Choice and Duration of Oral Anticoagulants for VTE

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Overview

Oral Anticoagulants

- Warfarin과 DOAC(Direct Oral Anticoagulants)는 모두 혈전 형성을 방지하기 위해 사용되는 항응고제

- 하지만 **작용 기전, 약물 특성, 모니터링 필요성, 음식 및 약물 상호작용, 임상적 특성** 등에서 중요한 차이가 있습니다.

  => Choice 결정인자

Overview

항응고제 분류 및 주요 약물

분류	작용기전	주요 약물	비고
비타민 K 길항제(VKA)	Factor II, VII, IX, X 생성 억제	**Warfarin**	혈중 INR 모니터링 필요, 식이·약물 상호작용 多
헤파린계	항트롬빈(AT-III) 활성화 → Xa, IIa 억제	**UFH**, **LMWH (Enoxaparin, Dalteparin)**	UFH: 정맥주사, LMWH: 피하주사, 입원환자/임산부
합성 펜타사카라이드	선택적 Xa 억제	**Fondaparinux**	HIT 환자에서 사용 가능
직접 경구 항응고제 (DOACs/NOACs)	직접 Xa 또는 IIa 억제	Xa 억제제: **Apixaban, Rivaroxaban, Edoxaban** IIa 억제제: **Dabigatran**	고정 용량, 모니터링 불필요, 빠른 효과 발현
기타 (injectable DTI)	직접 트롬빈 억제	**Argatroban**, **Bivalirudin**	HIT 환자 치료에 사용됨

Overview

Properties of an **ideal anticoagulant** versus currently available agents

	Oral	No significant food/drug interactions	Predictable response	No routine coagulation monitoring	Fixed dosing	No risk of HIT
IDEAL	✔	✔	✔	✔	✔	✔
LMWH		✔	✔	✔	✔	
UFH		✔				
Fondaparinux		✔	✔	✔	✔	✔
VKAs	✔					✔
Rivaroxaban	✔	✔	✔	✔	✔	✔
Dabigatran	✔	✔	✔	✔	✔	✔
Apixaban	✔	✔	✔	✔	✔	✔
Edoxaban	✔	✔	✔	✔	✔	✔

http://dx.doi.org/10.3904/kjm.2013.84.5.659

Guidelines : ESC, 2019

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 543–603
doi:10.1093/eurheartj/ehz405

ESC GUIDELINES

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)

Authors/Task Force Members: Stavros V. Konstantinides* (Chairperson) (Germany/Greece), Guy Meyer* (Co-Chairperson) (France), Cecilia Becattini (Italy), Héctor Bueno (Spain), Geert-Jan Geersing (Netherlands), Veli-Pekka Harjola (Finland), Menno V. Huisman (Netherlands), Marc Humbert[1] (France), Catriona Sian Jennings (United Kingdom), David Jiménez (Spain), Nils Kucher (Switzerland), Irene Marthe Lang (Austria), Mareike Lankeit (Germany), Roberto Lorusso (Netherlands), Lucia Mazzolai (Switzerland), Nicolas Meneveau (France), Fionnuala Ní Áinle (Ireland), Paolo Prandoni (Italy), Piotr Pruszczyk (Poland), Marc Righini (Switzerland), Adam Torbicki (Poland), Eric Van Belle (France), and José Luis Zamorano (Spain)

Guidelines : ESC, 2019

주요 권고사항 (PE)

- **초기 치료**
  - 고위험 PE → UFH 추천
  - 안정적 PE → LMWH/DOAC 사용 권고

- **치료 기간**
  - **최소 3개월 치료,**
    => 이후 유발성 + 낮은 출혈 위험이면 중단 고려
    => 비유발성 또는 지속 위험인자 있는 경우는 **연장 치료 권고**

- **연장치료 전략**
  - **DOAC 감량용량** 사용 가능
    (예: rivaroxaban 10 mg QD, apixaban 2.5 mg BID)
  - ESC/ERS recommend *extended anticoagulation*
    : for **persistent or minor transient risk factors**

Guidelines : ESC, 2023

ESC European Society of Cardiology

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Treatment of cancer-associated venous thromboembolism

09 Jun 2023

Prof. Lucia Mazzolai

Dr. Adriano Alatri

Venous thromboembolism (VTE) is one of the major causes of morbidity and mortality in cancer patients, who may also be at increased risk of bleeding. We review current knowledge and recommendations about the treatment of cancer-associated VTE.

Topic(s): *Cardio-Oncology;*

Keywords

cancer, treatment, venous thromboembolism

Guidelines : ESC, 2023

핵심 내용

- **암환자는 VTE 발생 위험이 증가,** ***증상이 있는 경우*** 영상 진단과 항응고 치료 필요

- **초기 및 유지 치료(6개월 이상)**
  : LMWH 또는 DOAC (Edoxaban, Rivaroxaban, Apixaban) 사용 권장
  (CrCl ≥ 30 mL/min, 약물 상호작용 고려)
  : **단, 위장관계(GI/GU)암 환자는 출혈 위험으로 DOAC 주의**

- **치료 기간**
  : 암이 **활동 중**이면 **최소 3–6개월 이상 지속**, 암이 비활성화 되면 중단 고려

- **검진 목적 1차 예방**
  : 고위험군 (예: 췌장암, Khorana score ≥2)에서 주기적 LMWH 또는
  DOAC (예: rivaroxaban, apixaban) 고려

- **관련 임상 연구들 (Hokusai-VTE, SELECT-D, Caravaggio)** 을 기반으로 매우 강력한 추천 근거가 제시됨.

Guidelines : Chest, 2021

[Pulmonary Vascular Guidelines and Consensus Statements]

CHEST

Antithrombotic Therapy for VTE Disease

Check for updates

Second Update of the CHEST Guideline and Expert Panel Report

Scott M. Stevens, MD; Scott C. Woller, MD; Lisa Baumann Kreuziger, MD; Henri Bounameaux, MD; Kevin Doerschug, MD; Geert-Jan Geersing, MD, PhD; Menno V. Huisman, MD; Clive Kearon, MD, PhD; Christopher S. King, MD; Andrew J. Knighton, PhD; Erica Lake, MLS; Susan Murin, MD; Janine R. E. Vintch, MD; Philip S. Wells, MD; and Lisa K. Moores, MD

BACKGROUND: This is the 2nd update to the 9th edition of these guidelines. We provide recommendations on 17 PICO (Population, Intervention, Comparator, Outcome) questions, four of which have not been addressed previously.

METHODS: We generate strong and weak recommendations based on high-, moderate-, and low-certainty evidence, using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.

RESULTS: The panel generated 29 guidance statements, 13 of which are graded as strong recommendations, covering aspects of antithrombotic management of VTE from initial management through secondary prevention and risk reduction of postthrombotic syndrome. Four new guidance statements have been added that did not appear in the 9th edition (2012) or 1st update (2016). Eight statements have been substantially modified from the 1st update.

CONCLUSION: New evidence has emerged since 2016 that further informs the standard of care for patients with VTE. Substantial uncertainty remains regarding important management questions, particularly in limited disease and special patient populations.

CHEST 2021; 160(6):e545-e608

KEY WORDS: antithrombotic therapy; DVT; guidelines; pulmonary embolism; thrombosis

Guidelines : Chest, 2021

2nd update of the chest guideline and expert pannel report
핵심 내용

- **초기 치료**: 모든 급성 VTE 환자에게 **최소 3개월** 항응고 치료
- **연장 치료**:
  - **Unprovoked VTE** 또는 지속 위험 요소 있는 경우 → **연장 치료 권고**
  - **Provoked VTE** (일시적 위험) → 3개월 후 **중단 고려**
- **항응고제 선택**:
  - **DOAC** (Apixaban, Rivaroxaban, Edoxaban, Dabigatran) **우선 사용**
  - **Warfarin**은 **APS, 심한 신부전, 고비용환자** 등 특수 상황에서 고려
- **APS(항인지질증후군)**: **Warfarin 우선**, DOAC 사용은 권장되지 않음
- **Reduced-dose DOAC 연장**:
  - Rivaroxaban 10 mg QD 또는 Apixaban 2.5 mg BID 사용 가능

Guidelines : ISTH, 2021-2022

jth

RECOMMENDATIONS AND GUIDELINES

Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation

Karlyn A. Martin[1] | Jan Beyer-Westendorf[2] | Bruce L. Davidson[3] | Menno V. Huisman[4] | Per Morten Sandset[5] | Stephan Moll[6]

DOI: 10.1002/rth2.12726

rpth research & practice in thrombosis & haemostasis

ORIGINAL ARTICLE

Management of cancer-associated thrombosis with thrombocytopenia: Impact of the ISTH guidance statement

Nicole Held DO[1] | Benjamin Jung PharmD, MS[2] | Lisa Baumann Kreuziger MD, MS[1,3]

Guidelines : ISTH, 2021-2022
핵심 내용

1. DOAC 사용 가이드 – 비만 및 고체중 대상(updated ISTH-SSC 2021)

: ISTH-SSC 발표 (2021)

- **BMI ≤40 kg/m²** 또는 **체중 ≤120 kg** 환자에서 **모든 DOAC 사용 적합**
- **BMI >40 kg/m²** 또는 **체중 >120 kg**인 경우
  - **: Rivaroxaban, Apixaban은 권장**
  - **: Dabigatran, Edoxaban, Betrixaban은 비권장**
  - : DOAC 혈중농도(peak/trough) 모니터링도 **정기적 권고하지 않음**

📌 *임상적 의미*

: 고체중 환자에서도 Rivaroxaban/Apixaban은 안전하게 사용할 수 있으며, 나머지는 주의 필요

Guidelines : ISTH, 2021-2022
핵심 내용

2. 암환자의 혈전증 및 혈소판 감소증 (CAT with Thrombocytopenia)

- **Held N. et al., *Res Pract Thromb Haemost*. 2022**

  : ISTH SSC 가이드라인에 따라 암환자 혈소판 감소증에서의 **항응고 전략을 구현한 결과**:

  - 혈소판 수 ≥50 × 10^3/μL: **표준 용량 항응고 + 수혈 지원**
  - 혈소판 25–50 × 10^3/μL: **감량 항응고 용량 유지**
  - 혈소판 <25 × 10^3/μL: **항응고 중단 권고**

- **결과**: 항응고 중단 후 혈전재발율과 출혈율 차이 없음, **알고리즘 준수 91%**

📌 *임상적 의미*

: 암환자가 혈소판 저하 시에도 안전하게 항응고 용량 조절을 통해 치료 지속 가능

Guidelines : ASH, 2020

CLINICAL GUIDELINES

blood advances

Check for updates

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

Thomas L. Ortel,[1] Ignacio Neumann,[2] Walter Ageno,[3] Rebecca Beyth,[4,5] Nathan P. Clark,[6] Adam Cuker,[7] Barbara A. Hutten,[8] Michael R. Jaff,[9] Veena Manja,[10,11] Sam Schulman,[12,13] Caitlin Thurston,[14] Suresh Vedantham,[15] Peter Verhamme,[16] Daniel M. Witt,[17] Ivan D. Florez,[18,19] Ariel Izcovich,[20] Robby Nieuwlaat,[19] Stephanie Ross,[19] Holger J. Schünemann,[19,21] Wojtek Wiercioch,[19] Yuan Zhang,[19] and Yuqing Zhang[19]

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Guidelines : ASH, 2020

핵심 요약

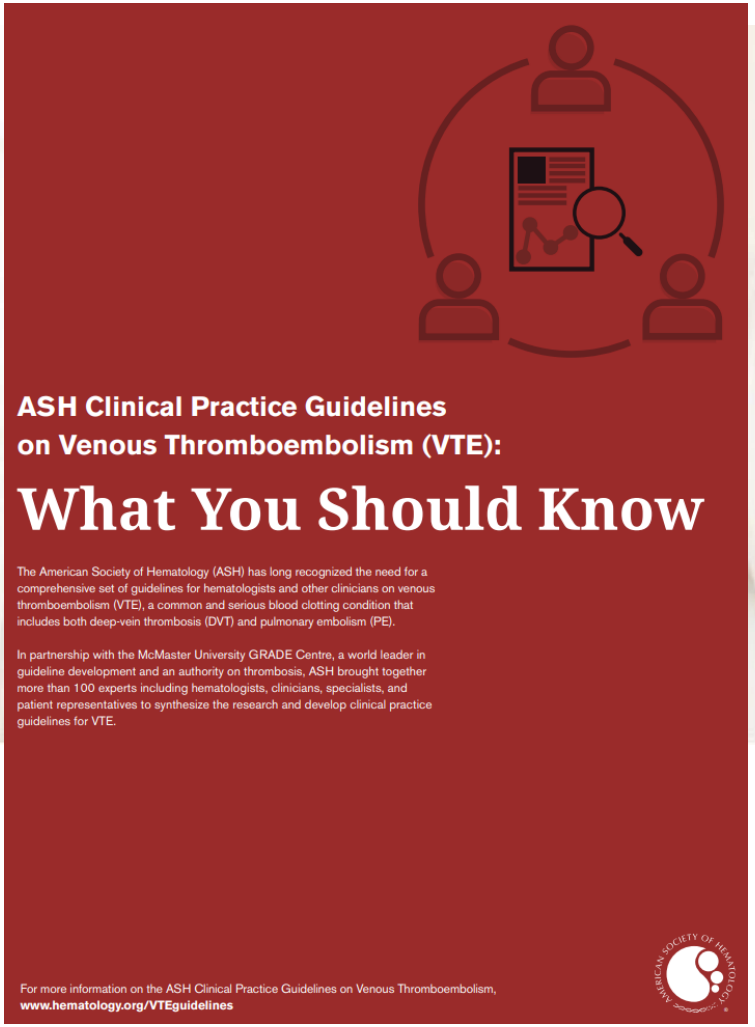
구간	추천 치료 기간	권고 약제/용량
초기 치료	5–21일	DOAC 선호 (예: rivaroxaban, apixaban)
1차 치료	3–6개월	DOAC or VKA
연장 치료	무기한(**재발/발병 위험 높음**)	DOAC (표준 또는 저용량) or Warfarin (APS, 신기능 저하 시)
APS 환자	-	Warfarin 우선, DOAC 자제
DOAC 용량 전략	-	rivaroxaban 10 mg QD, apixaban 2.5 mg BID

Guidelines : ASH, 2020

핵심 요약

- **임상 적용 포인트**
  - **일반 DVT/PE**
    : **DOAC이 1차 치료** 및 연장 치료에서 우선 선택지
  - **Provoked VTE (일시적 위험요인)**
    : 3–6개월 치료 후 보통 중단 가능
  - **Unprovoked VTE 또는 지속/재발 고위험군**
    : 항응고제를 **무기한 유지**하고, **DOAC 저용량 전략**이 유용
  - **APS 환자**
    : Warfarin 유지가 안전상 보장되고 DOAC은 피해야 한다

Guidelines : ASH, 2023



Blood Advances, 2023 Nov 28;7(22):7101–7138

Guidelines : ASH, 2023

핵심 요약

- **비유발성** VTE: **Low-bleeding risk**인 경우 **무기한 항응고 치료 권고**
- **초기 치료**: **DOAC** 또는 **헤파린 계열** 항응고제로 **3개월 이상** 사용
- **추가 권고**
  - 기저 질환/재발 요인 있는 경우 치료 연장
  - **고출혈 위험**이 있거나 **유발 인자 명확** 시 단기 치료 → **중단 가능**
- **Thrombophilia 검사의 역할**
  : 일부 혈전성 질환에서 조기 진단 및 치료 계획에 고려

Guidelines : ASH, 2023

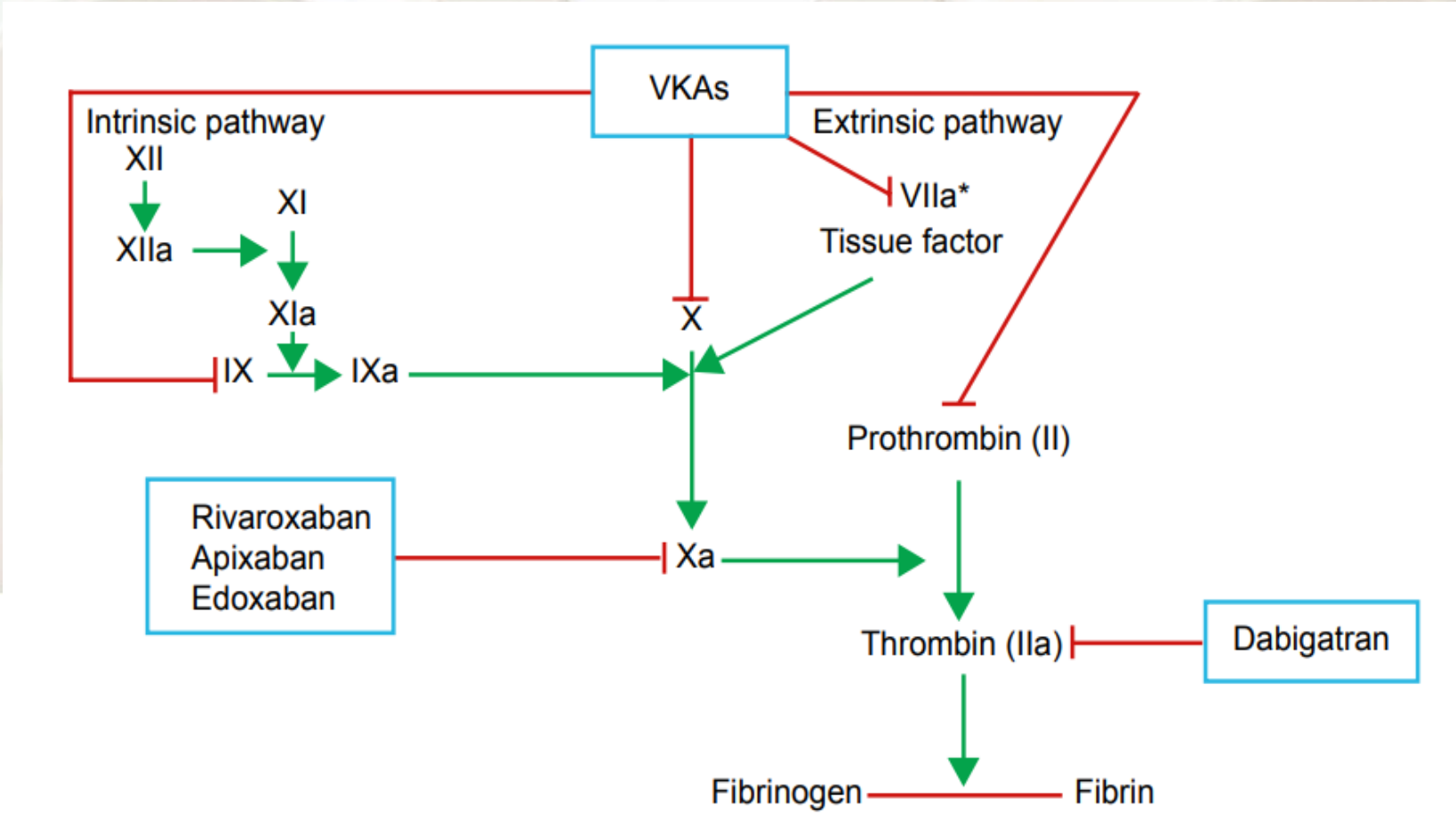
전체 내용

- **초기 치료** – DVT/PE 급성기
- **1차 치료** – 최소 3개월
- **2차 예방** – 재발 위험 고려하여 연장 여부 평가
- **Thrombophilia testing** – ***적응증 있는 환자에게 선별 권고***

  ➞ ASH는 매년 모니터링 및 최신 연구 반영 방식으로 지침을 **"리빙(living)" 형태로 유지** 중

가장 최신 ASH 지침은 2023년 기준으로 **비유발성 VTE의 indefinite 치료 권고**와 **thrombophilia testing 가이드라인**을 포함

Mx of anticoagulants effect of indirect (VKAs) and direct anti-IIa and anti-Xa anticoagulants (DOACs)



Warfarin vs DOAC: 작용기전 비교

구분	**Warfarin**	**DOAC**
분류	비타민 K 길항제 (VKA)	직접 작용 항응고제 (Direct oral anticoagulant)
작용 위치	간(Liver)	혈액 내(Plasma) 직접 작용
작용 표적	비타민 K 의존 응고인자 **II, VII, IX, X** (합성 억제)	**Dabigatran**: 트롬빈 (Factor IIa) 직접 억제 **Rivaroxaban, Apixaban, Edoxaban** : Factor Xa 직접 억제
작용 시작	느림 (2~3일 후 효과)	빠름 (1~4시간 내 효과)
작용 지속시간	긴 반감기 (40시간 이상)	약제별 반감기 다양 (약 12시간 내외)
혈중 모니터링 필요성	필요 (INR 측정)	대부분 불필요
해독제	**Vitamin K, PCC (Prothrombin Complex Concentrate)**	**Dabigatran**: Idarucizumab **Xa 억제제**: Andexanet alfa (제한적 사용)

Warfarin vs DOAC: 주요 차이점

항목	**Warfarin**	**DOAC** **(Apixaban, Rivaroxaban, Dabigatran, Edoxaban)**
작용 기전	비타민 K 길항제 (VKAs)	특정 응고 인자 직접 억제 (Xa 또는 IIa 억제)
약물 모니터링	필수 (INR 측정 필요)	대부분 필요 없음
시작 작용 시간	느림 (효과 나타나기까지 수일 소요)	빠름 (1~4시간 이내 효과 시작)
음식 상호작용	많음 (특히 비타민 K 풍부한 음식 주의)	적음
약물 상호작용	많음	비교적 적음
해독제	Vitamin K, FFP 등 사용 가능	일부 해독제 있음 (예: Idarucizumab for Dabigatran, Andexanet alfa for Xa inhibitors)
복용 횟수	1일 1회	약제에 따라 1~2회
비용	저렴함	상대적으로 고가

선택 기준 요약

1. 환자의 신장 기능
: **DOAC**는 대부분 **신장을 통해 배설**되므로 **신부전이 심한 경우에는 Warfarin이 선호**.
단, DOAC 중 Apixaban은 신장 의존도가 낮아 일부 환자에서 사용 가능.

2. 모니터링 가능성
: 모니터링이 어렵거나, 정기 병원 방문이 힘든 경우 DOAC 선호
: 환자가 INR 모니터링을 잘할 수 있다면 Warfarin도 가능

3. 출혈 위험
: 전반적으로 **DOAC가 뇌출혈 위험이 더 낮음**.
: 위장관 출혈 위험은 약제에 따라 Warfarin보다 높을 수도 있음 (예: Dabigatran)

4. 비용 및 보험
: DOAC는 비용이 높아 **경제적 제약이 있는 경우 Warfarin 선택**

5. 특수 상황
: 기계판막 환자: **Warfarin만 사용 가능**, DOAC는 금기
: 항인지질증후군: **Warfarin 선호**
: 임신: Warfarin은 기형 유발 가능 → 필요 시 **저분자량 헤파린** 사용

DVT/PE 치료 시 사용 가능한 주요 항응고제

약제	종류	기전	용량 특성	신장 기능 고려	해독제	투약 빈도
Warfarin	VKA	비타민 K 길항	INR 모니터링 필요	사용 가능 (**신기능 무관**)	Vitamin K, PCC	하루 1회
Rivaroxaban **(자렐토)**	DOAC (Xa억제)	직접 Xa 억제	**초기 15mg 1일 2회** **→ 20mg 1일 1회**	**CrCl <30 주의**	Andexanet alfa	하루 1~2회
Apixaban **(엘리퀴스)**	DOAC (Xa억제)	직접 Xa 억제	**초기 10mg 1일 2회** → 5mg 1일 2회	**CrCl <25** **또는 ESRD 주의**	Andexanet alfa	하루 2회
Dabigatran **(프라닥사)**	DOAC (IIa억제)	직접 트롬빈 억제	**초기 헤파린 병용 필요** → 150mg 1일 2회	**CrCl <30 금기**	Idarucizumab	하루 2회
Edoxaban **(릭시아나)**	DOAC (Xa억제)	직접 Xa 억제	**초기 헤파린 병용 필요** **→ 60mg 1일 1회**	**CrCl <15 금기**	없음 (응급 시 PCC)	하루 1회

요약

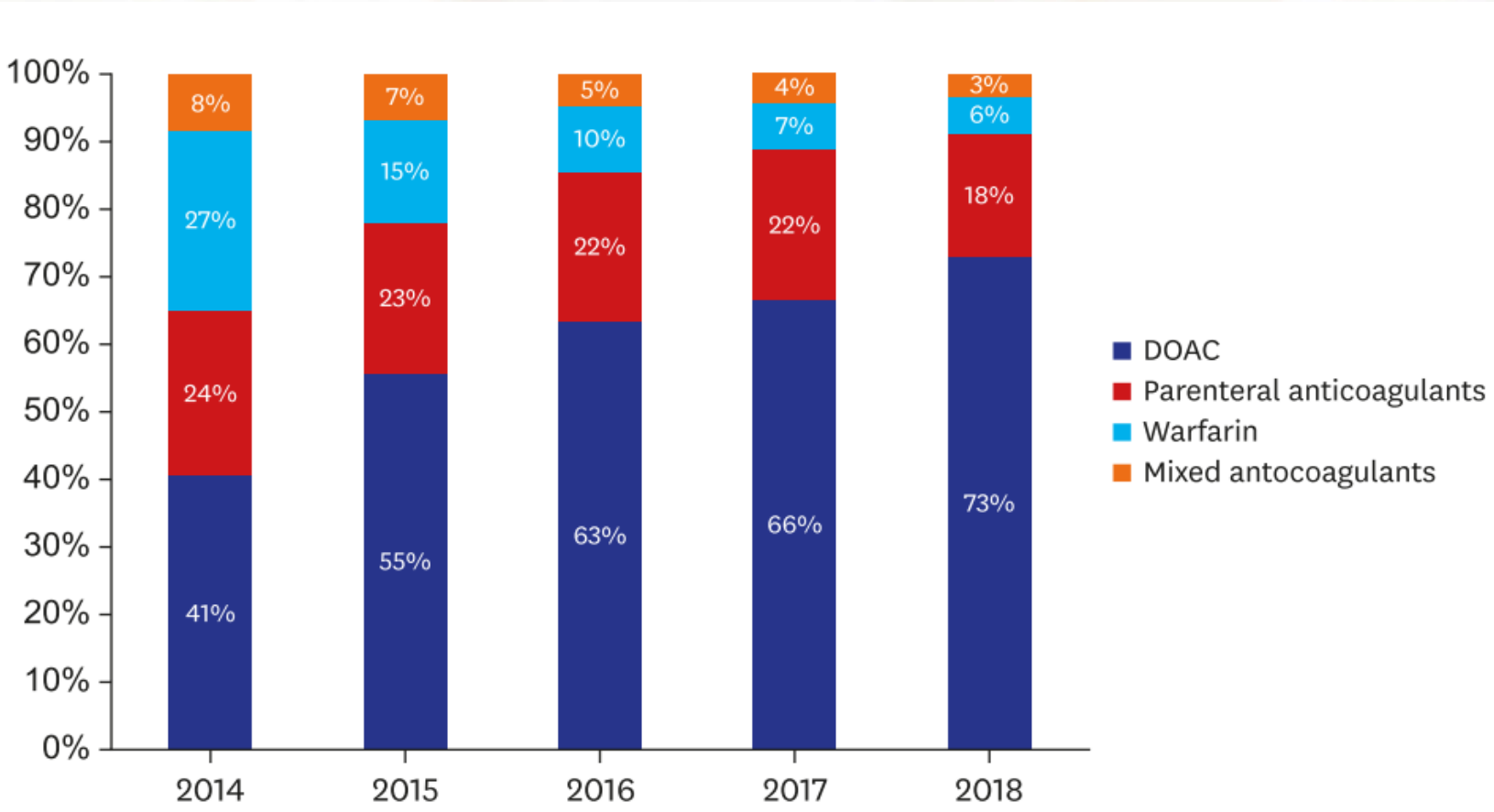
- **Warfarin**
  : 저렴하지만 모니터링과 식이조절 필요.
  : 신장 기능 매우 나쁜 환자에서도 사용 가능
  : 기계판막, 항인지질증후군 등 특수 상황에서 필수
  : 장기간 데이터 축적

- **DOAC**
  : 편리하고 출혈 위험 낮으며 상호작용 적음.
  => 다만, 비용이 높고 **일부 환자(신부전, 기계판막 등)에 사용 제한 있음**.
  : 빠른 효과 발현 → 초기 병원 입원 기간 단축
  : 고정 용량, 모니터링 불필요
  : 출혈 위험 (특히 뇌출혈) 낮음
  : 음식/약물 상호작용 적음

DVT/PE 환자 맞춤 약제 선택 가이드

상황	권장 약제	설명
초기 외래치료 or 조기 퇴원 목표	**Rivaroxaban, Apixaban**	입원 없이 경구치료 시작 가능 (헤파린 필요 없음)
신장기능 저하 (CrCl <30)	**Warfarin**	대부분 DOAC 사용 제한, Warfarin 사용
환자 모니터링 어렵고 복용 간단한 게 필요	**Rivaroxaban (1일 1회)**	복용 편의성 우수
출혈 위험 높은 환자	**Apixaban**	DOAC 중 가장 낮은 출혈 위험으로 보고됨
경제적 부담 큰 환자	**Warfarin**	비용 저렴, 보험 적용 범위도 넓음
암 관련 혈전증	**Apixaban, Edoxaban, LMWH**	DOAC도 일부 권장됨 (예: ASCO 가이드라인)
체중이 매우 낮거나 높음	**Warfarin or 용량 조절 가능한 DOAC (Apixaban)**	극단적 체중일 경우 DOAC 효과 불확실 가능성

Anticoagulation trend for VTEbolism from 2014 to 2018



치료 기간

상황	권장 치료 기간
첫 VTE, 유발 인자 있음 (예: 수술, 외상)	3개월
첫 VTE, 유발 인자 없음 (idiopathic)	최소 3개월 → 위험도 따라 연장 고려
재발성 VTE	장기 항응고 치료 고려
암 관련 VTE	최소 3~6개월, 활동성 암인 경우 연장 고려

Overview of Anticoagulation RCTs in VTE

Clinical Trial (Ref. # (Study Drug)	Included Patients	Trial Design	Length of follow-up	N	Treatment Groups	TTR	Primary Efficacy Outcome	Rate of Primary Outcome	Rate of Major Bleeding
RE-COVER (15) (dabigatran)	Acute symptomatic proximal DVT or PE	Double-blind, double-dummy RCT	6 months	2,564	Dabigatran 150 mg twice daily. After 5-10 days of parenteral anticoagulation versus parenterally bridged, adjusted-dose warfarin targeting INR 2.0-3.0	60%	Composite of symptomatic VTE or death associated with VTE	Dabigatran: 2.4% Warfarin: 2.1% HR: 1.10 (0.65-1.84)	Dabigatran: 1.6% Warfarin: 1.9% HR: 0.82 (0.45-1.48)
RE-COVER II (16) (dabigatran)	Acute symptomatic proximal DVT or PE	Double-blind, double-dummy RCT	6 months	2,568	Dabigatran 150 mg twice daily after 5-10 days of parenteral anticoagulation versus parenterally bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	57%	Composite of symptomatic VTE or death associated with VTE	Dabigatran: 2.3% Warfarin: 2.2% HR: 1.08 (0.64-1.8)	Dabigatran: 1.2% Warfarin 1.7% HR: 0.69 (0.36-1.32%)
EINSTEIN DVT (17) (rivaroxaban)	Acute symptomatic proximal DVT without PE	Open-label RCT	3, 6, or 12 months	3,449	Rivaroxaban 15 mg twice daily x 21 days, then 20 mg daily versus enoxaparin-bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	58%	Recurrent symptomatic VTE	Rivaroxaban: 2.1% Warfarin: 3.0% HR: 0.68 (0.44-1.04)	Rivaroxaban: 0.8% Warfarin: 1.2% HR: 0.65 (0.33-1.30)
EINSTEIN PE (18) (rivaroxaban)	Acute symptomatic PE with or without DVT	Open-label RCT	3, 6, or 12 months	4,832	Rivaroxaban 15 mg twice daily x 21 days, followed by 20 mg daily versus enoxaparin-bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	63%	Recurrent symptomatic VTE	Rivaroxaban: 2.1% Warfarin: 1.8% HR: 1.12 (0.75-1.68)	Rivaroxaban: 1.1% Warfarin: 2.2% **HR: 0.49 (0.31-0.79)**
AMPLIFY (19) (apixaban)	Acute symptomatic proximal DVT or PE	Double-blind double-dummy RCT	6 months	5,395	Apixaban 10 mg twice daily x 7 days followed by 5 mg twice daily versus enoxaparin-bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	61%	Composite of symptomatic VTE or death associate with VTE	Apixaban: 2.3% Warfarin: 2.7% HR: 0.84 (0.6-1.18)	Apixaban: 0.6% Warfarin: 1.8% **HR: 0.31 (0.17-0.55)**
Hokusai VTE (20) (edoxaban)	Acute symptomatic DVT of popliteal, femoral or iliac veins, or acute symptomatic PE	Double-blind double-dummy RCT	3-12 months	8,240	Edoxaban 60 mg daily after 5-10 days of parenteral anticoagulation versus parenterally bridged, adjusted-dose warfarin targeting INR: 2.0-3.0	64%	Composite of recurrent symptomatic VTE or VTE-related death	Edoxaban: 3.2% Warfarin: 3.5% HR: 0.89 (0.70-1.13)	Edoxaban: 1.4% Warfarin: 1.6% HR: 0.81 (0.59-1.21)

Bold refers to values that are statistically significant.

DVT = deep vein thrombosis; HR = hazard ratio; INR = international normalized ratio; PE = pulmonary embolism; RCT = randomized controlled trial; TTR = time in therapeutic range; VTE = venous thromboembolism.

J Am Coll Cardiol. 2020 Nov 3;76(18):2142-2154.

Examples of VTE provoking risk factors

Major Transient Risk Factors	Minor Transient Risk Factors	Persistent Risk Factors
-Cesarean section. -Confined to hospital bed for 3 days. -Surgery with general anesthesia for >30 min.	-Confined to bed out of hospital for 3 days. -Hospitalization < 3 days. -Leg injury. -Pregnancy. -Estrogen therapy. -Acute infectious illness (e.g., COVID-19) without hospitalization.	-Active cancer. -Inflammatory bowel disease. -Obesity. -Chronic inflammatory condition. -Advanced age. -Previous venous thromboembolism. -Genetic/acquired thrombophilia (APS, protein C&S deficiency, etc.).

Malik et al, J. Clin. Med. 2024, 13, 301.

RCTs of OACs in Secondary Prevention

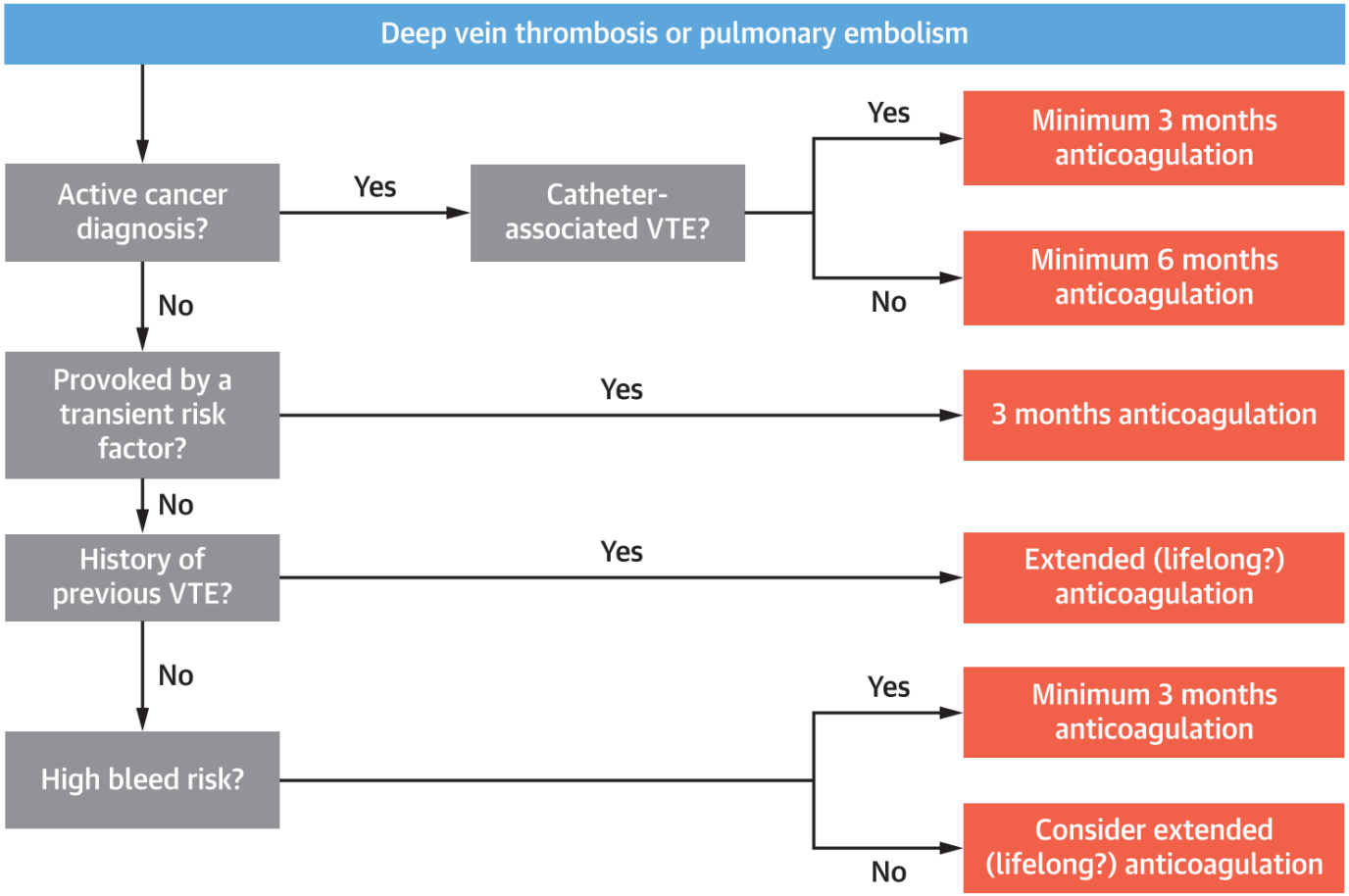
Trial (Ref. #) (Study Drug)	Included Patients	Design	Treatment Duration	N	Treatment Groups	TTR	Primary Efficacy Outcome	Rate of Primary Outcome	Rate of Major Bleeding
RE-MEDY (39) (dabigatran)	Patients previously enrolled in RE-COVER or RE-COVER II at with continued risk of VTE after 3–12 months	Double-blind, double-dummy RCT	6-36 months	2,866	Dabigatran 150 mg twice daily vs. adjusted-dose warfarin targeting INR: 2.0–3.0	65%	Composite of symptom-atic VTE or death associated with VTE	Dabigatran: 1.8% Warfarin: 1.3% HR: 1.44 (0.78-2.64)	Dabigatran: 0.9% Warfarin: 1.8% HR: 0.52 (0.27-1.02)
RE-SONATE (39) (dabigatran)	Patients previously in RE-COVER or RE-COVER II being considered for therapy discontinuation after 6–18 months	Double-blind RCT	6 months	1,353	Dabigatran 150 mg twice daily versus placebo	n/a	Composite of symptom-atic VTE or death associated with VTE	Dabigatran: 0.4% Placebo: 5.6% **HR: 0.08 (0.02–0.25)**	Dabigatran: 0.3% Placebo: 0% HR: nonestimable
EINSTEIN-EXT (17) (rivarox-aban)	Patients on warfarin 6–12 months after a VTE (may have been in EINSTEIN program) or rivaroxaban (all from EINSTEIN)	Open-label RCT	6 or 12 months	1,197	Rivaroxaban 20 mg daily vs. placebo	n/a	Recurrent symptomatic VTE	Rivaroxaban: 1.3% Placebo: 7.1% **HR: 0.18 (0.09–0.39)**	Rivaroxaban: 0.7% Placebo: 0% HR: nonestimable
AMPLIFY-EXT (40) (apixaban)	Patients on apixaban who had received 6–12 months of treatment after VTE	Double blind, double dum-dum RCT	12 months	2,486	Apixaban 5 mg twice daily, 2.5 mg twice daily, or placebo	n/a	Symptomatic recurrent VTE or death	Apixaban 5 mg twice daily: 4.2% Apixaban 2.5 mg twice daily: 3.8% Placebo: 11.6% **Placebo HR 0.33 (0.22–0.48) for 2.5 mg BID vs. placebo**	Apixaban 5 mg twice daily: 0.1% Apixaban 2.5 mg twice daily: 0.2% Placebo: 0.05% HR: 0.25 (0.03–2.24) for apixaban 5 mg twice daily vs. placebo HR: 0.49 (0.09–2.64) for apixaban 2.5 mg twice daily vs. placebo
EINSTEIN (41) CHOICE (rivarox-aban)	Patients who were on an anticoagulant 6–12 months after a VTE	Double-blind RCT	Up to 12 months	3,365	Rivaroxaban 20 mg daily, 10 mg daily, or aspirin 100 mg daily	n/a	Symptomatic recurrent fatal or nonfatal VTE	Rivaroxaban 20 mg daily: 1.5% Rivaroxaban 10 mg daily: 1.2% Aspirin 100 mg daily: 4.4% **HR: 0.34 (0.20–0.59) for 20 mg daily vs. aspirin** **HR: 0.26 (0.14–0.47) for 10 mg daily vs. aspirin**	Rivaroxaban 20 mg daily: 0.5% Rivaroxaban 10 mg daily: 0.4% Aspirin 100 mg daily: 0.3% HR: 2.01 (0.50–8.04) for rivaroxaban 20 mg daily vs. aspirin HR: 1.64 (0.39–6.84) for rivaroxaban 10 mg daily vs. aspirin

Bold refers to values that are statistically significant.

HR = hazard ratio; INR = international normalized ratio; RCT = randomized-controlled trial; TTR = time in therapeutic range; VTE = venous thromboembolism.

J Am Coll Cardiol. 2020 Nov 3;76(18):2142-2154.

Decision Tool for Shorter Versus Longer Course of Anticoagulation

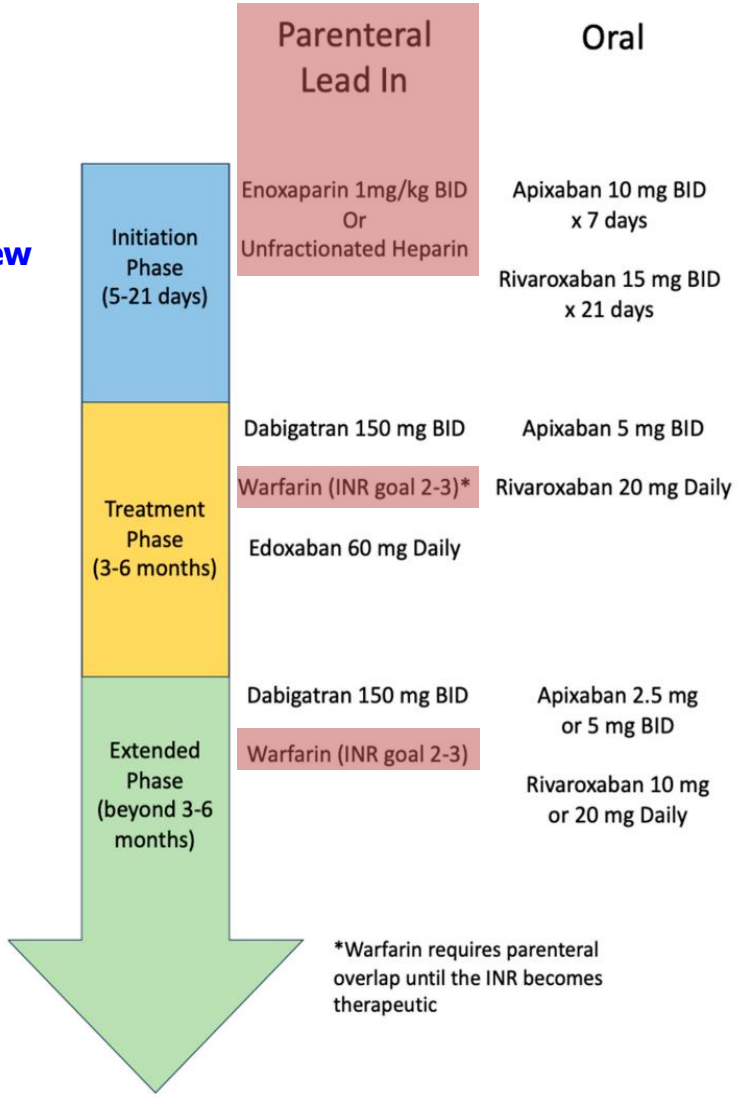


J Am Coll Cardiol. 2020 Nov 3;76(18):2142-2154.

Choice and duration of anticoagulation for VTE

1) initiation phase is to **slow down any active thrombus formation**, helping to **prevent new thrombus** from forming while allowing the **body's natural thrombolytic process** to proceed and restore/maintain venous blood flow.

3) Extended phase is the risk vs. benefit of **full dose** anticoagulation vs. **reduced-dose** anticoagulation vs. **no anticoagulation** will need to be considered depending on the **patient's risk factors**



2) For the treatment phase, all patients are recommended to receive 3–6 months of treatment with anticoagulation. This is the time when patients are at the **highest risk of recurrence** as an **acute thrombus is being converted to fibrin**

Malik et al, J. Clin. Med. 2024, 13, 301.

Choice in Subgroup or Special Population

Subgroup : 극단 체중군, 암환자, 신장 기능 저하
핵심요약

1. 극단 체중군 (고도비만·저체중)

(1) 고도 비만 (BMI > 40 kg/m² 또는 체중 > 120 kg)

: ISTH 권고 (2021): Rivaroxaban 또는 Apixaban의 표준용량 권장

- 다만, BMI ≥ 50 kg/m² 또는 체중 ≥ 150 kg에 대한 데이터 부족으로 그 이상 체중에서는 주의 필요
- **실제 임상 실증: Rivaroxaban 사용 고도 비만군(VTE, 약 8600명)에서 재발률 감소(HR 0.85), 출혈 위험 유사**

: **Apixaban도 저체중·고도비만 모두에서 안전·효과 유사**

(2) 저체중 (< 60 kg)

: 표준 용량 DOAC 사용 가능하지만, 심한 신기능 감소나 고령 일부 승인을 위해 **Apixaban 감량(2.5 mg BID) 고려 가능**

Effectiveness, safety, and healthcare costs associated with rivaroxaban versus warfarin among venous thromboembolism patients with obesity: a real-world study in the United States

Jeffrey S. Berger[1] · François Laliberté[2] · Akshay Kharat[3] · Dominique Lejeune[2] · Kenneth Todd Moore[4] · Young Jung[2] · Patrick Lefebvre[2] · Veronica Ashton[3]

Accepted: 18 April 2022 / Published online: 13 May 2022

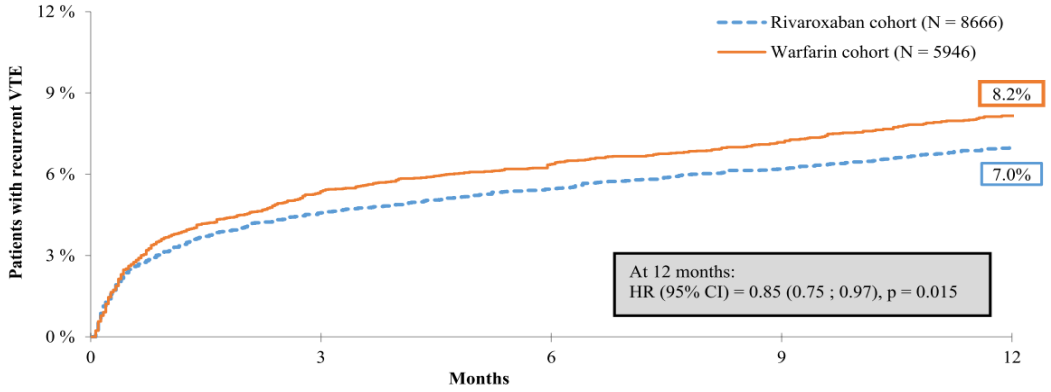
- A **retrospective**, **observational cohort study** was conducted.
- the date of initiation of **rivaroxaban or warfarin ≤ 30 days after a first VTE** event
- (1) ≥ 12 months of continuous health plan enrollment pre-index date,
- (2) ≥ 1 medical claim with a diagnosis of **obesity/BMI ≥ 30 kg/ m2**
- (3) ≥ 18 years old at index date.

Table 1 Baseline demographics and clinical characteristics of the vte patients with obesity treated with rivaroxaban or warfarin

	Unweighted cohorts			Weighted cohorts[a]		
	Rivaroxaban N = 8666	Warfarin N = 5946	Std. diff.[b,c] (%)	Rivaroxaban N = 8666	Warfarin N = 5946	Std. diff.[b,c] (%)

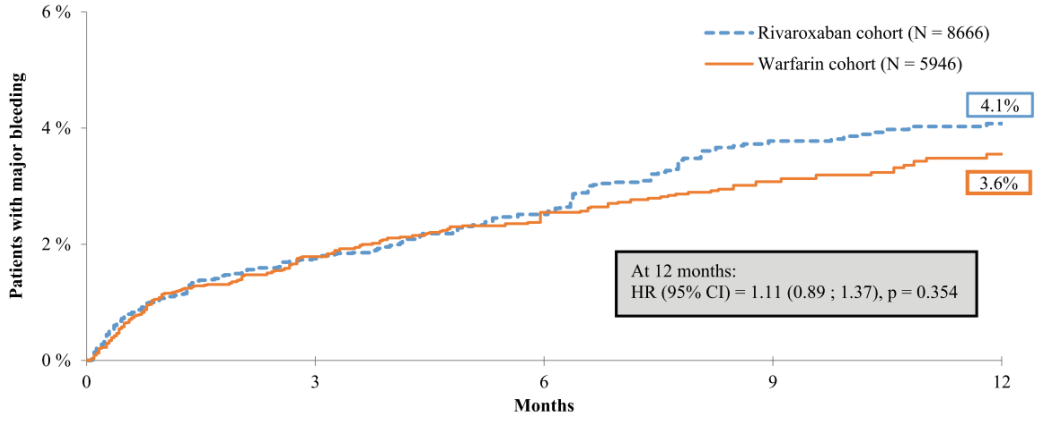
https://doi.org/10.1007/s11239-022-02661-1

Kaplan–Meier Rates of Recurrent VTE1—Intention-to-Treat



Patients at risk[2]			
Rivaroxaban	8666	6508	5045
Warfarin	5946	4404	3391

Kaplan–Meier Rates of Major Bleeding1—On-Treatment



Patients at risk[2]			
Rivaroxaban	8666	3844	1808
Warfarin	5946	2748	1221

https://doi.org/10.1007/s11239-022-02661-1

Subgroup : 극단 체중군, 암환자, 신장 기능 저하
핵심요약

2. 암환자 대상 서브그룹

- 주요 연구 및 비교

1) CARAVAGGIO (Apixaban vs Dalteparin)

: 재발률과 주요 출혈 모두 비슷. HR 재발 0.63, 출혈 0.82

2) SELECT-D (Rivaroxaban vs Dalteparin) & HOKUSAI-VTE (Edoxaban vs Dalteparin)

: **Rivaroxaban, Edoxaban** *모두 재발률 비열등*,
다만 일부 GI암 환자에서 출혈 증가 관찰

- ASH 2021 가이드라인

: **암관련 VTE 초치료로 Apixaban 또는 Rivaroxaban 권장**.
LMWH 고려 가능

: 종양 위치·치료제 상호작용·출혈 위험·환자 선호 등 고려한 개별 치료 알고리즘 제안.

RCTs of OAC Use on Cancer Pts With VTE

Clinical Trial (Ref. #) (Study Drug)	Included Patients	Trial Design	Length of Follow-Up	N	Treatment Groups	Efficacy Outcome	Rate of Efficacy Outcome	Rate of Major Bleeding
Hokusai VTE Cancer (28) (edoxaban)	Patients with active cancer and symptomatic or incidental popliteal, femoral or iliac or IVC DVT, symptomatic or incidental PE	Open-label RCT	12 months	1,050	Edoxaban 60 mg daily after 5-10 days of parenteral anticoagulation versus dalteparin 200 IU/kg x 30 days, then 150 IU/kg	Recurrent VTE (secondary)	Edoxaban: 7.9% Dalteparin: 11.3% HR: 0.71 (0.48-1.06)	Edoxaban: 6.9% Dalteparin: 4.0% **HR: 1.77 (1.03-3.04)**
SELECT-D (29) (rivaroxaban)	Patients with active cancer and symptomatic DVT, symptomatic PE, or incidental PE	Open-label RCT	6 months	406	Rivaroxaban 15 mg twice daily x 21 days, then 20 mg daily versus dalteparin 200 IU/kg x 30 days, then 150 IU/kg	Recurrent VTE	Rivaroxaban: 4% Dalteparin: 11% **HR: 0.43 (0.19-0.99)**	Rivaroxaban: 6% Dalteparin: 4% HR: 1.83 (0.68-4.96)
ADAM VTE (30) (apixaban)	Active cancer patients with acute DVT (including upper extremity), PE, splanchnic or cerebral vein thrombosis	Open-label RCT	6 months	300	Apixaban 10 mg twice daily x 7 days then 5 mg twice daily versus dalteparin 200 IU/kg x 30 days, then 150 IU/kg	Venous or arterial thrombo-embolism (secondary outcome)	Apixaban: 6% Dalteparin: 6% HR: 0.931 (0.43-2.02)	Apixaban: 0% Dalteparin: 1.4% HR: not estimable
Caravaggio (31) (apixaban)	Patients with active or recent cancer and acute DVT or PE	Open-label RCT	6 months	1,155	Apixaban 10 mg twice daily x 7 days then 5 mg twice daily versus dalteparin 200 IU/kg x 30 days, then 150 IU/kg	Recurrent VTE	Apixaban: 5.6% Dalteparin: 7.9% HR: 0.63 (0.37-1.07)	Apixaban: 3.8% Dalteparin: 4.0% HR: 0.82 (0.40-1.69)

Bold refers to values that are statistically significant.

DVT = deep vein thrombosis; HR = hazard ratio; IVC = inferior vena cava; PE = pulmonary embolism; RCT = randomized controlled trial; VTE = venous thromboembolism.

J Am Coll Cardiol. 2020 Nov 3;76(18):2142-2154.

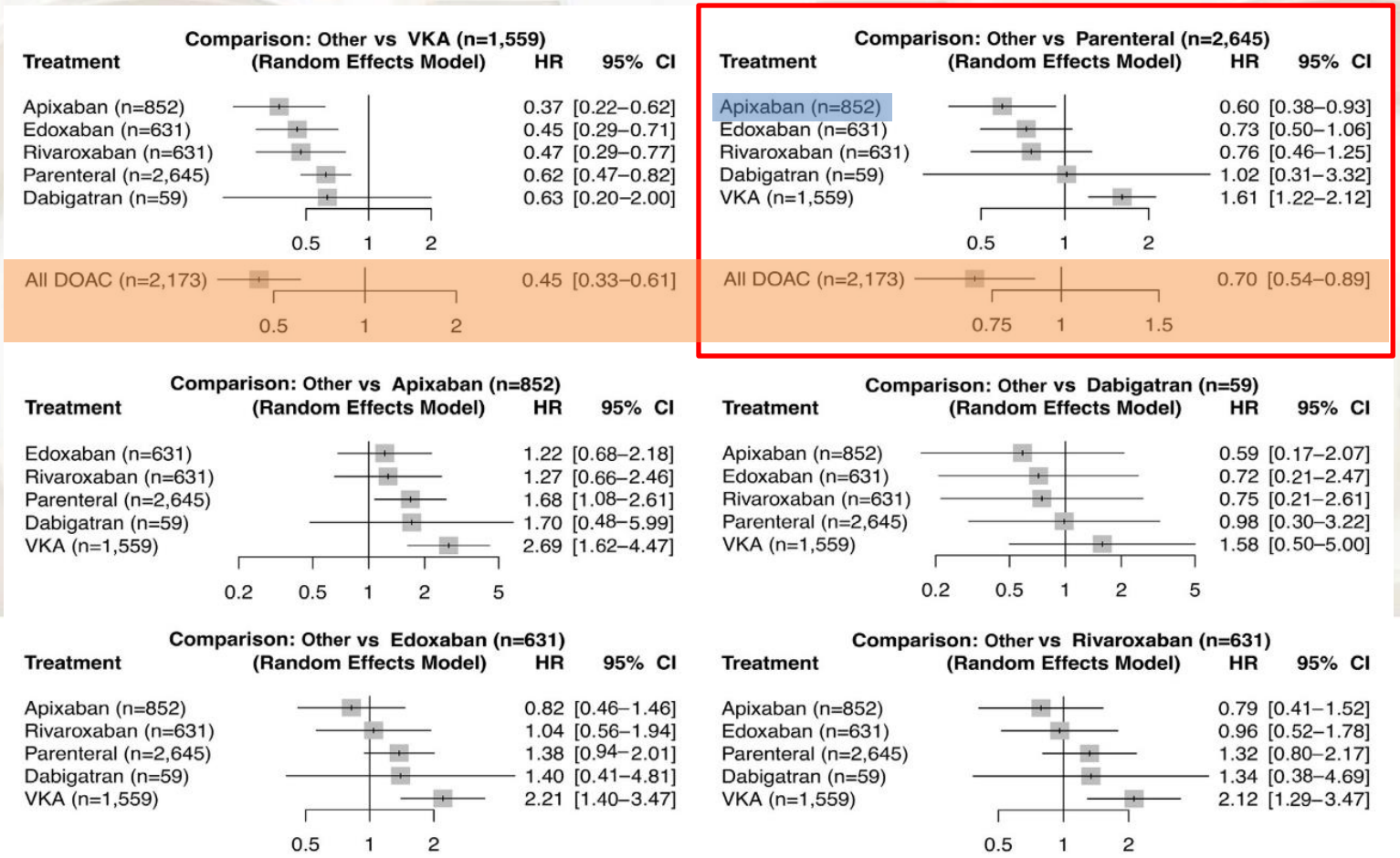
The efficacy and safety of DOACs in patients with active cancer

Comparing Anticoagulation Strategies for Venous Thromboembolism Associated With Active Cancer

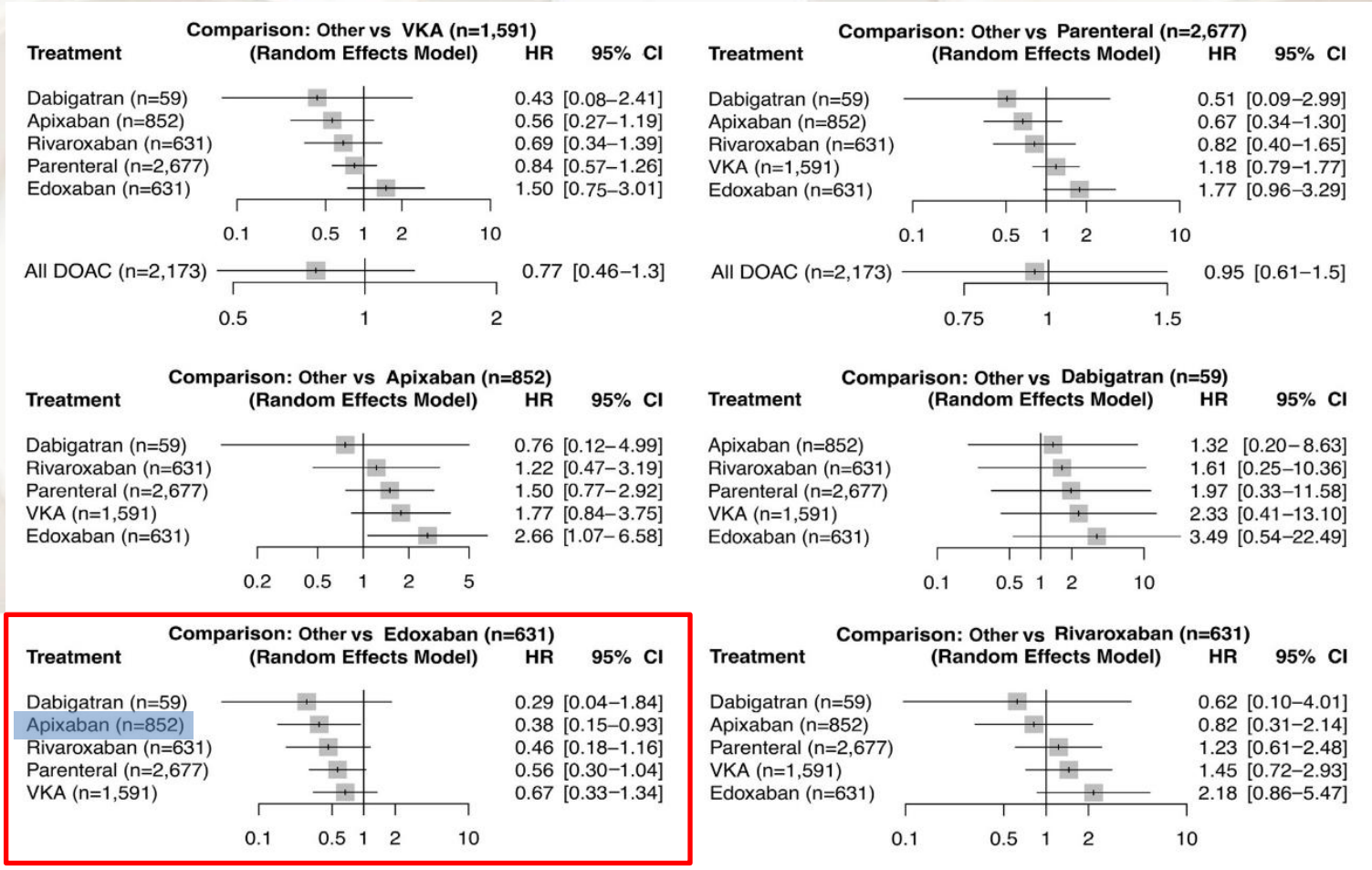
A Systematic Review and Meta-Analysis

Tomohiro Fujisaki, MD,[a,b] Daisuke Sueta, MD, PhD,[a] Eiichiro Yamamoto, MD, PhD,[a] Conor Buckley, MD,[c] Guilherme Sacchi de Camargo Correia, MD,[d] Julia Aronson, MD,[e] Paulino Tallón de Lara, MD, PhD,[f] Koichiro Fujisue, MD, PhD,[a] Hiroki Usuku, MD, PhD,[a] Kenichi Matsushita, MD, PhD,[a] Roxana Mehran, MD,[g] George D. Dangas, MD, PhD,[g] Kenichi Tsujita, MD, PhD[a]

Results for the Primary Efficacy Outcome (Recurrent Venous Thromboembolism)



Results for the Primary Safety Outcome (Major Bleeding)



Subgroup : 극단 체중군, 암환자, 신장 기능 저하

핵심요약

3. 신장 기능 저하 및 ESRD (말기 신부전·투석)

- DOAC들은 CrCl ≥30 mL/min에서 정상적 사용 가능

- 중증 신부전 (CrCl 15–29 mL/min)

: **Apixaban, Rivaroxaban 감량 사용 가능**하나,

=> 눈에 띄는 RCT 근거는 부족

: Dabigatran, Edoxaban은 금기이거나 사용 제한

- ESRD & 투석

: 소규모 RCT 및 후향적 연구에서 Apixaban 또는 감량

: Rivaroxaban은 와파린 대비 뇌졸중 감소·출혈 유사 추세

: FDA 및 심장학회에서는 Apixaban(일부 감량) 또는 Rivaroxaban(감량) 고려, **그러나 RCT 근거는 여전히 제한적**

Subgroup : 극단 체중군, 암환자, 신장 기능 저하 요약

상황	권장 항응고제
극단 체중 (BMI>40, 체중>120kg)	Rivaroxaban 또는 Apixaban 표준용량
저체중 (<60kg, 고령)	Apixaban 감량 필요 시 고려
암환자	Apixaban 우선 (출혈 적고 재발 예방 우수), Rivaroxaban/Edoxaban도 가능, GI암은 주의
CrCl 30–50	Apixaban, Rivaroxaban, Edoxaban(감량), Dabigatran (감량)
CrCl 15–<30 / 투석	Apixaban 또는 감량 Rivaroxaban 가능. Dabigatran/Edoxaban 금기.
Bariatric 수술 후 급성 VTE	초기 4주간 parenteral 권고, 이후 DOAC 고려

RCT of OAC for APS patients with VTE

Clinical Trial (Ref. #)	Included Patients	N	Trial Design	Length of Follow-Up	Treatment Groups	Primary Efficacy Outcomes	Efficacy Outcomes	Major Bleeding Outcomes
RAPS [23]	Patients with APS who were taking warfarin for previous VTE	116	Open-label RCT	210 days	Continue warfarin vs. rivaroxaban 20 mg daily	Percentage change in endogenous thrombin potential at day 42, with non-inferiority set at less than 20% difference from warfarin	ETP (nmol/L per min): Rivaroxaban 1086 vs. warfarin 548 Treatment effect (ratio): 2.0 (1.7–2.4)	Rivaroxaban: 0 Warfarin: 0
TRAPS [24]	Patients with APS (triple positivity) with history of thrombus	120	Open-label RCT	569 days (mean)	Rivaroxaban 20 mg or 15 mg daily (dependent on creatine clearance) vs. warfarin	Cumulative incidence of thromboembolic events, major bleeding, and vascular death	Rivaroxaban: 19% Warfarin: 3% HR: 6.7 (1.5–30.5)	Rivaroxaban: 7% Warfarin: 3% HR: 2.5 (0.5–13.6)
Ordi-Ros et al. [25]	Patients with APS (positive result on aPL testing on 2 occasions at least 3 months apart) with history of thrombus	190	Open-label RCT	36 months	Rivaroxaban 20 mg or 15 mg daily (dependent on creatine clearance) vs. warfarin	Proportion of patients with new thrombotic event	Rivaroxaban: 11.6% Warfarin: 6.3% HR: 1.94 (0.72–5.24)	Rivaroxaban: 6.3% Warfarin: 7.4% HR: 0.88 (0.3–2.63)
ASTRO-APS [26]	Patients with thrombotic antiphospholipid syndrome on anticoagulation for secondary prevention	48	Open-label RCT	12 months	Apixaban 2.5 mg BID then increased to 5 mg BID (after 25 patient was randomized) vs. warfarin	Thrombosis and vascular death	Apixaban: 6 thrombotic events Warfarin: no thrombotic events	Apixaban: 0 Warfarin: 1 event

APS = antiphospholipid syndrome; BID = twice daily; ETP = endogenous thrombin potential; HR = hazard ratio; RCT = randomized control trial; VTE = venous thromboembolism.

Malik et al, J. Clin. Med. 2024, 13, 301.

Subgroup : APS

핵심요약

- **ISTH 2020 SSC**
- **증거 부족으로 triple-positive 또는 동맥혈전 병력이 있는 고위험 환자에서는 DOAC 사용을 권하지 않으며, Warfarin이 계속 첫 선택**
- **그러나 single/double-positive, 비고위험 환자에 대해서는 DOAC 사용을 상호의료진-환자와 협의 후 고려**

- **요약**
  - **High-risk APS (triple+, 동맥 혈전, 심장판막 이상 등)**
    : **Warfarin 유지가 첫 선택**
  - **Low-risk APS (single- 또는 double-positive, 경정맥 혈전만)**
    : **DOAC 투여 가능**, 단 환자와 심혈관팀 간 협의 필요

DOAC dosages and precautions in liver disease

Condition and direct oral anticoagulant	Child-Pugh class		
	A	B	C
Nonvalvular atrial fibrillation			
Apixaban	5 mg twice daily or 2.5 mg twice daily[a]	Limited clinical experience; recommendations cannot be provided	Avoid
Edoxaban	60 mg once daily	Avoid	Avoid
Rivaroxaban	20 mg once daily	Avoid[b]	No clinical data available; avoid[b]
Dabigatran	150 mg twice daily	Large intersubject variability, but no evidence of a consistent change in drug exposure; use with caution or avoid	No clinical data available; avoid
Venous thromboembolism			
Apixaban	10 mg twice daily; transition to 5 mg twice daily after 7 days	Limited clinical experience; recommendations cannot be provided	Avoid
Edoxaban	60 mg once daily	Avoid	Avoid
Rivaroxaban	15 mg twice daily; transition to 20 mg once daily after 21 days	Avoid[b]	No clinical data available; avoid[b]
Dabigatran	150 mg twice daily	Large intersubject variability, but no evidence of a consistent change in drug exposure; use with caution or avoid	No clinical data available; avoid

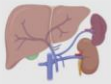
Note: Class A is mild hepatic impairment, B is moderate impairment, and C is severe liver disease. Additional adjustments needed for concomitant use of P-glycoprotein or cytochrome P450 3A4 inhibitors, or both, are not included.

[a]Reduce dose in patients with at least 2 of the following: age ≥ 80, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL.[17]

[b]Drug exposure and bleeding risk may be increased.[17,37]

Based on information from reference 36.

Indications for Which the Tradeoffs of Using DOACs Are Uncertain

	Study	Study Design	Topline Study Results	Key Knowledge Gaps
 Catheter-Associated DVT	Brandt et al[52] 2022	Subgroup analysis of AVERT RCT[103]	Apixaban 2.5 mg twice daily, when compared with placebo, was associated with lower rates of VTE (HR: 0.26; 95% CI: 0.14-0.47) and no difference in major bleeding (HR: 0.69; 95% CI: 0.20-2.35).	Limited evidence, RCTs urgently needed. Pivotal VTE trials should present breakdown of results according to presence of CVCs.
	TRIM-Line[104] 2021	Pilot RCT	Thromboprophylaxis with rivaroxaban 10 mg daily, when compared with placebo, resulted in no significant different rate of VTE in patients with cancer and central venous catheters (HR: 0.66; 95% CI: 0.11-3.90). One major bleeding in rivaroxaban arm.	
	TRIM-Line Ongoing	RCT	Ongoing trial, planning to enroll 1,828 patients, is comparing rivaroxaban 10 mg daily with placebo for primary thromboprophylaxis in cancer patients with central venous catheters (CVCs).	
 Cerebral Venous Sinus Thrombosis	RE-SPECT CVT[54] 2022	RCT	Dabigatran 150 mg twice daily, when compared with warfarin with an INR of 2 to 3, resulted in no recurrent VTE in both groups, with 1 major bleeding event recorded in the dabigatran arm and 2 in the warfarin arm at 25 weeks.	Small sample size and low event rates. Other DOACs need to be studied.
 Splanchnic Vein Thrombosis	RIPORT[106] 2022	RCT	Rivaroxaban 15 mg daily, when compared with placebo, resulted in a significantly lower rate of recurrent VTE (0 per 100 person-years vs 19.71 per 100 person-years; 95% CI: 7.49-31.92) in patients with noncirrhotic chronic portal vein thrombosis.	Small sample size. Need to study rates of recurrent VTE. Further RCTs needed.
 Left Ventricular Thrombus	Zhang et al[96] 2022	RCT	For *prevention* of LV thrombus following anterior MI, combination of rivaroxaban 2.5 mg twice daily and DAPT, when compared with DAPT alone, was associated with lower rates of LVT formation at 30 days (HR: 0.08; 95% CI: 0.01-0.62).	More RCTs with larger sample sizes are needed and other agents tested.
	Sayed et al[101] 2021	Meta-analysis	For *treatment* of LV thrombus post-MI, a pooled analysis of 3 small trials suggested no difference in stroke (OR: 0.14; 95% CI: 0.01-1.27) or LVT resolution (OR: 1.17; 95% CI: 0.37-3.45) between DOACs and warfarin, but major bleeding was lower in DOACs (OR: 0.16; 95% CI: 0.02-0.82).	Trials were underpowered. Further RCTs are needed, including for LV thrombus other than post-MI.
	REWARF-STEMI Ongoing	RCT	Ongoing trial, aiming to enroll 50 patients, is comparing rivaroxaban 15 mg daily vs warfarin in patients with LV thrombus follow acute ST-segment elevation myocardial infarction.	

https://doi.org/10.1016/j.jacc.2023.10.038

VTE 치료 종료 후 재발 위험도 평가

- VTE(정맥혈전색전증) 치료 종료 후 **재발 위험도 평가**는 항응고제 치료의 **지속 여부, 기간, 약제 선택**에 매우 중요한 결정 요소
- **재발 위험도 평가 항목과 사용 가능한 임상 도구**를 체계적으로 정리해본다

1. 재발 위험을 높이는 주요 임상 인자

항목	재발 위험도 영향
유발 인자 여부	
▸ 수술, 외상 등 일시적 유발 인자	**낮은 재발 위험** (3–5%)
▸ 항암 치료 중 / 활동성 암	**매우 높은 위험 (15–20%/년)**
▸ 명확한 유발 요인 없는 비유발성 (unprovoked)	**중간~높은 위험 (7–10%/년)**
성별	**남성** > 여성 (여성은 위험 요인 없으면 낮은 편)
D-dimer 수치 (치료 종료 후 1개월)	상승 시 재발 위험 증가 (이하 도구 참고)
초기 VTE 위치	PE 또는 **근위 DVT** > 원위 DVT
초기 VTE 횟수	**재발 1회 이상이면 위험 ↑**
고위험 혈전성 질환 보유	예: 항인지질 증후군, 중증 유전성 혈전성 질환
비만, 연령↑, 흡연, 호르몬제 복용 등	소인성 요인 다수 → 위험 ↑

Risk scoring algorithms for VTE recurrence.

Prediction model	Elements	Points	Findings
HERDOO-2[23]	Sex	NA	High risk:
	Signs of post-thrombotic syndrome	1	• Men (13.7%, 95% CI 10.8–17%)
	• Hyperpigmentation		• Women with ≥2 risk factors (14.1%, 95% CI 10.9–17.3%)
	• Erythema		Low risk:
	• Redness		• Women with 0–1 risk factors (1.6%, 95% CI 0.3–4.6%)
	Elevated d-dimer on anticoagulation	1	
	BMI >30 kg/m^2	1	
	Age ≥65	1	
Vienna[20]	Male sex	NA	Continuous HR 1.27–2.6 based on nomogram
	Proximal DVT		
	PE		
	Elevated d-dimer (3 weeks post-VKA discontinuation)		
DASH[22]	Elevated d-dimer (3–5 weeks post-anticoagulation discontinuation)	2	Annualized recurrence risk:
	Age ≤50	1	• ≤1 point (3.1%, 95% CI 2.3–3.9%)
	Male sex	1	• 2 points (6.4%, 95% CI 4.8–7.9%)
	Hormone replacement therapy	−2	• ≥3 points (12.3%, 95% CI 9.9–14.7%)
Louzada[55]	Female sex	1	Recurrence risk at 3–6 months:
	Prior VTE	1	• Low risk: ≤ −1 point (5.1%)
	Primary lung cancer	1	• Intermediate: 0 points (9.9%)
	Primary breast cancer	−1	• High: ≥1 point (15.8%)
	Tumor stage (TNM 1)	−2	

Vasc Med. 2015 April ; 20(2): 143–152.

2. D-dimer 기반 평가

- **D-dimer 검사**를 **치료 종료 후 3–5주 시점**에 시행
  => 정상일 경우 재발 위험 ↓

- **DULCIS 연구**
  : D-dimer가 정상인 환자에서 항응고 치료 중단 후 재발률은 연 3% 이하였음
  (Palareti et al., Blood, 2014)

Full Length Article

D-dimer and risk of venous thromboembolism recurrence: Comparison of two studies with similar designs but different laboratory and clinical results

Gualtiero Palareti [a,*], Cristina Legnani [a], Alberto Tosetto [b], Daniela Poli [c], Sophie Testa [d], Walter Ageno [e], Vittorio Pengo [f], Benilde Cosmi [g], Paolo Prandoni [a]

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- Background
  : Two management studies on this issue have been published (**DULCIS** in 2014 and **APIDULCIS** in 2022).

- Methods
  : Both studies were finalized to extend anticoagulation [with VKAs in DULCIS or apixaban 2.5 mg BID (kindly provided by BMS-Pfizer Collaboration) in APIDULCIS] only in patients with positive D-dimer results.
  T0/T15/T30/T60/T90 check

- Results
  : More D-dimer assays resulted positive in APIDULCIS than in DULCIS (61.1 % vs 47.7 %, $p < 0.0001$).
  : The incidence of bleeding was low in those receiving apixaban vs those who resumed VKAs (0.4 vs 2.3 per 100 person-years, respectively; IRR 0.17;).
  : While the recurrence rate was low and similar in the studies in subjects who resumed anticoagulation, it was significantly higher in APIDULCIS than in DULCIS in those who stopped anticoagulation for negative D-dimer (5.6 vs 3.0 per 100 person-years, respectively; IRR 1.9).

- Conclusion: The low dose Apixaban for extended VTE treatment is effective and safe, and well accepted by patients. Why subjects who stopped anticoagulation for negative D-dimer had a higher recurrence rate in APIDULCIS than in DULCIS remains to be explained.

Palareti et al., Blood Adv. 2022 Dec 13;6(23):6005-6015.

3. 임상 위험도 점수 도구(1)

- **HERDOO2 Score** (여성대상, 비유발성 **VTE**)

항목	점수
Hyperpigmentation, Edema, or Redness in legs	1
D-dimer ≥250 ng/mL (치료 중단 후 측정)	1
BMI ≥30	1
Age ≥65세	1

•**여성에서 HERDOO2 score = 0점 → 저위험** (재발률 1.6%/년)
•1점 이상이거나 남성 → 고위험군으로 간주 (Rodger et al., BMJ, 2017)

3. 임상 위험도 점수 도구(2)

- **DASH Score** (비유발성 VTE 재발예측 d-dmer 전략)

항목	기준	점수
D-dimer	항응고 중단 1개월 후 양성 (e.g., >500 ng/mL)	+2
Age	나이 ≤50세	+1
Sex	남성	+1
Hormone	여성 환자에서 호르몬 치료 중이지 않음 (비호르몬 치료)	+1

DASH 점수	1년 재발률
0–1	약 3.9%
2	약 6.3%
≥3	약 10.8%

Tosetto et al., J Thromb Haemost, 2012

4. 복합적 판단: 치료 지속 여부 결정

상황	권고사항
유발성 VTE + 일시적 위험 인자 (예: 수술 후)	**3개월 후 중단** 권장
비유발성 VTE + 낮은 재발 위험 (여성, D-dimer 음성 등)	**중단 고려 가능**
비유발성 VTE + 남성 또는 위험 요인 존재	**장기 치료 고려**
암환자, APS, 중증 유전성 질환 등	**장기 항응고 치료 권장**

요약

- **D-dimer 검사 + HERDOO2 or DASH score**를 통해 재발 위험도를 수치화 가능
- **암, APS, 남성 비유발성 VTE, 고령자** 등은 장기 치료 고려
- 낮은 위험군(여성 + D-dimer 음성 + HERDOO2 0점 등)은 치료 중단 고려 가능

기본치료이후 연장치료

1. 기본 치료 기간 (Initial treatment)

단계	기간	설명
초기 치료	**5~10일**	- **Warfarin**: 반드시 **heparin 병용** 필요 (overlap) - **DOAC (rivaroxaban/apixaban)**: 단독 사용 가능
중기 치료	**3개월**	- 대부분의 환자에서 최소 3개월 치료 권장 - 이후는 재발 위험과 출혈 위험에 따라 결정

기본치료이후 연장치료

2. 3개월 이후: 연장 치료 필요 여부 결정

=> 치료 종료 여부는 다음 요소에 따라 판단합니다

기준	연장 치료 고려	치료 중단 가능
유발 요인 없는 첫 VTE	✅	❌
영구적 위험요인 (암, APS 등)	✅	❌
일시적 유발요인 (수술, 외상 등)	❌	✅
출혈 위험 매우 높음	❌	✅ 또는 저용량 유지
재발 VTE 병력	✅	❌

기본치료이후 연장치료

3. 연장 치료 시 DOAC vs. Warfarin 사용과 기간

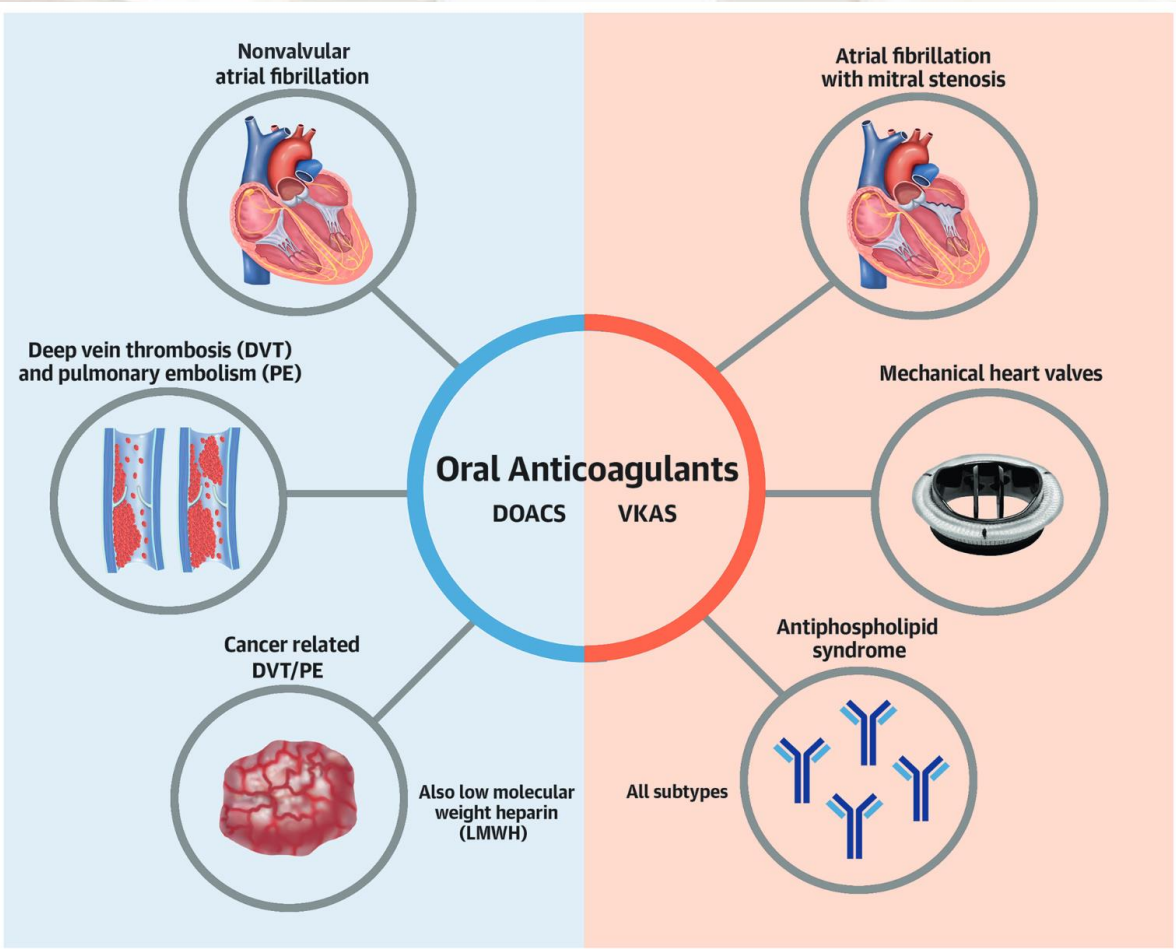
약제	연장 치료 가능 여부	기간	용량 예시
Warfarin	가능	수년 또는 평생	INR 2–3 유지
Apixaban	가능	무기한 가능	2.5mg BID (저용량)
Rivaroxaban	가능	무기한 가능	10mg QD (저용량)
Dabigatran	가능	150mg BID 유지	-

DOAC은 저용량으로 연장 치료 시, 출혈 위험을 낮추면서도 재발 예방 효과 유지됨

치료 연장 / 중단 결정 시 고려 요소

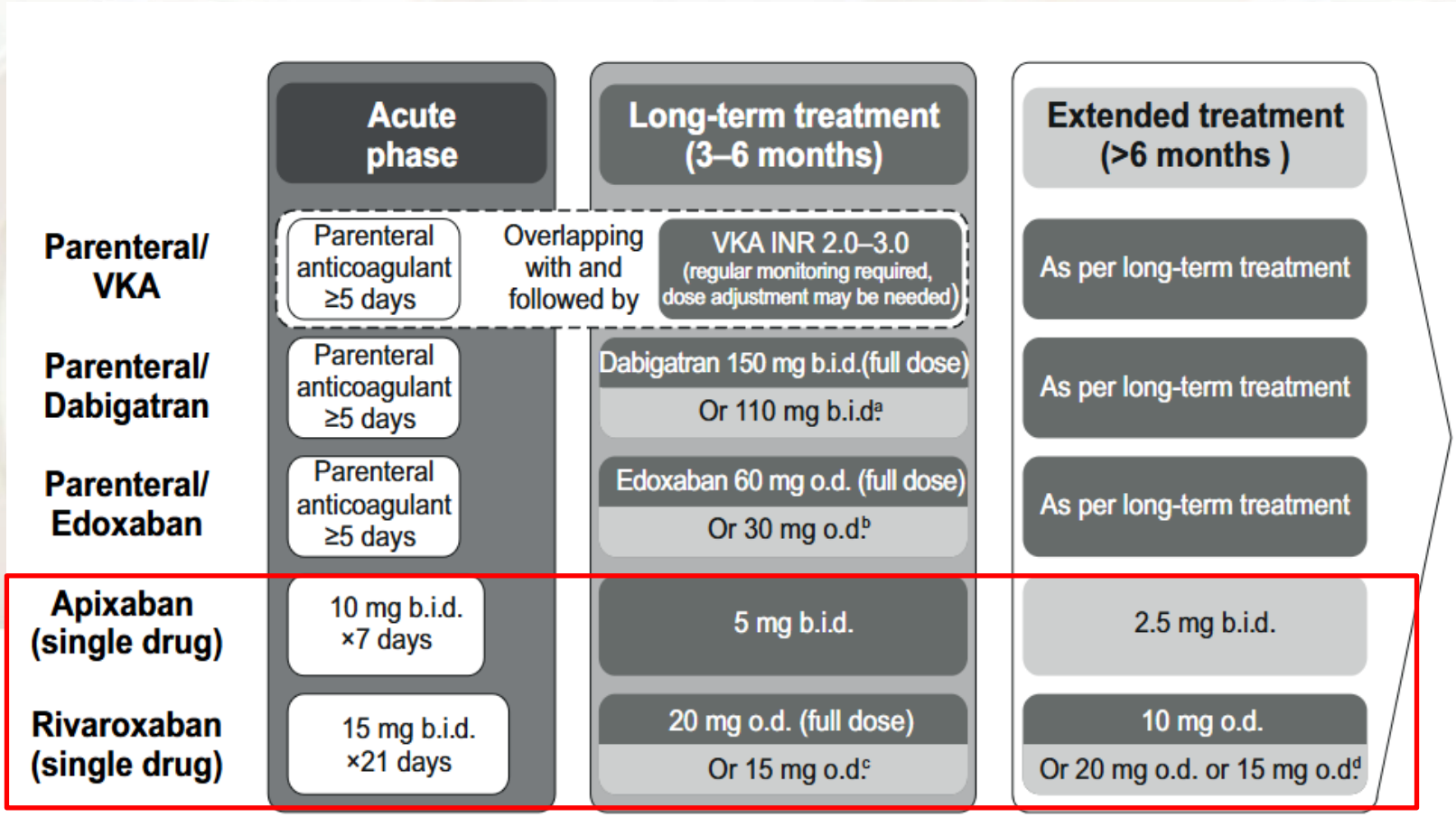
항목	치료 연장 고려 시	치료 중단 고려 시
VTE 유발 원인	없음 또는 지속 요인	명확한 일시적 원인
재발력	과거 재발 있음	첫 VTE, d-dimer 음성
출혈 위험	낮음	높음
암, APS, 유전성 혈전증	있음	없음
d-dimer (치료 중단 후 측정)	양성	음성

Summary : Current Evidence-Based Indications for Warfarin or Other Anticoagulant Medication



Mark A. et al, JACC 2023 Jan, 81 (1) 31–33

Summary : Dosing schemas of OACs approved for the treatment and/or secondary prevention of VT



감사합니다.