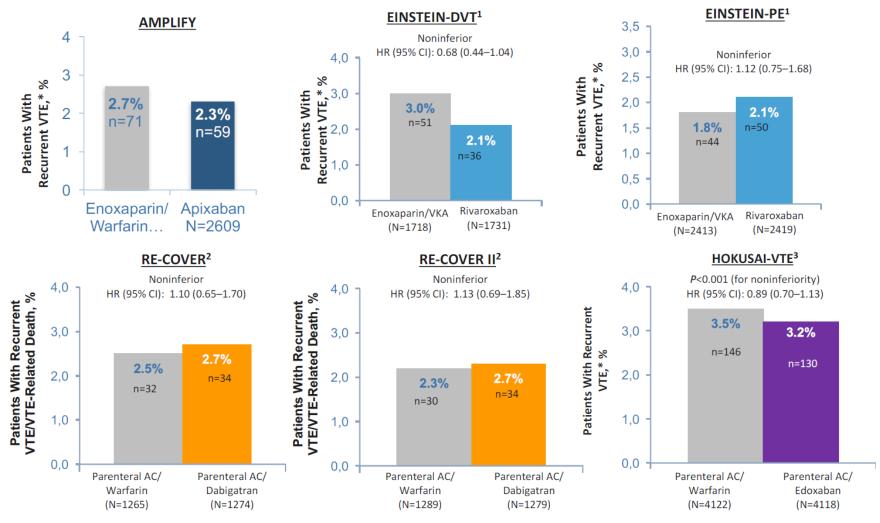
Best available evidence regarding the DOAC use in patients with Renal impairment

Parham Sadeghipour, MD
Rajaie Cardiovascular Medical and Research Center

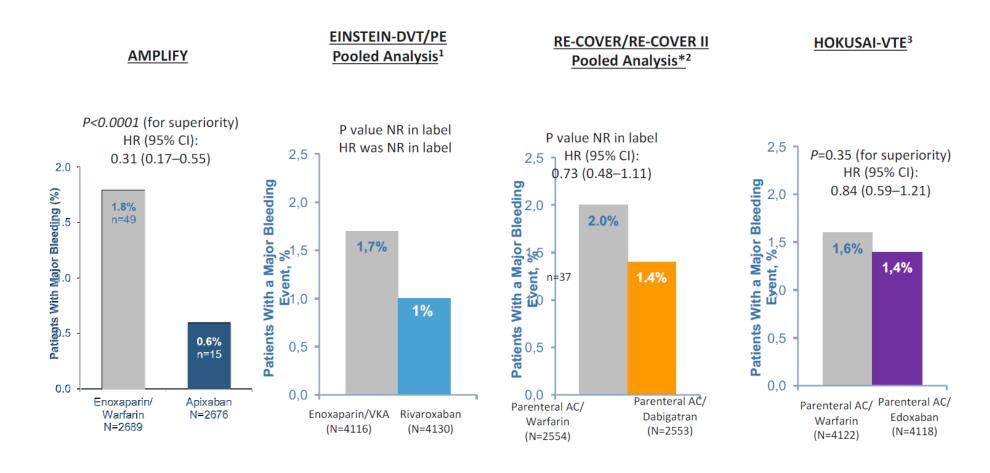
Disclosures

- 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)

	Dabiga (RE-L) 150 mg BID	A STATE OF THE STA	Apixaban (ARISTOTLE ^{4,5}) 5/2.5 mg BID	Rivaroxaban (ROCKET AF6) 20/15 mg OD	Edoxaban (ENGAGE AF-TIMI 48 ⁷) 60/30 mg OD
Stroke/SE	₹ 35%	Similar	1 21%	Similar	Similar
Ischemic stroke	↓ 24%	Similar	Similar	Similar	Similar
CV mortality	15%	Similar	Similar	Similar	1 14%
Major bleeding	Similar	1 20%	↓ 31%	Similar	₽ 20%
ICH	↓ 70%	\$ 59%	↓ 58%	↓ 33%	↓ 53%

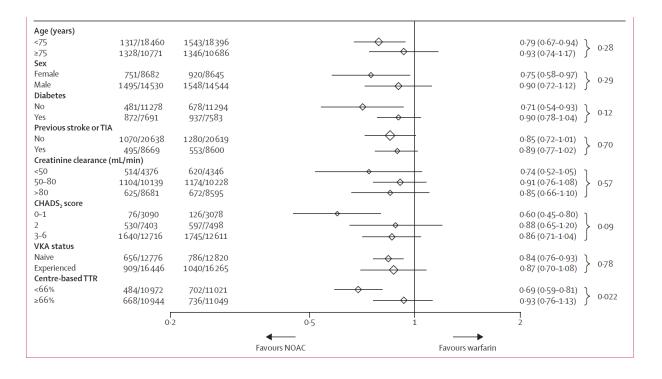


Ruff CT et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014 Mar 15;383(9921):955-62.



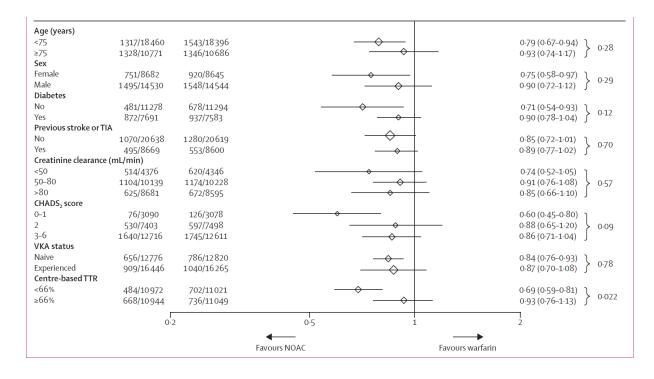
Ruff CT et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014 Mar 15;383(9921):955-62.

Α	Pooled NOAC (events)	Pooled warfarin (events)		RR (95% CI)	P _{interactio}
Age (years)					
<75	496/18073	578/18004		0.85 (0.73-0.99)	٠
≥75	415/11188	532/11095		0.85 (0.73-0.99) 0.78 (0.68-0.88)	} 0.38
Sex					
Female	382/10941	478/10839		0.78 (0.65-0.94)	١
Male	531/18371	634/18390	-	0.78 (0.65-0.94) 0.84 (0.75-0.94)	} 0.52
Diabetes	33 / 31	J ., JJ	*	.,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
No	622/20216	755/20238	\longrightarrow	0.83 (0.74-0.93))
Yes	287/9096	356/8990		0.83 (0.74-0.93) 0.80 (0.69-0.93)	0.73
Previous stroke or	TIA			(5 55)	
No	483/20699	615/20637		0.78 (0.66-0.91)	1
Yes	428/8663	495/8635	<u> </u>	0.78 (0.66-0.91) 0.86 (0.76-0.98)	0.30
Creatinine clearan		155/ = -55	Ť	(=, = = 3=,)	,
<50	249/5539	311/5503		0.79 (0.65-0.96)	1
50-80	405/13055	546/13155		0.75 (0.66-0.85)	0.12
>80	256/10626	255/10533	<u> </u>	0.98 (0.79–1.22)	
CHADS, score	,	33, 333		3 (, 5 , 7 ,	
0-1	69/5058	90/4942 ——	→	0.75 (0.54–1.04))
2	247/9563	290/9757		0.86 (0.70–1.05)	> 0.76
3-6	596/14690	733/14528		0.80 (0.72-0.89)	[","
VKA status	33-7-1-3-	7 3 3 7 - 1 3	Ť	(-,3)	
Naive	386/13789	513/13834		0.75 (0.66-0.86)	1
Experienced	522/15514	597/15395	<u> </u>	0.75 (0.66–0.86) 0.85 (0.70–1.03)	} 0.31
Centre-based TTR	3 ,-33-1		*	3 (- , 3)	
<66%	509/16219	653/16297		0.77 (0.65–0.92)	1 -
≥66%	313/12642	392/12904		0.82 (0.71–0.95)	} 0.60
		0.5	1	2	



Ruff CT et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014 Mar 15;383(9921):955-62.

Α	Pooled NOAC (events)	Pooled warfarin (events)		RR (95% CI) p _{inte}
Age (years)				
<75	496/18073	578/18004		0.85 (0.73-0.99)
≥75	415/11188	532/11095		0.85 (0.73-0.99) 0.78 (0.68-0.88) } 0.3
Sex				
Female	382/10941	478/10839		0.78 (0.65-0.94)
Male	531/18371	634/18390		0.78 (0.65-0.94) 0.84 (0.75-0.94) } 0.5
Diabetes			·	1, 12 - 1, 1
No	622/20216	755/20238		0.83 (0.74-0.93)
Yes	287/9096	356/8990		0.83 (0.74-0.93) 0.80 (0.69-0.93) } 0.7
Previous stroke or		55 , 55	·	(3 33,)
No	483/20699	615/20637		0.78 (0.66-0.91)
Yes	428/8663	495/8635		0.78 (0.66-0.91) 0.86 (0.76-0.98) } 0.3
Creatinine clearand	ce (mL/min)	1557 55	•	(, , , ,
<50	249/5539	311/5503		0·79 (0·65-0·96))
50-80	405/13055	546/13155		0.75 (0.66-0.85) > 0.1
>80	256/10626	255/10533	<u> </u>	0.98 (0.79–1.22)
CHADS, score				
0-1	69/5058	90/4942 ——	→	0·75 (0·54−1·04))
2	247/9563	290/9757		0.86 (0.70-1.05) > 0.7
3-6	596/14690	733/14528		0.80 (0.72-0.89)
VKA status		, , , , , ,	·	(, , , , ,
Naive	386/13789	513/13834		0.75 (0.66-0.86)
Experienced	522/15514	597/15395	· •	0.75 (0.66-0.86) 0.85 (0.70-1.03) } 0.3
Centre-based TTR			·	5 (· · · · · · · · · · · · · · · · · ·
<66%	509/16219	653/16297		0.77 (0.65-0.92)
≥66%	313/12642	392/12904		0.77 (0.65-0.92) 0.82 (0.71-0.95) } 0.6
	'		·	
		0.5	1	2



Ruff CT et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014 Mar 15;383(9921):955-62.

	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)

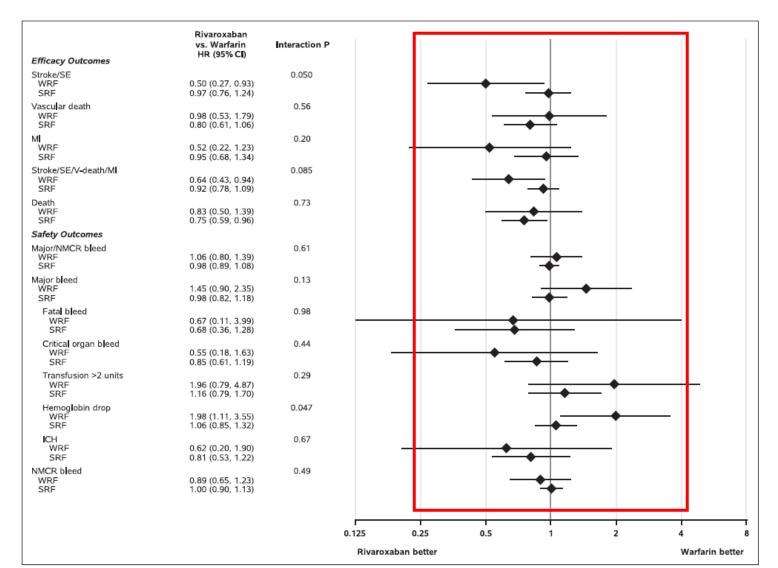
Efficacy and Safety of Dabigatran Compared With Warfarin in Relation to Baseline Renal Function in Patients With Atrial Fibrillation

A RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) Trial Analysis

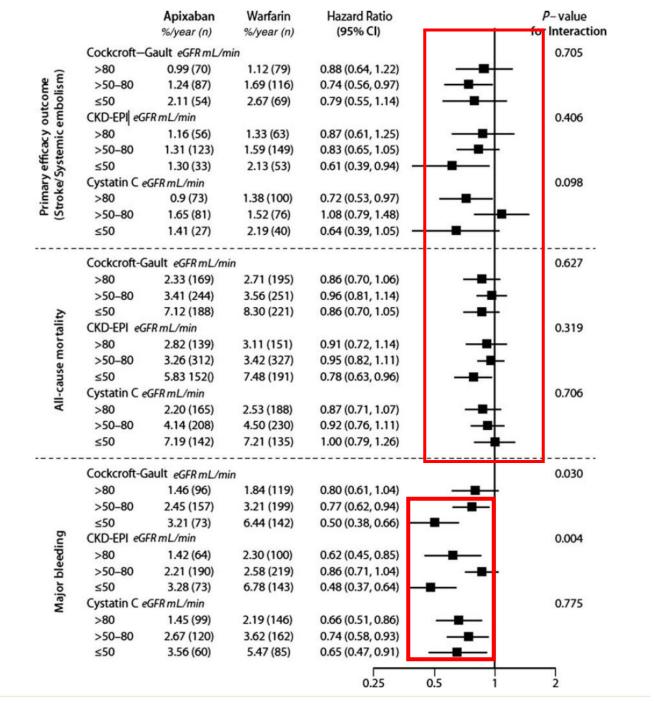
		Events, n (%/y)		Dabigatran 11 BID vs Warfa		Dabigatran 15 BID vs Warfa	-	Dabigatran 15 Dabigatran 110	
Outcome According to Renal Function Level (in mL/min)	Dabigatran 110 mg BID Events/n (%/y)	Dabigatran 150 mg BID Events/n (%/y)	Warfarin Events/n (%/y)	HR (95% CI)	P Value (Inter)	HR (95% CI)	P Value (Inter)	HR (95% CI)	P Value (Inter)
Stroke or systemic embolism									0.8337
≥80	35/1958 (0.88)	28/1945 (0.71)	41/1941 (1.05)	0.84 (0.54-1.32)	0.9108	0.67 (0.42-1.09)	0.7522	0.80 (0.49-1.32)	
50 to <80	94/2803 (1.69)	70/2852 (1.25)	103/2898 (1.83)	0.93 (0.70-1.23)		0.68 (0.50-0.92)		0.73 (0.54-1.00)	
<50	52/1196 (2.32)	36/1232 (1.53)	57/1126 (2.70)	0.85 (0.59-1.24)		0.56 (0.37-0.85)		0.66 (0.43-1.01)	
All-cause mortality									0.1941
≥80	89/1958 (2.24)	81/1945 (2.04)	97/1941 (2.48)	0.90 (0.68-1.20)	0.0074	0.82 (0.61-1.11)	0.3610	0.91 (0.68-1.23)	
50 to <80	175/2803 (3.15)	198/2852 (3.53)	244/2898 (4.32)	0.72 (0.60-0.88)		0.81 (0.67-0.98)		1.12 (0.91-1.37)	
<50	176/1196 (7.86)	159/1232 (6.77)	143/1126 (6.77)	1.16 (0.93-1.44)		1.00 (0.80-1.25)		0.86 (0.69-1.07)	
Major bleed									0.3439
≥80	59/1958 (1.48)	81/1945 (2.04)	95/1941 (2.43)	0.61 (0.44-0.84)	0.0607	0.84 (0.62-1.13)	0.6393	1.38 (0.99–1.93)	
50 to <80	158/2803 (2.84)	188/2852 (3.35)	209/2898 (3.70)	0.76 (0.62–0.94)		0.91 (0.75–1.11)		1.19 (0.96–1.47)	
<50	122/1196 (5.45)	129/1232 (5.50)	116/1126 (5.49)	0.99 (0.77–1.28)		1.01 (0.79–1.30)		1.02 (0.79–1.30)	
Life-threatening bleed									0.2565
≥80	17/1958 (0.43)	31/1945 (0.78)	50/1941 (1.28)	0.33 (0.19–0.58)	0.0169	0.61 (0.39-0.95)	0.4254	1.83 (1.01-3.30)	
50 to <80	74/2803 (1.33)	87/2852 (1.55)	107/2898 (1.90)	0.70 (0.52–0.94)		0.82 (0.62-1.08)		1.17 (0.86–1.59)	
<50	56/1196 (2.50)	60/1232 (2.56)	61/1126 (2.89)	0.86 (0.60-1.24)		0.88 (0.62-1.26)		1.02 (0.71–1.47)	
Intracranial bleed									0.2113
≥80	2/1958 (0.05)	7/1945 (0.18)	15/1941 (0.38)	0.13 (0.03–0.57)	0.4022	0.46 (0.19–1.13)	0.6930	3.52 (0.73–16.92)	
50 to <80	14/2803 (0.25)	22/2852 (0.39)	49/2898 (0.87)	0.29 (0.16-0.52)		0.45 (0.27-0.74)		1.56 (0.80-3.05)	
<50	11/1196 (0.49)	9/1232 (0.38)	26/1126 (1.23)	0.40 (0.20-0.80)		0.31 (0.14-0.66)		0.78 (0.32-1.88)	
Net clinical benefit*									
≥80	186/1958 (4.68)	182/1945 (4.59)	207/1941 (5.29)	0.88 (0.72–1.07)	0.1252	0.87 (0.71–1.06)	0.8534	0.98 (0.80-1.20)	0.3042
50 to <80	376/2803 (6.77)	396/2852 (7.05)	453/2898 (8.03)	0.84 (0.73–0.96)		0.88 (0.77–1.01)		1.05 (0.91–1.21)	
<50	291/1196 (12.99)	269/1232 (11.46)	260/1126 (12.31	1.05 (0.89–1.24)		0.93 (0.78-1.10)		0.88 (0.75-1.04)	

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

Insights From ROCKET AF

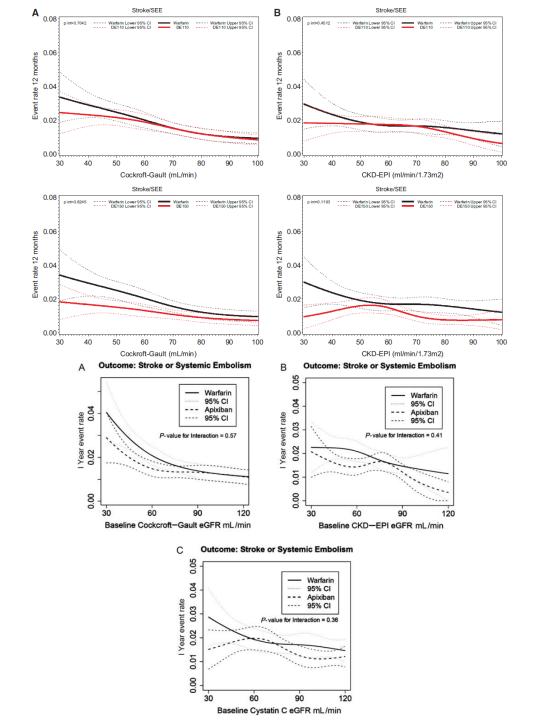


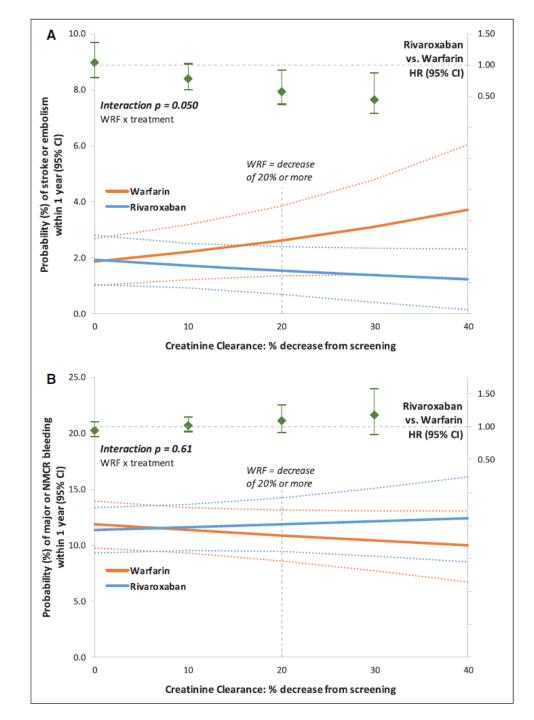
Efficacy of apixaban when compared with warfarin in relation to renal function in patien with atrial fibrillation: insights from the ARISTOTLE trial



Definition of CKD

Method	Equation	Additional Variables
Cockroft and Gault	$GFR\;(ml/min)\;=\frac{(140-age)\timesweight\;(kg)}{7.2\timesSCr\;(mg/dl)}$	\times 0.085 if female
MDRD 4-Variable study equation	$GFR \; (ml \; /min/1.73 \; m^2) \; = \; 186 \times \; SCr \; (mg/dl)^{-1.154} \times \; age^{-0.203} \times \; 0.742 \; (if \; female)$	× 1.21 if Black-American × 0.763 if Japanese × 1.233 if Chinese
MDRD 4-Variable study equation (IDMS traceable)	$\label{eq:GFR} \text{GFR } (\text{ml /min}/\text{1.73 m}^2) \ = \ 175 \times \text{SCr } \left(\text{mg/dl}\right)^{-1.154} \times \text{age}^{-0.203} \times 0.742 \left(\text{if female}\right)$	× 1.21 if Black-American × 0.763 if Japanese × 1.233 if Chinese
CKD – EPI creatinine equation	$\begin{aligned} \text{GFR} &= 141 \times \text{min} \bigg(\frac{\text{SCr}}{\kappa}, 1 \bigg)^{\alpha} \times \text{max} \bigg(\frac{\text{SCr}}{\kappa}, 1 \bigg)^{-1209} \times 0.993^{age} \\ \alpha &= \text{-0.329 if female, -0.411 if male} \end{aligned}$	× 1.018 if female × 1.159 if Black
	$\kappa = 0.7$ if female, 0.9 if male min = the minimum of $\frac{SCr}{\kappa}$ or 1	
	max = the maximum of $\frac{\overset{\kappa}{SCr}}{\kappa}$ or 1	





Accepted Manuscript

Variability In NOAC Dose Adjustment In Atrial Fibrillation Patients With Renal Dysfunction: The Influence Of Renal Function Estimation Formulae

Jason G. Andrade, MD, Nathaniel M. Hawkins, MD, Christopher B. Fordyce, MD MHS MSc, Marc W. Deyell, MSc MD, Lee Er, Ognjenka Djurdjev, Laurent Macle, MD, Sean A. Virani, MD MSc MPH, Adeera Levin, MD



18,209 adult non-dialysis CKD patients alive between January 1 2011 and January 1 2014

17,145 patients with CKD but no documented atrial fibrillation

1,064 patients with CKD and documented atrial fibrillation

203 patients excluded
due to lack of creatinine within 6m
1002 patients excluded
due to follow-up duration <4m
98 patients excluded
due to pre-emptive transplant

3 patients excluded due to lack of creatinine within 6m 41 patients excluded due to lack of weight data 189 patients excluded due to AF documentation only after transition to dialysis

15,842 patients with CKD but no documented atrial fibrillation

Primary Cohort

831 patients with CKD and documented atrial fibrillation

		MDRD		
CG	<30	30-50	>50	Total
<30	318	60	3	381 (46%)
30-50	110	167	14	291 (35%)
>50	14	100	45	159 (19%)
Total	442 (53%)	327 (39%)	62 (7%)	831

Agreement=63.8% [95% CI: 59.6%, 67.7%]

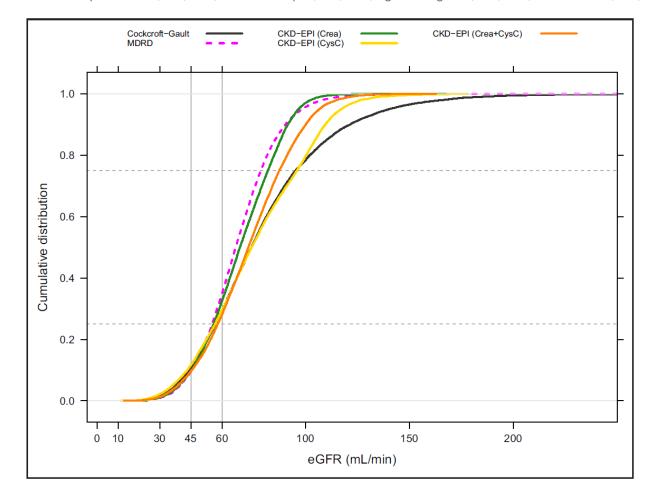
Under-treated=26.9% [95% CI: 23.3%, 30.9%]

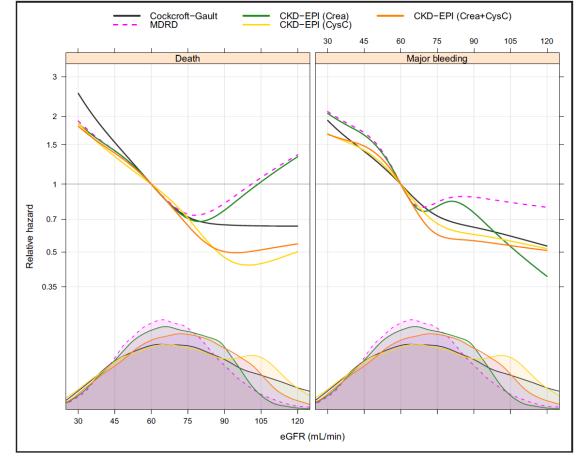
Over-treated=9.3% [95% CI: 7.1%, 12.0%]

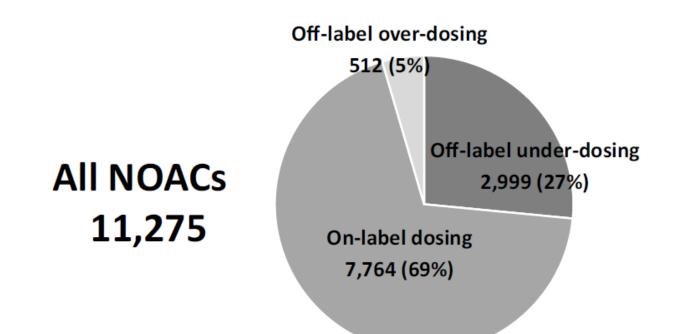
ORIGINAL RESEARCH

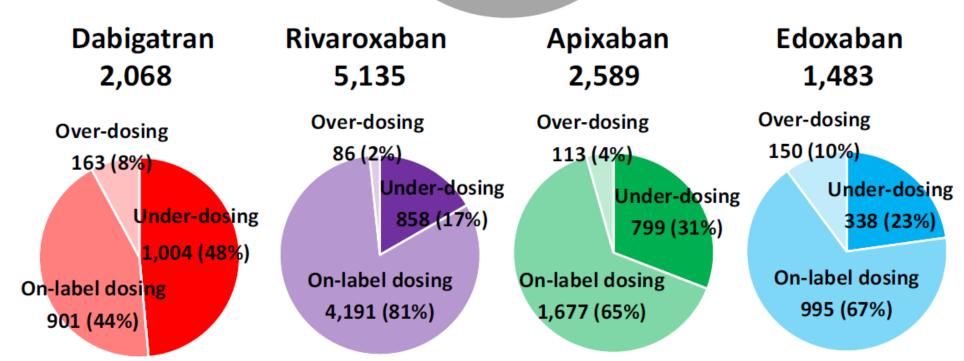
Association of Different Estimates of Renal Function With Cardiovascular Mortality and Bleeding in Atrial Fibrillation

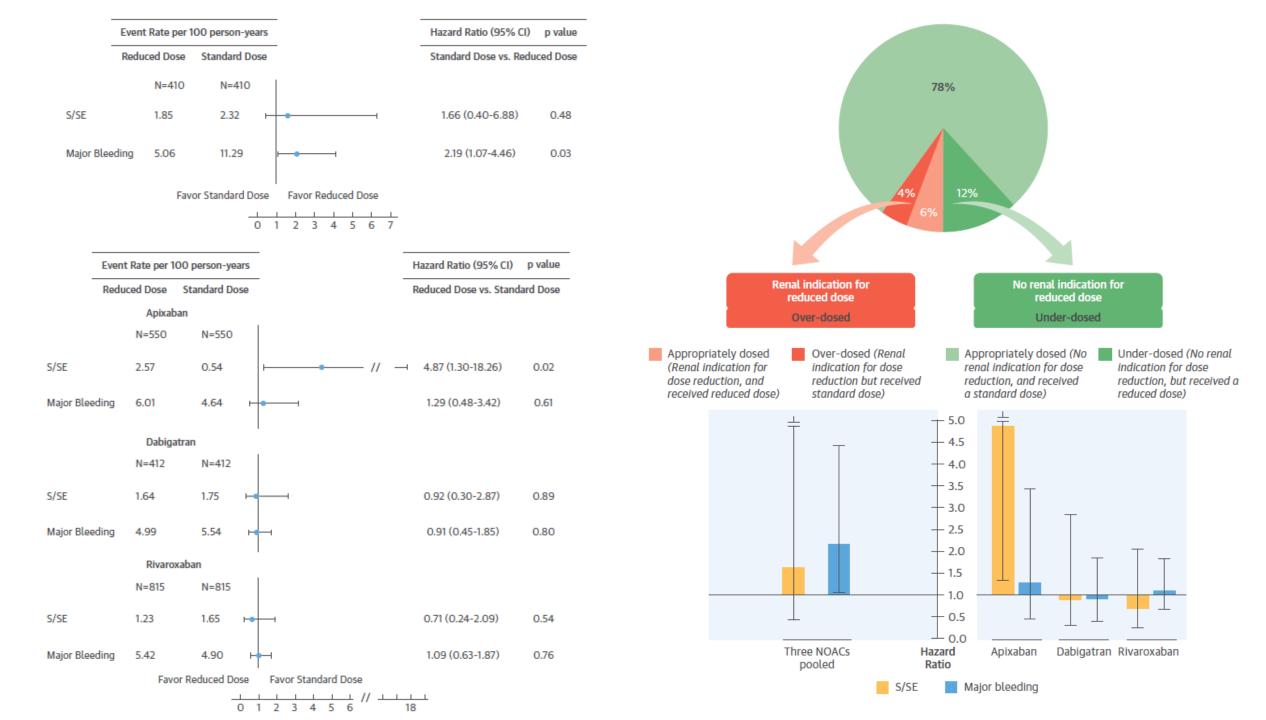
Ziad Hijazi , MD, PhD; Christopher B. Granger, MD; Stefan H. Hohnloser , MD; Johan Westerbergh, MSc; Johan Lindbäck , MSc; John H. Alexander , MD, MHS; Matyas Keltai, MD, DSc; Alexander Parkhomenko, MD, PhD; José L. López-Sendón, MD, PhD; Renato D. Lopes, MD, PhD; Agneta Siegbahn, MD, PhD; Lars Wallentin, MD, PhD



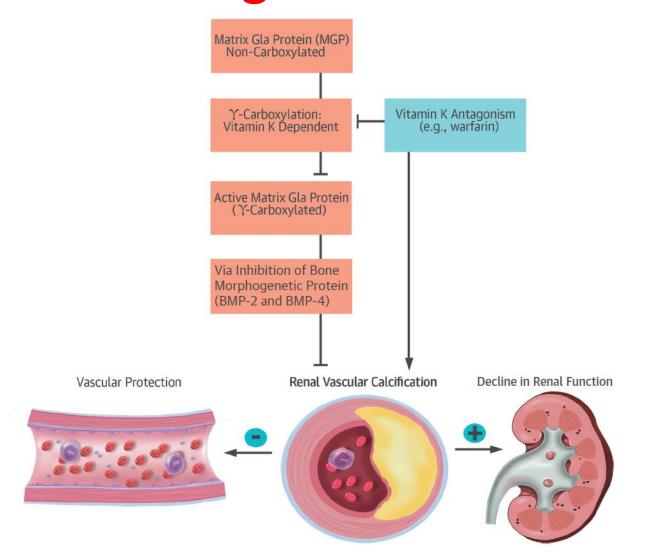


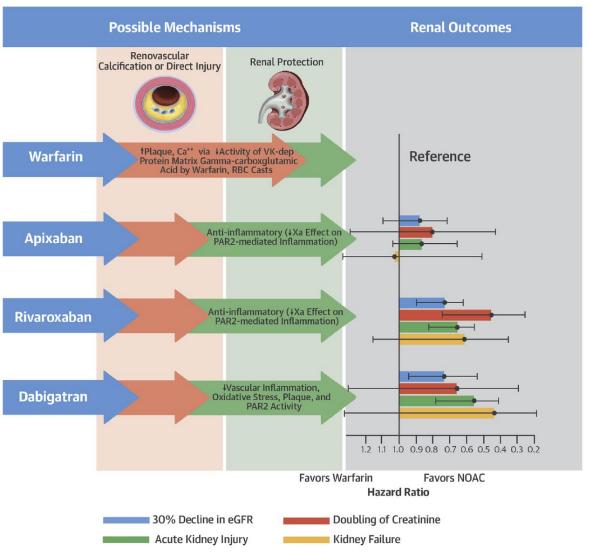




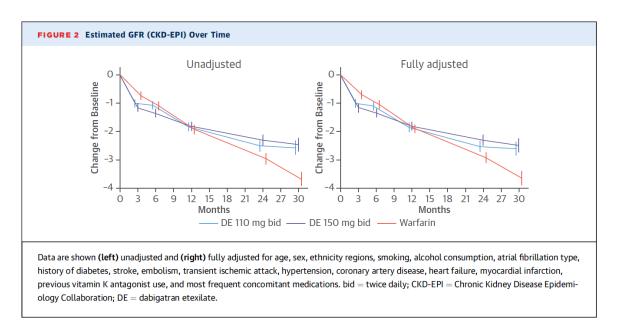


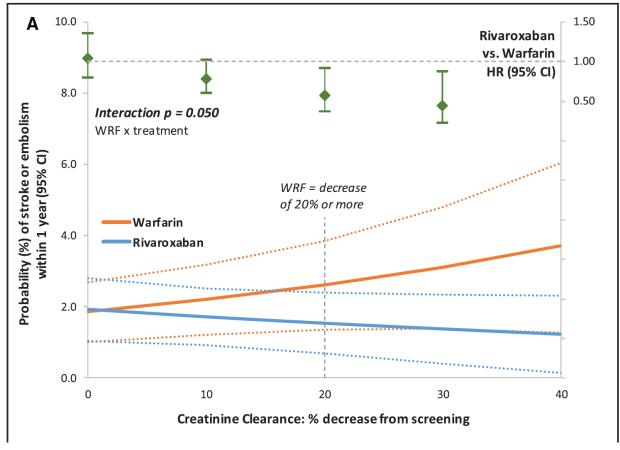
Renal monitoring in patients taking anticoagulation





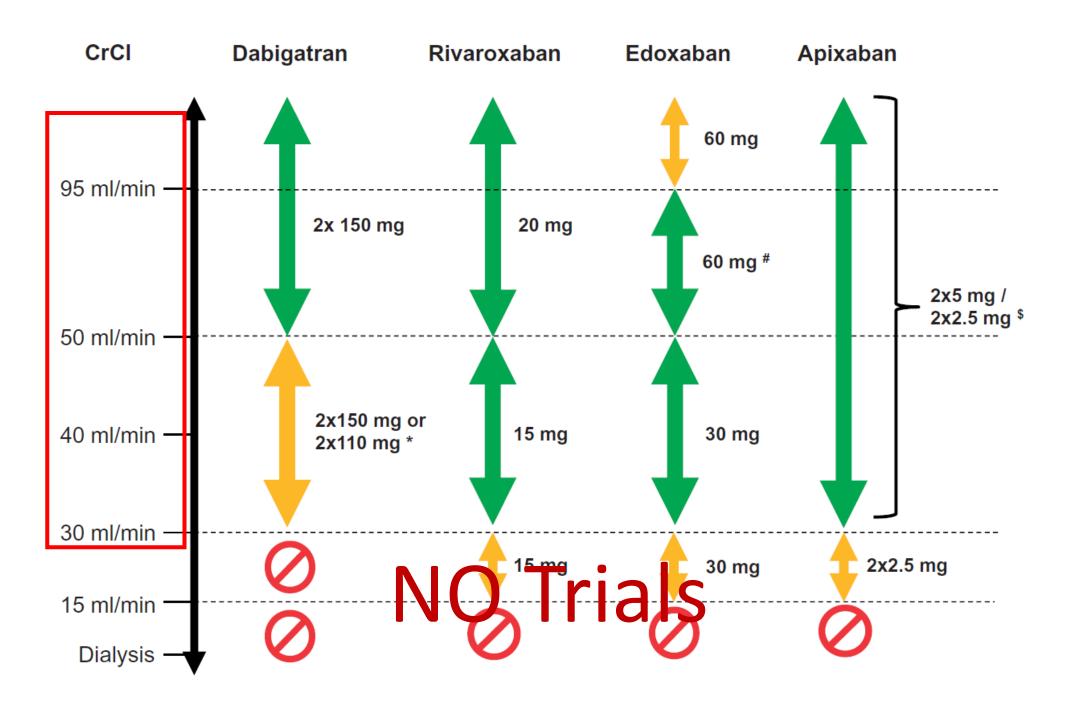
Renal monitoring in patients taking anticoagulation





Böhm et al. Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial. J Am Coll Cardiol. 2015 Jun 16;65(23):2481-93.

Fordyce et al.. On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin: Insights From ROCKET AF. Circulation. 2016 Jul 5;134(1):37-47



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

Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

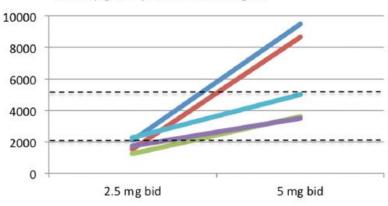
Table 2. PK parameters of apixaban after administration of 5 mg twice daily for a week and comparison with expected levels in the general population

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	_

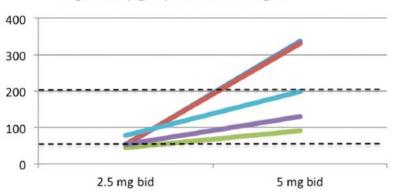
This table shows the PK parameters of apixaban 5 mg twice daily at steady state (day 8). Results are presented as mean \pm coefficient of variation (range), median (10th–90th percentile), or median (5th–95th percentile). For AUC₀₋₁₂, the geometric mean (in brackets) is also depicted. P values are comparing 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.

*Median (5th–95th percentile).

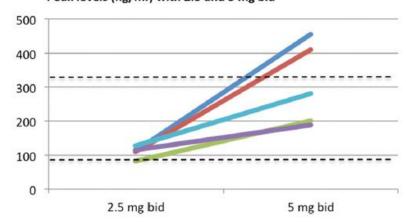
AUCss (ng.h/ml) with 2.5 and 5 mg bid



Trough levels (ng/ml) with 2.5 and 5 mg bid



Peak levels (ng/ml) with 2.5 and 5 mg bid

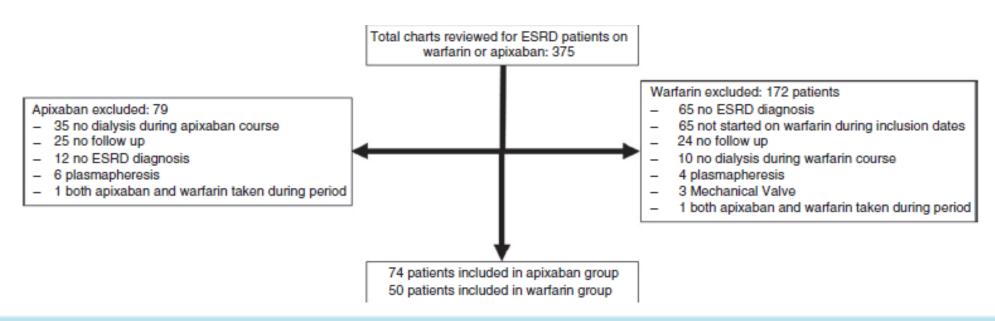


Limitations of pharmacokinetics study

- Small sample sizes
- Ideal patients with few comorbidities



Safety and effectiveness of apixaban compared to warfarin in dialysis patients



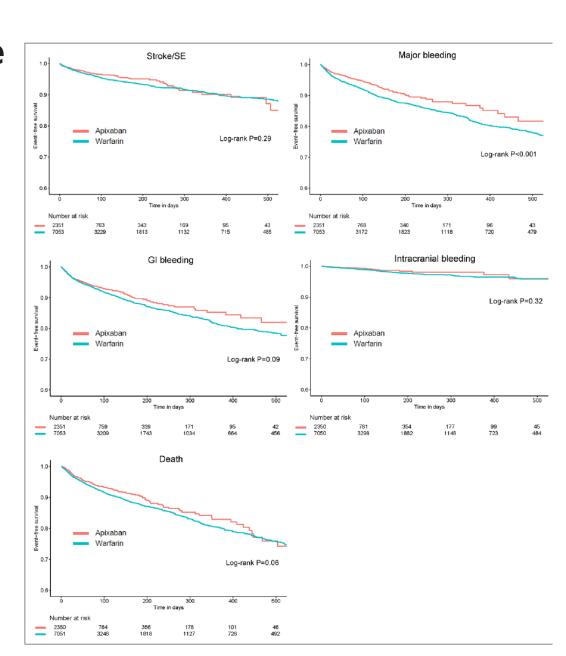
Characteristic	Apixaban	Warfarin	P-value
Bleeding event			
Any	14 (18.9%)	21 (42%)	.01
Major (among all patients)	4 (5.4%)	11 (22%)	.01
Recurrent venous thromboembolism*	2 (4.4%)	6 (28.6%)	.99

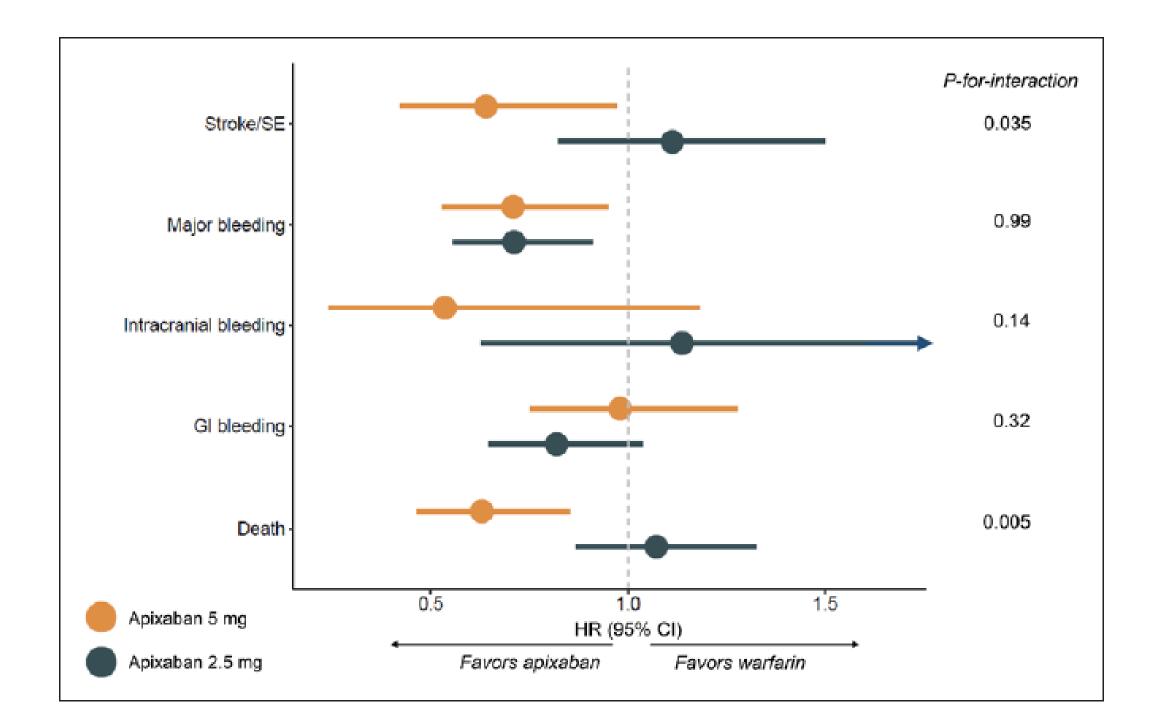
ORIGINAL RESEARCH ARTICLE



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

Outcome	Overall	Anivahan	Warfarin	Hazard Ratio (95% CI)	P Value
	Overall	Apixaban	vvariarin	(95% CI)	P value
Stroke/systemic embolism				I	T.
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		





Original Study Design

Selected inclusion criteria

- Atrial fibrillation
- CHA2DS2-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





Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: Meta-analysis

Ronpichai Chokesuwattanaskul ¹, Charat Thongprayoon ², Tanyanan Tanawuttiwat ³, Wisit Kaewput ⁴, Pavida Pachariyanon ⁵, Wisit Cheungpasitporn ⁶

Affiliations + expand

PMID: 29577340 DOI: 10.1111/pace.13331

Erratum in

Erratum.

[No authors listed]

Pacing Clin Electrophysiol. 2018 Jul;41(7):879. doi: 10.1111/pace.13431.

PMID: 31651055 No abstract available.

Abstract

Background: At the present, apixaban is the only nonvitamin K oral anticoagulant approved by the Food and Drug Administration for use with patients with creatinine clearance <15 mL/min or end-stage renal disease (ESRD). However, the recommendations are based on pharmacokinetic and pharmacodynamic data and there was lack of clinical trial evidence. We aimed to assess safety and efficacy of apixaban in patients with advanced chronic kidney disease (CKD) or ESRD.

Methods: Databases were searched through November 2017. Studies that reported incidence or odd ratios of bleeding complications or thromboembolic events in the use of apixaban in patients with CKD stage 4-5 or ESRD on dialysis were included. Effect estimates from the individual study were extracted and combined using random-effect, generic inverse variance method of DerSimonian and laird.

Results: Five studies were included into the analysis consisting of 43,850 patients in observational cohort studies. The majority of patients (87%) used apixaban for atrial fibrillation. The pooled estimated incidence of any bleeding complications on apixaban was 17.4% (95% confidence interval [CI]: 13.0%-23.0%). Compared to warfarin, apixaban was significantly associated with reduced risk of major bleeding (pooled odds ratio [OR], 0.42; 95% CI, 0.28-0.61). In studies in ESRD patients on dialysis, the pooled OR of major bleeding was 0.27 (95% CI, 0.07-0.95). There was no significant difference in risk of thromboembolic events in advanced CKD or ESRD patients on apixaban versus vitamin K antagonists (pooled OR, 0.56; 95% CI, 0.23-1.39).

Conclusions: Among patients with advanced CKD and ESRD, the use of apixaban was associated with lower risk of major bleeding compared to warfarin, and was found to be relatively effective with no excess risk of thromboembolic events.

A) Incidence of major bleeding in advanced CKD and/or ESRD on dialysis

Study name	Sta	tistics fo	or each s	tudy	Event rate and 95% CI
	Event rate	Lower limit	Upper limit	p-Value	Relative
Sarratt et al	0.012	0.001	0.167	0.002	3.93
Day et al	0.133	0.051	0.306	0.000	22.95
Stanton et al	0.096	0.046	0.188	0.000	■ 36.09
Steuber et al	0.061	0.030	0.123	0.000	37.03
	0.082	0.043	0.135	0.000	•
					-0.50 -0.25 0.00 0.25 0.50 No Bleeding Bleeding

B) Risk of bleeding in advanced CKD and/or ESRD on dialysis

Study name	Statistics for each study					Odds ra	P.			
	Odda ratio	Lower	Upper	p-Value						Relative
Sarratt et al	0.19	9.01	3.35	0.25	-		-	- 1	- 1	1.84
Stanton et al	0.49	9.18	1.31	0.15	- 1	1	-		- 1	19.00
No seworthy et al	0.41	9.27	0.03	0.00		- 3		- 1	- 1	82.30
	0.42	9.20	0.81	0.00			•			
					0.01	0.1	1	10	100	
					W	/arfarin	22	Apixab	an	

C) Risk of bleeding in ESRD on dialysis

Study name	St	atistics f	or each	tudy		Odda n	ACCRECATE VALUE OF THE PARTY OF			
	Odds	Lower	Upper	p-Value						Relative
Sarratt et al	0.15	0.01	3.55	0.25	1		-	- 1	- 1	1933
No seworthy et al	0.29	0.07	1.19	0.09		+	-			89.07
	0.27	0.07	0.95	0.04	1	-		- 1	- 12	
					0.01	0.1		10	100	
					144	arfaria.		Aniva	han	

Accepted Manuscript

Stroke, Major Bleeding and Mortality Outcomes in Warfarin Users with Atrial Fibrillation and Chronic Kidney Disease: A Meta-analysis of Observational Studies

Khagendra Dahal, MD, Sumit Kunwar, MD, Jharendra Rijal, MD, Peter Schulman, MD, Juyong Lee, MD, PHD



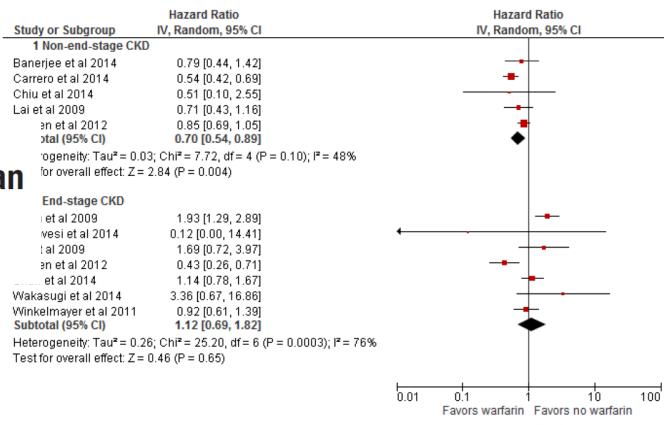
Efficacy and Safety of Dabigatran Compared With Warfarin in Relation to Baseline Renal Function in Patients With Atrial Fibrillation

A RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy)
Trial Analysis

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 patients with atrial fibrillation: insights from the ARISTOTLE trial



Original Investigation | Cardiology

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)	Favors warfarin	Favors control	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)	_	<u> </u>	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: 1 ² = 52.6%	0.96 (0.82-1.13)	_		100.00
			 	
		0.1	1	10
		HR (9	5% CI)	

B Hemorrhagic stroke

Source	HR (95% CI)	Favors Favors warfarin control	Weight, %
Chan et al,8 2009	2.22 (1.01-4.91)	1	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: 12 = 37.0%	1.46 (1.05-2.04)	\Diamond	100.00
	0.1	1 1(0 100
		HR (95% CI)	

A Major bleeding

Source	HR (95% CI)	Favors Favors warfarin control	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: 1 ² = 66.0%	1.20 (0.99-1.47)	♦	100.00
	0.1	1 HR (95% CI)	10

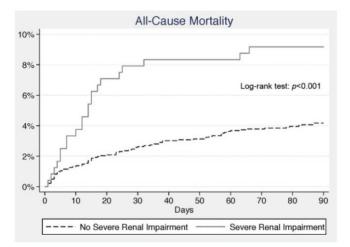
B Mortality

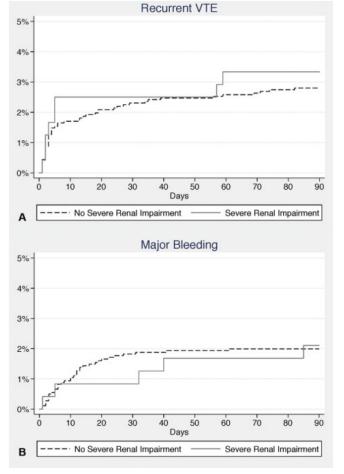
Source	HR (95% CI)	Favors Favors warfarin control	Weight, %
Winkelmayer et al, ⁹ 2011	1.06 (0.90-1.24)	=	12.65
Genovesi et al, ¹⁴ 2015	0.91 (0.56-1.48)	_	5.08
Wakasugi et al, ¹³ 2014	1.00 (0.40-2.52)		1.86
Shen et al, ¹⁵ 2015	1.01 (0.92-1.11)		14.36
Garg et al, 16 2016	1.03 (0.91-1.15)	į.	13.82
Kai et 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: 12 = 85.3%	0.95 (0.83-1.09)	\	100.00
	0.1	1	10
		HR (95% CI)	

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

David Spirk, MD¹ Tim Sebastian, MD² Martin Banyai, MD² Jürg H. Beer, MD³ Lucia Mazzolai, MD⁴ Thomas Baldi, MD⁵ Drahomir Aujesky, MD, MSc⁶ Daniel Hayoz, MD⁷ Rolf P. Engelberger, MD⁷ Thomas Kaeslin, MD⁸ Wolfgang Korte, MD⁹ Robert Escher, MD¹⁰ Marc Husmann, MD² Annette Mollet, PhD¹¹ Thomas D. Szucs, MD¹¹ Nils Kucher, MD²

		No severe RI N = 1,822		Severe RI N=240		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, 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	

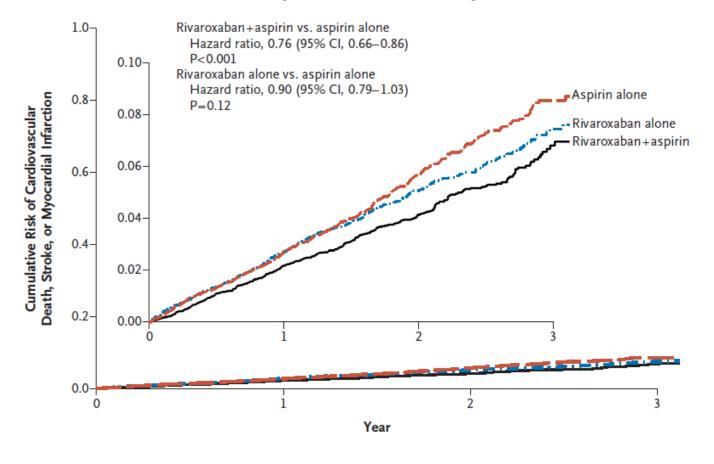




Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

COMPASS Trial

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A.K. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*



No. at Risk				
Aspirin alone	9126	7808	3860	669
Rivaroxaban alone	9117	7824	3862	670
Rivaroxaban+aspirin	9152	7904	3912	658

Characteristic	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Subgroup	Rivaroxaban+ Aspirin no. of even	Aspirin Alone ts/total no. (%)		Ratio for Cardiovascular Death, or Myocardial Infarction (95% CI)	P Value Interact
Coronary artery disease — no. (%)‡	8313 (90.8)	8250 (90.5)	8261 (90.5)	All participants	379/9152 (4.1)	496/9126 (5.4)	-	0.76 (0.66–0.86	
Peripheral arterial disease — no. (%)∫	2492 (27.2)	2474 (27.1)	2504 (27.4)	Age <65 yr	79/2150 (3.7)	126/2184 (5.8)		0.63 (0.48–0.84	0.20
Estimated GFR — no. (%)¶	()	()	()	65–74 yr ≥75 yr	179/5078 (3.5) 121/1924 (6.3)	238/5045 (4.7) 132/1897 (7)		0.74 (0.61–0.90 0.89 (0.69–1.14)
<30 ml/min	77 (0.8)	80 (0.9)	86 (0.9)	Sex	121/1724 (0.5)	132/1037 (7)	_	0.05 (0.05 1.14	0.75
· ·	, ,	, ,	` ′	Male	300/7093 (4.2)	393/7137 (5.5)	-	0.76 (0.66–0.89	
30 to <60 ml/min	1977 (21.6)	2028 (22.2)	2028 (22.2)	Female Geographic region	79/2059 (3.8)	103/1989 (5.2)		0.72 (0.54–0.97) 0.56
≥60 ml/min	7094 (77.5)	7005 (76.8)	7012 (76.8)	North America	63/1304 (4.8)	80/1309 (6.1)		0.78 (0.56–1.08	
,	,	()	()	South America	93/2054 (4.5)	111/2054 (5.4)		0.84 (0.63–1.10	
Race — no. (%)				Western Europe	117/2855 (4.1)	141/2855 (4.9)		0.82 (0.64–1.05	•
White	5673 (62.0)	5672 (62.2)	5682 (62.3)	Eastern Europe Asia-Pacific	59/1607 (3.7) 47/1332 (3.5)	90/1604 (5.6) 74/1304 (5.7)		0.65 (0.46-0.90 0.62 (0.43-0.89	
Black	76 (0.8)	04 (1.0)	02 (1.0)	Race	47/1332 (3.3)	74/1504 (5.7)		0.02 (0.43 0.03	0.37
ыаск	76 (0.8)	94 (1.0)	92 (1.0)	White	235/5673 (4.1)	306/5682 (5.4)	-	0.76 (0.64-0.90	
Asian	1451 (15.9)	1421 (15.6)	1397 (15.3)	Black	2/76 (2.6)	8/92 (8.7)	4	0.30 (0.06–1.46	
Other	1952 (21.3)	1930 (21.2)	1955 (21.4)	Asian Other	54/1451 (3.7)	81/1397 (5.8)		0.64 (0.45-0.90	•
Otilei	1932 (21.3)	1930 (21.2)	1933 (21.4)	Body weight	88/1952 (4.5)	101/1955 (5.2)		0.87 (0.65–1.16	0.64
Geographic region — no. (%)				≤60 kg	41/901 (4.6)	45/836 (5.4)		0.83 (0.55–1.27	
North America	1304 (14.2)	1305 (14.3)	1309 (14.3)	>60 kg	335/8241 (4.1)	448/8285 (5.4)		0.75 (0.65–0.86	
	, ,	` '	` ,	Estimated GFR	122/2054 (6.4)	177/2114 (0.4)		0.75 (0.00 0.04	0.95
South America	2054 (22.4)	2036 (22.3)	2054 (22.5)	<60 ml/min ≥60 ml/min	132/2054 (6.4) 247/7094 (3.5)	177/2114 (8.4) 319/7012 (4.5)		0.75 (0.60–0.94 0.76 (0.64–0.90	•
Western Europe, Israel, Australia,	2855 (31.2)	2845 (31.2)	2855 (31.3)	Baseline tobacco use	247/7054 (5.5)	313/7012 (4.3)		1	0.29
or South Africa	2000 (01.2)	20 10 (31.2)	2000 (01.0)	Yes	80/1944 (4.1)	122/1972 (6.2)		0.66 (0.50-0.88)
				No	299/7208 (4.1)	374/7154 (5.2)		0.79 (0.68–0.92	•
Eastern Europe	1607 (17.6)	1612 (17.7)	1604 (17.6)	Baseline diabetes Yes	179/3448 (5.2)	239/3474 (6.9)		0.74 (0.61–0.90	0.77
Asia-Pacific	1332 (14.6)	1319 (14.5)	1304 (14.3)	No	200/5704 (3.5)	257/5652 (4.5)		0.77 (0.64–0.93	
			()	History of hypertension	, , ,	, , ,			0.68
Medication — no. (%)				Yes	317/6907 (4.6)	409/6877 (5.9)	-	0.76 (0.66–0.89	•
ACE inhibitor or ARB	6475 (70.7)	6581 (72.2)	6462 (70.8)	No	62/2245 (2.8)	87/2249 (3.9)		0.71 (0.51–0.98	•
Calcium-channel blocker	, ,			Baseline dyslipidemia Yes	325/8239 (3.9)	428/8158 (5.2)		0.74 (0.64–0.86	0.47
Calcium-channel blocker	2413 (26.4)	2374 (26.0)	2482 (27.2)	No	54/913 (5.9)	68/968 (7)		0.85 (0.60–1.22	•
Diuretic	2727 (29.8)	2666 (29.2)	2746 (30.1)	Coronary artery disease					0.47
Beta-blocker	6389 (69.8)	6401 (70.2)	6394 (70.1)	Yes	347/8313 (4.2)	460/8261 (5.6)	-	0.74 (0.65–0.86	-
	,		, ,	No Peripheral arterial disease	32/839 (3.8)	36/865 (4.2)	-	0.89 (0.55–1.43) 0.61
Lipid-lowering agent	8239 (90.0)	8204 (90.0)	8158 (89.4)	Yes	126/2492 (5.1)	174/2504 (6.9)		0.72 (0.57–0.90	
NSAID	531 (5.8)	466 (5.1)	473 (5.2)	No	253/6660 (3.8)	322/6622 (4.9)	_	0.77 (0.66–0.91)
Nontrial PPI	3268 (35.7)	3266 (35.8)	3264 (35.8)				0.5	2.0	
	(55)	(55.5)	(55.5)				Rivaroxaban+	Aspirin Alone	

Aspirin Better

Better