26-06-20 폐혈관school 14:00-14:25

Updates in Pulmonary Embolism Management and Unresolved issues

중앙대학교 광명병원
호흡기알레르기내과 허진영

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Contents

- Terminology for risk factors of venous thromboembolism (VTE)
- Extended anticoagulation in VTE
- Ultrasound-facilitated, catheter-directed fibrinolysis
- Unresolved issues

Contents

- Terminology for risk factors of venous thromboembolism (VTE)
- Extended anticoagulation in VTE
- Ultrasound-facilitated, catheter-directed fibrinolysis
- Unresolved issues

Terminology for risk factors of VTE

- Idiopathic VTE & secondary VTE

The New England
Journal of Medicine

©Copyright, 1999, by the Massachusetts Medical Society

VOLUME 340 MARCH 25, 1999 NUMBER 12

A COMPARISON OF THREE MONTHS OF ANTICOAGULATION WITH EXTENDED ANTICOAGULATION FOR A FIRST EPISODE OF IDIOPATHIC VENOUS THROMBOEMBOLISM

CLIVE KEARON, M.B., PH.D., MICHAEL GENT, D.SC., JACK HIRSH, M.D., JEFFREY WEITZ, M.D., MICHAEL J. KOVACS, M.D., DAVID R. ANDERSON, M.D., ALEXANDER G. TURPIE, M.B., DAVID GROSS, M.D., PH.D., JEFFREY S. GINSBERG, M.D., PHILIP WELLS, M.D., BETSY MACKINNON, M.SC., AND JIM A. JULIAN, M.MATH.

ABSTRACT

Background Patients who have a first episode of venous thromboembolism in the absence of known risk factors for thrombosis (idiopathic thrombosis) are often treated with anticoagulant therapy for three months. Such patients may benefit from longer treatment, however, because they appear to have an increased risk of recurrence after anticoagulant therapy is stopped.

Methods In this double-blind study, we randomly assigned patients who had completed three months of anticoagulant therapy for a first episode of idiopathic venous thromboembolism to continue receiving warfarin, with the dose adjusted to achieve an international normalized ratio of 2.0 to 3.0, or to receive placebo for a further 24 months. Our goal was to determine the effects of extended anticoagulant therapy on the prevention of symptomatic venous thromboembolism and bleeding.

Results A prespecified interim analysis of efficacy led to the early termination of the trial after 162 patients had been enrolled and followed for an average of 10 months. Of 83 patients assigned to continue to receive placebo, 17 had a recurrent episode of venous thromboembolism (27.4 percent per patient-year), as compared with 1 of 78 patients assigned to receive warfarin (1.3 percent per patient-year; P<0.001). Warfarin resulted in a 95 percent reduction in the risk of recurrent venous thromboembolism (95 percent confidence interval, 83 to 99 percent). Three patients assigned to the warfarin group had nonfatal major bleeding (two had gastrointestinal bleeding and one genitourinary bleeding), as compared with none of the patients assigned to placebo (4.0 versus 0.0 percent vs. 0 percent per patient-year, P=0.09).

Conclusions Patients with a first episode of idiopathic venous thromboembolism should be treated with anticoagulant agents for longer than three months. (N Engl J Med 1999;340:901-7.)

©1999, Massachusetts Medical Society.

ACUTE venous thromboembolism is usually treated with a five-to-seven-day course of unfractionated or low-molecular-weight heparin, followed by a three-month course of oral anticoagulant therapy.[1] Subgroup analyses of the results of a number of recent studies suggest that, after anticoagulant therapy is stopped, the risk of recurrent venous thromboembolism is greater among patients who have a persistent risk factor for thrombosis and those whose initial episode of thrombosis occurred in the absence of an apparent risk factor than it is among patients in whom thrombosis develops in association with a transient risk factor, such as surgery.[2-5] On the basis of such observations, we hypothesized that patients with a first episode of idiopathic venous thromboembolism would benefit from a course of anticoagulant therapy lasting more than three months.

To test this hypothesis, we performed a double-blind, randomized trial comparing an additional 24 months of warfarin therapy (target international normalized ratio [INR], 2.0 to 3.0) with placebo in patients who had completed three months of anticoagulant therapy for a first episode of idiopathic venous thromboembolism.

From McMaster University, Hamilton, Ont., Canada (C.K., M.G., J.H., J.W., M.J.K., D.R.A., A.G.T., D.G., J.S.G., P.W., B.M., J.A.J.); the University of Ottawa, Ottawa, Ont., Canada (J.H., A.G.T., J.S.G.); the University of Western Ontario, London, Ont., Canada (M.J.K.); Dalhousie University, Halifax, N.S., Canada (D.R.A.); Northwestern University Medical School, Chicago (D.G.); and the University of Missouri, Columbia (P.W.). Address reprint requests to Dr. Kearon at the Thrombosis and Health Sciences Corporation, Henderson Pavilion, 711 Concession St., Hamilton, ON L8V 1C3, Canada.

Supported by a grant from Astra Pharmaceuticals, A.B.T.; Hamilton Civic Hospitals Research Center, Hamilton, Ont.; James Hoskins, M.D., and Robin Roberts, M.Litch., McMaster University, Hamilton, Ont.; Dixi via Siguoni, M.D., Ospedale Regionale, Aosta, Italy; Jean-Yves Lefebvre, M.D., Hôpital Notre-Dame, H.-Dieu, Montreal; Université de Sherbrooke, Sherbrooke, Que.; Clarence Demers, M.D., and Louis Desjardins, M.D., Laval University, Quebec, Que.; Jean Brisset, M.D., Hôpital Laval, Quebec, Que.; Jacques Turcot, M.D., Centre Hospitalier Régional de Lanaudière, Joliette, Que.; and Thrombosis Canada, Montreal.

The institutions that participated in the study are listed in the Appendix.

Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study

Gwen J. Zornberg, Hershel Jick

Summary

Background Antipsychotic drugs have been associated with an increased risk of adverse events such as venous thromboembolism. Our aim was to assess this risk in users of conventional antipsychotic drugs who had been diagnosed with first-time, idiopathic venous thromboembolism.

Methods From a baseline population of 29 952 recipients of conventional and atypical antipsychotic drugs aged younger than 60 years, we identified 42 individuals with idiopathic venous thromboembolism and 172 matched controls. We compared risk of current and recent use of antipsychotic drugs with non-use before the index date in cases and controls.

Findings Current exposure to conventional antipsychotic drugs was associated with a significantly increased risk of idiopathic venous thromboembolism compared with non-use (adjusted odds ratio 7·1, [95% CI 2·3–21·97]). Although we found no difference between phenothiazines, thioxanthenes, or other conventional antipsychotic drugs, low potency antipsychotic drugs (such as chlorpromazine) were more strongly and significantly associated with venous thromboembolism (odds ratio 24·1, [3·3–172·7]) than were high potency antipsychotic drugs such as haloperidol (3·3 [0·6–13·2]). The risk for venous thrombosis was highest during the first few months of conventional antipsychotic drug use.

Interpretation Current exposure to conventional antipsychotic drugs significantly increases the risk of idiopathic venous thromboembolism in men and women younger than 60 years of age.

Lancet 2000; **356**: 1219–23
See Commentary page xxx

Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, MA 02421, USA (G J. Zornberg MD, H Jick MD)

Correspondence to: Dr Gwen J. Zornberg (e-mail: zornberg@bu.edu)

Introduction

Antipsychotic drugs are widely used in medicine and psychiatry. Since their introduction, the newer atypical antipsychotic drugs have become more commonly prescribed, often replacing conventional drugs. Consequently, interest in their side-effect profiles has grown. Most attention has been paid to adverse effects such as agranulocytosis, which has been associated with clozapine use, and more common adverse neurological reactions such as tardive dyskinesia.[1] Little attention has been given to the risk of venous thrombosis and resection of venous thromboembolism, which includes pulmonary embolism and deep-vein thrombosis.

In a mortality study of the atypical antipsychotic drug clozapine, Walker and colleagues[2] reported that pulmonary embolism occurred more frequently in patients given this drug in past years. In addition to sporadic case reports,[3] a cohort study[4] documented cases of myocardial infarction, cerebral infarction, and pulmonary embolism in users of clozapine,[5] case reports[6] and observational studies[7,8] have documented positive associations with venous thromboembolism in recipients of conventional antipsychotic drugs, with a particular focus on the phenothiazine subclass.

In a retrospective review of phenothiazines, investigators reported that the frequency of thromboembolic complications associated with antipsychotic drug use was unrelated to psychiatric diagnosis and was greater than all other potentially fatal drug effects (ie, hepatotoxicity, agranulocytosis, or heart failure).[7] Pulmonary embolism is often misdiagnosed as sudden death, and Sweeney and Kay[8] reported that unsuspected pulmonary embolism were diagnosed in psychiatric patients only at necropsy.[9] Spontaneous reports have described an association between sudden cardiac death and antipsychotic drug use.[10,11] However, the evidence for a causal link between antipsychotic drugs and risk of venous thromboembolism remains inconclusive.

To assess the risk of venous thromboembolism drugs, patients were not free from cardiovascular and other thrombogenic risk factors,[12] and many recent spontaneous reports[13] lacked controls. Since antipsychotic drugs are common medications (particularly in psychiatric, chronically ill, and geriatric populations) and venous thromboembolism is a potentially fatal event, we undertook a case-control study to investigate need to further explore the findings of previous research on antipsychotic drug use. This led us to carry out a population-based, nested case-control analysis to explore the relation between antipsychotic drugs and the risk of developing first-episode, idiopathic venous thromboembolism in a large cohort of antipsychotic drug users by using the UK-based General Practice Research Database (GPRD).

Methods

Study population and data source

The baseline population from which the GPRD data were derived has been described in detail elsewhere.[14] The GPRD database encompasses about 3 million

CAIM 중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Terminology for risk factors of VTE

Journal of Thrombosis and Haemostasis, **14**: 1480–1483 DOI: 10.1111/jth.13336

RECOMMENDATIONS AND GUIDELINES

Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH

C. KEARON,* W. AGENO,† S. C. CANNEGIETER,‡ B. COSMI,§ G.-J. GEERSING¶ and P. A. KYRLE,** FOR THE SUBCOMMITTEES ON CONTROL OF ANTICOAGULATION, AND PREDICTIVE AND DIAGNOSTIC VARIABLES IN THROMBOTIC DISEASE

*McMaster University, Hamilton, ON, Canada; †University of Insubria, Varese, Italy; ‡Leiden University, Leiden, the Netherlands; §University of Bologna, Bologna, Italy; ¶Utrecht University, Utrecht, the Netherlands; and **Medical University of Vienna, Vienna, Austria

To cite this article: Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing G-J and Kyrle PA, for the Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost* 2016; **14**: 1480–3.

Whether an episode of venous thromboembolism (VTE) was unprovoked or provoked by an environmental (or acquired) risk factor and, if it was provoked, whether the provoking factor was transient or persistent, has important prognostic and treatment implications [1,2]. If thrombosis was provoked by a major transient risk factor, such as recent surgery, there is a very low risk of recurrence after stopping therapy [1]. At the other extreme, if thrombosis was provoked by a persistent and progressive risk factor, such as metastatic cancer, there is a high risk of recurrence after stopping therapy [3,4]. Patients with neither an important transient nor persistent provoking risk factor for thrombosis, who are often referred to as having 'unprovoked' VTE, have an intermediate risk of recurrence after stopping therapy [1,2].

Because of the implications for risk of recurrence and how long patients should be treated, it is often important to be able to categorize episodes of VTE as being provoked or unprovoked. This SSC statement discusses issues that are relevant to this categorization and proposes criteria (Table 1) that can be used in clinical practice and for clinical research to categorize episodes of VTE as provoked by a transient risk factor, provoked by a persistent risk factor or unprovoked. Our goal is to standardize what is meant by these terms, identify the strengths and limitations of this terminology, and improve the consistency with which patients are categorized into one of these three groups. Greater consistency in the use of this categorization is expected to benefit clinical practice and investigation.

Correspondence: Clive Kearon, Hamilton Health Sciences, Juravinski Hospital, AE-73, 711 Concession Street, Hamilton, ON L8V 1C3, Canada.
Tel.: +1 905 521 2100 ext2420; fax: +1 905 528 1862.
E-mail: kearonc@mcmaster.ca

Received 4 December 2015
Manuscript handled by: P. H. Reitsma.
Final decision: P. H. Reitsma, 18 March 2016

Nomenclature: 'unprovoked' or 'idiopathic' VTE

In relationship to assessment of the risk of recurrence, we prefer the term 'unprovoked' over 'idiopathic' to describe patients with VTE that is not associated with an environmental risk factor (either transient or persistent). The word 'unprovoked' focuses attention on whether there is an important environmental provoking factor for the VTE, which is the single variable that most influences the risk of recurrent VTE after anticoagulants are stopped [2,5]. The word 'idiopathic' suggests that there is no reason for thrombosis. However, whether or not there was an environmental provoking factor, patients may have non-environmental risk factors for thrombosis, such as a hereditary thrombophilia, older age or male sex, which do not qualify the event as provoked but may influence the risk of recurrence [6,7].

Categorization of VTE as 'unprovoked' vs. 'provoked by a transient risk factor'

Many episodes of VTE can readily be categorized as having been provoked by a transient risk factor (e.g. recent major surgery) or, alternatively, as being unprovoked (no environmental risk factor). However, when VTE occurs in a patient with a weak transient risk factor for thrombosis (e.g. minor soft tissue injury of the leg) or occurs many months after a major risk factor, it can be difficult to decide if the risk factor is prognostically important enough to justify categorizing the VTE as having been provoked. The degree to which risk factors are associated with thrombosis varies from very weak to very strong, and the point along this continuum that is used to

© 2016 International Society on Thrombosis and Haemostasis

- Provoked by a major transient risk factor
- Provoked by a minor transient risk factor
- Provoked by a persistent risk factor
- Unprovoked

Kearon, et al. J Thromb Haemostat 2016; 14:1480-1483

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Terminology for risk factors of VTE

- Provoked by a transient risk factor
  - Major: Transient risk factor during the 3 months before diagnosis of VTE
  - Half the risk of recurrent VTE after stopping anticoagulation therapy, when the risk factor occurred up to 3 months before VTE, or a greater than 10-fold increase in the risk of having a first VTE
    - Surgery with general anesthesia for greater than 30 min
    - Confined to bed in hospital for at least 3 days with an acute illness
    - Cesarean section

Kearon, et al. J Thromb Haemostat 2016; 14:1480-1483

Terminology for risk factors of VTE

- Provoked by a transient risk factor
  - Minor: Transient risk factor during the 2 months before diagnosis of VTE
  - Half the risk of recurrent VTE after stopping anticoagulation therapy, when the risk factor occurred up to 2 months before VTE, or a 3 to 10-fold increase in the risk of having first VTE
    - Surgery with general anesthesia for less than 30 min
    - Admission to hospital for less than 3 days with an acute illness
    - Estrogen therapy
    - Pregnancy or puerperium
    - Confined to bed out of hospital for at least 3 days with an acute illness
    - Leg injury associated with reduced mobility for at least 3 days

Kearon, et al. J Thromb Haemostat 2016; 14:1480-1483

Terminology for risk factors of VTE

- Provoked by a persistent risk factor
  - Active cancer
    - Has not received potentially curative treatment
    - There is evidence that treatment has not been curative
    - Treatment is ongoing

Kearon, et al. J Thromb Haemostat 2016; 14:1480-1483

Terminology for risk factors of VTE

- Unprovoked
  - No provoking risk factor (transient or persistent)

- “Idiopathic”
  - No reason for thrombosis
  - Not considered non-environmental risk factors
    - Hereditary thrombophilia, older age, male sex

Kearon, et al. J Thromb Haemostat 2016; 14:1480-1483

Terminology for risk factors of VTE

Circulation

Check for updates

ON MY MIND

Let's Stop Dichotomizing Venous Thromboembolism as Provoked or Unprovoked

Ida Ehlers Albertsen, MD
Gregory Piazza, MD, MS
Samuel Z. Goldhaber, MD

The optimal duration of anticoagulation for venous thromboembolism (VTE) remains uncertain. The benefit of anticoagulation to prevent recurrent VTE must be weighed against the risk of bleeding. Current guidelines dichotomize VTE as unprovoked or provoked. Guidelines for unprovoked VTE recommend extended-duration anticoagulation with no scheduled stop date and yearly assessment of bleeding risk, risk of recurrence, and patient preference. Guidelines for provoked VTE recommend 3 months of anticoagulation except for cancer patients, who generally receive extended-duration anticoagulation.

Dichotomizing VTE into provoked and unprovoked categories to guide decisions about the duration of anticoagulation is appealing because of its simplicity. However, optimal VTE management frequently requires a more nuanced approach. VTE is a systemic vascular disease that can no longer be characterized as a red clot disease because the thrombus usually contains abundant polymorphonuclear leukocytes, neutrophil extracellular traps, and activated platelets. This pathophysiological observation ties together the longstanding epidemiological link between inflammatory disorders, such as psoriasis, rheumatoid arthritis, and Crohn's disease, and VTE. When these inflammatory illnesses remain clinically or subclinically active, the risk of VTE recurrence remains high, although associated VTE is categorized as provoked rather than unprovoked.

In 2016, the International Society of Thrombosis and Haemostasis made recommendations on how to define transient provoking and persistent risk factors. They defined minor transient risk factors as "associated with a ≥ to 10-fold increased risk of having a first VTE" or "associated with half the risk of recurrent VTE after stopping anticoagulant therapy (compared with if there was no transient risk factor), when the risk factor occurred up to 2 months before the VTE."[1] According to these definitions, clinicians must estimate a patient's risk of recurrence. However, such estimates are hampered by a paucity of data to serve as the foundation for calculating risk of recurrence. Consequently, this International Society of Thrombosis and Haemostasis statement, although well intentioned, can be difficult to translate into clinical practice.

Defining unprovoked and provoked VTE is further challenged by the fact that there is a large grey zone for which precise categorization is not possible. Many VTE patients have multiple persistent (predisposing) and transient provoking factors. These factors carry large differences in recurrence risk. A history of minor persistent and transient risk factors can be based on analyses of randomized trials (Figure).

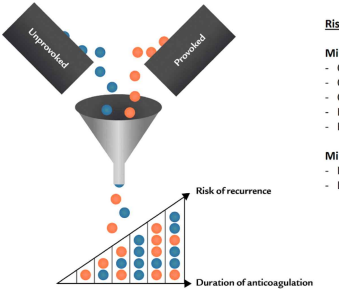
The EINSTEIN CHOICE trial (Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism) randomized patients with prior provoked (59%) or unprovoked (41%) VTE to either rivaroxaban (20 mg or 10 mg) or low-dose aspirin after they had received 6 to 12 months of anticoagulation.[2]

The opinions expressed in this article are not necessarily those of the American Heart Association.

Key Words: provoked ■ recurrence ■ risk stratification ■ unprovoked ■ venous thromboembolism

© 2018 American Heart Association, Inc.

https://www.ahajournals.org/journal/circ



Risk factors

Minor persistent (predisposing):
- Congestive heart failure
- Obesity
- Chronic kidney disease
- Family history of VTE
- Hereditary thrombophilia

Minor transient:
- Immobilization
- Leg injury with impaired mobility

- Against dichotomization of VTE
- "*Optimal VTE management frequently require a more nuanced approach*"

Albertsen, et al. Circulation 2018;138:2591-2593

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Terminology for risk factors of VTE

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† (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)

* Corresponding authors: Stavros V. Konstantinides, Center for Thrombosis and Hemostasis, Johannes Gutenberg University Mainz, Building 403, Langenbeckstr. 1, 55131 Mainz, Germany. Tel: +49 613 117 6255, Fax: +49 613 117 3956, Email: stavros.konstantinides@unimedizin-mainz.de; and Department of Cardiology, Democritus University of Thrace, 68100 Alexandroupolis, Greece. Email: stavros@med.duth.gr. Guy Meyer, Respiratory Medicine Department, Hôpital Européen Georges Pompidou, 20 Rue Leblanc, 75015 Paris, France. Tel: +33 156 093 165, Fax: +33 156 093 330, Email: guy.meyer@aphp.fr; and Université Paris Descartes, 15 rue de l'école de médecine 75006 Paris, France.

Author/Task Force Member Affiliations: listed in the Appendix.

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers: listed in the Appendix.

†**Representing the ERS.**

ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), Heart Failure Association (HFA).

Councils: Council on Cardiovascular Primary Care.

Working Groups: Aorta and Peripheral Vascular Diseases, Cardiovascular Surgery, Pulmonary Circulation and Right Ventricular Function, Thrombosis.

The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the European Heart Journal and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oup.com).

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge, and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy, and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic, or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the healthcare professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

© The European Society of Cardiology 2019. All rights reserved. For permissions please email: journals.permissions@oup.com.

Downloaded from https://academic.oup.com/eurheartj/article/41/4/543/5556160 by guest on 17 August 2023

- "*Terminology such as 'provoked' vs. 'unprovoked' PE/VTE is no longer*

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

onstantinides, et al. Eur Heart J 2020;41:543-603

CAVE 중앙대학교의료원 CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Terminology for risk factors of VTE

Circulation

CLINICAL PRACTICE GUIDELINES

2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American College of Clinical Pharmacy, American College of Emergency Physicians, American College of Chest Physicians, Society for Cardiovascular Angiography & Interventions, Society of Hospital Medicine, Society of Interventional Radiology, Society for Vascular Medicine, and the Society of Vascular Nursing

Writing Committee Members*

Mark A. Creager, MD, FACC, FAHA, MSVM, Chair; Geoffrey D. Barnes, MD, MSc, FACC, FAHA, FSVM, Co–Vice Chair; Jay Giri, MD, MPH, FACC, FAHA, FSCAI, Co–Vice Chair; Debabrata Mukherjee, MD, MS, FACC, FAHA, FSVM, MSCAI, JC Liaison†; William Schuyler Jones, MD, FACC, JC Liaison†; Allison E. Burnett, PharmD, PhC, CACP‡; Teresa Carman, MD, RPVI, MSVM; Ana I. Casanegra, MD, MS, FAHA, FSVM; Lana A. Castellucci, MD, MSc; Sherrell M. Clark§; Mary Cushman, MD, MSc, FAHA; Kerstin de Wit, MBChB, MSc, MD, MRCP, FRCEM, FRCPC; Jennifer M. Eaves, DNP, MSN, RN; Margaret C. Fang, MD, MPH‖; Joshua B. Goldberg, MD; Stanislav Henkin, MD, FACC, FAHA; Hillary Johnston-Cox, MD, FACC; Sabeeda Kadavath, MD, FACC¶; Daniella Kadian-Dodov, MD, FACC, FAHA, FSVM; William Brent Keeling, MD, FACC; Andrew JP Klein, MD, FACC, FSCAI#; Jun Li, MD; Michael C. McDaniel, MD, FACC, FSCAI; Lisa K. Moores, MD, FCCP, FRCP**; Gregory Piazza, MD, MS, FACC, FAHA; Karen S. Pieper, MS, APRN-CNS, CV-BC, CPHQ, CCNS††; Steven C. Pugliese, MD; Mona Rahaiu, MD‡‡; Rachel P. Rosovsky, MD, MPH; Faria Russo§§; Eric A. Secemsky, MD, MSc, RPVI, FACC, FAHA, FSCAI, FSVM; Akhilesh K. Sista, MD, FAHA, FSIR; Leben Tefera, MD, FACC; Ido Weinberg, MD, FACC, FSVM‖‖; Lauren M. Westafer, DO, MPH, MSB‖ Michael N. Young, MD, RPVI, FACC, FSCAI

AIM: The "2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults" is a de novo guideline that provides comprehensive recommendations for the evaluation, management, and follow-up of adult patients (≥18 years of age) with acute pulmonary embolism (PE). A key feature of this guideline is the introduction of the AHA/ACC Acute Pulmonary Embolism Clinical Categories, which enhance the precision of severity classification, prognosis assessment, and evidence-based therapeutic decision-making.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for recusal information. †ACC/AHA Joint Committee on Clinical Practice Guidelines liaison. ‡American College of Clinical Pharmacy representative. §AHA Patient representative. ‖Society of Hospital Medicine representative. ¶AHA/ACC Joint Committee on Performance Measures liaison. #Society for Cardiovascular Angiography and Interventions representative. **American College of Chest Physicians representative. ††Society of Vascular Nursing representative. ‡‡Society of Interventional Radiology representative. §§Society of Vascular Medicine representative. ‖‖American College of Emergency Physicians representative.

Peer Review Committee Members and AHA/ACC Joint Committee on Clinical Practice Guidelines Members, see page e1031.

The American Heart Association requests that this document be cited as follows: Creager MA, Barnes GD, Giri J, Mukherjee D, Jones WS, Burnett AE, Carman T, Casanegra AI, Castellucci LA, Clark SM, Cushman M, de Wit K, Eaves JM, Fang MC, Goldberg JB, Henkin S, Johnston-Cox H, Kadavath S, Kadian-Dodov D, Keeling WB, Klein AJP, Li J, McDaniel MC, Moores LK, Piazza G, Pieper KS, Pugliese SC, Rahaiu M, Rosovsky RP, Russo F, Secemsky EA, Sista AK, Tefera L, Weinberg I, Westafer LM, Young MN. 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN guideline for the evaluation and management of acute pulmonary embolism in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;153:e977–e1051. doi: 10.1161/CIR.0000000000001415

© 2026 by the American Heart Association, Inc and the American College of Cardiology Foundation.

Circulation is available at www.ahajournals.org/journal/circ

- "*The likelihood of recurrent VTE after an initial episode of PE depends on whether risk factors for VTE were present at the time of the initial PE*"

- Risk factors
  - Major reversible
  - Minor reversible
  - Persistent
  - No identifiable

Creager, et al. Circulation 2026; 153:e977-e1051

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Terminology for risk factors of VTE

Table 9. Risk Factors for Venous Thromboembolism

Major Reversible Risk Factor	Minor Reversible Risk Factor	Persistent Risk Factor
Surgery with general anesthesia ≥30 minutes	Surgery with general anesthesia <30 minutes	Active cancer with or without ongoing treatment
Hospitalization for acute medical illness ≥72 hours while confined to hospital bed	Hospitalization for acute medical illness <72 hours	Autoimmune disease (eg, rheumatoid arthritis, systemic lupus erythematous)
Cesarean section	Out-of-hospital acute medical illness ≥72 hours while confined to bed	Inflammatory bowel disease
Lower limb fracture	Estrogen therapy (hormone replacement or contraceptive)	Chronic immobility
	Peripartum period	
	Trauma with decreased mobility ≥72 hours	

Creager, et al. Circulation 2026; 153:e977-e1051

Contents

- Terminology for risk factors of venous thromboembolism (VTE)
- Extended anticoagulation in VTE
- Ultrasound-facilitated, catheter-directed fibrinolysis
- Unresolved issues

Long-term treatment with low dose DOAC in unprovoked VTE

Extended treatment of venous thromboembolism with reduced-dose versus full-dose direct oral anticoagulants in patients at high risk of recurrence: a non-inferiority, multicentre, randomised, open-label, blinded endpoint trial

Francis Couturaud, Jeannot Schmidt, Olivier Sanchez, Alice Ballerie, Marie-Antoinette Severine, Nicolas Meneveau, Laurent Bertoletti, Jérôme Coumaros, Ygal Benhamou, Joël Constans, Thomas Quermenec, François-Xavier Lapébie, Gilles Pernod, Gaël Picart, Antoine Elias, Caroline Doutelaux, Claire Neveux, Lina Khider, Pierre-Marie Roy, Stéphane Zuily, Nicolas Falvo, Philippe Lacroix, Joseph Emmerich, Isabelle Mahé, Julien Bisbleau, Azzedine Yazi, Sylvain Leyeux, Dominique Sotiphan, Pierre Plouvenou-Duquesne, Valérie Roy, Marc Donsay-des Déserts, Rafik Belhadj-Chaidi, Bouchra Lamia, Yves Gruel, Emilie Perelet, Philippe Girard, Cécile Tromeur, Farès Moustafa, Vincent Rothstein, Karine Lacut, Solen Mellac, Sophie Barillet, Patrick Mismetti, Silvy Laporte, Dominique Mottier, Guy Meyer, Christophe Leroyer, for the RENOVE Investigators*

Summary

Background In patients with venous thromboembolism at high risk of recurrence for whom extended treatment with direct oral anticoagulants has been indicated, the optimal dose is unknown. We aimed to assess efficacy and safety of reduced-dose versus full-dose direct oral anticoagulants in patients in whom extended anticoagulation has been indicated.

Methods RENOVE was a non-inferiority, investigator-initiated, multicentre, randomised, open-label, blinded endpoint trial done in 47 hospitals in France. Ambulatory patients aged 18 years or older with acute symptomatic venous thromboembolism (pulmonary embolism or proximal deep vein thrombosis) who had received 6–24 uninterrupted months of full-dose anticoagulation and for whom extended anticoagulation has been indicated were eligible. Eligible participants were categorised as having either a first unprovoked venous thromboembolism, recurrent venous thromboembolism, presence of persistent risk factors, or other clinical situations considered to be a high risk of recurrence. Participants were randomly assigned (1:1) to receive oral treatment with either a reduced dose of apixaban (2·5 mg twice daily) or rivaroxaban (10 mg once daily) or a full dose of apixaban (5 mg twice daily) or rivaroxaban (20 mg once daily) using a centralised randomisation procedure with an interactive web response system. The sequence generation method was a computerised random number generator and was balanced by blocks of different sizes. Randomisation was stratified by centre, type of direct oral anticoagulant, and antiplatelet drug. Physicians and participants were unmasked to treatment allocation; recurrent venous thromboembolism, clinically relevant bleeding, and all-cause death were adjudicated by an independent committee blinded to treatment allocation. The primary outcome was symptomatic recurrent venous thromboembolism, including recurrent fatal or non-fatal pulmonary embolism or isolated proximal deep vein thrombosis (non-inferiority hypothesis 90% power to exclude a hazard ratio [HR] of 1·7). The primary outcome and first two secondary outcomes were included in a hierarchical testing procedure. This trial is registered with ClinicalTrials.gov, NCT03285438.

Findings From Nov 2, 2017, to July 6, 2022, 2768 patients were enrolled and randomly assigned to the reduced-dose group (n=1383) or the full-dose group (n=1385). 970 (35·0%) participants were female, 1797 (65·0%) were male, and one (<0·1%) had sex not reported. Median follow-up was 37·1 months (IQR 24·0–48·3). Recurrent venous thromboembolism occurred in 19 of 1383 patients in the reduced-dose group (5-year cumulative incidence 2·2% [95% CI 1·1–3·3]) versus 15 of 1385 patients in the full-dose group (5-year cumulative incidence 1·8% [0·8–2·7]; adjusted HR 1·32 [95% CI 0·67–2·62]; absolute difference 0·40% [95% CI −1·05 to 1·85]; p=0·23 for non-inferiority). Major or clinically relevant bleeding occurred in 96 patients in the reduced-dose group (5-year cumulative incidence 9·9% [95% CI 7·7–12·1]) and 154 patients in the full-dose group (5-year cumulative incidence 15·2% [12·8–17·6]; adjusted HR 0·61 [95% CI 0·48–0·79]). 1136 (82·1%) of 1383 patients in the reduced-dose group and 1150 (83·0%) of 1385 in the full-dose group had an adverse event; 374 (27·0%) patients in the reduced-dose group and 420 (30·3%) in the full-dose group has a serious adverse event. 35 (5-year cumulative incidence 4·3% [95% CI 2·6–6·0]) patients in the reduced-dose group and 54 (5-year cumulative incidence 6·1% [4·3–8·0]) patients in the full-dose group died during the study period.

Interpretation In patients with venous thromboembolism requiring extended anticoagulation, reduction of the direct oral anticoagulant dose did not meet the non-inferiority criteria. However, the low recurrence rates in both groups and substantial reduction of clinically relevant bleeding with the reduced dose could support this regimen as an option. Further research will be needed to identify subgroups for whom the anticoagulation dose should not be reduced.

Lancet 2025; **405**: 725–35

See Comment page 676

*The RENOVE Investigators are listed in the appendix (pp 2–5)

Univ Brest, INSERM U1304-GETBO, CIC1412IBM, SAILL Brest, France (F Couturaud MD PhD, C Thomas MD PhD, K Lacut MD PhD, G Mottier MD PhD); C Leroyer MD PhD); **Centre Hospitalier Universitaire Brest, Département de Médecine Interne et Pneumologie, Brest, France** (F Couturaud, C Thomas, K Lacut, S Mellac RN, S Barillet RN, O Mottier, C Leroyer); **FCRIN INNOVTE Network, Saint-Etienne, France** (F Couturaud, J Schmidt MD PhD, O Sanchez MD PhD, A Ballerie MD, M-A Severine MD PhD, N Meneveau MD PhD, L Bertoletti MD PhD, J Coumaros MD PhD, Y Benhamou MD PhD, J Constans MD PhD, F-X Lapébie MD PhD, G Pernod MD PhD, G Picart MD, A Elias MD PhD, C Neveux MD, P-M Roy MD PhD, S Zuily MD PhD, N Falvo MD, P Lacroix MD PhD, J Emmerich MD PhD, I Mahé MD PhD, D Sotiphan MD PhD, M Donjay-des Déserts MD PhD, Y Gruel MD PhD, E Perelet MS, P Girard BSc, C Tromeur, F Moustafa MD PhD, K Lacut, P Mismetti MD PhD, S Laporte PhD, D Mottier, G Meyer MD*); **Service d'urgences, Centre Hospitalier Universitaire de Clermont-Ferrand, Lapsco UMR 1071 - UMR 6024, Université Clermont-Auvergne,**

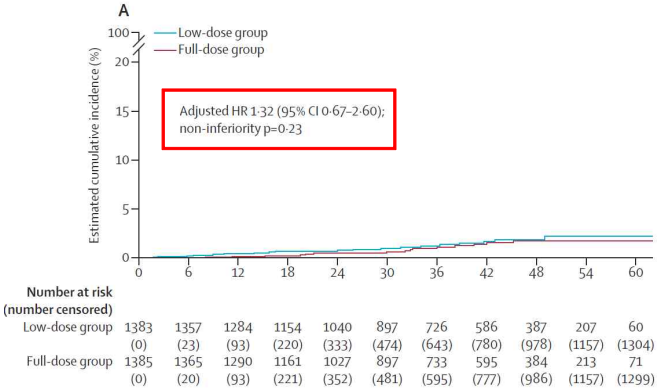
- 47 hospitals in France
- Randomized open-label blinded endpoint trial
- Patients with unprovoked VTE, persistence of risk factors
- 1383 reduced-dose DOAC vs. 1385 full-dose apixaban
- Primary outcome:
  - Recurrent venous thromboembolism during treatment
- Secondary outcome:
  - Major & clinically relevant non-major bleeding

Couturaud F, et al. Lancet 2025;405:725-35

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

	Reduced-dose group (n=1383)	Full-dose group (n=1385)
Age, years	62·2 (14·3)	63·1 (14·3)
<50	277/1382 (20·0%)	264/1385 (19·1%)
50–64	451/1382 (32·6%)	428/1385 (30·9%)
≥65	654/1382 (47·3%)	693/1385 (50·0%)
Sex		
Female	489/1383 (35·4%)	481/1385 (34·7%)
Male	893/1383 (64·6%)	904/1385 (65·3%)
Not reported	1/1383 (0·1%)	0/1385
BMI, kg/m²	28·6 (7·6)	28·3 (5·1)
BMI ≥30 kg/m²	428/1379 (31·0%)	416/1385 (30·0%)
Creatinine clearance, mL/min*		
<30	1/1264 (0·1%)	2/1280 (0·2%)
30–49	70/1264 (5·5%)	89/1280 (7·0%)
50–79 mL/min	370/1264 (29·3%)	378/1280 (29·5%)
≥80 mL/min	823/1264 (65·1%)	811/1280 (63·4%)
Medical conditions		
Chronic respiratory disease	155/1382 (11·2%)	144/1384 (10·4%)
Coronary artery disease or chronic heart failure	50/1382 (3·6%)	49/1384 (3·5%)
Arrhythmia	41/1382 (3·0%)	35/1384 (2·5%)
Stroke	30/1382 (2·2%)	24/1384 (1·7%)
Hypercholesterolaemia	257/1382 (18·6%)	272/1384 (19·7%)
Type 1 or type 2 diabetes	105/1382 (7·6%)	117/1384 (8·5%)
Previous cancer ≥6 months before index event	140/1382 (10·1%)	129/1384 (9·3%)
Family history of venous thromboembolism†	499/1382 (36·1%)	481/1384 (34·7%)
Thrombophilia (all tests)‡	234/625 (37·4%)	234/641 (36·5%)
Major thrombophilia‡	107/623 (17·2%)	111/641 (17·3%)
Previous distal deep, muscular, or superficial vein thrombosis	316/1382 (22·9%)	296/1384 (21·4%)
Characteristics of index event§		
Symptomatic pulmonary embolism with or without deep vein thrombosis	1178/1379 (85·4%)	1192/1381 (86·3%)
Pulmonary embolism with deep vein thrombosis	627/1379 (45·5%)	609/1381 (44·1%)
Pulmonary embolism without deep vein thrombosis	551/1379 (40·0%)	583/1381 (42·2%)
Pulmonary embolism at intermediate–high risk of death	198/1176 (16·8%)	203/1191 (17·0%)
Pulmonary embolism at high risk of death	32/1176 (2·7%)	44/1191 (3·7%)
Symptomatic isolated proximal deep vein thrombosis	201/1379 (14·6%)	189/1381 (13·7%)
Circumstances of index event		
First episode of unprovoked venous thromboembolism	836/1382 (60·5%)	845/1382 (61·1%)
Multiple episodes (≥2) of venous thromboembolism	463/1382 (33·5%)	453/1382 (32·8%)
Index and previous unprovoked venous thromboembolism	290/461 (62·9%)	310/449 (69·0%)
Index unprovoked and previous provoked venous thromboembolism	135/461 (29·3%)	111/449 (24·7%)
Index provoked and previous unprovoked venous thromboembolism	18/461 (3·9%)¶	20/449 (4·5%)
Index and previous provoked venous thromboembolism	18/461 (3·9%)	8/449 (1·8%)
Venous thromboembolism associated with persistent risk factor	64/1382 (4·6%)	67/1382 (4·8%)
Active cancer	34/64 (53·1%)	37/67 (55·2%)
Chronic inflammatory disease	11/64 (17·2%)	22/67 (32·8%)
Known major thrombophilia‖	7/64 (10·9%)	5/67 (7·5%)
Permanent immobilisation	7/64 (10·9%)	1/67 (1·5%)
Other	5/64 (7·8%)	2/67 (3·0%)
Estimated high risk of recurrence by physicians	19/1382 (1·4%)**	17/1382 (1·2%)††
Venous thromboembolism bleed score[27] at inclusion		
Low (<2 risk factors)	876/1264 (69·3%)	873/1277 (68·4%)
High (≥2 risk factors)	388/1264 (30·7%)	404/1277 (31·6%)
Treatment of venous thromboembolism before randomisation		
Anticoagulation duration, months	8·2 (6·4–12·2)	8·0 (6·4–12·3)
Direct oral anticoagulant alone	681/1380 (49·3%)	671/1383 (48·5%)
Heparin followed by direct oral anticoagulant	617/1380 (44·7%)	641/1383 (46·3%)
Low-molecular-weight heparin or fondaparinux alone	41/1380 (3·0%)	40/1383 (2·9%)
Heparin plus bridge to vitamin K antagonist	41/1380 (3·0%)	31/1383 (2·2%)
Thrombolytic agent	39/1380 (2·8%)	46/1384 (3·3%)
Inferior vena cava filter	10/1381 (0·7%)	8/1384 (0·6%)
Study treatment stratification at inclusion		
Apixaban and no antiplatelet drug	613 (44·3%)	613 (44·3%)
Rivaroxaban and no antiplatelet drug	742 (53·7%)	735 (53·1%)
Apixaban and antiplatelet drug	12 (0·9%)	17 (1·2%)
Rivaroxaban and antiplatelet drug	16 (1·2%)	20 (1·4%)

Long-term treatment with low dose DOAC in unprovoked VTE

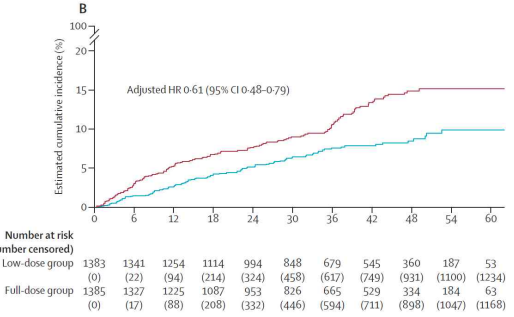


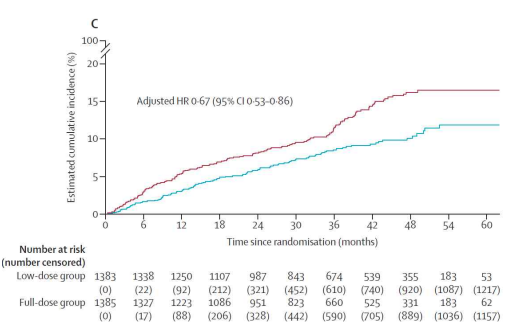
Cumulative incidence of symptomatic recurrent venous thromboembolism

Couturaud F, et al. Lancet 2025;405:725-35

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Long-term treatment with low dose DOAC in unprovoked VTE





Major and clinically relevant non-major bleeding

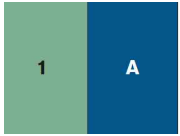
Symptomatic recurrent venous thromboembolism, major bleeding, clinically non-major bleeding

Couturaud F, et al. Lancet 2025;405:725-35

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

▶Long-term treatment with low dose DOAC in unprovoked VTE

- Non-inferiority not reached for reduced dose at median follow-up 37.1-months
  - 2.2% vs. 1.8%
- Better safety
- Active cancer patients not included



7. For patients with a PE who are offered anticoagulation beyond the initial treatment phase (3-6 months) into the extended treatment phase, treatment with half-dose apixaban or rivaroxaban is recommended to reduce the risk of bleeding.[8,9,19,20]

Couturaud F, et al. Lancet 2025;405:725-35

Long-term treatment with low dose DOAC in cancer VTE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2025 VOL. 392 NO. 14

Extended Reduced-Dose Apixaban for Cancer-Associated Venous Thromboembolism

I. Mahé, M. Carrier, O. Mayeur, J. Chidiac, E. Vicaut, N. Falvo, G. Sanchez, C. Granger, M. Monreal, J. López-Núñez, B. Otero-Candelera, L. Le Gal, E. Yeo, M. Righini, H. Robert-Ebadi, M.V. Huisman, F.A. Klok, P. Westerweel, G. Agnelli, C. Becattini, A. Bamias, K. Syrigos, S. Szmit, A. Torbicki, P. Verhamme, A. Marouyeux, A.T. Cohen, C. Ay, C. Chapelle, G. Meyer, Investigators*

ABSTRACT

BACKGROUND

In patients with active cancer and venous thromboembolism, whether extended treatment with a reduced dose of an oral anticoagulant is effective in preventing recurrent thromboembolic events and decreasing bleeding is unclear.

METHODS

We conducted a randomized, double-blind, noninferiority trial with blinded central outcome adjudication. Consecutive patients with active cancer and proximal deep-vein thrombosis or pulmonary embolism who had completed at least 6 months of anticoagulant therapy were randomly assigned in a 1:1 ratio to receive oral apixaban at a reduced (2.5 mg) or full (5.0 mg) dose twice daily for 12 months. The primary outcome was centrally adjudicated fatal or nonfatal recurrent venous thromboembolism, assessed in a noninferiority analysis (margin of 2.00 for the upper boundary of the 95% confidence interval of the subhazard ratio). The key secondary outcome was clinically relevant bleeding, assessed in a superiority analysis.

RESULTS

A total of 1766 patients underwent randomization at a median time since the index event of 8.0 months (interquartile range, 6.5 to 12.6); 866 patients were assigned to the reduced-dose group, and 900 to the full-dose group. The median treatment duration was 11.0 months (interquartile range, 8.3 to 12.1). Recurrent venous thromboembolism occurred in 38 patients (cumulative incidence, 2.7%) in the reduced-dose group and in 24 (cumulative incidence, 2.8%) in the full-dose group (adjusted subhazard ratio, 0.76; 95% confidence interval [CI], 0.41 to 1.41; P<0.001 for noninferiority). Clinically relevant bleeding occurred in 102 patients (cumulative incidence, 12.0%) in the reduced-dose group and in 136 (cumulative incidence, 15.6%) in the full-dose group (adjusted subhazard ratio, 0.75; 95% CI, 0.58 to 0.97; P=0.03). Mortality was 17.7% in the reduced-dose group and 19.6% in the full-dose group (adjusted hazard ratio, 0.86; 95% CI, 0.66 to 1.06).

CONCLUSIONS

Extended anticoagulation with reduced-dose apixaban was noninferior to full-dose apixaban for the prevention of recurrent venous thromboembolism in patients with active cancer. The reduced dose led to a lower incidence of clinically relevant bleeding complications than the full dose. (Funded by the Bristol-Myers Squibb–Pfizer Alliance; AIM-CAT ClinicalTrials.gov number, NCT03620865.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Le Gal can be contacted at isabelle.mahe@aphp.fr or at Hôpital Louis Mourier, Service de Médecine Interne, Assistance Publique–Hôpitaux de Paris, Université Paris Cité, 178 Rue des Renouilliers, 92700 Colombes, France.

*Deceased.

†A list of the AIM-CAT investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 29, 2025, at NEJM.org.

N Engl J Med 2025;392:1363-73.
DOI: 10.1056/NEJMoa2412113

Copyright © 2025 Massachusetts Medical Society.

CME

- 121 centers in 11 countries
- Randomized double-blind noninferiority trial
- Patients with active cancer
- 866 reduced-dose apixaban vs. 900 full-dose apixaban
- Primary outcome:
  - Fatal or nonfatal recurrent VTE over 12 months
- Secondary outcome:
  - Clinically relevant bleeding over 12 months

Mahe I, et al. N Engl J Med 2025;392(14):1363-1373

CAUH 중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Lon DOAC in cancer VTE

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

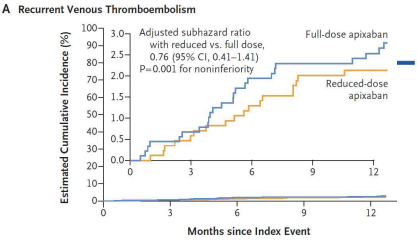
Characteristic	Reduced-Dose Apixaban (N=866)	Full-Dose Apixaban (N=900)
Age — yr	67.2±11.0	67.7±11.4
Male sex — no. (%)	375 (43.3)	391 (43.4)
Body weight — kg	75.7±16.3	75.7±16.4
Body-mass index†	27.0±5.3	27.0±5.4
Platelet count <100,000/mm³ — no./total no. (%)	18/863 (2.1)	15/899 (1.7)
Creatinine clearance <50 ml/min — no./total no. (%)	115/864 (13.3)	127/900 (14.1)
Qualifying diagnosis of venous thromboembolism — no. (%)		
Pulmonary embolism with or without lower-limb proximal deep-vein thrombosis	669 (77.3)	665 (73.9)
Lower-limb proximal deep-vein thrombosis only	197 (22.7)	235 (26.1)
Clinical manifestation of index venous thromboembolism — no./total no. (%)		
Symptomatic deep-vein thrombosis or pulmonary embolism	528/856 (61.7)	580/888 (65.3)
Incidental pulmonary embolism	290/856 (33.9)	275/888 (31.0)
Incidental deep-vein thrombosis only	38/856 (4.4)	33/888 (3.7)
History of venous thromboembolism — no. (%)	157 (18.1)	170 (18.9)
Active cancer — no. (%)‡	864 (99.8)	897 (99.7)
Stage of cancer — no. (%)		
Localized	111 (12.8)	117 (13.0)
Locally advanced	115 (13.3)	113 (12.6)
Metastatic	574 (66.3)	584 (64.9)
Other	64 (7.4)	83 (9.2)
Unknown	2 (0.2)	3 (0.3)
Site of cancer — no. (%)		
Breast	199 (23.0)	202 (22.4)
Prostate	77 (8.9)	87 (9.7)
Colon or rectum	123 (14.2)	148 (16.4)
Lung	99 (11.4)	100 (11.1)
Other	368 (42.5)	363 (40.3)
ECOG performance-status score — no. (%)§		
0	456 (52.7)	504 (56.0)
1	342 (39.5)	329 (36.6)
2	67 (7.7)	63 (7.0)
Unknown	1 (0.1)	4 (0.4)

Mahe I, et al. N Engl J Med 2025;392(14):1363-1373

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Table 2. **Clinical Outcomes during the Trial Period.***

Outcome	Reduced-Dose Apixaban (N=866)	Full-Dose Apixaban (N=900)	Treatment Effect (95% CI)	P Value
	number (percent)			
Primary efficacy outcome: recurrent venous thromboembolism†	18 (2.1)	24 (2.8)	0.76 (0.41–1.41)	0.001
Recurrent symptomatic venous thromboembolism	17 (2.0)	18 (2.1)	0.97 (0.50–1.88)	—
Lower-limb deep-vein thrombosis‡	8 (0.9)	6 (0.7)	—	
Pulmonary embolism	9 (1.1)	10 (1.2)	—	
Fatal pulmonary embolism	0	0	—	
Unexplained sudden death§	3 (0.4)	2 (0.3)	—	
Upper-limb deep-vein thrombosis	1 (0.1)	3 (0.4)	—	
Central venous catheter–related thrombosis	1 (0.1)	2 (0.2)	—	
Incidental venous thromboembolism¶	1 (0.1)	6 (0.7)	—	
Recurrent major venous thromboembolism‖	17 (2.0)	21 (2.4)	0.83 (0.44–1.57)	—
Key secondary safety outcome: major or clinically relevant non-major bleeding**	102 (12.1)	136 (15.6)	0.75 (0.58–0.97)	0.03
Major bleeding	24 (2.9)	37 (4.3)	0.66 (0.40–1.10)	—
Fatal bleeding	2 (0.2)	2 (0.2)	—	
Major gastrointestinal bleeding	12 (1.4)	25 (2.9)	—	
Upper gastrointestinal bleeding	6 (0.7)	13 (1.5)	—	
Lower gastrointestinal bleeding	7 (0.8)	13 (1.5)	—	
Clinically relevant nonmajor bleeding	84 (10.0)	107 (12.3)	0.79 (0.59–1.05)	
Other secondary outcomes				
Death from any cause	148 (17.7)	168 (19.6)	0.96 (0.86–1.06)	—
Recurrent symptomatic venous thromboembolism, major bleeding, or death from any cause††	167 (19.9)	191 (22.1)	0.96 (0.87–1.07)	—
Major venous thromboembolism or major bleeding‡‡	41 (5.2)	55 (6.8)	0.96 (0.87–1.06)	—



▶Long-term treatment with low dose DOAC in cancer VTE

- No efficacy difference for stepping dose down after 6 months
- Benefit in terms of bleeding

- Patients who survived 6 months
- Follow-up of 12 months

Mahe I, et al. N Engl J Med 2025;392(14):1363-1373

Extended treatment for provoked VTE with enduring risk factors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban for Extended Treatment of Provoked Venous Thromboembolism

Gregory Piazza, M.D.,[1,2] Behnood Bikdeli, M.D.,[1,3] Arvind K. Pandey, M.D.,[1] Darsiya Krishnathasan, M.S.,[1] Candrika D. Kharaeni, M.D.,[1] Antoine Bejjani, M.D.,[1,4] Ruth H. Morrison, R.N., B.S.N.,[1] Heather Hogan, R.N., B.S.N.,[1] Sina Rasheed, M.D., M.P.H.,[1] Mariana Pfefferman, M.D.,[1] Junyang Lou, M.D., Ph.D.,[1,5] John Fanikos, R.P.H.,[1,5] Nicole Porio, B.A.,[1] Lisa Rosenbaum, M.D.,[6] Piotr Sobieszczyk, M.D.,[7] Zhou Lan, Ph.D.,[1,7] Marie Gerhard-Herman, M.D.,[1] Umberto Campia, M.D.,[1,2] and Samuel Z. Goldhaber, M.D.,[1,2] for the HI-PRO Trial Investigators*

ABSTRACT

BACKGROUND

The appropriate duration of anticoagulation for venous thromboembolism (VTE) in patients who have a transient provoking factor (e.g., surgery, trauma, or immobility) and concomitant enduring risk factors is uncertain.

METHODS

In this single-center, double-blind, randomized trial, adults with VTE after the occurrence of a transient provoking factor who had at least one enduring risk factor and had completed at least 3 months of anticoagulation were assigned to receive oral apixaban (at a dose of 2.5 mg twice daily) or placebo for 12 months. The primary efficacy outcome was the first symptomatic recurrent VTE. The primary safety outcome was the first episode of major bleeding according to the criteria of the International Society on Thrombosis and Hemostasis.

RESULTS

A total of 600 patients underwent randomization (mean age, 59.5 years; female sex, 57.0%; non-White race, 19.2%). The trial population had a broad range of provoking factors and enduring risk factors. Symptomatic recurrent VTE occurred in 4 of the 300 patients (1.3%) in the apixaban group and in 20 of the 300 patients (10.0%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.04 to 0.36; P<0.001). Major bleeding occurred in 1 patient in the apixaban group and none in the placebo group. Clinically relevant nonmajor bleeding was observed in 14 of 294 patients (4.8%) in the apixaban group and in 5 of 294 patients (1.7%) in the placebo group (hazard ratio, 2.68; 95% CI, 0.96 to 7.45; P=0.06). One patient in the apixaban group and 3 patients in the placebo group died, with no deaths attributed to cardiovascular or hemorrhagic causes. Nonhemorrhagic, nonfatal adverse events occurred in 6 patients (2.0%) in each group.

CONCLUSIONS

Among patients with provoked VTE and enduring risk factors, low-intensity therapy with apixaban for 12 months resulted in a lower risk of symptomatic recurrent VTE than placebo, with a low risk of major bleeding. (Funded by Bristol-Myers Squibb–Pfizer Alliance; HI-PRO ClinicalTrials.gov number, NCT04168203.)

Author affiliations are listed at the end of the article. Dr. Piazza can be contacted at gpiazza@bwh.harvard.edu or at the Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

*A complete list of the HI-PRO trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 30, 2025, at NEJM.org.

N Engl J Med 2025;393:1166-76.
DOI: 10.1056/NEJMoa2509426
Copyright © 2025 Massachusetts Medical Society.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org at Chungang University on June 7, 2026.

- Single-center, double-blind randomized trial (Brigham and Women's hospital)
- Patients with VTE after the occurrence of a transient provoking factor and **enduring risk factor**
- 300 apixaban 2.5 mg BID vs. 300 placebo 12 months
- Primary outcome
  - First symptomatic, recurrent, objectively confirmed VTE
- Secondary outcome
  - Composite of death from cardiovascular causes, nonfatal myocardial infarction, stroke or transient ischemic attack, systemic embolism, major adverse limb event or coronary or peripheral ischemia resulting in revascularization

Piazza, et al. N Engl J Med. 2025;393:1166-1176

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

E ith enduring risk factors

Characteristic	All Patients (N=600)	Apixaban (N=300)	Placebo (N=300)	Standardized Difference†
				%
Age — yr	59.5±15.2	59.1±15.2	59.9±15.2	5.8
Female sex — no. (%)	342 (57.0)	176 (58.7)	166 (55.3)	6.7
Race — no. (%)‡				
White	485 (80.8)	246 (82.0)	239 (79.7)	5.9
Black	70 (11.7)	33 (11.0)	37 (12.3)	4.2
Asian	5 (0.8)	4 (1.3)	1 (0.3)	11.0
Other	18 (3.0)	9 (3.0)	9 (3.0)	0
Unknown	27 (4.5)	9 (3.0)	18 (6.0)	14.5
Hispanic or Latino ethnic group — no. (%)‡	55 (9.2)	26 (8.7)	29 (9.7)	3.5
BMI§	30.6±6.7	30.7±6.8	30.4±6.6	3.5
Current smoker — no. (%)	32 (5.3)	15 (5.0)	17 (5.7)	3.0
Coexisting conditions — no. (%)¶				
Previous VTE‖	125 (20.8)	67 (22.3)	58 (19.3)	7.4
Diabetes	71 (11.8)	40 (13.3)	31 (10.3)	9.3
Hypertension	296 (49.3)	146 (48.7)	150 (50.0)	2.7
Coronary artery disease	104 (17.3)	50 (16.7)	54 (18.0)	3.5
Peripheral artery disease	23 (3.8)	12 (4.0)	11 (3.7)	1.7
Stroke or TIA	31 (5.2)	17 (5.7)	14 (4.7)	4.5
Heart failure	15 (2.5)	10 (3.3)	5 (1.7)	10.7
Dyslipidemia	317 (52.8)	164 (54.7)	153 (51.0)	7.4
Carotid occlusive disease	13 (2.2)	6 (2.0)	7 (2.3)	2.3
Family history of VTE — no. (%)	154 (25.7)	78 (26.0)	76 (25.3)	1.5
Use of aspirin at ≤81 mg/day — no. (%)				
At baseline	125 (20.8)	55 (18.3)	70 (23.3)	12.3
During follow-up period	119 (19.8)	54 (18.0)	65 (21.7)	9.2

iazza, et al. N Engl J Med 2025;393:1166-1176

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Characteristic	Total (N = 600)	Apixaban (N = 300)	Placebo (N = 300)	Standardized Difference
				%
VTE diagnosis for eligibility — no. (%)				
Only deep-vein thrombosis	288 (48.0)	142 (47.3)	146 (48.7)	2.7
Isolated calf deep-vein thrombosis	119 (19.8)	48 (16.0)	71 (23.7)	19.3
Only pulmonary embolism	140 (23.3)	77 (25.7)	63 (21.0)	11.1
Right ventricular dysfunction	80 (13.3)	38 (12.7)	42 (14.0)	3.9
Both pulmonary embolism and deep-vein thrombosis	172 (28.7)	81 (27.0)	91 (30.3)	7.4
Provoking factors for VTE — no. (%)†				
Acute medical illness‡	110 (18.3)	56 (18.7)	54 (18.0)	1.7
Surgery	201 (33.5)	102 (34.0)	99 (33.0)	2.1
Trauma	115 (19.2)	62 (20.7)	53 (17.7)	7.6
Pregnancy	11 (1.8)	7 (2.3)	4 (1.3)	7.5
Infection	99 (16.5)	45 (15.0)	54 (18.0)	8.1
Hormonal contraceptive or replacement therapy	69 (11.5)	42 (14.0)	27 (9.0)	15.7
Hospitalization ≤3 mo before the VTE event	56 (9.3)	25 (8.3)	31 (10.3)	6.9
Immobility	188 (31.3)	81 (27.0)	107 (35.7)	18.8
Blood transfusion§	2 (0.3)	1 (0.3)	1 (0.3)	0
Coronavirus disease 2019§	49 (8.2)	23 (7.7)	26 (8.7)	3.7
Long-haul travel§	100 (16.7)	46 (15.3)	54 (18.0)	7.2
Other factor¶	53 (8.8)	26 (8.7)	27 (9.0)	1.2
Enduring risk factors for VTE — no. (%)†				
Persistent immobility	39 (6.5)	15 (5.0)	24 (8.0)	12.2
Obesity: BMI ≥30	289 (48.2)	141 (47.0)	148 (49.3)	4.7
Heart failure	15 (2.5)	10 (3.3)	5 (1.7)	10.7
Chronic lung disease	134 (22.3)	78 (26.0)	56 (18.7)	17.7
Chronic inflammatory or autoimmune disorder	313 (52.2)	152 (50.7)	161 (53.7)	6.0
Atherosclerotic cardiovascular disease	176 (29.3)	86 (28.7)	90 (30.0)	2.9
Chronic kidney disease	64 (10.7)	32 (10.7)	32 (10.7)	0
Chronic liver disease	23 (3.8)	10 (3.3)	13 (4.3)	5.2
Median duration of anticoagulant treatment before randomization — mo (IQR)	6.6 (3.7–35.3)	7.6 (3.9–39.6)	5.9 (3.5–32.5)	6.9

with enduring risk factors

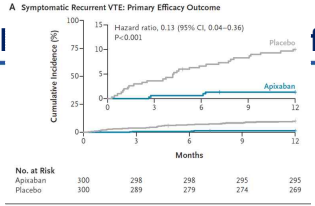
- Enduring risk factors
  - Persistent immobility
  - Obesity: BMI ≥30
  - Heart failure
  - Chronic lung disease
  - Chronic inflammatory or autoimmune disorder
  - Atherosclerotic cardiovascular disease
  - Chronic kidney disease
  - Chronic liver disease

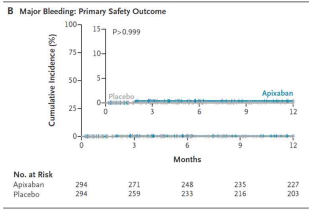
Piazza, et al. N Engl J Med 2025;393:1166-1176

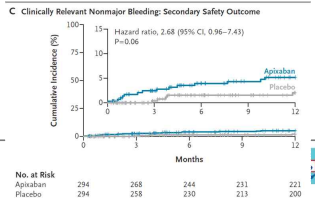
중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Extended treatment for provoked VTE

Outcome	Apixaban	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no. (%)			
Efficacy outcome				
Symptomatic recurrent VTE: primary efficacy outcome	4/300 (1.3)	30/300 (10.0)	0.13 (0.04–0.36)	<0.001
Pulmonary embolism				
Any	0	11/300 (3.7)		
Isolated subsegmental	0	1/300 (0.3)		
Deep-vein thrombosis				
Any	4/300 (1.3)	23/300 (7.7)		
Isolated calf	2/300 (0.7)	10/300 (3.3)		
Secondary efficacy composite outcome	2/300 (0.7)	3/300 (1.0)†	0.67 (0.11–3.98)‡	
Nonfatal myocardial infarction	1/300 (0.3)	0		
Stroke, TIA, or systemic embolism§	1/300 (0.3)	2/300 (0.7)		
Coronary or peripheral ischemia resulting in revascularization	0	2/300 (0.7)		
Other outcome				
Additional efficacy composite outcome¶	6/300 (2.0)	32/300 (10.7)	0.18 (0.07–0.43)‡	
Composite thrombotic outcome‖	6/300 (2.0)	31/300 (10.3)	0.19 (0.08–0.44)‡	
Death from any cause	1/300 (0.3)	3/300 (1.0)		
Safety outcome				
Major bleeding: primary safety outcome**	1/294 (0.3)	0	NE	>0.999
Clinically relevant nonmajor bleeding: secondary safety outcome**	14/294 (4.8)	5/294 (1.7)	2.68 (0.96–7.43)	0.06







HR 0.13, P<0.001

Piazza, et al. N Engl J Med 2025;393:1166-1176

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Extended treatment for provoked VTE with enduring risk factors

- Risk reduction with extended anticoagulation
- Challenges the concept
  - “provoked = stop at 3 months, unprovoked = extend”

- Single-center design
- Comparison with placebo
  - Dose, aspirin not considered
- Follow-up of 12 months

Piazza, et al. N Engl J Med 2025;393:1166-1176

Meta-analysis for reduced-dose vs. full-dose DOAC for extended trea

Thrombosis Research 254 (2025) 109476

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Efficacy and safety of reduced-dose versus full-dose direct oral anticoagulants for extended treatment of venous thromboembolism: A meta-analysis with trial sequential analysis and reconstructed time-to-event data

Ahmed Ibrahim [a], Laila Shalabi [b], Sofian Zreigh [c], Abdelrahman M. Tawfik [a], Belal Mohamed Hamed [d], Mohamed Elsawy [d], Atul Pathak [e], Mamas A. Mamas [f], Giuseppe Andò [g,*], Islam Y. Elgendy [h], Pierre Sabouret [i,j]

[a] Faculty of Medicine, Alexandria University, Alexandria, Egypt
[b] Faculty of Medicine, Gharyan University, Gharyan, Libya
[c] Faculty of Medicine, Ankara Yildirim Beyazit University, Ankara, Turkey
[d] Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[e] National Institute of Cardiology, Cardiac Surgery and Interventional Cardiology (INCCI), Luxembourg
[f] Keele Cardiovascular Research Group, Keele University, Stoke-on-Trent, UK
[g] Department of Clinical and Experimental Medicine, University of Messina and Azienda Ospedaliera Universitaria Policlinico "Gaetano Martino", Messina, Italy
[h] Division of Cardiovascular Medicine, Gill Heart and Vascular Institute, University of Kentucky, Lexington, KY, USA
[i] National College of French Cardiologists, Paris, France
[j] Heart Institute and Action Group, Pitié-Salpêtrière, Sorbonne University, 75013, Paris, France

ARTICLE INFO

Keywords:
Anticoagulants
Apixaban
Rivaroxaban
Venous thromboembolism
Reduced-dose
Meta-analysis

ABSTRACT

Background: While current guidelines recommend extended therapeutic anticoagulation for venous thromboembolism (VTE), the optimal dosing strategy for direct oral anticoagulants (DOACs) remains uncertain, particularly in cancer-associated VTE. This meta-analysis evaluates the efficacy and safety of reduced-dose versus full-dose DOACs for extended VTE treatment.

Methods: We conducted a comprehensive search of major electronic databases through April 2025 for randomized controlled trials (RCTs) comparing reduced-dose versus full-dose DOACs for VTE treatment. Pooled risk ratios (RR) with 95 % confidence intervals (CI) were calculated using random-effects models. Time-to-event data were reconstructed from Kaplan-Meier curves. Trial sequential analysis (TSA) was employed to assess the conclusiveness of the evidence.

Results: Our analysis included five RCTs involving 8781 patients. Reduced-dose DOACs were associated with comparable efficacy to full-dose therapy in preventing recurrent VTE (RR, 0.94; 95 % CI, 0.65–1.29; $P = 0.70$), supported by time-to-event analysis (HR, 0.89; 95 % CI 0.78–1.02; $p = 0.10$). However, reduced-dose regimens significantly reduced major or clinically relevant non-major bleeding (RR, 0.71; 95 % CI 0.61–0.82; $P < 0.0001$), with consistent findings on Kaplan-Meier analysis (HR, 0.61; 95 % CI 0.57–0.66; $P < 0.001$). Subgroup analyses showed consistent results in patients with and without active cancer, and also across different DOAC types (apixaban and rivaroxaban). No differences were observed in all-cause mortality. TSA confirmed sufficient evidence for both efficacy and safety outcomes.

Conclusion: Reduced-dose DOACs were as effective as full-dose regimens in preventing recurrent VTE, with a better safety profile, suggesting they may be preferred for patients requiring extended anticoagulation, especially those at high risk of recurrence.

Prospero ID: CRD42025104675.

- 5 RCTs, 8781 patients
- Efficacy outcome
  - Recurrent venous thromboembolism
- Safety outcome
  - Clinically relevant bleeding

Ibrahim, et al. Thromb Res 2025;254:109476

CAVE 중앙대학교의료원 CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Meta-analysis for reduced-dose vs. full-dose DOAC for extended trea

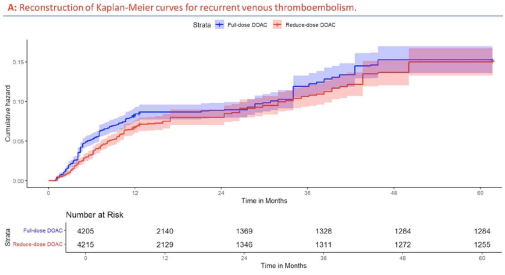
Baseline characteristics and comorbidities of included patients.

Trial	Age, mean (SD), y		Male, No. (%)		BMI (kg/m^2)		Diabetes mellitus, No. (%)		Active cancer, No. (%)[a]		Known thrombophilia, No. (%)[b]		PE, No. (%)		DVT, No. (%)		CrCl <30 ml/min, No. (%)		CrCl 30 to <50 ml/min, No. (%)		CrCl 50 to <80 ml/min, No. (%)		CrCl ≥80, No. (%)	
	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose	Reduced-dose	Full-dose
AMPLIFY-EXT	56.6 (15.3)	56.4 (15.6)	487 (58.0 %)	469 (57.7 %)	29.3 ± 6.1	29.2 ± 5.7	100 (11.9 %)	82 (10.1 %)	15 (1.8 %)	9 (1.1 %)	–	–	296 (35.2 %)	286 (35.2 %)	544 (64.8 %)	527 (64.8 %)	1 (0.1 %)	3 (0.4 %)	47 (5.6 %)	41 (5.0 %)	174 (20.7 %)	168 (20.7 %)	595 (70.8 %)	580 (71.3 %)
EINSTEIN CHOICE	58.8 (14.7)	57.9 (14.7)	620 (55.0 %)	602 (54.4 %)	BMI ≥ 30: 376 (33.4 %)	BMI ≥ 30: 394 (35.6 %)	–	–	27 (2.4 %)	25 (2.3 %)	74 (6.6)	79 (7.1)	381 (33.8 %)[c]	381 (34.4 %)[c]	565 (50.1 %)[c]	565 (51.0 %)[c]	2 (0.2 %)	1 (0.1 %)	49 (4.3 %)	40 (3.6 %)	302 (26.8 %)	279 (25.2 %)	774 (68.7 %)	787 (71.1 %)
EVE trial	63.6 (11.0)	64.3 (10.7)	87 (48.6 %)	74 (40.9 %)	29.2 (6.6)	29.5 (6.8)	104 (58.1 %)	111 (61.3 %)	179 (100 %)	181 (100 %)	–	–	106 (59.2)[c]	102 (56.4)[c]	88 (49.2)	92 (50.8)	–	–	–	–	–	–	–	–
RENOVE	62.2 (14.3)	63.1 (14.3)	893 (64.6 %)	904 (65.3 %)	28.6 (7.6)	28.3 (5.1)	105 (7.6 %)	117 (8.5 %)	34/1382 (2.5 %)	37/1382 (2.7 %)	234/625 (37.4 %)	234/641 (36.5 %)	1178 (85.4 %)[c]	1192 (86.3 %)[c]	201 (14.6 %)[c]	189 (13.7 %)[c]	1/1264 (0.1 %)	2/1280 (0.2 %)	70/1264 (5.5 %)	89/1280 (7.0 %)	370/1264 (29.3 %)	378/1280 (29.5 %)	823/1264 (65.1 %)	811/1280 (63.4 %)
API-CAT	67.2 (11.0)	67.7 (11.4)	375 (43.3)	391 (43.4)	27.0 (5.3)	27.0 (5.4)	–	–	864 (99.8)	897 (99.7)	–	–	669 (77.3)[d]	665 (73.9)[d]	197 (22.7)[e]	235 (26.1)[e]	–	–	115/864 (13.3)[e]	127/900 (14.1)[e]	–	–	–	–

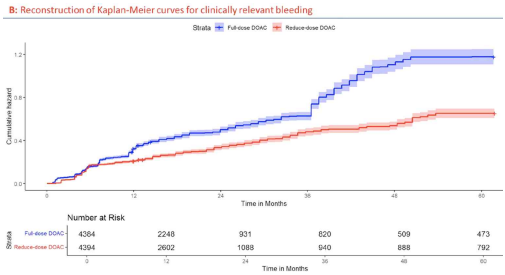
Ibrahim, et al. Thromb Res 2025;254:109476

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Meta-analysis for reduced-dose vs. full-dose DOAC for extended trea



RR 0.97, 95% CI 0.61-1.53, P = 0.89



RR 0.71, 95% CI 0.61-0.83, P<0.0001

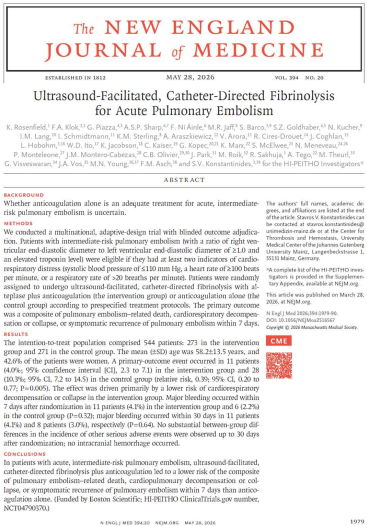
Ibrahim, et al. Thromb Res 2025;254:109476

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

Contents

- Terminology for risk factors of venous thromboembolism (VTE)
- Extended anticoagulation in VTE
- Ultrasound-facilitated, catheter-directed fibrinolysis
- Unresolved issues

US-facilitated, catheter-directed fibrinolysis



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 28, 2026 VOL. 394 NO. 20

Ultrasound-Facilitated, Catheter-Directed Fibrinolysis for Acute Pulmonary Embolism

K. Rosenfield,[1] F.A. Klok,[2] G. Piazza,[3] A.S.P. Sharp,[4] F. Ni Ainle,[5] M.R. Jaff,[6] S. Barco,[7,8] S.Z. Goldhaber,[1,9] N. Kucher,[9] I.M. Lang,[10] J. Schmidtmann,[11] K.M. Sterling,[6] A. Arazalinevicz,[12] V. Arora,[13] R. Cires-Drouet,[14] J. Coghlan,[15] L. Hobohm,[7,16] W.D. Ito,[17] K. Jacobson,[18] C. Kaiser,[19] G. Kopec,[20,21] K. Man,[22] S. McElwee,[23] N. Meneveau,[24,25] P. Monteleone,[26] J.M. Montero-Cabezas,[26] C.B. Olivier,[27,28] J. Park,[29] M. Roik,[30] R. Saikhuja,[1] A. Tegos,[31] M. Theurl,[32] G. Visveswaran,[33] J.A. Vos,[34] M.N. Young,[35,36] F.M. Asch,[37] and S.V. Konstantinides,[7,38] for the HI-PEITHO Investigators*

ABSTRACT

BACKGROUND

Whether anticoagulation alone is an adequate treatment for acute, intermediate-risk pulmonary embolism is uncertain.

METHODS

We conducted a multinational, adaptive-design trial with blinded outcome adjudication. Patients with intermediate-risk pulmonary embolism (with a ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter of ≥1.0 and an elevated troponin level) were eligible if they had at least two indicators of cardiorespiratory distress (systolic blood pressure of ≤110 mm Hg, a heart rate of ≥100 beats per minute, or a respiratory rate of ≥20 breaths per minute). Patients were randomly assigned to undergo ultrasound-facilitated, catheter-directed fibrinolysis with alteplase plus anticoagulation (the intervention group) or anticoagulation alone (the control group) according to prespecified treatment protocols. The primary outcome was a composite of pulmonary embolism–related death, cardiorespiratory decompensation or collapse, or symptomatic recurrence of pulmonary embolism within 7 days.

RESULTS

The intention-to-treat population comprised 544 patients: 273 in the intervention group and 271 in the control group. The mean (±SD) age was 58.2±13.5 years, and 42.6% of the patients were women. A primary-outcome event occurred in 11 patients (4.0%; 95% confidence interval [CI], 2.3 to 7.1) in the intervention group and 28 (10.3%; 95% CI, 7.2 to 14.5) in the control group (relative risk, 0.39; 95% CI, 0.20 to 0.77; P=0.005). The effect was driven primarily by a lower risk of cardiorespiratory decompensation or collapse in the intervention group. Major bleeding occurred within 7 days after randomization in 11 patients (4.1%) in the intervention group and 6 (2.2%) in the control group (P=0.32); major bleeding occurred within 30 days in 11 patients (4.1%) and 8 patients (3.0%), respectively (P=0.64). No substantial between-group differences in the incidence of other serious adverse events were observed up to 30 days after randomization; no intracranial hemorrhage occurred.

CONCLUSIONS

In patients with acute, intermediate-risk pulmonary embolism, ultrasound-facilitated, catheter-directed fibrinolysis plus anticoagulation led to a lower risk of the composite of pulmonary embolism–related death, cardiopulmonary decompensation or collapse, or symptomatic recurrence of pulmonary embolism within 7 days than anticoagulation alone. (Funded by Boston Scientific; HI-PEITHO ClinicalTrials.gov number, NCT04790370.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Stavros V. Konstantinides can be contacted at stavros.konstantinides@unimedizin-mainz.de or at the Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany.

*A complete list of the HI-PEITHO investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 28, 2026, at NEJM.org.

N Engl J Med 2026;394:1979-90.
DOI: 10.1056/NEJMoa2510567

Copyright © 2026 Massachusetts Medical Society.

CME

- 59 centers in the US & Europe
- Multinational, adaptive-design trial with blinded outcome adjudication
- Patients with intermediate-risk pulmonary embolism
  - RV:LV ≥ 1.0
  - Elevated troponin
    - Systolic blood pressure ≤110 mm Hg
    - Heart rate ≥100 betas per min
    - Respiratory rate >20 breaths per min
- 273 interventions vs. 271 controls
- Primary outcome
  - Composite of pulmonary embolism-related death, cardiorespiratory collapse or decompensation, or nonfatal, symptomatic recurrence of pulmonary embolism within 7 days

Rosenfield et al. N Engl J Med 2026;394(20):1979-1990

CAUH 중앙대학교의료원 CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

US-facilitated, catheter-directed fibrinolysis

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

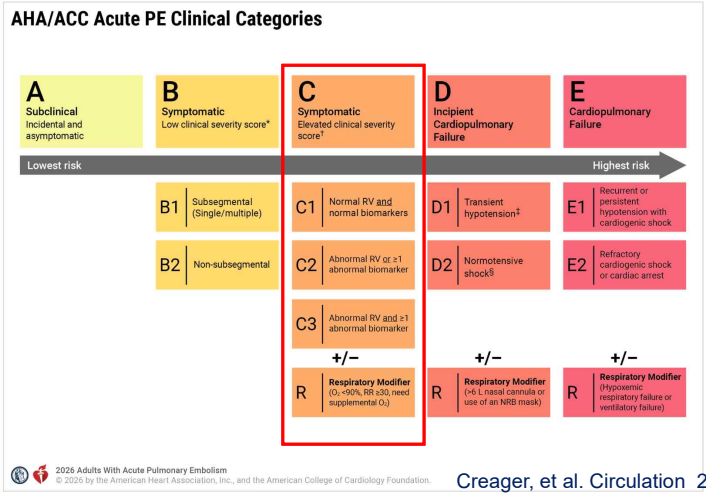
Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low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

©ESC 2019

Konstantinides, et al. Eur Heart J 2020;41:543-603

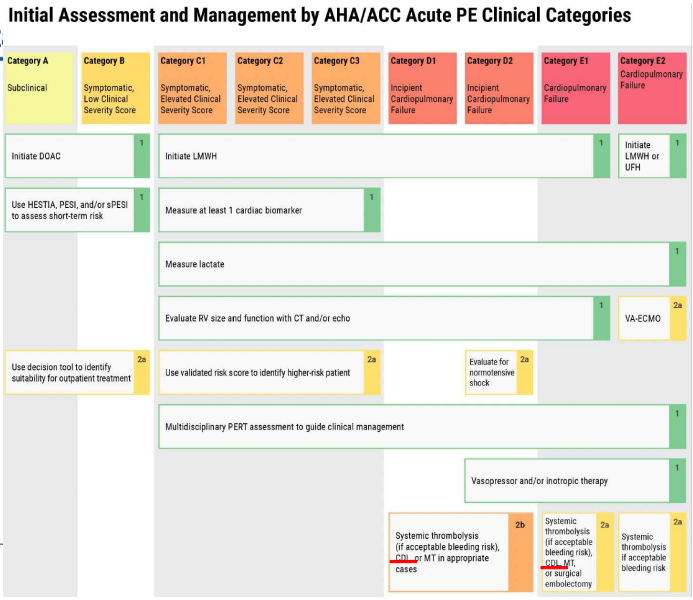
중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

▶US-facil[illegible] catheter-directed fibrinolysis



Creager, et al. Circulation 2026; 153:e977-e1051

US-facilit



026; 153:e977-e1051

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

ed fibrinolysis

Characteristic	Intervention (N=273)	Control (N=271)	Standardized Difference†
			percent
Demographic data			
Age — yr	58.2±13.6	58.2±13.4	0.2
Female sex — no. (%)	114 (41.8)	118 (43.5)	3.6
Clinical status			
Body-mass index‡	32.9±8.5	33.4±8.2	5.0
Frailty index§	1.9±0.7	1.9±0.7	2.0
Duration of symptoms (current episode) — days¶	3.5±3.3	3.9±3.5	12.5
Dyspnea — no. (%)	254 (93.0)	242 (89.3)	13.2
Chest pain — no. (%)	87 (31.9)	101 (37.3)	11.4
Syncope — no. (%)	67 (24.5)	64 (23.6)	2.2
Tachycardia — no. (%)‖	210 (76.9)	215 (79.3)	5.8
Prolonged hypotension — no. (%)	4 (1.5)	6 (2.2)	5.6
Tachypnea — no. (%)**	118 (43.2)	142 (52.4)	18.4
Hypoxemia — no. (%)	135 (49.5)	130 (48.0)	3.0
National Early Warning Score††	6.0±1.9	6.0±1.9	2.2
Concomitant ultrasound-confirmed, lower-extremity deep-vein thrombosis — no. (%)			
Yes	107 (39.2)	109 (40.2)	2.1
No	82 (30.0)	86 (31.7)	
Ultrasound not performed	84 (30.8)	76 (28.0)	
Imaging findings			
Bilateral pulmonary embolism — no. (%)‡‡	251 (91.9)	262 (96.7)	20.6
RV:LV ratio§§	1.6±0.5	1.5±0.4	12.5
Medical history — no. (%)			
Congestive heart failure			
Yes	4 (1.5)	9 (3.3)	12.2
No	267 (97.8)	259 (95.6)	
Unknown	2 (0.7)	3 (1.1)	
Transient ischemic attack or stroke			
Yes	7 (2.6)	11 (4.1)	8.4
No	266 (97.4)	259 (95.6)	
Unknown	0	1 (0.4)	
Current or previous cancer¶¶			
Yes	29 (10.6)	21 (7.7)	10.0
No	236 (86.4)	249 (91.9)	
Unknown	8 (2.9)	1 (0.4)	
Chronic obstructive pulmonary disease			
Yes	13 (4.8)	14 (5.2)	1.9
No	256 (93.8)	247 (91.1)	
Unknown	4 (1.5)	10 (3.7)	

Rosenfield et al. N Engl J Med 2026;394(20):1979-1990

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

▶US-facilitated, catheter-directed fibrinolysis

Outcome	Intervention (N = 273)		Control (N = 271)		Relative Risk (95% CI)†
	no. of patients	*% (95% CI)†*	*no. of patients*	*% (95% CI)†*	
Any primary-outcome event	11	4.0 (2.3–7.1)	28	10.3 (7.2–14.5)	0.39 (0.20–0.77);
Components of the primary outcome					
Pulmonary embolism–related death	3	1.1 (0.4–3.2)	1	0.4 (0.1–2.1)	3.0 (0.3–28.5)
Cardiorespiratory decompensation or collapse	10	3.7 (2.0–6.6)	28	10.3 (7.2–14.5)	0.4 (0.2–0.7)
Recurrence of pulmonary embolism	1	0.4 (0.1–2.0)	1	0.4 (0.1–2.1)	1.0 (0.1–15.8)

Rosenfield et al. N Engl J Med 2026;394(20):1979-1990

CAU 중앙대학교의료원 CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

US-facilitated, catheter-directed fibrinolysis

Table 3. Cumulative Major Bleeding Events through 30 Days (Treated Population).*

Event	Intervention (N=271)	Control (N=271)	Relative Risk (95% CI)†	P Value‡
	no. of patients (%)			
Major bleeding according to ISTH criteria				
Within 72 h	10 (3.7)	4 (1.5)	2.5 (0.8–7.9)	0.17
Within 7 days	11 (4.1)	6 (2.2)	1.8 (0.7–4.9)	0.32
Within 30 days	11 (4.1)	8 (3.0)	1.4 (0.6–3.4)	0.64
Moderate-to-severe bleeding within 7 days according to GUSTO criteria	9 (3.3)	4 (1.5)	2.3 (0.7–7.2)	0.26
Ischemic stroke				
Within 7 days	1 (0.4)	0	NE	1.00
Within 30 days	1 (0.4)	0	NE	1.00
Intracranial hemorrhage				
Within 7 days	0	0	NE	1.00
Within 30 days	0	0	NE	1.00

Table 4. Mortality, Recurrence of Pulmonary Embolism, and Serious Adverse Events through 30 Days (Treated Population).*

Event	Intervention (N=271)	Control (N=271)	Relative Risk (95% CI)†
	no. of patients (%)		
Death from any cause through 7 days	3 (1.1)	2 (0.7)	1.5 (0.3–8.9)
Outcomes through 30 days			
Death from any cause	5 (1.8)	3 (1.1)	1.7 (0.4–6.9)
Symptomatic recurrence of pulmonary embolism	1 (0.4)	2 (0.7)	0.5 (0.0–5.5)
Any serious adverse event‡	40 (14.8)	44 (16.2)	0.9 (0.6–1.3)§

Rosenfield et al. N Engl J Med 2026;394(20):1979-1990

중앙대학교의료원
CHUNG-ANG UNIVERSITY HEALTHCARE SYSTEM

▶ US-facilitated, catheter-directed fibrinolysis

- Efficacy benefits of low-dose, locally-delivered fibrinolytics achieve decompensation
- No increase in major hemorrhage including intracranial hemorrhage

- Soft end-point
- Bleeding numerically higher
- Highly selected population

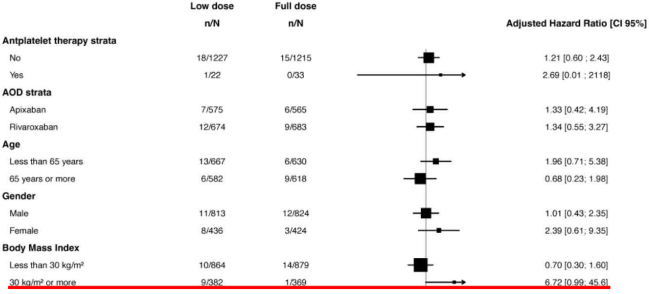
Rosenfield et al. N Engl J Med 2026;394(20):1979-1990

Contents

- Terminology for risk factors of venous thromboembolism (VTE)
- Extended anticoagulation in VTE
- Ultrasound-facilitated, catheter-directed fibrinolysis
- Unresolved issues

Unresolved issues

- Safety of reduced dose for each risk factors
  - Obesity
  - Intermediate-high or high risk of death



Incidence of symptomatic recurrent venous thromboembolism

Couturaud F, et al. Lancet 2025;405:725-35

Unresolved issues

- Duration of extended anticoagulation
  - Still life-long anticoagulation?

- Safety of reduced dose for cancer-associated VTE beyond 12 months
  - Study duration of 12 months

Unresolved issues

- US-facilitated catheter directed fibrinolysis
  - Patient selection
  - Lack of mortality benefit