



# ICT 2023

28th International  
Congress on Thrombosis

# Bleeding Risk Assessment in End-Stage Kidney Disease

*Daniel Caldeira, MD PhD FESC, Portugal*

## Declaration of interests

In last 5 years participated in educational events and/or congresses or conference (which included travel/hospitality) with Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Merck Serono, Ferrer, Pfizer, Novartis and Roche.



CENTRO HOSPITALAR  
UNIVERSITÁRIO  
LISBOA NORTE, EPE



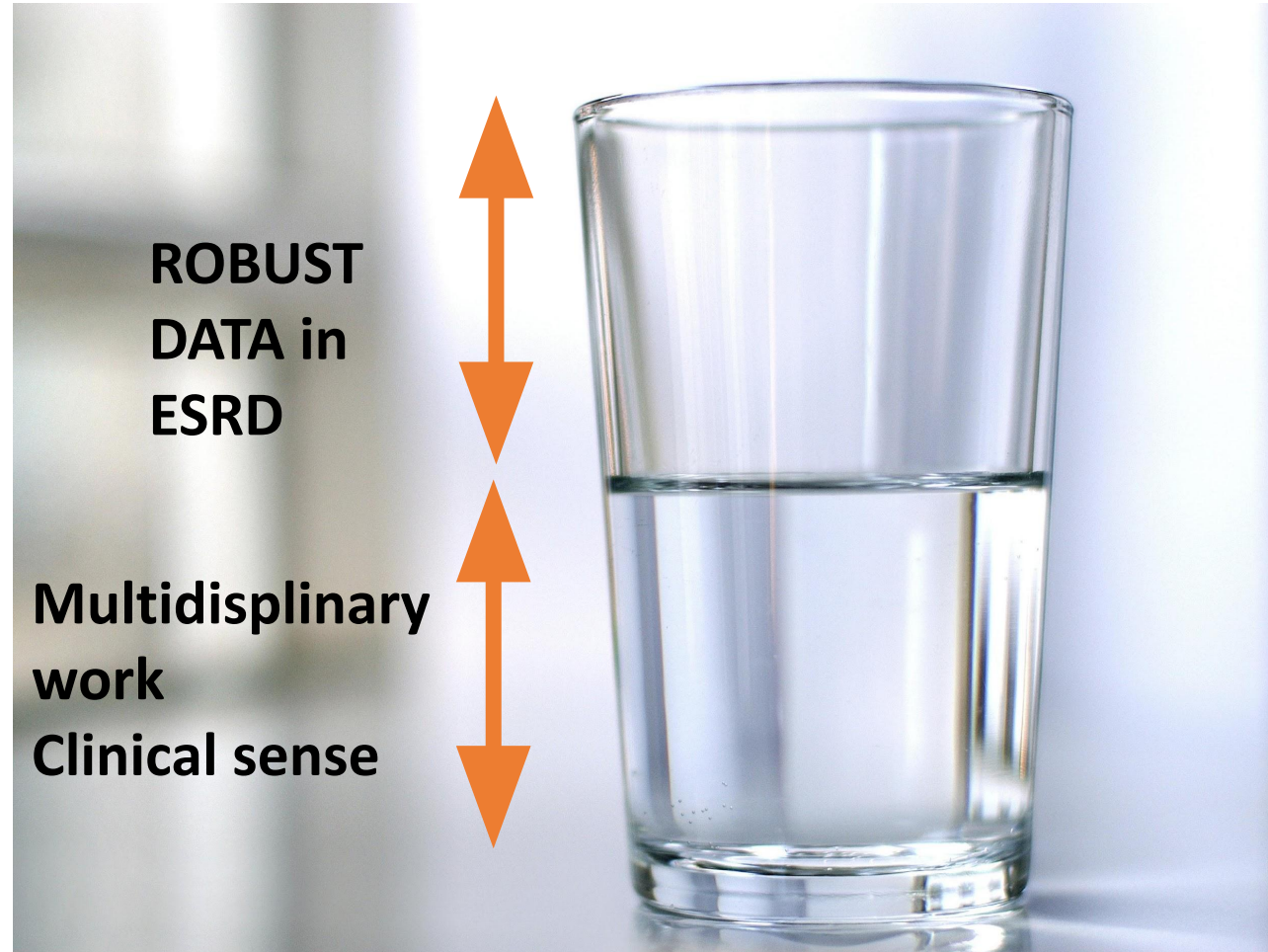
# My opinion

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# My opinion

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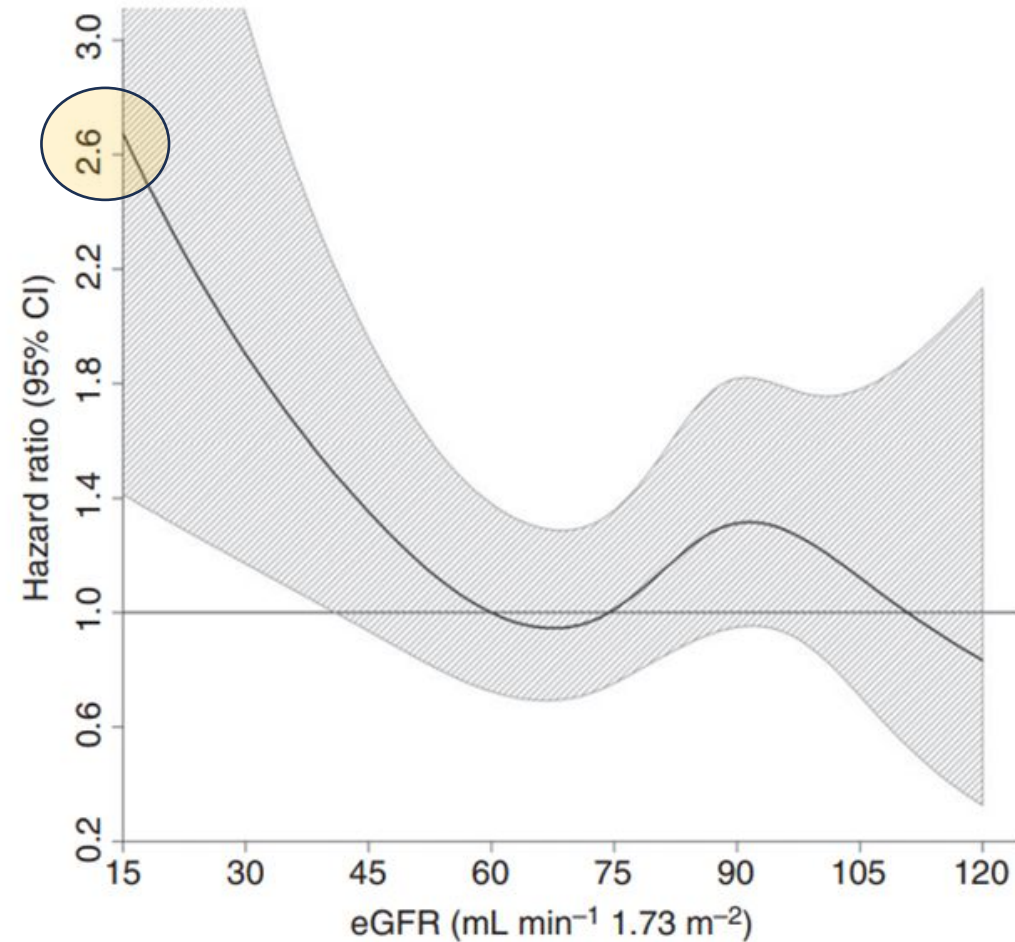
# Topics

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- Bleeding, Atrial Fibrillation (Afib), Stroke in ESRD
- Bleeding factors in ESRD
- Oral anticoagulation in Afib & ESRD
  - New trials
- Bleeding risk prediction in Afib & ESRD

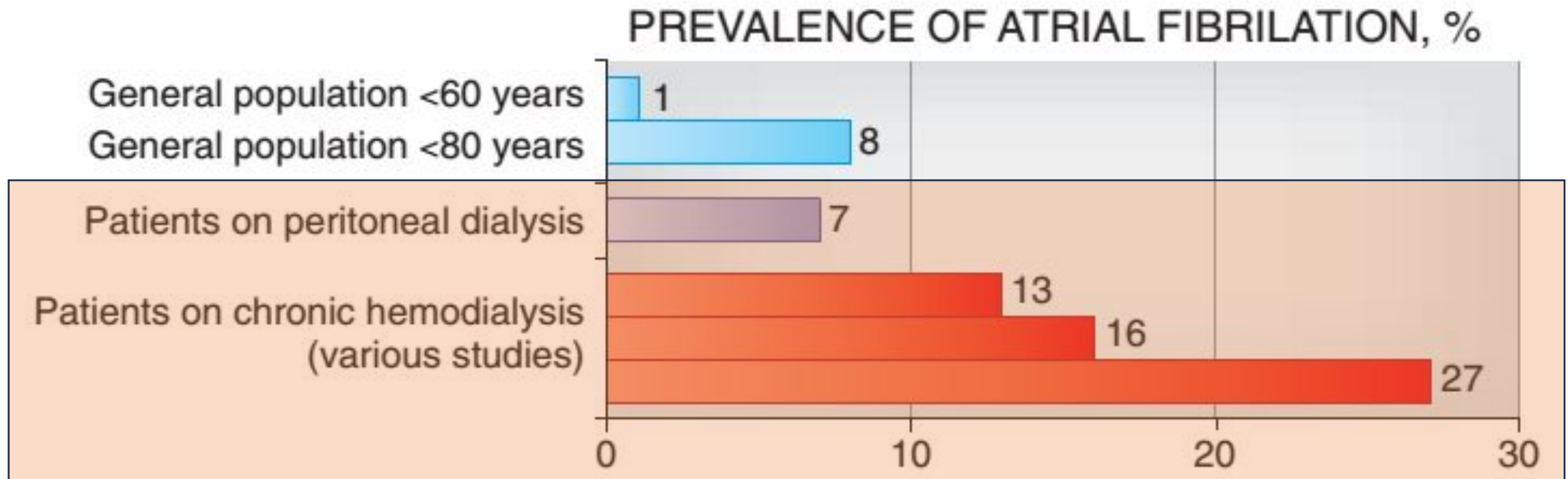
# Bleeding in Renal Disease

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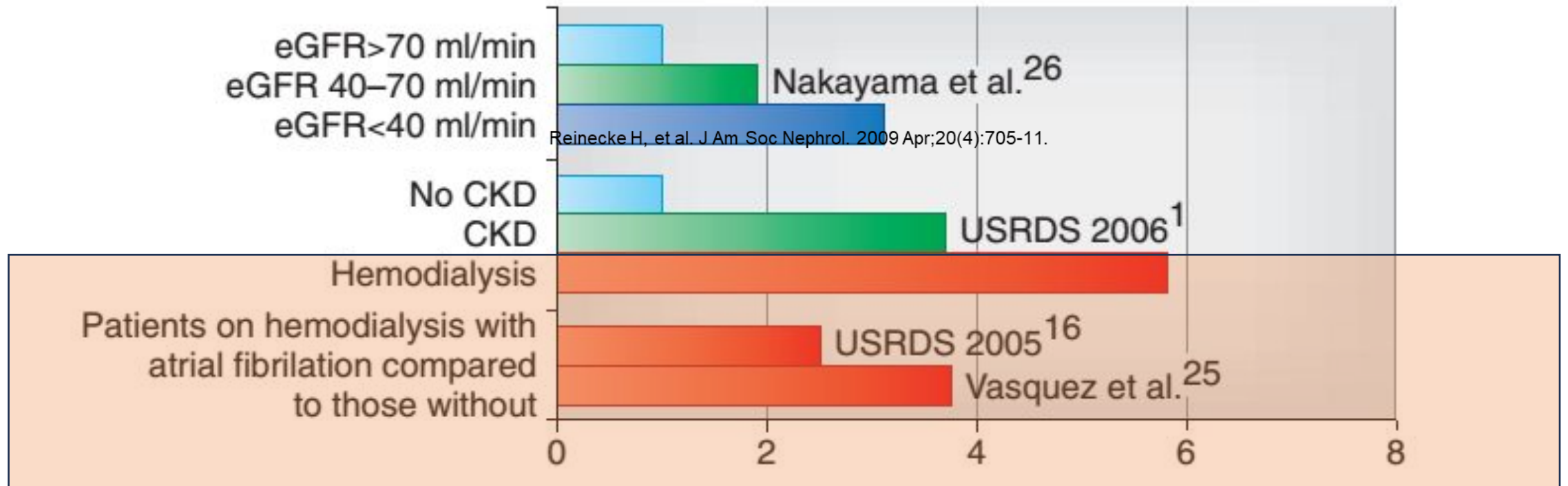
# AFib in ESRD

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# Stroke in ESRD

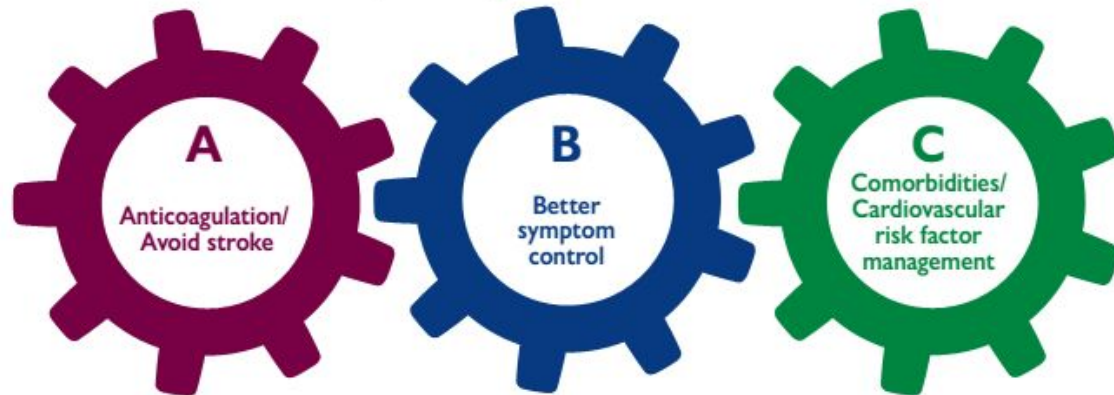
RELATIVE RISK OF STROKE IN DIFFERENT SUBGROUPS OF CKD



# WHEN A ESRD HAS ATRIAL FIBRILLATION

## 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

### Treat AF: The ABC pathway



1. Identify low-risk patients  
CHA<sub>2</sub>DS<sub>2</sub>-VASc 0(m), 1(f)
2. Offer stroke prevention if  
CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥1(m), 2(f)  
Assess bleeding risk, address  
modifiable bleeding risk factors
3. Choose OAC (NOAC or VKA  
with well-managed TTR)

- Assess symptoms,  
QoL and patient's  
preferences
- Optimize rate  
control
- Consider a rhythm  
control strategy  
(CV, AADs, ablation)

- Comorbidities and  
cardiovascular risk  
factors
- Lifestyle changes  
(obesity reduction,  
regular exercise,  
reduction of alcohol use,  
etc.)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease <sup>2</sup>	1
Age 65–74	1
Sex category (i.e. female sex)	1
<b>Maximum score</b>	<b>9</b>

# Clinical prediction rules - Bleeding

Risk Stratification Schemes for Bleeding Prediction in Atrial Fibrillation			
Risk score	HEMORR <sub>2</sub> HAGES	HAS-BLED	ATRIA
Variables	Age	Age	Age
	Hepatic/renal disease	Abnormal renal/liver function	Renal disease
	Hypertension	Hypertension	Hypertension
	Prior bleeding	Prior bleeding	Prior bleeding
	Stroke	Stroke	Anemia
	Alcohol abuse	Drugs/alcohol	
	Anemia	Labile INR	
	Cancer		
	Reduced platelet count/function		
	Genetic factors		
	Fall risk		

# Bleeding factors in ESRD

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## Factors Predisposing for Bleeding

Platelet abnormalities including subnormal dense granule content  
Reduction in intracellular ADP and serotonin  
Impaired release of the platelet  $\alpha$ -granule protein and  $\beta$ -thromboglobulin  
Enhanced intracellular cAMP and abnormal mobilization of platelet  $\text{Ca}^{2+}$   
Abnormal platelet arachidonic acid metabolism  
Defective cyclo-oxygenase activity  
Abnormality of the activation-dependent binding activity of GPIIb/IIIa  
Increased formation of vascular PGI<sub>2</sub>  
Altered von Willebrand factor

## Dilemmas in the Management of Atrial Fibrillation in Chronic Kidney Disease

Holger Reinecke,\* Eva Brand,<sup>†</sup> Rolf Mesters,<sup>‡</sup> Wolf-Rüdiger Schäbitz,<sup>§</sup> Marc Fisher,<sup>||</sup> Hermann Pavenstädt,<sup>†</sup> and Günter Breithardt\*

### Indirectly:

Presence of uremic toxins, especially parathyroid hormone  
Anemia/altered blood rheology  
Erythropoietin deficiency  
Specific drug treatment (e.g., nonsteroidal anti-inflammatory drugs)  
Catheter; Heparin in dialysis

# Guidelines

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...or just lines that do not guide that much...

## Anticoagulation guidelines in ESRD patients with AF

Scientific society (reference)	Year	Guideline
K-DOQI <sup>49</sup>	2005	Antithrombotic therapy (warfarin and aspirin) should be considered, based on an assessment of the risk of embolism and of bleeding complications. Dialysis patients are at increased risk for bleeding and careful monitoring should accompany intervention.
KDIGO <sup>50</sup>	2011	Weighing the available evidence, the benefit of warfarin anticoagulation for primary prevention of stroke in CKD 5D patients is questionable.
European Society of Cardiology <sup>51</sup>	2012	AF patients with severe renal failure have not been adequately studied and their risk assessment is complex.
Canadian Society of Cardiology <sup>52</sup>	2014	There are no randomized trials data for nonvalvular AF patients who are dialysis dependent, and we therefore cannot recommend their routine anticoagulation.
American Heart Association/ American College of Cardiology/Heart Rhythm Society <sup>2</sup>	2014	For patients with nonvalvular AF with a CHA2DS2-VASc score of $\geq 2$ and who have end-stage CKD (creatinine clearance $< 15$ mL/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0-3.0) for oral anticoagulation. (Level of Evidence: B)



ESC

European Society  
of Cardiology

European Heart Journal (2020) 00, 1–125

doi:10.1093/eurheartj/ehaa612

ESC GUIDELINES

# 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC)

## 11.8 Atrial fibrillation and chronic kidney disease

excluded from the major RCTs. The evidence for the benefits of OAC in patients with end-stage kidney disease with  $\text{CrCl} \leq 15 \text{ mL/min}$  or on dialysis is even more limited, and to some extent controversial. There are no RCTs, whereas observational data question the benefit of OAC in this patient population. Data from observational

### DATA

- LIMITED / OBSERVATIONAL
- CONTROVERSIAL

# OAC in ESRD

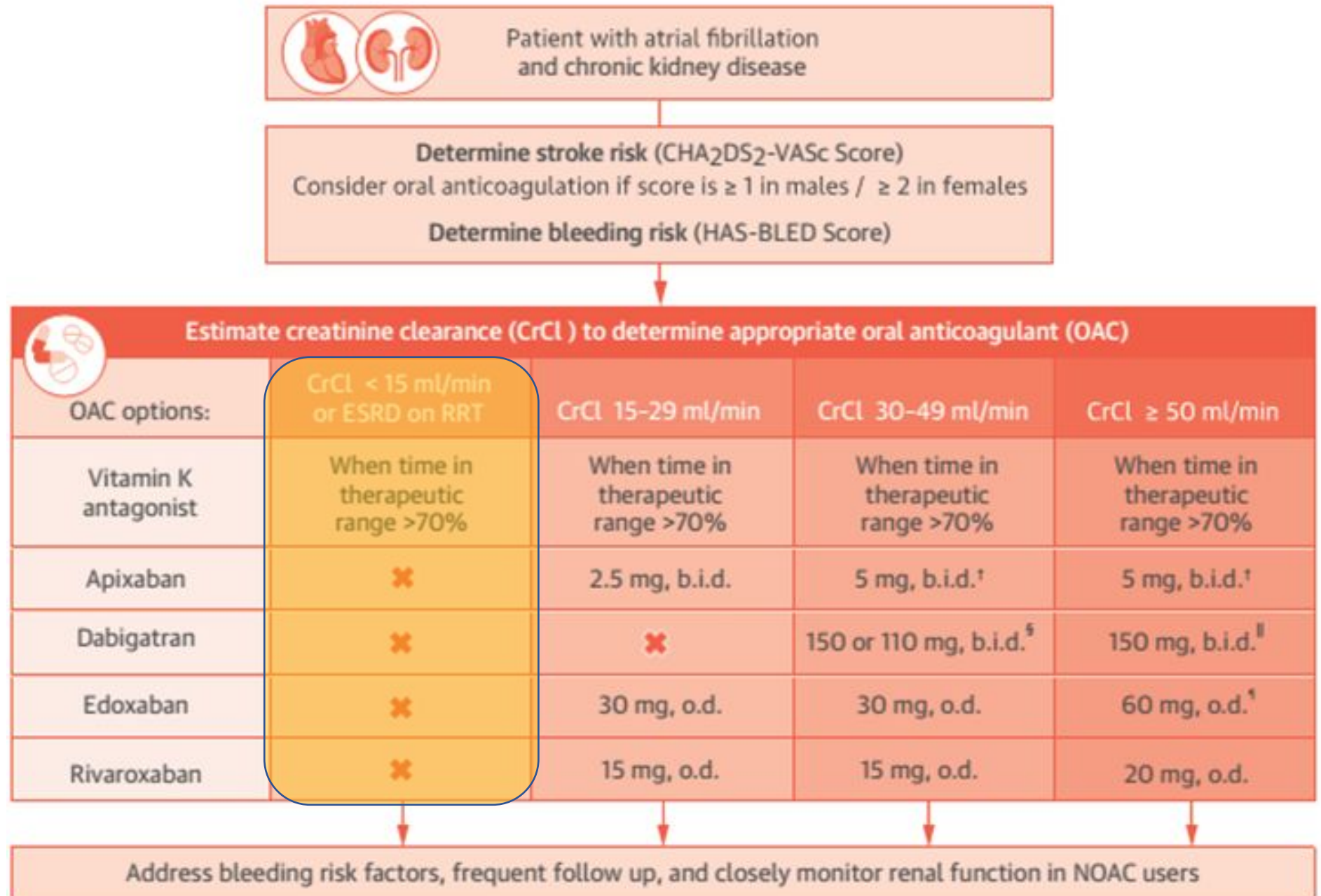
Study (reference)	Population	Outcome	HR (95% CI)
<b>Benefit</b>			
Olesen et al <sup>17</sup>	1074 hemodialysis, 212 peritoneal dialysis, 92 kidney transplant	Total stroke	0.44 (0.26-0.74)
Bonde et al <sup>11</sup>	1026 hemodialysis, 344 peritoneal dialysis, 25 kidney transplant with CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2*	All cause mortality	0.85 (0.72-0.33)
Carrero et al <sup>18</sup>	478 post-MI with eGFR ≤15 mL/min	Composite of death, MI, ischemic stroke	0.57 (0.37-0.86)
Shen et al <sup>14</sup>	12,284 prevalent hemodialysis	Ischemic stroke	0.68 (0.47-0.99)
<b>No benefit</b>			
Wizemann et al <sup>4</sup>	1001 prevalent hemodialysis ≤65 y	Total stroke	1.29 (0.45-3.68)
	1137 prevalent hemodialysis 65-75 y	Total stroke	1.35 (0.69-2.63)
Winkelmayer et al <sup>19</sup>	2313 prevalent hemodialysis >65 y	Total stroke	1.08 (0.76-1.55)
		Ischemic stroke	0.92 (0.61-1.37)
		Hemorrhagic stroke	2.38 (1.15-4.96)
Wakasugi et al <sup>20</sup>	60 prevalent hemodialysis	Ischemic stroke	1.94 (0.63-5.93)
Shah et al <sup>21</sup>	1626 prevalent hemodialysis and peritoneal dialysis	Ischemic stroke	1.14 (0.78-1.67)
Genovesi et al <sup>22</sup>	290 prevalent hemodialysis	Ischemic stroke	0.12 (0.00-3.59)
<b>Harm</b>			
Chan et al <sup>23</sup>	1671 incident hemodialysis	Total stroke	1.93 (1.29-2.90)
		Ischemic stroke	1.81 (1.12-2.92)
		Hemorrhagic stroke	2.22 (1.01-4.91)
Wizemann et al <sup>4</sup>	1107 prevalent hemodialysis >75 y	Total stroke	2.17 (1.04-4.53)

**Table 14** Dose adjustment for NOACs as evaluated in the PHASE III trials (adapted from Hart et al.<sup>316</sup>)

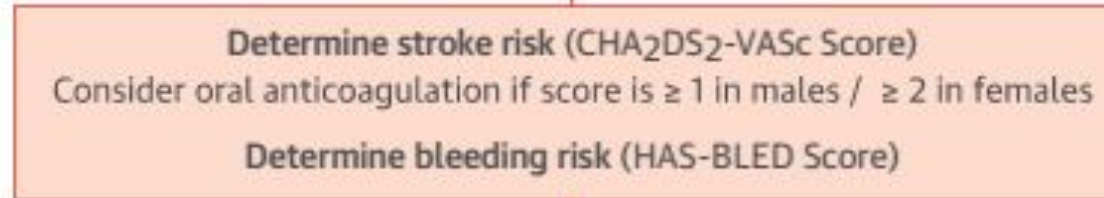
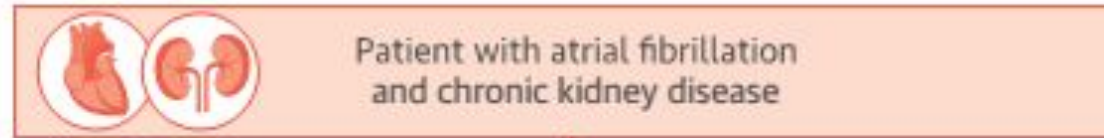
	Dabigatran (RE-LY) <sup>318, 425</sup>	Rivaroxaban (ROCKET-AF) <sup>320, 426</sup>	Apixaban (ARISTOTLE) <sup>319, 427</sup>	Edoxaban (ENGAGE AF-TIMI 48) <sup>321</sup>
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 mL/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl <30–49 mL/min	2.5 mg twice daily if serum creatinine ≥1.5 mg/dL (133 µmol/L) plus age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

CKD = chronic kidney disease; CrCl = creatinine clearance; GFR = glomerular filtration rate; NA = not available.

# Europe



# United States

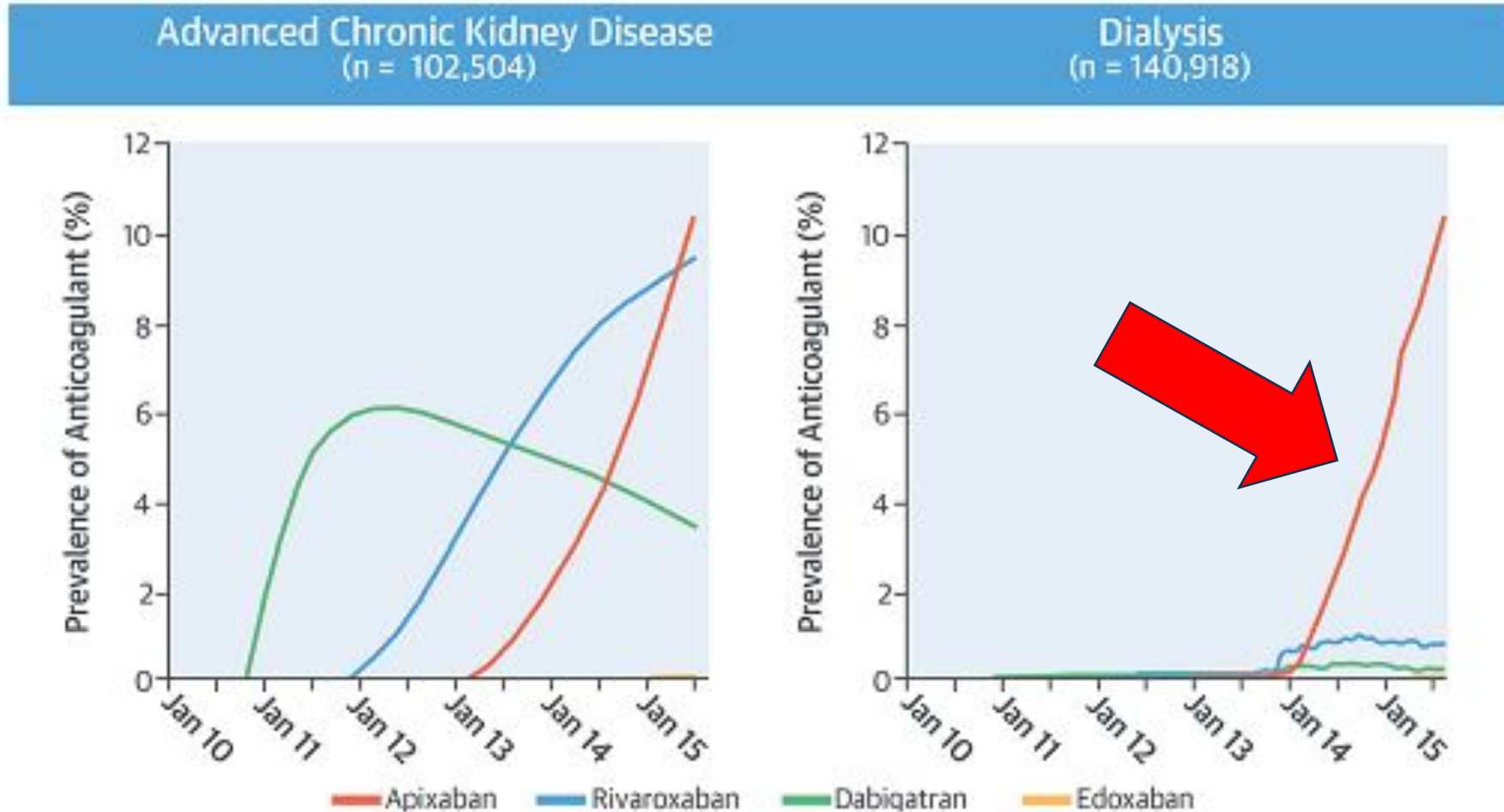


Estimate creatinine clearance (CrCl ) to determine appropriate oral anticoagulant (OAC)

OAC options:	CrCl < 15 ml/min or ESRD on RRT	CrCl 15-29 ml/min	CrCl 30-49 ml/min	CrCl ≥ 50 ml/min
Vitamin K antagonist	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%
Apixaban	5 mg, b.i.d.*	2.5 mg, b.i.d.	5 mg, b.i.d. <sup>†</sup>	5 mg, b.i.d. <sup>†</sup>
Dabigatran	×	75 mg, b.i.d. <sup>†</sup>	150 or 110 mg, b.i.d. <sup>§</sup>	150 mg, b.i.d. <sup>  </sup>
Edoxaban	×	30 mg, o.d.	30 mg, o.d.	60 mg, o.d. <sup>§</sup>
Rivaroxaban	×	15 mg, o.d.	15 mg, o.d.	20 mg, o.d.

Address bleeding risk factors, frequent follow up, and closely monitor renal function in NOAC users

# NOACs in US / ESRD



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

# JASN

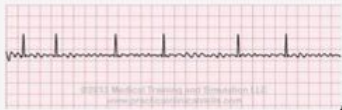
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

## VALKYRIE TRIAL

### METHODS



N=132



VKA INR 2-3

Rivaroxaban 10 mg od

Rivaroxaban+vitamin K2

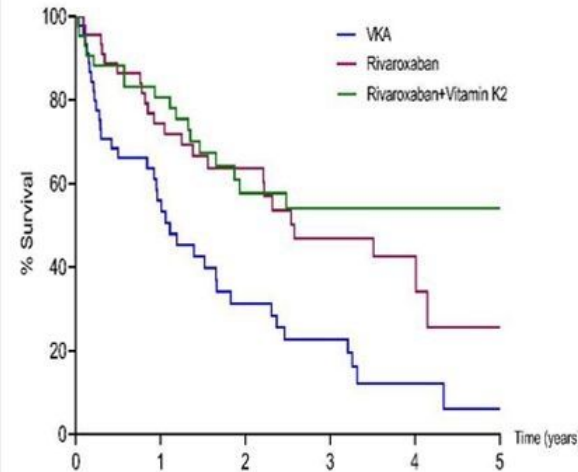
### OUTCOME

#### 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 <sub>Cox-adj</sub>
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

ORIGINAL RESEARCH ARTICLE



# A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study

Holger Reinecke<sup>1</sup>, MD; Christiane Engelbertz<sup>2</sup>, PhD; Rupert Bauersachs, MD; Günter Breithardt<sup>3</sup>, MD; Hans-Herbert Echterhoff, MD; Joachim Gerß<sup>4</sup>, PhD; Karl Georg Haeusler<sup>5</sup>, MD; Bernd Hewing, MD; Joachim Hoyer, MD; Sabine Juergensmeyer, PhD; Thomas Klingenhöfen, MD; Guido Knapp, PhD; Lars Christian Rump, MD; Hans Schmidt-Guertler, MD; Christoph Wanner<sup>6</sup>, MD; Paulus Kirchhof<sup>7</sup>, MD\*; Dennis Goerlich, PhD\*

**METHODS:** From June 2017 through May 2022, AXADIA-AFNET 8 (Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease), an investigator-initiated PROBE (prospective randomized open blinded end point) outcome assessment trial, randomized patients with AF on chronic hemodialysis to either apixaban (2.5 mg BID) or the vitamin K antagonist (VKA) phenprocoumon (international normalized ratio, 2.0 to 3.0). The composite primary safety outcome was defined by a first event of major bleeding, clinically relevant nonmajor bleeding, or all-cause death. The primary efficacy outcome was a composite of ischemic stroke, all-cause death, myocardial infarction, and deep vein thrombosis or pulmonary embolism. Our hypothesis was that apixaban is noninferior to VKA.

**RESULTS:** Thirty-nine sites randomized 97 patients (30% women; mean age 75 years; mean CHA<sub>2</sub>DS<sub>2</sub>-VASc [congestive heart

**CONCLUSIONS:** In this randomized trial comparing apixaban and VKA in patients with AF on hemodialysis with long follow-up, no differences were observed in safety or efficacy outcomes. Even on oral anticoagulation, patients with AF on hemodialysis remain at high risk of cardiovascular events. Larger randomized trials are needed to determine the optimal anticoagulation regimen for patients with AF on hemodialysis.

ORIGINAL RESEARCH ARTICLE



# Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial

Sean D. Pokorney<sup>1</sup>, MD, MBA; Glenn M. Chertow, MD; Hussein R. Al-Khalidi<sup>2</sup>, PhD; Dianne Gallup, MS; Pat Dignacco, BA; Kurt Mussina, MBA; Nisha Bansal, MD; Crystal A. Gadegbeku, MD; David A. Garcia, MD; Samira Garonzik, PharmD; Renato D. Lopes<sup>3</sup>, MD, PhD; Kenneth W. Mahaffey, MD; Kelly Matsuda, PharmD; John P. Middleton, MD; Jennifer A. Rymer<sup>4</sup>, MD, MBA; George H. Sands, MD; Ravi Thadhani, MD; Kevin L. Thomas<sup>5</sup>, MD; Jeffrey B. Washam, PharmD; Wolfgang C. Winkelmayer, MD; Christopher B. Granger<sup>6</sup>, MD; on behalf of the RENAL-AF Investigators

**METHODS:** The RENAL-AF trial (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation) was a prospective, randomized, open-label, blinded-outcome evaluation (PROBE) of apixaban versus warfarin in patients receiving hemodialysis with AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ . Patients were randomly assigned 1:1 to 5 mg of apixaban twice daily (2.5 mg twice daily for patients  $\geq 80$  years of age, weight  $\leq 60$  kg, or both) or dose-adjusted warfarin. The primary outcome was time to major or clinically relevant nonmajor bleeding. Secondary outcomes included stroke, mortality, and apixaban pharmacokinetics. Pharmacokinetic sampling was day 1, day 3, and month 1.

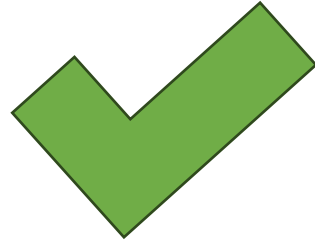
**RESULTS:** From January 2017 through January 2019, 154 patients were randomly assigned to apixaban (n=82) or warfarin (n=72). The trial stopped prematurely because of enrollment challenges. Time in therapeutic range (international normalized

**CONCLUSIONS:** There was inadequate power to draw any conclusion regarding rates of major or clinically relevant nonmajor bleeding comparing apixaban and warfarin in patients with AF and end-stage kidney disease on hemodialysis. Clinically relevant bleeding events were  $\approx 10$ -fold more frequent than stroke or systemic embolism among this population on anticoagulation, highlighting the need for future randomized studies evaluating the risks versus benefits of anticoagulation among patients with AF and end-stage kidney disease on hemodialysis.

# NOACs in AF and ESRD

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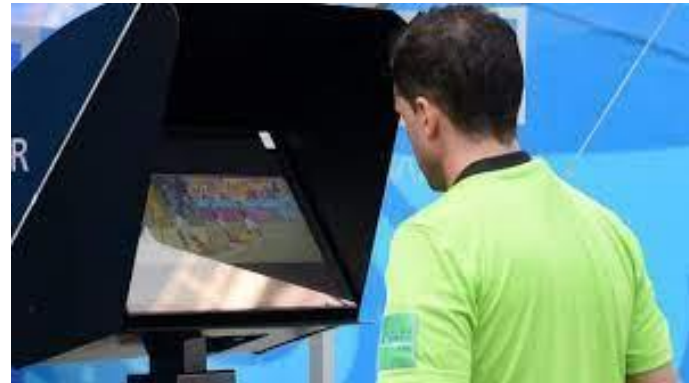
VALKYRIE TRIAL



AXADIA-AFNET 8



RENAL-AF



# Bleeding Risk Assessment in End-Stage Kidney Disease: Validation of Existing Risk Scores and Evaluation of a Machine Learning-Based Approach

Stephan Nopp<sup>1</sup> Clemens P. Spielvogel<sup>2,3</sup> Sabine Schmaldienst<sup>4</sup> Renate Klauser-Braun<sup>5</sup>  
Matthias Lorenz<sup>6</sup> Benedikt N. Bauer<sup>1</sup> Ingrid Pabinger<sup>1</sup> Marcus Säemann<sup>7</sup> Oliver Königsbrügge<sup>1</sup>  
Cihan Ay<sup>1</sup>

Bleeding risk score	Total study cohort (n = 625) C-statistics (95% CI)	Subgroup of patients with atrial fibrillation (n = 165) C-statistic (95% CI)
HAS-BLED	0.59 (0.53–0.66)	0.54 (0.42–0.66)
ATRIA	0.55 (0.48–0.62)	0.58 (0.46–0.70)
HEMORR <sub>2</sub> HAGES	0.58 (0.51–0.65)	0.56 (0.44–0.69)
ORBIT	0.59 (0.52–0.66)	0.61 (0.47–0.74)
OBRI	0.54 (0.47–0.61)	0.54 (0.44–0.64)
mOBRI	0.54 (0.47–0.60)	0.55 (0.44–0.65)
Shireman et al	0.59 (0.52–0.67)	0.62 (0.50–0.74)

## Modest prediction estimates in ESRD

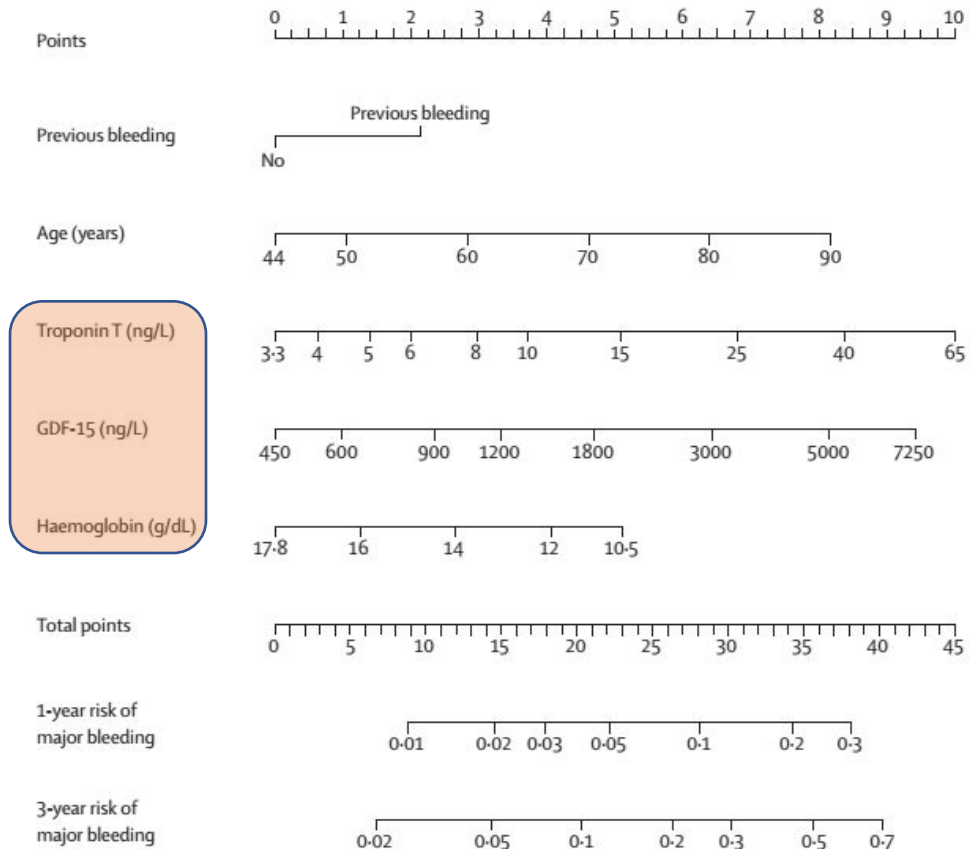
### Review

The HAS-BLED Score for Predicting Major Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis

Score	Synthesis of C Statistic (95% CI)
HAS-BLED	0.65 (0.61-0.69)

# The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study

Ziad Hijazi, Jonas Oldgren, Johan Lindbäck, John H Alexander, Stuart J Connolly, John W Eikelboom, Michael D Ezekowitz, Claes Held, Elaine M Hylek, Renato D Lopes, Agneta Siegbahn, Salim Yusuf, Christopher B Granger, Lars Wallentin, on behalf of the ARISTOTLE and RE-LY Investigators



Hemoglobin  
High-sensitivity troponin  
GDF-15

# Growth differentiation factor-15 predicts major bleeding, major adverse cardiac events and mortality in patients with end-stage kidney disease on haemodialysis: findings from the VIVALDI study

Get access >

Stephan Nopp, Oliver Königsbrügge, Sabine Schmaldienst, Renate Klauser-Braun, Matthias Lorenz, Ingrid Pabinger, Marcus Säemann, Cihan Ay ✉

*Nephrology Dialysis Transplantation*, gfac321, <https://doi.org/10.1093/ndt/gfac321>

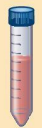
Published: 06 December 2022 Article history ▾

## Growth differentiation factor-15 predicts major bleeding, major adverse cardiac events and mortality in patients with end-stage kidney disease on haemodialysis: findings from the VIVALDI study

### Methods



**Hemodialysis patients** in Vienna  
n=594



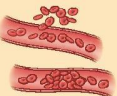
#### Biomarker GDF-15

- Linked with oxidative stress and inflammation
- Associated with kidney function



#### Follow-up:

Median follow-up 3.5 years



#### Primary endpoints



#### Secondary endpoints

### Results

#### GDF-15 levels

Median 5475 ng/L (25th–75th percentile: 3964–7533)

#### Bleeding



**SHR 1.31**

95% CI 1.00–1.71  
per doubling of GDF-15

#### Mortality



**SHR 1.58**

95% CI 1.28–1.95  
per doubling of GDF-15

#### MACE



**SHR 1.47**

95% CI 1.11–1.94  
per doubling of GDF-15

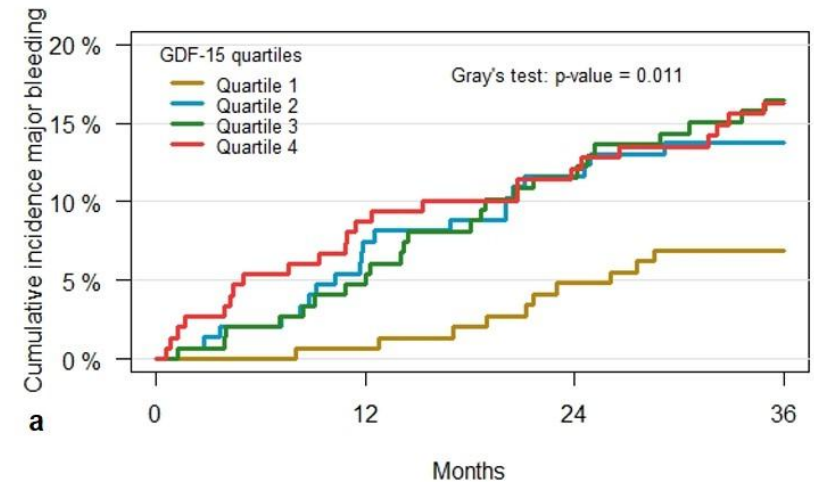
#### GDF-15 improves prediction of major bleeding in ESKD

C-statistic of the HAS-BLED score improved from 0.61 to 0.68 with the addition of GDF-15

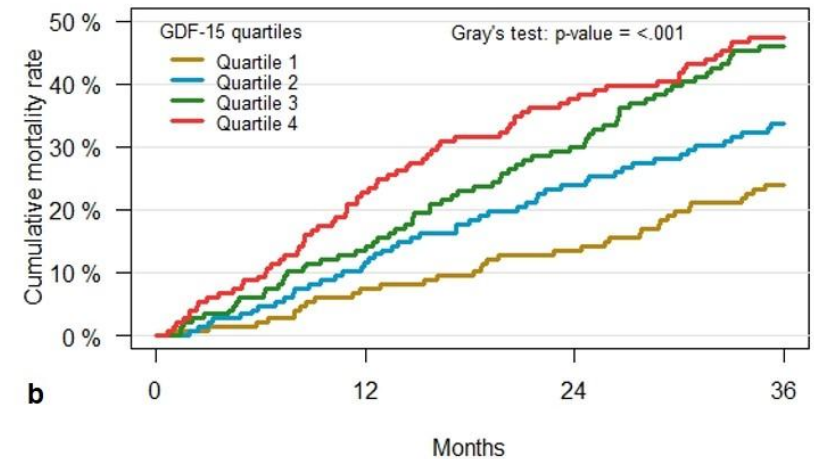
#### GDF-15 improves prediction of MACE and death in ESKD

GDF-15 adds predictive value to current models on MACE and death risk prediction

Nopp S., et al. *NDT* (2023)  
@NDTSocial



Quartile 1:	149	143	134	124	115	106	99	92	82	75	68
Quartile 2:	148	141	134	119	110	101	92	82	75	70	62
Quartile 3:	148	139	125	113	103	91	77	68	61	53	45
Quartile 4:	149	135	120	106	92	83	72	67	61	54	50



Quartile 1:	149	143	134	125	117	109	103	98	89	81	74
Quartile 2:	148	143	138	127	120	112	106	95	86	81	72
Quartile 3:	148	140	129	118	111	99	86	79	70	60	53
Quartile 4:	149	139	128	116	101	90	79	75	69	60	57

# Bleeding risk assessment in ESRD/ My conclusion

Potentially modifiable	Modifiable
Extreme frailty ± excessive risk of falls <sup>a</sup>	Hypertension/elevated SBP
Anaemia	Concomitant antiplatelet/NSAID
Reduced platelet count or function	Excessive alcohol intake
Renal impairment with CrCl <60 mL/min	Non-adherence to OAC
VKA management strategy <sup>b</sup>	Hazardous hobbies/occupations
	Bridging therapy with heparin
	INR control (target 2.0 - 3.0), target TTR >70% <sup>c</sup>
	Appropriate choice of OAC and correct dosing <sup>d</sup>

- Type of dialysis
- Treatment/prevention of comorbidities that lead to bleeding complications (peptic ulcer)
- Vascular access issues – malfunction, infection...
- Overall functional status
- Mobility and ability to comply with medical regimens
- Frailty or impaired mobility

