Management following diagnosis of Pulmonary Embolism

ESC/ERS 2019 & ASH 2020 guidelines

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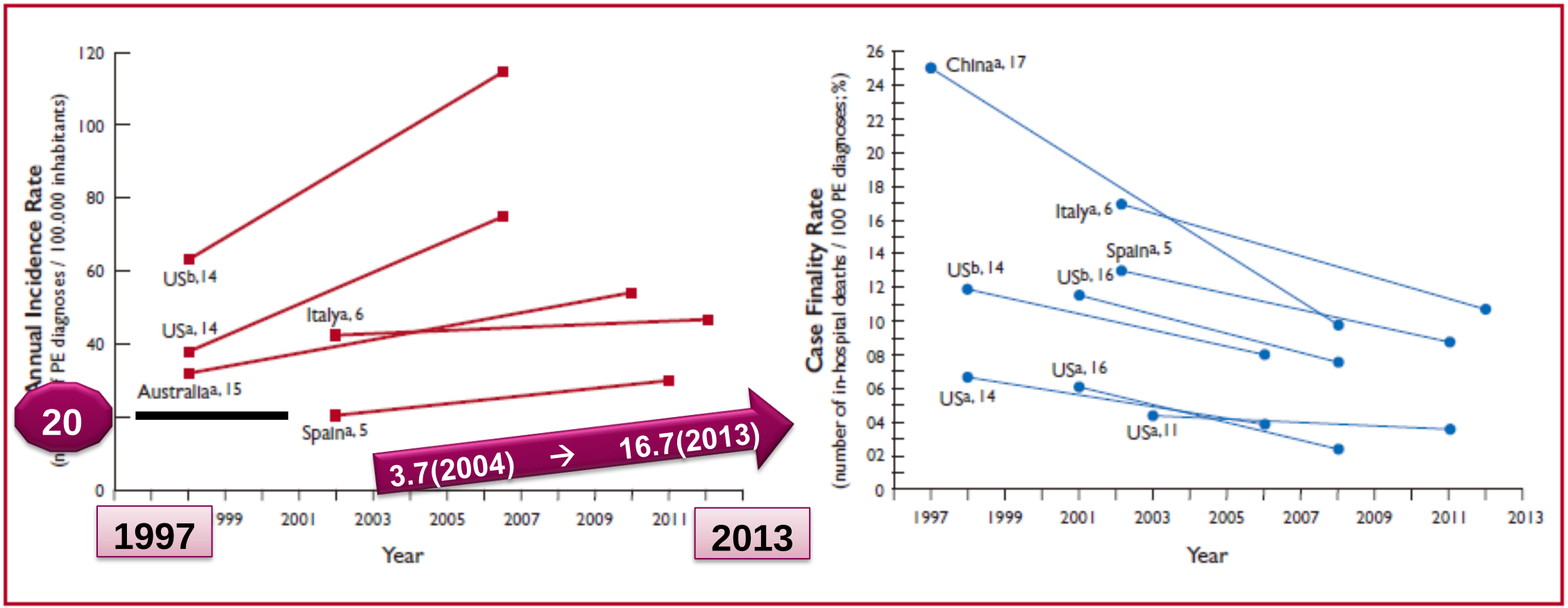
장소: SC Convention, 서울

Contents

- 한국의 혈전현황
- Case
- High-risk PE patients & Massive PE
- 30-day mortality in PE
- Maintenance therapy
- Home management
- Provoked vs Unprovoked (Risk stratification)

Annual incidence & Case fatality rate of PE

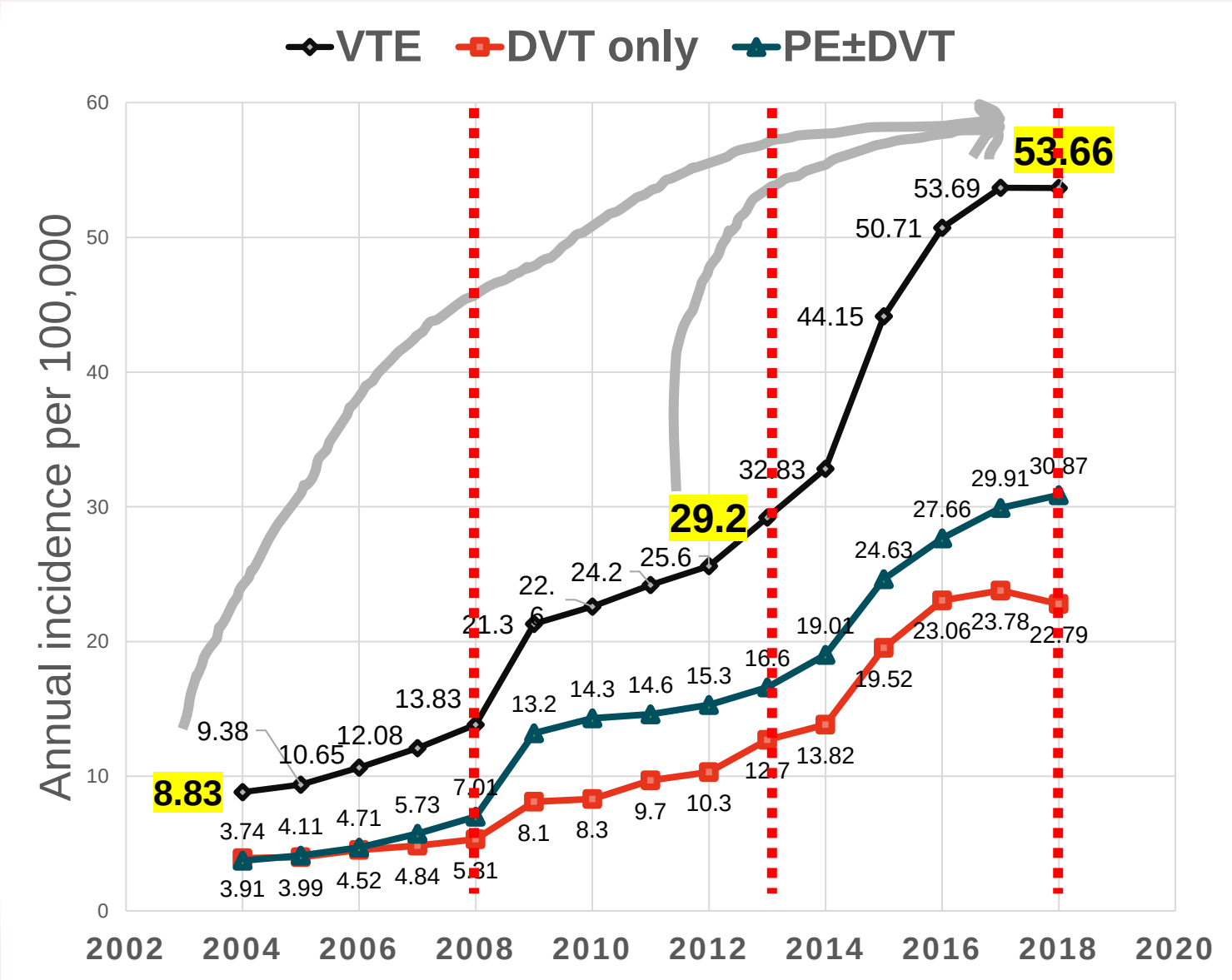


Jang J thrombo Haemost 2011;9:85-91
Hong et al. PLoS One 2018
Modified from JACC 2016;67:976-90
Konstantinides Eur Heart J 2019;00:1-61

Annual incidence of VTE in Korea from 2004 to 2018

Rate ratio for VTE:

- 1.8 (= 53.66/29.2)
- 6.07 (= 53.66/8.83)



Hwang, Bang 2021 In progress

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Case 1. 수술 후 호흡곤란발생한 경우

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1. Proper management (thrombolysis or anticoagulants)
2. 30-day mortality (simplified Pulmonary embolism severity index, PESI)
3. Maintenance therapy
4. Provoked vs Unprovoked
5. Thrombophilia test

Frequency and timing of clinical VTE after major joint surgery

Hip fracture: 60- 80 d

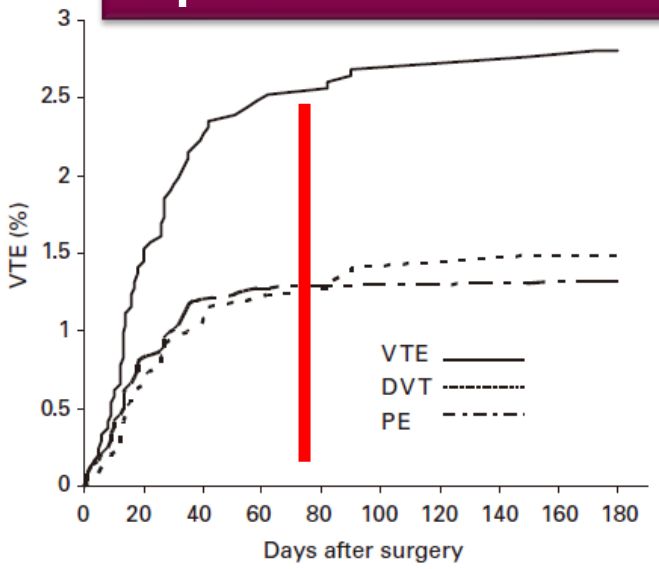


Fig. 1a

THR: 60-80 d

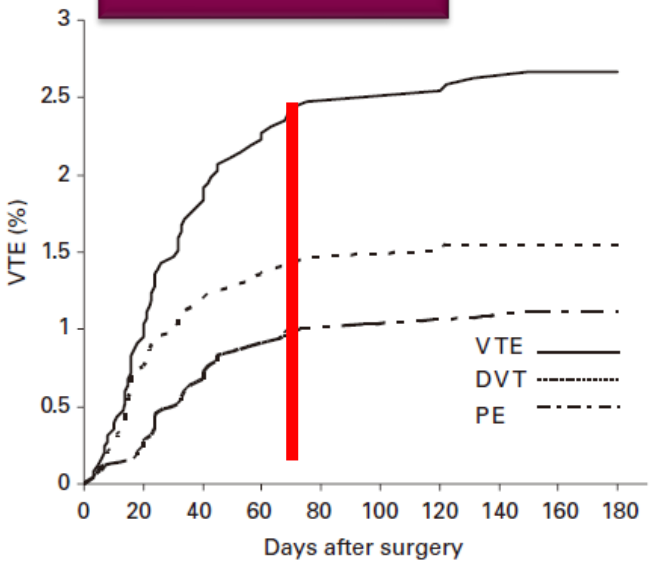
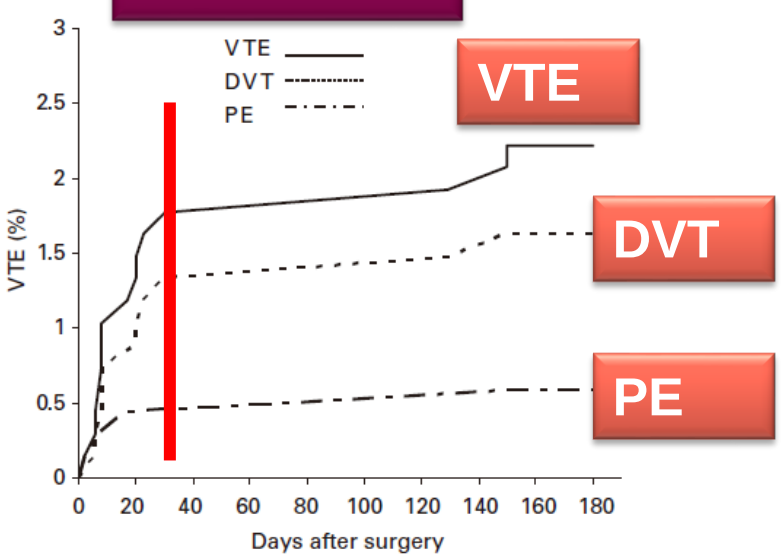


Fig. 1b

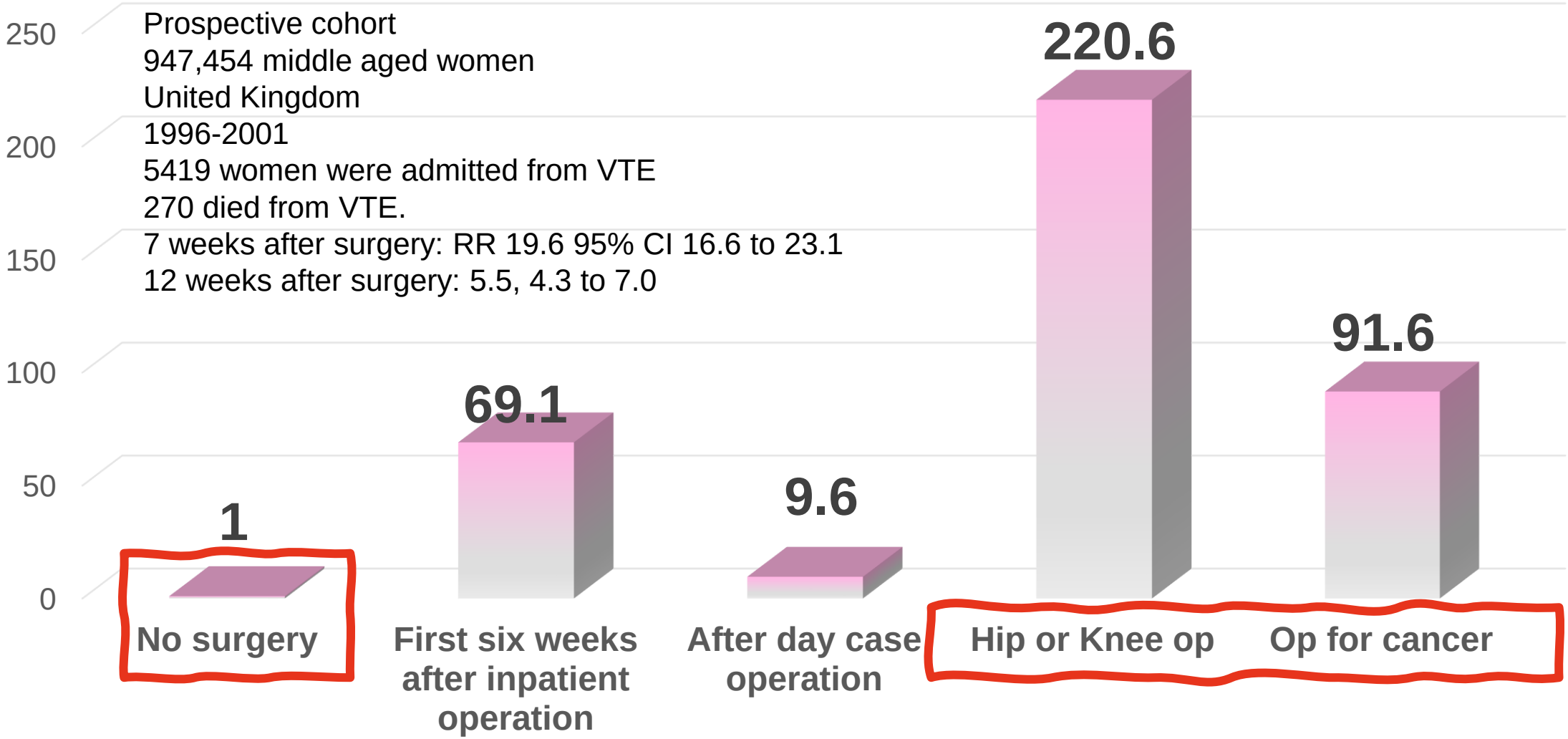
TKR: 30 d



Group showing the cumulative incidence of VTE *vs* time after a) surgery for fracture of the hip, b) total hip replacement and c) total knee replacement

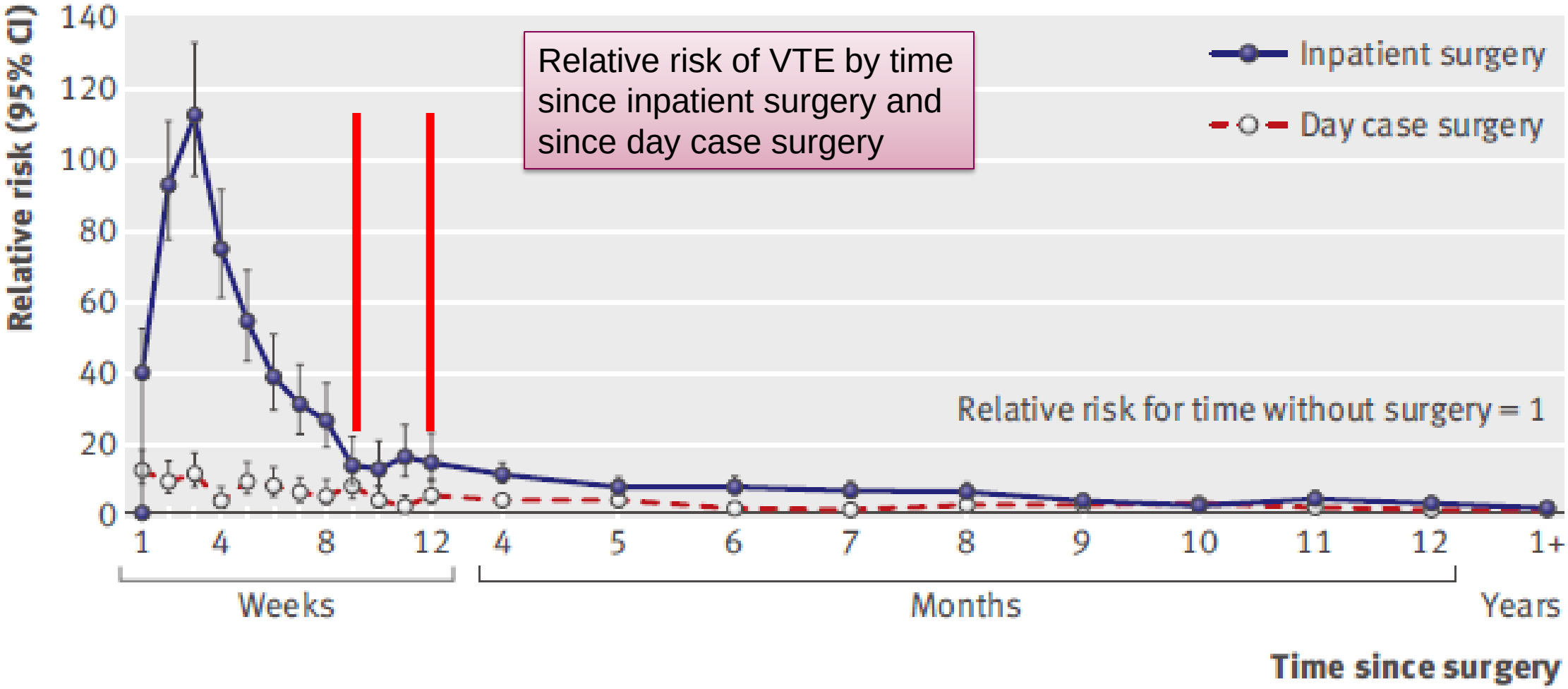
Bjornara 2006

Relative risk of VTE: Million Women Study



1. Sweetland et al BMJ 2009;339:b4583

Relative risk of VTE: Million Women Study



1. Sweetland et al BMJ 2009;339:b4583

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1. Proper management

- ❑ Thrombolysis
- ❑ Catheter-directed thrombolysis
- ❑ LMWH
- ❑ DOACs

2014

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI ≥I[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	–	+	Both positive	
	Intermediate–low	–	+	Either one (or none) positive[e]	
Low		–	–	Assessment optional; if assessed, both negative[e]	

2019

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/ or comorbidity: PESI class III–V or sPESI ≥I	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

Classification of PE severity and the risk of early (30-day) death

Recommendations
Rescue thrombolytic therapy is recommended for patients who deteriorate haemodynamically.
II a (2014) → I (2019)

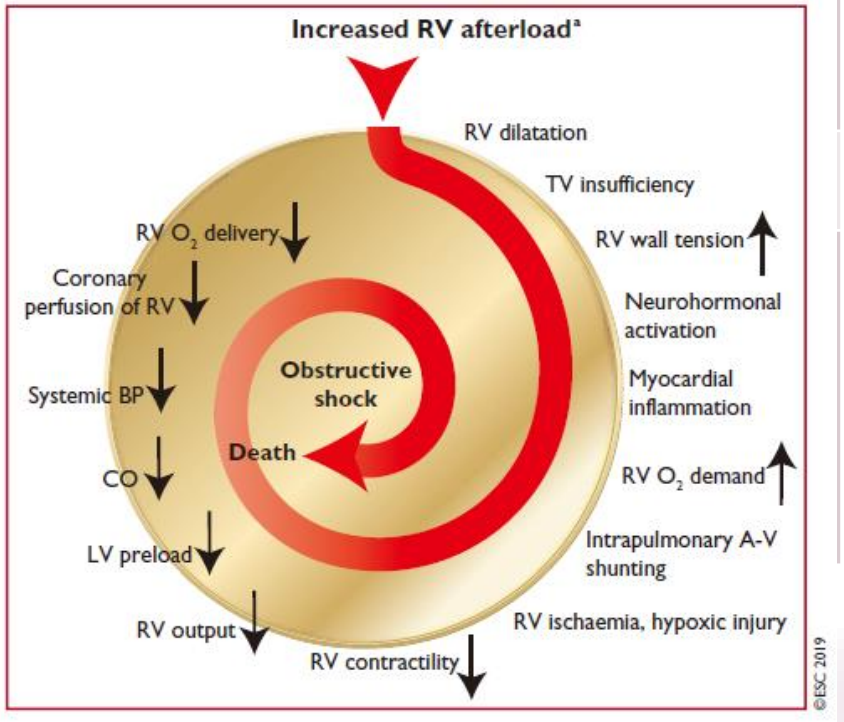
Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

©ESC 2019

Eur Respir J 2019;54(3):1901647

Definition of haemodynamic instability

(1) Cardiac arrest	(2) Obstructive shock[1-3]	(3) Persistent hypotension
Need for cardiopulmonary resuscitation (CPR)	Systolic BP < 90 mmHg or vasopressors required to achieve a BP >=90 mmHg despite adequate filling status	Systolic BP < 90 mmHg or systolic BP drop >=40 mmHg, lasting longer than 15 min and not caused **by new-onset arrhythmia, hypovolemia, or sepsis**
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	



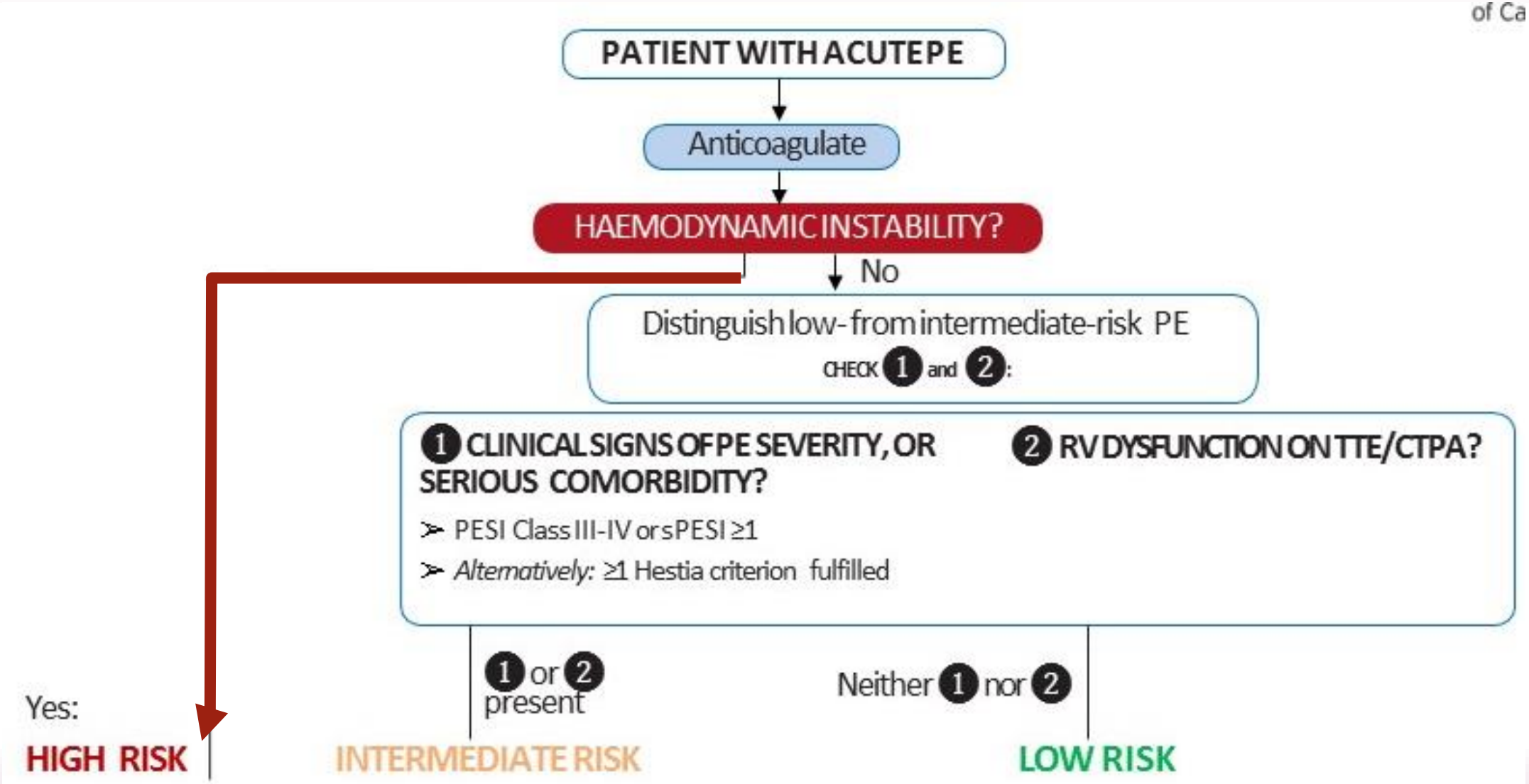
1. Harjola et al Eur J Heart Fail 2016;18:226-241
2. Mebazaa et al Intensive Care Med 2016;42:147-163
3. Thiele et al Eur Heart J 2015;36:1223-1230
4. Konstanides Eur Heart J 2019

폐색전증에서 중증도의 분류

ASH guideline	ESC/ERS guideline
❑ **Massive PE** accounts for 5–10% of cases, and is characterized by extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE.	High risk PE for early mortality (35-58%)[4-6]
❑ **Submassive PE** accounts for 20–25% of patients, and is characterized by RV dysfunction despite normal systemic arterial pressure.	Intermediate-high
❑ **Low-risk PE** constitutes about 65–75% of cases. These patients have an excellent prognosis.	Low-risk (1%)

1. Ortel et al Blood Adv 2021;4(19):4693-4738
2. Eur Respir J 2019;54(3):1901647
3. Harrison 20th edition
4. Tapson NEJM 2008;358(10):1037-1052
5. Meyer Annals of Intensive Care 2016
6. Aujesky AJRCCM 2005;172(8):1041-1046

Risk-adjusted management strategy for acute PE



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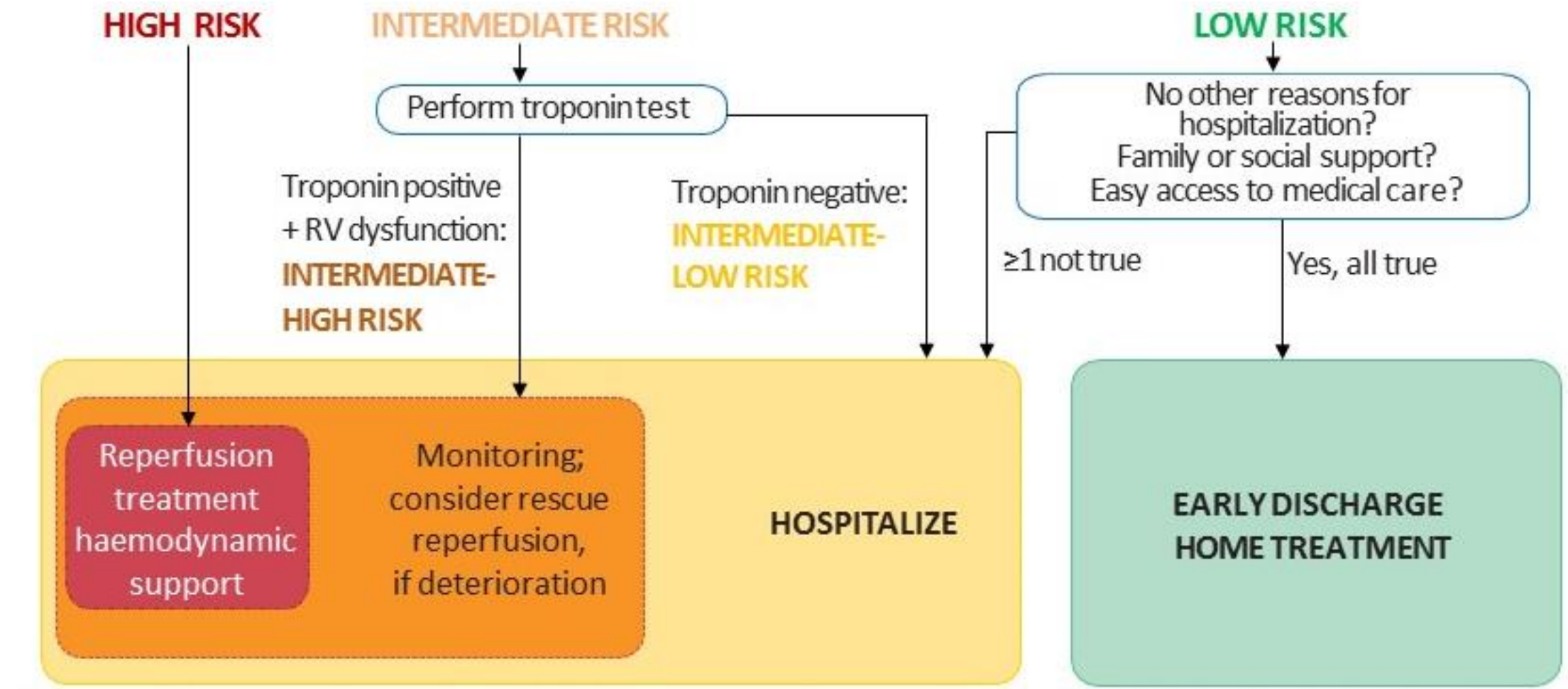
Risk-adjusted management strategy for acute PE



CTPA = computed tomography pulmonary angiography; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; TTE = transthoracic echocardiography.

Eur Respir J 2019;54(3):1901647

Risk-adjusted management strategy for acute PE (ERS 2019 and ASH 2020)

Recommendations	2014	2019
Rescue thrombolytic therapy is recommended for patients who deteriorate haemodynamically.	IIa	I
Surgical embolectomy or catheter-directed treatment should be considered as alternatives to rescue thrombolytic therapy for patients who deteriorate haemodynamically.	IIb	IIa

Eur Respir J 2019;54(3):1901647

Management strategy for acute PE (ASH 2020)

- For patients with acute PE in whom thrombolysis is considered appropriate→
- For patients with extensive DVT in whom thrombolysis is considered appropriate→
- For patients with acute PE and evidence of right ventricular dysfunction (by echocardiography and/or biomarkers), →

1. Eur Respir J 2019;54(3):1901647
2. Ortel et al. Blood Adv 2021;4(19): 4693-4738

Management strategy for acute PE (ERS 2019 and ASH 2020)

- For patients with acute PE in whom thrombolysis is considered appropriate, the ASH guidelines suggest using systemic thrombolysis over catheter-directed thrombolysis partially due to a paucity of randomized trial data. (ASH)

- For patients with extensive DVT in whom thrombolysis is considered appropriate, the ASH guidelines suggest using catheter-directed thrombolysis over systemic thrombolysis.

- For patients with acute PE and evidence of right ventricular dysfunction (by echocardiography and/or biomarkers), the ASH guidelines suggest anticoagulation alone over routine use of thrombolysis. Thrombolysis is reasonable to consider for patients at low bleeding risk who are at high risk for decompensation. (ASH 2020)

1. Eur Respir J 2019;54(3):1901647
2. Ortel et al. Blood Adv 2021;4(19): 4693-4738

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1. Proper management—thrombolysis (tPA 100mg)
2. **30-day mortality (simplified Pulmonary embolism severity index, PESI)**

Parameter	Simplified PESI score
CHF, Chronic pulmonary disease	1 point
Cancer	1 point
Pulse rate >=110 bpm	1 point
Systolic BP < 100mmHg	1 point
O2 saturation < 90%	1 point
Age > 80	1 point (if age >80 years)

30-day mortality—Simplified pulmonary embolism severity index (sPESI score)

Parameter	Simplified PESI score
Age	1 point (if age >80 years)
Cancer	1 point
CHF, Chronic pulmonary disease	1 point
Pulse rate >=110 bpm	1 point
Systolic BP < 100mmHg	1 point
O2 saturation < 90%	1 point

0 point = 30 day mortality risk 1.0% (95% CI 0.0—2.1%)

>=1 point(s) = 30 day mortality risk 10.9% (95% CI 8.5—13.2%)

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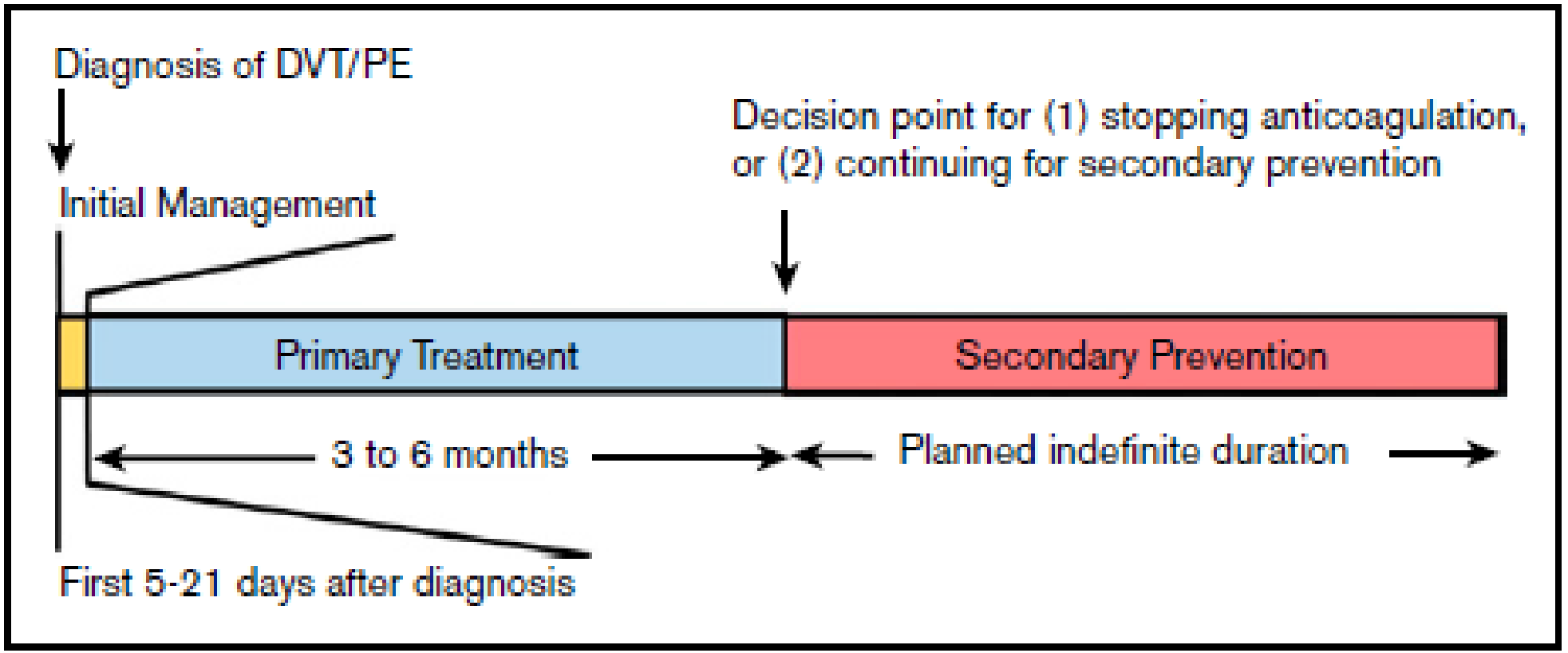
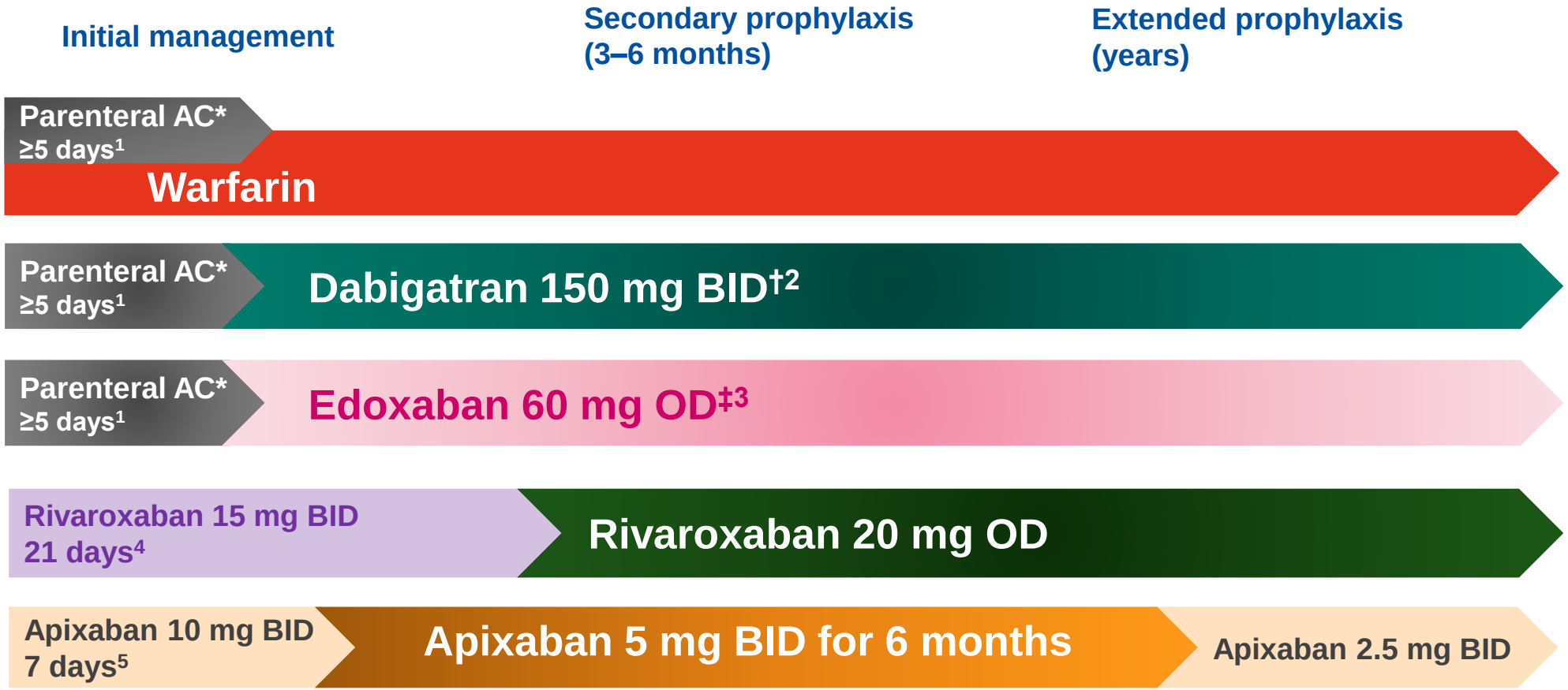
1. Proper management—thrombolysis (tPA 100mg)
2. 30-day mortality: 35~58% & 10.9% based on sPESI score(=3)
3. **Maintenance therapy**
4. Provoked vs Unprovoked
5. Thrombophilia test

Time frame of the decisions for anticoagulation



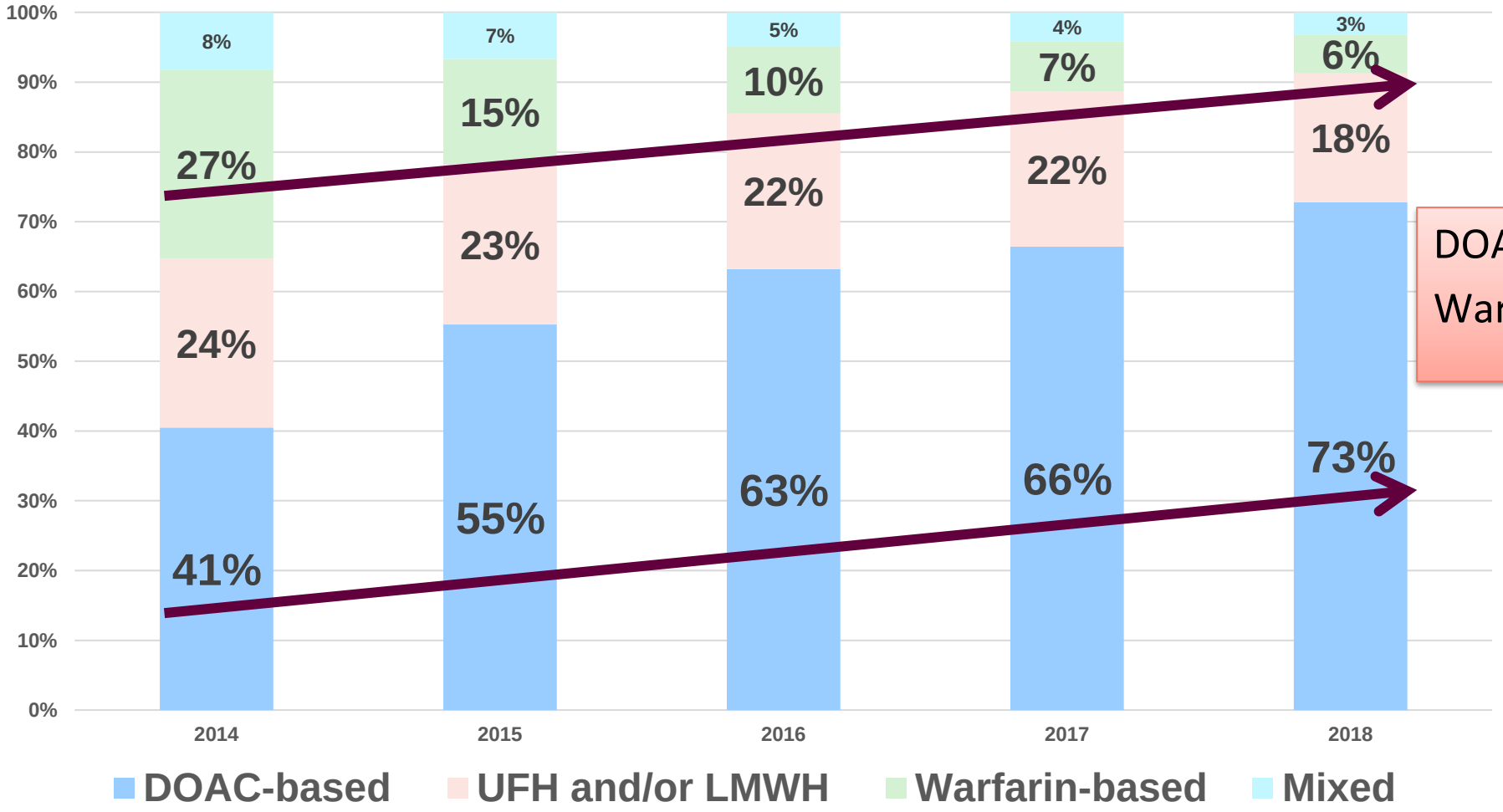
Ortel et al. Blood Adv 2021;4(19): 4693-4738

Option among DOACs



1. *LMWH, fondaparinux or UFH; †Dabigatran 110 mg BID for aged ≥80 years, concomitant verapamil, or based on individual assessment of thromboembolic/bleeding risk; ‡Edoxaban 30 mg OD for CrCl 15–50 mL/min, weight ≤60 kg, certain concomitant P-gp inhibitors
2. **1.** Kearon et al. Chest 2012;141(2 Suppl):e419S–94S; **2.** Pradaxa SPC; **3.** Lixiana SPC; **4.** Xarelto SPC; **5.** Eliquis SPC. Current versions available online at: http://www.medicines.org.uk/emc/

Trend of anticoagulants for the treatment of VTE from 2014 to 2018



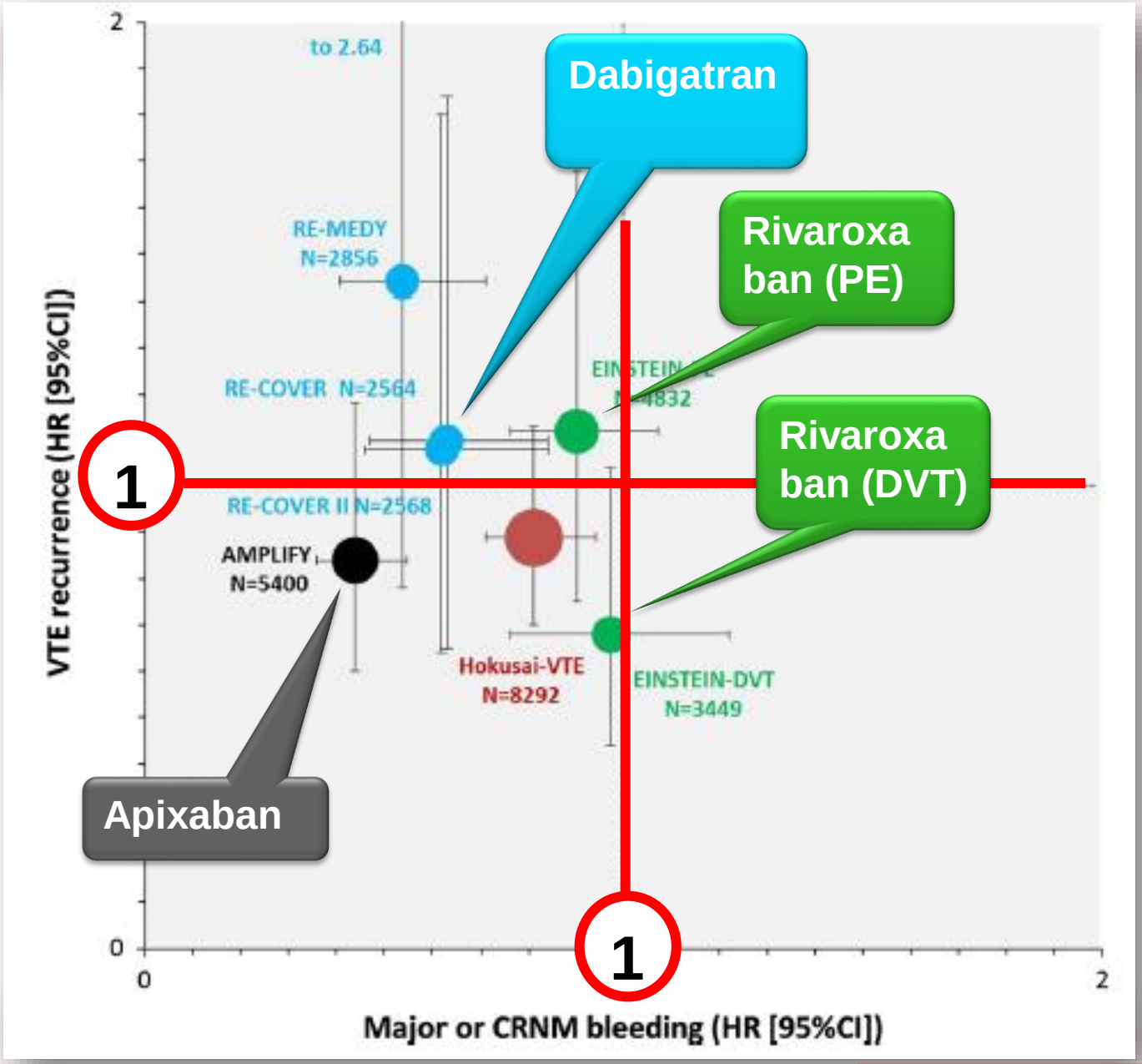
DOACs 1.78배 증가
Warfarin 88%감소

Hwang, Bang 2021 In progress

Selection among anticoagulants

- Bleeding complication
- Once daily versus bid
- Body weight
- Renal function
- Patient's preference

Therapeutic anticoagulation for at least 3 months is recommended for all patients with PE (Class I, level A) (ERS)



1. Cohen et al. Adv Ther 2014; (31): 473-493

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Home treatment based on Risk stratification for PE to predict 30-day mortality

The ASH guidelines suggest offering home treatment instead of hospitalization for patients with acute PE at low risk for complications. This includes patients at low risk based on the **Pulmonary Embolism Severity Index (PESI) or its simplified version**.

Component	Score[a]
Age >80 y	1 p
History of cancer	1 p
Chronic cardiopulmonary disease	1 p
Pulse > 110/min	1 p
Systolic blood pressure <100 mm Hg	1 p
Oxygen saturation <90%	1 p

[a]A total score of 0 p indicates low risk for fatal pulmonary embolism.

- Simplified pulmonary embolism severity index
- Low-risk –negative predictive value for fatal PE is 99%
- 40-50% of patients can be sent home from the Emergency room
- 30 day mortality: 1.1% (0.7-1.5) vs 10.9% (8.5-13.2)
- Class II a Level A (ERS) [2]

1. Jiménez D, et al. Arch Intern Med 2010;170(15):1383–1389
2. Aujesky et al Lancet 2011;378:41-48

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1. 호흡곤란의 원인
2. High likelihood of PE→ CT angiogram
3. Proper management—thrombolysis (tPA 100mg)
4. 30-day mortality =10.9%, (sPESI score)=3
5. Maintenance therapy
6. **Provoked vs Unprovoked**
7. **Thrombophilia test**

Terminology such as 'provoked' vs. 'unprovoked' PE/VTE is no longer supported by the Guidelines, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation. (ERS, 2019)

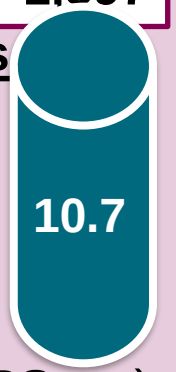
Recurrence after stopping anticoagulation

	After 1 year		After 5 years
Provoked by surgery	1	x 3=	3
Provoked by nonsurgical reversible	5	x 3=	15
Unprovoked	10	x 3=	30

- Risk of recurrence after stopping Tx[1]
- Estimated annualized risk of recurrence in Cancer-associated VTE: 15%
- By 3 months, 14% of patients with a proximal DVT and 17.5% with PE will have died[2,3]

1) Kearon Chest 2012;141:e419s-494s
2) Vaitkus PT et al. Thromb Haemost 2005;93:76-9
3) Goldahber SZ et al. Lancet 1999; 353:1386-9
4) Khan et al. BMJ 2019;366

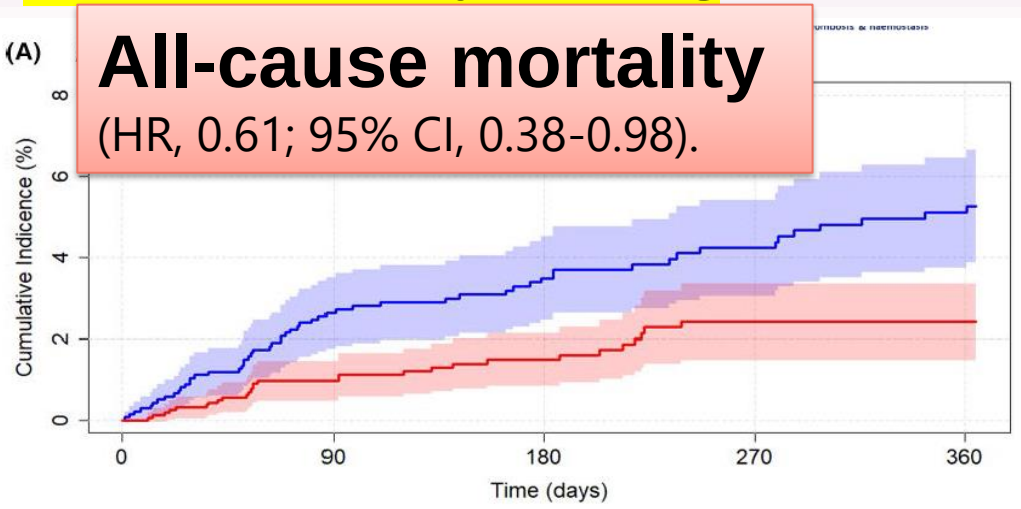
VTE recurrent rate at 1 year after anticoagulation

	Major	Minor
Persistent	N=147 Active cancer Excluding basal cell or squamous cell skin cancer 	N=1,897 **Inflammatory bowel (lower extremity paralysis** CHF BMI >30 kg/m2 **CrCl <50 ml/min**, family history of VTE, **known thrombophilia (APS** etc) 
Transient	N=179 Major surgery Trauma Cesarian section 	N=445 **Immobilization** **Travel > 8 hrs** Pregnancy Puerperium Estrogen use **Lower limb trauma with transient with impairment of mobility** 

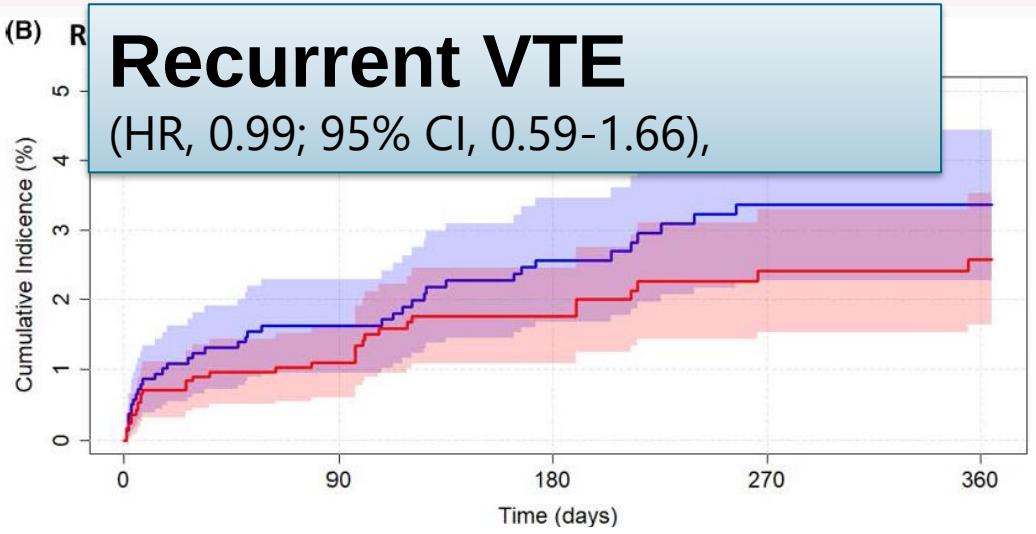
Prins et al Blood 2018:2(7):788
Kearon et al J Thromb Haemost 2016;14:1480-1483

Cumulative incidence curves for primary outcomes in patients with major or minor transient provoking risk factors

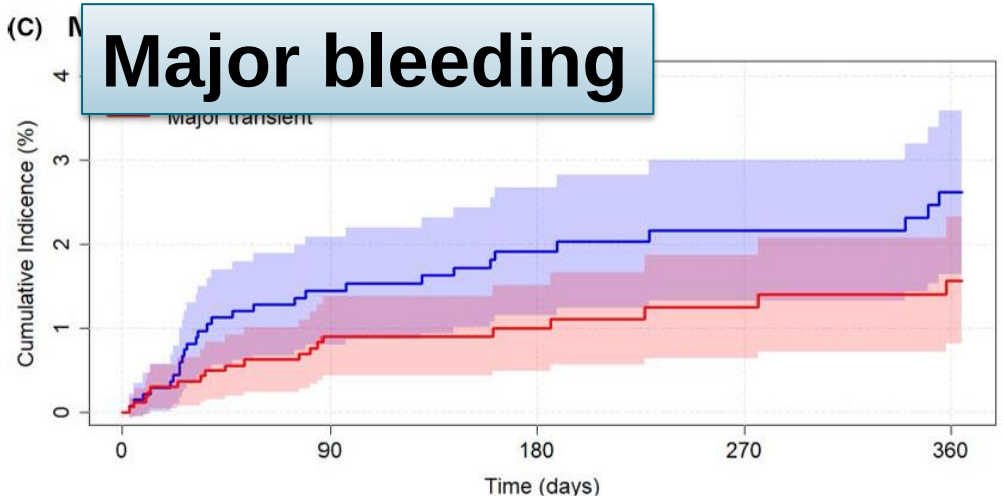
All-cause mortality
(HR, 0.61; 95% CI, 0.38-0.98).



Recurrent VTE
(HR, 0.99; 95% CI, 0.59-1.66),



Major bleeding



----Minor transient

----Major transient

Ageno et al. Res Pract Thromb 2021;5(2):326-341

Anticoagulation (ERS 2019)

- Therapeutic anticoagulation for at least 3 months is recommended for all patients with PE (Class I, level A) (ESC)
- For patients with first PE/VTE secondary to a major transient/reversible risk factor, discontinuation of therapeutic oral anticoagulation is recommended after 3 months. (Same Class I, level B ← IB) (ESC)
  - Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and no identifiable risk factor. (IIa,A(2019) ←IIaB (2014)
  - Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a persistent risk factor other than APS. (class IIa, level C)
  - Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE associated with a minor transient or reversible risk factor. (class IIa, level C)

Anticoagulation (ERS 2019)

- Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with recurrent VTE (that is, with at least one previous episode of PE or DVT) not related to a major transient or reversible risk factor. (I,B)

- Oral anticoagulant treatment with a VKA for an indefinite period is recommended for patients with the antiphospholipid antibody syndrome (I, B)

- Follow-up: It is recommended to reassess drug tolerance and adherence, hepatic and renal function, and the bleeding risk at regular intervals.(Same I,C ← I,C)

APS에 대하여

Rivaroxaban vs warfarin in high-risk patients with APS

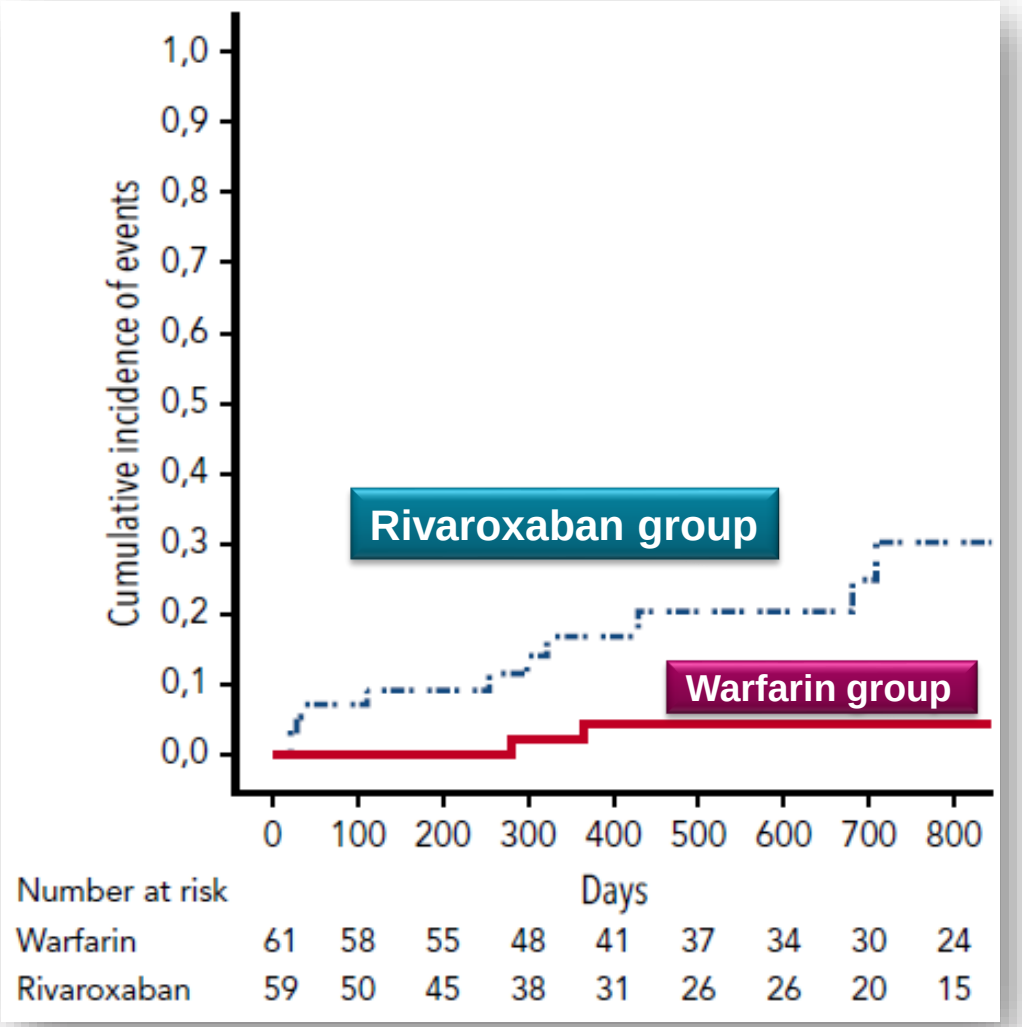
Outcome, n	"As treated" analysis				ITT analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01	13 (22)	2 (3)	7.4 (1.7-32.9)	.008
Arterial thrombosis	7 (12)	0	—	—	7 (12)	0	—	—
Ischemic stroke	4 (7)	0			4 (7)	0		
Myocardial infarction	3 (5)	0			3 (5)	0		
Venous thromboembolism	0	0			1 (2)	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3	4 (7)	2 (3)	2.3 (0.4-12.5)	.3
Death	0	0	—	—	1 (2)	0	—	—

HR 7.4 (1.7-32.9)

Early termination due to increased thrombotic and bleeding events in rivaroxaban group

1. Pengo et al. Blood. 2018;132(13):1365-1371

Rivaroxaban vs warfarin in high-risk patients with APS



Early termination due to increased thrombotic and bleeding events in rivaroxaban group

1. Pengo et al. Blood. 2018;132(13):1365-1371

APS-related VTE vs non-APS VTE in HIRA

국내연구 (24명 vs 44명, 서울아산)

- Age (39.7± 18.4 vs 60.4 ±14.0)
- OR 0.93; 95% CI 0.893-0.969)

Piette and Cacoub

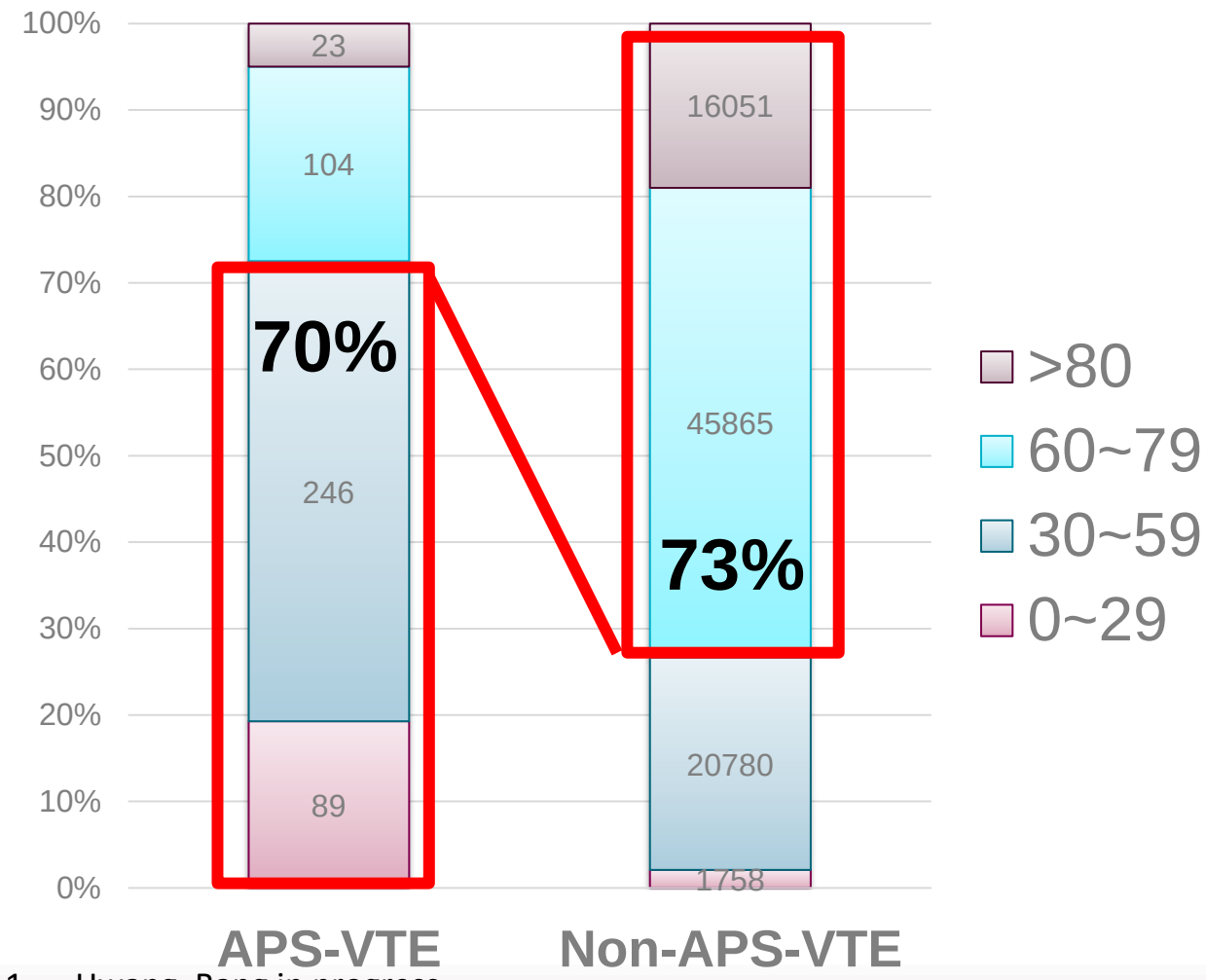
- < 50에서 first thrombosis발생

Anderson and Spencer

- >40에서 VTE risk증가

1. Na et all Turberc Respir Dis 2019
2. Piette Circulation 1998;97(22):2195-6

APS-related VTE vs non-APS VTE in HIRA



	APS-VTE on DOACs	APS-VTE On warfarin
VTE		
Arterial thrombosis		
Major bleeding		

1. Hwang, Bang in progress
2. Na et all Turberc Respir Dis 2019
3. Piette Circulation 1998;97(22):2195-6

Cancer screening in unprovoked VTE patients

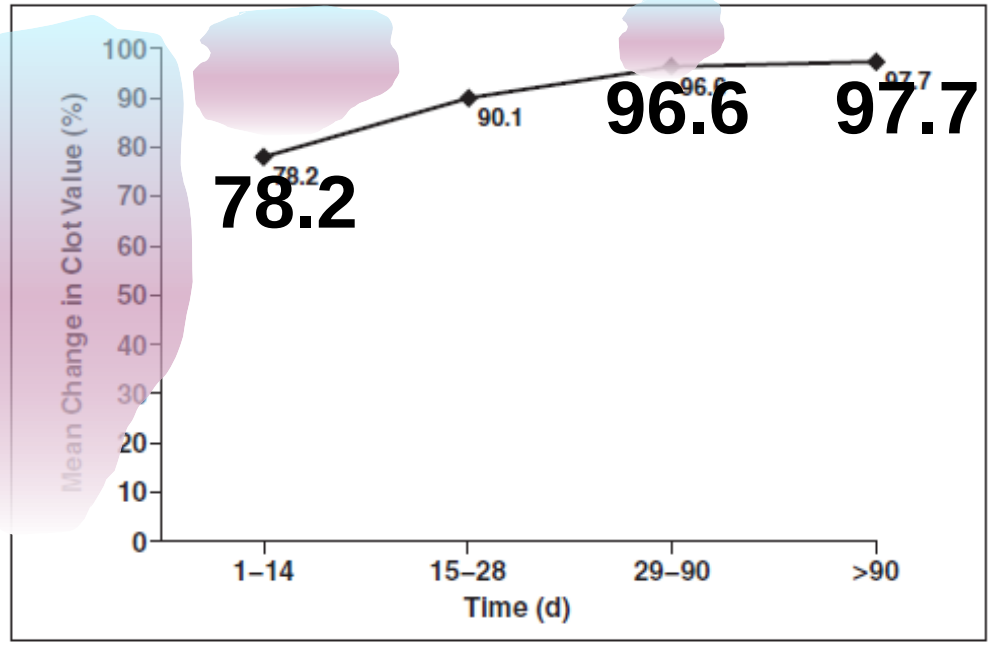
	Trousseau N=630	SOME N=854	D'Acquapendente N=195	MVTEP N=399
Method	Center-specific	randomized	randomized	Randomized
Extensive = limited screening +@	Basic blood test and X-ray + **CT chest/abdomen, mammography**	Basic blood test and X-ray **and mammography/ Pap semar/PSA** + **CT abdomen/pelvis**	Basic blood test, X-ray, **investigations by patients' signs and symptoms** + **CT chest/abdomen/pelvis**	Basic blood tests, chest X-ray and **mammography/ Pap semar/PSA** + **PET scan**
Extensive vs **limited** (no)	342 vs. 288	423 vs. 431	98 vs. 97	197 vs 197
Cancer detection at baseline (%)	3.5 ≈ 2.5	3.3 ≈ 2.3	10.2 ≈ 8.2	8.2 ≈ 5.6
New cancer at follow-up (%)	3.7 ≈ 5.3	1.2 ≈ 0.9	2.0 ≈ 2.1	0.5 < 4.7
Overall mortality	No difference	No difference	No difference	No difference

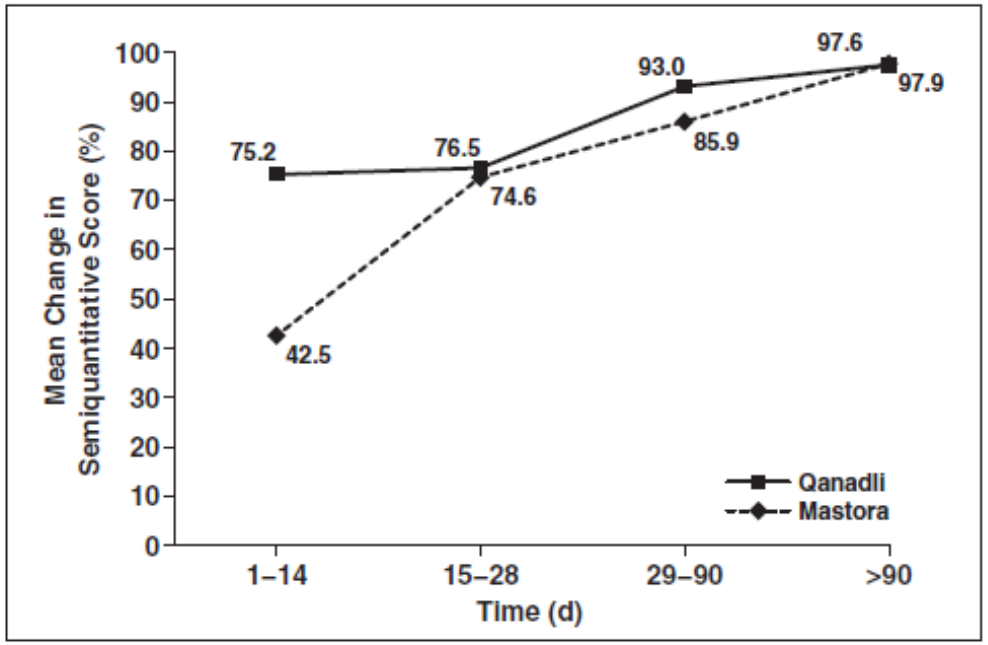
1. Van Doormaal J Thromb Haemost 2011;9:79-84
2. Carrier NEJM 2015;373:697-704
3. Prandoni Semin Thromb Hemost 2016;42:884-890
4. Robin Lancet Oncol 2016;17:193-199

Timing of operation in patients with acute PE

외상이나 암수술을 앞둔 환자가 수술을 시행하기도 전에 이미 혈전이 발생한다면 수술전에 얼마동안 혈전을 치료하고 수술을 시행할 것인가?

The rate of resolution of clot burden measured by pulmonary CT angiography





	1-14 days	29-90 days	After 90 days
Complete resolution	56.7%	77.4%	94.1%
Total clot volume	**Decreased by** 78%	96.6% at 90 days	97.7% after 90 days

Aghayes et al. Am J Roentgenol 2019

Take home message

Take-Home message

- 한국의 혈전은 지속적으로 증가해왔고, 고령화 시대에 더 증가할 것으로 예상된다.
- 수술환자 6주에 VTE위험도는 RR 69.1배, OS major surger후 220배, 암수술후91배증가한다.
- Hemodynamic compromise(5-10%)경우 mortality 35-58%증가하며 Thrombolysis적응증이다.
- Therapeutic anticoagulation 적어도3개월요법 (Class I, Level A) (ERS 2019)
- Home treatment in patient with low-risk PE (Class II a, Level A) (ERS 2019)
- Major, minor, persistent, & transient, ERS) vs (Provoked vs Unprovoked, ASH)

경청해 주셔서 감사합니다.