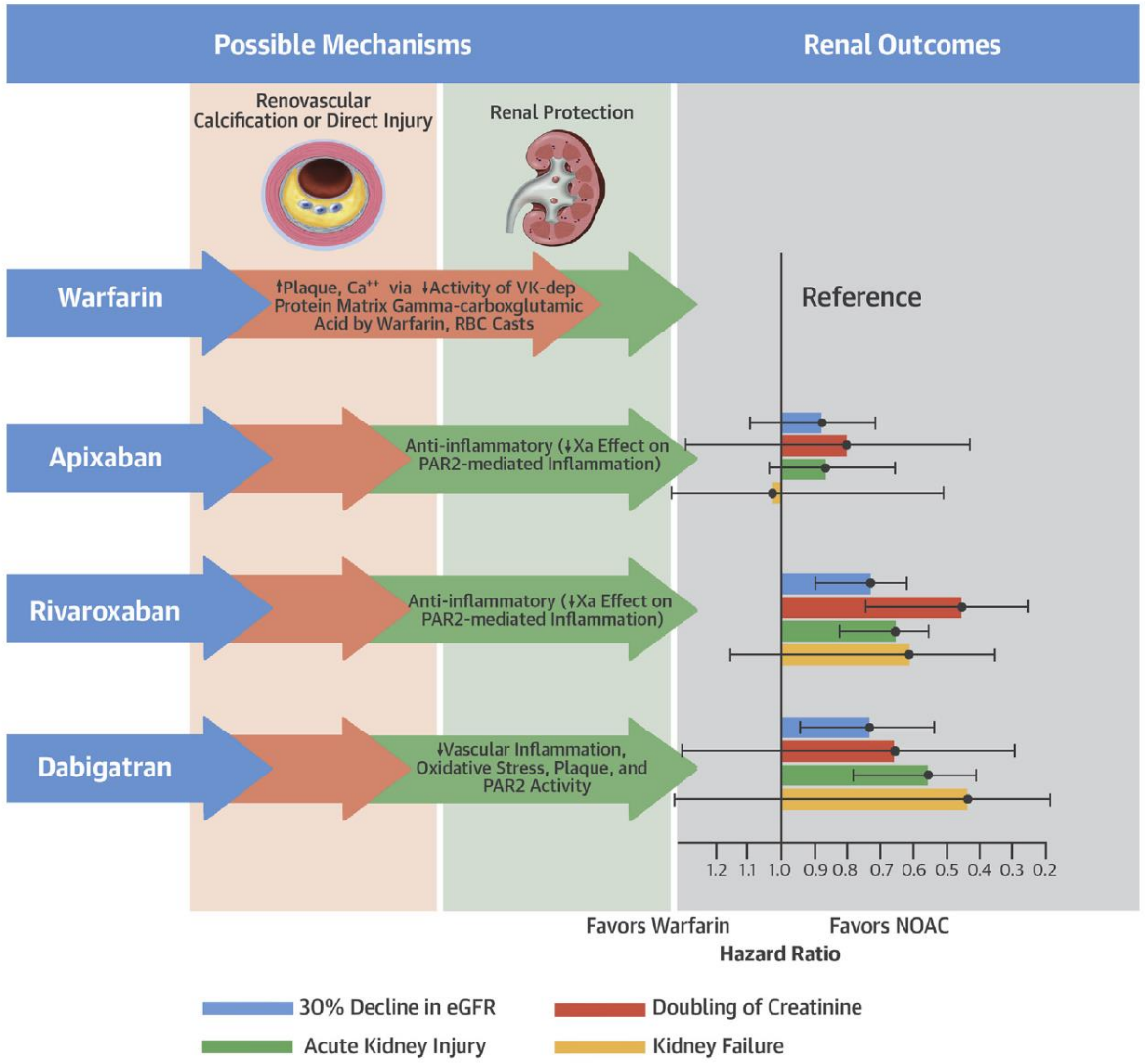
DOAC trough RCT

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Number of patients	18,113	14,264	18,201	21,105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg or 30 mg once daily
Moderate CKD Definition (CrCl)	31–49 mL/min	25–50 mL/min	30–49 mL/min	30–50 mL/min
Dose adjustment for moderate CKD	75 mg twice daily	15 mg once daily	2.5 mg twice daily	30 mg once daily
Number of patients with moderate CKD	3554 (20%)	2950 (21%)	3017 (17%)	2740 (19.5%)
Exclusion criteria based on CrCl	< 30 mL/min	< 30 mL/min	Serum Cr > 2.5 mg/dL or CrCl <25 mL/min	< 30 mL/min
Primary efficacy outcome: stroke and SE vs. warfarin (HR, 95% CI)	150 mg: 0.56 (0.37–0.85) 110 mg: 0.85 (0.59–1.24)	0.84 (0.57–1.23)	0.79 (0.55–1.14)	0.87 (0.64–1.19)
Primary safety outcome: major bleeding (HR, 95% CI)	150 mg: 1.02 (0.79–1.30) 110 mg: 0.99 (0.77–1.28)	0.95 (0.72–1.26)	0.5 (0.38–0.66)	0.76 (0.58–0.98)


CrCl
Dabigatran
Rivaroxaban
Edoxaban
Apixaban
95 ml/min
50 ml/min
40 ml/min
30 ml/min
15 ml/min
Dialysis
2x 150 mg
20 mg
60 mg
60 mg #
2x5 mg /
2x2.5 mg $
2x150 mg or
2x110 mg *
15 mg
30 mg
15 mg
30 mg
2x2.5 mg
NO Trials

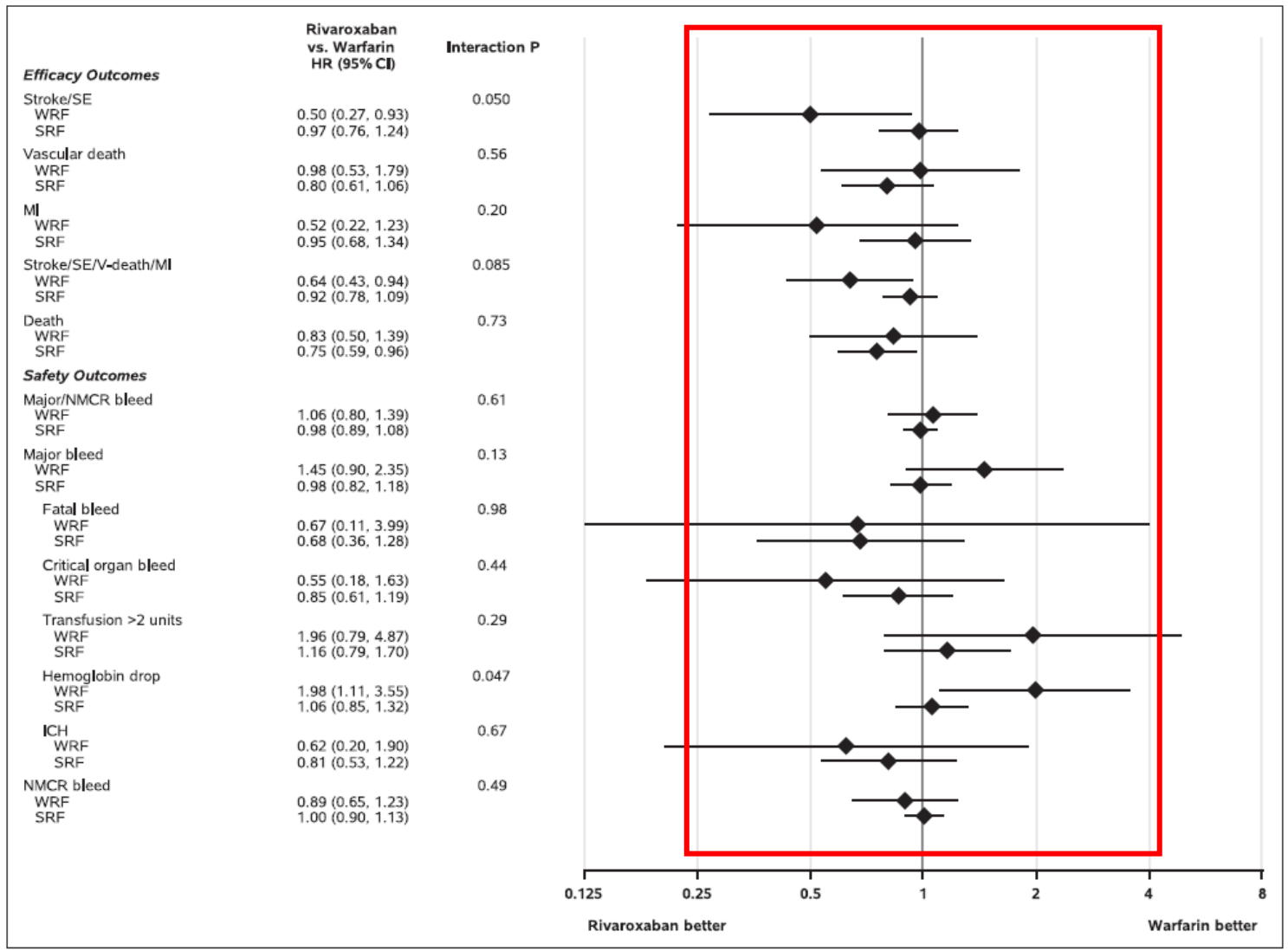
Renal monitoring in patients taking anticoagulation



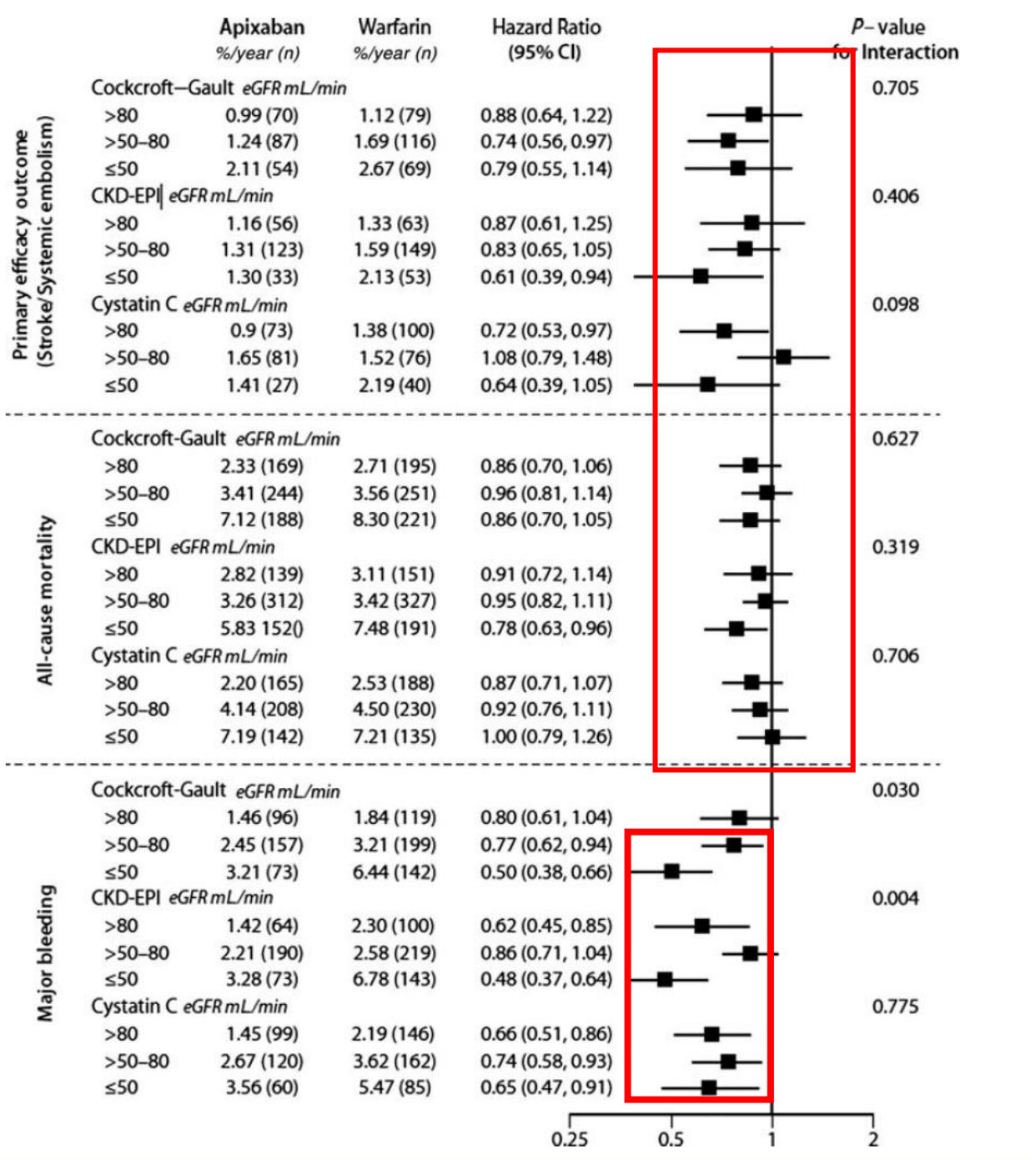


On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin

Insights From ROCKET AF



Efficacy of apixaban when compared with warfarin in relation to renal function in patien with atrial fibrillation: insights from the ARISTOTLE trial



CrCl 15–29 ml/min	AHA/ACC/HRS (2019) (5)	Adjusted dose INR 2–3	75 mg BID	5.0 or 2.5 mg BID*	15 mg QD	Not recommended
	CHEST Guideline (2018) (4)	Adjusted dose TTR >70%	75 mg BID (U.S. only) Not recommended outside U.S.	2.5 mg BID	15 mg QD	30 mg QD
	KDIGO (2018)† (2)	Consider adjusted dose INR 2–3	Unknown (consider 75 mg BID)	Consider 2.5 mg BID	Consider 15 mg QD	Consider 30 mg QID
	EHRA practical guide (2018) (3)	Not discussed	Not recommended	2.5 mg BID	15 mg QD	30 mg QD
	ESC (2016) (1)	Adjusted dose INR 2–3	Not recommended	Not recommended if CrCl <25	Not recommended	Not recommended
CrCl <15 ml/min (Dialysis)	AHA/ACC/HRS (2019) (5)	Adjusted dose INR 2–3	Not recommended	5.0 or 2.5 mg BID*	Not recommended	Not recommended
	CHEST guideline (2018) (4)	Adjusted dose TTR >70%	Not recommended	5 mg BID‡	Not recommended	Not recommended
	KDIGO (2018)† (2)	Equipoise	Not recommended	Consider 2.5 mg BID	Unknown (15 mg QD mentioned)	Not recommended
	EHRA practical guide (2018) (3)	Not discussed	Not recommended	Not recommended	Not recommended	Not recommended
	ESC (2016) (1)	Not discussed	Not recommended	Not recommended	Not recommended	Not discussed

		Dabigatran	Apixaban	Rivaroxaban	Edoxaban
CrCl 15-30 ml/min	FDA	75 mg BID	5 or 2.5 mg BID*	15 mg QD	30 mg QD
	EMA	Contraindicated	2.5 mg BID	Limited clinical data –15 mg QD	30 mg QD
CrCl < 15 ml/min	FDA	Not approved	5 mg BID	Limited clinical data–15 mg QD	Not approved
	EMA	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Dialysis	FDA	Not approved	5 mg BID	Limited clinical data–15 mg QD	Not approved
	EMA	Contraindicated	Contraindicated	Contraindicated	Contraindicated

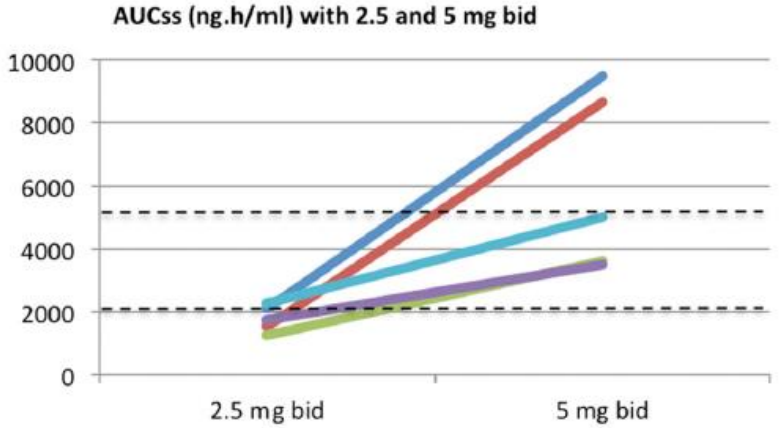
1. Do we have solid evidence for the efficacy and safety of DOAC in ESRD patients with AF?

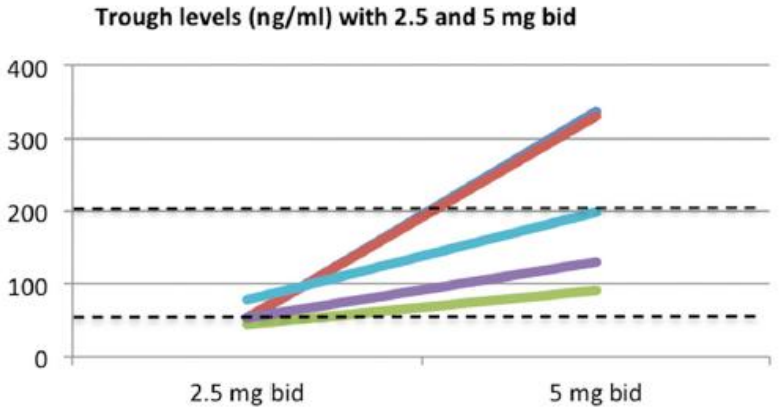
Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

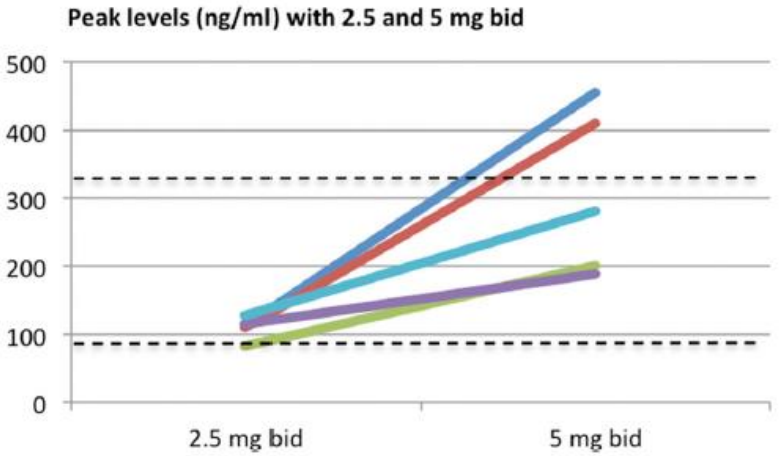
Table 2. PK parameters of apixaban after administration of 5 mg twice daily for a week and comparison with expected levels in the general population

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][18]
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)[a20]
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).





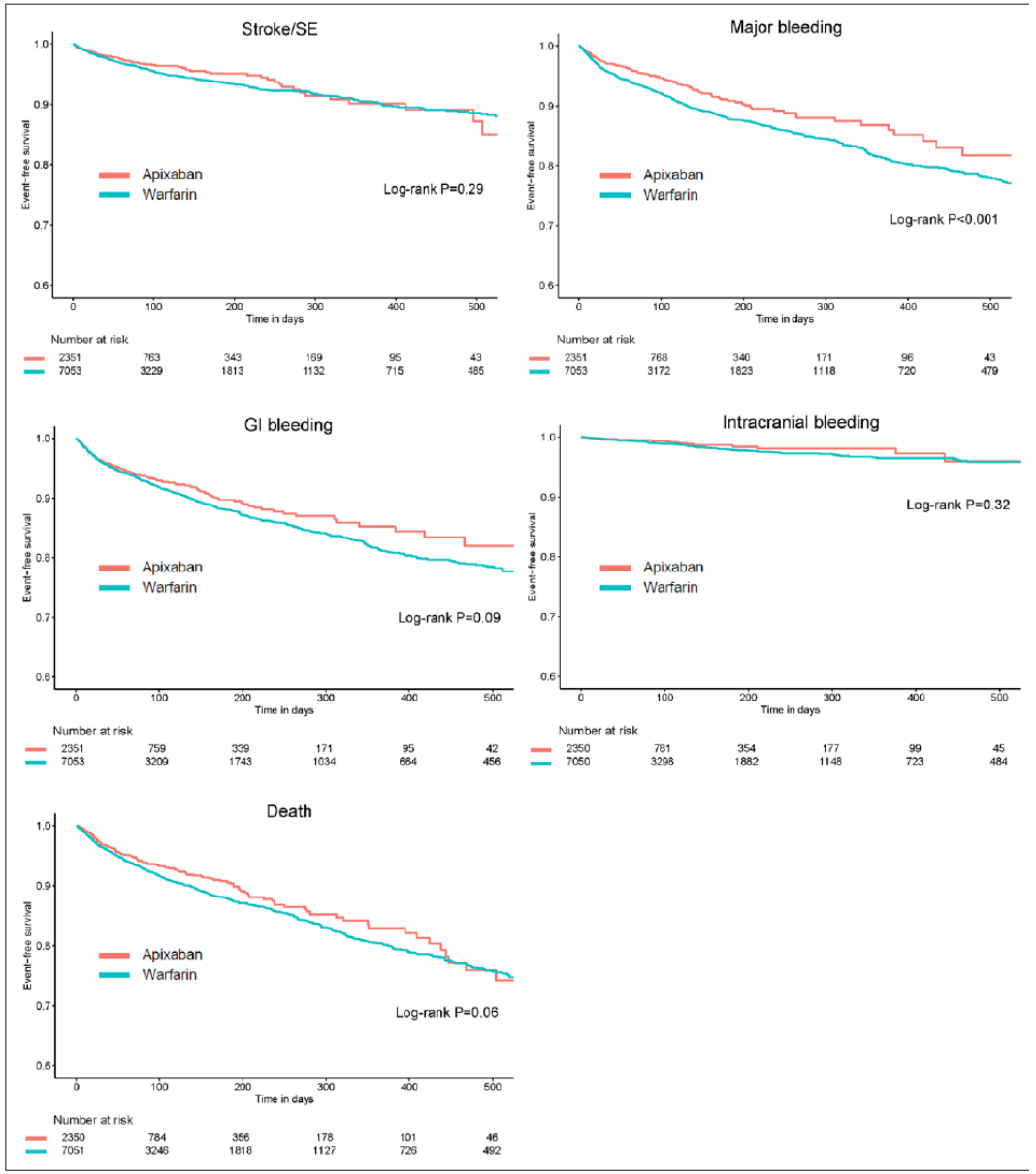


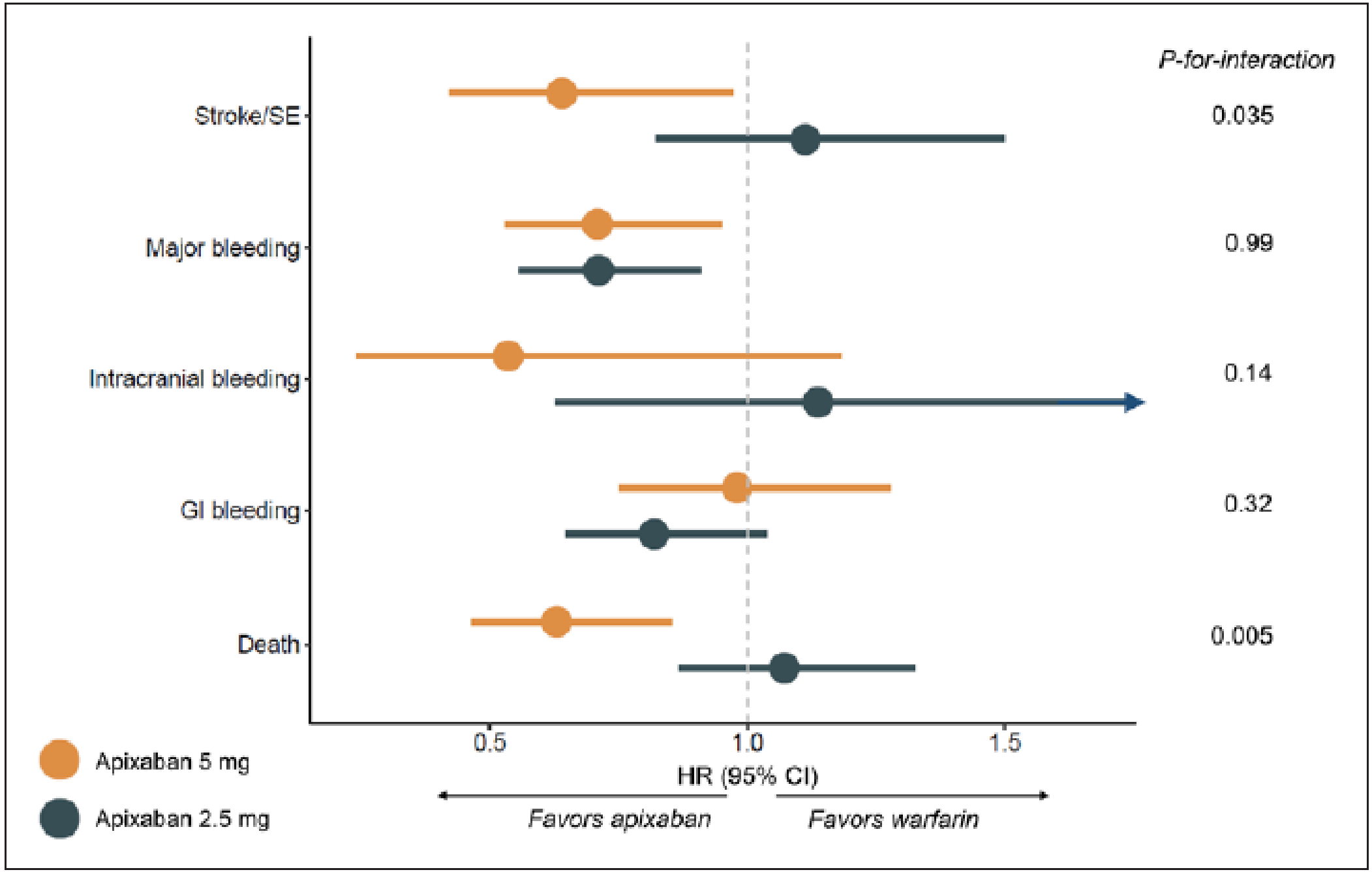
Limitations of *pharmacokinetics* study

- Small sample sizes
- Ideal patients with few comorbidities

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

Outcome	Overall	Apixaban	Warfarin	Hazard Ratio (95% CI)	*P* Value
Stroke/systemic embolism					
No. of patients	9404	2351	7053	0.88 (0.69–1.12)	0.29
No. of events	454	81	373		
Event rate per 100 PY	11.9	12.4	11.8		
Major bleeding					
No. of patients	9404	2351	7053	0.72 (0.59–0.87)	<0.001
No. of events	844	129	715		
Event rate per 100 PY	22.3	19.7	22.9		
Gastrointestinal bleeding					
No. of patients	9404	2351	7053	0.86 (0.72–1.02)	0.09
No. of events	865	155	710		
Event rate per 100 PY	23.4	23.8	23.4		
Intracranial bleeding					
No. of patients	9400	2350	7050	0.79 (0.49–1.26)	0.32
No. of events	132	21	111		
Event rate per 100 PY	3.4	3.1	3.5		
Death					
No. of patients	9404	2351	7053	0.85 (0.71–1.01)	0.06
No. of events	912	159	753		
Event rate per 100 PY	24.7	23.7	24.9		




P-for-interaction
Stroke/SE
0.035
Major bleeding
0.99
Intracranial bleeding
0.14
GI bleeding
0.32
Death
0.005
0.5
1.0
1.5
HR (95% CI)
Favors apixaban
Favors warfarin
Apixaban 5 mg
Apixaban 2.5 mg

Original Study Design

Selected inclusion criteria
- **Atrial fibrillation**
- **CHA_2DS_2-VASc ≥2**
- **Hemodialysis**
- **Candidate for OAC**

Randomize (n ≈ 760)

Selected exclusion criteria
- **Moderate or severe mitral stenosis**
- **OAC needed for reason other than AF**
- **Need for aspirin > 81 mg**
- **Need for dual antiplatelet therapy**
- **Life expectancy < 3 months**

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

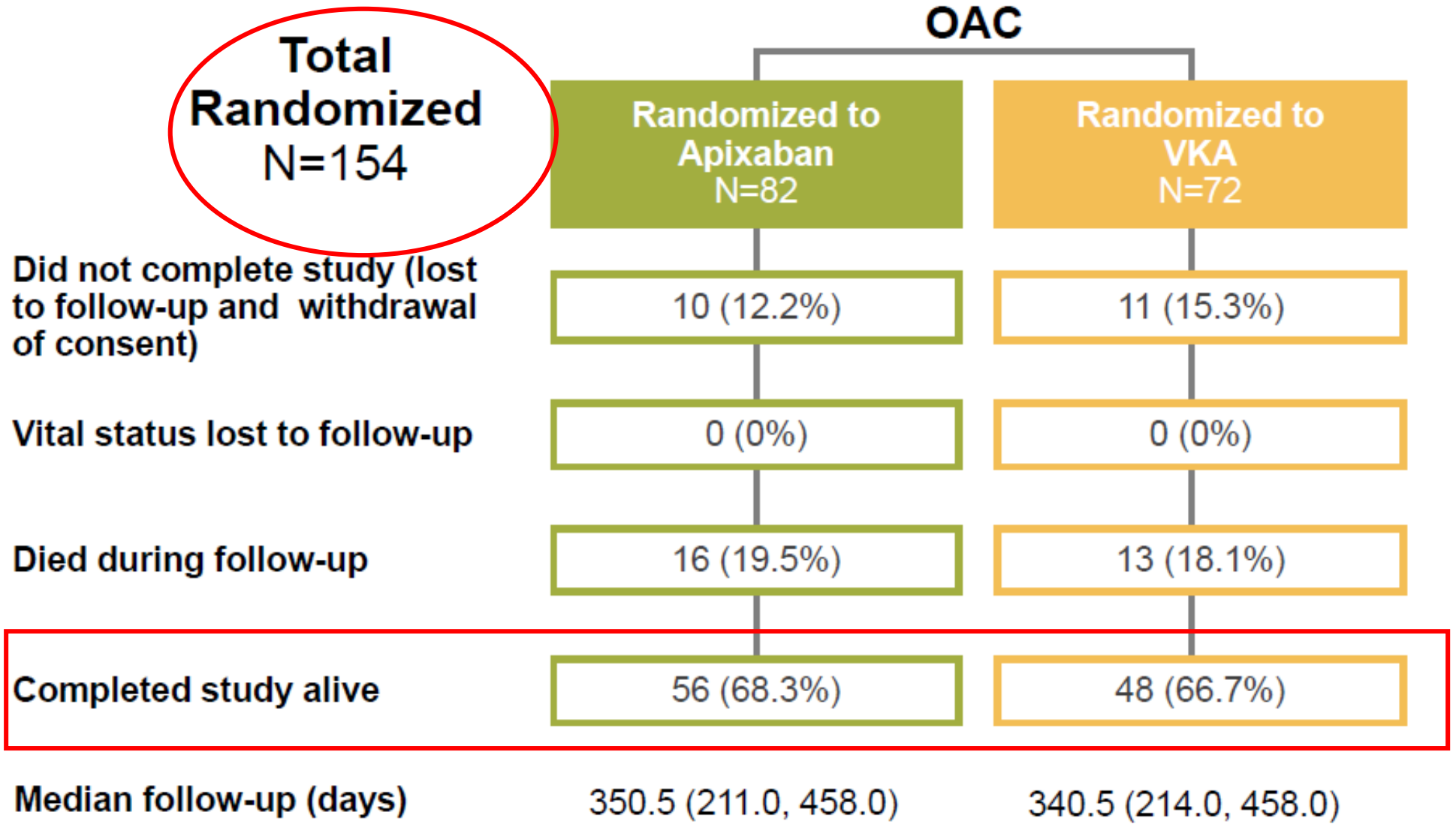
Warfarin
(target INR 2–3)

Open label with blinded event adjudication

Primary outcome: ISTH major and clinically relevant non-major bleeding

Secondary outcomes:
- ***PK in patients randomized to apixaban***
- ***Stroke and systemic embolism***
- ***Death***
- ***Tolerability/persistence/adherence parameters***

CONSORT Diagram



Patient Baseline Characteristics

	Apixaban (N=82)	Warfarin (N=72)
Age (years), Median	69.0 (61.0, 76.0)	68.0 (60.5, 72.5)
≥ 75 years old	24 (29.3%)	15 (20.8%)
Female	34 (41.5%)	22 (30.6%)
Black	35 (42.7%)	34 (47.2%)
CHA_2DS_2-VASc, Median (Q1, Q3)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)
Stroke	17 (20.7%)	12 (16.7%)
Warfarin or NOAC naïve	10 (12.2%)	4 (5.6%)
Type of atrial fibrillation		
Paroxysmal	45 (54.9%)	40 (55.6%)
Persistent/Permanent	37 (45.1%)	32 (44.4%)
Prior clinically relevant or spontaneous bleeding	18 (22.0%)	14 (19.4%)
Bleeding the past year requiring hospitalization	8 (9.8%)	2 (2.8%)
Aspirin	29 (36.7%)	32 (45.7%)

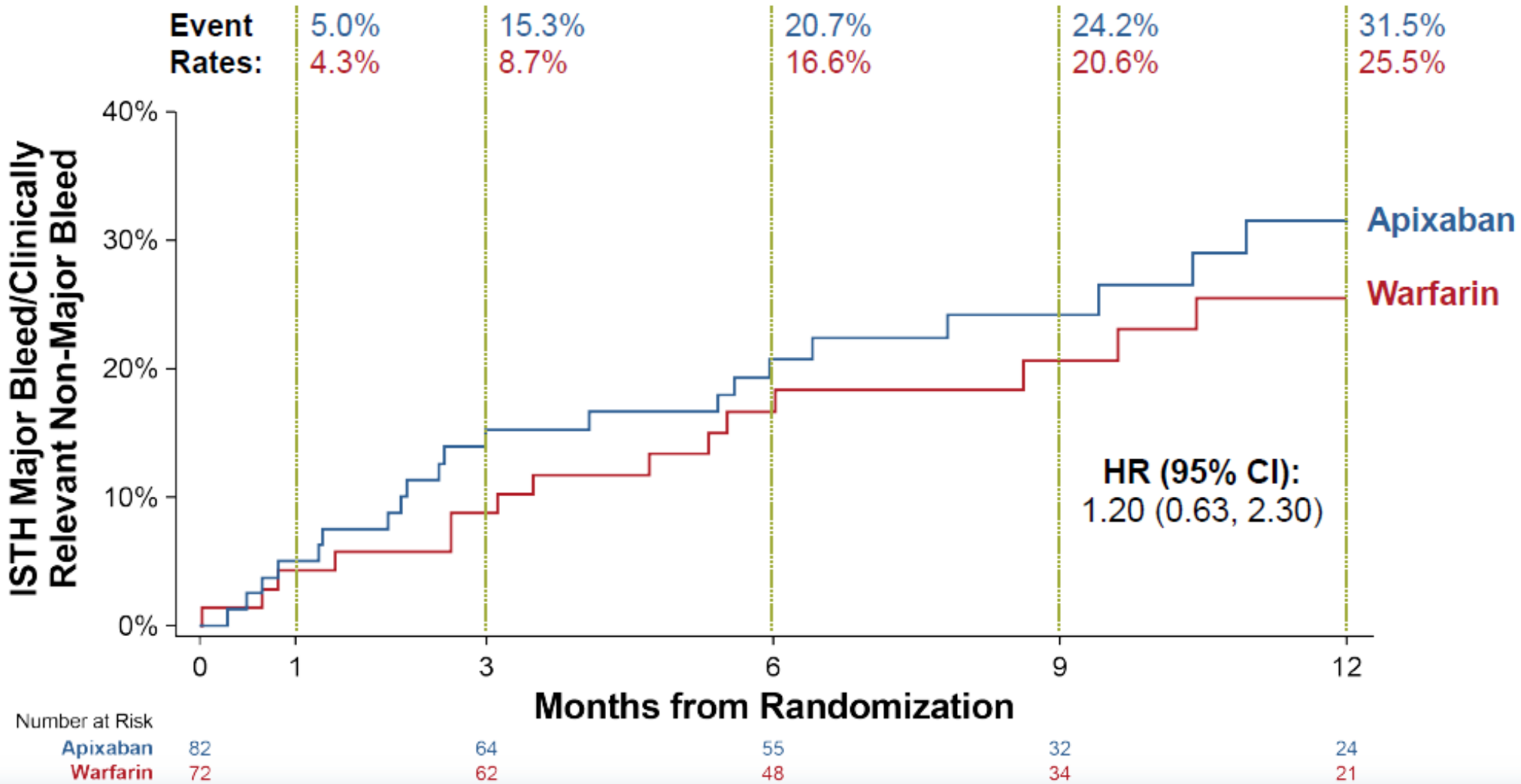
Apixaban and Warfarin Dosing in Modified ITT

Patients randomized to apixaban and received at least one dose	Apixaban N = 77
First apixaban dose	
2.5 mg BID	22 (28.6%)
5.0 mg BID	55 (71.4%)
Apixaban dose reduction from 5.0 mg to 2.5 mg BID	15 (27.3%)
Patients randomized to warfarin and received at least one dose	**Warfarin N = 68**
Time in therapeutic range (2.0-3.0), Median (Q1, Q3)[1]	44.3% (23.2%, 59.0%)

- Patients were 3 times as likely to be subtherapeutic (INR <2.0) relative to supratherapeutic (>3.0)

1 Time in therapeutic range was calculated by the Rosendaal method

Time to Major or Clinically Relevant Non-Major Bleed for Intention to Treat



Primary Safety Endpoint: ITT Analysis

	Apixaban N = 82	Warfarin N = 72
ISTH major bleed/clinically relevant non-major bleed[1]	21 (25.6%)	16 (22.2%)
Intracranial	1 (1.2%)	1 (1.4%)
Gastrointestinal	2 (2.4%)	6 (8.3%)
Hemodialysis access site	11 (13.4%)	6 (8.3%)
ISTH major bleed[1]	7 (8.5%)	7 (9.7%)
Intracranial	1 (1.2%)	1 (1.4%)
Gastrointestinal	2 (2.4%)	5 (6.9%)
Hemodialysis access site	1 (1.2%)	0 (0.0%)
ISTH clinically relevant non-major bleed[1]	14 (17.1)	9 (12.5%)
Gastrointestinal	0 (0.0%)	1 (2.8%)
Hemodialysis access site	10 (12.2%)	6 (8.3%)

1 Per protocol, heparin during dialysis was minimized

Secondary Endpoints

	Apixaban N = 82	Warfarin N = 72
Stroke	2 (2.4%)	2 (2.8%)
Ischemic	1 (1.2%)	2 (2.8%)
Hemorrhagic	1 (1.2%)	0 (0.0%)
Systemic embolism	0 (0.0%)	0 (0.0%)
Death	21 (25.6%)	13 (18.1%)
Cardiovascular	9 (11.0%)	4 (5.6%)
Non-cardiovascular	5 (6.1%)	8 (11.1%)
Undetermined	7 (8.5%)	1 (1.4%)
Bleeding related death	1 (1.2%)	0 (0%)

- Analyses of pharmacokinetic (PK) data from 50 patients randomized to apixaban are ongoing

Multicenter RCT of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: the Valkyrie study

METHODS

N=132

VKA INR 2-3

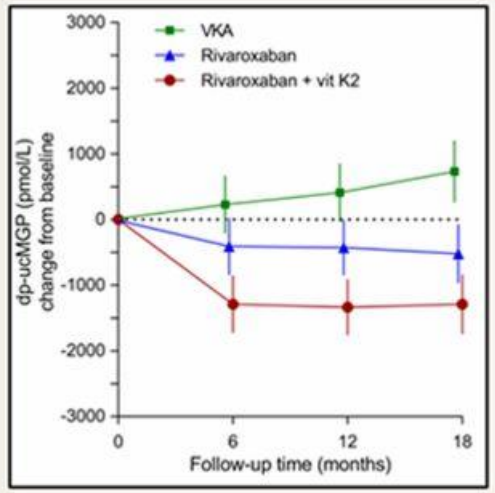
Rivaroxaban 10 mg od

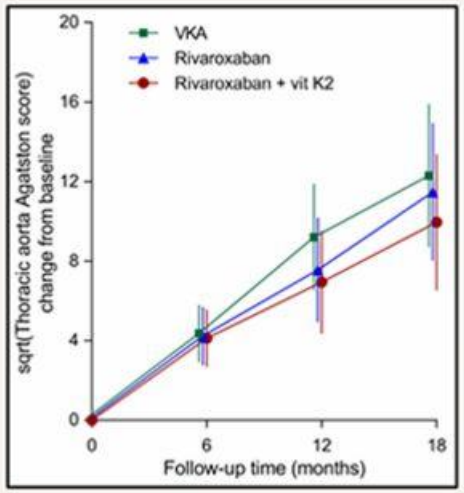
Rivaroxaban + Vit K2

0m* 6m* 12m* 18m*

*VitK status, PWV and CAC score

OUTCOME





Bleeding type	Rate per 100 person-years (number)		
	VKA (n=44)	Rivaroxaban (n=46)	Rivaroxaban + VitK2 (n=42)
Life-threatening	13.3 (7)	3.5 (2)	9.5 (5)
Major	22.7 (12)	13.8 (8)	3.8 (2)
Life-threatening + major	36.0 (19)	17.3 (10)	13.2 (7)
Minor	26.5 (14)	31.1 (18)	30.3 (16)
Gastro-intestinal	22.7 (12)	17.3 (10)	24.6 (13)

CONCLUSION

Withdrawal of VKA and high-dose Vitamin K2 improve Vitamin K status in hemodialysis patients, but have no significant favorable effect on VC progression. Severe bleeding complications may be lower with rivaroxaban than with VKA.

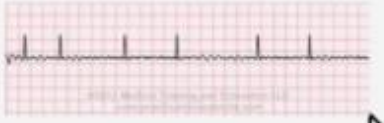
JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter RCT

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

N=132



VKA INR 2-3

Rivaroxaban 10 mg od

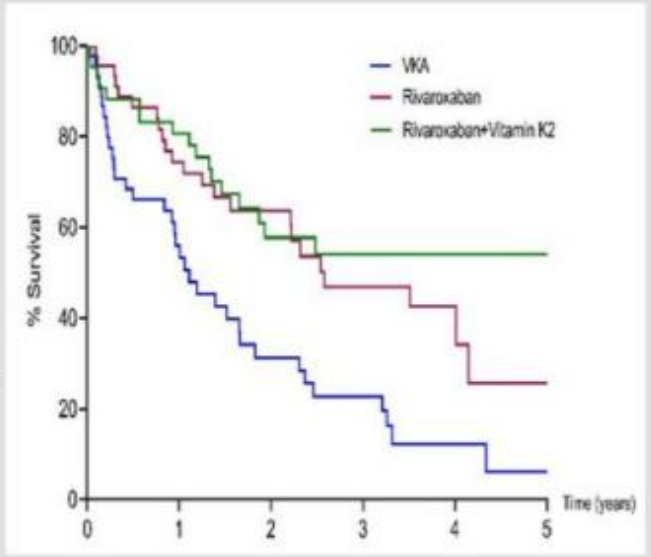
Rivaroxaban+vitamin K2

OUTCOME

Primary efficacy end point:

HR for composite of fatal and non-fatal stroke, cardiac events and other vascular events (95% CI, P-value vs VKA):

- Rivaroxaban: 0.41 (0.25-0.68, P=0.0006)
- Rivaroxaban+vitamin K2: 0.34 (0.19-0.61, P=0.0003)



Safety end point:

Outcome parameter	VKA (n=44)	Rivarox (n=46)	Rivarox + vit K2 (n=42)	$P_{Cox-adj}$
Life-threatening or major bleeding	17 (30)	8 (11)	9 (12)	P=0.048
Minor bleeding	13 (19)	16 (27)	16 (22)	P=0.639
Gastrointestinal bleeding	12 (23)	9 (16)	13 (19)	P=0.478

number of patients with at least one bleeding episode (total number bleeding episodes)

Conclusion

In hemodialysis patients with AF, rivaroxaban reduced the composite of fatal and non-fatal cardiovascular events and major bleeding complications in comparison to VKA.

doi: 10.1681/ASN.2020111566

2. Do we have solid evidence for the efficacy and safety of OAC in ESRD patients with AF?

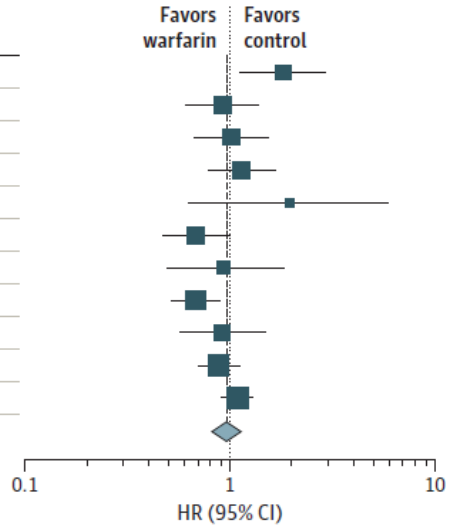
Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Renal Disease

A Systematic Review and Meta-analysis

Mandeep S. Randhawa, MD; Rohanlal Vishwanath, BSc; Manoj P. Rai, MD; Ling Wang, PhD; Amritpal K. Randhawa, MD; George Abela, MD; Gaurav Dhar, MD

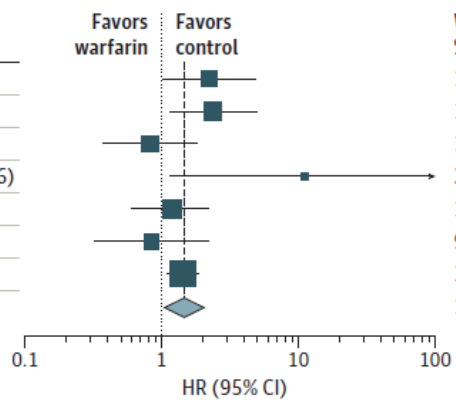
A Ischemic stroke

Source	HR (95% CI)	Weight, %
Chan et al,[8] 2009	1.81 (1.12-2.92)	7.19
Winkelmayer et al,[9] 2011	0.92 (0.61-1.37)	8.79
Chen J et al,[11] 2014	1.02 (0.67-1.53)	8.65
Shah et al,[12] 2014	1.14 (0.78-1.67)	9.39
Wakasugi et al,[13] 2014	1.94 (0.63-5.93)	1.87
Shen et al,[15] 2015	0.68 (0.47-0.99)	9.61
Garg et al,[16] 2016	0.93 (0.49-1.82)	4.61
Kai et al,[20] 2017	0.68 (0.52-0.90)	12.57
Lee et al,[22] 2017	0.92 (0.57-1.48)	7.22
Tan et al,[19] 2019	0.88 (0.70-1.11)	14.08
Yoon et al,[21] 2017	1.09 (0.90-1.28)	16.01
Overall: I^2 = 52.6%	0.96 (0.82-1.13)	100.00



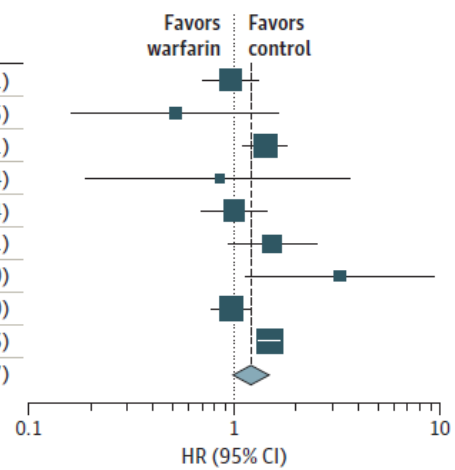
B Hemorrhagic stroke

Source	HR (95% CI)	Weight, %
Chan et al,[8] 2009	2.22 (1.01-4.91)	12.55
Winkelmayer et al,[9] 2011	2.38 (1.15-4.96)	13.98
Shen et al,[15] 2015	0.82 (0.37-1.81)	12.48
Wang et al,[17] 2016	11.11 (1.15-107.16)	2.06
Kai et al,[20] 2017	1.20 (0.60-2.20)	16.27
Lee et al,[22] 2017	0.84 (0.32-2.19)	9.39
Yoon et al,[21] 2017	1.44 (1.10-1.88)	33.26
Overall: I^2 = 37.0%	1.46 (1.05-2.04)	100.00



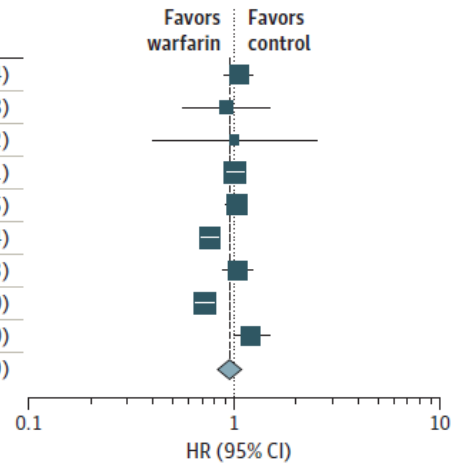
A Major bleeding

Source	HR (95% CI)	Weight, %
Winkelmayer et al,[9] 2011	0.96 (0.70-1.31)	14.60
Carrero et al,[10] 2014	0.52 (0.16-1.65)	2.62
Shah et al,[12] 2014	1.41 (1.09-1.81)	16.64
Wakasugi et al,[13] 2014	0.85 (0.19-3.64)	1.71
Shen et al,[15] 2015	1.00 (0.69-1.44)	12.87
Garg et al,[16] 2016	1.53 (0.94-2.51)	9.63
Wang et al,[17] 2016	3.26 (1.13-9.40)	3.11
Kai et al,[20] 2017	0.97 (0.77-1.20)	17.74
Tan et al,[19] 2019	1.48 (1.32-1.66)	21.08
Overall: I^2 = 66.0%	1.20 (0.99-1.47)	100.00



B Mortality

Source	HR (95% CI)	Weight, %
Winkelmayer et al,[9] 2011	1.06 (0.90-1.24)	12.65
Genovesi et al,[14] 2015	0.91 (0.56-1.48)	5.08
Wakasugi et al,[13] 2014	1.00 (0.40-2.52)	1.86
Shen et al,[15] 2015	1.01 (0.92-1.11)	14.36
Garg et al,[16] 2016	1.03 (0.91-1.15)	13.82
Kai et al,[20] 2017	0.76 (0.69-0.84)	14.26
Lee et al,[22] 2017	1.04 (0.88-1.23)	12.44
Tan et al,[19] 2019	0.72 (0.65-0.80)	14.14
Voskamp et al,[23] 2018	1.20 (1.00-1.50)	11.40
Overall: I^2 = 85.3%	0.95 (0.83-1.09)	100.00



Secondary Endpoints

	Apixaban N = 82	Warfarin N = 72
Stroke	2 (2.4%)	2 (2.8%)
Ischemic	1 (1.2%)	2 (2.8%)
Hemorrhagic	1 (1.2%)	0 (0.0%)
Systemic embolism	0 (0.0%)	0 (0.0%)
Death	21 (25.6%)	13 (18.1%)
Cardiovascular	9 (11.0%)	4 (5.6%)
Non-cardiovascular	5 (6.1%)	8 (11.1%)
Undetermined	7 (8.5%)	1 (1.4%)
Bleeding related death	1 (1.2%)	0 (0%)

- Analyses of pharmacokinetic (PK) data from 50 patients randomized to apixaban are ongoing

Venous Thromboembolism and Renal Impairment: Insights from the SWIss Venous ThromboEmbolism Registry (SWIVTER)

David Spirk, MD[1] Tim Sebastian, MD[2] Martin Banyai, MD[2] Jürg H. Beer, MD[3] Lucia Mazzolai, MD[4] Thomas Baldi, MD[5] Drahomir Aujesky, MD, MSc[6] Daniel Hayoz, MD[7] Rolf P. Engelberger, MD[7] Thomas Kaeslin, MD[8] Wolfgang Korte, MD[9] Robert Escher, MD[10] Marc Husmann, MD[2] Annette Mollet, PhD[11] Thomas D. Szucs, MD[11] Nils Kucher, MD[2]

	No severe RI $N = 1{,}822$		Severe RI $N = 240$		HR	95% CI	p^a
Mortality, *n* (%)	76	4.2	22	9.2	2.27	1.41–3.65	0.001
VTE related, *n* (%)	20	1.1	4	1.7	1.54	0.53–4.50	0.43
Bleeding related, *n* (%)	3	0.2	2	0.8	5.25	0.88–31.42	0.07
Nonfatal recurrent VTE, *n* (%)	31	1.7	4	1.7	0.98	0.35–2.77	0.97
Nonfatal recurrent PE,[b] *n* (%)	20	1.1	4	1.7	1.52	0.52–4.45	0.44
Nonfatal recurrent DVT,[b] *n* (%)	18	1.0	3	1.2	1.27	0.37–4.31	0.70
Nonfatal major bleeding, *n* (%)	33	1.8	3	1.3	0.69	0.21–2.25	0.53
Nonfatal bleeding requiring medical attention, *n* (%)	64	3.6	9	3.8	1.06	0.53–2.14	0.86
Recurrent VTE, *n* (%)	51	2.8	8	3.3	1.19	0.57–2.52	0.64
Major bleeding, *n* (%)	36	2.0	5	2.1	1.05	0.41–2.68	0.92
Bleeding requiring medical attention, *n* (%)	67	3.7	11	4.6	1.24	0.66–2.35	0.50