Anticoagulation in End-Stage Kidney Disease (ESKD)

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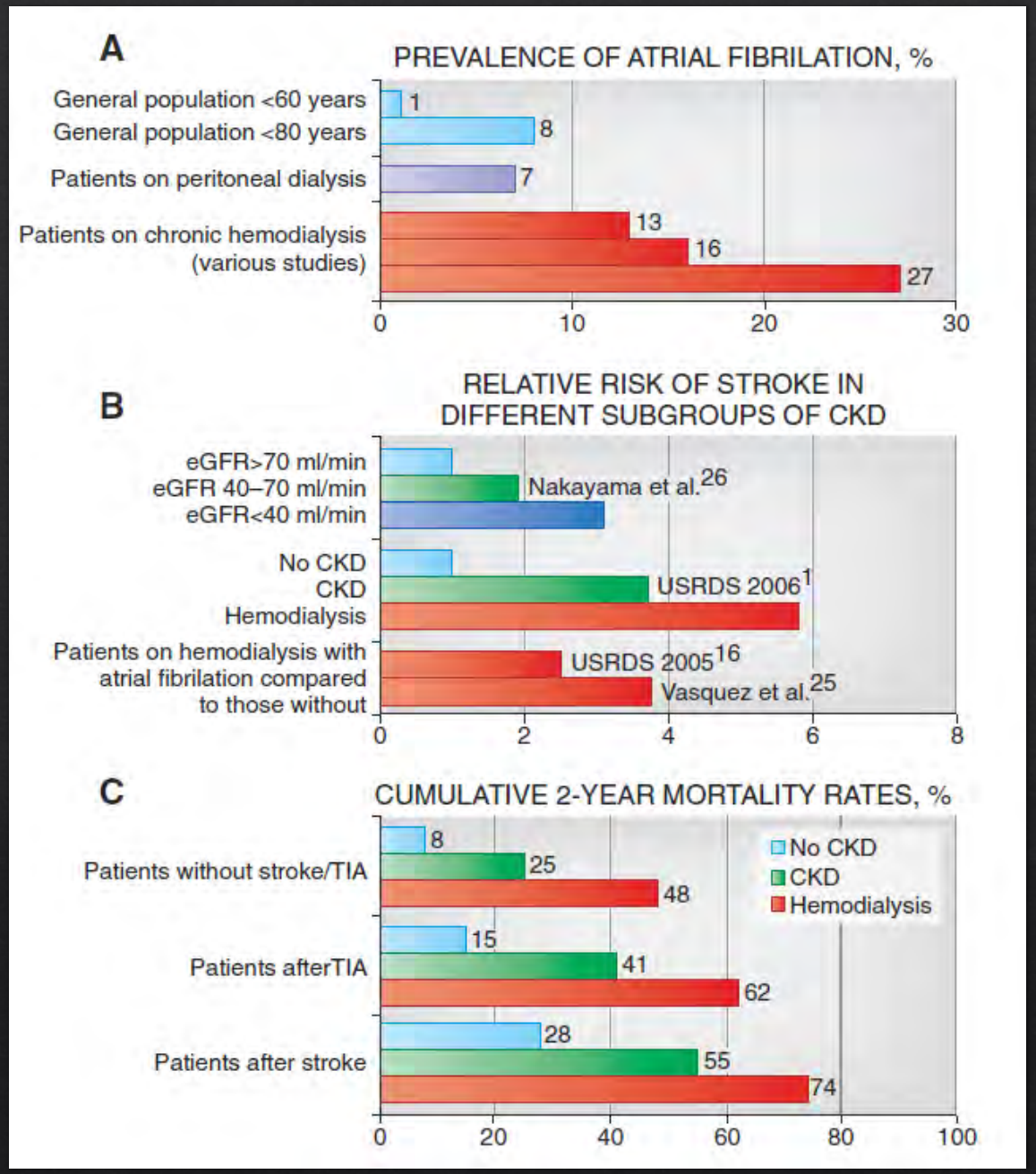
Atrial fibrillation in ESKD

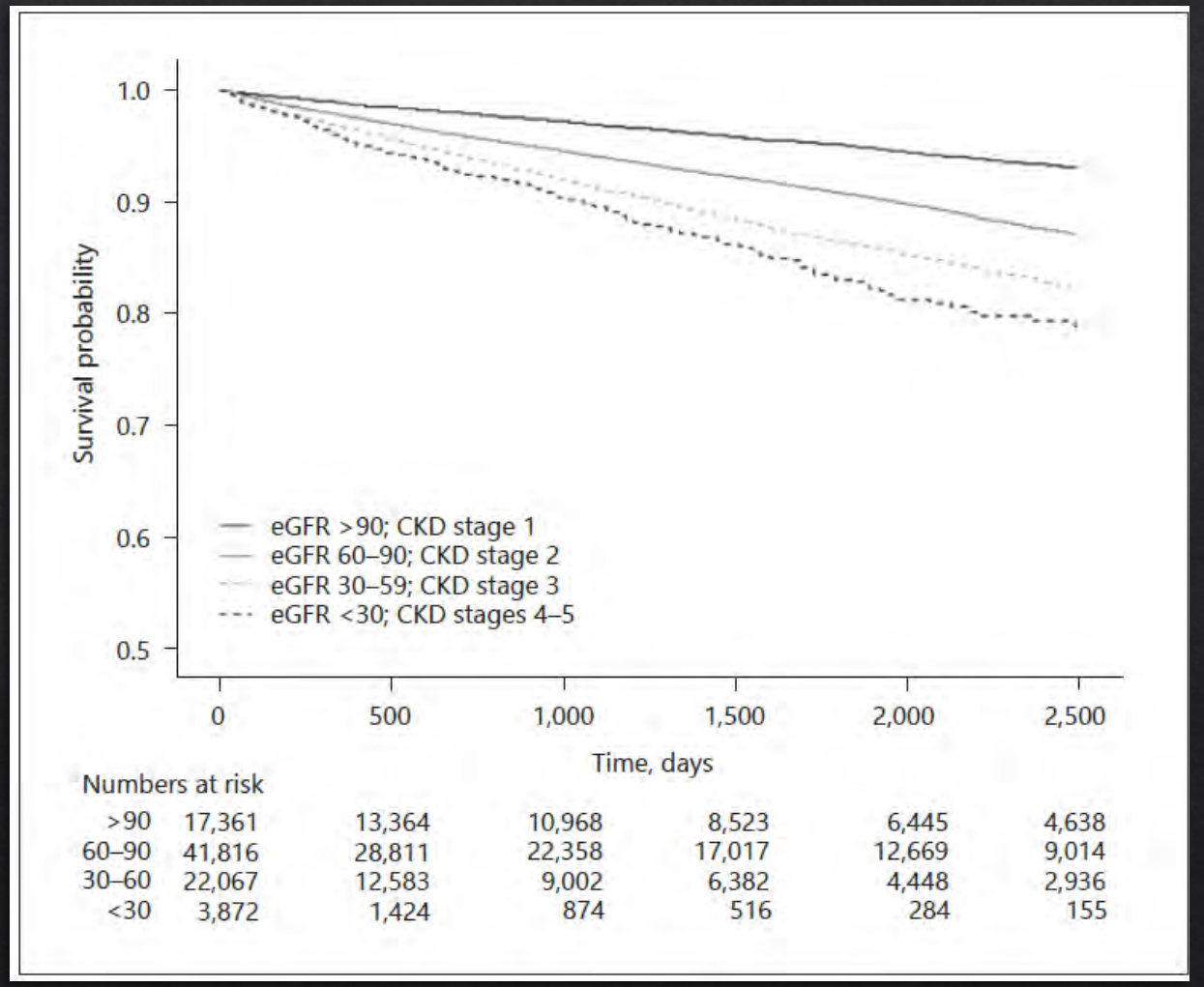
- High prevalence of AF in HD patients, reported 12-25% [1]
  - ? due to LVH, vascular & valvular calcification, volume overload, electrolyte shifts during HD, sympathetic nervous system activation
- Higher risk of thromboembolic complications
- Associated with increased mortality
  - USRDS study: One-year mortality was twice as high among HD patients with AF compared with those without (39% versus 19%) [2]

1. Zimmerman et al. *NDT* 2012;27:3816-22.
2. Winkelmayer et al. *JASN* 2011; 22(2):349-357.



Reinecke et al. JASN 2009, 20: 705–711

Increasing risk of ischaemic stroke as eGFR declines



Numbers at risk

>90	17,361	13,364	10,968	8,523	6,445	4,638
60–90	41,816	28,811	22,358	17,017	12,669	9,014
30–60	22,067	12,583	9,002	6,382	4,448	2,936
<30	3,872	1,424	874	516	284	155

Arnson et al. *Cardiology* 2020;145:178–186.

Anticoagulation for AF in CKD patients

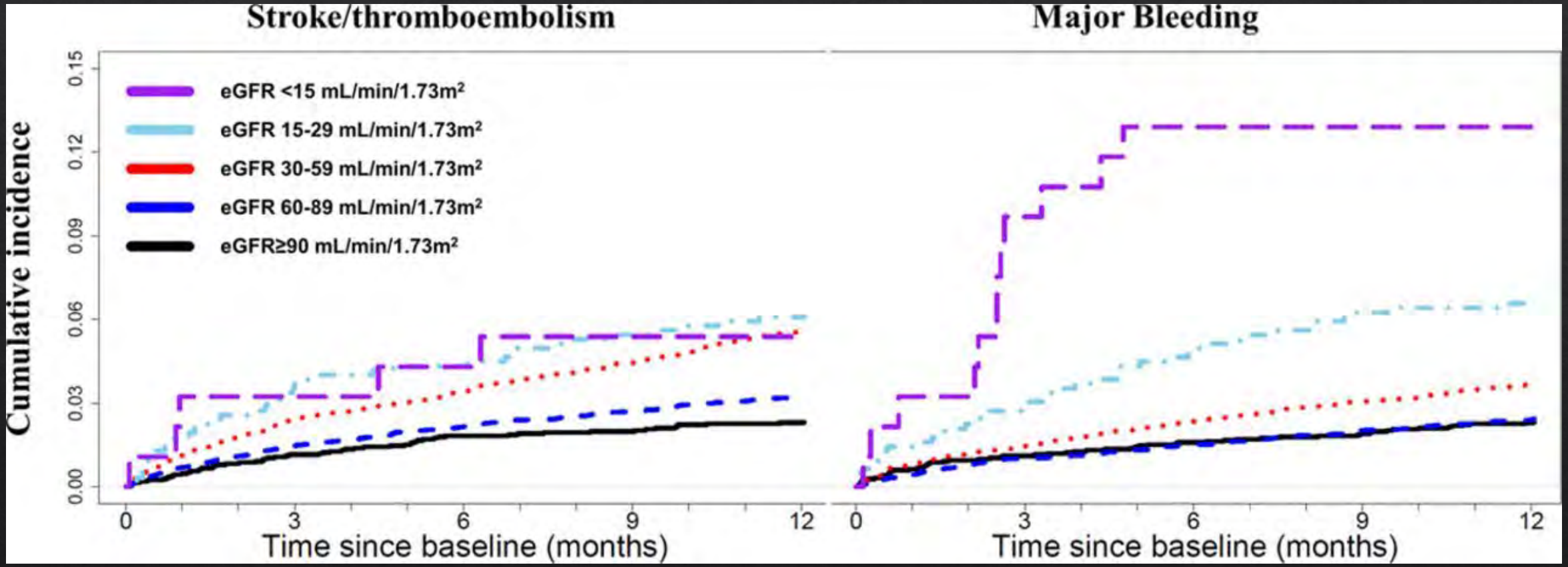
- 2018 Australian guidelines on AF recommend use of warfarin in patients with advanced CKD (CrCl <30ml/min) who require anticoagulation [1]
- In patients with CKD Stage 3-4, warfarin therapy appears to lower the risk of ischaemic stroke & systemic embolism [2,3]

Things to consider:

- Bleeding risk?
- What about use of NOACs?

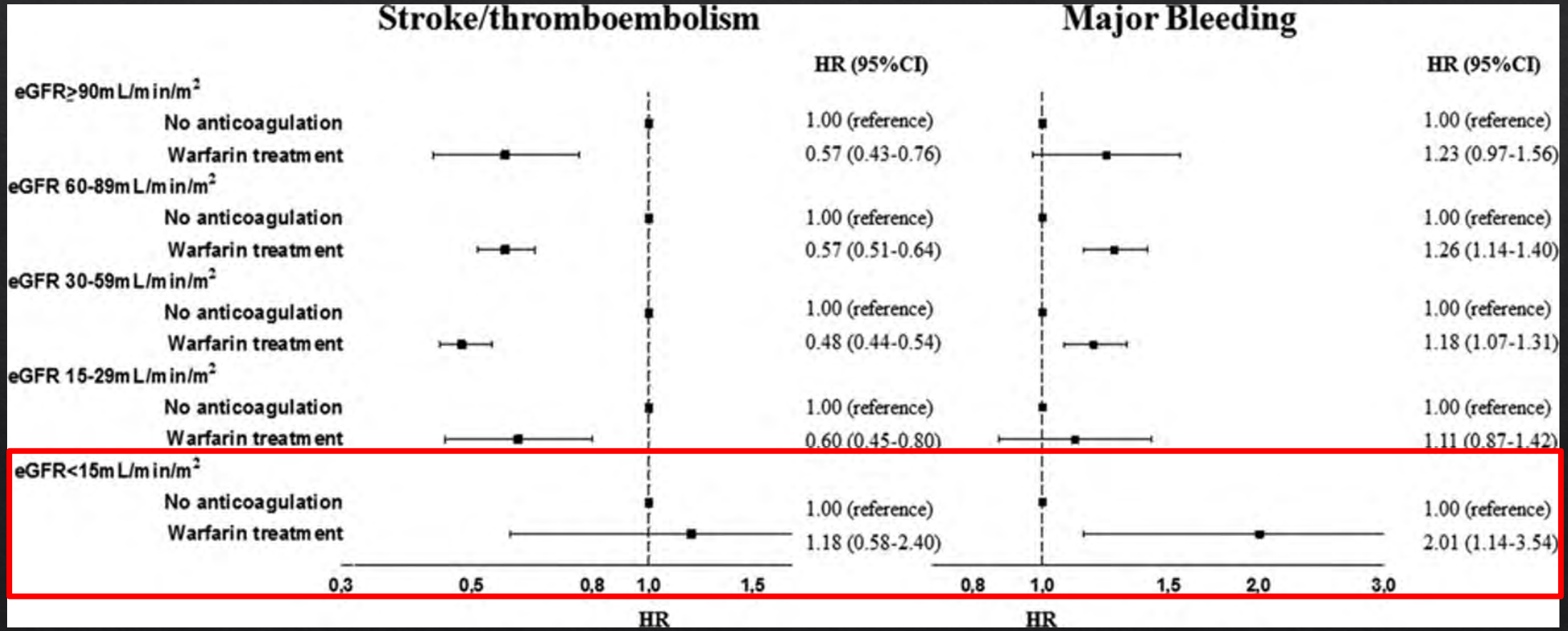
1. Brieger et al. *Heart, Lung & Circulation* 2018; 27(10): 1209-1266.
2. Hart et al. *CJASN* 2011;6: 2599–2604
3. Friberg et al. *Eur Heart J* 2014:36:297–306

ESKD – higher risk of stroke, but also higher risk of major bleeding



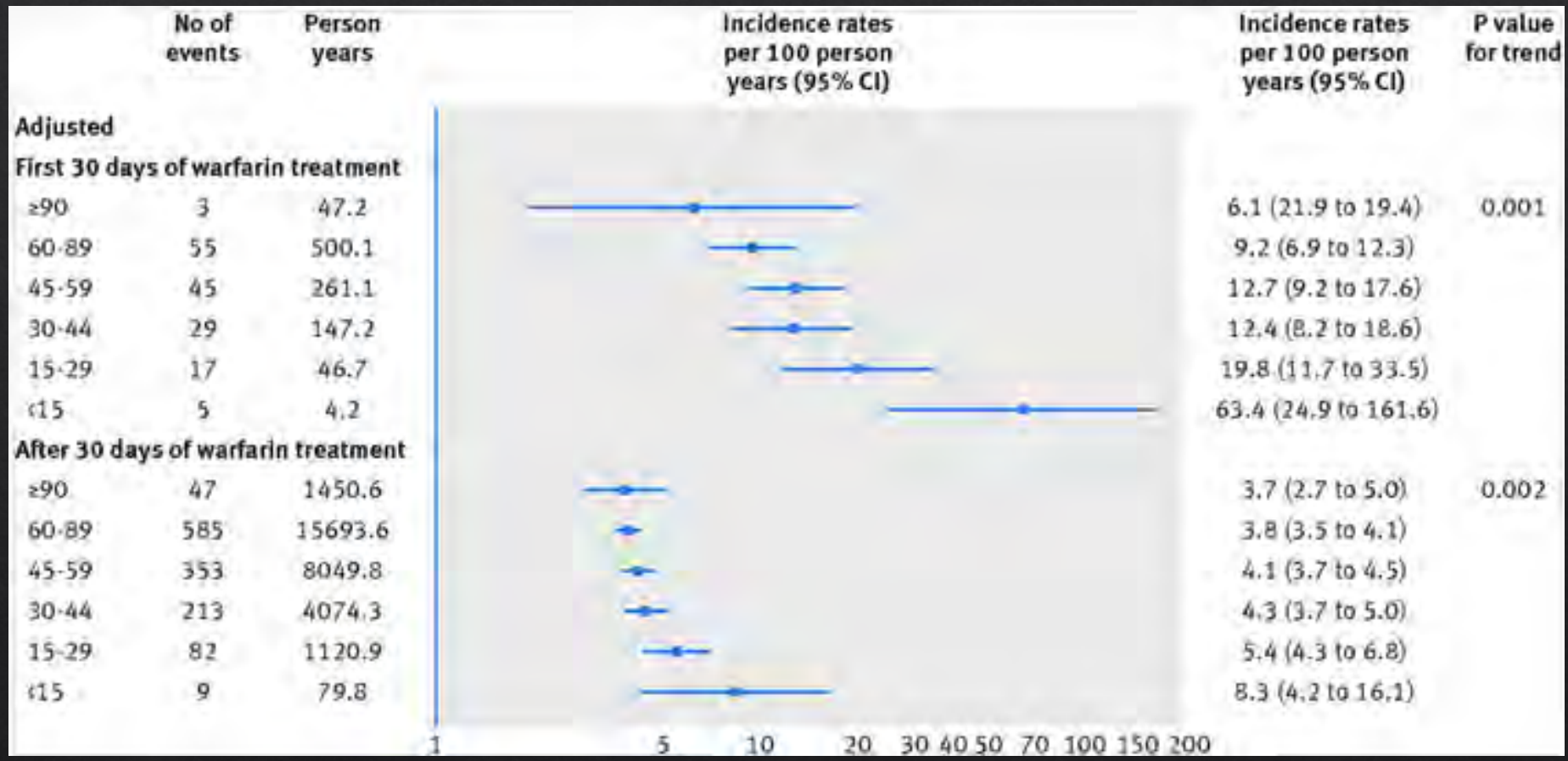
Bonde et al. *Stroke* 2016; 47(11), 2707-2713.

Warfarin may be no better than no anticoagulation for stroke prevention in ESKD?



Bonde et al. *Stroke* 2016; 47(11), 2707-2713.

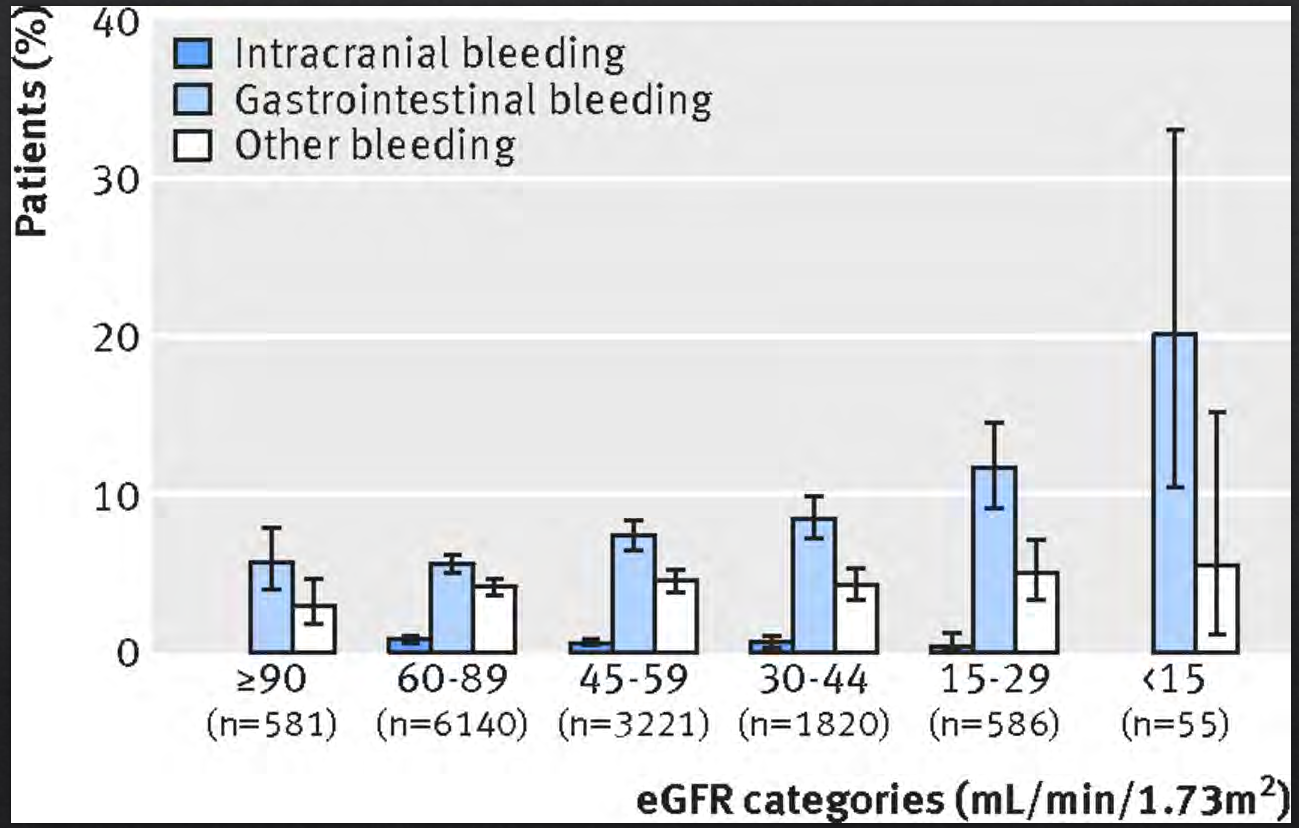
Increasing rate of major bleeding as eGFR decreases



	No of events	Person years	Incidence rates per 100 person years (95% CI)	P value for trend
Adjusted				
First 30 days of warfarin treatment				
≥90	3	47.2	6.1 (21.9 to 19.4)	0.001
60-89	55	500.1	9.2 (6.9 to 12.3)	
45-59	45	261.1	12.7 (9.2 to 17.6)	
30-44	29	147.2	12.4 (8.2 to 18.6)	
15-29	17	46.7	19.8 (11.7 to 33.5)	
<15	5	4.2	63.4 (24.9 to 161.6)	
After 30 days of warfarin treatment				
≥90	47	1450.6	3.7 (2.7 to 5.0)	0.002
60-89	585	15693.6	3.8 (3.5 to 4.1)	
45-59	353	8049.8	4.1 (3.7 to 4.5)	
30-44	213	4074.3	4.3 (3.7 to 5.0)	
15-29	82	1120.9	5.4 (4.3 to 6.8)	
<15	9	79.8	8.3 (4.2 to 16.1)	

Jun et al. *BMJ* 2015;350:h246

Increases in major bleeding rates were largely due to GI bleeding



Jun et al. *BMJ* 2015;350:h246

Warfarin use in HD patients

- Systematic review of 12 observational studies in HD patients
- N = 17,380 hemodialysis patients of whom 4,010 (23.1%) received VKA
- Time in the therapeutic range or mean INR was generally low

- Treatment with VKA was associated with:
  - No significant reduction in risk of ischemic stroke (HR 0.74; 0.51-1.06)
  - Increased total bleeding risk (HR 1.21; 1.03-1.43)
  - Almost 2x risk of hemorrhagic stroke, but not statistically significant (HR 1.93; 0.93-3.98)
  - No effect on mortality (HR 1.00; 0.92-1.09)

Van Der Meersch et al. *American Heart Journal* 2017; 184: 37-46.

NOACs

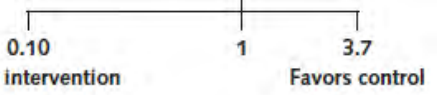
- Significantly reduced risk of stroke and systemic embolism with lower bleeding rates compared to warfarin
- More rapid onset of action, shorter half-life, lack the need for regular laboratory monitoring and lack diet and drug interactions
- Recommended as first-line anticoagulation therapy for patients with non-valvular AF, over warfarin (includes apixaban, dabigatran or rivaroxaban)
- CKD patients (eGFR <30 mL/min) excluded from original RCTs

Meta-analysis of 45 RCTs on anticoagulation for AF in CKD

- Only 8 trials included pts with CrCl <20 mL/min or eGFR <15 mL/min
- In early-stage CKD, NOACs had a risk-benefit profile superior to that of VKAs
- Insufficient evidence in pts with advanced CKD or ESKD

Figure 2. Treatment effects in trials involving participants with atrial fibrillation on stroke or systemic embolism, nonhemorrhagic stroke, hemorrhagic stroke, myocardial infarction, all-cause death, and bleeding outcomes.

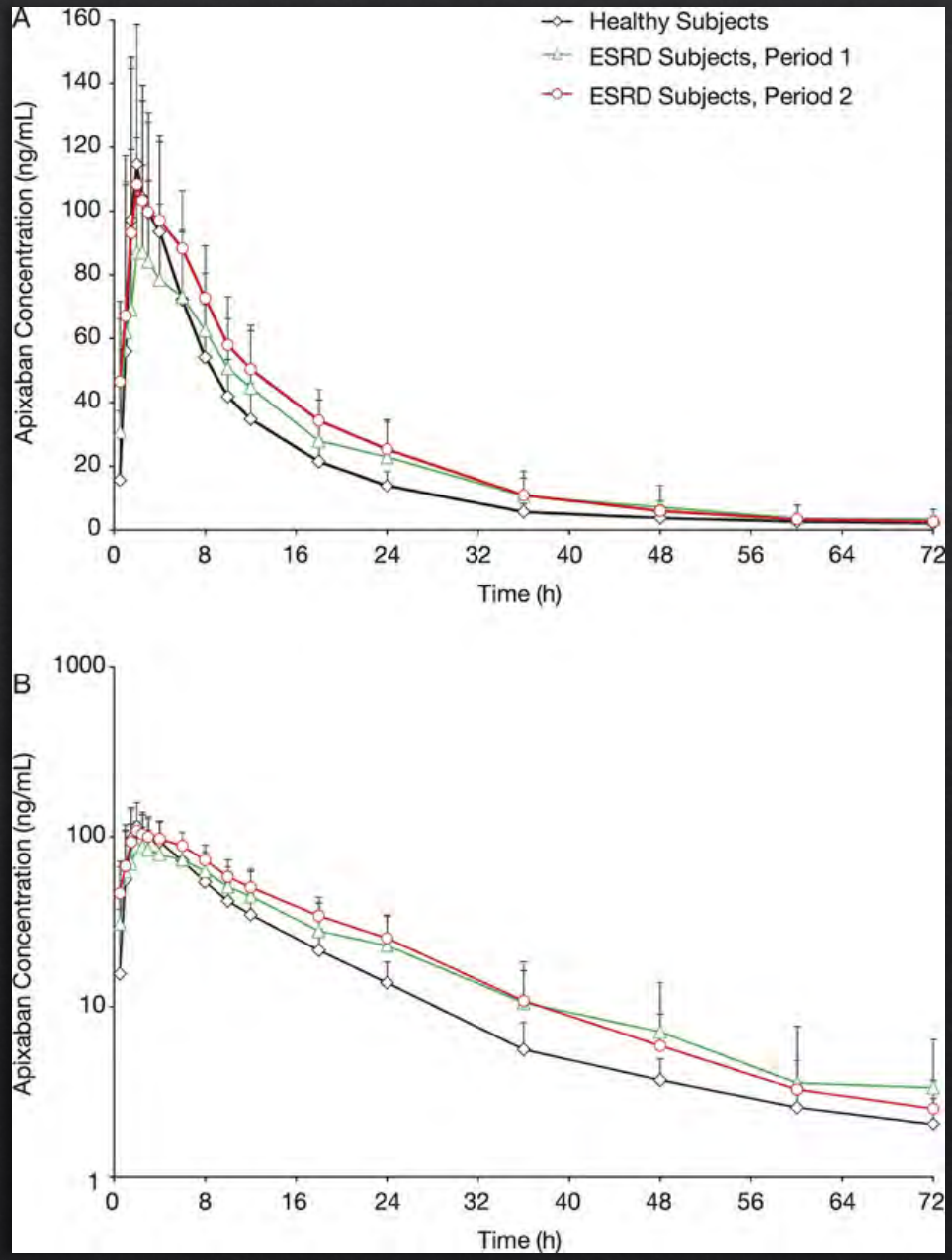
Comparison, by Outcome	Trials, *n*	Events/Participants, *n/N* Intervention	Control	RR (95% CI)	I^2, %	GRADE Certainty of Evidence
Stroke or systemic embolism						
VKA vs. ASA	1	6/267	23/249	0.24 (0.10–0.59)	NA	Very low
NOAC vs. ASA	1	17/857	51/840	0.33 (0.19–0.56)	NA	Very low
Any OAC vs. ASA	2	23/1124	74/1089	0.30 (0.19–0.48)	0	Moderate
High-dose NOAC vs. VKA	5	227/5735	283/5597	0.79 (0.66–0.93)	0	High
High- and low-dose NOAC vs. VKA	5	389/8265	283/5597	0.87 (0.74–1.02)	8	High
Nonhemorrhagic stroke						
High-dose NOAC vs. VKA	3	151/4362	144/4328	1.04 (0.83–1.30)	0	Moderate
Hemorrhagic stroke						
High-dose NOAC vs. VKA	3	27/4362	57/4328	0.48 (0.30–0.76)	0	Moderate
Myocardial infarction						
High-dose NOAC vs. VKA	1	34/1379	38/1361	0.88 (0.56–1.39)	NA	Very low
All-cause death						
VKA vs. ASA	1	21/267	22/249	0.89 (0.50–1.58)	NA	Very low
NOAC vs. ASA	1	59/857	66/840	0.88 (0.62–1.23)	NA	Very low
Any OAC vs. ASA	2	80/1124	88/1089	0.88 (0.66–1.18)	0	Low
High-dose NOAC vs. VKA	3	598/4113	664/4002	0.88 (0.78–0.99)	22	Moderate
Death or ischemic event after PCI/ACS						
High-dose NOAC vs. VKA	2	13/73*	8/72*	0.91 (0.33–2.56)	75	Very low
Major bleeding						
VKA vs. ASA	1	5/267	6/249	0.78 (0.24–2.51)	NA	Very low
NOAC vs. ASA	1	24/857	20/840	1.18 (0.65–2.11)	NA	Very low
Any OAC vs. ASA	2	29/1124	26/1089	1.08 (0.64–1.83)	0	Low
High-dose NOAC vs. VKA	5	402/5600	491/5473	0.80 (0.61–1.04)	75	Low
High- and low-dose NOAC vs. VKA	5	574/8121	491/5473	0.74 (0.55–1.00)	83	Low
Major or nonmajor clinically relevant bleeding						
High-dose NOAC vs. VKA	5	401/1792*	396/1762*	0.97 (0.76–1.23)	28	Low
Intracranial hemorrhage						
High-dose NOAC vs. VKA	3	41/4102	81/3954	0.49 (0.30–0.80)	36	Moderate
Gastrointestinal bleeding						
High-dose NOAC vs. VKA	1	51/1372	43/1356	1.17 (0.79–1.75)	NA	Very low
Fatal bleeding						
High-dose NOAC vs. VKA	1	9/1372	19/1356	0.47 (0.21–1.03)	NA	Very low
Minor bleeding						
High-dose NOAC vs. VKA	1	120/1372	150/1356	0.79 (0.63–0.99)	NA	Very low



Ha et al. *Ann Intern Med.* 2019;171:181-189.

Pharmacokinetics of Apixaban in ESKD

- Out of the NOACs, Apixaban has the lowest renal clearance (25%)
- Open-label study in 8 subjects with ESKD on HD, compared with 8 healthy controls
- ESKD resulted in a modest increase (36%) in apixaban AUC and no increase in Cmax
- HD had limited impact on apixaban clearance

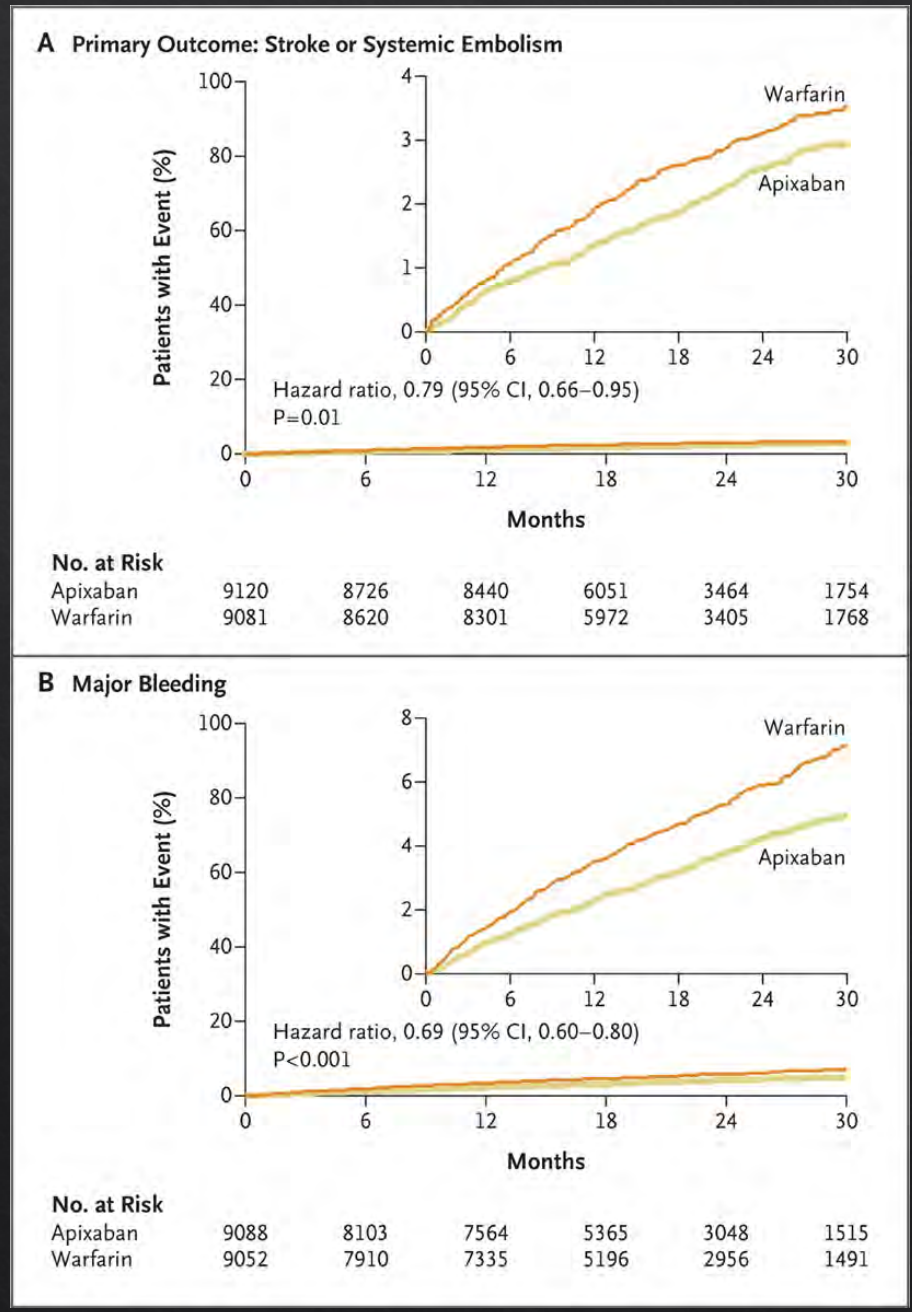


Wang et al. *The Journal of Clinical Pharmacology*, *56*(5), 628-636.

ARISTOTLE (2011)

- Apixaban was superior to warfarin in preventing stroke or systemic embolism (HR 0.79), caused less bleeding (HR 0.69), and resulted in lower mortality (HR 0.89)

- Patients with significant renal impairment were excluded (serum creatinine >221µmol/L or CrCl <25 mL/min)



Granger et al. *NEJM*, 2011; 365:981-992.

Questions raised

AF in CKD – high prevalence, higher risk of stroke, higher mortality

Risk increases as eGFR declines

ESKD patients have higher risk of major bleeding (especially GI)

Unclear whether warfarin is better than no anticoagulation for stroke prevention in AF in ESKD patients

NOACs better than Warfarin in general population

No data on NOACs in CKD

Circulation

ORIGINAL RESEARCH ARTICLE

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

Editorials, see p 1530 and p 1534

Konstantinos C. Siontis, MD
Xiaosong Zhang, MS
Ashley Eckard, MS
Nicole Bhave, MD
Douglas E. Schaubel, PhD
Kevin He, PhD
Anca Tilea, MPH
Austin G. Stack, MBBCh,

BACKGROUND: Patients with end-stage kidney disease (ESKD) on dialysis were excluded from clinical trials of direct oral anticoagulants for atrial fibrillation (AF). Recent data have raised concerns regarding the safety of dabigatran and rivaroxaban, but apixaban has not been evaluated despite current labeling supporting its use in this population. The goal of this study was to determine patterns of apixaban use and its associated outcomes in dialysis-dependent patients with ESKD and AF.

Methods

- Retrospective cohort study using the US Renal Data System (USRDS)
  - Medicare prescription information to identify patients prescribed dabigatran, rivaroxaban, apixaban, or warfarin between Oct 2010 and Dec 2015
- N = 25,523 patients with ESKD and AF undergoing dialysis who initiated treatment with an oral anticoagulant
- Patients were followed until study end (Dec 2015) or until death or censoring
- Study outcomes: ischaemic stroke or systemic embolism, major bleeding, GI bleeding, intracranial bleeding, and death
- Matched cohorts for apixaban and warfarin based on a prognostic score

Table 1. Baseline characteristics

Of the apixaban group:

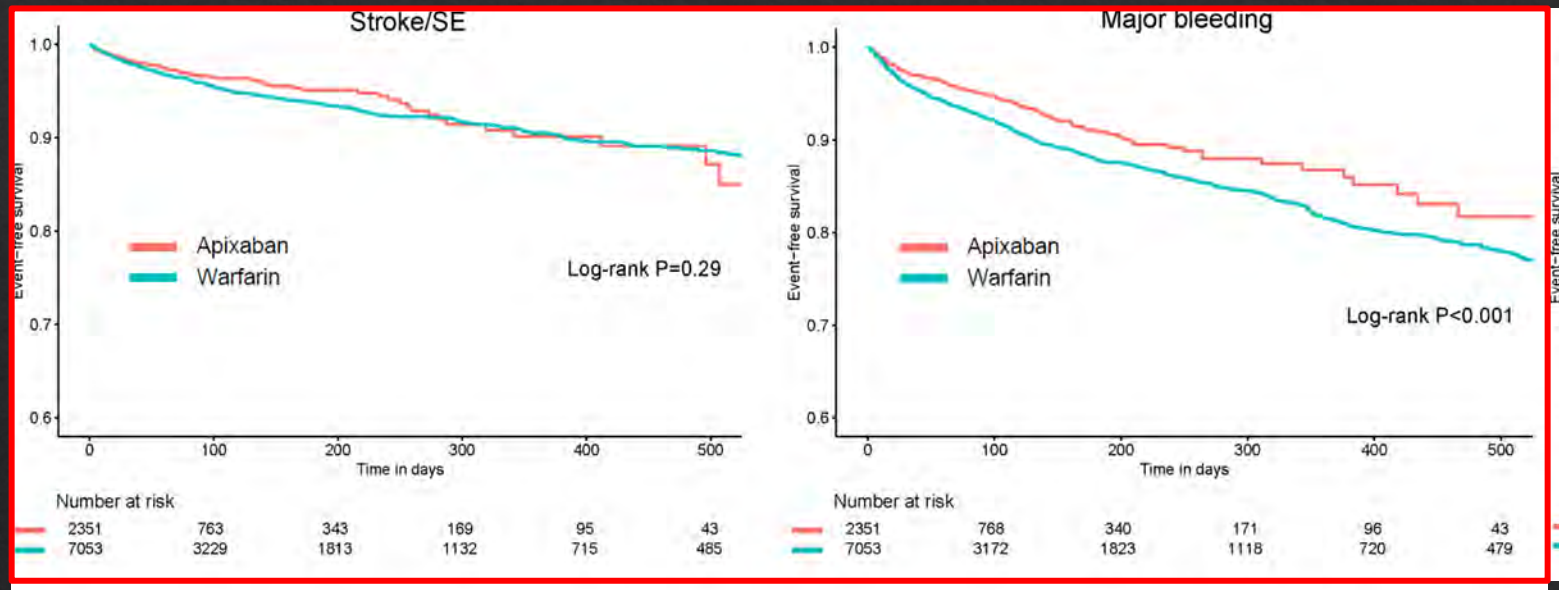
- 1034 (44%) were prescribed 5mg BD
- 1317 (56%) patients were 2.5 mg BD

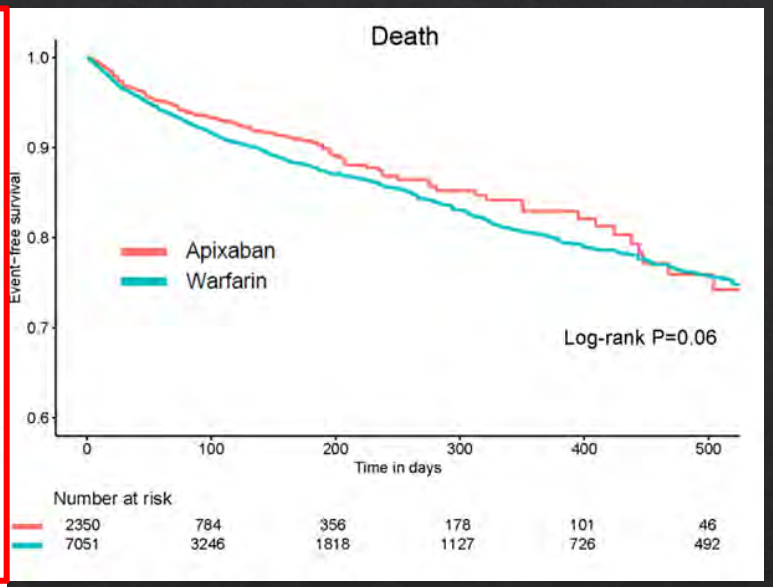
Variable	Overall (n=25 523)	Apixaban (n=2351)	Warfarin (n=23 172)
Demographics			
Age, y	68.22 (11.89)	68.87 (11.49)	68.15 (11.93)
Male	13 852 (54.3)	1280 (54.4)	12 572 (54.3)
Race			
White	16 837 (66.0)	1595 (67.8)	15 242 (65.8)
Black	7458 (29.2)	604 (25.7)	6,854 (29.6)
Other	1228 (4.8)	152 (6.5)	1076 (4.6)
Nephrology care			
Dialysis modality			
Hemodialysis	24 146 (94.6)	2216 (94.3)	21 930 (94.6)
Peritoneal dialysis	1377 (5.4)	135 (5.7)	1242 (5.4)
Time on dialysis, y			
<1	7196 (28.2)	656 (27.9)	6540 (28.2)
1 to <2	2949 (11.6)	240 (10.2)	2709 (11.7)
2 to <3	2759 (10.8)	256 (10.9)	2503 (10.8)
≥3	12 619 (49.4)	1199 (51.0)	11 420 (49.3)
Private insurance	3898 (15.3)	416 (17.7)	3482 (15.0)
Pre-ESKD nephrology care, mo			
None	12 010 (47.1)	1012 (43.0)	10 998 (47.5)
<6	2842 (11.1)	283 (12.0)	2559 (11.0)
6 to <12	4374 (17.1)	422 (17.9)	3952 (17.1)
≥12	6297 (24.7)	634 (27.0)	5663 (24.4)
Comorbidities			
Hypertension	25 421 (99.6)	2342 (99.6)	23 079 (99.6)
Cerebrovascular event*	8461 (33.2)	778 (33.1)	7683 (33.2)
Diabetes mellitus	19 121 (74.9)	1773 (75.4)	17 348 (74.9)
Congestive heart failure	19 827 (77.7)	1868 (79.5)	17 959 (77.5)
Sudden cardiac death/ ventricular arrhythmia	3339 (13.1)	279 (11.9)	3060 (13.2)
Peripheral arterial disease	11 521 (45.1)	1084 (46.1)	10 437 (45.0)
Smoking	9797 (38.4)	978 (41.6)	8819 (38.1)
Hypothyroidism	461 (1.8)	90 (3.8)	371 (1.6)
Liver disease	2580 (10.1)	221 (9.4)	2359 (10.2)
Obesity	5526 (21.7)	590 (25.1)	4936 (21.3)
Venous thromboembolism	4658 (18.3)	279 (11.9)	4379 (18.9)
Cancer	3848 (15.1)	330 (14.0)	3518 (15.2)
Anemia	25 336 (99.3)	2334 (99.3)	23 002 (99.3)
Myocardial infarction	6850 (26.8)	632 (26.9)	6218 (26.8)
Sleep apnea	5399 (21.2)	550 (23.4)	4849 (20.9)
Prior major bleeding	2536 (9.9)	217 (9.2)	2319 (10.0)
Prior gastrointestinal bleeding	2966 (11.6)	249 (10.6)	2717 (11.7)
CHA_2DS_2-VASc score	5.24 (1.79)	5.27 (1.77)	5.24 (1.79)

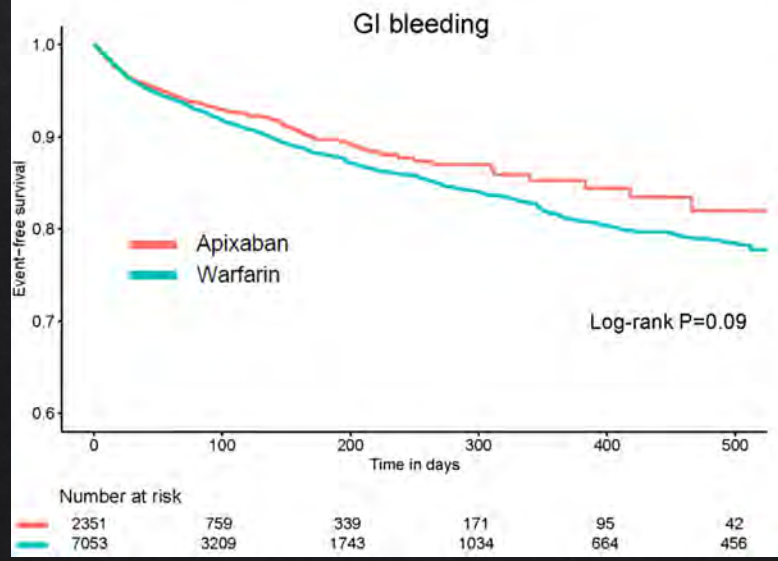
Table 1. Baseline characteristics

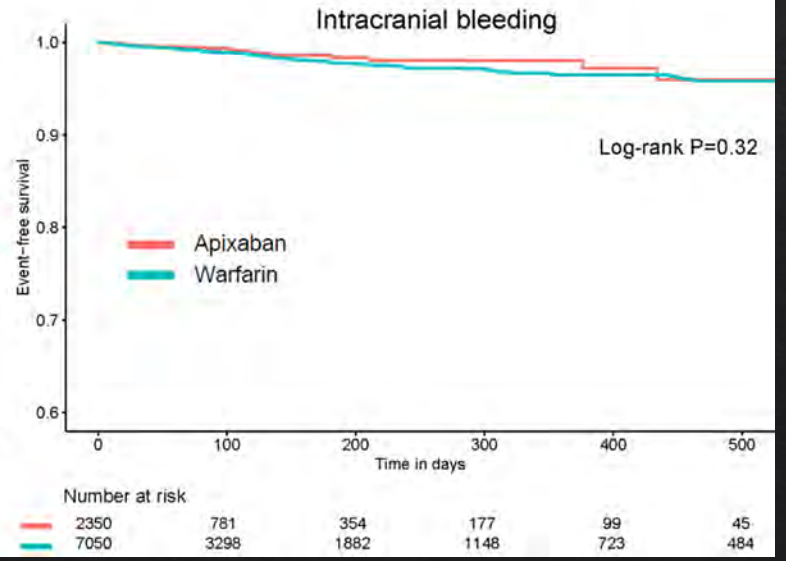
Variable	Overall (n=25 523)	Apixaban (n=2351)	Warfarin (n=23 172)
Statin	6174 (24.2)	553 (23.5)	5621 (24.3)
Nonstatin lipid lowering	649 (2.5)	44 (1.9)	605 (2.6)
Angiotensin-converting enzyme inhibitor	3195 (12.5)	213 (9.1)	2982 (12.9)
Angiotensin receptor blocker	1474 (5.8)	156 (6.6)	1318 (5.7)
β-Blocker	10645 (41.7)	925 (39.3)	9720 (41.9)
Calcium channel blocker	5946 (23.3)	530 (22.5)	5416 (23.4)
Diuretic	2329 (9.1)	214 (9.1)	2115 (9.1)
Other antihypertensive	3689 (14.5)	332 (14.1)	3357 (14.5)
Antiarrhythmics	5616 (22.0)	538 (22.9)	5078 (21.9)
Antianginal vasodilator	2365 (9.3)	206 (8.8)	2159 (9.3)
Antiplatelet†	1866 (7.3)	154 (6.6)	1,712 (7.4)
Nonsteroidal antiinflammatory drugs	357 (1.4)	32 (1.4)	325 (1.4)
Insulin	3419 (13.4)	283 (12.0)	3136 (13.5)
Noninsulin diabetes mellitus drug	1320 (5.2)	126 (5.4)	1194 (5.2)
Proton pump inhibitor	5036 (19.7)	408 (17.4)	4628 (20.0)
Antidepressant	3787 (14.8)	307 (13.1)	3480 (15.0)

Figure 2. Kaplan–Meier survival curves for the apixaban group and matched warfarin cohort



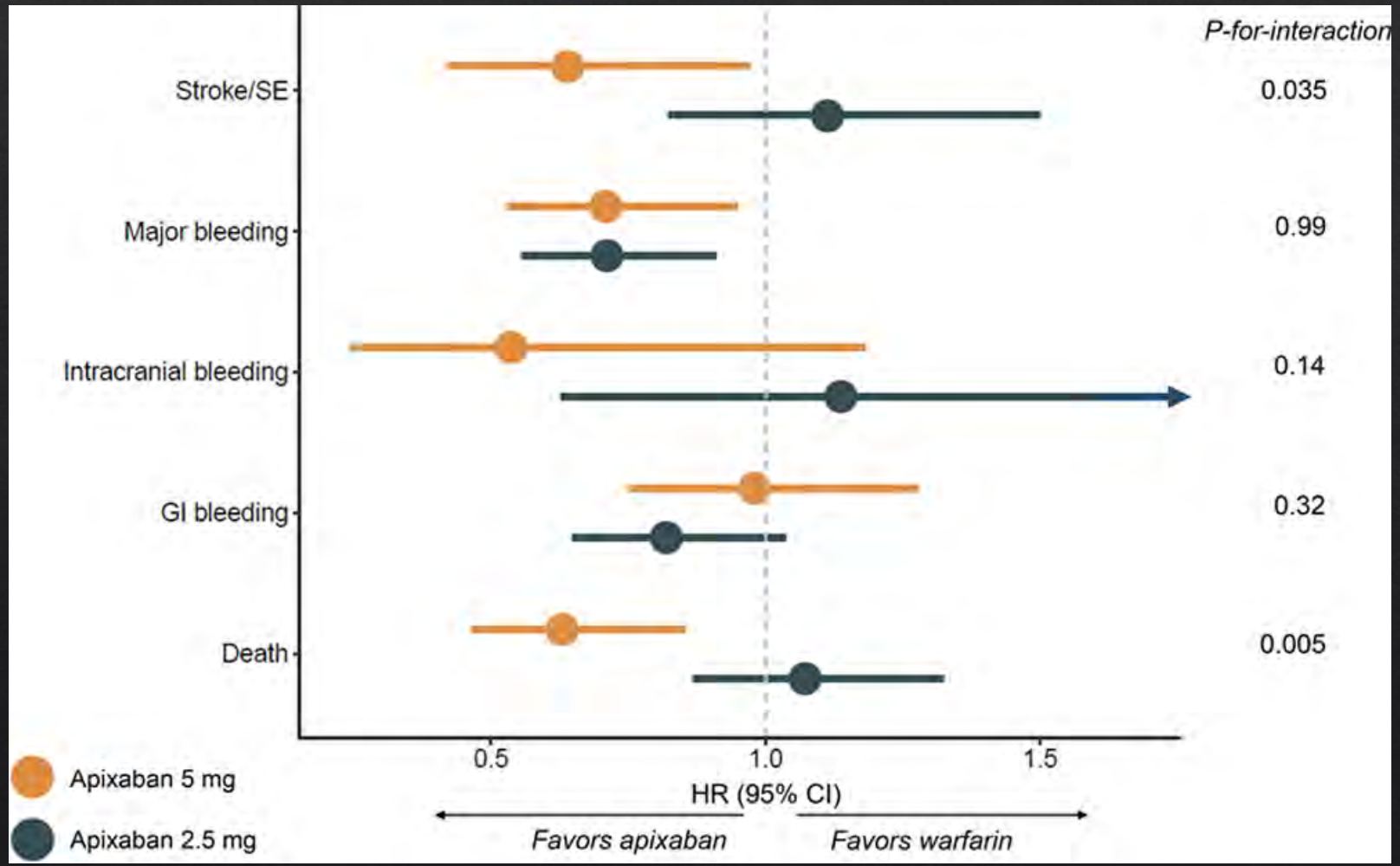






Apixaban had lower rates of major bleeding compared with warfarin (HR 0.72), and no difference in stroke or systemic embolism

Figure 3. Association estimates from dose-specific comparisons of apixaban versus warfarin



Standard-dose apixaban (5 mg BD) was associated with lower risks of stroke/systemic embolism and death, compared to reduced-dose apixaban (2.5mg BD) or warfarin

No difference between 2 doses for major bleeding

Discussion

- Limitations - observational design and reliance on administrative data (reliance on diagnostic coding), unmeasured confounding
- High discontinuation rates for both drugs (mean time on apixaban 105 days, warfarin 157 days)
- Lack of advantage of apixaban versus warfarin in terms of intracerebral hemorrhage
- Bleeding rates were high even in the apixaban group – intracranial bleeding 3.1 per 100 patient-years (vs 0.33 in ARISTOTLE)

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Article

Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation

Thomas A. Mavrakanas,[1,2] *Katherine Garlo*,[1] *and David M. Charytan*[3]

Abstract

Background and objectives The relative efficacy and safety of apixaban compared with no anticoagulation have not been studied in patients on maintenance dialysis with atrial fibrillation. We aimed to determine whether apixaban is associated with better clinical outcomes compared with no anticoagulation in this population.

[1]Renal Division, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts

Methods

- Retrospective cohort study using USRDS data (2012-2015)
- N = 2082 (512 maintenance HD patients with incident non-valvular AF treated with apixaban, vs 1561 matched control patients not on any anticoagulant)
  - 207 patients received standard dose (5 mg BD), 257 patients received reduced dose (2.5 mg BD), and 57 patients switched doses
- Primary outcome: hospital admission for new stroke, TIA, or systemic thromboembolism
- Secondary outcome: fatal or intracranial bleeding

Table 1. Baseline characteristics of the unmatched and matched cohort

Characteristics	Unmatched Cohort			Matched Cohort		
	No Treatment	Apixaban	Standardized Difference	No Treatment	Apixaban	Standardized Difference
No. of patients	10,976	521		1561	521	
Demographics						
Age	67±13	68±11	−0.03	68±13	68±11	0.04
Men	5920 (54%)	281 (54%)	0.00	824 (53%)	281 (54%)	0.02
Black race	3378 (31%)	116 (22%)	−0.19	333 (21%)	116 (22%)	0.02
Hemodialysis	9831 (90%)	453 (87%)	−0.08	1374 (88%)	453 (87%)	−0.03
Dialysis vintage, mo	26 (10–57)	19 (6–33)	0.33	19 (6–38)	19 (6–33)	0.01
Comorbidities						
Hypertension	10,916 (100%)	520 (100%)	0.05	1557 (100%)	520 (100%)	0.02
Diabetes	8778 (80%)	419 (80%)	0.01	1251 (80%)	419 (80%)	0.01
Coronary disease	8302 (76%)	387 (74%)	−0.03	1150 (74%)	387 (74%)	0.01
Heart failure	8243 (75%)	397 (76%)	0.03	1187 (76%)	397 (76%)	0.00
Myocardial infarction	2953 (27%)	110 (21%)	−0.14	349 (22%)	110 (21%)	−0.03
Stroke history	4375 (40%)	178 (34%)	−0.12	564 (36%)	178 (34%)	−0.04
PVD	6571 (60%)	285 (55%)	−0.11	854 (55%)	285 (55%)	0.00
Dyslipidemia	9333 (85%)	472 (91%)	0.17	1420 (91%)	472 (91%)	−0.01
Malignancy	3163 (29%)	149 (29%)	0.00	457 (29%)	149 (29%)	−0.02
Alcohol-related disease	1603 (15%)	59 (11%)	−0.10	175 (11%)	59 (11%)	0.00
Liver disease	3550 (32%)	134 (26%)	−0.15	371 (24%)	134 (26%)	0.04
COPD	4755 (43%)	207 (40%)	−0.07	606 (39%)	207 (40%)	0.02
Bleeding history	6346 (58%)	254 (49%)	−0.18	752 (48%)	254 (49%)	0.01
Medication						
ACEI	3301 (30%)	134 (26%)	−0.10	384 (25%)	134 (26%)	0.03
ARB	2030 (19%)	97 (19%)	0.00	293 (19%)	97 (19%)	−0.01
Antiplatelet agent	2688 (25%)	117 (23%)	−0.05	356 (23%)	117 (23%)	−0.01
β-Blocker	7564 (69%)	379 (73%)	0.08	1126 (72%)	379 (73%)	0.01
Statin	5806 (53%)	313 (60%)	0.15	942 (60%)	313 (60%)	0.00

Results are presented as mean ± SD, median (interquartile range), or number (percentage). PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

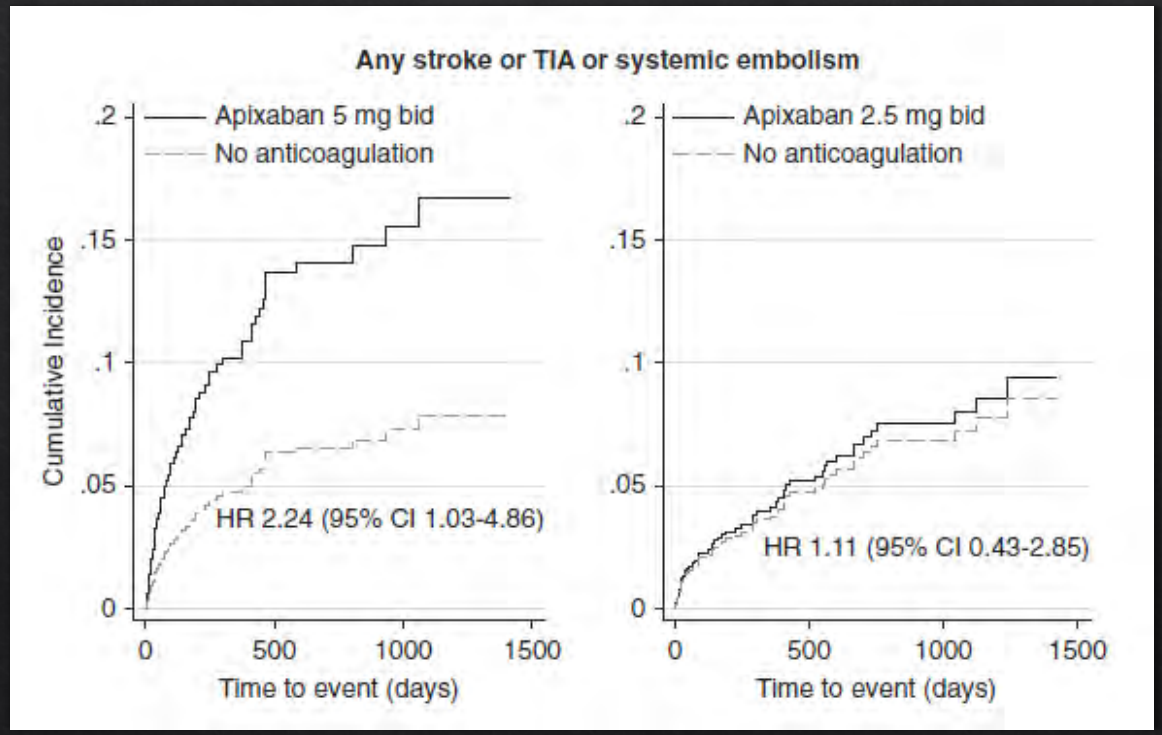
Results

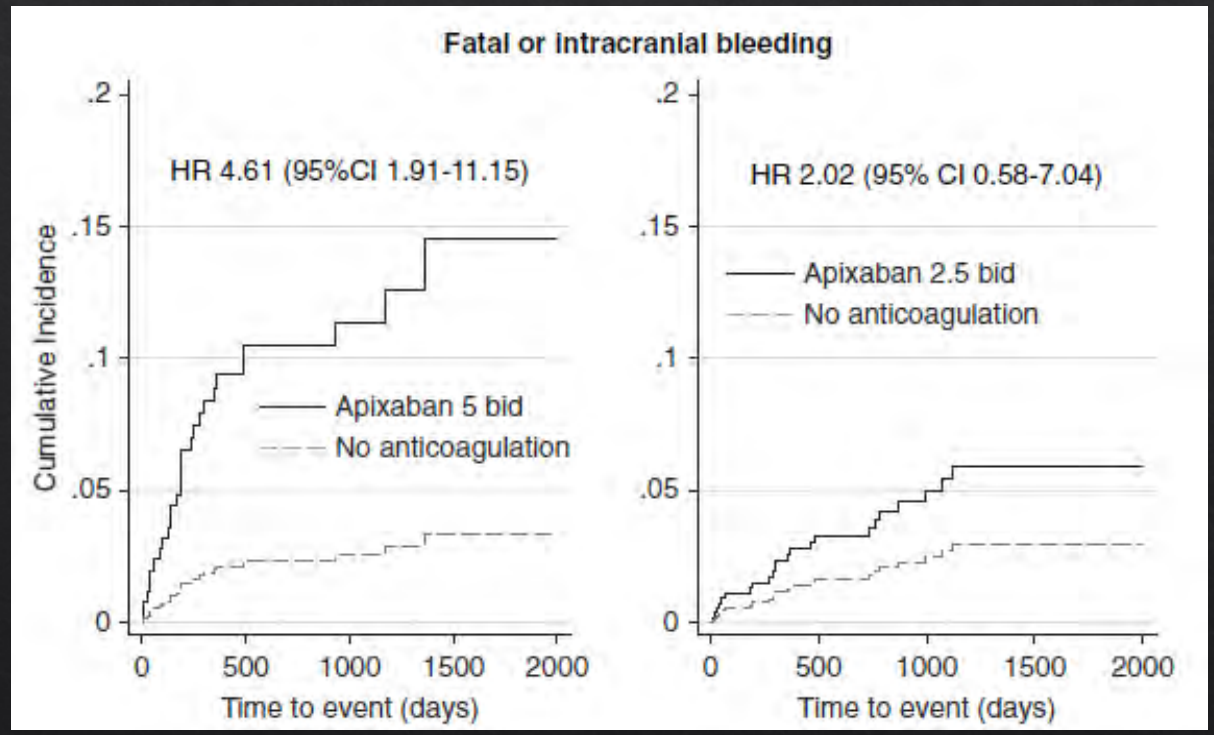
Table 2. Clinical outcomes in the "as-treated" population (main analysis)

Outcome	Incidence in Apixaban Users	Incidence in Nonusers	Crude Hazard Ratio (95% Confidence Interval)	*P* Value	Adjusted[a] Hazard Ratio (95% Confidence Interval)	*P* Value
Any stroke, TIA, or embolism	7.5 (13)	7.0 (114)	1.24 (0.69 to 2.23)	0.47	1.29 (0.72 to 2.33)	0.39
Any stroke	5.8 (<11)	5.8 (96)	1.13 (0.58 to 2.19)	0.72	1.17 (0.60 to 2.28)	0.64
Major bleeding	4.9 (<11)	1.6 (45)	**2.74 (1.37 to 5.47)**	**0.004**	**2.76 (1.38 to 5.52)**	**0.004**
Clinically important bleeding	59.2 (77)	56.9 (695)	1.15 (0.90 to 1.47)	0.26	1.15 (0.90 to 1.46)	0.26
Ischemic stroke or MI	27.6 (43)	25.1 (373)	1.24 (0.90 to 1.71)	0.18	1.25 (0.91 to 1.72)	0.17
Ischemic stroke	3.5 (<11)	5.0 (81)	0.81 (0.35 to 1.89)	0.63	0.85 (0.36 to 1.98)	0.71
Hemorrhagic stroke	2.3 (<11)	1.3 (22)	1.89 (0.65 to 5.47)	0.24	1.89 (0.65 to 5.49)	0.24

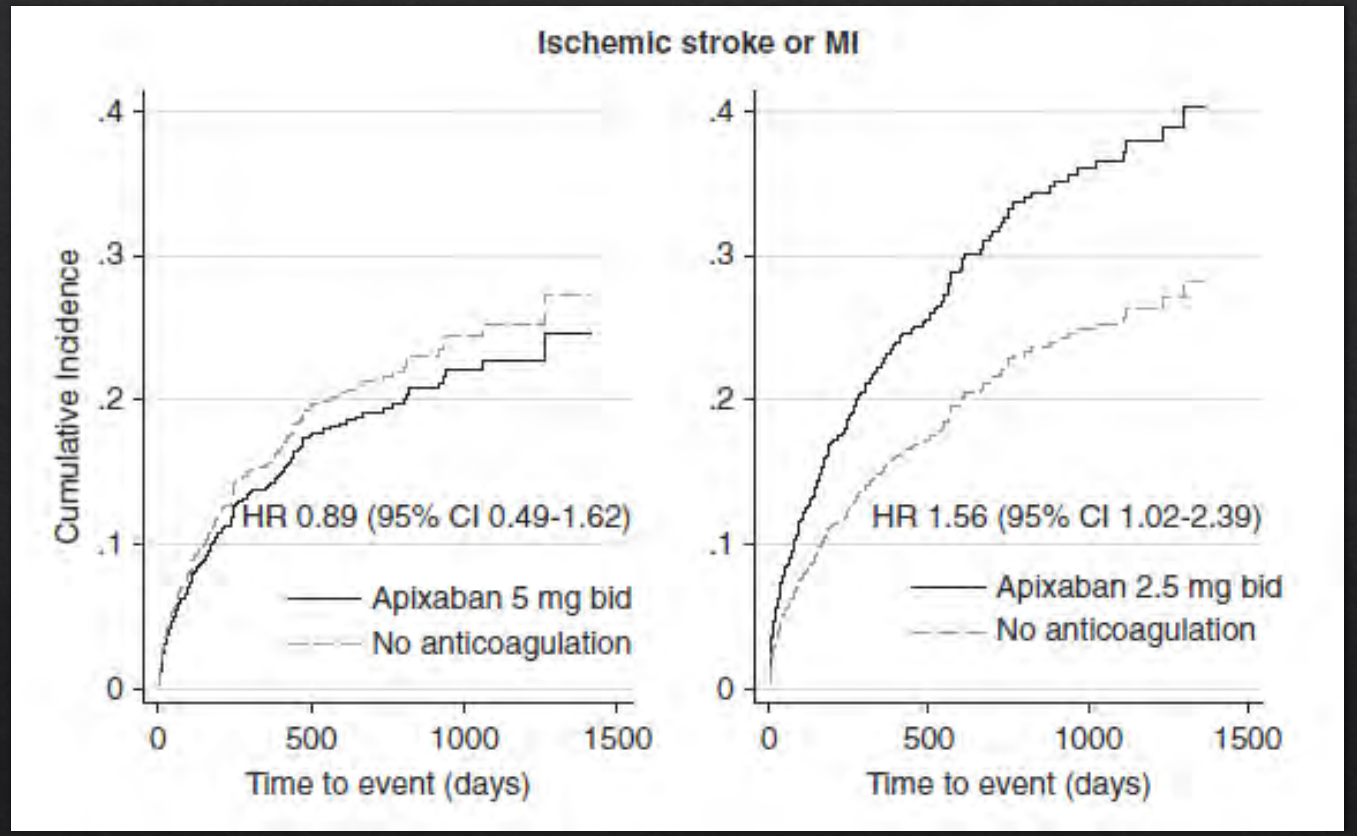
- Apixaban was not associated with a lower risk of stroke / thromboembolism
- It was associated with higher incidence of fatal or intracranial bleeding events, but lower all-cause mortality rates (HR 0.58; 95% CI 0.43 to 0.78)

Apixaban 5mg vs 2.5mg BD





Apixaban 5mg vs 2.5mg BD



Discussion

- Compared to no anticoagulation, Apixaban use was associated with significantly higher rates of haemorrhagic stroke and ICH (especially at standard dose)
- Lower all-cause mortality due to selection bias?
  - Lower incidence of pneumonia (HR 0.77) and hip fractures (HR 0.19) in Apixaban users
- Bleeding events were observed at very high rates even without anticoagulation
- Limitations: observational retrospective study using diagnostic codes, number & proportion of patients treated with apixaban were small, presence of residual confounding

Take-home messages

- Risk-benefit profile of anticoagulation for AF in patients with ESKD remains unclear
- Unclear whether apixaban or warfarin significantly reduce stroke incidence
- Apixaban associated with lower major bleeding risk than warfarin (but higher than no anticoagulation)
- In conservative pathway patients, who are often frail and elderly – should we consider stopping anticoagulation?