Why Does Kidney Matter: New Insight from RENOVATOR study

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Disclosure

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Abbott, Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daewoong Pharmaceutical Co., Daiichi-Sankyo, DeepQure, Dreamtech Co., Ltd., Jeil Pharmaceutical Co. Ltd, Medtronic, Samjinpharm, Seers Technology, and Skylabs.
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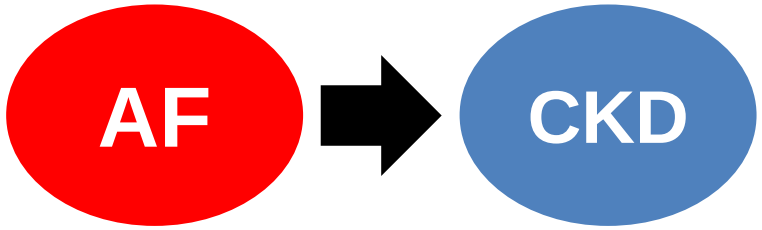
AF and CKD



Outcome	Studies	Relative risk (95% CI)	I^2 (%)
Peripheral arterial disease	1	1.31 (1.19 to 1.45)	NA
All cause mortality	66	1.46 (1.39 to 1.53)	93
Ischaemic heart disease	16	1.61 (1.38 to 1.87)	86
Chronic kidney disease	3	1.64 (1.41 to 1.91)	50
Sudden cardiac death	7	1.88 (1.36 to 2.60)	78
Major cardiovascular events	9	1.96 (1.53 to 2.51)	98
Haemorrhagic stroke	3	2.00 (0.67 to 5.96)	73
Cardiovascular mortality	14	2.03 (1.79 to 2.30)	76
Ischaemic stroke	12	2.33 (1.84 to 2.94)	87
Stroke	38	2.42 (2.17 to 2.71)	96
Heart failure	6	4.99 (3.04 to 8.22)	93

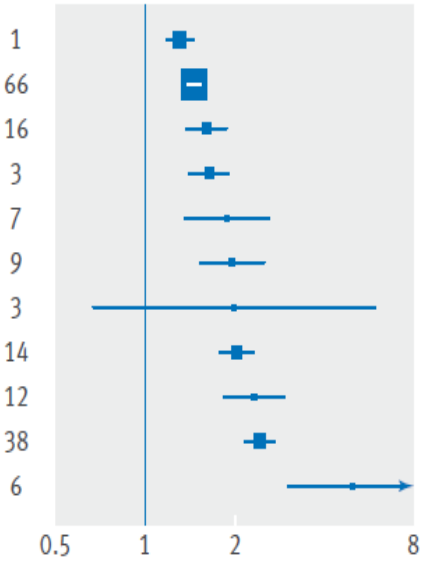
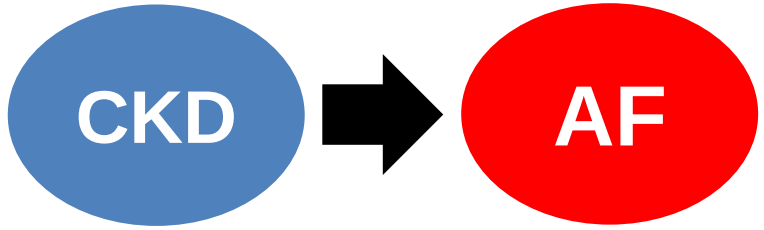
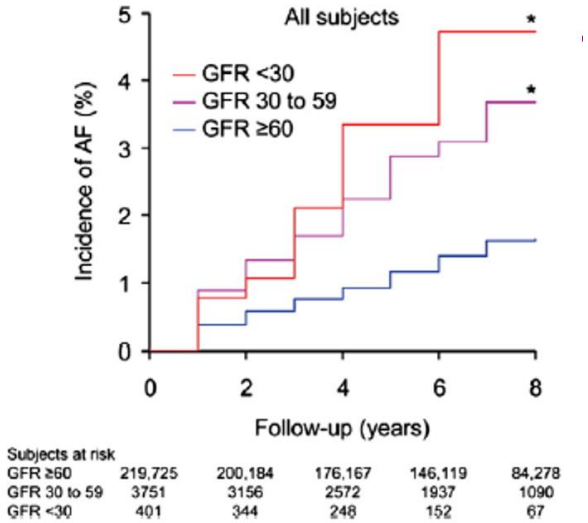


Fig 2 | Association between atrial fibrillation and all cause mortality and cardiovascular and renal disease, showing summary relative risks for each outcome examined. NA=not available





	Estimated GFR at baseline, mL/min/1.73m²		
Age-adjusted incidence of AF per 1000 person-years (95% CI)	≥60	30-59	<30
	2.2 (2.1-2.3)	5.1 (4.1-6.1)	6.6 (2.9-10.3)

BMJ 2016, AHJ 2009

Rates of stroke and bleeding in patients with both AF and CKD

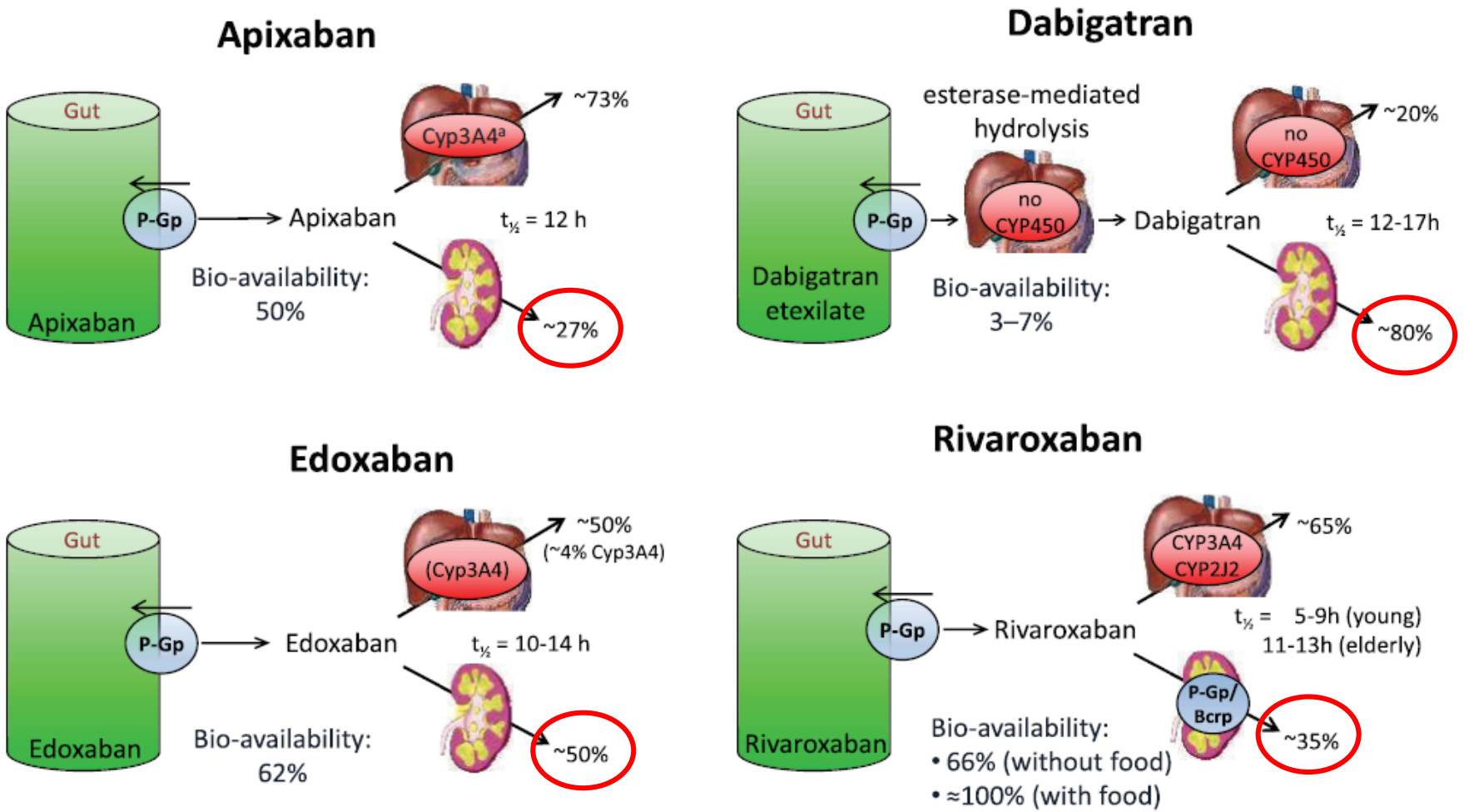
- Danish national registry data, 1997–2008
  - 132,372 patients included, 3,587 patients (2.7%) with non-end-stage CKD

	Number	No. of PY	No. of Events	Event rate per 100 PY (95% CI)
Stroke/thromboembolism				
No renal disease	127,884	461,734	16,648	3.61 (3.55-3.66)
Non-end-stage CKD	3587	13,078	842	6.44 (6.02-6.89)
Disease Requiring RRT	901	2,922	164	5.61 (4.82-6.54)
Bleeding				
No renal disease	127,884	16,195	16,195	3.54 (3.48-3.59)
Non-end-stage CKD	3587	1,097	1,097	8.77 (8.26-9.30)
Disease Requiring RRT	901	243	243	8.89 (7.84-10.08)

* CHA_2DS_2-VASc ≥2: No renal disease 77.6%, Non-end-stage CKD 91.1%, Disease requiring RRT 77.0%
* Warfarin treatment: No renal disease 37%, Non-end-stage CKD 25.1%, Disease requiring RRT 24.8%

Olesen JB, et al. N Engl J Med 2012; 367:625–635

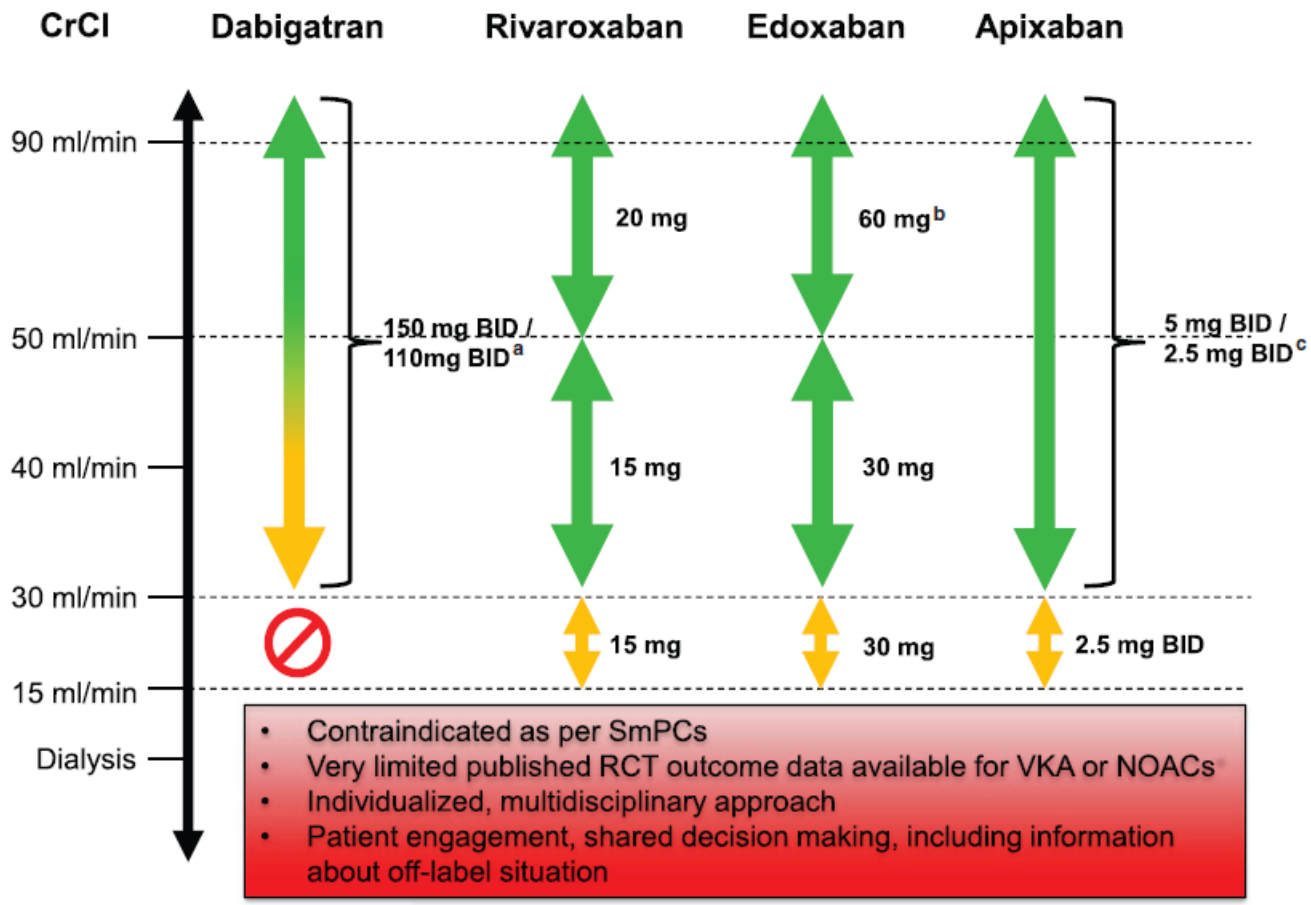
Absorption and metabolism of the different NOACs



Renal Excretion of NOACs

D>E>R>A

Labels for NOACs and dosing in CKD

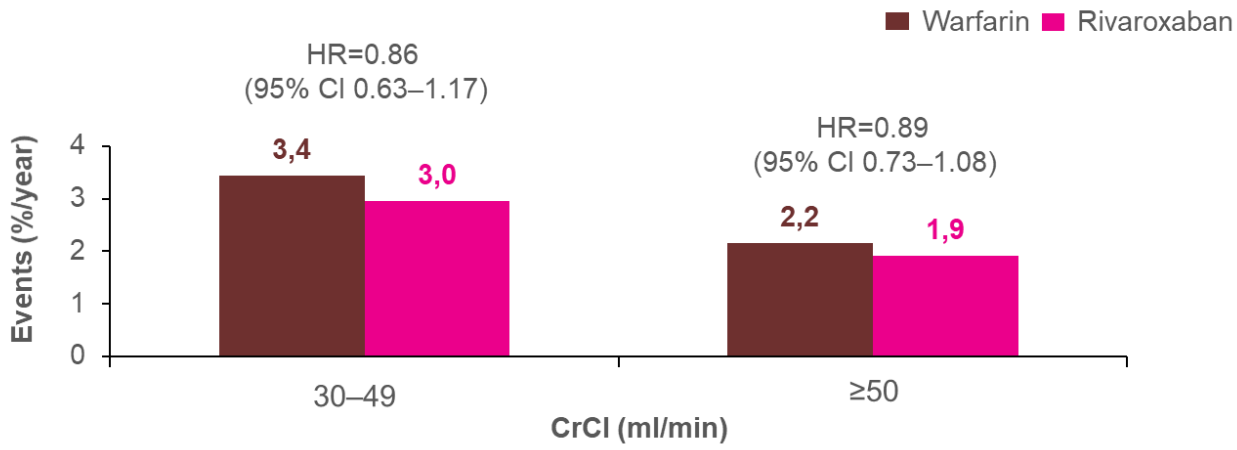


Use of NOACs according to renal function. [a]110 mg BID in patients at high risk of bleeding (per SmPc). [b]Other dose reduction criteria may apply (weight <_ 60 kg, concomitant potent P-Gp inhibitor therapy). According to EMA, SmPc edoxaban should be used in 'high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk'.473 See text for details. [c]2 x 2.5 mg only if at least two out of three fulfilled: age >_80 years, body weight <_60 kg, creatinine >_1.5 mg/dL (133 mmol/L). Orange arrows indicate cautionary use; see text for details. BID, twice daily;
CrCl, creatinine clearance; EMA, European Medicines Agency; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.

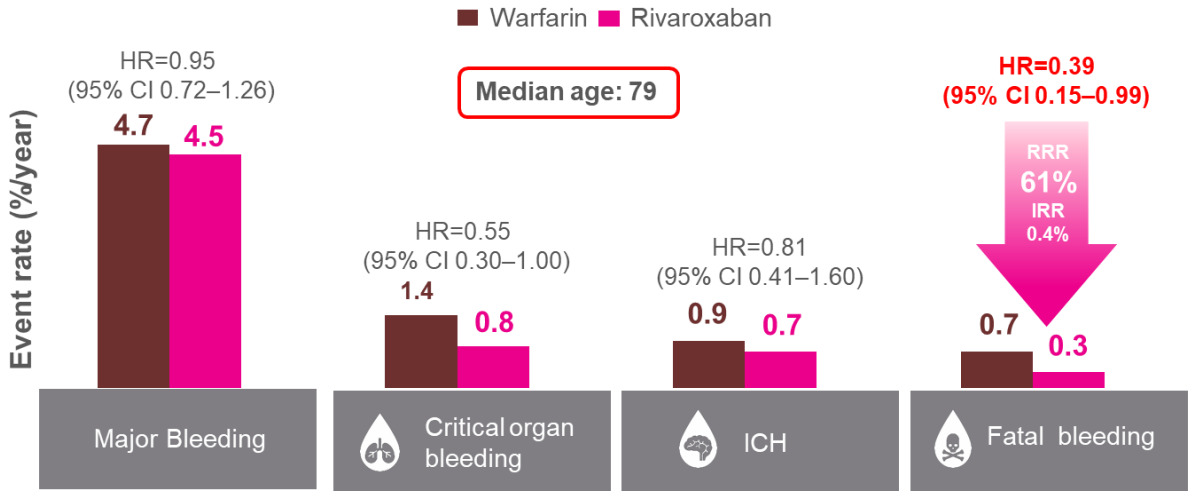
Rivaroxaban showed consistent efficacy between normal/mild and moderate renally impaired patients

ROCKET AF

Primary efficacy endpoint: Stroke/SE



Safety endpoint



- Safety and efficacy results support the use of rivaroxaban as an alternative to warfarin for stroke prevention in patients with moderate renal impairment
- There were fewer fatal bleeds with rivaroxaban

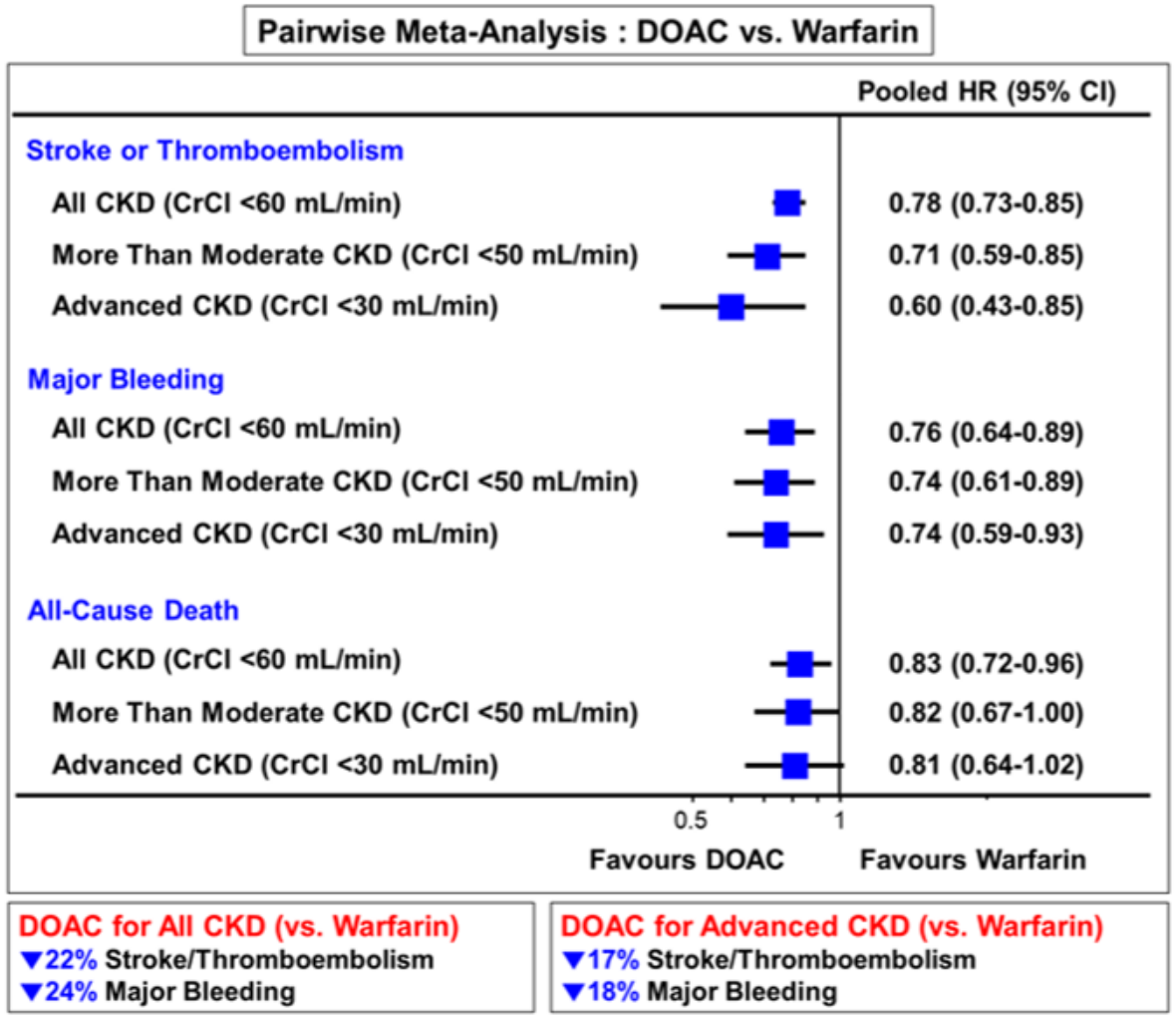
Fox KAA et al, Eur Heart J 2011;32:2387–2394

NOACs in patients with chronic kidney disease or advanced liver disease

Oral anticoagulant therapy in patients with end-stage CKD (CrCl of 15 mL/min and/or dialysis)

- lack of strong evidence the decision on anticoagulation and (if so) whether to use a NOAC or VKA in patients with end-stage renal failure or on dialysis requires a high degree of individualization
- Measurements of NOAC plasma levels
  - Plasma levels while on treatment with apixaban 2.5mg BID (as well as with 5mg, Pokorney et al., presented at ESC 2020), edoxaban 15 mg QD, and rivaroxaban 10mg QD or 15mg were found to be similar to patients with the full dose and normal renal function

OAC for patients with CKD & AF : DOAC > Warfarin



Rhee TM, Lee SR, Choi EK, et al. FCM 2022

Decreasing Renal Function:
Risk of Major Bleeding and Death

Risk factors		Effect on risk of major bleeding		Effect on risk of death	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Baseline age (years)		1.01 (0.99–1.02)	0.088	1.07 (1.06–1.09)	<0.001
eGFR over time* (ml/min/1.73 m^2)		**1.02 (1.01–1.04)**	**<0.001**	**1.01 (1.01–1.02)**	**0.036**
Heart failure		1.26 (0.63–2.49)	0.515	1.28 (0.70–2.36)	0.420
Diabetes		1.47 (0.75–2.86)	0.258	2.99 (1.72–5.2)	<0.001
Type of NOAC (reference to dabigatran)	Rivaroxaban	0.96 (0.48–1.93)	0.906	1.20 (0.57–2.51)	0.631
	Apixaban	0.45 (0.18–1.15)	0.096	1.04 (0.45–2.38)	0.926

Every 1 ml/min/1.73 m^2 decrease in eGFR
was associated with a **2% increase in risk of MB** and a **1% increase in risk of death**

*as assessed by Cockroft–Gault formula

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MB, major bleeding; NOAC, non-vitamin K antagonist oral anticoagulant

Becattini C *et al*, *J Thromb Haemost* 2018;16:833–841

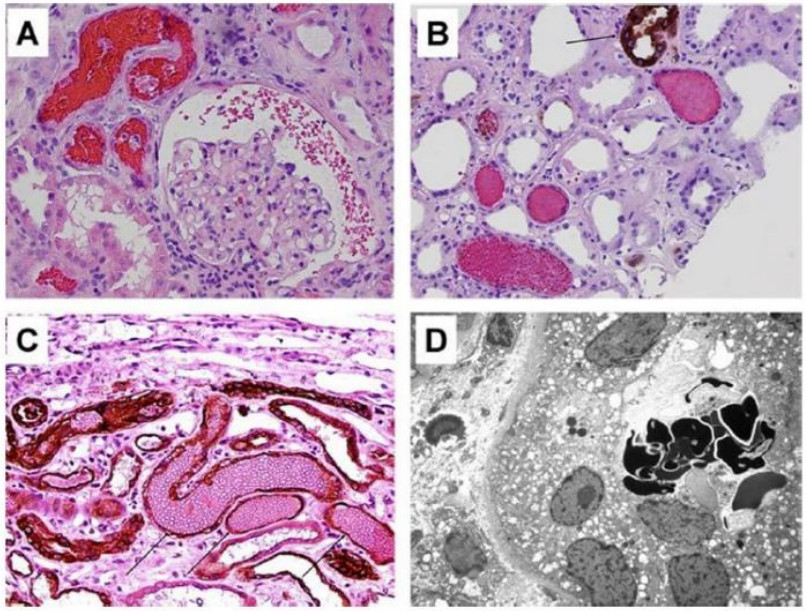
Xarelto rivaroxaba

Warfarin related nephropathy

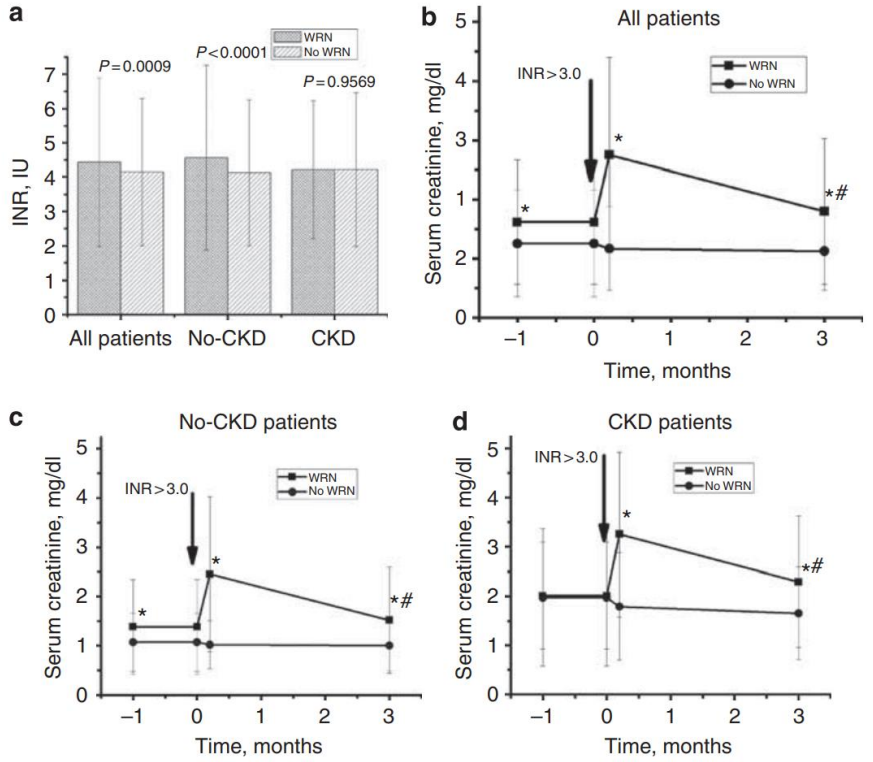
- ✓ Warfarin may induce AKI by causing **glomerular hemorrhage** and **renal tubular obstruction by RBC casts**.

Acute Kidney Injury During Warfarin Therapy Associated With Obstructive Tubular Red Blood Cell Casts: A Report of 9 Cases

Sergey V. Brodsky, MD, PhD,[1,2] Anjali Satoskar, MD,[1] Jun Chen, MD,[2] Gyongyi Nadasdy, MD,[1] Jeremiah W. Eagen, MD,[3] Mirza Hamirani, MD,[4] Lee Hebert, MD,[5] Edward Calomeni, MS,[1] and Tibor Nadasdy, MD[1]



American Journal of Kidney Diseases, Vol 54, No 6 (December), 2009: pp 1121-1126



Kidney International (2011) 80, 181–189

WRN occurred in 20.5% of the entire cohort, 33.0% of the CKD cohort, and 16.5% of the no-CKD cohort.

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Renal outcome in AF patients with OAC

Changes in Renal Function in Patients With Atrial Fibrillation

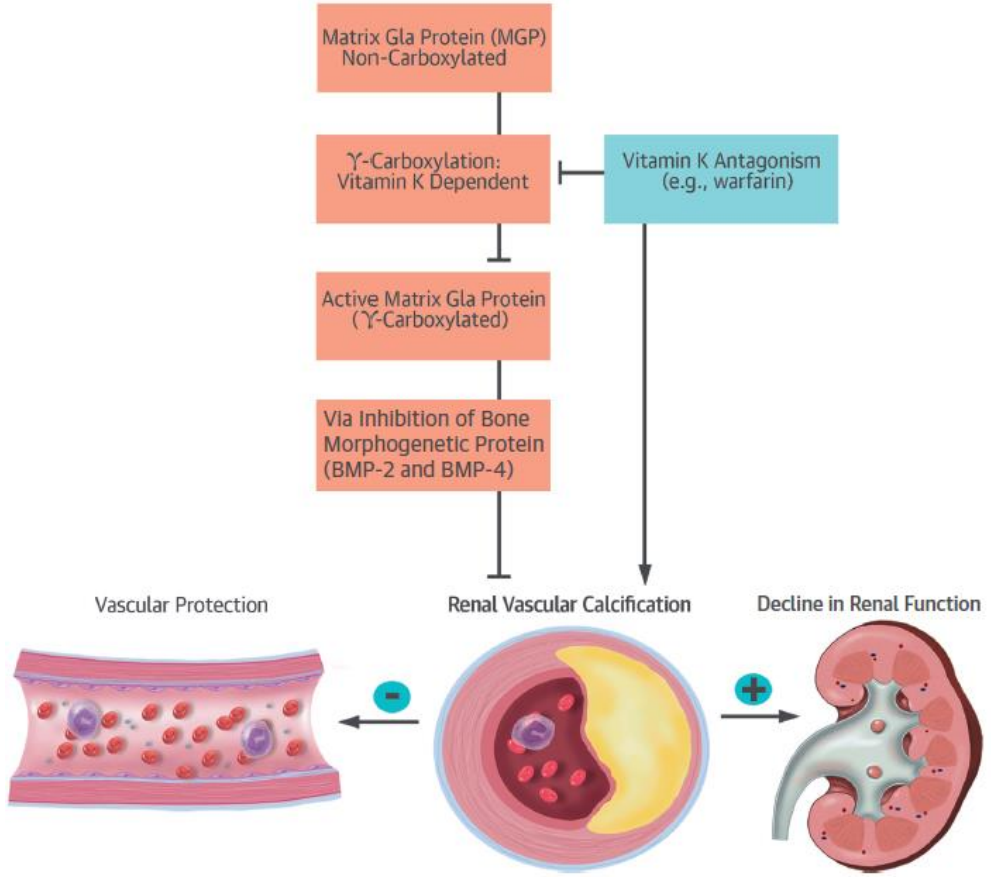
An Analysis From the RE-LY Trial

Michael Böhm, MD,* Michael D. Ezekowitz, MD, ChB, DPhil,†‡ Stuart J. Connolly, MD,§ John W. Eikelboom, MBBS,§ Stefan H. Hohnloser, MD,‖ Paul A. Reilly, PhD,¶ Helmut Schumacher, PhD,# Martina Brueckmann, MD,#** Stephan H. Schirmer, MD, PhD,* Mario T. Kratz, MD,* Salim Yusuf, MD, DPhil,§ Hans-Christoph Diener, MD,†† Ziad Hijazi, MD,‡‡ Lars Wallentin, MD, PhD‡‡

METHODS Of the 18,113 patients in the RE-LY study randomized to receive DE (110 mg or 150 mg twice daily) or warfarin, 16,490 patients with atrial fibrillation had creatinine values measured at baseline and at least 1 follow-up visit. Changes in GFR for up to 30 months were evaluated.

RESULTS GFR declined in all treatment groups. After an average of 30 months, the mean ± SE decline in GFR was significantly greater with warfarin (-3.68 ± 0.24 ml/min) compared with DE 110 mg (-2.57 ± 0.24 ml/min; p = 0.0009 vs. warfarin) and DE 150 mg (-2.46 ± 0.23 ml/min; p = 0.0002 vs. warfarin). A decrease in GFR >25% was less likely with DE 110 mg (hazard ratio: 0.81 [95% confidence interval: 0.69 to 0.96]; p = 0.017) or DE 150 mg (hazard ratio: 0.79 [95% confidence interval: 0.68 to 0.93]; p = 0.0056) than with warfarin in the observation period >18 months. Patients with poor international normalized ratio control (i.e., time in therapeutic range <65%) exhibited a faster decline in GFR. A more pronounced decline in GFR was associated with previous warfarin use and with the presence of diabetes.

CONCLUSIONS Patients with atrial fibrillation receiving oral anticoagulation exhibited a decline in renal function that was greater in those taking warfarin versus DE, and it was amplified by diabetes and previous vitamin K antagonist use. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY] With Dabigatran Etexilate; NCT00262600)
(J Am Coll Cardiol 2015;65:2481-93)

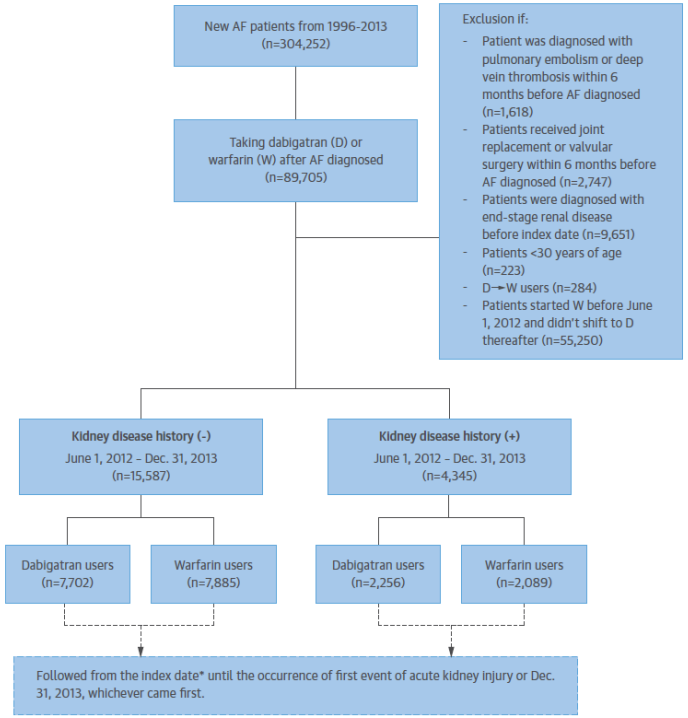


Böhm M, et al. JACC 2015

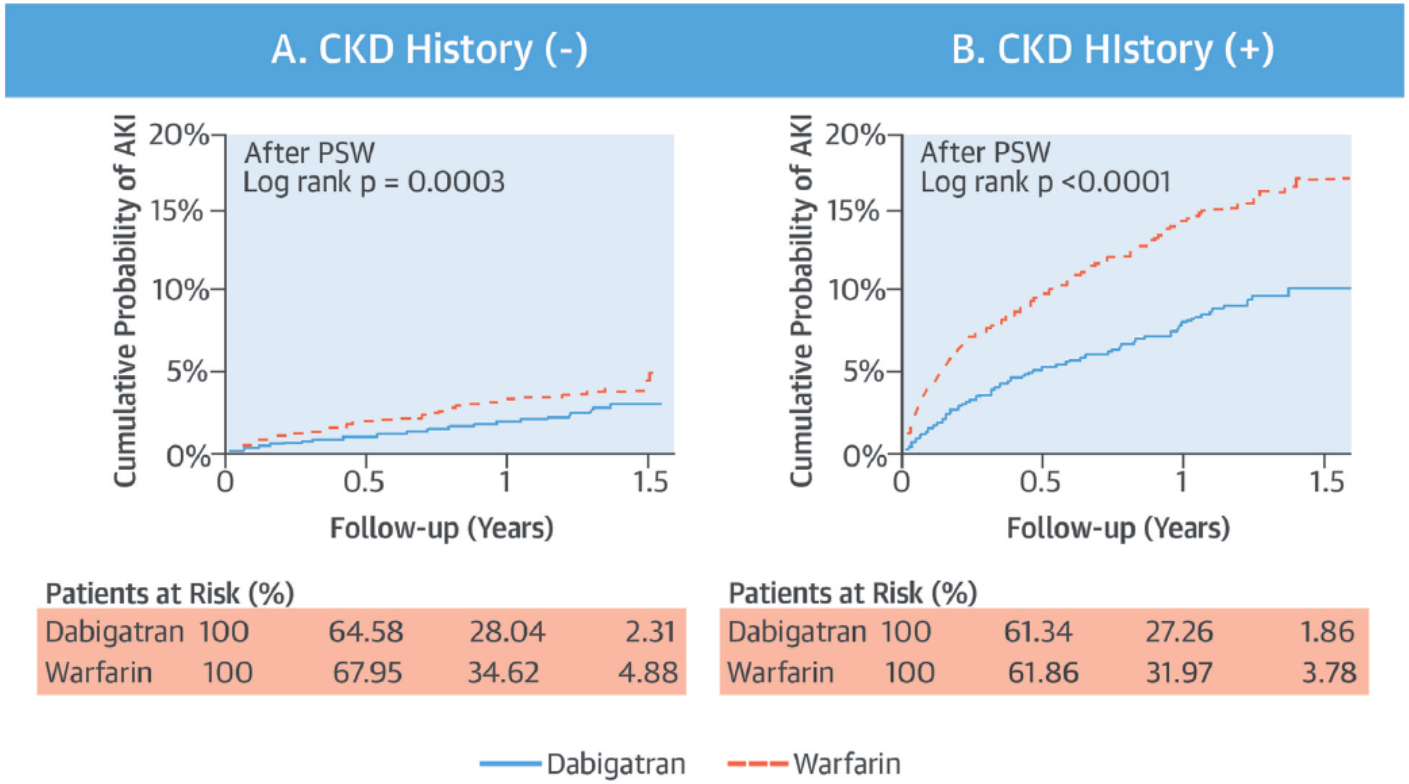
Renal outcome in AF patients with OAC

Acute Kidney Injury in Asians With Atrial Fibrillation Treated With Dabigatran or Warfarin

Yi-Hsin Chan, MD,[a,b] Yung-Hsin Yeh, MD,[a,b] Lai-Chu See, PhD,[c,d,e] Chun-Li Wang, MD,[a,b] Shang-Hung Chang, MD, PhD,[a,b] Hsin-Fu Lee, MD,[a,b] Lung-Sheng Wu, MD,[a,b] Hui-Tzu Tu, MS,[c] Chi-Tai Kuo, MD[a,b]



CENTRAL ILLUSTRATION AKI in Patients With Nonvalvular AF Treated With Dabigatran or Warfarin: Cumulative Probability After PSW



Chan, Y.-H. et al. J Am Coll Cardiol. 2016;68(21):2272-83.

Dabigatran users **(solid line)** had a significantly lower risk of acute kidney injury (AKI) than warfarin users **(dashed line)** after propensity score weighting (PSW) in both the chronic kidney disease (CKD)-free **(A)** and CKD **(B)** cohorts. AF = atrial fibrillation.

Chan YH, et al. JACC 2016

Renal outcome in AF patients with OAC

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Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation

Xiaoxi Yao, PhD,[a,b] Navdeep Tangri, MD, PhD,[c] Bernard J. Gersh, MB, ChB, DPhil,[d] Lindsey R. Sangaralingham, MPH,[a] Nilay D. Shah, PhD,[a,b,e] Karl A. Nath, MB, ChB,[f] Peter A. Noseworthy, MD[a,d]

ABSTRACT

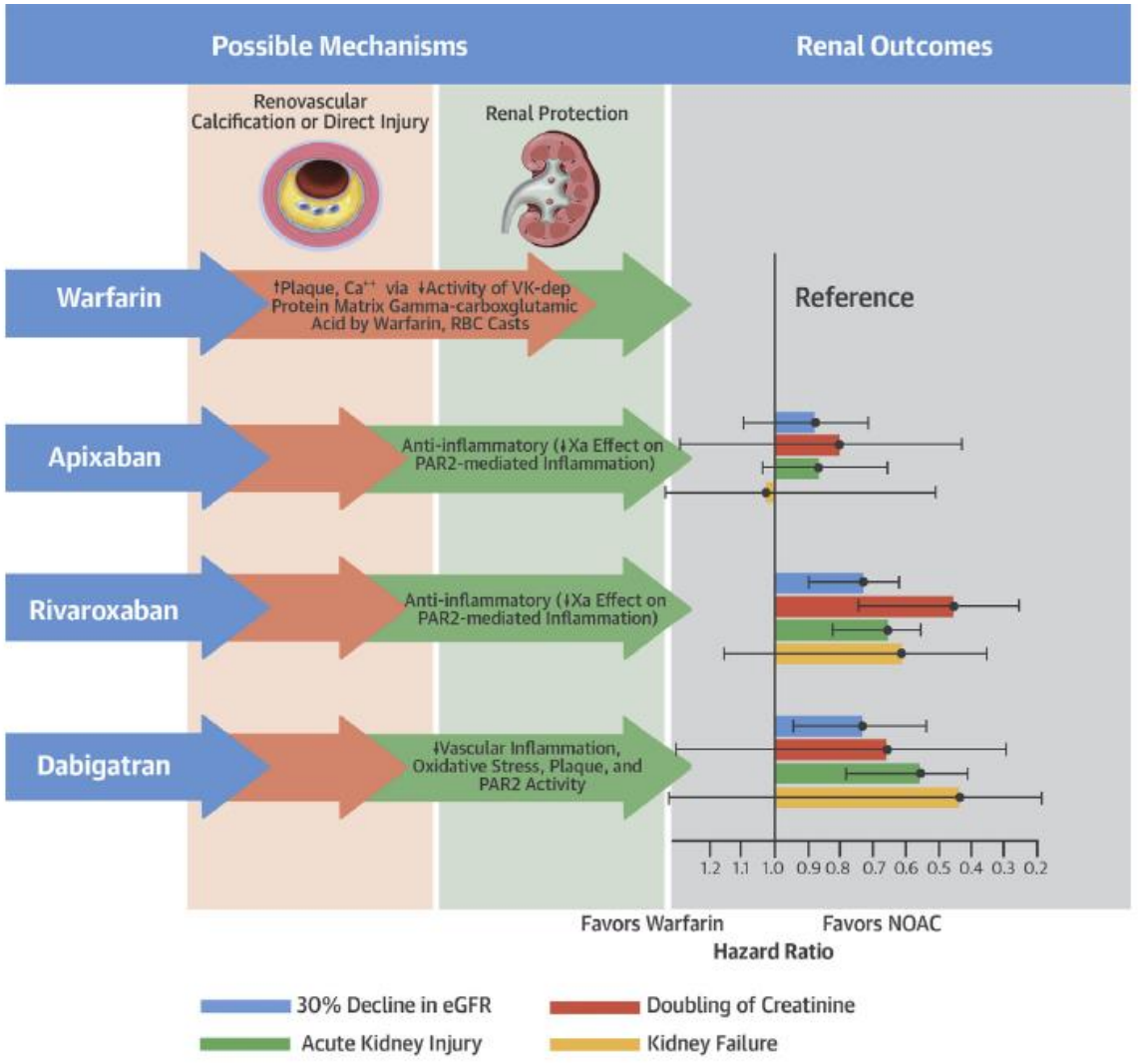
BACKGROUND Lifelong oral anticoagulation, either with warfarin or a non-vitamin K antagonist oral anticoagulant (NOAC), is indicated for stroke prevention in most patients with atrial fibrillation (AF). Emerging evidence suggests that NOACs may be associated with better renal outcomes than warfarin.

OBJECTIVES This study aimed to compare 4 oral anticoagulant agents (apixaban, dabigatran, rivaroxaban, and warfarin) for their effects on 4 renal outcomes: ≥30% decline in estimated glomerular filtration rate (eGFR), doubling of the serum creatinine level, acute kidney injury (AKI), and kidney failure.

METHODS Using a large U.S. administrative database linked to laboratory results, the authors identified 9,769 patients with nonvalvular AF who started taking an oral anticoagulant agent between October 1, 2010 and April 30, 2016. Inverse probability of treatment weighting was used to balance more than 60 baseline characteristics among patients in the 4 drug cohorts. Cox proportional hazards regression was performed in the weighted population to compare oral anticoagulant agents.

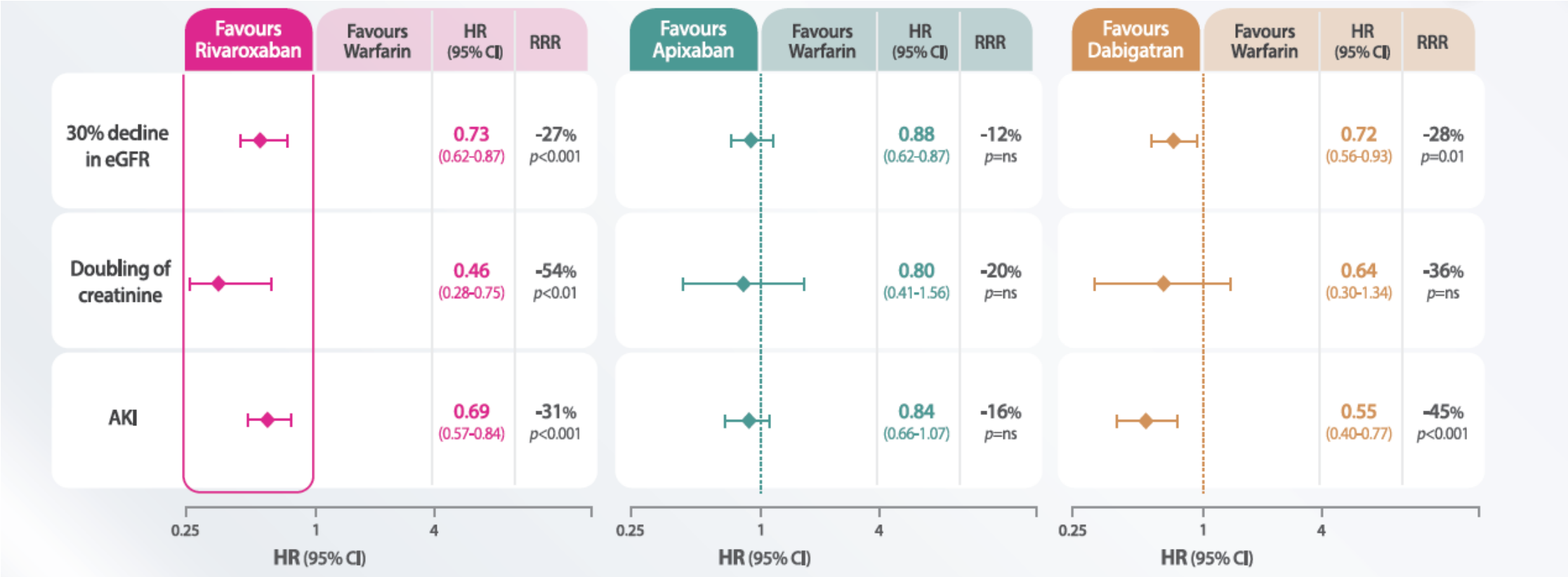
RESULTS The cumulative risk at the end of 2 years for each outcome was 24.4%, 4.0%, 14.8%, and 1.7% for ≥30% decline in eGFR, doubling of serum creatinine, AKI, and kidney failure, respectively. When the 3 NOACs were pooled, they were associated with reduced risks of ≥30% decline in eGFR (hazard ratio [HR]: 0.77; 95% confidence interval [CI]: 0.66 to 0.89; $p < 0.001$), doubling of serum creatinine (HR: 0.62; 95% CI: 0.40 to 0.95; $p = 0.03$), and AKI (HR: 0.68; 95% CI: 0.58 to 0.81; $p < 0.001$) compared with warfarin. When comparing each NOAC with warfarin, dabigatran was associated with lower risks of ≥30% decline in eGFR and AKI; rivaroxaban was associated with lower risks of ≥30% decline in eGFR, doubling of serum creatinine, and AKI; however, apixaban did not have a statistically significant relationship with any of the renal outcomes.

CONCLUSIONS Renal function decline is common among patients with AF treated with oral anticoagulant agents. NOACs, particularly dabigatran and rivaroxaban, may be associated with lower risks of adverse renal outcomes than warfarin. (J Am Coll Cardiol 2017;70:2621-32) © 2017 by the American College of Cardiology Foundation.



Yao X, et al. JACC 2017

Effect on Renal Function: NOACs vs VKA in AF patients



Study design: US administrative database를 사용하여 후향적으로 2010년부터 2016년까지 항응고제제(apixaban, dabigatran, rivaroxaban, warfarin) 복용을 시작한 9,769명의 NVAF 환자를 10.7개월 동안 추적관찰하였으며, 4개의 renal outcome을 평가하였음(≥30% decline in eGFR, doubling of the serum creatinine level, AKI, and kidney failure)

*After inverse probability of treatment weighting

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation

Yao X et al. *J Am Coll Cardiol* 2017;70:2621–2632

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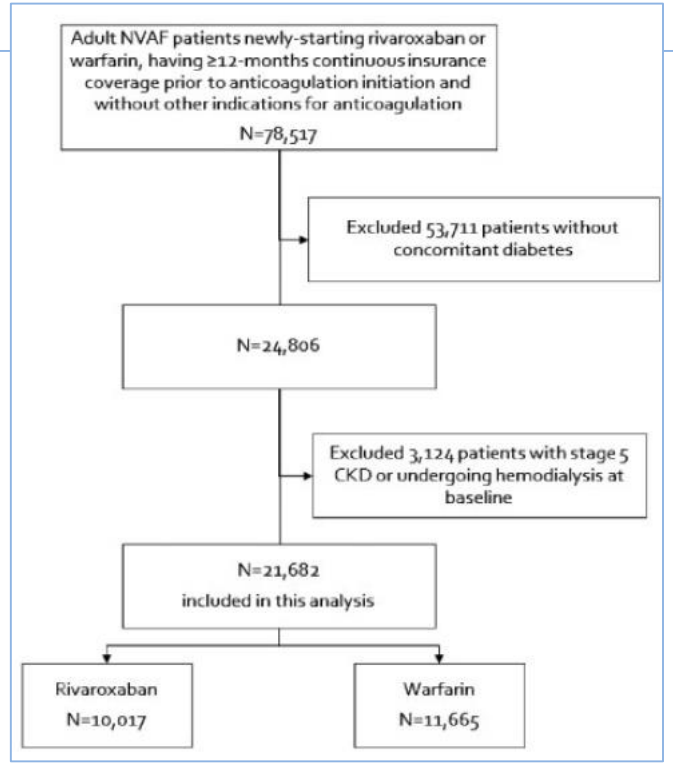
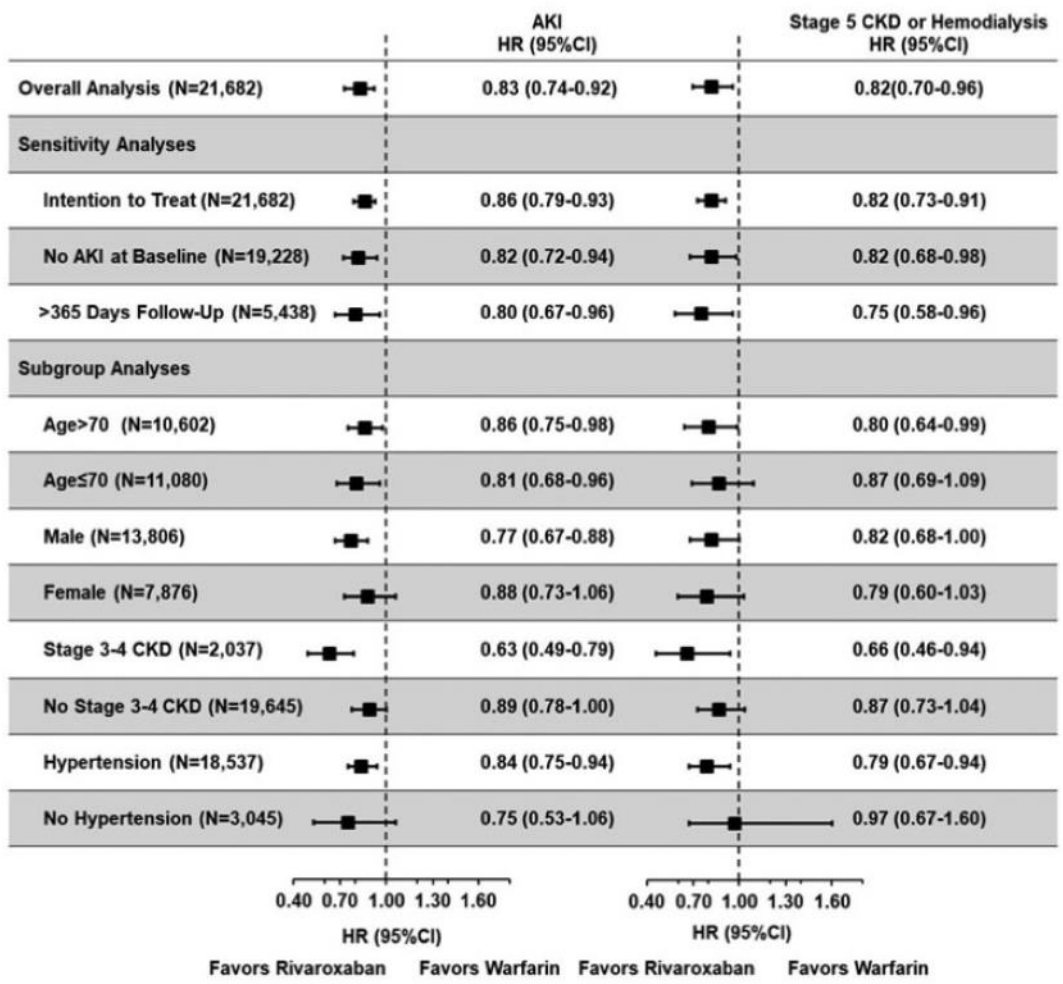
Renal outcome in AF DM patients : rivaroxaban vs. warfarin

ESC European Society of Cardiology
European Heart Journal - Quality of Care and Clinical Outcomes (2020) 6, 301–307
doi:10.1093/ehjqcco/qcz047
ORIGINAL ARTICLE

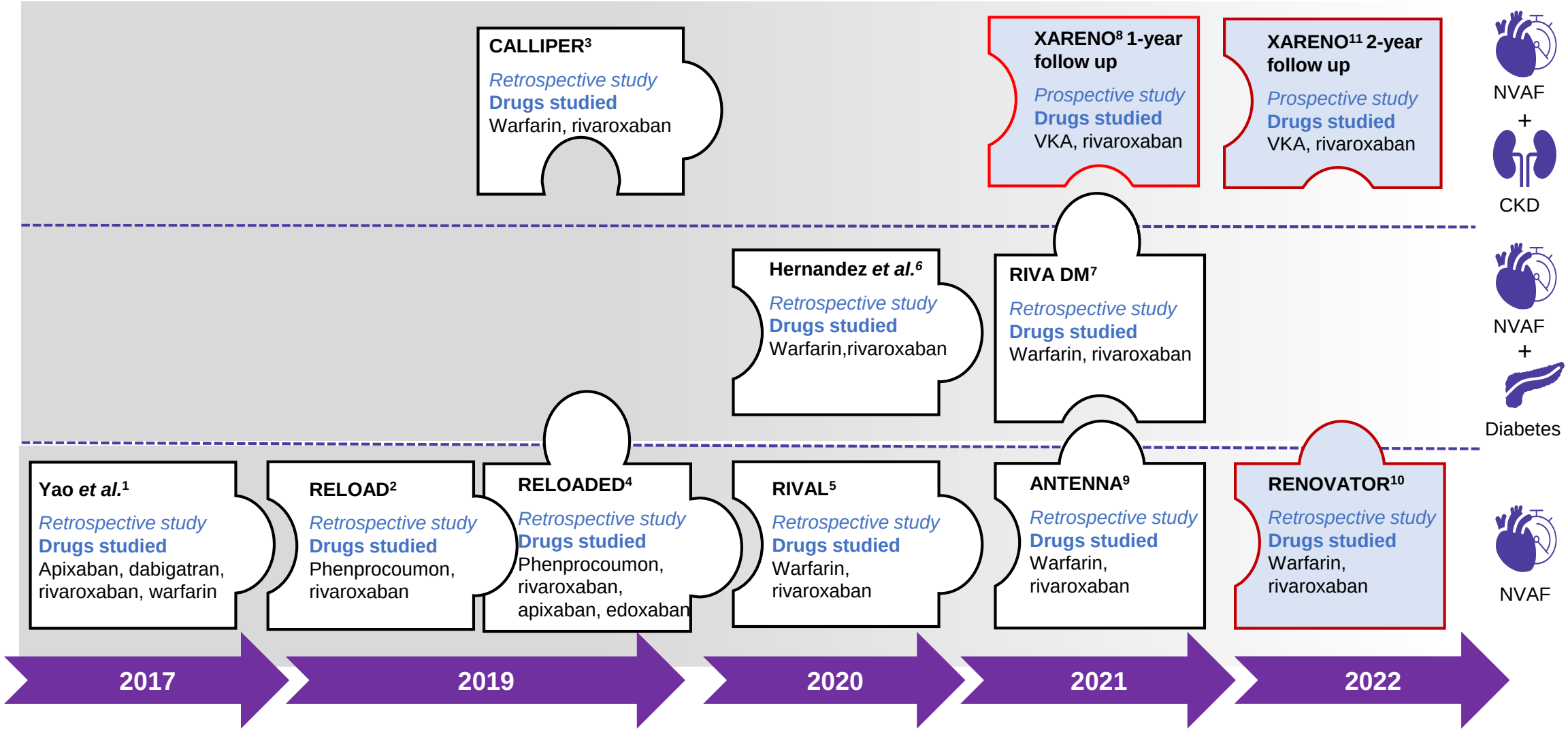
Rivaroxaban vs. warfarin and renal outcomes in non-valvular atrial fibrillation patients with diabetes





Hernandez AV, et al. EHJ QCCO 2020

A Growing Body of Evidence Supports the Use of Rivaroxaban in Patients with Kidney Disease



1. Yao X et al. *J Am Coll Cardiol* 2017;70:2621–2632. 2. Bonnemeier H et al. *Int J Cardiol Heart Vasc* 2019;23:100367. 3. Vaitsiakhovich T et al. *Eur Heart J* 2019;40:ehz745.1122.
4. Bonnemeier H et al. *Eur Heart J* 2019; ehz745.1125. 5. Coleman CI et al. *Clin Appl Thromb Hemost* 2019;25:1–8. 6. Hernandez AV et al. *Eur Heart J Qual Care Clin Outcomes* 2020;6:301–307.
7. Costa OS et al. *Curr Med Res Opin* 2021 Sep;37(9):1493-1500. **8.** Kreutz R et al. *ACC.* Washington DC, USA, 2–4 April 2022.
9. González Pérez A, et al. *Int J Cardiol* 2022;352:165–171. 10. Lee SR et al. *Front Cardiovasc Med* 2023;10:1040834. 11. Kreutz R et al. *ACC.* New Orleans, USA, 4–6 March 2023

Xarelto rivaroxaban

Renal Outcomes of Rivaroxaban Compared with Warfarin in Asian Patients with Nonvalvular Atrial Fibrillation: A Korean Nationwide Population-Based Cohort Study

The RENOVATOR Study

- So-Ryoung Lee, Eue-Keun Choi, Sang-Huan Park, Kyung-Do Han, Seil Oh, Khaled Abdelgawwad and Gregory Y.H. Lip

RENOVATOR Investigated the Differences in Adverse Kidney Outcomes Between Rivaroxaban and Warfarin-Treated Patients with Atrial Fibrillation

Background

- Several studies have shown that rivaroxaban may be associated with improved kidney function preservation compared with warfarin
- However, additional evidence is required, especially in an Asian patient population

Study aim

- To determine whether there are differences in adverse kidney outcomes between rivaroxaban- and warfarin-treated patients with AF in Korea

Methods

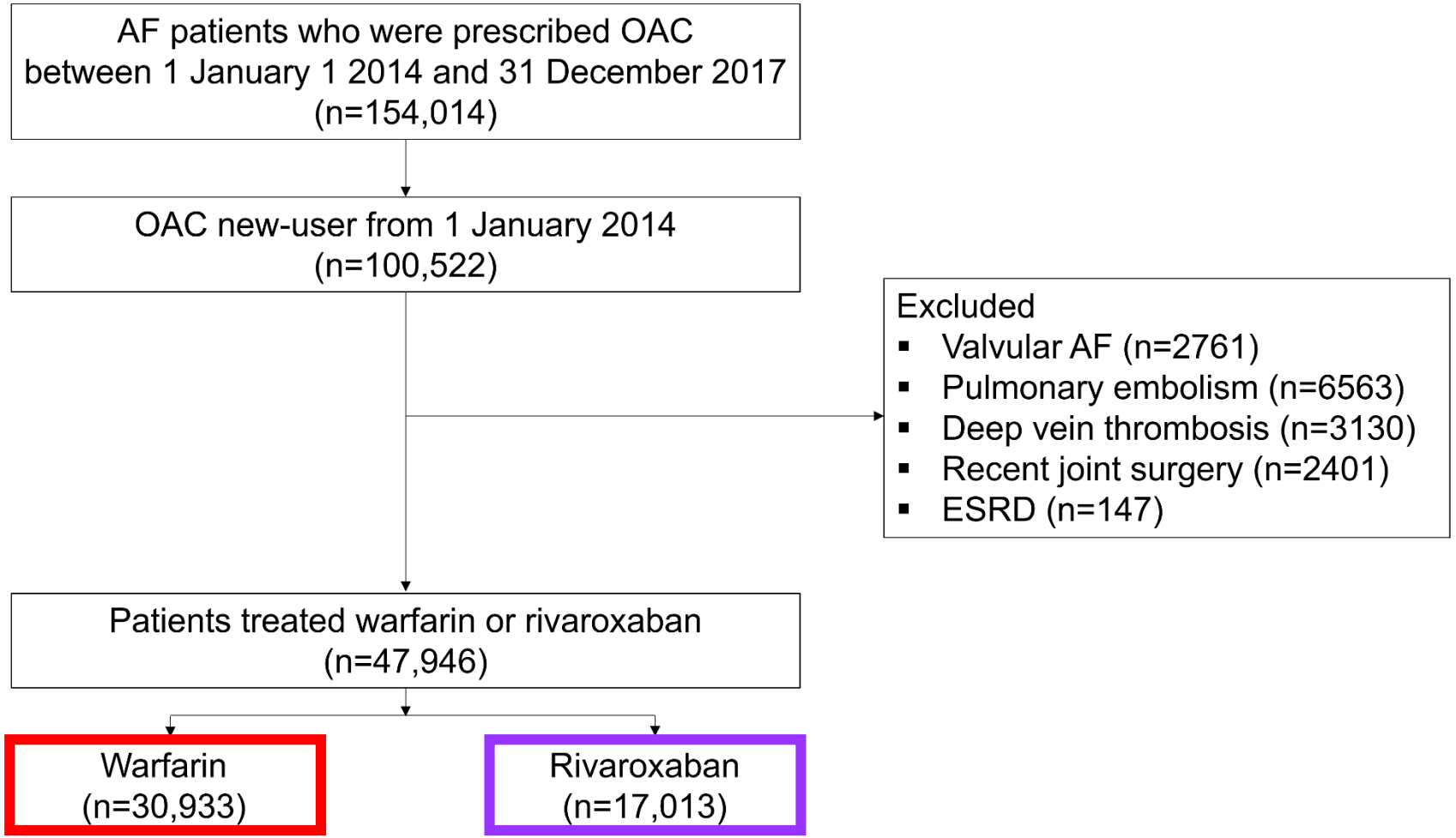
- **Study type:** Retrospective, observational, nationwide population-based cohort study
- **Population:** Adult patients with AF newly using OAC and newly initiated on rivaroxaban or warfarin
- **Treatment:** Rivaroxaban 20 mg od, rivaroxaban 15 mg od or warfarin
- **Study procedures:** Treatment groups from the Korean NHIS database were compared with propensity score methods and IPTW weighting was used to adjust for potential confounding due to imbalances between populations
- **Primary outcome:** Incident kidney failure, defined as the need for maintenance dialysis or having kidney transplantation
- **Secondary outcome:** Incident ischaemic stroke, ICH, major GI bleeding, major bleeding and all-cause death

This study was conducted using NHIS data in retrospective observation manner.
Rivaroxaban is not approved to use for renal function preservation. Bayer does not recommend off-label use of products. Before prescribing any products, please consult the relevant local prescribing information.

Lee SR et al. *Front Cardiovasc Med* 2023;10:1040834.

Xarelto rivaroxaba

Study flow



Lee SR et al. *Front Cardiovasc Med* 2023;10:1040834.

Baseline Characteristics Were Balanced Between Treatment Groups

Baseline characteristics (after IPTW)	Rivaroxaban (n=17,006)	Warfarin (n=30,946)
Age, median ± SD	70.4 ± 11.2	70.2 ± 11.9
Female sex, %	41.6	41.9
CHA_2DS_2-VASc	3.9 ± 1.9	3.9 ± 1.9
Chronic kidney disease, %	5.7	5.5
eGFR, ml/min/1.73 m^2	81.6	81.6
Rivaroxaban dose, %		
15 mg od	52.8	N/A
20 mg od	47.2	N/A
Prior stroke, %	29.5	29.0
Hypertension, %	82.6	82.6
Diabetes, %	26.8	26.5
Heart failure, %	41.8	42.0
Charlson Comorbidity Index	4.0 ± 2.5	4.0 ± 2.5

Lee SR et al. *Front Cardiovasc Med* 2023;10:1040834.

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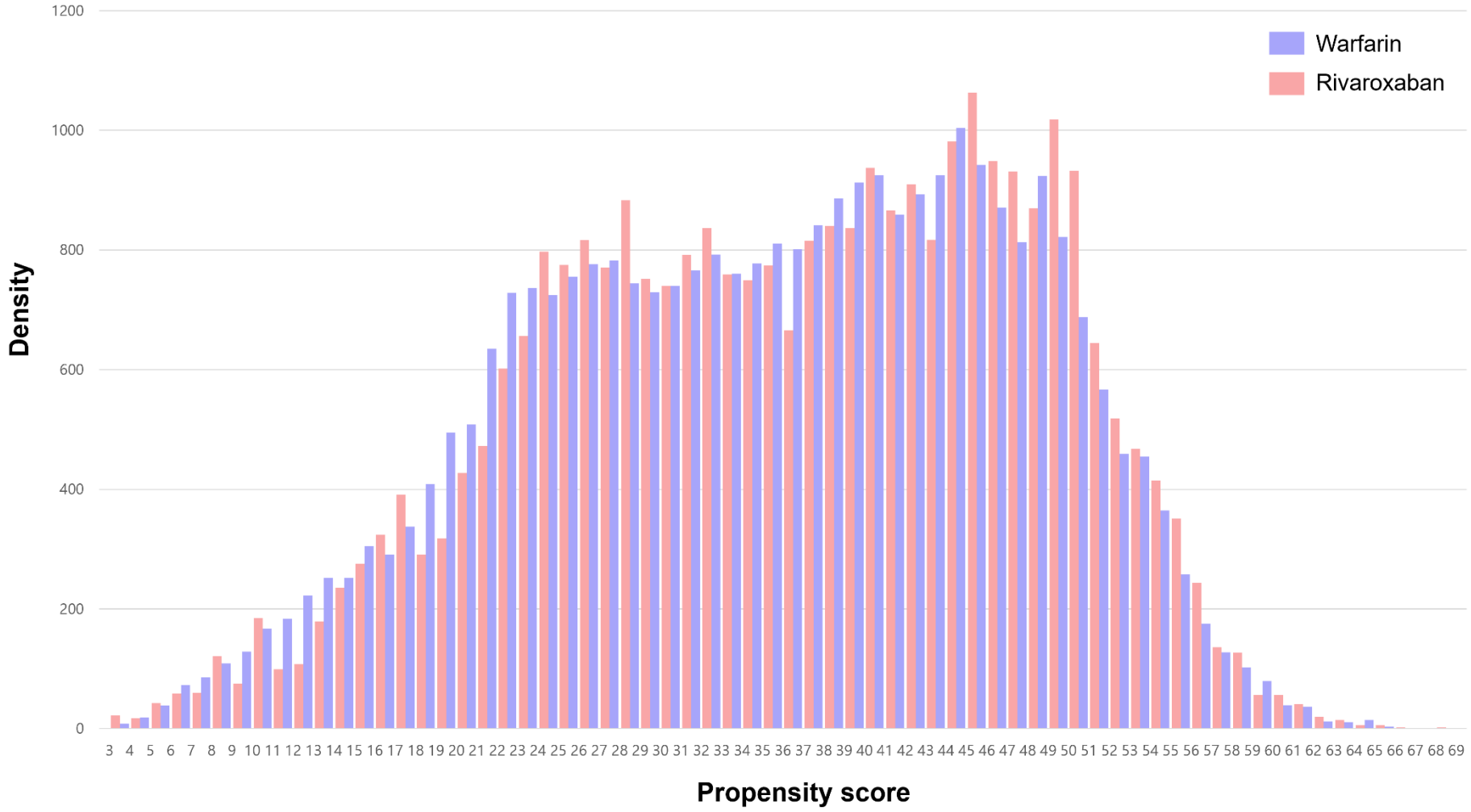
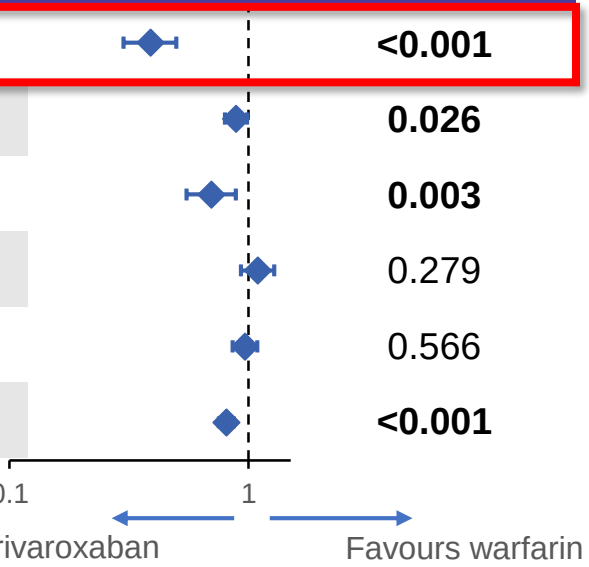
Balancing baseline characteristics between the two group



Lee SR et al. *Front Cardiovasc Med* 2023;10:1040834.

Patients with NVAF Receiving Rivaroxaban Had a Lower Risk of Kidney Failure, ICH and All-Cause Mortality than Those Receiving Warfarin

	Weighted IR				
	Rivaroxaban (n=17,006)	Warfarin (n=30,946)	HR (95% CI)	HR (95% CI)	*p*-value
Kidney failure	0.32	0.83	0.389 (0.300–4.99)		**<0.001**
Ischaemic stroke	2.30	2.70	0.887 (0.797–0.986)		**0.026**
ICH	0.43	0.61	0.699 (0.550–0.883)		**0.003**
Major GI bleeding	1.11	1.05	1.092 (0.930–1.279)		0.279
Major bleeding	1.96	2.04	0.966 (0.858–1.086)		0.566
All-cause death	4.78	6.08	0.807 (0.751–0.867)		**<0.001**



*Kidney failure, defined as the need for maintenance dialysis or having kidney transplantation

This study was conducted using NHIS data in retrospective observation manner.
Rivaroxaban is not approved to use for renal function preservation. Bayer does not recommend off-label use of products. Before prescribing any products, please consult the relevant local prescribing information.

Lee SR et al. *Front Cardiovasc Med* 2023;10:1040834.

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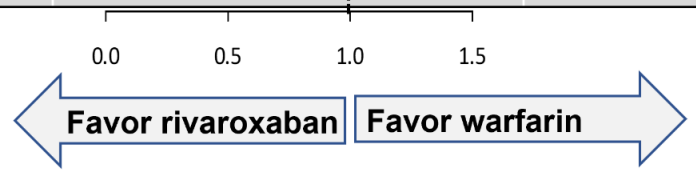
Sensitivity analyses for primary outcome

Primary outcome: ESRD	IR		HR (95% CI)	p-value
	W	R		
Main analysis (IPTW OT)	0.83	0.32	0.389 (0.300-0.499)	<0.001
IPTW ITT	0.61	0.42	0.625 (0.520-0.746)	<0.001
Multivariable adjusted Cox (OT)*	0.89	0.29	0.409 (0.313-0.534)	<0.001
Multivariable adjusted Cox (ITT)*	0.64	0.37	0.592 (0.489-0.718)	<0.001
IPTW OT, 5% trimmed	0.84	0.27	0.323 (0.240-0.427)	<0.001
IPTW ITT, 5% trimmed	0.63	0.38	0.533 (0.434-0.651)	<0.001
6-month lag period (OT)*	0.69	0.22	0.422 (0.294-0.605)	<0.001
12-month follow-up restriction (OT)*	1.05	0.35	0.348 (0.247-0.480)	<0.001
In patients with baseline eGFR value (OT)†	0.70	0.28	0.545(0.391-0.759)	<0.001



*Adjusted for age, sex, CHA_2DS_2-VASc, CCI, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, prior stroke, peripheral artery disease, chronic kidney disease, cancer, chronic obstructive pulmonary disease, use of antiplatelet agents

†Adjusted for age, sex, CHA_2DS_2-VASc, CCI, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, prior stroke, peripheral artery disease, chronic kidney disease, cancer, chronic obstructive pulmonary disease, use of antiplatelet agents + eGFR

Lee SR et al. *Front Cardiovasc Med* 2023;10:1040834.

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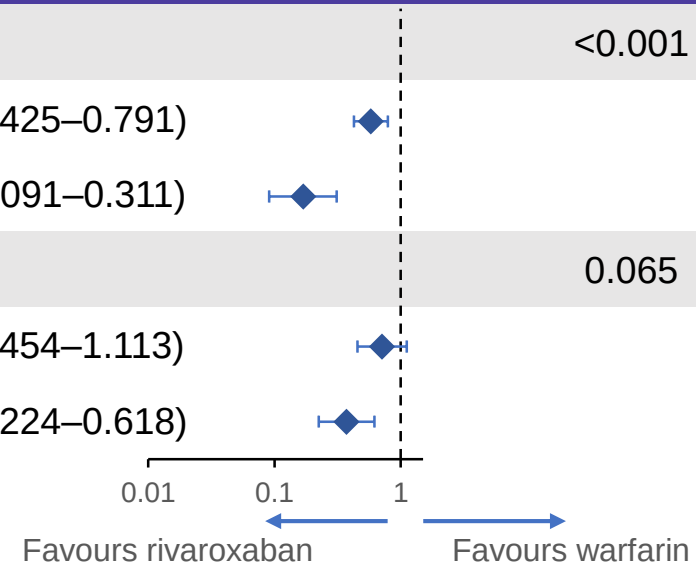
Subgroup analyses for primary outcome

Subgroup	Number of events/total number (IR per 100 patient-years) Rivaroxaban	Warfarin	HR (95% CI)	HR (95% CI)	*p*-value
Chronic kidney disease					<0.001
No	57/16,289 (0.25)	166/29,034 (0.46)	0.580 (0.425–0.791)		
Yes	11/724 (1.32)	176/1899 (8.41)	0.169 (0.091–0.311)		
eGFR*					0.065
>60 ml/min/1.73 m²	29/9723 (0.20)	69/16,989 (0.31)	0.711 (0.454–1.113)		
≤60 ml/min/1.73 m²	18/1942 (0.66)	119/3570 (2.61)	0.372 (0.224–0.618)		



*Among patients with baseline eGFR value.

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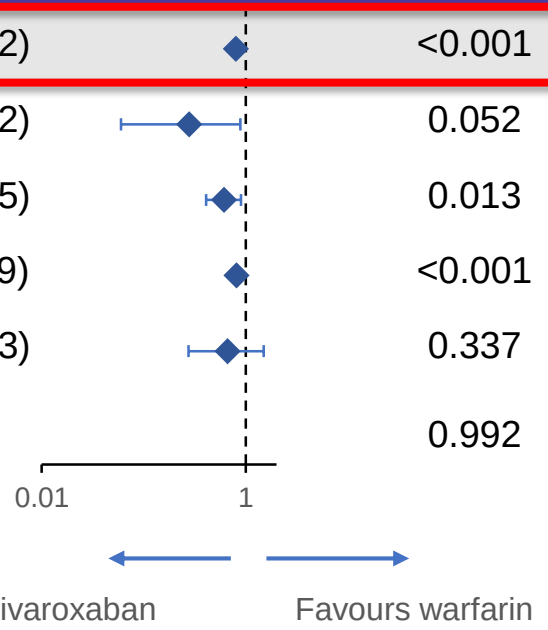
Exploratory analysis : subset of pts with baseline and follow-up laboratory results

	Weighted IR				
	Rivaroxaban (n=4,745)*	Warfarin (n=6,453)*	IPTW HR (95% CI)	HR (95% CI)	*p*-value
Composite of 1–5	5.13	5.73	0.798 (0.713–0.892)		<0.001
1. eGFR <15 ml/min/1.73 m²	0.04	0.09	0.278 (0.060–0.882)		0.052
2. AKI (N17x)	0.36	0.52	0.610 (0.408–0.895)		0.013
3. eGFR 30%↓	4.81	5.3	0.811 (0.722–0.909)		<0.001
4. Serum Cr ≥ twofold↑	0.08	0.10	0.665 (0.274–1.493)		0.337
5. Dialysis or kidney transplantation#	0.00	0.06	N/A		0.992



*This exploratory analysis included only patients with baseline eGFR measurements. #No patients in the exploratory analysis population underwent kidney transplantation or dialysis.

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In RENOVATOR study

Korean Patients Receiving Rivaroxaban Had Consistent Safety and Efficacy Profiles as Observed in Other Studies

- Rivaroxaban was associated with a lower risk of kidney failure than warfarin in Korean patients with NVAF
- The findings from this study were consistent with previous studies of kidney outcomes in both Asian and non-Asian patients with NVAF receiving anticoagulation
- The risk of all-cause death, ICH and ischaemic stroke was lower in patents receiving rivaroxaban vs. warfarin
- Patients with CKD at baseline saw an especially high reduction in the risk of kidney failure when treated with rivaroxaban vs warfarin

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Advanced Age and Preferential Use of Vitamin K Antagonists in Severe Renal Impairment: First Results of the XARENO Registry in Patients With Non-valvular Atrial Fibrillation and Non-dialysis Dependent Advanced Chronic Kidney Disease

Reinhold Kreutz, Gilbert Deray, Juergen Floege, Marianne Gwechenberger, Andreas Luft, Hahn Kai, Pontus Persson and Jan Beyer-Westendorf

Originally published12 Nov 2020 https://doi.org/10.1161/circ.142.suppl_3.13927 *Circulation*. Nov 17, 2020;142 A13927

XARENO Explored How Patients with NVAF and Advanced CKD Benefit from Treatment with Rivaroxaban Versus a VKA[1,2]

XARENO was a multicentre, prospective, non-interventional registry study based in Germany, Austria, Switzerland, France, Belgium and Luxembourg

The objective was to assess CKD progression and net clinical benefit of different anticoagulation strategies (rivaroxaban versus VKA) in patients with NVAF and CKD in routine clinical practice

XARENO measured the progression of CKD by monitoring decline in eGFR and tracking safety outcomes*

*Safety outcomes are major bleeding; all-cause mortality; TIA, stroke or systemic arterial embolism; MACE; symptomatic VTE; and net clinical benefit (stroke and other thromboembolic events, major bleeding and all-cause mortality).

Rivaroxaban is not approved to use for renal function preservation. Bayer does not recommend off-label use of products. Before prescribing any products, please consult the relevant local prescribing information.

1. Kreutz R et al. *Circulation* 2020;142:A13927. Abstract 13927. 2. Kreutz R et al. ACC. Washington DC, USA, 2–4 April 2022..

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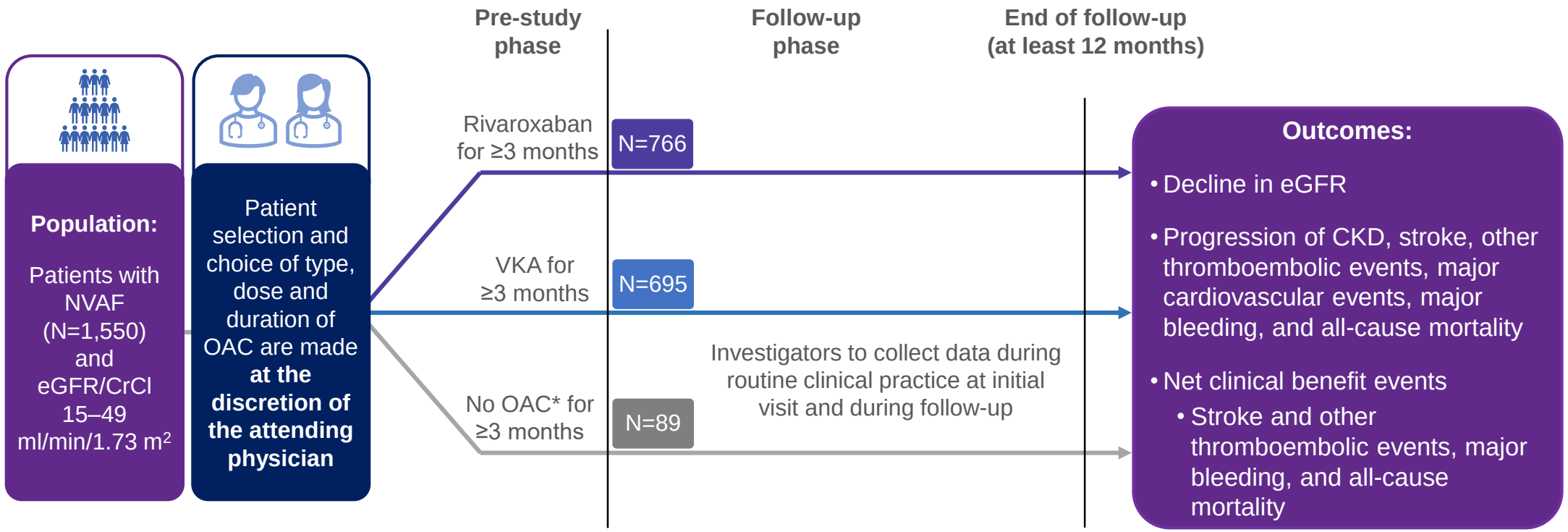
XARENO: Study Design[1–3]

Prospective, multicentre, non-interventional study



*Antiplatelet therapy allowed.

1. Kreutz R et al. *Circulation* 2020;142:A13927. Abstract 13927. 2. Kreutz R et al. *ACC.* Washington DC, USA, 2–4 April 2022. 3. GWT-TUD GmbH et al. 2019. https://clinicaltrials.gov/ct2/show/study/NCT02663076 [accessed 25 Feb 2022].

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Patients with Worse Baseline Kidney Function Are More Likely to Be Prescribed a VKA than Rivaroxaban

	Rivaroxaban (n=764)	VKA (n=691)	ASD
Age, years, mean ± SD	77.7±7.4	78.5±7.6	10.7
Male, n (%)	54.3	57.5	6.3
eGFR (ml/min/1.73 m²), %			
<15	0.1	1.3	13.9
15–19.9	1.7	8.1	30.0
20–29.9	11.1	26.5	40.1
30–39.9	33.1	25.6	16.5
40–49.9	35.2	21.7	30.3
≥50	7.1	3.9	13.9
Unknown	11.6	12.9	3.8
Co-morbidities, n (%)			
Hypertension	79.7	80.6	2.2
Diabetes	39.3	41.7	4.9
Ischaemic stroke	8.2	7.1	4.3
Heart failure	21.7	22.7	2.4
Myocardial infarction	11.9	14.3	7.2

Kreutz R et al. ACC. New Orleans, USA, 4–6 March 2023.

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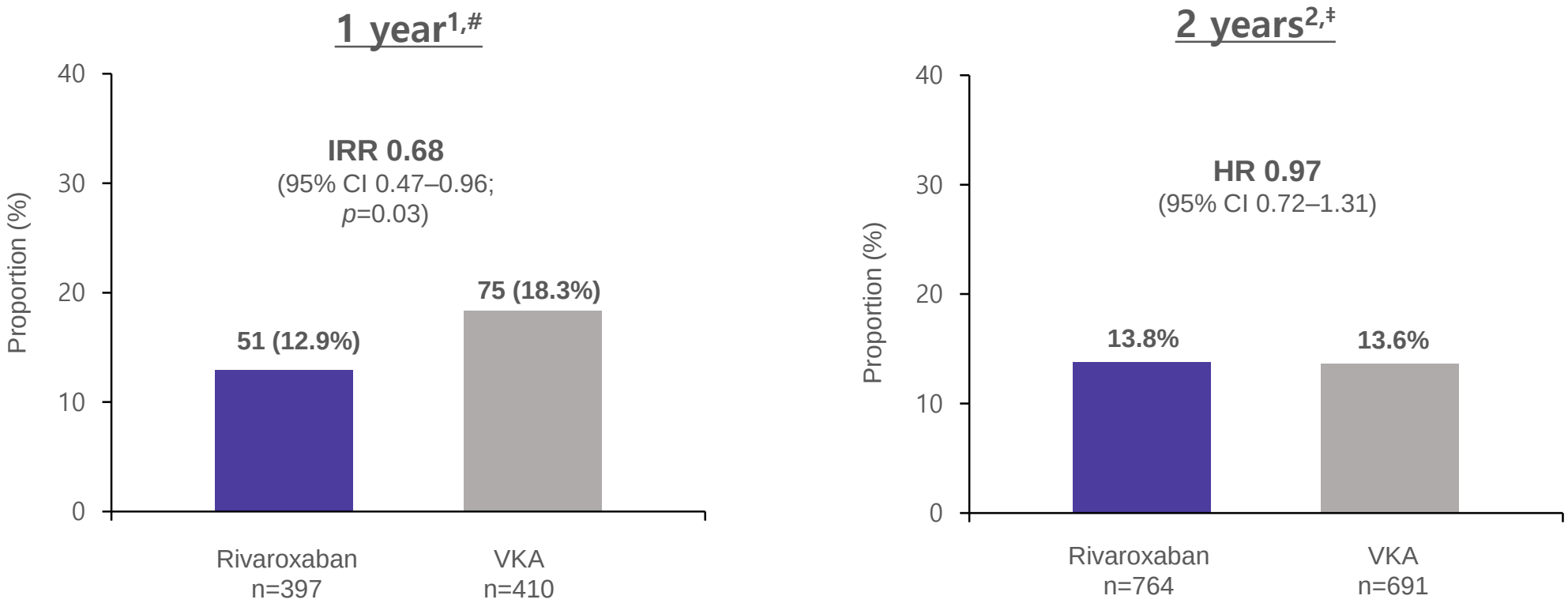
Patients Prescribed Rivaroxaban Experienced a Greater Net Clinical Benefit than Those Prescribed a VKA at 1 Year

Frequency of net clinical benefit events*



*Net clinical benefit (stroke and other thromboembolic events, major bleeding and all-cause mortality). #PSMA. ‡OLW.

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1. Kreutz R et al. ACC. Washington DC, USA, 2–4 April 2022. 2. Kreutz R et al. ACC. New Orleans, USA, 4–6 March 2023.

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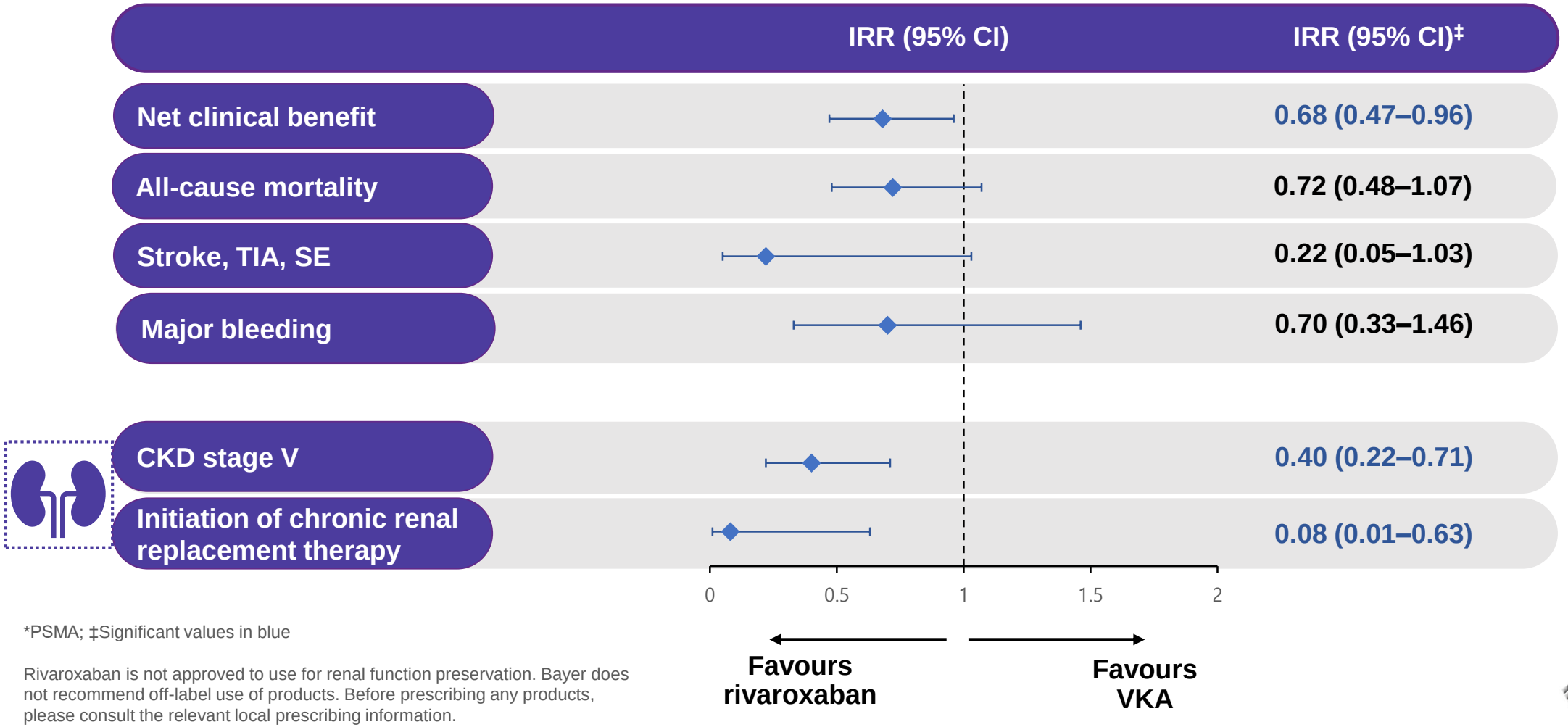
Patients Prescribed Rivaroxaban Had Significantly Better End-Stage Kidney Outcomes at 1 Year

Incidence Risk Ratios and 95% Confidence Intervals After 1 Year of Follow-up*



*PSMA; ‡Significant values in blue

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Kreutz R et al. ACC. New Orleans, USA, 4–6 March 2023.

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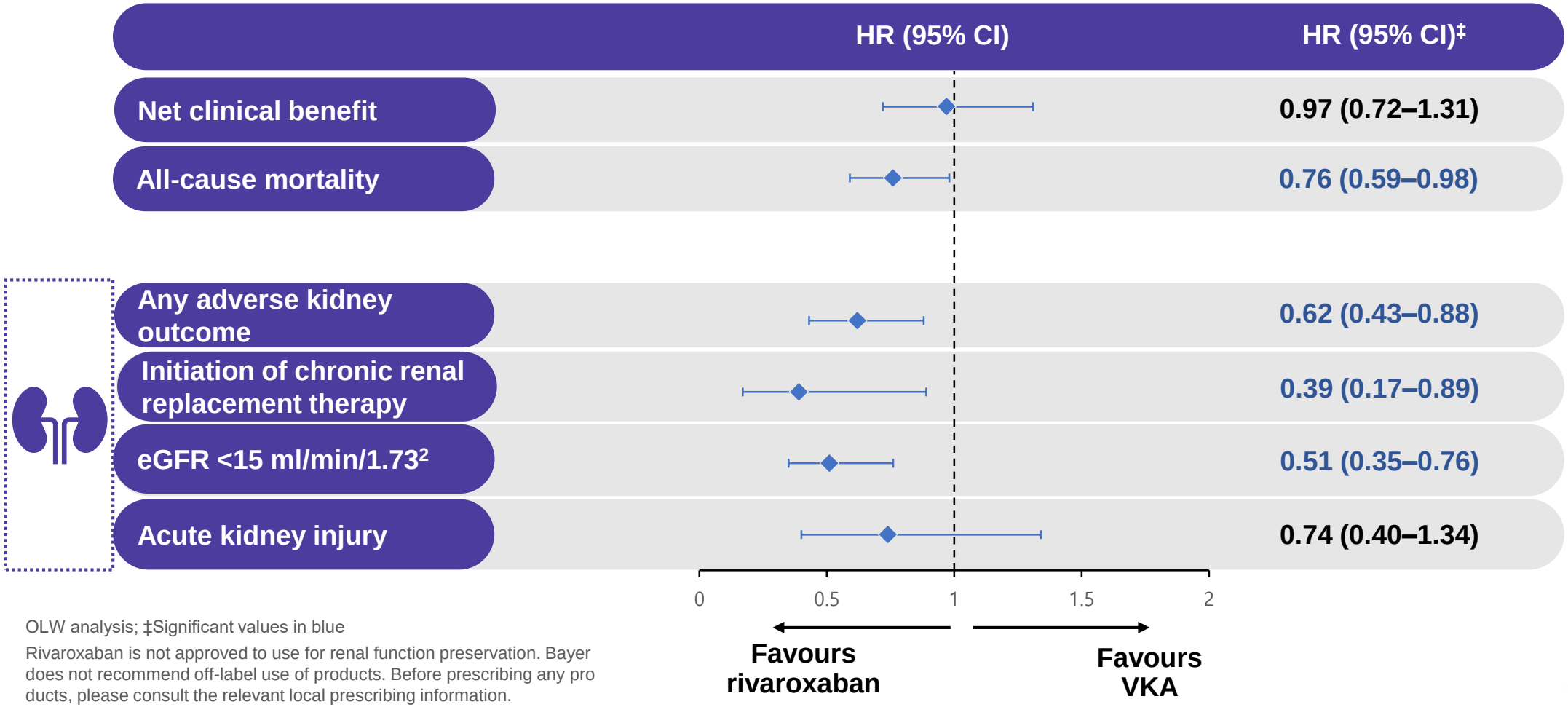
Favorable Kidney Outcomes in Patients Treated with Rivaroxaban Persisted Through 2 Years

Hazard Ratios and 95% Confidence Intervals After 2 Years of Follow-up*



OLW analysis; ‡Significant values in blue

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Kreutz R et al. ACC. New Orleans, USA, 4–6 March 2023.

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In XARENO study

- More patients with advanced CKD were treated with VKAs than rivaroxaban[1,2]
- After propensity-score matching, baseline eGFR was similar between the two groups, and numerically higher in the rivaroxaban group after follow-up[1,2]
- **Patients treated with rivaroxaban** experienced a lower rate of the composite of stroke and other thromboembolic events, major bleeding, and all-cause mortality at 1 year, and a significant all-cause mortality benefit was observed at 2 years[1,2]
- **Patients with CKD** who were prescribed rivaroxaban had significantly better adverse kidney outcomes than those treated with a VKA at both 1 and 2 years[1,2]

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1. Kreutz R et al. ACC. Washington DC, USA, 2–4 April 2022. 2. Kreutz R et al. ACC. New Orleans, USA, 4–6 March 2023.

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Conclusion

- ROCKET AF demonstrated consistent efficacy and safety profile in NVAF patients with moderate renal impairment[1]
- In Yao data, compared to warfarin, rivaroxaban was associated with reduced risks of:
  - ≥30% decline in eGFR (HR 0.73; 95% CI 0.62–0.87; p<0.001)
  - Doubling of serum creatinine (HR 0.46; 95% CI 0.28–0.75; p<0.01)
  - AKI (HR 0.69; 95% CI 0.57–0.84; p<0.001)
- Rivaroxaban significantly prevented the reduction in CrCl over time vs. warfarin in real world evidence
  - In RENOVATOR study, Korean patients receiving Rivaroxaban had consistent safety and efficacy profiles as observed in other studies
  - In XARENO study, Patients with CKD who were prescribed rivaroxaban had significantly better adverse kidney outcomes than those treated with a VKA at 1 year
- Rivaroxaban (15 mg OD) can be prescribed in NVAF patients with ESRD on dialysis as well as moderate to severe renal impairment in US (FDA approval in 2018).

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Thank you for your attention