

Debate: DOACs are a reasonable and safe alternative to LMWH in the treatment of CAT. No

SIR Noble

Marie Curie Professor of Supportive and Palliative Medicine

Marie Curie Palliative Care Research Centre

Cardiff University



A truly great man



ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Rasikob, 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. Marcuri, M.D., Guy Meyer, M.D., Annalise Sagars, M.D.,
 Minggao Shi, Ph.D., Tzu-Fai Wang, M.D., Erik Yoo, M.D., George Zhang, Ph.D.,
 Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Buller, M.D.,
 for the Hokusai VTE Cancer Investigators*

ABSTRACT

BACKGROUND

Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulant agents is unclear.

METHODS

In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

RESULTS

Of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.9%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; $P=0.006$ for noninferiority; $P=0.87$ for superiority). Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, -3.4 percentage points; 95% CI, -7.0 to 0.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).

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.)

From the University of Oklahoma Health Sciences Center, College of Public Health, Oklahoma City (G.E.R.); the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam (N.E., H.R.B.), and IREAS Academic Research Organization (A.S.)—both in Amsterdam; the Department of Vascular Medicine and Hemostasis, University Hospitals Leuven, Leuven, Belgium (P.V.); Ottawa Hospital Research Institute, Ottawa (M.C.); London Health Sciences Centre-Victoria Hospital, London, ON (M.J.K.); University Health Network, University of Toronto, Toronto (E.Y.); and McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON (J.I.W.)—all in Canada; the Department of Medicine and Aging Sciences, University G. d'Annunzio, Chieti, Italy (M.D.N.); the Department of Medicine, Division of Hematology, University of Washington, Seattle (D.G.); Daiichi Sankyo Pharma Development, Basking Ridge, NJ (M.A.G., M.F.M., M.S., G.Z.); Thrombotic Research Institute and University College London, London (A.K.K.); the Department of Respiratory Disease, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Paris (G.M.); the Department of Internal Medicine, Division of Hematology, Ohio State University Wexner Medical Center, Columbus (T.-F.W.); and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston (J.I.Z.). Address reprint requests to Dr. Rasikob at the University of Oklahoma Health Sciences Center, College of Public Health, 800 NE 13th St., Oklahoma City, OK 73104, or at gary-rasikob@ouhsc.edu.

*A complete list of Hokusai VTE Cancer Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

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SUMMARY

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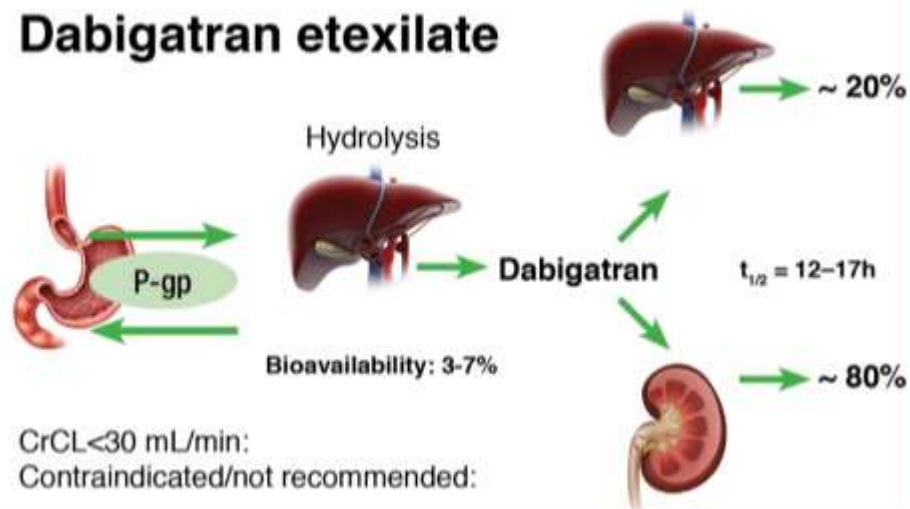
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The New England Journal of Medicine

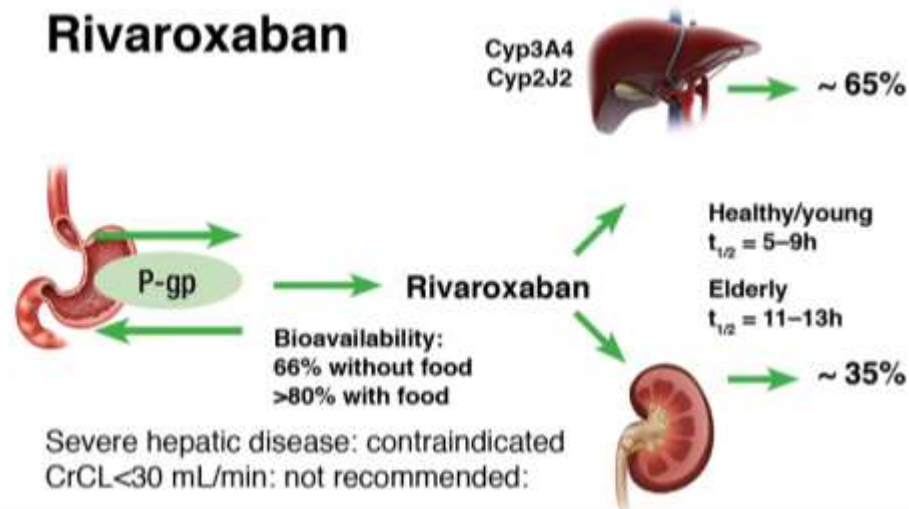
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DOAC Pharmacology

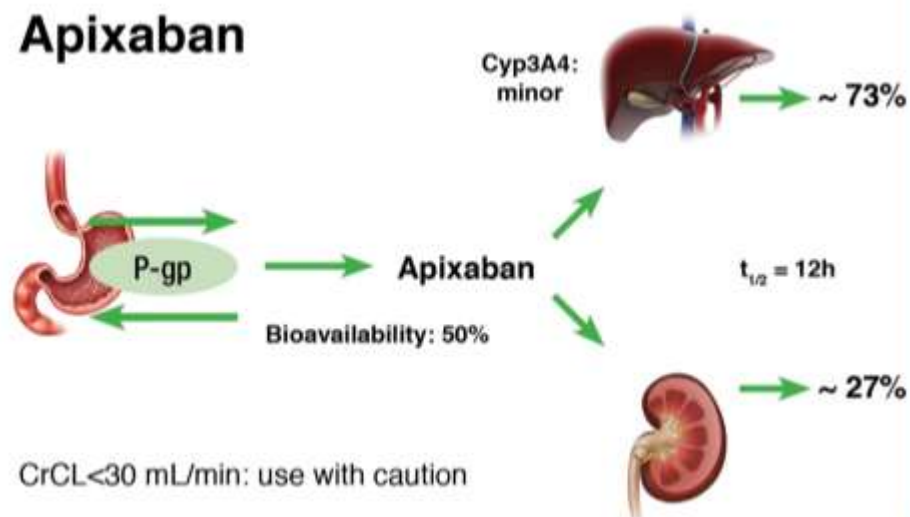
Dabigatran etexilate



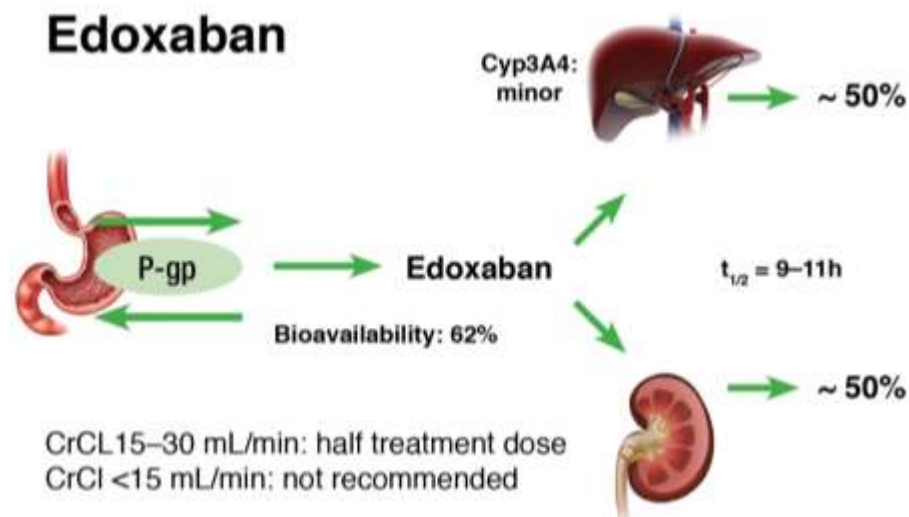
Rivaroxaban



Apixaban

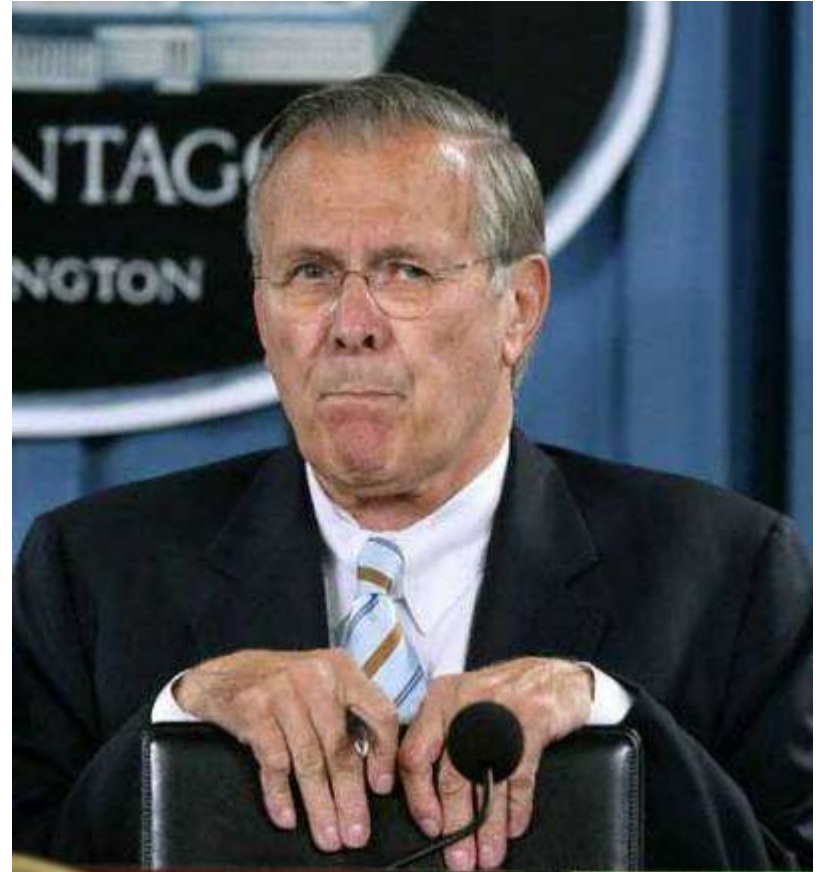


Edoxaban



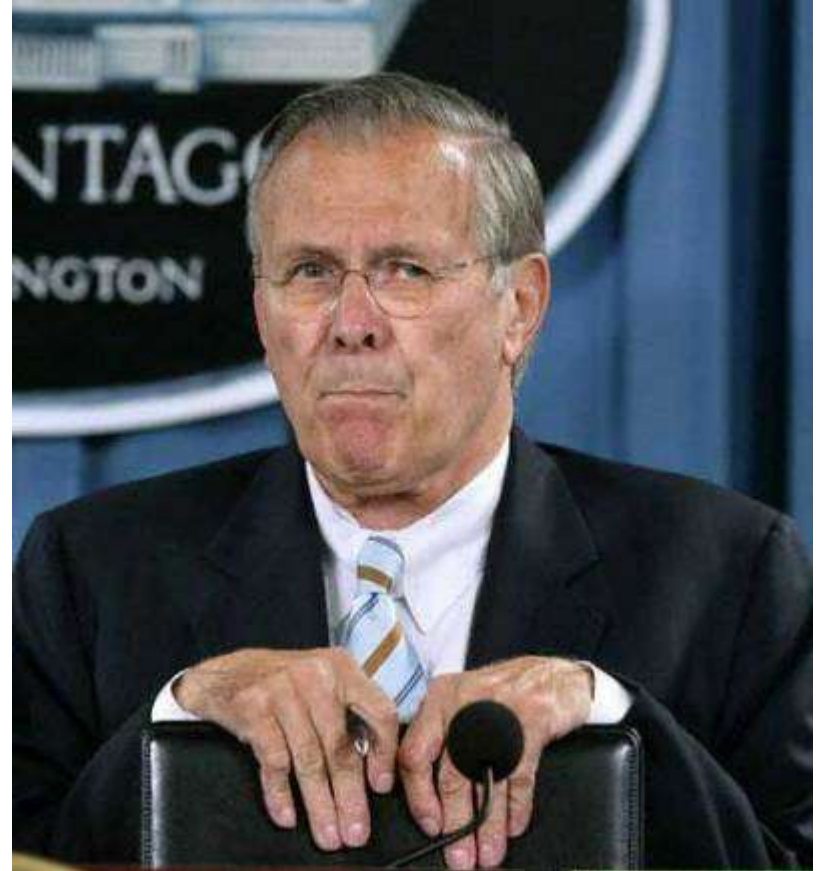
Not everyone is as clever as Harry

“As we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns -- the ones we don't know we don't know.”



Not everyone is as clever as Harry

“As we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns -- the ones we don't know we don't know.”



**DOACs are only as safe as the
stupidest person allowed to prescribe
them**

DOACs are not just a tablet form of heparin.



DOACs and the jobbing oncologist



Extremes of bodyweight



Oral anticoagulant recommendations for patients with renal insufficiency (RI)

DOACs ¹	Mild RI CrCl 51–79 ml/min	Moderate RI CrCl 30–50 ml/min	Severe RI CrCl 15–29 ml/min	Severe RI < 15 ml/min
Apixaban	No dose adjustment	No dose adjustment	Use with caution	Not recommended
Edoxaban	No dose adjustment	Half dose	Half dose	Not recommended
Rivaroxaban	No dose adjustment	No dose adjustment	Use with caution	Not recommended
Dabigatran	No dose adjustment	Consider lowering dose	Contraindicated	Contraindicated

1. Apixaban, edoxaban, rivaroxaban and dabigatran: EMA Summary of Product Characteristics

CrCl = creatinine clearance; DOAC = direct oral anticoagulants; EMA = European Medicines Agency; TTR = time in therapeutic range

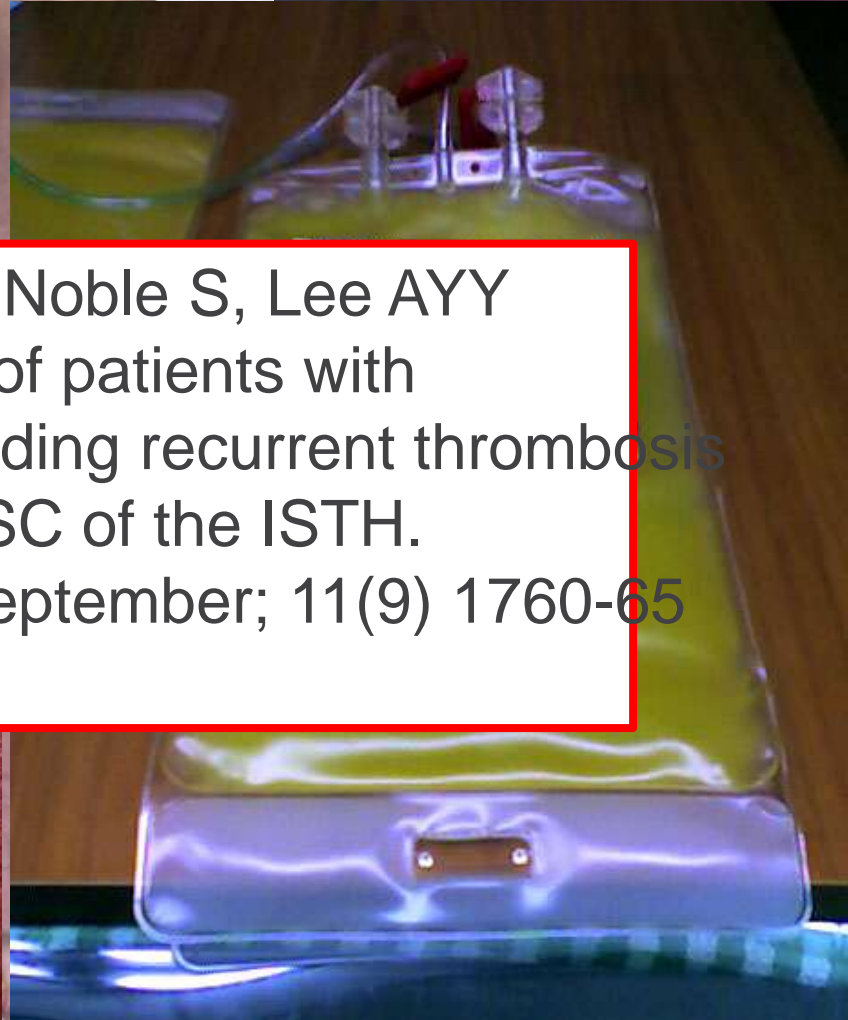
Inducers and inhibitors of CYP3A4 and P-gp

Kinase inhibitors	CYP3A4	P-gp
Afatinib		↓
Alectinib		↓
Ceritinib	↓	
Crizotinib	↓	
Dasatinib	↓	
Ibrutinib		↓
Idelalisib	↓	↓
Imatinib	↓	
Lapatinib	↓	↓
Nilotinib	↓	↓
Osimertinib	↓	
Vemurafenib	↑	↓
Lenvatinib	↑	↑

Chemotherapy	CYP3A4	P-gp
Doxorubicin	↓	
Topotecan	↓	
Vinblastine	↓	
Mitotane	↑	
Venetoclax		↓

Supportive care	CYP3A4	P-gp
Aprepitant	↓	
Methylprednisolone	↓	
Dexamethasone	↑	↑

Inhibitors of CYP3A4 and/or P-gp may increase risk of bleeding on DOACs.

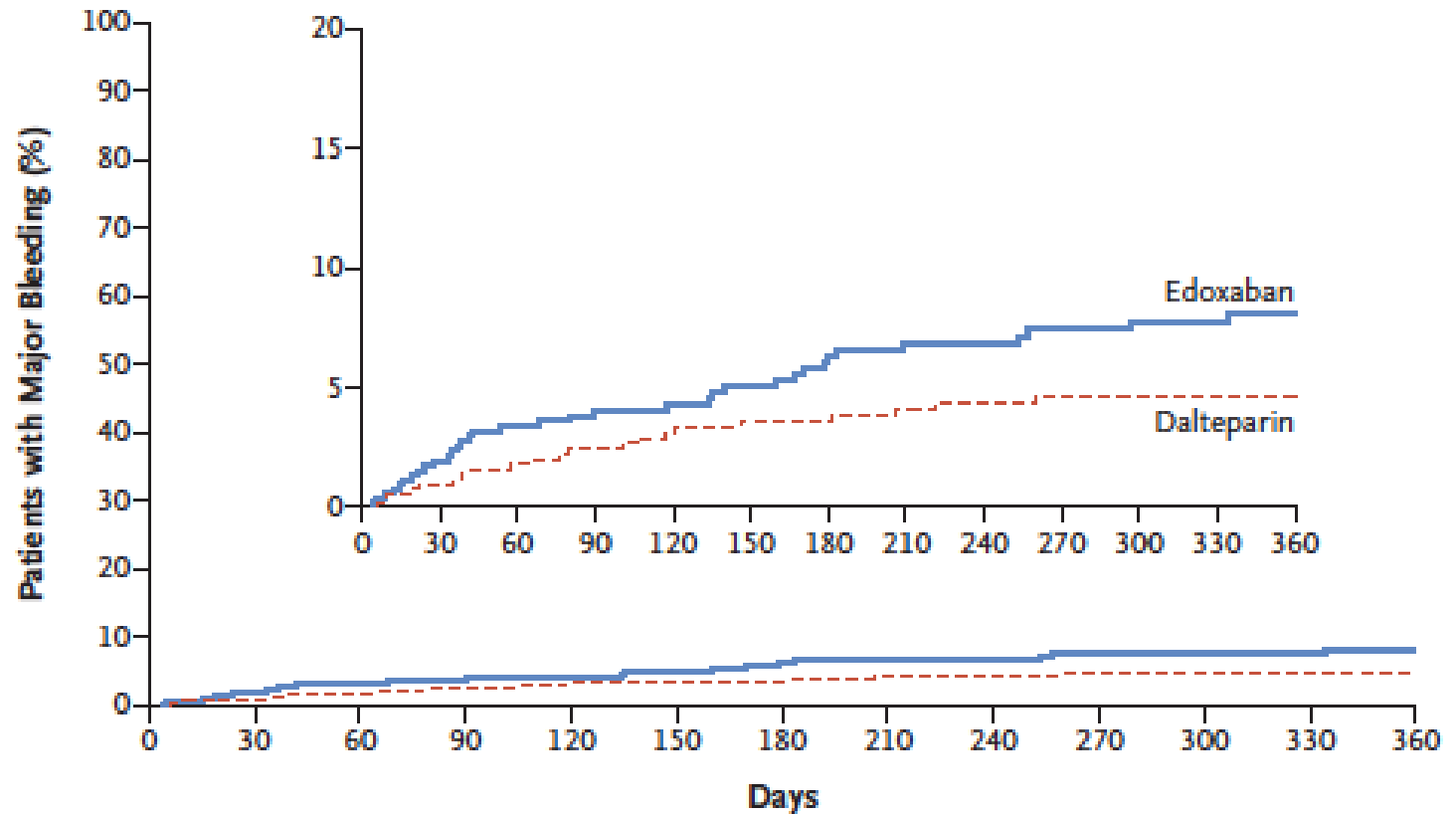


Carrier M, Khorana AA, Zwicker JI, Noble S, Lee AYY
Management of challenging cases of patients with
cancer-associated thrombosis including recurrent thrombosis
and bleeding: guidance from the SSC of the ISTH.
Journal Thromb and Haem 2013 September; 11(9) 1760-65



Bleeding

B



No. at Risk

Edoxaban	522	484	447	426	404	375	358	343	323	308	282	248	168
Dalteparin	524	497	466	436	409	390	378	356	346	335	298	262	183

Appendix: page 16/32

Dose Adj and Bleed Risk (EXRS)				
Dose Adj w/ Bld Risk	99 16 (16.2)	98 14 (14.3)	-	
Dose Adj w/out Bld Risk	22 6 (26.1)	19 2 (10.5)		
Not Dose Adj w/ Bld Risk	331 44 (13.3)	324 47 (12.9)		
Not Dose Adj w/out Bld Risk	69 1 (1.4)	73 12 (16.4)		
Number of Bleeding Risk (EXRS)				
0	92 7 (7.6)	92 14 (13.2)	0.0878	
1	148 12 (8.1)	151 15 (9.9)		
2	174 26 (14.9)	159 23 (13.7)		
3	89 19 (21.3)	98 11 (11.2)		
≥4	19 3 (13.8)	24 6 (25.0)		
Surg 200ks Prior to Rand (EXRS)				
Yes	16 2 (12.5)	15 2 (13.3)	-	
No	504 65 (12.8)	509 69 (13.6)		
Antiplatelet Agts at Rand (EXRS)				
Yes	26 3 (19.2)	31 3 (16.1)	0.6183	
No	496 62 (12.5)	493 66 (13.1)		
Brain Tumor/Metas at Rand (EXRS)				
Yes	31 6 (19.4)	43 8 (18.6)	0.6766	
No	491 61 (12.4)	481 63 (13.1)		
Metastatic Disease at Rand (EXRS)				
Yes	308 42 (14.0)	317 46 (14.5)	0.8558	
No	222 25 (11.3)	207 25 (12.1)		
Req Adv Cancer at Rand (EXRS)				
Yes	273 40 (14.7)	267 31 (11.6)	0.0383	
No	249 27 (10.8)	257 40 (15.6)		
Gastroint Cancer at Rand (EXRS)				
Yes	136 26 (19.1)	125 18 (14.4)	0.1810	
No	306 41 (10.8)	359 33 (13.3)		
Urothelial Cancer at Rand (EXRS)				
Yes	38 9 (23.7)	31 3 (16.1)	0.4846	
No	494 50 (12.0)	493 66 (13.1)		
Avastin Use at Rand (EXRS)				
Yes	19 3 (13.8)	30 7 (23.3)	0.6352	
No	503 64 (12.7)	494 64 (13.0)		
Survival in Study				
Died<3 Months	88 15 (18.8)	71 11 (15.5)	-	
Alive and Early Discc3 Months	8 1 (12.5)	8 1 (12.5)		
Stay in Study>3 Months	434 51 (11.8)	445 59 (13.3)		
Type of Cancer at Rand #				
Solid Tumor	465 61 (13.1)	467 65 (13.9)	-	
Haematological Malignancy	36 3 (8.9)	55 6 (10.9)		
Solid Tumor and Haemat Malign	1 1 (100.0)	2 0		
Active Cancer at Rand #				
Yes	513 66 (12.8)	511 69 (13.5)	-	
No	9 1 (11.1)	13 2 (13.4)		
Distant Metastasis at Rand #				
Yes	274 36 (13.1)	280 42 (15.0)	0.6850	
No	192 26 (13.5)	169 23 (12.2)		
Receiving Cancer Trt at Rand #				
Yes	374 42 (11.2)	383 45 (11.7)	0.9282	
No	148 25 (16.9)	141 26 (18.4)		
Recurring Cancer at Rand #				
Yes	163 25 (13.2)	152 24 (13.8)	0.8243	
No	359 42 (11.7)	372 47 (12.6)		
Cancer Cured #				
Yes	125 10 (8.0)	114 12 (10.5)	0.4374	
No	397 37 (14.4)	410 39 (14.8)		
Baseline ECOG				
0	155 14 (9.0)	148 17 (11.5)	0.3911	
1	243 38 (15.6)	246 33 (13.8)		
≥2	123 15 (12.2)	124 21 (16.9)		
Init Hosp Dur On/Off Rand				
None	5 0	- -	-	
<=3 days	449 55 (12.2)	- -		
> 3 days	68 12 (17.6)	- -		
<= Median	311 40 (12.9)	- -	-	
> Median	204 27 (13.1)	- -		
<= 25th Percentile	158 13 (8.2)	- -	-	
>25-50th Percentile	153 27 (17.6)	- -		
>50-75th Percentile	136 15 (10.9)	- -		
>75th Percentile	68 12 (17.6)	- -		
Heparin Use Prior to Rand				
Yes	393 50 (12.7)	412 58 (14.1)	0.5564	
No	129 17 (13.2)	112 13 (11.6)		

Appendix: page 16/32

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Yes	26 3 (19.2)	31 3 (16.1)		
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Brain Tumor/Metas at Rand (EXRS)			0.6766	
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Metastatic Disease at Rand (EXRS)			0.8558	
Yes	308 42 (14.0)	317 46 (14.5)		
No	222 25 (11.3)	207 25 (12.1)		
Req Adv Cancer at Rand (EXRS)			0.0303	
Yes	273 40 (14.7)	267 31 (11.6)		
No	249 27 (10.8)	257 40 (15.6)		

GI cancers: 13.1% major bleeding
Urothelial cancers 8% major bleeding

Receiving Cancer Trt at Rand B			0.9282	
Yes	374 42 (11.2)	383 45 (11.7)		
No	148 25 (16.9)	141 26 (18.4)		
Recurring Cancer at Rand B			0.8243	
Yes	163 25 (13.2)	152 24 (13.8)		
No	359 42 (11.7)	372 47 (12.6)		
Cancer Cured B			0.4374	
Yes	125 10 (8.0)	114 12 (10.5)		
No	397 37 (14.4)	410 39 (14.8)		
Baseline ECOG			0.3911	
0	155 14 (9.0)	148 17 (11.5)		
1	243 38 (15.6)	246 33 (13.8)		
≥2	123 15 (12.2)	124 21 (16.9)		
Init Hosp Dur On/Off Rand			-	
None	5 0	- -		
<= 5 days	449 55 (12.2)	- -		
> 5 days	68 12 (17.6)	- -		
<= Median	311 40 (12.9)	- -		
> Median	204 27 (13.1)	- -		
<= 25th Percentile	158 13 (8.2)	- -		
>25-50th Percentile	153 27 (17.6)	- -		
>50-75th Percentile	138 15 (10.9)	- -		
>75th Percentile	68 12 (17.6)	- -		
Heparin Use Prior to Rand			0.5564	
Yes	393 50 (12.7)	412 58 (14.1)		
No	129 17 (13.2)	112 13 (11.6)		

Select-d pilot study

430 patients randomized

Protocol change implemented to exclude patients with esophageal and gastro-esophageal cancer by safety committee due to excessive bleeding in the rivaroxaban arm.

Six month outcomes	Rivaroxaban (n = 203)	Dalteparin (n = 203)
Recurrent VTE, n (%)	8 (4)	18 (11)
Major bleeding, n (%)	11 (5)	6 (3)
CRNMB, n (%)	25 (12)	6 (3)
Major and CRNMB, n (%)	36 (17)	12 (6)

ISTH definition major bleeding

Major bleeding event

A major bleeding event will be confirmed when it is a clinically overt bleeding event that meets at least one of the following:

a) Fatal bleeding

b) Bleeding in a critical area or organ such as:

- Retroperitoneal
- Intracranial
- Intraocular
- Intraspinal
- Intra-articular
- Pericardial
- Intramuscular with compartment syndrome

c) A clinically overt bleeding event

- that is associated with a fall in hemoglobin of 2.0 g/dL (>1.24 mMol/L) or more, or
- leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood.

Classification of clinical presentation

Category	Description
1	Bleeding events presenting without any clinical emergency
2	All bleeding events that could not be classified to any of the other three
3	Bleeding events presenting with great medical emergency
4	Bleeding events already fatal before or almost immediately upon entering the hospital

CLINICAL STUDY PROTOCOL
A PHASE 3B, PROSPECTIVE, RANDOMIZED,
OPEN-LABEL, BLIND EVALUATOR (PROBE)
STUDY EVALUATING THE EFFICACY AND
SAFETY OF (LMW) HEPARIN/EDOXABAN
VERSUS DALTEPARIN IN VENOUS
THROMBOEMBOLISM ASSOCIATED WITH
CANCER
DU176b-D-U311
IND/EUDRACT NUMBER 63,266/2014-004708-30

VERSION 1.0, 15 DEC 2014
DAIICHI SANKYO PHARMA DEVELOPMENT
399 THORNALL STREET
EDISON, NJ 08837
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Notes: further d
Source: details

**VERSUS DALTEPARIN IN VENOUS
THROMBOEMBOLISM ASSOCIATED WITH
CANCER**

DUI76b-D-U311

IND/EUDRACT NUMBER 63,266/2014-004708-30

VERSION 3.0, 20 JAN 2016

VERSION 2.0, 17 DEC 2015

VERSION 1.0, 15 DEC 2014

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EDISON, NJ 08837

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STATISTICAL ANALYSIS PLAN

A PHASE 3B, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLIND EVALUATOR (PROBE) STUDY EVALUATING THE EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN (LMWH)/EDOXABAN VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

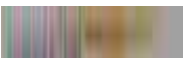
Protocol Number: DU176b-D-U311

- Version 1.0, 29 February 2016

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STATISTICAL ANALYSIS PLAN

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5.3. Safety Endpoints

The primary safety endpoint is major bleeding, and the secondary safety endpoints include the following:

- Major + clinically relevant non-major bleeding;
- Clinically relevant non-major bleeding;
- All bleeding;
- Mortality from all causes.

CEC adjudication results will form the basis for the final analysis. Healthcare resource utilization for potential recurrent VTE and bleed events will also be analyzed.

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Protocol Number: DU176b-D-U311

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ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nicky 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., Annalisa Sagers, M.D., Minggao Shi, Ph.D., Tzu-Fai 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*

ABSTRACT

BACKGROUND

Low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulants agents is unclear.

METHODS

In this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

RESULTS

Of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; $P=0.006$ for noninferiority; $P=0.87$ for superiority). Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 39 patients (11.3%) in the dalteparin group (difference in risk, -3.4 percentage points; 95% CI, -7.0 to 0.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).

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. (Registered at ClinicalTrials.gov number, NCT02073682.)

From the Sciences of Oklahoma of Vascular Center, U.H.R.B., *Organized the Department Hemostasis, Leuven, 1 Research Health Sciences London, Network, (E.Y.), and Thrombosis Institute, Canada, 4 Aging Sci Ohio, 5 Medicine University of Ich Sankyo Ridge Thrombosis Center, the Department Hospital Leuven, 6 (G.M.), 6 Ohio University, 7 (T.F.) Medical Center Boston (J.I.W.), 8 Dr. Raskob, 9 Public Health City, 10 (G.M.), 11 (G.M.), 12 (G.M.), 13 (G.M.), 14 (G.M.), 15 (G.M.), 16 (G.M.), 17 (G.M.), 18 (G.M.), 19 (G.M.), 20 (G.M.), 21 (G.M.), 22 (G.M.), 23 (G.M.), 24 (G.M.), 25 (G.M.), 26 (G.M.), 27 (G.M.), 28 (G.M.), 29 (G.M.), 30 (G.M.), 31 (G.M.), 32 (G.M.), 33 (G.M.), 34 (G.M.), 35 (G.M.), 36 (G.M.), 37 (G.M.), 38 (G.M.), 39 (G.M.), 40 (G.M.), 41 (G.M.), 42 (G.M.), 43 (G.M.), 44 (G.M.), 45 (G.M.), 46 (G.M.), 47 (G.M.), 48 (G.M.), 49 (G.M.), 50 (G.M.), 51 (G.M.), 52 (G.M.), 53 (G.M.), 54 (G.M.), 55 (G.M.), 56 (G.M.), 57 (G.M.), 58 (G.M.), 59 (G.M.), 60 (G.M.), 61 (G.M.), 62 (G.M.), 63 (G.M.), 64 (G.M.), 65 (G.M.), 66 (G.M.), 67 (G.M.), 68 (G.M.), 69 (G.M.), 70 (G.M.), 71 (G.M.), 72 (G.M.), 73 (G.M.), 74 (G.M.), 75 (G.M.), 76 (G.M.), 77 (G.M.), 78 (G.M.), 79 (G.M.), 80 (G.M.), 81 (G.M.), 82 (G.M.), 83 (G.M.), 84 (G.M.), 85 (G.M.), 86 (G.M.), 87 (G.M.), 88 (G.M.), 89 (G.M.), 90 (G.M.), 91 (G.M.), 92 (G.M.), 93 (G.M.), 94 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for the Hokusai VTE Cancer Investigators*

Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists

An individual patient data meta-analysis

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¹Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; ²Department of Haematological Medicine, Guy's and St Thomas' Hospital, King's College London, London, UK; ³College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

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Special circumstances

	LMWH	DOACs
Extremes of body weight	Commonly used	Not recommended
Chemotherapy	Few drug-drug interactions	Avoid in strong inducers/ inhibitors of p-GP or CYP3A4
Renal impairment	Dose adjustment	Dose adjustment
Thrombocytopenia	Dose adjustment	Dose adjustment

	LMWH	DOACs
Heparin induced thrombocytopenia	Contraindicated	Not contraindicated
Upper GI/ urothelial cancers	Commonly used	Increased bleeding risk: avoid
Needle phobia	Not advised	Acceptable
Liver disease	Used with caution	Used with caution

**DOACs are only as safe as the
stupidest person allowed to prescribe
them**

**So how do we inform the unknowingly
unknowing about the safe prescribing?**

Through the universal language of hip-hop





CAT RAP

**I said-a hip, hop, the hippie, the hippie
To the hip hip hop-a you don't stop the rock,
It to the bang-bang boogie, say up jump the boogie
To the rhythm of the boogie, the beat**

**Now what you hear is not a test: I'm rappin' to the beat
And me, the groove, and my friends are gonna try to
move your feet**

**I am Noble MC, in Bergamo
And I'm rapping with my peers
There's Benny, Anna, Freddy Ricks
The ICTHIC musketeers**

I'm called Notorious TRM
Thrombosis Renegade Master
Cost I seen what cancer clots can do
Don't need no news forecaster
They . disaster,
They gonna kill you faster
By bleed or big PE
The bleeding don't stop when you get a clot
That's Coagulopathy

**Now he-par-ins have been the bomb
Since CLOT by Aggie Lee
More efficacious than warfarin
And that sounds good to me**

**A daily prick is all it takes
Pinch fat, inject and boom
But some folk say
They got no space
They running out of room**

**In the longterm I say no fear
In time we'll have evolved
To all have nice big guts like me
Crack on guys
Problem solved**

**Now I got no beef with Buller
He's a wise man, He's a sage
He been fighting clots since time began
When leeches were the rage''**

**He says relax Prescribe DOACs
There safe and they're reliable
Well I read that paper too my friend
And I think you're certifiable.**

**Now I aint clever like Buller
But even I have seen
With an iddy biddy microscope
Zoomed in on page 16
Of the *32 page online appendix*
A tiny forest plot
which shows a breakdown of major bleeds
Who bleeds and who does not**

13 percent major bleed

13! Unlucky for some

**For GI cancers starting from your gullet to your
bum**

Urothelial bleeding cancers

Likewise Not so great

Major bleeding incident percentages of 8

**I know Buller says these bleedings aren't bad
Has a new score to address
But if you torture the data long enough,
It will eventually confess.**

**Now one last thing before I go
And drive you to distraction
Think of those patients on chemo
And drug-drug interactions**

***Inhibit or induce PGP or CYP 3A4*
Gonna produce damage to your juice
That you aint looking for**

Stay off methyl pred unless you wanna see red
Afatinib Alelectininb too
Watch your backs with Venetoclax
Or you'll get malaena poo

**Aprepitant, Ceritinib,
Crizotinib, Dasatinib,
Ibrutinib
Idelalisib
Imatinib
Lapatinib**

**Lenvatinib
Mitotave
Nilotinib
Tropotecan
Dexafrikinmethasone**

**Now some of us were born to rap
And others born to waltz
With CAT this aint no binary choice of what is true and
false
We know this wide wide world to don't move to the
beat of just one drum
DOACs might be right for you
But not be right for some**

DOACs will be fine in cancer

(pause) so long as you

Check their kidneys, liver and platelets are doing, what they're meant to do

Avoid in GI cancers

Avoid in urothelial

Ensure when chemo given

They're interaction free ya'll

**Each patients is different
Each with value and preferences
So embrace individuality
And think beyond the references**





**Care and support
through terminal illness**