Treatment of Venous Thromboembolism in Patients with Cancer

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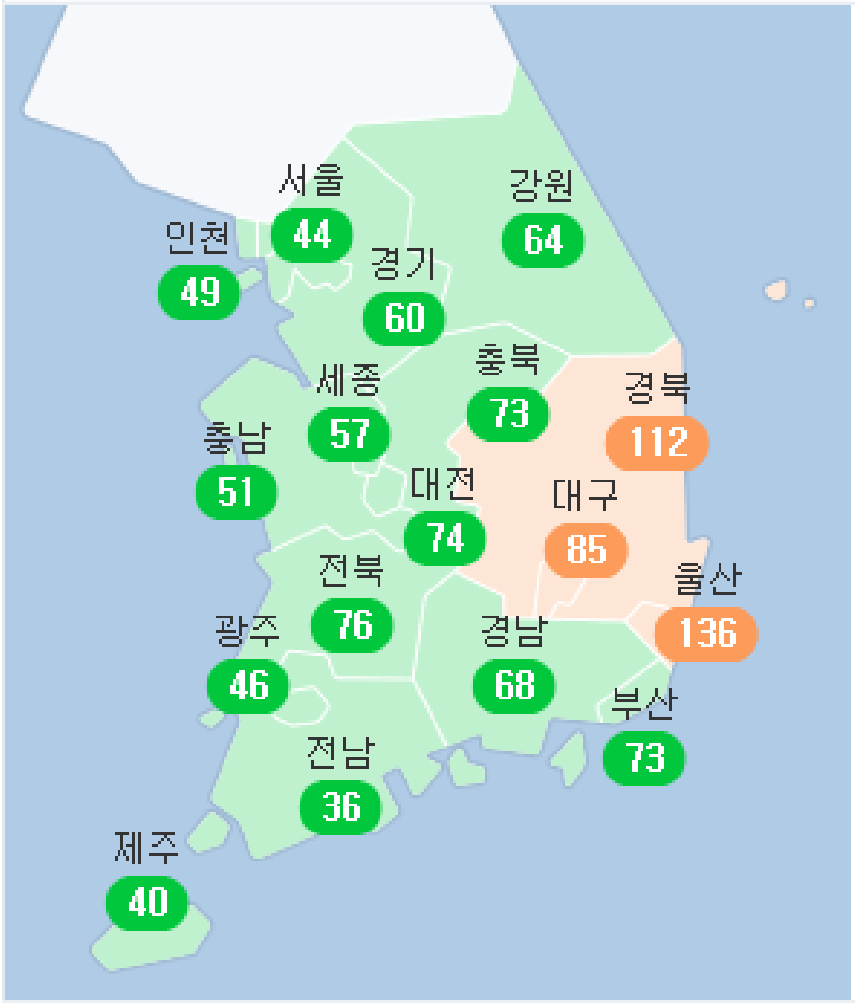
미세먼지 초미세먼지 오존 자외선 황사

현재 내일 모레 주간



관측지점	현재	오전예보	오후예보
서울	44	나쁨	한때나쁨
경기	60	나쁨	한때나쁨
인천	49	나쁨	한때나쁨
강원	64	나쁨	한때나쁨
세종	57	나쁨	한때나쁨
충북	73	나쁨	한때나쁨
충남	51	나쁨	한때나쁨
대전	74	나쁨	한때나쁨

VTE and Cancer

- VTE: Deep vein thrombosis + Pulmonary embolism

Up to 6-fold risk of VTE

Cancer → **VTE**

- **Of all patients who present with VTE, about 20% of them already have cancer**
- **5-10% of patients presenting with idiopathic VTE will be diagnosed with cancer within next 12-24 months**

VTE and Cancer

- **Cancer increases risk of VTE by 4- to 6-fold.**
  - Hypercoagulable state by cancer itself
  - Systemic chemotherapy (cisplatin, anthracycline, lenalidomide, bevacizumab)
  - Hormone therapy
  - Supportive care (erythropoietin stimulating factor)
  - Decreased performance → decreased ambulation

Risk assessment model of VTE in ambulatory cancer patients

Patient Characteristics	Risk score
Site of primary cancer	
- Very high risk (stomach, pancreas)	2
- High risk (Lung, Lymphoma, Gynecologic, bladder, testicular)	1
Prechemotherapy PLT >350x10^9/l	1
Hb <10g/L or Erythropoiesis-stimulating agent	1
Prechemotherapy WBC >11x10^9/l	1
BMI ≥ 35kg/m^2	1

Total score	Risk category	Risk of symptomatic VTE
0	Low	0.3-0.8%
1,2	Intermediate	1.3%-2.0%
3 or higher	High	6.7-7.1%

Khorana AA et al. Blood 2008;111:4902-7

VTE and Cancer

Up to 6-fold risk of VTE

Cancer ⇄ **VTE**

Worse outcomes

- Delay or discontinuation of chemotherapy

- Increased hospitalizations (mean duration 11 days)

- Need for ≥ 3-6 months of anticoagulation

Risk factors for bleeding with anticoagulation therapy in VTE

Age> 65 y	Cancer	Anti-platelet therapy
Age >75y	Metastatic cancer	Poor anticoagulant control
Previous bleeding	Renal failure	Recent surgery
Comorbidity and reduced functional capacity	Thrombocytopenia	Frequent falls
Previous stroke	Anemia	Alcohol abuse
Diabetes		

0 risk factor : low risk

1 risk factor- moderate risk

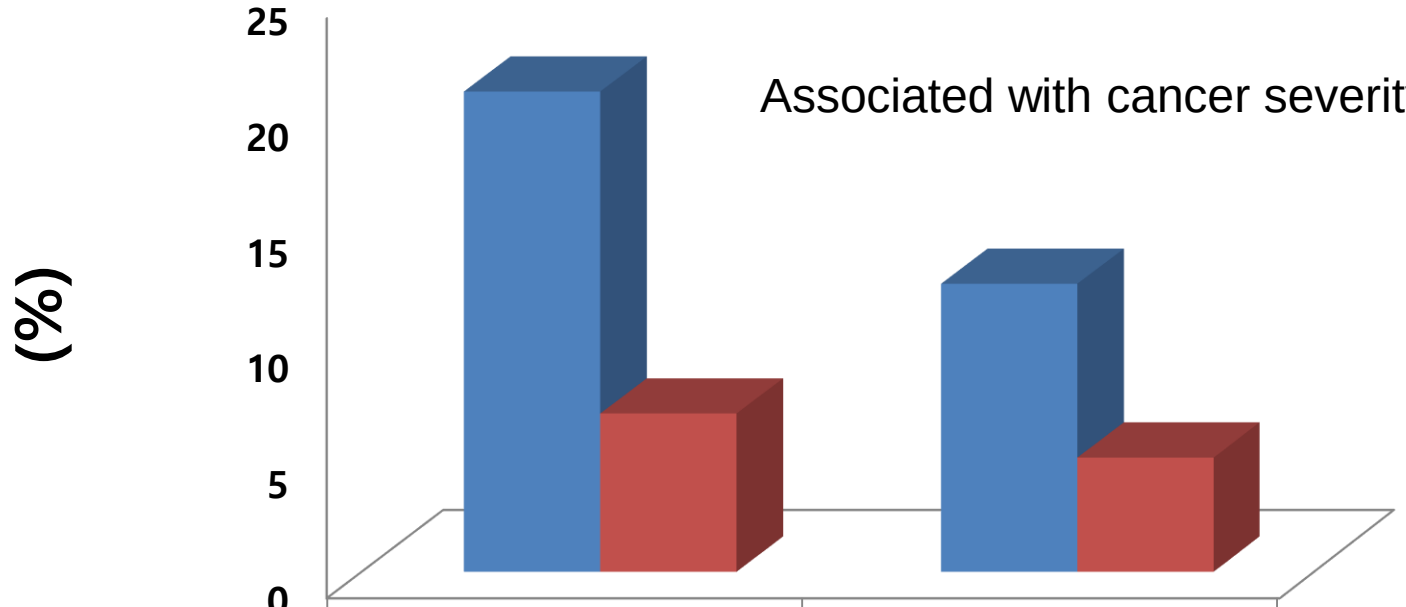
2 risk factors: High risk

Chest 2012;141 :e419-e494

Recurrent VTE and bleeding in Cancer Pts during treatment

Threefold higher risk of recurrent VTE and major bleeding

during 3-6 months of Tx

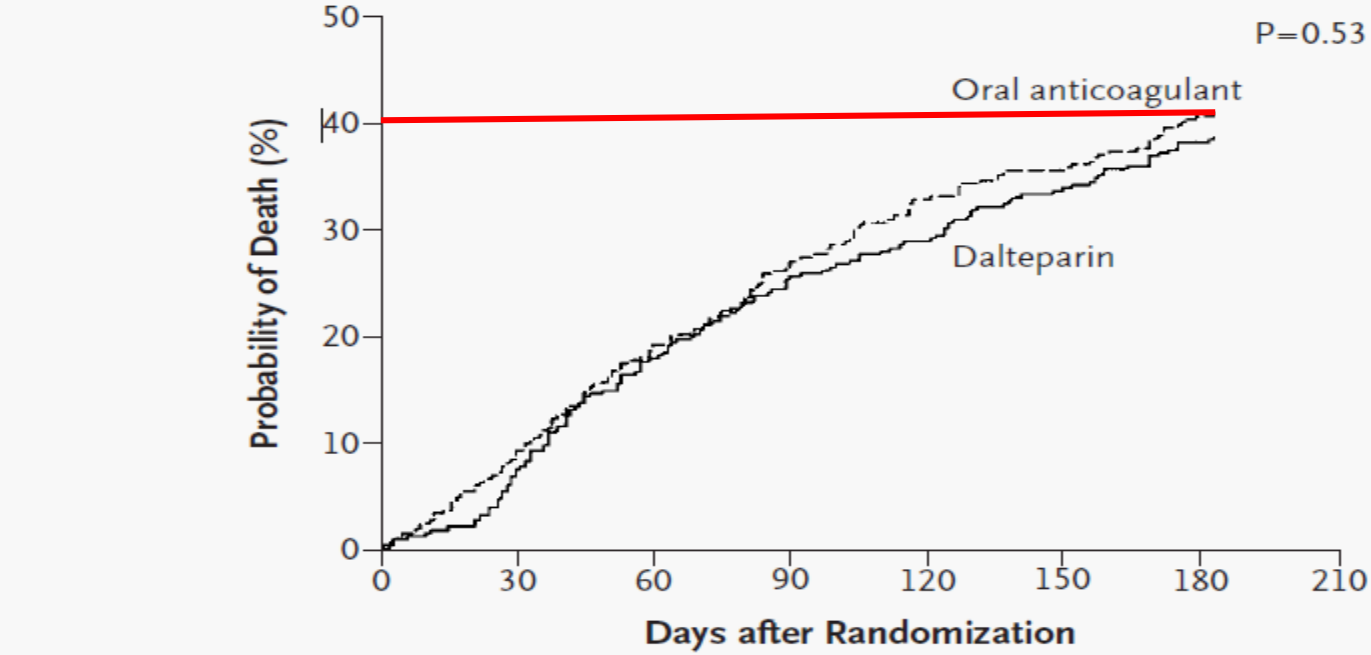


	Recurrent VTE	Major bleeding
VTE with Cancer	20.7	12.4
VTE without Cancer	6.8	4.9

Prandoni et al Blood;2002;100:3484-3488.

Mortality in VTE and cancer

6 month mortality in patients with VTE and cancer : 40%



No. at Risk

Dalteparin	336	310	274	248	237	220	206
Oral anticoagulant	336	301	268	240	220	211	194

CLOT study

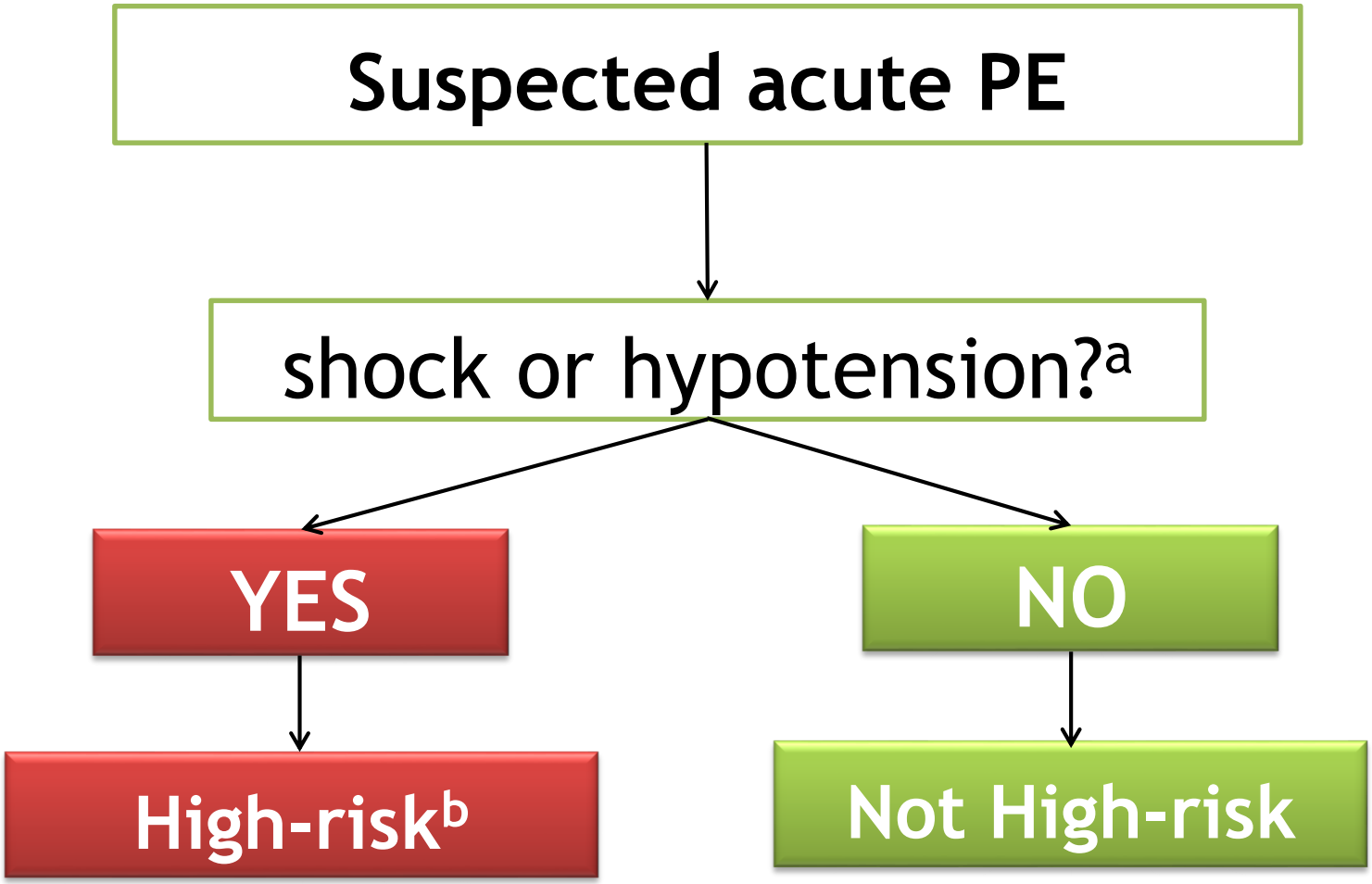
VTE & Cancer

Initial Treatment

Extended Treatment

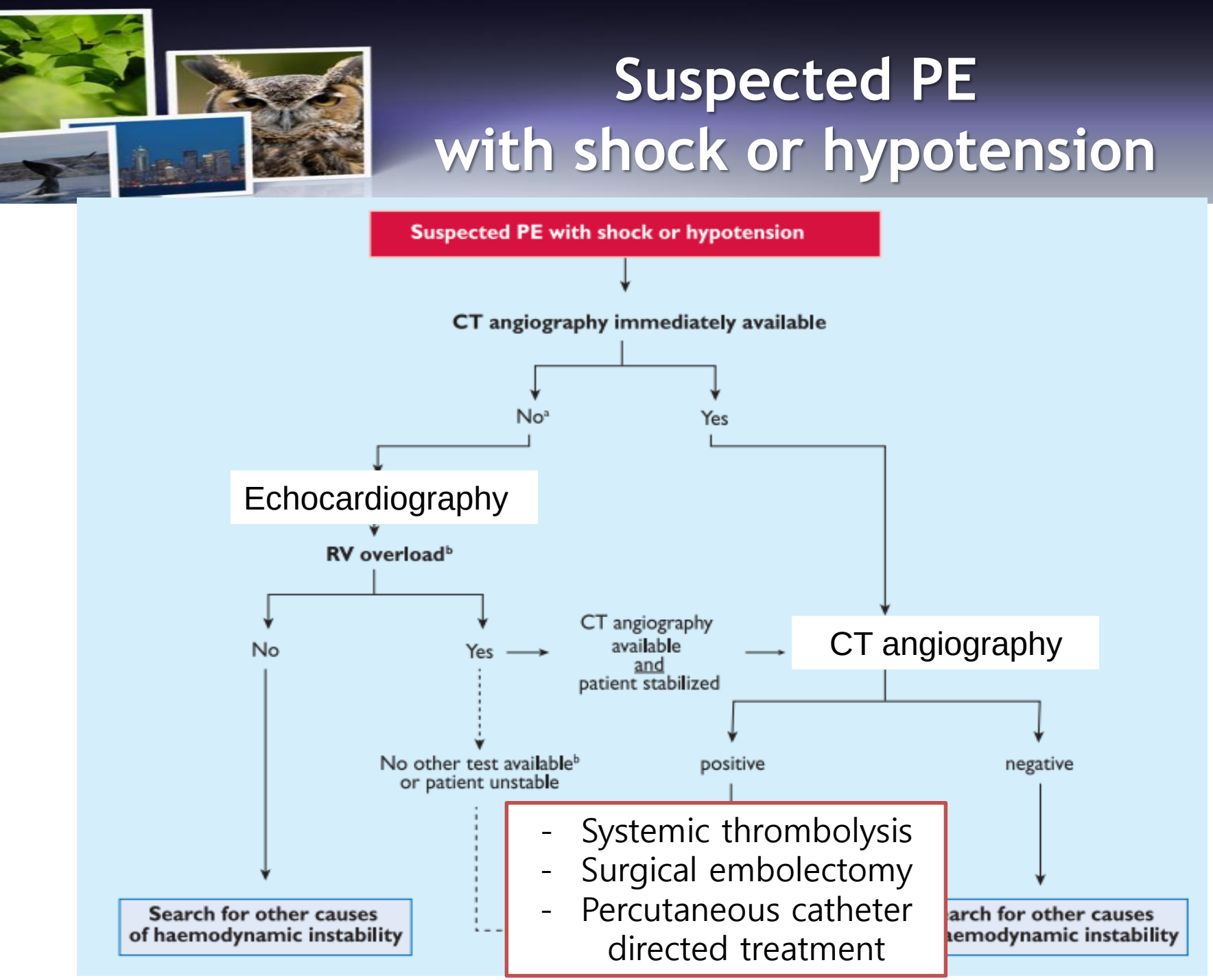
Unsuspected PE

Initial risk stratification of acute PE

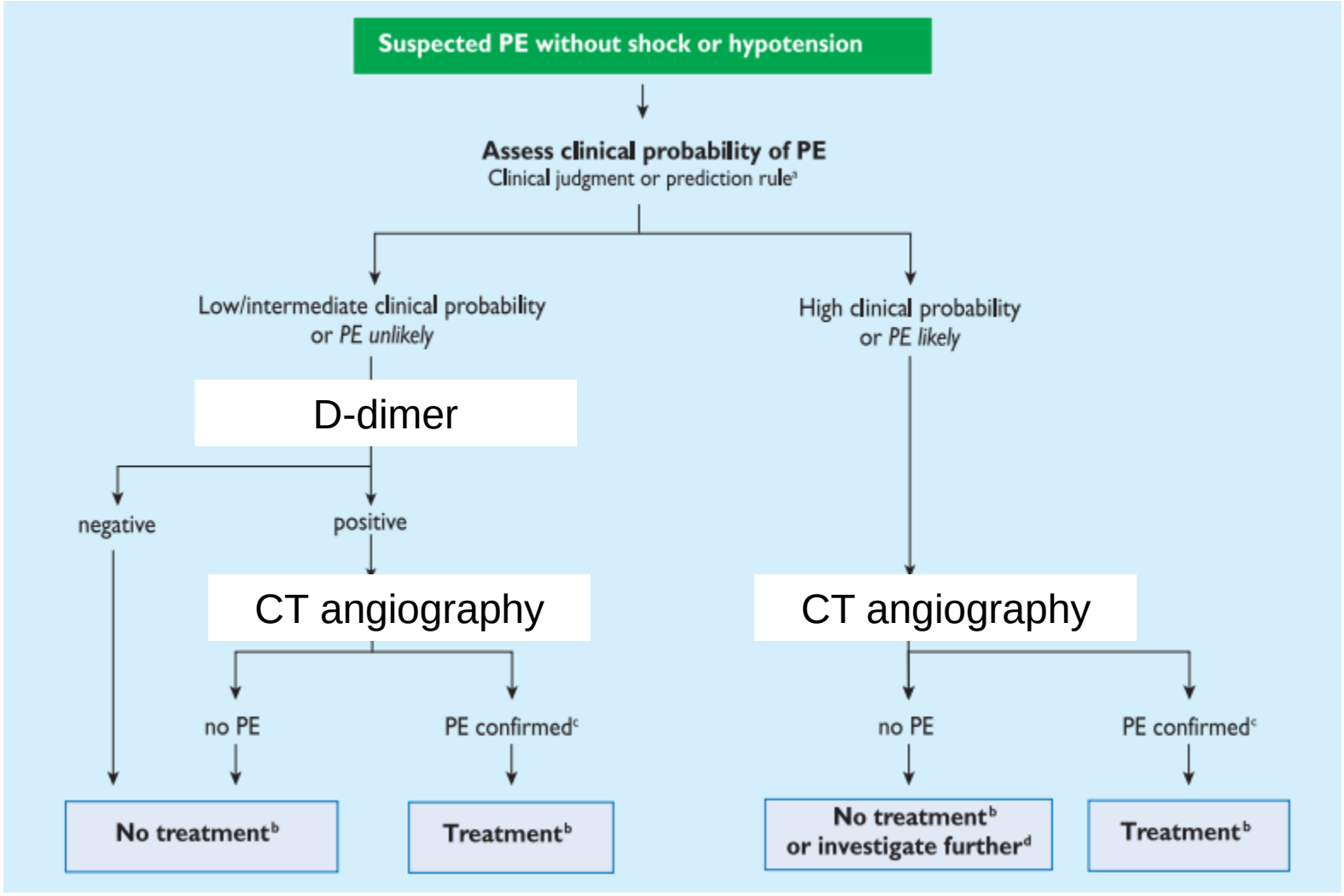


[a]Defined as SBP <90mmHg, or a SPB drop by ≥ 40mmgHg, for > 15 mins
[b]Based on the estimated PE-related in-hospital or 30-day mortality

Suspected PE with shock or hypotension



Suspected PE without shock or hypotension



Contraindications for Tx in patients with cancer and VTE

Absolute contraindications

- Active major, serious, or potentially life-threatening bleeding not reversible with medical or surgical intervention, including but not limited to any active bleeding in a critical site (ie, intracranial, pericardial, retroperitoneal, intraocular, intra-articular, intraspinal)
- Severe, uncontrolled malignant hypertension
- Severe, uncompensated coagulopathy (eg, liver failure)
- Severe platelet dysfunction or inherited bleeding disorder
- Persistent, severe thrombocytopenia (< 20,000/μL)
- Surgery or invasive procedure, including but not limited to lumbar puncture, spinal anesthesia, and epidural catheter placement

Patients for whom anticoagulation is of uncertain benefit

- Patient receiving end-of-life/hospice care
- Very limited life expectancy with no palliative or symptom reduction benefit
- Asymptomatic thrombosis with concomitant high risk of serious bleeding

IVC filter

- Indication
  - Absolute contraindication to anticoagulation (eg, active bleeding)
  - Recurrent PE despite adequate anticoagulant therapy
  - Complication of anticoagulation (eg, severe bleeding)
  - Severe enough PE that another PE may be lethal
- Outcome
  - Reduced PE incidence but increased DVT incidence
  - No gain of mortality
- If temporary CIx, implant retrievable filter and removal within retrieval window

VTE treatment on cancer

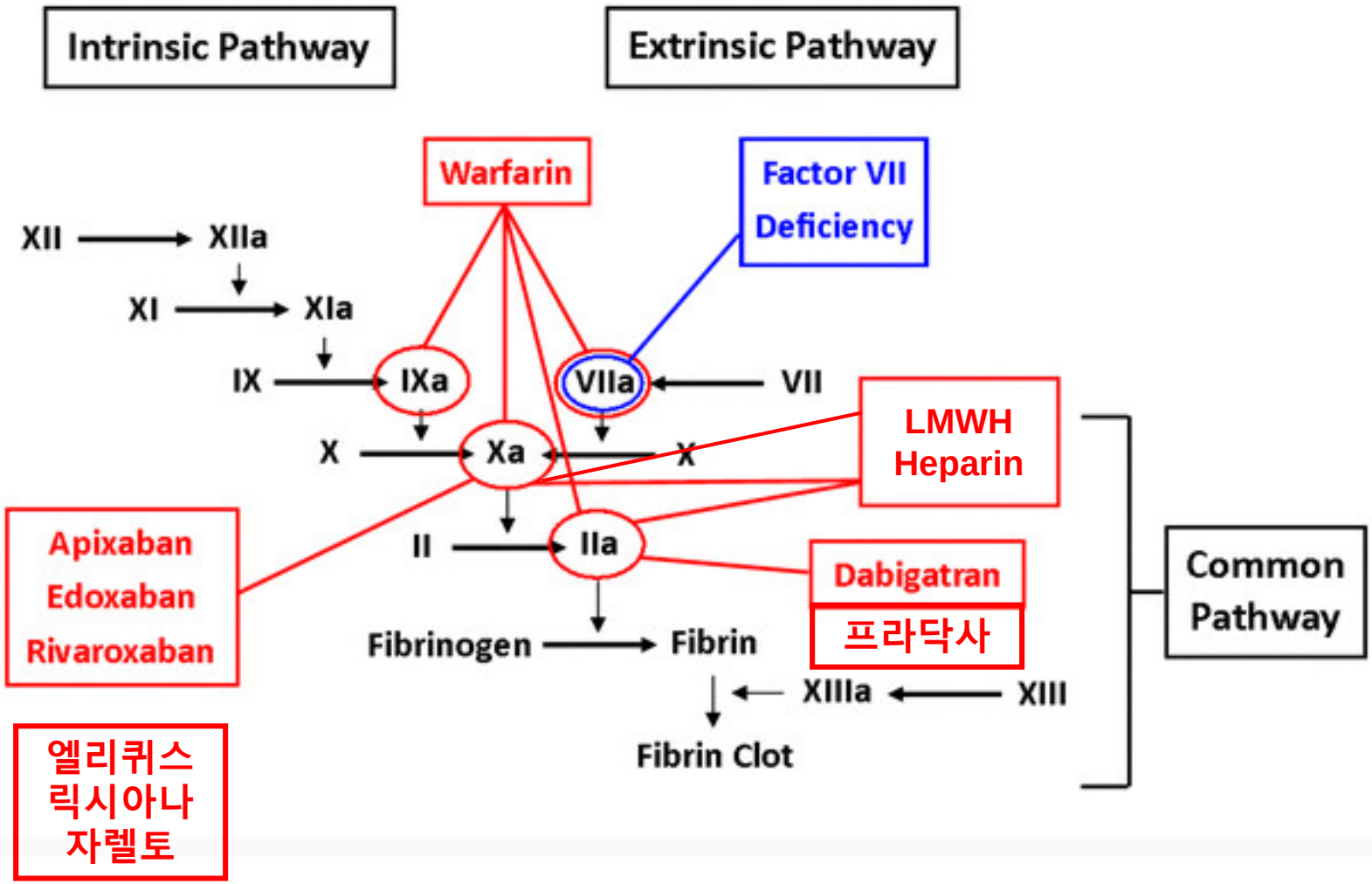
Nonpharmacologic
(Prophylaxis & Treatment)

- Intermittent Pneumatic Compression
- Elastic Stockings
- Inferior Vena Cava Filter

Pharmacologic
(Prophylaxis & Treatment)

- Unfractionated Heparin (UH)
- Low Molecular Weight Heparin (LMWH)
- Oral Anticoagulants

Mechanism of action



용량

Drug by Class	Treatment Dosage	Pharmacokinetics: Half-Life	Pharmacokinetics: Renal Clearance, %	Pharmacokinetic Drug Interactions
Direct factor Xa inhibitors				All drugs in this class have increased levels with strong inhibitors of CYP3A4 and P-Gp and decreased levels with inducers of CYP3A4 and P-Gp
Rivaroxaban	15 mg orally, twice daily for 3 wk, then 20 mg orally every 24 h	7-11 h	33[a]	
Apixaban	10 mg orally, twice daily for 10 d, then 5 mg twice daily	8-12 h	25[a]	
Edoxaban	60 mg orally every 24 h after 7 to 10 d of low-molecular-weight heparin	6-11 h	35[a]	
Direct factor IIa inhibitors				Increased levels with strong inhibitors of P-Gp and amiodarone; decreased levels with inducers of P-Gp
Dabigatran	150 mg orally, twice daily after 7 to 10 d of low-molecular-weight heparin	14-17 h	80[a]	
Indirect factor Xa inhibitors				None
Fondaparinux	Weight <50 kg: 5 mg subcutaneously every 24 h Weight 50-100 kg: 7.5 mg subcutaneously every 24 h Weight >100 kg: 10 mg subcutaneously every 24 h	17-21 h	100	
Low-molecular-weight heparins				None
Dalteparin	200 IU/kg subcutaneously every 24 h or 100 IU/kg twice daily	3-4 h	Approximately 80	
Enoxaparin	1 mg/kg subcutaneously twice daily or 1.5 mg/kg subcutaneously every 24 h	3-4 h	Approximately 80	

VTE & Cancer

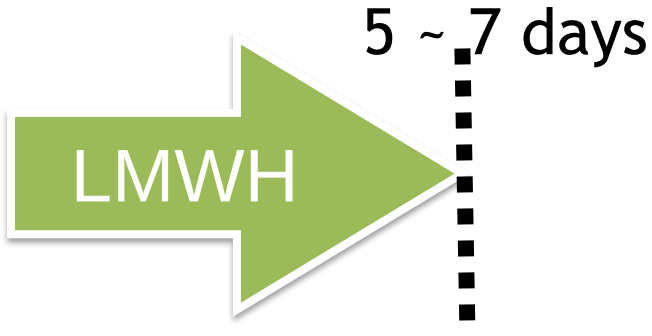
Initial Treatment

Extended Treatment

Unsuspected PE

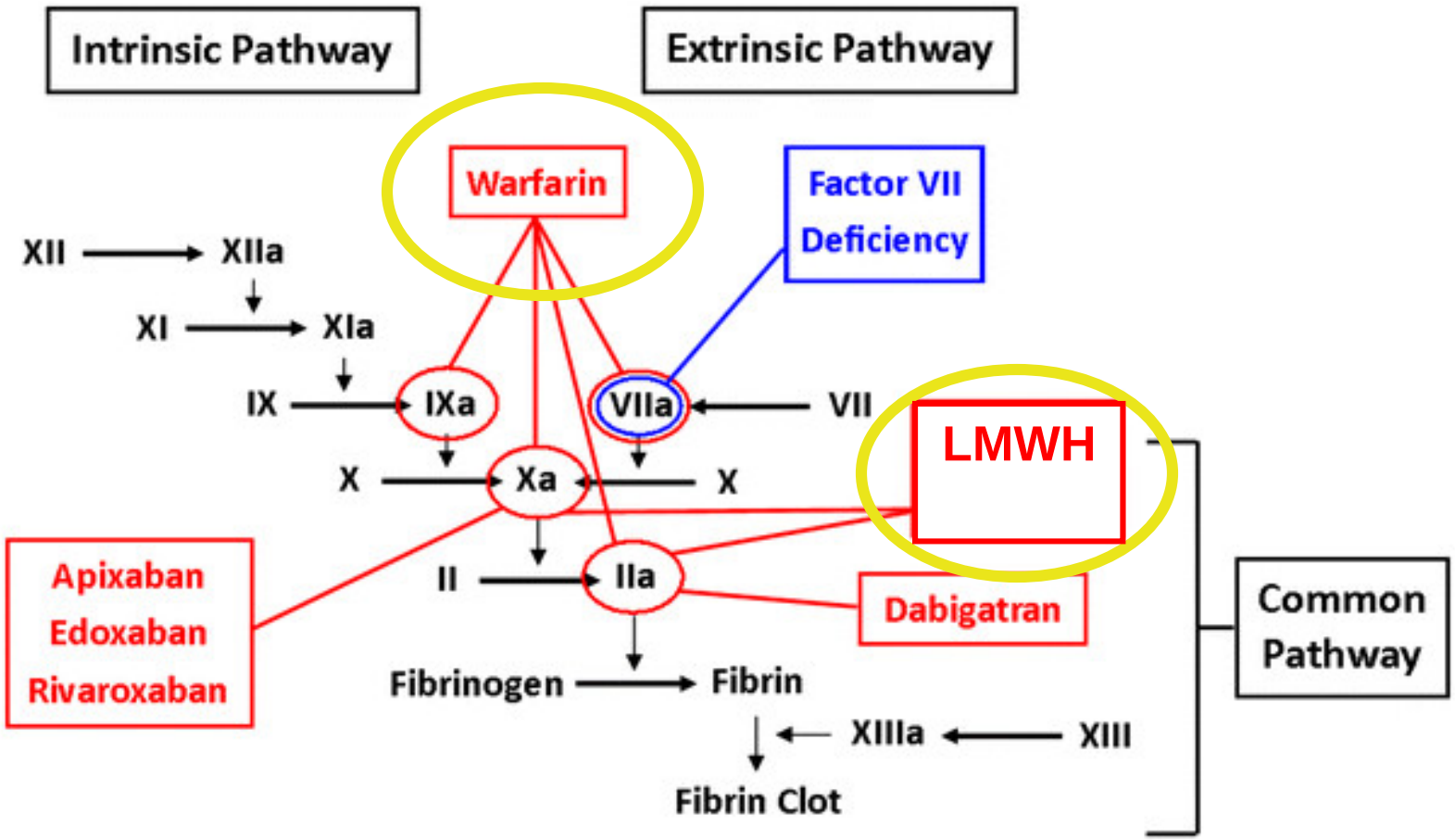
Conventional Treatment of VTE

Initial treatment



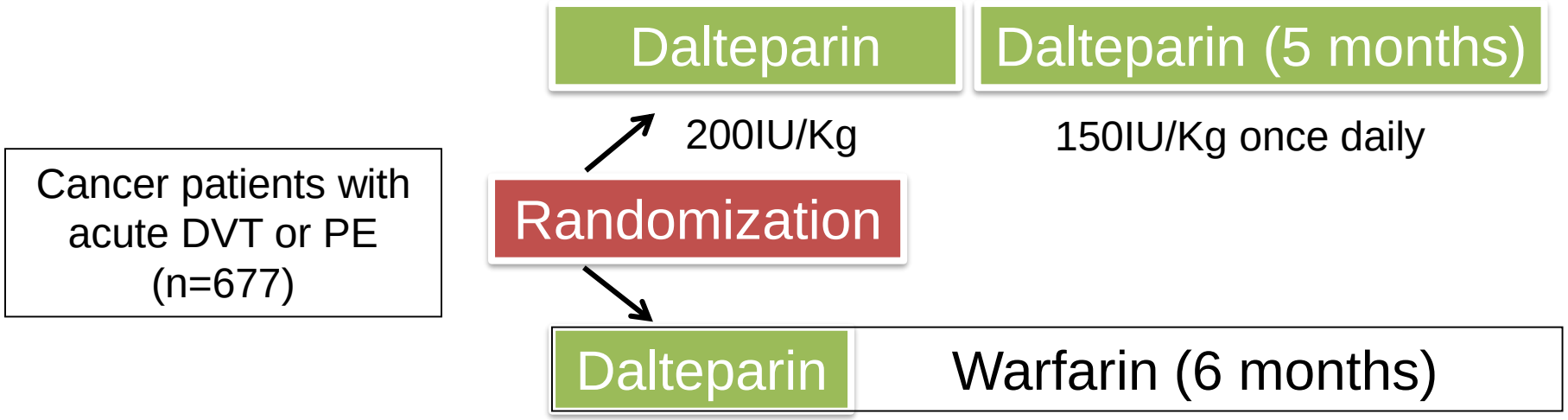
Long-term therapy

Mechanism of action



Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

CLOT study

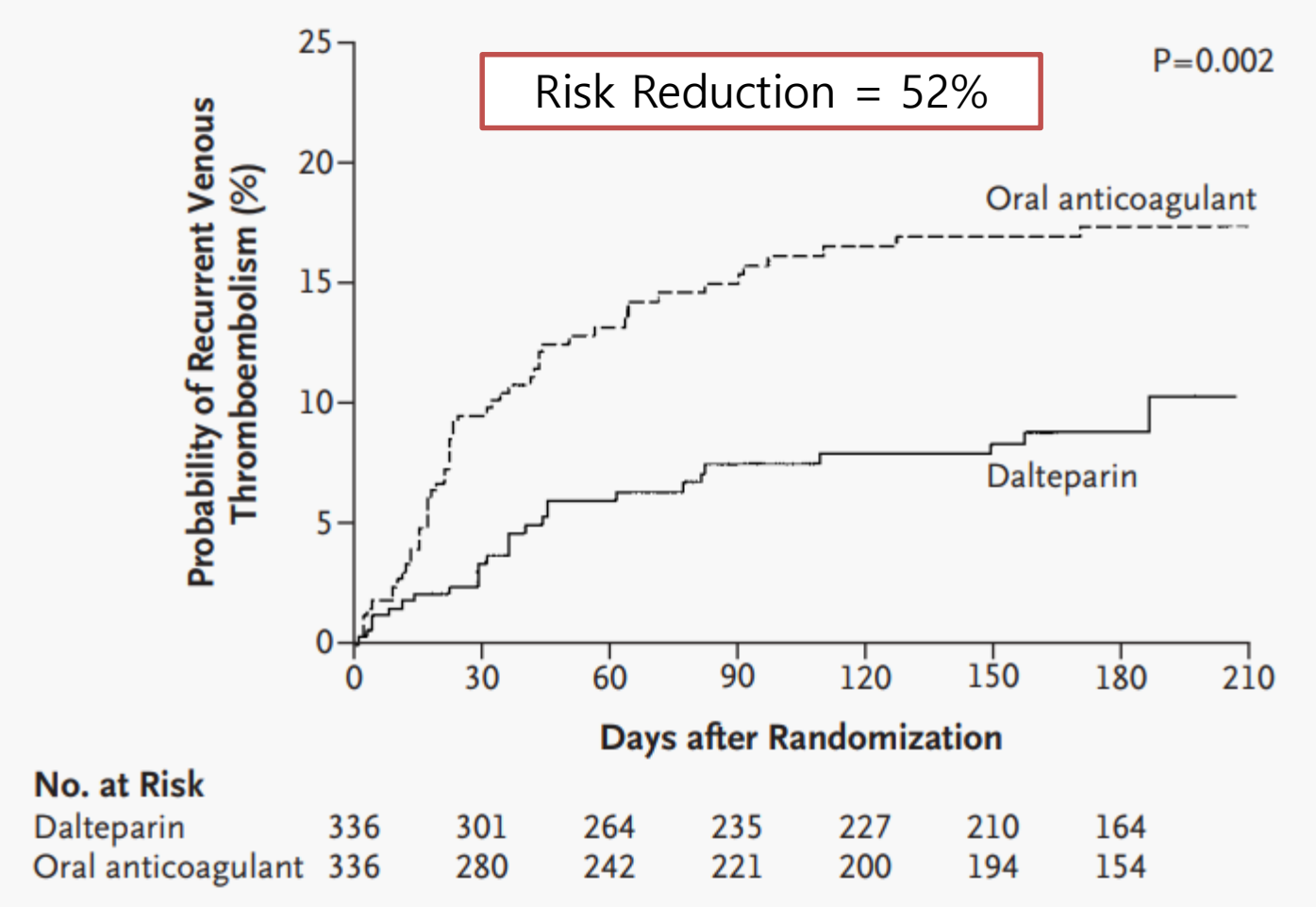


Primary Endpoints : Recurrent VTE and Bleeding

Secondary Endpoint : Survival

Dalteparin over warfarin

No difference of major bleeding (6% vs. 4%), any bleeding (14% vs. 19%, Dal vs. War)

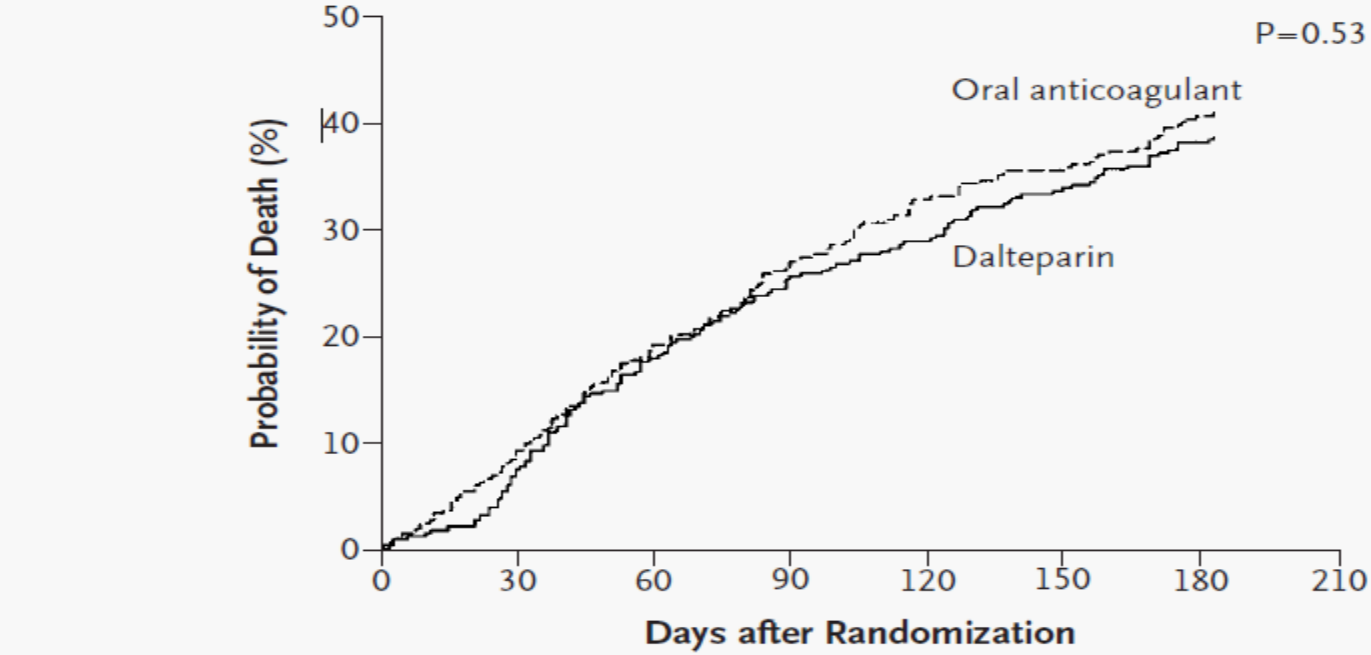


n=53/336
15.8%

n=27/336
8.0%

Mortality in VTE and cancer

6 month mortality : no difference, 39% vs. 41%



No. at Risk

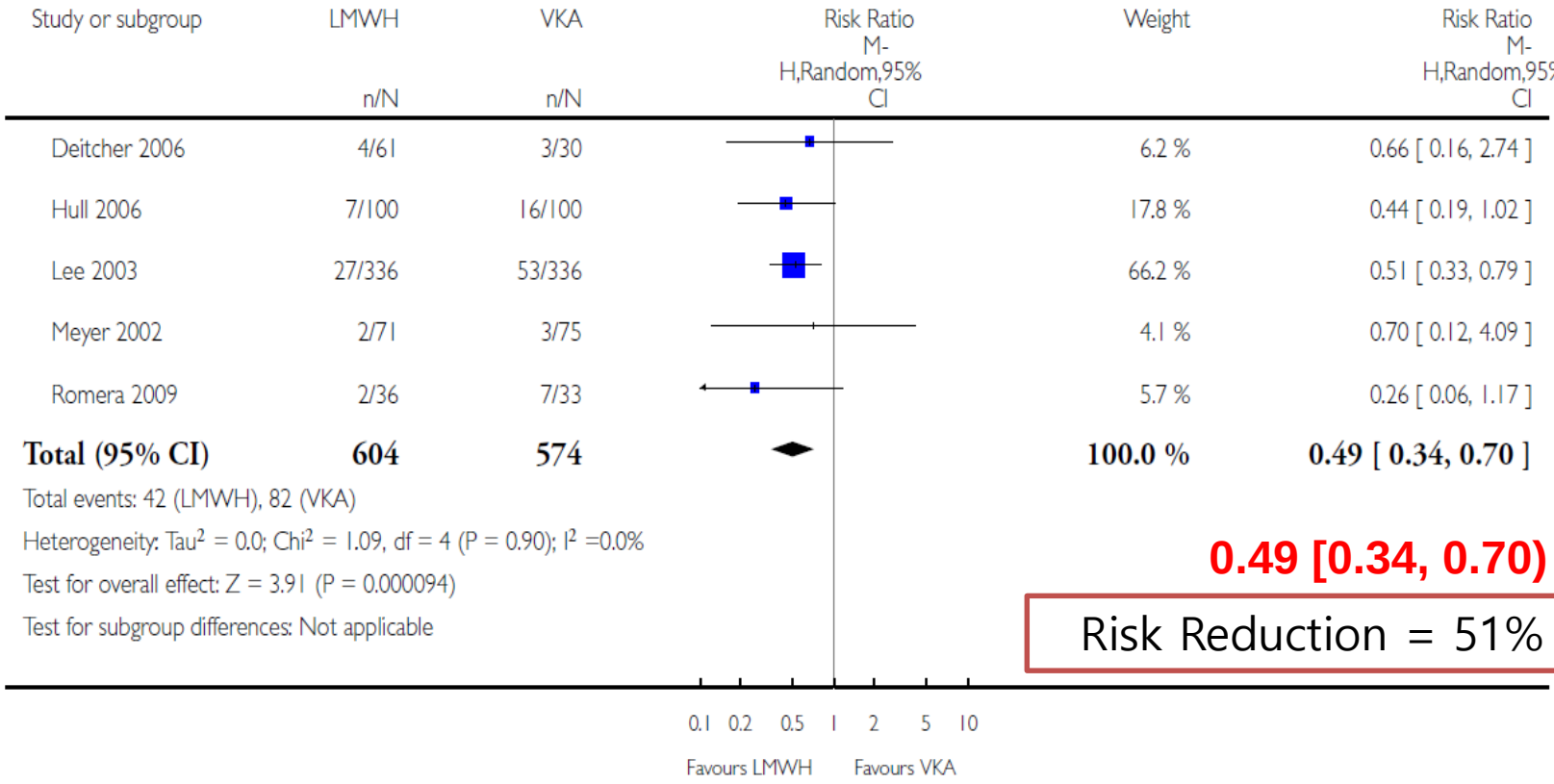
Dalteparin	336	310	274	248	237	220	206
Oral anticoagulant	336	301	268	240	220	211	194

CLOT study

Dalteparin>>Warfarin

- D > W	-VTE control
- D = W	-Less Bleeding episodes
- D > W	-No delay of invasive procedure
- D > W	-Convenient monitoring
- D > W	-Low interaction c chemo-drug
- D > W	-Independent of GI problem
- W > D	-Renal damaged pts
- W > D	-Extreme weights
- W > D	-Convenient administration

LMWH >> Warfarin
Recurrent VTE



0.49 [0.34, 0.70)

Risk Reduction = 51%

Akl EA et al. Cochrane Database Syst Rev 2014

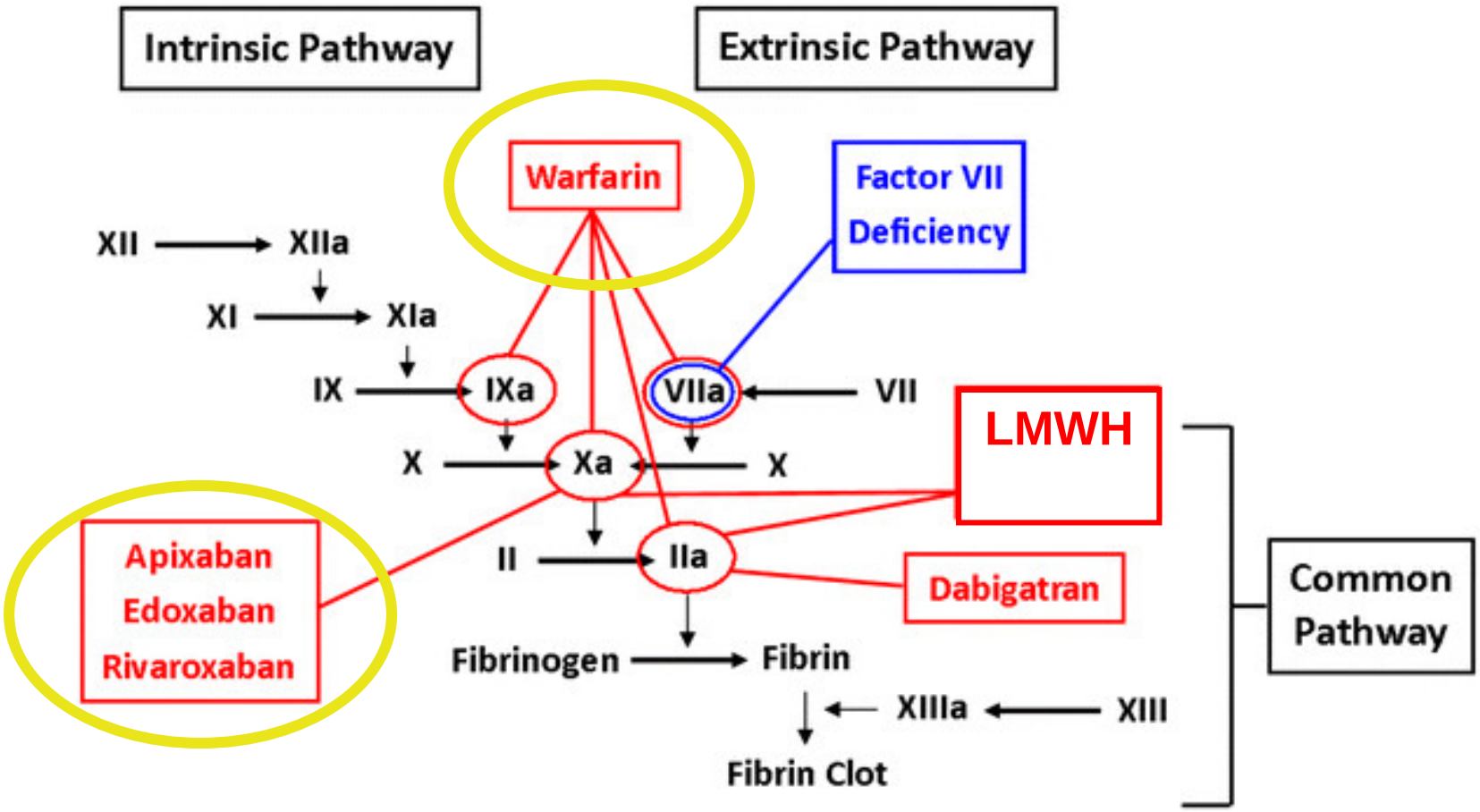
LMWH = Warfarin Mortality

Comparison 1. LMWH versus VKA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival (time-to-event)	3	1018	HR (Random, 95% CI)	0.96 [0.81, 1.14]
2 Mortality (at 3 months)	3	538	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.46, 1.30]
3 Mortality (at 6 months)	3	919	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.11]
4 Mortality (at any time point)	6	1346	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.81, 1.11]
5 Recurrent venous thromboembolism (time-to-event)	3	1018	HR (Random, 95% CI)	0.47 [0.32, 0.71]
6 Recurrent venous thromboembolism	5	1178	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.34, 0.70]
7 Minor bleeding	4	1120	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.53, 1.35]
8 Major bleeding	4	1120	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.53, 2.10]
9 Thrombocytopenia	2	346	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.60, 1.74]

Akl EA et al. Cochrane Database Syst Rev 2014

Mechanism of action



Original Investigation

Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism

A Systematic Review and Meta-analysis

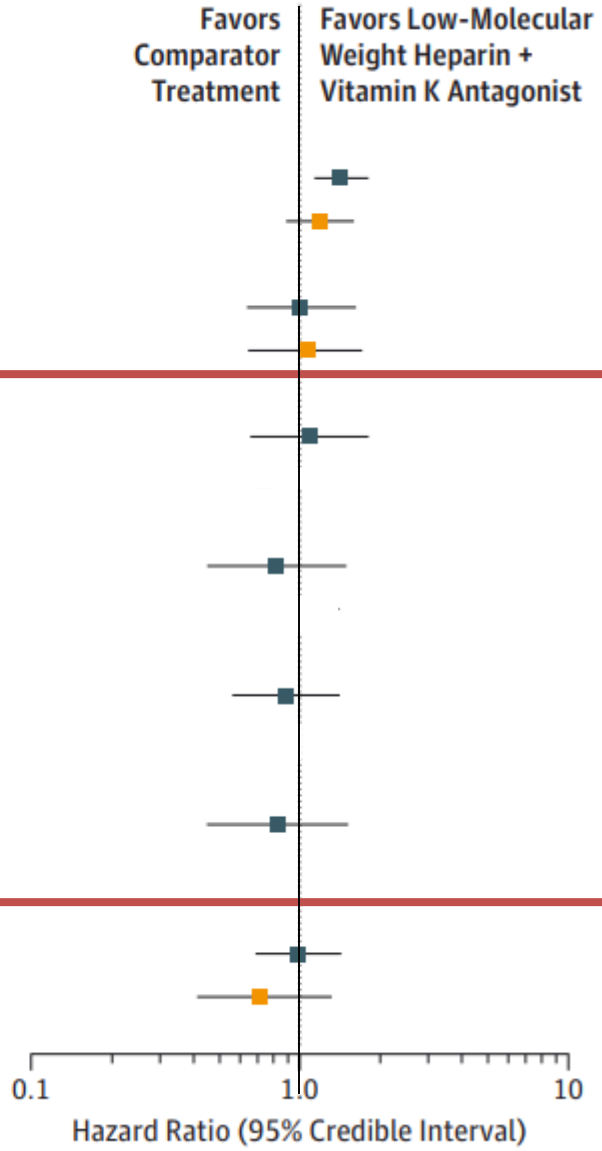
Lana A. Castellucci, MD; Chris Cameron, MSc; Grégoire Le Gal, MD, PhD; Marc A. Rodger, MD, MSc; Doug Coyle, PhD; Philip S. Wells, MD, MSc; Tammy Clifford, PhD; Esteban Gandara, MD, MSc; George Wells, PhD; Marc Carrier, MD, MSc

Clinical and Safety Outcomes Associated With Treatment

Lan
Dou
Geo

A Recurrent venous thromboembolism and major bleeding

Comparator Treatment	Hazard Ratio (95% Credible Interval)
Unfractionated heparin + vitamin K antagonist	
Recurrent VTE	1.42 (1.15-1.80)
Major bleeding	1.19 (0.90-1.58)
Fondaparinux + vitamin K antagonist	
Recurrent VTE	1.01 (0.65-1.62)
Major bleeding	1.07 (0.65-1.70)
Low-molecular-weight heparin + dabigatran	
Recurrent VTE	1.11 (0.67-1.80)
Major bleeding	0.74 (0.46-1.26)
Low-molecular-weight heparin + edoxaban	
Recurrent VTE	0.83 (0.46-1.49)
Major bleeding	0.84 (0.51-1.39)
Rivaroxaban	
Recurrent VTE	0.90 (0.57-1.41)
Major bleeding	0.55 (0.35-0.89)
Apixaban	
Recurrent VTE	0.84 (0.46-1.51)
Major bleeding	0.31 (0.15-0.62)
Low-molecular-weight heparin alone	
Recurrent VTE	0.99 (0.70-1.42)
Major bleeding	0.71 (0.42-1.31)



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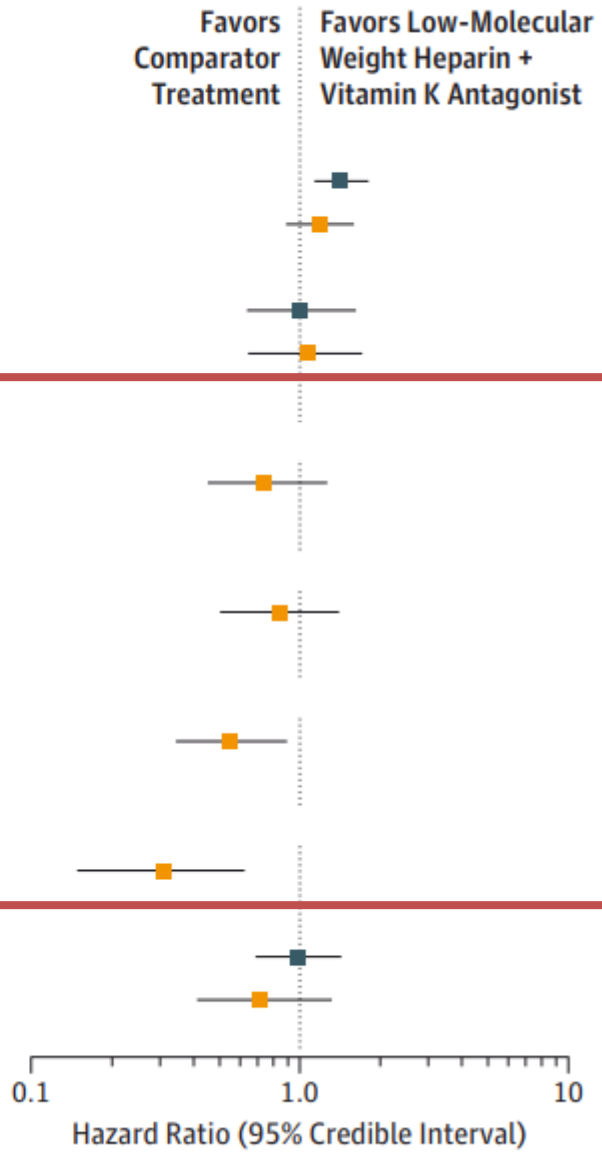

Original Investigation

Clinical and Safety Outcomes Associated With Treatment

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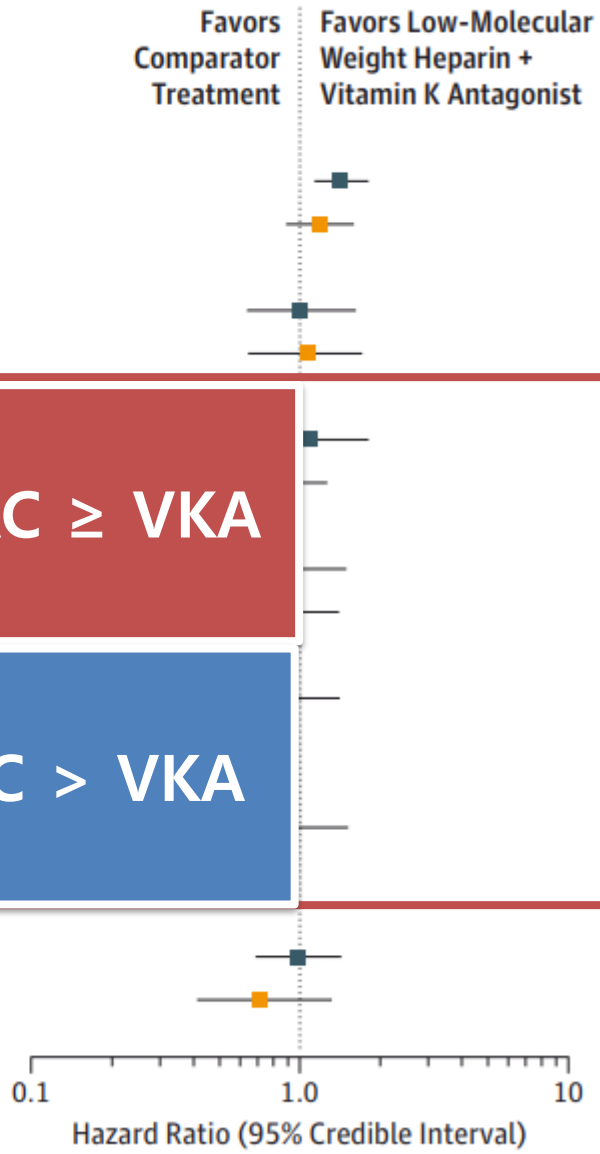


Benefit-Risk profile: NOAC ≥ VKA

Patient preference: NOAC > VKA

NOAC vs. VKA in VTE & Cancer (subgroup analysis)

VTE recurrence

	Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Api	AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]
Riv	EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]
Riv	EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]
Edox	HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]
Dab	RECOVER I & II 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]
	Total (95% CI)		**595**		**537**	**100.0%**	**0.63 [0.37, 1.10]**
	Total events						
	Heterogeneity: Chi²						
	Test for overall effe						

Odds Ratio M-H, Fixed, 95% CI

1 10 100

DA Favors comparator

Benefit-Risk profile: NOAC = VKA

Clinically Rele

Patient preference: NOAC > VKA

B

Study or Subgroup						
AMPLIFY 2013						
EINSTEIN-DVT 2010						
EINSTEIN-PE 2012						
HOKUSAI 2013						
RECOVER I & II 2013	23	159	20	152	22.4%	1.12 [0.59, 2.13]
Total (95% CI)		**587**		**527**	**100.0%**	**0.85 [0.62, 1.18]**
Total events	85		87			

Heterogeneity: Chi² = 4.04, df = 4 (P = 0.40); I² = 1%

Test for overall effect: Z = 0.96 (P = 0.34)

ds Ratio

xed, 95% CI

0.01 0.1 1 10 100

Favors DOA Favors comparator

2016 ACCP Recommendation

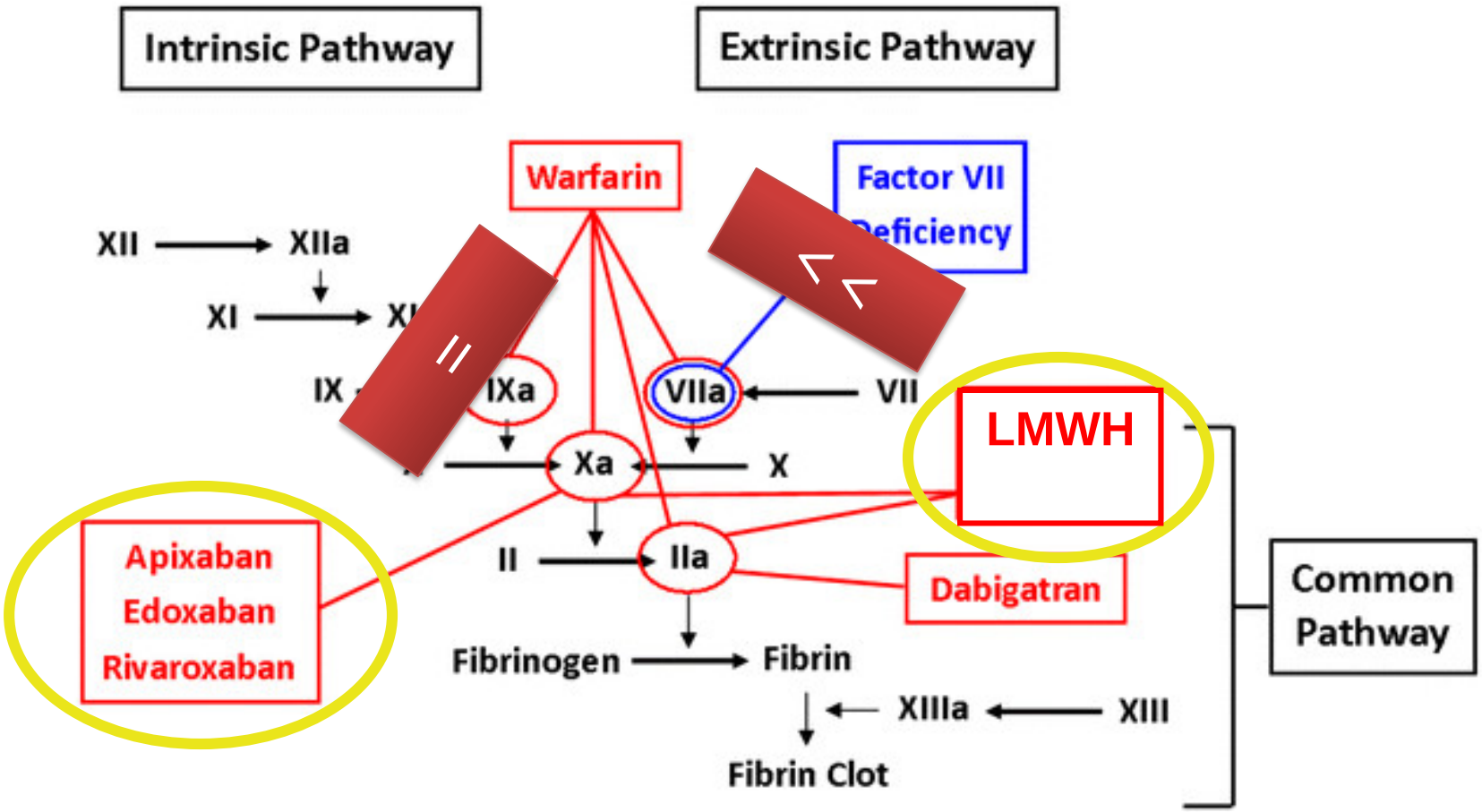
TABLE 6] Factors That May Influence Which Anticoagulant Is Chosen for Initial and Long-Term Treatment of VTE

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.

In patients with DVT of the leg or PE and cancer (“cancer-associated thrombosis”), as long-term (first 3 months) anticoagulant therarpy

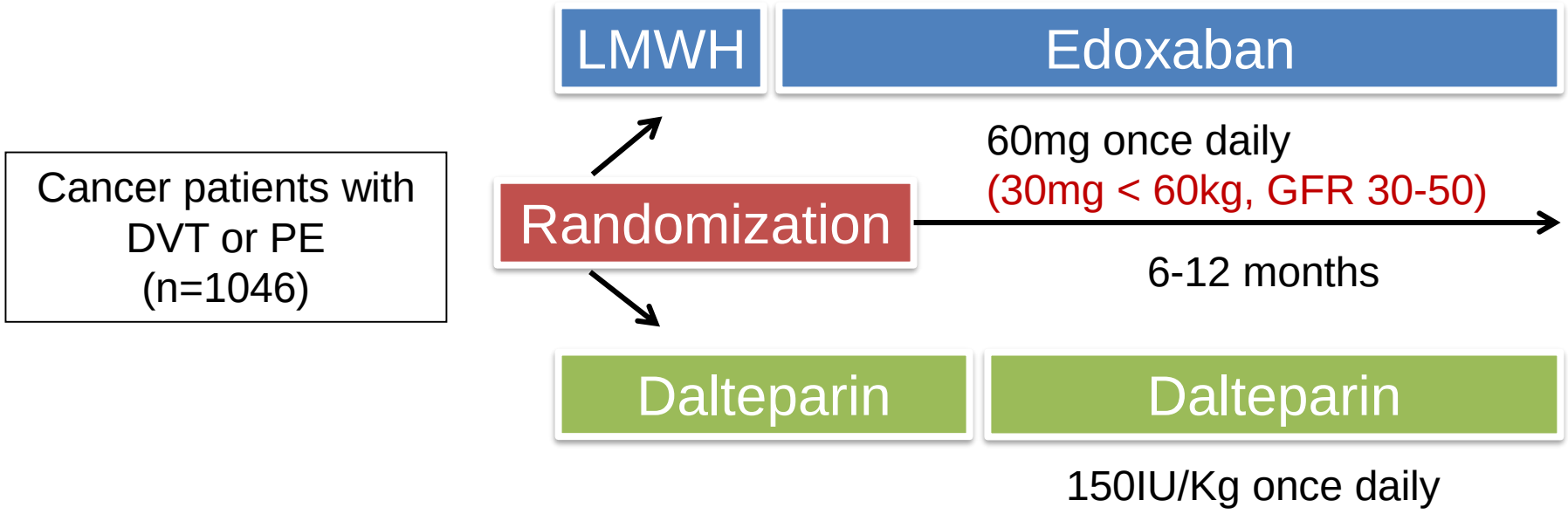
LMWH over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban

Mechanism of action



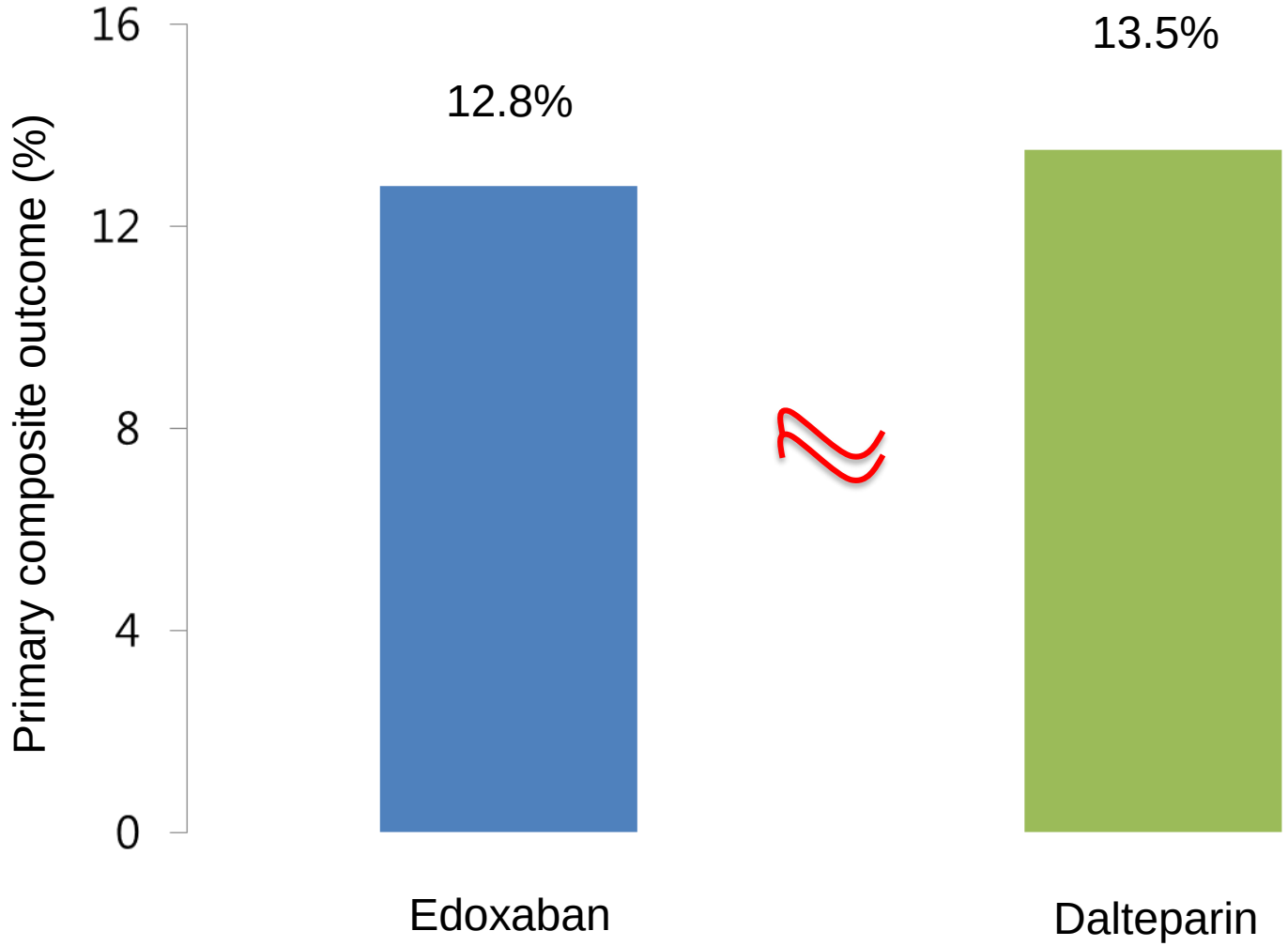
Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

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*

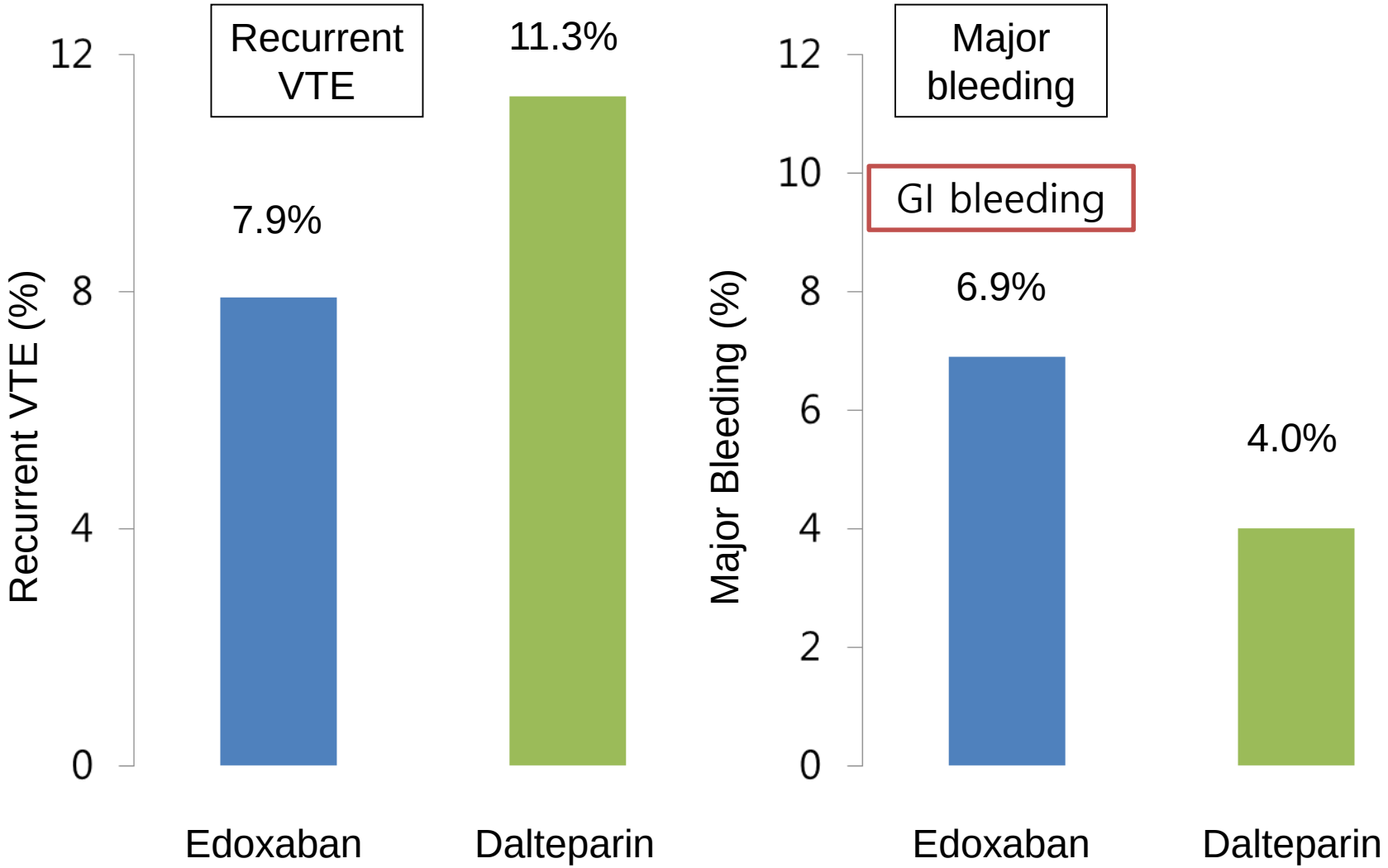


Primary Endpoints : Recurrent VTE or Bleeding during 12 months

Primary outcome



Recurrent VTE/Major Bleeding



Edoxaban = Dalteparin

is non-inferior to

↓Recurrent VTE

↑risk of bleeding

Summary

- The treatment of VTE in cancer
  - LMWH >> VKA therapy
  - DOACs = VKA therapy in cancer

    : DOACs ≥ VTA therapy in the patient's preference
  - Edoxaban = LMWH

    : consider benefit/risk and patient's preference

VTE & Cancer

Initial Treatment

Extended Treatment

Unsuspected PE

Treatment Duration

Duration	Cases
3 months	VTE provoked by a nonsurgical transient risk factor (eg, estrogen therapy, pregnancy, leg injury, flight of >8 h) 15% recurrence at 5 years
≥3 months (usually 6 or 12 months)	Unprovoked (also termed “idiopathic”) VTE; not meeting criteria for provoked by a transient risk factor or by cancer 30% recurrence at 5 years
Extended (also termed “indefinite”)	VTE associated with cancer (also termed “cancer associated thrombosis”) 15% annualized risk of recurrence

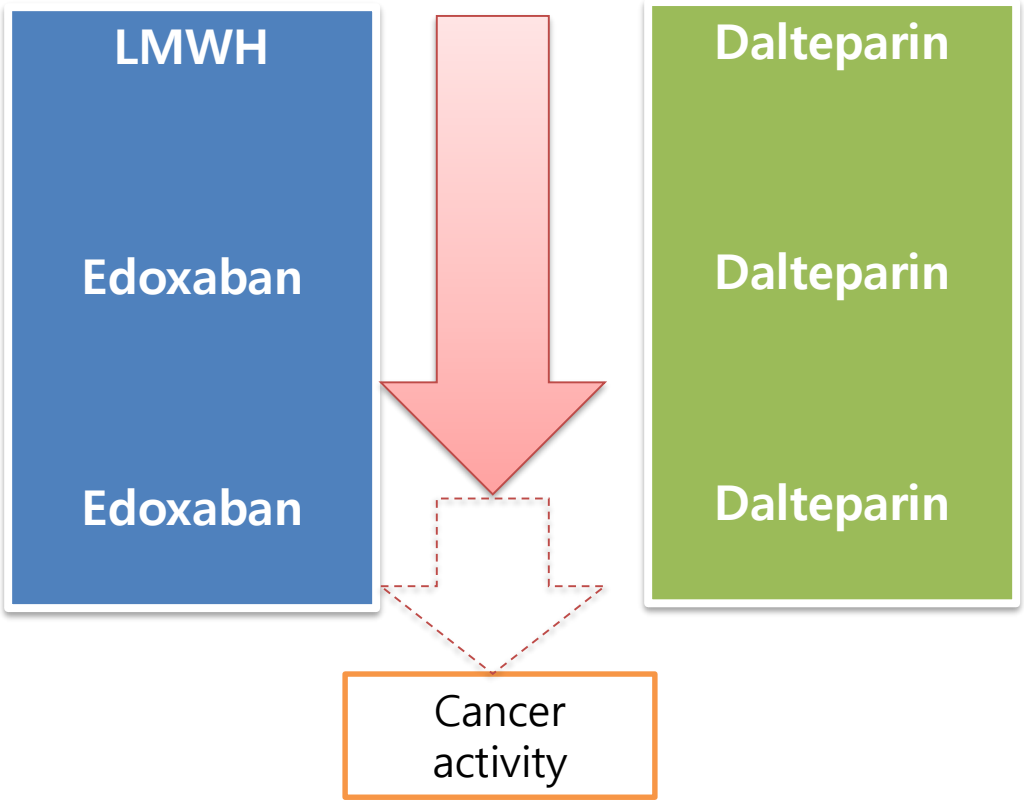
Duration

Cancer - VTE

Initial phase

Maintenance phase: up to 3 months

Extended phage: ≥ 3months Life-long phase



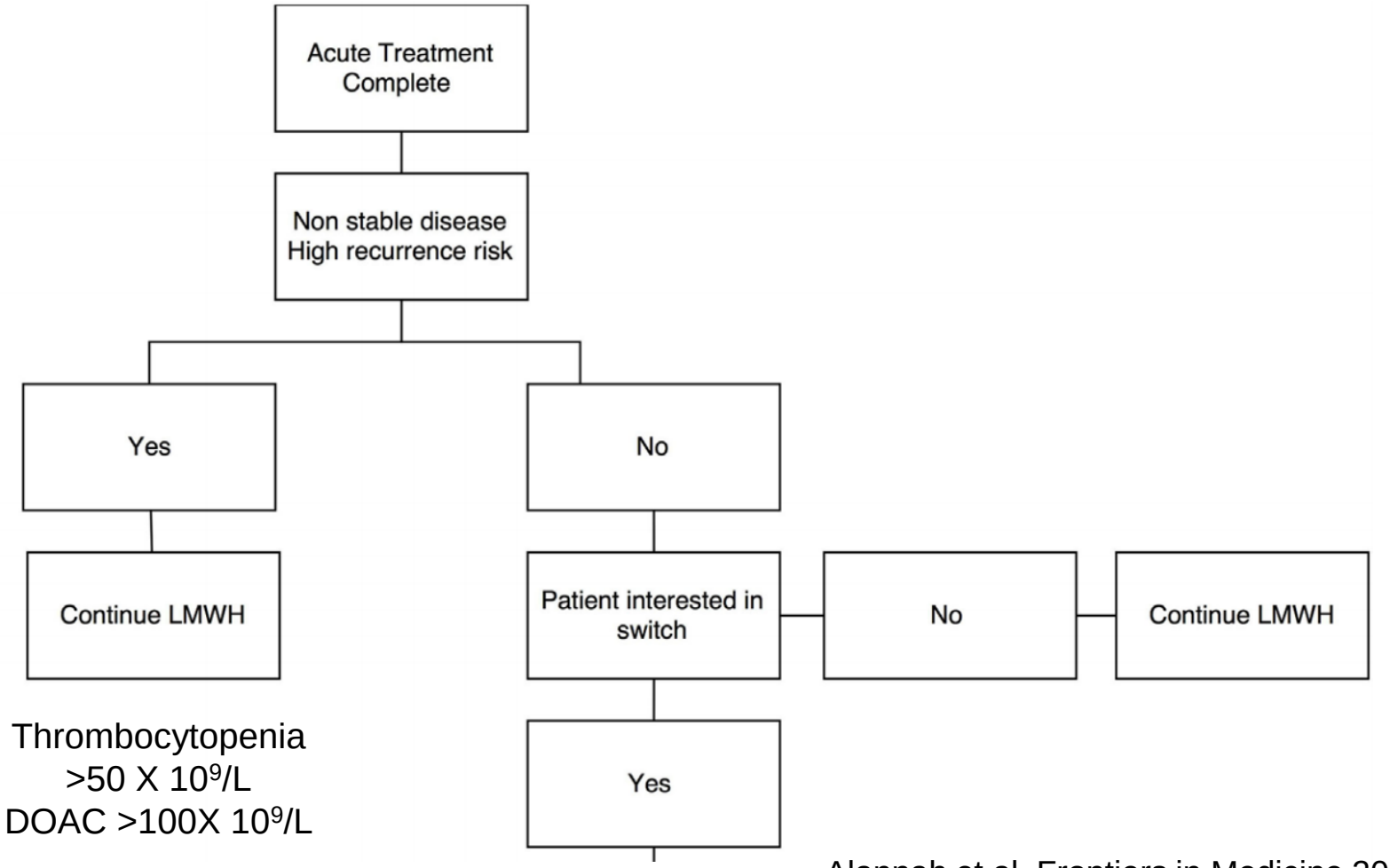
Median 17 months in SMC

Extended Treatment of VTE

Extended treatment with dabigatran, rivaroxaban, and apixaban markedly reduces recurrent VTE without being associated with much bleeding.

	Dabigatran	Rivaroxaban	Apixaban
All-cause mortality	Moderate	Moderate RR 0.49 (0.04-5.43)	Moderate RR 0.49 (0.2-1.22)
Recurrent VTE	High RR 0.08 (0.02-0.25)	High RR 0.19 (0.09-0.04)	High RR 0.19 (0.11-0.3)
Major Bleeding	Moderate	Moderate	Moderate RR 0.49 (0.09-2.64)

Extended Treatment plan



Thrombocytopenia
>50 X 10^9/L
DOAC >100X 10^9/L

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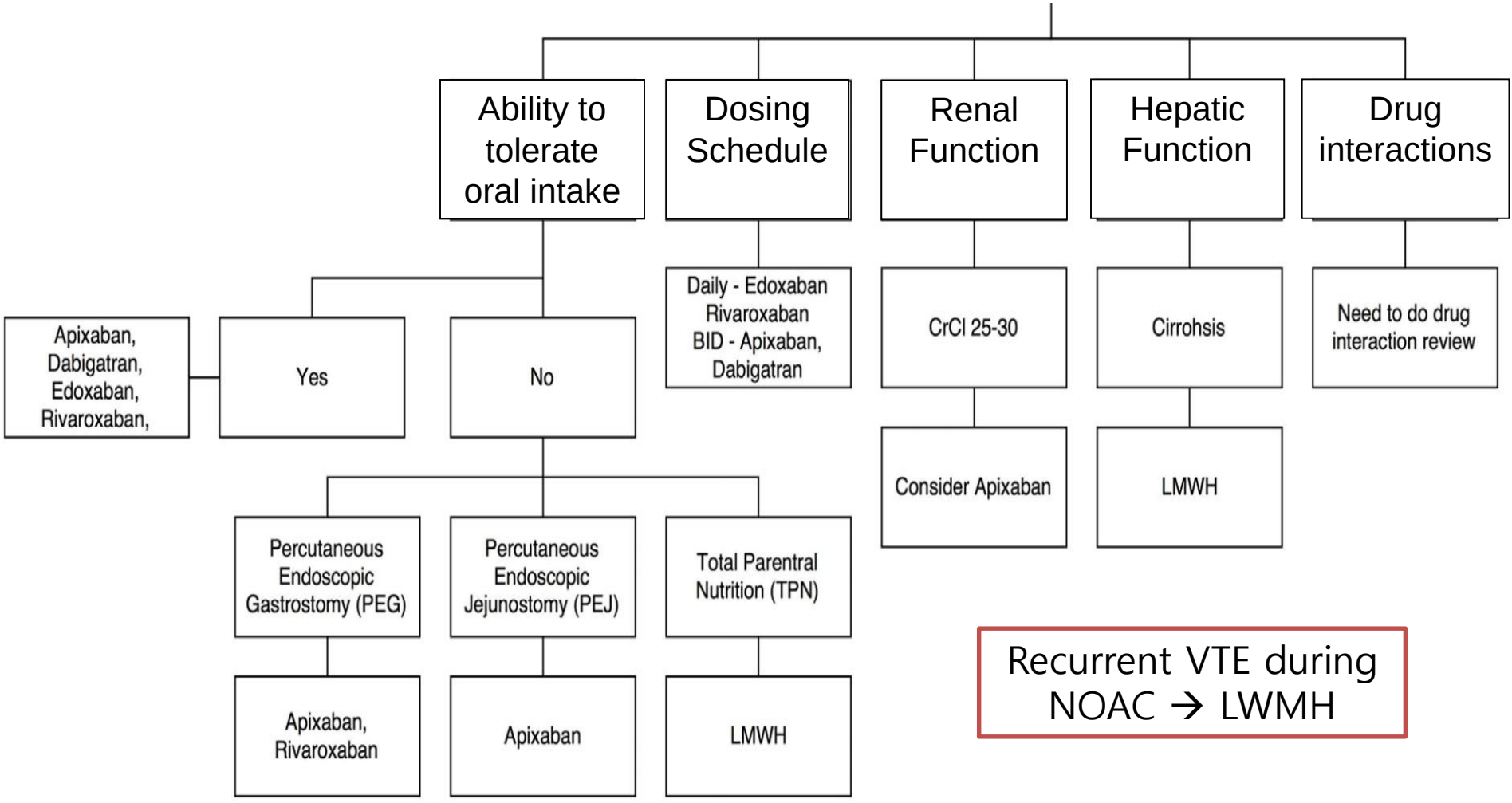
A switch to DOAC from LMWH

A relatively lower risk of recurrent VTE and bleeding

Probably	Probably not
• Stable metastatic cancer on oral or maintenance intravenous treatment • Metastatic cancer stable post immunotherapy treatment • Metastatic malignancy with expected long survival (ER + breast cancer on oral agent, low-grade lymphoma)	• Metastatic cancer on immunotherapy treatment • Metastatic cancer progressing on treatment • Metastatic malignancy with expected short survival (pancreatic cancer, esophageal cancer, and refractory high-grade lymphoma)

Alannah et al. Frontiers in Medicine 2017



Recurrent VTE during NOAC → LWMH

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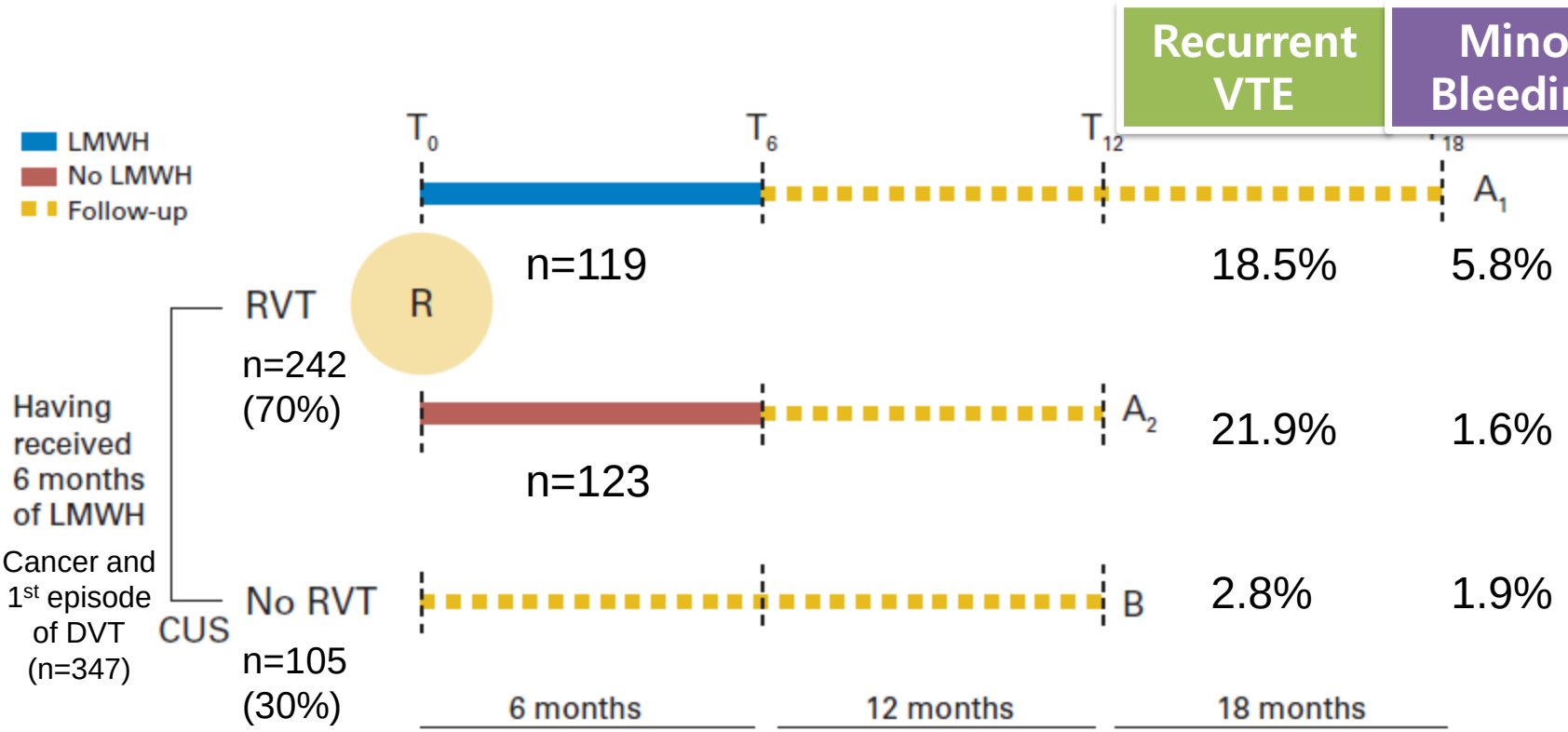
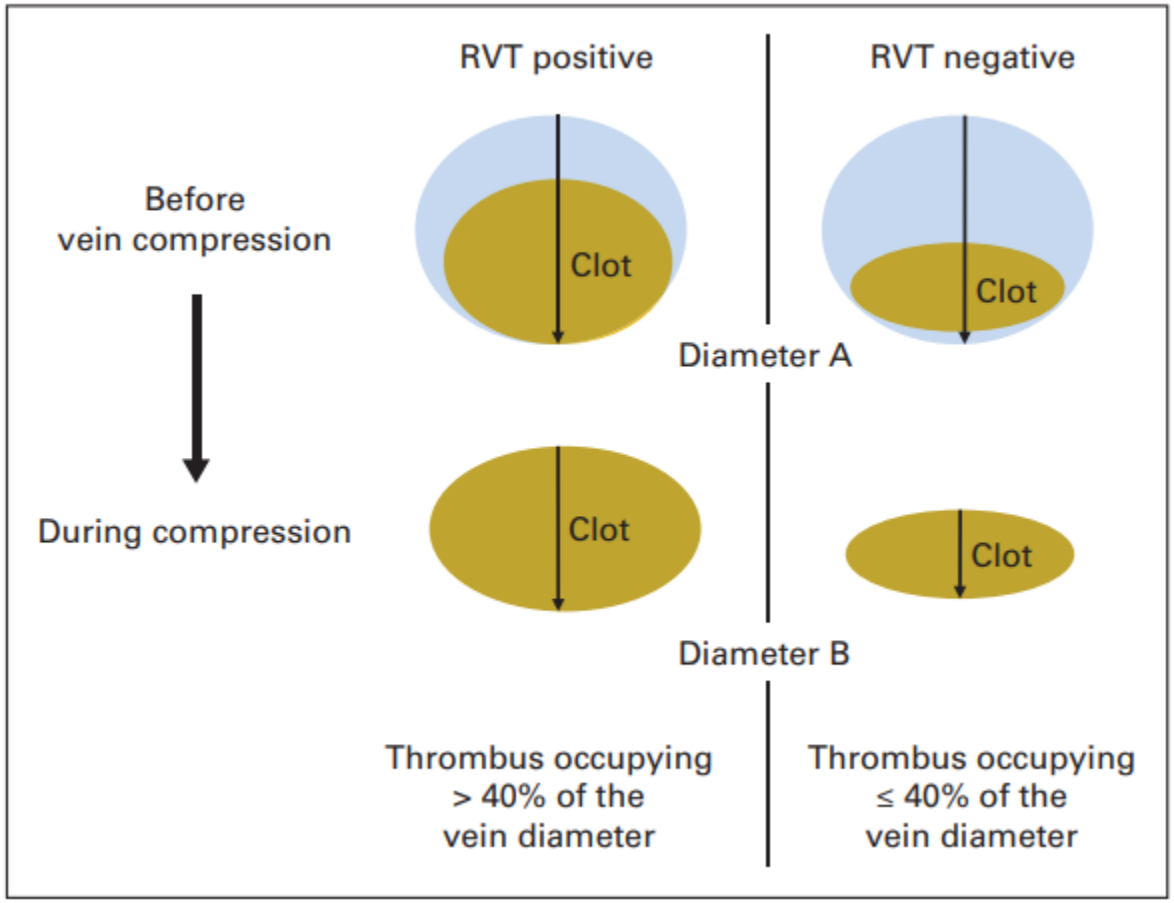
Cancer-related DVT (DACUS)



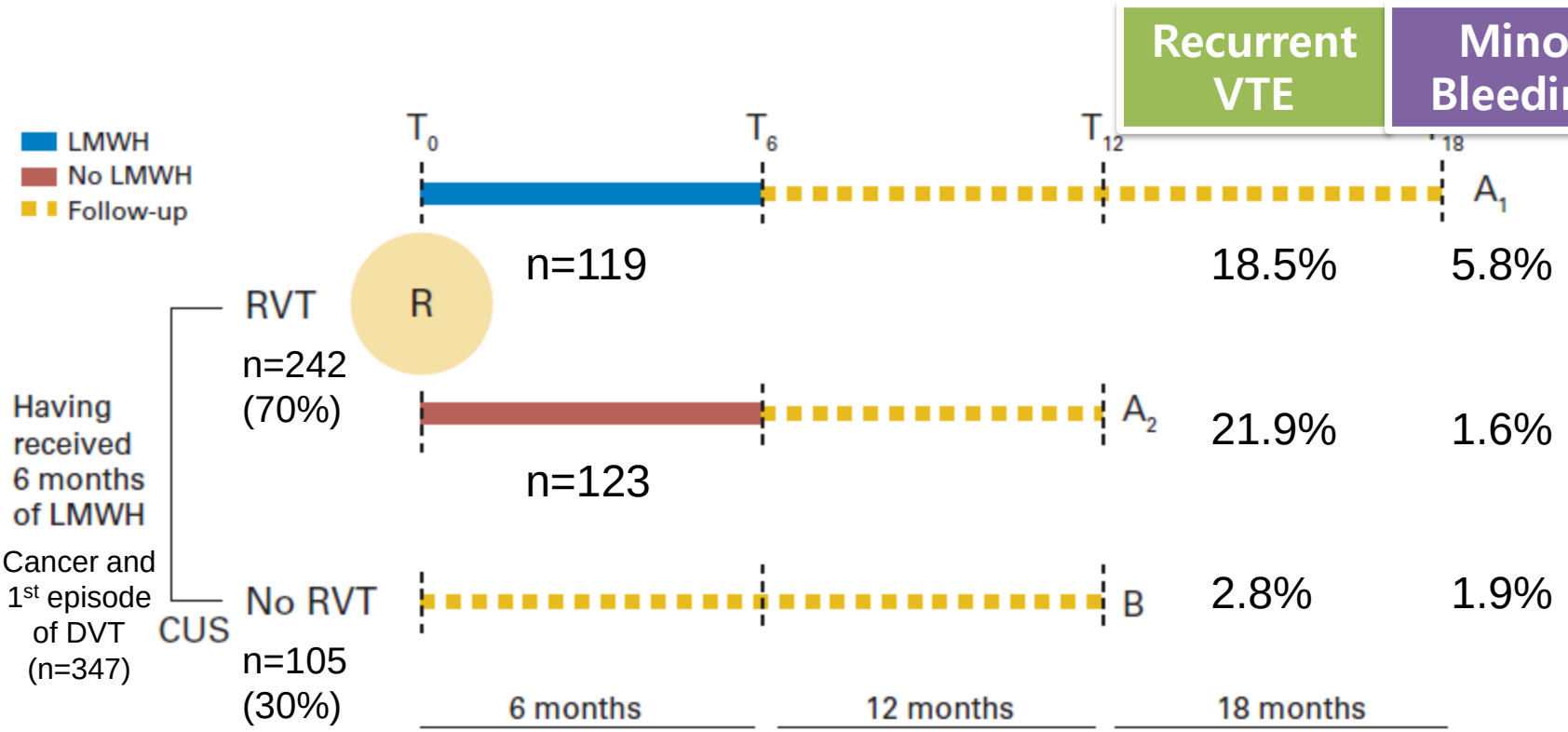
	6 months				12 months				18 months			
	VTE	BI		F	VTE	BI		F	VTE	BI		F
Group		Major	Minor			Major	Minor			Major	Minor	
A1	4	4	2	108	10	2	4	91	8	1	3	78
A2	18	1	4	94	9	1	4	77				
B	2	1	3	97	1	1	2	91				

JCO 2014: 32

Evaluation of residual vein thrombosis



Cancer-related DVT (DACUS)



	6 months				12 months				18 months			
	VTE	BI		F	VTE	BI		F	VTE	BI		F
Group		Major	Minor			Major	Minor			Major	Minor	
A1	4	4	2	108	10	2	4	91	8	1	3	78
A2	18	1	4	94	9	1	4	77				
B	2	1	3	97	1	1	2	91				

JCO 2014: 32

Summary

- Life-long therapy
  - LMWH >> VKA therapy
  - Edoxaban = LMWH

    : consider benefit/risk and patient's preference
  - LMWH → DOACs in the appropriately selected patient

VTE & Cancer

Initial Treatment

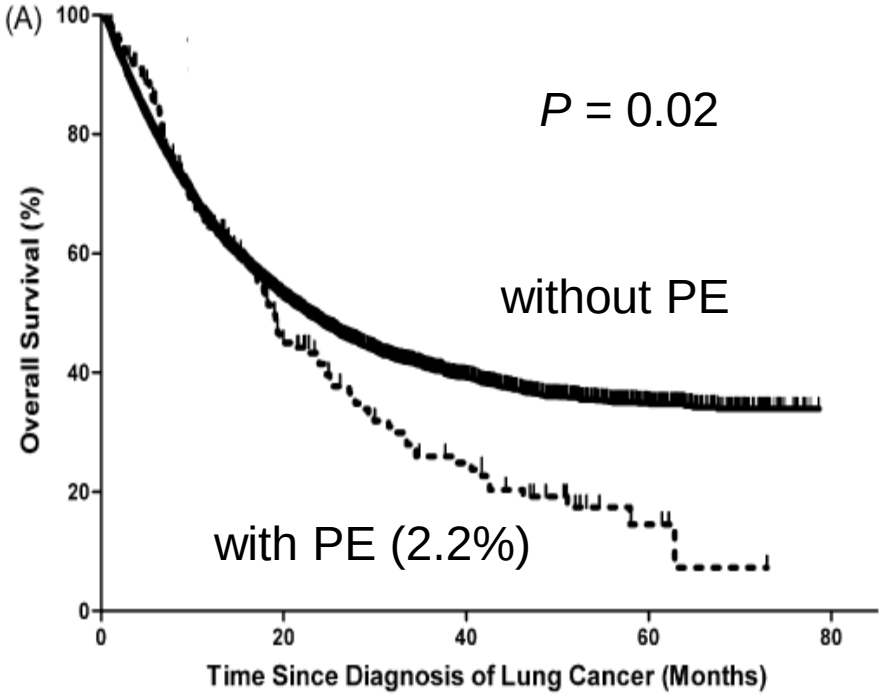
Extended Treatment

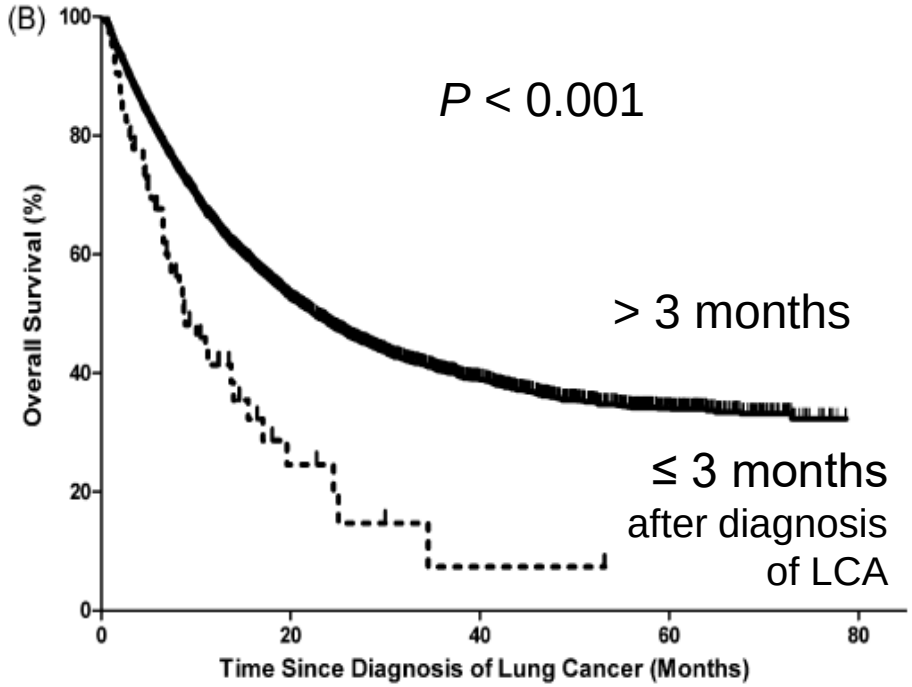
Unsuspected PE

Unsuspected PE

Incidentally detected PE in regular follow up chest CT without associated symptoms

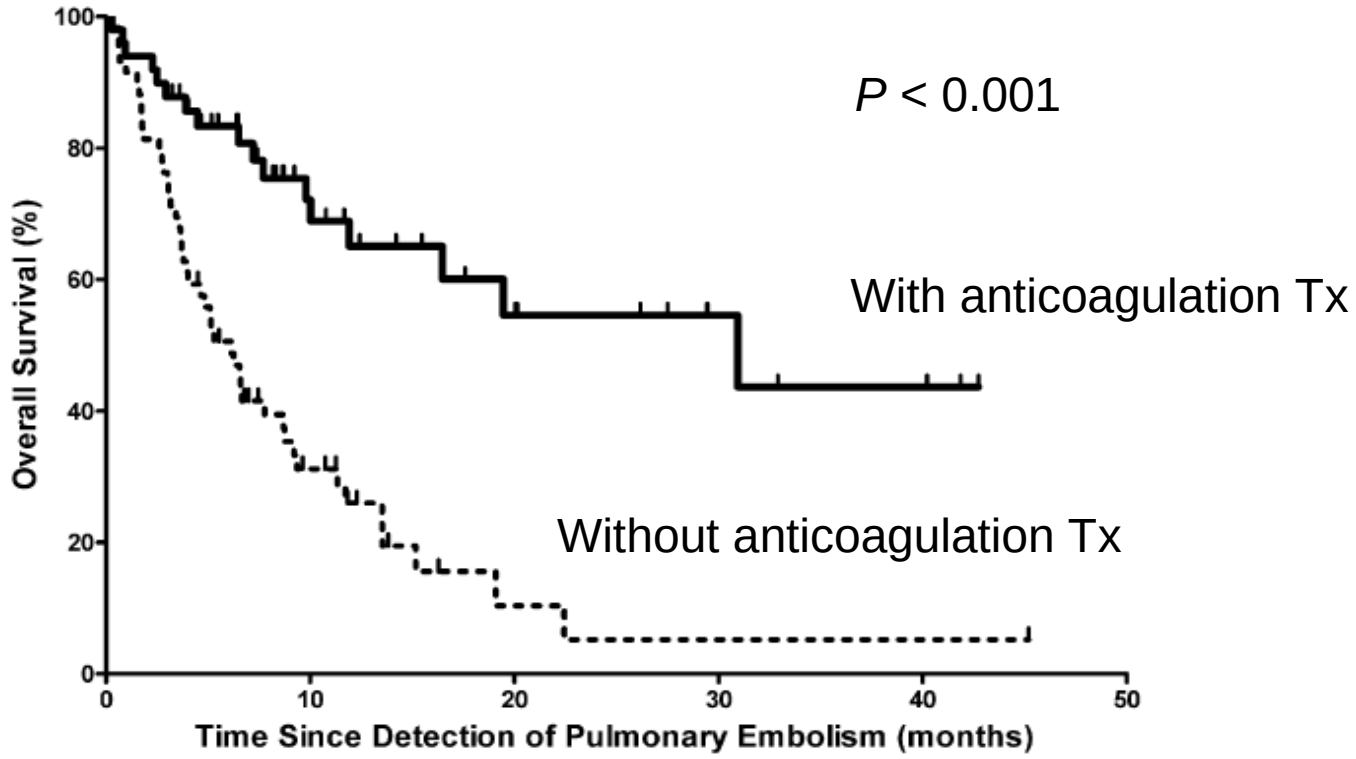
n=8014 at SMC
180/8014 (2.2%) of PE, Incidental PE: 63%





Unsuspected PE

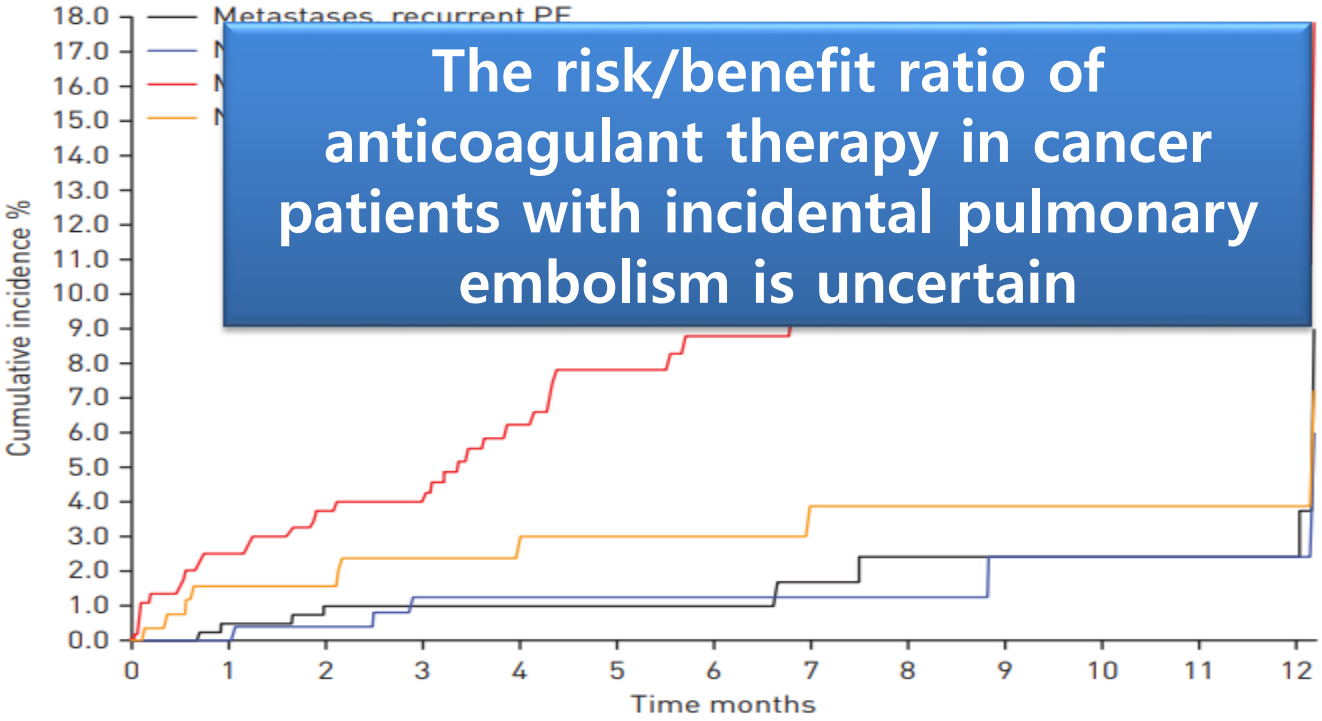
Of 113 unsuspected PE lung cancer patients, 51 received anticoagulation and 62 did not



Unsuspected PE

715 with unsuspected PE and treatment from RIETE

- Major bleeding >> Symptomatic pulmonary embolism (10.1 vs. 3.17 events per 100 patient–years)
- Fatal bleeding >> symptomatic PE (2.7 vs. 0.7 events per 100 patient–years)
- After discontinuing anticoagulation, major bleeding << symptomatic PE (3.0 vs. 8.37)

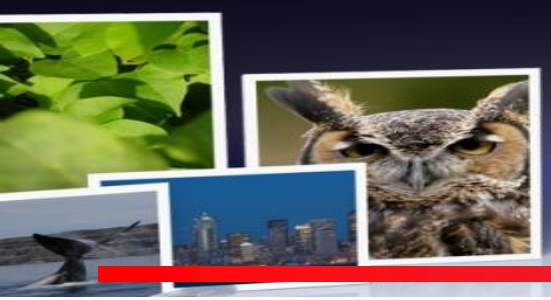


경청해 주셔서
감사합니다.

Dalteparin>>Warfarin

- More predictable dose response
- Less drug interaction c chemo drugs
- High compliance d.t unnecessary monitoring via venous access
- Less complication in cessation of anticoagulation prior to surgical intervention

More bleeding in renal impaired patients



Dalteparin Dose

	1일 1회 dalteparin용량 (IU)	
체중 (kg)	초기 1개월 (induction) 200 IU/kg	후기 5개월 (maintenance) 150 IU/Kg
<46	7,500	7,500
46-56	10,000	7,500
57-68	12,500	10,000
69-82	15,000	12,500
83-98	18,000	15,000
>99	18,000	18,000

	1일 1회 dalteparin용량 (IU)	
체중 (kg)	초기 1개월 (induction) 200 IU/kg	후기 5개월 (maintenance) 150 IU/Kg
<60	10,000 (7,500)	7,500
≥60	12,500 (15,000 or 10,000)	10,000

Available dose at Korea: 2,500 IU, 7,500 IU, and 10,000 IU

VTE treatment on cancer

Leg elevation and Early ambulation

Nonpharmacologic
(Prophylaxis & Treatment)

- Intermittent Pneumatic Compression
- Elastic Stockings
- Inferior Vena Cava Filter

Pharmacologic
(Prophylaxis & Treatment)

- Unfractionated Heparin (UH)
- Low Molecular Weight Heparin (LMWH)
- Oral Anticoagulants

Korean guideline (General Surgery)

Risk group	Procedures	Thromboprophylaxis
Very low	Breast cancer surgery Gastric cancer surgery (< 60 yr of age) Hepatobiliary cancer surgery (< 60 yr of age)	Early ambulation
Low	Gastric cancer surgery (>= 60 yr of age) Hepatobiliary cancer surgery (>= 60 yr of age)	Mechanical prophylaxis
Moderate	Colorectal cancer surgery Pancreatic cancer surgery	Mechanical prophylaxis or pharmacological prophylaxis
High	Any major cancer surgery in patients with previous VTE or thrombophilia	pharmacological prophylaxis (+/- Mechanical prophylaxis)

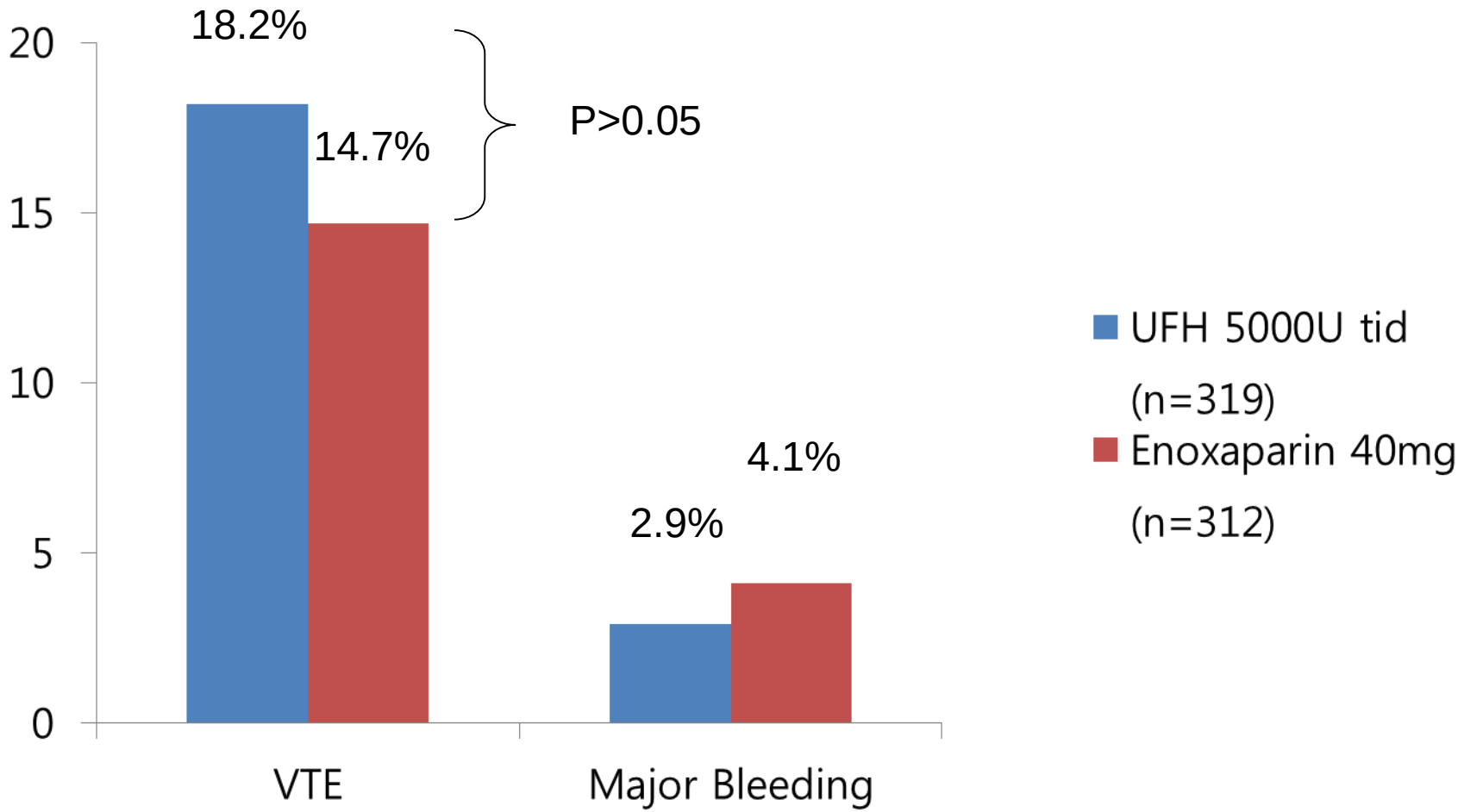
SM Bang, 2014, J Korean Med Sci

Surgical Pateints

- LMWH vs. UFH
  - Abdominal or pelvic surgery for cancer (mostly colorectal)
  - LMWH once daily vs. UFH tid for 7–10 days post-op
  - DVT on venography at day 5, 9 and symptomatic VTE

Study	N	Design	Regimens
ENOXACAN	631	double-blind	enoxaparin vs. UFH
Canadian Colorectal DVT Prophylaxis	475	double-blind	enoxaparin vs. UFH

Prophylaxis in Surgical patients



ENOXACAN Study Group. *Br J Surg* 1997;84:1099–103

Prophylaxis in Surgical patients with cancer

- Extended prophylaxis
  - Abdominal or pelvic surgery for cancer
  - **LMWH** for ~ 7 days vs. 28 days post-op
  - Routine bilateral venography at ~day 28

Study	N	Regimens	VTE rate	
ENOXACAN II	332	Enoxaparin 28 D vs. ~7D	4.8% vs 12.0%	60%
FAME	198	Dalteparin 28 D vs. ~7D	7.3% vs 16.3%	55%

1. Bergqvist D, 2002, N Engl J Med
2. Rasmussen M, 2003, Blood