대한결핵 및 호흡기학회- 49th Workshop

Pulmonary Vascular Disease: Review of 2020

Prophylaxis beyond Treatment of VTE

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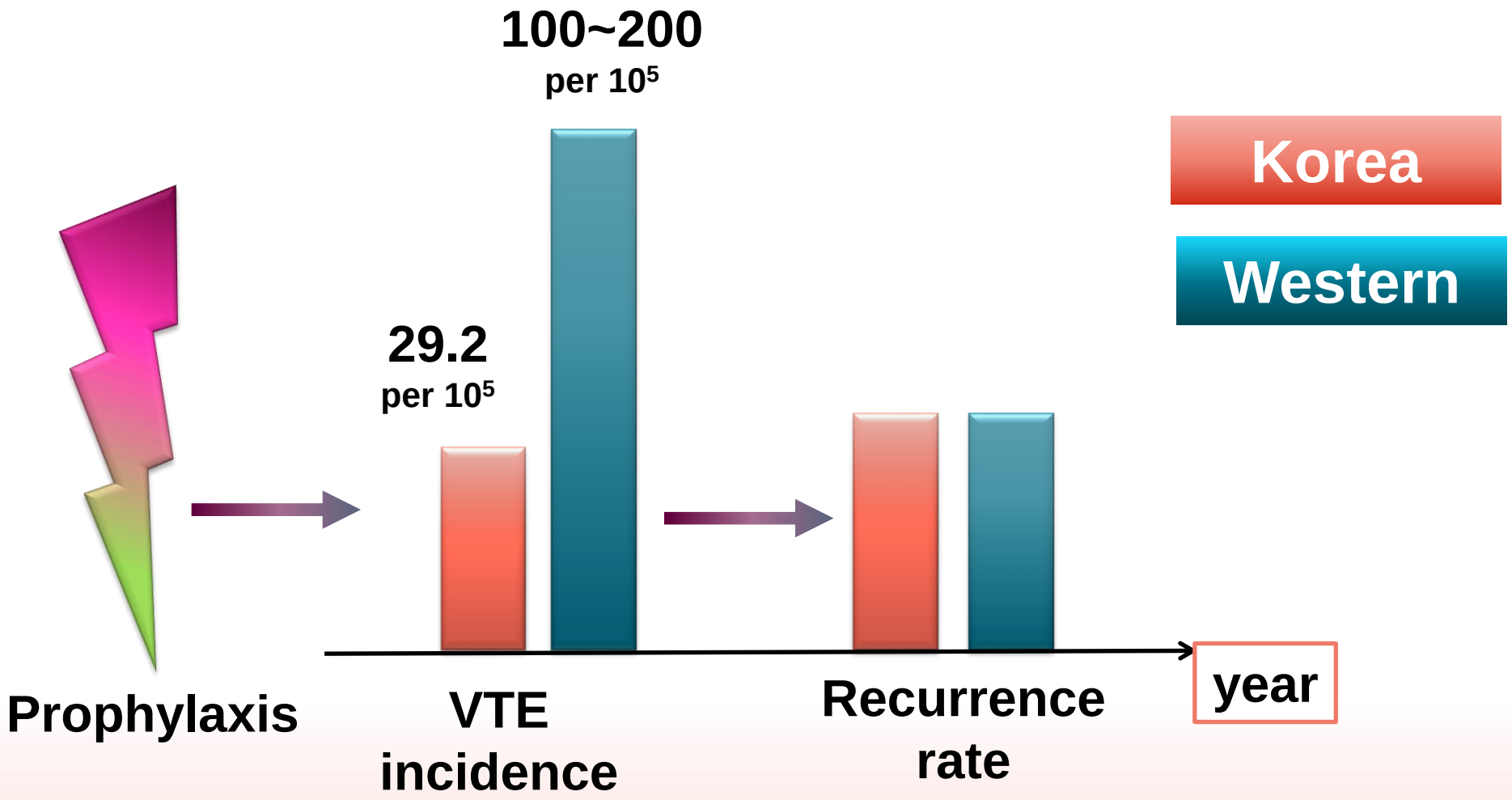
시간: 2020.7.25(토) 09:55-10:20

장소: 서울

Thromboprophylaxis beyond VTE treatment in medical part



1. Jang J thrombo Haemost 2011;9:85-91
2. Hong et al. PLoS One 2018
3. Hwang et al Tuberc Respir Dis 2019, 2020

Search & Priority

- Period: 2018.1~2020.5
- Keyword: venous thromboembolism, pulmonary embolism
- Clinical trials
- Impact factors

Contents

1. Anticoagulation in cancer-associated VTE

Treatment in patient with Cancer-associated VTE: Overview

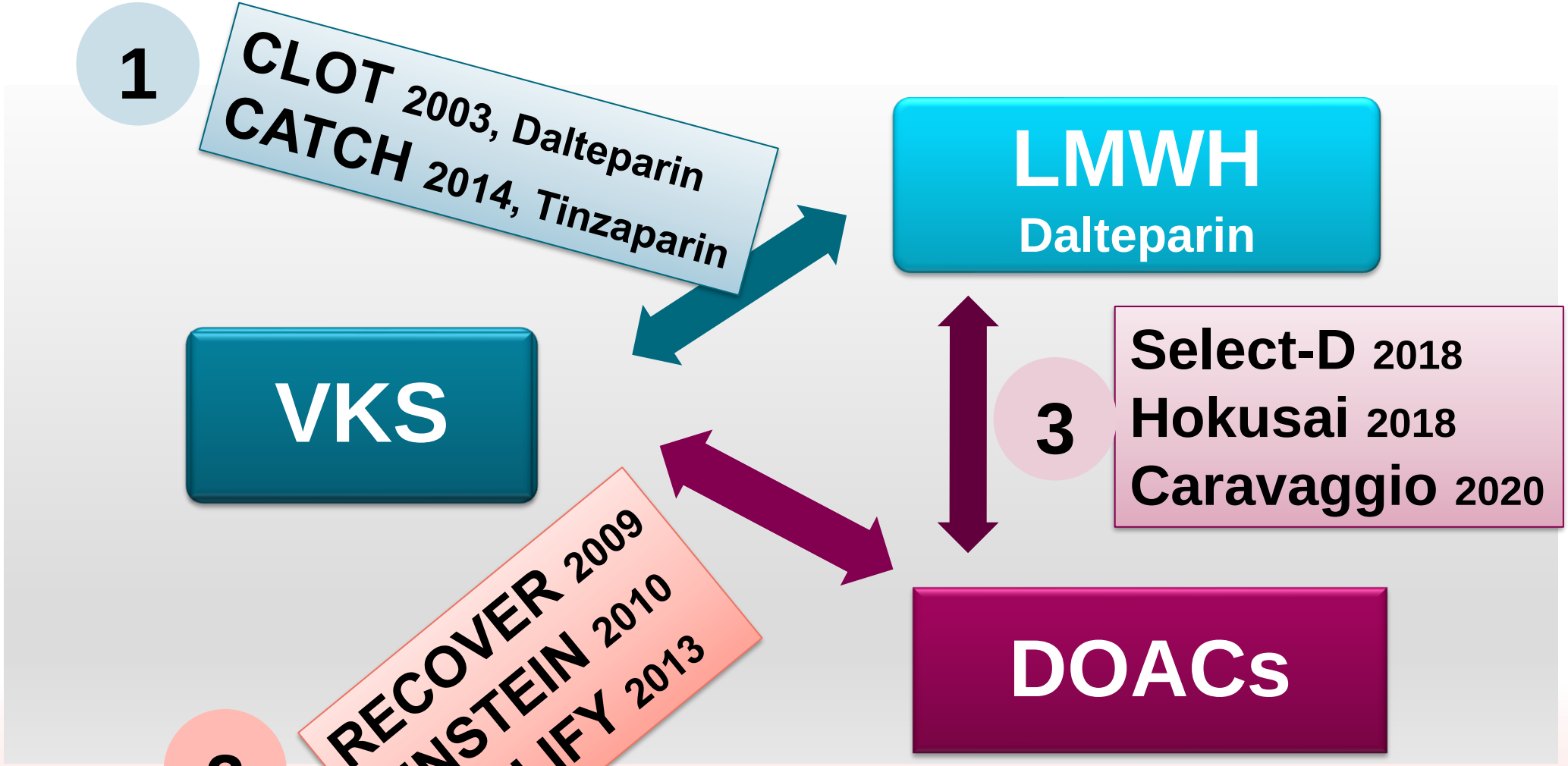
	SELECT-D study[1]	Hokusai VTE cancer[2]	Caravaggio study[3]
Year	2018	2018	2020
Agent	Rivaroxaban	Edoxaban	Apixaban
Comparator LMWH			

Dalteparin

Cancer VTE의 치료에 대한 CLOT연구에서 Dalteparin이 Warfarin에 비하여 VTE재발을 유의(9% vs 17%)하게 줄여주어 Standard regimen으로 각 연구의 Comparator에 사용되었다.

1. Young et al. J Clin Oncol 2018
2. Raskob GE et al. NEJM 2018
3. Agnelli et al. Thromb Haemost 2020

Treatment in Cancer-associated VTE



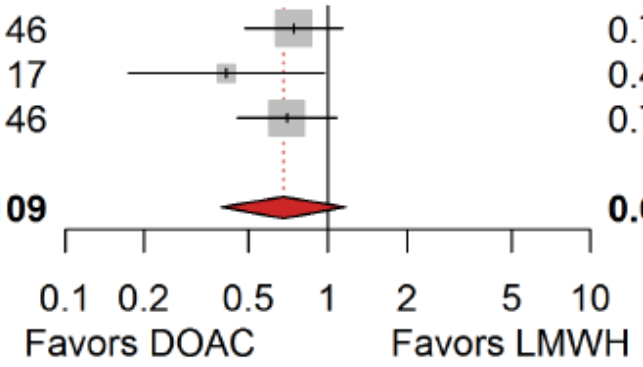
1. Kearon Chest 2016; 149(2): 315-352

Cancer-associated VTE: Meta-analysis

Recurrent VTE

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	34	524	46	0.74	[0.48; 1.14]	45.4%
SELECT-D	rivaroxaban	203	7	203	17	0.41	[0.17; 0.97]	11.2%
Caravaggio	apixaban	576	32	579	46	0.70	[0.45; 1.08]	43.4%
Random effects model		**1301**	**73**	**1306**	**109**	**0.68**	**[0.39; 1.17]**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.0001$, $p = 0.48$



앞선 두연구에서 bleeding에 대한 concern이 있었다. Hokusai에서 Edoxaban group에 major bleedin이 많았고, SELECT-D연구의 Rivaroxaban group에서 CRNMB이 많은점을 보여주었다.

Mulder et al. Blood 2020

How to manage the bleeding in treatment of CAV patient

Select-D Rivaroxaban

Table 3. Bleeding Events

Type of Bleed	Dalteparin (n = 203)	Rivaroxaban (n = 203)
Major bleeding	6	11
Criteria to define major bleeding*		
Clinically overt and decrease in hemoglobin level of ≥ 2 g/dL over 24 hours	5	6
Clinically overt and transfusion of ≥ 2 units of packed red cells	3	10
Clinically overt and critical site (eg, intracranial, retroperitoneal)	0	0
Clinically overt and contributes to death	1	1
Sites of major bleed*		
GI		
Esophageal	1	3
Stomach	3	2
Lower GI	0	1
Site unknown	0	2

이 연구의 Bleeding 세부내용 보면 rivaroxaban군에서도 severity가 높지 않은 출혈이었고, 출혈의 부위도 소화기암에 집중되어 있었다.

1. Raskob et al. N Engl J Med 2018;378:615-24
2. Young et al J Clin Oncol 2018:36:2017-2023

How to manage the bleeding in treatment of Cancer-associated VTE (CAT) patient

	Edoxaban (N = 522)	Dalteparin (N = 524)
Category 1	0	0
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)

Hokusai Edoxaban

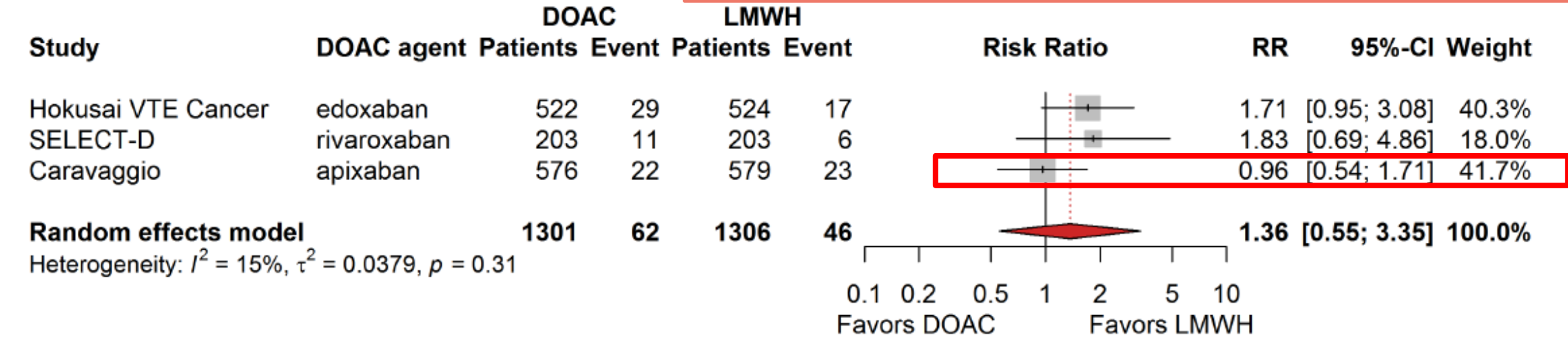
Hokusai 연구의 Bleeding 세부내용 보면 Edoxaban 군에서 severity가 낮은 category 2에서 출혈이 많았고, catetory 3, 4에서는 dalteparin군이 출혈이 더 발생함을 볼 수 있다.

1. Raskob et al. N Engl J Med 2018;378:615-24
2. Young et al J Clin Oncol 2018:36:2017-2023

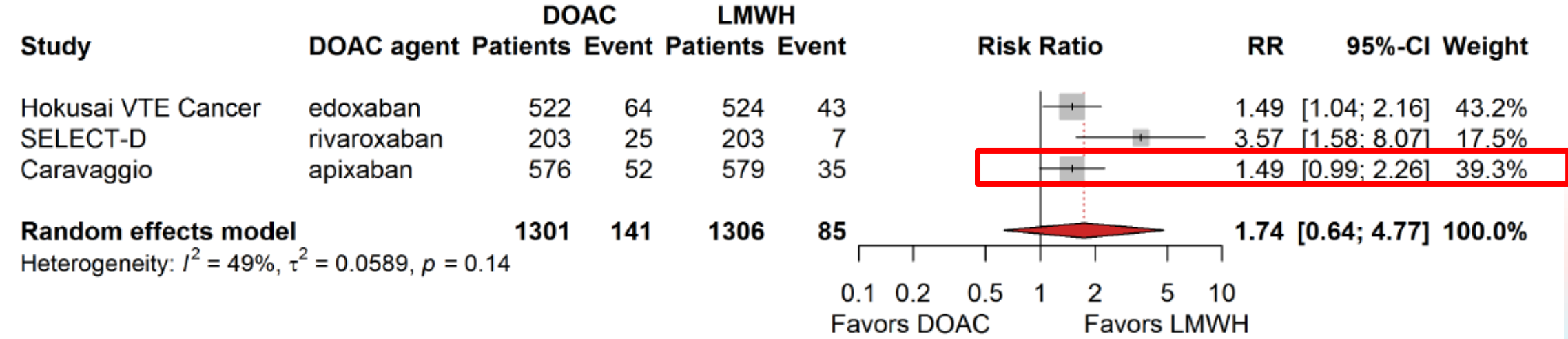
Cancer-associated VTE: Meta-analysis

이번에 나온 Caravaggio 연구에서 DOACs vs LMWH군의 bleeding 차이가 없음을 보여주었고, 3연구에 대한 메타분석에서 두군간에 출혈의 유의한 차이가 없었다.

Major bleeding



Clinically relevant non-major bleeding

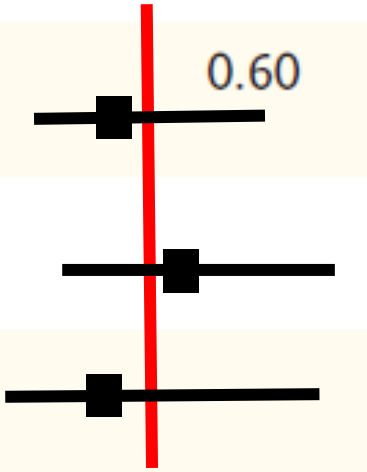


Mulder et al. Blood 2020

Caravaggio study

이번에 발표된 Caravaggio 연구에서 major bleedin(safety outcome)은 두군(Apixaban vs Dalteparin)간에 차이를 보이지 않았다.

	Apixaban (N=576)	Dalteparin (N=579)	Hazard Ratio (95% CI)	P Value
Primary safety outcome — no. (%)				
Major bleeding¶	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)	0.60
Major gastrointestinal bleeding	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)	
Major nongastrointestinal bleeding	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)	



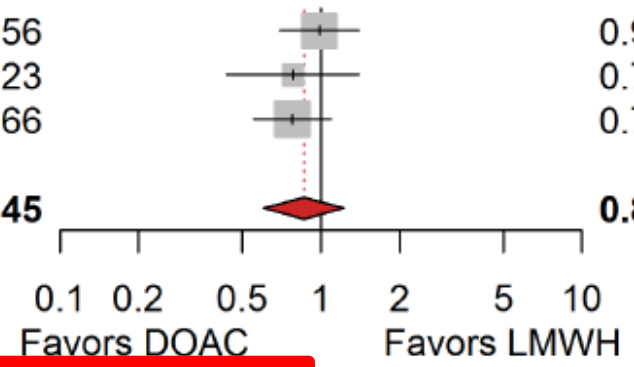
1. Agnelli N Engl J Med 2020

Cancer-associated VTE: Meta-analysis

Composite of first major bleeding or recurrent VTE

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	55	524	56	0.99	[0.69; 1.40]	41.8%
SELECT-D	rivaroxaban	203	18	203	23	0.78	[0.44; 1.41]	15.1%
Caravaggio	apixaban	576	51	579	66	0.78	[0.55; 1.10]	43.1%
Random effects model		**1301**	**124**	**1306**	**145**	**0.86**	**[0.60; 1.23]**	**100.0%**

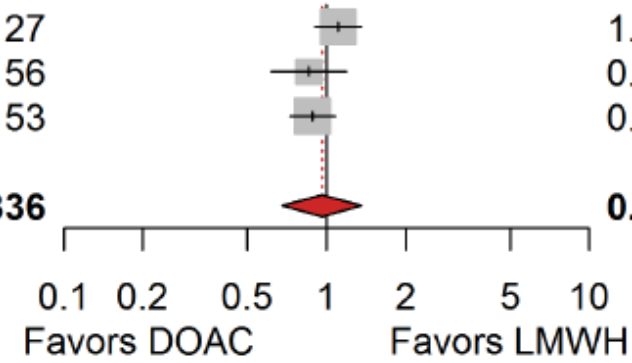
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.60



All-cause mortality

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	140	524	127	1.11	[0.90; 1.36]	39.2%
SELECT-D	rivaroxaban	203	48	203	56	0.86	[0.61; 1.20]	20.1%
Caravaggio	apixaban	576	135	579	153	0.89	[0.73; 1.08]	40.7%
Random effects model		**1301**	**323**	**1306**	**336**	**0.96**	**[0.68; 1.36]**	**100.0%**

Heterogeneity: I^2 = 30%, τ^2 = 0.0074, p = 0.24



Mulder et al. Blood 2020

VTE prophylaxis in cancer

Prevention of VTE in patients with cancer: DOACs vs Placebo

	CASSINI study[1]	AVERT study[2]
Year	2019	2019
Agent	Rivaroxaban	Apixaban
Comparator	placebo	placebo

- Routine thromboprophylaxis is not recommended in previous guidelines. That is why comparator was placebo in those studies.[1]

Cancer 환자에서 혈전예방 요법에 대한 참고하실 선행 연구들

- PROTECHT study (Agnelli) nadroparin 2009
- SAVE-ONCO trial (Agnelli) Semuloparin 2012

1. Khorana et al NJEM 2019
2. Carrier et al NEJM 2019

Prevention of VTE in patients with cancer: DOACs vs Placebo

	CASSINI study[1]	AVERT study[2]
Khorana score (0-6)	≥2	≥2
	Ambulatory Initiating chemotherapy	Ambulatory, **ECOG 0 or 1: 85%** Initiating chemotherapy
Number	Rivaroxaban(420) vs 421	Apixaban (n = 291) vs 283
Agents	Rivaroxabn 10 mg vs **placebo**	Apixaban 2.5 mg bid vs **placebo**
F/U period	180 days (210)	Up to 180 days
	Intervention period	
Lung cancer	15% (14-17%)	10%

Exclusion

- **Basal-cell or Squamous-cell skin cancer, acute leukemia, myeloproliferative neoplasm, planned Stem-cell transplantation,**
- **a life expectancy of less than 6 months,**
- **GFR < 30, Plat < 50,000 etc**

1. Khorana et al NJEM 2019
2. Carrier et al NEJM 2019

Prevention of VTE in patients with cancer: Khorana risk score (0 ~ 6)

Khorana risk score.

Cancer type	
Very high risk: pancreatic, gastric	2
High risk: lung, lymphoma, gynecologic, bladder, testicular	1
Complete count biomarkers	
Pre-chemotherapy platelet count $\geq 350 \times 10^9$/L	1
Hemoglobin count < 100 g/L or use of red cell growth factors	1
Pre-chemotherapy leucocyte count $> 11 \times 10^9$/L	1
Patient factor	
BMI ≥ 35 kg/m^2	1

Low risk: 0 points; Intermediate-risk 1–2 points; High-risk: $\geq$ 3 points.

1. Khorana et al NJEM 2019
2. Carrier et al NEJM 2019

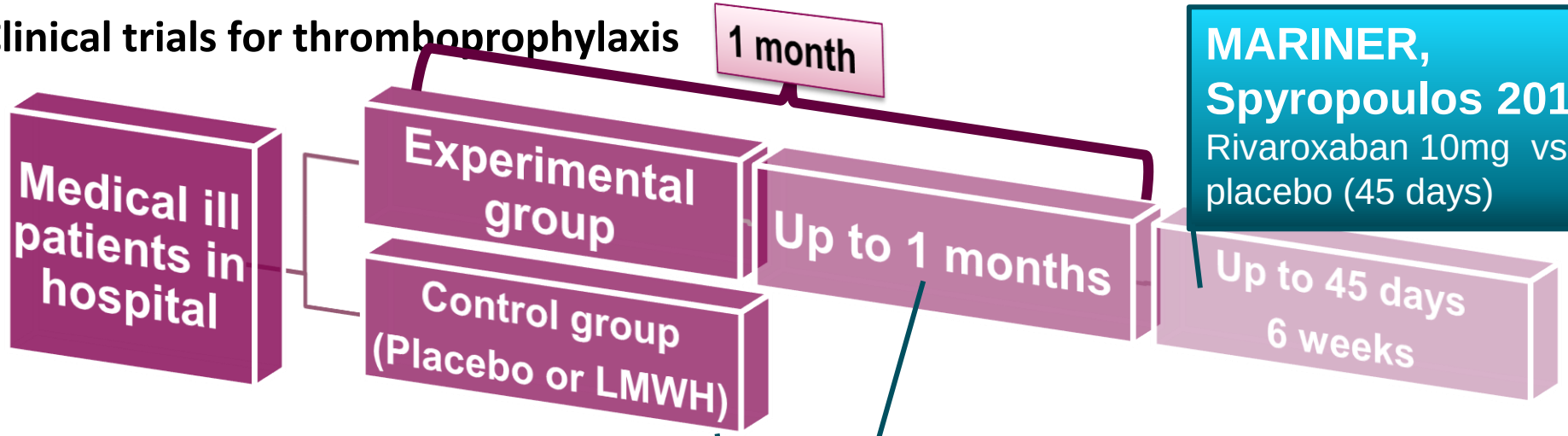
Prevention of VTE in patients with cancer: DOACs vs Placebo

	CASSINI study[1]	AVERT study[2]
Intention-to-treat		
VTE	25/420(6.0%) in rivaroxaban vs 37/421(8.8%) HR 0.66; 95%CI 0.4-1.09 p=0.10	12/288 (4.2%) in Apixaban vs 28/275 (10.2%) **HR 0.41; 95CI 0.26-0.65, p<0.001★**
Major bleeding	8/405(2.0%) vs 4/404(1.0%) HR 1.96; 95%CI 0.59-6.49	10 (3.5%) vs 5 (1.8%) HR 2.0;9% CI 1.01-3.95 p=0.046
Intervention period	11(2.6%) vs 27(6.4%) **HR 0.4; 95%CI 0.2-0.8 VTE★**	
		6(2.1%) vs 3 (1.1%) **HR 1.89; 95% CI 0.39-9.24 Major Bleeding★**
Risk difference	**4 %** point in **CASSINI**	**6%** in **AVERT**
	2.2 % point in **SAVE-ONCO**	
	1.9 % point in **PROTECHT**	

1. Khorana et al NJEM 2019
2. Carrier et al NEJM 2019

Thromboprophylaxis in medically ill patients

Clinical trials for thromboprophylaxis



MARINER, Spyropoulos 2018
Rivaroxaban 10mg vs placebo (45 days)

Samama 1999

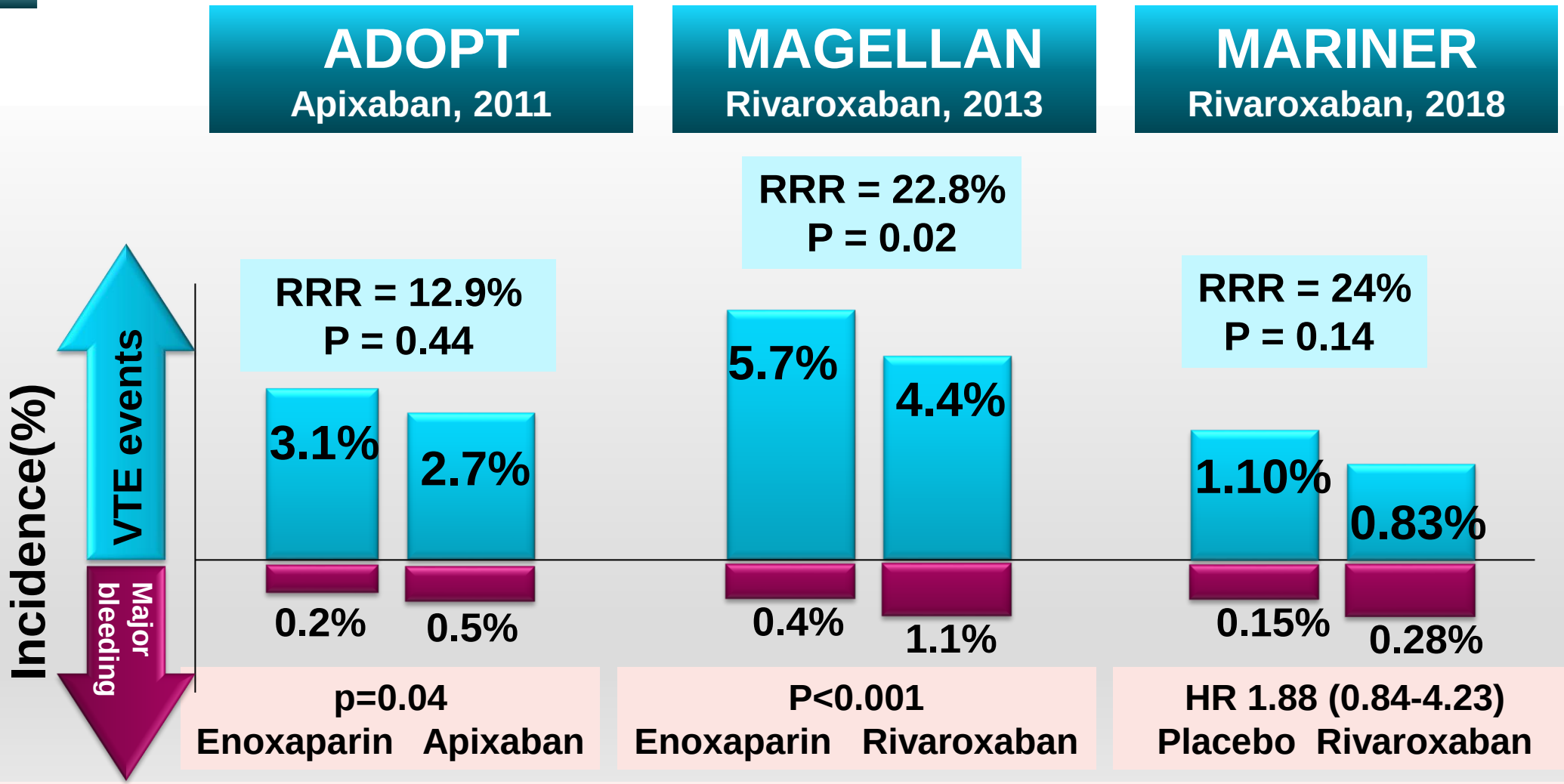
Enoxaparin 40mg, Enoxaparin 20mg or placebo for 6 to 14 days
5.5%(16 of 291) vs 14.9%(43 of 288)
RR 0.37; 97.6%CI 0.22-0.63, p<0.001
ARR=9.4%, RRR=,63% NNT=11

MAGELLAN, Cohen 2013

Subcutaneous placebo(10 ± 4)
Rivaroxaban 10mg (35±4)
versus
Enoxaparin 40mg (10±4) plus placebo (35±4)

1. Samama et al NEJM 1999
2. Goldhaber et al NEJM 2011
3. Cohen NEJM 2013;368(6):513-23
4. Spyropoulos NEJM 2018;379(12):1118-27

Comparison of extended thromboprophylaxis in acute medically ill patients



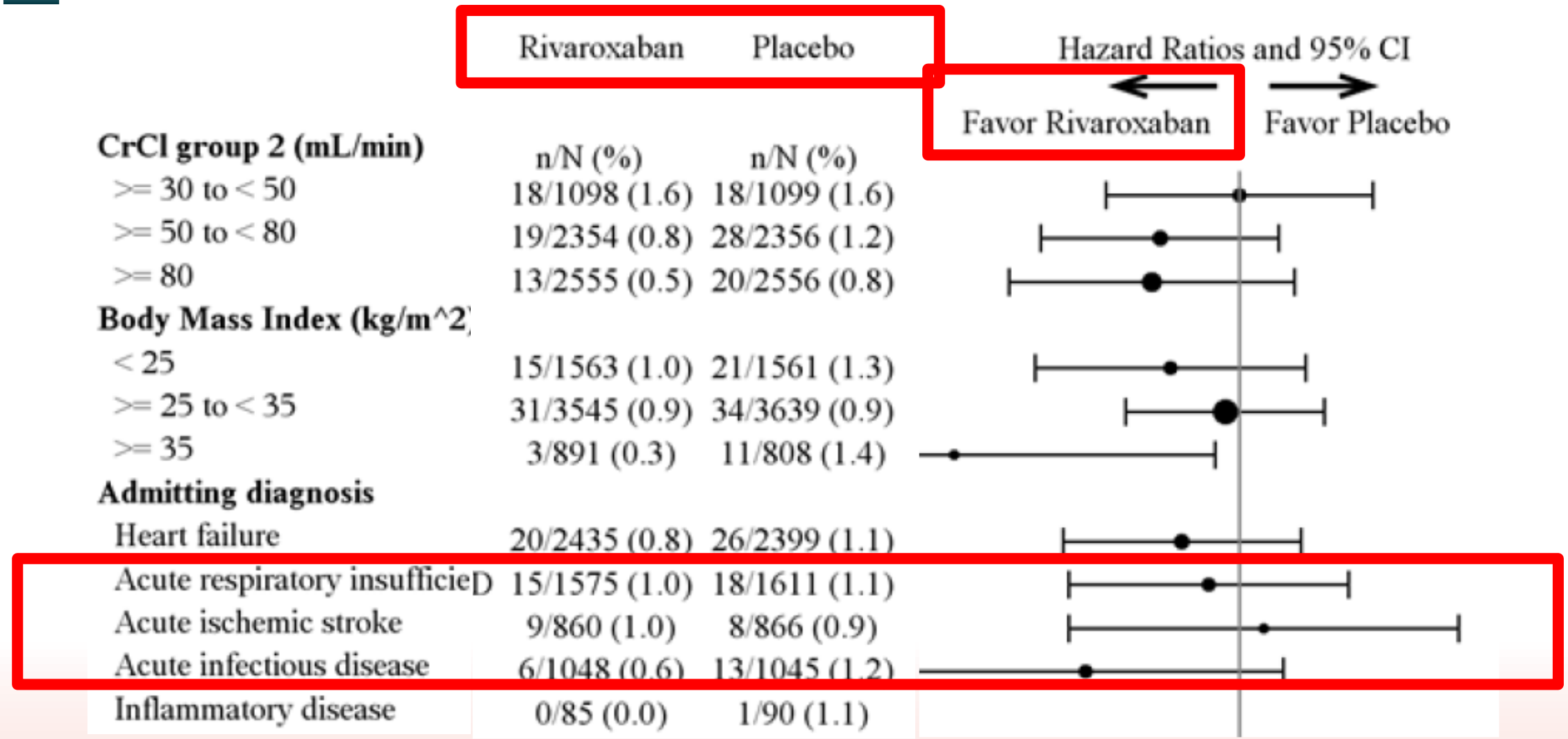
1. Goldhaber et al NEJM 2011
2. Cohen NEJM 2013;368(6):513-23
3. Spyropoulos NEJM 2018;379(12):1118-27

Thromboprophylaxis in medically ill patients: Clinical trials

	Cohen[1]	Spyropoulos[2]	Mahlab[3]
Year	2013	2018	2020
Study	Clinical trial MAGELLAN trial	Clinical trial MARINER trial	Real-life
	Rivaroxaban (35±4) vs Enoxaparin (10±4)	Rivaroxaban vs placebo	
Duration	35 days	45 days	
Comorbidity			
Infection	45.8% vs 45.1%	17.5% vs 17.4%	25.1%
Respiratory insufficiency or ECOPD	27.3% vs 28.7%	26.2% vs 26.8%	***
2 or more	30.6% vs 31.4%		

1. Cohen NEJM 2013;368(6):513-23
2. Spyropoulos NEJM 2018;379(12):1118-27
3. Mahlab-Guri Medicine 2020;99(7):e19127

Subgroup of primary efficacy endpoint in MARINER study (45 days)

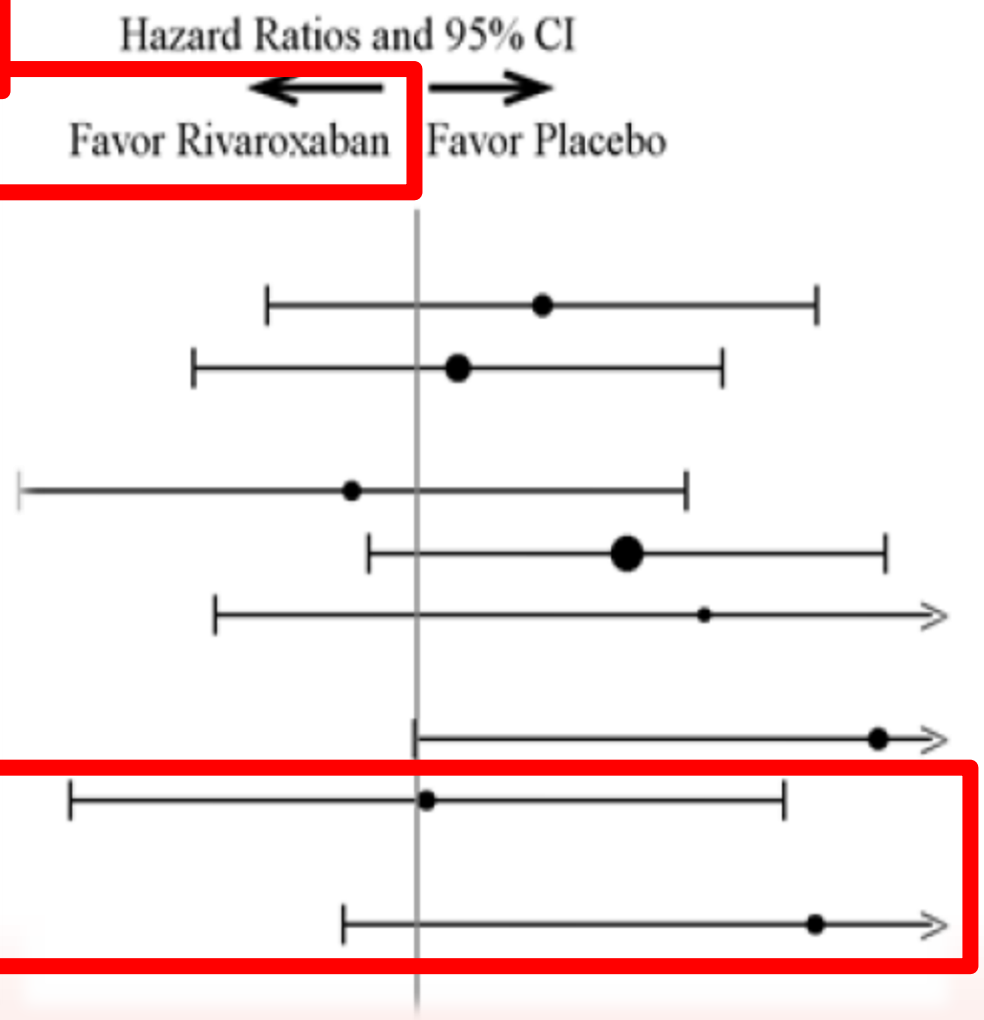


	Rivaroxaban n/N (%)	Placebo n/N (%)
CrCl group 2 (mL/min)		
>= 30 to < 50	18/1098 (1.6)	18/1099 (1.6)
>= 50 to < 80	19/2354 (0.8)	28/2356 (1.2)
>= 80	13/2555 (0.5)	20/2556 (0.8)
Body Mass Index (kg/m^2)		
< 25	15/1563 (1.0)	21/1561 (1.3)
>= 25 to < 35	31/3545 (0.9)	34/3639 (0.9)
>= 35	3/891 (0.3)	11/808 (1.4)
Admitting diagnosis		
Heart failure	20/2435 (0.8)	26/2399 (1.1)
Acute respiratory insufficiency	15/1575 (1.0)	18/1611 (1.1)
Acute ischemic stroke	9/860 (1.0)	8/866 (0.9)
Acute infectious disease	6/1048 (0.6)	13/1045 (1.2)
Inflammatory disease	0/85 (0.0)	1/90 (1.1)

1. Spyropoulos et al NEJM 2018, supplement

Subgroup of Major bleeding in MARINER study (45 days)

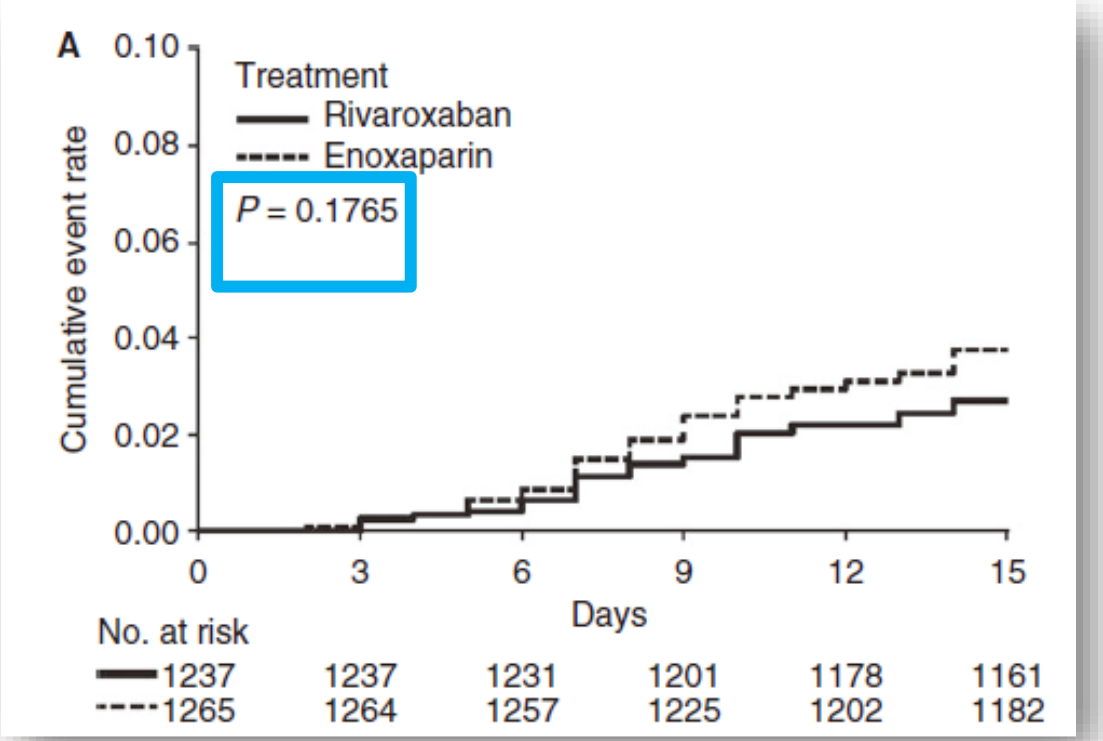
	Rivaroxaban	Placebo
CrCl group 2 (mL/min)	n/N (%)	n/N (%)
>= 30 to < 50	4/1092 (0.4)	0/1091 (0.0)
>= 50 to < 80	7/2347 (0.3)	4/2346 (0.2)
>= 80	6/2543 (0.2)	5/2543 (0.2)
Body Mass Index (kg/m^2)		
< 25	3/1557 (0.2)	4/1554 (0.3)
>= 25 to < 35	10/3532 (0.3)	4/3618 (0.1)
>= 35	4/885 (0.5)	1/804 (0.1)
Admitting diagnosis		
Heart failure	8/2432 (0.3)	1/2389 (0.0)
Acute respiratory insufficien	3/1563 (0.2)	3/1606 (0.2)
Acute ischemic stroke	0/858 (0.0)	4/863 (0.5)
Acute infectious disease	6/1041 (0.6)	1/1032 (0.1)
Inflammatory disease	0/85 (0.0)	0/90 (0.0)



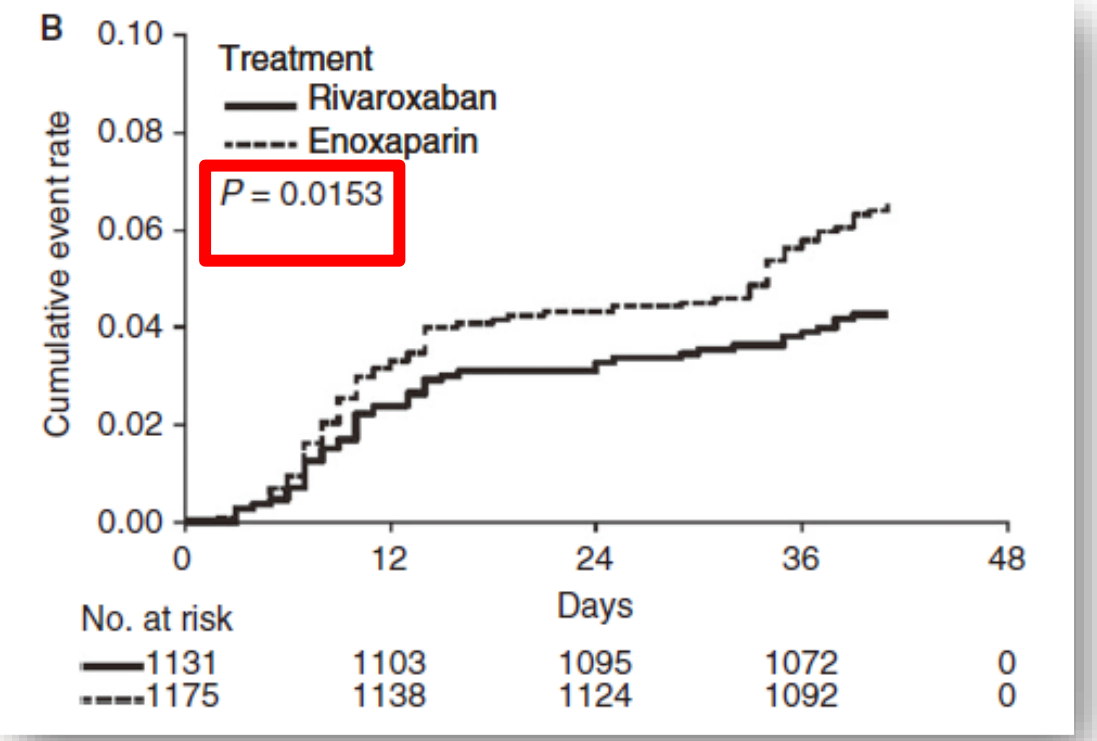
1. Spyropoulos et al NEJM 2018, supplement

Subgroup analysis in MAGELLAN study: Patients hospitalized for acute infection.

- VTE events at day 10



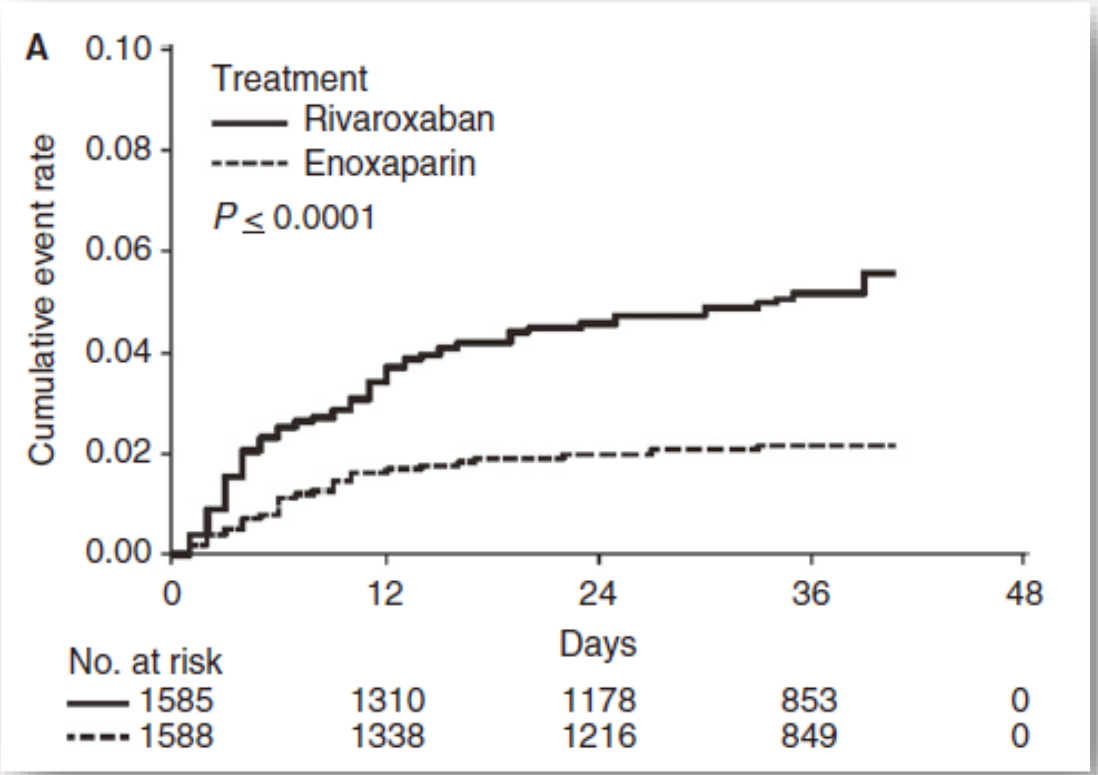
- VTE events at day 35



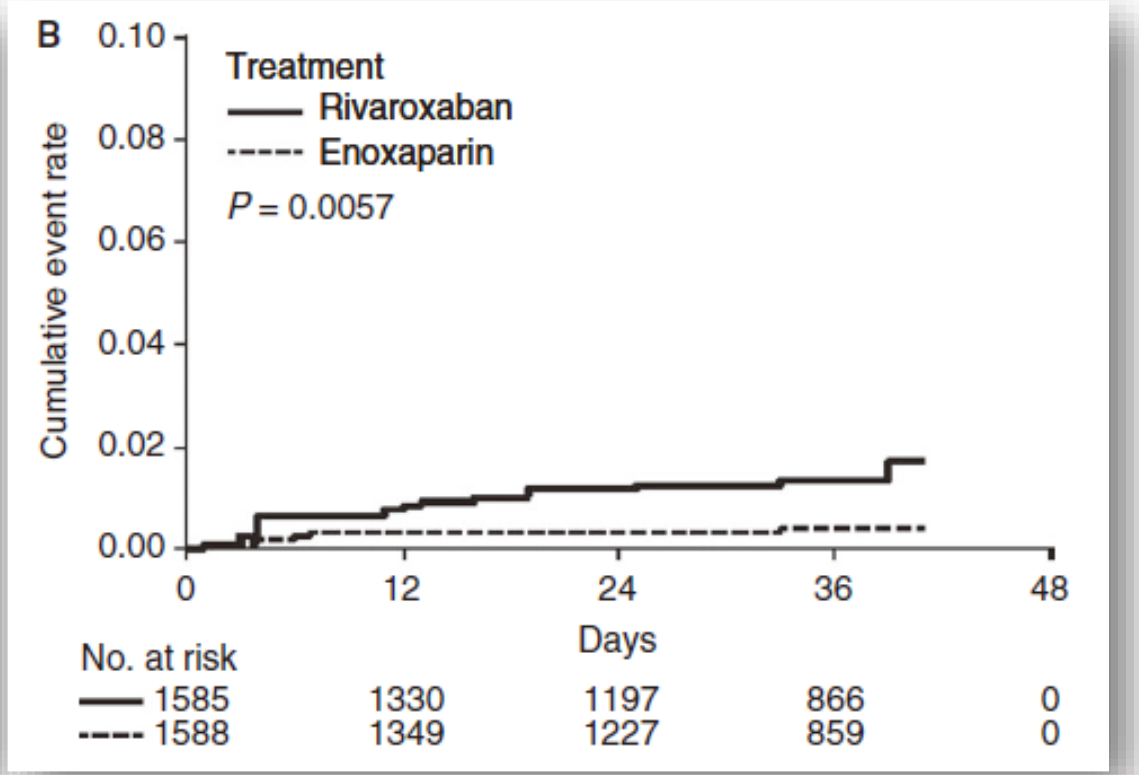
1. Cohoon et al J Thromb Haemost 2018

Subgroup analysis in MAGELLAN study: Patients hospitalized for acute infection.

- Major or CRNMB at day 35



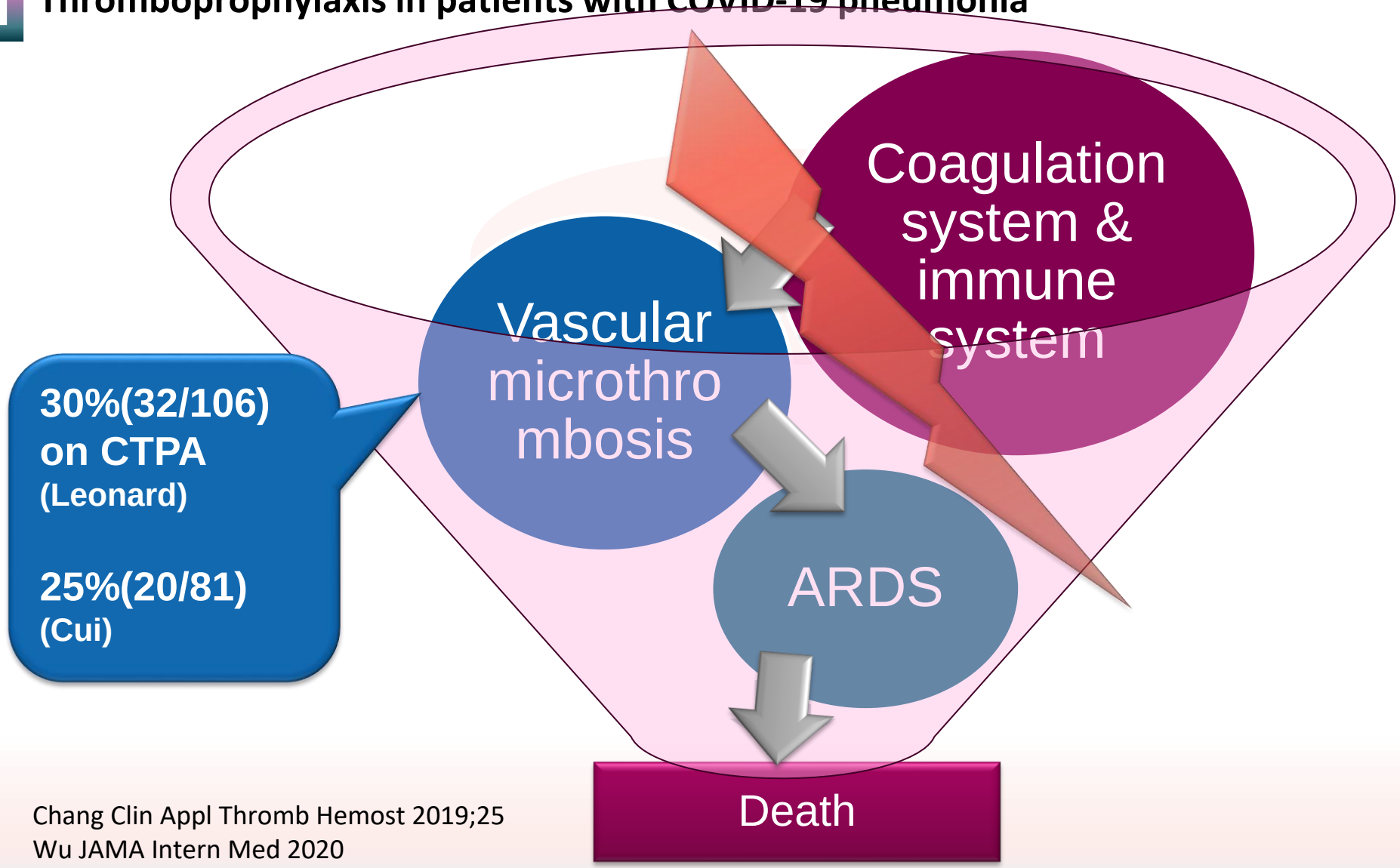
- Major bleeding at day 35



1. Cohoon et al J Thromb Haemost 2018

Thromboprophylaxis in patients with COVID-19 infection

Thromboprophylaxis in patients with COVID-19 pneumonia



1. Chang Clin Appl Thromb Hemost 2019;25
2. Wu JAMA Intern Med 2020
3. Leonard-Lorant Radiology 2020
4. Cui J Thromb Haemost 2020
5. Antoniak Res Pract Thromb Haemost 2018;2(3):549-557

Padua score

Items	Score
Active cancer (metastases and/or chemoradiotherapy in the previous 6 months)	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Bedrest for ≥3 days	3
Thrombophilia	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥30 kg/m^2)	1
Ongoing hormonal treatment	1

High risk of VTE: ≥4 points. VTE: Venous thromboembolism; BMI: Body mass index.

IMPROVE score (International Medical Prevention Registry of Venous thromboembolism)

The IMPROVE risk-assessment model

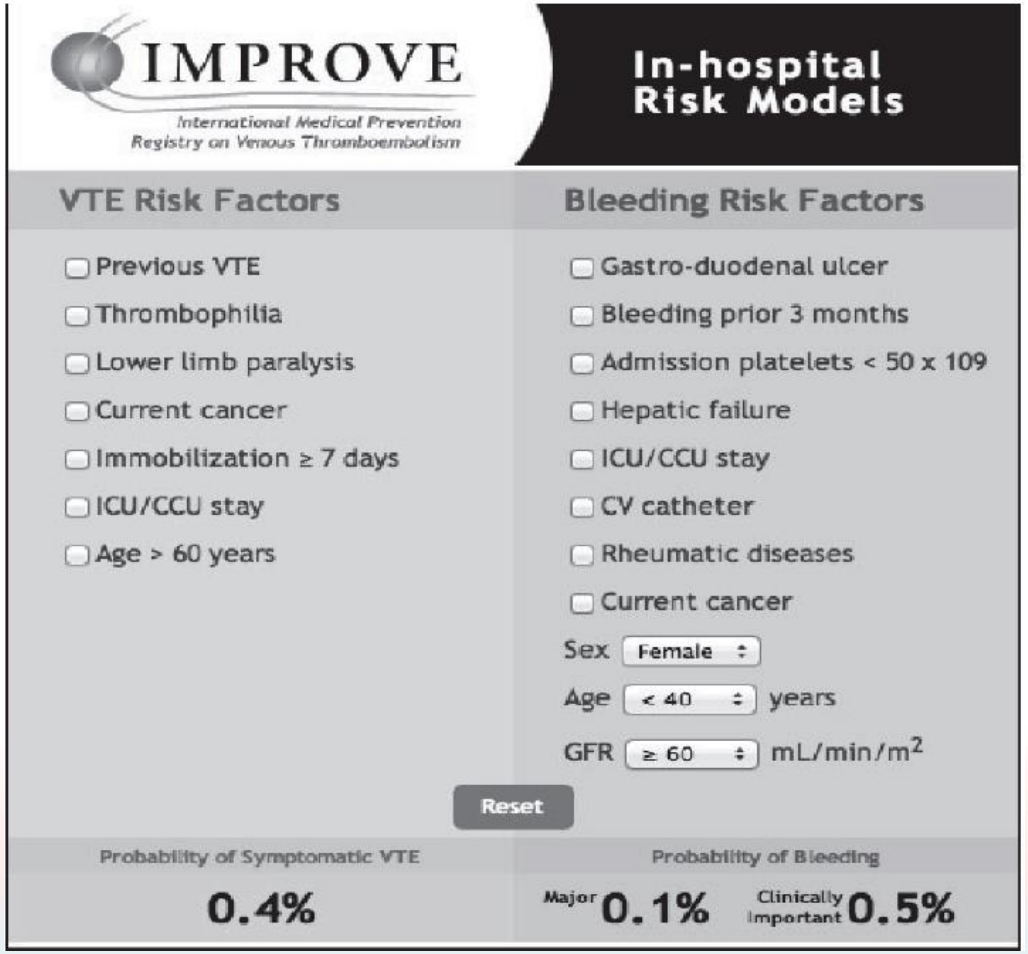
Risk factor	Points
Prior venous thromboembolism	3
Diagnosed thrombophilia	2
Current lower-limb paralysis	2
Current cancer	2
Immobilized for at least 7 days	1
Stay in the ICU or coronary care unit	1
More than 60 years old	1

Note: In 2011, the authors of IMPROVE set a total score of 0 or 1 as low risk and not needing anticoagulant prophylaxis and a score of 2 or more as appropriate for prophylaxis.

Source: Chest 2011;140:705-14

IMNS Medical Media

IMPROVE Risk Calculator: http://www.outcomes.org/improve



1. Spyropoulos Thrombosis and Haemostasis 2017

ISTH
International Society on Thrombosis and Haemostasis

22 June 2020

A Systematic Approach for Managing Venous Thromboembolism in COVID-19 Patients: A Multinational Consensus Statement from the International Society on Thrombosis and Haemostasis on Behalf of the International Thrombosis Community

Deep learning in thromboprophylaxis

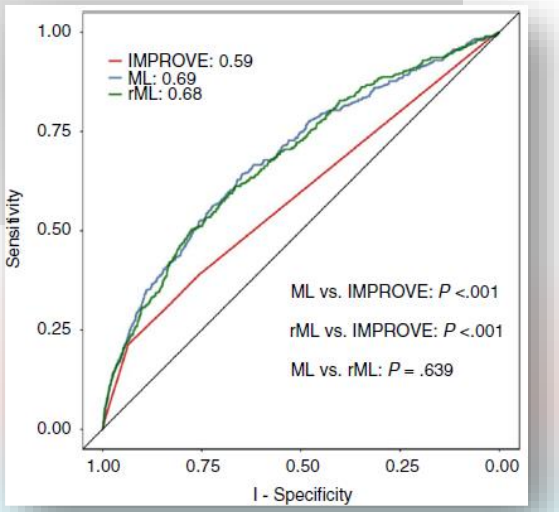
Machine learning to predict VTE in acute ill medical patients (c-statistics)

APEX trial

7513 Acute medical ill patients

	C-statistics
IMPROVE score	0.59
Super learner model (ML) (68 variables)	0.69
Reduced model (rML) (16 variables)	0.68

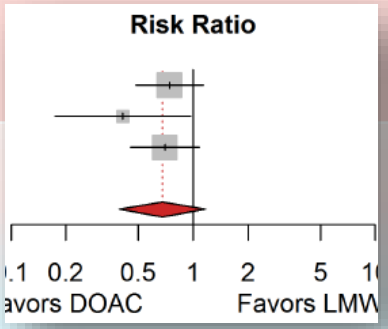
VTE



1. Nafee et al. Res Pract Thromb Haemost 2020;4:230-237

Summary

	Anticoagulation in cancer-associated VTE	Thromboprophylaxis in cancer patient	Thromboprophylaxis in medically ill patients	Thromboprophylaxis in COVID-19
Clinical trials	**Select-D** (Riva 2018) **Hokusai** (Edoxa 2018) **Caravaggio**(Apixa 2020)	**CASSINI** (Riva 2019) **AVERT** (Apixaban2019)	**MARINER** (45d) (2018) **MAGELLAN** (35d) (2013) …	**Ongoing**
Model	Modified Well's criteria	Khorana score ≥2 (0-6)	IMPROVE score ≥4 Padua score ≥4	---
Comparator	Dalteparin	Placebo	Enoxaparin/placebo	---
	GI bleeding**주의** Caravaggio**(차이없음)**			
VTE	**0.68 (0.39-1.17) in 3 trials**	**Risk difference** **4% in CASSINI** **6% in AVERT**	**RRR=24%, p=0.14** **0.83% vs 1.10% MARINER** **RRR=22.8, p=0.02** **4.4% vs 5.7% MAGELLAN**	---



Prophylaxis beyond Treatment of VTE

경청해 주셔서 감사합니다.