Belgrade University *Clinical Centre of Serbia, Belgrade, Serbia*

October 16 - 18
14th EDITION 2015

CHRONIC KIDNEY DISEASE (CKD) IN THE PATIENT WITH ATRIAL FIBRILLATION

CKD and atrial fibrillation: warfarin, NOAC or nothing?

KLINIČKI CENTAR SRBIJE

Tatjana S. Potpara, MD, PhD, FESC

Assist. Prof. in Cardiology, School of Medicine, Belgrade University;

Head of the Department for arrhythmia intensive care, Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia;

President of the Serbian Atrial Fibrillation Association (SAFA);

The EHRA Scientific Initiatives Committee co-chair;

Past Chair of the Working Group on Cardiac Arrhythmias, Serbian Cardiology Society.

October 16 - 18
14th EDITION 2015

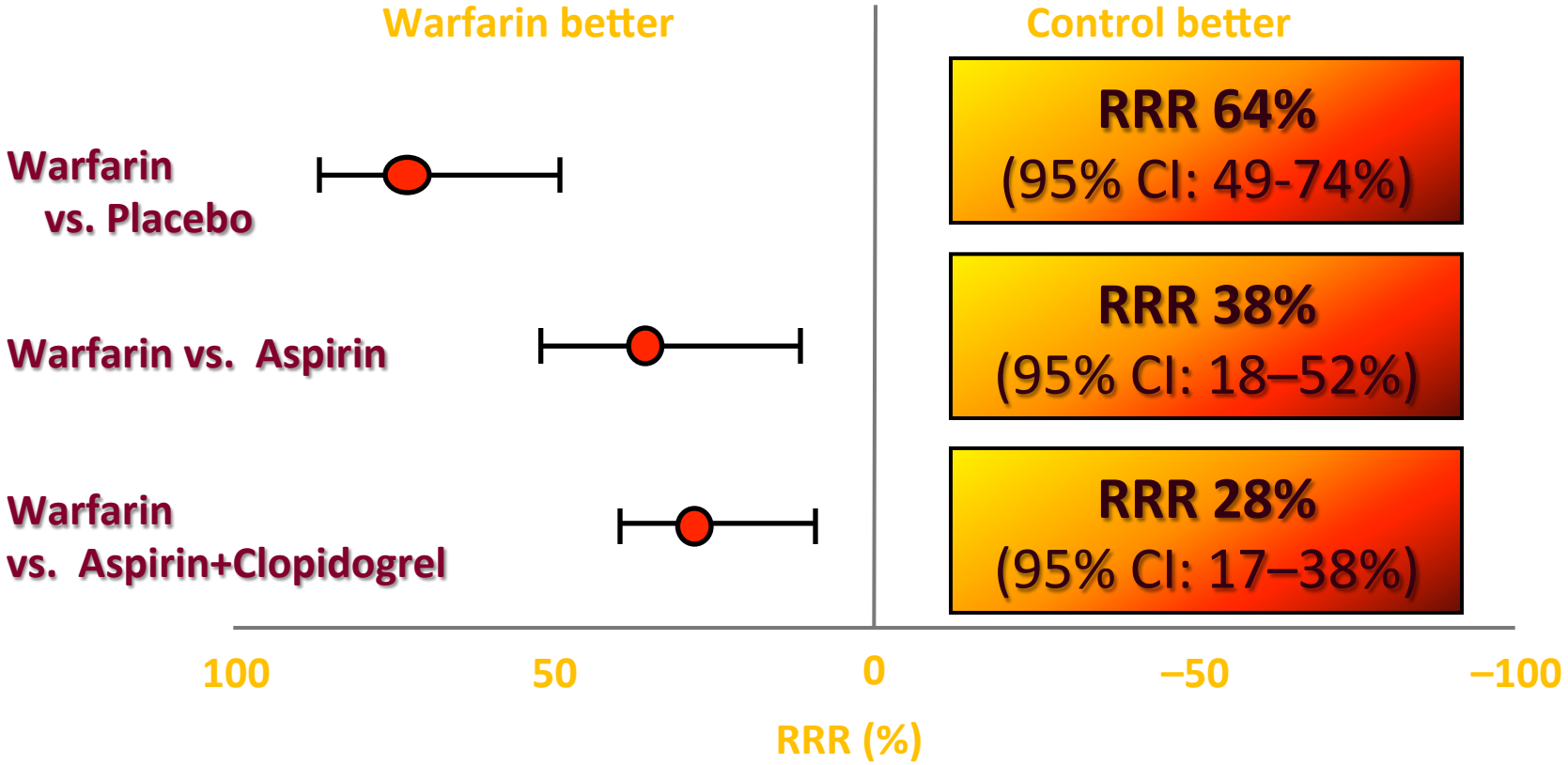
MY CONFLICTS OF INTEREST:

Consultant and speaker for

- **Bayer,**
- **Pfizer and**
- **Boehringer Ingelheim**

Oral anticoagulant therapy (vitamin K antagonists) in non-valvular AF patients

Warfarin for stroke prevention in AF (*Randomized trials*)

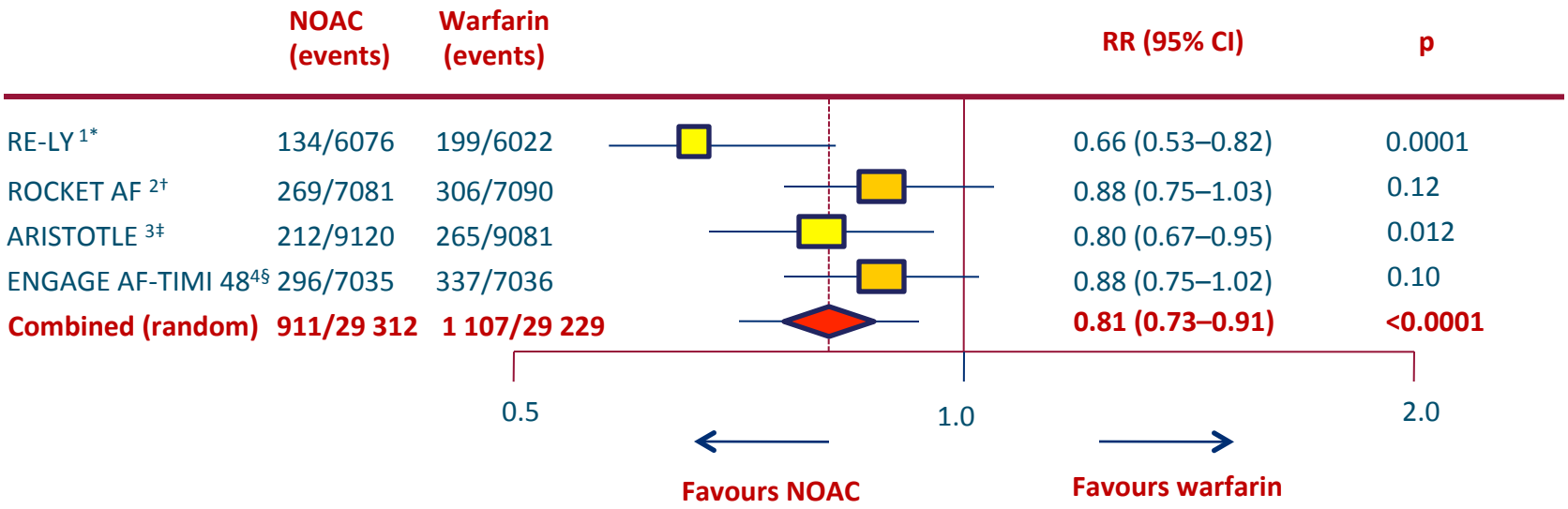


Relative risk reduction (RRR) for all strokes (ischaemic and haemorrhagic)

Hart RG et al. *Ann Intern Med* 2007;146:857–67

NOACs for STROKE PREVENTION in AF

Stroke or systemic embolic events



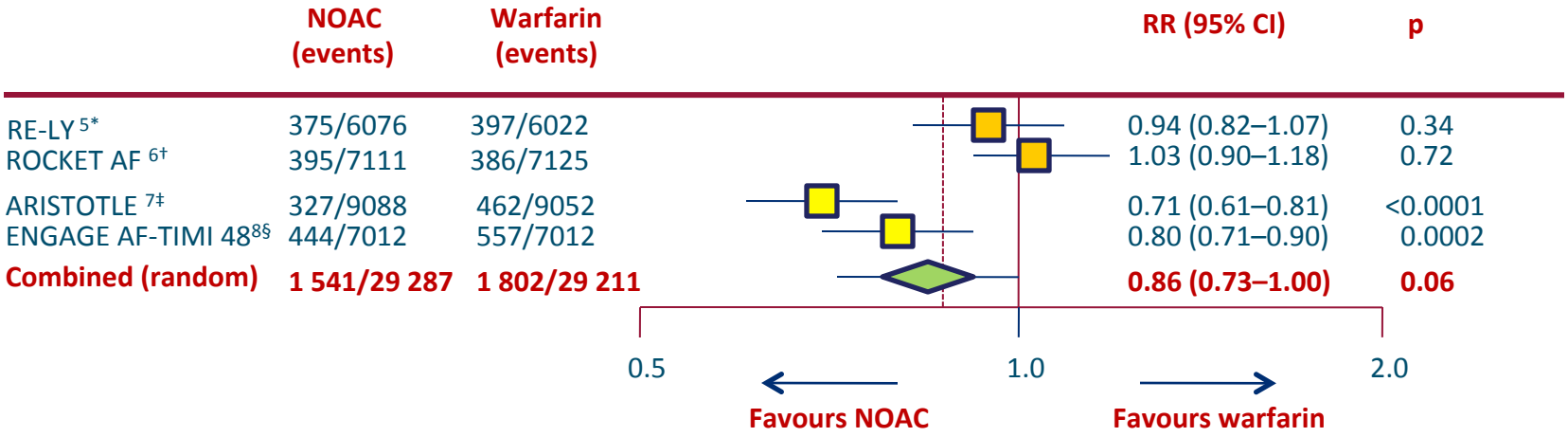
*Dabigatran 150mg twice daily; †Rivaroxaban 20mg once daily; ‡Apixaban 5mg twice daily; §Edoxaban 60mg once daily.

A 19% RR reduction in stroke or SE

[1]N Engl J Med 2009;361:1139-1151; [2]N Engl J Med 2011;365:883-891; [3]N Engl J Med 2011;365:981-992; [4]N Engl J Med 2013;369:2093-2104.

NOACs for STROKE PREVENTION in AF

Major bleeding



*Dabigatran 150mg twice daily; †Rivaroxaban 20mg once daily; ‡Apixaban 5mg twice daily; §Edoxaban 60mg once daily.

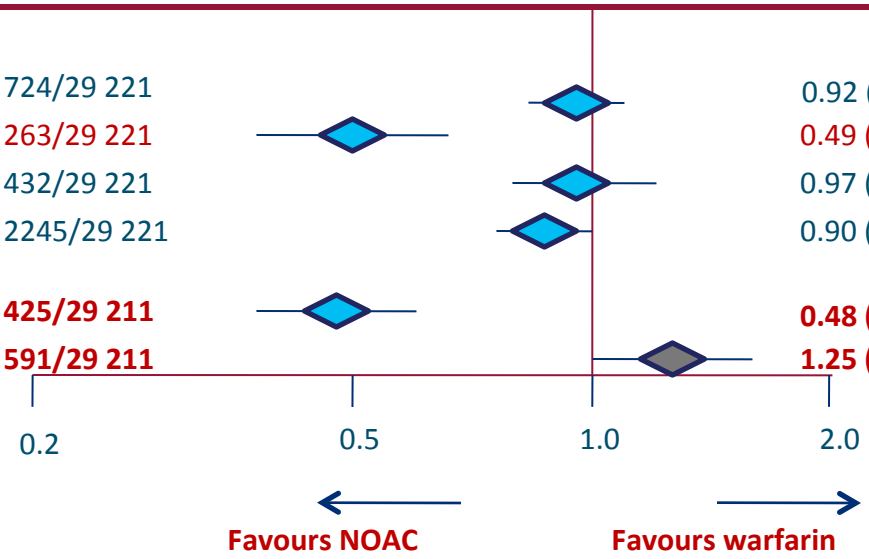
A 14% RR reduction in major bleeding

[1]N Engl J Med 2009;361:1139-1151; [2]N Engl J Med 2011;365:883-891; [3]N Engl J Med 2011;365:981-992; [4]N Engl J Med 2013;369:2093-2104.

NOACs for STROKE PREVENTION in AF

Secondary efficacy and safety outcomes

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p
Efficacy				
Ischaemic stroke	665/29 292	724/29 221	0.92 (0.83–1.02)	0.10
Haemorrhagic stroke	130/29 292	263/29 221	0.49 (0.38–0.64)	<0.0001
Myocardial infarction	413/29 292	432/29 221	0.97 (0.78–1.20)	0.77
All-cause mortality	2022/29 292	2245/29 221	0.90 (0.85–0.95)	0.0003
Safety				
Intracranial haemorrhage	**204/29 287**	**425/29 211**	**0.48 (0.39–0.59)**	**<0.0001**
Gastrointestinal bleeding	**751/29 287**	**591/29 211**	**1.25 (1.01–1.55)**	**0.043**



*Dabigatran 150mg twice daily; †Rivaroxaban 20mg once daily; ‡Apixaban 5mg twice daily; §Edoxaban 60mg once daily.

A 51% RR reduction in haemorrhagic stroke

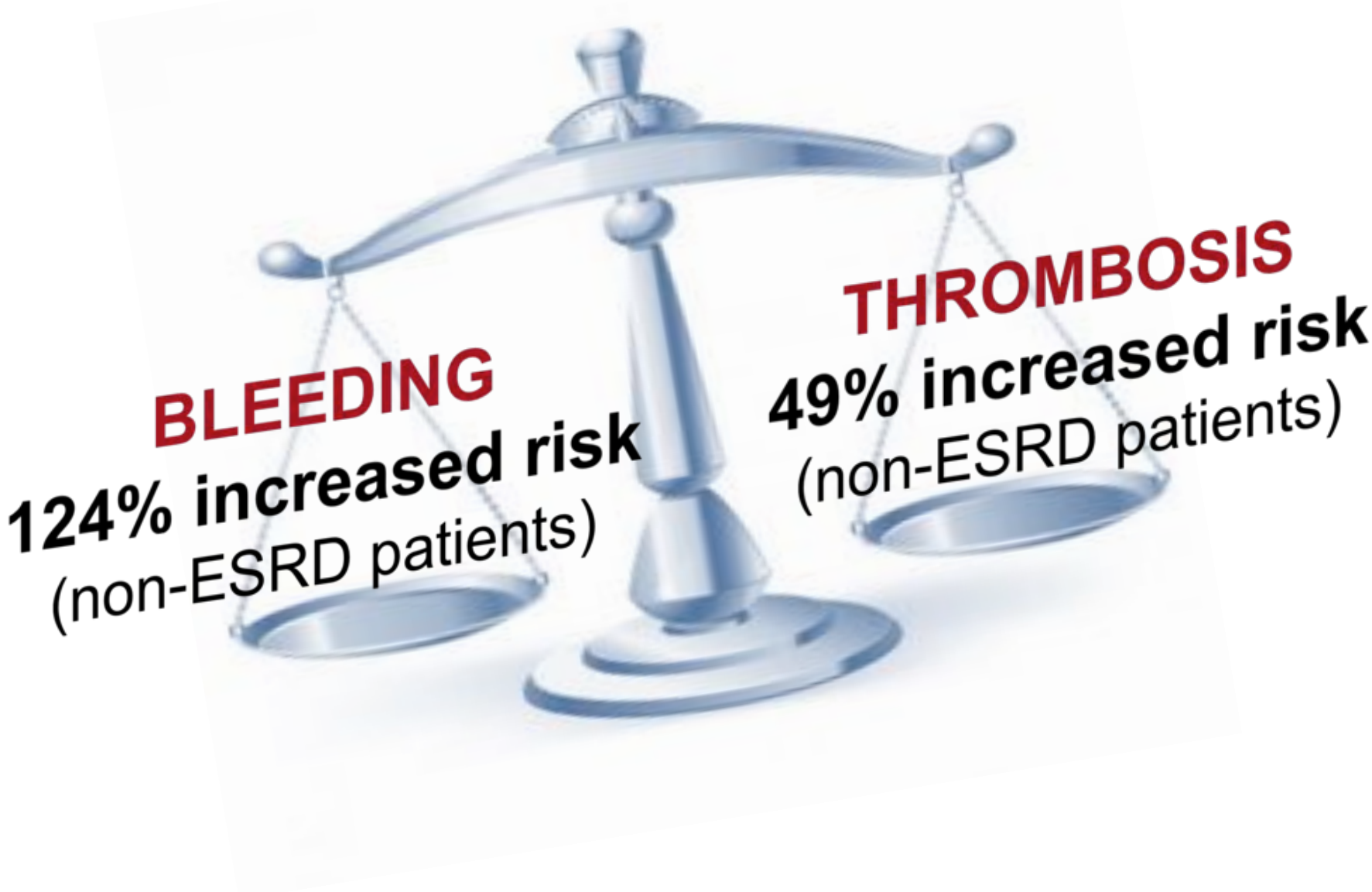
A 10% RR reduction in all-cause mortality

[1]N Engl J Med 2009;361:1139-1151; [2]N Engl J Med 2011;365:883-891; [3]N Engl J Med 2011;365:981-992; [4]N Engl J Med 2013;369:2093-2104.

The use of oral anticoagulant therapy for stroke prevention in atrial fibrillation

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

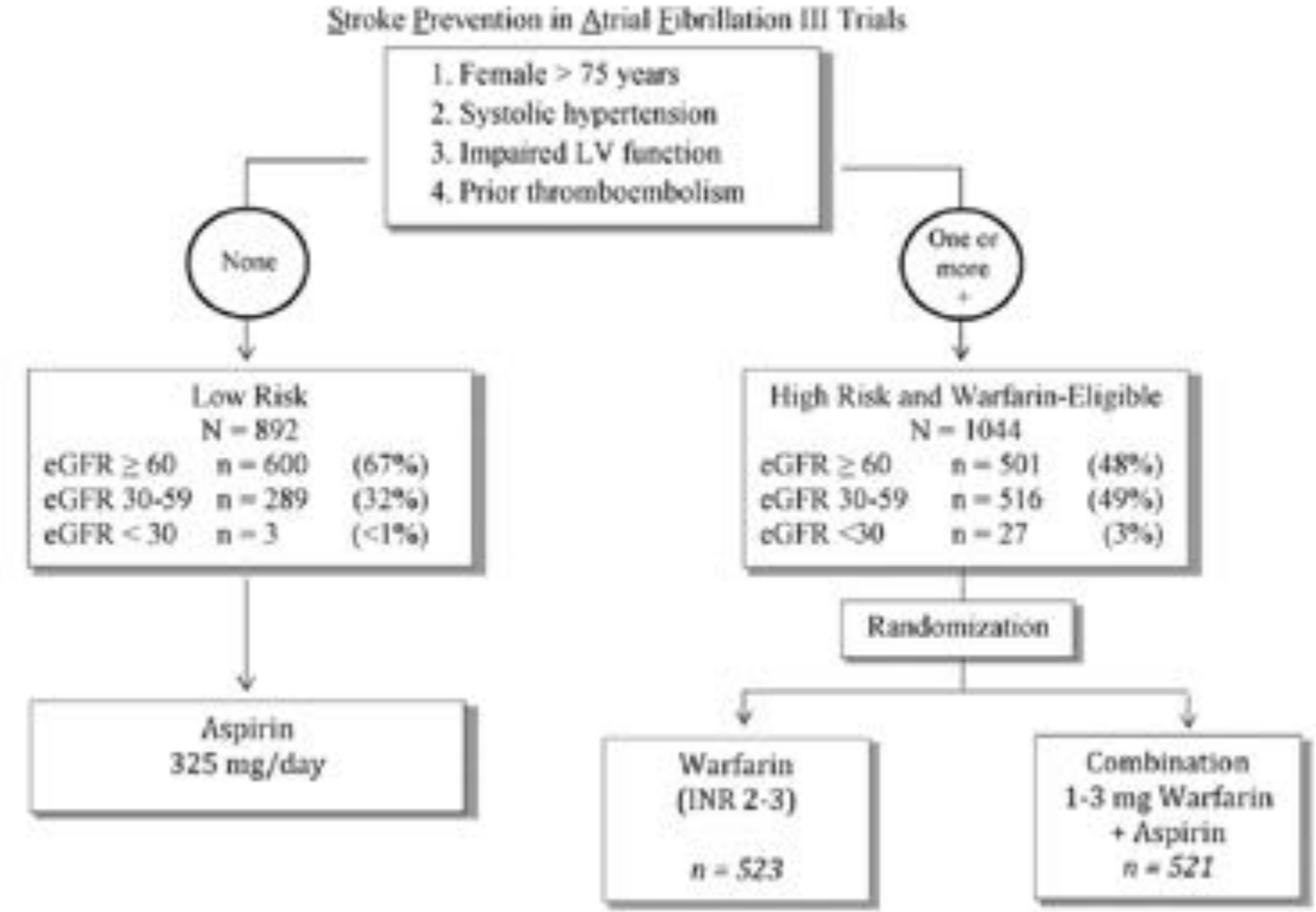
Olesen JB, Lip GYH, Kamper A., et al. NEJM 2012;367:625.



Warfarin in Atrial Fibrillation Patients with Moderate Chronic Kidney Disease

Robert G. Hart, Lesly A. Pearce,† Richard W. Asinger,‡ and Charles A. Herzog‡*

Clin J Am Soc Nephrol 6: 2599–2604, 2011.



Warfarin in Atrial Fibrillation Patients with Moderate Chronic Kidney Disease

Robert G. Hart, Lesly A. Pearce,† Richard W. Asinger,‡ and Charles A. Herzog‡*

Clin J Am Soc Nephrol 6: 2599–2604, 2011.

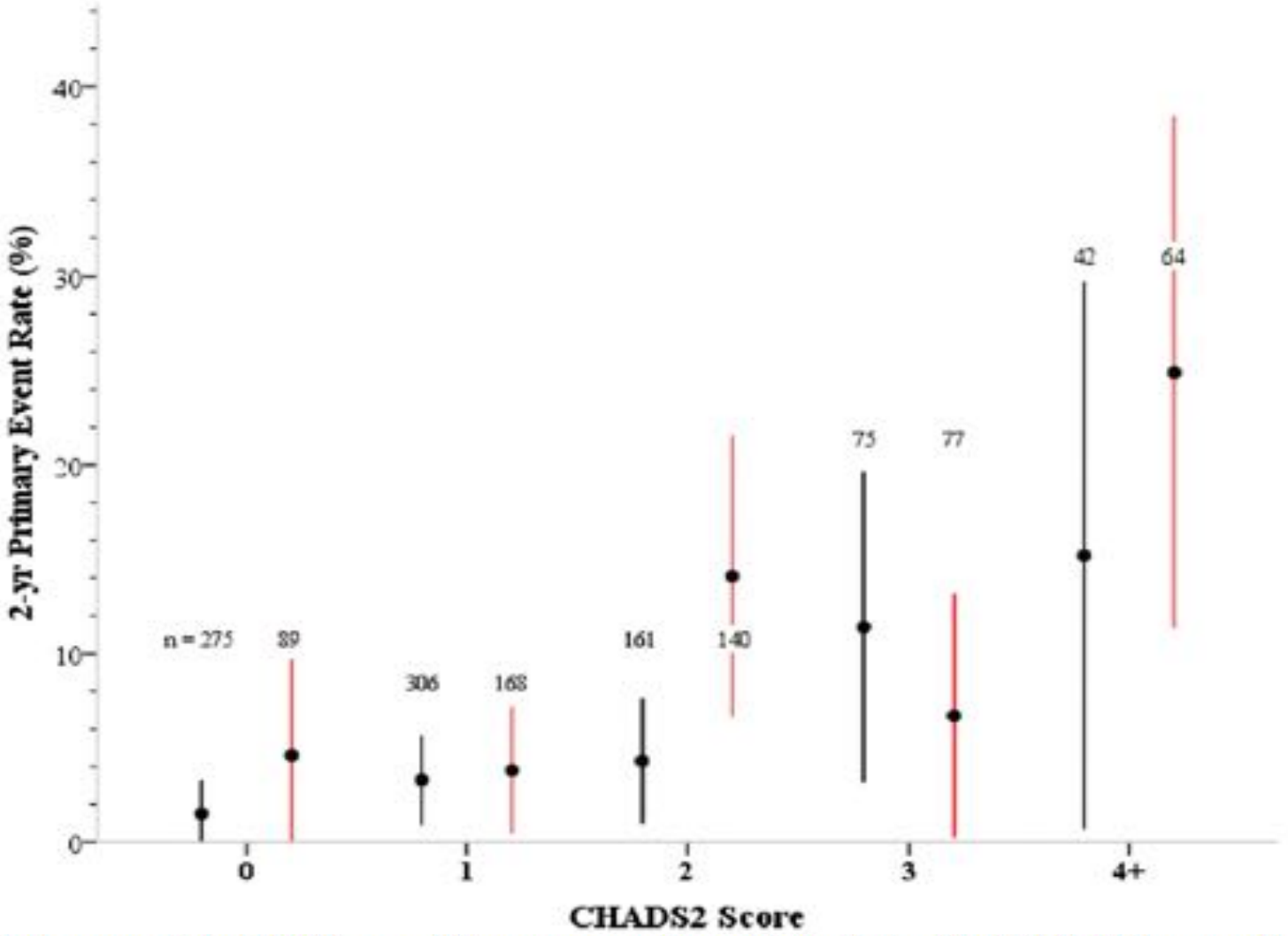


Figure 2. | Rate of primary events by CHADS2 score (18) among non-anticoagulated patients with atrial fibrillation according to chronic kidney disease status. Stage 3 CKD = red; eGFR>60 = black.

Warfarin in Atrial Fibrillation Patients with Moderate Chronic Kidney Disease

Robert G. Hart, Lesly A. Pearce,† Richard W. Asinger,‡ and Charles A. Herzog‡*

Clin J Am Soc Nephrol 6: 2599–2604, 2011.

The value of vitamin K antagonists in patients with less advanced CKD and AF resembles that of non-CKD patients

Table 3. Effect of adjusted-dose warfarin in patients with stage 3 CKD[a]

	Adjusted-Dose Warfarin			Fixed, Low-Dose Warfarin + Aspirin			Relative Risk Reduction[c] (%) (95% CI); *P*
	n	No. of Events	2-year Rate (%)	*n*	No. of Events	2-year Rate (%)	
Ischemic stroke/systemic embolism[b]							
eGFR ≥60 ml/min per 1.73 m^2	242	5	5.1	259	16	8.5	67 (10, 88); $P = 0.02$
Stage 3 CKD	267	6	2.9	249	23	14.1	76 (42, 90); $P < 0.01$
All major bleeds							
eGFR ≥60 ml/min per 1.73 m^2	242	5	6.3	259	7	6.3	21 (−151, 75); $P = 0.69$
Stage 3 CKD	267	5	2.5	249	6	3.6	24 (−150, 77); $P = 0.65$
Deaths							
eGFR ≥60 ml/min per 1.73 m^2	242	10	7.9	259	15	10.1	26 (−64, 67); $P = 0.45$
Stage 3 CKD	267	21	13.7	249	22	17.7	15 (−55, 53); $P = 0.60$

See Methods for definitions of stages of CKD. Features of stage 3 CKD participants did not differ significantly by treatment arm (see Supplmentary Table 1). CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated GFR.

[a]27 participants with stage 4 CKD are excluded.

[b]Almost all (96%) were ischemic strokes.

[c]Relative risk reduction estimated as 1 minus the hazard ratio.

Vitamin K antagonists in end-stage CKD patients with AF

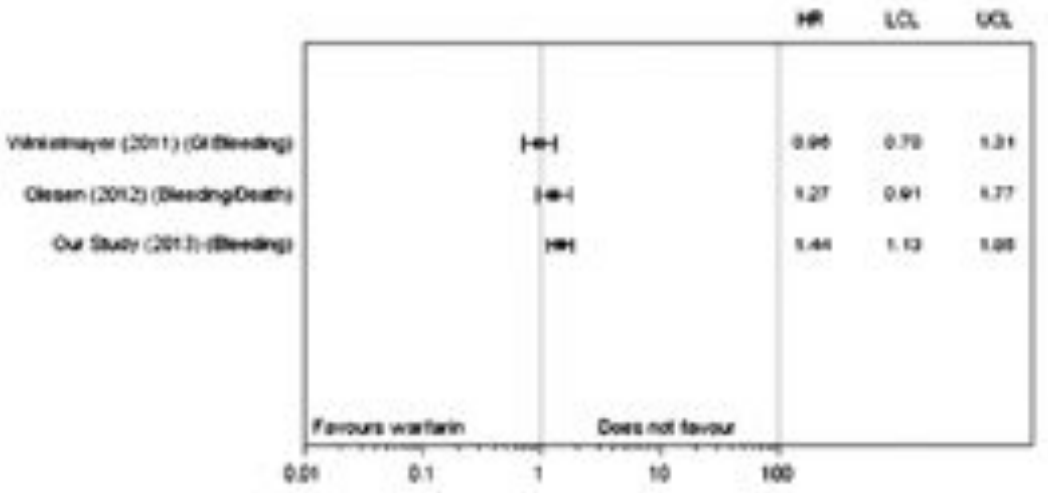
No relevant data from randomized clinical trials!

Large database analyses (a number of limitations!):

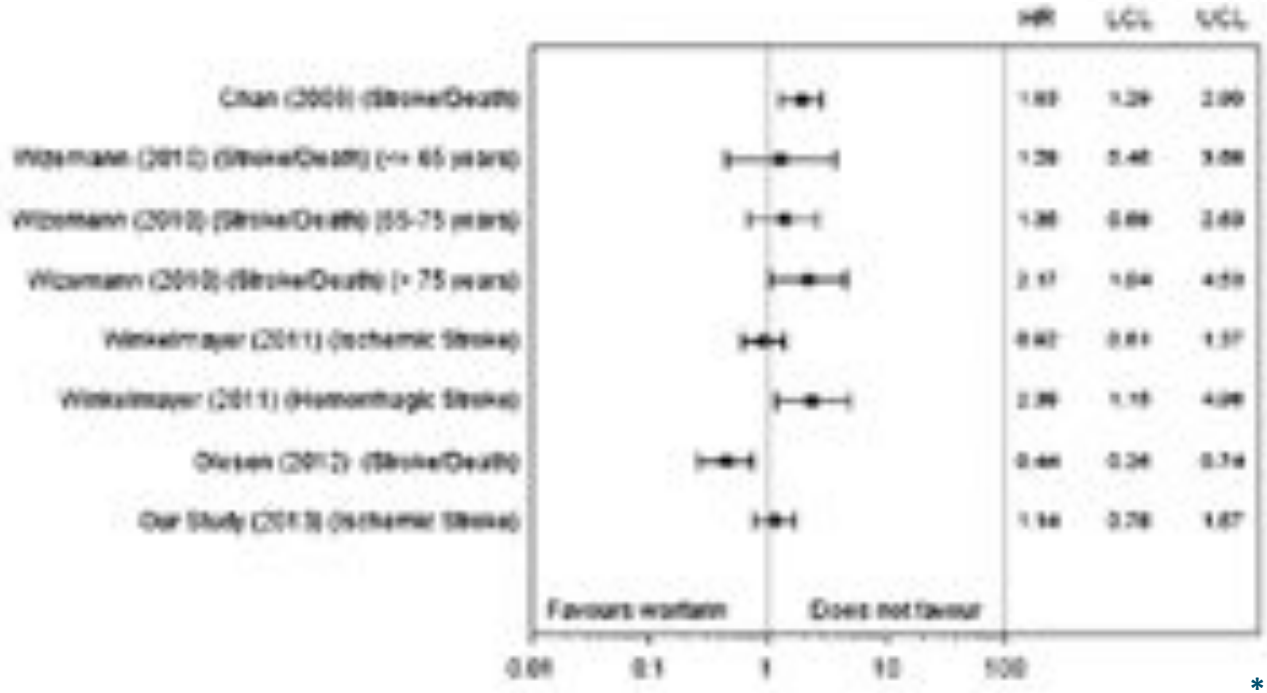
•***Chan et al***. *J Am Soc Nephrol 2009;20:2223*: in 1671 incident he
warfarin use was associated with a significantly increased risk
monitoring, INR reporting, drug discontinuation, etc.

•**The DOPPS* data** (1996-2004) on 2188 patients with prevalent
≥75 y **(HR 2.17; 95%CI, 1.04-4.53)**.

•***Winkelmayer et al.*** *Clin J Am Soc Nephrol 2011;6:2662:* No diff
with incident AF and taking warfarin vs. 948 propensity matched
haemorrhagic stroke with warfarin (HR 2.38; 95%CI, 1.15-4.96)



Circulation. 2014;129:1196-1203.



*Dialysis Outcomes and Practice Patterns study

Warfarin Use and the Risk for Stroke and Bleeding in Patients With Atrial Fibrillation Undergoing Dialysis

Mitesh Shah, MBBS MSc; Meytal Avgil Tsadok, PhD; Cynthia A. Jackevicius, PharmD, MSc; Vidal Essebag, MD, PhD; Mark J. Eisenberg, MD, MPH; Elham Rahme, PhD; Karin H. Humphries, DSc; Jack V. Tu, MD, PhD; Hassan Behlouli, PhD; Helen Guo, MSc; Louise Pilote, MD, PhD

Circulation. 2014;129:1196-1203.

A retrospective analysis

Dialysis Patients N=1626		Nondialysis Patients N=204 210	
Warfarin Users n=756	No-Warfarin Users, n=870	Warfarin Users, n=103 473	No-Warfarin Users, n=100 737

Table 3. Association between Warfarin Use and the Risk for Stroke and Bleeding in Patients with Atrial Fibrillation

Patients With AF	Outcomes	Adjusted* HR (95% CI)	Propensity Score† Adjusted HR (95% CI)
Dialysis (n=1626)	Stroke‡	1.14 (0.78–1.67)	1.17 (0.79–1.75)
	Bleeding§	1.44 (1.13–1.85)	1.41 (1.09–1.81)
Nondialysis (n=204 210)	Stroke‡	0.87 (0.85–0.90)	0.89 (0.87–0.92)
	Bleeding§	1.19 (1.16–1.22)	1.20 (1.17–1.23)

†Propensity score was derived from the following variables: age ≥75 y, sex, type of AF (primary vs secondary), $CHADS_2$ scores (1 and ≥2), liver disease, congestive heart failure, hypertension, diabetes mellitus, history of stroke/TIA, history of bleeding, use of rate control drug, rhythm control drug, aspirin, clopidogrel, and NSAIDs.

Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study

Leif Friberg[1*], Lina Benson[2], and Gregory Y.H. Lip[3]

European Heart Journal (2015) **36**, 297–306

307,351 AF patients identified in national Patient register

13,039 excluded because of mitral stenosis or valvular surgery

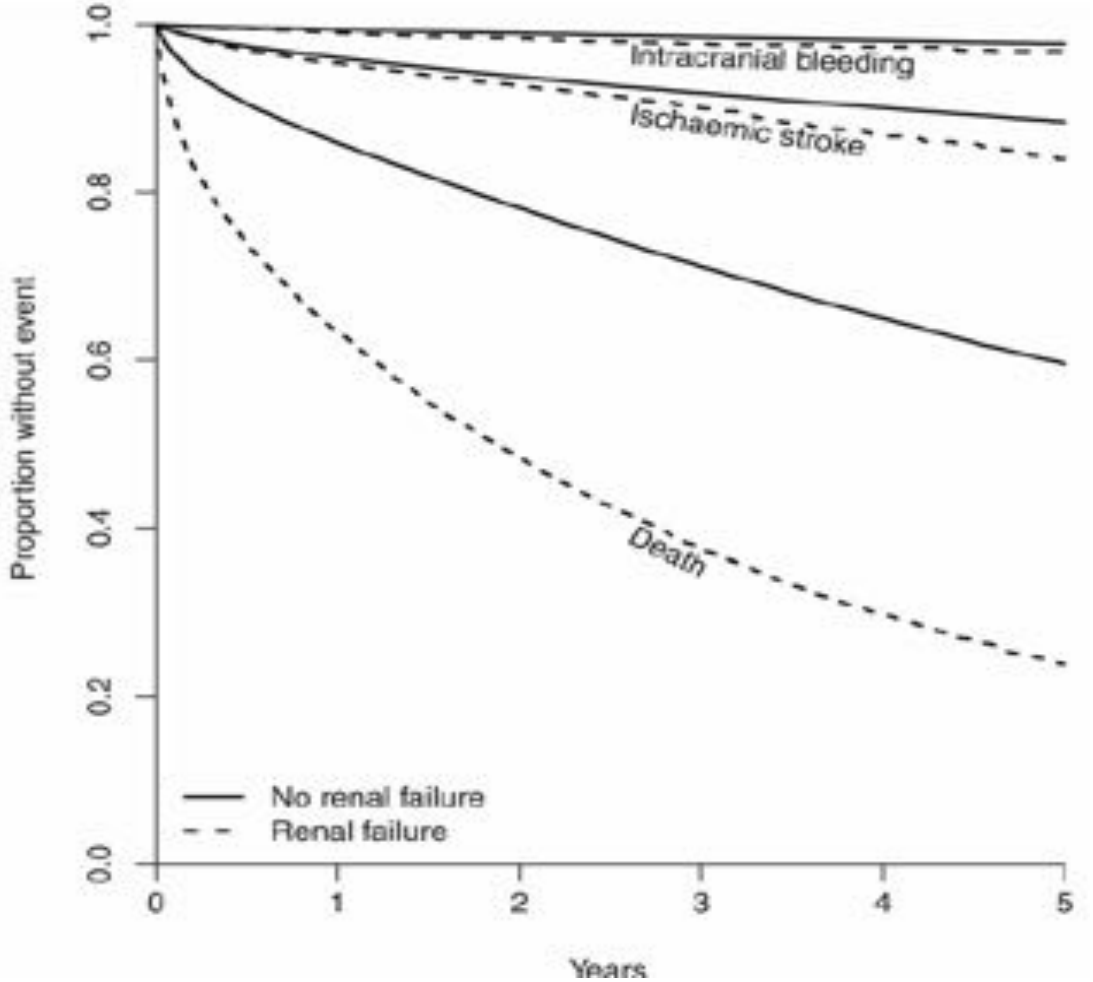
294,312 remaining

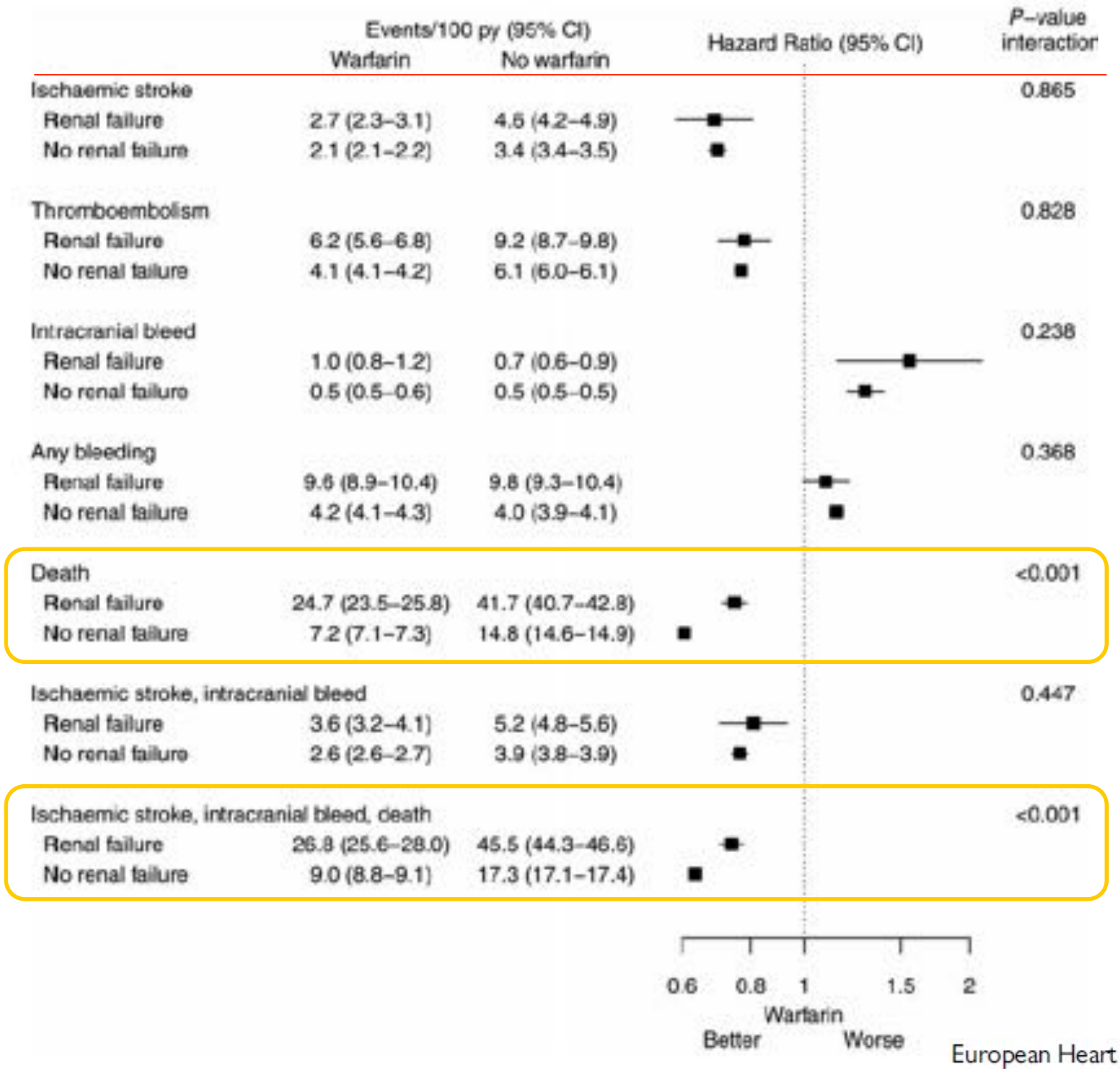
10,343 exluded because of death <14 days from index

283,969 remaining for study

13,435 with renal failure

270,534 without renal failure





European Heart Journal (2015) **36**, 297–306

Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study

Leif Friberg[1*], Lina Benson[2], and Gregory Y.H. Lip[3]

European Heart Journal (2015) **36**, 297–306

Table 4 Combined endpoints among 13 435 patients with renal failure in relation warfarin use and bleeding risk

	Ischaemic stroke or intracranial bleed			Ischaemic stroke, intracranial bleed, or death		
	Events per 100 years at risk (95% CI)		Multivariable	Events per 100 years at risk (95% CI)		Multivariable
HAS-BLED	Warfarin (n = 3766)	No warfarin (n = 9669)	HR (95% CI)	Warfarin (n = 3766)	No warfarin (n = 9669)	HR (95% CI)
1–2	2.1 (1.4–2.9)	2.8 (2.0–3.7)	0.81 (0.51–1.27)	24.1 (21.8–26.7)	34.4 (31.6–37.3)	0.86 (0.75–0.98)
3–5	4.0 (3.5–4.6)	5.3 (4.9–5.7)	0.83 (0.70–0.99)	27.5 (26.1–28.9)	46.1 (44.9–47.4)	0.75 (0.70–0.80)
6–8	6.8 (3.4–12.1)	10.2 (7.8–13–1)	0.74 (0.39–1.40)	30.2 (22.3–39.9)	65.1 (58.8–72.0)	0.56 (0.42–0.76)
All	3.6 (3.2–4.1)	5.2 (4.8–5.6)	0.82[b] (0.70–0.97)	26.8 (25.6–28.0)	45.5 (44.4–46.6)	0.76[a] (0.72–0.80)

Multivariable adjustments have been made for the same cofactors as in the full model in Table 2. P-value interaction between warfarin and HAS-BLED: 0.940 (ischaemic stroke or intracranial bleed) and 0.558 (ischaemic stroke, intracranial bleed, or death).

[b]Stratified for HAS-BLED.

Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study

Leif Friberg[1*], Lina Benson[2], and Gregory Y.H. Lip[3]

European Heart Journal (2015) **36**, 297–306

Table 5 Events per 100 years at risk in relation to time in therapeutic range among warfarin-treated atrial fibrillation patients with and without renal failure

	Events per 100 years at risk					
	Renal failure			No renal failure		
	TTR <60% (*n* = 167)	TTR 60–69% (*n* = 109)	TTR ≥70% (*n* = 266)	TTR <60% (*n* = 3506)	TTR 60–69% (*n* = 3079)	TTR ≥70% (*n* = 14 528)
Stroke	3.3 (1.8–5.7)	3.8 (1.8–7.0)	2.2 (1.2–3.6)	2.8 (2.5–3.2)	2.5 (2.2–2.9)	1.7 (1.6–1.8)
Thrombo- embolism	8.4 (5.7–12.1)	7.5 (4.5–11.7)	4.7 (3.1–6.7)	5.0 (4.6–5.5)	4.3 (4.0–4.8)	3.4 (3.2–3.6)
Intracranial bleed	1.0 (0.3–2.6)	0.7 (0.1–2.6)	0.4 (0.1–1.3)	0.5 (0.4–0.7)	0.4 (0.3–0.6)	0.2 (0.2–0.3)
Any bleeding	11.5 (8.2–15.6)	9.2 (5.8–13.8)	5.9 (4.1–8.2)	4.9 (4.5–5.4)	4.1 (3.7–4.5)	2.7 (2.6–2.9)
Death	9.3 (6.5–12.8)	9.0 (5.8–13.3)	5.9 (4.2–8.0)	4.5 (4.1–5.0)	3.1 (2.8–3.5)	1.6 (1.5–1.7)
Ischaemic stroke or intracranial bleeding	3.9 (2.2–6.4)	4.2 (2.1–7.5)	2.5 (1.4–4.0)	3.3 (3.0–3.7)	2.9 (2.5–3.3)	1.9 (1.8–2.1)
Ischaemic stroke, intracranial bleeding, or death	11.8 (8.7–15.8)	12.6 (8.6–17.6)	8.0 (6.0–10.5)	7.2 (6.6–7.8)	5.5 (5.1–6.1)	3.3 (3.2–3.6)

Note that TTR values only were available for 21 655 patients

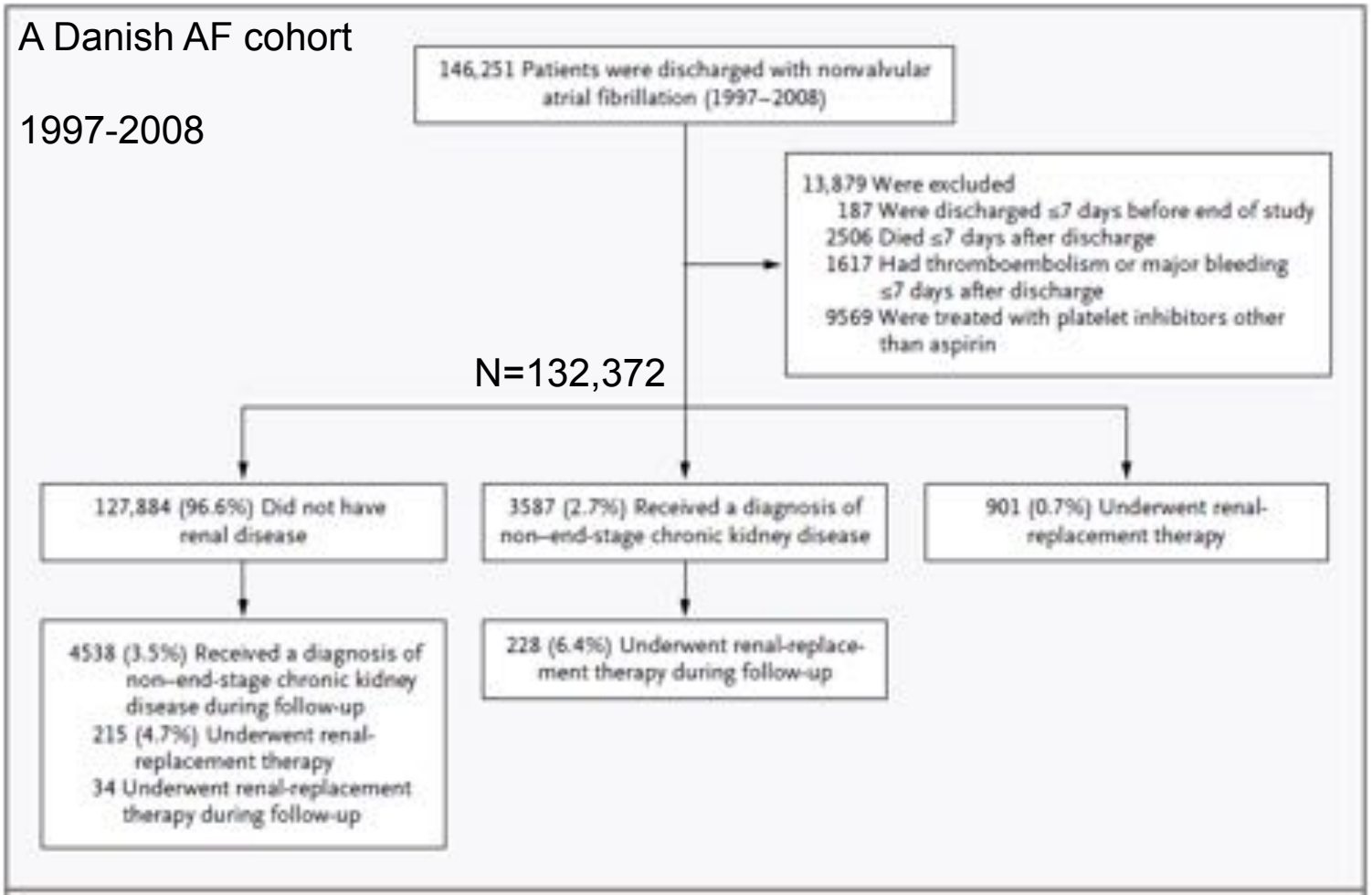
Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Jonas Bjerring Olesen, M.D., Gregory Y.H. Lip, M.D., Anne-Lise Kamper, M.D., D.M.Sc., Kristine Hommel, M.D., Lars Køber, M.D., D.M.Sc., Deirdre A. Lane, Ph.D., Jesper Lindhardsen, M.D., Gunnar Hilmar Gislason, M.D., Ph.D., and Christian Torp-Pedersen, M.D., D.M.Sc.

N Engl J Med 2012;367:625-35.

A Danish AF cohort

1997-2008



Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

N Engl J Med 2012;367:625-35.

Characteristic	No Renal Disease (N = 127,884)	Non–End-Stage Chronic Kidney Disease (N = 3587)	Disease Requiring Renal-Replacement Therapy (N = 901)	P Value
Antithrombotic medication — no. (%)				
Warfarin only	36,638 (28.6)	609 (17.0)	178 (19.8)	<0.001
Aspirin only	23,952 (18.7)	879 (24.5)	153 (17.0)	<0.001
Warfarin and aspirin	10,745 (8.4)	290 (8.1)	45 (5.0)	<0.001
CHA_2DS_2-VASc score†				<0.001
0	11,720 (9.2)	70 (2.0)	42 (4.7)	
1	16,926 (13.2)	251 (7.0)	165 (18.3)	
≥2	99,238 (77.6)	3266 (91.1)	694 (77.0)	
HAS-BLED score‡				<0.001
0 or 1	51,262 (40.1)	883 (24.6)	390 (43.3)	
2	46,159 (36.1)	1336 (37.2)	312 (34.6)	
≥3	30,463 (23.8)	1368 (38.1)	199 (22.1)	

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

N Engl J Med 2012;367:625-35.

Table 3. Hazard Ratios for Stroke or Systemic Thromboembolism.*

Characteristic	Total Population (N = 132,372)		No Renal Disease (N = 127,884)†		Non–End-Stage Chronic Kidney Disease (N = 3587)†		Disease Requiring Renal-Replacement Therapy (N = 901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants			1.00		1.49 (1.38–1.59)	<0.001	1.83 (1.57–2.14)	<0.001
Antithrombotic therapy								
None	1.00		1.00		1.00		1.00	
Warfarin	0.59 (0.57–0.62)	<0.001	0.59 (0.56–0.61)	<0.001	0.84 (0.69–1.01)	0.07	0.44 (0.26–0.74)	0.002
Aspirin	1.11 (1.07–1.15)	<0.001	1.10 (1.06–1.14)	<0.001	1.25 (1.07–1.47)	0.01	0.88 (0.59–1.32)	0.54
Warfarin and aspirin	0.70 (0.65–0.75)	<0.001	0.69 (0.64–0.74)	<0.001	0.76 (0.56–1.03)	0.08	0.82 (0.37–1.80)	0.62
Risk factors for thromboembolism‡								
Congestive heart failure	1.03 (0.99–1.07)	0.18	1.03 (0.99–1.08)	0.11	0.98 (0.84–1.14)	0.78	0.96 (0.64–1.43)	0.84
Hypertension	1.06 (1.03–1.09)	<0.001	1.05 (1.02–1.09)	0.002	1.13 (0.98–1.30)	0.10	1.05 (0.76–1.45)	0.78
Age								
≥75 yr	3.48 (3.31–3.66)	<0.001	3.56 (3.38–3.76)	<0.001	1.87 (1.48–2.36)	<0.001	2.46 (1.60–3.79)	<0.001
65–74 yr	2.02 (1.91–2.14)	<0.001	2.03 (1.92–2.16)	<0.001	1.52 (1.18–1.94)	0.001	2.18 (1.46–3.24)	<0.001
Diabetes	1.32 (1.26–1.38)	<0.001	1.32 (1.25–1.39)	<0.001	1.16 (0.99–1.36)	0.07	1.41 (0.95–2.10)	0.09
History of stroke or systemic thromboembolism	3.20 (3.10–3.31)	<0.001	3.24 (3.14–3.35)	<0.001	2.71 (2.34–3.15)	<0.001	1.99 (1.36–2.91)	<0.001
Vascular disease	1.10 (1.06–1.15)	<0.001	1.12 (1.07–1.16)	<0.001	0.89 (0.76–1.05)	0.17	1.11 (0.78–1.58)	0.57
Female sex	1.12 (1.08–1.15)	<0.001	1.12 (1.08–1.15)	<0.001	1.06 (0.92–1.22)	0.44	1.34 (0.97–1.85)	0.08

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

N Engl J Med 2012;367:625-35.

Table 4. Hazard Ratios for Bleeding.*

Characteristic	Total Population (N = 132,372)		No Renal Disease (N = 127,884)†		Non–End-Stage Chronic Kidney Disease (N = 3587)†		Disease Requiring Renal-Replacement Therapy (N = 901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants			1.00		2.24 (2.10–2.38)	<0.001	2.70 (2.38–3.07)	<0.001
Antithrombotic therapy								
None	1.00		1.00		1.00		1.00	
Warfarin	1.28 (1.23–1.33)	<0.001	1.28 (1.23–1.33)	<0.001	1.36 (1.17–1.59)	<0.001	1.27 (0.91–1.77)	0.15
Aspirin	1.21 (1.16–1.26)	<0.001	1.21 (1.16–1.26)	<0.001	1.12 (0.96–1.30)	0.14	1.63 (1.18–2.26)	0.003
Warfarin and aspirin	2.15 (2.04–2.26)	<0.001	2.18 (2.07–2.30)	<0.001	1.63 (1.32–2.02)	<0.001	1.71 (0.98–2.99)	0.06
Risk factors for bleeding‡								
Hypertension	1.01 (0.98–1.04)	0.52	1.01 (0.98–1.04)	0.58	0.99 (0.87–1.11)	0.81	0.92 (0.71–1.20)	0.55
Abnormal liver function	1.37 (1.23–1.52)	<0.001	1.40 (1.25–1.57)	<0.001	1.31 (0.90–1.91)	0.16	0.74 (0.34–1.64)	0.46
History of stroke or systemic thromboembolism	1.23 (1.18–1.28)	<0.001	1.24 (1.19–1.30)	<0.001	1.04 (0.89–1.22)	0.62	0.93 (0.63–1.36)	0.70
History of bleeding	2.44 (2.33–2.55)	<0.001	2.54 (2.42–2.67)	<0.001	1.70 (1.45–1.99)	<0.001	2.09 (1.50–2.91)	<0.001
Age ≥65 yr	2.09 (2.00–2.17)	<0.001	2.12 (2.03–2.20)	<0.001	1.61 (1.35–1.92)	<0.001	1.36 (1.03–1.80)	0.03
Use of NSAIDs	1.12 (1.08–1.16)	<0.001	1.12 (1.08–1.17)	<0.001	1.10 (0.96–1.26)	0.19	0.91 (0.62–1.33)	0.63
Alcohol abuse	1.40 (1.30–1.52)	<0.001	1.43 (1.32–1.56)	<0.001	1.01 (0.73–1.39)	0.97	1.33 (0.70–2.54)	0.39

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

October 16 - 18
14th EDITION 2015

N Engl J Med 2012;367:625-35.

All patients with any CKD compared to no CKD

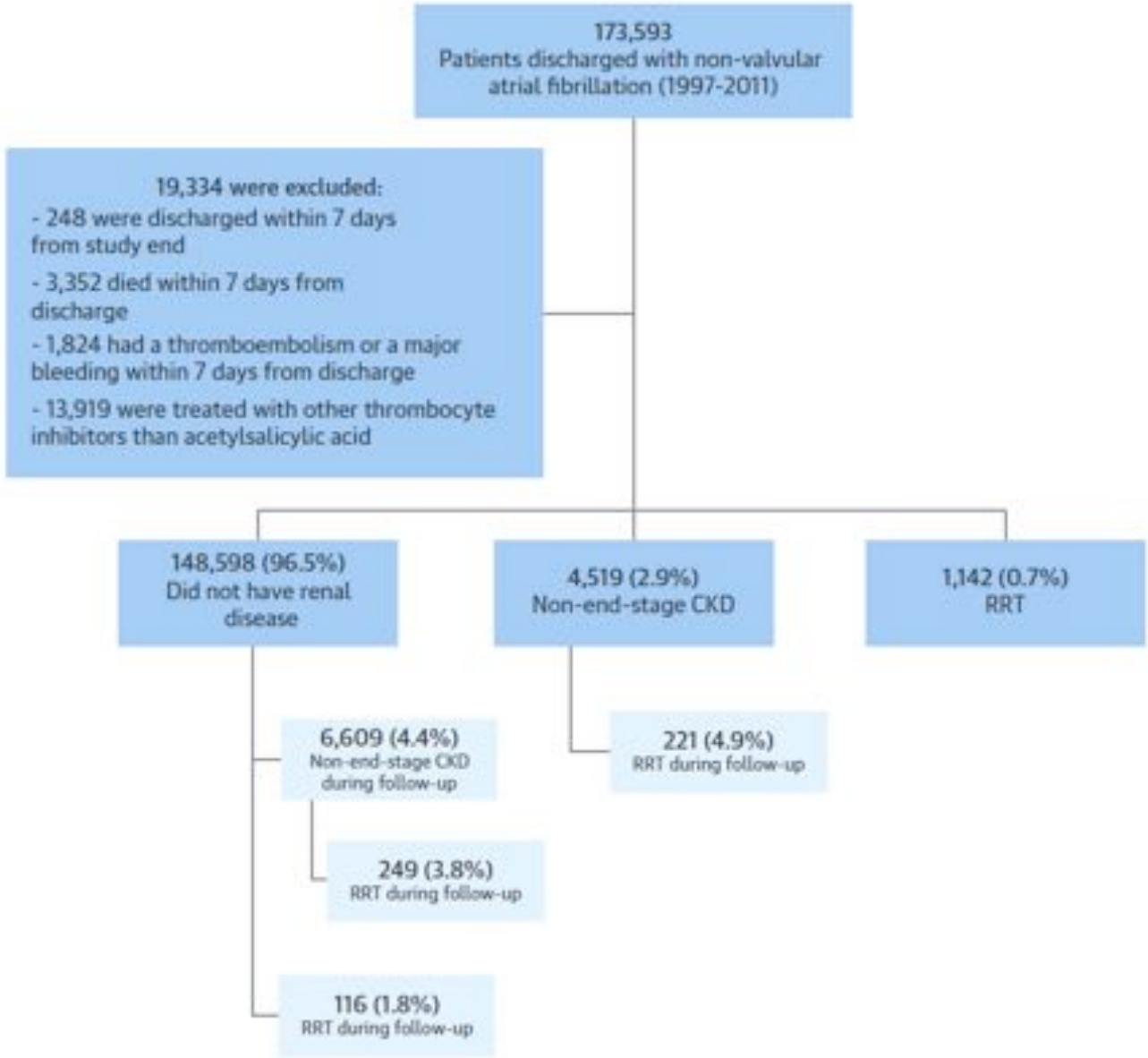
	Stroke or SE HR (95%CI)	**P**	**Major bleeding** HR (95%CI)	**P**
Warfarin	0.76 (0.64-0.91)	0.003	1.33 (1.16-1.53)	<0.001
Aspirin	1.17 (1.01-1.35)	0.04	1.17 (1.02-1.34)	0.03
Warfarin plus aspirin	0.74 (0.56-0.98)	0.04	1.61 (1.32-1.96)	<0.001

those patients with moderate chronic kidney disease.[14,15] We found that warfarin therapy was associated with a significant reduction in the risk of stroke or thromboembolism among patients with chronic kidney disease but that the risk of bleeding among such patients was significantly increased. Thus, the net clinical effect of warfarin treatment requires careful assessment in patients with chronic kidney disease,[16] and the data do not provide clear guidance regarding indications for anticoagulant therapy in patients with both atrial fibrillation and chronic kidney disease.

Net Clinical Benefit of Antithrombotic Therapy in Patients With Atrial Fibrillation and Chronic Kidney Disease

A Nationwide Observational Cohort Study

Bonde, A.N. et al. J Am Coll Cardiol. 2014; 64(23):2471–82.



Net Clinical Benefit of Antithrombotic Therapy in Patients With Atrial Fibrillation and Chronic Kidney Disease

A Nationwide Observational Cohort Study

Bonde, A.N. et al. J Am Coll Cardiol. 2014; 64(23):2471–82.

	No Renal Disease (N = 148,598)	Non-End-Stage CKD (n = 4,519)	RRT (n = 1,142)
CHA_2DS_2-VASc			
Low, score 0	12,404 (8.35)	100 (2.21)	53 (4.64)
Intermediate, score 1	18,571 (12.50)	283 (6.26)	191 (16.73)
High, score 2-9	117,623 (79.16)	4,136 (91.52)	898 (78.63)
HAS-BLED			
0 or 1	65,914 (44.36)	1,278 (28.28)	536 (46.94)
2	56,176 (37.80)	1,947 (43.08)	399 (34.94)
≥3	26,508 (17.84)	1,294 (28.63)	207 (18.13)
Concomitant medication			
Warfarin	35,127 (23.64)	635 (14.05)	186 (16.29)
Warfarin and aspirin	16,992 (11.43)	495 (10.95)	74 (6.48)
Aspirin	41,956 (28.23)	1,668 (36.91)	299 (26.18)

Net Clinical Benefit of Antithrombotic Therapy in Patients With Atrial Fibrillation and Chronic Kidney Disease

A Nationwide Observational Cohort Study

Bonde, A.N. et al. J Am Coll Cardiol. 2014; 64(23):2471–82.

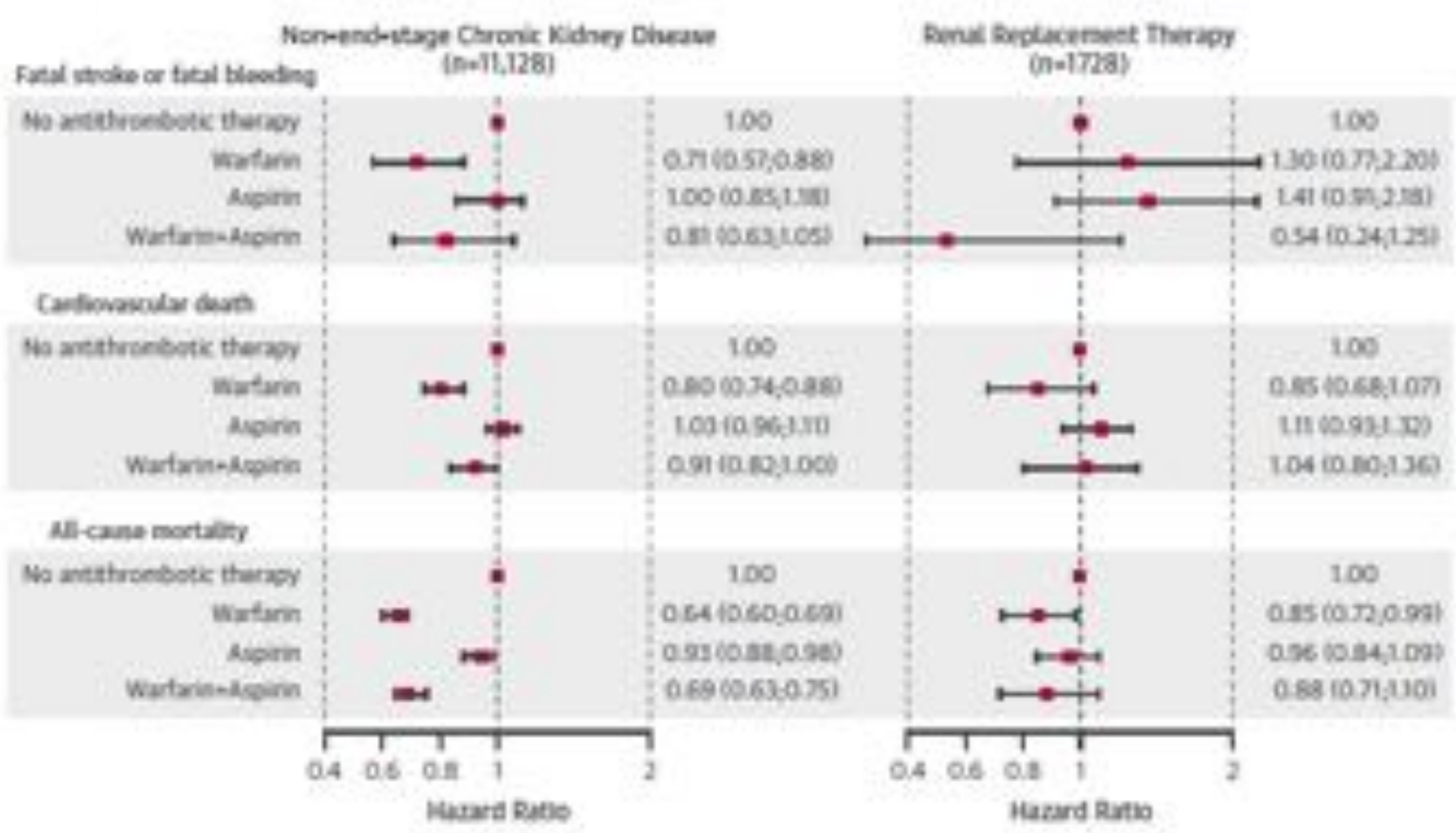
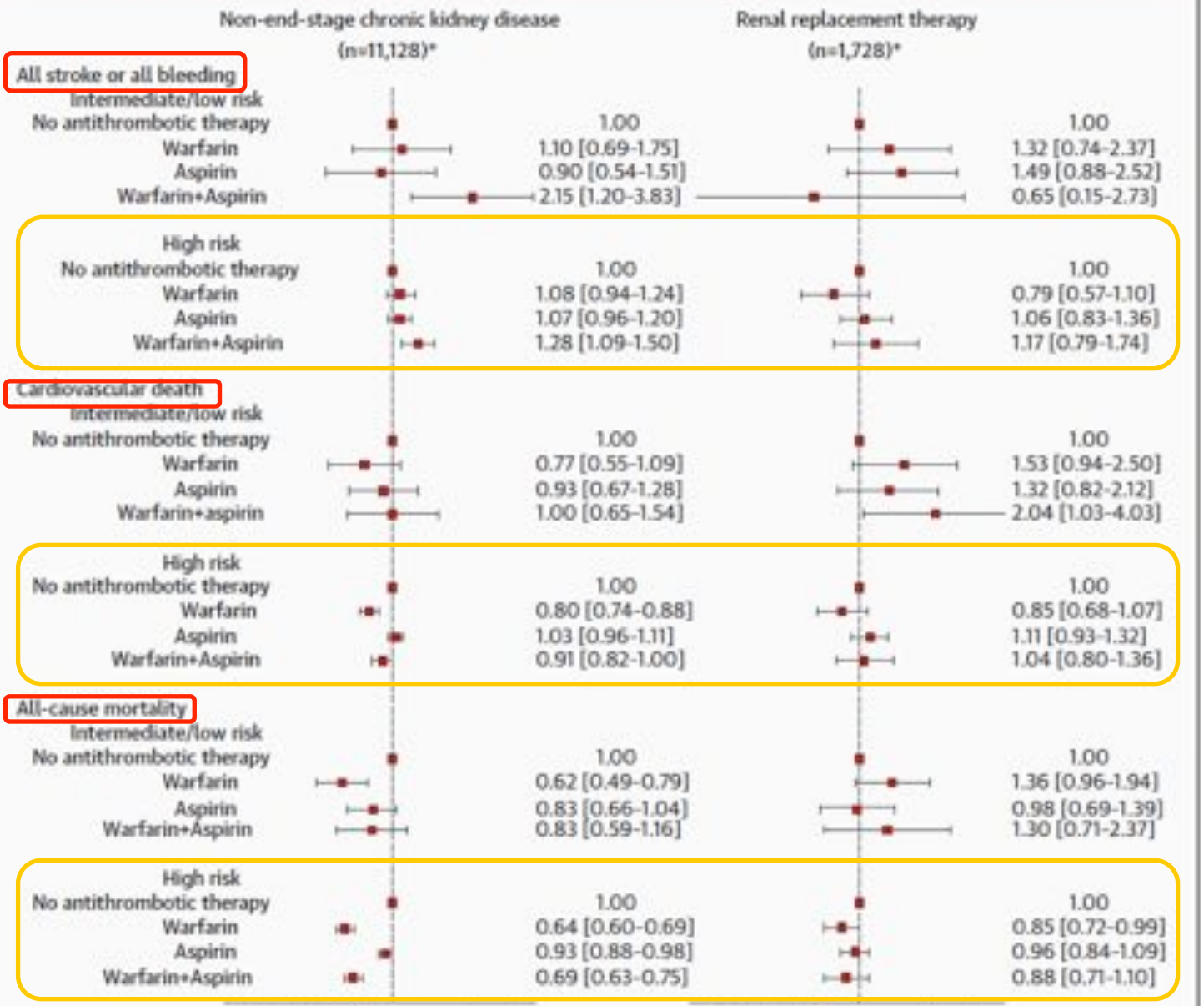
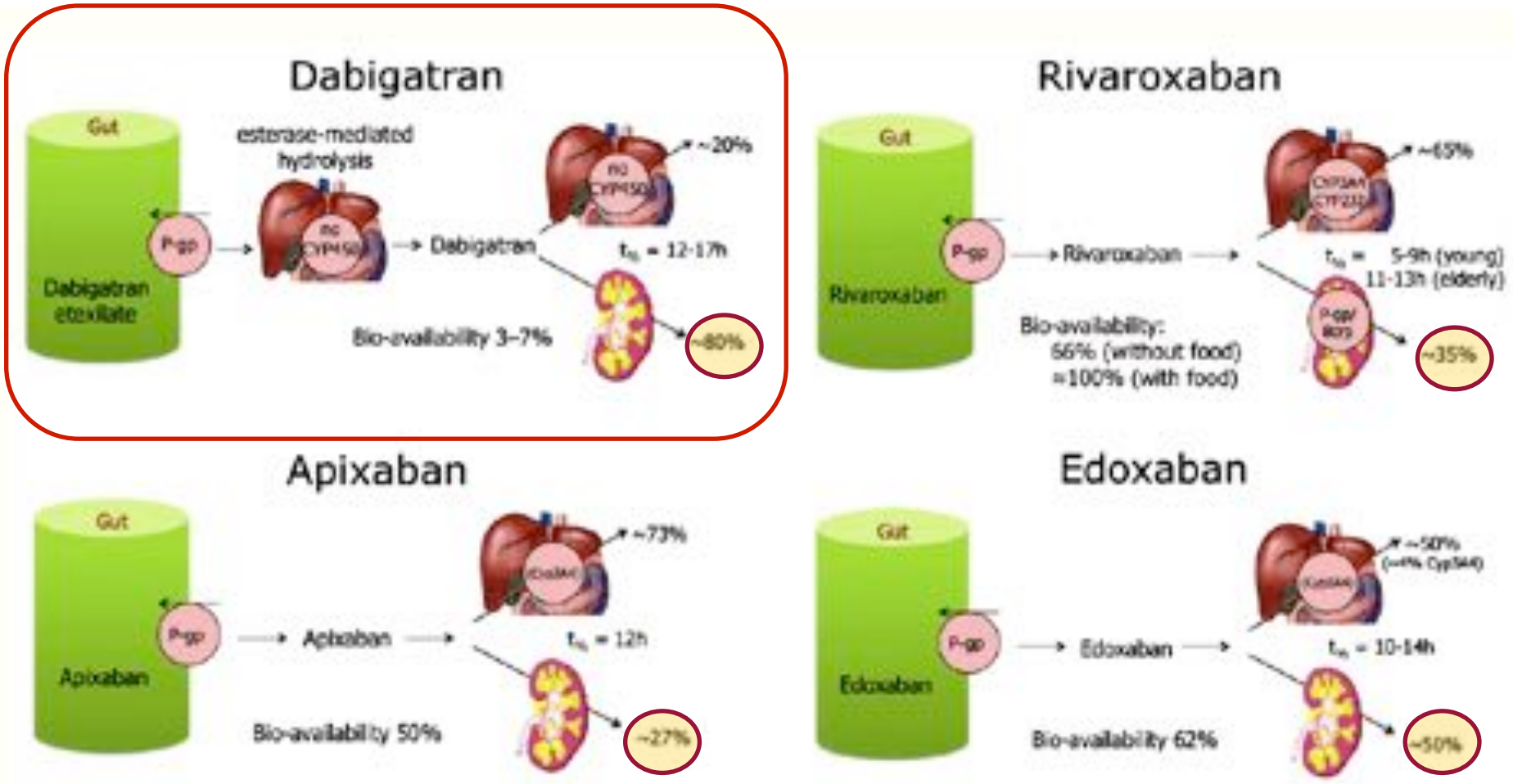


FIGURE 2 Net Clinical Benefit of Antithrombotic Therapy in Patients With AF and CKD



All NOACs are partly eliminated via the kidneys
Dabigatran has the greatest extent of renal elimination



H. Heidbuchel *et al.* Updated EHRA practical guide for use of the non-VKA oral anticoagulants Europace
doi:10.1093/europace/euv309

Prolongation of the NOACs half-lives is proportional to the degree of renal dysfunction

Table 7 Estimated drug half lives and effect on AUC NOAC plasma concentrations in different stages of CKD compared to healthy controls

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl >80 mL/min	12–17 h	12 h	10–14 h	5–9 h (young) 11–13 h (elderly)
CrCl 50–80 mL/min CKD Stages I and II	~17 h (+50%)	~14.6 h (+16%)	~8.6 h (+32%)[SmPC]	~8.7 h (+44%)[1]
CrCl 30–50 mL/min CKD Stage III	~19 h (+320%)	~17.6 h (+29%)	~9.4 h (+74%)[SmPC]	~9.0 h (+52%)[1]
CrCl 15–30 mL/min CKD Stage IV	~28 h (+530%)	~17.3 h (+44%)	~16.9 h (72%)[SmPC]	~9.5 h (+64%)[1]
CrCl ≤ 15 mL/min CKD Stage V; off-dialysis	No data	– (+36%)	– (+93%)[SmPC]	– (+70%)[1]

CKD, chronic kidney disease; CrCl, creatinine clearance.

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

Ziad Hijazi, MD, PhD; Stefan H. Hohnloser, MD; Jonas Oldgren, MD, PhD; Ulrika Andersson, MSc; Stuart J. Connolly, MD; John W. Eikelboom, MD; Michael D. Ezekowitz, MB, ChB, PhD; Paul A. Reilly, PhD; Agneta Siegbahn, MD, PhD; Salim Yusuf, MD, PhD; Lars Wallentin, MD, PhD

A pre-specified sub-analysis

Estimation of GFR:

1. **Cockcroft-Gault** formula
2. **CKD-EPI** equation (Chronic Kidney Disease Epidemiology Collaboration)
3. **Cystatin C** equation
4. **MDRD** equation (Modification of Diet in Renal Disease)

eGFR	Cockcroft-Gault	CKD-EPI
≥ 80 mL/min	5844 (32.6%)	3880 (21.6%)
50-79 mL/min	8553 (47.6%)	10697 (59.6%)
30-49 mL/min	3554 (19.8%)	3374 (18.8%)

eGFR <30mL/min (Cockcroft-Gault) was an exclusion criterion in the RE-LY

Circulation. 2014;129:961-970.

Table 2. Interaction Between Categorical Renal Function According to Cockcroft-Gault Formula and Treatment in a Cox Model for Outcome

Outcome According to Renal Function Level (in mL/min)	Events, n (%/y)			Dabigatran 110 mg BID vs Warfarin		Dabigatran 150 mg BID vs Warfarin		Dabigatran 150 vs Dabigatran 110 mg BID	
	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)	

CI indicates confidence interval; HR, hazard ratio; and *P* Value (Inter), *P* value for interaction.

*Net clinical benefit: Composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleed.

Table 3. Interaction Between Categorical Renal Function According to CKD-EPI Equation and Treatment in a Cox Model for Outcome

Outcome According to Renal Function Level (in mL/min)	Events, n (%/y)			Dabigatran 110 mg BID vs Warfarin		Dabigatran 150 mg BID vs Warfarin		Dabigatran 150 vs Dabigatran 110 mg BI	
	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin	HR (95% CI)	*P* Value (Inter)	HR (95% CI)	*P* Value (Inter)	HR (95% CI)	*P* Value (Inter)
Stroke or systemic embolism									0.9902
≥80	28/1284 (1.09)	21/1296 (0.81)	32/1300 (1.25)	0.87 (0.53–1.45)	0.7782	0.65 (0.37–1.12)	0.7521	0.74 (0.42–1.31)	
50 to <80	116/3547 (1.65)	86/3576 (1.21)	124/3574 (1.76)	0.94 (0.73–1.21)		0.69 (0.52–0.90)		0.73 (0.55–0.97)	
<50	37/1126 (1.71)	27/1157 (1.21)	45/1091 (2.17)	0.78 (0.51–1.21)		0.55 (0.34–0.89)		0.71 (0.43–1.16)	
All-cause mortality									0.5983
≥80	71/1284 (2.77)	61/1296 (2.36)	86/1300 (3.37)	0.82 (0.60–1.12)	0.6554	0.70 (0.50–0.97)	0.1532	0.85 (0.61–1.20)	
50 to <80	233/3547 (3.31)	229/3576 (3.22)	265/3574 (3.76)	0.88 (0.74–1.05)		0.85 (0.71–1.02)		0.97 (0.81–1.17)	
<50	136/1126 (6.28)	148/1157 (6.64)	133/1091 (6.41)	0.97 (0.77–1.24)		1.03 (0.82–1.30)		1.06 (0.84–1.33)	
Major bleed									0.5485
≥80	32/1284 (1.25)	46/1296 (1.78)	77/1300 (3.01)	0.41 (0.27–0.62)	0.0012	0.59 (0.41–0.84)	0.0050	1.43 (0.91–2.25)	
50 to <80	196/3547 (2.78)	217/3576 (3.05)	238/3574 (3.38)	0.82 (0.68–0.99)		0.90 (0.75–1.09)		1.10 (0.91–1.33)	
<50	111/1126 (5.13)	135/1157 (6.06)	105/1091 (5.06)	1.02 (0.78–1.33)		1.22 (0.95–1.58)		1.20 (0.93–1.54)	
Life-threatening bleed									0.2662
≥80	13/1284 (0.51)	20/1296 (0.77)	42/1300 (1.64)	0.30 (0.16–0.57)	0.0178	0.47 (0.27–0.80)	0.0040	1.53 (0.76–3.08)	
50 to <80	87/3547 (1.24)	89/3576 (1.25)	125/3574 (1.78)	0.69 (0.53–0.91)		0.70 (0.54–0.92)		1.01 (0.75–1.36)	
<50	47/1126 (2.17)	69/1157 (3.10)	51/1091 (2.46)	0.88 (0.59–1.31)		1.27 (0.89–1.83)		1.44 (0.99–2.08)	
Intracranial bleed									0.3252
≥80	1/1284 (0.04)	5/1296 (0.19)	13/1300 (0.51)	0.08 (0.01–0.58)	0.2745	0.38 (0.14–1.07)	0.9635	4.98 (0.58–42.53)	
50 to <80	18/3547 (0.26)	26/3576 (0.37)	60/3574 (0.85)	0.30 (0.18–0.50)		0.43 (0.27–0.68)		1.43 (0.78–2.61)	
<50	8/1126 (0.37)	7/1157 (0.31)	17/1091 (0.82)	0.45 (0.19–1.04)		0.38 (0.16–0.92)		0.85 (0.31–2.35)	
Net clinical benefit*									0.4059
≥80	122/1284 (4.76)	117/1296 (4.53)	161/1300 (6.30)	0.74 (0.59–0.94)	0.1774	0.71 (0.56–0.90)	0.0371	0.96 (0.74–1.23)	
50 to <80	489/3547 (6.94)	464/3576 (6.52)	519/3574 (7.37)	0.94 (0.83–1.07)		0.89 (0.78–1.00)		0.94 (0.83–1.07)	
<50	242/1126 (11.18)	266/1157 (11.94)	240/1091 (11.57)	0.96 (0.80–1.15)		1.04 (0.88–1.24)		1.09 (0.91–1.29)	

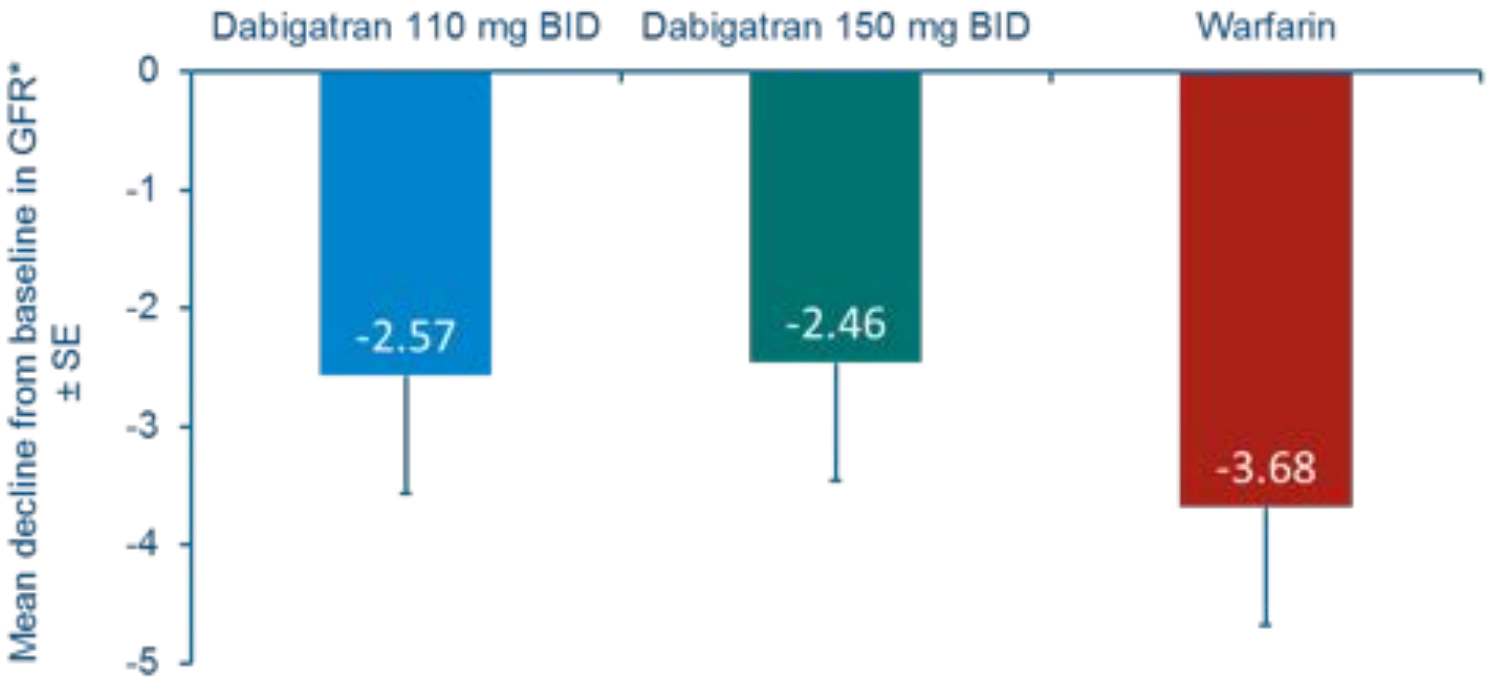
CI indicates confidence interval; HR, hazard ratio; and *P* Value (Inter), *P* value for interaction.

*Net clinical benefit: Composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleed.

Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial

October 16 - 18
14th EDITION 2015

Bohm M, et al. J Am Coll Cardiol 2015;65(23):2481-93.



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

Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment

Keith A.A. Fox*, Jonathan P. Piccini, Daniel Wojdyla, Richard C. Becker, Jonathan L. Halperin, Christopher C. Nessel, John F. Paolini, Graeme J. Hankey, Kenneth W. Mahaffey, Manesh R. Patel, Daniel E. Singer, and Robert M. Califf

European Heart Journal (2011) **32**, 2387–2394

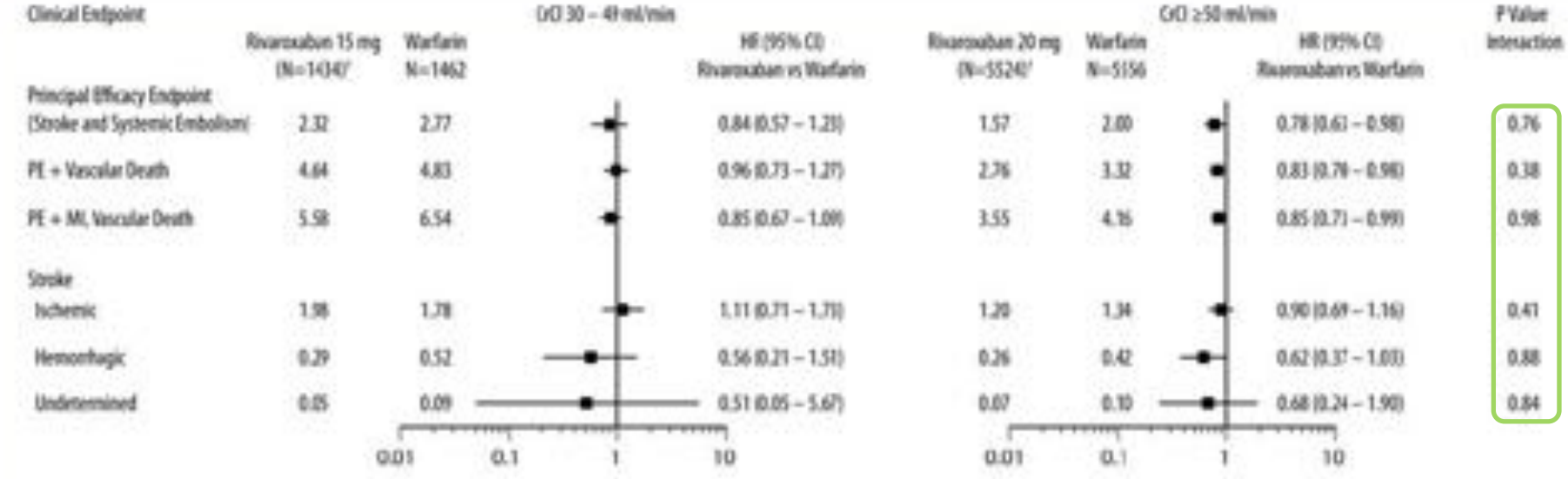
A pre-specified secondary analysis

- Renal function was estimated using the Cockcroft-Gault equation
- 2950 of 14264 patients (20.7%) had a CrCl of 30-49mL/min

- Rivaroxaban dose was reduced to 15mg once daily
- Patients with a CrCl of 30-49mL/min on warfarin (n=1476) had a median TTR of 57.7 (IQR 42.2-69.9)

eGFR <30mL/min (Cockcroft-Gault) was an exclusion criterion in the ROCKET AF

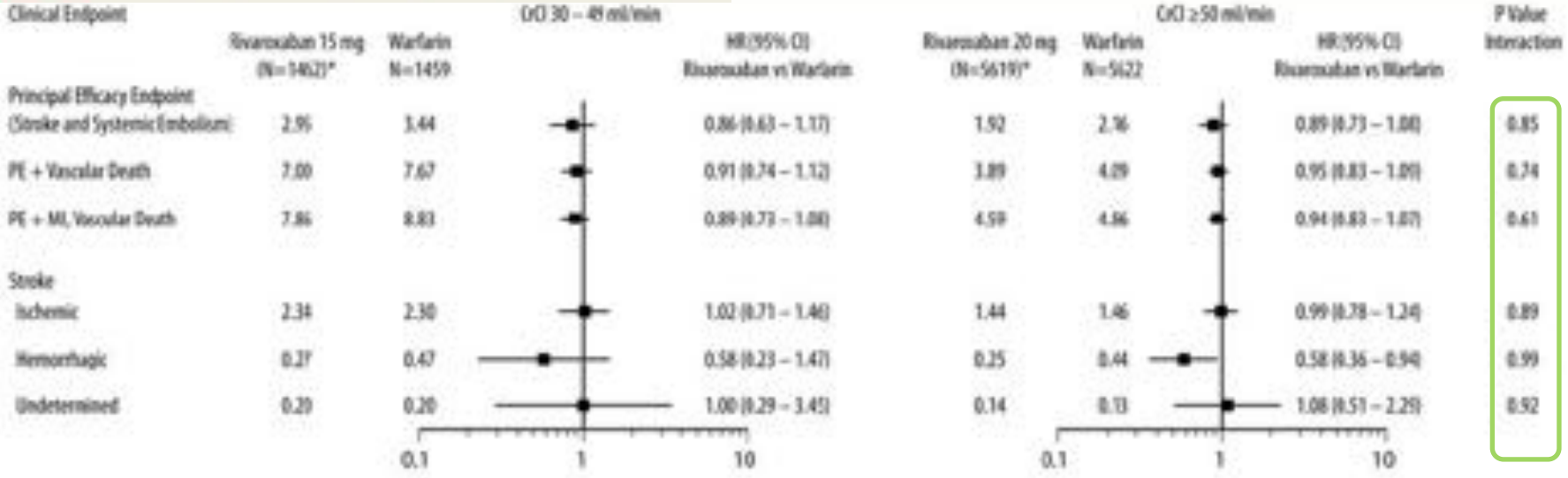
Figure 1 Efficacy events in the per-protocol (on-treatment) population.



* The primary analysis was pre-specified to be performed in the per-protocol population on treatment, which included all patients who received at least 1 dose of study drug, did not have major protocol violations, and were followed for events while on study drug or within 2 days of last dose.

† Event rates per 100 pt/yrs of follow-up

Figure 2 Efficacy endpoints according to the intention to treat.



* Event rates per 100 pt/yrs of follow-up

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

Stefan H. Hohnloser[1*], Ziad Hijazi[2,3], Laine Thomas[4], John H. Alexander[4], John Amerena[5], Michael Hanna[6], Matyas Keltai[7], Fernando Lanas[8], Renato D. Lopes[4], Jose Lopez-Sendon[9], Christopher B. Granger[4], and Lars Wallentin[2]

European Heart Journal (2012) **33**, 2821–2830

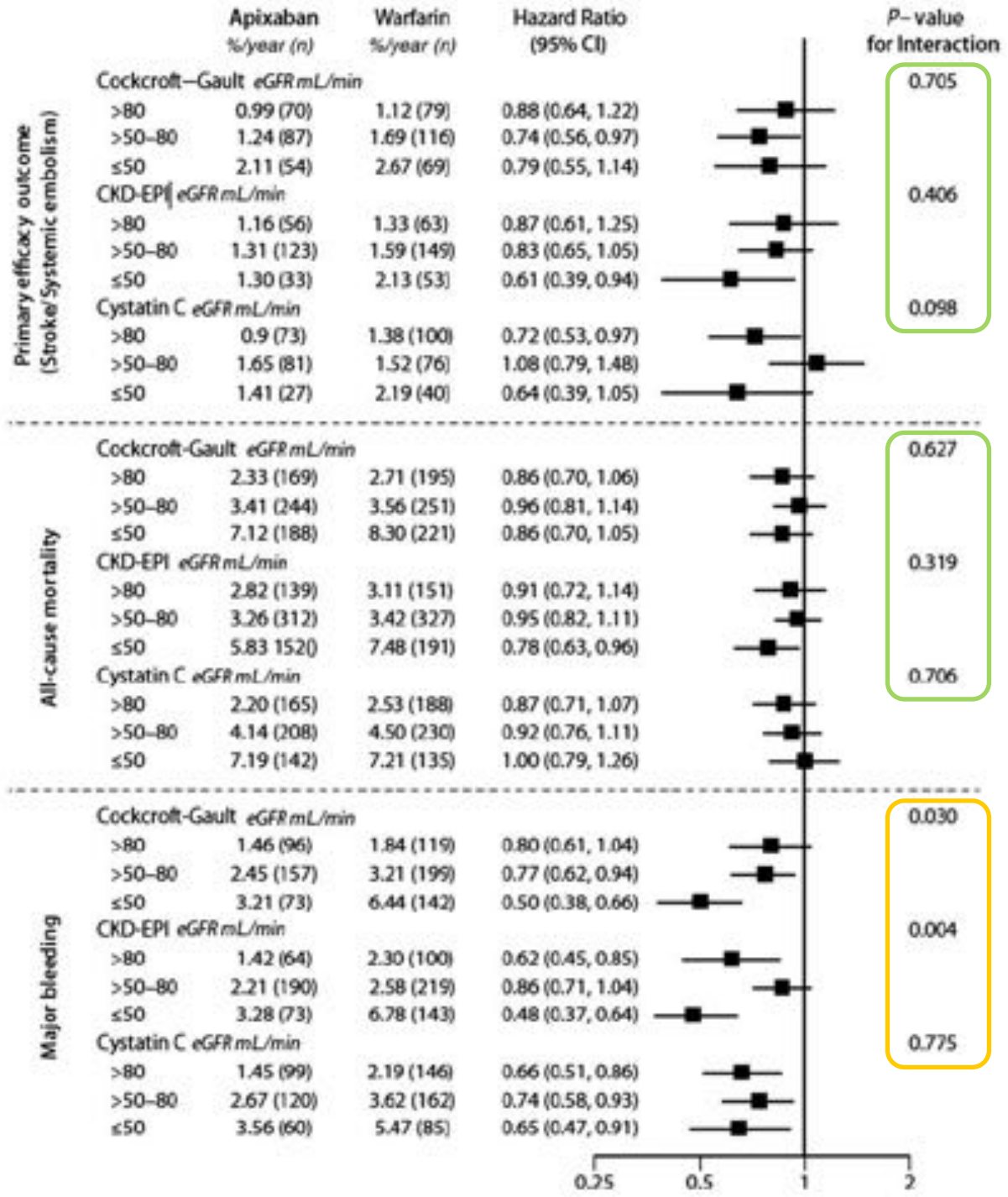
A pre-specified secondary analysis

Apixaban dose was reduced to 2.5 bid if 2 of 3 of the following criteria were met:

- age of ≥80 years
- body weight of ≤60kg
- serum creatinine of ≥1.5mg/dL (133μmol/L)

eGFR	Cockcroft-Gault	CKD-EPI
> 80 mL/min	7518 (42%)	5190 (29%)
51-80 mL/min	7587 (42%)	10151 (56%)
30-50 mL/min	3017 (15%)	2843 (16%)

Serum Cr >2.5mg/dL or calculated CrCl <25mL/min (Cockcroft-Gault) was an exclusion criterion in the ARISTOTLE


Apixaban %/year (n)
Warfarin %/year (n)
Hazard Ratio (95% CI)
P– value for Interaction
Primary efficacy outcome (Stroke/Systemic embolism)
Cockcroft–Gault eGFR mL/min
>80 0.99 (70) 1.12 (79) 0.88 (0.64, 1.22)
>50–80 1.24 (87) 1.69 (116) 0.74 (0.56, 0.97)
≤50 2.11 (54) 2.67 (69) 0.79 (0.55, 1.14)
0.705
CKD-EPI eGFR mL/min
>80 1.16 (56) 1.33 (63) 0.87 (0.61, 1.25)
>50–80 1.31 (123) 1.59 (149) 0.83 (0.65, 1.05)
≤50 1.30 (33) 2.13 (53) 0.61 (0.39, 0.94)
0.406
Cystatin C eGFR mL/min
>80 0.9 (73) 1.38 (100) 0.72 (0.53, 0.97)
>50–80 1.65 (81) 1.52 (76) 1.08 (0.79, 1.48)
≤50 1.41 (27) 2.19 (40) 0.64 (0.39, 1.05)
0.098
All-cause mortality
Cockcroft-Gault eGFR mL/min
>80 2.33 (169) 2.71 (195) 0.86 (0.70, 1.06)
>50–80 3.41 (244) 3.56 (251) 0.96 (0.81, 1.14)
≤50 7.12 (188) 8.30 (221) 0.86 (0.70, 1.05)
0.627
CKD-EPI eGFR mL/min
>80 2.82 (139) 3.11 (151) 0.91 (0.72, 1.14)
>50–80 3.26 (312) 3.42 (327) 0.95 (0.82, 1.11)
≤50 5.83 152() 7.48 (191) 0.78 (0.63, 0.96)
0.319
Cystatin C eGFR mL/min
>80 2.20 (165) 2.53 (188) 0.87 (0.71, 1.07)
>50–80 4.14 (208) 4.50 (230) 0.92 (0.76, 1.11)
≤50 7.19 (142) 7.21 (135) 1.00 (0.79, 1.26)
0.706
Major bleeding
Cockcroft-Gault eGFR mL/min
>80 1.46 (96) 1.84 (119) 0.80 (0.61, 1.04)
>50–80 2.45 (157) 3.21 (199) 0.77 (0.62, 0.94)
≤50 3.21 (73) 6.44 (142) 0.50 (0.38, 0.66)
0.030
CKD-EPI eGFR mL/min
>80 1.42 (64) 2.30 (100) 0.62 (0.45, 0.85)
>50–80 2.21 (190) 2.58 (219) 0.86 (0.71, 1.04)
≤50 3.28 (73) 6.78 (143) 0.48 (0.37, 0.64)
0.004
Cystatin C eGFR mL/min
>80 1.45 (99) 2.19 (146) 0.66 (0.51, 0.86)
>50–80 2.67 (120) 3.62 (162) 0.74 (0.58, 0.93)
≤50 3.56 (60) 5.47 (85) 0.65 (0.47, 0.91)
0.775
0.25
0.5
1
2

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

N Engl J Med 2013;369:2093-104.

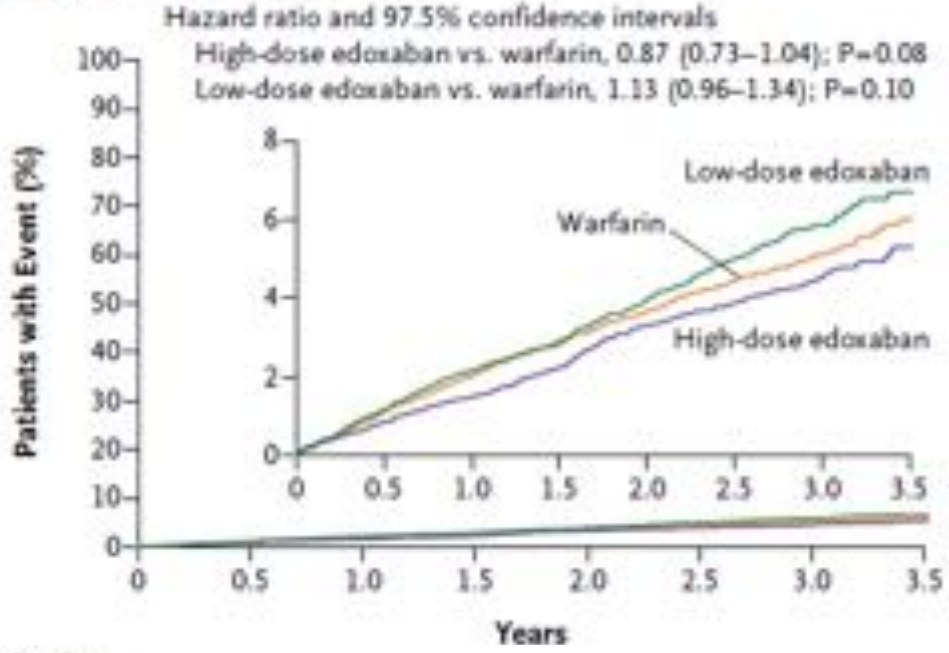
Edoxaban 60mg and 30mg once daily

Edoxaban dose reduction criteria (at least one of the following):

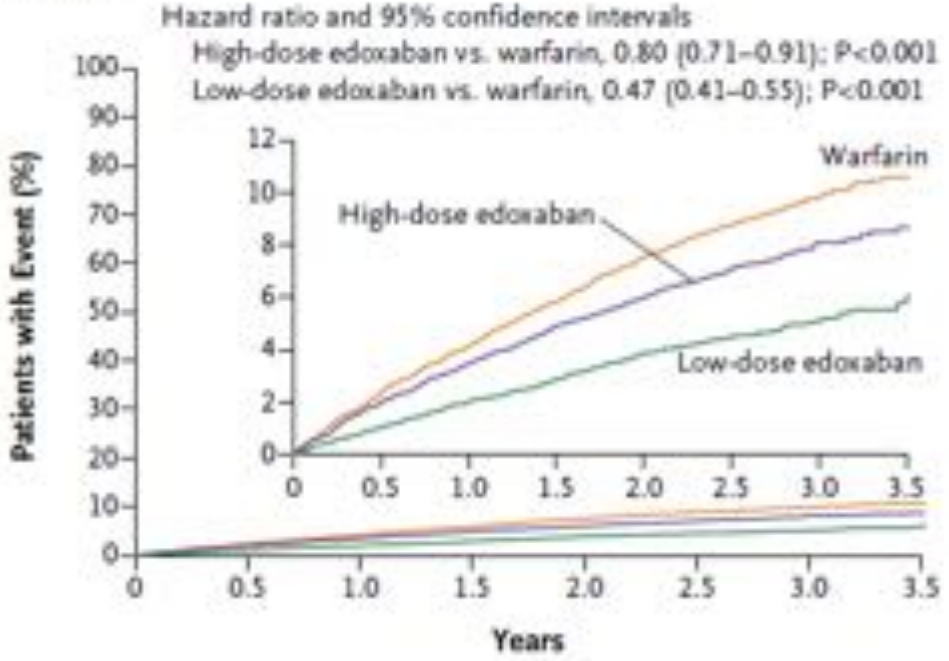
- CrCl <50mL/min (30-49mL/min),
- body weight ≤60kg or
- concomitant therapy with verapamil or quinidine or dronedarone

CrCl <50mL/min at randomization: n=1361 patients (19.3%)

A Stroke or Systemic Embolic Event

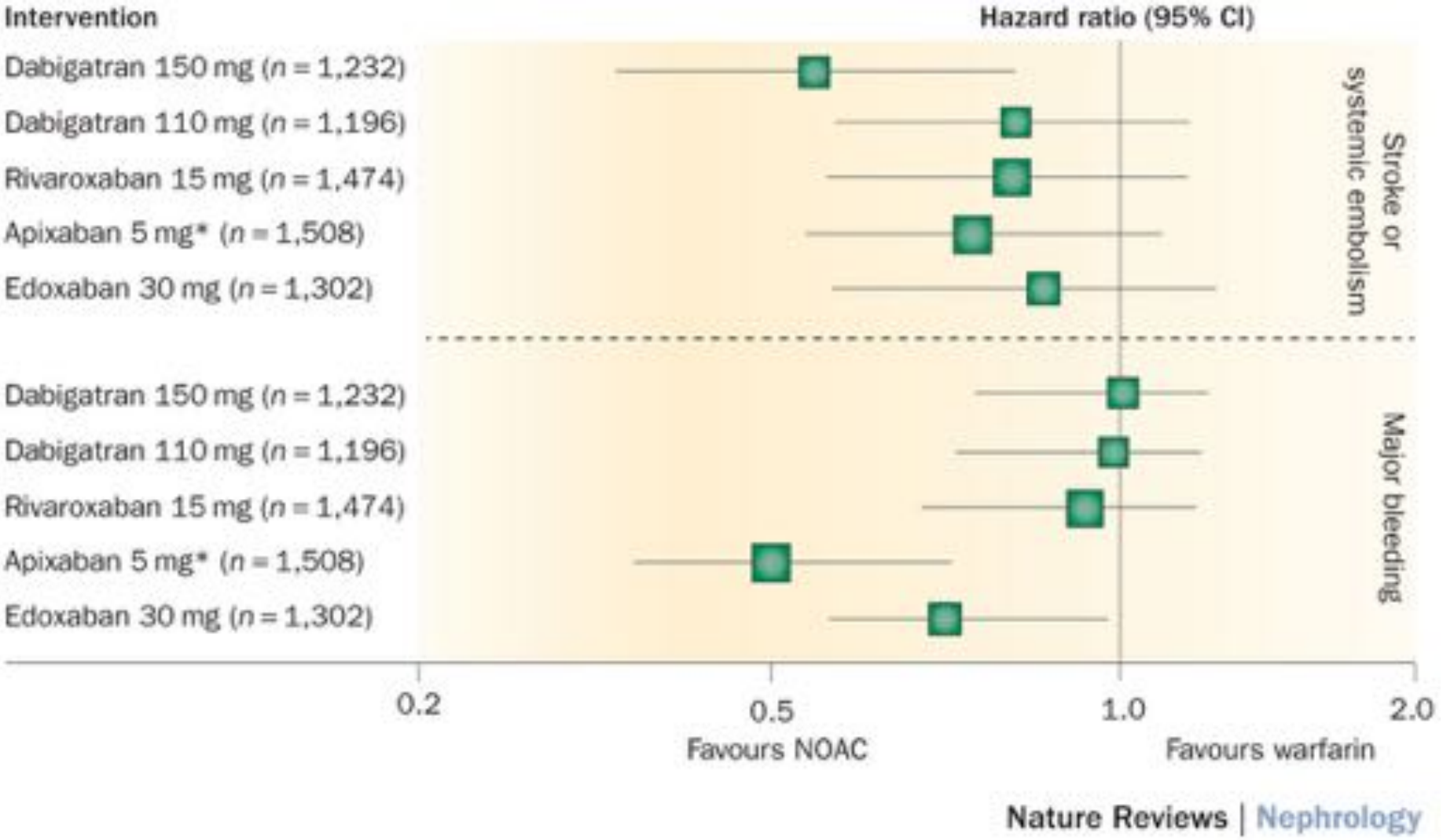


B Major Bleeding



Efficacy and safety of NOACs vs. warfarin in patients with moderate CKD

Qamar A, Bhatt, D. L. *Nat. Rev. Nephrol.* 2015; doi:10.1038/nrneph.2015.14



Stroke Risk and Efficacy of Apixaban in Atrial Fibrillation Patients with Moderate Chronic Kidney Disease

John W. Eikelboom, MBBS,* Stuart J. Connolly, MD,* Peggy Gao, MSc,*
Ernesto Paolasso, MD,† Raffaele De Caterina, MD,‡ Steen Husted, MD,§
Martin O'Donnell, MD,* Salim Yusuf, MBBS, DPhil,* and Robert G. Hart, MD*

Journal of Stroke and Cerebrovascular Diseases, Vol. 21, No. 6 (August), 2012: pp 429-435

All patients* (n = 5525)	eGFR ≥60 mL/min per 1.73 m^2 (n = 3828)	Stage III CKD eGFR <60 mL/min per 1.73 m^2 (n = 1697)	*P* value for stage III *v* eGFR ≥60 mL/min per 1.73 m^2

Table 3. *Event rates with apixaban versus aspirin according to chronic kidney disease status**

	Apixaban rates (n/N)	Aspirin rates (n/N)	Hazard ratio (95% CI)	*P* value
Primary events†				
eGFR ≥60 mL/min per 1.73 m^2	1.7% per year (34/1917)	2.8% per year (60/1911)	0.57 (0.37-0.87)	.009
Stage III CKD	1.8% per year (17/857)	5.6% per year (51/840)	0.32 (0.18-0.55)	<.001; *P* for interaction = .10
Major hemorrhage				
eGFR ≥60 mL/min per 1.73 m^2	0.9% per year (19/1917)	0.8% per year (18/1911)	1.1 (0.56-2.0)	.85
Stage III CKD	2.5% per year (24/857)	2.2% per year (20/840)	1.2 (0.65-2.1)	.58; *P* for interaction = .82
All deaths				
eGFR ≥60 mL/min per 1.73 m^2	2.3% per year (49/1917)	3.3% per year (71/1911)	0.70 (0.49-1.0)	.05
Stage III CKD	6.2% per year (59/857)	7.1% per year (66/840)	0.86 (0.61-1.2)	.42; *P* for interaction = .39

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; stage III CKD, eGFR 30 to 59 mL/min per 1.73 m^2.

*Event rates for 70 patients with stage IV CKD assigned to apixaban (n = 31) versus aspirin (n = 39), respectively: primary events 0% per year (n = 0) versus 5% per year (n = 2), major hemorrhage 3.0% per year (n = 1) versus 2.5% per year (n = 1), and death 9.1% per year (n = 3) versus 7.4% per year (n = 3).

†Most (95%) were ischemic strokes.

Updated EHRA Practical Guide on NOACs (Heidbuchel et al, Europace 2015)
Approved European labels for NOACs and their dosing in CKD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[3] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

Red: contra-indicated/not recommended. **Orange**: reduce dose as per label. **Yellow**: consider dose reduction if two or more 'yellow' factors are present (see also *Table 6*).
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.
[a]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine >1.5 mg/dL.
[b]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high CrCl after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.
[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

ESC 2012 focused update: NOACs in patients with renal impairment

Recommendation	Class	Level
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year	IIa	A
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min)	III	A

Camm AJ et al. Eur Heart J 2012;33:2719–47

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

TABLE 7 Dose Selection of Oral Anticoagulant Options for Patients With Nonvalvular AF and CKD (Based on Prescribing Information for the United States)*

Renal Function	Warfarin (92)	Dabigatran† (74)	Rivaroxaban† (75)	Apixaban† (76)
Normal/mild impairment	Dose adjusted for INR 2.0-3.0	150 mg BID (CrCl >30 mL/min)	20 mg QD with the evening meal (CrCl >50 mL/min)	5.0 or 2.5 mg BID‡
Moderate impairment	Dose adjusted for INR 2.0-3.0	150 mg BID (CrCl >30 mL/min)	15 mg QD with the evening meal (CrCl 30-50 mL/min)	5.0 or 2.5 mg BID‡
Severe impairment	Dose adjusted for INR 2.0-3.0§	75 mg BID‖ (CrCl 15-30 mL/min)	15 mg QD with the evening meal (CrCl 15-30 mL/min)	No recommendation. See Section 4.2.2.2 in the full-text guideline¶
End-stage CKD not on dialysis	Dose adjusted for INR 2.0-3.0§	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation. See Section 4.2.2.2 in the full-text guideline¶
End-stage CKD on dialysis	Dose adjusted for INR 2.0-3.0§	Not recommended¶ (CrCl <15 mL/min)	Not recommended¶ (CrCl <15 mL/min)	No recommendation. See Section 4.2.2.2 in the full-text guideline¶ #

Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society

Giuseppe Boriani (Chair, Italy)*, Irina Savelieva (Co-chair, UK), Gheorghe-Andrei Dan (Romania), Jean Claude Deharo (France), Charles Ferro (UK), Carsten W. Israel (Germany), Deirdre A. Lane (UK), Gaetano La Manna (Italy), Joseph Morton (Australia), Angel Moya Mitjans (Spain), Marc A. Vos (The Netherlands), Mintu P. Turakhia (USA), and Gregory Y.H. Lip (UK)

Europace (2015) **17**, 1169–1196

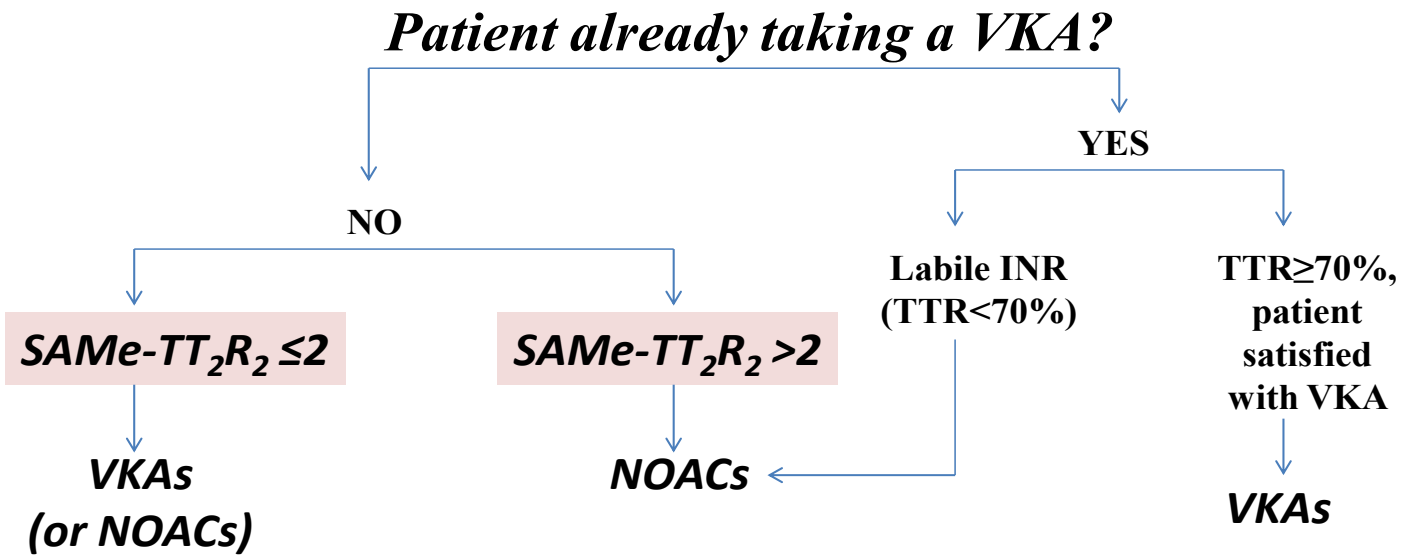
4. Patients with AF and associated CKD have a high risk of stroke and thromboembolism, as well as major bleeding, and these risks are particularly high in patients with renal replacement therapy, whether dialysis or renal transplantation. In patients with CKD, choice and monitoring of thromboprophylaxis deserves special clinical surveillance.

- All the NOACs have a degree of renal excretion, and should not be used where severe renal impairment (creatinine clearance <25–30 mL/min) is evident. In this setting, warfarin is at present time the anticoagulant of choice.
- The SAMe-TT_2R_2 score can be considered to identify patients less likely to achieve good TTRs while on VKAs, who should be targeted for more regular review and follow-up, with additional efforts (e.g. education) to improve the TTR.

Oral Anticoagulant Therapy in Atrial Fibrillation Patients at High Stroke and Bleeding Risk

Tatjana S. Potpara[a,b], Gregory Y.H. Lip[a,c,*]

PROGRESS IN CARDIOVASCULAR DISEASES 58 (2015) 177–194



	Component	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history*	1
T	Treatment (interacting drugs, e.g., amiodarone)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2

*More than two of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease.

Conclusions:

1. Patients with AF and CKD taking OAC have increased rates of stroke and bleeding compared with non-CKD patients, irrespective of the OAC type (VKAs or NOACs)

2. Benefits of OAC are evident for patients with a non-end-stage CKD, and NOACs broadly offer additional net clinical benefit over VKAs in these patients

3. More data are needed to guide the use of OAC in patients requiring RRT. Whilst available data suggest that these patients may benefit from VKAs, experience with NOAC is lacking

4. Patients with advanced CKD taking OAC require close and regular clinical follow-up and monitoring of renal function, and achieving a good TTR in CKD patients taking VKA is essential.