Oral Anticoagulation in Dialysis Patients: Uncertainties and Opportunities

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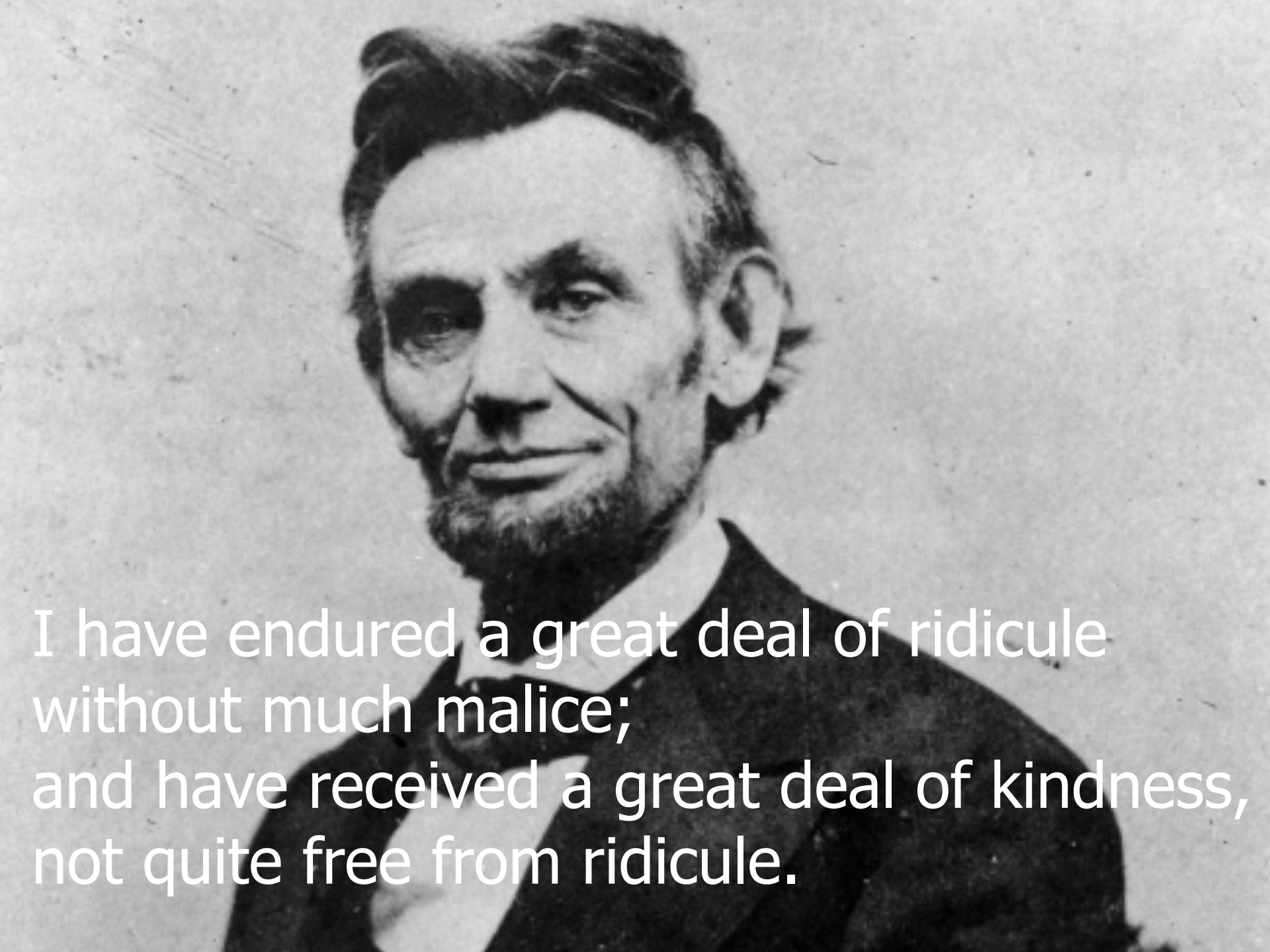
An De Vriese
Division of Nephrology
AZ Sint-Jan Brugge
Belgium


I have endured a great deal of ridicule
without much malice;
and have received a great deal of kindness,
not quite free from ridicule.

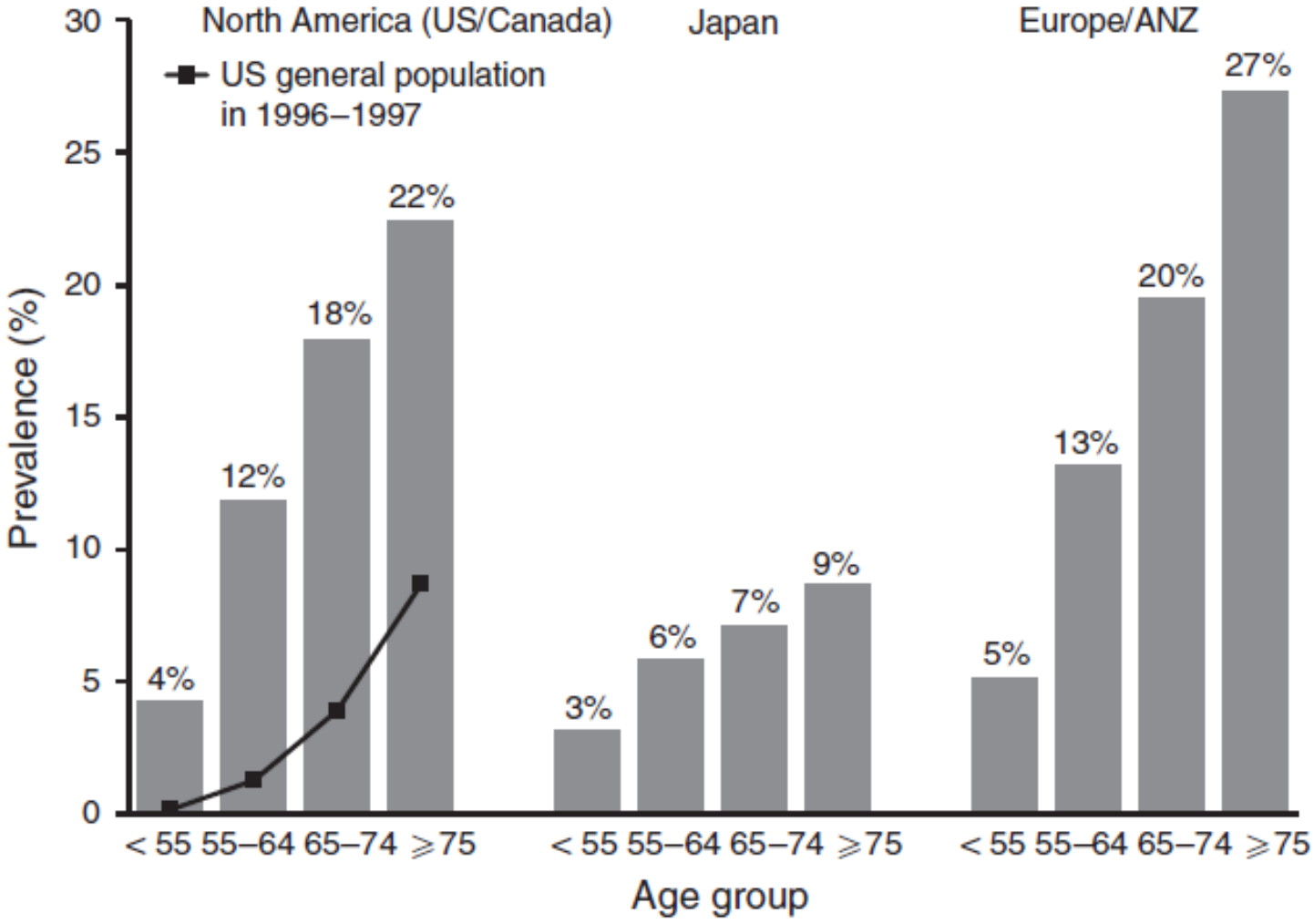
Oral anticoagulants in Dialysis: Navigating between Scylla and Charybdis

An De Vriese
Nephrology & Infectious Diseases
AZ Sint-Jan Brugge
Belgium

AF in Dialysis

DOPPS I (1996–2001) and DOPPS II (2002–2004)

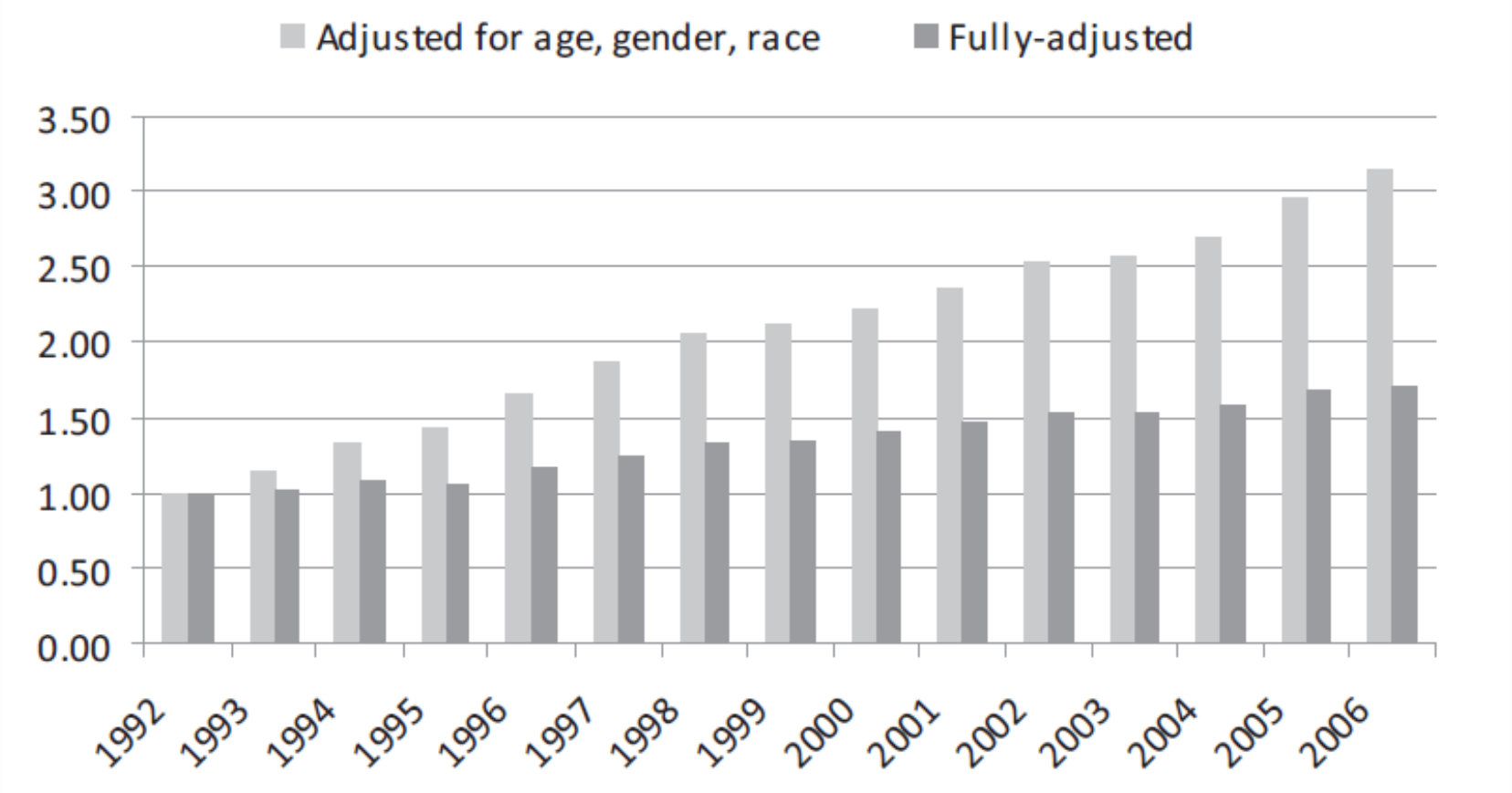
Wizeman V *et al*. Kidney Int 2010; 77: 1098-1106



Belgium:
Mean Age =74y
Prevalence = 24.7%

AF in Dialysis

Winkelmayer W *et al*. J Am Soc Nephrol 2011; 22: 349–357



Fully adjusted = +dialysis vintage, Medicaid eligibility, all available indicators of comorbidity

Ischemic Stroke in Dialysis

Vazquez *et al*. Kidney Int 2009; 76: 324-330

Risk x4-10

Table 8 | Factors independently associated with the presence of ischemic stroke in the course of the dialysis period

	Odds ratio	95% CI	*P*
Previous stroke or transient ischemic attack	6.98	1.24–39	0.027
AF at any time	17.3	1.99–150	0.010

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

JACC 2014;64(21):e1-76

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For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include: warfarin (INR 2.0 to 3.0) *(Level of Evidence: A)*, dabigatran *(Level of Evidence: B)*, rivaroxaban *(Level of Evidence: B)*, or apixaban. *(Level of Evidence: B)*

For patients with nonvalvular AF with a CHA2DS2-VASc score of 2 or greater and who have endstage CKD (creatinine clearance [CrCl] <15 mL/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation. *(Level of Evidence: B)*

2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

Can J Cardiol 2014;30:1114–1130

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There are no randomized trials data for nonvalvular AF patients who are dialysis-dependent,
and we therefore cannot recommend their routine anticoagulation.

Variation in Facility use of Antithrombotic Agents in Dialysis

Sood *et al*. Kidney Int 2013; 84, 600–608

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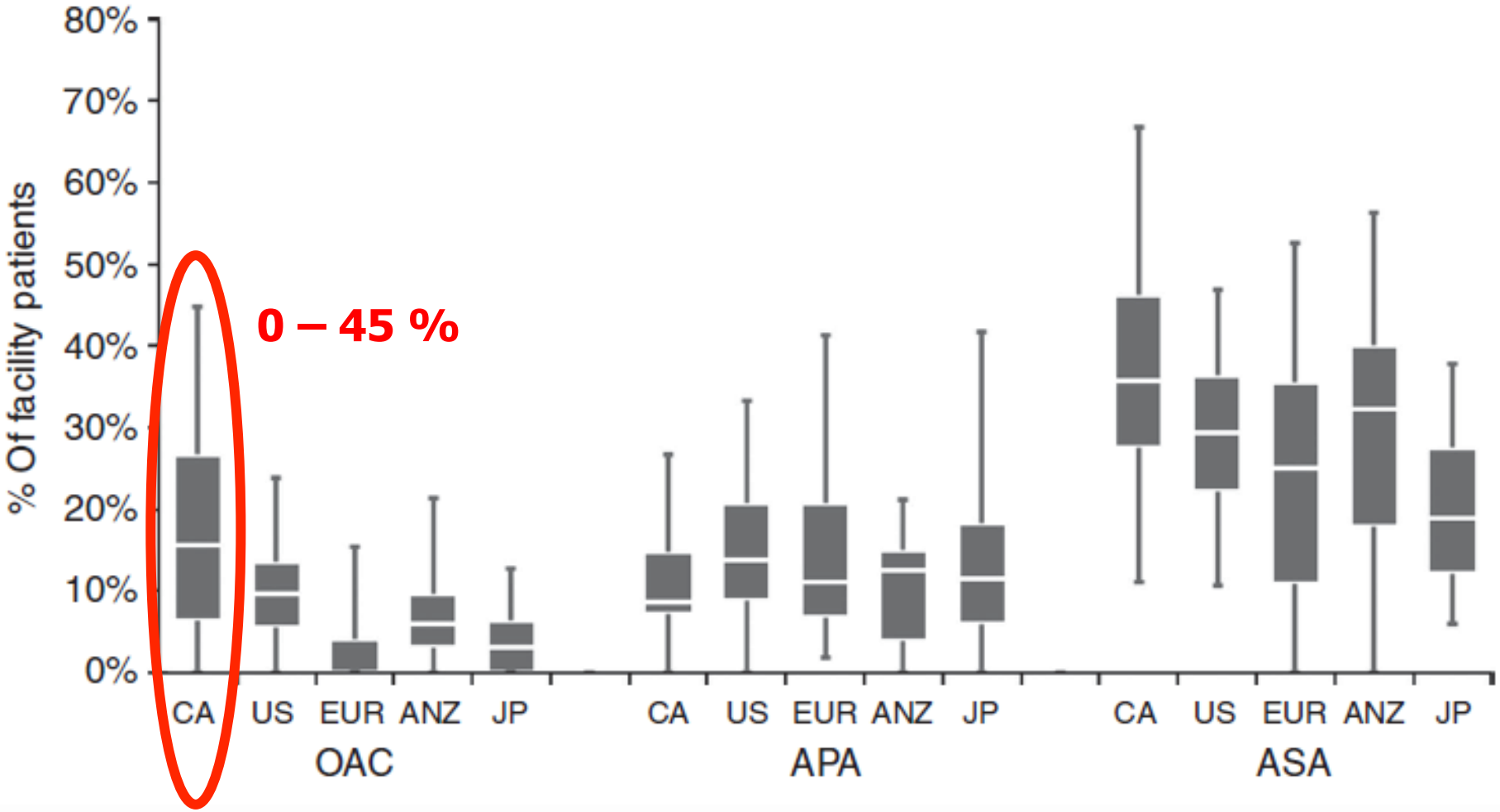


Vitamin K antagonists and Dialysis: Indirect Evidence

1) Prevention of stroke and systemic embolism

2) Major Bleeding

3) Vascular Calcifications

Risk for Stroke or Systemic Thromboembolism

Olesen *et al*. New Engl J Med 2012; 367: 625-35

Characteristic	No Renal Disease (N=127,884)†		Non–End-Stage Chronic Kidney Disease (N=3587)†		Disease Requiring Renal-Replacement Therapy (N=901)†	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants	1.00		1.49 (1.38–1.59)	<0.001	1.83 (1.57–2.14)	<0.001
Antithrombotic therapy						
None	1.00		1.00		1.00	
Warfarin	0.59 (0.56–0.61)	<0.001	0.84 (0.69–1.01)	0.07	0.44 (0.26–0.74)	0.002
Aspirin	1.10 (1.06–1.14)	<0.001	1.25 (1.07–1.47)	0.01	0.88 (0.59–1.32)	0.54
Warfarin and aspirin	0.69 (0.64–0.74)	<0.001	0.76 (0.56–1.03)	0.08	0.82 (0.37–1.80)	0.62

Risk for Stroke and Bleeding

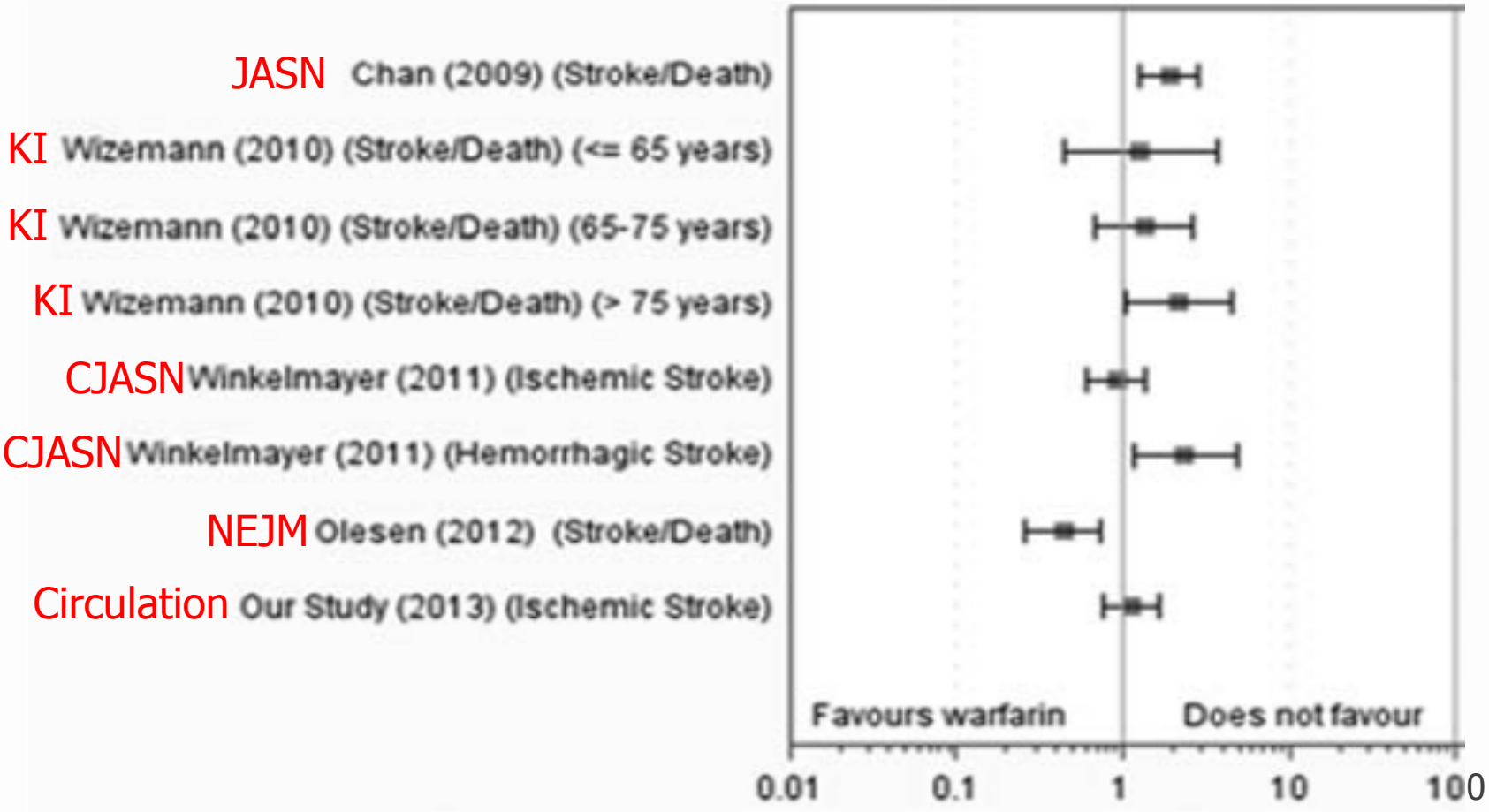
Shah *et al*. Circulation 2014; 129: 1196-1203

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

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

Warfarin and risk for Stroke

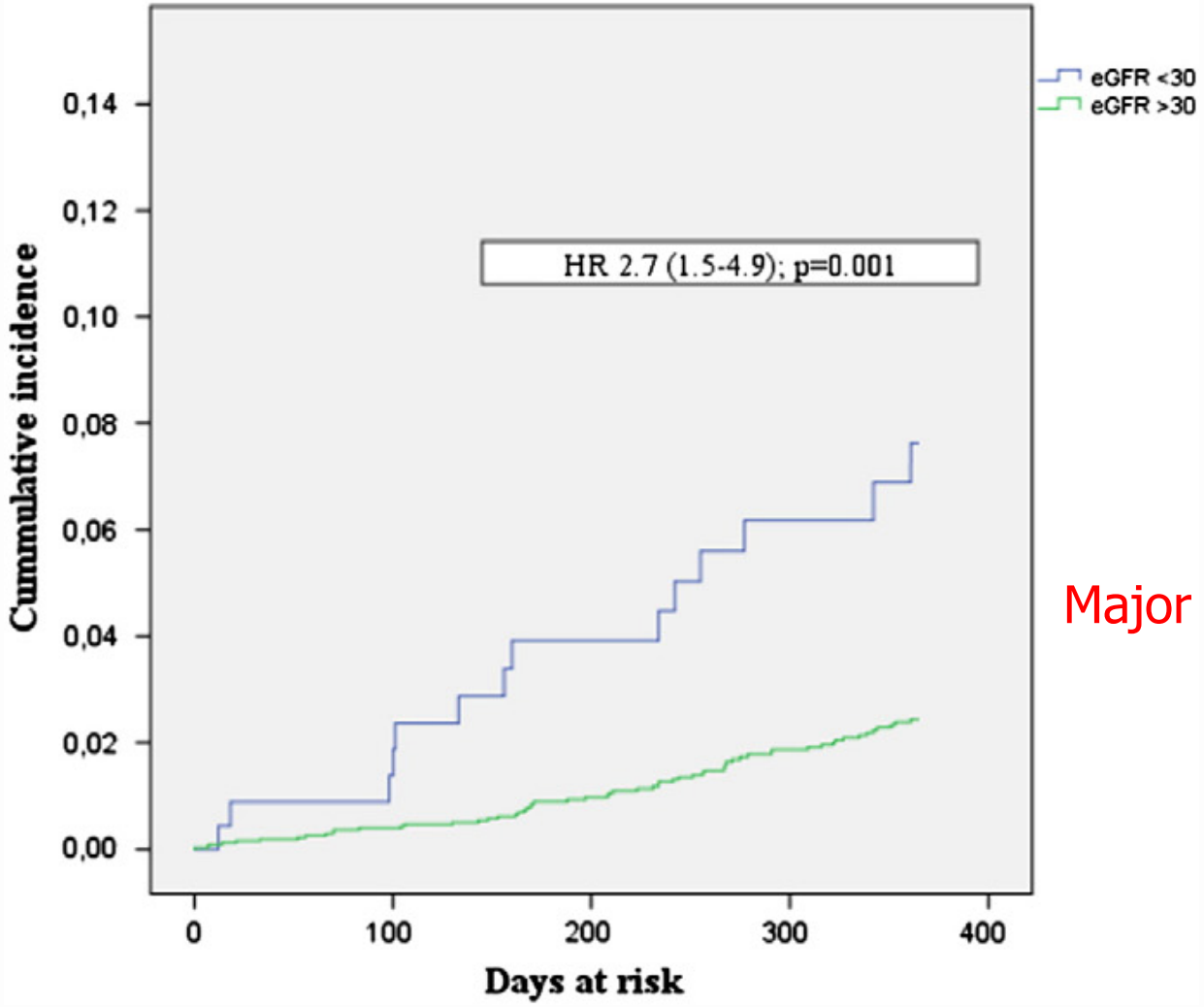
Shah *et al*. Circulation 2014; 129: 1196-1203



NDT - Genovesi 2015: favours warfarin

Major Bleeding in Patients taking Warfarin

Wieloch *et al*. Thromb Res 2013; 131: 481-6

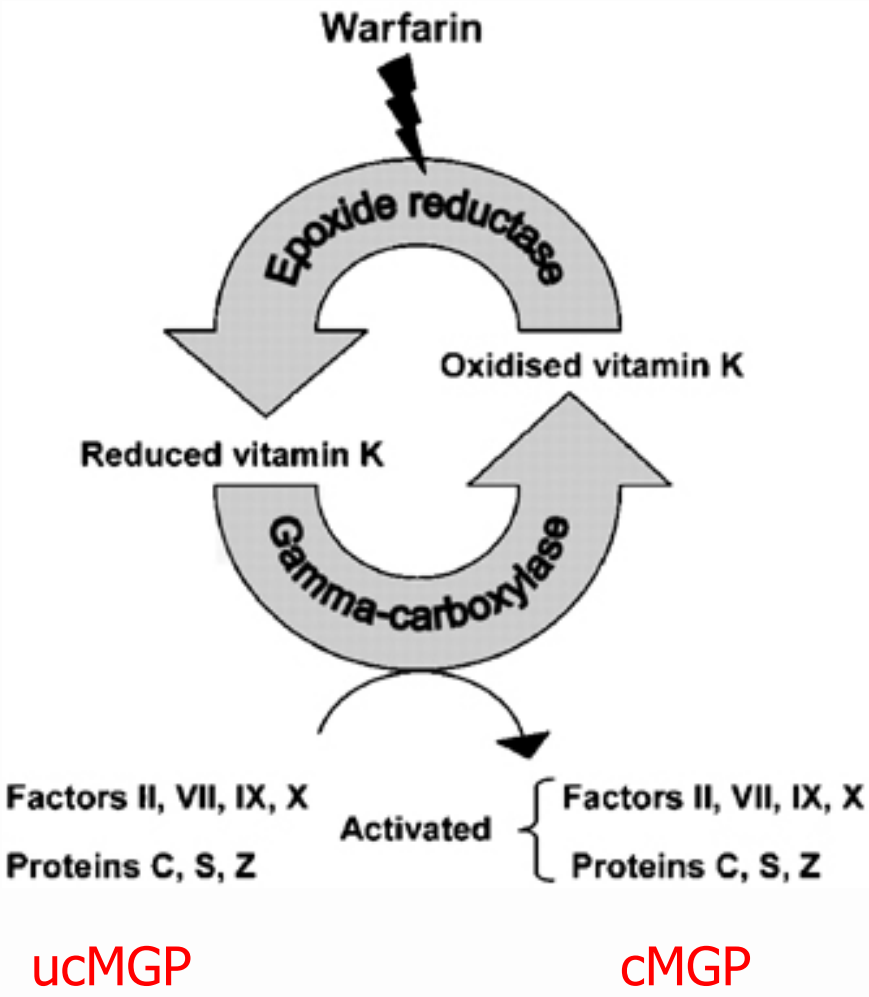


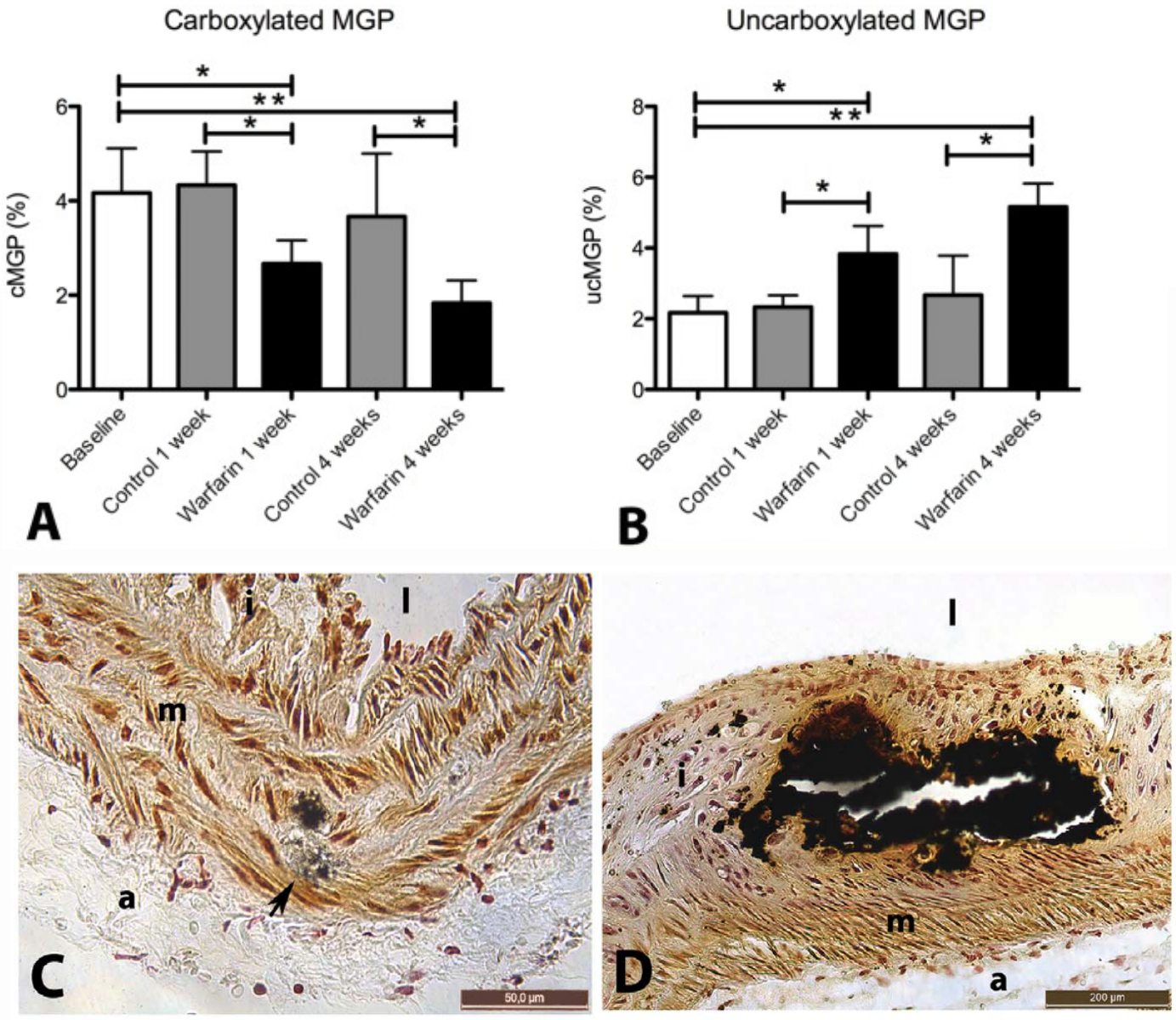
Major bleeding on OAC: x10

Warfarin and Vascular calcification

Matrix Gla protein (MGP):

- Most potent local inhibitor of ectopic calcification
- Locally produced by VSMC

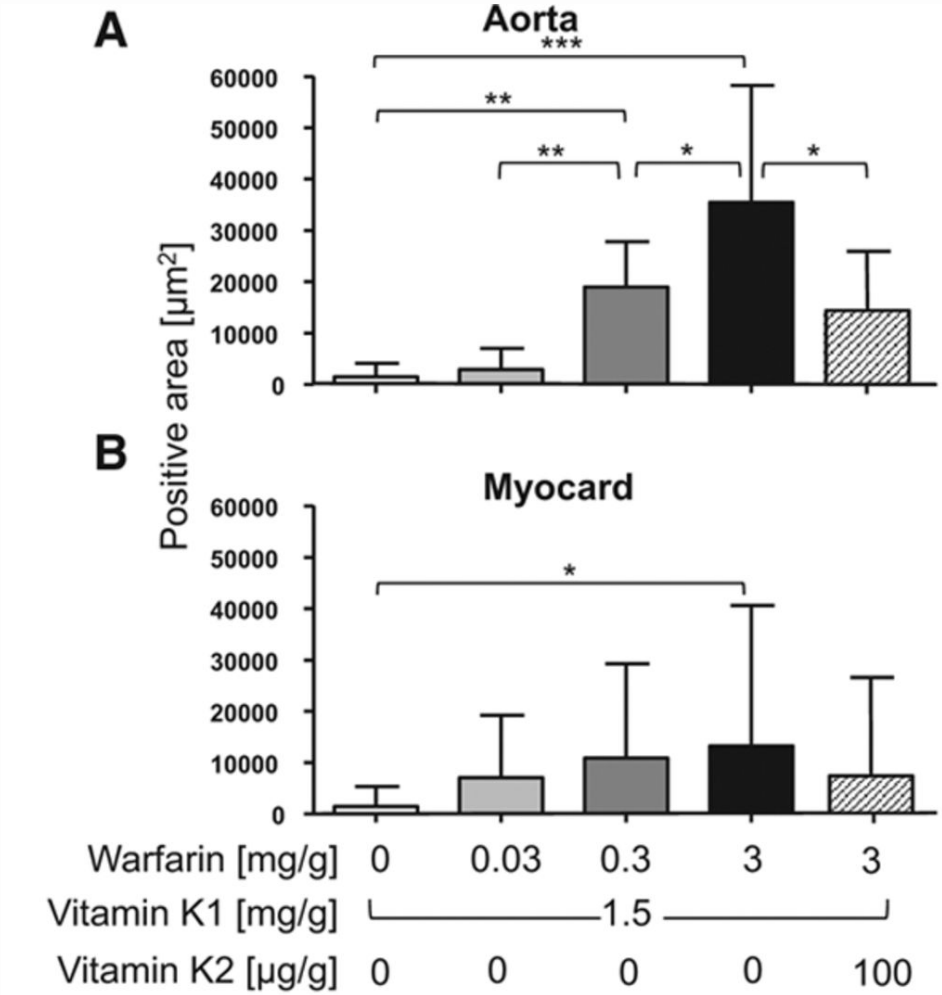




Schurgers L et al.
PLoS ONE 2012; 7(8): e43229

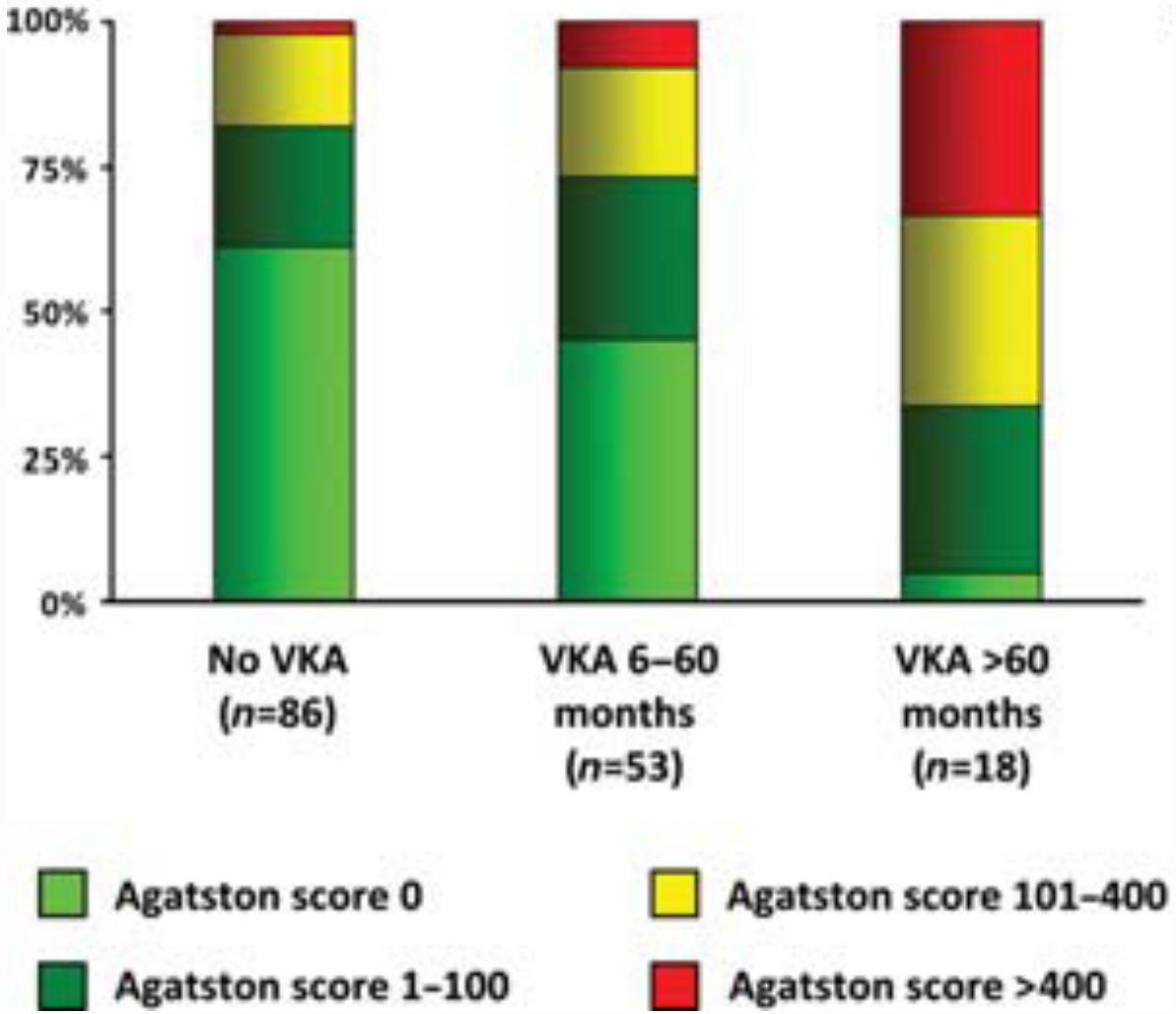
Warfarin and Vascular calcification

Krüger T et al. *Arterioscler Thromb Vasc Biol* 2013; 33: 2618-2624



Warfarin and Vascular calcification

Weijs et al. *Eur Heart J* 2011; 32: 2555-2562



Warfarin and Vascular calcification

Tantisatamo et al. *Arterioscler Thromb Vasc Biol* 2015;35:237-242

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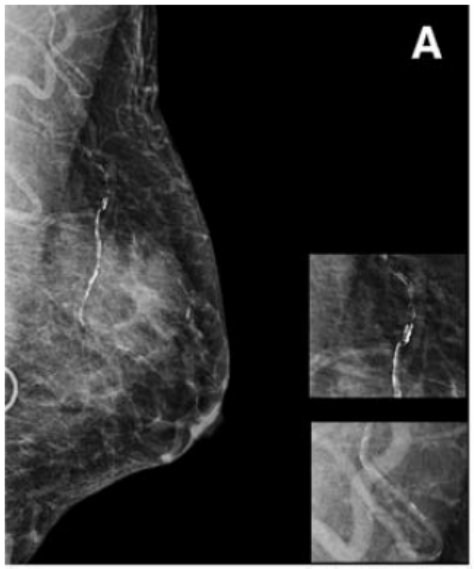

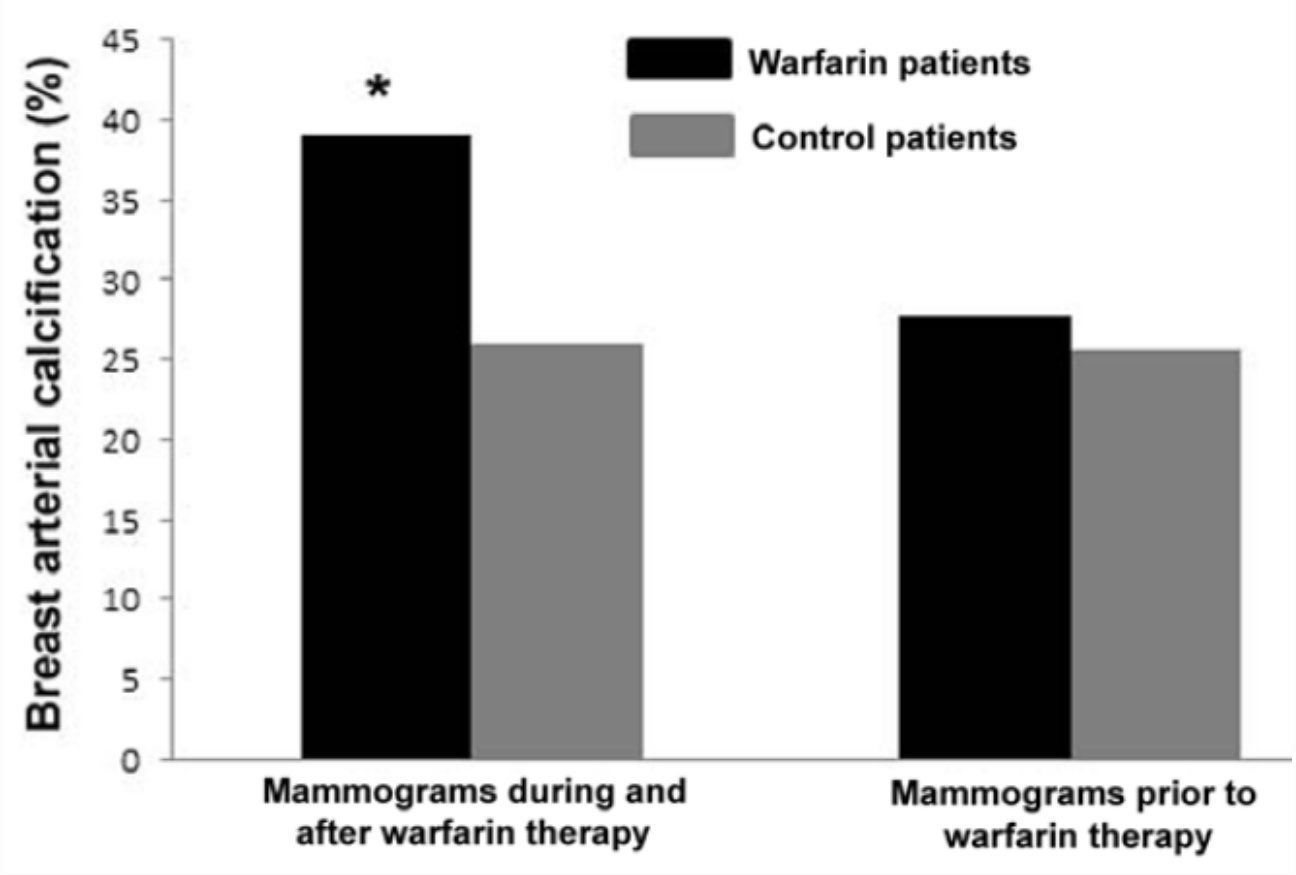

Dialysis = Vitamin K-deficient state

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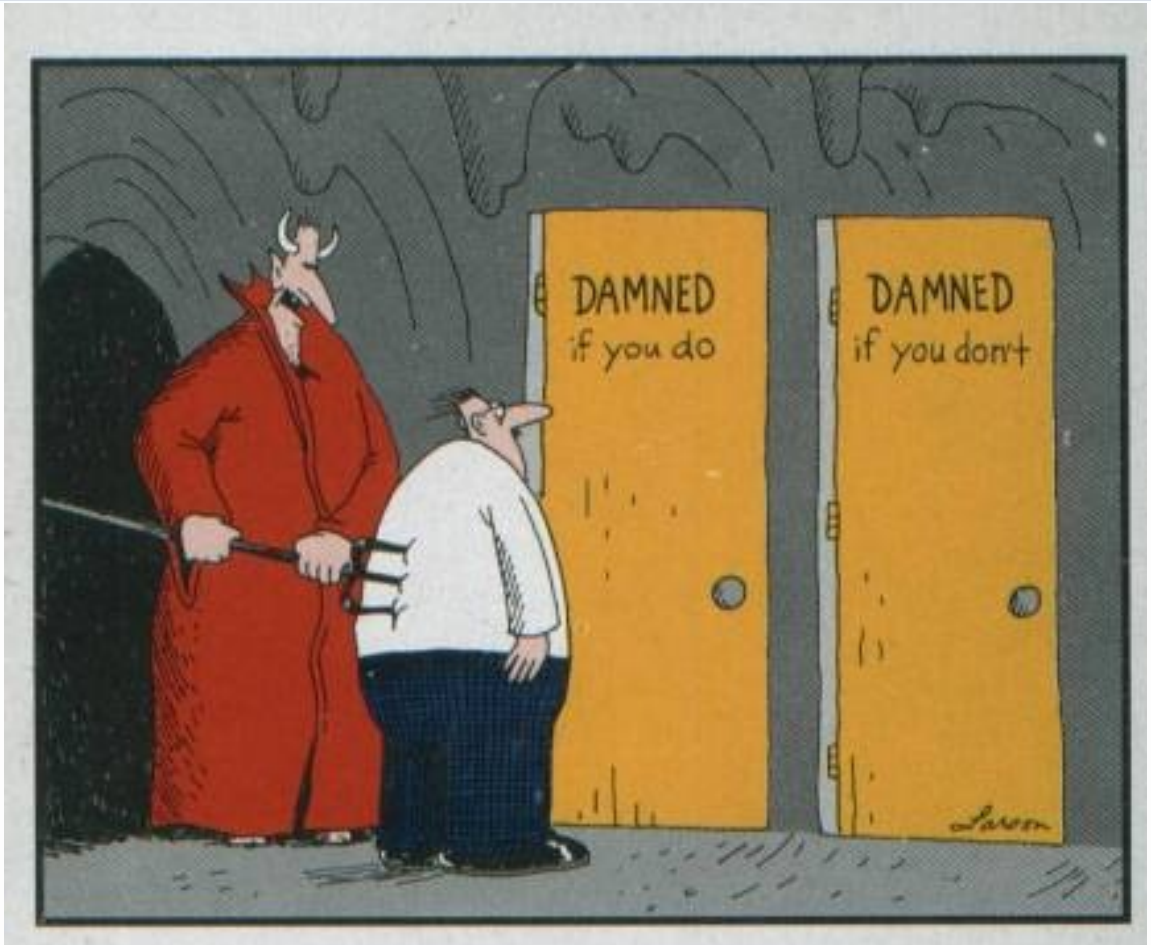

"C'mon, c'mon — it's either one or the other."

1) Dialysis diet is deficient in vitamin K
2) Vitamin K2 intake correlates inversely with dp-uc-MGP

Caluwé & De Vriese. Nephrol Dial Transplant 2014;29:1385-90.

Cranenburg. Kidney Int 2012; 82: 605–610

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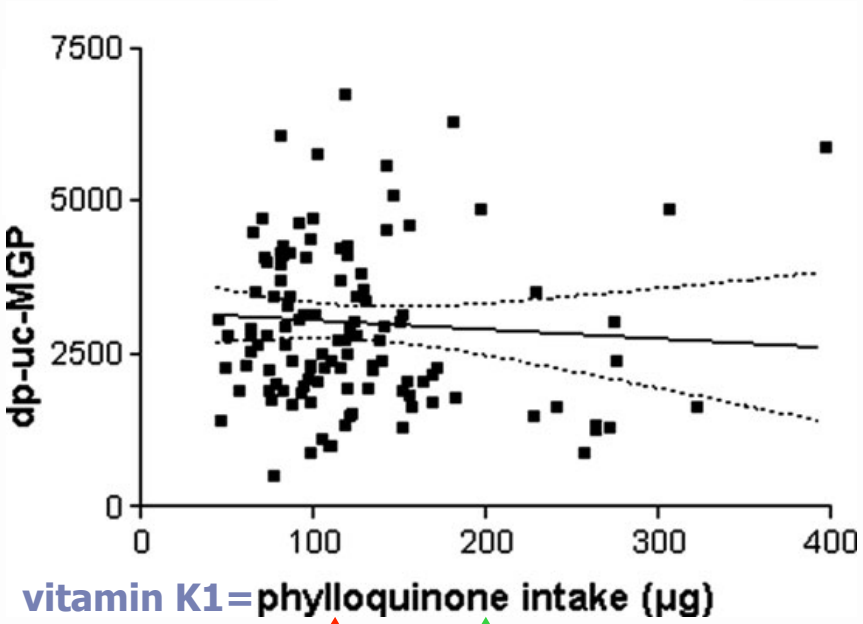

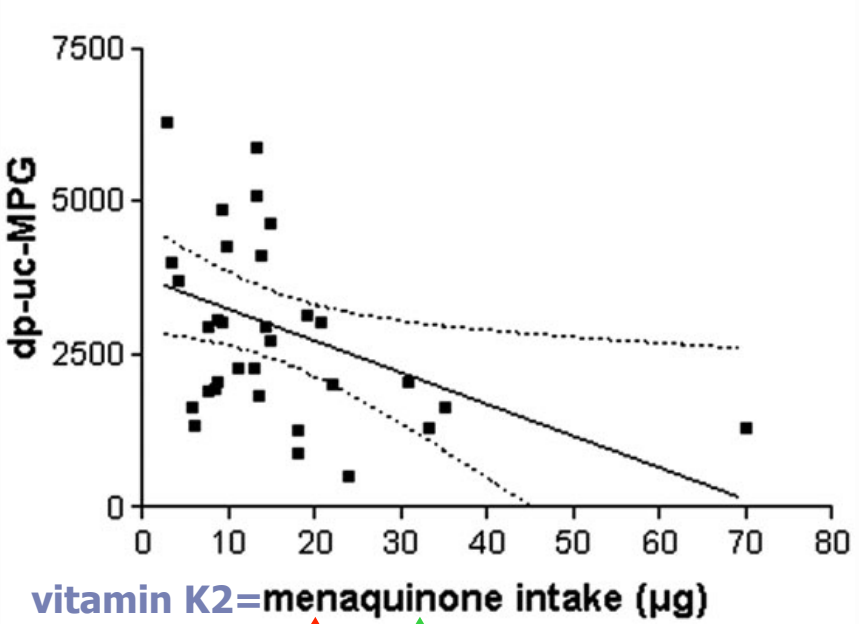

Dutch Hemodialysis=118µg

Normal=200µg

Dutch Hemodialysis=21µg

Normal=31µg

Vitamin K2 supplementation in dialysis patients

Caluwé & De Vriese. Nephrol Dial Transplant 2014;29:1385-90

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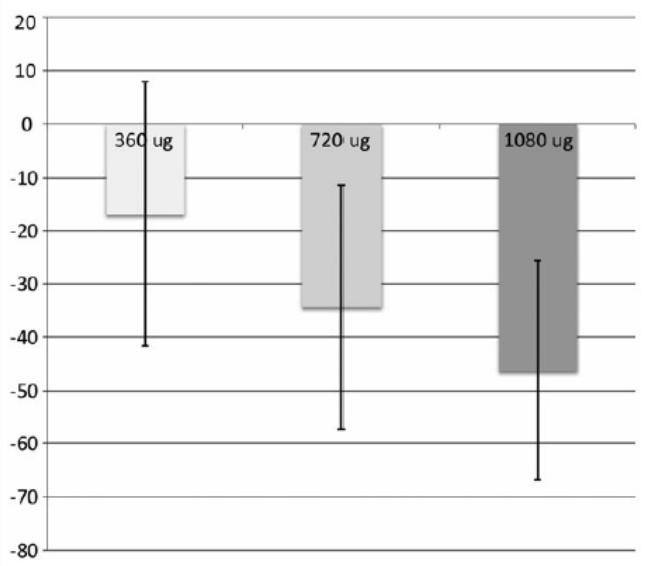
Table 2. Circulating dephosphorylated-uncarboxylated-MGP (pmol/L)

	Treatment group (MK-7) ($N = 165$)		
	360 µg ($n = 59$)	720 µg ($n = 53$)	1080 µg ($n = 53$)
Baseline	2872 (123–7539)	2897 (500–7567)	3206 (857–7337)
After treatment	2306 (105–6618)	1935 (130–6132)	1719 (116–6047)
% Change	17[a]	33[a]	46[a]



NB: vitamin K2 intake healthy population = 31 µg/d

NB: dp-uc-MGP healthy population = 447±188 pmol/L

Vitamin K antagonists and Dialysis: Indirect Evidence

1) Prevention of Stroke: equivocal

2) Major Bleeding: increased

3) Vascular Calcifications: increased

Sicilia

Messina

Calabria

Navigating between Scylla and Charybdis

Comorbidity
- Valve replacement
- Pulmonary embolism

Coumarins

No clear indication / contraindication

⇩ Risk Embolism ischem. stroke?

⇧ Risk Bleeding (GI, cerebral..)

⇧ Risk Cardio-vascul. calcific.

⇧ Risk Calci-phylaxis

No coumarins

Comorbidity
- Falls
- Bleeding
- etc.

No coumarins

NOAC

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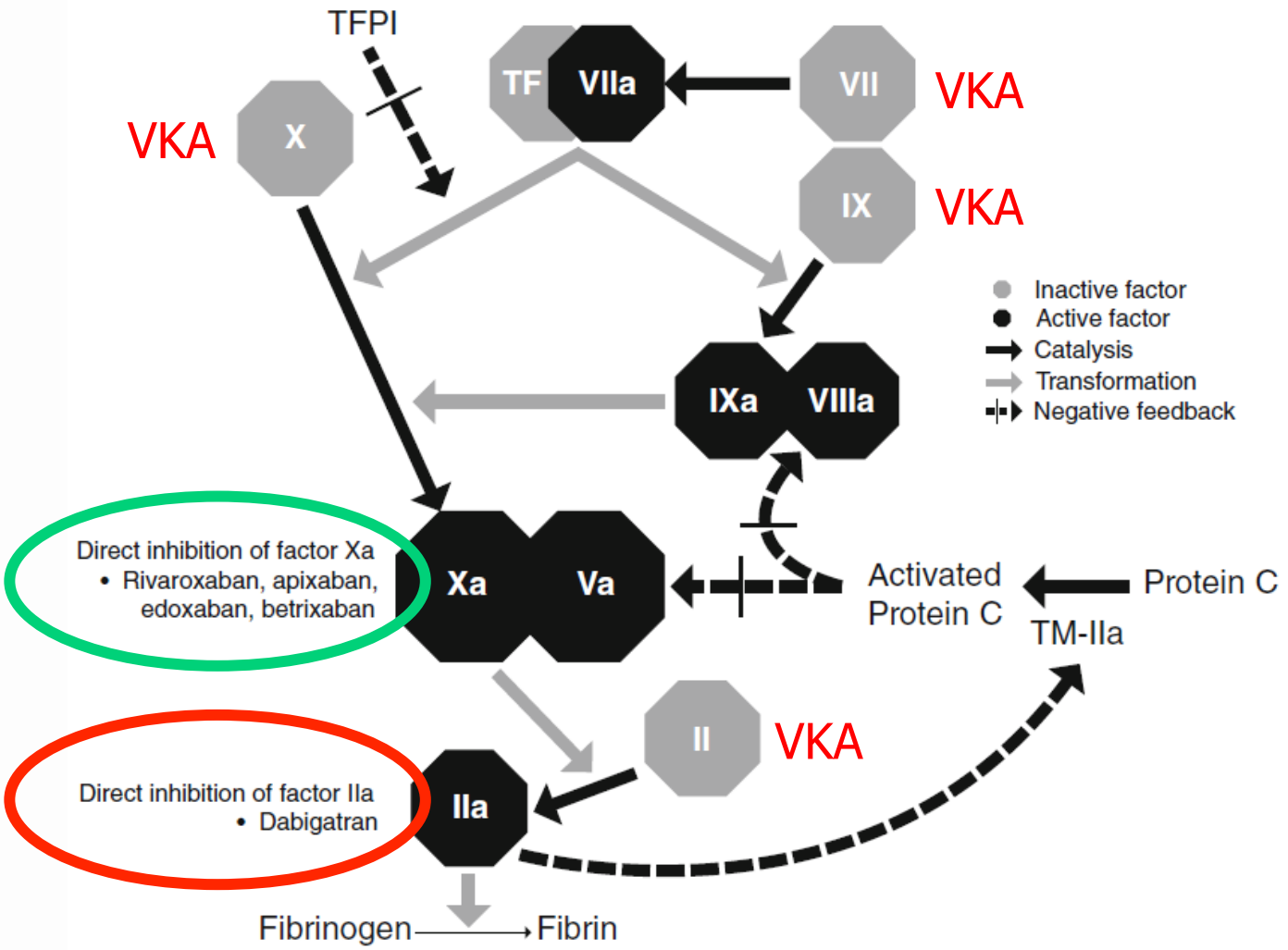

NOAC in non-valvular AF

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE-AF
Molecule	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
N	18,113	14,264	18,201	21,105
Factor	IIa	Xa	Xa	Xa
Study design	Open-label	Double-blind	Double-blind	Double-blind
Dosing	110 mg BID 150 mg BID	20 mg OD 15 mg OD (renal)	5 mg BID 2.5 mg BID (+80 y; <60 kg, renal)	60 mg OD 30 mg OD (<60 kg, renal, Pgp inhibitor)
Age (years)	72	73	70	72
$CHADS_2$	2.1	3.5	2.1	2.8
Stroke/embolism (ITT!)	110 mg: Non-inferior 150 mg: Superior	Non-inferior	Superior	Non-inferior
Major Bleeding	Warfarin: 3.36% Dabig 110 mg: 2.71% Dabig 150 mg: 3.11%	Warfarin: 3.4% Rivaroxaban: 3.6%	Warfarin: 3.09% Apixaban: 2.13%	Warfarin: 3.43% Edox 60 mg: 2.75% Edox 30 mg: 1.61%

Features of Novel Oral Anticoagulants

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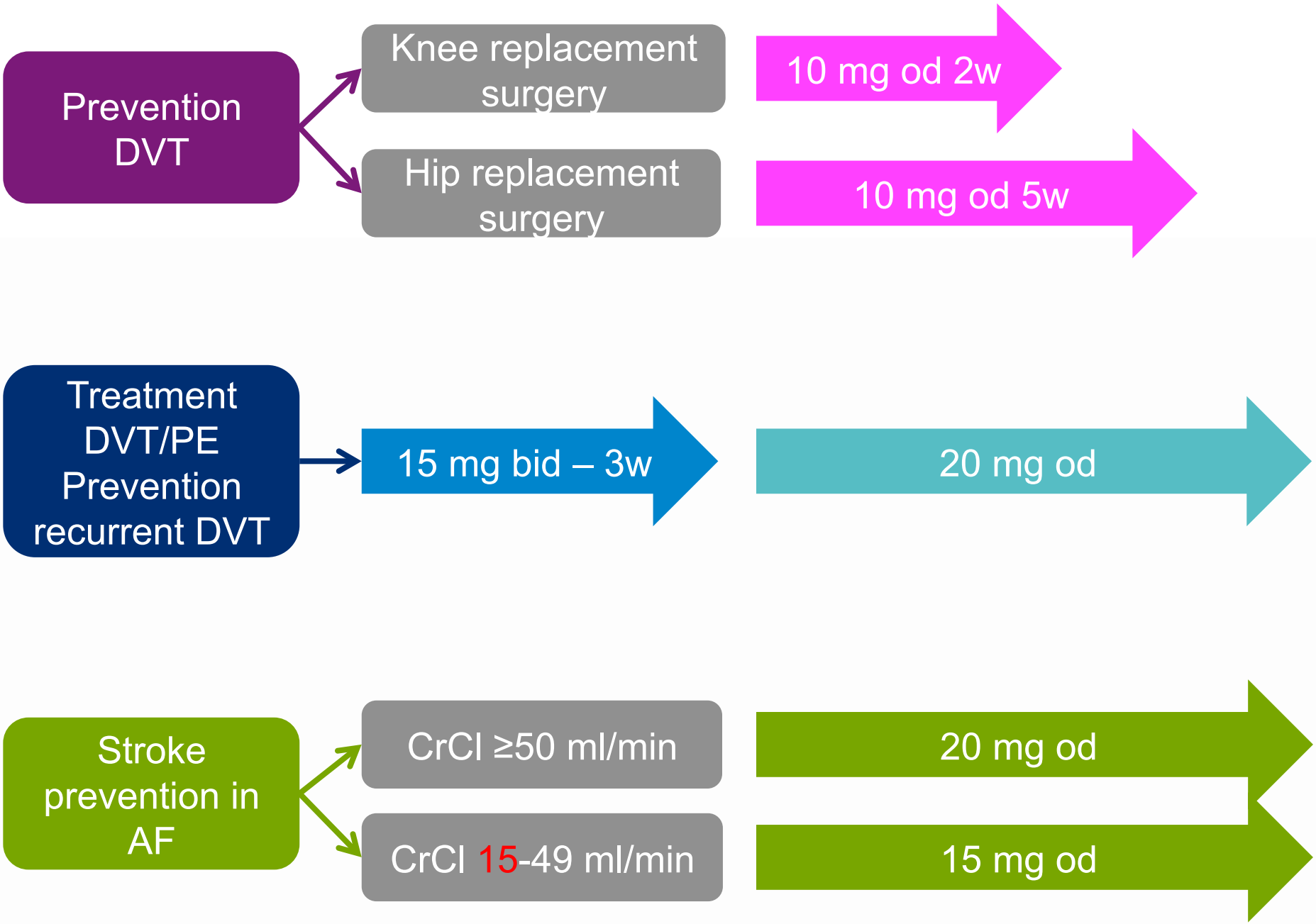
	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to Cmax	1.25 – 3	2 – 4	3 – 4	1 – 2
CYP metabolism	None	32%	Minimal	< 4%
Bioavailability	3-7%	80% (with food)	50%	62%
Protein binding	35%	93%	87%	50%
Half-life	14 – 17 h	7 – 11h	8 – 15 h	8 – 10 h
Renal elimination	80%	35%	27%	50%



Mueck *et al*. Clin Pharmacokinet 2014; 53: 1-16

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AJKD

Original Investigation

Dose-Finding Study of Rivaroxaban in Hemodialysis Patients

An S. De Vriese, MD, PhD,[1] Rogier Caluwé, MD,[2] Els Bailleul, MD,[3]
Dirk De Bacquer, PhD,[4] Daniëlle Borrey, PhD,[5] Bruno Van Vlem, MD, PhD,[2]
Stefaan J. Vandecasteele, MD, PhD,[1] and Jan Emmerechts, MD, PhD[5]

Rivaroxaban
Dose –finding Hemodialysis

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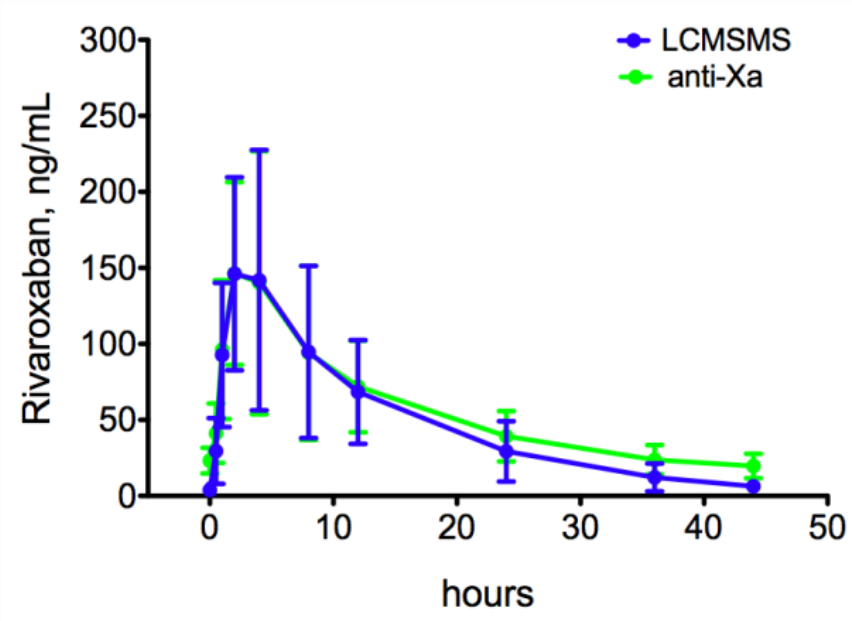
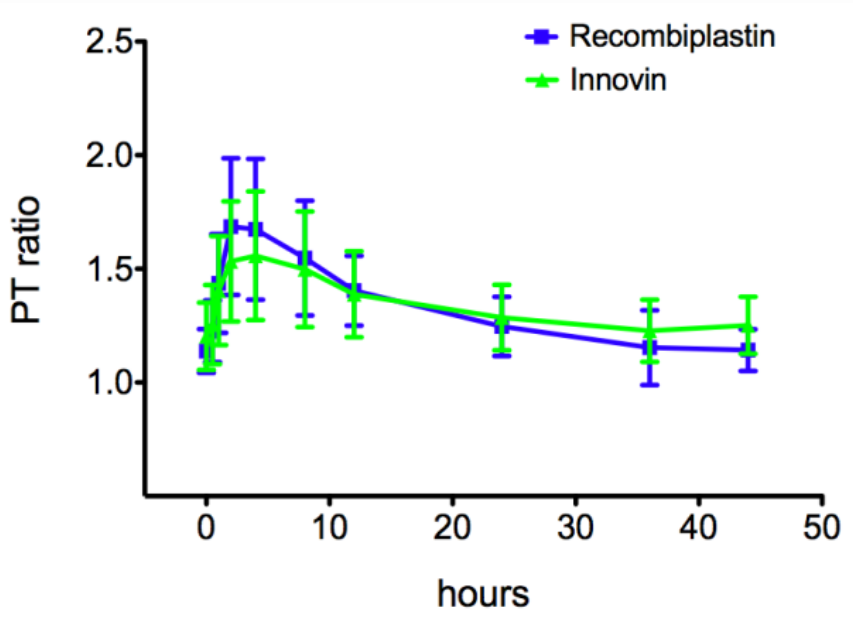
Chronic hemodialysis patients
No residual renal function
Single dose of 10 mg after dialysis





Single dose of rivaroxaban

(1) Stampfuss et al. Int J Clin Pharmacol Ther 2013; 51: 549-61
(2) Our data

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	Healthy Controls 20 mg (1)	Hemodialysis 10 mg (2)
AUC, µg/L/h	2294 (19) [1464-3227]	2072 (54.7) [1141-4946]
C_{max}, µg/L	294.4 (15) [225.4-360.6]	172.6 (45.5) [103-394]

Values are geometric mean (% coefficient of variation), [range]

Rivaroxaban: Effect of Dialysis

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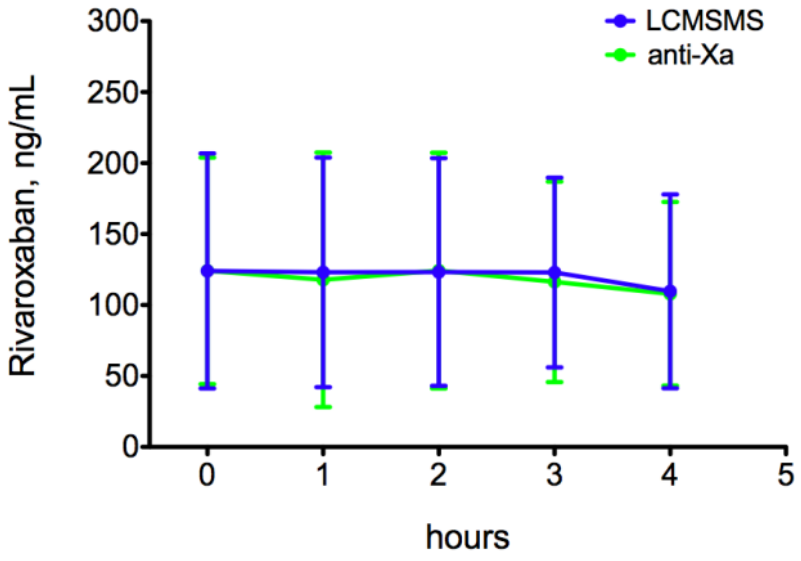
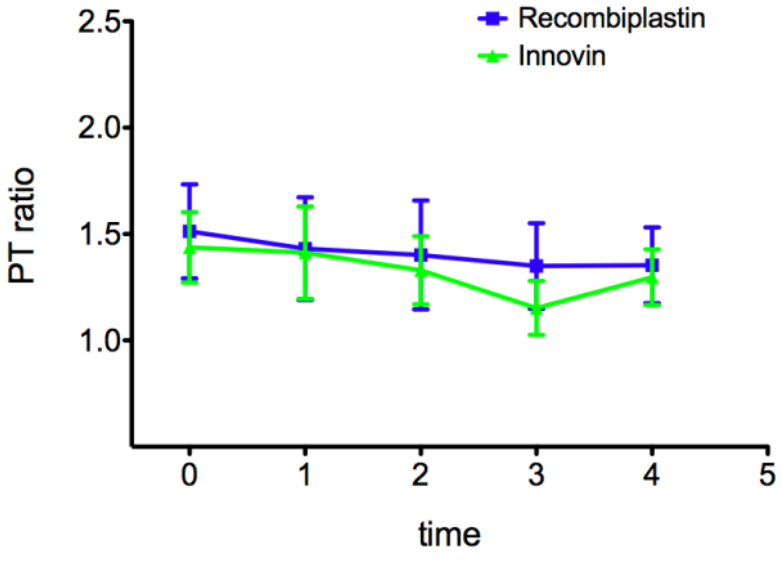
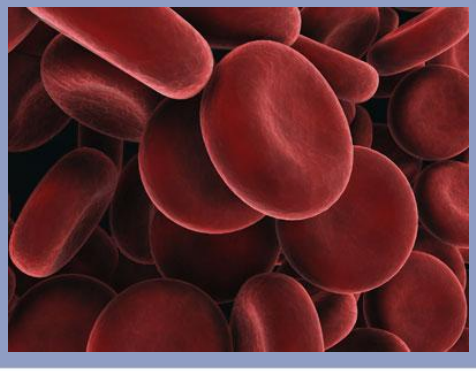




Current Status of Antidote Development

Greinacher et al. Thromb Haemost 2015; 113: 931–942



=Recombinant activated FX

=Fab-fragment humanised monoclonal antibody

=Small molecule

Antidote	Data available for	Ex vivo	Animal	Phase 1 & 2 trials*	Phase 3
andexanet alpha, PRT064445	apixaban	+	+	+[#]	+
	betrixaban	+	+	+	+
	rivaroxaban	+	+	+	+
	edoxaban	n.d.	n.d.	+	+
	fondaparinux	+	+	n.d.	+
	enoxaparin	+	+	+	+
idarucizumab	dabigatran	+	+	+	+
modified thrombin (γT -S195A-IIa)	dabigatran	+	+	n.d.	n.d.
aripazine (PER977)	apixaban	+	+	n.d.	n.d.
	rivaroxaban	+	+	n.d.	n.d.
	edoxaban	+	+	+	n.d.
	enoxaparin	+	+	n.d.	n.d.
	dabigatran	+	+	n.d.	n.d.
	heparin	n.d.	n.d.	planned	n.d.

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

Eerenberg L *et al*. Circulation 2011; 124:1573-1579

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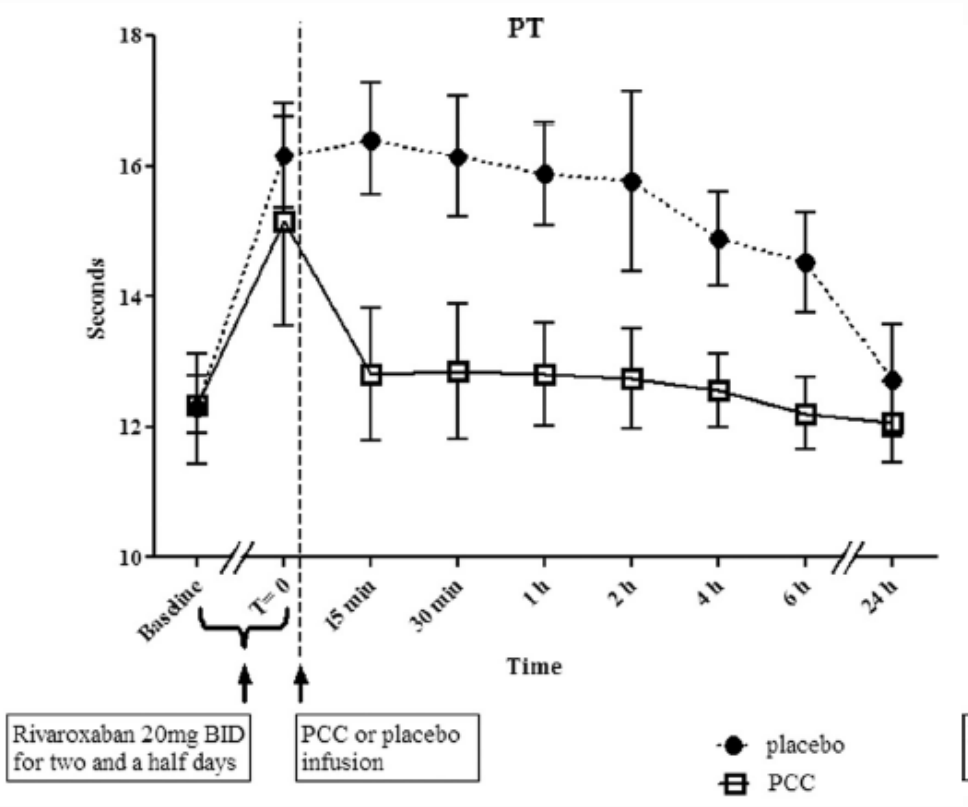
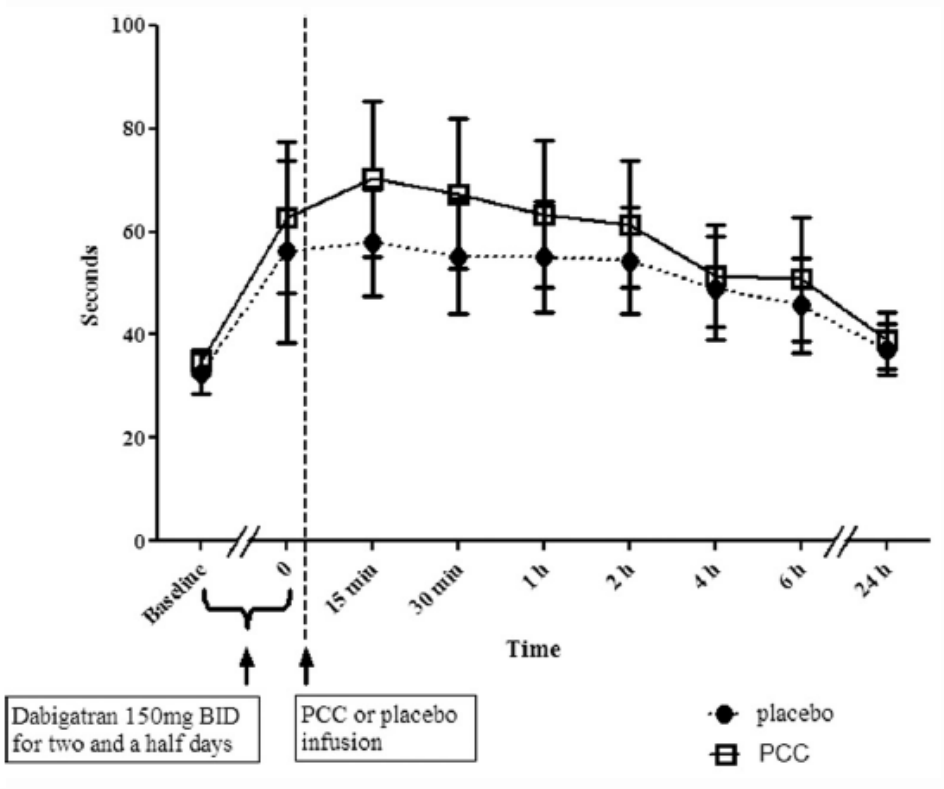
RIVAROXABAN



DABIGATRAN



NB: PCC=II, VII, IX, X

RCT in Hemodialysis patients with non-valvular AF

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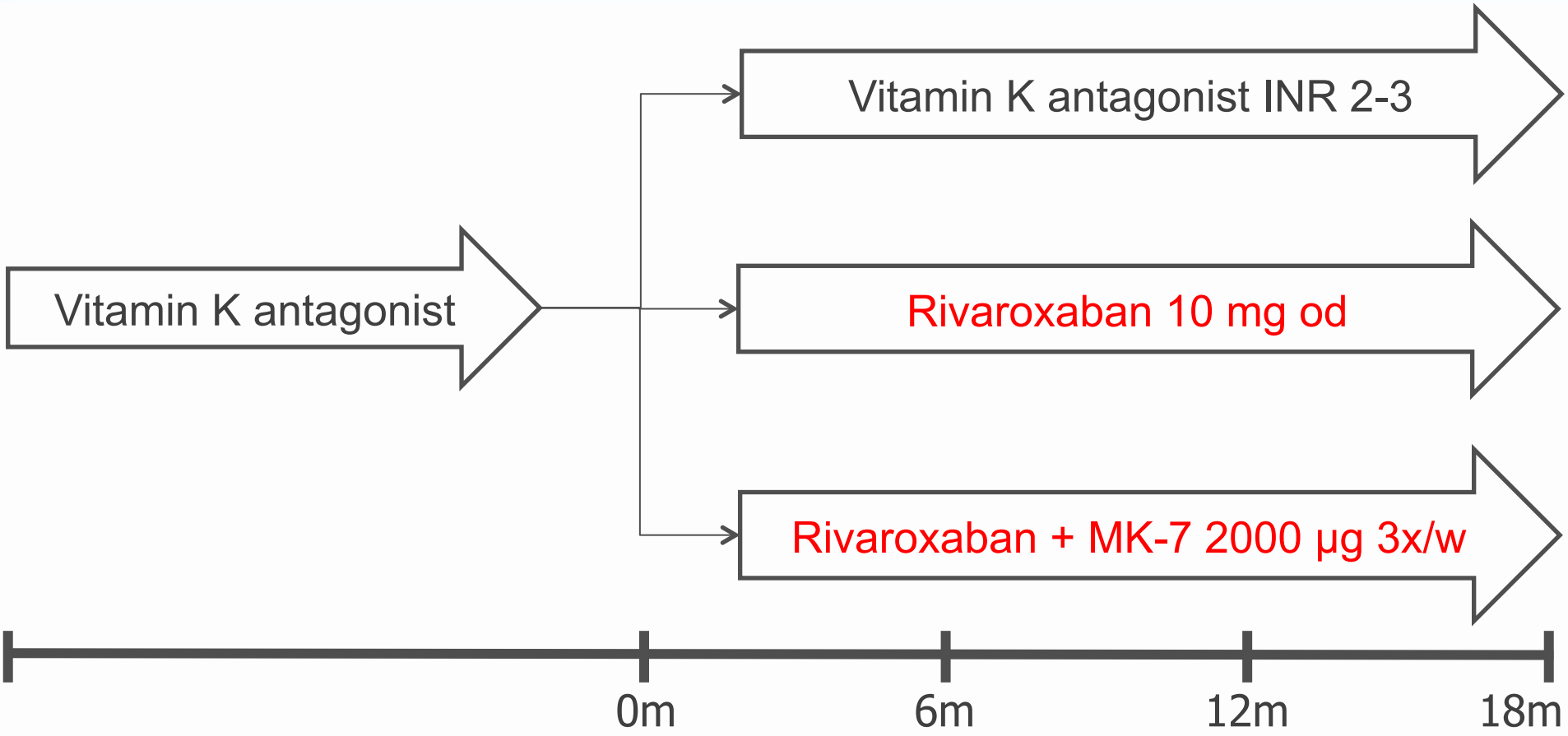
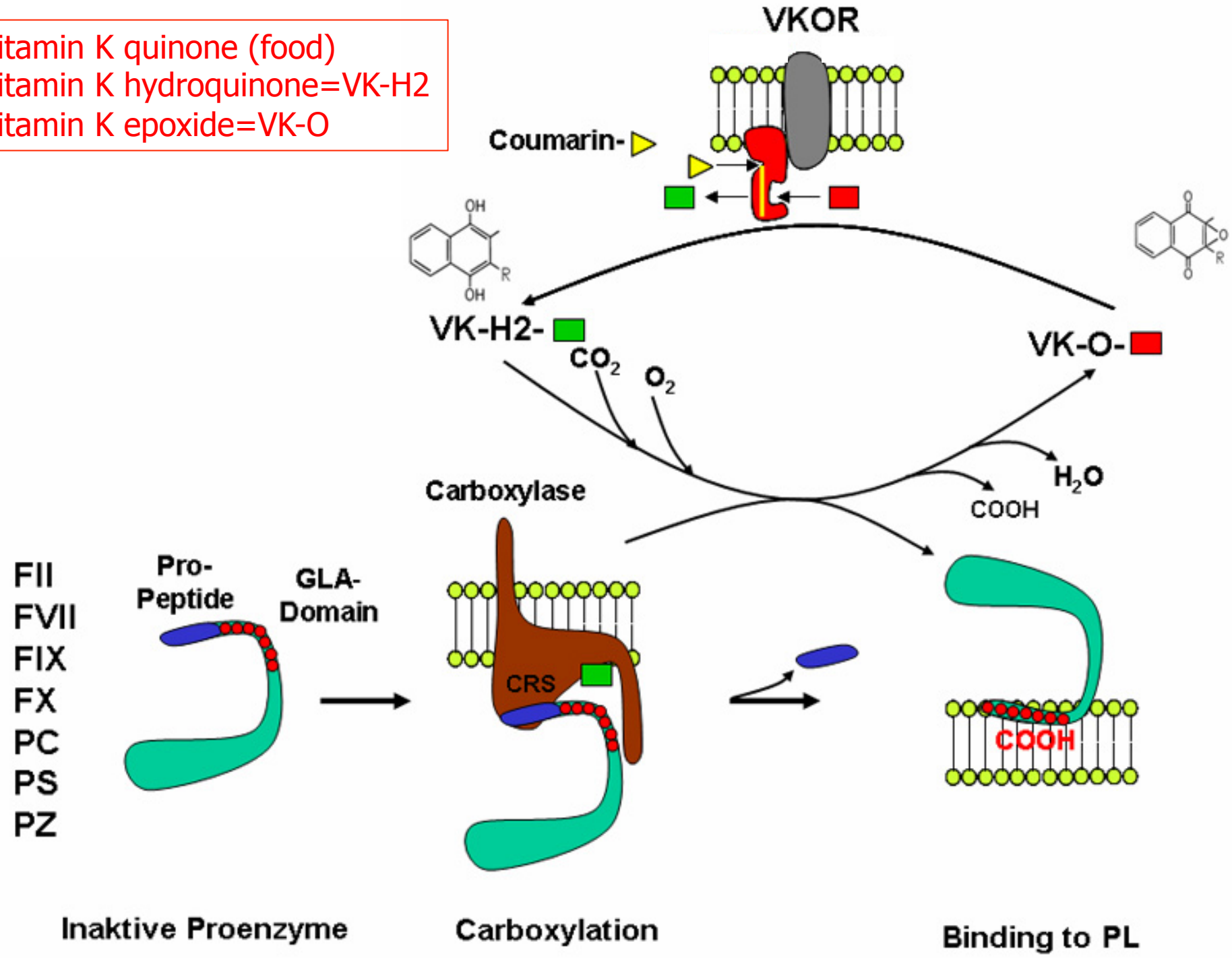


Progression of cardiovascular calcification and PWV


H. Draper

Vitamin K quinone (food)
Vitamin K hydroquinone=VK-H2
Vitamin K epoxide=VK-O



Ongoing RCTs Vitamin K versus Placebo

	Population	Vitamin K – duration	Endpoint
VitaVasK study (Europe)	348 prevalent hemodialysis patients	5 mg K1 3x/w – 18m	Thoracic aortic and coronary artery calcification
iPACK HD study (Canada)	80 incident hemodialysis patients	10 mg K1 3x/w – 12m	cardiovascular events and progression of cardiovascular calcification
Our study (Belgium)	117 prevalent hemodialysis patients with non-valvular AF	2000 µg K2 (MK7) – 18m	Thoracic aortic and coronary artery calcification, PWV
NCT00785109 (Aachen)		2 mg K1 1x/d -12m	progress of aortic valve calcification
NCT01002157 (Maastricht)	Patients with established CAC	360 µg K2 (MK7) – 24m	Coronary arterial calcification
NCT01922804 (Denmark)	Postmenopausal women	375 µg K2 (MK7) – 12m	bone mineral density, insulin sensitivity, arterial calcification

Ongoing RCTs VKA versus NOAC

	Population	NOAC (vs. VKA) duration	Endpoint
IRIVASC (Aachen)	253 AF or pulmonary embolism, CreaClear > 15 ml/min	Rivaroxaban 15/20 mg – 12m	Progression of coronary or valvular Agatston Score, IMT of carotid artery, FMD of brachial artery
Victoria (Angers)	150 AF, pulmonary embolism or venous thrombosis, CreaClear > 15 ml/min	Rivaroxaban 15/20 mg – 12m	Progression of coronary calcification, PWV, progression of calcification at the lower limbs
NCT02090075		Apixaban	Progression of coronary calcification
Our study (Belgium)	117 prevalent hemodialysis patients with non-valvular AF	Rivaroxaban 10 mg – 18m	Thoracic aortic and coronary artery calcification, PWV

$CHADS_2$	Score	CHA_2DS_2-VASc	Score
Congestive HF	1	Congestive HF	1
Hypertension	1	Hypertension	1
Age ≥ 75 y	1	Age ≥ 75 y	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
		Vascular disease (prior MI, PAD, aortic plaque)	1
		Age 65-74 y	1
		Sex category (i.e. female sex)	1
Maximum score	6	Maximum score	9

PS1: Application to dialysis population would result in the recommendation of anticoagulation in the vast majority of cases
PS2: Patients with severe kidney disease were excluded from the validation studies

Vitamin K ATG in dialysis: Decisions based on uncertainty

Juma *et al*. BMCN 2013; 14: 174

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Table 1 Nephrologist responses, depending on stroke and fall risk, and history of GI bleed

Case	CHADS2	CHADS-Vasc	Hemodialysis	GI bleed	Risk for falls	Likely to start warfarin (%)	Unlikely to start warfarin (%)	Uncertain (%)
1	2	3	No	No	No	80.4	3.6	16.1
2	2	3	Yes	No	No	50.0	14.3	35.7
3	5	6	Yes	No	No	76.7	3.6	19.6
4	5	8	Yes	No	Yes	23.2	28.6	48.2
5	5	8	Yes	Yes	No	48.2	8.9	42.9
6	5	8	Yes	Yes	Yes	3.6	67.9	28.6

Dominant driver of treatment:
provider preference/belief rather than patient factors

Rivaroxaban Clearance

Kubitza *et al*. Brit J Clin Pharmacol 2010; 70: 703-712

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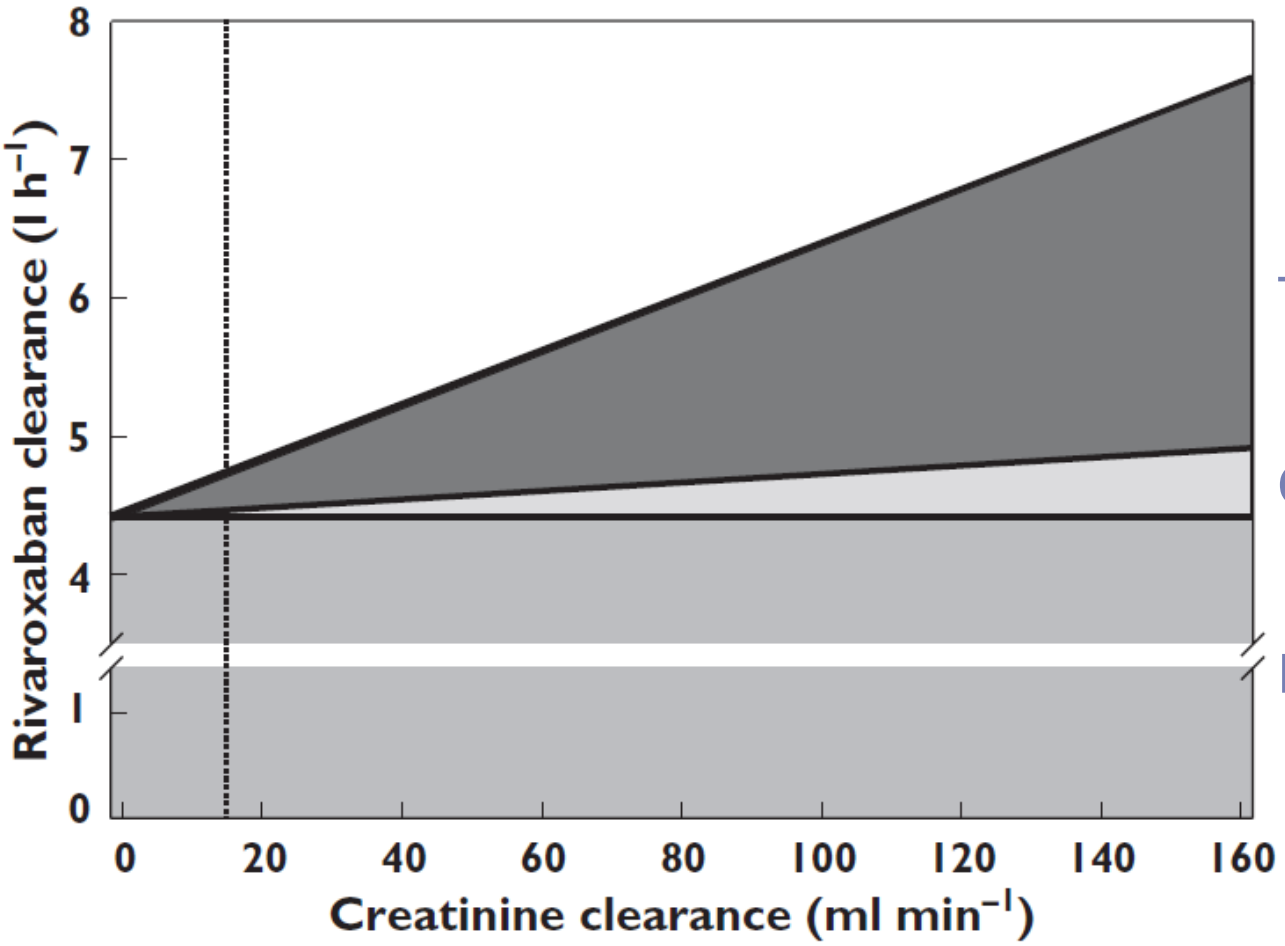

Tubular Secretion

Glomerular Filtration

Non-renal Clearance

Rivaroxaban at Steady State in Hemodialysis Patients

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6 chronic hemodialysis patients
No residual renal function
10 mg daily
24h AUC at day 1 and day 7