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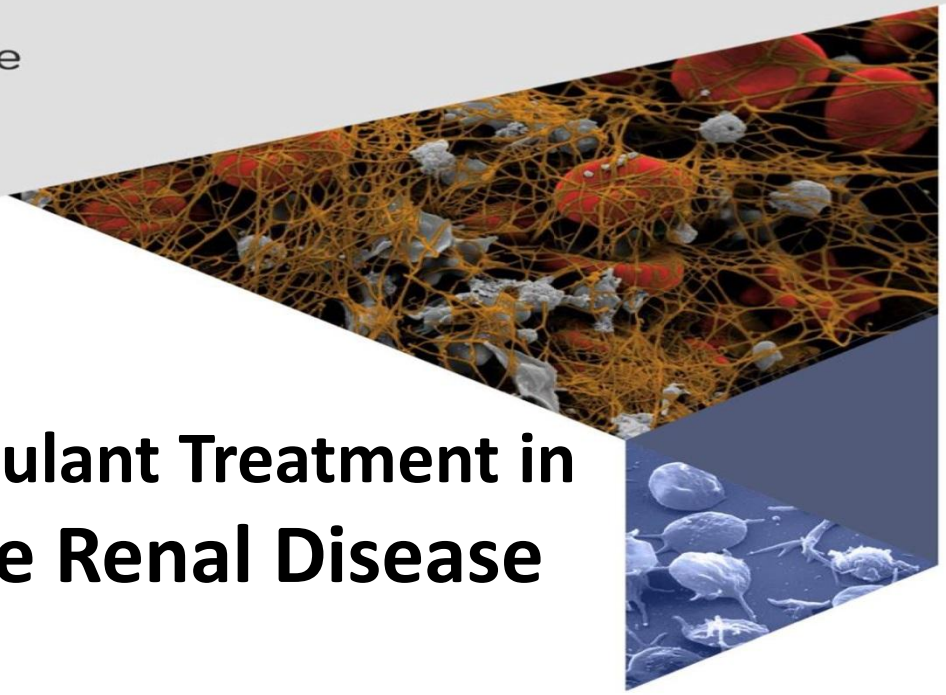

How to Approach Anticoagulant Treatment in Patients with End Stage Renal Disease

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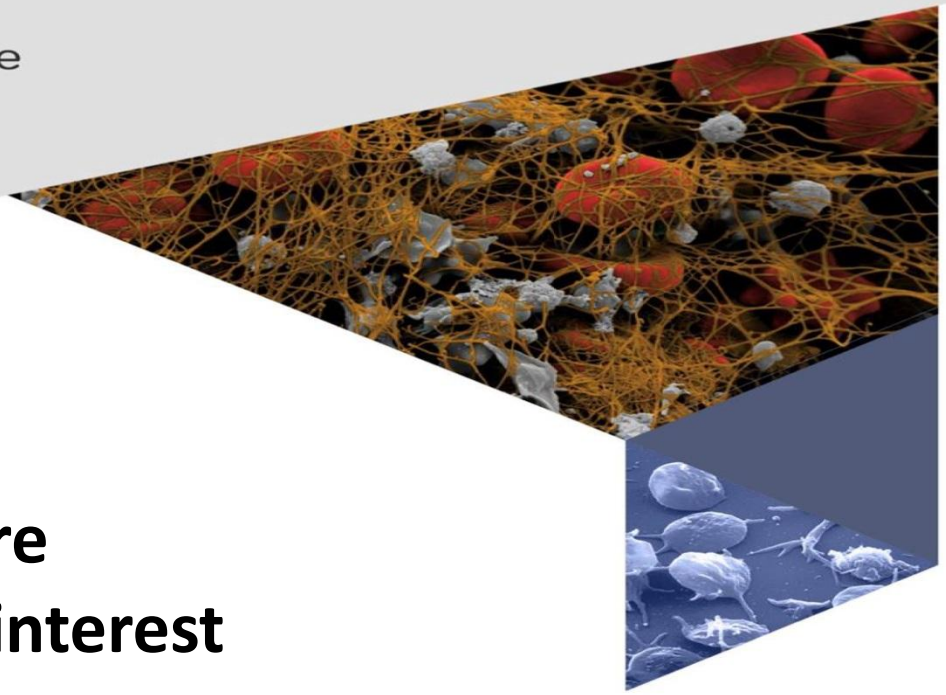


Disclosure

No conflict of interest

Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m²)
1	Kidney damage with normal or GFR	≥ 90
2	Kidney damage with mild GFR	89-60
3A	Mild to moderate GFR	59-45
3B	Moderate GFR	45-30
4	Severe GFR	30-15
5	Kidney failure	< 15 or dialysis

Chronic Kidney Disease

ESRD: End Stage Renal Disease

Renal Association (www.renal.org). Accessed Feb 2019

CKD and ESRD patients

Simultaneously Prothrombotic and Haemorrhagic

- **Prothrombotic Risk**
  - Prothrombotic changes in the vascular endothelium
  - Increase in coagulation factors (fibrinogen, factor VIII and von Willebrand factor) as part of chronic inflammation
  - Increase in antifibrinolytic proteins (plasminogen activator inhibitor)
  - Hyperlipidaemia which predisposes patients to cardiovascular thrombosis
  - Haemoconcentration with effects on blood rheology
  - Changes in platelet membrane ⇨ proaggregatory

Hughes S et al. *Clin Kidney J.* 2014; 7:442-449
Lau et al. *J Am Coll Cardiol*. 2016; 68: 1452-64

CKD and ESRD patients

Simultaneously Prothrombotic and Haemorrhagic

- **Haemorrhagic Risk**
  - Platelet dysfunction
    - Uremic toxins inhibit release of platelet factors
    - Impaired GP IIb/IIIa receptor activation
  - Anaemia which can impact on the interaction of platelets with the vessel wall
  - Stress ulcers
  - Need for frequent interventions
  - Drugs (antiplatelets and frequent heparin exposure)

Hughes S et al. *Clin Kidney J.* 2014; 7:442-449

Exacerbated Risk for Stroke and Bleeding in AF and ESRD
Epidemiological Data

- Patients with ESRD requiring renal replacement therapy
  - **Double** the risk to experience stroke and thromboembolism compared to patients without renal dysfunction
  - Relative risk of intracerebral hemorrhage **>10-fold** higher

Lau et al. *J Am Coll Cardiol*. 2016; 68: 1452-64

TABLE 2 Epidemiological Insight Into Stroke Risk in Patients With AF and CKD

First Author (Year) (Ref. #)	Study Type	N	Findings
Go et al. (2009) (55)	Retrospective	10,908 AF with CKD	Compared with GFR ≥60 ml/min/1.73 m^2: eGFR: 45-59 ml/min; RR: 1.16 (95% CI: 0.95-1.40) eGFR <45 ml/min; RR: 1.39 (95% CI: 1.13-1.71) (p = 0.0082 for trend).
Friberg et al. (2012) (138)	Retrospective	182,678 AF patients (8,113 with CKD)	CKD stage 1 and below: multivariate HR: 1.11 (95% CI: 0.99-1.25)
Olesen et al. (2012) (56)	Retrospective	132,372 AF patients (3,587 with NDD CKD; 901 with ESRD)	Compared with GFR ≥90 ml/min/1.73 m^2: NDD CKD HR: 1.49 (95% CI: 1.38-1.59) ESRD, HR: 1.83 (95% CI: 1.57-2.14)
Guo et al. (2013) (18)	Prospective	617 AF patients	Risk of stroke or death: HR: 2.90 (95% CI: 1.88-4.48) Risk of stroke in 6 months: Absolute decrease in eGFR ≥25 ml/min/1.73 m^2: HR: 2.77 (95% CI: 1.26-6.09) Relative decrease in eGFR ≥25%: HR: 2.57 (95% CI: 1.14-5.80)
Roldán et al. (2013) (61)	Prospective	978 AF patients on VKA	Every decrease in eGFR of 30 ml/min/1.73 m^2: HR: 1.42 (95% CI: 1.11-1.83)
Bonde et al. (2014) (57)	Retrospective	154,254 nonvalvular AF patients (148,598 with NRD; 4,519 with NDD; 1,142 receiving RRT)	Compared with GFR ≥60 ml/min/1.73 m^2: NDD CKD, HR: 1.32 (95% CI: 1.23-1.42) RRT, HR: 2.01 (95% CI: 1.74-2.33)
Chao et al. (2014) (139)	Retrospective	10,999 AF patients with ESRD in Taiwan	11.7% of patients experienced ischemic stroke Absolute stroke and thromboembolism event rate: 6.9/100 patient-years
Banerjee et al. (2014) (140)	Prospective	8,962 AF patients (2,982 with CKD)	Compared with GFR ≥60 ml/min/1.73 m^2: eGFR 30-59 ml/min HR: 1.53 (95% CI: 1.10-2.12) eGFR <30 ml/min HR: 1.78 (95% CI: 0.99-3.19)

CI = confidence interval; HR = hazard ratio; NDD = nondialysis-dependent; RR = relative risk; RRT = renal replacement therapy; other abbreviations as in Table 1.

Lau et al. *J Am Coll Cardiol*. 2016; 68: 1452-64

Pursuing "Net Clinical Benefit" with Anticoagulation in AF and ESRD

Balance the risks of ischemic stroke and bleeding on oral anticoagulation

- **CHA_2DS_2-VASc score** determines thromboembolic risk (≥2 threshold for anticoagulation)
  - Score derived from non-renal patients
  - Moderate-severe renal impairment not included as a factor
  - May not be valid in ESRD
- **HAS-BLED score** to formally assess the bleeding risk and enable risk stratification
  - Abnormal renal function included in the score (? vs ESRD)
  - Correct potentially reversible risk factors for bleeding
  - ***ESRD is a non-modifiable factor for bleeding***

Schwartzenberg S et al. *Am J Cardiol.*2016; 117:477-482

Anticoagulation for AF in Dialysis Patients

ANTICOAGULATION IS NOT UNIVERSALLY ACCEPTED

- 2005 Guidelines from Kidney Disease Improving Global Outcomes (KDIGO)
  - Do not recommend warfarin for primary prevention of stroke in ESRD and NVAF
  - Recommendation for warfarin for secondary prevention of stroke
- AHA 2014 Guidelines
  - CHAD2DS2-VASc score ≥2: reasonable to consider anti-coagulation with warfarin (IIb)
- Canadian Cardiovascular Society 2014 Guidelines
  - Recommend not routinely anti-coagulating non-valvular AF in patients with eGFR <30 ml/min or on dialysis
- ESC 2016 Guidelines EHRA 2015 Consensus documents
  - Lack of data on VKAs and NOACs
  - They suggest the use of warfarin but with debatable benefit
  - NOACs not recommended for CrCl <15 ml/min

McCullough PA et al. *Clin J Am Soc Nephrol.* 2016; 11:2079-2084
Muster H and Alcorn H. *Am J Nephrol.* 227-228

Anticoagulation in Dialysis Patients
Available Randomized Data

Randomized Trials assessing OAC in haemodialysis patients	0
Controlled trials of NOACs in patients with severe CKD (CrCl <25-30 ml/min)	0

Oral Anticoagulation in CKD/ESRD: Vitamin K Antagonists

- Prescription of oral anticoagulants in patients with severe renal impairment varies

- UNCERTAINTY about the risks and benefits of VKA anticoagulation in this patient group

AF pts with ESRD

- Conflicting findings from observational studies
- Equivocal results about efficacy and safety of VKAs
- Potential harm from VKA use in some studies
- Higher risk of hemorrhagic stroke than thromboembolic events
- **Good quality anticoagulation with TTR>70% is vital**

Lau et al.
J Am Coll Cardiol: 2016; 68: 1452-64

TABLE 3 VKA Use and Stroke Rates in ESRD

First Author (Year) (Ref. #)	Study Type	Number (% With AF)	Findings
Wiesholzer et al. (2001) (103)	Retrospective observational	430 (14.3%)	Stroke rate/100 patient-years: AF with VKA: 4.46 AF without VKA: 1.0
Abbott et al. (2003) (95)	Retrospective observational	3,374 (1.25%)	3-year survival rate: AF with VKA: 70% AF without VKA: 55%
Chan et al. (2009) (104)	Retrospective observational	48,825 (3.42%)	90-day HR: AF with VKA: 1.93 (95% CI: 1.29–2.90)*
Wizemann et al. (2010) (105)	Observational (DOPPS)	17,513 (12.5%)	Stroke rate in subjects >75 yrs of age: Warfarin user: 2.17 (95% CI: 1.04–4.53)
Phelan et al. (2011) (106)	Retrospective	845 requiring dialysis (141 on warfarin)	Stroke rate/100 patient-years: VKA user: 1.7 vs. non-VKA user: 0.7 ($p = 0.636$) Major hemorrhage rate/100 patient-years: VKA user: 10.8 vs. non-VKA user: 8.0 ($p = 0.593$)
Winkelmayer et al. (2011) (107)	Retrospective observational	2,313 ESRD patients with new AF	HR for ischemic stroke: VKA user 0.92 (95% CI: 0.61–1.37) HR for hemorrhagic stroke: VKA user 2.38 (95% CI: 1.15–4.96)
Olesen et al. (2012) (56)	Subgroup analysis	901 patients with AF requiring dialysis	HR compared with no antithrombotic agent, dialysis-dependent patients: VKA: 0.44 (95% CI: 0.69–1.01)
Knoll et al. (2012) (100)	Prospective	235 patients on dialysis (19.6% on VKA)	No stroke or bleed experienced HR for mortality in VKA user: 0.80 (95% CI: 0.28–2.29)
Sood et al. (2013) (108)	Observational (DOPPS)	41,844 (9.71%)	Stroke rate/100 patient-years: VKA: 3.3 No VKA or antiplatelet: 2.1†
Bonde et al. (2014) (57)	Retrospective	154,254 nonvalvular AF patients (1,142 on RRT and 260 receiving VKA)	Stroke and thromboembolic risk in non-VKA users: HR: 1.82 (95% CI: 1.58–2.12)‡
Shah et al. (2014) (109)	Retrospective	1,626 patients with AF on RRT (756 VKA users)	HR for ischemic stroke comparing VKA vs. non-VKA users: 1.14 (95% CI: 0.78–1.67) HR for bleeding: 1.44 (95% CI: 1.13–1.85)
Chen et al. (2014) (102)	Retrospective	500 with AF and ESRD (250 receiving VKA)	Compared with control group (no VKA or antiplatelet agent): HR for ischemic stroke: 1.017 (95% CI: 0.673–1.537)
Wakasugi et al. (2014) (110)	Prospective	60 Japanese patients with AF requiring dialysis (28 VKA users)	Comparing VKA vs. non-VKA users HR for ischemic stroke: 3.36 (95% CI: 0.67–16.66)
Chan et al. (2015) (98)	Retrospective	271 patients with AF on peritoneal dialysis (70 on VKA)	Comparing VKA vs. aspirin users: HR for ischemic stroke: 0.16 (95% CI: 0.04–0.66) Comparing VKA vs. nonusers of antithrombotic agents: HR for ischemic stroke: 0.19 (95% CI: 0.06–0.65)
Findlay et al. (2015) (99)	Retrospective	1.382 patients with ESRD, of whom 293 with AF (118 on VKA; 175 without VKA)	Stroke rate: AF with VKA: 11.4% AF without VKA: 14.4%
Genovesi et al. (2015) (97)	Prospective	290 patients with AF requiring dialysis (134 on VKA at recruitment)	Comparing VKA vs. non-VKA users: HR for stroke/thromboembolic events: 0.12 (95% CI: 0.00–3.59)
Shen et al. (2015) (101)	Retrospective	12,284 patients on RRT (1,383 started on VKA)	Comparing VKA vs. non-VKA users: HR for ischemic stroke: 0.68 (95% CI: 0.47–0.99) HR for mortality: 0.84 (95% CI: 0.73–0.97)

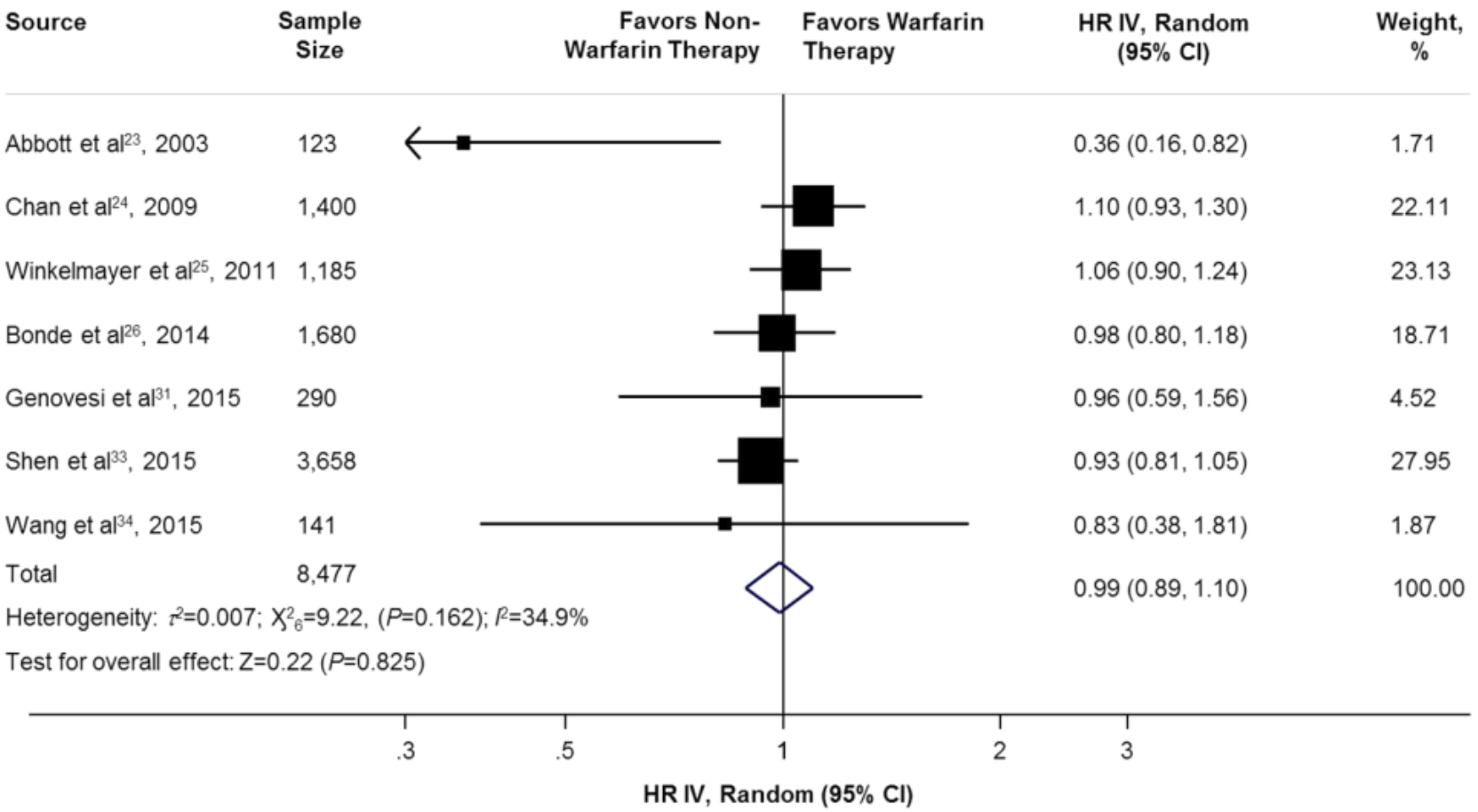
*AF with VKA covariate adjusted model: adjusted for $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack [TIA], or thromboembolism) score, sex, race, Charlson comorbidity index, entry date, body mass index, facility standardized mortality ratio, cardiovascular drugs, dialysis adequacy, baseline laboratory values, heparin dosage, and heparin regimes. †VKA users include patients with AF, thromboembolic disease, or central vascular catheter. ‡Adjusted for aspirin treatment and all risk factors included in CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack [TIA], or thromboembolism, vascular disease [prior myocardial infarction, peripheral arterial disease or aortic plaque], age 65–74 years, sex category [female]) score.

DOPPS = Dialysis Outcomes and Practice Pattern Study; VKA = vitamin K antagonist; other abbreviations as in Tables 1 and 2.

openheart

Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis

MORTALITY



Nochaiwong S et al. *Open Heart* 2016; 3:e000441

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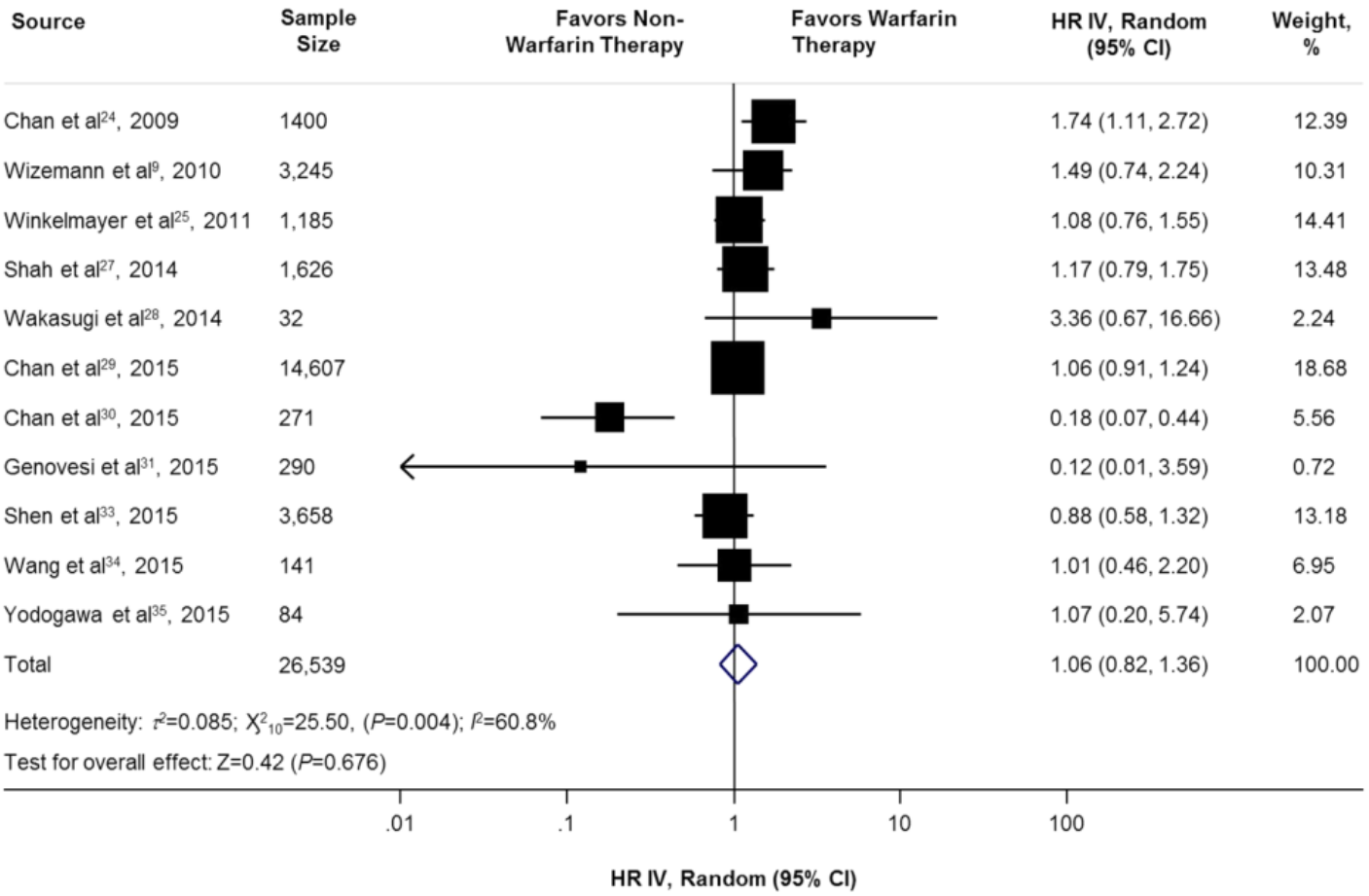
Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis

STROKE/THROMBOEMBOLISM



Nochaiwong S et al. *Open Heart* 2016; 3:e000441

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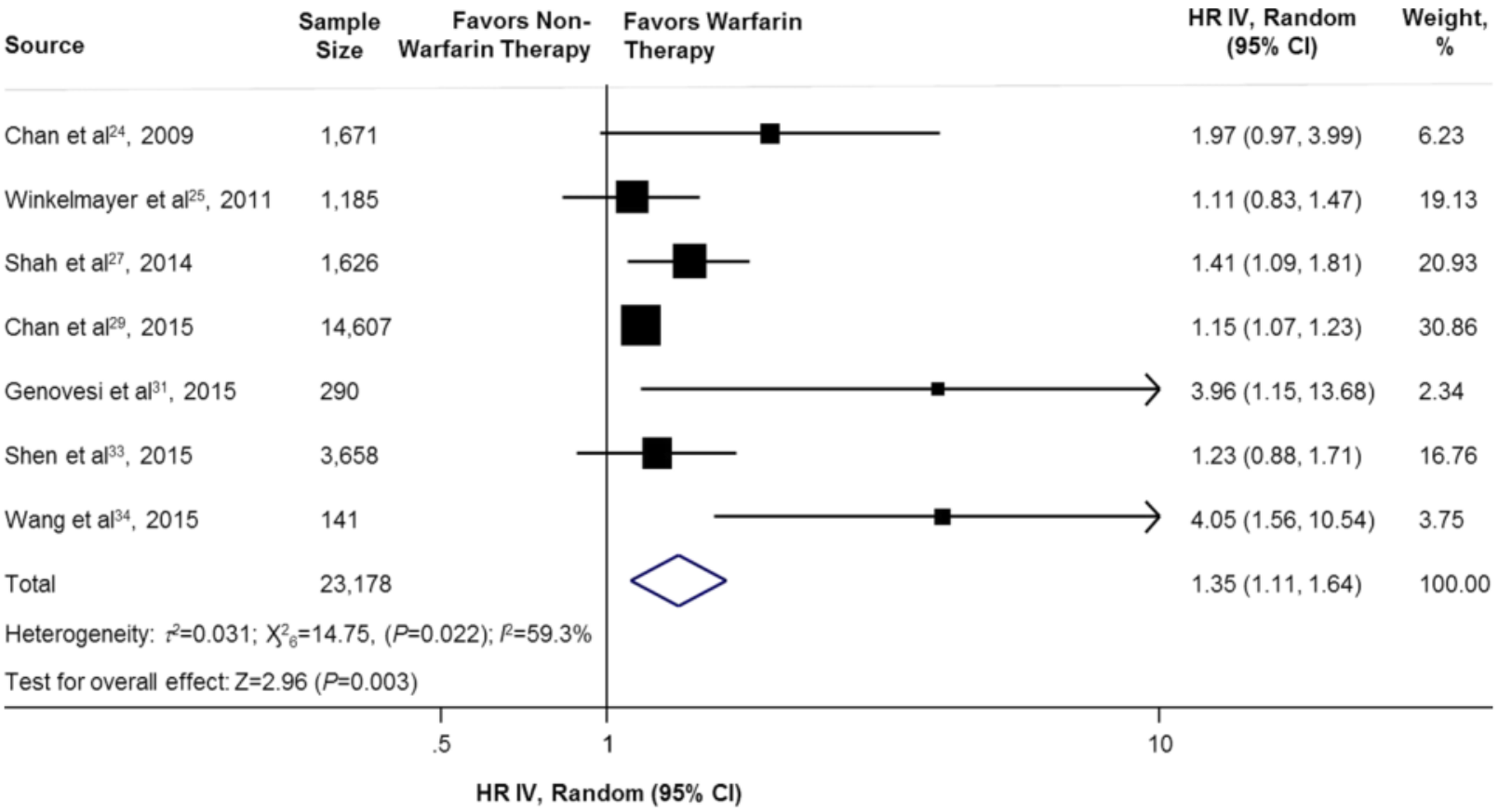
Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis

INCREASED BLEEDING WITH WARFARIN



Nochaiwong S et al. *Open Heart* 2016; 3:e000441

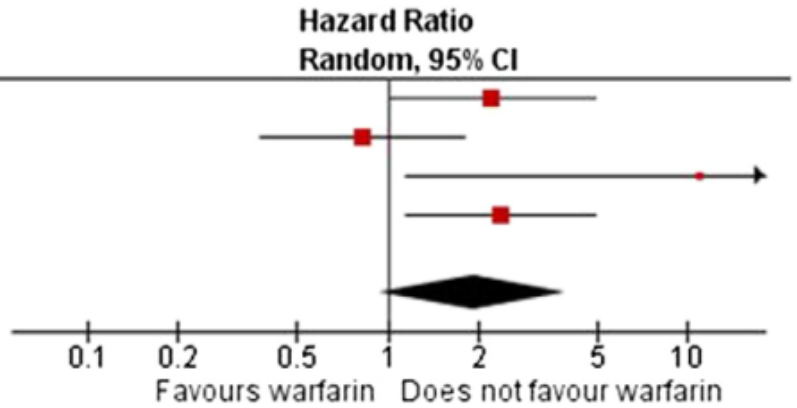
Vitamin K antagonists for stroke prevention in hemodialysis patients with atrial fibrillation: A systematic review and meta-analysis

Hans Van Der Meersch, MD,[a] Dirk De Bacquer, PhD,[b] and An S. De Vriese, MD, PhD[a] *Brugge and Ghent University, Belgium*

INCREASED *INTRACRANIAL BLEEDING* WITH WARFARIN

Study	Weight	Hazard Ratio Random, 95% CI
Chan 2009	30.0%	2.22 [1.01, 4.91]
Shen 2015	30.1%	0.82 [0.37, 1.81]
Wang 2015	8.4%	11.10 [1.14, 107.84]
Winkelmayer 2011	31.6%	2.38 [1.15, 4.96]
Total (95% CI)	**100.0%**	**1.93 [0.93, 3.98]**

Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 7.08$, $df = 3$ ($P = .07$); $I^2 = 58\%$
Test for overall effect: $Z = 1.77$ ($P = .08$)



Warfarin use and the risk of intracranial bleeding in hemodialysis patients with AF.

Van Der Meersch H et al. *Am Heart J* 2017; 184:37-46

Oral Anticoagulation in CKD: NOACs

- NOACs: non-inferior (sometimes superior) efficacy/safety to VKA
- All NOACs have a degree of renal excretion
- Severe CKD and ESRD patients not included in pivotal RCTs

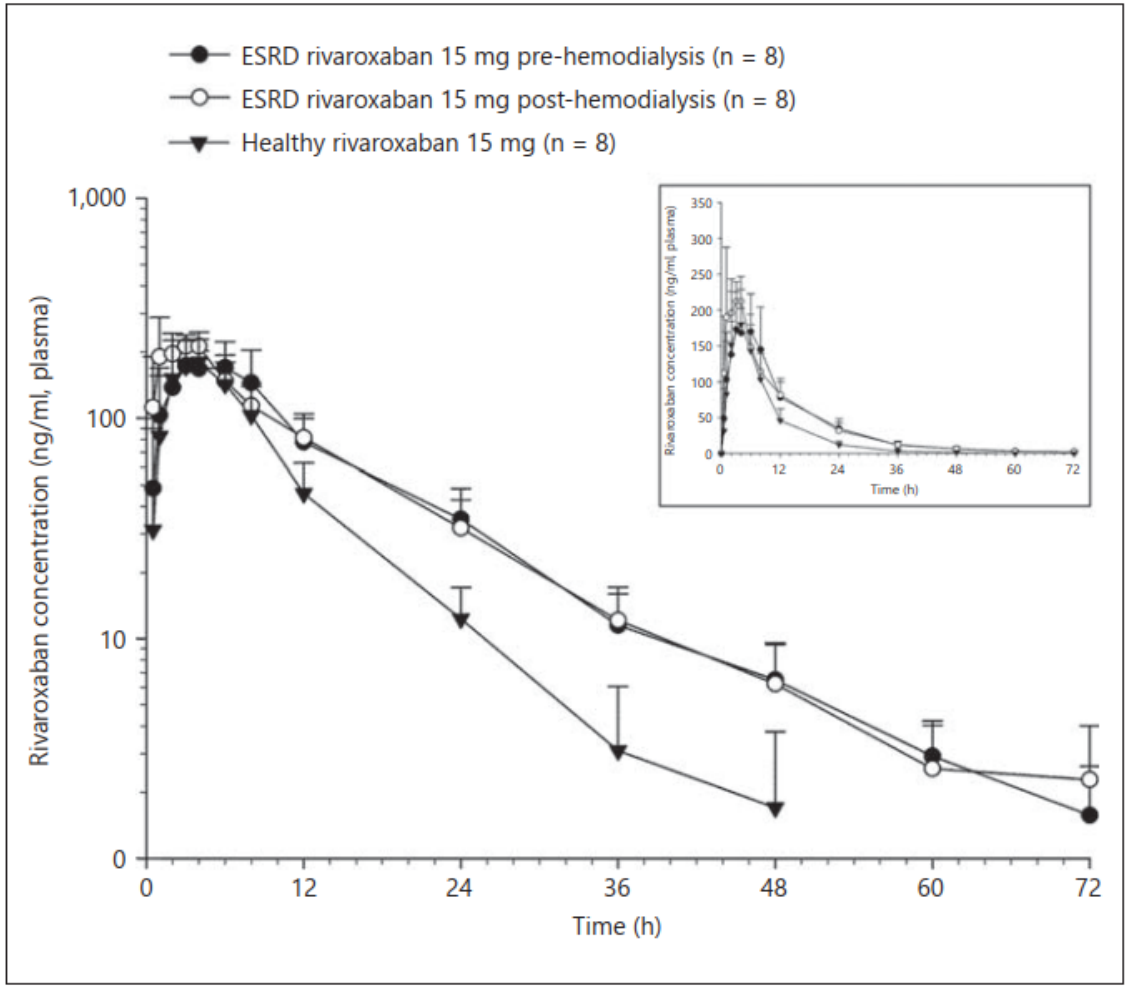
Table 5 Main PK characteristics for oral anticoagulants and dosing recommendations, according to regulatory approvals (modified from refs[79,80])

	Warfarin	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose		80%	27%	50%	35%
Bioavailability	95–100%	3–7%	50%	62%	66% without food Almost 100% with food
Fraction renally excreted of administered dose		4%	14%	37%	33%
Approved for CrCl		≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥30 mL/min: no adjustment	CrCl ≥50 mL/min: no adjustment (i.e. 150 mg b.i.d.)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg b.i.d.)	60 mg daily for CrCl 50–95 mL/min, 30 mg daily for CrCl 15–50 mL/min, weight ≤60 kg; not recommended for CrCl >95 mL/min	CrCl ≥50 mL/min: no adjustment (i.e. 20 mg qd)
Dosing if CKD	When CrCl <30 mL/min: use lower doses and monitor closely	When CrCl 30–49 mL/min, 150 mg b.i.d. is possible (SmPC) but 110 mg b.i.d. is recommended if high risk of bleeding[79]	CrCl 15–29 mL/min: 2.5 mg b.i.d. Serum creatinine ≥1.5 mg/dL in combination with age of ≥80 years or weight ≤60 kg. (SmPC) or with other factors that increase bleeding risk (e.g. diltiazem): 2.5 mg b.i.d.	60 mg daily for CrCl 50–95 mL/min, 30 mg daily for CrCl 15–50 mL/min, weight ≤60 kg; not recommended for CrCl >95 mL/min	15 mg q.d. when CrCl 15–49 mL/min

Boriani G et al. *Europace* 2015; 17:1169-1196

ESRD on Dialysis: Rivaroxaban Pharmacokinetics

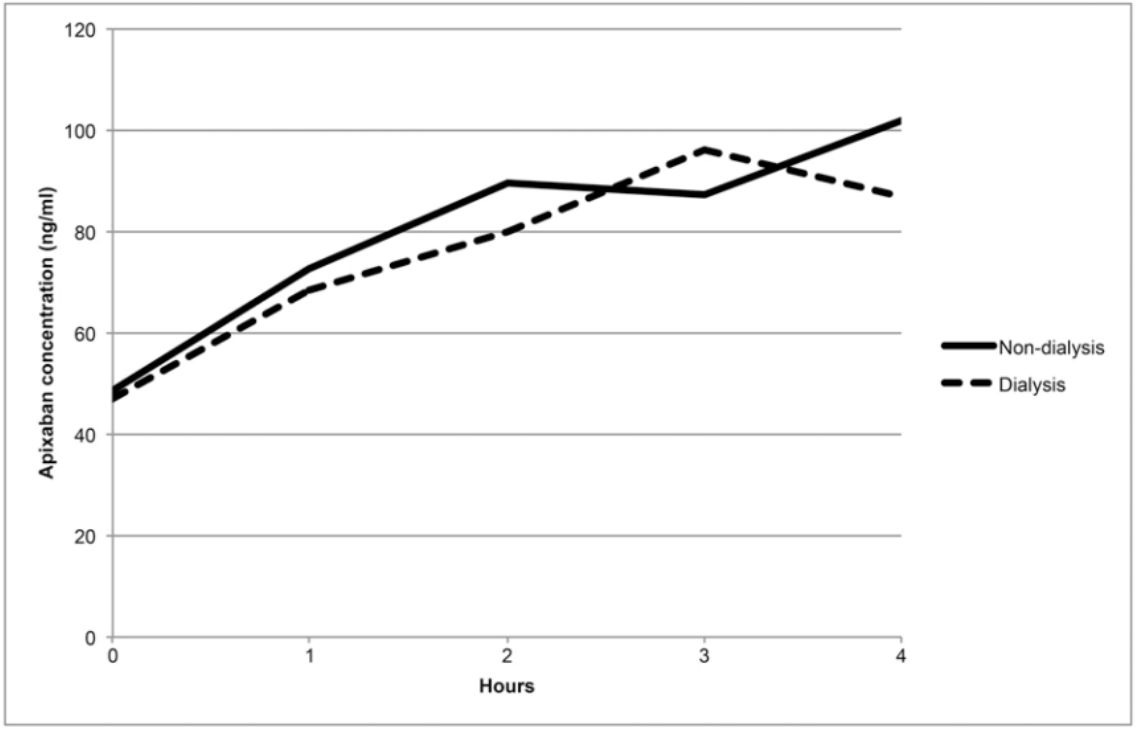
- **Dialysis has a minimal impact on the pharmacokinetics of rivaroxaban**
- **Bioavailability of rivaroxaban is similar between ESRD subjects and healthy volunteers**
- **The changes in PK and PD parameters were generally comparable to those observed in patients with moderate-to-severe renal impairment who were not undergoing dialysis**



Dias C et al. *Am J Nephrol* 2016; 43:229-236

ESRD on Dialysis: Apixaban Pharmacokinetics

- **Minimal effect of Dialysis on Apixaban PK**
- **Apixaban 2.5-mg twice daily had similar PK indices in dialysis patients as 5 mg twice daily in patients with preserved renal function**



Mavrakanas T et al. *J Am Soc Nephrol* 2017; 28:2241-2248

US FDA Approved Labels for NOACs in ESRD on Dialysis

Revised Approval based on very limited data from small (<n=10) pharmacokinetic studies in patients with ESRD on dialysis without clinical safety data

Apixaban Package Insert for Atrial Fibrillation (Revised Oct 2017)

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1)]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Rivaroxaban Package Insert for Atrial Fibrillation (Revised Feb 2018)

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study *[see Clinical Pharmacology (12.2, 12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF.

These sentences open the door for clinicians to consider apixaban or rivaroxaban in patients with ESRD

Approved European Labels for NOACs in CKD

Table 8 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)[5] 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.

Heidbuchel G et al. *Europace* 2015; 17:1467-1507

Do we have any clinical experience with NOACs in ESRD ?

CLINICAL EXPERIENCE *Off-Label*

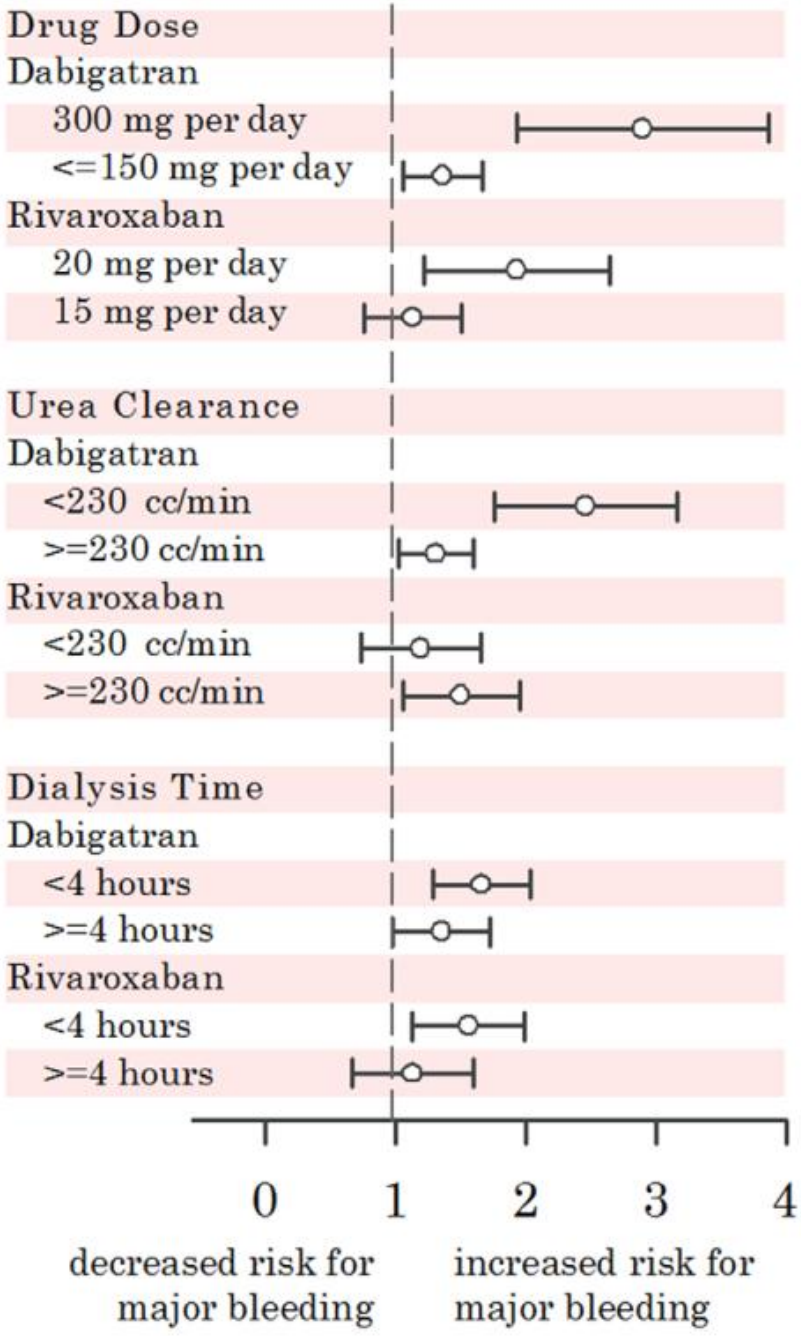
Dabigatran and Rivaroxaban in AF and ESRD on Hemodialysis

- Fresenius Medical Care North America ESRD Database
- 8064 pts Warfarin, 281 pts Dabigatran, 244 pts Rivaroxaban

Compared to Warfarin:

- Dabigatran and Rivaroxaban associated with **higher risk of hospitalization or death from bleeding**
- Differences in stroke and arterial embolism could not be assessed due to very low number of events

Chan KE et al. *Circulation* 2015; 131:972-979

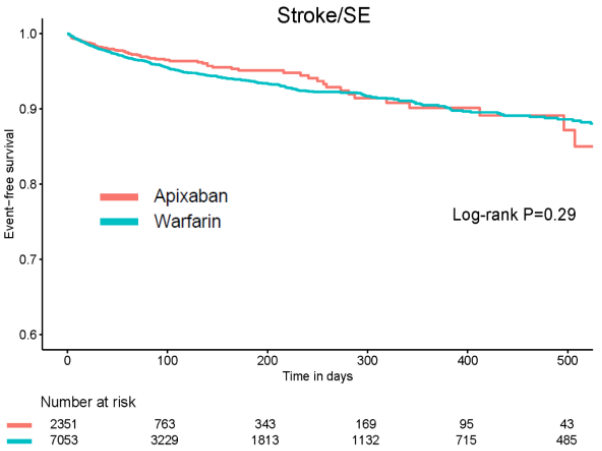


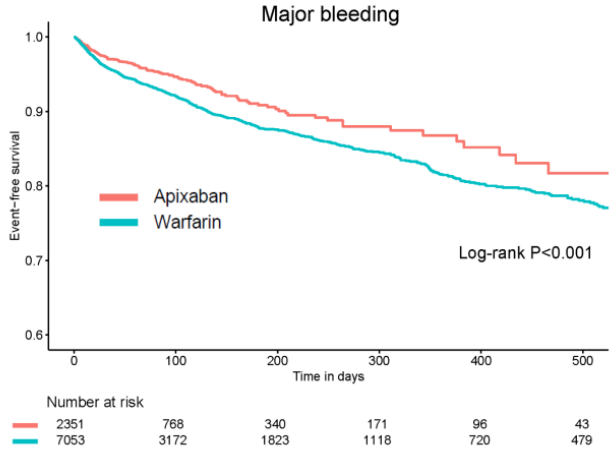
Compared to warfarin

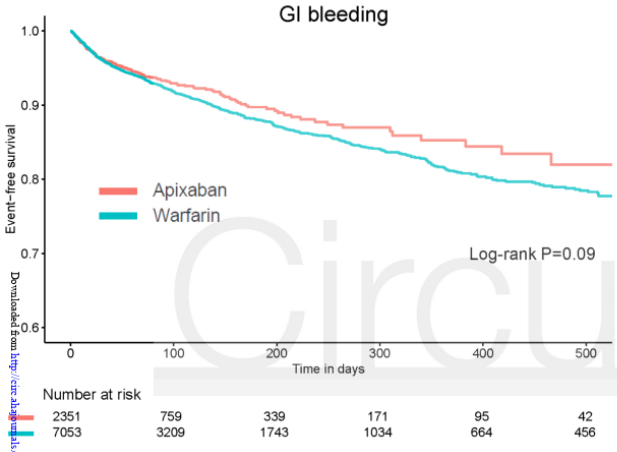
Apixaban in Pts with ESRD on Dialysis and AF in the US

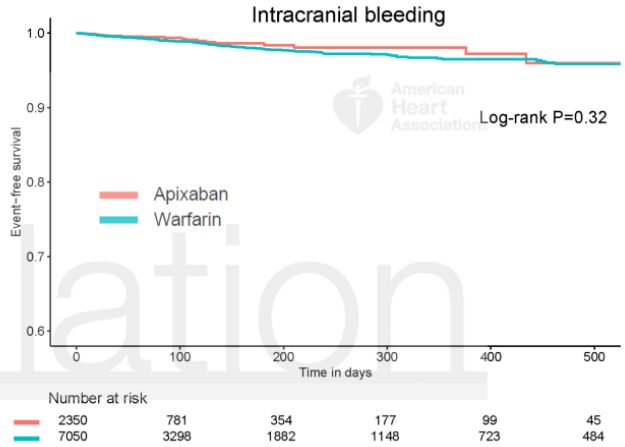
- **Retrospective study** of Medicare beneficiaries included in the US Renal Data System (Oct 2010 to Dec 2015) – AF & ESRD on dialysis

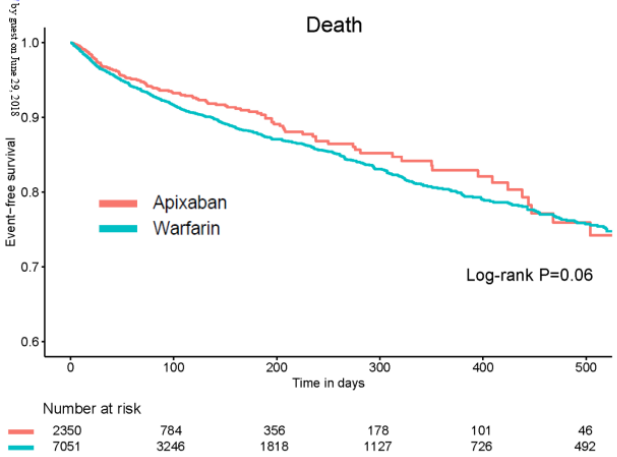
- Apixaban
  44%: 5 mg BD
  56%: 2.5 mg BD









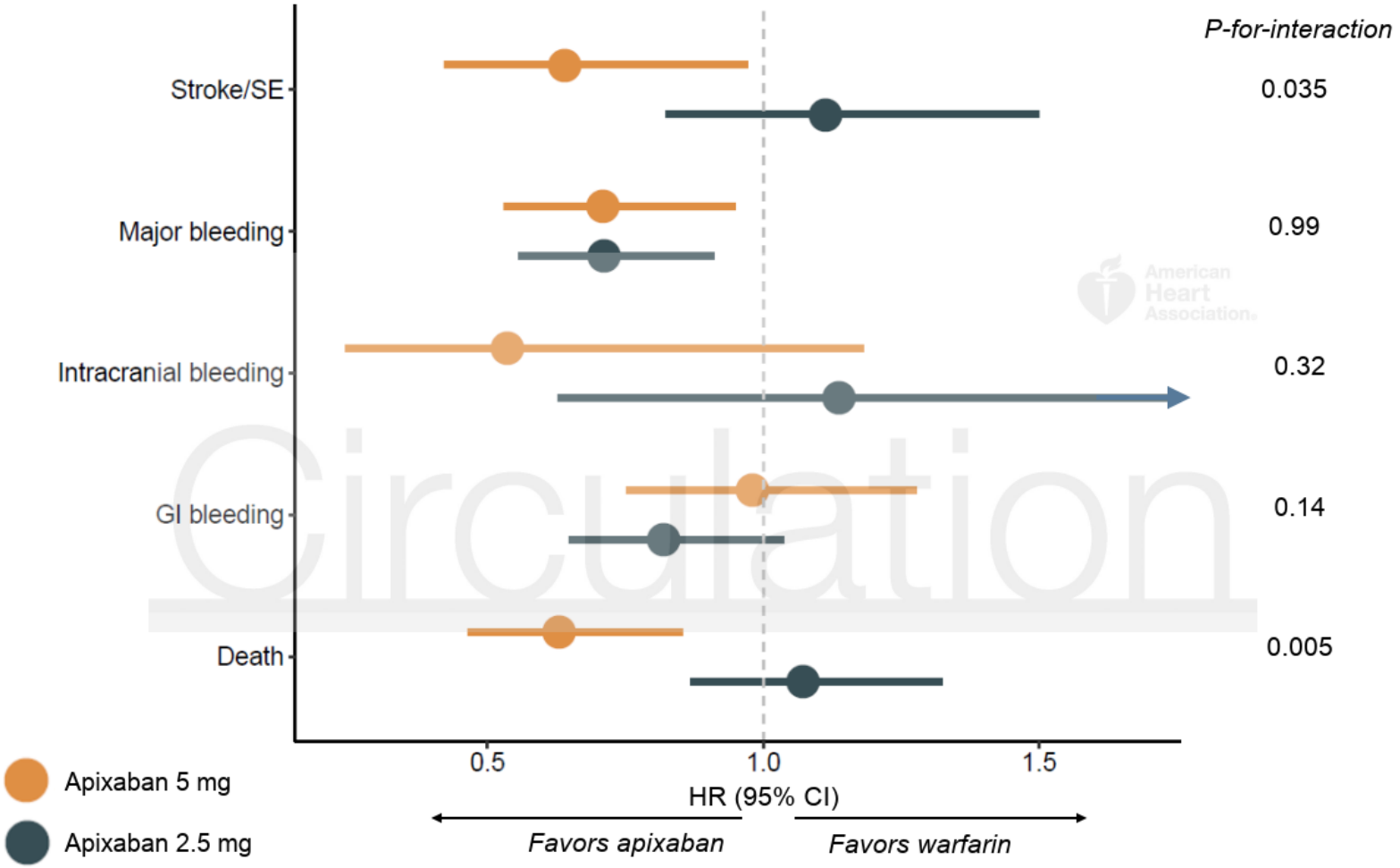


2351 patients on Apixaban vs 23172 matched patients on Warfarin

Siontis K et al. *Circulation* 2018; 138:1519-1529

Apixaban in Pts with ESRD and AF in the US

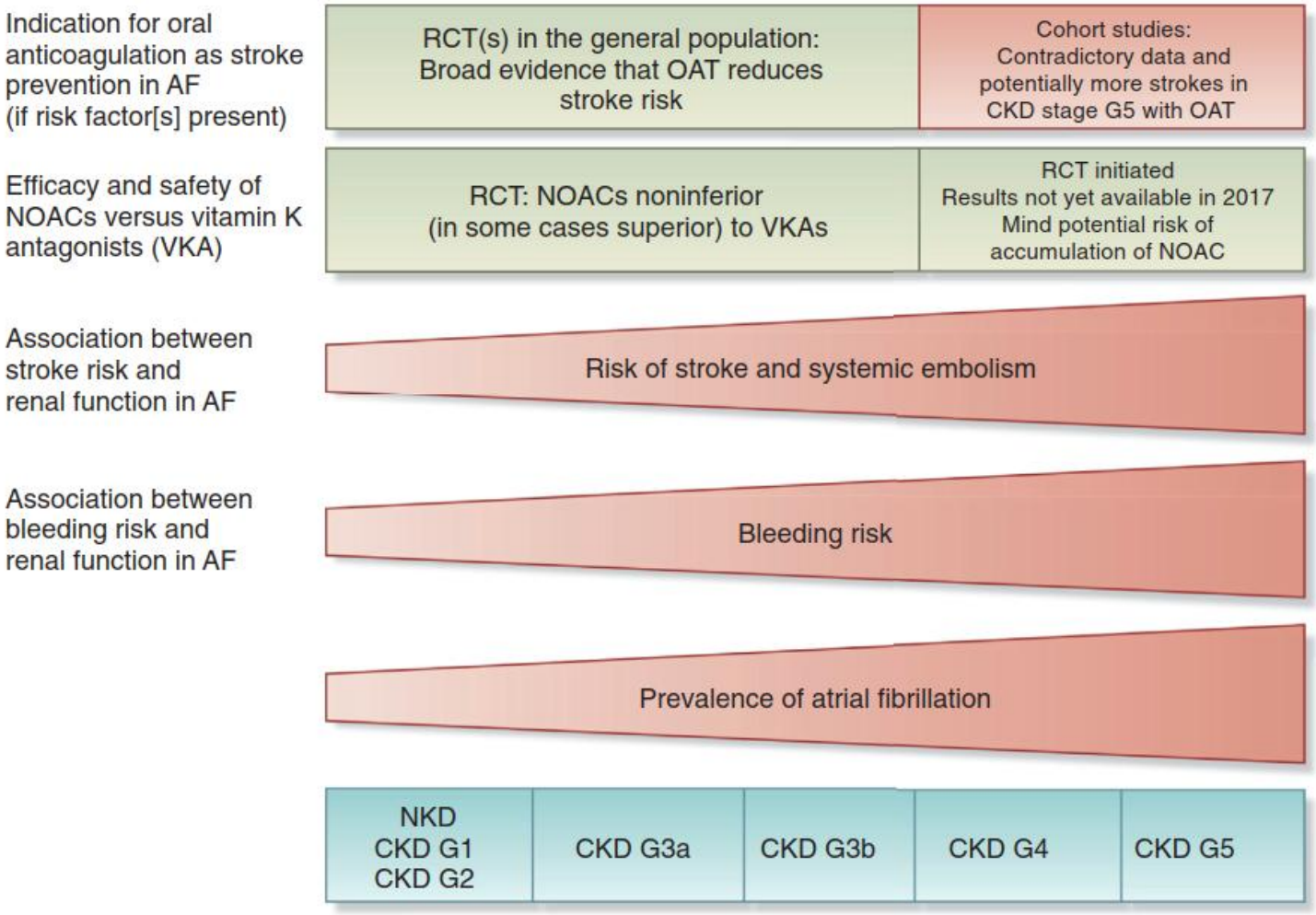
Benefit with 5 mg vs 2.5 mg BD ?



Siontis K et al. *Circulation* 2018; 138:1519-1529

Anticoagulation according to CKD stage

What Do We Know?



Heine GH and Brandeburg V. *Kidney International* 2017; 91:778-780

How we can we approach anticoagulation in a patient with AF and ESRD?

CENTRAL ILLUSTRATION **Proposed Algorithm for Oral Anticoagulant Choices in Patients With Atrial Fibrillation and Chronic Kidney Disease**

Patient with atrial fibrillation and chronic kidney disease

Determine stroke risk (CHA_2DS_2-VASc Score)
Consider oral anticoagulation if score is ≥ 1 in males / ≥ 2 in females

Determine bleeding risk (HAS-BLED Score)

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.†	5 mg, b.i.d.†
Dabigatran	✖	75 mg, b.i.d.‡	150 or 110 mg, b.i.d.§	150 mg, b.i.d.‖
Edoxaban	✖	30 mg, o.d.	30 mg, o.d.	60 mg, o.d.¶
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

Lau, Y.C. et al. J Am Coll Cardiol. 2016;68(13):1452-64.

Pragmatic Considerations to Reduce Bleeding in ESRD Patients on Anticoagulation

- Minimize heparin with dialysis
- Use of citrate locks for dialysis catheters
- Consideration of prophylaxis for gastrointestinal bleeding when clinically indicated
- Tight blood pressure control
- Discontinuation of concurrent antiplatelet agents if clinically reasonable

Reversal of Anticoagulation

- Vitamin K antagonists (VKAs)
  - Vitamin K and/or plasma
- NOACs
  - Factor concentrates for reversal (?)
  - Rivaroxaban and Apixaban
    - Andexanet alpha: FDA US approval in May 2018
      Reduction of anti-Xa activity by 92% (rivaroxaban) and 94% (apixaban)
  - Dabigatran
    - Idarucizumab

Heo YA. *Drugs* 2018; 78:1049-1055

LACK OF RANDOMIZED DATA
Anticoagulation in ESRD

KDIGO= Kidney Disease: Improving Global Outcomes
Recommendations after KDIGO International Conference

Table 2 Chronic kidney disease categories lacking randomized clinical trial data on the utility of anticoagulation[4,63,64]

eCrCl (mL/min)[a]	Warfarin	Apixaban[b]	Dabigatran	Edoxaban	Rivaroxaban
15–30	Adjusted dose for INR 2–3 could be considered	2.5 mg PO b.i.d. could be considered	Unknown (75 mg PO b.i.d.)[c,d]	30 mg QD[e] could be considered	15 mg QD could be considered
<15 not on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO b.i.d.)[c]	Not recommended	Not recommended	Unknown (15 mg QD)[c]
<15 on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO b.i.d.)[c]	Not recommended	Not recommended	Unknown (15 mg QD)[c]

INR, international normalized ratio.
Dosing of direct oral anticoagulants (DOACs) based solely on limited pharmacokinetic and pharmacodynamic data (no randomized efficacy or safety data exist).
[a]Cockcroft-Gault estimated creatinine clearance.
[b]Apixaban dose needs modification to 2.5 mg b.i.d. if patient has any two of the following: serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg.
[c]DOAC doses listed in parenthesis are doses that do not currently have any clinical safety or efficacy data. The doses of DOACs apixaban 5 mg b.i.d.[b], rivaroxaban 15 mg QD and dabigatran 75 mg b.i.d. are included in the United States Food and Drug Administration approved labelling based on limited dose pharmacokinetic and pharmacodynamics data with no clinical safety data. We suggest consideration of the lower dose of apixaban 2.5 mg PO b.i.d. in CKD G5/G5D to reduce bleeding risk until clinical safety data are available.
[d]Dabigatran 75 mg available only in the USA.
[e]The dose was halved if any of the following: estimated CrCl of 30–50 mL/min, body weight of ≤60 kg, or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors).

Turakhia MP et al. *Eur Heart J* 2018; 39:2314-2325

Upcoming OAC Clinical Trials in ESRD

- **VKAs vs no oral anticoagulation**
  - AVKDIAL (NCT02886962)
- **Apixaban vs VKAs in ESRD**
  - RENAL-AF (NCT02942407)
  - AXADIA (NCT02933697)
- **Left Atrial Appendage occlusion vs VKAs in CKD stages 4 and 5**
  - WatchAFIB (NCT02039167)

Thank you !