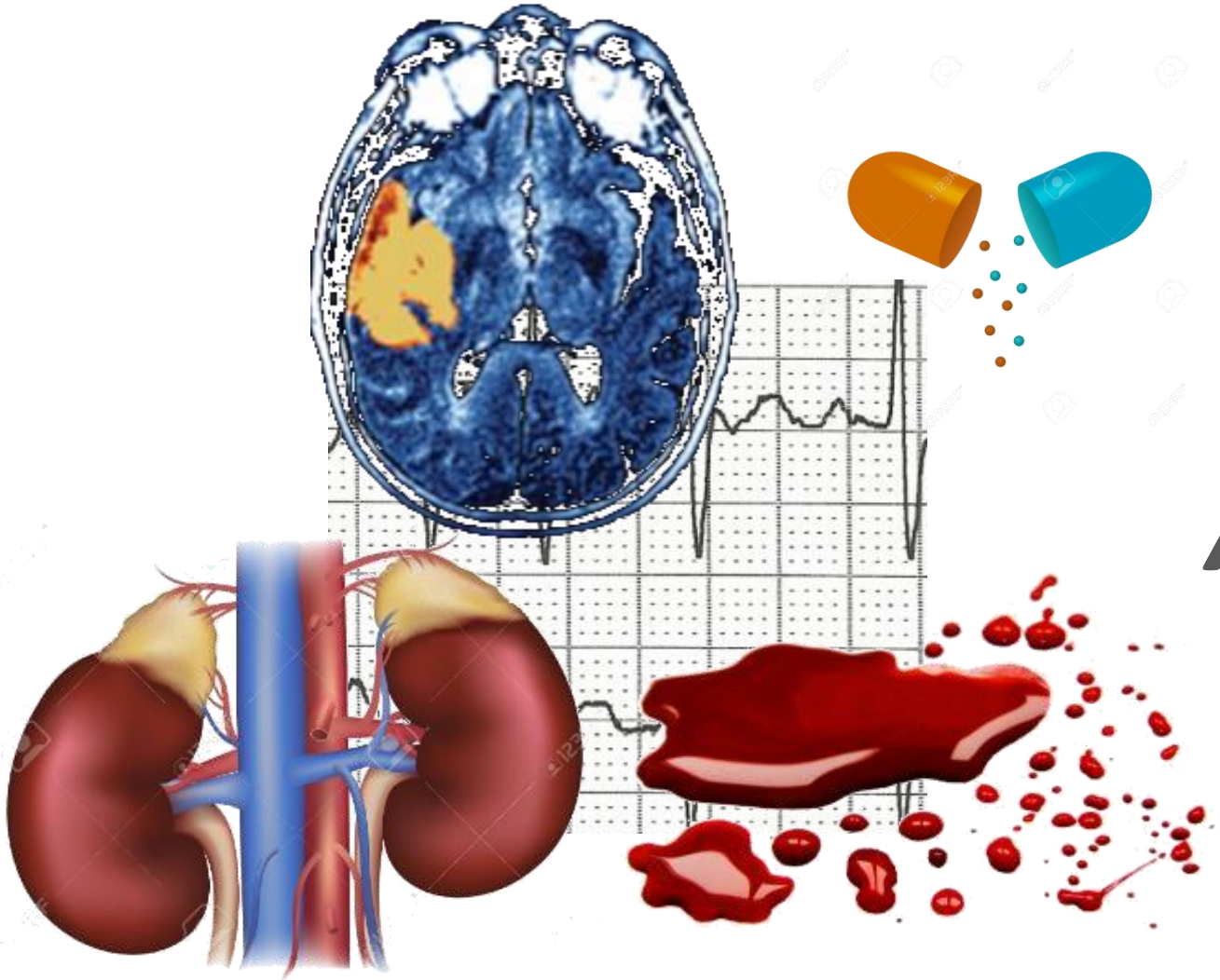
Friday & Saturday
December 5-7, 2019
Sofitel Chicago
Magnificent Mile

AF, VT, VF Summit 2019

This year's Summit dedicated to Masood Akhtar, MD

In Memoriam



Anticoagulation Therapy in 2019

Are we There Yet?

A. John Camm

St George's University of London

Declaration of Competing Interests

Guidelines: Chairman: ESC Guidelines on Atrial Fibrillation, 2010 and Update, 2012; ACC/AHA/ESC Guidelines on VAs and SCD; 2006; NICE Guidelines on ACS and NSTEMI, 2012; NICE Guidelines on Heart Failure, 2008; Member: NICE Guidelines on AF, 2006; ESC VA and SCD Guidelines, 2015; Reviewer: AHA/ACC/HRS Guidelines on AF, 2014; ACC/AHA/HRS SVT Guidelines, 2015; ESC AF Guidelines, 2016.

Steering Committees: multiple trials involving antiarrhythmic agents, heart failure drugs, novel anticoagulants, ablation [illegible]
Data Safety Management Boards: multiple trials of devices and drugs.
Events Co[illegible] [illegible] CV adverse effects.

Editorial Role: Editor-in-Chief, EHJ-Case Reports and Clinical Cardiology; Editor, European Textbook of Cardiology, Europea[illegible]diology.

Consultant/Advisor/Speaker: Allergan, Acesion, Huya, Incarda, Menarini, Milestone, Sanofi, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Portola, Boston Scientific, Abbott, Biotronik, Medtronic, Johnson and Johnson

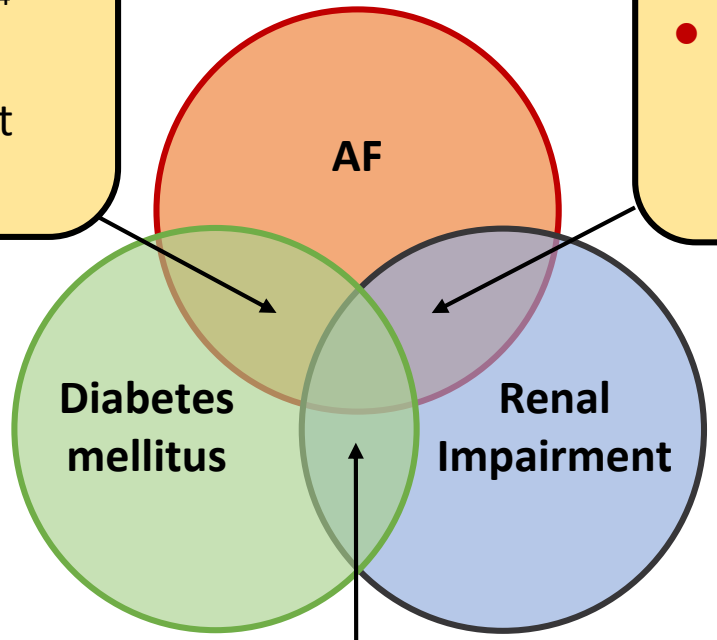
Charities: Trustee of the Drug Safety Research Unit, the Atrial Fibrillation Association and the Arrhythmia Alliance
Directorship: Richmond Pharmacology limited

Consultant/Advisor/Speaker: Allergan, Alta Thera, Astellas, Acesion, Huya, Incarda, Merck, Menarini, Milestone, Sanofi, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Portola, Boston Scientific, Abbott, Biotronik, Medtronic, GlaxoSmithKline, InfoBionic, Cardiac Insight, Johnson and Johnson, Radius

Overlapping Comorbidities Increase the Complexity of Stroke Prevention in AF Patients

- Up to **40%** of AF patients have DM[1–3]
- DM is an independent risk factor for stroke in patients with AF (RR: 1.7)[4]
- Risk of death following a stroke is greater for patients with vs without DM[5]

- **25-35%** of patients with AF have renal impairment[6]
- CKD is associated with an increased risk of developing AF and vice versa[7], as well as bleeding [8,9]

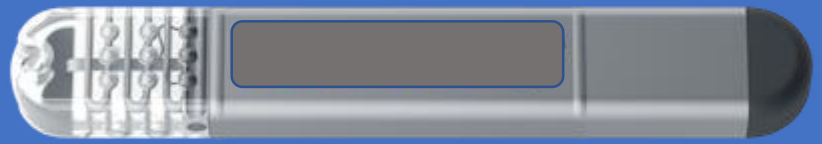


- Microvascular complications in DM can damage the kidneys[10]
- Diabetic kidney disease occurs in around one-third of patients with type 2 DM[11]

1. Patel MR et al. N Engl J Med 2011;365:883–891; 2. Giugliano RP et al. N Engl J Med 2013;369:2093–2104; 3. Granger CB et al. N Engl J Med 2011;365:981–992; 4. The Stroke Risk in Atrial Fibrillation Working Group. Neurology 2007;69:546–554; 5. Bansilal S et al. Am Heart J 2015;170:675–682.e8; 6. Boriani G et al. Sci Rep 2016;6:30271; 7. Boriani G et al. Europace 2015;17:1169–1196; 8. Kirchhof P et al. Eur Heart J 2016;37;2893–2962; 9. Olesen JB et al. N Engl J Med 2012;367:625–635; 10. Beckman JA et al. JAMA 2002;287:2570–2581; 11. Pecoits-Filho P et al. Diabetol Metab Syndr 2016;8:50.

AF on ILR Recordings during Dialysis
Number and Rate of AF Events

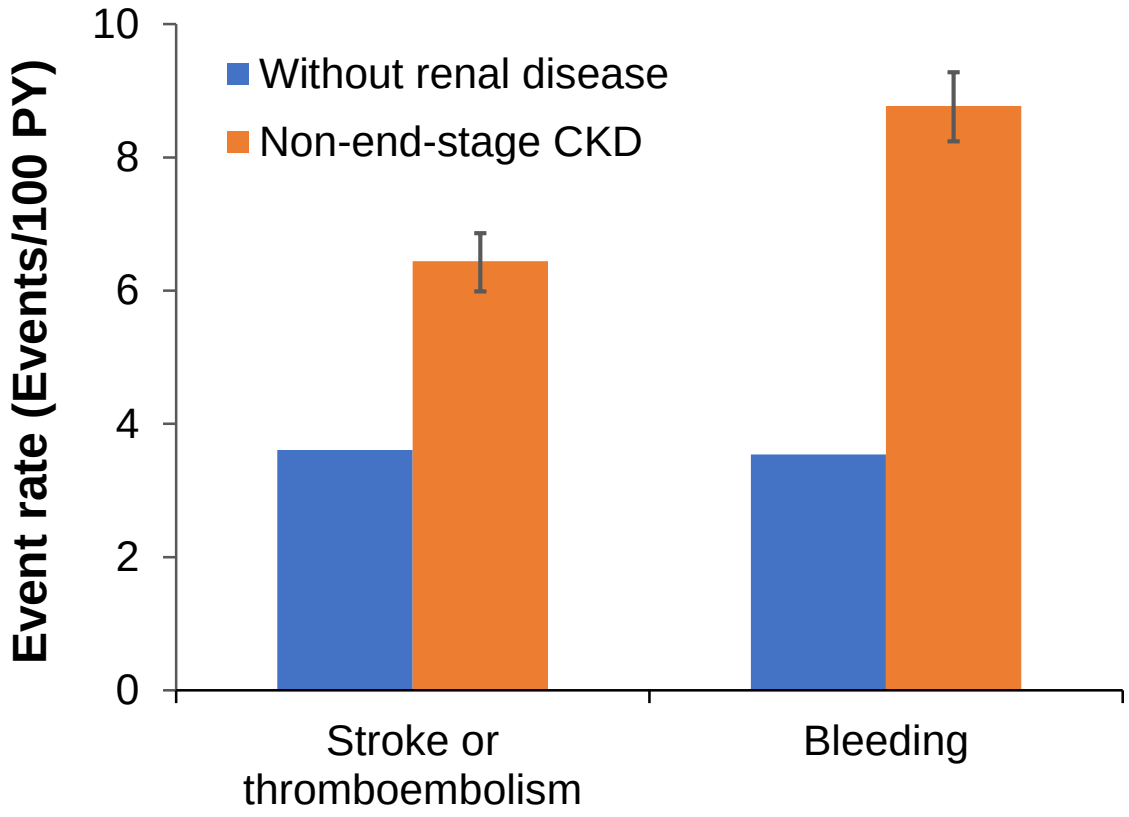
66 patients on maintenance hemodialysis (mean age 56, 70% male) underwent ILR placement.

	ILR detected AF	ILR Detected AF ≥6 Minutes
Number of Events	**4419**	**1710**
Subjects with Events (% of Subjects with Any ILR Data)	**27 (41%)**	**23 (35%)**
Estimated Events Per Patient Month [95% CI Bounds]	**11.9 [4.9,28.7]**	**4.62 [1.8,11.5]**

Koplan et al –Clinical Cardiology – in press

Why Does Kidney Disease Matter?

Patients with NVAF and renal impairment are at higher risk of bleeding and stroke

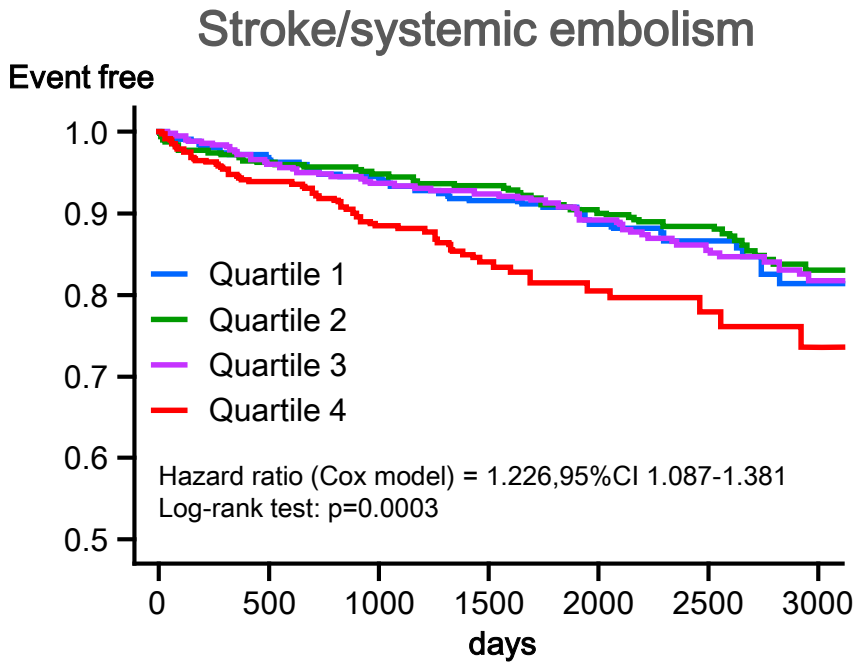


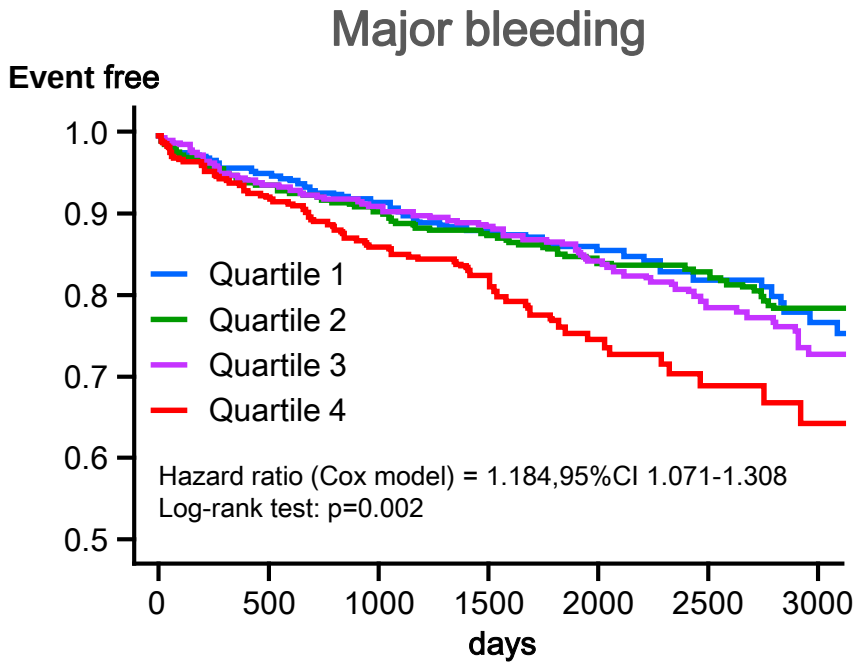
Large Danish cohort study (N=132,372) in AF patients with chronic kidney disease. 28% of patients with no renal disease received warfarin.

Olesen JB et al. N Engl J Med 2012;367:625–635.

CV Risk (Stroke or Bleeding) is Aggravated by deterioration of Renal Function

Event non-incidence rates in AF patients by quartile of annual eGFR change





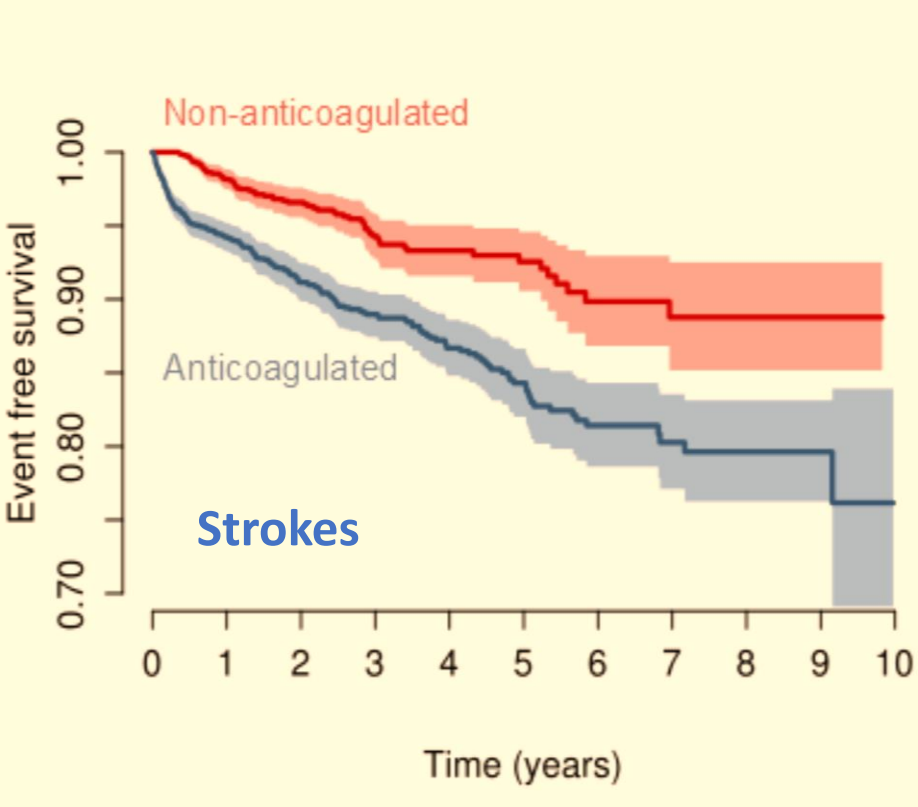
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
No. of patients	661	662	666	664
eGFR change (mL/min/1.73m²/year)	> 1.56	1.56 to -1.25	-1.25 to -4.81	< -4.81

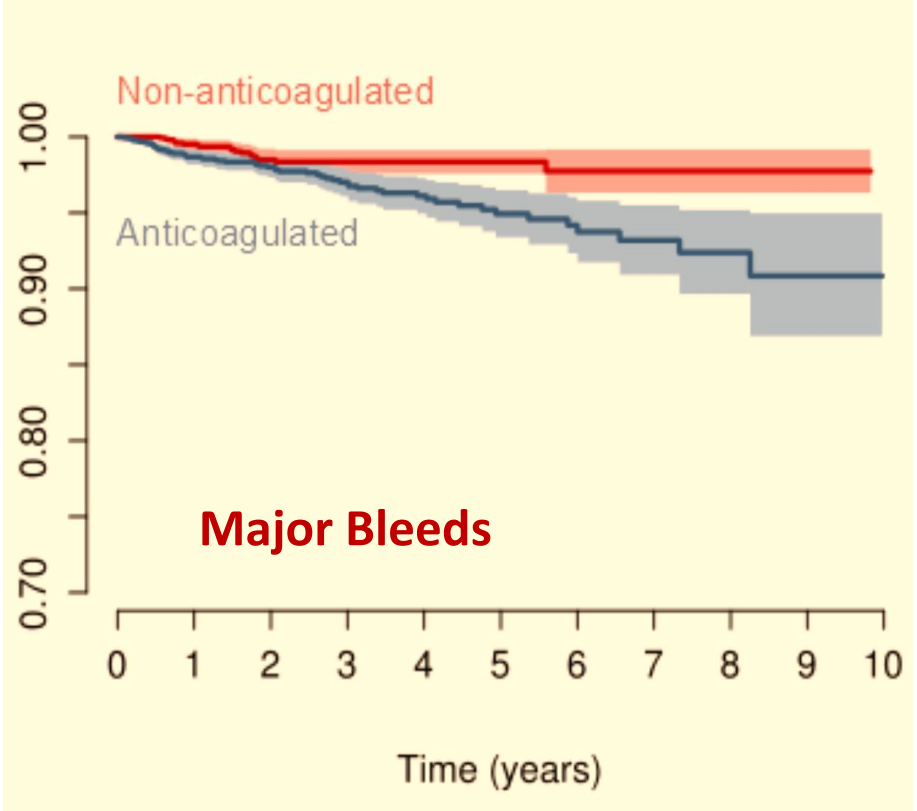
Subjects and methods: We retrospectively analyzed 2,653 patients with AF at a single site in France between 2000 and 2010. Mean observation period: 1499 days. Treatment with VKA: 62-68%.

Fauchier L et al, Am Heart J 2018;198:39-45

Elderly AF Patients with Chronic Kidney Disease receiving Anticoagulation

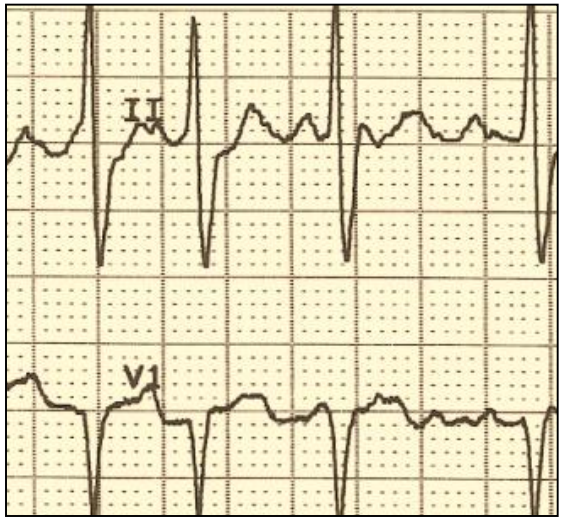
Patients aged 65 years and over with a new diagnosis of AF and eGFR of <50 ml/min/1.73 m^2
2,434 pairs using propensity scores by exposure to anticoagulant and followed for a median of 506 days

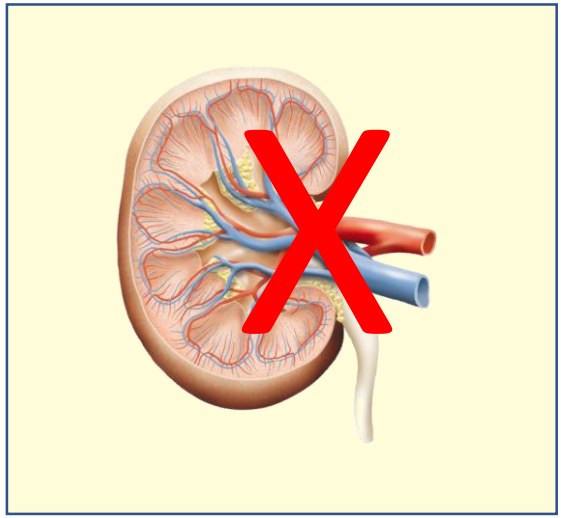




Kumar S, et al. BMJ 2017

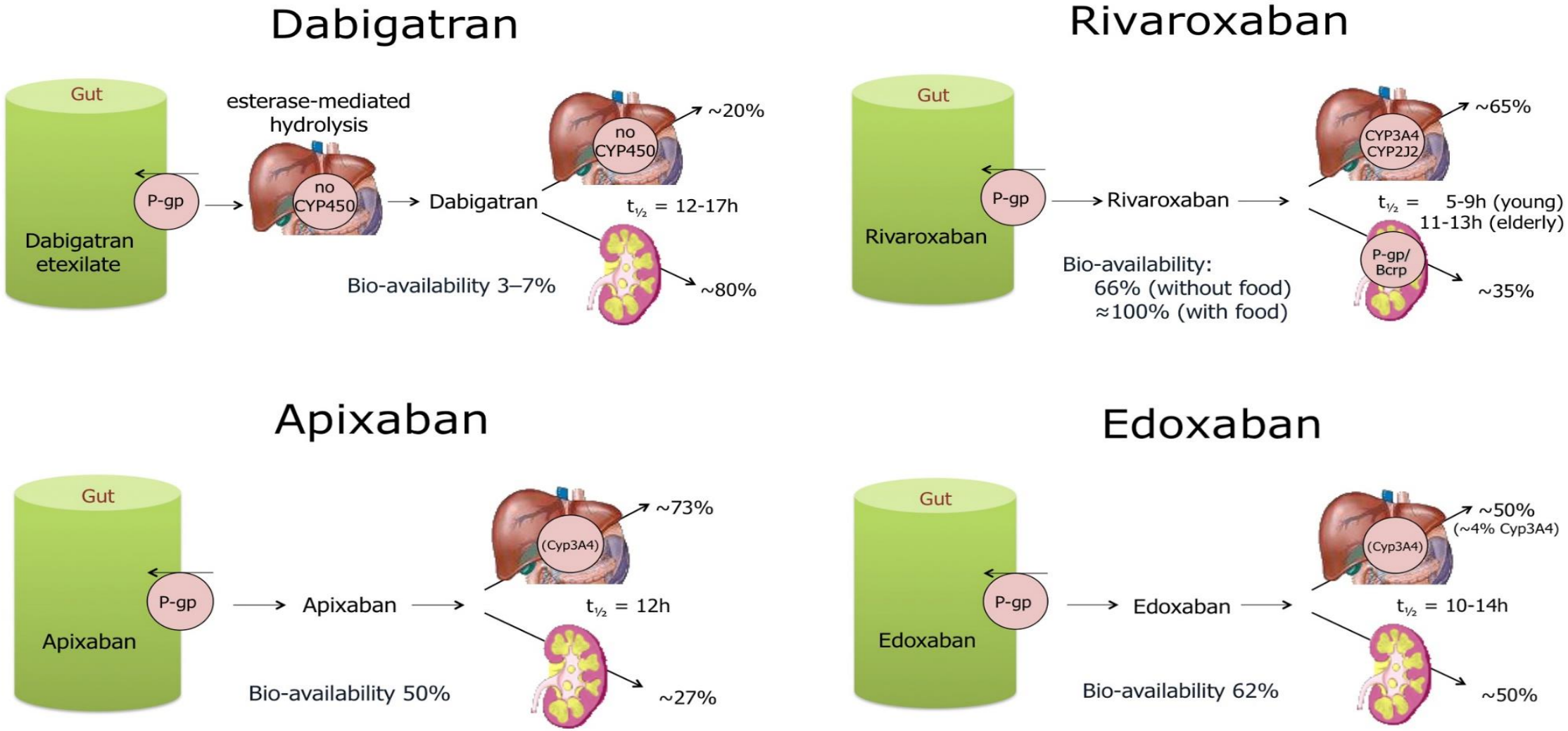
Warfarin in Patients with AF and ESRD





Study	Design	Number of patients	Outcome on warfarin vs no warfarin
Lai, 2010	Retrospective cohort	93	Warfarin effective against ischemic stroke
Winkelmayer, 2011	Prospective cohort	1185	No effect on overall stroke
Wizemann, 2010	Prospective cohort	17,513	Warfarin increased risk of stroke 2-fold in over 75 y.o.
Phelan, 2011	Retrospective cohort	845	Warfarin increased risk of hemorrhagic stroke 2-fold
Chan, 2009	Retrospective cohort	1671	Warfarin increased risk of stroke 2-fold
Wiesholzer, 2001	Retrospective cohort	430	Warfarin increased risk of stroke 3-fold
Wang, 2016	Prospective cohort	141	Warfarin increased risk of ICH 11-fold; no difference in SE
Dahal, 2016	Meta-analysis of 6 retro- and 5 prospective cohorts	48,500	No effect on stroke/SE, 1.3-fold risk of ICH
Liu, 2016	Meta-analysis of 11 studies	25,407	No effect on stroke/SE, 1.27-fold risk of MB

Absorption, Metabolism and Elimination
Different NOACs



Heidbuchel H et al. Europace 2013;15:625-651

Oral Anticoagulants
Pharmacokinetics in Renal Disease

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	VKA	IIa	Xa	Xa	Xa
Hours to C_{max}	3 days	1.25–3	2–4	3–4	1–2
Half-life: normal renal function	**35 h**	**14 – 17 h**	**7 – 8 h**	11-12 h	**9-10 h**
Half life: CrCl<30 ml/min	**35 h**	**27 h**	**10 h**	N/A	**17 h**
Dose for SPAF	Variable	150 mg BID	20 mg OD	5 mg BID	60 mg OD
Dose in CKD	Variable OD	110 mg BID CrCl<50	15 mg OD CrCl<50	2.5 mg BID **CrCl<30***	30mg OD CrCl<50
Lowest allowed CrCL	-	**30ml/min**	15ml/min	15ml/min	15ml/min
Dialysis effect	Not effective	62-68% drug removal	Not effective	Not effective	Not effective

*If accompanied by one of the following criteria: 1) Age >80 years, body weight ≤60 kg
As there have been no head to head trials; it is not possible to make comparisons between the DOACs

- In the absence of hard endpoint studies it is advised to avoid the routine use of NOACs in patients with severe renal dysfunction (CrCl <15 mL/min) as well as in patients on dialysis[1]

Table adapted from Mar et al. Int J Cardiol 2016; 202:578–85

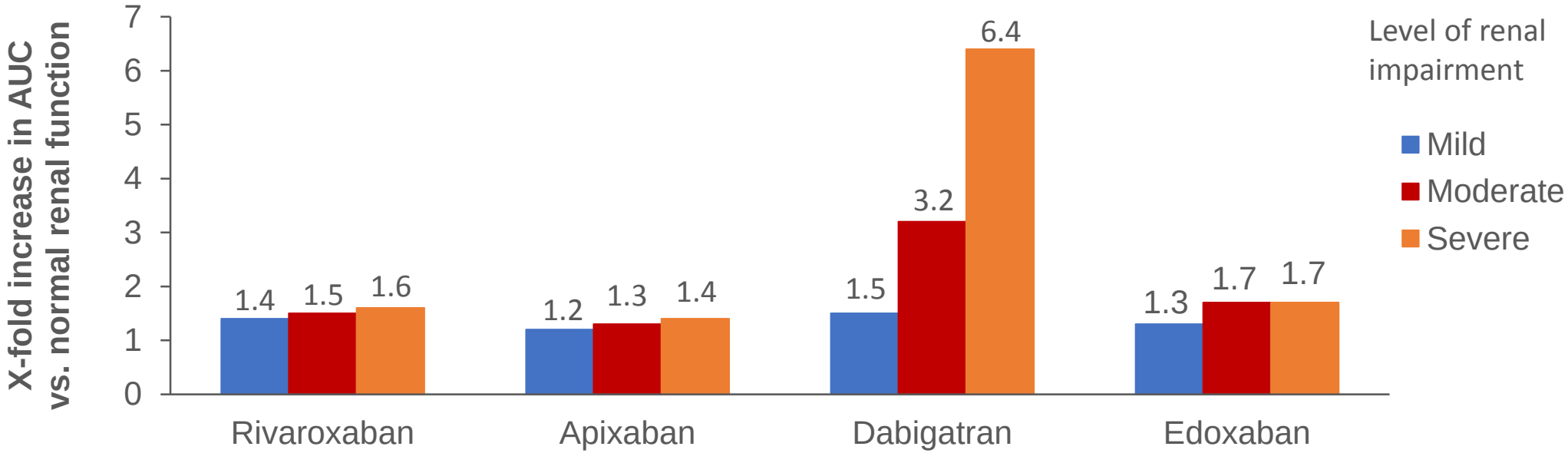
1. Steffel J, et al. Eur Heart J. 2018;39:1330–93.

Patients With Renal Impairment:

Higher Exposure for Dabigatran vs Factor Xa Inhibitors

Renal clearance (of absorbed dose)[1]	33%	27%	80%	~50%

Dabigatran is predominantly renally excreted



Dabigatran is contraindicated for patients with CrCl <30ml/min

NOTE: Graphs based on data in respective SmPCs. No head to head comparison. Data for edoxaban are currently not available.

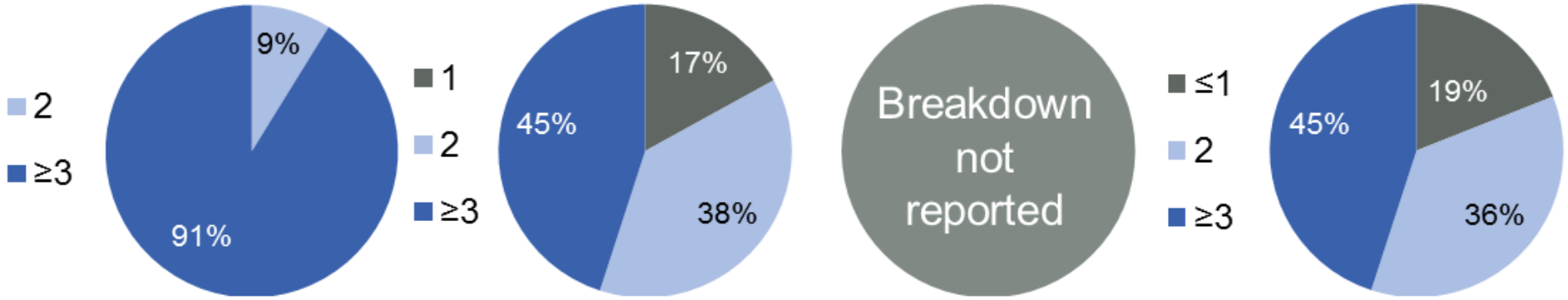
1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3. Dabigatran SmPC; 4. Stangier J et al. Clin Pharmacokinet. 2010;49(4):259–268;

Patients with Renal Impairment in the Phase III NOAC Trials

Renal impairment

	ROCKET AF[1]	ARISTOTLE[2]	ENGAGE AF[3]	RE-LY[4]
Proportion of patients	**N=2950 (20.7%)**	**N=3017 (16.6%)**	**N=2740 (19.5%)**	**N=3374 (18.9%)**
Mean $CHADS_2$ score	**3.7**	**2.6**	**3.1**	–
CHF, %	65.7	32.7	55	32.6
Hypertension, %	91.9	84.9	92	85.6
Diabetes mellitus, %	32.5	21.1	28	29.1
Prior stroke/TIA/SE, %	49.6	25.1	30	20.1[#]

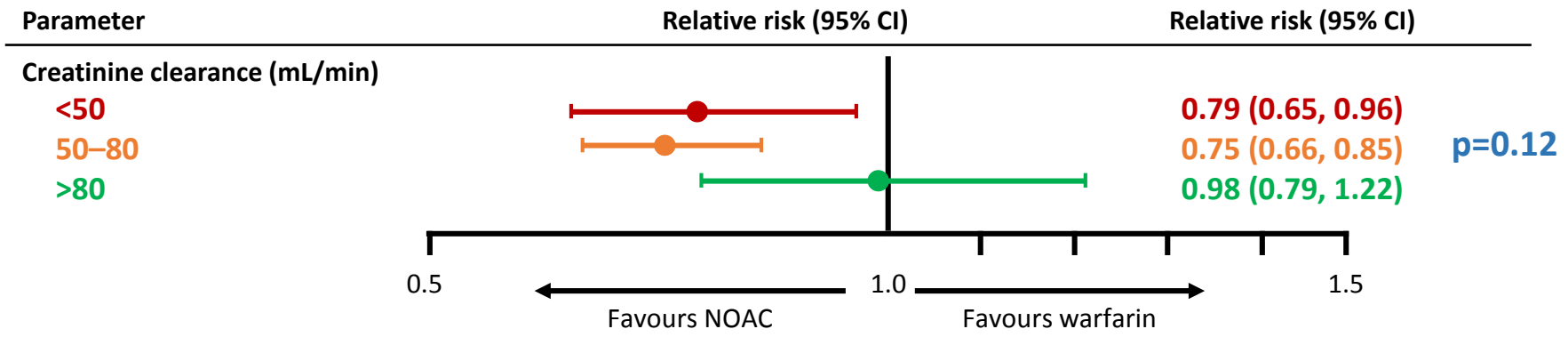
$CHADS_2$ score



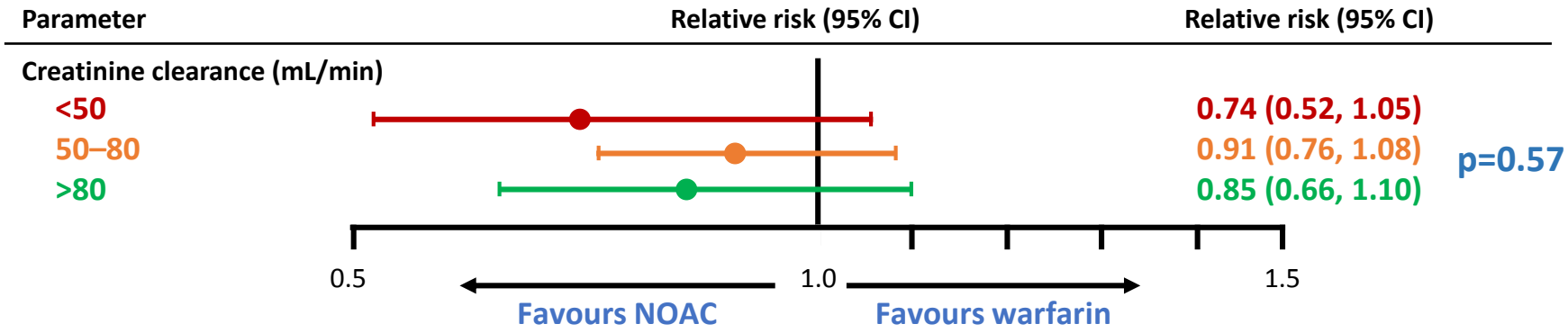
1. Fox KAA et al, Eur Heart J 2011;32:2387–2394; 2. Hohnloser SH et al, Eur Heart J 2012;33:2821–2830; 3. Bohula EA et al, Circulation 2016;134:24–36
4. Hijazi Z et al, Circulation 2014;129:961–970

Meta-analysis of All NOACs vs Warfarin
Renal Function Subgroups

Stroke or SEE



Major bleeding

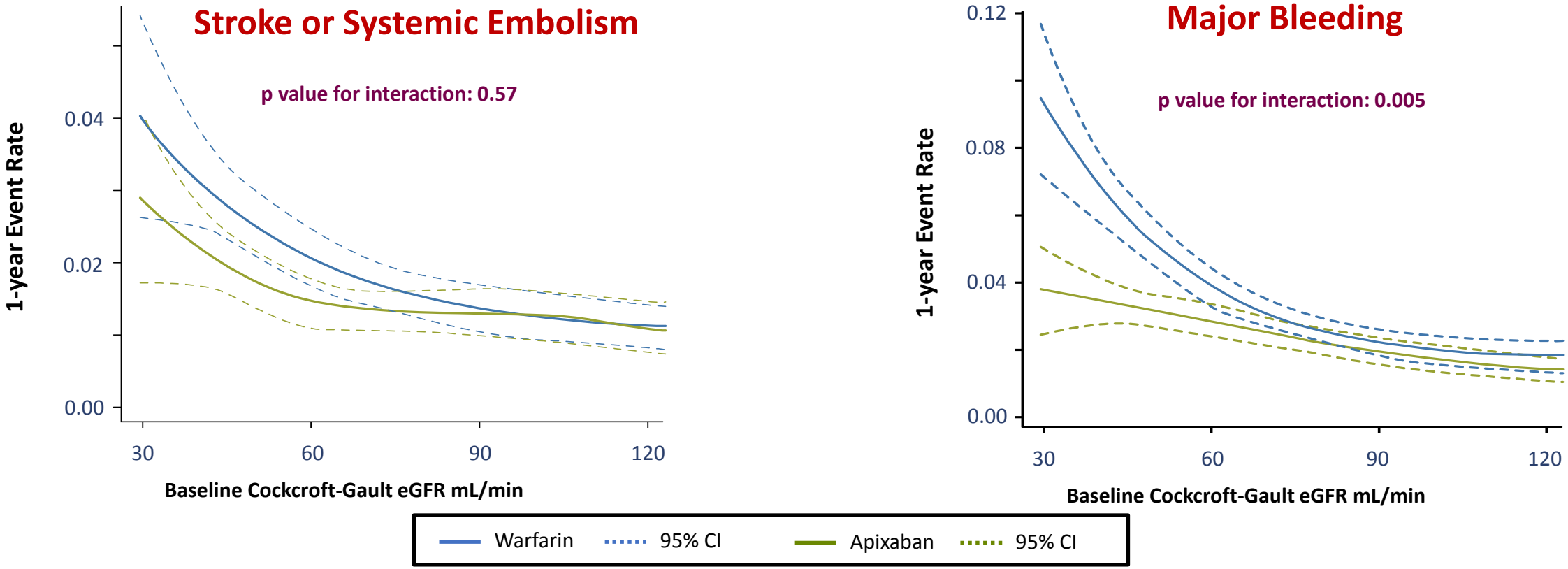


CI, confidence interval; NOAC, novel oral anticoagulants; SEE, systemic embolic events

Ruff CT, et al. Lancet 2014;383:955-62

ARISTOTLE: Apixaban versus Warfarin According to Renal Function

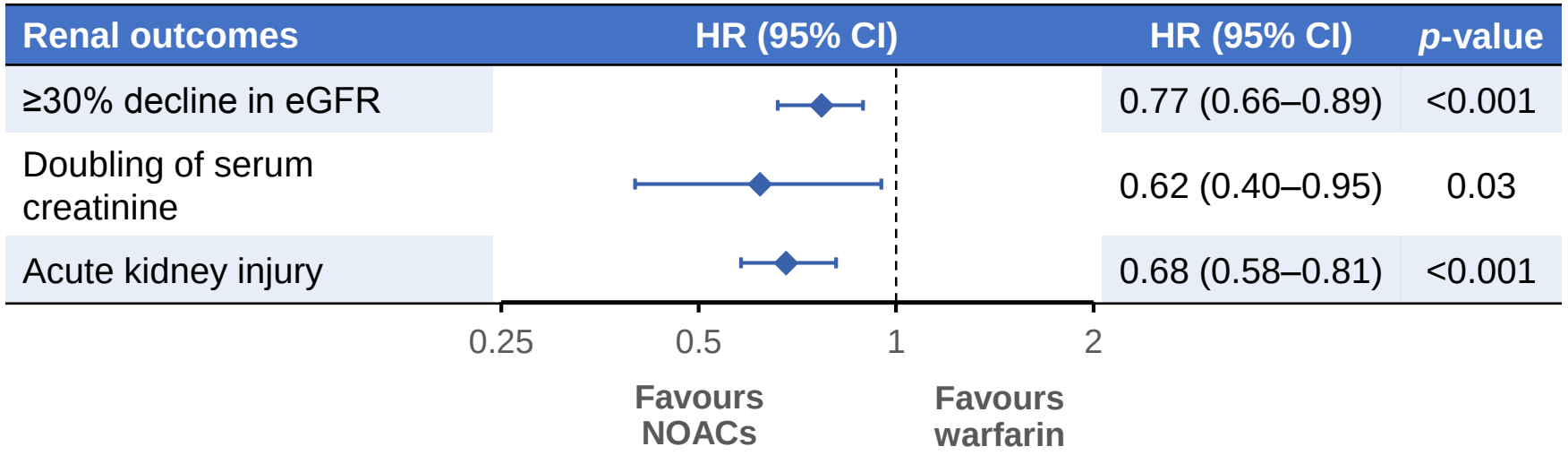
7518 patients (42%) with an estimated GFR (eGFR) of >80 mL/min, 7587 (42%) between 50 and 80 mL/min, and 3017 (15%) with an eGFR of ≤50 mL/min



Hohnloser SH, et al. Eur Heart J 2012;33:2821–2830

Renal Outcomes in AF Patients on NOACs

- At 2 years, the cumulative risk was
  - 24.4% for ≥30% decline in eGFR
  - 4.0%, doubling of serum creatinine
  - 14.8% for AKI
  - 1.7% for kidney failure
- Compared with warfarin, the use of NOACs was associated with reduced risks of ≥30% decline in eGFR, doubling of serum creatinine and acute kidney disease



Yao X et al, J Am Coll Cardiol 2017;70:2621–2632

RIVAL: Rivaroxaban Associated with Lower Risk of Acute Kidney Injury or Progression to Stage 5 CKD Than Warfarin

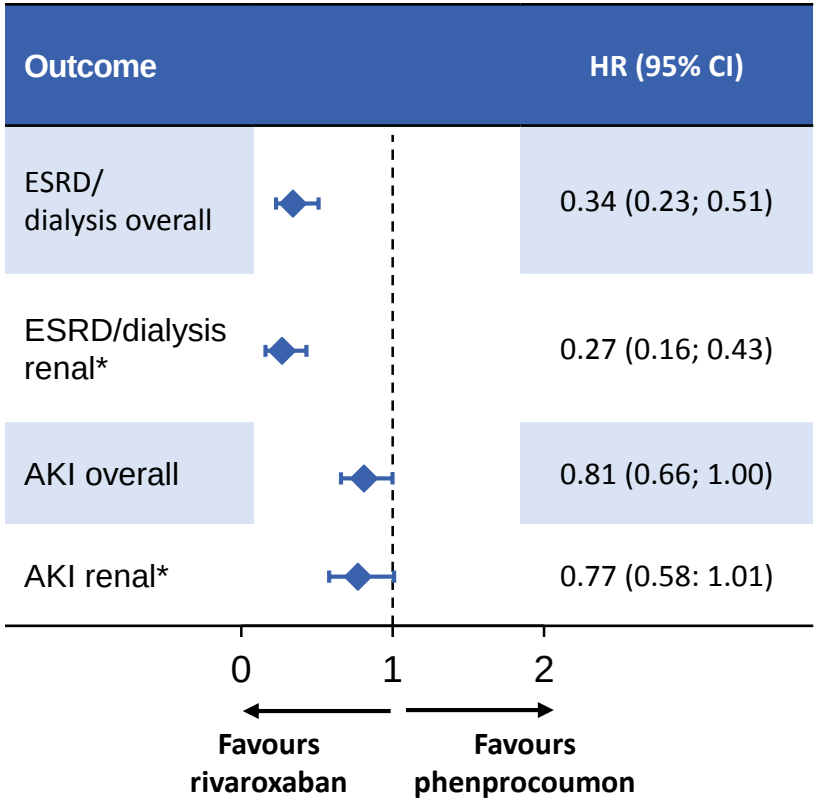
- Analysis of US Truven MarketScan claims data for patients with NVAF initiating rivaroxaban or warfarin
  - Patients with stage 5 CKD or on haemodialysis at baseline excluded

	Event rate (per 100 person-years)		HR (95% CI)	HR (95% CI)
	Rivaroxaban N=36,318	Warfarin N=36,281		
AKI	**4.91**	**8.45**		**0.81 (0.75–0.87)**
Stage 5 CKD or dialysis	**2.67**	**4.12**		**0.82 (0.74–0.91)**

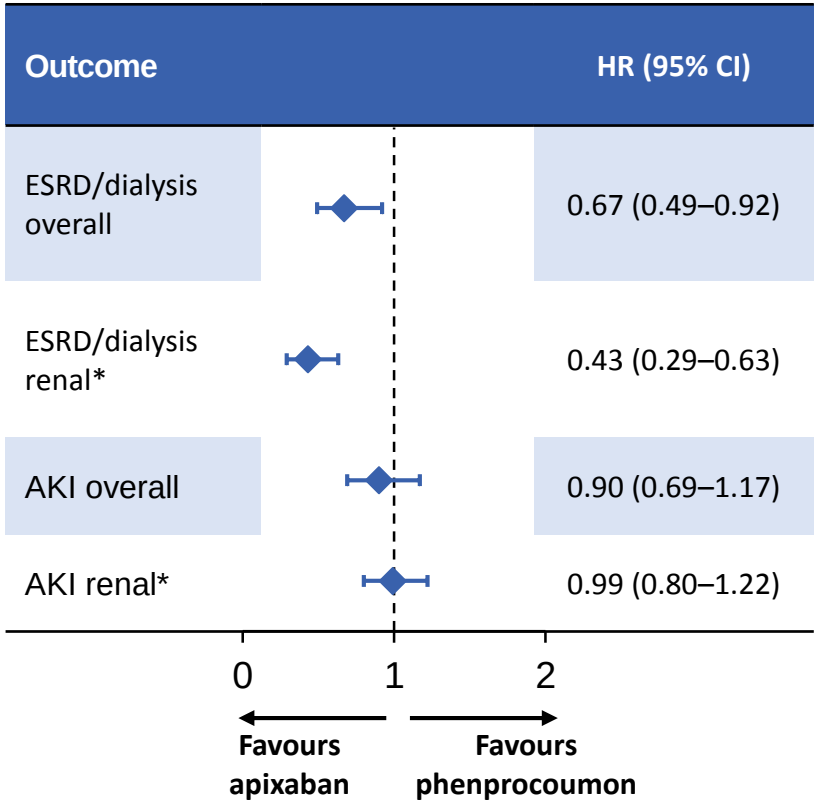
Coleman CI et al, presented at ESOC 2019 (Abstract AS25-017)

RELOADED: Rivaroxaban and Apixaban Showed Risk Reductions for ESRD/Dialysis, and Only Rivaroxaban Showed Benefit for AKI

Rivaroxaban vs phenprocoumon



Apixaban vs phenprocoumon



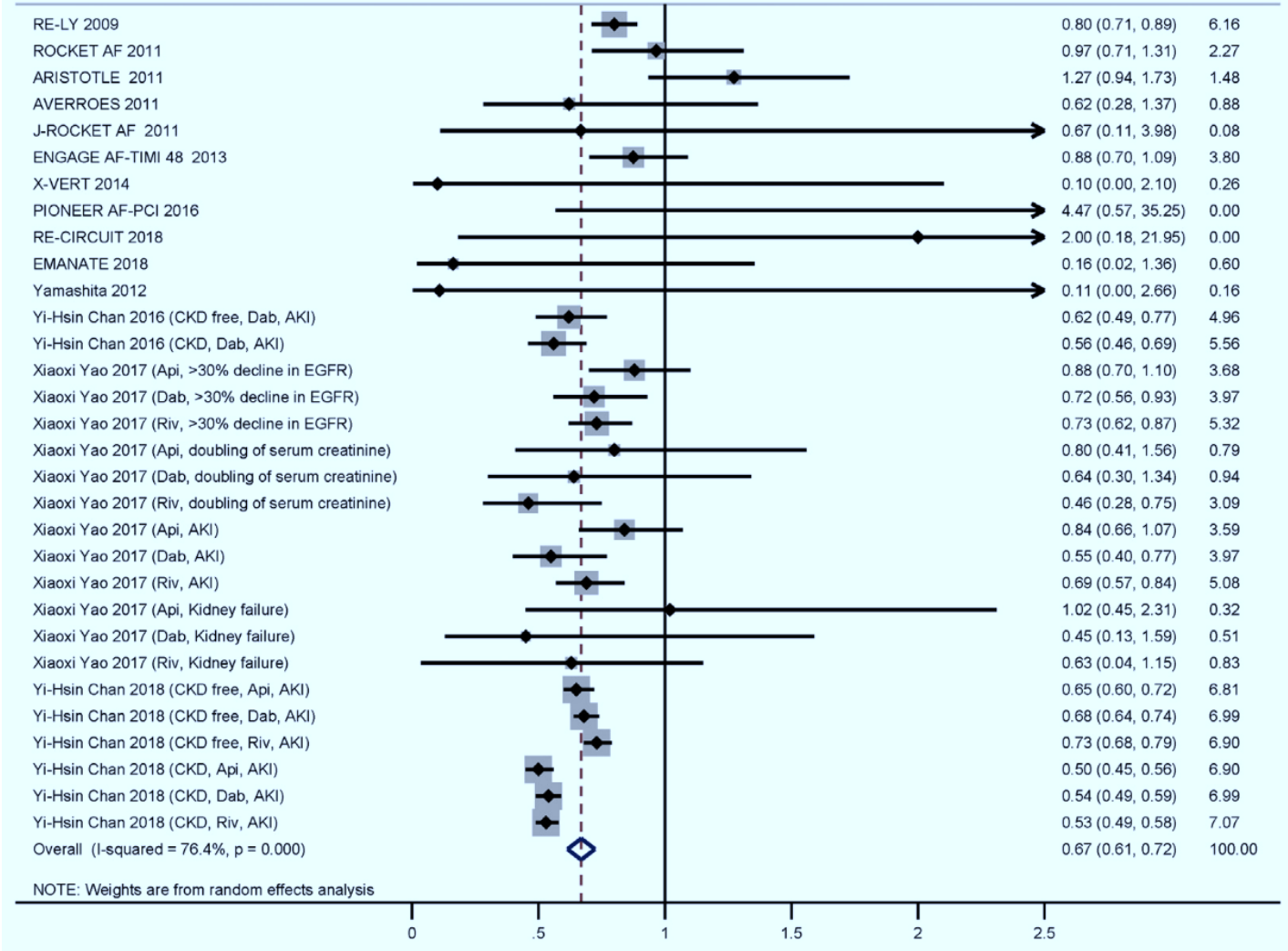
*Renal insufficiency subgroup defined by following ICD-10 codes: D63.1, E10.2, E11.2, E13.2, I12, I13, N02, N03, N04, N05, N07, N08, N14, N18.1-N18.4, N18.9, N19, Q61.

Bonnemeier H et al. Presented at ESOC 2019, Milan, Italy, AS25-066.

Risk of Renal Impairment in Patients with NOACs vs. VKAs/ASA

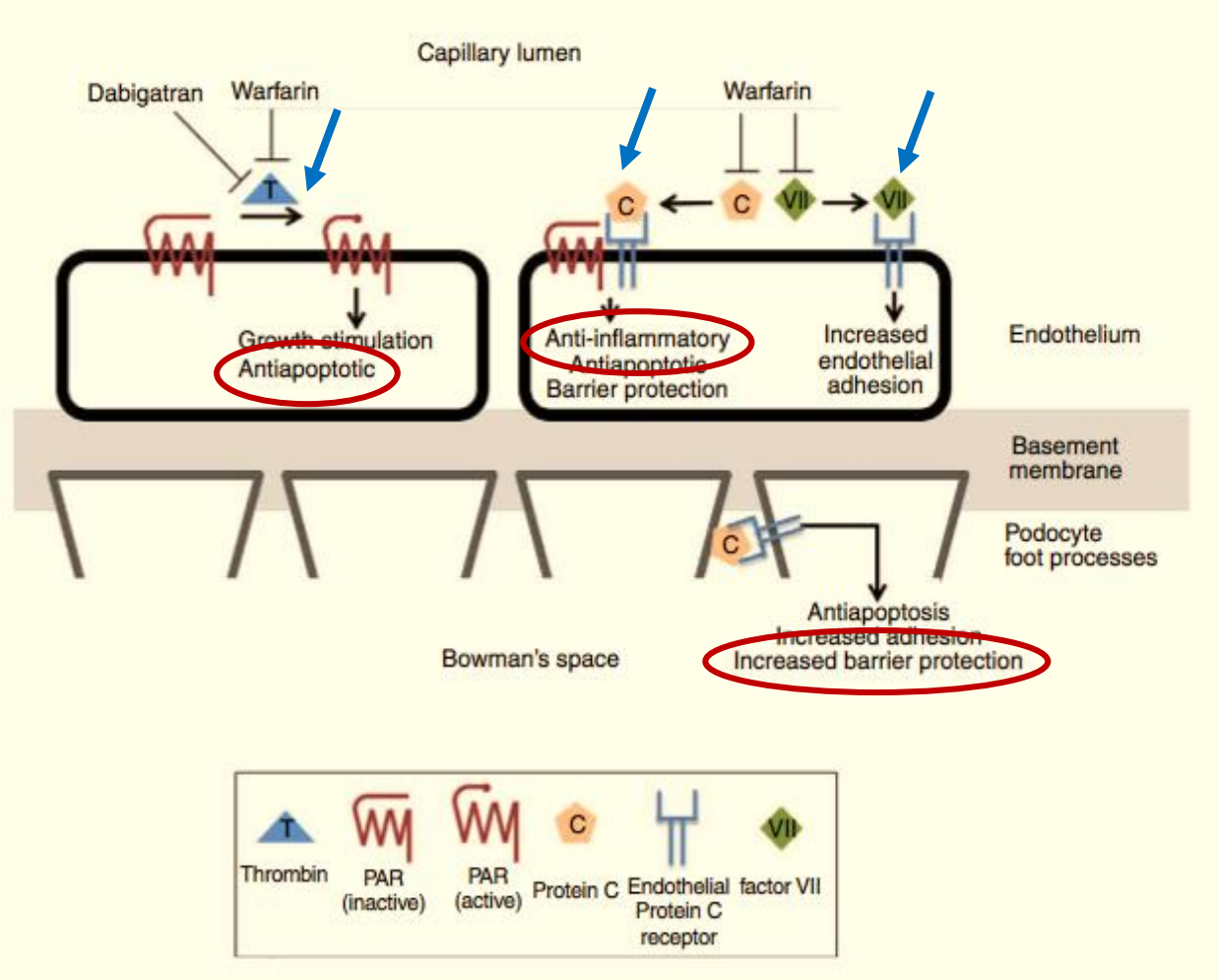
11 RCTs and
3 observational studies
189,483 (119,188 patients with NOACs and 70,295 patients with VKA/ASA)

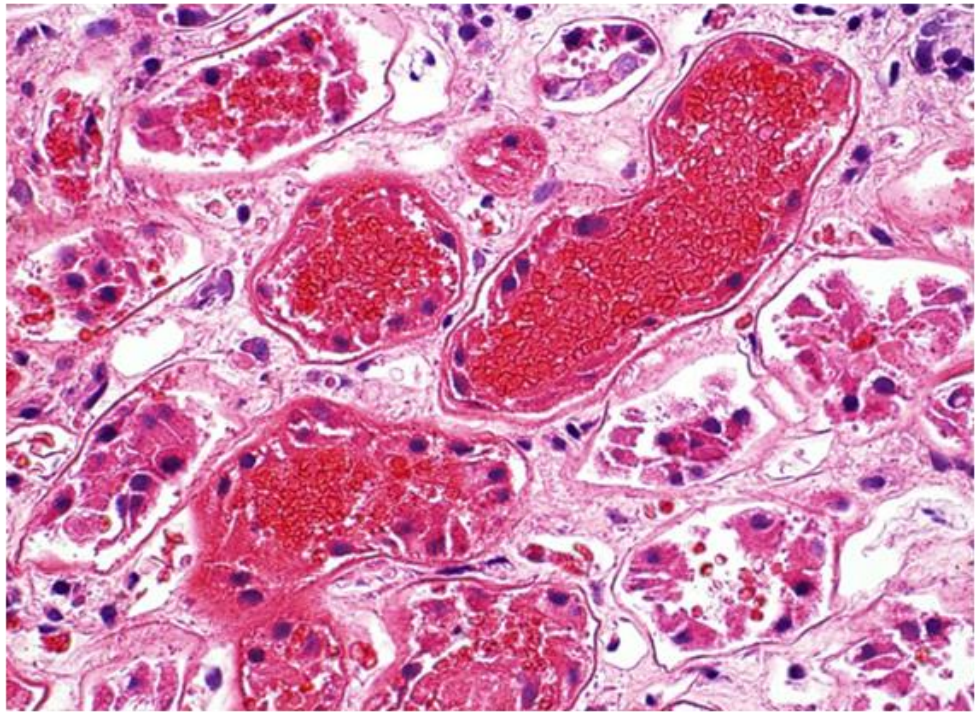
33% reduction in renal impairment with NOACs



Zhang C, et al. Thrombosis Research 2019;174:16-23

Anticoagulation-Related Nephropathy and AKI

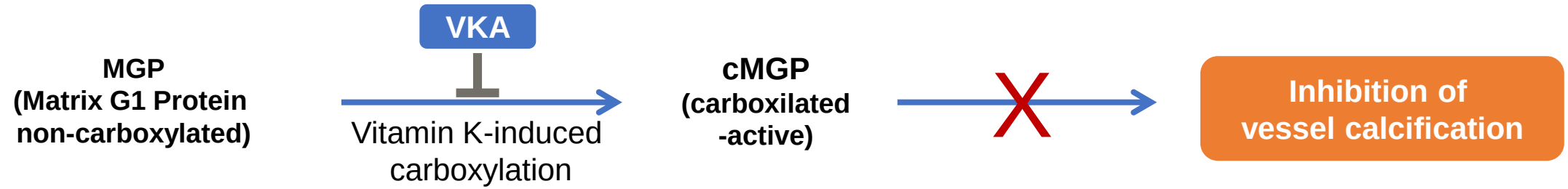




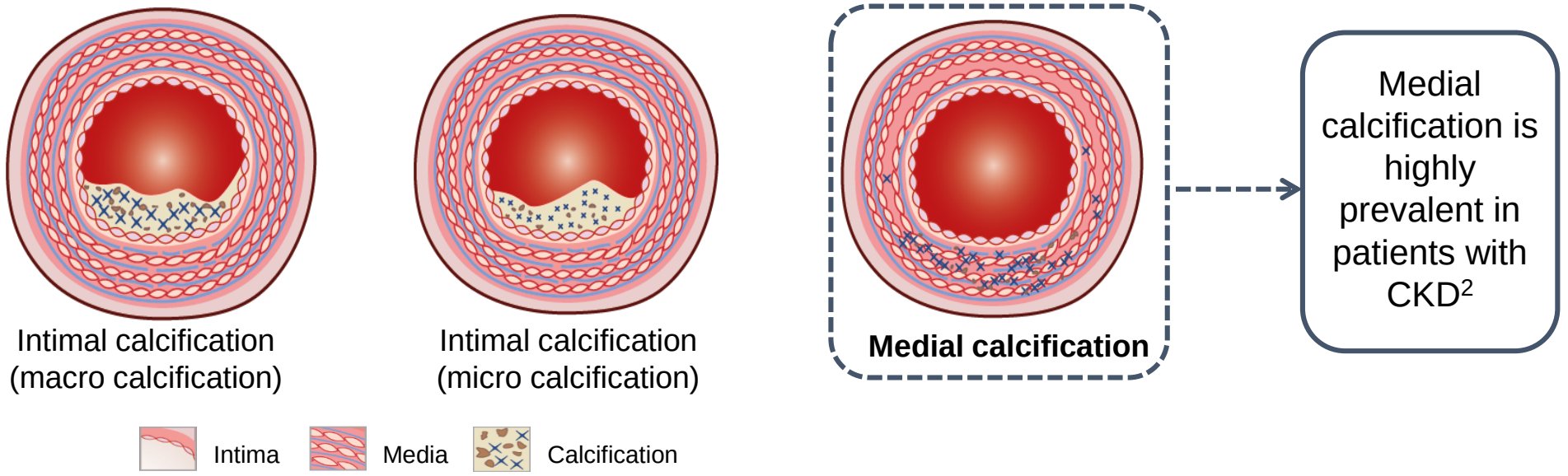
Microscopic pathology of patient with anticoagulation-related nephropathy

Wheeler DS et al. J Thromb Haemost 2016;14:461–467

VKAs Promote Vascular Calcification and Decline in Renal Function

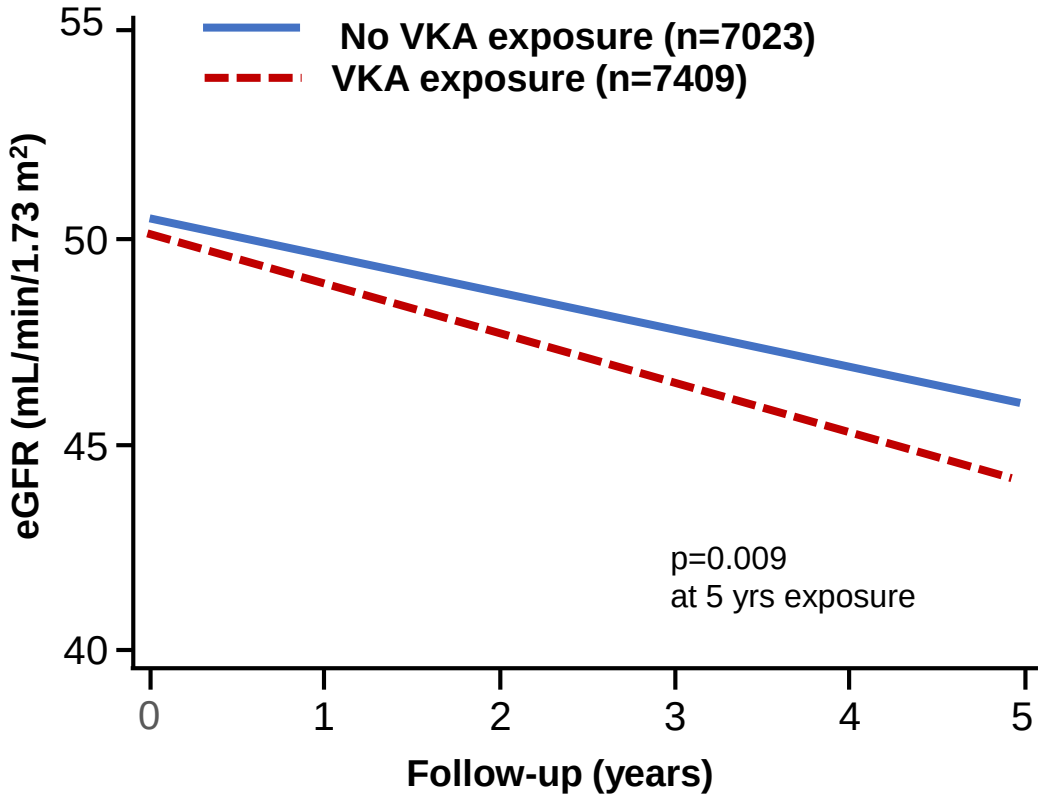


MGP is the main inhibitor of vascular calcification, and vitamin K is required for full activity of MGP[1]

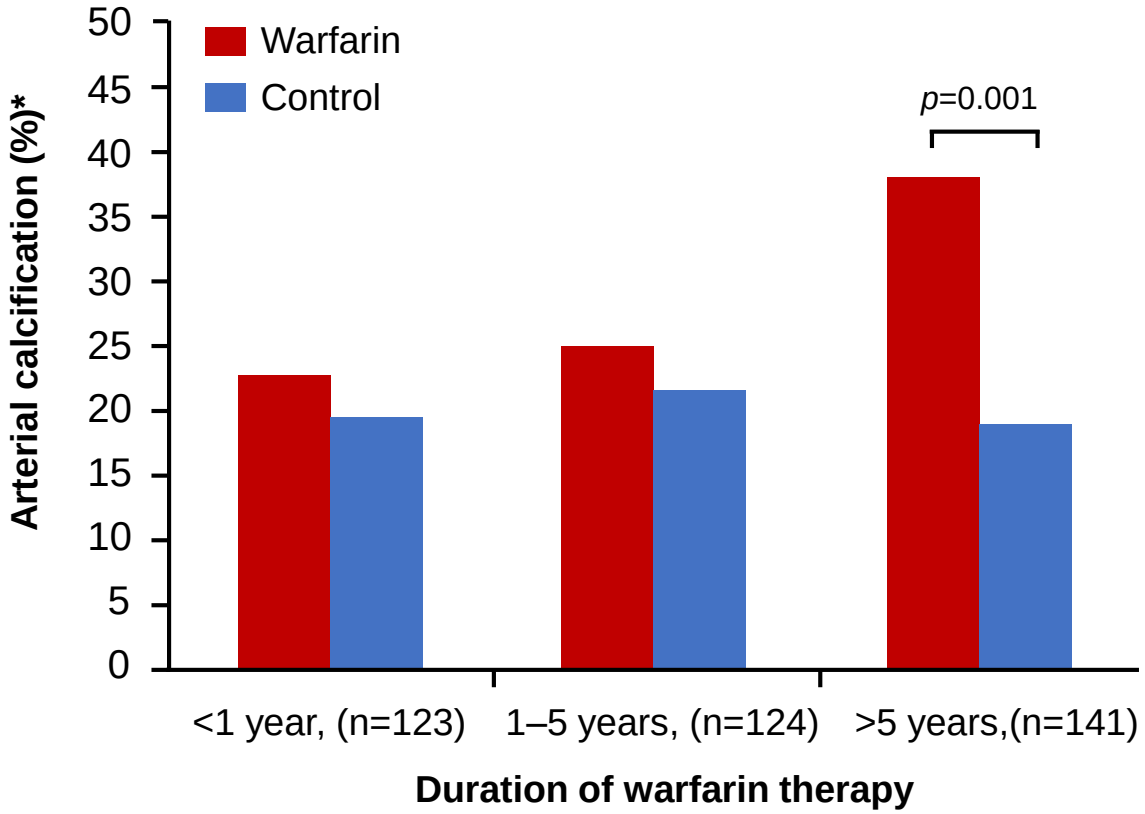


1. Van Gorp RH, Schurgers LJ. Nutrients 2015;7:9538–9557; 2. Willems BAG et al. Mol Nutr Food Res 2014;58:1620–1635.

Effects of VKA on Calcification



In patients with AF and CKD, renal function declines faster in those with VKA exposure vs no VKA exposure[1]



Arterial calcification is increased in warfarin-treated patients vs control patients[2]

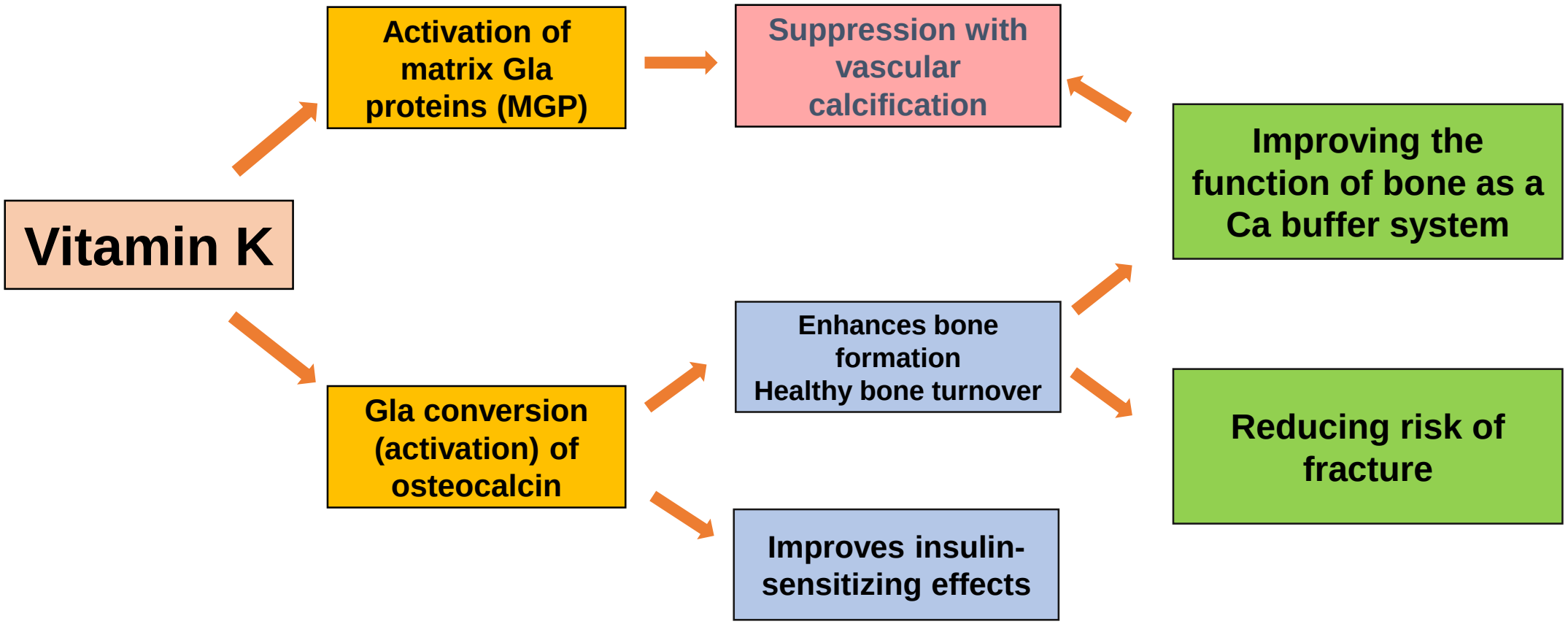
*Calcification analysis in X-rays of lower extremity arteries at knee level and below.

chi-square test

1. Posch F, et al. Presented at ÖGIM 2017, poster 07; 2. Han KH, O'Neill WC. *J Am Heart Assoc* 2016;5:e002665.

Vitamin K is Required to Inhibit Vascular Calcification

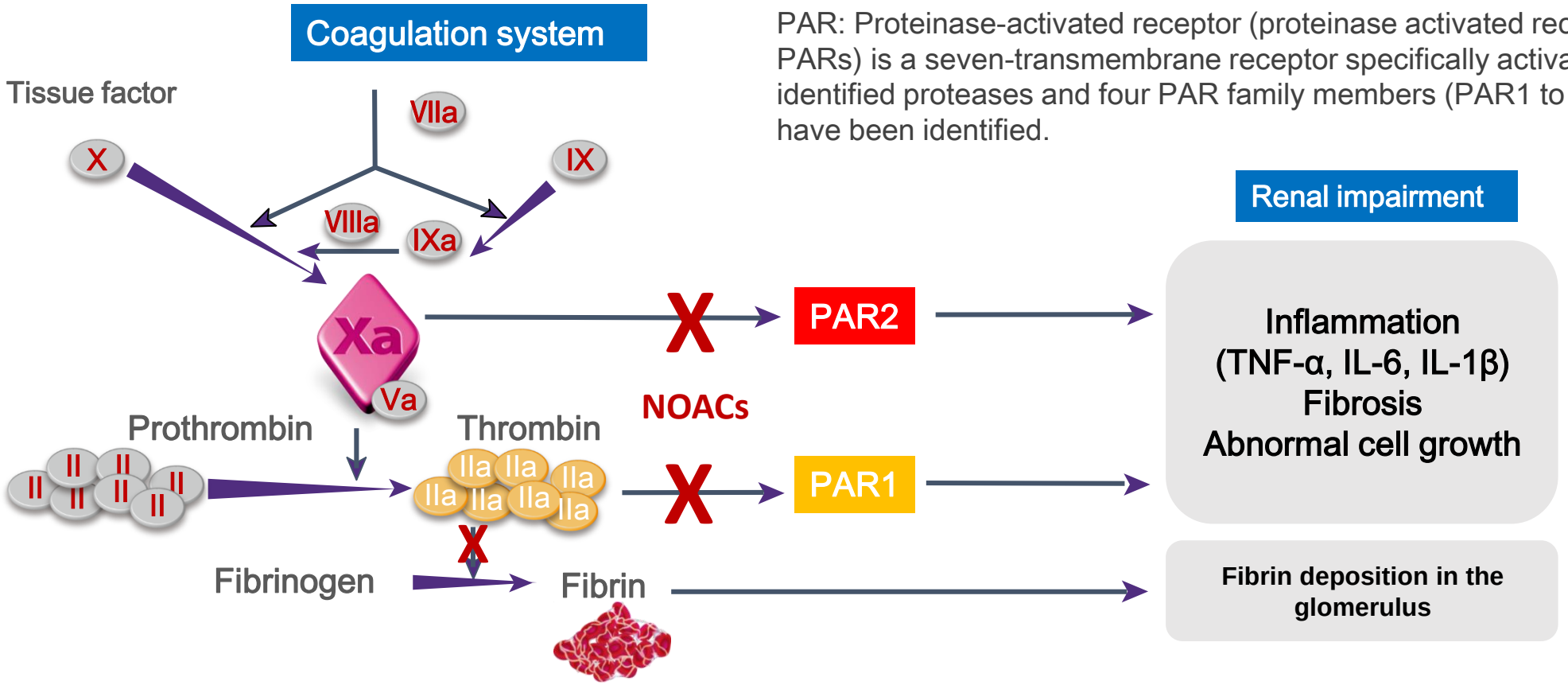
Warfarin Antagonizes the Activity of Vitamin K



Potential of Vitamin K in CKD-MBD: Ayumu Nakajima; Chronic Kidney Disease associated with CKD-MBD;revised edition, p276-281

Coagulation System and Renal Impairment

In IgA nephropathy and diabetic nephropathy, it has been suggested that the coagulation system is involved in the disease state formation of renal impairment

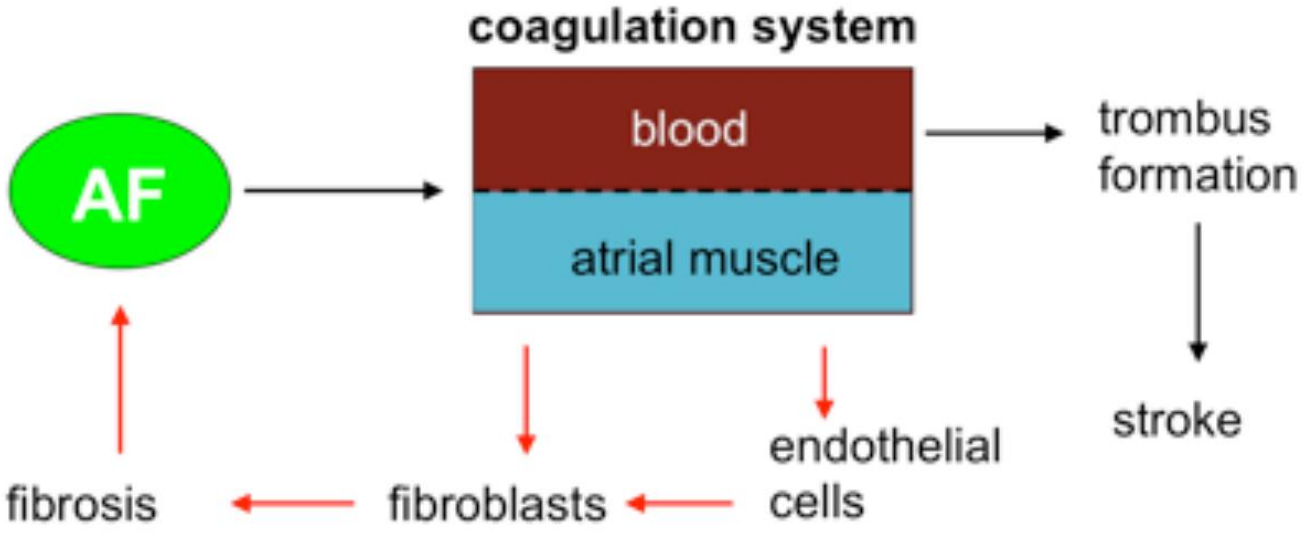


PAR: Proteinase-activated receptor (proteinase activated receptors: PARs) is a seven-transmembrane receptor specifically activated by identified proteases and four PAR family members (PAR1 to 4) have been identified.

Hertig A et al, J Am Soc Nephrol 2004;15:844-53, Farquhar A et al, J Clin Path 1972;25:657-67, Tanaka M et al, Kidney Int 2005;67:2123-33, Sumi A et al, Biol Pharm Bull 2011;34:824-30, Amdur RL et al, Clin J Am Soc Nephrol 2016;11:1546-56

Hypercoagulability Causes Atrial Fibrosis and Promotes Atrial Fibrillation?

Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodeling, and Vascular Destabilisation in the Progression of AF (RACE V)



Spronk HM et al. Eur Heart J 2017;38:38-50

The hypercoagulable state during AF causes pro-fibrotic and pro-inflammatory responses in adult atrial fibroblasts.

Inhibition of coagulation may not only prevent strokes but also inhibit the development of a substrate for AF.

In isolated rat atrial fibroblasts, thrombin enhanced the phosphorylation of the pro-fibrotic signalling molecules….. All effects could be attenuated by the thrombin inhibitor dabigatran.

2019 ACC Guideline Recommendations

- Section 4.2.2.2 – Anticoagulant options – “Over time, NOACs (particularly dabigatran and rivaroxaban) may be associated with **lower risks of adverse renal outcomes** than warfarin in patients with AF (S4.2.2.2-16).”

January CT *et al*, *Circulation* 2019; 140:e125–e151

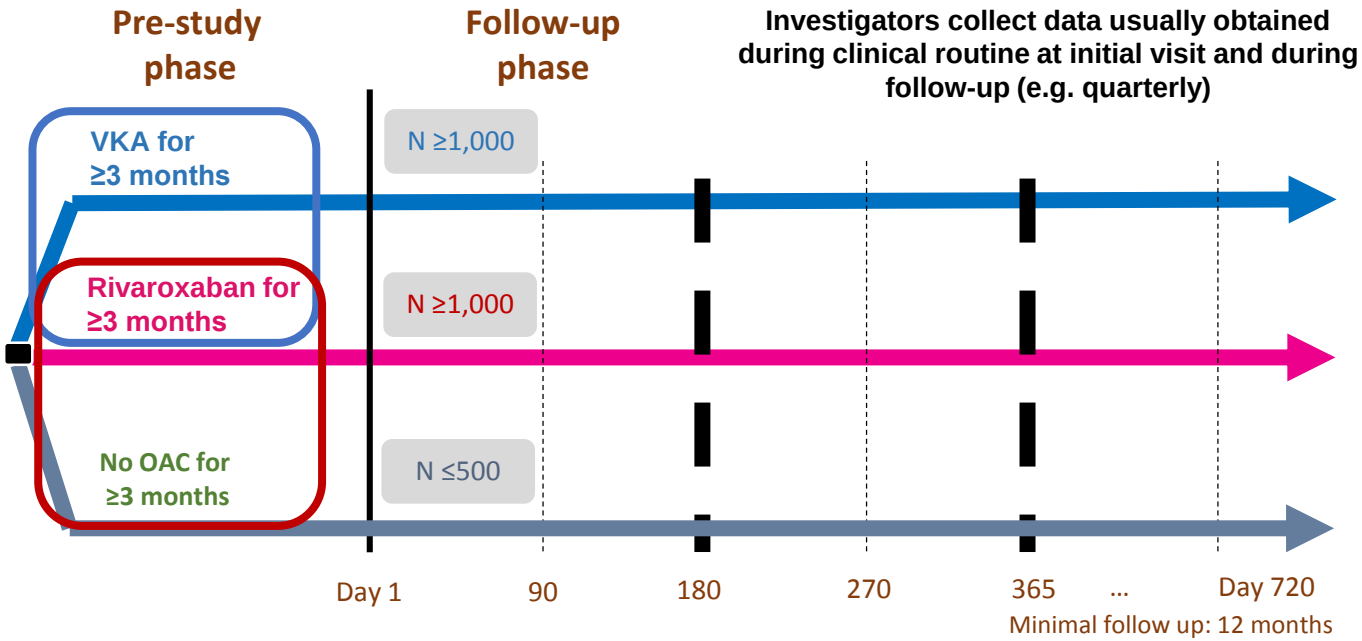
Factor XA – inhibition in RENal patients with non-valvular atrial fibrillation Observational registry

XARENO

Study population:

Patients with NVAF (N ≥2,500) and eGFR/CrCl 15–49 ml/min

Patient selection and choice of type, dose and duration of drug used at discretion of attending physician

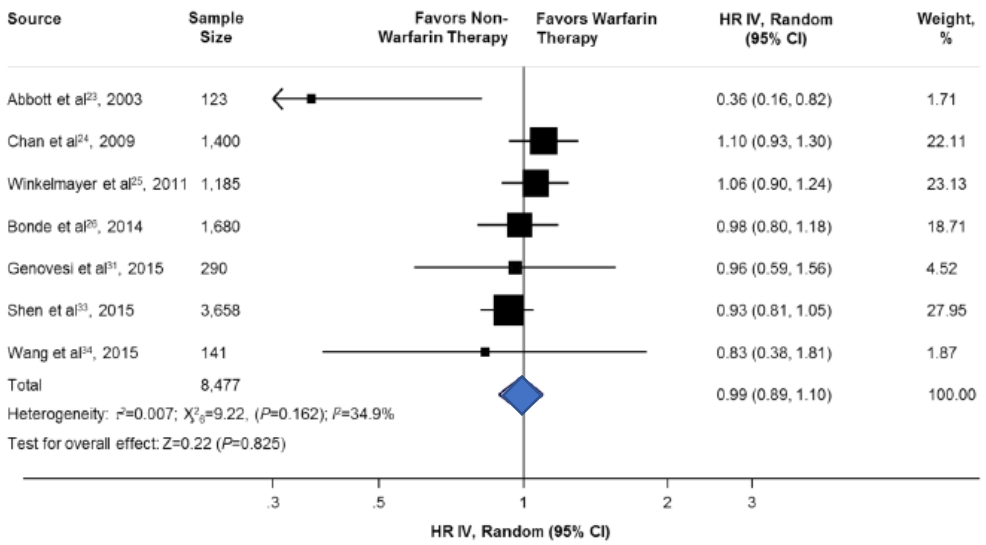


AC, anticoagulation; APT, antiplatelet therapy; VKA, vitamin K antagonist. Patients in the rivaroxaban or VKA arm can also receive APT in addition to AC

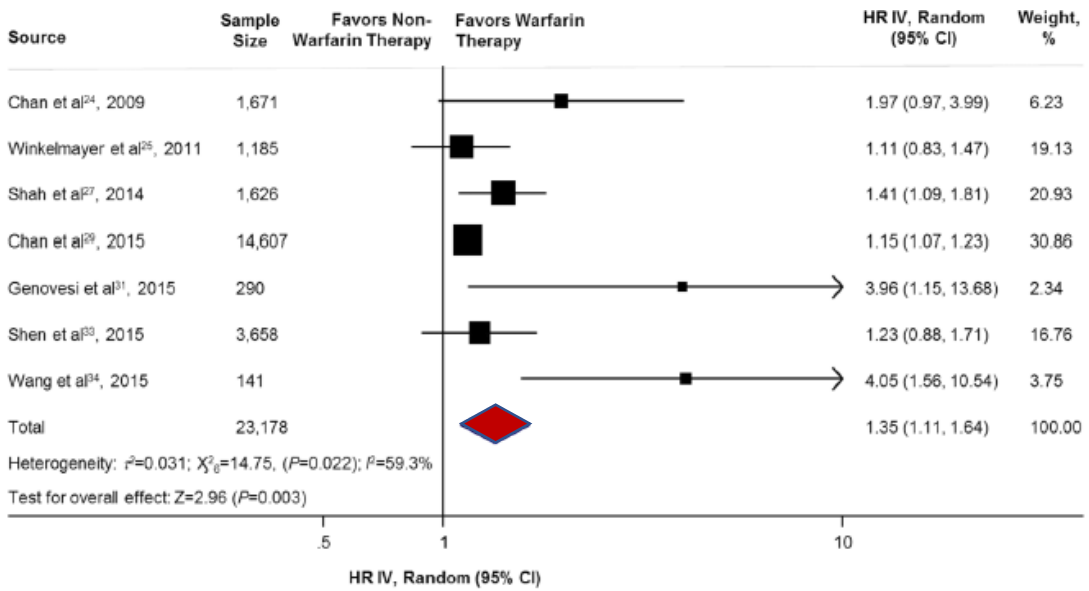
XARENO Clinicaltrials.gov. NCT NCT02663076. Available at https://clinicaltrials.gov/ct2/show/NCT02663076 (accessed November 2017)

What is the Evidence for Warfarin in AF Patients undergoing Haemodialysis?

All-cause mortality



Major bleeding



Systematic review and meta-analysis

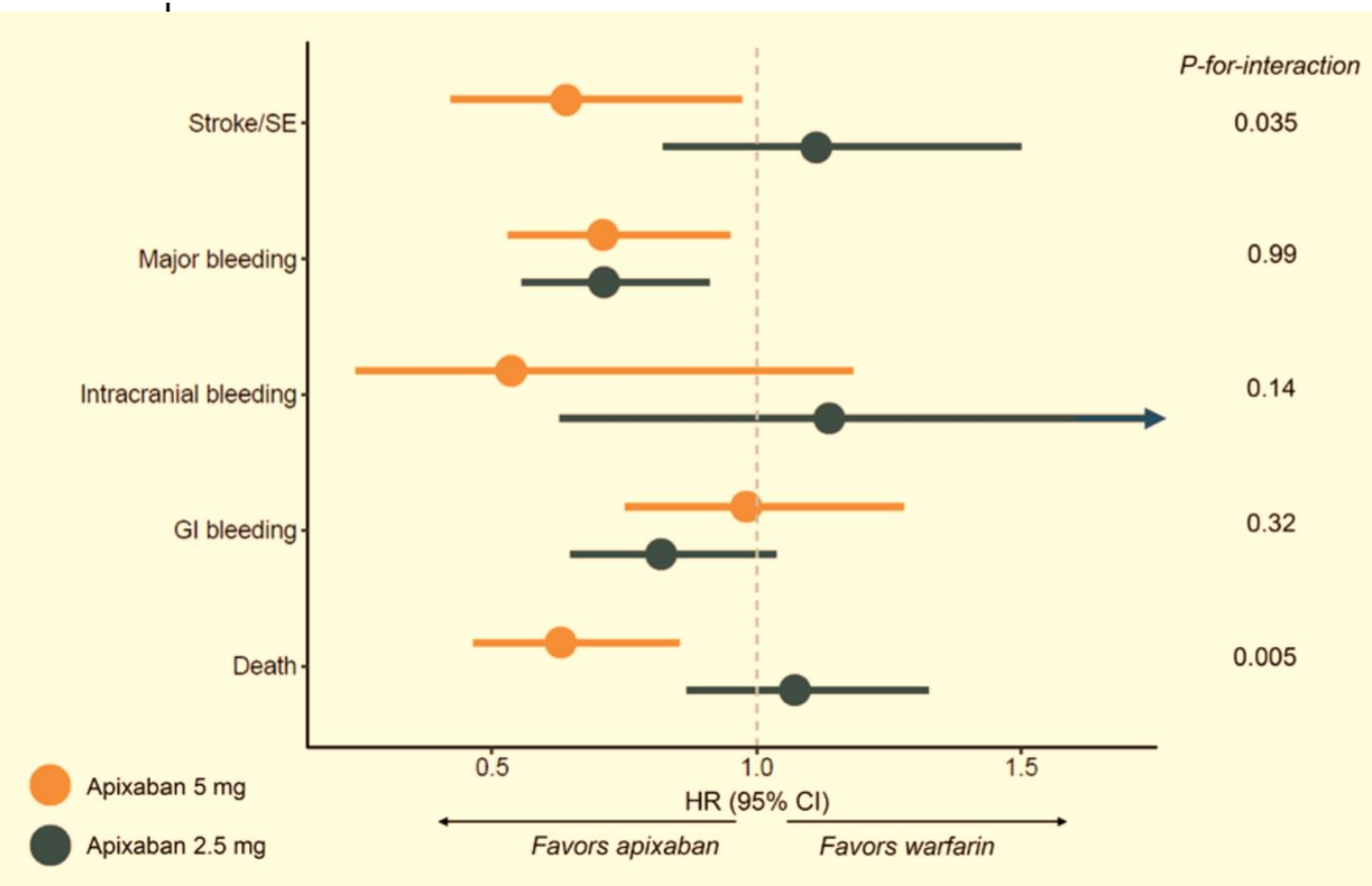
In AF patients undergoing dialysis, warfarin therapy (vs nothing or placebo) was **not associated with and increase of mortality and stroke/thromboembolism**, but **significantly increased the risk of major bleeding**

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

Apixaban Use in End-Stage Kidney Disease

Retrospective cohort study of Medicare beneficiaries: 25,523 patients (45.7% women; age 68.2±11.9 years), including 2,351 patients on apixaban and 23,172 patients on warfarin

Matched cohorts - Apixaban 1:3 Warfarin

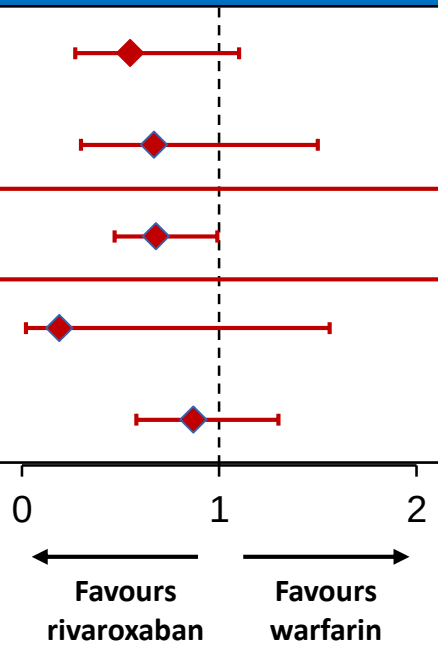


All Apixaban
N= 2321
Apixaban 5 mg BID
N = 1004
Apixaban 2.5 mg BID
N= 1317

Siontis et al. Circulation 2018 DOI: 10.1161/CIRCULATIONAHA.118.035418

Rivaroxaban Appears to be Associated with Similar Efficacy and Significantly Less Major Bleeding vs Warfarin in ERSD Patients

	Event rate (per 100 PYs)		HR (95% CI)
	Rivaroxaban (N=1896)	Warfarin (N=4848)	
Stroke or SE	1.10	2.16	0.55 (0.27–1.10)
Ischaemic stroke	0.85	1.44	0.67 (0.30–1.50)
Major bleeding	3.73	6.16	0.68 (0.47–0.99)
Intracranial	0.08	0.28	0.19 (0.02–1.56)
Gastrointestinal	3.39	4.52	0.87 (0.58–1.30)



Coleman CI et al. Am J Med 2019; doi: 10.1016/j.amjmed.2019.04.013.

US FDA Labeling on ESRD

Apixaban[1]

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.

Hemodialysis in ESRD subjects: Systemic exposure to apixaban administered as a single 5 mg dose in ESRD subjects dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 36% higher when compared to subjects with normal renal function (Figure 3).

The systemic exposure to apixaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min is 17% higher compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min. The systemic exposure of apixaban is 14% lower on dialysis when compared to not on dialysis.

Protein binding was similar (92%-94%) between healthy controls and ESRD subjects during the on-dialysis and off-dialysis periods.

Rivaroxaban[2]

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.

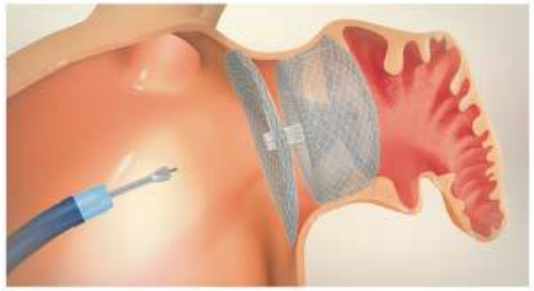
Hemodialysis in ESRD subjects: Systemic exposure to rivaroxaban administered as a single 15 mg dose in ESRD subjects dosed 3 hours after the completion of a 4-hour hemodialysis session (post-dialysis) is 56% higher when compared to subjects with normal renal function (see Table 9). The systemic exposure to rivaroxaban administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 600 mL/min and a blood flow rate in the range of 320 to 400 mL/min is 47% higher compared to those with normal renal function. The extent of the increase is similar to the increase in patients with CrCl 15 to 50 mL/min taking XARELTO 15 mg. Hemodialysis had no significant impact on rivaroxaban exposure. Protein binding was similar (86% to 89%) in healthy controls and ESRD subjects in this study.

1. Eliquis FDA label Suppl-20 2. Xarelto FDA label Suppl-32

2019 AHA/ACC/HRS Focused Update: Management of Patients with Atrial Fibrillation

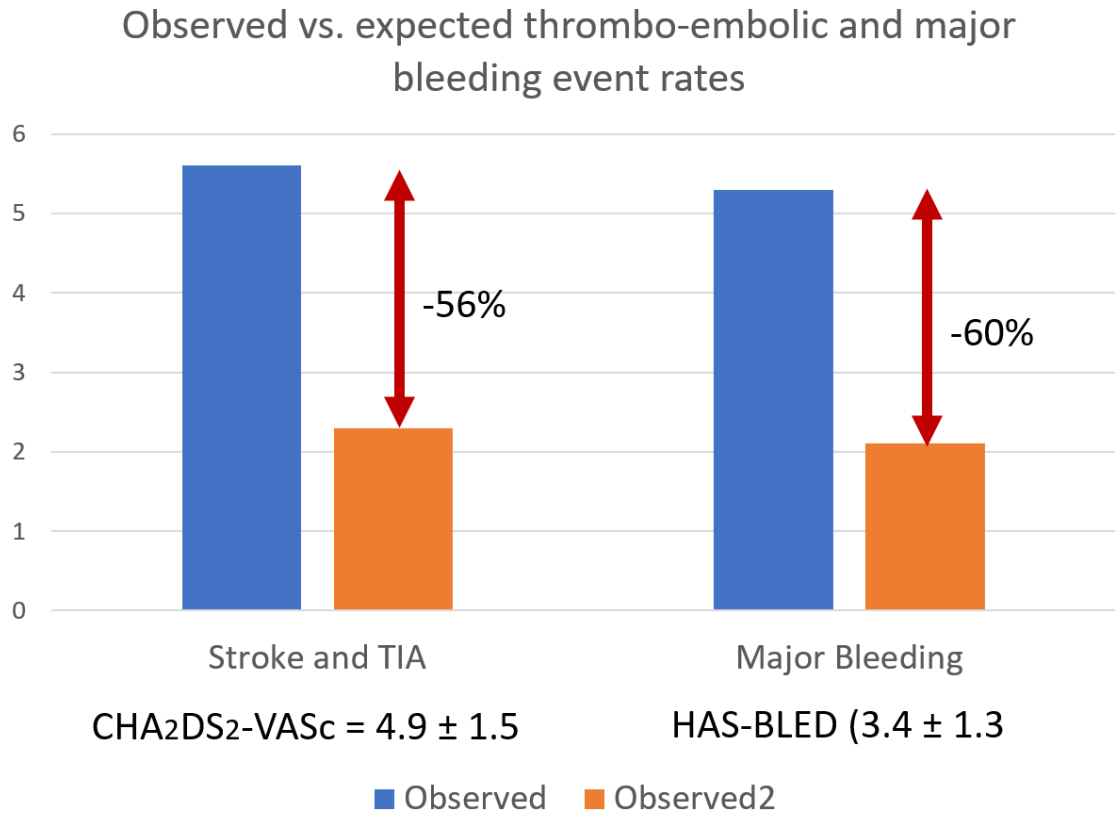
IIb	B-R	14. For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD (serum creatinine ≥1.5 mg/dL [apixaban], CrCl 15 to 30 mL/min [dabigatran], CrCl ≤50 mL/min [rivaroxaban], or CrCl 15 to 50 mL/min [edoxaban]) with an elevated CHA_2DS_2-VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, apixaban, or edoxaban) (S4.1.1-11). **MODIFIED**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve, and this recommendation has been changed in response to the approval of edoxaban. LOE was updated from C to B-R. (Section 4.1. in the 2014 AF Guideline)
IIb	B-NR	13. For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation (S4.1.1-26, S4.1.1-29, S4.1.1-30). **MODIFIED**: New evidence has been added. LOE was updated from B to B-NR. (Section 4.1. in the 2014 AF Guideline)

LAAO for AF Patients with CKD
AMPLATZER European Registry



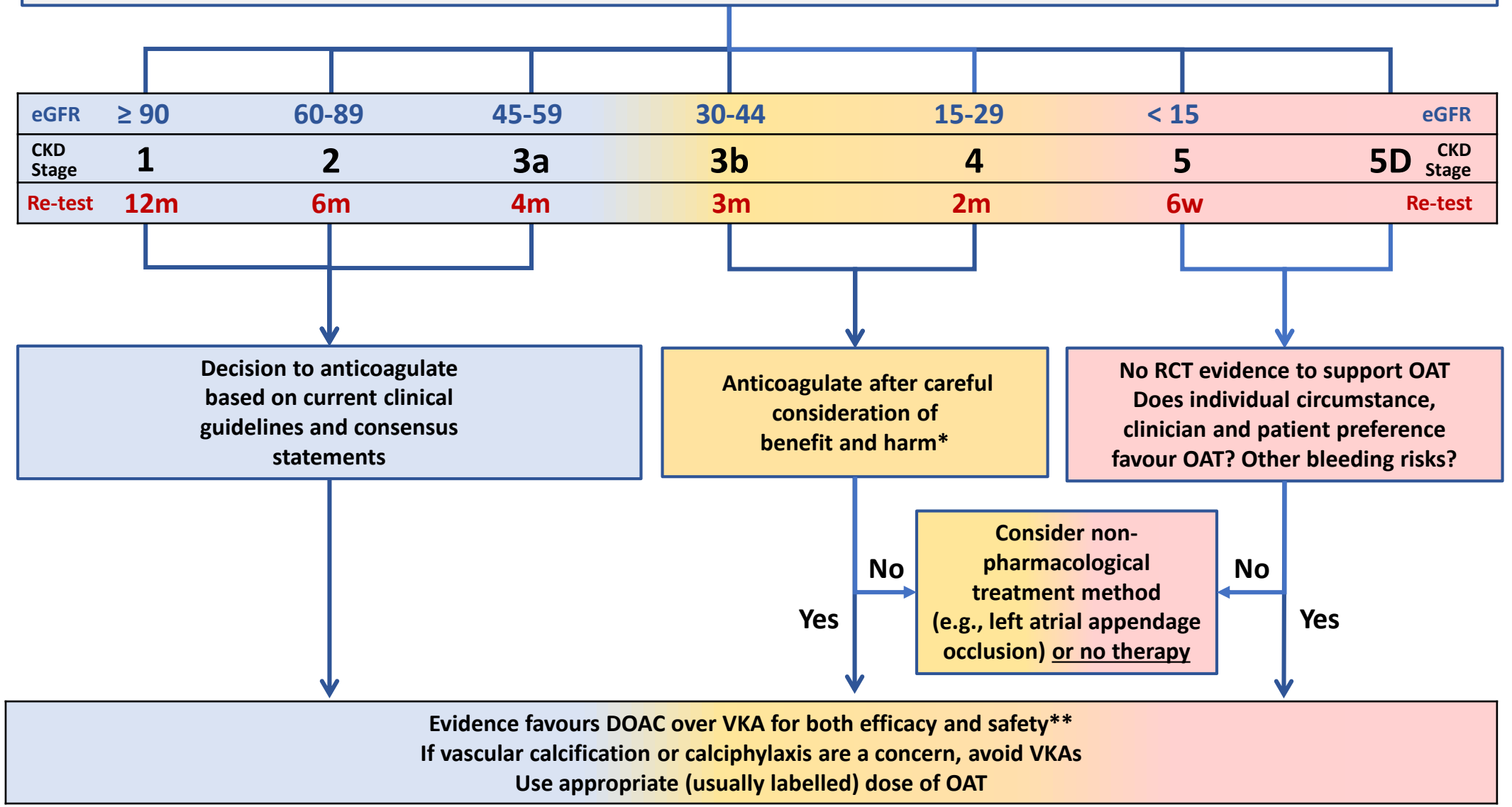
- ACP multicentre registry, 1014 pts (75±8yrs)
- CKD (N=375, CHA_2DS_2-VASc: 4.9±1.5, HASBLED: 3.4±1.3)
- High procedural (97%) and occlusion (99%) success
- Peri-procedural major adverse events:
  - 5.1% of patients,
  - 0.8% death
  - No difference between patients with and without CKD (6.1 vs 4.5%, p=0.47)
- 1319 patient years follow up
- Survival:
  - 1 yr: 84 vs 96%
  - 2 yr: 84 vs 93%; p<0.001)

} patients with an eGFR <30ml/min/1.73m



Kefer J, et al. Int J Cardiol. 2016;207:335-40

Chronic Kidney Disease and Non-Valvular Atrial Fibrillation

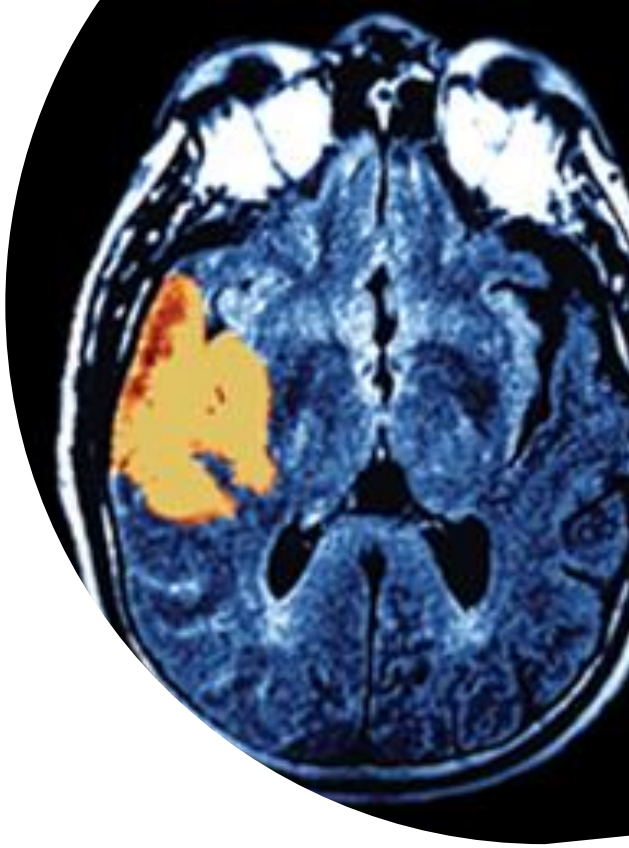


* Existing scoring systems are not validated in this setting; ** Please refer to current dosage recommendations

Conclusions

- Renal impairment increases the likelihood of AF and the consequent stroke and bleeding risks
- Vitamin K antagonists (VKA) have not been shown to be advantageous in t provide net clincal benefit to patients with modest to severe chronic kidney disease (CKD)
- All non vitamin K oral anticoagulants (NOACs) are partially excreted via the kidney and dose reduction strategies are often needed in patients with renal impairment
- Anticoagulation with vitamin K antagonist therapy may lead to further impairment of renal function via a variety of mechanisms, and factor Xa inhibitors may themselves reduce progressive renal impairment
- NOAC therapy is generally preferred in patients with moderate renal impairment, particularly when diabetes is also present
- For patients with ESRD/CKD class 5, OAC may be possible but LAAO may be preferable

Thank you for your attention…



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University of London