Novara 7 Giugno 2018

DOACS nel 2018: a che punto siamo?

Fabrizio UGO

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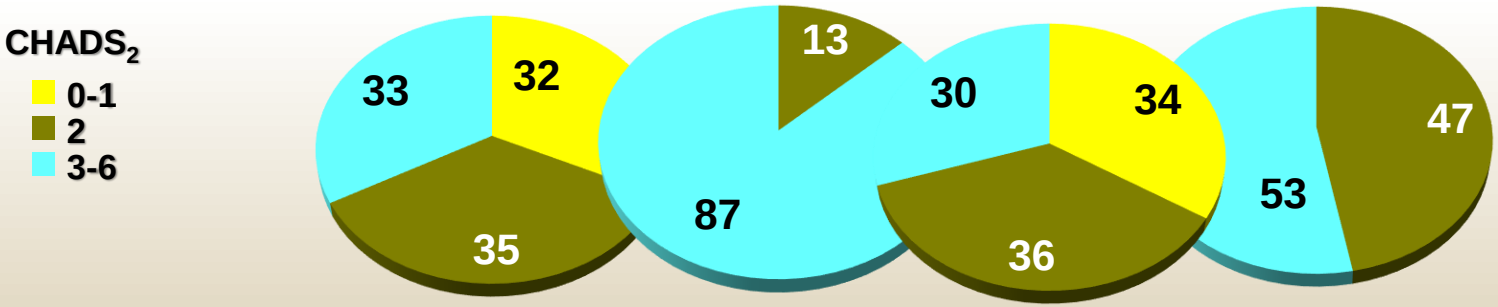
Baseline characteristics in AF trials

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
Randomized, n	18,113	14,264	18,201	21,105
Age, years	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	36	39
$CHADS_2$ score	2.1	3.5	2.1	2.8
Paroxysmal AF, %	32	18	15	25
Prior stroke/TIA, %	20	55	19	28
VKA naïve, %	50	38	43	41
Aspirin use, %	40	36	31	29
Median follow-up, years	2.0	1.9	1.8	2.8
Median TTR, %	66	58	66	68



1. Connolly SJ et al. N Engl J Med 2009;361:1139-1151; 2. Patel MR et al. N Engl J Med 2011;365:883-891;
3. Granger CB et al. N Engl J Med 2011;365:981-992; 4. Giugliano RP et al. N Engl J Med 2013;369:2093-2104.

NOAC AF studies

	RE-LY[1]	ROCKET-AF[2]	ARISTOTLE[3]	ENGAGE AF[4]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
N	18,113	14,264	18,201	21,105
Dose (mg)	150, 110	20	5	60, 30
Frequency	BID	QD	BID	QD
Initial dose reduction	No	20→15 mg	5→2.5 mg	60→30 mg 30→15 mg
Dose reduction at baseline, %	0	21	5	25
Dose modification after randomization	No	No	No	Yes (7%)
Target INR (warfarin)	2.0–3.0	2.0–3.0	2.0–3.0	2.0–3.0
Design	PROBE	2x blind	2x blind	2x blind
Follow up (years)	2.0	1.9	1.8	2.8

PROBE = prospective, randomized, open-label, blinded end-point evaluation

1. Connolly et al. N Engl J Med 2009;361:1139–1151; 2. Patel et al. N Engl J Med 2011;365:883–891
3. Granger et al. N Engl J Med 2011;365:981–992; 4. Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Dose reduction for patient characteristics in NOAC studies

RE-LY[1]	ROCKET-AF[2]	ARISTOTLE[3]	ENGAGE-AF[4]
• None	• 20→15 mg QD for: – Creatinine clearance <30–49 mL/min	• 5→2.5 mg BID for ANY TWO of: – Age ≥80 years – body weight ≤60 kg – Serum creatinine ≥1.5 mg/dL	• 60→30 mg QD for: – Creatinine clearance 30–50 mL/min – body weight ≤60 kg – Use of quinidine, verapamil or dronedarone

BID=twice daily; QD=once daily

1. Connolly et al. New Engl j Med 2009;361:1139–1151. 2. Patel et al. N Engl J Med 2011;365:883–891.
3. Granger et al. N Engl J Med 2011;365:981–992. 4. Giugliano et al. N Engl J Med 2013; e-pub ahead of print

DOACs 2018: update

- Fibrillazione atriale e valvole
- Insufficienza renale – calcifilassi – pazienti in dialisi
- Pz oncologico
- Soggetti con FA ed obesi
- Gestione dei sanguinamenti
- Aderenza

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Selected indications and contraindication for DOACs in AF pts

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Severe aortic stenosis	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post operatively)	Not advised if for rheumatic mitral stenosis
	Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post operatively)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

2018 EHRA Pratical Guide on NOACs in AF

Findings of studies with AF pts and bioprosthetic valves

Authors	Study design	NOACs	Bioprosthesis, *n* (%)	Surgical valve repair, *n* (%)	Stroke/TIA/SE	Major bleedings	Follow-up
Breithardt et al[14]	Posthoc analysis phase III trial	Rivaroxaban	–	64 valvuloplasty (60.4%) 42 other cardiac procedure (39.6%)	2.01% per year	6.14% per year	1.9 y
Avezum et al[15]	Posthoc analysis phase III trial	Apixaban	132 previous valve surgery		1.31% per year	4.55% per year	1.8 y
Carnicelli et al[16]	Posthoc analysis phase III trial	Edoxaban	191 Aortic bioprosthesis (31.4%) Mitral bioprosthesis (68.6%)	–	1.19% per year (60 mg od) 2.57% per year (30 mg od)	Similar to warfarin 6.27% per year 0.76% per year (30 mg od)	2.8 y
Durães et al[17]	Phase II prospective, open-label, randomized, pilot study	Dabigatran	15 Isolated mitral bioprosthesis (73.3%)	–	6.7%	–	90 d
Yadlapati et al[11]	Retrospective single-center cohort study	Dabigatran (60.3%) Rivaroxaban (34.2%) Apixaban (5.5%)	60 Aortic bioprosthesis (65.8%) Mitral bioprosthesis (16.4%)	13 Root reconstruction with aortic bioprosthesis (17.8%)	1.4%	6.9%	511.8 ± 400.8 d
Di Biase et al[12]	Prospective single-center cohort study	Rivaroxaban (70%) Apixaban (30%)	127 Aortic bioprosthesis (59%) Mitral bioprosthesis (41%)	–	0% per year	1.6% per year	1 y
Russo et al (current study)	Retrospective multicenter cohort study	Apixaban (54%) Dabigatran (31%) Rivaroxaban (15%)	76 Aortic bioprosthesis (42.6%) Mitral bioprosthesis (19.7%)	46 Aortic repair (33.6%) Mitral repair (4.1%)	0.8% per year	1.3% per year	835 ± 203 d

Abbreviation: AF, atrial fibrillation; NOACs, nonvitamin K antagonist oral anticoagulants; od, once a day; TIA, transient ischemic attack.

Russo V. et al. Semin Thromb Hemost. 2018; 44: 312- 314

Accepted Manuscript

Oral anti-Xa anticoagulation after Trans-Aortic Valve Implantation for Aortic Stenosis: The randomized ATLANTIS trial

Jean-Philippe Collet, Sergio Berti, Angel Cequier, Eric Van Belle, Thierry Lefevre, Pascal Leprince, Franz-Josef Neumann, Eric Vicaut, Gilles Montalescot

PII: S0002-8703(18)30080-2
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Reference: YMHJ 5647

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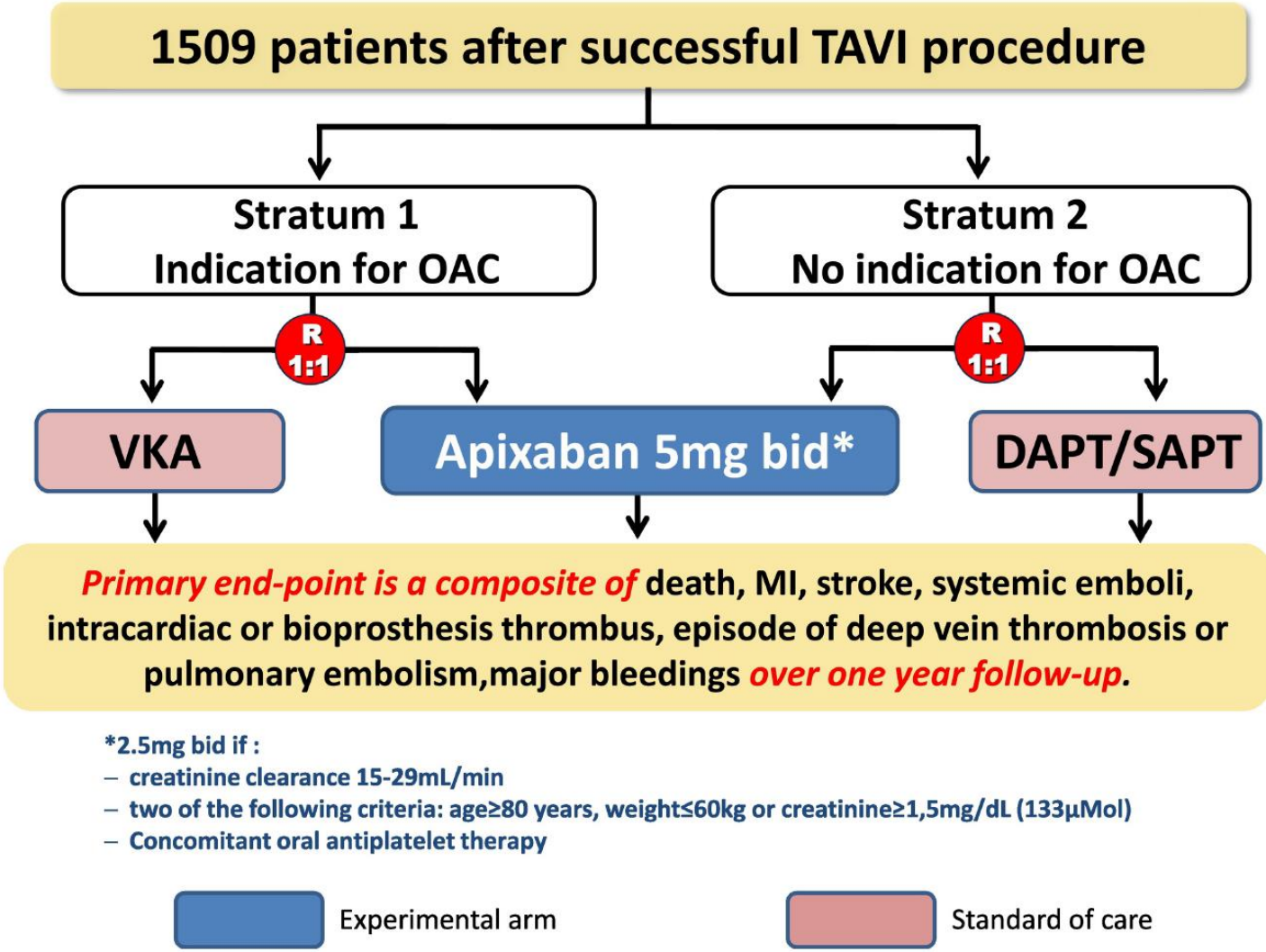
ATLANTIS: Study design



DOACs 2018: update

- Fibrillazione atriale e valvole
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Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation

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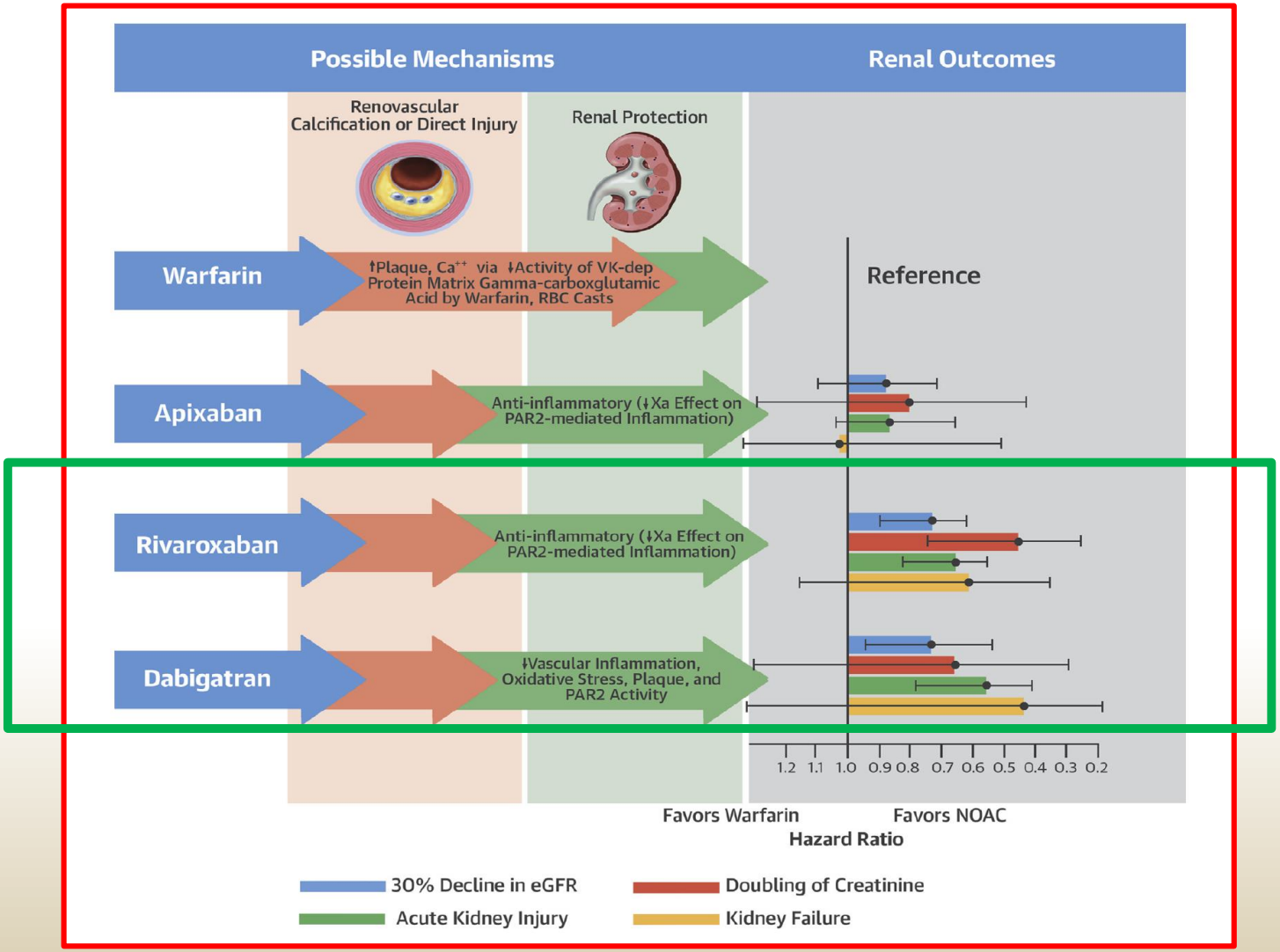
OBJECTIVES This study aimed to compare 4 oral anticoagulant agents (apixaban, dabigatran, rivaroxaban, and warfarin) for their effects on 4 renal outcomes: ≥30% decline in estimated glomerular filtration rate (eGFR), doubling of the serum creatinine level, acute kidney injury (AKI), and kidney failure.

METHODS Using a large U.S. administrative database linked to laboratory results, the authors identified 9,769 patients with nonvalvular AF who started taking an oral anticoagulant agent between October 1, 2010 and April 30, 2016.

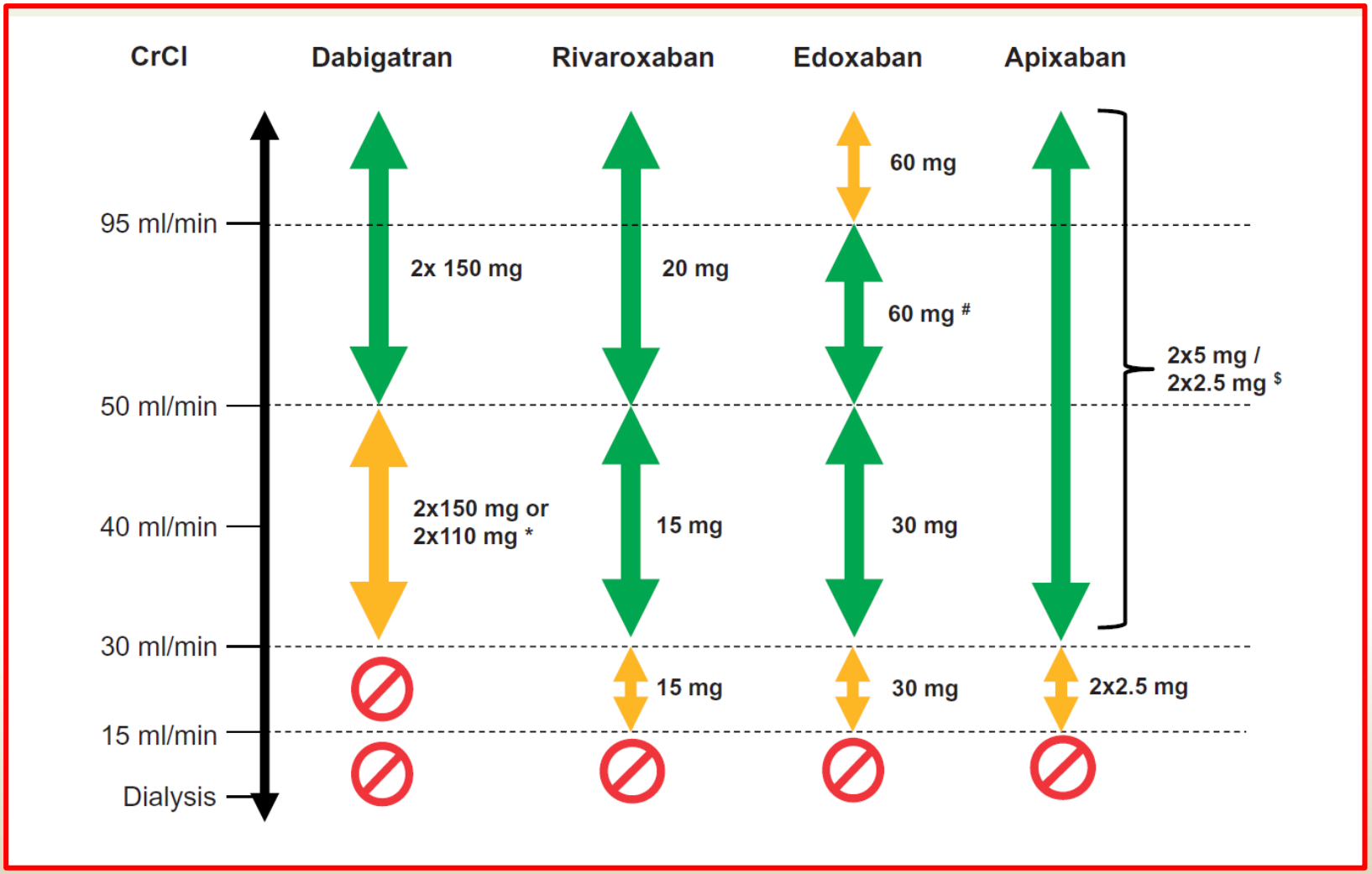
Yao X. Et al. JACC 2017;70: 2621 - 32

Renal Outcomes Associated With the Various Oral Anticoagulant Agents



Yao X. Et al. JACC 2017;70: 2621 - 32

Use of DOACs according to renal function



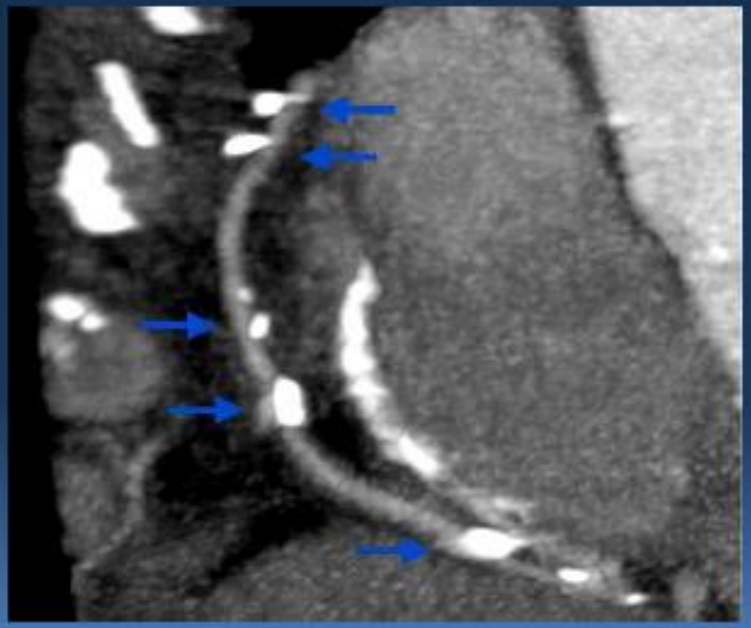
2018 EHRA Pratical Guide on NOACs in AF

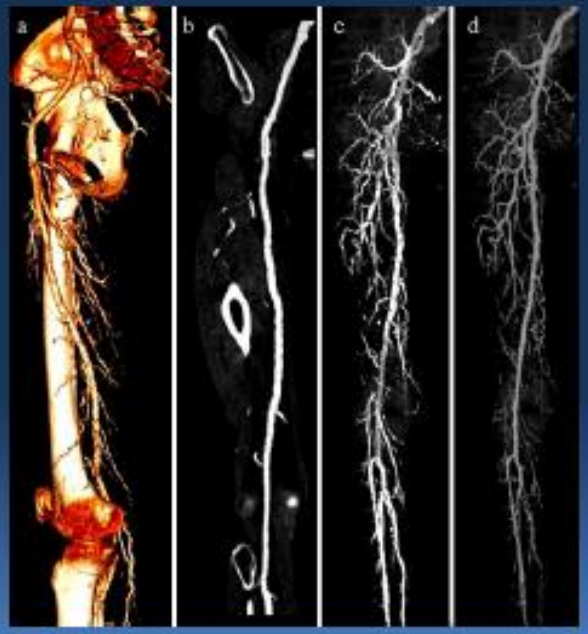
WARFARIN IN CKD PATIENTS

Calcific uremic arteriopathy occurs in 1–4% of dialysis patients and portends a poor prognosis (45% mortality at 12 months).

Vitamin K antagonists affect the synthesis and function of the matrix Gla protein, which is a potent inhibitor of tissue calcification.

In dialysis patients, warfarin has been linked to calcific uraemic arteriopathy (calciphylaxis) as well as aortic valve calcification.





Koos R, Mahnken AH, Muhlenbruch G, Brandenburg V, Pflueger B, Wildberger JE *et al.*
Relation of oral anticoagulation to cardiac valvular and coronary calcium assessed by multislice spiral computed tomography.
Am J Cardiol 2005;96:747–9.

Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2017;46:249–256
DOI: 10.1159/000481207

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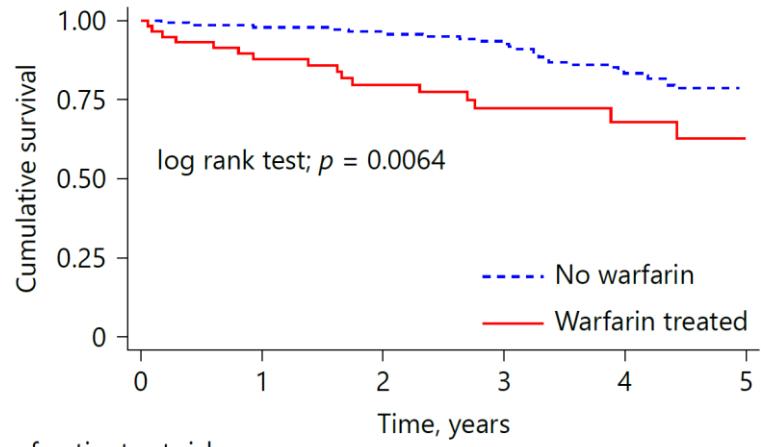
Accepted: September 02, 2017
Published online: September 15, 2017

Warfarin Use and Increased Mortality in End-Stage Renal Disease

Mark C. Lin[a] Elani Streja[b, c] Melissa Soohoo[b, c] Medhat Hanna[a] Javad Savoj[d] Kamyar Kalantar-Zadeh[b, c] Wei Ling Lau[b, c]

[a]School of Medicine, [b]Division of Nephrology and Hypertension, Department of Medicine, and [c]Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California, Irvine, CA and [d]Department of Internal Medicine, Riverside Community Hospital, University of California, Riverside School of Medicine, Riverside CA, USA

A retrospective matched cohort study,
Follow-up 5.8 years



Number of patients at risk, *n*

No warfarin	144	137	132	115	92	0
Warfarin treated	59	49	38	28	16	0

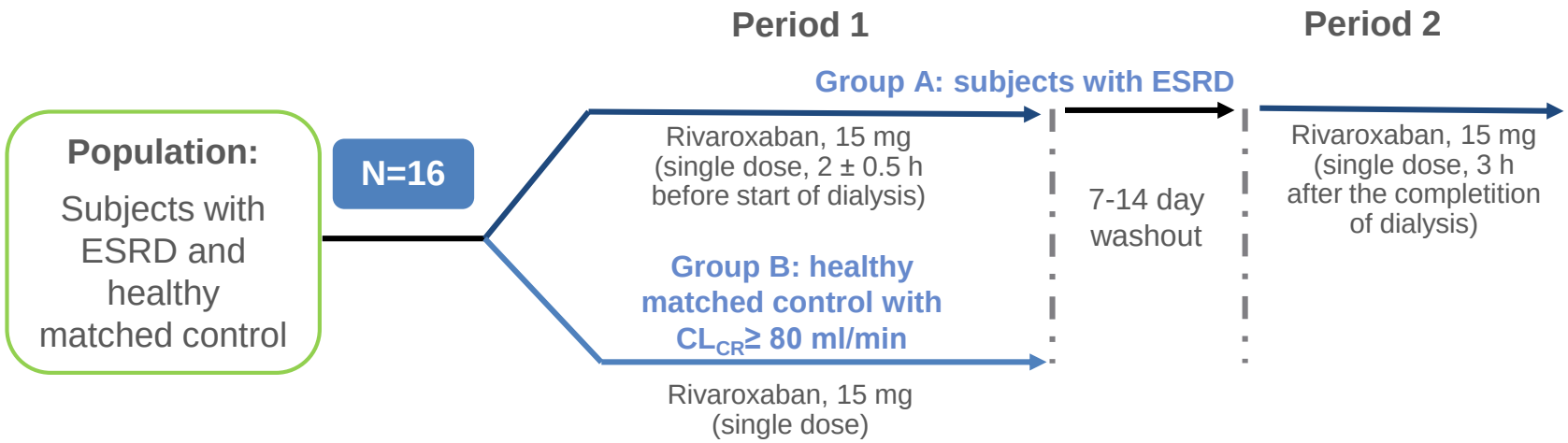
AMONG WARFARIN USERS:

Significant bleeding (incident rate ratio, IRR 3.57 with 95% CI 1.51–8.45; $p < 0.01$)

Myocardial infarction (IRR 4.20 with 95% CI 1.78–9.91; $p < 0.01$)

PK, PD and Safety of Single-Dose Rivaroxaban in Chronic Hemodialysis

Objective: (1) to characterize the single-dose PK and PD of rivaroxaban administered as a 15-mg dose, both once before and once after dialysis, in subjects with ESRD, and (2) to compare this PK and PD profile in subjects with ESRD to that in healthy control subjects with CL CR ≥ 80 ml/min



Results:

- rivaroxaban plasma AUC increased by 56% administered post-dialysis. This reflects an approximate 35% decrease in overall clearance due to ESRD;
- rivaroxaban administration prior to a 4-hour hemodialysis session resulted in only a 5% lowering of plasma AUC as compared to the AUC with post-dialysis dosing, indicating that dialysis has a minimal impact on the PK of rivaroxaban;
- No bleeding events occurred during the study

Dias C. *et al. Am J Nephrol*. 2016;43:229-36

CLINICAL RESEARCH www.jasn.org

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

7 pts

dose in patients with preserved renal function. Apixaban 2.5 mg twice daily in patients on hemodialysis resulted in drug exposure comparable with that of the standard dose (5 mg twice daily) in patients with preserved renal function and might be a reasonable alternative to warfarin for stroke prevention in patients on dialysis. Apixaban 5 mg twice daily led to supratherapeutic levels in patients on hemodialysis and should be avoided.

CLINICAL RESEARCH www.jasn.org

Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

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

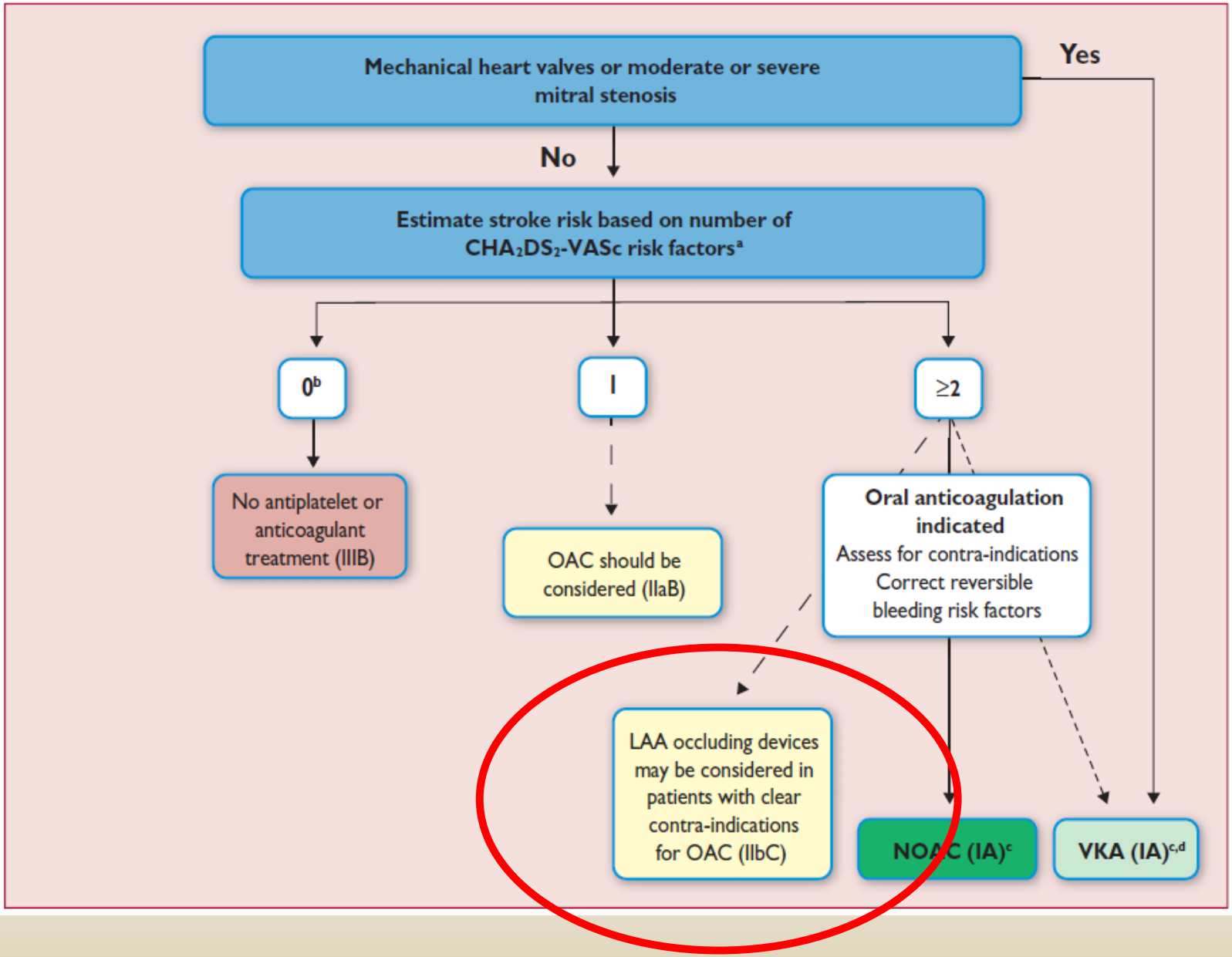
*Division of N ... IcGill ... ec, Canada; and †Division of General Intern ... cal Pha ..., Geneva University Hospitals, Geneva, Switz

Apixaban 2,5mg TD

7 pts

dose in patients with preserved renal function. Apixaban 2.5 mg twice daily in patients on hemodialysis resulted in drug exposure comparable with that of the standard dose (5 ... ts with preserved renal function and might be ... r stroke ... n dialysis. Apixaban 5 mg twice daily led to su ... emodia ... led.

Apixaban 5mg TD



2016 ESC Guidelines for AF

DOACs 2018: update

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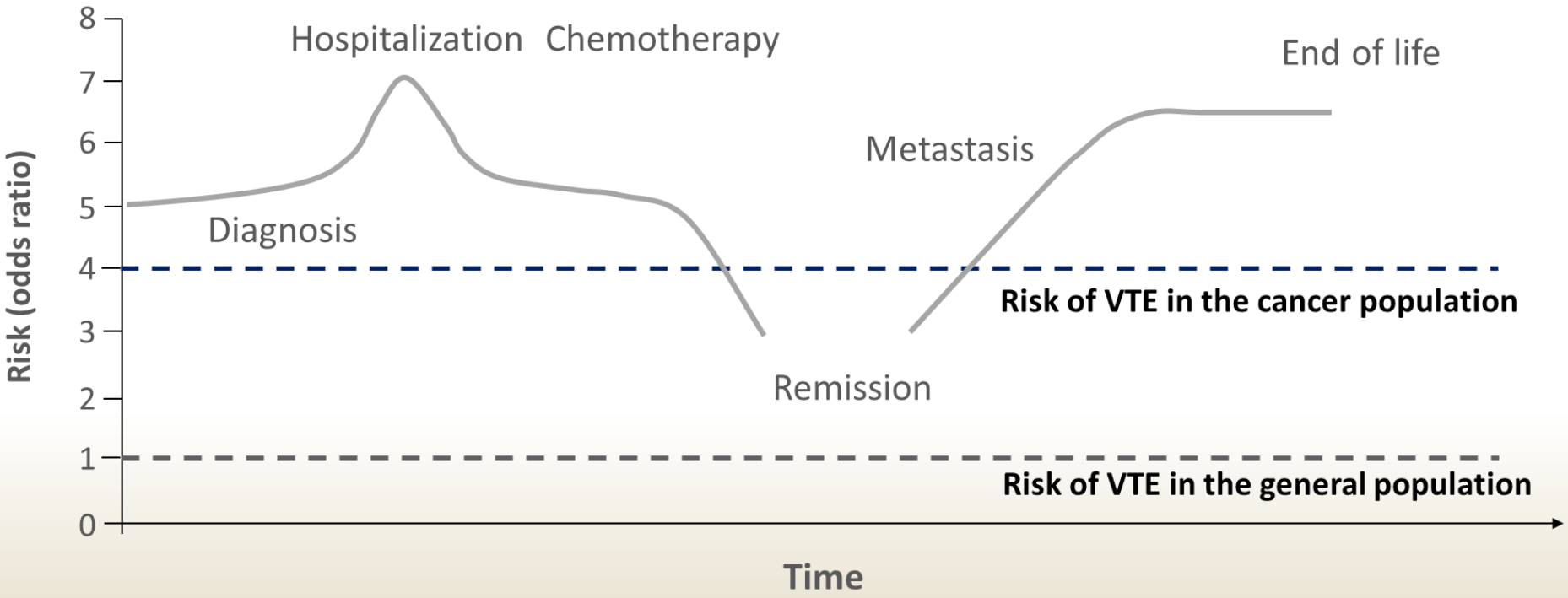
Atrial fibrillation and malignacy

Interdisciplinary teamwork
(1) Estimate individual patient risk profile • AF-related risk factors (CHA_2DS_2-VASc, bleeding risk) • Cancer-related risk factors (type, liver metastases, coagulopathy, renal/hepatic function etc. • Treatment-related risk factors (thrombocytopenia, surgery, radiation, central lines etc.) (2) Choose anticoagulant • Current standard of care: VKA/(LMWH)[a] • NOACs: Available data scarce, but encouraging • Consider patient preference (VKA vs. NOAC) (3) Protect the patient • Gastric protection (PPI/H2 blockers) • Beware of drug–drug interactions (*Table 4*) • Dose reduction/treatment interruption (if platelets <50k, renal dysfunction, bleeding, . . .)
Beware • Risk of thromboembolism ↑ • Risk of bleeding ↑

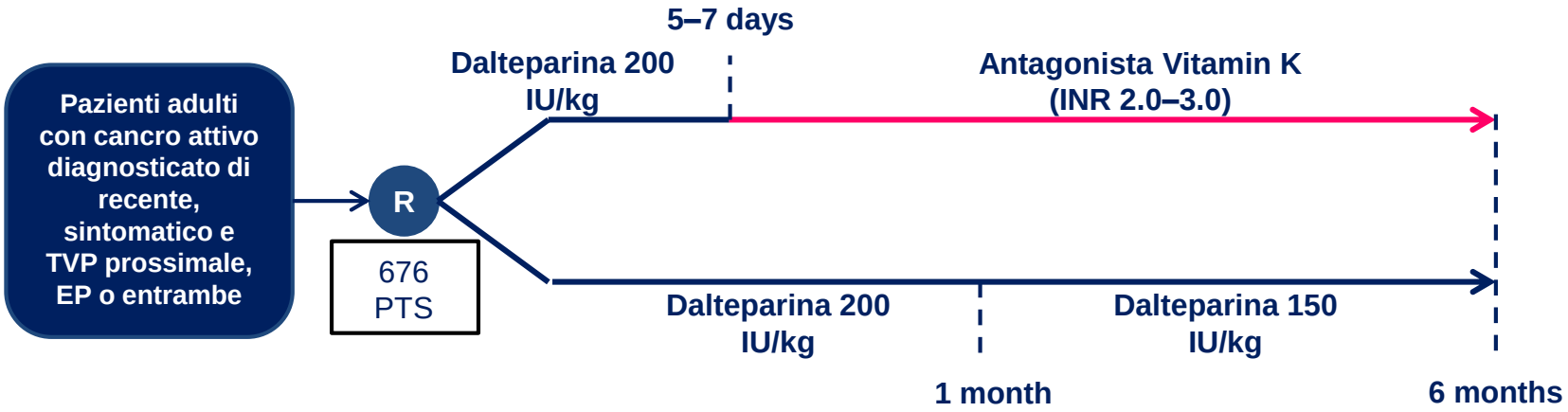
2018 EHRA Pratical Guide on NOACs in AF

VTE Risk varies over the natural history of cancer



Adapted from Lyman GH, *Cancer* 2010;7:1334–1349

CLOT: disegno dello studio



Outcome Primario: Primo episodio di recidiva di TVP, EP o entrambi sintomatici durante il periodo di trattamento di 6 mesi

Criteri di inclusione

- Pazienti adulti con cancro attivo e recentemente diagnosticato e TVP, EP o entrambi erano eleggibili.
- Il cancro attivo era definito come:
  - tumori, ad esclusione dei tumori baso cellulari e squamo cellulari della pelle, diagnosticati entro 6 mesi dall'arruolamento,
  - Tumori in trattamento nei 6 mesi precedenti l'arruolamento
  - Recidiva di cancro o cancro metastatico

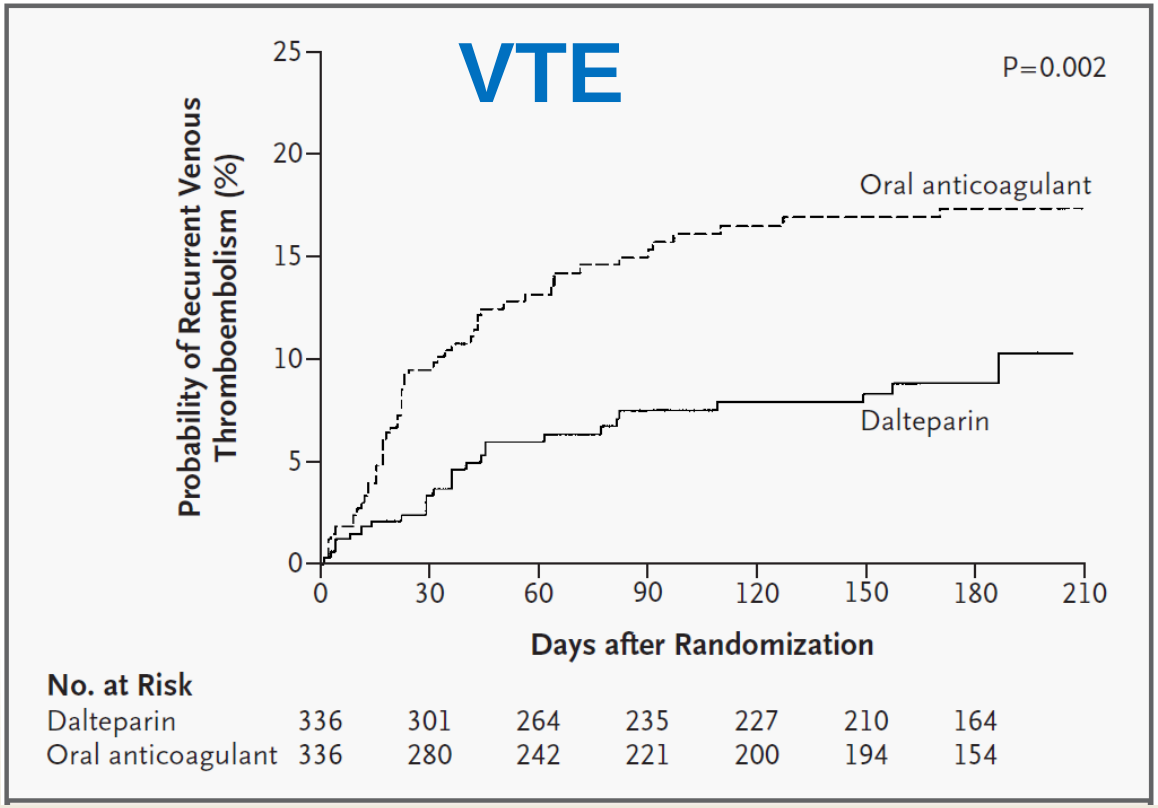
DVT, deep vein thrombosis; INR, international normalised ratio; PE, pulmonary embolism

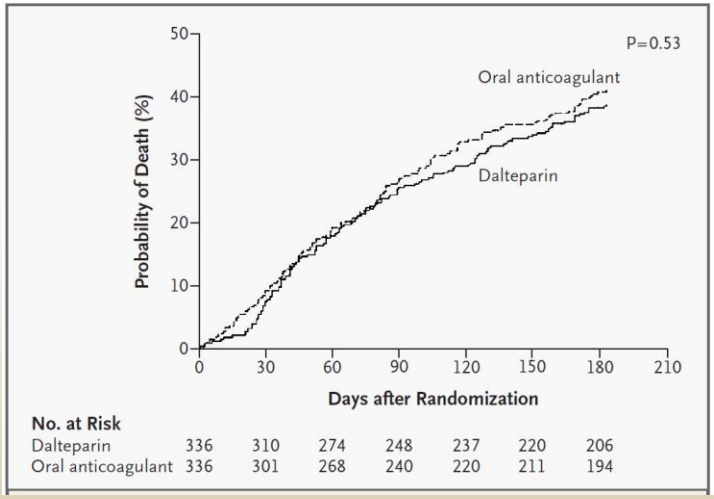
Lee AYY. Et al. NEJM 2003; 349: 146 - 53

Outcome events

Table 3. Primary Efficacy Outcome Events.

Event	Dalteparin (N=336)	Oral Anticoagulant (N=336)
	no. of patients	
Deep-vein thrombosis alone	14	37
Nonfatal pulmonary embolism	8	9
Fatal pulmonary embolism	5	7
Total	27	53





Lee AYY. Et al. NEJM 2003; 349: 146 - 53

REGULAR ARTICLE

blood advances

Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation

Surbhi Shah,[1] Faye L. Norby,[2] Yvonne H. Datta,[1] Pamela L. Lutsey,[2] Richard F. MacLehose,[2] Lin Y. Chen,[1] and Alvaro Alonso[3]

[1]Department of Medicine, University of Minnesota Medical School, Minneapolis, MN; [2]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN; and [3]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA

Effectiveness and associated risk of DOACs vs warfarin, as well as comparisons of DOACs, in a large population of cancer patients with nonvalvular atrial fibrillation (AF).

MarketScan databases.

16 096 AF patients (mean age, 74 years) initiating oral anticoagulant and being actively treated for cancer between 2010 and 2014.

Anticoagulant users were matched by age, sex, enrollment date, and drug initiation date.

Study end points were identified with diagnostic codes and included ischemic stroke, severe bleeding, other bleeding, and venous thromboembolism (VTE).

Shah S. et al. Blood advances 2018; 2: 200 - 209

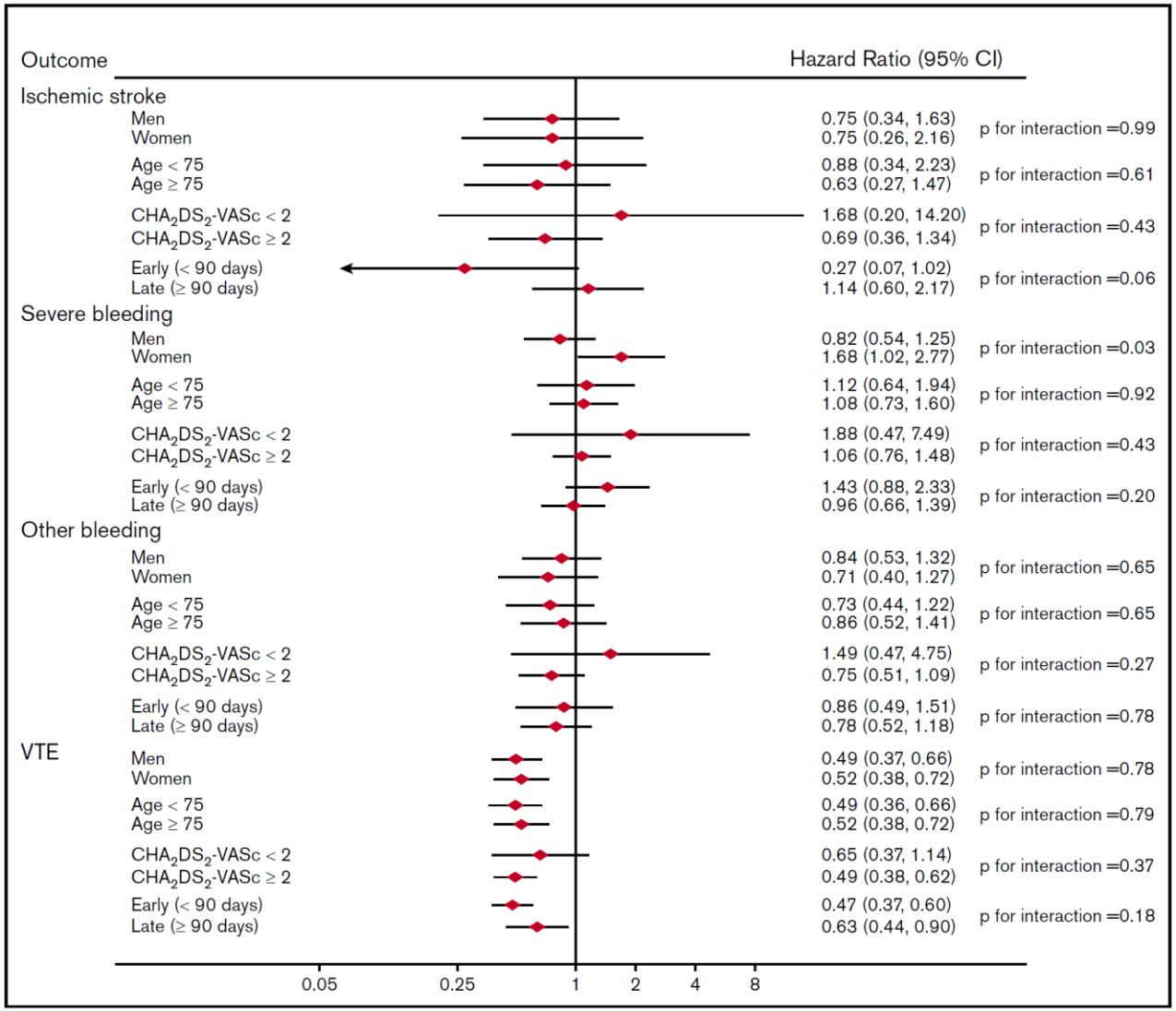
Characteristics of population

	Rivaroxaban	Dabigatran	Apixaban	Warfarin
N	2808	2189	1078	10 021
Age, y	73.8 ± 10.2	74.0 ± 10.3	74.9 ± 10.3	75.4 ± 10.1
Female, %	40.7	38.3	42.5	39.4
CHA_2DS_2-VASc score	4.0 ± 2.0	4.3 ± 2.0	4.2 ± 1.9	4.6 ± 2.0
Comorbidities, %				
Hypertension	82.3	83.4	85.6	85.4
Prior ischemic stroke	27.4	33.9	28.8	35.6
Metastatic brain lesion	2	1.5	1.2	2.4
Prior gastrointestinal bleed	12.1	14.4	11.6	16.6
Prior other bleed	8	10.2	7.2	13
Liver disease	9.6	10.3	9.8	11.5
Renal disease	13.8	13.3	17.5	24.4
Heart failure	32.4	36.3	34.6	42.5
Medications (pharmacy), %				
Antiplatelet agents	2.6	3.5	4.1	3.1
Nonsteroidal anti-inflammatory drugs	27.3	32.6	28	28.8
Chemotherapy	21.7	18.1	16.3	23.4
Hormonal therapy	13.4	11.5	11.7	12.8
Radiation therapy	12.3	10.3	8.1	11.7
Other cancer therapy/procedures	65.7	69.7	71.4	64.7
Type of cancer, %				
Breast	21.4	20.8	23.4	17.8
Lung	12.5	10.4	8.6	13.1
Gastrointestinal	10.3	10.7	11.6	13.9
Genitourinary	29.0	31.3	29.8	28.7
Gyneco-oncological	2.6	2.2	2.0	2.5
Hematological	9.6	9.2	8.8	10.1
Other	14.6	15.4	15.8	13.9

Values are mean ± standard deviation or percentage. Gastrointestinal malignancies (stomach, esophagus, colon cancer, rectal cancer, pancreatic cancer, hepatocellular carcinoma, small intestine cancer), genitourinary malignancies (prostate cancer, testicular cancer, bladder cancer, kidney cancer, and penile cancer), gyneco-oncological malignancies (cancer of cervix, ovary, and uterus), hematological malignancies (leukemia and lymphomas), and "Other" for any remaining nonmelanoma rare cancers.

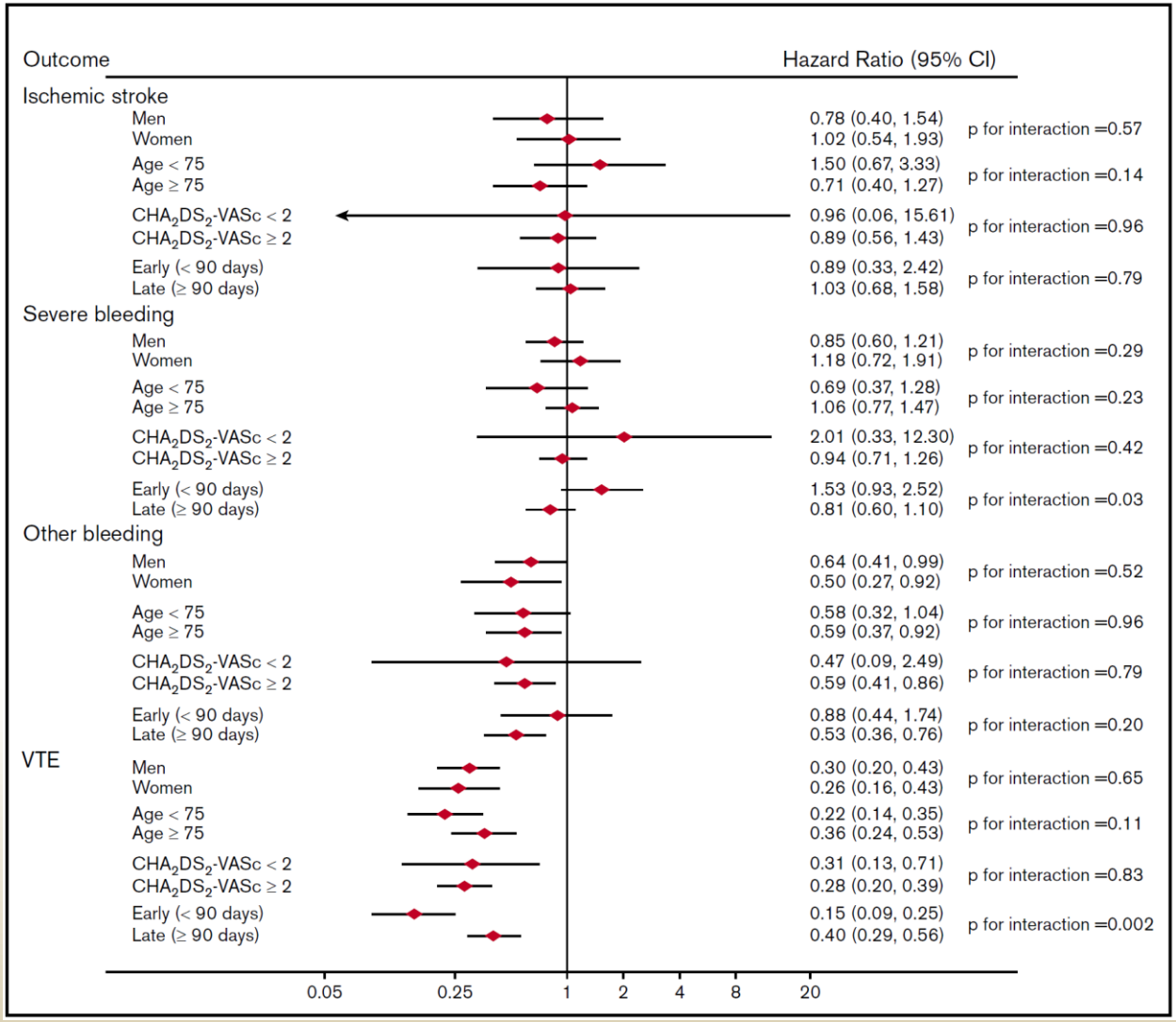
Shah S. et al. Blood advances 2018; 2: 200 - 209

Outcomes among AF pts with cancer:
Rivaroxaban vs Warfarin



Shah S. et al. Blood advances 2018; 2: 200 - 209

Outcomes among AF pts with cancer:
Dabigatran vs Warfarin



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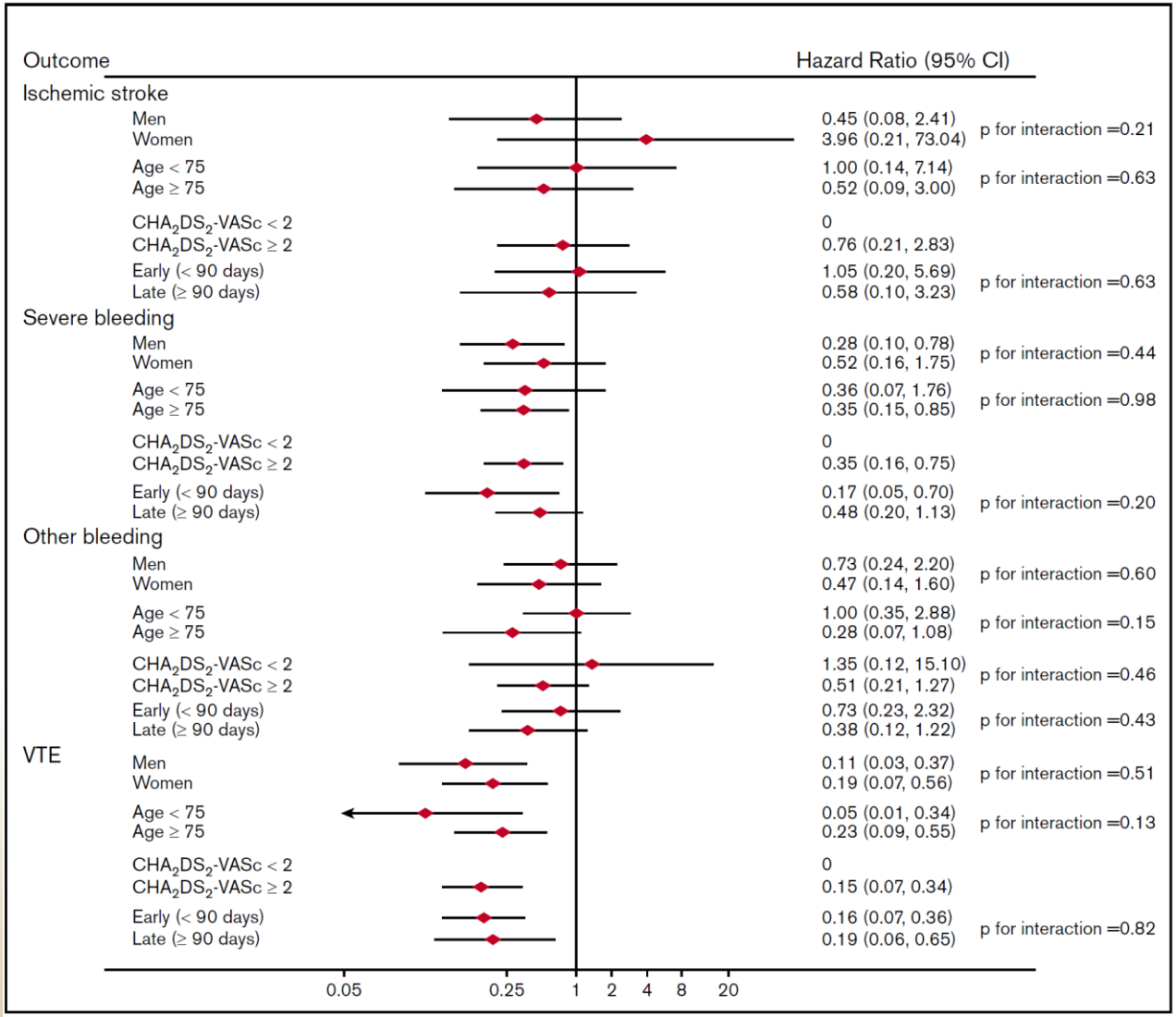
Outcomes among AF pts with cancer:
Apixaban vs Warfarin



Shah S. et al. Blood advances 2018; 2: 200 - 209

Outcomes among AF pts with cancer:

- In AF and cancer patients, rate of bleeding is lower with apixaban, similar in dabigatran and rivaroxaban users, compared to warfarin users.
- Ischemic stroke rates did not differ among anticoagulant users.
- Incident VTE risk was lower in all DOAC compared with warfarin users.

Shah S. et al. Blood advances 2018; 2: 200 - 209

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

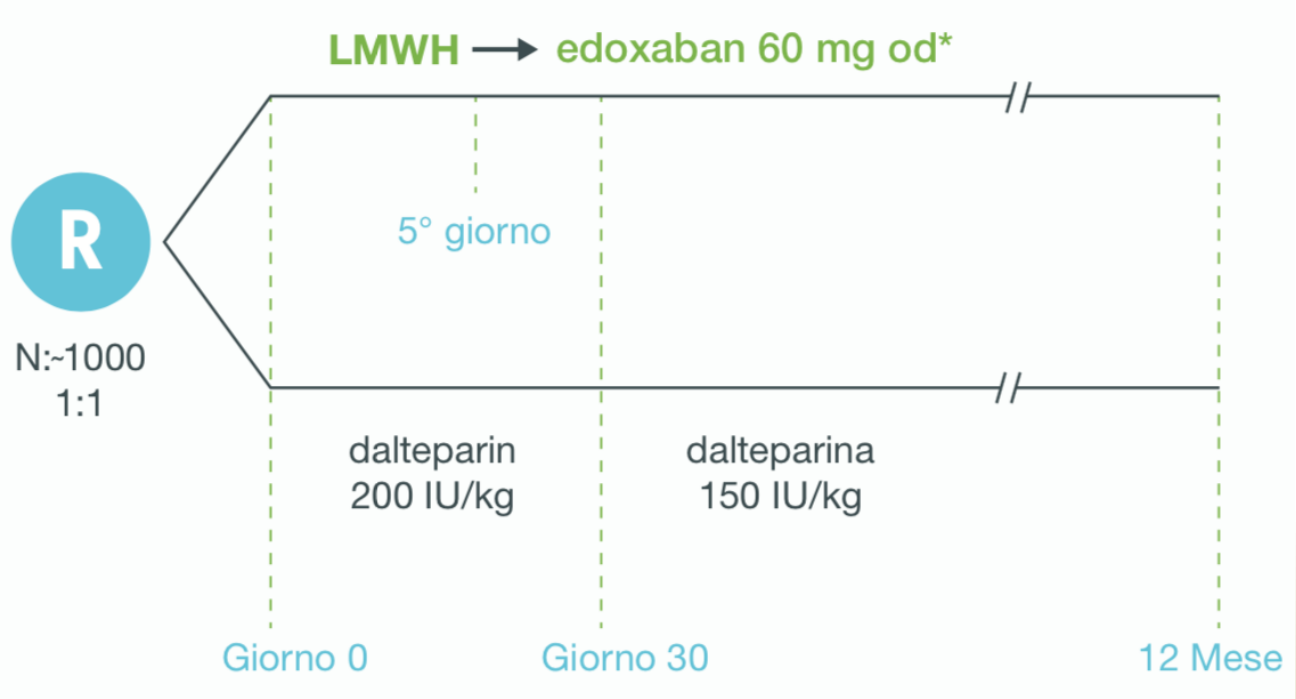
Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

Raskob G.E et al. NEJM 2018; 378: 615 - 624

Hokusai VTE Cancer: Design of study

TEV Confermato da obiettività

1050 pz randomizzati e stratificati per rischio di sanguinamento e necessità di riduzione del dosaggio*



** Aggiustamento a 30 mg per pz con peso < 60 kg, ClCr compresa fra 30 e 50 mL/min, e uso concomitante di potenti inibitori della p-Gp*

Raskob G.E et al. NEJM 2018; 378: 615 - 624

Clinical Characteristics of pts at baseline

Characteristic	Edoxaban (N = 522)	Dalteparin (N = 524)
Age — yr	64.3±11.0	63.7±11.7
Male sex — no. (%)	277 (53.1)	263 (50.2)
Weight		
Mean — kg	78.8±17.9	79.1±18.1
≤60 kg — no. (%)	83 (15.9)	78 (14.9)
Creatinine clearance of 30–50 ml/min — no. (%)	38 (7.3)	34 (6.5)
Platelet count of 50,000–100,000 per μl — no. (%)	32 (6.1)	23 (4.4)
Met criteria to receive lower dose of edoxaban — no. (%)†	122 (23.4)	117 (22.3)
Qualifying diagnosis of venous thromboembolism — no. (%)		
Pulmonary embolism with or without deep-vein thrombosis	328 (62.8)	329 (62.8)
Deep-vein thrombosis only	194 (37.2)	195 (37.2)
Symptomatic deep-vein thrombosis or pulmonary embolism	355 (68.0)	351 (67.0)
Incidental deep-vein thrombosis or pulmonary embolism‡	167 (32.0)	173 (33.0)
Active cancer — no. (%)	513 (98.3)	511 (97.5)
Metastatic disease — no. (%)	274 (52.5)	280 (53.4)
Recurrent cancer — no. (%)	163 (31.2)	152 (29.0)
Cancer treatment within previous 4 wk — no. (%)§	374 (71.6)	383 (73.1)
ECOG performance status — no. (%)¶		
0	155 (29.7)	148 (28.2)
1	243 (46.6)	246 (46.9)
2	123 (23.6)	124 (23.7)
Previous venous thromboembolism — no. (%)	49 (9.4)	63 (12.0)
Risk factors for bleeding — no. (%)‖		
0	92 (17.6)	92 (17.6)
1	148 (28.4)	151 (28.8)
2	174 (33.3)	159 (30.3)
≥3	108 (20.7)	122 (23.3)

Raskob G.E et al. NEJM 2018; 378: 615 - 624

Outcomes during the overall trial period

Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for

CONCLUSIONS

Oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban than with dalteparin. (Funded by Daiichi Sankyo; Hokusai VTE Cancer ClinicalTrials.gov number, NCT02073682.)

Category 2	24/36 (66.7)	8/21 (38.1)	
Category 3	12/36 (33.3)	12/21 (57.1)	
Category 4	0	1/21 (4.8)	
Clinically relevant nonmajor bleeding — no. (%)§	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)
Major or clinically relevant nonmajor bleeding — no. (%)§¶	97 (18.6)	73 (13.9)	1.40 (1.03–1.89)
Death from any cause — no. (%)	206 (39.5)	192 (36.6)	1.12 (0.92–1.37)
Event-free survival — no. (%)‖	287 (55.0)	296 (56.5)	0.93 (0.77–1.11)

Raskob G.E et al. NEJM 2018; 378: 615 - 624

DOACs 2018: update

- Fibrillazione atriale e valvole
- Insufficienza renale – calcifilassi – pazienti in dialisi
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- Aderenza

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Weight-based analysis for efficacy and Obese patients in major phase III 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)

BMI, body mass index.

Martin K. Et al. Journal of Thrombosis and Heamost. 2016; 14: 1308 - 1313

Guidance statements
for
VTE treatment; VTE prevention and AF pts

BMI ≤ 40 kg/m2
and
Weight ≤ 120 kg

→ Appropriate standard dosing of the DOACs

BMI ≥ 40 kg/m2
and
Weight ≥ 120 kg

→ DOACs should not be used

Martin K. Et al. Journal of Thrombosis and Heamost. 2016; 14: 1308 - 1313

DOACs in obese patients

Concerns have been expressed about the reliability of the anticoagulant effect of NOACS in obese patients.[427,428] Weight was not an exclusion criterion in any of the NOAC trials in AF or VTE.

Because of limited data in extreme obesity, the use of VKA in patients with a BMI $\geq$40 kg/m^2 or weight >120 kg should be considered (in line with recommendations from the International Society on Thrombosis and Haemostasis).[427] In rare case when a

Relation of Risk of Stroke in Patients With Atrial Fibrillation to Body Mass Index (from Patients Treated With Rivaroxaban and Warfarin in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation Trial)

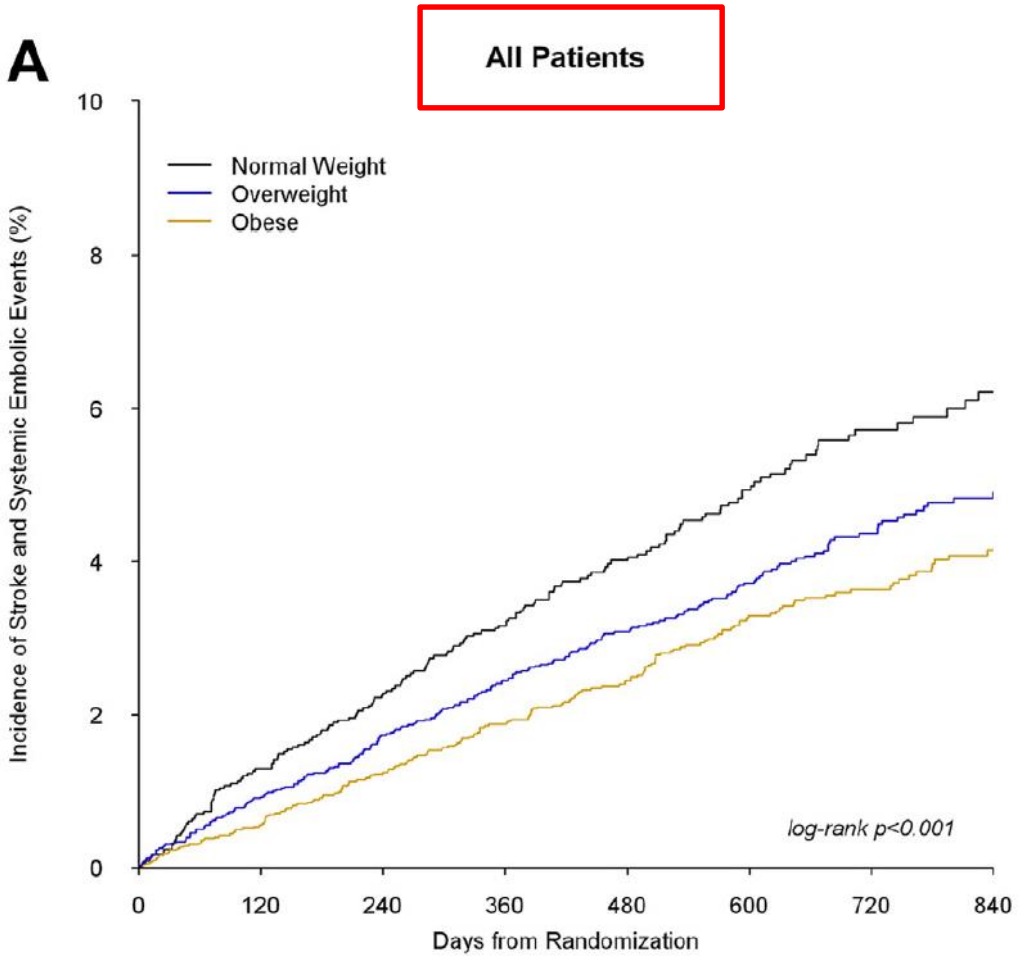
Somasekhara R. Balla, MD[a], Derek D. Cyr, PhD[b], Yuliya Lokhnygina, PhD[b], Richard C. Becker, MD[c], Scott D. Berkowitz, MD[d], Günter Breithardt, MD[e], Keith A.A. Fox, MB, ChB[f], Werner Hacke, MD, PhD[g], Jonathan L. Halperin, MD[h], Graeme J. Hankey, MD[i], Kenneth W. Mahaffey, MD[j], Christopher C. Nessel, MD[k], Jonathan P. Piccini, MD, MHS[b], Daniel E. Singer, MD[l], and Manesh R. Patel, MD[b,*]

Incidence of stroke and systemic embolic events as well as bleeding events in normal weight (n[3,289), overweight (n [5,535), and obese (n [5,206) patients.

Post hoc analysis of the ROCKET-AF trial.

Balla S.R. et al. Am J Cardiol 2017; 119: 1989 - 1996

Primary endpoint and anticoagulant therapy



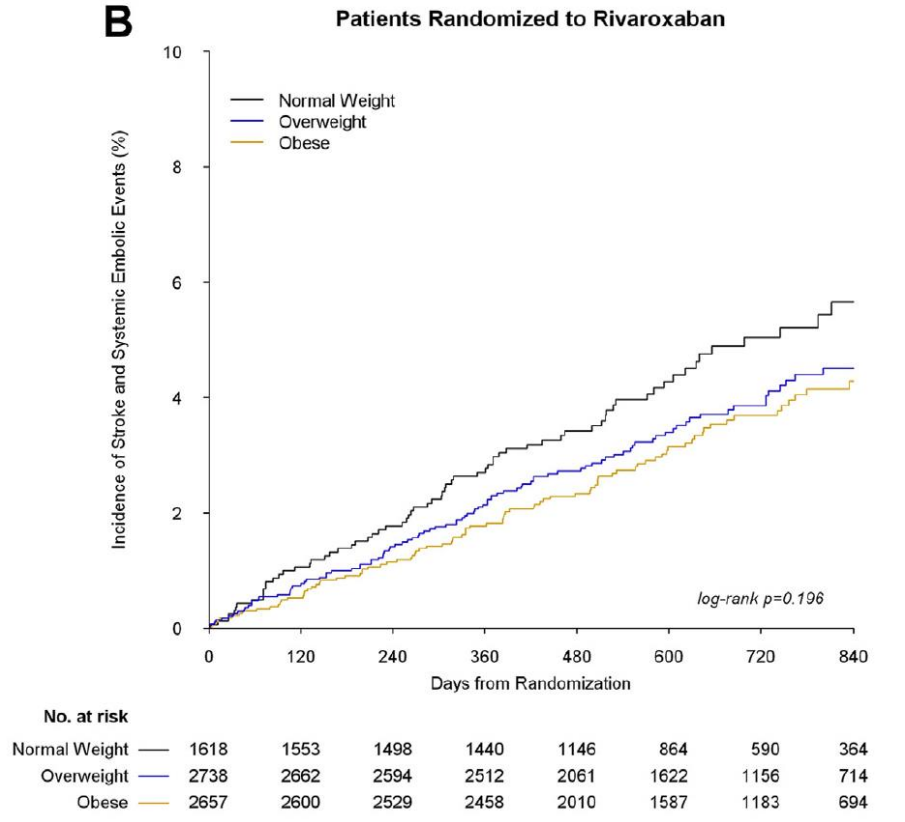
No. at risk

Normal Weight	3289	3146	3034	2924	2344	1781	1230	763
Overweight	5535	5371	5220	5051	4109	3221	2309	1403
Obese	5206	5099	4959	4813	3941	3118	2307	1372

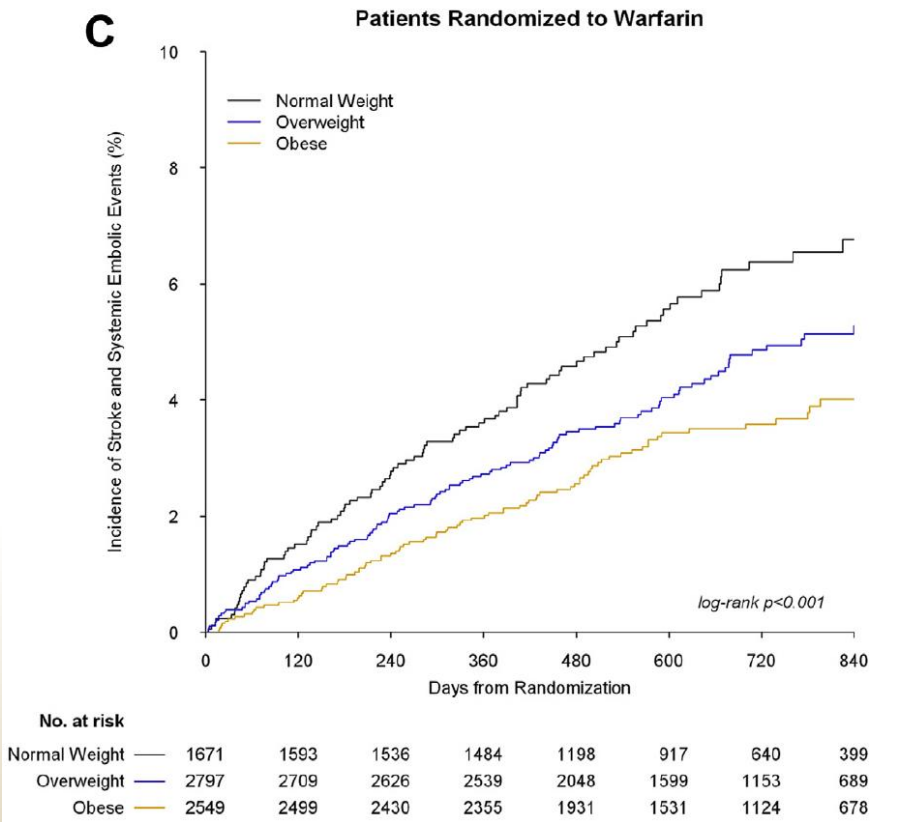
Balla S.R. et al. Am J Cardiol 2017; 119: 1989 - 1996

Primary endpoint and anticoagulant therapy

Rivaroxaban



Warfarin



Balla S.R. et al. Am J Cardiol 2017; 119: 1989 - 1996

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European Heart Journal (2016) **37**, 2869–2878
doi:10.1093/eurheartj/ehw124

CLINICAL RESEARCH
Atrial fibrillation

The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial

Roopinder K. Sandhu[1]*, Justin Ezekowitz[1,2], Ulrika Andersson[3], John H. Alexander[4], Christopher B. Granger[4], Sigrun Halvorsen[5], Michael Hanna[6], Ziad Hijazi[3,7], Petr Jansky[8], Renato D. Lopes[4], and Lars Wallentin[3,7]

Sandhu RK et al. EHJ 2016; 37: 2869 - 2878

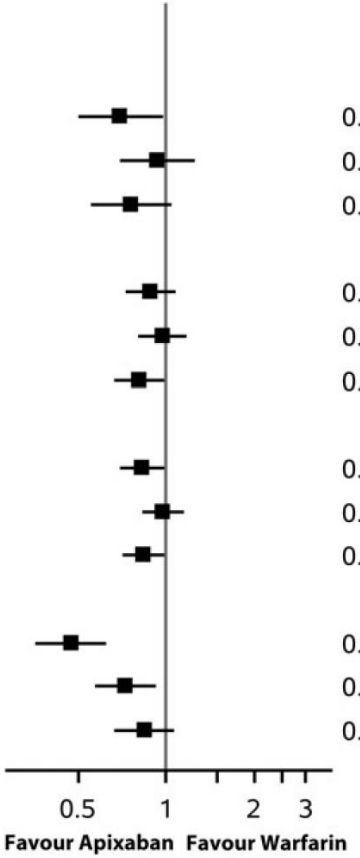
Outcomes according to categories of BMI

Outcome BMI category (kg/m^2)	Number of patients in analysis	Events (%/year)	HR (95% CI) *BMI 18.5-<25 kg/m^2 as reference*	*P*-value *Effect of BMI category*
Stroke/SE				
18.5–<25	4038	142 (2.01)		
25–<30	6671	174 (1.43)	0.86 (0.68–1.08)	0.18
≥30	7131	150 (1.11)	0.79 (0.61–1.02)	
Death				
18.5–<25	4038	397 (5.45)		
25–<30	6671	429 (3.44)	0.67 (0.59–0.78)	<.0001
≥30	7131	398 (2.90)	0.63 (0.54–0.74)	
Stroke/SE/MI/Death				
18.5–<25	4038	510 (7.23)		
25–<30	6671	598 (4.92)	0.74 (0.65–0.84)	<.0001
≥30	7131	554 (4.13)	0.68 (0.60–0.78)	
Major bleeding				
18.5–<25	3984	217 (3.44)		
25–<30	6618	270 (2.44)	0.82 (0.68–0.99)	0.11
≥30	7074	281 (2.30)	0.91 (0.74–1.10)	

Sandhu RK et al. EHJ 2016; 37: 2869 - 2878

Outcomes according to categories of BMI stratified by study treatment

Outcome BMI category (kg/m^2)	No of patients	Apixaban Events (%/year)	Warfarin Events (%/year)	HR (95% CI)	*P*-value Interaction
Stroke/SE					
18.5–<25	4052	59 (1.65)	83 (2.36)	0.70 (0.50–0.97)	0.41
25–<30	6702	84 (1.37)	90 (1.47)	0.93 (0.69–1.26)	
≥30	7159	66 (0.97)	86 (1.28)	0.76 (0.55–1.05)	
Death					
18.5–<25	4052	188 (5.11)	210 (5.78)	0.89 (0.73–1.08)	0.45
25–<30	6702	212 (3.38)	218 (3.48)	0.97 (0.80–1.17)	
≥30	7159	181 (2.61)	220 (3.21)	0.81 (0.67–0.99)	
Stroke/SE/MI/Death					
18.5–<25	4052	234 (6.55)	277 (7.91)	0.83 (0.70–0.99)	0.31
25–<30	6702	296 (4.84)	303 (4.97)	0.97 (0.83–1.14)	
≥30	7159	256 (3.78)	302 (4.51)	0.84 (0.71–0.99)	
Major bleeding					
18.5–<25	4035	72 (2.22)	147 (4.70)	0.47 (0.36–0.63)	0.006
25–<30	6687	115 (2.04)	156 (2.82)	0.73 (0.57–0.92)	
≥30	7134	132 (2.12)	153 (2.51)	0.84 (0.67–1.07)	



Sandhu RK et al. EHJ 2016; 37: 2869 - 2878

DOACs 2018: update

- Fibrillazione atriale e valvole
- Insufficienza renale – calcifilassi – pazienti in dialisi
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Measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening major bleeding	• Inquire about last intake + dosing regimen • Local haemostatic measures • Fluid replacement • RBC substitution, if necessary • Platelet substitution (in case of thrombocytopenia ≤60 × 109/L or thrombopathy) • Fresh frozen plasma not as reversal agent (may be considered as plasma expander) • Tranexamic acid can be considered as adjuvant (1 g i.v., repeat every 6 h, if necessary) • Desmopressin can be considered in special cases such as coagulopathy or thrombopathy; 0.3 μg/kg i.v. infusion (max dose 20 μg)	

	• Estimate normalization of plasma levels:
	  • Normal renal function: 12–24 h
	  • CrCl 50–80 mL/min: 24–36 h
	  • CrCl 30–50 mL/min: 36–48 h
	  • CrCl <30 mL/min: ≥48 h
	• Maintain diuresis
	• Consider idarucizumab (see below)
		• Normalization of plasma levels: 12–24 h

2018 EHRA Pratical Guide on NOACs in AF

DOACs 2018: update?

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)

Life-threatening bleeding	• All of the above
	• Direct reversal: Idarucizumab 5 g i.v. in two doses a 2.5 g i.v. no more than 15 min apart
		• All of the above
		• Direct reversal: Andexanet alpha (if available and approved)[a]
		  • Bolus over 15–30 min, followed by 2-h infusion
		  • Rivaroxaban (last intake >7 h before) or apixaban: 400 mg bolus, 480 mg infusion @ 4 mg/min
		  • Rivaroxaban (last intake <7 h before or unknown) or enoxaparin or edoxaban: 800 mg bolus, 960 mg infusion @ 8 mg/min

	• Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) • Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC, if available	

RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate.
[a]Andexanet alpha is currently neither approved nor available and final results of the ANNEXA-4 study are pending.

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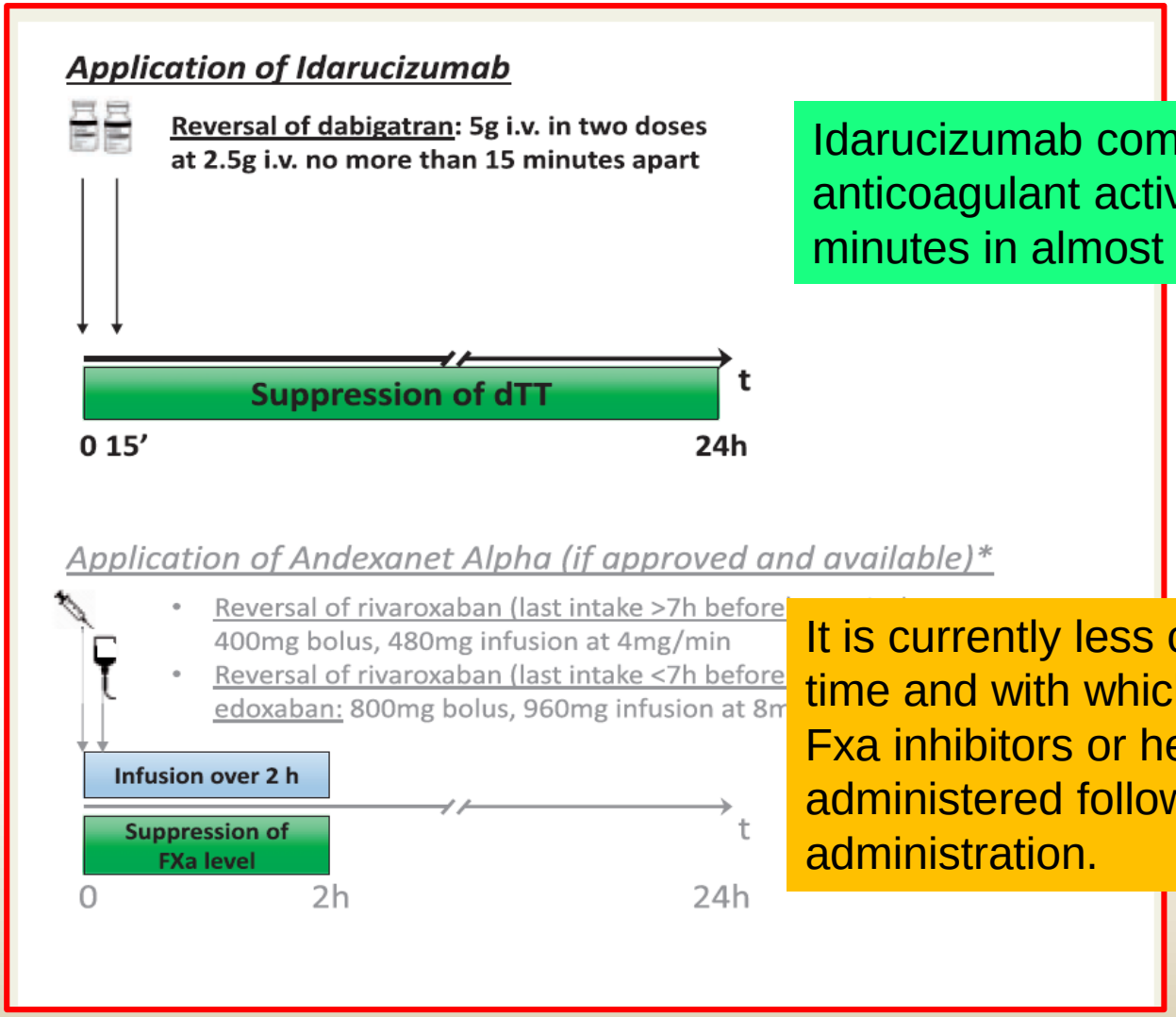
Application and effect of reversal DOACs



Idarucizumab completely reversed the anticoagulant activity of dabigatran within minutes in almost all patients

It is currently less clear at what point in time and with which anticoagulant effect Fxa inhibitors or heparin can be re-administered following andexanet alpha administration.

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DOACs 2018: update

- Fibrillazione atriale e valvole
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- Aderenza

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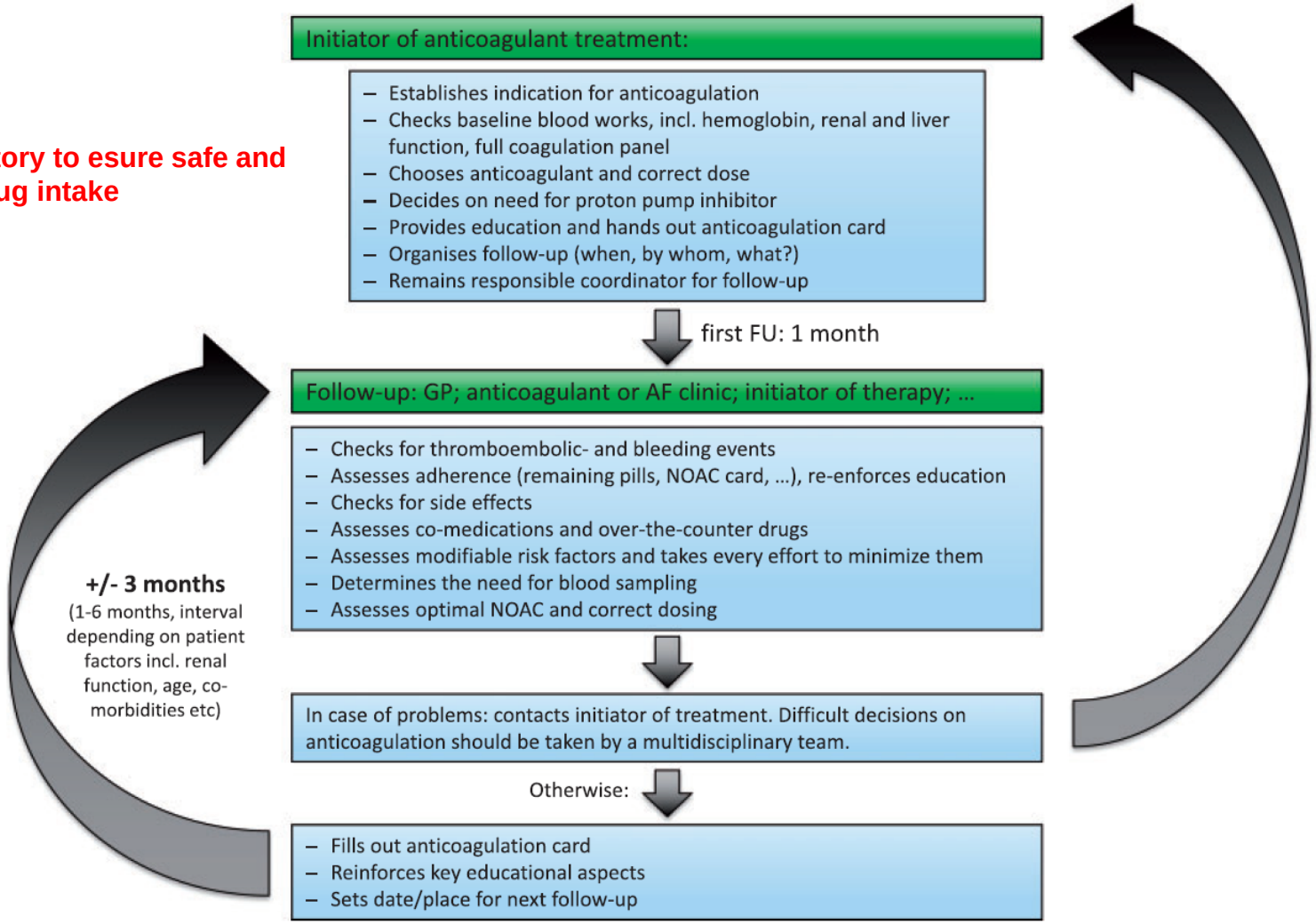
Structured follow-up

It is mandatory to esure safe and effective drug intake



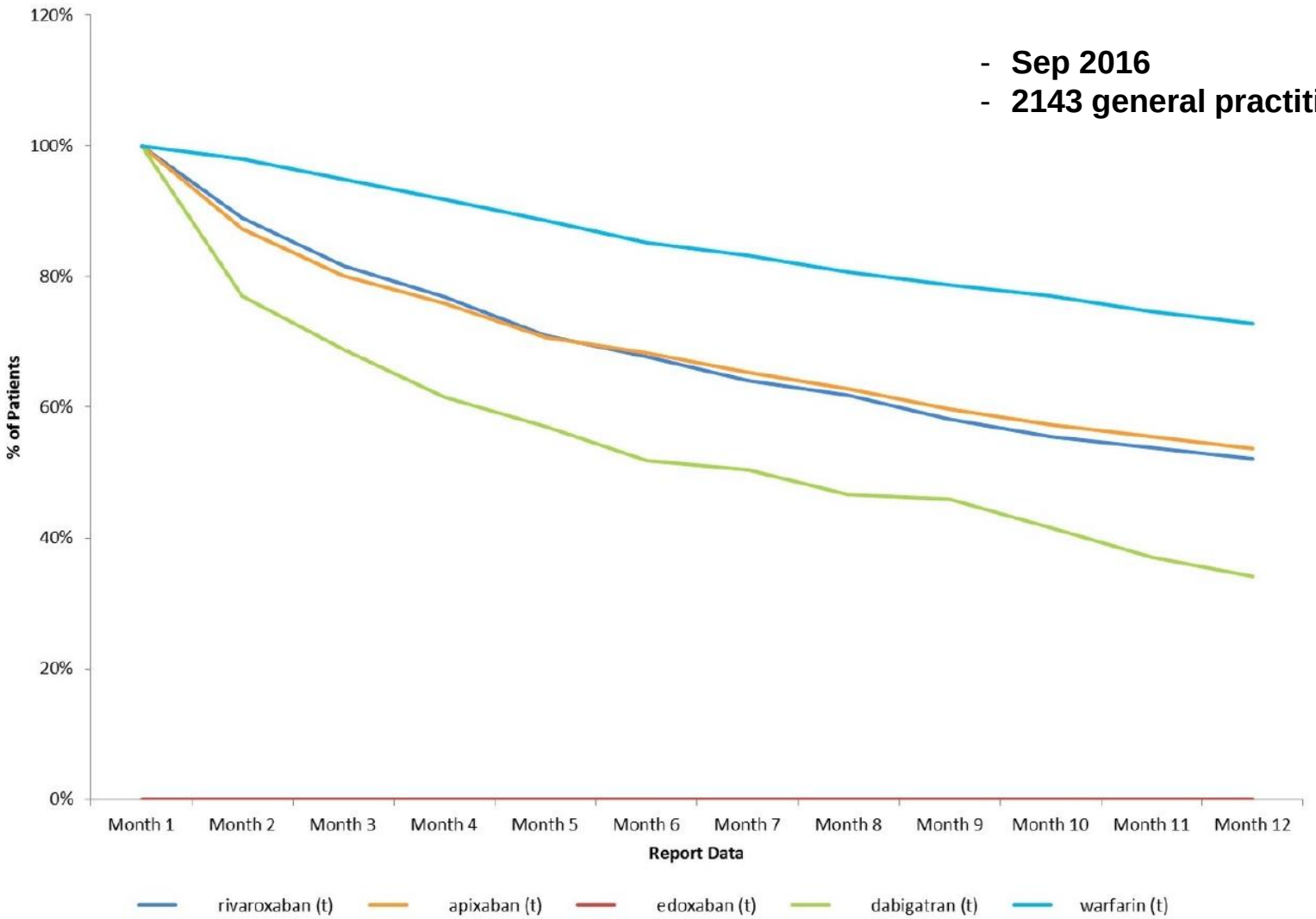
2018 EHRA Pratical Guide on NOACs in AF

Checklist during follow-up contacts

	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess average adherence • Re-educate on importance of strict intake schedule • Inform about adherence aids (special boxes; smartphone applications; . . .). Consider specific adherence measuring interventions (review of pharmacy refill data; electronic monitoring[51]; special education session; . . .)
2. Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
3. Bleeding	Each visit	• 'Nuisance' bleeding: preventive measures possible? Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication, dose or timing?
4. Other side effects	Each visit	Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation, or change of anticoagulant drug
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs (Pharmacokinetics and drug–drug interactions of non-vitamin K antagonist oral anticoagulants section). • Careful interval history: also temporary use can be risky
6. Blood sampling (incl. hemoglobin, renal and liver function)	Yearly	Patients other than those specified below
	6-monthly	≥75 years (especially if on dabigatran) or frail (see **chapter 2**)
	x-monthly	If renal function CrCl ≤60 mL/min: recheck interval = CrCl/10
	If needed	If intercurrent condition that may impact renal or hepatic function
7. Assessing and minimizing modifiable risk factors for bleeding	Each visit	• As recommended by current guidelines[3] • Particularly: uncontrolled hypertension (systolic >160 mmHg), medication predisposing for bleeding (e.g. aspirin, NSAIDs), labile INR (if on VKA), excessive alcohol intake)
8. Assess for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether a. The chosen NOAC is the best for the patient b. The chosen dose is correct

2018 EHRA Pratical Guide on NOACs in AF

Adherence data for oral anticoagulans in England



Burn J. Et al. Open Heart (BMJ). 2018;5:e000712

Take home message

- I DOACs nei pazienti con FA e protesi valvolari biologiche si possono usare. Recenti evidenze e trials ongoing per TAVI

- La terapia anticoagulante con Warfarin deteriora la funzionalità renale. I DOACs (soprattutto Dabigatran e Rivaroxaban) hanno effetto più protettivo per il rene

- Nel paziente neoplastico i DOACs si sono dimostrati efficaci nel ridurre la VTE (in particolare Edoxaban per RCT) e sicuri (apixaban) rispetto a warfarin

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Take home message

- Il soggetto obeso è gravato da minor tasso di stroke/SE. Recenti evidenze indicano che i DOACs (in particolare dabigatran, apixaban e rivaroxaban) non sono inferiori a Warfarin

- Nei sanguinamenti Life-threatening l'utilizzo di un «antidoto» può essere importante. Ad oggi solo l'idarucizumab (per dabigatran) è disponibile

- E' fondamentale mantenere un'aderenza terapeutica elevata al fine di beneficiare degli effetti positivi dei DOACs

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Grazie

Grazie

Grazie