DOAC Use in CKD- Is It Safe?

Marisa Battistella, Pharm D
Pharmacy Clinician Scientist
Nephrology Pharmacist-UHN
Associate Professor-University of Toronto

Disclosures

- Speaking Honorarium – Pfizer

Learning Objectives

By the end of the presentation participants should be able to:

1. Discuss the literature on the use of DOACs in the CKD population.
2. Compare and Contrast the pharmacology and pharmacokinetics of the various DOACs in CKD patients
3. Identify knowledge gaps regarding use of these medications in the CKD patient population.

Case

Mrs V. is a 55 year old lady on HD since 2007. She has ESKD from unknown origin.

- PMH:
  - CAD- MI and ischemic cardiomyopathy
  - AF- right occipital infarct in 2015
  - PVD
  - Hepatitis C (treated with interferon)
- Medications:
  - rosuvastatin, ramipril, metoprolol, clopidogrel, ASA, **warfarin**, pantoprazole, replavite, cinacalcet, Aranesp, Venofer
- She is admitted with calciphylaxis of her left foot

Question

What do we do about her anticoagulation for AF?

A) Continue warfarin
B) D/C warfarin and start a DOAC
C) D/C warfarin and start a LMWH
D) D/C warfarin

Question

What is the prevalence of AF in the general population?

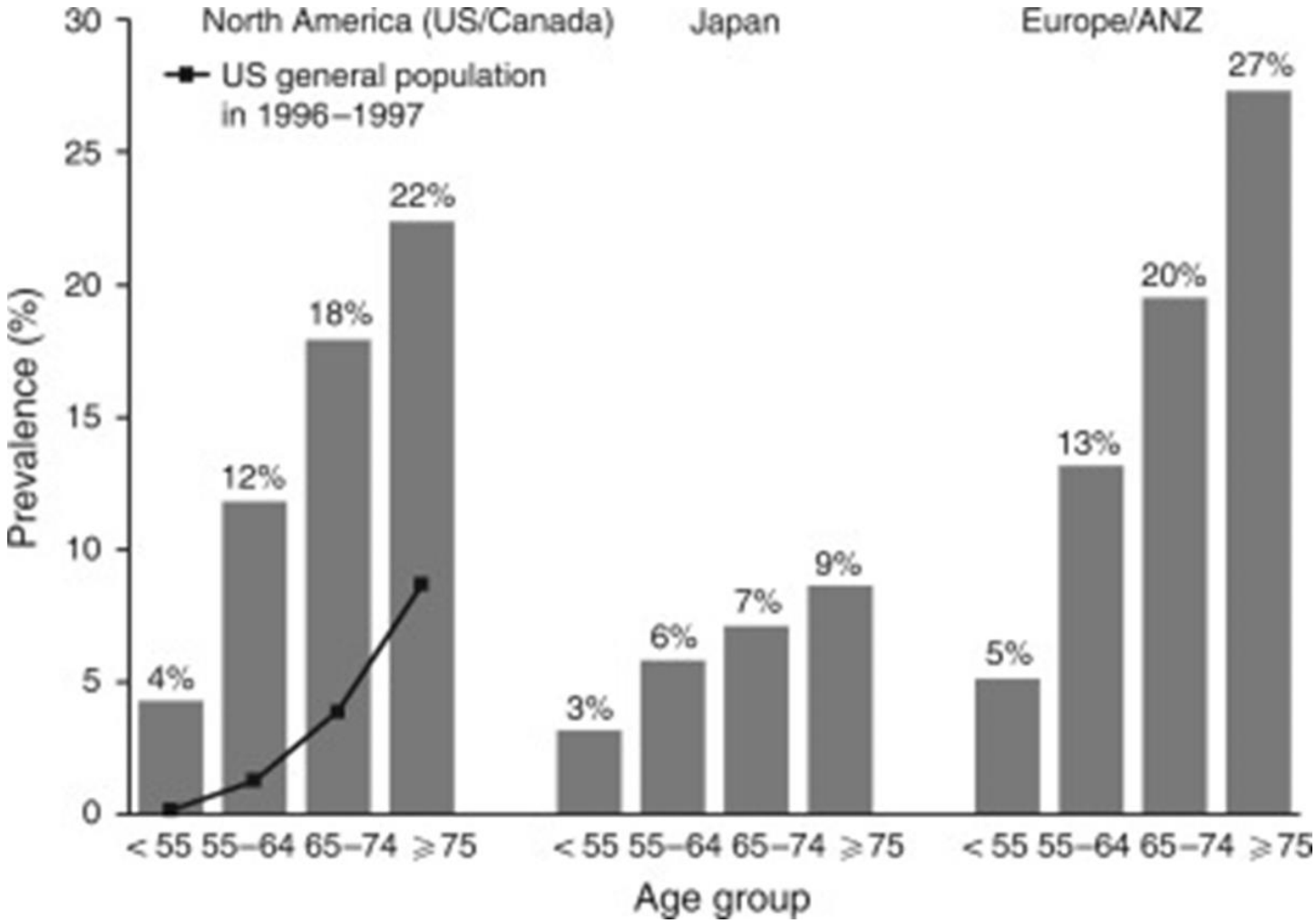
a) 1%
b)10%
c) 3%
d)18%

Question

What is the prevalence of AF in the HD population?

a) 1%
b) 10%
c) 3%
d) 18%

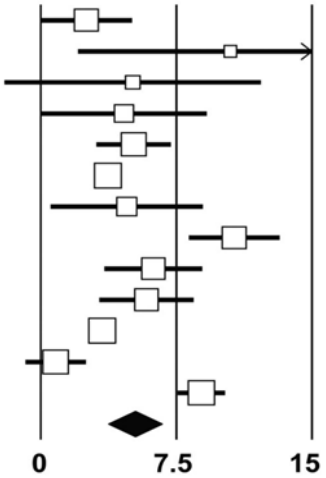
Prevalence of AF in HD



Wizemann. KI 2010 (77): 1098-1106

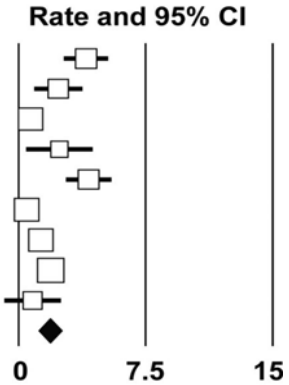
Ischemic Stroke in Dialysis

Study name	Year	Events/Total N
Weisholzer	2001	4 / 158
Vazquez	2003	6 / 57
Vazquez	2006	2 / 39
To	2007	4 / 87
Genovesi	2008	25 / 486
Chan	2009	102 / 2740
Vazquez	2009	5 / 105
Chou	2010	72 / 673
Lai	2010	21 / 337
Sanchez-Perales	2010	20 / 342
Wizemann	2010	148 / 4348
Fujii	2011	1 / 120
Winkelmayer(cJASN)	2011	188 / 2116
Summary Event Rate (events per 100 patient years)		5.2



Sroke in patients with Atrial Fibrillation (per 100 patient years)

Study name	Year	Events/Total N
Wiesholzer	2001	38 / 954
Vazquez	2003	11 / 468
Vazquez	2006	4 / 564
To	2007	6 / 249
Genovesi	2008	39 / 942
Vazquez	2009	2 / 411
Sanchez-Perales	2010	14 / 1061
Wizemann	2010	695 / 36552
Fujii	2011	1 / 120
Summary Event Rate (events per 100 patient years)		1.9

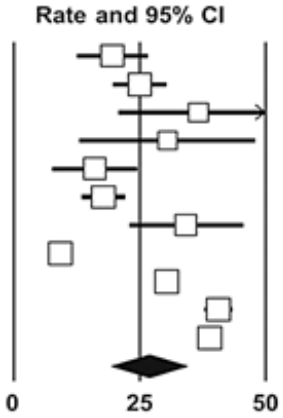


Stroke in patients without Atrial Fibrillation (per 100 patient years)

Zimmerman, D., *et al*. Nephrol Dial Transplant. 2012; 27:3816-3822

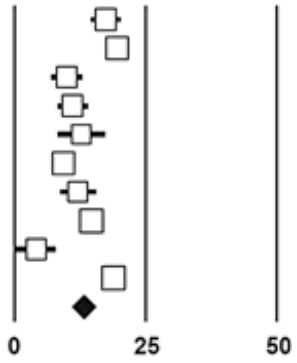
Mortality in Dialysis

Study name	Year	Events/Total N
Wiesholzer	2001	31 / 158
Abbott	2003	90 / 359
Vazquez	2003	21 / 57
Vazquez	2006	12 / 39
To	2007	14 / 87
Genovesi	2008	68 / 381
Vazquez	2009	36 / 105
Chou	2010	63 / 673
Wizemann	2010	1342 / 4412
Winkelmayer(cJASN)	2011	931 / 2287
Winkelmayer(JASN)	2011	7180 / 18410
Summary Event Rate (events per 100 patient years)		**26.9**



Mortality in patients with Atrial Fibrillation (per 100 patient years)

Study name	Year	Events/Total
Wiesholzer	2001	167 / 954
Abbott	2003	1871 / 9493
Vazquez	2003	47 / 468
Vazquez	2006	63 / 564
To	2007	32 / 249
Genovesi	2008	99 / 1047
Vazquez	2009	50 / 411
Wizemann	2010	5464 / 36931
Fujii	2011	5 / 120
Winkelmayer(JASN)	2011	34940 / 183893
Summary Event Rate (events per 100 patient years)		**13.4**



Mortality in patients without Atrial Fibrillation (per 100 patient years)

Zimmerman, D., *et al*. Nephrol Dial Transplant. 2012; 27:3816-3822

Mortality Due to Bleeding, MI and Stroke in Dialysis Patients

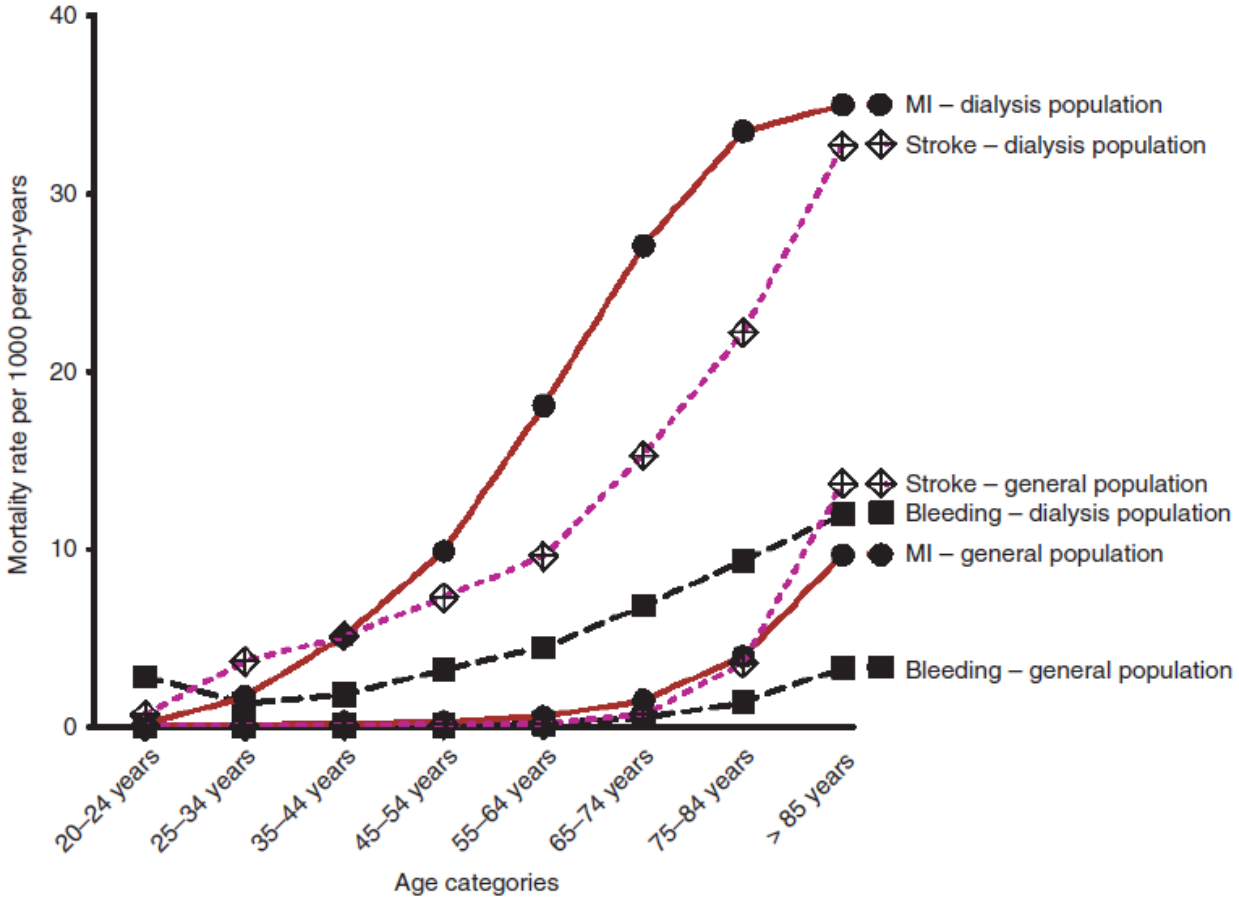


Fig. 1. Mortality rates attributable to bleeding, myocardial infarction (MI) and stroke in dialysis patients and in the general population, stratified by age group. [Color figure can be viewed at wileyonlinelibrary.com]

Ocak, JTH 2018;16:1953-1963

Management of AF in HD patients

TABLE 1 Society guidelines for anticoagulation in AF by CKD stage

CKD stage	AHA/ACC/HRS	ESC	CCS
Mild to moderate Stages 2-3 (eGFR 30-90 mL/min/1.73 m^2)	Warfarin (class 1, LOE A) DOACs (class 1, LOE B) with dose adjustment for moderate CKD (class lib, LOE C)	DOACs recommended in general (mild to moderate CKD not mentioned)	DOACs recommended in general (mild to moderate CKD not mentioned)
Severe Stage 4 (eGFR 15-29 mL/min/1.73 m^2)	Warfarin recommended, DOACs may be considered (class lib, LOE C)	Anticoagulation may safely be given (specific drugs not mentioned)	Warfarin recommended
End stage renal disease Stage 5 (eGFR <15 mL/min/1.73 m^2 or on hemodialysis)	Warfarin recommended (class IIa, LOE B), recommend against dabigatran and rivaroxaban (class III, LOE C)	No specific recommendation given	Cannot recommend routine anticoagulation for dialysis patients due to lack of data

Abbreviations: ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Associated; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; LOE, level of evidence.

Bjhatia et al Clin Cardio 2018

Kidney Disease: Improving Global Outcomes- Update

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).

KDIGO Update: EHJ 2018

Study	Design	Risk of Stroke HR (95% CI)		Risk of Major Bleeding HR (95% CI)
		Ischemic	Hemorrhagic	
Chan et al. 2009	Retrospective cohort, n=1671	**1.81 (1.12-2.92)**	**2.22 (1.01-4.91)**	1.04 (0.73-1.46)
Winkelmayer et al. 2011	Prospective cohort, n=2313	0.92 (0.61-1.37)	**2.38 (1.15-4.96)**	0.96 (0.70-1.31) (GI bleed)
Garg et al 2016	Retrospective cohort, n=302	0.93 (0.49-1.82)	Not specified	1.53 (0.94-2.51)
Genovesi et al 2015	Prospective cohort,n=296	0.12 (0.00-3.59)	Not specified	**3.96 (1.15-13.68)**
Wakasugi et al	Prospective cohort, n=60	3.36 (0.67-16.66)	Not specified	0.85 (0.19-3.64)
Shah et al 2014	Retrospective cohort, n=1626	1.17(0.79-1.75)	Not specified	**1.41 (1.09-1.81)**
Yodagawa et al 2016	Retrospective cohort, n=84	1.07 (0.2-5.74)	Not specified	Not specified

Systematic Review Discussion

Conclusion

- Our review suggested a lack of association between warfarin use and reduced risk of stroke
- And an association between warfarin use and increased risk of bleeding in patients with AF on HD

Limitations

- Differences in definitions and reporting of outcomes make direct comparison difficult
- INR not recorded in studies

Battistella et al. CJKHD 2017

Research Question

- **What is the anticoagulation control in our HD unit?**
  - Time in Therapeutic Range (TTR) is a common way to evaluate anticoagulation
  - TTR measurement methods:
    1. Rosendaal (linear interpolation model)
    2. *Fraction of INRs in Range*

Question

What TTR is acceptable for patients taking warfarin?

A) 40%

B) 55%

C) 65%

D)100%

Methods

- **Study Design:** Retrospective chart review (2006-2012)
- **Study Population:** All HD patients in a single center on warfarin
  - for a minimum of **one year** for VTE or AF with a target INR of 2-3
- **Data Collection:**– Weekly INR measurements from the most recent full year
  - Patient demographics, medication histories, clinical outcomes

Quin et al. Clin Nephro 2014

Results

Table 2. Time in Therapeutic Range		
	Rosendaal Method (n=46)	Fraction of INRs in Range Method (n=46)
TTR (%), mean (SD)	49.2 (±14.6)	44.2 (±13.5)
Percentage of INRs below 2, mean (SD)	39.3 (±16.2)	41.3 (±15.5)
Percentage of INRs above 3, median (IQR)	10 (6-15.5)	13.5 (9-17.5)
Poor Control TTR <60%, n (%) mean TTR (SD) or median TTR (IQR)	39 (84.9) 50 (38-55)	39 (84.9) 40.5 (±10.5)
Moderate Control TTR 60-75%, n (%) median TTR (IQR)	5 (10.9) 69 (60.5-70.5)	6 (13.0) 60 (60-63.5)
Good Control TTR >75%, n (%) median TTR (IQR)	2 (4.3) 83.5 (77-90)	1 (2.2) 87
Standard Deviation of INR values, mean (SD)	0.898 (± 0.39)	

Quin et al. Clin Nephro 2014

Clinical Outcomes

Table 3. Rosendaal TTR and Clinical Outcomes			
Clinical Outcomes	Poor Control TTR <60%	Moderate Control TTR 60-75%	Good Control TTR >75%
	n=39	n=5	n=2
Serious Bleed, n (%)	9 (23.1)	0 (0)	0 (0)
Minor Bleed, n (%)	5 (12.8)	0 (0)	1 (50)
Total Bleeds, n (%)	14 (35.9)	0 (0)	1 (50)
Ischemic Stroke, n (%)	2 (5.1)	0 (0)	0 (0)
TIA, n (%)	1 (2.6)	0 (0)	0 (0)
MI, n (%)	2 (5.1)	0 (0)	0 (0)
VTE, n (%)	4 (10.3)	0 (0)	0 (0)
Total Thrombotic Events, n (%)	9 (23.1)	0 (0)	0 (0)

Quin et al. Clin Nephro 2014

Serious Bleeding Events

Table 4. Serious Bleeding Events			
Patient ID	INR on day of Bleed	SD of INR values	Description of Bleed
2	N/A*	0.627	Lower GI bleed, Hb drop=37g/L, *INR=1.6 2 days prior
10	3.01	0.954	Upper GI bleed, 2 units PRBCs
12	2.05	0.779	Upper GI bleed, 2 units PRBCs, warfarin d/c
15	1.86	1.490	NYD, Hb drop 148 to 80g/L
16	3.63	1.389	Hemorrhagic cholecystitis, 2 units PRBCs, warfarin d/c
18	2.48	1.189	Upper GI bleed, 2 units PRBCs
25	2.04	0.547	Upper GI bleed, 2 units PRBCs
28	1.76	0.524	Left AV fistula bleed, 2 units PRBCs
41	2.14	0.531	Lower GI bleed (ischemic colitis), 2 units PRBCs
Median	2.10	0.779	

Quin et al. Clin Nephro 2014

Summary so far….

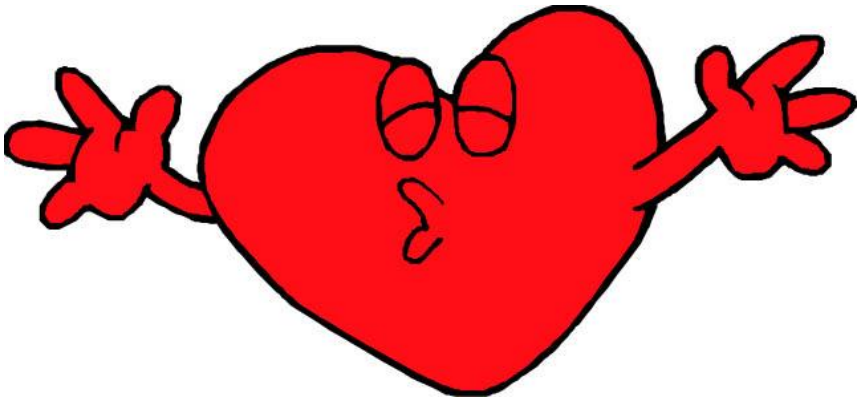
- Clinical equipoise to use warfarin in HD patients
- TTR is low
- INRs are labile- many reasons

- So what do we do with this?

Important Question

How do Clinicians feel about warfarin use in CKD/HD patients?

Nephrologist



Cardiologist

Methods

Study Design:

- Cross-sectional survey of nephrologists and cardiologists in Canada

Sampling Frame:

1. Nephrologists:
   a. Members of the Canadian Society of Nephrology (CSN), **n = 400**
2. Cardiologists:
   a. Members of the Canadian Cardiovascular Society (CCS), **n = 900**
      - Members of the Canadian Heart Rhythm Society (CHRS), **n = 204**
   c. Cardiologists affiliated with the Division of Cardiology at:
      - University of Calgary, **n = 60**
      - University of Alberta, **n = 30**
      - University of Toronto, **n = 103**

Questionnaire Structure

1. **Patient Cases**
   - 4 scenarios which vary in severity of stroke and bleeding risk
   - respondents asked to decide on the management of AF-related stroke risk and report their level of certainty for each case
     - 6 drug therapy options for stroke risk management
     - certainty scale of zero to ten (0 being very uncertain, 5 being neutral, 10 being very certain)
2. **Demographics**

Stroke and Bleeding Risk Matrix

		Low Stroke	High Stroke
Low Bleed		Case 1	Case 3
	CHA_2DS_2-VASc	1	8
	HAS-BLED	1	3
High Bleed		Case 2	Case 4
	CHA_2DS_2-VASc	1	8
	HAS-BLED	3	7

Sample Questionnaire Case

Case 3: A 79-year-old female on HD with non-valvular AF, previous ischemic stroke, hypertension, type 2 diabetes and congestive heart failure.

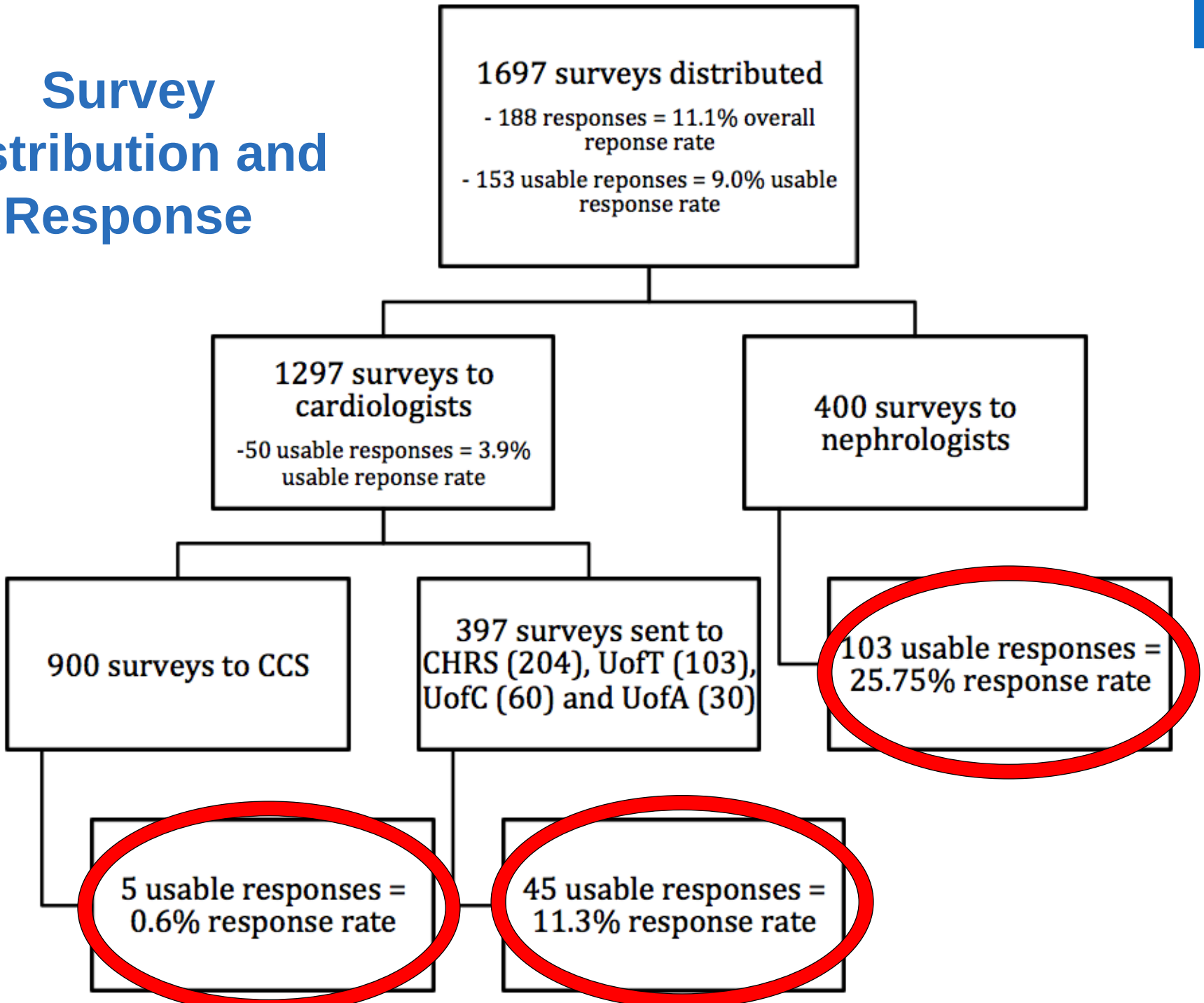
a. **Aspirin**
b. **Other anti-platelet agent (clopidogrel, dipyridamole, etc)**
c. **Dual anti-platelet therapy (Aspirin plus other)**
d. **Warfarin**
e. **One of the new oral anticoagulant therapies (apixaban, rivaroxaban or dabigatran)**
f. **No drug therapy**

Level of CERTAINTY (0 being very uncertain, 5 being neutral, 10 being very certain):

0 1 2 3 4 5 6 7 8 9 10

RESULTS

Survey Distribution and Response



Summary

Anticoagulant vs antiplatelet/no drug therapy

- Both cardiologists and nephrologists recommend anticoagulant therapy **less** when bleeding risk is high and **more** when stroke risk is high.
- Cardiologists are **3 times more likely** to recommend anticoagulant therapy than nephrologists, regardless of the bleeding/stroke risk profile.

Certainty

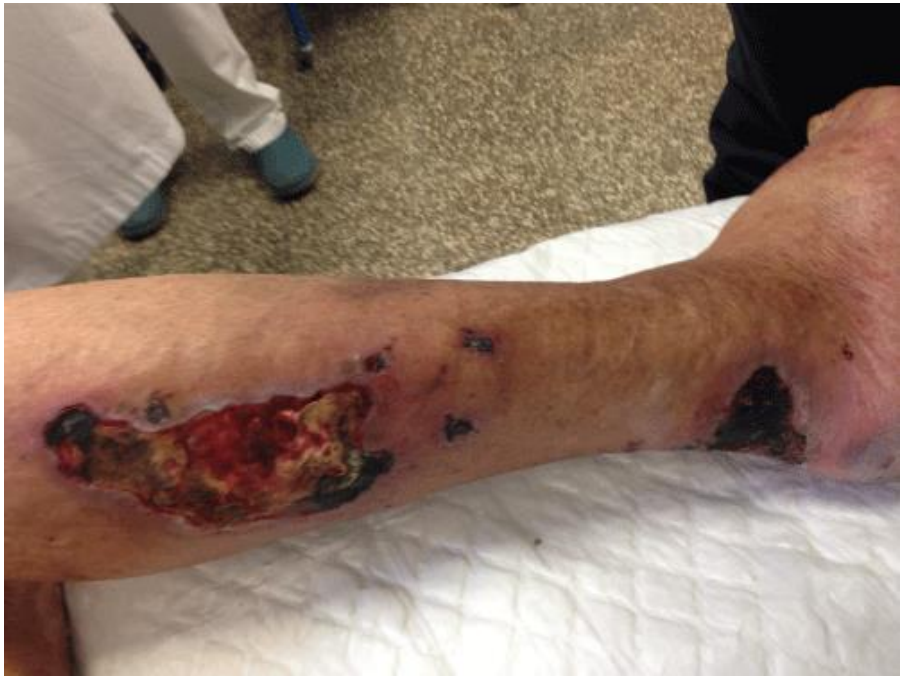
- When bleeding risk is low (scenarios 1 and 3), there is **no difference** in certainty between cardiologists and nephrologists (6.8 vs 6.2, p=0.078).

- When bleeding risk is high (scenarios 2 and 4), nephrologists have **higher** certainty than cardiologists (6.7 vs 5.4, p=0.001).

Clinical Dilemma

Calciphylaxis
Calcific Uremic Arteriolopathy (CUA)

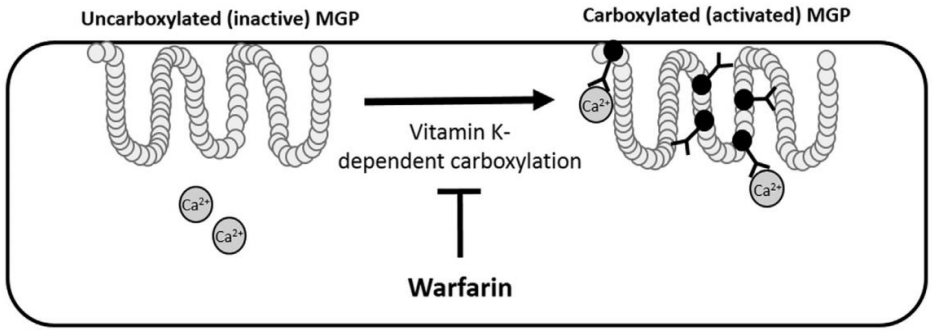
- Rare and serious disorder presenting with skin ischemia and necrosis
  - Reduced blood flow caused by calcification, fibrosis, and thrombus formation
- Most commonly occurs in ESRD and dialysis
  - CKD-mineral bone disorder
  - CKD-MBD treatment
  - Chronic inflammation
  - **Deficiencies in inhibitors of vascular calcifications**



Nigwekar SU, *N Engl J Med.* 2018;378:1704.

Warfarin and Vascular Calcification

- Matrix gamma-carboxyglutamate Gla protein (MGP)
  - Highly insoluble protein synthesized by vascular smooth muscle cells
  - Binds calcium phosphate, preventing calcification
  - MGP requires vitamin K to be converted to its active form
- Vitamin K antagonists (VKAs) such as Warfarin ↑ systemic calcification → stroke



Poterucha TJ, *Am J Med*. 2016;129:635.e1–635.e4.

What about the Direct Oral Anticoagulants (DOACS)?

DOACs

dabigatran

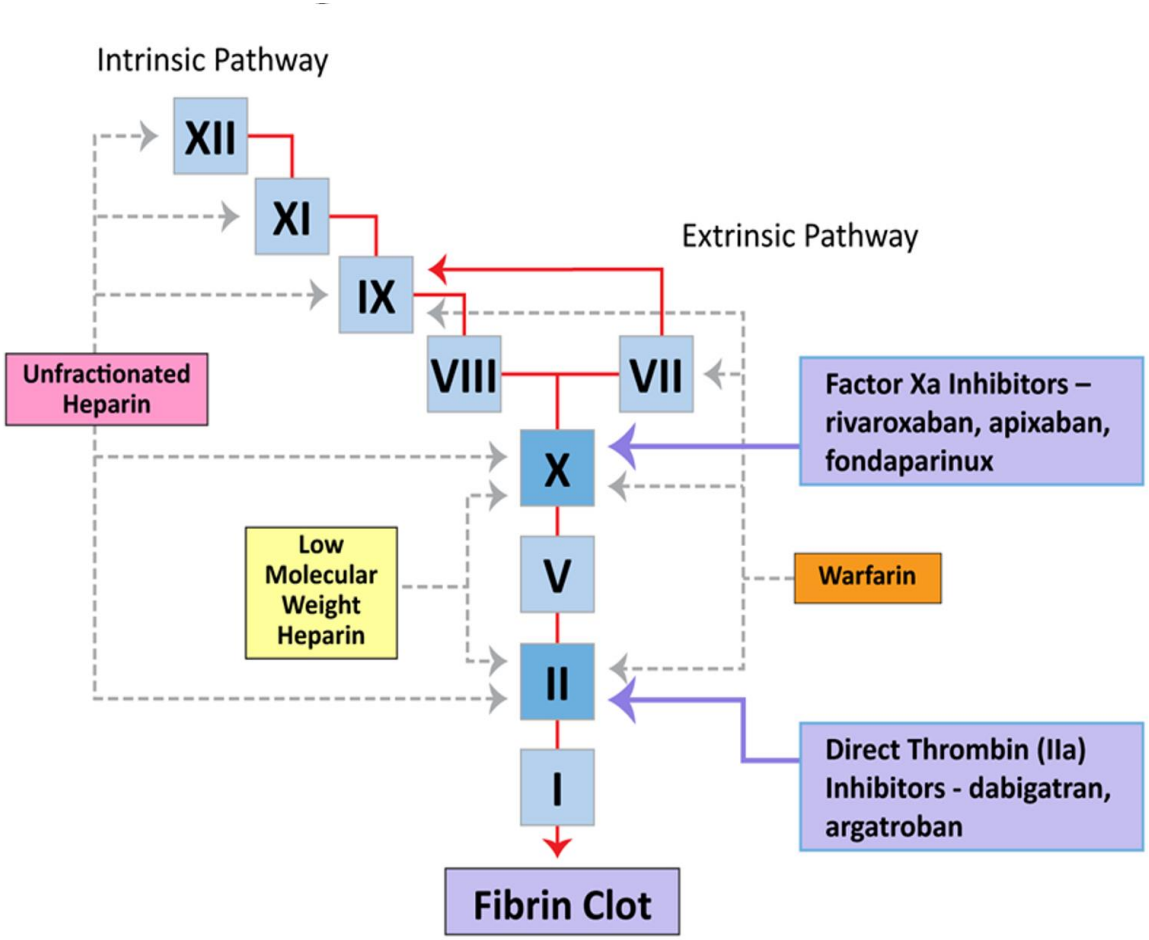
rivaroxaban

apixaban

edoxaban

Indications: DVT/PE, NVAF, post-op thromboprophylaxis **

Mechanism of Action of the DOACs



Dabiga**t**ran
(Pradaxa)

Rivaro**xa**ban
(Xarelto)

Api**xa**ban
(Eliquis)

Edo**xa**ban
(Lixiana)

Phase III Trials of DOACs approved for AF

Drug	Dabigatran 150mg, 110mg	Rivaroxaban 20mg, 15mg	Apixaban 5mg, 2.5mg	Edoxaban 60mg, 30mg, 15mg
Study	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
No. of patients	18,113	14,264	18,201	21,105
Warfarin (INR 2-3)	Open label	Double blind	Double blind	Double blind
Average $CHADS_2$	2.1	3.5	2.1	2.8
Median age (yrs)	71	73	70	72
Median follow-ups	2.0	1.9	1.8	2.8
Dose adjustment	None; patients were randomized to 150mg or 110mg BID	15mg OD if CrCl 30-49 mL/min	2.5mg BID if CrCl >25 and 2/3 criteria: age ≥80, weight ≤60kg, creatinine ≥133µmol/L	Randomized to 60 or 30mg; dose halved if CrCl 30-50mL/min, weight ≤60kg, concomitant use of verapamil or quinidine
Warfarin in therapeutic range	67 (54-78)	58 (43-71)	66 (52-77)	68 (55-77)
Exclusion criteria related to CKD	CrCl <30mL/min	CrCl <30mL/min	CrCl <25mL/min	CrCl <30mL/min

Stroke or Systemic Events

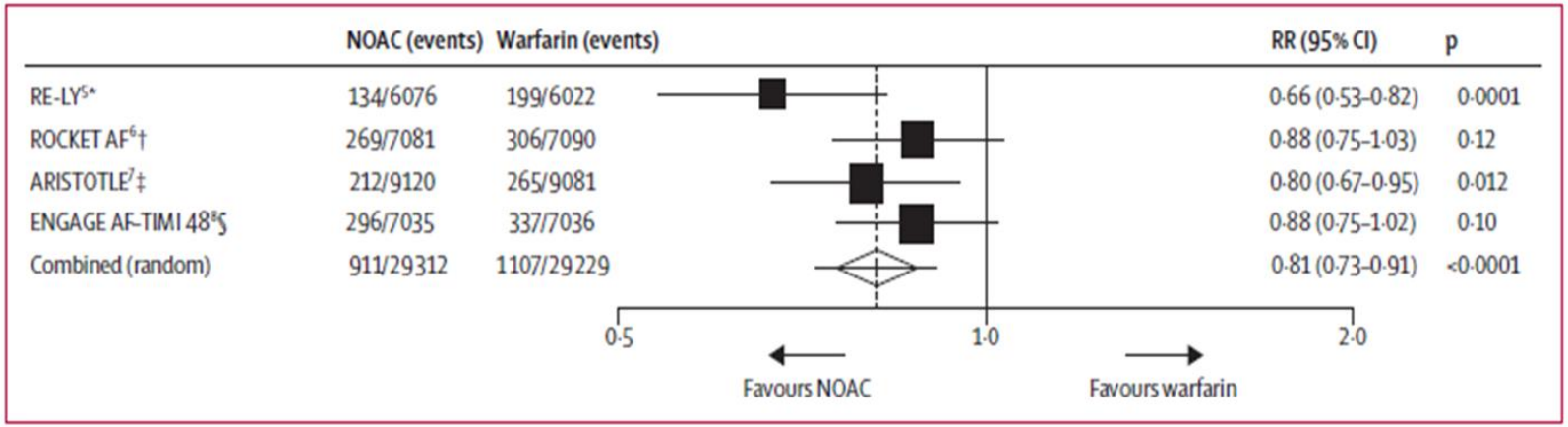


***Figure 1*: Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Ruff et al. Lancet 2014; 383

Major Bleeding

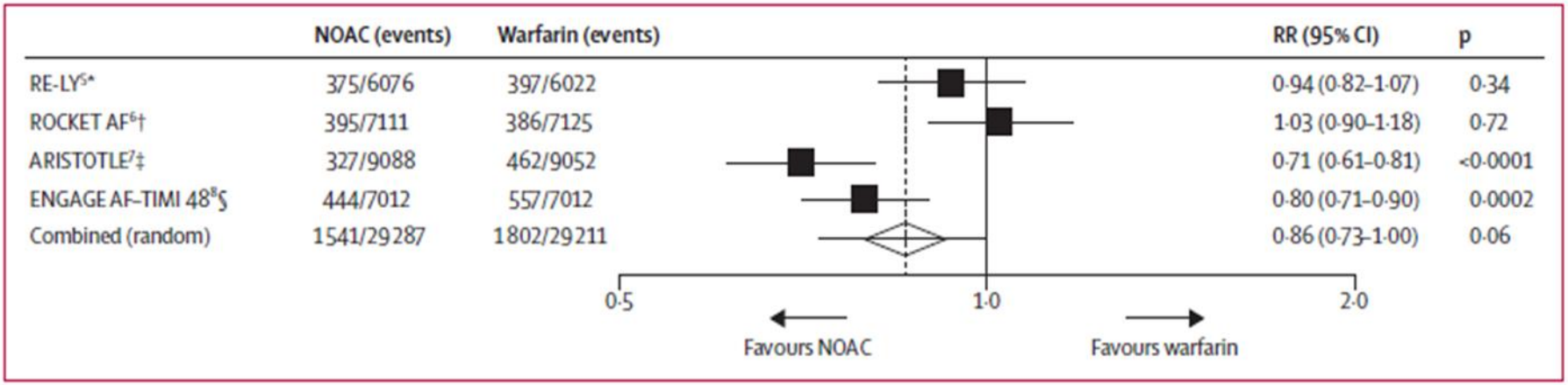
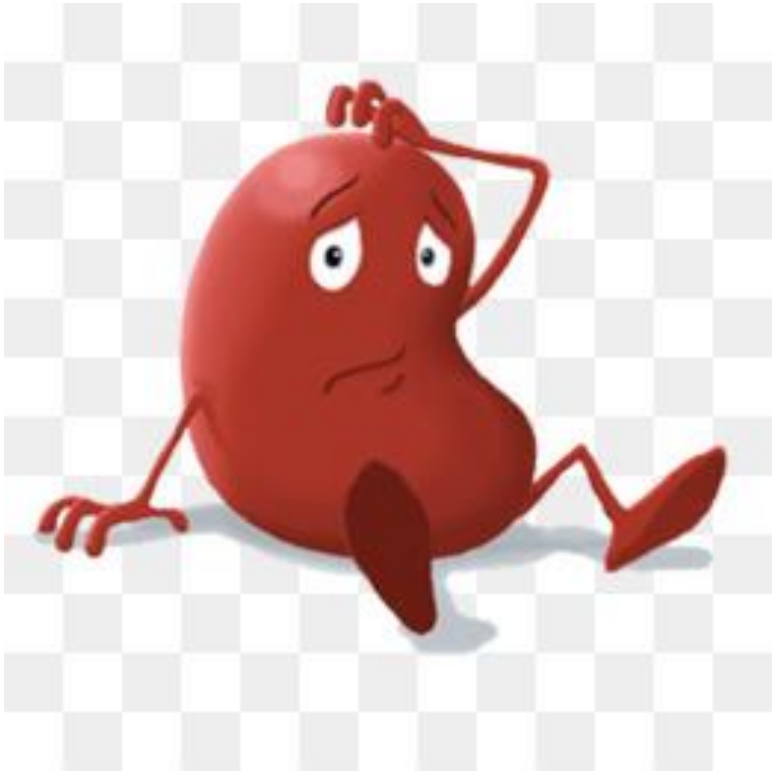


***Figure* 3: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Ruff et al. Lancet 2014; 383

What about Patients with CKD?



Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral Anticoagulants for Atrial Fibrillation

Freddy Del-Carpio Munoz, MD, MSc[a,*], S. Michael Gharacholou, MD, MSc[a], Thomas M. Munger, MD[a], Paul A. Friedman, MD[a], Samuel J. Asirvatham, MD[a], Douglas L. Packer, MD[a], and Peter A. Noseworthy, MD[a,b]

Novel oral anticoagulants (NOACs) are safe and effective for the prevention of stroke or systemic embolism (S/SE) in atrial fibrillation. The efficacy and safety of NOACs compared with warfarin has not been systematically assessed in subjects with mild or moderate renal dysfunction. We performed a meta-analysis of the randomized clinical trials that compared efficacy and safety (major bleeding) outcomes of NOACs compared to warfarin for the treatment of nonvalvular atrial fibrillation and had available data on renal function. We estimated the pooled relative risk (RR) of S/SE and major bleeding in relation to renal function (assessed by baseline estimated glomerular filtration rate divided in 3 groups: normal [estimated glomerular filtration rate >80 ml/min], mildly impaired [50 to 80 ml/min], and moderate impairment [<50 ml/min]). We included 4 randomized clinical trials enrolling a total of 58,338 subjects. The RRs of S/SE and major bleeding were higher

Del-Carpio Munoz, F., *et al. Am J Cardiol.* 2016; 117: 69-75

Stroke Outcomes

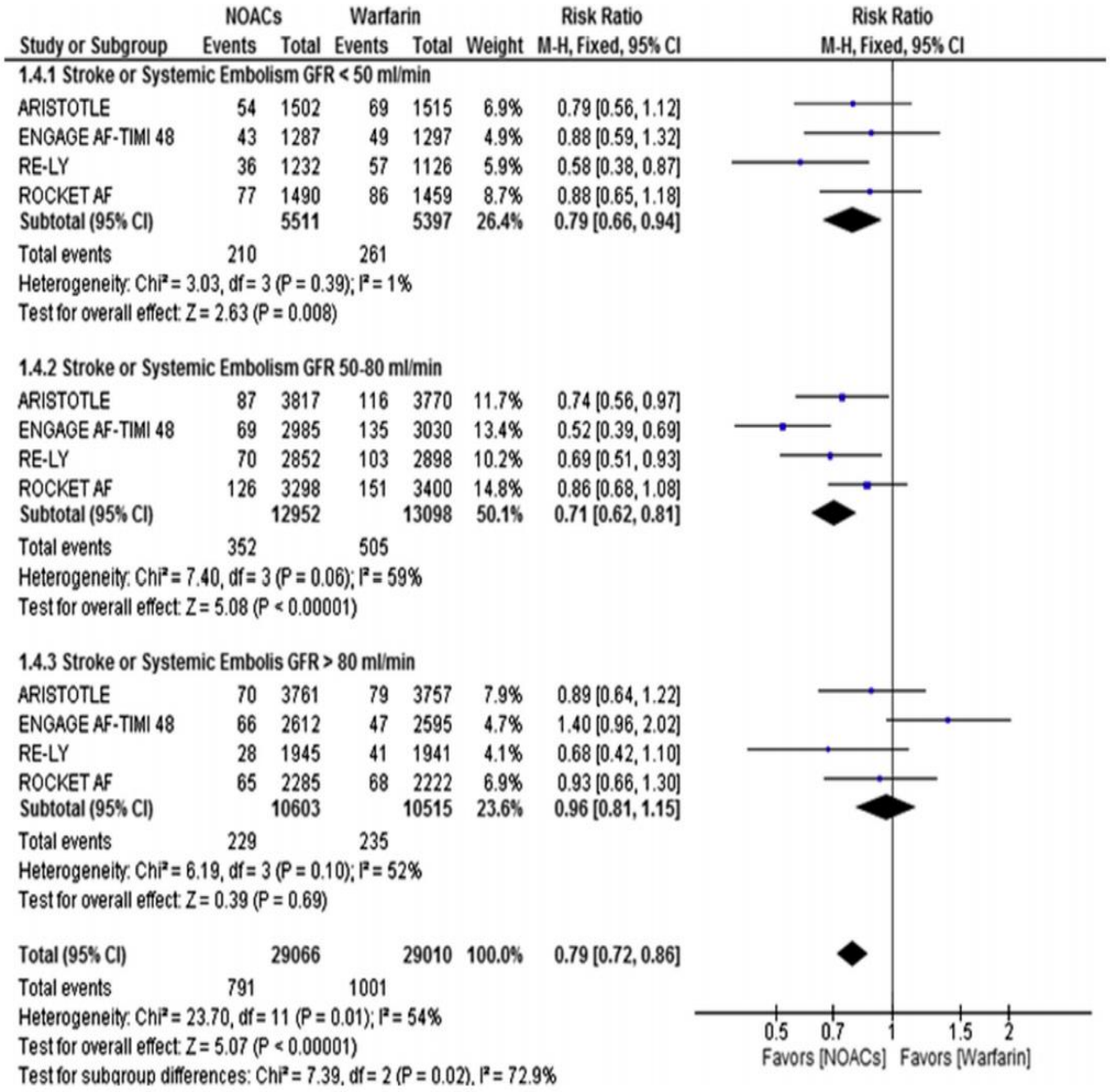


Figure 2. Risk of stroke or systemic embolism and use of NOACs versus warfarin in atrial fibrillation in relation to renal function.

Del-Carpio Munoz, F., *et al. Am J Cardiol.* 2016; 117: 69-75

Bleeding Outcomes

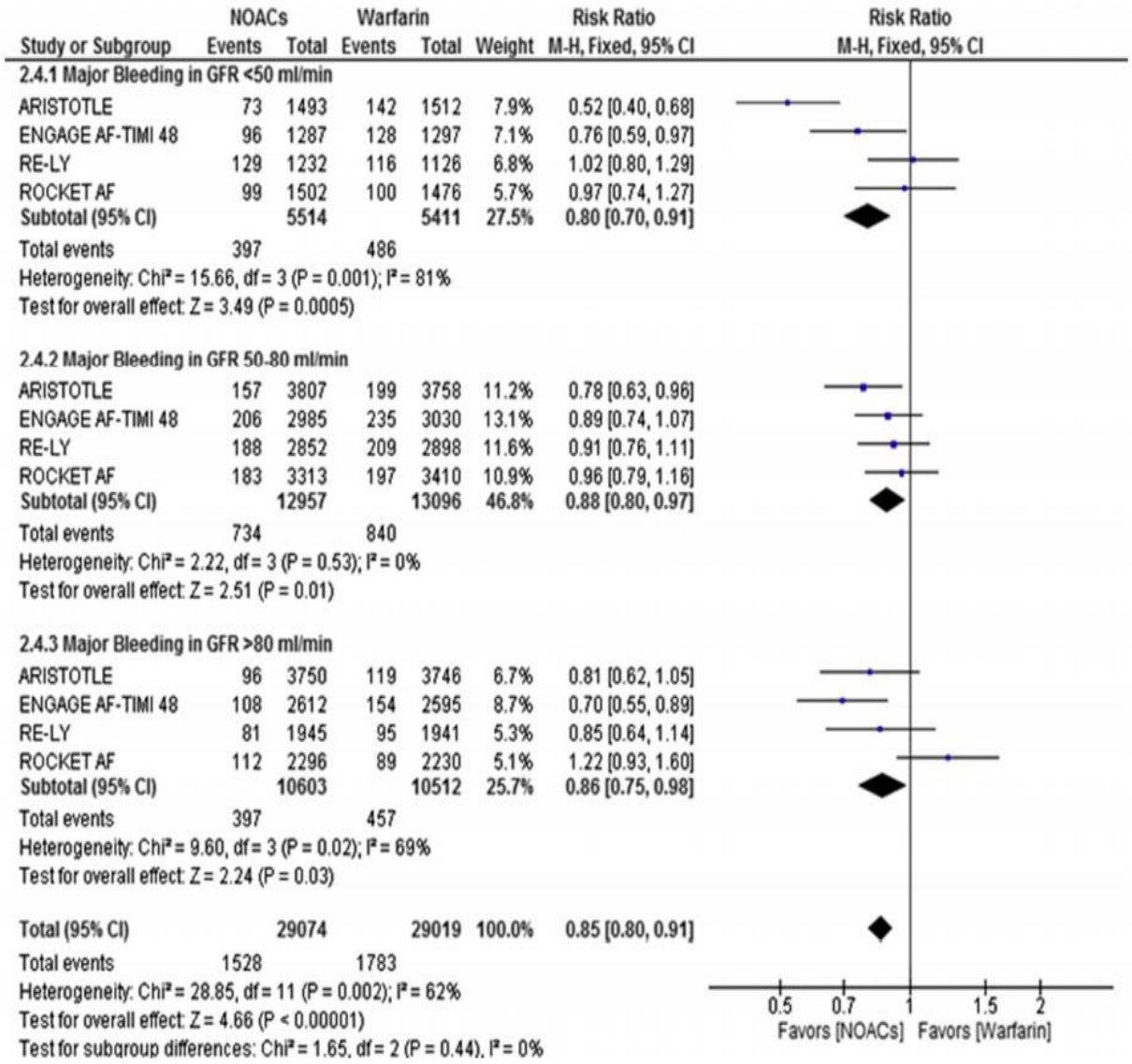


Figure 3. Risk of major bleeding and use of NOACs versus warfarin in relation to renal function.

Del-Carpio Munoz, F., *et al. Am J Cardiol.* 2016; 117: 69-75

What about Patients with “Real” Chronic Kidney Disease?

Question

Which DOAC would you use in patients with eGFR < 30ml/min?

A) dabigatran

B) rivaroxaban

C) apixaban

D) Edoxaban

E) None

Question

Which DOAC would you use in patients on HD?

A) dabigatran
B) rivaroxaban
C) apixaban
D) edoxaban
E) none

Drug Properties of the DOACs

	Warfarin	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
Renal clearance of parent drug	<1%	27%	36%	80%	50%
Removal with 4h of hemodialysis	<1%	7%	<1%	50-60%	9%
Volume of distribution	8	21	50	50-70	107
Protein binding	99%	87%	92-95%	35%	55%
Metabolism	CYP2C9 Minor: CYP2C8, 2C18, 2C19, 1A2, 3A4	CYP3A4/5	CYP3A4/5, CYP2J2	Activated by esterases	Minimal: hydrolysis, CYP3A4

Potential Drug Interactions

P-gp +/- CYP3A4 Inhibitors*

- Azole antifungals*
  - Ketoconazole, itraconazole, voriconazole, posaconazole
  - Fluconazole - caution
- Protease inhibitors*
  - Ritonavir
- Dronedarone
- Calcineurin Inhibitors
  - cyclosporine, tacrolimus
- Amiodarone
- Diltiazem*, verapamil
- Clarithromycin*, erythromycin*
- Quinidine

- P-gp inhibitors – reduce dabigatran or edoxaban dose or avoid, if possible
- Edoxaban - verapamil & amiodarone OK

P-gp + CYP3A4 Inducers

- Rifampin
- Phenytoin
- Carbamazepine
- Phenobarbital
- St. John's Wort

P-gp = P-glycoprotein efflux transporter; *CYP = cytochrome P450

Dosing of DOACS in CKD

- What is the evidence?

Kidney Disease: Improving Global Outcomes- Update

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).

KDIGO Update: EHJ 2018

Edoxaban Dosing

Drug	Canada	US
Edoxaban	50-80ml/min: 60mg daily[1] 30-50ml/min: 30mg daily <30ml/min: Not recommended HD: Not recommended	51-95ml/min:60mg daily 15-50ml/min: 30mg daily <15ml/min: Not recommended HD: Not recommended

1. If ≤60kg or P-gp inhibitors except amiodarone and verapamil

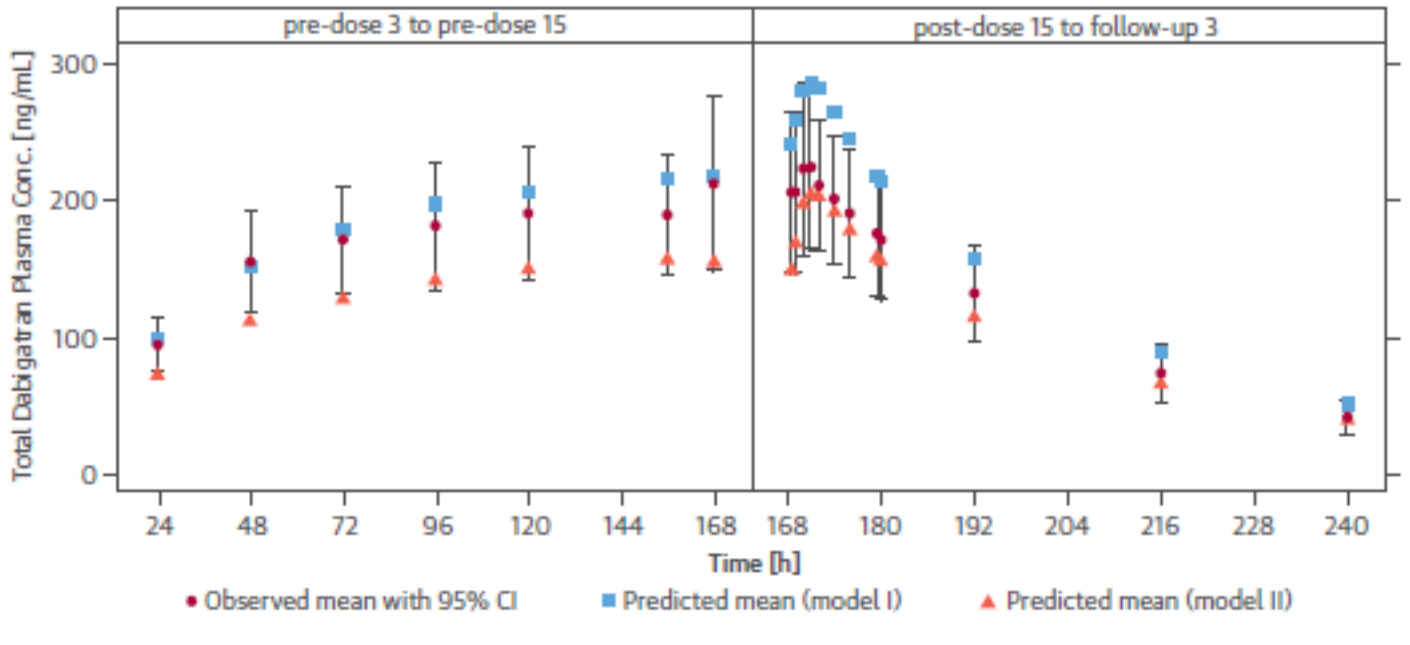
Dosing for Dabigatron

Drug	Canada	US
Dabigatran	>30ml/min: 150mg bid[1] or 110mg bid[3] <30ml/min: Avoid HD: Avoid	>50ml/min: 150mg bid 30-50ml/min:150mg bid[1] 15-30ml/min:75mg bid[2] <15ml/min: Avoid HD: Avoid

1. 75mg BID if concomitant dronedarone or ketoconazole
2. Avoid if concomitant P-gp inhibitor
3. Patients with high risk of bleeding including patients >75 years with 1 or more risk factors for bleeding

Dosing of Dabigatran

FIGURE 1 Observed (Mean and 95% CI) and Predicted (Mean) Total Dabigatran Plasma Concentration Profiles Following 75 mg b.i.d. in Patients With Severe CKD



Predictions marked "model I" were derived from a model (1) on the basis of mean data from severe chronic kidney disease (CKD) patients participating in a single-dose dabigatran trial. Predictions marked "model II" were derived from a model (3) on the basis of data from the RE-LY (Dabigatran versus Warfarin in Patients with Atrial Fibrillation) trial. CI = confidence interval.

- 15 patients with eGFR 23 ml/min- 75mg bid for 7 days
- Observed compared to PK modeling

Kooiman et al. JACC 2016

Removal of Dabigatran by Dialysis

- PK Case Study show 50% removal by HD
- Used in overdoses

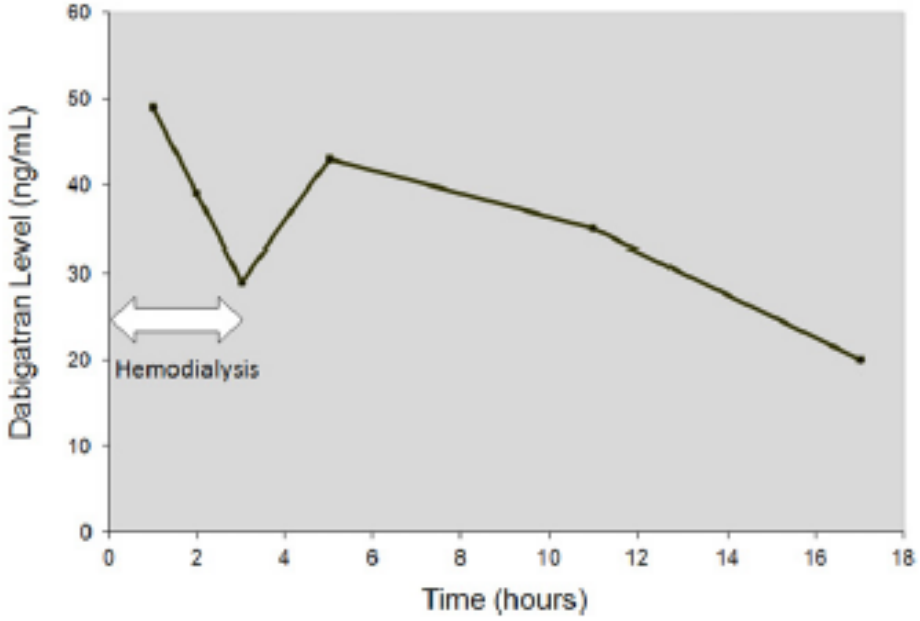


Figure 1. Decrease in dabigatran levels during hemodialysis and rebound after treatment.

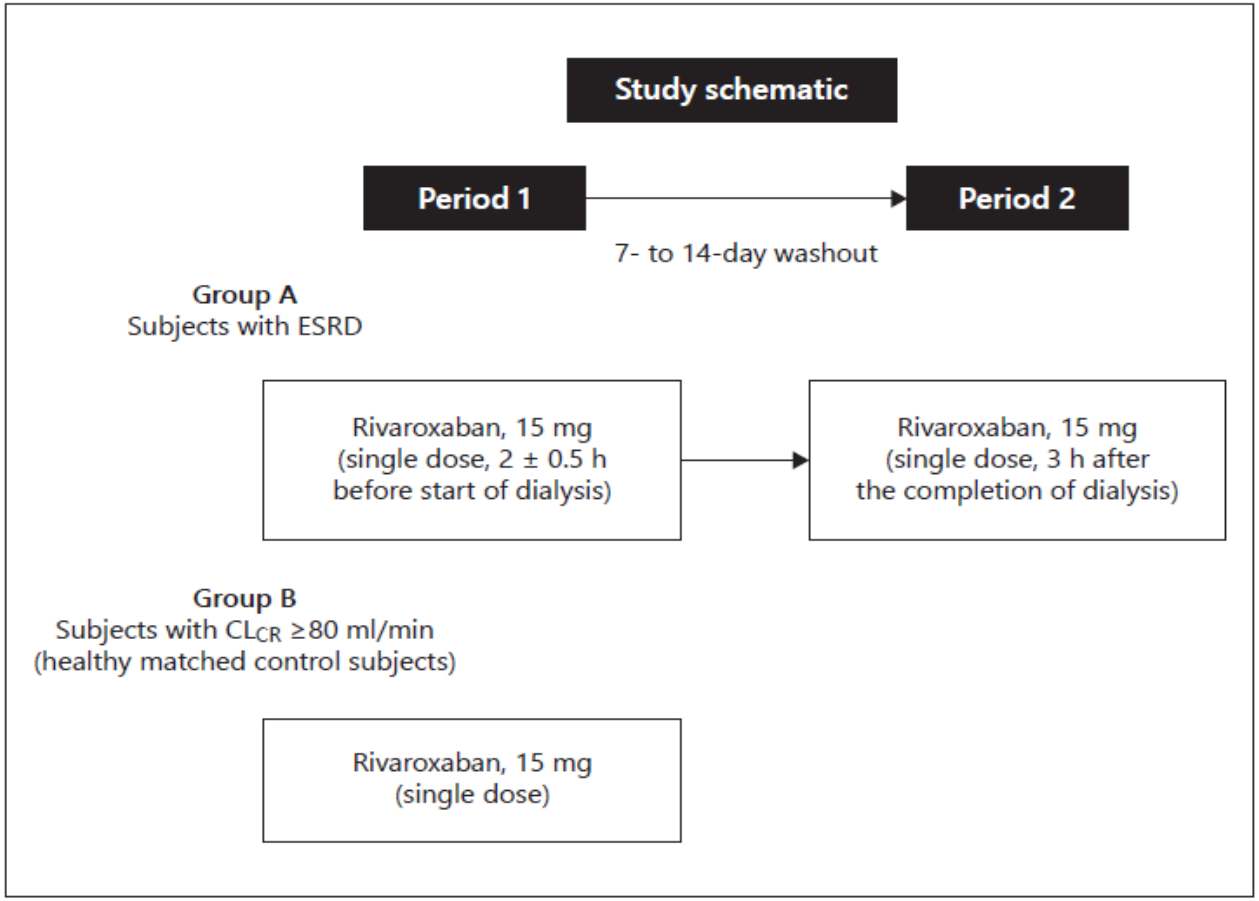
Chang, AJKD 2013

Dosing for Rivaroxaban

Drug	Canada	US
Rivaroxaban*	>50ml/min: 20mg daily 15-50ml/min: 15mg daily < 15ml/min: Avoid HD: Avoid	>50ml/min: 20mg daily 15-50ml/min: 15mg daily <15ml/min: Avoid HD: Avoid

* Rivaroxaban updated monograph for VTE (15-50ml/min): 15mg bid x 3weeks then 20mg od; prevention: 10-20mg daily

Rivaroxaban Dosing



- 8 patients in each group
- Single Dose study- PK parameters calculated on unknown number of blood samples

Dias et al. Am J Nephr 2016

Rivaroxaban Dosing

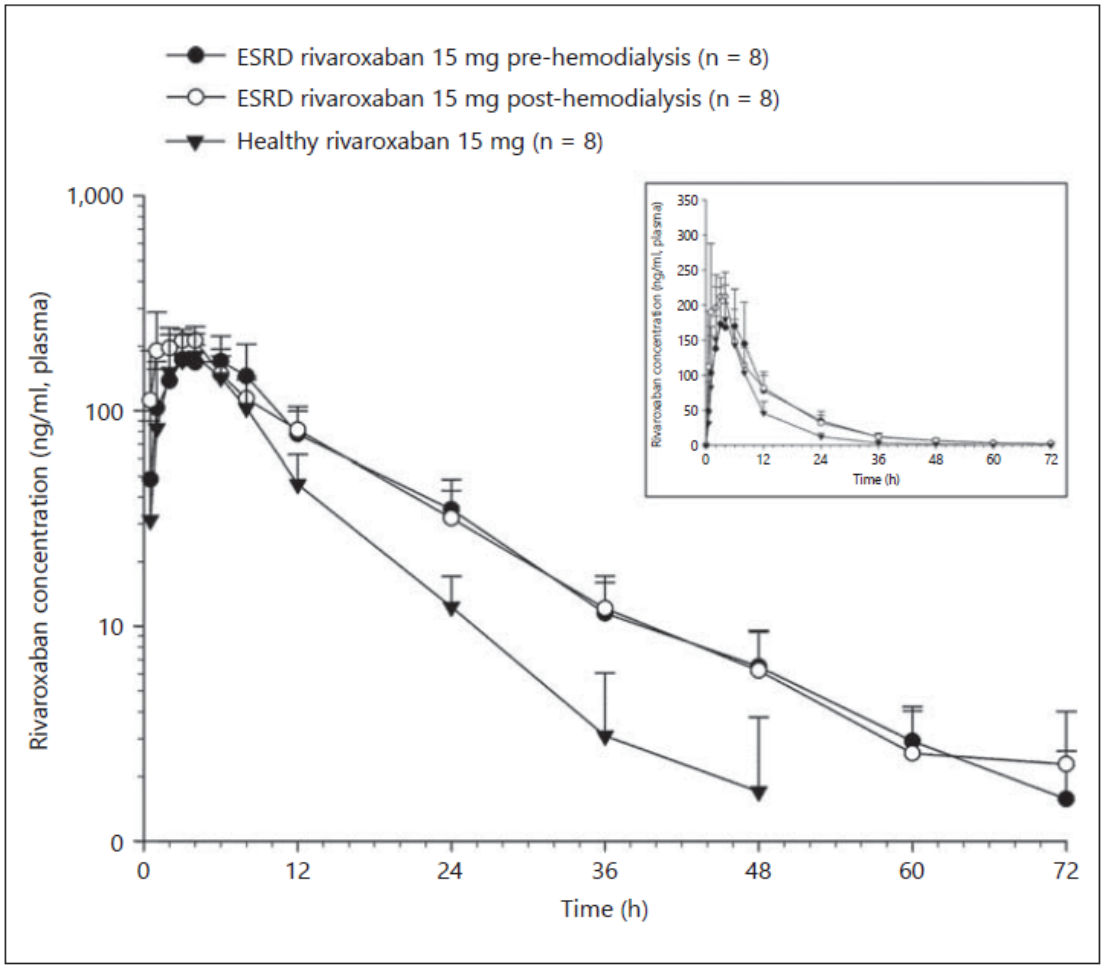
Table 2. Arithmetic mean (SD) plasma PK parameters following a single 15-mg dose of rivaroxaban in subjects with normal renal function and ESRD

Parameter	Normal renal function (CL_{CR} ≥80 ml/min; n = 8)	ESRD	
		pre-dialysis[a] (n = 8)	post-dialysis[b] (n = 8)
C_{max}, ng/ml	210 (30.8)	194 (47.2)	247 (40.2)
t_{max}, h[c]	3.0 (0.5–6.0)	3.0 (1.0–6.0)	2.0 (1.0–4.0)
AUC_{last}, ng·h/ml	1,848 (404)	2,740 (613)	2,857 (495)
AUC_{∞}, ng·h/ml	1,879 (432)[d]	2,770 (622)	2,907 (500)
$t_{1/2}$, h	6.2 (1.8)[d]	12.2 (3.8)	13.2 (5.7)
Vd/F, l	71.0 (8.9)[d]	101 (39)	101 (44)
CL/F, l/h	8.31 (1.70)[d]	5.69 (1.46)	5.34 (1.21)
Protein-bound rivaroxaban, %[c, e]	89 (87–93)	86 (80–94)	

[a] Pre-dialysis, subjects dosed 2 h before hemodialysis.
[b] Post-dialysis, subjects dosed 3 h after hemodialysis.
[c] Expressed as median (range).
[d] n = 7; healthy subject 220107 was excluded from $AUC_{(0-\infty)}$ PK parameter analysis due to variability in the terminal phase (r^2 adjustment <0.9000).
[e] Percentage of rivaroxaban that is protein-bound in pre-dose plasma.

Dias et al. AmJ Nephr 2016

Rivaroxaban Dosing



Dias et al. AmJ Nephr 2016

Dose-Finding Study of Rivaroxaban in Hemodialysis Patients

- PK study
- Groups
  - 10mg rivaroxaban at end of 3 consecutive dialysis sessions (n=12)
  - 10mg single dose 6-8hrs before dialysis (n=12)
  - 10mg once daily before dialysis for 7 days (n=6)

Am J Kidney Dis. 2015;66(1):91-98

Results of Rivaroxaban PK Study

- ↑AUC 1.7 fold compared to healthy volunteers receiving 10mg but similar to healthy volunteers receiving 20mg
- No effect of HD on plasma concentrations and anticoagulation effect
- No accumulation after multiple daily dosing

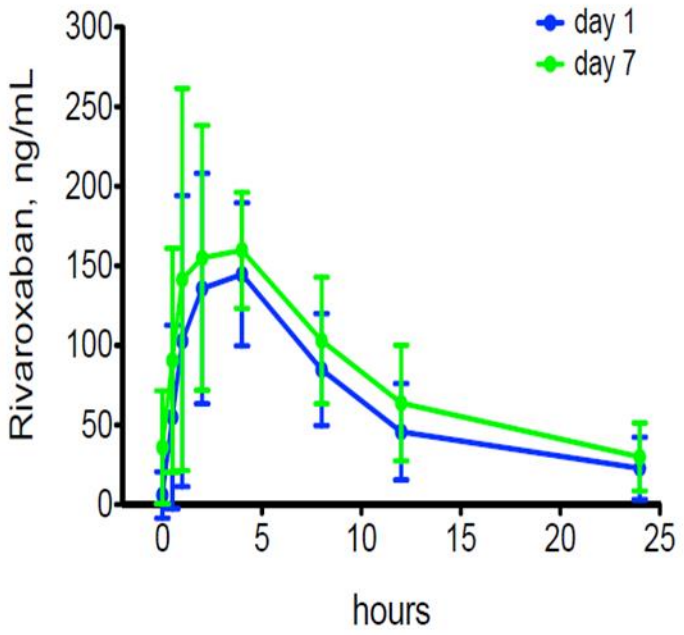


Figure 4. Rivaroxaban concentrations based on multiple-dose administration. Mean (± standard deviation) plasma rivaroxaban concentrations measured by liquid chromatography–tandem mass spectrometry on days 1 and 7 after administration of 10 mg of rivaroxaban in 6 patients.

Am J Kidney Dis. 2015;66(1):91-98

Apixaban dosing for atrial fibrillation

Drug	Canada	US
Apixaban	>30 ml/min: 5mg BID[1] 15-29 ml/min: Use with caution <15 ml/min: Not recommended HD: Not recommended	> 15ml/min: 5 mg BID[1] HD: 5 mg BID[1]

1. 2.5mg BID if any 2 of following: ≥80 years, weight≤60kg or SrCr≥1.5mg/dL (133 umol/L)

Pharmacokinetics and Safety of Apixaban in Subjects on Hemodialysis

- Open-label, single dose study (5mg)
- Groups: HD (n=8) vs CrCl >80 ml/min(n=8)
  - Matched according to age (±5 years), weight (±20% post dialysis weight) and sex
- Results
  - ↑AUC by 36% higher in ESRD
  - Similar protein binding
  - 4-hr dialysis session: ↓exposure by 14%
  - No difference in INR, PT and aPTT

The Journal of Clinical Pharmacology 2016. 56(5) 628-636

Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

Thomas A. Mavrakanas,*† Caroline F. Samer,‡ Sharon J. Nessim,* Gershon Frisch,* and Mark L. Lipman*

*Division of Nephrology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; and †Division of General Internal Medicine and ‡Department of Clinical Pharmacology and Toxicology, Geneva University Hospitals, Geneva, Switzerland

CJASN 2017; 28

Study Methods

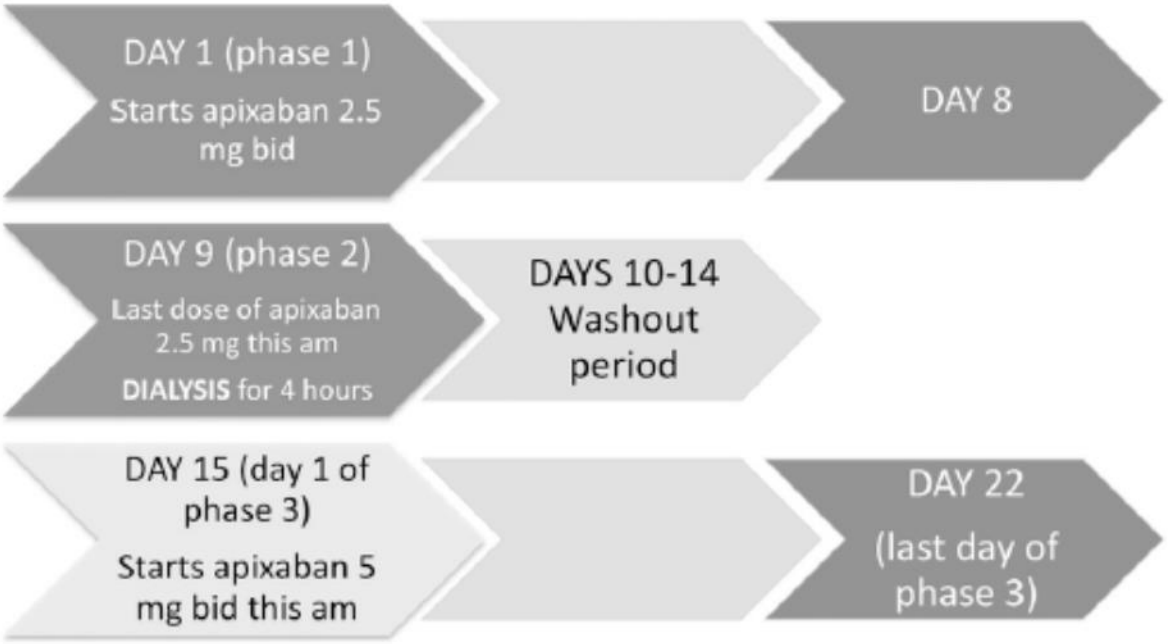
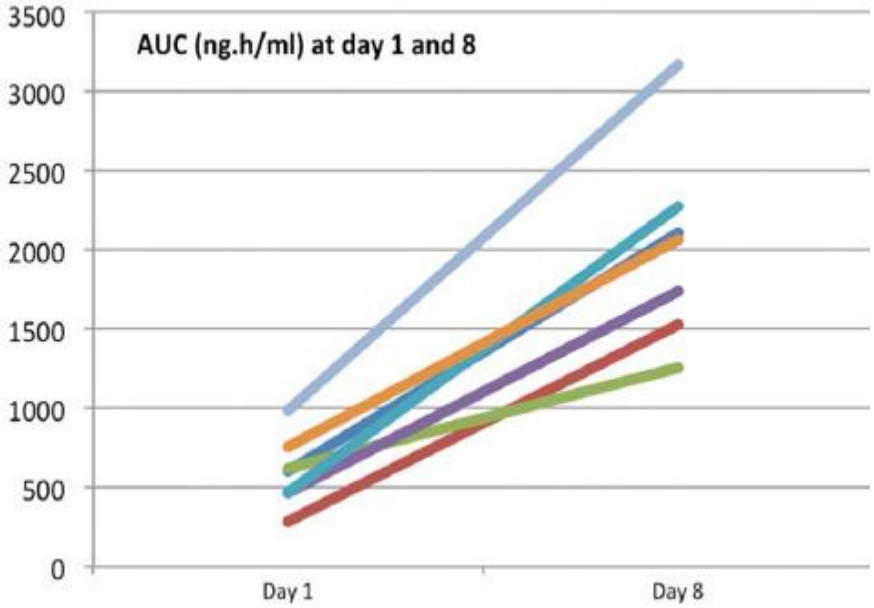
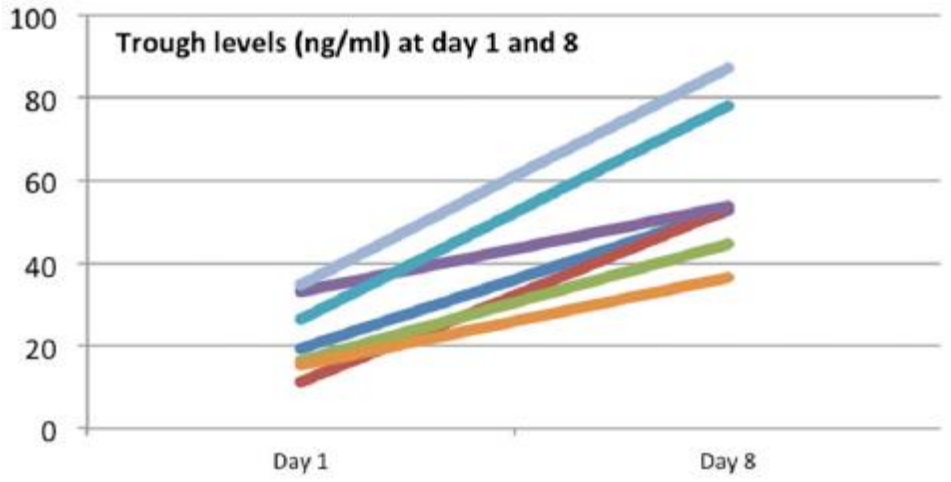


Figure 4. Schematic presentation of study interventions (phases 1–3). Phase 1: apixaban exposure after a 2.5 mg single dose and at steady state (day 8). Phase 2: effect of hemodialysis on apixaban concentration at steady state. Phase 3: apixaban exposure at steady state with a 5 mg bid dose. Bid, twice daily.

CJASN 2017; 28

Results





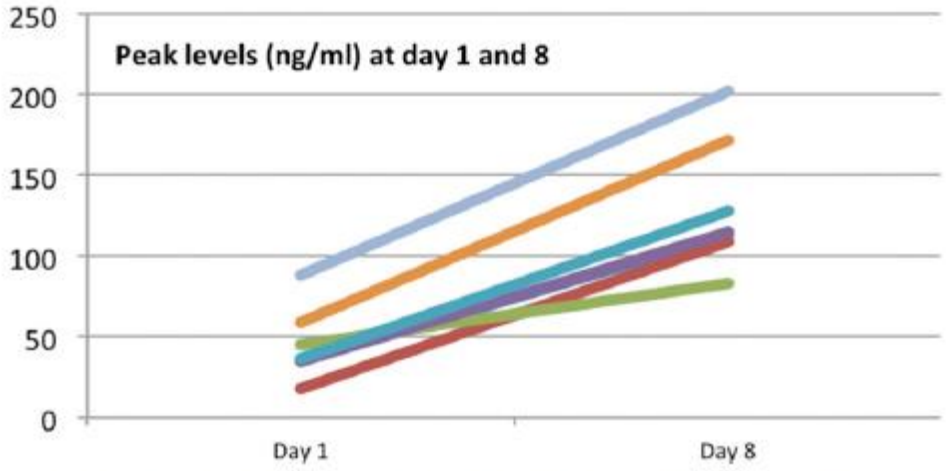


Table 1. PK parameters during phase 1

Apixaban 2.5 mg Twice Daily	Day 1	Day 8	*P* Value	Reference Levels (for the 2.5 mg twice daily dose)
AUC_{0-12}, ng h/ml	298.6 (38.0%)	1009.8 (30.7%)	<0.001	—
AUC_{0-24}, ng h/ml	597.3 (38.0%)	2019.7 (30.7%)	<0.001	1661 (1120–2620)[19]
C_{max}, ng/ml	45.2 (49.9%)	131.5 (31.1%)	<0.001	123 (69–221)[a,20]
t_{max}, h	4.4 (62%)	3.6 (48%)	0.32	—
C_{min}, ng/ml	22.3 (41.2%)	58.0 (31.2%)	<0.001	56 (24–103)[19]
$t_{1/2}$, h	5.9 (15.8%)	7.5 (64.3%)	0.94	—
AI	N/A	3.6 (33.9%) [3.4]	N/A	[1.3–1.7][14,22]

Results are presented as mean (coefficient of variation), median (10th–90th percentile), or median (5th–95th percentile). The geometric mean (in brackets) is also provided for the AI. t_{max}, Time to peak apixaban concentration; AI, accumulation index; N/A, not applicable.
[a]Median (5th–95th percentile).

Figure 1. Apixaban PK parameters with the 2.5-mg twice daily dose on days 1 and 8, showing significant accumulation of the drug.

CJASN 2017; 28

Results

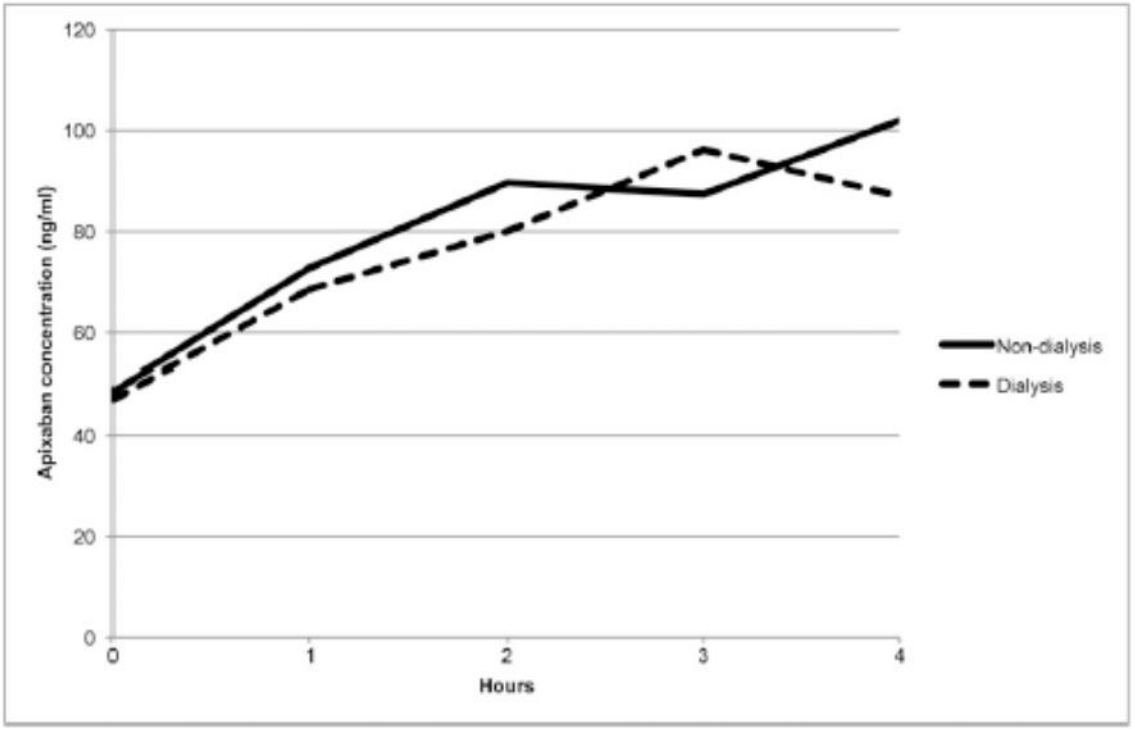


Figure 2. Effect of hemodialysis on apixaban levels. The solid line shows apixaban levels during the first 4 hours after drug administration (2.5 mg) on day 8 (nondialysis day). The dotted line shows apixaban levels during hemodialysis on day 9. The dialysis session started immediately after the drug administration (2.5 mg) and lasted for 4 hours.

CJASN 2017; 28

Results

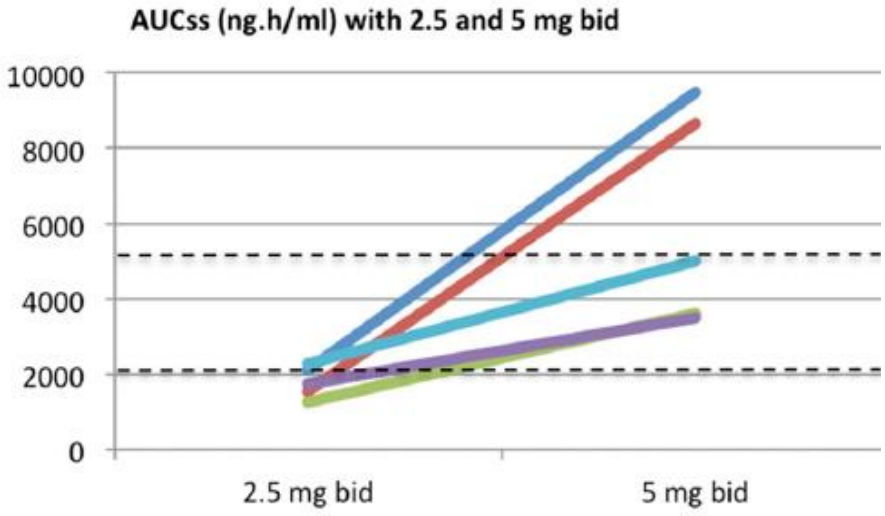


Table 2. PK parameters of apixaban after administration of 5 mg twice daily for a week and comparison with expected levels in the general population

Apixaban 5 mg Twice Daily	Day 22	*P* Value	Reference Levels (for the 5 mg twice daily dose)
AUC_{0-12}, ng h/ml	3026.6±46.6% [2770.4]	0.03	[1474–1717][18]
AUC_{0-24}, ng h/ml	6053.2±46.6% (3505.5–9469.7)	0.03	3370 (2070–5250)[19]
C_{max}, ng/ml	307.0±39.4% (189.0–455.0)	0.02	171 (91–321)[a][20]
t_{max}, h	3.8±35.6% (2.5–6.0)	0.89	—
C_{min}, ng/ml	217.5±51.9% (91.0–337.4)	0.03	107 (56–203)[19]
$t_{1/2}$, h	17.4±51.3% (7.1–29.8)	0.13	—

This table shows the PK parameters of apixaban 5 mg twice daily at steady state (day 8). Results are presented as mean ± coefficient of variation (range), median (10th–90th percentile), or median (5th–95th percentile). For AUC_{0-12}, the geometric mean (in brackets) is also depicted. *P* values are comparing apixaban 5 mg twice daily (day 22) with apixaban 2.5 mg twice daily at steady state (day 8; data depicted in Table 1, column 3). t_{max}, Time to peak apixaban concentration.
[a]Median (5th–95th percentile).

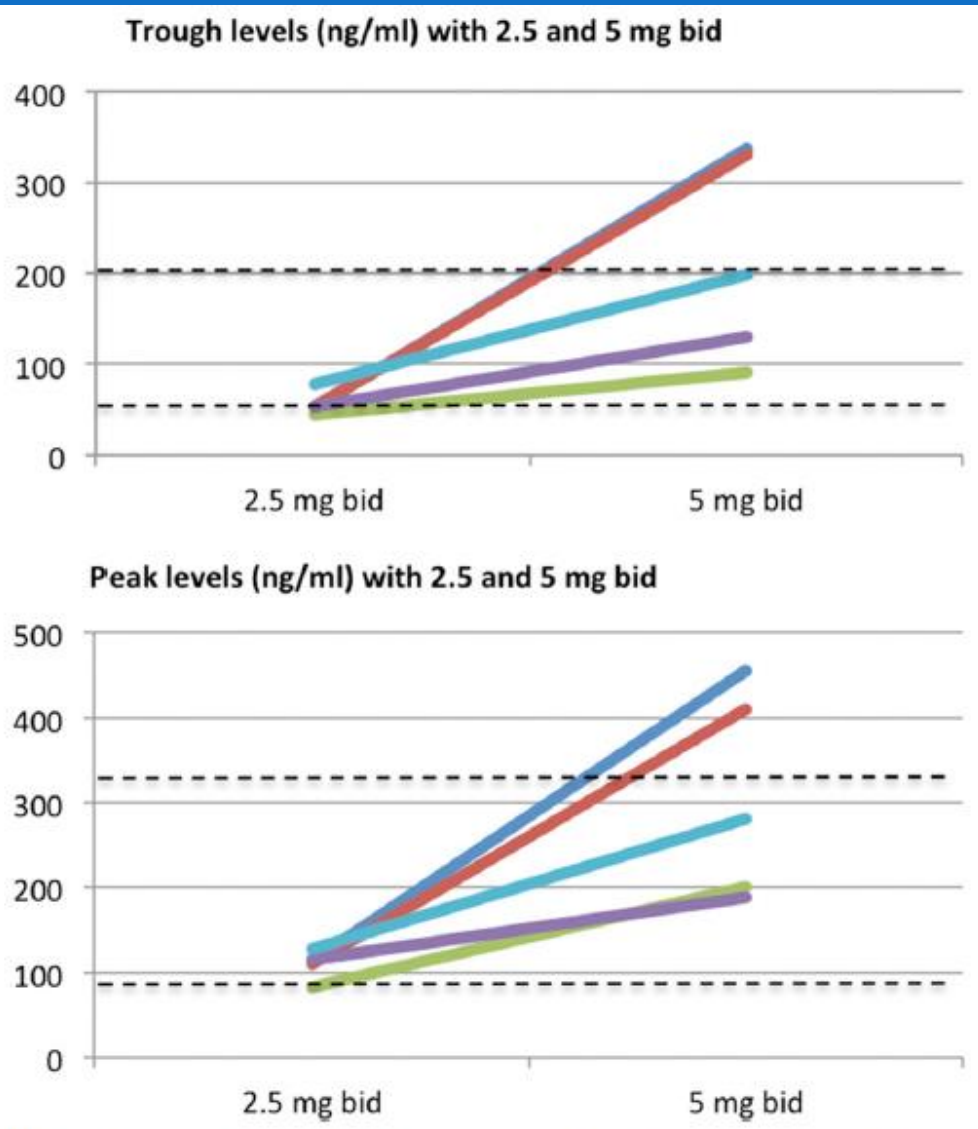


Figure 3. Comparison of the PK parameters at steady state (*i.e.*, after 8 days of apixaban administration) achieved with the reduced dose (2.5 mg twice daily) and with the standard dose (5 mg twice daily) of apixaban. The dotted lines represent the 10th and 90th percentiles of the predicted levels for the 5-mg twice daily dose in patients with preserved renal function (5th and 95th percentiles for C_{max}). AUCss, area under the concentration-time curve at steady state; bid, twice daily.

Is there any clinical evidence with the DOACs in CKD 4 or 5/Dialysis?

DOAC use in CKD and Dialysis with AF Systematic Review

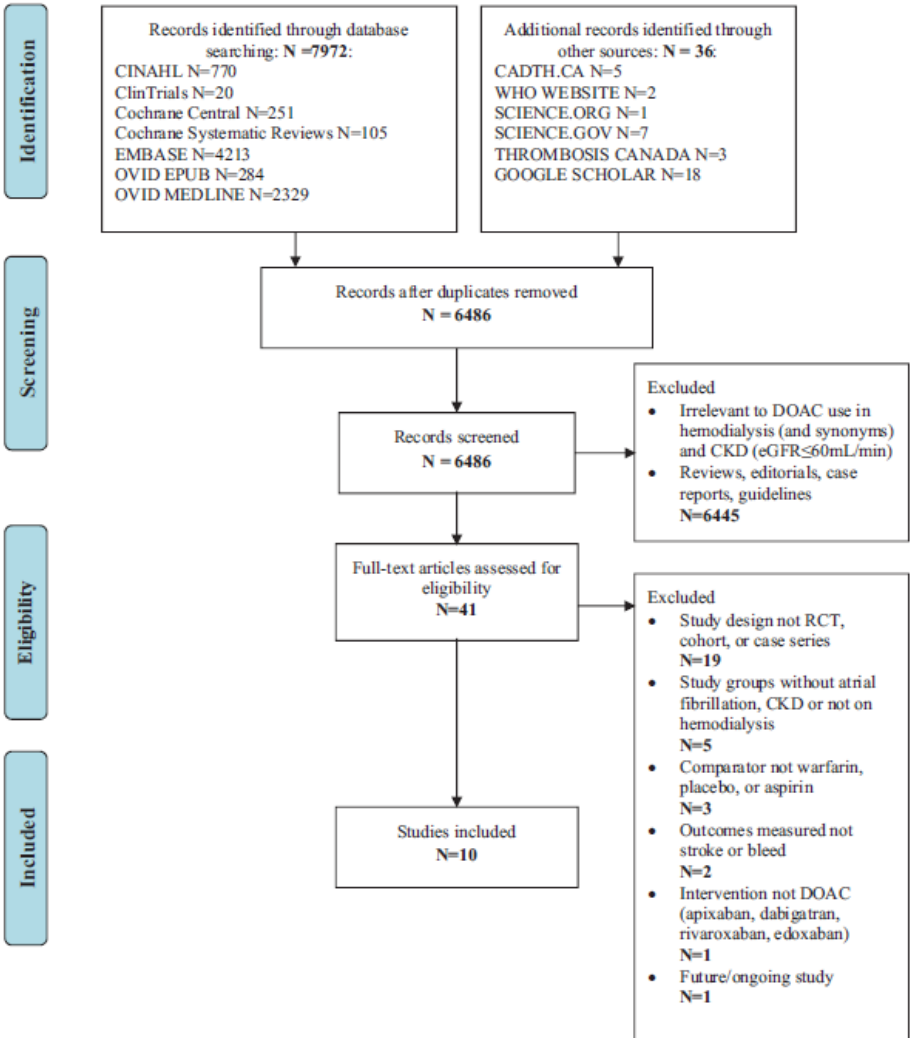
- **Background:** Lack of clear benefit and potential risk of bleeding with DOAC use in CKD and dialysis with AF

- **Aim:** Evaluate how treatment with DOACs affect stroke and bleeding outcomes compared with Warfarin or Aspirin in this population

Feldberg J, *Nephrol Dial Transplant*. 2018:1–13.

ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Flow Diagram of Study Selection



RCTs (6), cohort studies (3) and case series (1)

Feldberg J, *Nephrol Dial Transplant*. 2018:1–13.

DOACs vs. Warfarin in CKD with AF Systematic Review Results

DOAC	Stroke/Systemic Embolism	Major Bleeding
Apixaban 2.5–5mg BID	↓	↓
Dabigatran 110mg BID	↔	↔
Dabigatran 150mg BID	↓	↔
Rivaroxaban 10–20mg daily	↔	↔
Edoxaban 30–60mg daily	↔	↓

Feldberg J, *Nephrol Dial Transplant*. 2018:1–13.

DOACs vs. Warfarin in Dialysis with AF Systematic Review Results

DOAC	Stroke/Systemic Embolism	Major Bleeding
Apixaban 2.5–5mg BID	⟷	⟷
Dabigatran 75–150mg BID	⟷	↑
Rivaroxaban 15–20mg daily	⟷	↑

Feldberg J, *Nephrol Dial Transplant*. 2018:1–13.

Limitations

- Heterogeneity of the ten included studies.
  - the studies had varying definitions of major bleeding and stroke outcomes, and heterogeneous inclusion/exclusion criteria
- Each of the trials included had different definitions for kidney dysfunction and dose adjustments for the DOACs varied in the studies.
- Only two studies done comparing DOACs to warfarin for atrial fibrillation in HD patients
  - both were retrospective cohort studies.

Feldberg J, *Nephrol Dial Transplant*. 2018:1–13.

Circulation

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

Ziontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, et al.

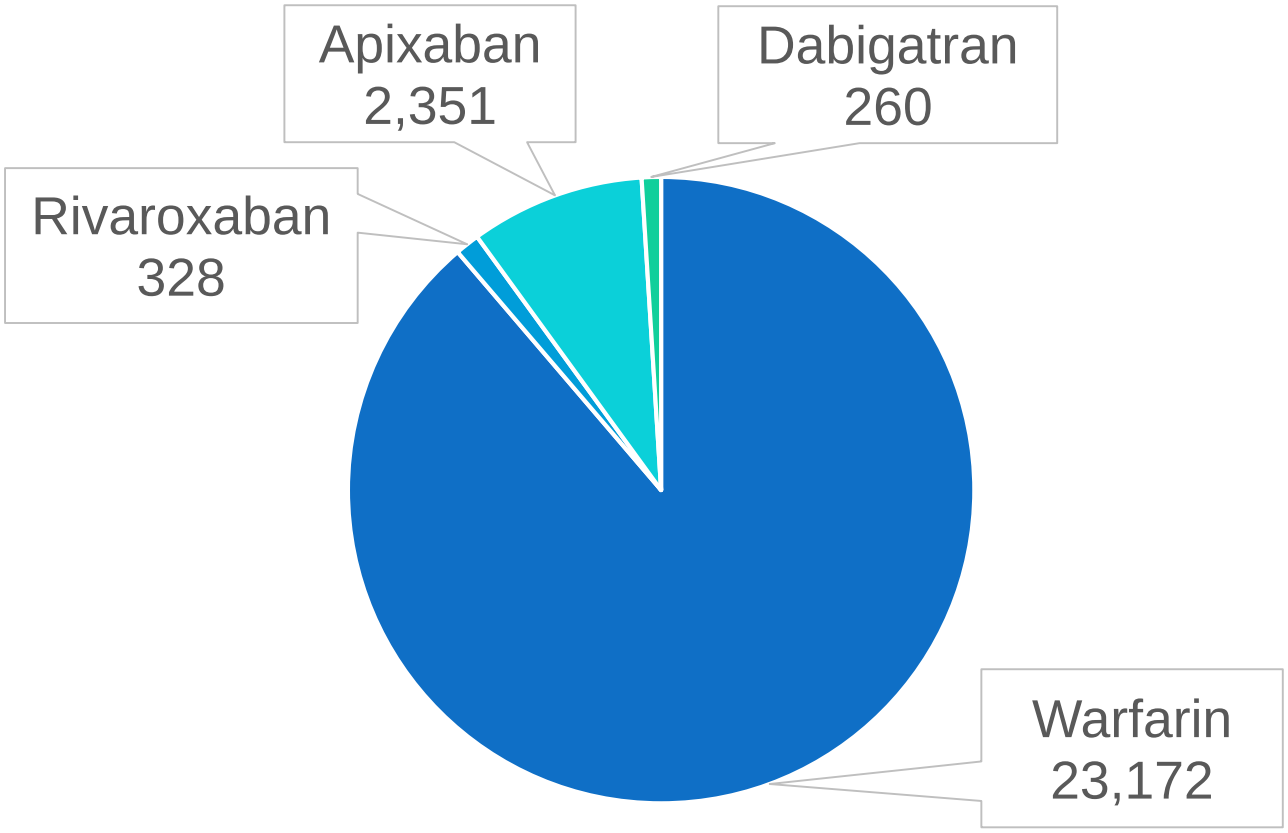
Circulation. 2018;138:1519–1529. DOI: 10.1161/CIRCULATIONAHA.118.035418

October 9, 2018

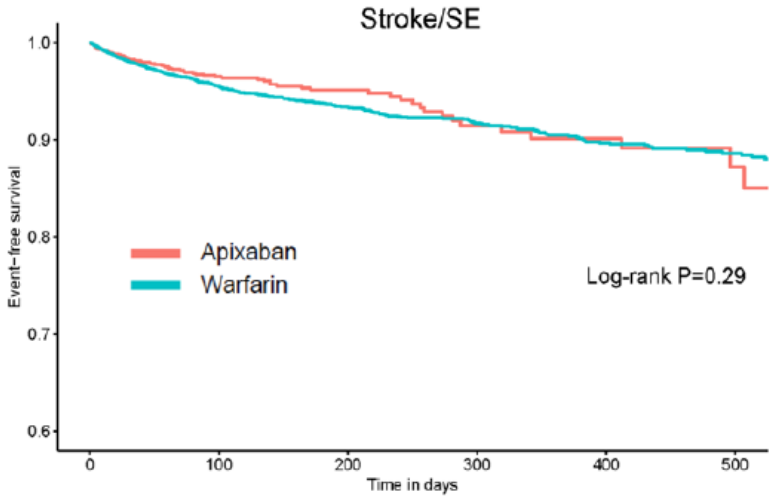
Study design and methodology

- Retrospective cohort study
- Data from United States Renal Data System (USRDS)
- 5 year period (Oct 2010 – Dec 2015)
- Two parts:
  - Study population and trends of DOAC use
  - Outcomes of matched cohorts 3:1 (based on prognostic score)

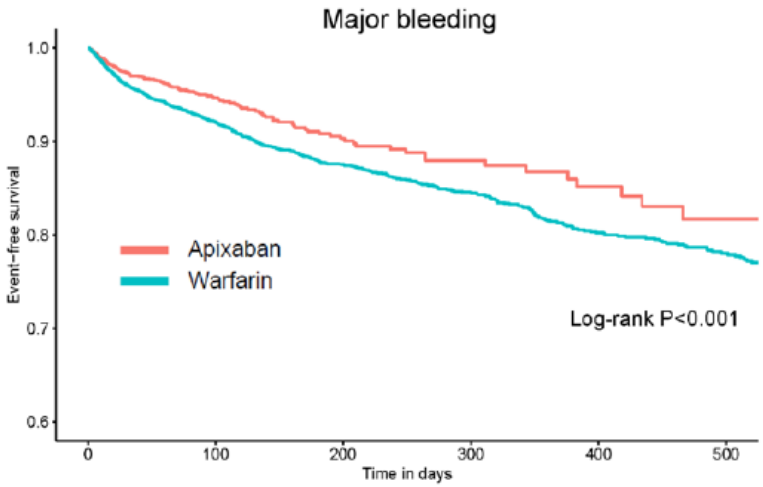
Sample size


Apixaban
2,351
Dabigatran
260
Rivaroxaban
328
Warfarin
23,172

Outcomes



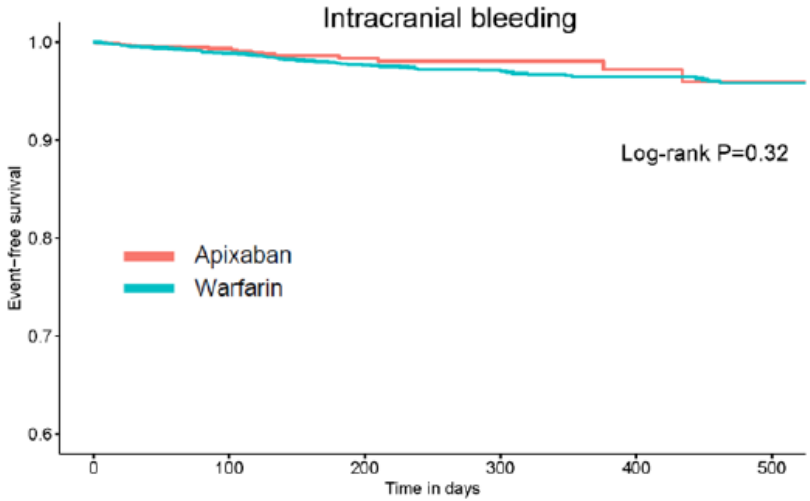
Apixaban: **12.4** per 100 patient-years
Warfarin: **11.8** per 100 patient-years



Apixaban: **19.7** per 100-patient years

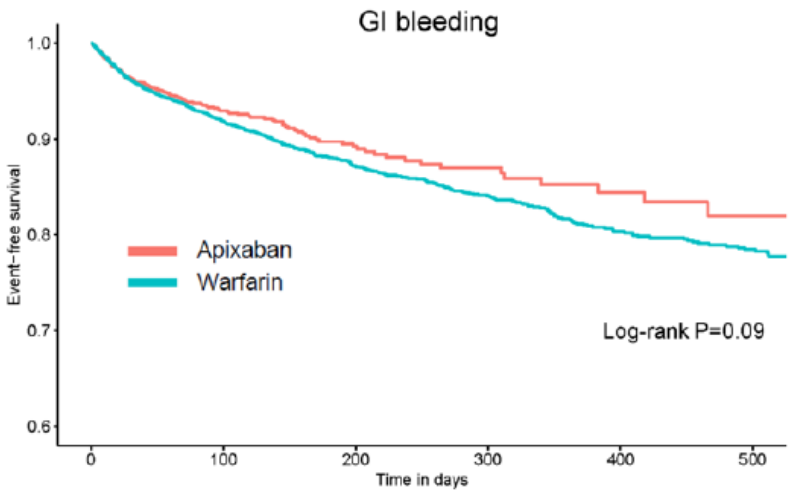
Warfarin: **22.9** per 100-patient years

Outcomes



Apixaban: **3.1** per 100 patient-years

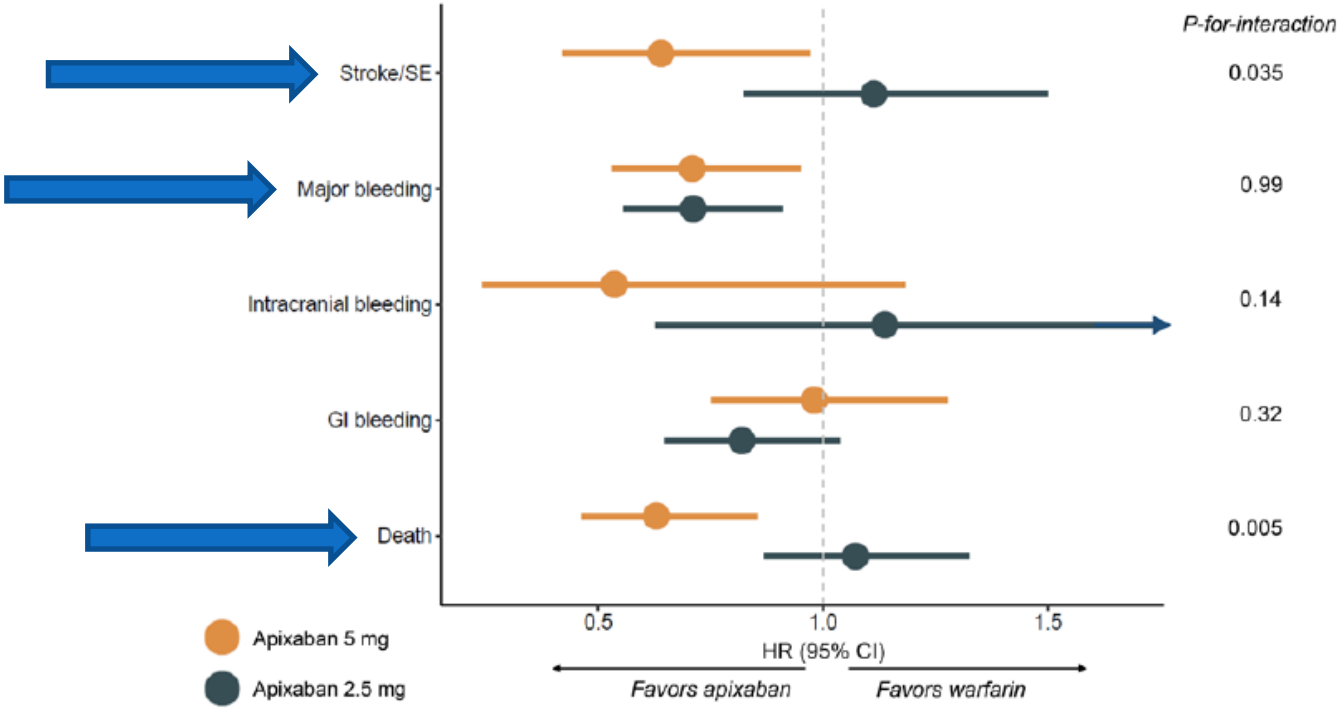
Warfarin: **3.5** per 100 patient-years



Apixaban: **23.8** per 100-patient years

Warfarin: **23.4** per 100-patient years

Apixaban Dosing



Limitations

- Confounding factors, e.g. selective prescribing
- Did not report minor bleeding
- No information on body weight, adherence to treatment, use of non-oral anticoagulants during dialysis (e.g. heparin), or time in therapeutic range/INRs
- High number of patients censored due to expiration of prescription or >30-day gap between prescriptions (62.4% apixaban, 72.5% warfarin)

Case

Mrs V. is a 55 year old lady on HD since 2007. She has ESKD from unknown origin.

- PMH:
  - CAD- MI and ischemic cardiomyopathy
  - AF- right occipital infarct in 2015
  - PVD
  - Hepatitis C (treated with interferon)
- Medications:
  - rosuvastatin, ramipril, metoprolol, clopidogrel, ASA, **warfarin**, pantoprazole, replavite, cinacalcet, Aranesp, Venofer
- She is admitted with calciphylaxis of her left foot

Question

What do we do about her anticoagulation for AF?

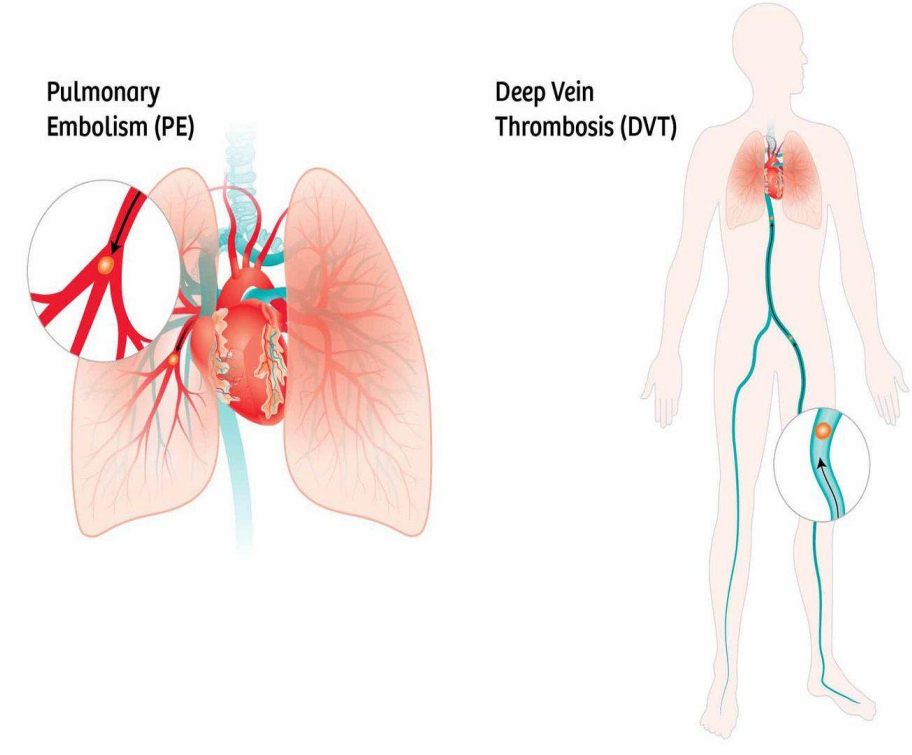
A) Continue warfarin

B) D/C warfarin and start a DOAC

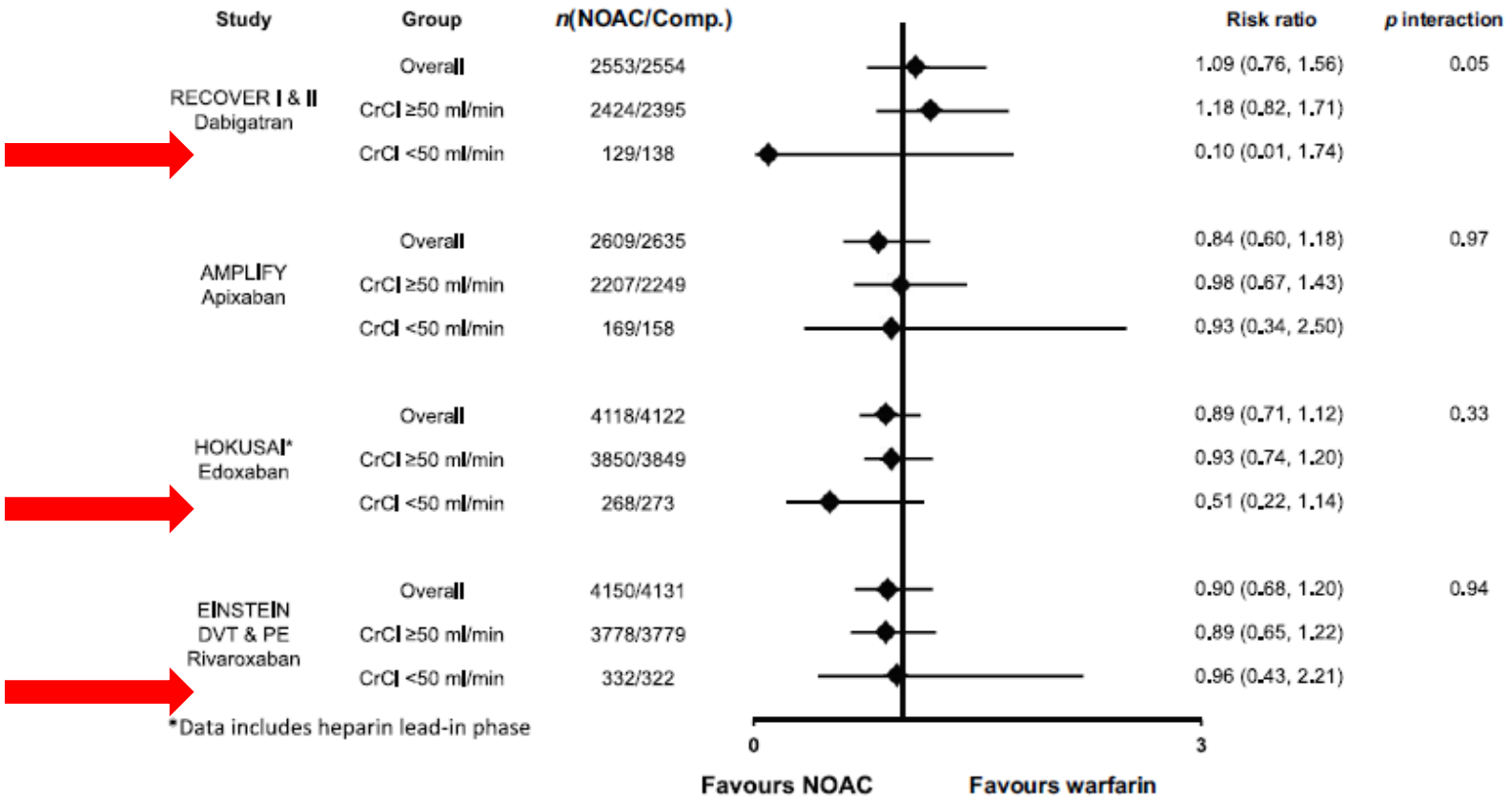
C) D/C warfarin and start a LMWH

D) D/C warfarin

DOACs for the management of DVT in CKD Patients

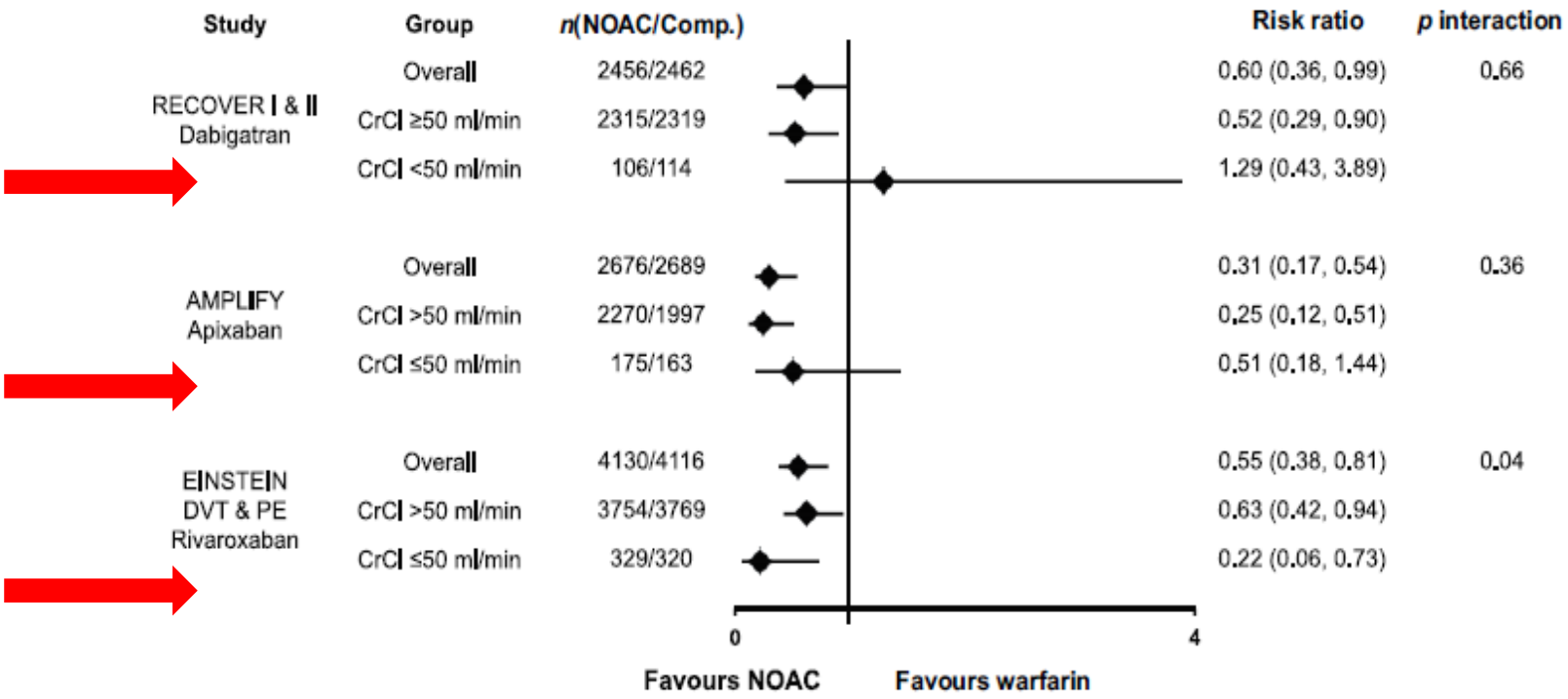


Recurrent DVT or Death related to VTE



Turpie, Ther Adv Crdiovasc Dis 2017 Sep; 11(9): 243–256.

Bleeding in VTE Treated Patients



Turpie, Ther Adv Crdiovasc Dis 2017 Sep; 11(9): 243–256.

What about Patients with “Real” Chronic Kidney Disease?

Safety and Efficacy of Apixaban Versus Warfarin in Patients With Advanced Chronic Kidney Disease

Joseph H. Schafer, PharmD[1], Ashley L. Casey, PharmD, BCPS[2], Kristina A. Dupre, PharmD[2], and Britta A. Staubes, PharmD, BCPS[2]

- Retrospective cohort design comparing CKD patients who received either warfarin or apixaban for Afib or DVT
- Primary outcome- bleeding at 3 months
- Secondary Outcomes- stroke or recurrent DVT at 3, 6 and 12 months

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Table 1. Baseline Demographic and Clinical Characteristics.

	Apixaban (n = 302)	Warfarin (n = 302)	*P* Value
Age, years, mean (SD)	73.5 (12.1)	70.6 (13.8)	0.006
Male sex, n (%)	139 (46)	163 (54)	0.01
Caucasian, n (%)	176 (58.3)	164 (54.3)	0.054
Weight, kg, median (IQR)	81.2 (68-95.6)	84.8 (68.7-99.8)	0.20
Height, inches, mean (SD)	66.5 (4.3)	67.1 (4.2)	0.08
Indication of AF, n (%)	254 (84.1)	234 (77.5)	0.039
Duration of administered medication in months, mean (SD)	8.8 (3.5)	9.7 (3.5)	0.003
CKD Stage 4, n (%)	197 (65.2)	182 (60.3)	0.21
CKD Stage 5, n (%)	105 (34.8)	120 (39.7)	0.21
Hemodialysis, n (%)	91 (30.1)	103 (34.1)	0.30
SCr, mg/dL, median (IQR)	2.3 (1.9-2.7)	2.5 (2.1-3)	0.002
CrCl, mL/min, mean (SD)	25.2 (7.9)	25.2 (8)	0.96
GFR, mL/min/1.73 m^2, median (IQR)	22 (12-26)	20.4 (11.1-26.1)	0.81
CHA_2DS_2-VASc, mean (SD)[a]	4.8 (1.6)	4.8 (1.6)	0.87
Hypertension, n (%)	248 (82.1)	234 (77.5)	0.16
Heart failure, n (%)	171 (56.6)	169 (56)	0.87
Diabetes, n (%)	142 (47)	138 (45.7)	0.74
Previous stroke, n (%)	58 (19.2)	61 (20.2)	0.76
HAS-BLED, mean (SD)[a]	3.4 (0.9)	3.3 (0.8)	0.15
Bleed previous year, n (%)	37 (12.3)	24 (8)	0.079
Aspirin, n (%)	147 (48.7)	152 (50.3)	0.68
P2Y12 inhibitors, n (%)	33 (10.9)	36 (11.9)	0.70
PPI/H2RA, n (%)	141 (46.7)	163 (54)	0.07
Apixaban dosing			
5 mg twice daily, n (%)	129 (43%)		
2.5 mg twice daily, n (%)	173 (57%)		
Apixaban dosing in AF (n = 254)			
5 mg twice daily, n (%)	104 (41%)		
Correct dosage	87 (84%)		
Incorrect dosage	17 (16%)		
2.5 mg twice daily, n (%)	150 (59%)		
Correct dosage	91 (61%)		
Incorrect dosage	59 (39%)		
Apixaban dosing in VTE (n = 48)			
5 mg twice daily, n (%)	25 (52%)		
Correct dosage	25 (100%)		
2.5 mg twice daily, n (%)	23 (48%)		
Correct dosage[b]	2 (9%)		
Incorrect dosage	21 (91%)		

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Bleeding, Stroke and Thromboembolism

Table 2. Major Bleeding, Stroke, and Thromboembolism Rates at Different Time Periods.

Outcome	Apixaban	Warfarin	
0-3 Months	n = 302	n = 302	*P* Value
Major bleeding, n (%)	25 (8.3)	30 (9.9)	0.48
Fatal bleeding, n (%)	2 (0.7)	6 (2)	0.45
Nonfatal major bleeding at a critical site, n (%)	4 (1.3)	4 (1.3)	
Other nonfatal major bleeding, n (%)	19 (6.3)	20 (6.6)	
Stroke, n (%)	1 (0.3)	2 (0.7)	1
Thromboembolism, n (%)	3 (1)	2 (0.7)	1
3-6 Months	n = 277	n = 277	
Major bleeding, n (%)	4 (1.4)	11 (4)	0.07
Fatal bleeding, n (%)	0 (0)	1 (0.4)	0.87
Nonfatal major bleeding at a critical site, n (%)	0 (0)	0 (0)	
Other nonfatal major bleeding, n (%)	4 (1.4)	10 (3.7)	
Stroke, n (%)	2 (0.7)	1 (0.3)	1
Thromboembolism, n (%)	0 (0)	2 (0.7)	0.5
6-12 Months	n = 273	n = 261	
Major bleeding, n (%)	4 (1.5)	22 (8.4)	<0.001
Fatal bleeding, n (%)	0 (0)	3 (1.1)	0.73
Nonfatal major bleeding at a critical site, n (%)	0 (0)	6 (2.3)	
Other nonfatal major bleeding, n (%)	4 (1.5)	13 (4.9)	
Stroke at 12 months, n (%)	2 (0.7)	1 (0.3)	1
Thromboembolism, n (%)	0 (0)	1 (0.3)	0.5

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What do we do with this data?

Clinicaltrials.gov

- Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation (RENAL-AF)

- Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) (AXADIA)

- Strategies for the management of Atrial Fibrillation in patiEnts receiving HemoDialysis (SAFE-HD)

Conclusion

- Increase risk of stroke and bleeding among CKD patients compared to general population

- Treatment of AF in Stage 5 CKD/dialysis is controversial
- Clinicians should continue to weigh the risk of stroke versus bleeding before prescribing warfarin or DOACs in the dialysis population with Afib.

- For DVT treatment- clinicians need to asses the risk of bleed and duration of treatment

Reversal Agents

- Idarucizumab: a specific reversal agent for dabigatran

- Andexanet for reversal of both direct and indirect Xa inhibitors