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

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Marie Curie
Care and support through terminal illness

A truly great man

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*

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 ITREAS, 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.); Thrombosis 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. Raskob at the University of Oklahoma Health Sciences Center, College of Public Health, 801 NE 13th St., Oklahoma City, OK 73104, or at gary-raskob@ouhsc.edu.

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

This article was published on December 12, 2017, at NEJM.org.

DOI: 10.1056/NEJMoa1711948

The NEW ENGLAND JOURNAL of MEDICINE

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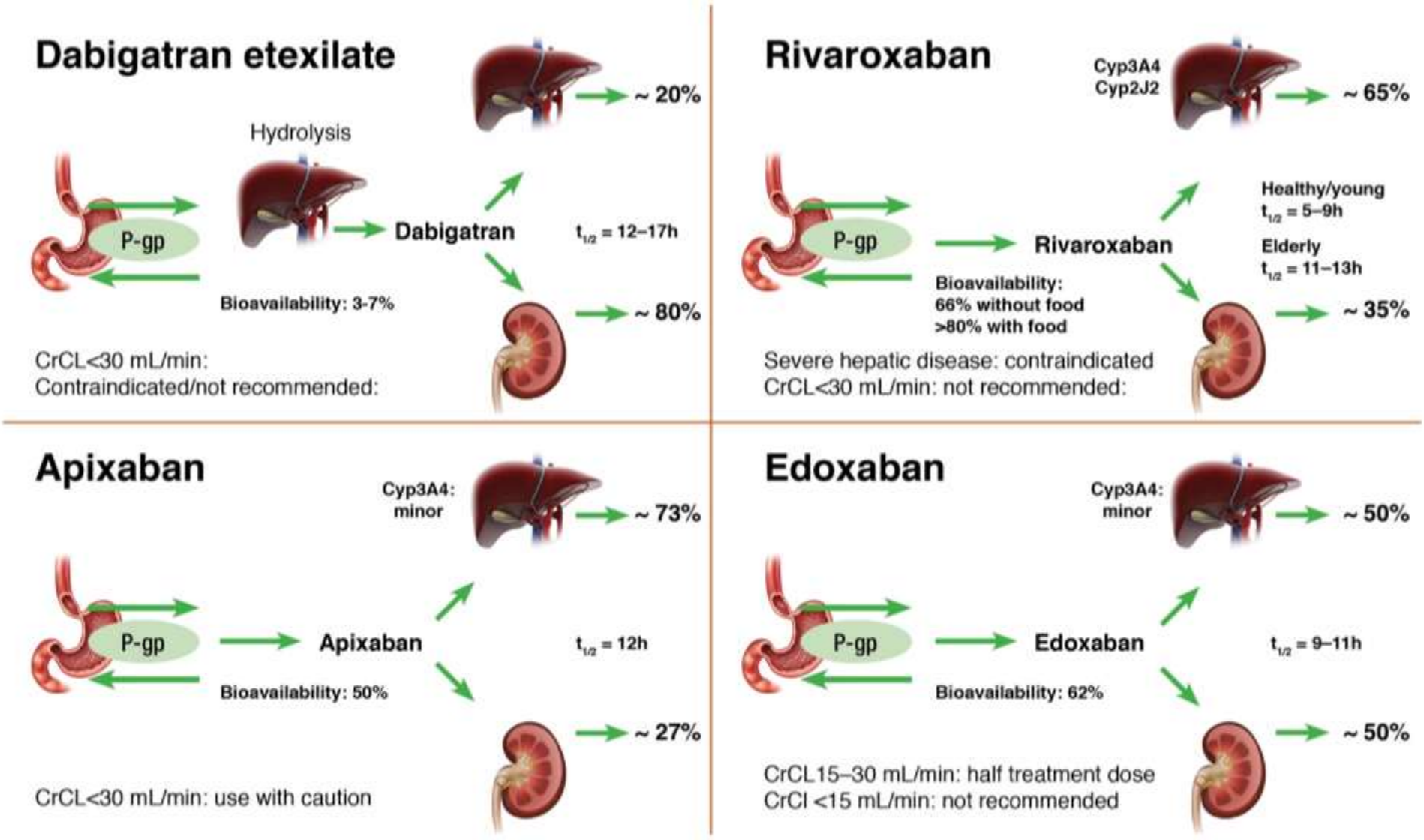
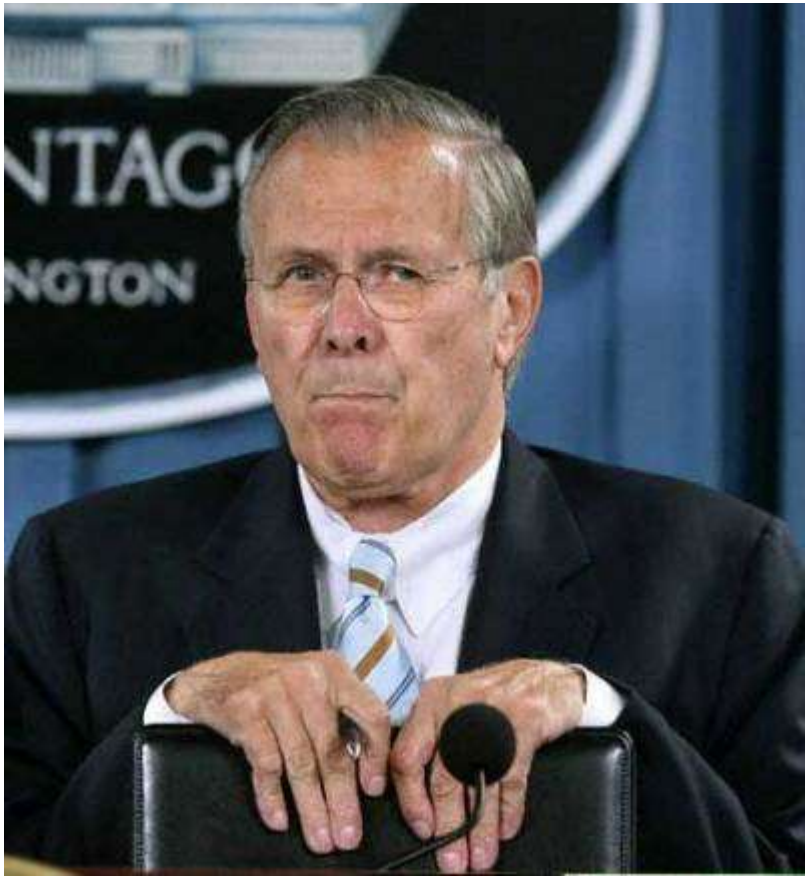
DOAC Pharmacology



Adapted from: Heidbuchel H *et al. Europace* 2013; U.S., Canadian Prescribing Information CrCl = creatinine clearance

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."



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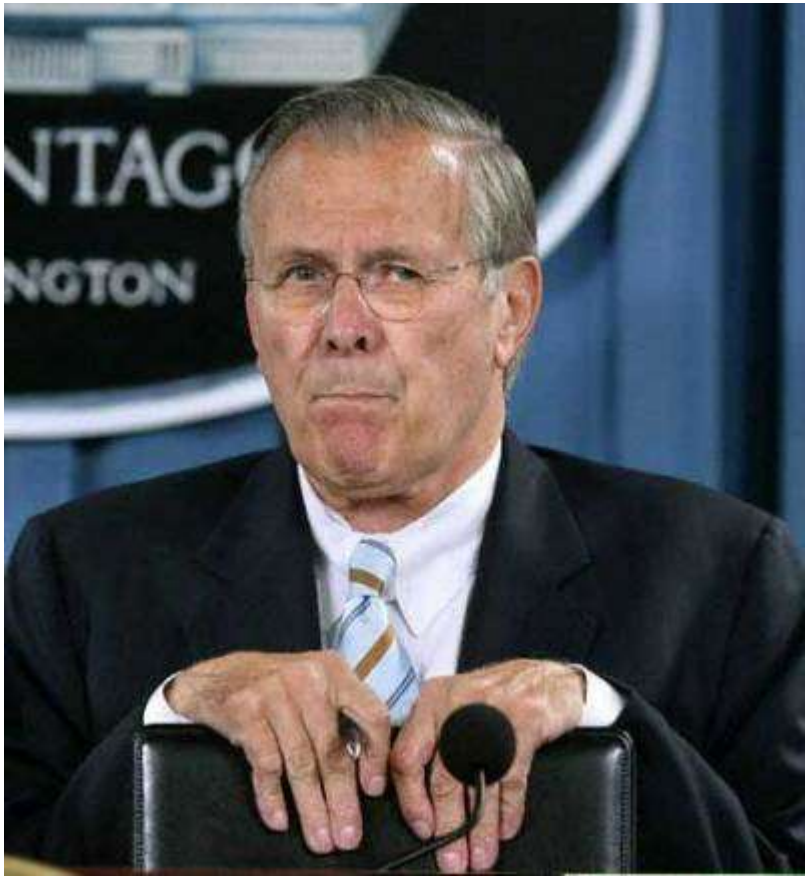


DOACs are only as safe as the stupidest person allowed to prescribe them

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	↑	↑

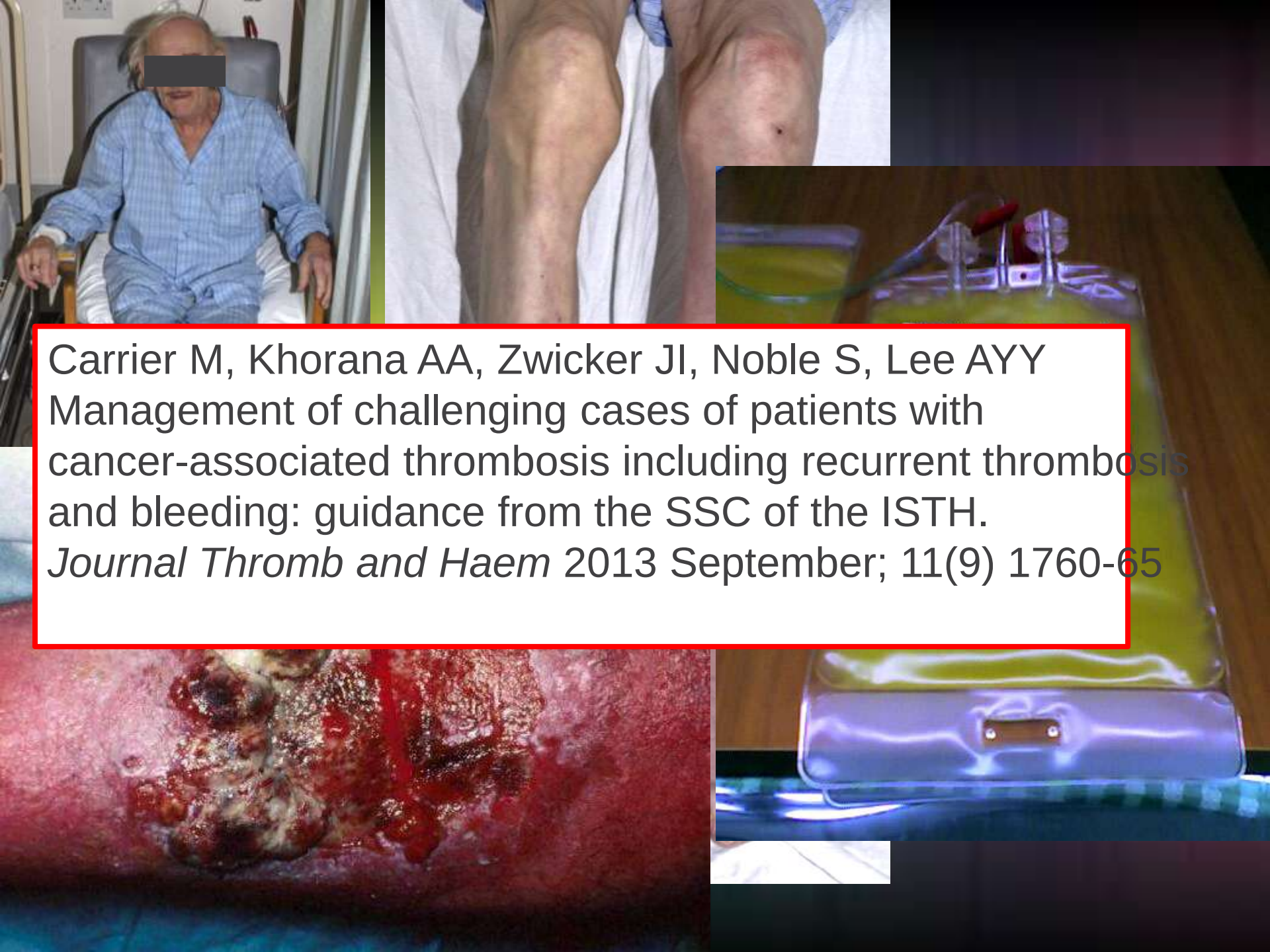
Chemotherapy	CYP3A4	P-gp
Doxorubicin	↓	
Topotecan	↓	
Vinblastine	↓	
Mitotane	↑	
Venetoclax		↓

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

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

Product Prescribing Information

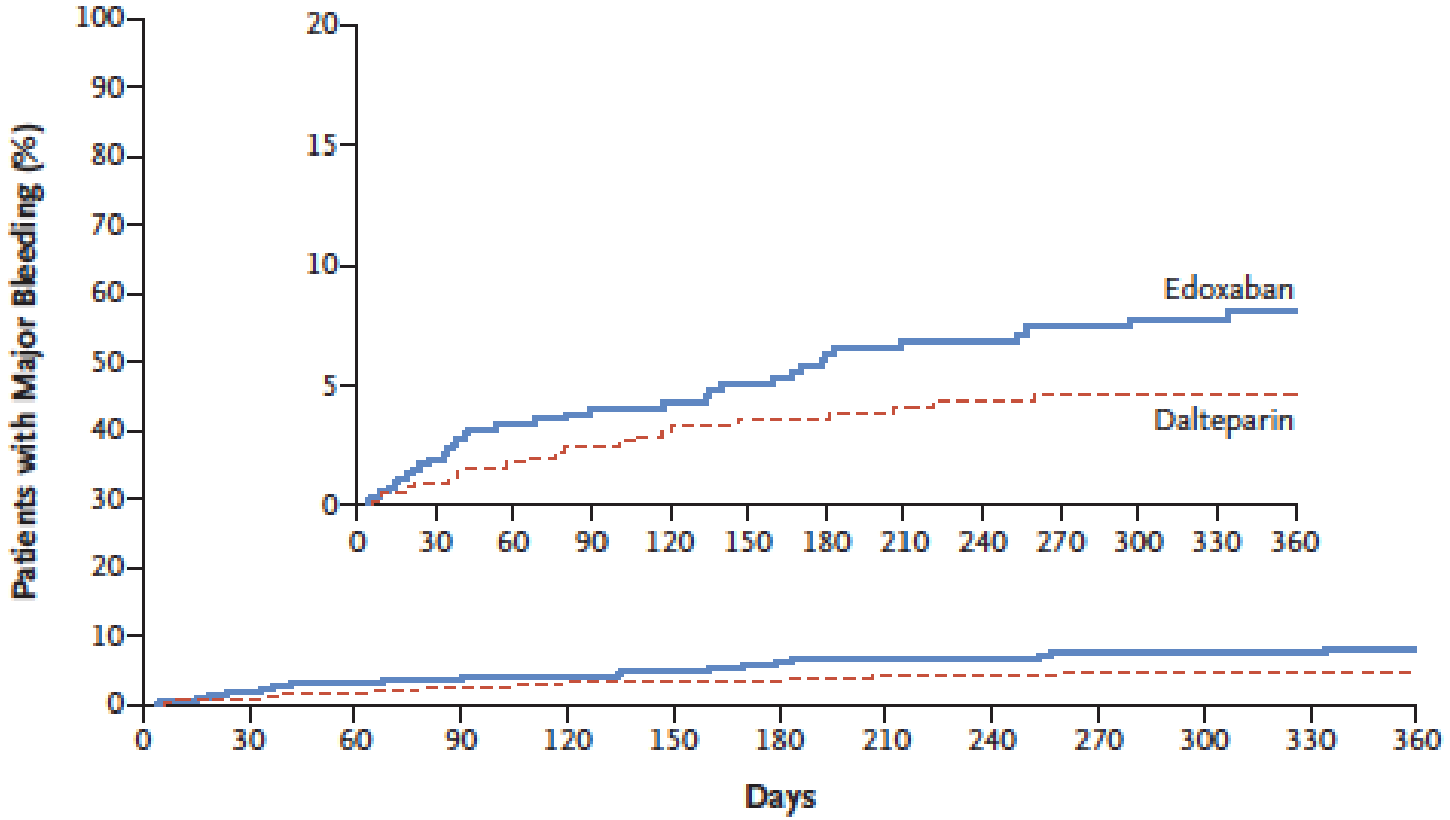
CYP = Cytochrome P; P-gp = p-glycoprotein



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

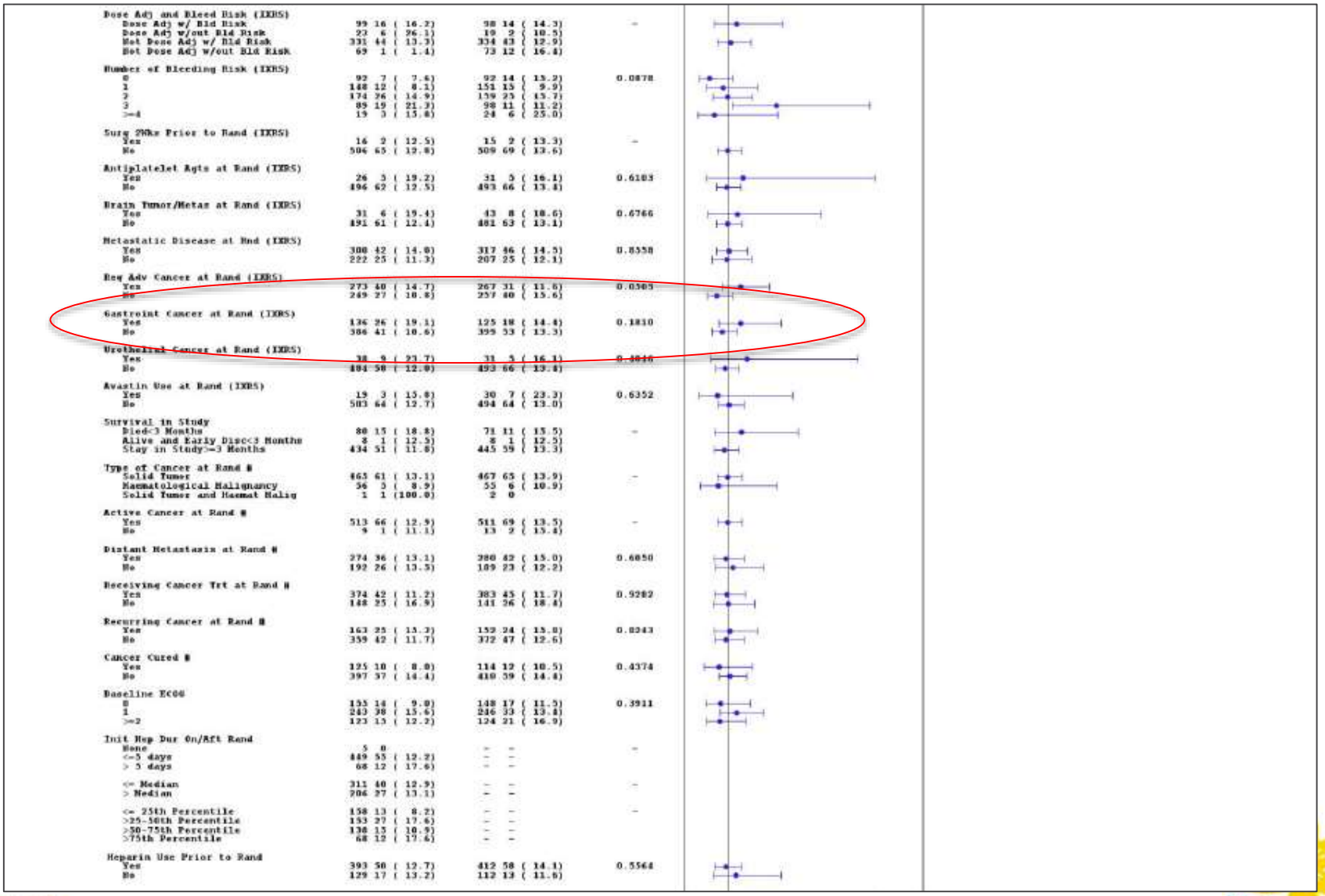
Bleeding

B

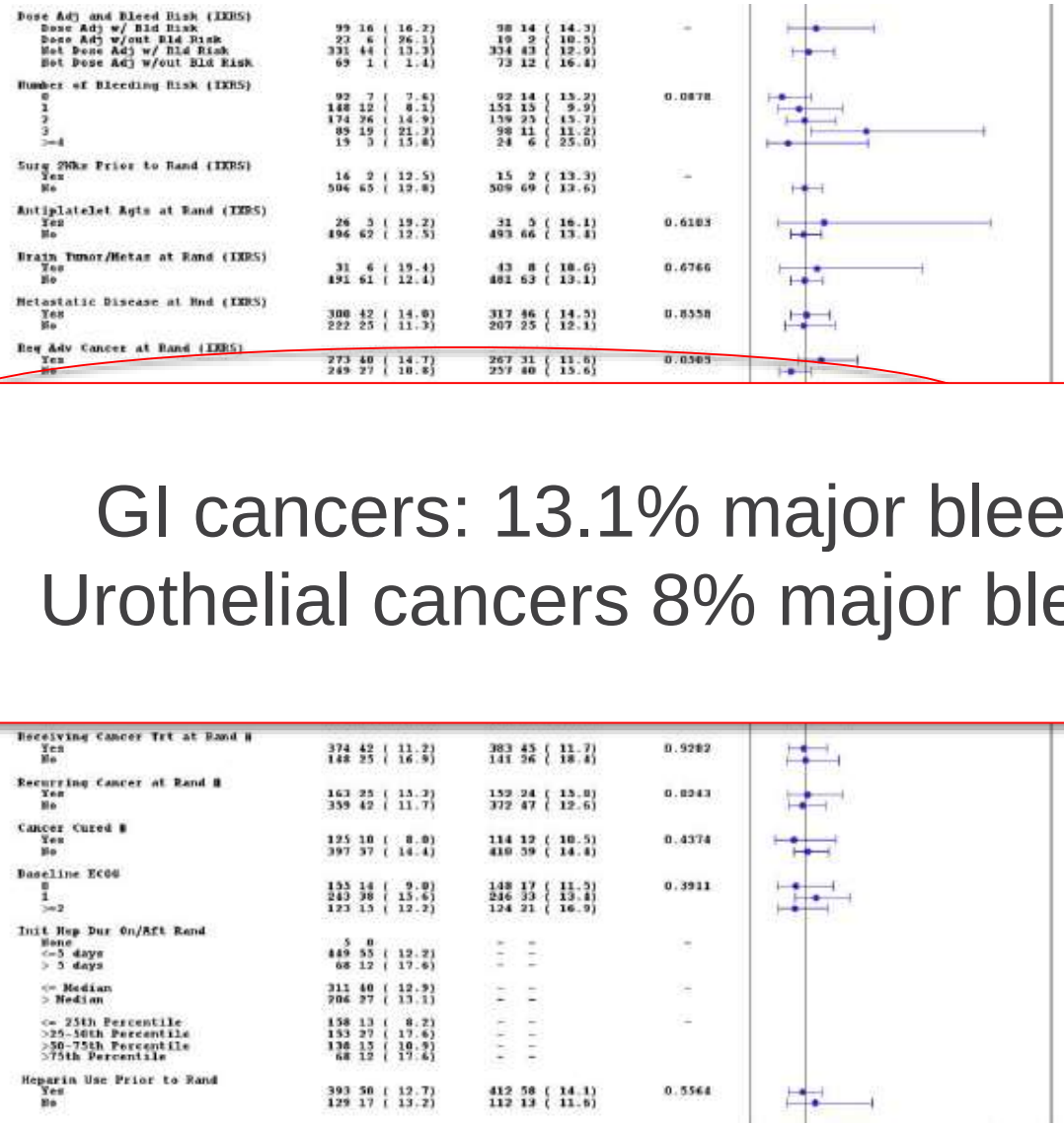


No. at Risk													
Edoxaban	522	484	447	426	404	375	358	343	323	308	282	248	168
Dalteparin	524	497	466	436	409	390	378	356	346	335	298	262	183

Appendix: page 16/32



Appendix: page 16/32



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

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)

Young A et al. Presented at: ASH 2017; Abstract 625.

CRNMB = clinically-relevant non-major bleeding

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

Bleker SM, et al. Thromb Haemost 2017;117:1944–51

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

Notes: further d

Source: details

VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

DU176b-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

DAIICHI SANKYO PHARMA DEVELOPMENT

399 THORNALL STREET
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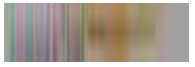
STATISTICAL ANALYSIS PLAN

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**

DAIICHI SANKYO PHARMA DEVELOPMENT



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

- **Version 3.0, 02 October 2017**

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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 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).

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N ENGL J MED NEJM.ORG

The New England Journal of Medicine

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

Suzanne M. Bleker[1*]; Marjolein P.A. Brekelmans[1*]; Elise S. Eerenberg[1]; Alexander T. Cohen[2]; Saskia Middeldorp[1]; Gary Raskob[3]; Harry R. Büller[1]

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

Summary

Factor Xa (fXa)-inhibitors are as effective and safer than vitamin-K–antagonists (VKA) in the treatment of venous thromboembolism (VTE). We previously classified the severity of clinical presentation and course of all major bleeding events from the EINSTEIN, AMPLIFY and HOKUSAI-VTE trials separately. The current aim was to combine these findings in order to increase precision, assess a class effect and analyse presentation and course for different types of bleeding, i.e. intracranial, gastro-intestinal, and other. We classified the clinical presentation and course of all major bleeding events using pre-defined criteria. Both classifications comprised four categories; one being the mildest, and four the most severe. Odds ratios (OR) were calculated for all events classified as category three or four between fXa-inhibitors and VKA recipients. Also, ORs were computed for different types of bleeding. Major bleeding occurred in 111 fXa-inhibitor recipients and in 187 LMWH/VKA recipients. The clinical presentation was classified as category three or four in 35% and 48% of the major bleeds in fXa inhibitor and VKA recipients, respectively (OR 0.59, 95% CI 0.36–0.97). For intracranial, gastro-intestinal and other bleeding a trend towards a less severe presentation was observed for patients treated with fXa inhibitors. Clinical course was classified as severe in 22% of the fXa inhibitor and 25% of the VKA associated bleeds (OR 0.83, 95% CI 0.47–1.46). In conclusion, FXa inhibitor associated major bleeding events had a significantly less severe presentation and a similar course compared to VKA. This finding was consistent for different types of bleeding.

Keywords

Major bleeding; factor Xa inhibitors; vitamin K antagonists; venous thromboembolism

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Thromb Haemost 2017; 117: 1944–1951

* Both authors contributed equally to this manuscript.

Introduction

Factor Xa (fXa) inhibitors are at least as effective as vitamin K antagonists (VKA) in the treatment of venous thromboembolism (VTE), and are associated with less bleeding (1–6). Furthermore, the pattern of bleeding complications has been observed to differ between patients receiving fXa inhibitors and VKA; those receiving fXa inhibitors less often experienced intracranial haemorrhages (ICH) whereas gastro-intestinal (GI) and urogenital bleeds appeared to occur more often in this group (7–10).

The uptake of fXa inhibitors in the treatment of VTE has been slow, partly due to concerns about the clinical impact and the best strategies for treatment of bleeding events (11,12). Therefore, there is a need for information about the presentation, development and management of bleeding events during the use of these new agents. Previously, we classified the severity of clinical presentation and course of all major bleeding events in the EINSTEIN, AMPLIFY and HOKUSAI-VTE trials for each study separately (13–15). Although small differences existed amongst the study results, all studies showed at least a trend for a less severe clinical presentation in fXa inhibitor recipients compared to VKA recipients. For clinical course either no or a minimal difference was found in favour of the fXa inhibitors.

In the present individual patient data meta-analysis, we combined the results from these three studies to increase precision and to be able to analyse the effects in different types of bleeding, with a special interest for ICH and GI bleeding. The aim of this study was to assess differences in bleeding pattern and to compare the clinical presentation and subsequent clinical course of major bleeding events associated with fXa inhibitors to those associated with the use of VKA.

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Stroke, Systemic or Venous Thromboembolism

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An individual patient data meta-analysis

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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

Care and support through terminal illness

Marie Curie

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 Alectininb too

Watch your backs with Venetoclax

Or you’ll get malaena poo

Aprepitant, Ceritinib, Crizorinib, 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


Marie
Curie
Care and support
through terminal illness