Parenteral anticoagulation and thrombolytic agent for the treatment of VTE

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VTE

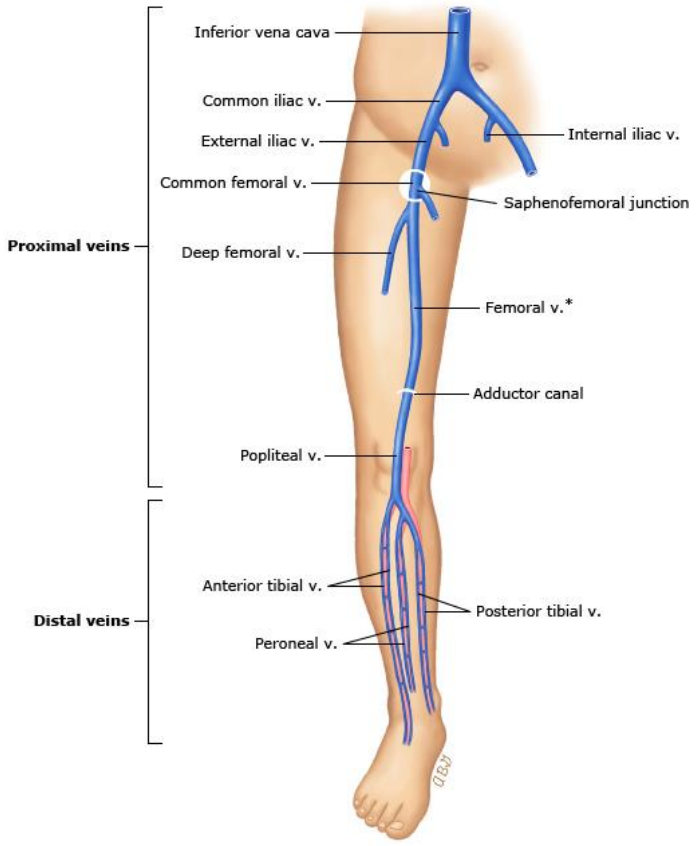
- Blood clots in the veins, also known as venous thromboembolism (VTE), are a serious medical condition that can cause disability and even death.
- Venous blood clots most often form in the deep veins of the leg, a condition referred to as **deep-vein thrombosis (DVT).**
- DVT can become life-threatening if the clot breaks free and becomes lodged in the arteries of the lung, which is called a **pulmonary embolism (PE).**

- **Prevalence**
  - US: 142-300 per 100,000 person-years (~33% recurrence within 10 years)
  - Korea: 53.7 per 100,000 person-years (21.5% recurrence with a 5 year cumulative incidence)

Nat Rev Cardiol. 2015 Jun 16;12(8):464–474.
Tuberculosis and Respiratory Diseases 2019; 82(4): 341-347.

Terminology

Deep veins of the lower extremity

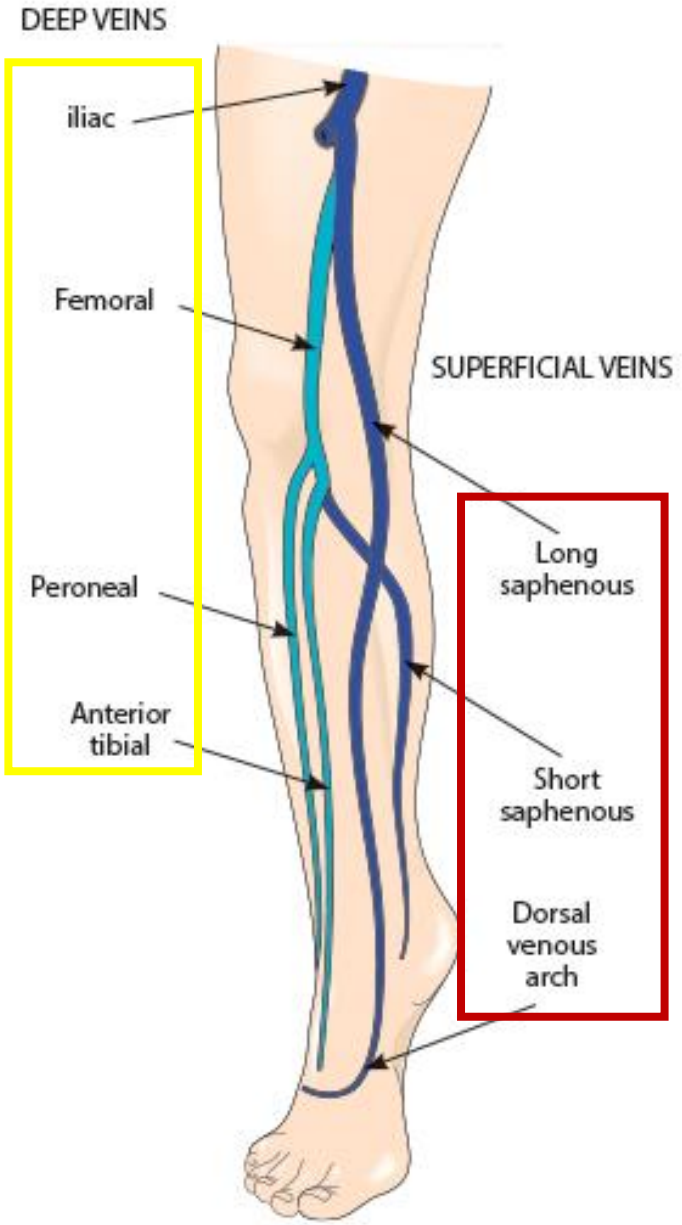


Deep veins of the right lower extremity. The paired tibial veins (anterior tibial, peroneal, and posterior tibial) are shown with their adjacent arteries. The bridging veins between the paired veins are also demonstrated. The popliteal and femoral veins are also sometimes duplicated (omitted from the diagram) with one of the duplicated segments frequently larger in caliber than the other.

v: vein.

* The femoral v. has been referred to in the past as the superficial femoral vein, which is a misnomer since it is a deep vein.

- **Proximal DVT** – A proximal DVT is located in the popliteal, femoral, or iliac veins; or the inferior vena cava
- **Distal DVT** –located below the knee, and is confined to the calf veins (peroneal, posterior, anterior tibial, and muscular veins). The popliteal vein is **not** involved.
- **Superficial DVT**
- **Deep DVT**



VTE guidelines

American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism

Blood Adv. 2020 Oct 2;4(19):4693–4738

[Pulmonary Vascular Special Features]

CHEST

Antithrombotic Therapy for VTE Disease

Compendium and Review of CHEST Guidelines 2012-2021

Check for updates

CHEST 2024; 166(2):388-404

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Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

NICE guideline | NG158 | Published: 26 March 2020 | Last updated: 02 August 2023

NICE NG158; 2023 update

ASH 2020 guideline - Summary

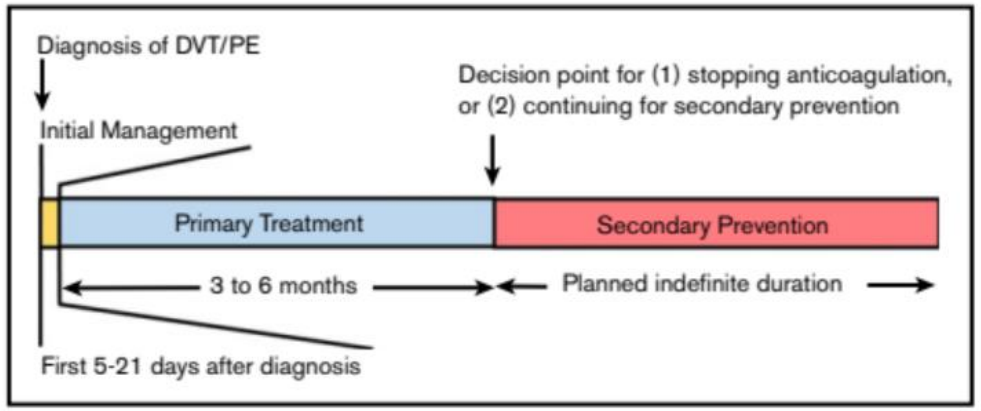

Figure 1. Time frame of the decisions. Initial management (yellow box) spans the first 5 to 21 days following diagnosis of a new VTE and includes issues concerning whether the patient can be treated at home or requires admission to the hospital, use of thrombolytic therapy, whether an IVC filter needs to be placed, and initial anticoagulant therapy. Primary treatment continues anticoagulant therapy for 3 to 6 months total and represents the minimal duration of treatment for the VTE. After completion of primary treatment, the next decision concerns whether anticoagulant therapy will be discontinued or if it will be continued for secondary prevention of recurrent VTE. Typically, secondary prevention is continued indefinitely, although patients should be reevaluated on a regular basis to review the benefits and risks of continued anticoagulant therapy. Our choice of terminology reflects the distinct clinical intentions of the different phases of VTE management, linking them to important clinical decisions addressed in the guidelines, rather than using terms reflecting the relative duration of therapy.

1. 치료 단계 구분
    1. Initial management: 첫 5-21일
    2. 1차 치료 (Primary treatment): 최소 3개월
    3. 2차 예방 (Secondary prevention): 무기한 또는 장기 치료 여부 결정

2. 항응고제 선택

- 대부분 DOAC > VKA

3. 치료 기간

4. 재발 위험

ASH guideline

Recommendation	Remarks
1. Uncomlicated 심부정맥혈전증(DVT) 환자에게는 → 입원 치료보다 가정 치료를 제공하는 것을 제안함 (조건부 권고, 근거 수준: 낮음)	
2. 합병증 위험이 낮은 폐색전증(PE) 환자에게는 입원 치료보다 가정 치료(home treatment)를 제안 (조건부 권고, 근거 수준 매우 낮음)	- PESI, sPESI 등 임상 예측 점수는 유용하지만, 임상 판단을 대체할 수 없음 - 입원 필요 상태(지원 부족, 약 복용 어려움, 출혈 위험, IV 진통 필요 등)는 예외
3. DVT 또는 PE 환자에서 비타민 K 길항제(VKA)보다 DOAC 사용을 제안 (조건부 권고, 근거 수준 보통)	신기능 저하(CrCl <30), 간질환, 항인지질항체증후군 환자에게는 적용되지 않을 수 있음
6. 저혈압 동반 PE 환자에게는 항응고제 단독보다 thrombolysis + 항응고제를 권장 (강한 권고, 근거는 낮음)	
7. Submassive PE(RV 기능 이상 있으나 저혈압 없음) 환자에게는 thrombolysis 병용보다는 항응고제 단독을 제안 (조건부 권고, 낮은 근거 수준)	
8. 광범위 DVT 환자 중 thrombolysis 고려되는 경우, 전신 thrombolysis보다 카테터 유도 thrombolysis를 제안 (조건부 권고, 근거 매우 낮음)	
9. PE 환자에서 thrombolysis 적응증이 있는 경우, 카테터 유도보다는 systemic thrombolysis를 제안 (조건부 권고, 매우 낮은 근거)	
12. **일과성 주요 유발요인(major transient risk factor)**에 의해 유발된 VTE 환자에게는 → 연장기 항응고 치료를 권장하지 않음 (강한 권고, 근거 중간)	
13. **경미한 일과성 유발요인(minor transient risk factor)**에 의해 유발된 VTE 환자에게는 → 연장기 항응고 치료를 제안하지 않음 (약한 권고, 근거 중간)	대부분의 일과성 요인 유발 DVT/PE 환자는 3~6개월 후 치료 종료 가능 비유발성 또는 만성 위험요인 동반 환자는 무기한 치료를 고려 연장 치료가 필요한 경우에는 6~12개월 이상 치료도 정당화될 수 있음
14. **비유발성 VTE 또는 지속성 유발요인(예: 항인지질항체증후군, 암)**에 의한 VTE 환자에게는 → DOAC을 이용한 연장기 치료를 권장 (강한 권고, 근거 중간)	

ASH guideline

Recommendation	Remarks
15. 유발성 DVT/PE 환자에게 **예후 예측 검사를 루틴으로 시행하는 것(예: D-dimer)**은 → 권장하지 않음 (조건부 권고, 근거 낮음)	
16. 예후 예측 목적으로 영상으로 잔여 혈전을 확인하는 것은 → 권장하지 않음 (조건부 권고, 근거 낮음)	
17. 예후 예측 검사(생체표지자 등) 결과에 따라 항응고 치료 연장 여부 결정 제안 (조건부 권고, 근거 낮음)	
18. **만성 위험요인(chronic provoking factor)**에 의해 유발된 DVT/PE 환자에서 → 1차 치료(primary treatment) 종료 후에도 무기한 항응고 치료를 권장 (조건부 권고, 근거 중간)	일과성 요인에 의한 VTE는 보통 무기한 치료 필요 없음 그러나 만성 위험요인(예: 활동성 암, 항인지질항체증후군 등)은 지속 치료 필요 출혈 위험 높은 환자는 제외
19. 비유발성 DVT/PE 환자에게도 → 무기한 항응고 치료를 권장 (조건부 권고, 근거 중간)	이 권고는 출혈 위험이 높지 않은 환자에게만 적용 항응고제 중단 여부는 환자 선호, 출혈 위험, 재발 위험 등을 종합 고려해야 함
22. 1차 치료 후 DOAC으로 2차 예방을 계속하는 환자에게는 → 표준 용량 또는 감량 DOAC 사용을 제안 (조건부 권고, 근거 중간)	감량 용량 예시: rivaroxaban 10mg/day, apixaban 2.5mg bid
23. VKA 치료 중 재발성 DVT/PE 발생한 경우, → LMWH로 변경을 제안 (조건부 권고, 근거 매우 낮음)	INR 조절이 잘 되었는지 확인 필요 재발 원인 평가 필수 (기저 질환, 악성 질환 등)
24a. 일과성 위험요인 + 과거 재발 경험이 있는 환자, 또는 비유발성 또는 지속 유발요인에 의한 VTE 환자에게는 → 무기한 항응고 치료를 제안 (조건부 권고, 근거 중간)	
24b. 과거 VTE 병력이 있는 환자에서 이번 VTE가 일과성 요인에 의해 유발된 경우, → 1차 치료 후 항응고 종료를 제안 (조건부 권고, 근거 중간)	
25. 재발성 비유발성 DVT/PE 환자에게는 → 1차 치료 후 무기한 항응고 치료를 권장 (강한 권고, 근거 중간)	

23. VKA 치료 중 재발성 DVT/PE 발생한 경우, → LMWH로 변경을 제안 (조건부 권고, 근거 매우 낮음)

Chest guideline

Question	Statement
1. Isolated Distal DVT를 치료해야 하는가?	
2. Isolated subsegmental PE는 치료해야 하는가?	Proximal PE 없이 subsegmental PE만 존재하고, 다리의 proximal DVT도 없음 (i) 재발 VTE 위험이 낮은 경우 → 항응고제보다는 임상적 감시 권장 (약한 권고, 낮은 근거) (ii) 재발 VTE 위험이 높은 경우 → 감시보다는 항응고제 권장 (약한 권고, 낮은 근거)
3. Incidentally 발견된 PE는 치료해야 하는가?	증상 있는 PE 환자와 동일하게 초기 및 장기 항응고 치료를 권장 (약한 권고, 중간 근거)
4. 급성 VTE가 의심되는 환자에서 진단 검사 전 경험적 치료를 시작해야 하는가?	1) 임상적으로 급성 VTE 가능성이 높은 환자: ➤ 진단 검사 결과를 기다리는 동안 정맥투여 항응고제 치료 시작 권장 (약한 권고, 낮은 근거) 2) 중간 정도의 VTE 가능성 있고, 진단 결과가 4시간 이상 지연될 경우: ➤ 정맥투여 항응고제 사용을 권장 (약한 권고, 낮은 근거) 3) VTE 가능성이 낮고, 진단 검사 결과가 24시간 내에 나올 것으로 예상되는 경우:

1) **저혈압(수축기 혈압 <90mmHg)**이 있는 급성 PE 환자 중 출혈 위험이 높지 않은 경우, ➤ 전신 투여 혈전용해제 사용을 권장 (약한 권고, 낮은 근거)
2) 혈전용해제를 사용할 급성 PE 환자에게는, ➤ 카테터 유도 혈전용해술보다는 정맥(말초정맥)을 통한 전신 혈전용해제를 권장 (약한 권고, 낮은 근거)
3) 저혈압 동반 PE 환자 중 다음에 해당하는 경우, ➤ 카테터 유도 혈전 제거술을 권장 (약한 권고, 낮은 근거)
- 출혈 위험이 높음
- 전신 혈전용해제 실패
- 쇼크로 수 시간 내 사망 위험 있음
- 그리고 전문 인력과 장비가 구비된 경우,

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Question	Statement
7. IVC 필터 삽입 여부	1) 항응고 치료가 가능한 **급성 DVT 또는 PE 환자**에서는 ➤ **항응고제 + IVC 필터 삽입을 하지 않도록 권장** (강한 권고, 중간 근거) **2) 항응고제 사용이 금기인** 급성 근위부 DVT 또는 PE 환자에게는 ➤ **IVC 필터 사용을 권장** (강한 권고, 중간 근거) 3) 항응고 치료 대신 **IVC 필터를 삽입했던 환자**에서 출혈 위험이 사라졌다면, ➤ **표준적인 항응고 치료를 시작할 것을 권장** (약한 권고, 중간 근거)
11. 치료기 항응고제로 어떤 약제를 사용할 것인가?	➤ **VKA(와파린 등)**보다는 **DOAC (apixaban, dabigatran, edoxaban, rivaroxaban)** 사용을 권장 (강한 권고, 중간 근거) **2) 암 관련 혈전증(CAT: cancer-associated thrombosis)** 환자에서는 ➤ **LMWH(저분자량 헤파린)**보다는 **경구용 Factor Xa 억제제 (apixaban, edoxaban, rivaroxaban)** 사용을 권장 (강한 권고, 중간 근거)
12-13. Extended-phase Anticoagulation 여부/약제/용량	**비유발성 VTE 또는 지속성 유발요인 존재 시,** DOAC을 이용한 연장기 치료 권장 암 관련 VTE (CAT), 무기한 치료 권장 DOAC 사용 불가 시 VKA 권장
14. **족부 압박 스타킹 (Graduated Compression Stockings)**	

1) **VKA(와파린 등)**으로 치료받는 급성 VTE 환자는
➤ 반드시 초기에는 정맥투여 항응고제 (LMWH, fondaparinux, IV UFH 또는 SC UFH) 병용 (강한 권고, 중간 근거)
2) 초기 항응고제를 사용하는 환자에서:
➤ LMWH 또는 fondaparinux > IV UFH, SC UFH (모두 약한 권고)
3) VKA를 사용하는 경우:
➤ VKA는 초기 항응고제 시작과 동시에 투여 시작,
➤ 최소 5일 이상 병용, INR ≥ 2.0을 24시간 이상 유지될 때까지 병용 유지 (강한 권고, 중간 근거)

CTEPH 환자에게 항응고 치료를 중단하기보다는 연장할 것을 권장 (강한 권고, 근거 중간), DOAC vs VKA 논란 있으며, 일부 자

16. Choice and Dose of Therapy for 표재정맥혈전증(Superficial Venous Thrombosis:)

1) DVT/PE로 진행 위험이 있는 하지 SVT 환자에게 45일간 항응고 치료 제안
2) 항응고 치료 시 fondaparinux 2.5 mg/day > LMWH (약한 권고, 근거 낮음)
3) 주사제 사용 불가능한 경우, rivaroxaban 10 mg/day 대안으로 제안 (약한

Chest guideline

Question	Statement
17. 상지 DVT의 Management	1) axillary 이상 혈관 침범 시 **항응고 단독 > thrombolysis** 제안 (약한 권고, 근거 낮음) 2) thrombolysis 시행한 환자도 **동일한 강도/기간의 항응고 치료 필요 (**강한 권고, 근거 중간) 3) axillary 이상 침범한 UEDVT는 **최소 3개월 이상 치료 제안 (**약한 권고, 근거 낮음) 4) 중심정맥관 제거한 경우, 3개월 치료 제안. 5) 중심정맥관 유지 중인 경우, **항응고 치료 지속 제안**
18. 뇌정맥(정맥동) 혈전증의 Management	뇌정맥 혈전증 환자에게 **최소 3개월 항응고 치료 권장 (강한 권고, 근거 낮음)**
19. 복부정맥혈전증 (Splanchnic vein thrombosis)의 Management	1) 증상 있는 복부정맥혈전증 환자: **항응고 치료 > 무치료 (강한 권고, 근거 중간) – 문맥, 장간막, 비장정맥 포함** 2) 우연히 발견된 복부정맥혈전증: **무치료 > 항응고 치료 제안 (약한 반대 권고, 근거 낮음)** 3) 증상 있는 간정맥 혈전증: **항응고 치료 제안 (약한 권고, 근거 낮음)**
20. 항인지질항체증후군(APS)	DOAC보다 VKA(INR 2.5 목표) 사용을 제안 (약한 권고, 근거 낮음): triple positive 환자에서는 DOAC 효과↓

Guideline 비교 (thrombolysis, parenteral anticoagulation)

ASH guideline	Chest guideline
1. 저혈압 동반 PE 환자에게는 항응고제 단독보다 thrombolysis + 항응고제를 권장 (강한 권고, 근거는 낮음) - PE 환자에서 thrombolysis 적응증이 있는 경우, **카테터 유도보다는 systemic thrombolysis**를 제안 (조건부 권고, 매우 낮은 근거)	1. 급성 PE 환자 중, 1) ****저혈압(수축기 혈압 <90mmHg)**이 있는 급성 PE 환자 중 출혈 위험이 높지 않은 경우, ➤ 전신 투여 혈전용해제 사용을 권장** (약한 권고, 낮은 근거) **2) 혈전용해제를 사용할 급성 PE 환자에게는, ➤ 카테터 유도 혈전용해술보다는 정맥(말초정맥)을 통한 전신 혈전용해제를 권장** (약한 권고, 낮은 근거)
2. **광범위 DVT 환자 중 thrombolysis 고려되는 경우,** 전신 thrombolysis보다 **카테터 유도 thrombolysis를 제안** (조건부 권고, 근거 매우 낮음)	2. **VKA(와파린 등)**으로 치료받는 급성 VTE 환자는 ➤ 반드시 초기에는 **정맥투여 항응고제 (LMWH, fondaparinux, IV UFH 또는 SC UFH)** 병용 (강한 권고, 중간 근거) - 초기 항응고제를 사용하는 환자에서: ➤ **LMWH 또는 fondaparinux > IV UFH, SC UFH** (모두 약한 권고)
3. VKA **치료 중 재발성 DVT/PE 발생한 경우, → LMWH로 변경**을 제안 (조건부 권고, 근거 매우 낮음)	3. DVT/PE로 진행 위험이 있는 하지 SVT 환자에게 **45일간 항응고 치료 제안** 1) 항응고 치료 시 **fondaparinux 2.5 mg/day > LMWH (약한 권고, 근거 낮음)** **2) 주사제 사용 불가능한 경우, rivaroxaban 10 mg/day 대안으로 제안 (약한 권고, 근거 낮음)**

Thrombolysis

1. 저혈압 동반된 PE 환자

- Summary of the evidence
  - 29 systemic review, 26 RCTc (n=2787), without hemodynamic compromise with RV dysfunction
  - Systemic thrombolysis except 1 catheter directed thrombolysis

- Benefits (thrombolytics)

Benefits	Relative risk (RR)	Absolute relative risk (ARR)	Evidence level
Reduced mortality	RR 0.61 (CI 0.40–0.94)	1,000명당 58명 감소 (CI 9–90명)	낮음
Reduced the risk of subsequent PE	RR 0.56 (CI 0.35–0.91)	1,000명당 7명 감소 (CI 2–10명)	매우 낮음
Reduced the risk of DVT	RR 0.92 (CI 0.14–6.03)	효과 불확실 (CI −8 ~ +46명)	매우 낮음

- Harm

Side effects	Relative risk (RR)	Absolute relative risk (ARR)	Evidence level
Major bleeding	RR 1.89 (CI 1.46–2.46)	1,000명당 31명 증가 (CI 16–51명)	높음
Intracranial hemorrhage	RR 3.17 (CI 1.19–8.41)	1,000명당 7명 증가 (CI 1–21명)	중간

- Conclusion
  - Low mortality > bleeding risk
  - 혈역학적 불안정 상태에서는 생명 구명 효과로 인해 비용 효과성도 높을 것으로 예상됨
  - thrombolysis는 현실적으로 대부분의 임상 상황에서 시행 가능함

Thrombolysis (PE)

- 저혈압(수축기 혈압 <90mmHg)을 동반한 급성 PE 환자 중 출혈 위험이 높지 않은 경우

- 항응고 치료를 시작한 이후 임상적으로 악화되는 급성 PE 환자(아직 저혈압은 없음)에서 → 출혈 위험이 허용 가능한 경우
  - SBP, HR, distal perfusion, RV function, cardiac marker monitor

- 혈전용해제를 사용하는 PE 환자는 → 카테터 유도 치료보다는 전신 정맥투여 방식을 제안

- 저혈압 동반 PE 환자 중, bleeding risk가 높거나, systemic thrombolysis 실패, 수 시간 내 사망 예상될 때는 카테터 혈전 제거술 제안

Whether to use interventional therapy in acute PE	6	**In patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy** (Weak Recommendation, Low-Certainty Evidence).[a]
	6.1	**In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy** (Strong Recommendation, Low-Certainty Evidence).[d]
	6.2	**In selected patients with acute PE who deteriorate (see text[4]) after starting anticoagulant therapy but have yet to develop hypotension and who have an acceptable bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy** (Weak Recommendation, Low-Certainty Evidence).[a]
	6.3	**In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over catheter-directed thrombolysis** (Weak Recommendation, Low-Certainty Evidence).[a]
	6.4	**In patients with acute PE associated with hypotension who also have (i) a high bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention** (Weak Recommendation, Low-Certainty Evidence).[a]

CHEST 2024; 166(2):388-404

Thrombolysis (PE)

- NICE guideline 2020 [Aug 2023 updated]
  - Consider pharmacological systemic thrombolytic therapy for people with PE and haemodynamic instability
  - Do not offer pharmacological systemic thrombolytic therapy to people with PE and haemodynamic stability with or without right ventricular dysfunction (see also the section on anticoagulation treatment for DVT or PE). If the person develops haemodynamic instability, Consider pharmacological systemic thrombolytic therapy
  - For people with confirmed PE and haemodynamic instability, offer continuous UFH infusion and consider thrombolytic therapy (see the section on thrombolytic therapy).

Risk stratification

Pulmonary embolism classification and risk stratification

Early mortality risk		Indicators of risk			
		Haemodynamic instability*	Clinical parameters of PE severity and/or comorbidty: PESI class III-V or sPESI ≥1	RV dysfunction on TTE or CTPA	Elevated cardiac troponin levels¶
High△		+	(+)◇	+	(+)
Intermediate§	Intermediate-high	–	+¥	+	+
	Intermediate-low	–	+¥	One (or none) positive	
Low		–	–	–	Assesment optional; if assessed, negative

From: Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019; 54(3):1901647. doi: 10.1183/13993003.01647-2019. Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Pulmonary-Embolism-Diagnosis-and-Management-of.

High-risk PE = Massive PE (one of the following clinical presentations)

- Cardiac arrest
- Obstructive shock (systolic BP <90mmHg or vasopressors required to achieve a BP > 90mmHg)
- Persistent hypotension (SBP <90 or SBP drop >=40 for > 15분, not caused by arrhythmia, hyp9ovolemia, or sepsis)

Pulmonary Embolism Severity Index

Table 7 Original and simplified Pulmonary Embolism Severity Index

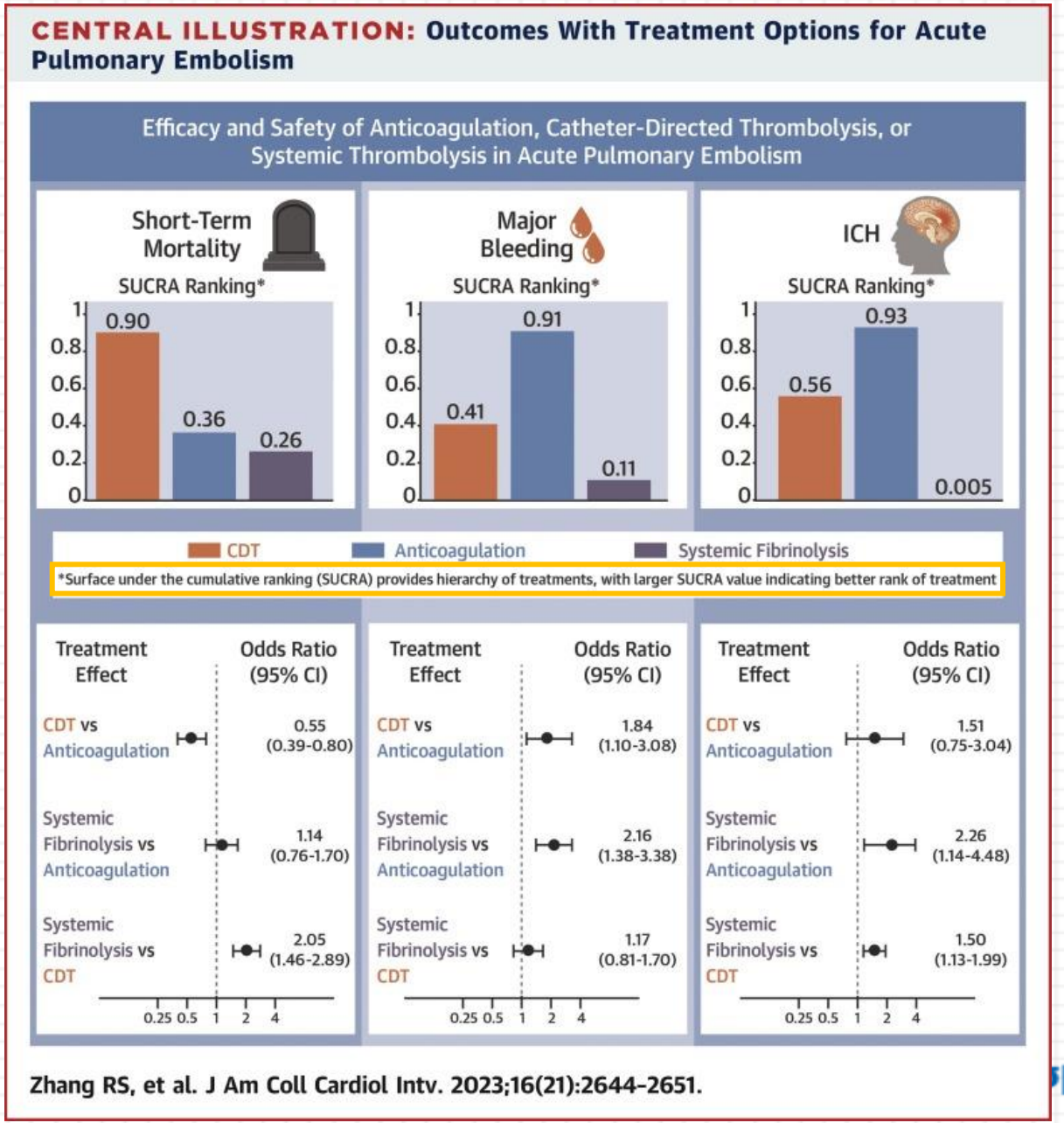
Parameter	Original version[226]	Simplified version[229]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic BP <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths per min	+20 points	–
Temperature <36°C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point

Risk strata[a]	
Class I: ≤65 points very low 30 day mortality risk (0–1.6%)	**0 points** = 30 day mortality risk 1.0% (95% CI 0.0–2.1%)
Class II: 66–85 points low mortality risk (1.7–3.5%)	
Class III: 86–105 points moderate mortality risk (3.2–7.1%)	**≥1 point(s)** = 30 day mortality risk 10.9% (95% CI 8.5–13.2%)
Class IV: 106–125 points high mortality risk (4.0–11.4%)	
Class V: >125 points very high mortality risk (10.0–24.5%)	

Thrombolysis (PE)

	ASH VTE Guideline (미국 혈액학회, 2020)	CHEST Guideline Compendium (2021, 2024 업데이트)	NICE NG158 (영국, 2020 개정)
	1차 권고 (Systemic thrombolysis): hemodynamic instability 시		
	- **hemodynamic compromise PE** - **T**hrombolytic therapy + 항응고제 - **Systemic thrombolysis** > CDT	- **Systemic thrombolysis** > CDT	- **Systemic thrombolysis** > CDT
Catheter-directed thrombolysis	- 전신 투여가 어렵거나 출혈 위험이 중간 이상인 환자 - 시술 경험・인프라가 갖춰진 센터에서 대안으로 고려 가능	(i) 고위험 출혈 (ii) 전신 thrombolysis 실패 (iii) 전신 투여 약효가 나타나기 전 쇼크로 사망 위험 등 특별 상황에서 고려 가능	언급 없음

CDT vs systemic fibrinolysis vs Anticoagulation



- Meta-analysis (45 study, N=81,705)
  - 무작위 대조 시험(RCT): 17편
  - 전향적 비무작위 연구: 2편
  - 후향적 관찰 연구: 26편

  - Anticoagulation alone (N=19,976)
  - Catheter directed thrombolysis (N=9,610)
  - Systemic fibrinolysis (N=52,119)

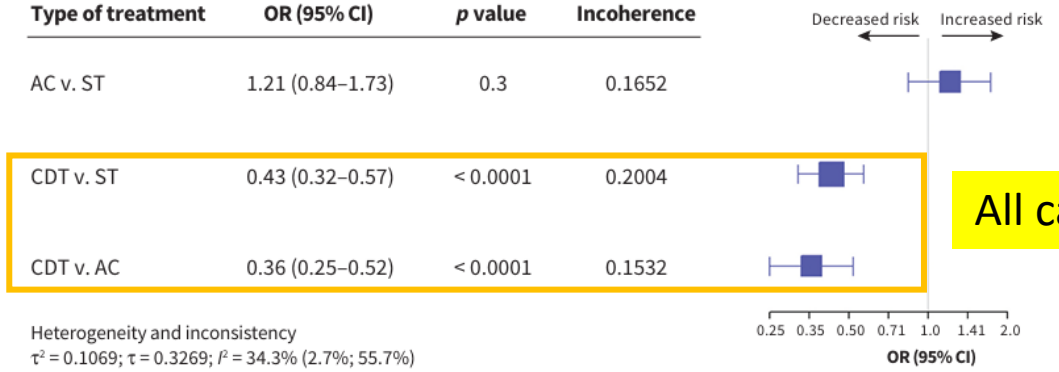
  - Mortality 감소 측면: CDT > 항응고 > systemic fibrinolysis
  - Major bleeding 안전성: 항응고 > CDT > systemic fibrinolysis
  - ICH 안전성: 항응고 > CDT > systemic fibrinolysis

J Am Coll Cardiol Intv. 2023;16(21):2652–4.

CDT vs systemic fibrinolysis vs Anticoagulation (PE)

Catheter-directed thrombolysis compared with systemic thrombolysis and anticoagulation in patients with intermediate- or high-risk pulmonary embolism: systematic review and network meta-analysis

David Planer MD MSc, Stav Yanko PharmD, Ilan Matok PhD, Ora Paltiel MDCM MSc, Rama Zmiro PharmD, Victoria Rotshild PharmD PhD, Offer Amir MD, Gabby Elbaz-Greener MD MHA, Bruria Hirsh Raccah PharmD PhD

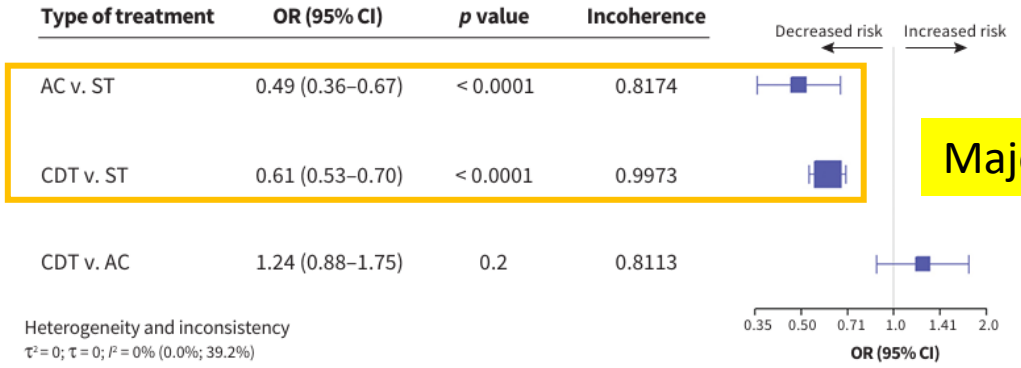


Type of treatment	OR (95% CI)	*p* value	Incoherence
AC v. ST	1.21 (0.84–1.73)	0.3	0.1652
CDT v. ST	0.43 (0.32–0.57)	< 0.0001	0.2004
CDT v. AC	0.36 (0.25–0.52)	< 0.0001	0.1532

Heterogeneity and inconsistency
$\tau^2 = 0.1069$; $\tau = 0.3269$; $I^2 = 34.3\%$ (2.7%; 55.7%)

All cause death

Figure 3: Network meta-analysis of the association between treatment for pulmonary embolism and all-cause death. Size of squares is proportional to the weight of each arm. Decreased or increased risk of the outcome is of the first type of treatment in comparison, relative to the second type of treatment. The *p* value indicates the probability of observing the differences between direct and indirect treatment effects. The presence of incoherence is indicated by a *p* value less than 0.05. Note: AC = anticoagulation, CDT = catheter-directed thrombolysis, CI = confidence interval, OR = odds ratio, ST = systemic thrombolysis.



Type of treatment	OR (95% CI)	*p* value	Incoherence
AC v. ST	0.49 (0.36–0.67)	< 0.0001	0.8174
CDT v. ST	0.61 (0.53–0.70)	< 0.0001	0.9973
CDT v. AC	1.24 (0.88–1.75)	0.2	0.8113

Heterogeneity and inconsistency
$\tau^2 = 0$; $\tau = 0$; $I^2 = 0\%$ (0.0%; 39.2%)

Major bleeding

Figure 4: Network meta-analysis of the association between treatment for pulmonary embolism and major bleeding. Size of squares is proportional to the weight of each arm. Decreased or increased risk of the outcome is of the first type of treatment in comparison, relative to the second type of treatment. The *p* value indicates the probability of observing the differences between direct and indirect treatment effects. The presence of incoherence is indicated by a *p* value less than 0.05. Note: AC = anticoagulation, CDT = catheter-directed thrombolysis, CI = confidence interval, OR = odds ratio, ST = systemic thrombolysis.

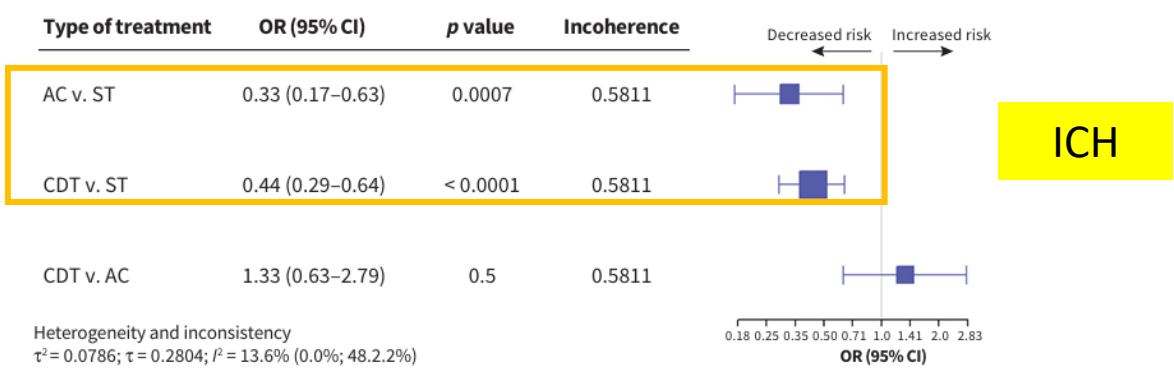
- Meta-analysis (44 study, N=20,006)
  - 무작위 대조 시험(RCT): 19편
  - 관찰 연구: 25편

- Anticoagulation alone (N=19,976)
- Catheter directed thrombolysis (N=9,610)
- Systemic fibrinolysis (N=52,119)

- Mortality 감소 : CDT > 항응고, systemic fibrinolysis
- Major bleeding 위험: systemic fibrinolysis > CDT

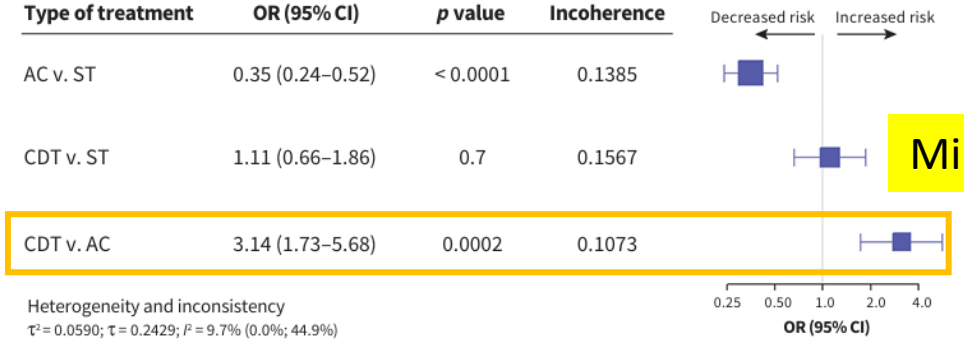
CMAJ 2023 June 19;195:E833-43.

CDT vs systemic fibrinolysis vs Anticoagulation (PE)



ICH

Figure 5: Network meta-analysis of the association between treatment for pulmonary embolism and intracranial hemorrhage. Size of squares is proportional to the weight of each arm. Decreased or increased risk of the outcome is of the first type of treatment in comparison, relative to the second type of treatment. The *p* value indicates the probability of observing the differences between direct and indirect treatment effects. The presence of incoherence is indicated by a *p* value less than 0.05. Note: AC = anticoagulation, CDT = catheter-directed thrombolysis, CI = confidence interval, OR = odds ratio, ST = systemic thrombolysis.



Minor bleeding

Figure 6: Network meta-analysis of the association between treatment for pulmonary embolism and minor bleeding. Size of squares is proportional to the weight of each arm. Decreased or increased risk of the outcome is of the first type of treatment in comparison, relative to the second type of treatment. The *p* value indicates the probability of observing the differences between direct and indirect treatment effects. The presence of incoherence is indicated by a *p* value less than 0.05. Note: AC = anticoagulation, CDT = catheter-directed thrombolysis, CI = confidence interval, OR = odds ratio, ST = systemic thrombolysis.

- ICH 위험: systemic fibrinolysis > CDT
- Minor bleeding: CDT > 항응고

- **Conclusion:**

가이드라인에서는 저혈압이 동반된 경우 thrombolysis를 권고하고 있으나 CDT 또는 systemic thrombolysis 등 방법에 대해서는 추가적인 RCT가 필요한 상태. CDT의 경우 실제 시행되는 경우가 적음.

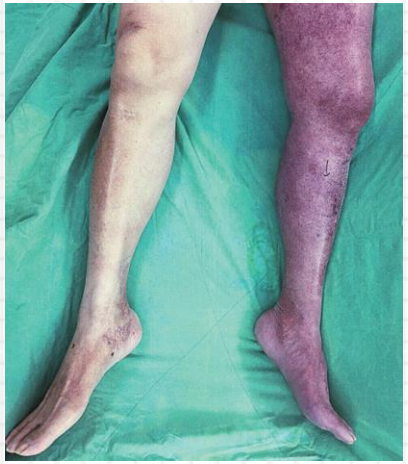
인하대학교

CMAJ 2023 June 19;195:E833-43.

Thrombolysis (DVT)

- 대부분의 근위부 DVT 환자에서는 **항응고요법 단독** 치료를 thrombolysis(혈전용해술) + 항응고요법보다 선호
- For patients with **extensive DVT** **in whom thrombolysis is considered** appropriate, the ASH guideline panel suggests using **catheter-directed thrombolysis** over systemic thrombolysis

Indication	권고안
Proximal DVT	항응고요법 단독 치료 선호
Limb-threatening DVT (사지 위협 DVT: phlegmasia, severe pain, edema)	thrombolysis + 항응고요법 고려 가능
(Low risk bleeding) iliofemoral DVT	thrombolysis + 항응고요법 고려 가능
Common femoral vein 이하 DVT	thrombolysis 사용 드물게
Thrombolysis 방법	catheter-directed thrombolysis 선호



N Engl J Med 2018;378:658

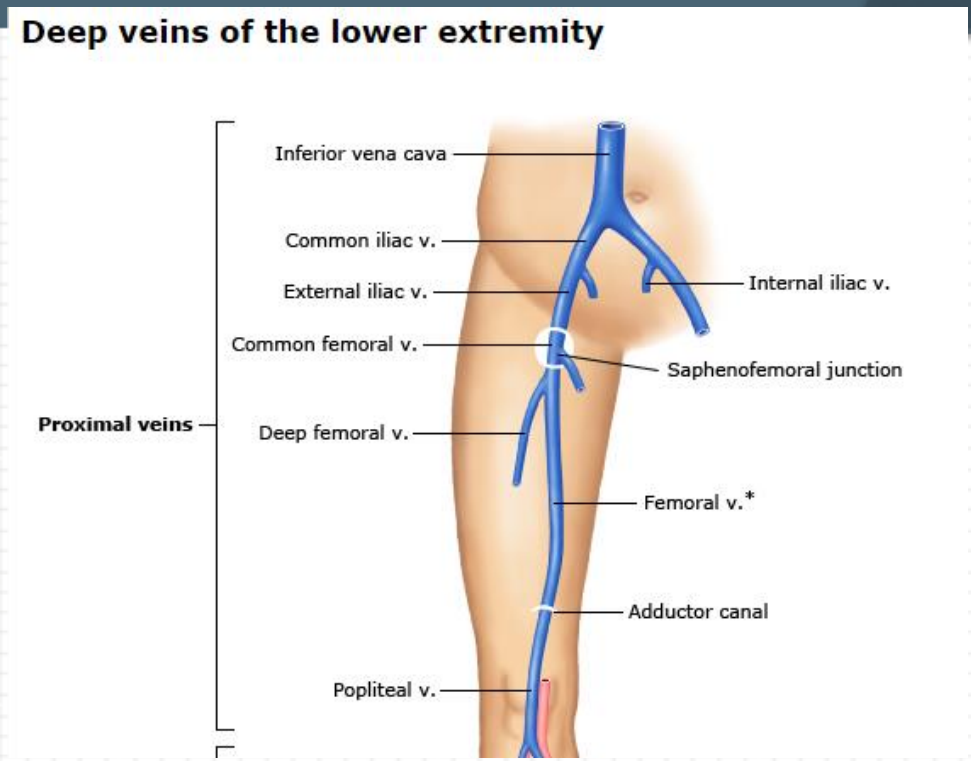
Extensive DVT definition / thrombolysis indication

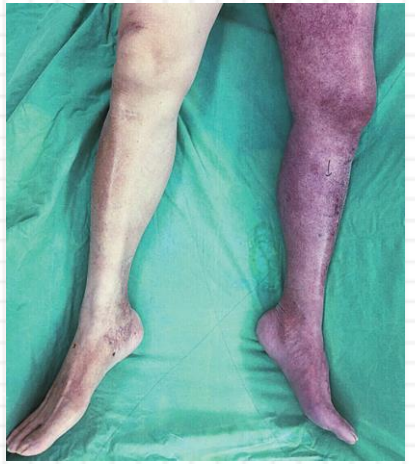
- **Extensive DVT** : a thrombus connecting to 2 or more segments of
  - inferior vena cava (IVC)
  - iliac vein
  - femoral vein
  - popliteal vein

Cf) **Localized DVT** : a thrombus confined to 1 segment of above

Ann Vasc Surg. 2022;85:246–252.

- Indications for thrombolytic therapy for lower extremity DVT include
  - extensive or large proximal lower extremity DVT (ie, popliteal or femoral DVT)
  - iliofemoral thrombosis associated with either or both of the following:
    - Severe symptomatic swelling (ie, considered "at risk" of ischemia)
    - Limb-threatening ischemia (ie, phlegmasia cerulea dolens [PCD])





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Thrombolysis (DVT)

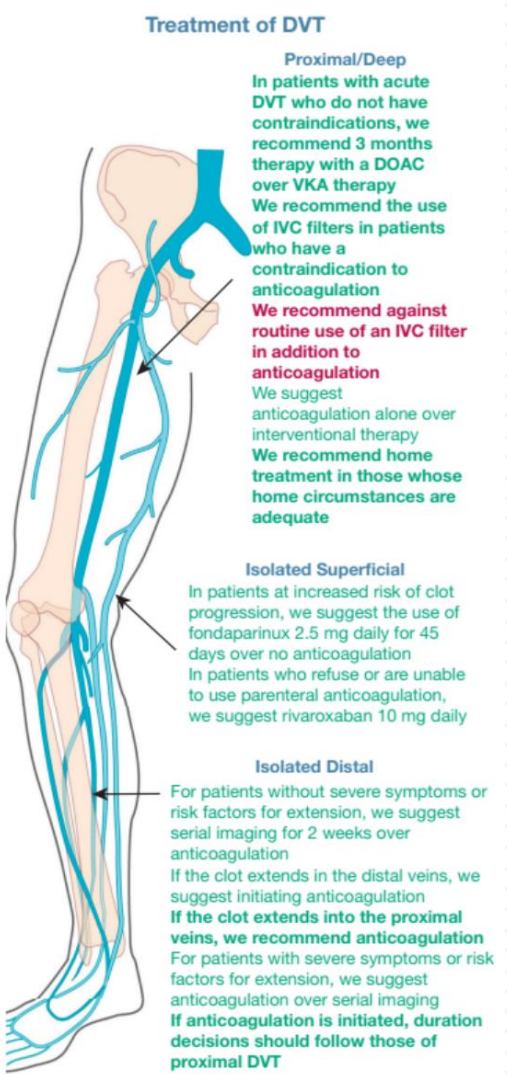


Figure 1 – *The venous anatomy of the lower extremity, and the relevant guidance statement to treat thrombosis in each venous distribution. DOAC = direct-acting oral anticoagulant; IVC = inferior vena cava; VKA = vitamin K antagonist. "Slagter - Drawing Deep and superficial veins of the lower extremity - no labels" at AnatomyTOOL.org by Ron Slagter, license: Creative Commons Attribution - NonCommercial-ShareAlike.*

Proximal/Deep DVT (근위부/심부 DVT)

(1) 항응고 치료 권고

- We recommend **against the use of thrombolytic** therapy in most patients with acute DVT.

(2) Thrombolysis

- Author consensus is that patients with **phlegmasia cerulea dolens**, characterized as DVT at risk of progression to critical limb ischemia and potential limb loss, are outside the scope of this guidance.

CHEST 2024; 166(2):388-404

Thrombolysis (DVT)

- NICE guideline [2020]
  - Consider **catheter-directed thrombolytic therapy** for people with symptomatic **iliofemoral DVT** who have:
    - symptoms lasting less than 14 days
    - good functional status
    - a life expectancy of 1 year or more
    - a low risk of bleeding

Thrombolysis (DVT)

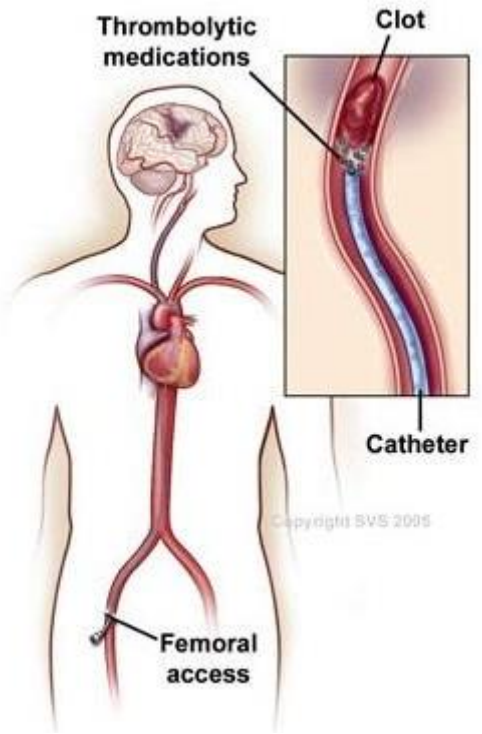
	ASH VTE Guideline (2020)	CHEST Guideline (2024 개정)	NICE NG158 (2020 개정)
	1차 권고 :anticoagulation		
Thrombolysis 적응증	- 'extensive' 또는 **limb-threatening**(phlegmasia cerulea dolens), - **iliac/common femoral** 침범, 젊은·저출혈 위험 환자 등 선택적 적용	- **Phlegmasia cerulea dolens** 등 위급 상황은 개별 판단	- **증상성 ilio-femoral DVT** - 증상 ≤ 14 일 - 양호한 기능 상태·예상 생존 ≥ 1 년 - 낮은 출혈 위험
comment	**CDT > Systemic**	DVT에서 CDT, systemic thrombolysis에 대한 언급 없음.	**CDT > Systemic**

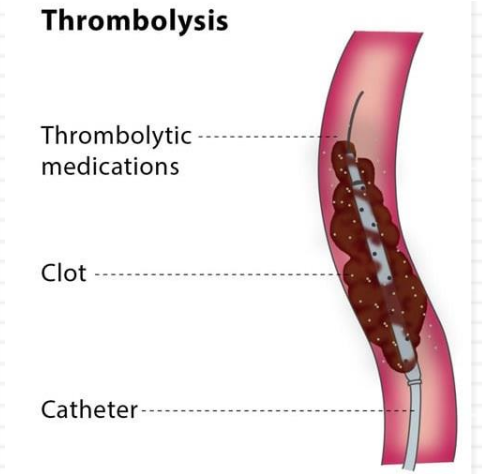
카테터 유도 치료(Catheter-directed therapies, CDTs)

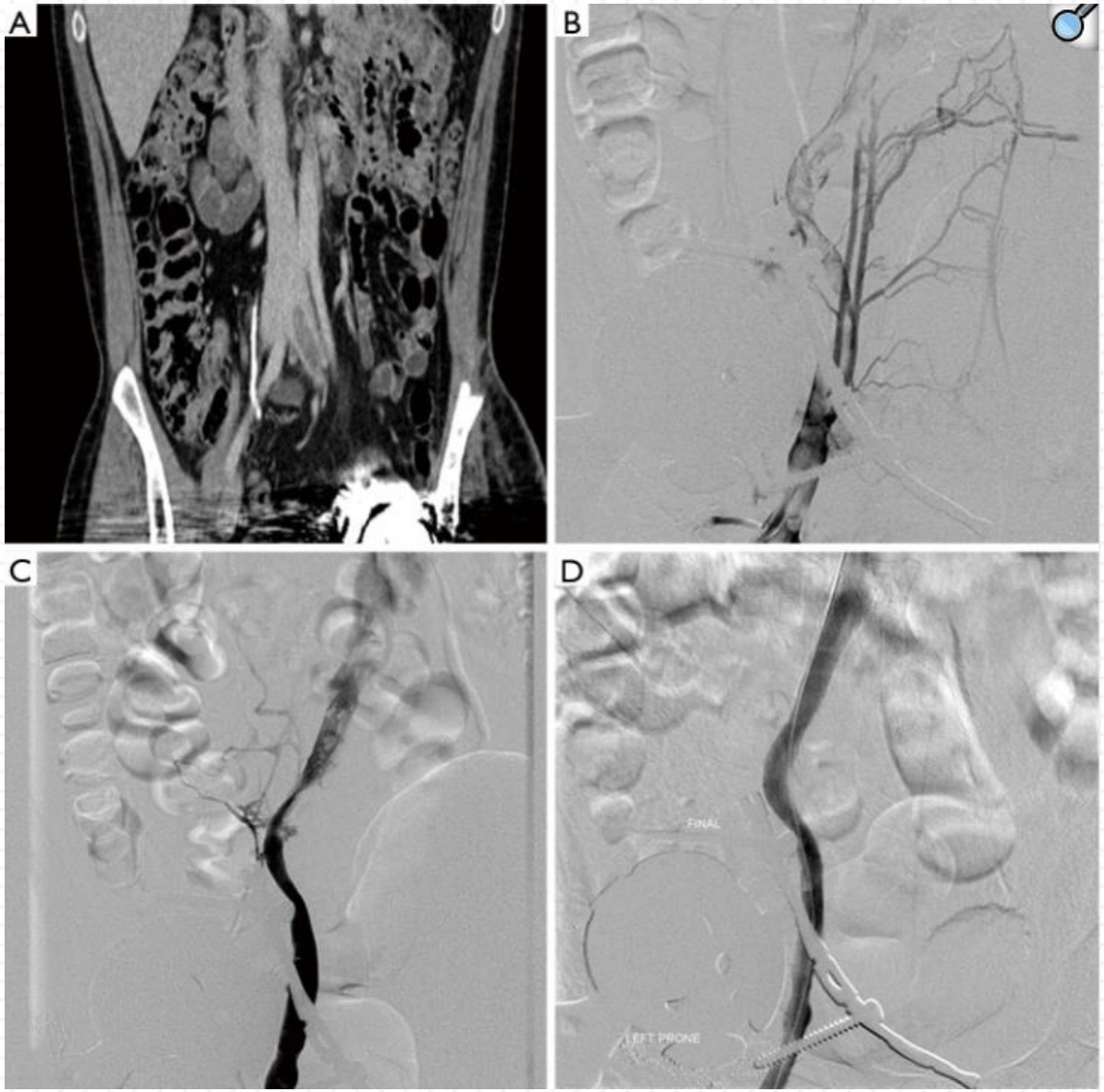
- **기계적 혈전 제거술** (예: 흡인 색전술, suction embolectomy)
- **카테터 유도 혈전용해술** (저용량의 혈전용해제를 카테터를 통해 주입, 초음파 병용 가능)

- **선택 기준**:
- **출혈 위험이 높고 thrombolysis 금기인 경우**: 흡인 색전술이 더 적절
- **흡인술 시행 불가 및 thrombolysis 일부 가능 시**: 저용량의 혈전용해제를 카테터를 통해 주입하는 방식 선택

Catheter directed thrombolysis (CDT)







- **PCDT** (pharmacomechanical catheter-directed thrombolysis) **with angioplasty and stenting.**

(A) Extensive DVT extending from the left popliteal vein to the common iliac vein;

(B) pulse-spray thrombolysis was performed with 0.1 mg/mL tPA preparation. A temporary IVC filter was placed prior to the procedure;

(C,D) mechanical thrombectomy with the AngioJet catheter followed by balloon angioplasty and deployment of several self-expanding stents. PCDT,

https://vascular.org/your-vascular-health/your-care-journey/treatments/catheter-directed-thrombolytic-therapy

Contraindication to fibrinolysis

Contraindications to fibrinolysis
Absolute
History of haemorrhagic stroke or stroke of unknown origin
Ischaemic stroke in previous 6 months
Central nervous system neoplasm
Major trauma, surgery, or head injury in previous 3 weeks
Bleeding diathesis
Active bleeding
Relative
Transient ischaemic attack in previous 6 months
Oral anticoagulation
Pregnancy or first post-partum week
Non-compressible puncture sites
Traumatic resuscitation
Refractory hypertension (systolic BP >180 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer

Parenteral anticoagulation

Parenteral anticoatulation – Indication (ASH, Chest, NICE)

1. VTE가 의심되지만 영상·D-dimer 결과가 4 시간 안에 나오지 않을 때 – 'Interim therapeutic anticoagulation'
   - NICE: 검사 지연 시 **LMWH/UFH/Fondaparinux/DOAC 중 하나를 즉시 시작**하고, 검사 결과는 나중에 확인하도록 권고

2. 재발'Breakthrough' **VTE가 VKA 치료 중 발생**
   - ASH: LMWH 전환 권고

3. 확진된 VTE에서 **VKA 치료를 시작하거나, Dabigatran·Edoxaban을 쓸 예정인 경우** 'Bridging'
   - CHEST : VKA 치료 시 **최소 5 일간 LMWH / UFH(+INR ≥ 2 × 24 h)** 먼저 사용(Strong)
   - ASH, NICE : Dabigatran·Edoxaban은 **UFH/LMWH 선투여 5–10 일** 뒤 경구 전환 필요

4. DOAC이 부적합하거나 금기인 특수군
   ① **CrCl < 15 mL/min** 또는 중증 신부전
   ② **체중 < 50 kg / > 120 kg** – 농도 모니터링 고려
   ③ **Triple-positive APS** – LMWH + VKA ≥ 5 일→VKA 단독
   ④ **활성 암**인데 DOAC이 맞지 않을 때 LMWH 단독·병용 허용

5. 특수 상황: 임산부, 수유부- LMWH 1차 선택 / isolated superficial thromboembolism – fondaparinux

Parenteral anticoagulation - 1. VKA 치료 중 재발성 DVT/PE

- **치료 중인 VKA (Vitamin K Antagonist) 복용 중 INR target level로 잘 유지되었음에도 불구하고 DVT 및/또는 PE가 발생한 환자에게 DOAC보다는 LMWH 사용을 제안** (조건부 권고, 효과에 대한 증거 수준: 매우 낮음)

- **재발성 혈전색전증 원인**:
  - 기저 질환 (예: cancer, APS, vasculitis 등)
  - 항응고제 선택/용량 부적절, 복약 순응도 저하, 약물 상호작용, 음식 상호작용 등

- **평가 시 우선 확인할 사항**:
  - 복약 순응도 확인
  - INR 검사로 치료 범위 내 VKA 복용 여부 확인
  - 적절한 약물 용량인지 검토

ASH guideline 2020

Parenteral anticoagulation – 2. VKA 치료받는 환자 초기 병용

- **급성 VTE 환자에서 VKA를 사용할 경우,**
  → 초기에는 반드시 병용으로 비경구 항응고제 (LMWH, fondaparinux, IV UFH, 또는 SC UFH)를 투여할 것을 권고

- 비경구 항응고제를 사용하는 경우,
  - IV UFH보다는 LMWH 또는 fondaparinux를 선호
  - LMWH vs SC UFH → LMWH 선호
  - fondaparinux vs SC UFH → fondaparinux 선호

- VKA를 사용할 경우,
  - 가능한 빨리 VKA를 시작(예: 비경구 항응고제 시작과 같은 날)하고,
  - 최소 5일간 비경구 항응고제를 유지하며
  - INR이 2.0 이상으로 최소 24시간 유지될 때까지 지속할 것을 권고

9	**In patients with acute VTE treated with VKA therapy, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or subcutaneous UFH) rather than no such initial treatment** (Strong Recommendation, Moderate-Certainty Evidence).[b]
9.1	**In patients with acute VTE initiated with a parenteral agent, we suggest LMWH or fondaparinux over IV UFH** (Weak Recommendation, Low-Certainty Evidence)**, and over subcutaneous UFH** (Weak Recommendation, Moderate-Certainty Evidence for LMWH; Weak Recommendation, Low-Certainty Evidence for fondaparinux).[a]
9.2	**In patients with acute VTE treated with VKA, we recommend early initiation (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 d and until the INR is ≥ 2.0 for at least 24 h** (Strong Recommendation, Moderate-Certainty Evidence).[b]

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Parenteral anticoagulation – 2. Dabigatran/Edoxaban 치료받는 환자 초기 병용

- NICE guideline 2020:
  - Offer either apixaban or rivaroxaban to people with confirmed proximal DVT or PE. If neither apixaban nor rivaroxaban is suitable offer:
    - **LMWH for at least 5 days followed by dabigatran or edoxaban** or
    - LMWH concurrently with a vitamin K antagonist (VKA) for at least 5 days, or until the international normalised ratio (INR) is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
  - Offer people with confirmed proximal DVT or PE and renal impairment (estimated creatinine clearance between 15 ml/min and 50 ml/min) one of
    - • apixaban • rivaroxaban • **LMWH for at least 5 days followed by edoxaban or dabigatran** if estimated creatinine clearance is 30 ml/min or above
    - LMWH or UFH, given concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
- ASH 2020:
  - **Dabigatran, edoxaban : administered after an initial treatment of 5 to 10 days with LMWH**, whereas rivaroxaban and apixaban were administered without initial parenteral anticoagulants

VKA + heparin 병용 이유

① 작용 발현 지연

- **Warfarin**: inhibits the vitamin K dependent coagulation (II, VII, IX, X) and anticoagulation factors (Protein C, Protein S).
  - Half life: VII (6 hrs), Protein C (8h), IX (24h), Protein S (30h), X (48h), **II (60h)**

② Initial 'hypercoagulable status'

- **Protein C, S**: 반감기가 짧아 (8-30h) warfarin 투약 후 빠르게 감소 → 항응고 억제 → 'hypercoagulable status' 특히 Factor II, X 는 아직 억제되지 않았기 때문에 더욱 위험함 -> Warfarin 시작 초기에 오히려 혈전이 악화될 수 있는 일시적 친응고 (prothrombotic) 상태가 발생. 기존 혈전이 있는 경우 반드시 병용 치료 필요.

Parenteral anticoagulation -3. Isolated Superficial DVT (표재정맥 혈전증)

(1) 혈전 진행 위험 높은 경우: fondaparinux 2.5mg/day × 45일 > 무치료

(2) 주사 치료 거부 또는 불가능한 경우: rivaroxaban 10mg/day 제안

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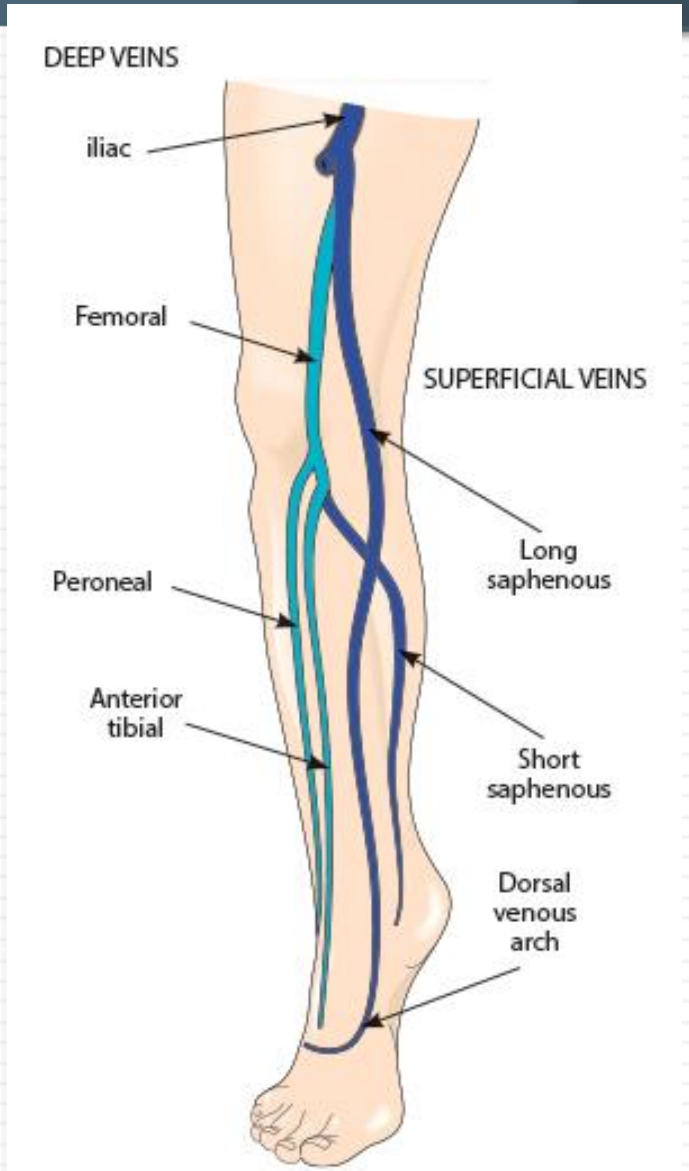
치료 권장되는 SVT의 조건	Remarks
>5 cm 이상 진행된 SVT	임상적으로 유의미한 길이
심부정맥과 가까운 위치	예: saphenofemoral junction 근처 (within 3cm) -> proximal DVT에 준하여 치료
증상 심하거나 재발성	염증, 통증, 붓기 동반
혈전성 소인 존재	암, 혈전성 체질 등
입원 또는 수술 후 발생	고위험군



Klauer KM. Emerg Med News. 2017 Jan 10.

Table 12. Randomised controlled trials examining superficial venous thrombosis treatment published during the last two decades

Study	Design	Patients – *n*	Treatment regimens	Main results
Marchiori, 2002,[310]	Open label	60	Intermediate *vs.* prophylactic SC doses of UFH for four weeks	Intermediate doses more effective in preventing VTE during a six month follow up.
Lozano, 2003,[306]	Open label	80	Saphenofemoral disconnection *vs.* outpatient LMWH SC enoxaparin (full dose for one week and intermediate dose for another three weeks)	LMWH treatment was less expensive, avoiding hospitalisation
STENOX, 2003,[25]	Double blind	427	LMWH enoxaparin in prophylactic or full SC doses, oral tenoxicam or placebo, for 8–12 days	The incidence of VTE and SVT recurrence combined by day 12 was significantly reduced from 30.6% in the placebo group to 8.3%, 6.9%, and 14.9% in the prophylactic dose, full dose, and tenoxicam groups, respectively
Vesalio, 2005,[311]	Double blind	164	LMWH nadroparin in prophylactic or body weight adjusted full SC doses for one month	SVT progression or VTE complications combined during the three month follow up period in the prophylactic and full dose groups occurred in 8.6% and 7.2%, respectively ($p = .74$)
CALISTO, 2010,[7]	Double blind	3 002	Fondaparinux in prophylactic doses or placebo, SC for 45 days	The primary efficacy outcome (composite of death from any cause or symptomatic pulmonary embolism, symptomatic deep vein thrombosis, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial vein thrombosis) at day 47 was 0.9% in the fondaparinux group and 5.9% in the placebo group (relative risk reduction with fondaparinux, 85%). Except for the outcome of death, each component of the primary efficacy outcome was significantly reduced in the fondaparinux group
STEFLUX, 2012,[313]	Double blind	664	LMWH parnaparin either intermediate dose for 10 days followed by placebo for 20 days or intermediate dose for 30 days or prophylactic dose for 30 days	The composite of symptomatic and asymptomatic DVT, recurrence and or symptomatic or asymptomatic local extension of SVT and symptomatic PE at 33 days and 93 days was significantly reduced with intermediate dose for 30 days
SURPRISE, 2017,[26]	Open label	472	Oral rivaroxaban or SC fondaparinux in prophylactic doses for 45 days	Composite of symptomatic DVT or PE, progression or recurrence of SVT, and all cause mortality at 45 days occurred equally frequently in the two groups

SC = subcutaneous; UFH = unfractionated heparin; LMWH = low molecular weight heparin; VTE = venous thromboembolism; SVT = superficial vein thrombosis; DVT = deep vein thrombosis; PE = pulmonary embolism.

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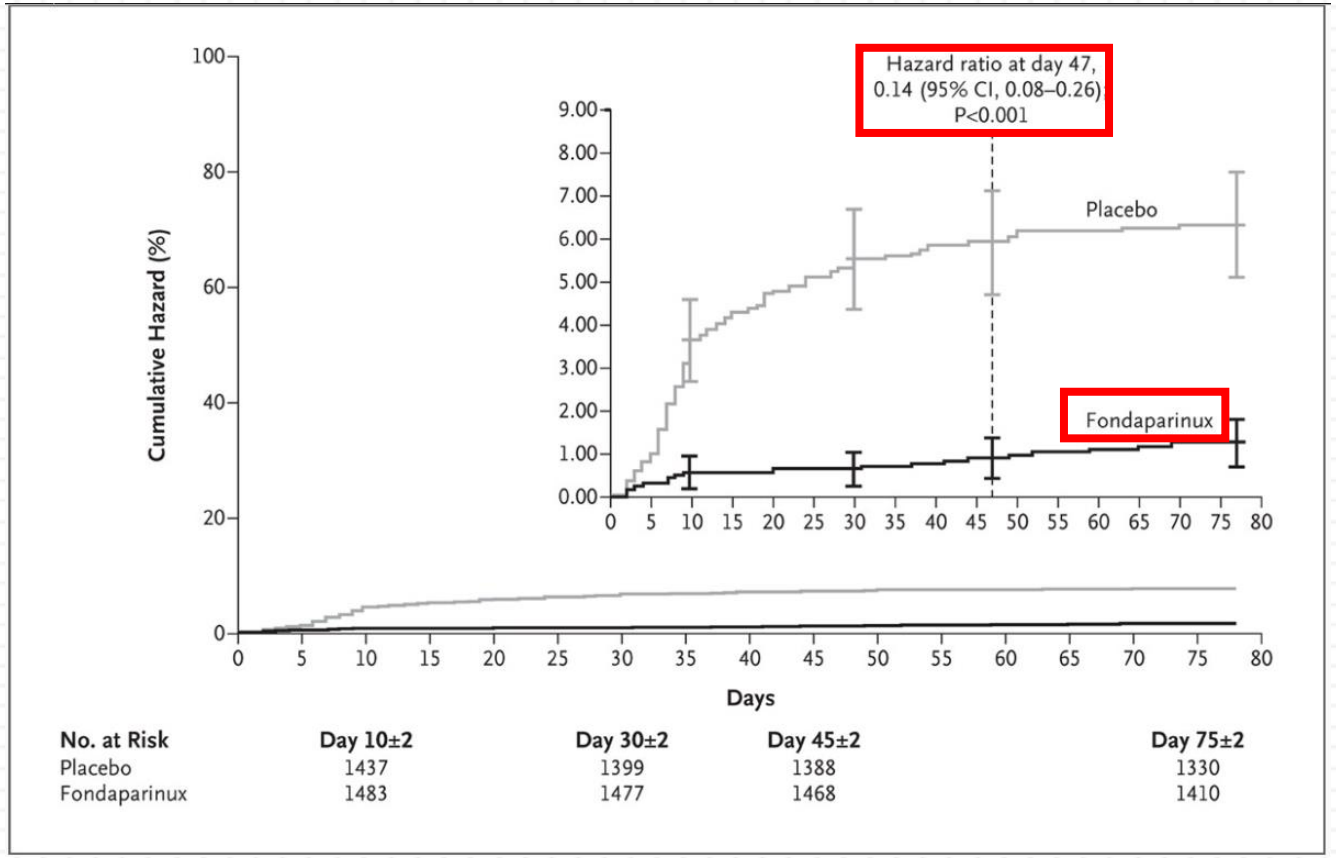
SVT – CALISTO trial

- 17 countries, 171 centers (Mar 2007-May 2009) RCT (N=3,002)
- Acute, symptomatic SVD without DVT or PE
- Fondaparinux 2.5mg SQ qd, 45 days vs. Placebo
- Primary endpoint
  - Mortality
  - Symptomatic PE
  - Symptomatic DVT
  - Recurrent SVT
- Primary endpoint 발생률: 0.9 vs 5.9% (p<0.001)

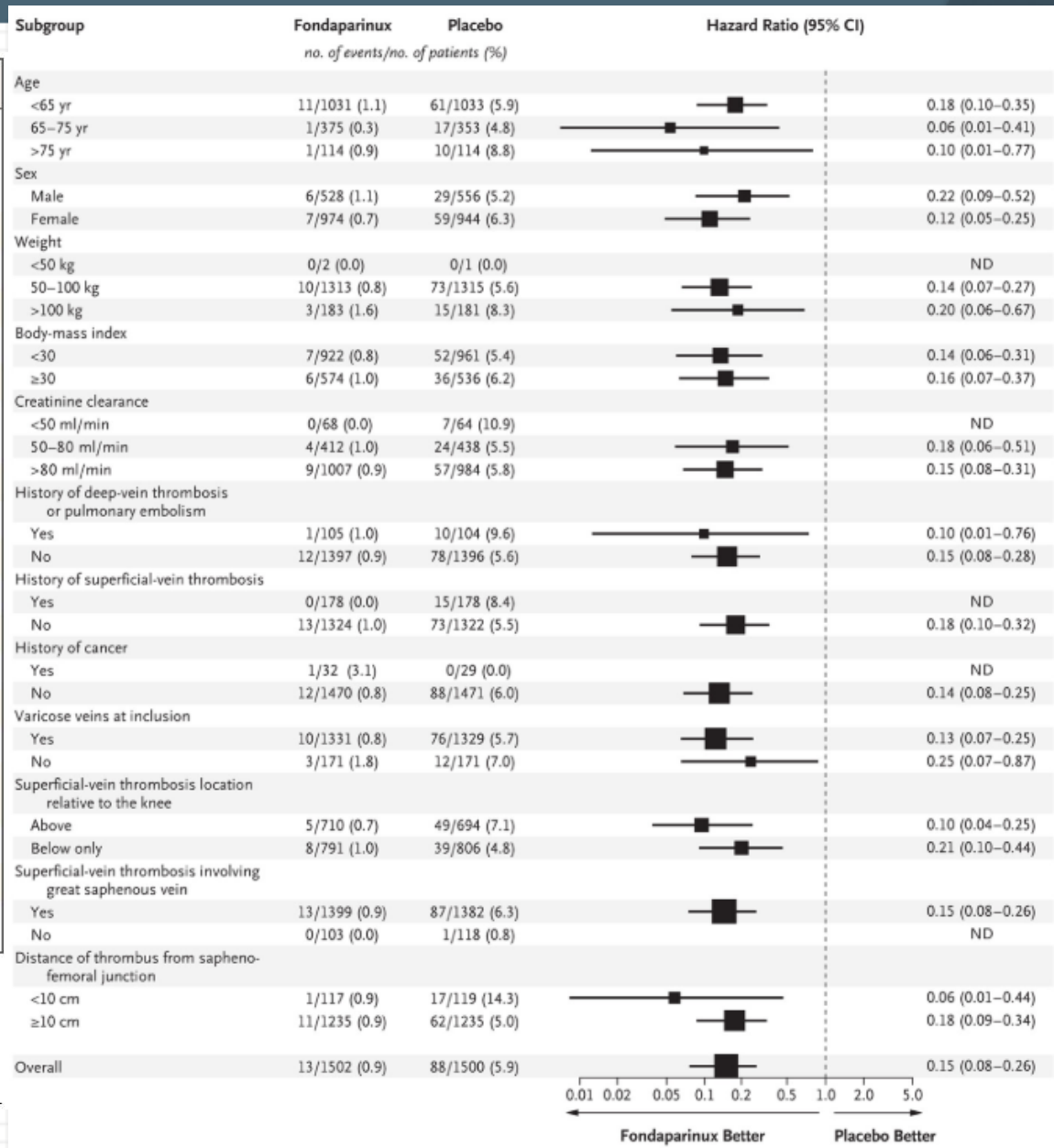


N Engl J Med 2010;363:1222-1232

Table 3. Efficacy Outcomes.

Efficacy Outcome	Fondaparinux (N=1502)	Placebo (N=1500)	Absolute Risk Reduction with Fondaparinux	Relative Risk with Fondaparinux	P Value*
	no. with event (%)		*percentage points (95% CI)*	*% (95% CI)*	
By Day 47					
Primary composite outcome†	13 (0.9)	88 (5.9)	−5.0 (−6.3 to −3.7)	0.15 (0.08 to 0.26)	<0.001
Death‡	2 (0.1)	1 (0.1)	0.1 (−0.2 to 0.3)	1.99 (0.18 to 21.87)	1.00
Pulmonary embolism§	0	5 (0.3)	−0.3 (−0.6 to 0.0)	Not calculated	0.03
Deep-vein thrombosis¶	3 (0.2)	18 (1.2)	−1.0 (−1.6 to −0.4)	0.17 (0.05 to 0.56)	<0.001
Extension of superficial-vein thrombosis to the saphenofemoral junction	4 (0.3)	51 (3.4)	−3.1 (−4.1 to −2.2)	0.08 (0.03 to 0.22)	<0.001
Recurrence of superficial-vein thrombosis	5 (0.3)	24 (1.6)	−1.3 (−2.0 to −0.6)	0.21 (0.08 to 0.54)	<0.001
Deep-vein thrombosis or pulmonary embolism	3 (0.2)	20 (1.3)	−1.1 (−1.8 to −0.5)	0.15 (0.05 to 0.50)	<0.001
Surgery for superficial-vein thrombosis	11 (0.7)	57 (3.8)	−3.1 (−4.1 to −2.0)	0.19 (0.10 to 0.37)	<0.001
By Day 77					
Composite outcome†	18 (1.2)	94 (6.3)	−5.1 (−6.4 to −3.7)	0.19 (0.12 to 0.32)	<0.001
Death‡	2 (0.1)	1 (0.1)	0.1 (−0.2 to 0.3)	1.99 (0.18 to 21.87)	1.00
Pulmonary embolism§	0	6 (0.4)	−0.4 (−0.7 to −0.1)	Not calculated	0.02
Deep-vein thrombosis	4 (0.3)	19 (1.3)	−1.0 (−1.6 to −0.4)	0.21 (0.07 to 0.62)	0.001
Extension of superficial-vein thrombosis to the saphenofemoral junction	5 (0.3)	54 (3.6)	−3.3 (−4.3 to −2.3)	0.09 (0.04 to 0.23)	<0.001
Recurrence of superficial-vein thrombosis	8 (0.5)	26 (1.7)	−1.2 (−2.0 to −0.4)	0.31 (0.14 to 0.68)	0.002
Deep-vein thrombosis or pulmonary embolism	4 (0.3)	22 (1.5)	−1.2 (−1.9 to −0.5)	0.18 (0.06 to 0.53)	<0.001
Surgery for superficial-vein thrombosis	15 (1.0)	61 (4.1)	−3.1 (−4.2 to −1.9)	0.25 (0.14 to 0.43)	<0.001

* P values were calculated with the use of Fisher's exact test.
† Some patients had more than one event.
‡ There were two deaths from cancer in the fondaparinux group and one death from acute heart failure in the placebo group.
§ No instance of pulmonary embolism was fatal.
¶ There were 11 cases of proximal deep-vein thrombosis: 1 in the fondaparinux group and 10 in the placebo group.



N Engl J Med 2010;363:1222-1232

SVT - SURPRISE Trial (rivaroxaban vs. fondaparinux)

- Open-label, randomized, 27 centers, non-inferiority, phase 3b (Germany)
- N=485 (per-protocol 435, each group 236)
- Symptomatic SVT (≥5cm)
- 1:1 rivaroxaban 10mg 경구 vs fondaparinux 2.5mg SC, 45일
- Primary efficacy outcome
  - DVT 또는 PE 발생
  - SVT recurrence or progression
  - All cause mortality
  - 비열등성 한계: 4.5%p (절대 차이 기준)
- Primary outcome 발생률:
  - Rivaroxaban군: 3% (7/211명; 95% CI: 1.6–6.7)
  - Fondaparinux군: 2% (4/224명; 95% CI: 0.7–4.5)
  - HR: 1.9 (95% CI: 0.6–6.4) → 비열등성 입증됨 (p=0.0025)
- Major bleeding: 두 군 모두 0건

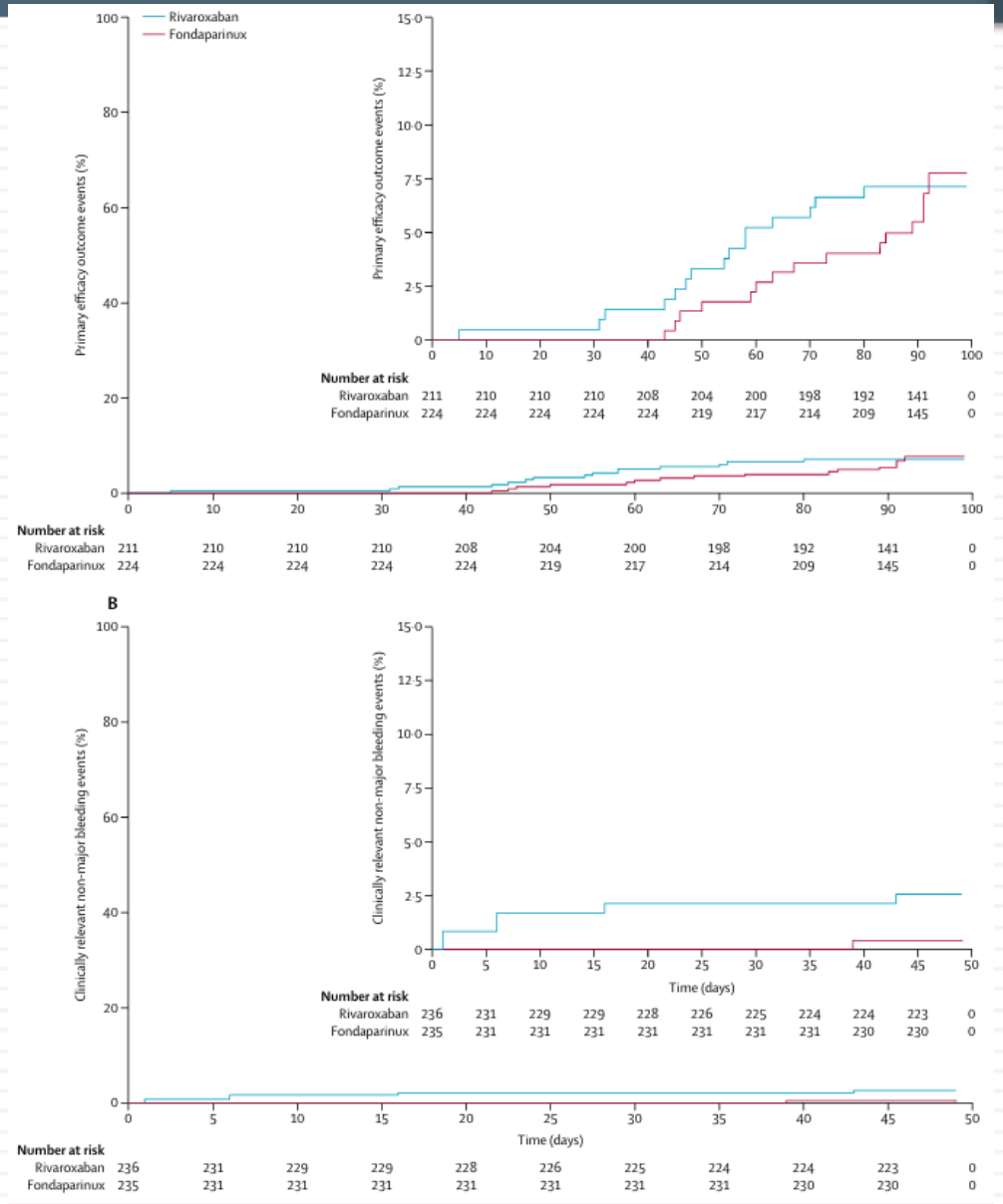


Figure 2: Kaplan-Meier cumulative event rates for the primary efficacy outcome at 45 and 90 days in the per-protocol analysis set (A), and for clinically relevant non-major bleeding at 45 days in the safety analysis set (B)

Lancet Haematol. 2017;4(3):e105–e113.

	Rivaroxaban group		Fondaparinux group	
	Day 45	Day 90	Day 45	Day 90
Efficacy (per-protocol analysis set)*				
Primary efficacy endpoint†	7 (3%; 1·6–6·7)	15 (7%; 4·4–11·4)	4 (2%; 0·7–4·5)	15 (7%; 4·1–10·8)
Superficial-vein thrombosis extension	0	2 (1%; 0·3–3·4)	0	1 (<1%; 0·1–2·5)
Superficial-vein thrombosis recurrence	4 (2%; 0·7–4·8)	8 (4%; 1·9–7·3)	3 (1%; 0·5–3·9)	12 (5%; 3·1–9·1)
Deep-vein thrombosis	3 (1%; 0·5–4·1)	6 (3%; 1·3–6·1)	1 (<1%; 0·1–2·5)	2 (1%; 0·3–3·2)
Pulmonary embolism	0	0	0	0
Death	0	0	0	0
Surgery for superficial-vein thrombosis	0	0	0	2
Safety (safety analysis set)‡				
Major bleeding	0	0	0	0
Clinically relevant non-major bleeding	6 (3%; 1·2–5·4)	6 (3%; 1·2–5·4)	1 (<1%; 0·1–2·4)	2 (1%; 0·2–3·1)
Minor bleeding	15 (6%; 3·9–10·2)	16 (7%; 4·2–10·7)	15 (6%; 3·9–10·3)	17 (7%; 4·6–11·3)
Any bleeding§	20 (9%; 5·5–12·7)	21 (9%; 5·9–13·2)	16 (7%; 4·2–10·8)	19 (8%; 5·2–12·3)

Data are n (%; 95% CI). Primary timpoint: day 45 (end of treatment). Secondary time point: day 90 (end of follow-up). 95% CI of proportions were calculated with the Wilson's score method. *n=211 in the rivaroxaban group, n=224 in the fondaparinux group. †Composite endpoint of extension or recurrence of superficial-vein thrombosis, symptomatic deep-vein thrombosis, or pulmonary embolism, or occurrence of all-cause death. ‡n=236 in the rivaroxaban group, n=235 in the fondaparinux group. §Patients with more than one bleeding event were only counted once.

Table 2: **Clinical outcomes**

SVT

16	**In patients with SVT of the lower limb at increased risk of clot progression to DVT or PE (see text[4]), we suggest the use of anticoagulation for 45 d over no anticoagulation** (Weak Recommendation, Moderate-Certainty Evidence).[a]
16.1	**In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg/d over other anticoagulant treatment regimens such as (prophylactic or therapeutic) dose of LMWH** (Weak Recommendation, Low-Certainty Evidence).[a]
16.2	**In patients with SVT who refuse or are unable to use parenteral anticoagulation, we suggest rivaroxaban 10 mg/d as a reasonable alternative for fondaparinux 2.5 mg/d** (Weak Recommendation, Low-Certainty Evidence).[a]

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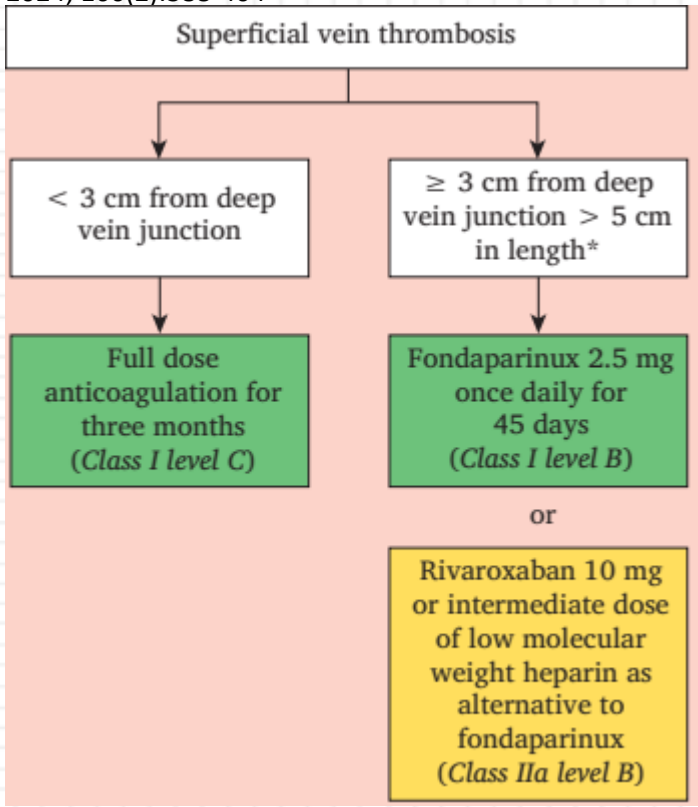

Recommendation 67

Patients with lower limb superficial vein thrombosis ≥ 3 cm away from the junction with the deep veins and extending ≥ 5 cm in length are recommended to have fondaparinux 2.5 mg once daily for 45 days to reduce the risk of further thromboembolic events.

Class	Level	References	ToE
I	B	Decousus *et al.* 2010[7]	

Recommendation 68

Patients with lower limb superficial vein thrombosis ≥ 3 cm away from the junction with the deep veins and extending ≥ 5 cm in length should be considered for rivaroxaban 10 mg or an intermediate dose of a low molecular weight heparin once daily as an alternative to fondaparinux to reduce the risk of further thromboembolic events.

Class	Level	References	ToE
IIa	B	Cosmi *et al.* (2012),[24] Decousus *et al.* (2010),[7] Beyer-Westendorf *et al.* (2017),[26] Di Nisio *et al.* (2018)[307]	

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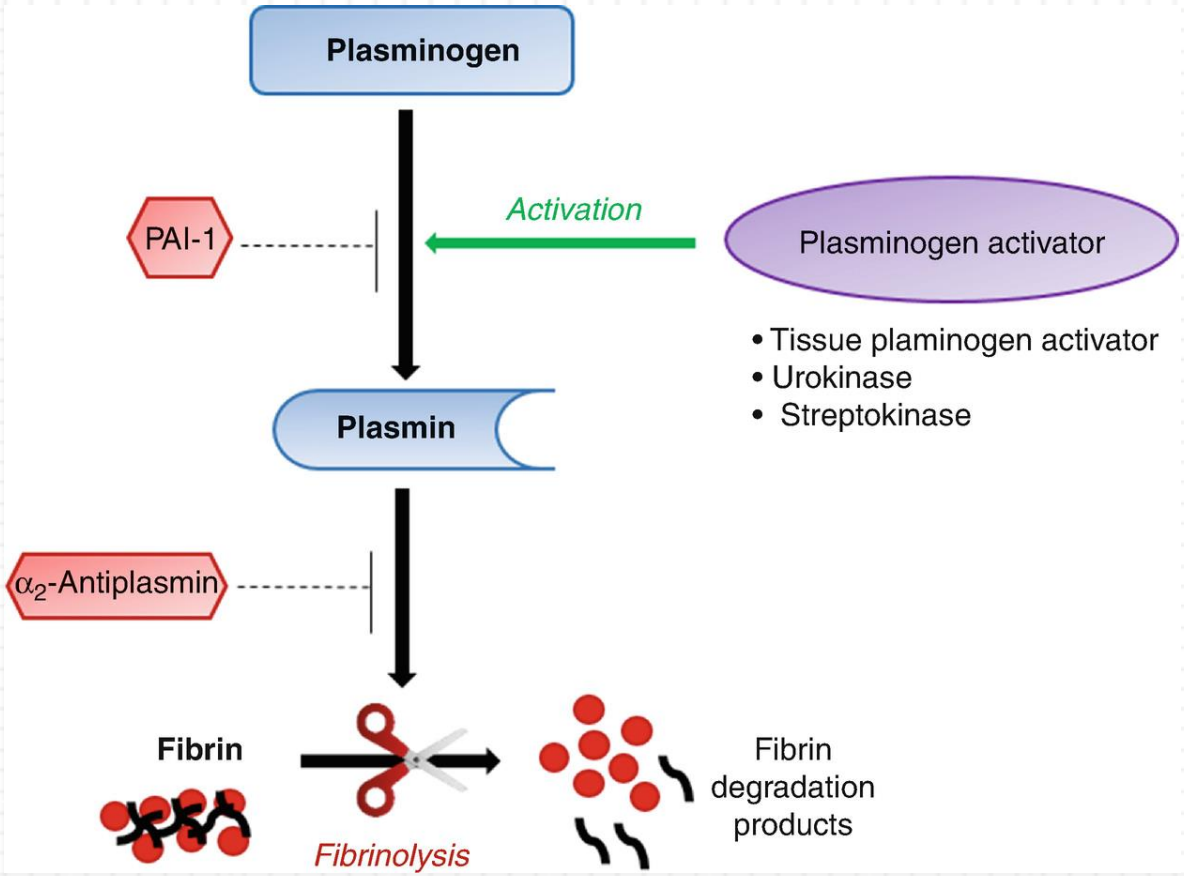
Special occasion, Agent, dose

특수 상황별 치료

	ASH VTE Guideline (2020)	CHEST Guideline (2024 개정)	NICE NG158 (2020 개정)
Cancer	**1차 : DOAC or LMWH** 위·췌·방광 등 **GI/GU 종양 ▶ LMWH 우선** (d/t bleeding risk, drug interaction)	**DOAC > LMWH**	**DOAC > LMWH 단독** 또는 VKA+LMWH bridge
CKD (CrCl <30)	**UFH** 또는 **용량-감량 LMWH (+ anti-Xa 모니터)** 우선	CrCl < 30 → **UFH or warfarin** 권고 (VKA는 신기능 영향 X)	CrCl < 15 → **UFH > LMWH** 15 <CrCl <50 → DOAC, LMWH, UFH
Liver disease (Child-Pugh B/C)	**LMWH or VKA** 선호 **DOAC 선호X**	**LMWH** **VKA**, DOAC 지양	-
Pregnancy/ Breast feeding	LMWH	LMWH	LMWH

FDA approved Thrombolytic agent, dose



Clin Exp Thromb Hemost 2017;3(1):8-11

Molecule	Regimen
rtPA	100 mg over 2 h
	0.6 mg/kg over 15 min (maximum dose 50 mg)[a]
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h
	Accelerated regimen: 1.5 million IU over 2 h
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h
	Accelerated regimen: 3 million IU over 2 h

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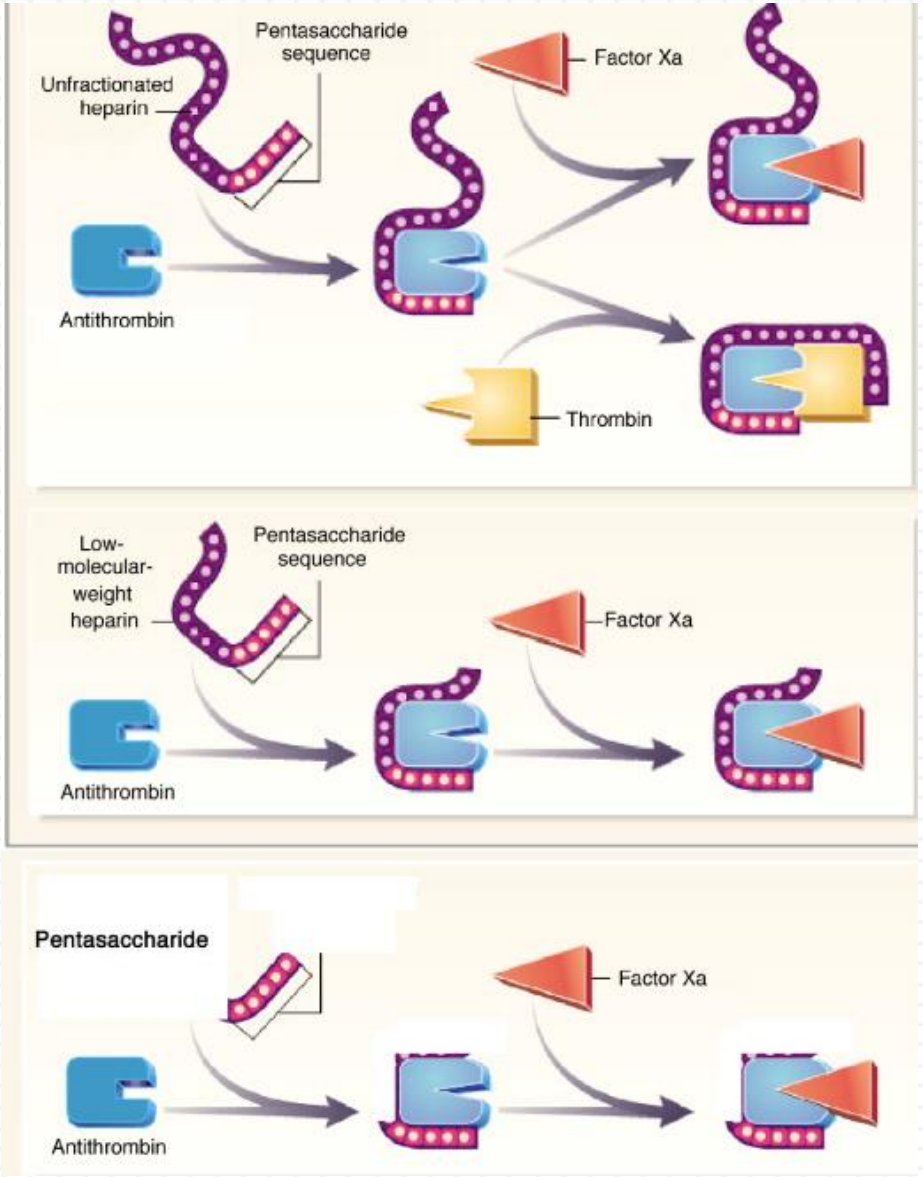
Cf) rtPA dose
- Stroke: 0.9mg/kg 1hr
- AMI: 체중 별 bolus+infusion
- PE: 100mg/2hr fixed

Mechanism of action



- **UFH**: 긴 분자구조 → AT와 Factor Xa, IIa **동시 억제**
  - 혈장 내 다양한 단백질 (fibrinogen, vWF)에 비특이적 결합 -> 이로 인해 용량-반응 예측이 어렵고, 일부 환자에서 heparin resistance 발생.
  - HIT (heparin-induced thrombocytopenia), osteoporosis 등 부작용.
- **LMWH**: 짧은 사슬이 많아 **2자 결합만 가능** → 대부분 **Xa 억제에만 작용**
  - 단백질 결합이 적어 용량-반응 예측성 좋음. (aPTT monitoring 불필요. Fixed dose)
  - osteoblast 결합 적어 골손실 위험 적음.
- **Fondaparinux** (Xa inhibitor, pentasaccharide): AT, Xa 억제만 가능.
  - Platelet이나 PF4와 결합하지 않아 HIT 유발하지 않으나, HIT 환자에서 사용한 임상 연구가 부족함.
  - Renal excretion되어 CKD환자에서 주의 필요.

N Engl J Med 1997;337:688-698

인하대학교

Circulation. 1998;98:1575-1582.
Eur J Cardiothorac Surg. 2023 Oct 4;64(4):ezad340

Agent, dose (Treatment of DVT with or without PE)

계열	약제	체중·신기능 기준 치료 용량	투여 간격	Remark
LMWH	**Enoxaparin (크렉산, 크녹산)**	• 1 mg/kg SC q12 h (1차 선택) • 1.5 mg/kg SC q24 h	12 h / 24 h	CrCl < 30 mL/min → 1 mg/kg q24 h 또는 UFH로 변경 CrCl < 15 mL/min / 투석 → UFH로 변경
	Dalteparin (프라그민)	200 IU/kg SC q24 h (최대 18 000 IU)	24 h	CrCl < 30 mL/min → 감량 권고 없으나 신중 사용. Anti-Xa monitoring 권고 CrCl < 15 mL/min / 투석→데이터 부족.
	Tinzaparin	175 IU/kg SC q24 h	24 h	CrCl < 20 mL/min 피함, UFH 권고
Indirect Xa inhibitor	**Fondaparinux**	1) DVT Tx < 50 kg → 5 mg 50–100 kg → 7.5 mg >100 kg → 10 mg SC q24 h 2) SVT Tx 2.5mg SC q24h	24 h	CrCl < 30 mL/min 금기 warfarin / DOAC 전환까지 최소 5 일 사용

J Thromb Thrombolysis. 2016 Jan;41(1):32-67.
Thromb Haemost. 1996 Aug;76(2):195-9.
Front Pharmacol. 2024 Mar 11;15:1352982

Summary

Parenteral Anticoagulation & Thrombolysis in VTE treatment	
1. Thrombolysis Indications	**1) Massive PE(쇼크/저혈압)** → **Systemic Alteplase 100 mg/2 h** Cf) CDT 우선 고려: ① 전신용해 금기·실패 ② 출혈 고위험 ③ 전문센터 가용 **2) Ilio-femoral DVT ≤14 일** + 증상 심함 → **CDT**
2. Parenteral anticoagulation	1) 영상·D-dimer 지연 > 4 h → LMWH/UFH/Fondaparinux 즉시 투여 2) VKA 치료 중 재발 → LMWH 전환 3) VKA·Dabigatran·Edoxaban 치료 시작 시 → LMWH/UFH 5-10 일 bridge 4) Isolated SVT → fondaparinux 2.5mg SC 5) DOAC 부적합한 특수 환자군 (CrCl < 15, pregnancy, 출혈 높은 일부 cancer)
3. Parenteral Treatment Doses	• Enoxaparin 1 mg/kg q12h (1.5 mg/kg q24h) • Dalteparin 200 IU/kg q24h / Tinzaparin 175 IU/kg q24h

Thank you for your attention.

Anticoagulation following thrombolysis

1. Agent selection

- 원칙: 혈전용해술 후 즉시 UFH로 anticoagulation 시작.
- 예외사항: 이미 LMWH 투여받은 경우, 다음 투여 예정 시간까지 UFH 시간 연기.
- 주의사항: LMWH, DOAC, Warfarin 등 longer-acting anticoagulants는 최소 24시간 이후에 시작. (to ensure that there is no delayed bleeding that would require immediate cessation of anticoagulation)

2. UFH 용량 및 투여 방식

- Bolus 생략 가능: Some experts start a heparin infusion without a bolus,
- aPTT 기준 적용:
  - aPTT < 2 × ULN: UFH 주입 바로 시작
  - aPTT ≥ 2 × ULN: 4시간마다 반복 측정 → 2 × ULN 미만 되면 UFH 시작

3. Transition to Oral agents

- Once stable for 24 to 48 hours, patients should be transitioned to an oral agent (eg, DOAC or warfarin).

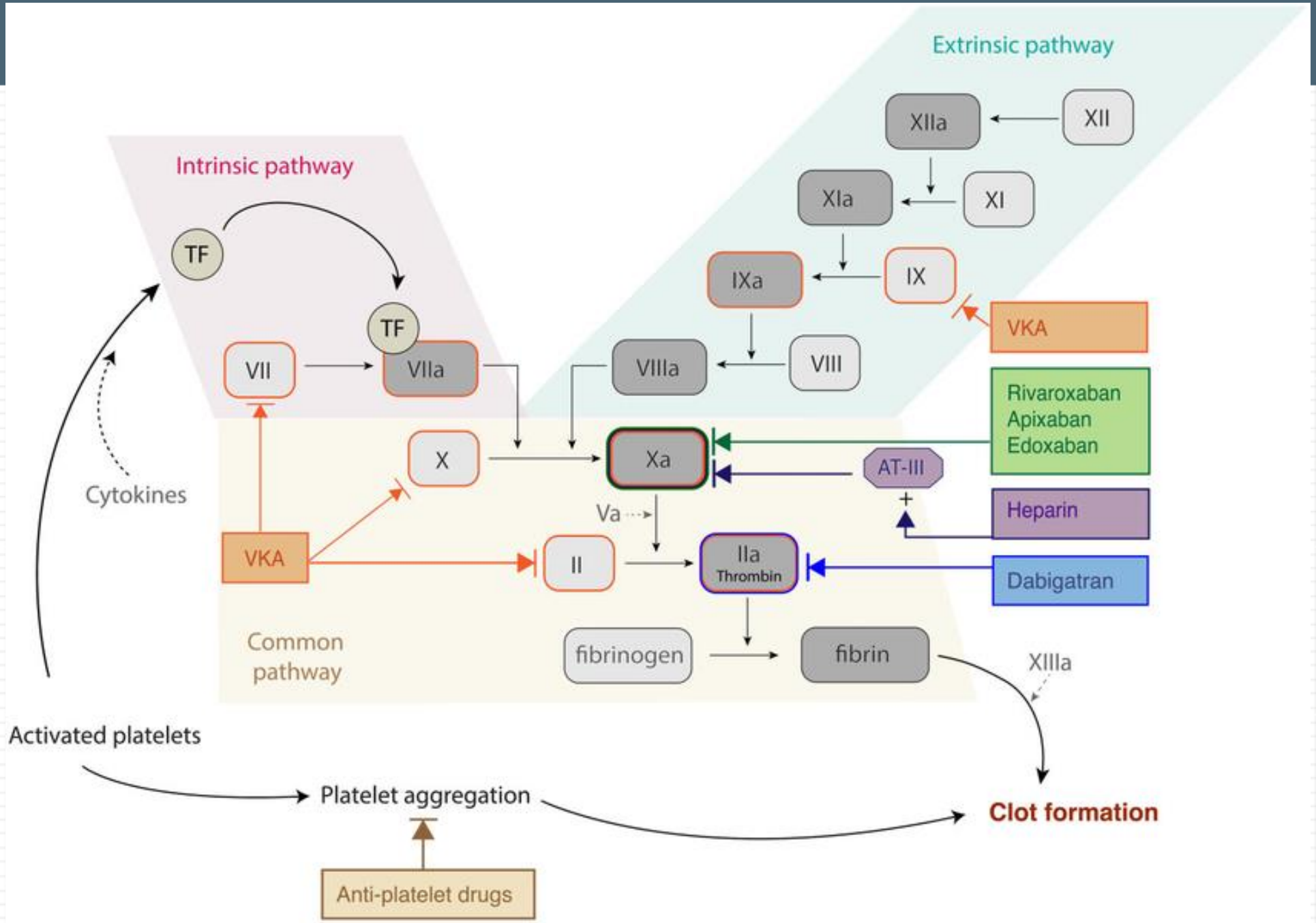

Extrinsic pathway
XIIa
XII
Intrinsic pathway
XIa
XI
TF
IXa
IX
TF
VKA
VII
VIIa
VIIIa
VIII
Rivaroxaban
Apixaban
Edoxaban
X
Xa
AT-III
Cytokines
Va
Heparin
VKA
II
IIa
Thrombin
Dabigatran
Common
pathway
fibrinogen
fibrin
XIIIa
Activated platelets
Platelet aggregation
Clot formation
Anti-platelet drugs

Table 1: Classification of pulmonary embolism according to European Society of Cardiology and American Heart Association guidelines

Classification	Definition
High-risk PE	Acute PE with signs of hemodynamic instability, presenting 1 of the following clinical manifestations: • Cardiac arrest (need for CPR) • Obstructive shock (SBP < 90 mm Hg or vasopressors required to achieve SBP ≥ 90 mm Hg, despite adequate filling status) and end-organ hypoperfusion (i.e., altered mental status; cold, clammy skin; oliguria or anuria; increased serum lactate) • Persistent hypotension (SBP < 90 mm Hg or SBP drop ≥ 40 mm Hg, lasting longer than 15 min and not caused by new onset arrhythmia, hypovolemia or sepsis)
Intermediate-risk (submassive) PE	• Acute PE without signs of hemodynamic instability, but with a PESI class III–IV or simplified PESI ≥ 1 • Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present
	Intermediate-high risk is defined if both of the following criteria are also present: • Signs of RV dysfunction on an imaging test (echo or CT) • Positive cardiac laboratory biomarkers of cardiac damage Intermediate-low risk is defined if 1 or none of these criteria are present
Low-risk PE*	Acute PE with no hemodynamic instability, no RV dysfunction and no comorbidity, with a PESI class I or simplified PESI score < 1

Note: CDT = catheter-directed thrombolysis, CPR = cardiopulmonary resuscitation, CT = computed tomography, CTPA = computed tomography pulmonary angiogram, PE = pulmonary embolism, PESI = Pulmonary Embolism Severity Index, RV = right ventricle, SBP = systolic blood pressure, TTE = transthoracic echocardiogram.
*Patients with low-risk PE are not candidates for systemic or catheter-directed thrombolysis and were not included in our study.

2019 ESC guideline

Table 8 **Classification of pulmonary embolism severity and the risk of early (in-hospital or 30 day) death**

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

BP = blood pressure; CTPA = computed tomography pulmonary angiography; H-FABP = heart-type fatty acid-binding protein; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = transthoracic echocardiogram.

[a]One of the following clinical presentations (*Table 4*): cardiac arrest, obstructive shock (systolic BP <90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP <90 mmHg or a systolic BP drop ≥40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis).

[b]Prognostically relevant imaging (TTE or CTPA) findings in patients with acute PE, and the corresponding cut-off levels, are graphically presented in *Figure 3*, and their prognostic value is summarized in Supplementary Data *Table 3*.

[c]Elevation of further laboratory biomarkers, such as NT-proBNP ≥600 ng/L, H-FABP ≥6 ng/mL, or copeptin ≥24 pmol/L, may provide additional prognostic information. These markers have been validated in cohort studies but they have not yet been used to guide treatment decisions in randomized controlled trials.

[d]Haemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the high-risk PE category. In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary.

[e]Signs of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of I–II or an sPESI of 0.[234] Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category.