Amsterdam UMC
University Medical Centers

DOACs in de dagelijkse praktijk

Antifosfolipiden syndroom

Overgewicht

Nierinsufficiëntie

Michiel Coppens internist vasculair geneeskundige

Conflict of Interest Disclosure Form

Name: Michiel Coppens **Affiliation:** Amsterdam UMC

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	Bayer, Roche, CSL Behring, Sanquin Blood Supply, Daiichi Sankyo, UniQure, Portola
Receipt of honoraria or consultation fees:	Bayer, CSL Behring, Sobi, NovoNordisk, Pfizer, Bureau Prevents, MeDTalks, MEDCON **Alle bedragen werden ontvangen door Amsterdam UMC**
Participation in a company sponsored speaker's bureau:	
Stock shareholder:	
Other support (please specify):	
Scientific advisory board	Richtlijn Antitrombotisch Beleid (2016, FMS/NIV) Richtlijn Atriumfibrilleren (verw. 2021, FMS/NVVC) Richtlijn Bloedtransfusie, onderdeel Trombocytentransfusie (2019, NIV) Update richtlijn Hemofilie 2020 (NVHB) ASH VTE Guideline Thrombophilia Testing (exp. 2020, ASH)

DOAC's 1e keuze boven VKA

Voor de *gemiddelde patiënt*

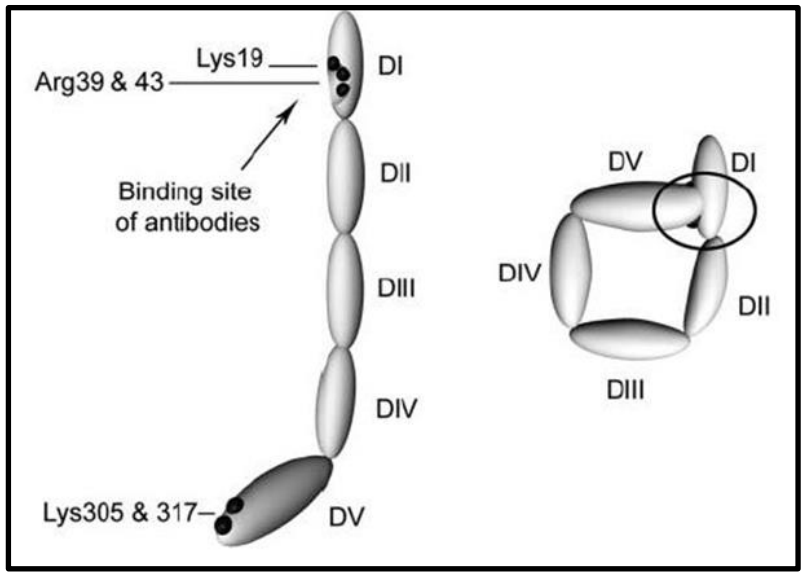
- 50% reductie intracraniële bloeding
  - 50% afname fatale bloeding
- 10% mortaliteitsafname

- 25% toename MDL bloeding

Federatie Medisch Specialisten
RICHTLIJNENDATABASE
Antitrombotisch beleid

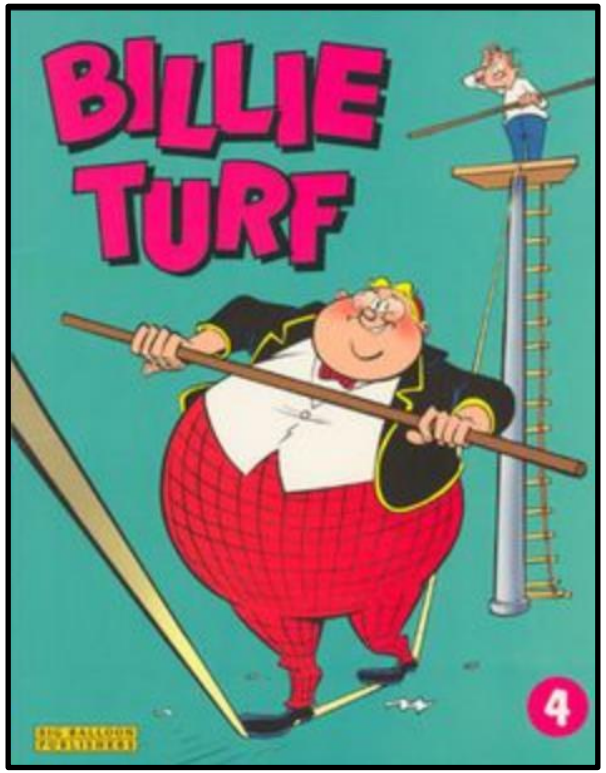
ESC GUIDELINES
European Society of Cardiology

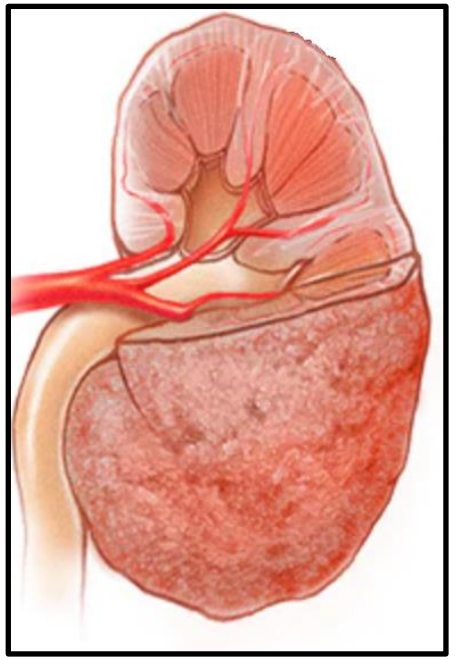
3 x Niet-gemiddeld



Antifosfolipidensyndroom

(Extreme) obesitas





Nierinsufficiëntie

Antifosfolipiden syndroom

Kliniek

- Trombose
  - Veneus
  - Arterieel
  - Microvasculair
- Zwangerschapscomplicaties
  - Miskraam AD ≥10 wkn
  - ≥3 miskramen AD <10 wkn
  - Prematuur (AD<34 wkn) tgv (pre)ecclampsie/placenta insuf

Laboratorium

- Lupus anticoagulans
- Cardiolipine a.s. (IgM, IgG)
- β2-Glycoproteïne-1 a.s. (IgM, IgG)
- Persisterend (12 wkn!!) aanwezig

EMA

Mogelijke praktische implicaties:

- Screenen APS a.s. bij
  - Acute VTE?
  - 2nd preventie, nu aan een DOAC?
  - (bij hart-/herseninfarct?)
- Initiële behandeling acute VTE
- Medico-legaal?

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Vittorio Pengo,[1] Gentian Denas,[1] Giacomo Zoppellaro,[1] Seena Padayattil Jose,[1] Ariela Hoxha,[2] Amelia Ruffatti,[2] Laura Andreoli,[3] Angela Tincani,[3] Caterina Cenci,[4] Domenico Prisco,[4] Tiziana Fierro,[5] Paolo Gresele,[5] Arturo Cafolla,[6] Valeria De Micheli,[7] Angelo Ghirarduzzi,[8] Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Doris Barcellona,[13] Maria Gerosa,[14] and Alessandra Banzato[1]

High-risk
=
Triple positive

Characteristic	Rivaroxaban (n = 59)	Warfarin (n = 61)
Females, n (%)	39 (66)	38 (62)
Age, y	46.5 ± 10.2*	46.1 ± 13.2*
APS laboratory test positivity, n		
LA: dRVVT/aPTT/both	16/5/38	14/7/40
aCL: IgG or IgG + IgM/IgM only	57/2	52/9
aβ2GPI: IgG or IgG + IgM/IgM only	57/2	52/9
Autoimmune disease, n (%)	24 (41)	25 (41)
Systemic lupus erythematosus	10	15
Other autoimmune disease	14	10

Previous thrombotic events, n (%)		
Arterial events	11 (19)	14 (23)
Stroke	8	8
Acute myocardial infarction	0	2
Other sites	3	4
Venous events	38 (64)	39 (64)
Deep vein thrombosis and/or pulmonary embolism	36	32
Other sites	2	7
Venous and arterial events	10 (17)	8 (13)
Pregnancy morbidity, n (%)†	16 (41)	12 (32)

Pengo, Blood 2018

TRAPS trial

Outcome, n	"As treated" analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	*P*
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01
Arterial thrombosis Ischemic stroke Myocardial infarction	7 (12) 4 (7) 3 (5)	0 0 0	—	—
Venous thromboembolism	0	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3
Death	0	0	—	—

- Vroegtijdig gestaakt
- Verschil zit in hart- en herseninfarct

Pengo, Blood 2018

Niet de enige trial

Annals of Internal Medicine ORIGINAL RESEARCH

Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome

A Randomized Noninferiority Trial

Josep Ordi-Ros, MD, PhD; Luis Sáez-Comet, MD, PhD; Mercedes Pérez-Conesa, MD; Xavier Vidal, MD, PhD; Antoni Riera-Mestre, MD, PhD; Antoni Castro-Salomó, MD, PhD; Jordi Cuquet-Pedragosa, MD; Vera Ortiz-Santamaria, MD; Montserrat Mauri-Plana, MD, PhD; Cristina Solé, PhD; and Josefina Cortés-Hernández, MD, PhD

Table 1. Characteristics of the Study Sample at Baseline

Characteristic	Rivaroxaban Group (n = 95)	VKA Group (n = 95)
Female sex, *n (%)*	61 (64.2)	60 (63.2)
Median age (IQR), *y*	47 (40–55)	51 (38–63)
Median duration of APS (IQR), *y*	7 (4–15)	6 (4–12)
Clinical criteria for initial anticoagulation, *n (%)*		
Venous thrombosis	69 (72.6)	70 (73.7)
Arterial thrombosis	37 (38.9)	34 (35.8)
Both arterial and venous thrombosis	11 (11.6)	9 (9.5)
Laboratory profile at inclusion, *n (%)*		
Lupus anticoagulant	93 (97.9)	90 (94.7)
Lupus anticoagulant alone	37 (38.9)	30 (31.6)
IgG/IgM antibodies		
aCL	62 (65.3)	65 (68.4)
Anti-β_2GPI	60 (63.2)	62 (65.3)
Anti-aPS/PT	31 (32.6)	33 (34.7)
Mean aCL/β_2GPI antibody level (SD)		
IgG aCL, *GPL units*	190.2 (6.5)	181.8 (275.5)
IgM aCL, *MPL units*	21.8 (30.4)	16.5 (20.3)
IgG anti-β_2GPI, *GPL units*	141.4 (241.9)	137.4 (262.8)
IgM anti-β_2GPI, *MPL units*	24.8 (31.9)	19.1 (31.6)
Lupus anticoagulant and IgG aCL and IgG anti-β_2GPI antibodies, *n (%)*	58 (61.1)	57 (60.0)

Lupus anticoagulans 96%
Triple positive 61%

Ordi-Ros, Ann Int Med 2019

Vergelijkbare resultaten:
Verschil arteriële events, niet veneus

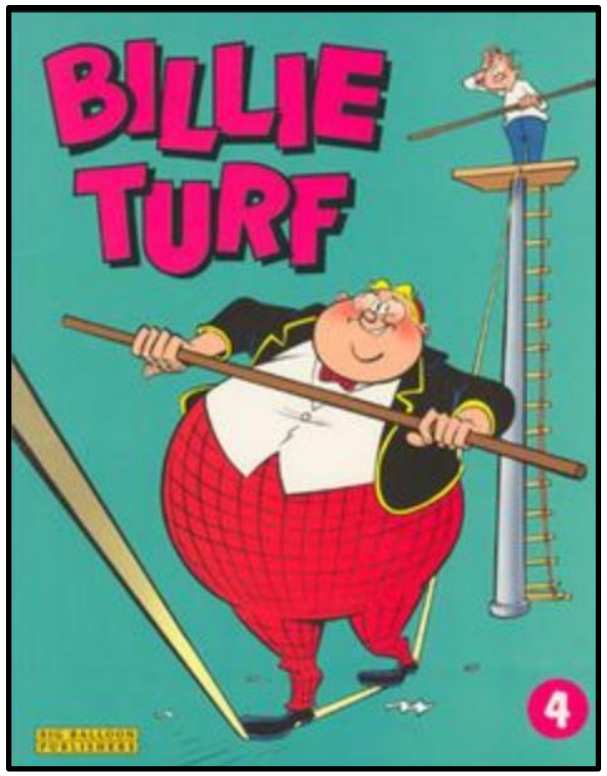
Study Population	Events, *n* (%)		Hazard Ratio (95% CI)‡	*P* Value
	Rivaroxaban Group (*n* = 95)	VKA Group (*n* = 95)†		
Per protocol, as treated				
All events	11 (11.6)	6 (6.3)	1.94 (0.72–5.24)	0.190
Arterial events§	10 (10.5)	3 (3.2)	3.52 (0.97–12.79)	0.060
Venous events§	2 (2.1)	3 (3.2)	0.70 (0.12–4.21)	0.70
Stroke	9 (9.5)	0 (0)	19.97 (1.00–400.0)	0.050

DOAC’s bij APS

- Minder bescherming tegen hart- en herseninfarct
- Bescherming tegen recidief VTE lijkt even goed
- Bij hoog-risico APS antistoffen (triple positive of tenminste lupus anticoagulans)
- Secundaire preventie studies, niet acute VTE

Mijn praktijk:

- Alleen APS testen bij clues
- Geen bezwaar tegen initieel DOAC
- Shared decision making



One size fits all?

Or does it?

Wat zeggen fase 3 trials?

Drug	Trial	Weight categories	Number of obese patients (%)
Dabigatran	RE-COVER I	≥ 100 kg	502/2539 (20)
		BMI ≥ 35	306/2539 (12)
	RE-COVER II	> 100 kg	438/1280 (34.2)
		BMI > 35	302/1280 (23.6)
	RE-LY	≥ 100 kg	3099/18 113 (17.1)
	RE-MEDY	≥ 100 kg	299/1430 (20.9)
	RE-SONATE	≥ 100 kg	122/681 (17.9)
Rivaroxaban	EINSTEIN DVT	> 100 kg	245/1731 (14.2)
	EINSTEIN PE	> 100 kg	345/2419 (14.3)
	EINSTEIN EXTENSION	> 100 kg	85/602 (14.1)
	ROCKET-AF	> 90 kg	2035/7131 (28.5)
		BMI > 35	972/7131 (13.6)
Apixaban	AMPLIFY	≥ 100 kg	522/2691 (19.4)
		BMI > 35	349/2691 (13.0)
	ARISTOTLE	None	
Edoxaban	ENGAGE AF TIMI 48	None	
	HOKUSAI VTE	> 100 kg	611/4118 (14.8)

Effectiviteit en veiligheid hetzelfde

MAAR

- Bulk patiënten milde range: 90/100 – 120 kg

ISTH SSC Scientific and Standardization Committee

Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH

K. MARTIN*, J. BEYER-WESTENDORF†, B. L. DAVIDSON‡, M. V. HUISMAN§, P. M. SANDSET¶, and S. MOLL*

1. Appropriate standard dosing in patients with a BMI ≤ 40 kg/m^2 or ≥120 kg

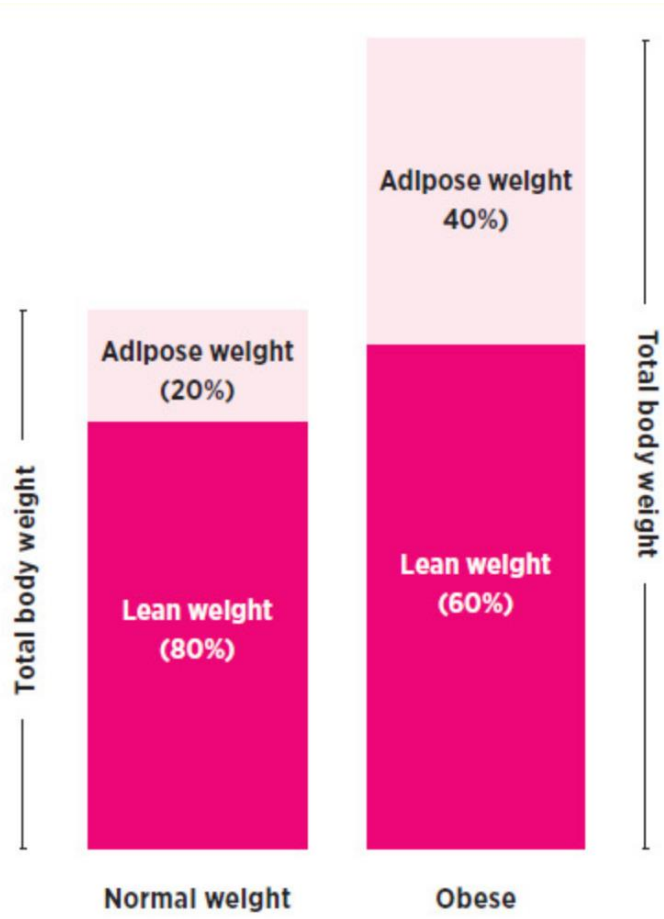
2. Suggest not to use DOACs should in patients with BMI > 40 kg/m^2 or >120 kg

3. If DOACs are used with BMI >40 kg/m^2 or weight >120 kg, suggest to check drug-specific peak and trough level

J Thromb Haemost 2016

Lichaamsgewicht vs. Verdelingsvolume (Vd)

- Toename gewicht geeft beperkte toename lean-body mass
- Zelfs lean-body mass ≠ Verdelingsvolume
  - Hydrofiele middelen: geen toename met obesitas
  - Lipofiele middelen:
    - Matige toename (aminoglycosides, caffeïne)
    - Geen toename (H2-receptor antagonisten, neuromusculaire blockers)
  - DOAC's…???



Cheymol, Clin Pharmacokinet 1993

PK van DOAC's mbt. lichaamsgewicht

	logP[b]	Volume of distribution (L)	Protein binding (%)
Apixaban	2.71	21	87
Dabigatran[a]	−2.4	60-70	35
Edoxaban	1.72	107	55
Rivaroxaban	2.18	50	94

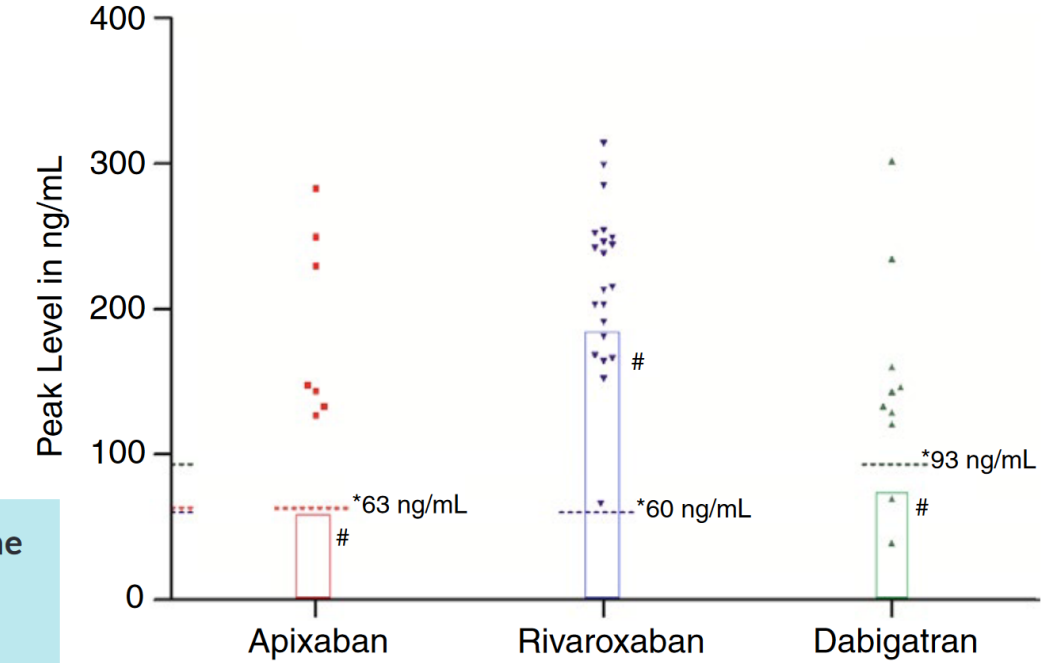
Piran, RPTH 2018 & Moll, RPTH 2018

BRIEF REPORT

rpth research & practice in thrombosis & haemostasis

Peak plasma concentration of direct oral anticoagulants in obese patients weighing over 120 kilograms: A retrospective study

Siavash Piran MD, MSc | Hugh Traquair MD | Noel Chan MD, MBBS | Vinai Bhagirath MD, MSc | Sam Schulman MD, PhD



DOAC	N	Median peak concentration from PK studies (ng/mL)[14-17]	Median peak plasma concentration ng/mL (IQR)	Peak plasma below the 5th percentile (10th percentile for dabigatran) peak concentration (N, %)
Apixaban	7	130 (5th-95th percentile range 59-302)	148 (138-240)	0 (0)
Dabigatran	10	184 (10th-90th percentile range 74-383)	138 (123-156.5)	2 (20)[a]
Rivaroxaban	21	249 (5th-95th percentile range 184-343)	215 (181-249)	6 (28)[b]
Overall	38	NA	NA	8 (21)

Piran, RPTH 2018 & Moll, RPTH 2018

DOAC’s en obesitas

- Toename lean-body mass en Vd << toename lichaamsgewicht

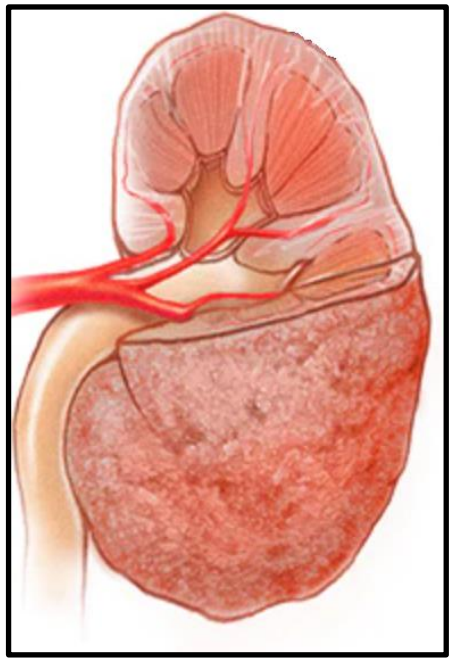
- < 120 kg / BMI 40 kg/m^2: geen afname effectiviteit

- > 120 kg / BMI 40 kg/m^2:
  - Lagere spiegel bij 0-30% van patiënten
  - Spiegelverificatie niet onredelijk

Typische bloedspiegels (ng/mL)

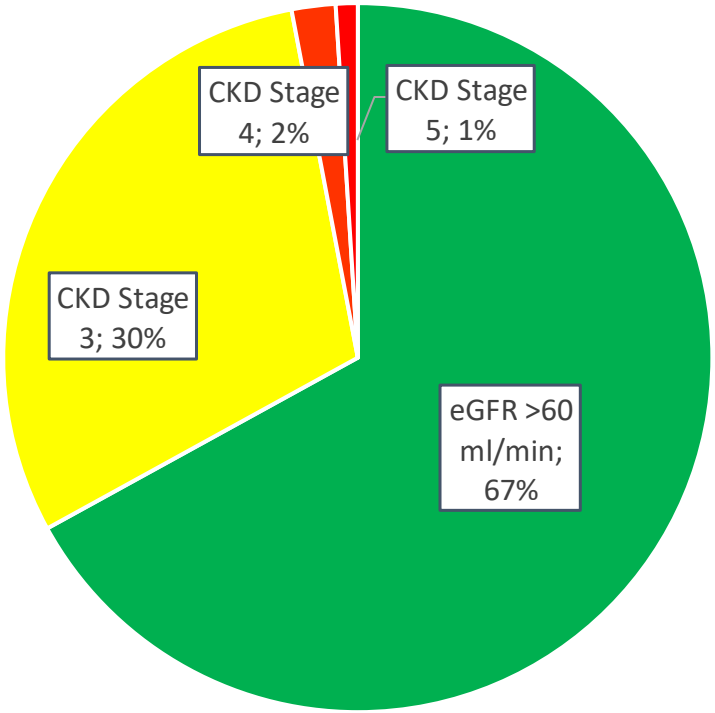
PIEKWAARDE	DALWAARDE
Dabigatran	
AF: 175 (p25-p75 117-275)	91 (p25-p75 61-143)
VTE: 175 (p25-p75 117-225)	60 (p25-p75 39-95)
Rivaroxaban	
AF: 249 (p5-p95 184-343)	44 (p5-p95 12-137)
VTE: 270 (p5-p95 189-419)	26 (p5-p95 6-87)
Apixaban	
AF: 171 (p5-p95 91-321)	103 (p5-p95 41-230)
VTE: 132 (p5-p95 59-203)	63 (p5-p95 22-177)
Edoxaban	
AF: 170 (+/- 1.5x IQR 125-245)	36 (p25-p75 19-62)
VTE: 234 (p25-p75 149-317)	19 (p25-p75 10-39)

Douxfils, J Thromb Haemost 2017



Chronische nierinsufficiëntie

CKD in AF patiënten



CKD 3 = 30-59 ml/min

30-44 ml/min 45-59 ml/min

30% 70%

'Slechts' 12% eGFR <45 ml/min

Hart, Can J Cardiol 2013

Hoger bloedingsrisico bij CKD?

Bleeding Risk with Dabigatran in the Frail Elderly

Table 1. Details of Episodes of Bleeding in 44 Patients Taking Dabigatran.*

Patient No.	Age	Sex	Weight	Daily Dose†	Site of Bleeding	Degree of Renal Impairment‡	Required Blood Products§
	yr		kg	mg			
3‖	77	M	60	300	Rectal	Moderate	Yes
4	78	F	NA	220	Rectal	Moderate	No
5‖	40	M	94	220	Rectal	Mild	Yes
6	65	F	79	300	Postoperative	Mild	Yes
7	71	M	73	300	Hematuria	Mild	No
8	75	F	NA	220	Rectal	Mild	No
9	75	F	NA	220	Rectal	Mild	Yes
10‖	67	M	69	220	Subdural hematoma	None	Yes
11¶	70	M	82	300	Rectal	None	No
12	70	F	70	NA	Hemarthrosis	None	No
13	71	M	74	300	Hematuria	None	No
14	73	F	67	300	Rectal	Severe	No
15‖	77	F	89	NA	Rectal	Severe	Yes
16‖**	82	M	50	220	Rectal	Severe	Yes
17	83	F	52	220	Hemoptysis	Severe	No
18	86	F	54	NA	Mucosal	Severe	No
19‖††	88	F	NA	300	Intracranial	Moderate	No
20¶‖	92	M	49	300	Rectal	Moderate	Yes
21‖	80	F	NA	NA	Subdural hematoma	Moderate	Yes
22	83	M	70	220	Rectal	Moderate	No

Harper, NEJM 2012

Case-series: alleen een teller…

… geen noemer

eGFR:
<50 ml/min: 58%
<30 ml/min: 14%

DOAC’s en nierfunctie

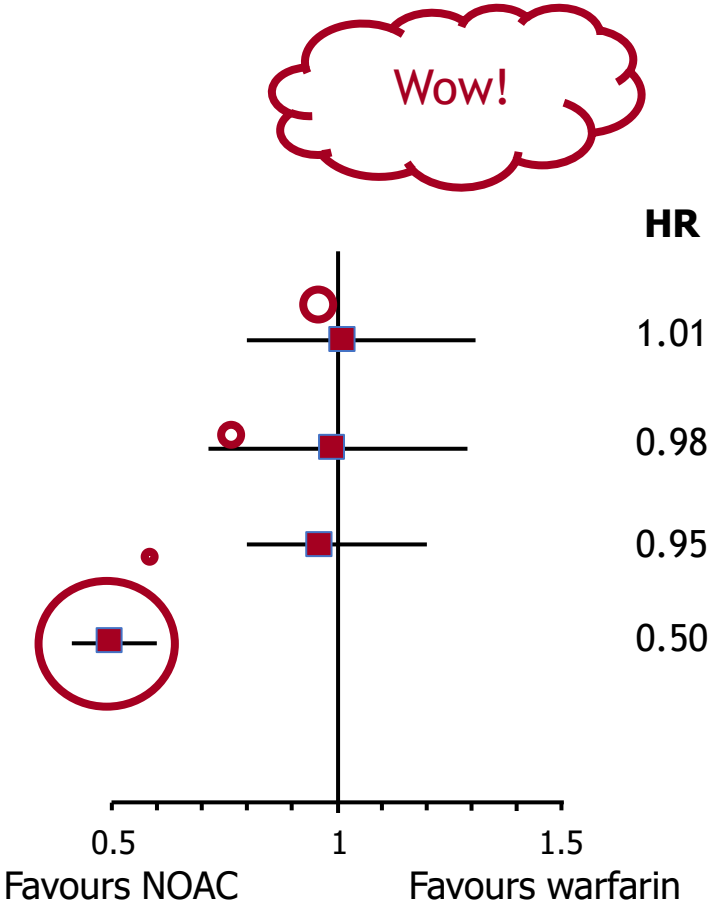
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
% renal clearance	80%	35%	25%	35%
eGFR exclusion criterion trials †	<30 ml/min	<30 ml/min	<25ml/min of kreat >221 uM	<30 ml/min
Ptn with eGFR < 50 ml/min, n (%)*†	3505 (19%)	3017 (17%)	2950 (21%)	4074 (19%)
Dose reduction eGFR < 50 ml/min†	— 26% for age 75-80 yrs; NOT for eGFR	— 25%	— 50% (with age ≥80 yr or weight ≤60kg)	— 50%

* in fase 3 AF trials † Cockcroft Gault

CKD 3 (eGFR 30-50 ml/min)

Major bleeding

	Study drug (%/yr)	Warfarin (%/yr)	HR
RE-LY®: Dabigatran 150 mg*[1,2]	5.44	5.41	1.01
RE-LY®: Dabigatran 110 mg*[1,2]	5.29	5.41	0.98
ROCKET AF: Rivaroxaban[3]	4.49	4.70	0.95
ARISTOTLE: Apixaban*[4]	3.21	6.44	0.50



1. Connolly S et al. NEJM 2009; 361:1139-51; **2.** Eikelboom J et al. Circulation 2011;123:2363-72;
3. Fox et al. Eur Heart J 2011; 32:2387-94; **4.** Hohnloser S et al. Eur Heart J 2012; 33:2821-31

CKD 4 (eGFR 15-30 ml/min)

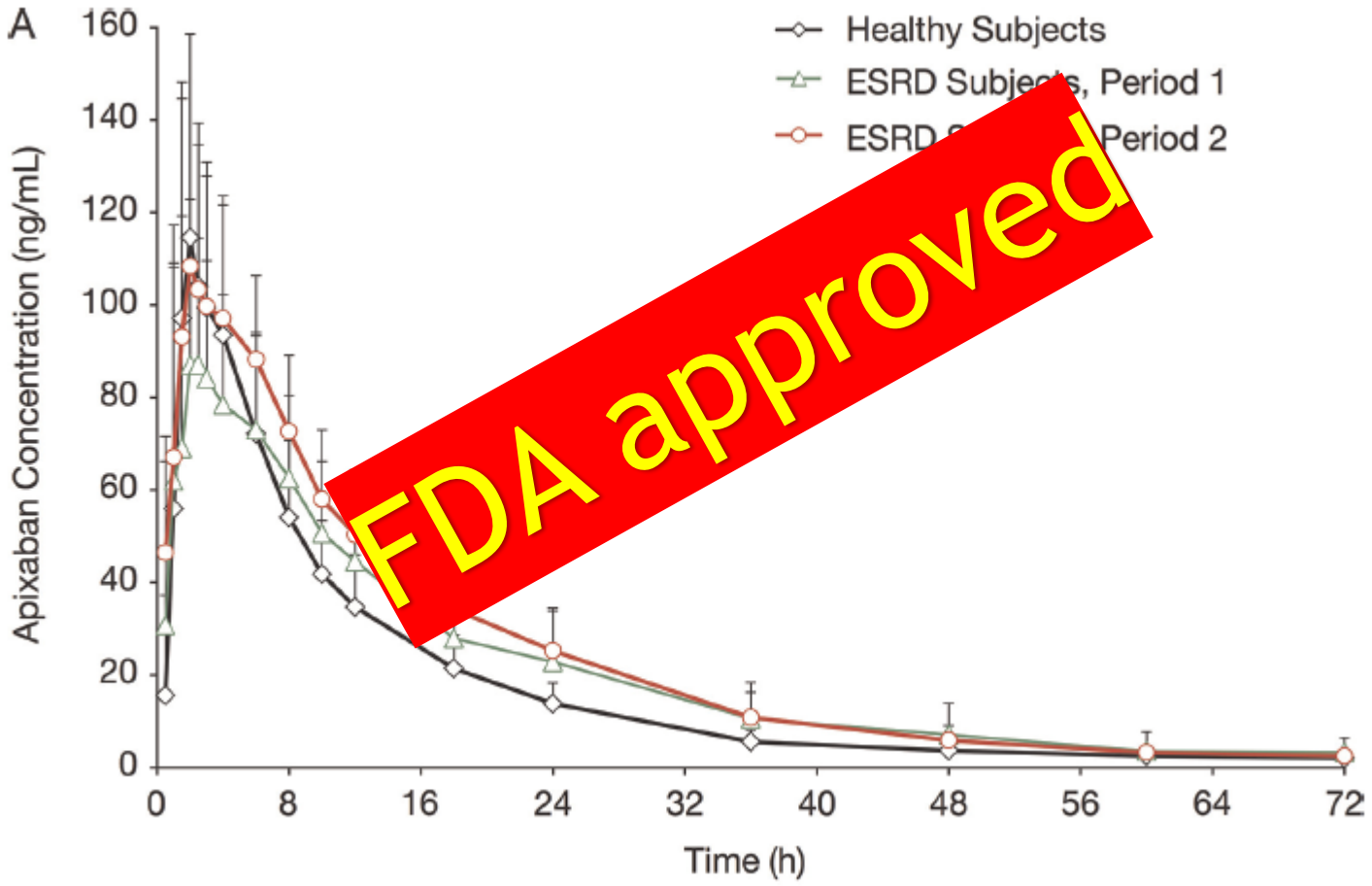
- Terra Incognita!
- Geen RCT's
  - Maar ook niet voor VKA

- Xa wel goedgekeurd voor CKD 4
  - Richtlijn AT Beleid 2016: GEBRUIK GEEN DOAC

- Richtlijnen AF bij eGFR <15-30 ml/min: primaire vs. secundaire preventie

[Acute VTE: LMWH 100% renaal geklaard…]

CKD 5 (eGFR <15 ml/min) met hemodialyse



- ESRD, N=8
- Single dose 5 mg
- Period 1: 2 h before dialysis
- Period 2: after dialyse

- 36% higher AUC
- Effect dialysis: - 13%

Wang, J Clin Pharmacol 2016

DOAC’s en chronische nierinsufficiëntie

- Hogere risico’s trombo-embolie én bloeding
- Überhaupt anticoagulantia bij eindstadium nierziekte??
- CKD = uiting van de broze patiënt
  - Misschien/waarschijnlijk belangrijker dan PK parameter
- Hoe belangrijk is nierfunctie bij 25%, 35%, 45% renale klaring voor cumulatie?

DOAC’s in niet-gemiddelde patiënten

- Logische en plausibele zorgen
- Op welk punt klapt “Voordelig voor gemiddelde patiënt” om naar “Neutraal” en om naar “Nadelig”…
- Beperkte evidence geen ondersteuning voor de zorgen
- *In dubio abstine* discutabel bij duidelijk voordeel voor de “gemiddelde patiënt”