



Extended anticoagulation in provoked VTE with persistent risk factors: A meta-analysis of randomised trials

Mohsin Raj Mantoo¹, Saadat Raj Mantoo², Mir Wajid Majeed³, Anushka Kulkarni⁴, Haziq Parveez Lone⁴, Mazin Mansoor⁴, Ambuj Roy^{1*}

Abstract

Background: Patients with venous thromboembolism (VTE) triggered by transient factors are typically treated with anticoagulants for 3–6 months. However, those with coexisting long-term non-malignant conditions may continue to carry a meaningful risk of recurrence beyond the initial treatment period. The benefit of extended anticoagulation in this subgroup remains uncertain.

Objectives: To evaluate the efficacy and safety of continued and reduced-dose direct oral anticoagulant (DOAC) therapy compared with no extended anticoagulation or aspirin in patients with provoked VTE and persistent non-malignant risk factors.

Methods: We performed a systematic review and meta-analysis of randomised controlled trials in accordance with PRISMA guidelines. MEDLINE, Embase and CENTRAL were searched from inception through 15 October 2025. Eligible trials enrolled adults with provoked VTE and persistent non-malignant risk factors who had completed initial anticoagulation and compared extended DOAC therapy with placebo, aspirin or discontinuation. Primary outcomes were recurrent VTE and major bleeding. Risk ratios (RRs) were pooled using random-effects models, with fixed-effects analyses as sensitivity.

Results: Three trials, including 2498 participants, were analysed. Continued DOAC therapy was associated with a lower incidence of recurrent VTE compared with placebo or aspirin (RR 0.25, 95% confidence interval [CI] 0.07–0.98; $P=34\%$). Reduced-dose regimens demonstrated comparable effectiveness (RR 0.21, 95% CI 0.11–0.41). Major bleeding events were infrequent across all groups, and no clear excess risk was observed with extended therapy (RR 2.38, 95% CI 0.87–6.53; $P=0\%$).

Conclusions: Among patients with provoked VTE and ongoing non-malignant risk factors, extended DOAC therapy appears to reduce recurrence without a definite increase in major bleeding. These findings support a more individualised approach to treatment duration in this intermediate-risk population.

Keywords

venous thromboembolism, direct oral anticoagulants, persistent risk factors, secondary prevention, meta-analysis, recurrent VTE, major bleeding

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), remains an important contributor to morbidity and mortality worldwide^[1,2]. The duration of anticoagulation traditionally depends on whether the index event is provoked – occurring in the setting of a transient risk factor such as surgery or trauma – or unprovoked, where no clear trigger is identified^[3]. While the duration of anticoagulation following a first episode of provoked VTE is generally limited to 3–6 months, unprovoked VTE often requires extended or indefinite anticoagulation due to a high annual recurrence risk (up to 10% within the first year and 25% within 5 years)^[4–6].

This dichotomous framework does not adequately reflect a subset of patients who present with transient provoking factors but also have underlying chronic conditions, such as obesity, chronic inflammatory or autoimmune disorders, cardiopulmonary disease, or chronic kidney

disease. In these individuals, the risk of recurrence may persist even after resolution of the initial trigger, placing them between the conventional “provoked” and “unprovoked” categories^[7].

Randomised trial data have begun to highlight the clinical implications of this gap. The HI-PRO trial demonstrated a 1-year recurrence rate of approximately 10% among placebo-treated patients with persistent provoking factors despite initial anticoagulation^[7]. Similarly, subgroup analyses of the EINSTEIN CHOICE trial (rivaroxaban vs aspirin) and EINSTEIN Extension trial (rivaroxaban vs placebo) suggest that extended low-intensity direct oral anticoagulant (DOAC) regimens significantly reduce VTE recurrence in this population without increasing the risk of major bleeding^[8,9].

We, therefore, conducted a systematic review and meta-analysis (SRMA) restricted to randomised evidence to evaluate the efficacy and safety of extended DOAC therapy – at both standard and reduced doses – in patients with provoked VTE and ongoing non-malignant risk factors.

Methods

1. Study design and registration

This SRMA was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

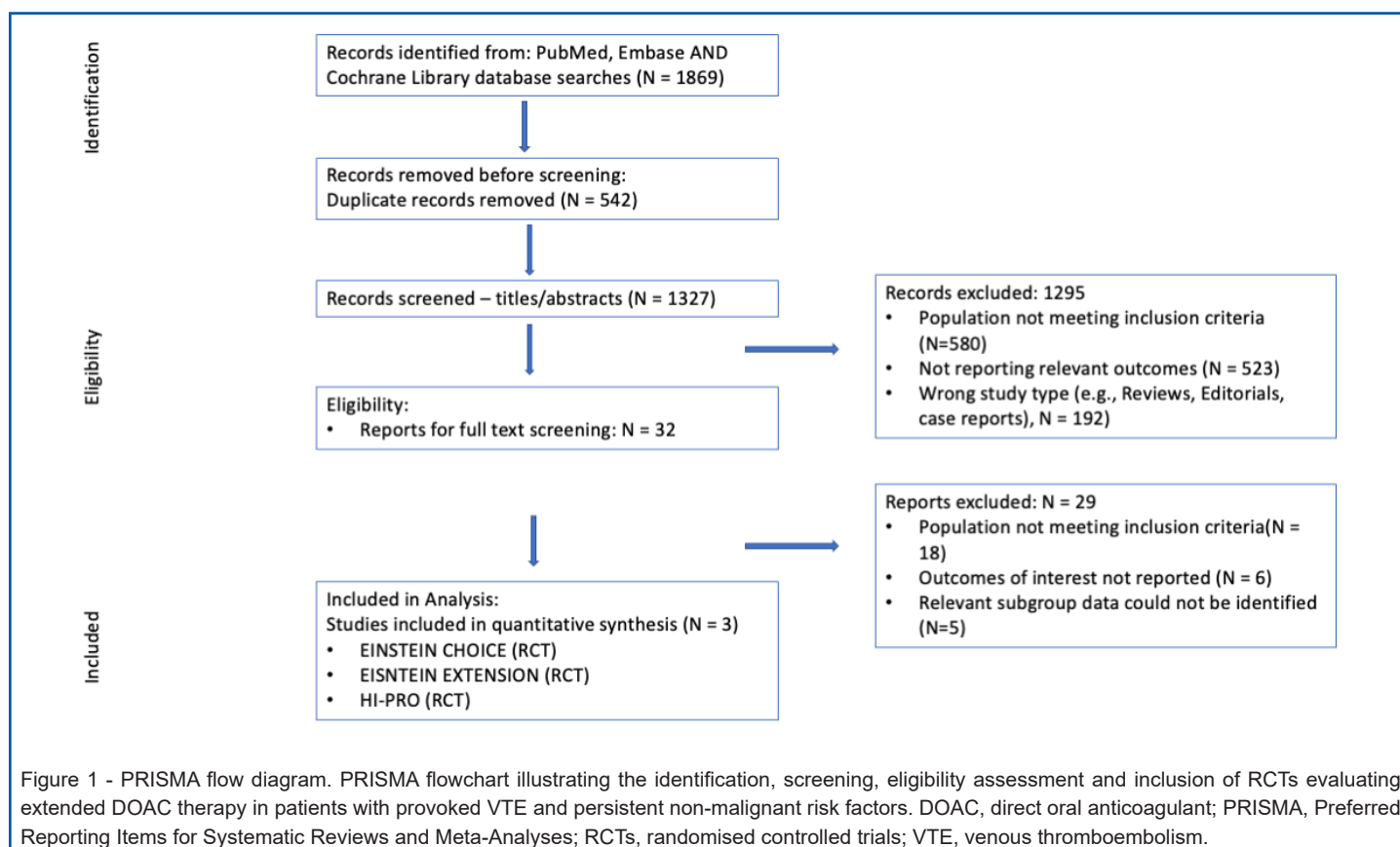
*Corresponding author: Ambuj Roy; E-mail address: drambujroy@gmail.com

¹Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India

²Department of Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India

³Vardhman Mahavir Medical College and Associated Safdarjung Hospital, New Delhi, India

⁴All India Institute of Medical Sciences, New Delhi, India



(PRISMA) guidelines. The protocol was prospectively developed using the PICO framework and registered in the PROSPERO database (CRD420251180371). As the study involved analysis of previously published data, ethical approval and informed consent were not required.

2. Data sources and search strategy

A comprehensive literature search was performed in PubMed/MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception through 15 October 2025. The search strategy combined controlled vocabulary (MeSH and Emtree terms) and free-text keywords encompassing DOACs, VTE and extended or reduced-dose regimens. The complete search syntax for each database is provided in the supplemental material. Reference lists of relevant trials and prior reviews were also screened to identify additional studies.

Three independent reviewers (MRM, HPL and MM) screened titles, abstracts and full-text articles for eligibility. Disagreements were resolved by MRM. The study selection process is summarised in the PRISMA flow diagram (Figure 1).

3. Eligibility criteria

Studies were selected based on the following pre-defined criteria derived from the focused clinical question:

- **P (Population):** Adults (≥ 18 years) with a first episode of VTE initially associated with a transient provoking factor, who also had

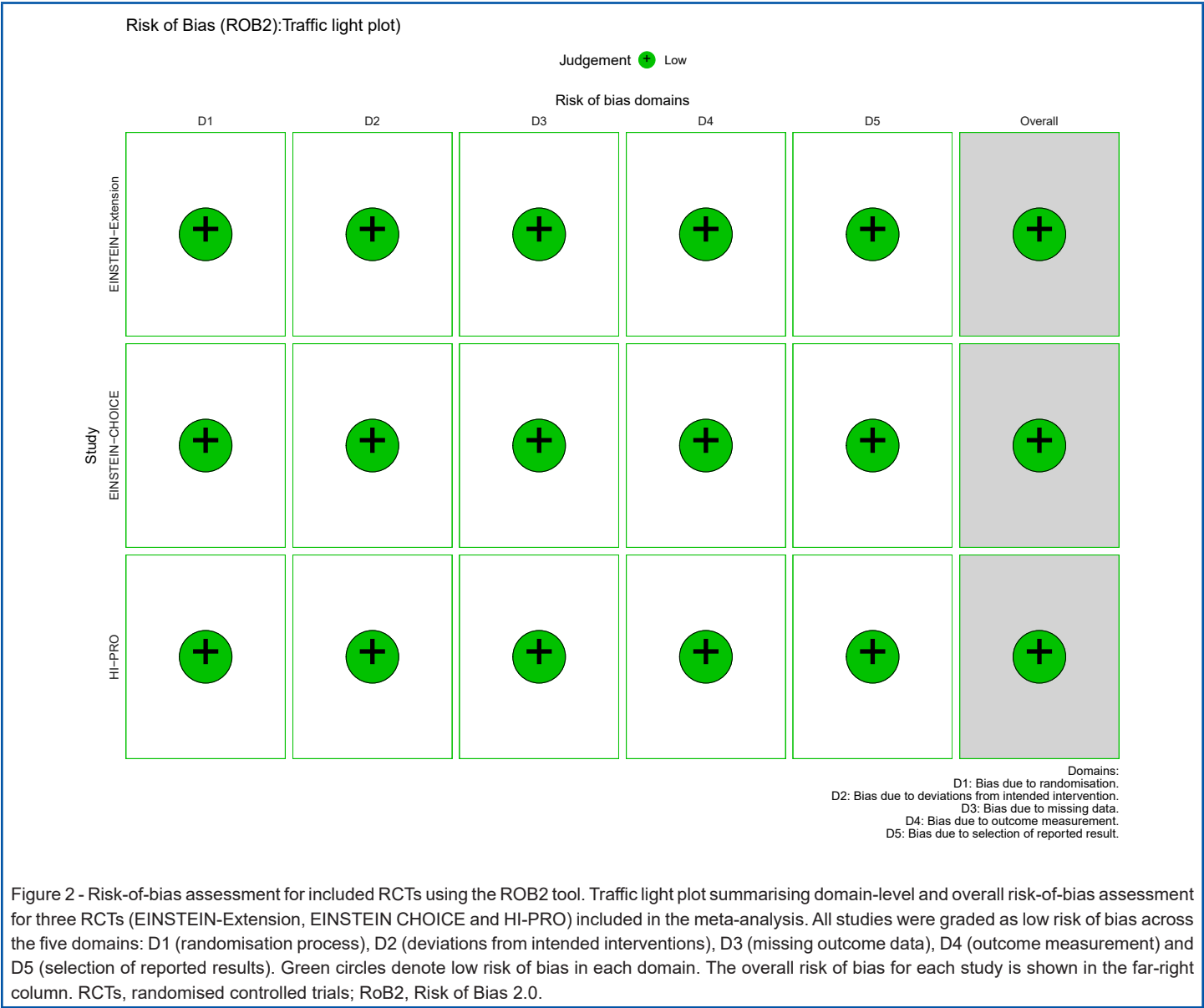
at least one persistent non-malignant risk factor and completed standard anticoagulation (3–6 months).

- **I (Intervention):** Continued DOAC therapy at any dose (therapeutic or reduced-dose). The primary reduced-dose regimens of interest were apixaban 2.5 mg twice daily or rivaroxaban 10 mg once daily.
- **C (Comparator):** No extended anticoagulation, defined as receiving placebo or switching to aspirin.
- **O (Outcomes):**
 - Primary Efficacy: Recurrent VTE.
 - Primary Safety: Major bleeding (defined by International Society on Thrombosis and Haemostasis [ISTH] criteria).
- **T (Study type):** Only randomised controlled trials (RCTs) and prespecified subgroup analyses from RCTs were included in the primary analysis.

Studies were excluded if:

- They did not report outcomes specifically for the target subgroup
- They were observational in design
- They included patients with active malignancy at baseline.

Clarification of subgroup data: For the EINSTEIN program, subgroup data were derived from a prespecified pooled analysis in which index VTE events were centrally classified as major or minor transient or persistent risk factors. Only patients classified as having persistent non-malignant risk factors were included in the present analysis.



4. Data extraction

Data were extracted independently by two reviewers (MRM and SRM) using a standardised form. Extracted variables included study characteristics, participant demographics, intervention details, comparator strategies and outcome events. Discrepancies were resolved by consensus.

5. Risk-of-bias assessment

The risk of bias for randomised trials was assessed by two independent reviewers (MWM and AK) using the Cochrane Risk of Bias 2.0 (RoB2) tool, which evaluates domains including the randomisation process, deviations from intended interventions, missing outcome data, outcome measurement and selection of reported results. Results are summarised using a traffic light plot (Figure 2).

6. Statistical analysis

Effect estimates were synthesised as risk ratios (RRs) with 95% confidence intervals (CIs) using the Mantel–Haenszel method. A random-effects model was prespecified for all primary analyses, with fixed-effects models reported as sensitivity analyses. Between-study heterogeneity was quantified using the I^2 statistic and Cochran’s Q test. Subgroup analyses were performed according to DOAC dose (reduced vs therapeutic) and comparator type (placebo vs aspirin). Meta-regression and publication bias assessment were not performed because of the limited number of included trials, consistent with best practice recommendations. All analyses were conducted using R (RStudio version 2025.09.1 + 401). A two-sided p -value <0.05 was considered statistically significant.

Results

1. Study selection and characteristics

A total of three RCTs met the inclusion criteria, comprising 2498 participants. These included the HI-PRO, EINSTEIN CHOICE and EINSTEIN Extension trials^[7–10]. All participants had completed initial anticoagulation for provoked VTE and had at least one persistent non-malignant risk factor. The evaluated interventions included both standard-dose and reduced-dose DOAC regimens, specifically apixaban 2.5 mg twice daily and rivaroxaban 10 mg once daily. Comparator strategies consisted of placebo or aspirin. Detailed study characteristics are shown in Table 1.

All included trials were judged to be at low risk of bias across all domains of the ROB-2 tool (Figure 2).

2. Baseline recurrence risk in the comparator group

Across comparator arms, recurrent VTE occurred in approximately 6.4% of patients, indicating a persistent risk of recurrence despite completion of standard anticoagulation. In the HI-PRO trial, the recurrence rate in the placebo arm reached 10% at 1 year, substantiating the high-risk phenotype of the study population.

3. Primary efficacy outcome – recurrent VTE

Overall continued DOAC (any dose) vs no treatment/aspirin

Pooling data from all included trials, extended DOAC therapy was associated with a lower risk of recurrent VTE compared with control strategies. Under the random-effects model, extended DOAC therapy reduced recurrent VTE by 75% (RR 0.25; 95% CI 0.07–

0.98). Results were consistent under a fixed-effects model (RR 0.24; 95% CI 0.15–0.40). Heterogeneity across studies was moderate ($P=34\%$). All trials demonstrated effect estimates favouring continued anticoagulation. (Figure 3)

When stratified by control type, the benefit of extended DOAC therapy remained consistent. In placebo-controlled trials (HI-PRO and EINSTEIN Extension), DOAC therapy was associated with a marked reduction in recurrence (RR 0.17; 95% CI 0.08–0.36). In the aspirin-controlled trial (EINSTEIN CHOICE), DOAC therapy also significantly reduced recurrent VTE (RR 0.39; 95% CI 0.19–0.77). There was no evidence of effect modification by comparator type (p for subgroup difference >0.10) (Figure 4).

4. Reduced-dose DOAC vs no treatment/aspirin

Two trials (HI-PRO and EINSTEIN CHOICE subgroup), comprising 1528 patients, evaluated reduced-dose DOAC therapy exclusively. Reduced-dose regimens resulted in a 79% reduction in recurrent VTE under a fixed-effects model (RR 0.21; 95% CI 0.11–0.41). Under a random-effects model, effect estimates were directionally consistent with wider CIs owing to the limited number of studies. Heterogeneity was moderate ($P=43\%$) (Figure 5).

5. Primary safety outcome – major bleeding

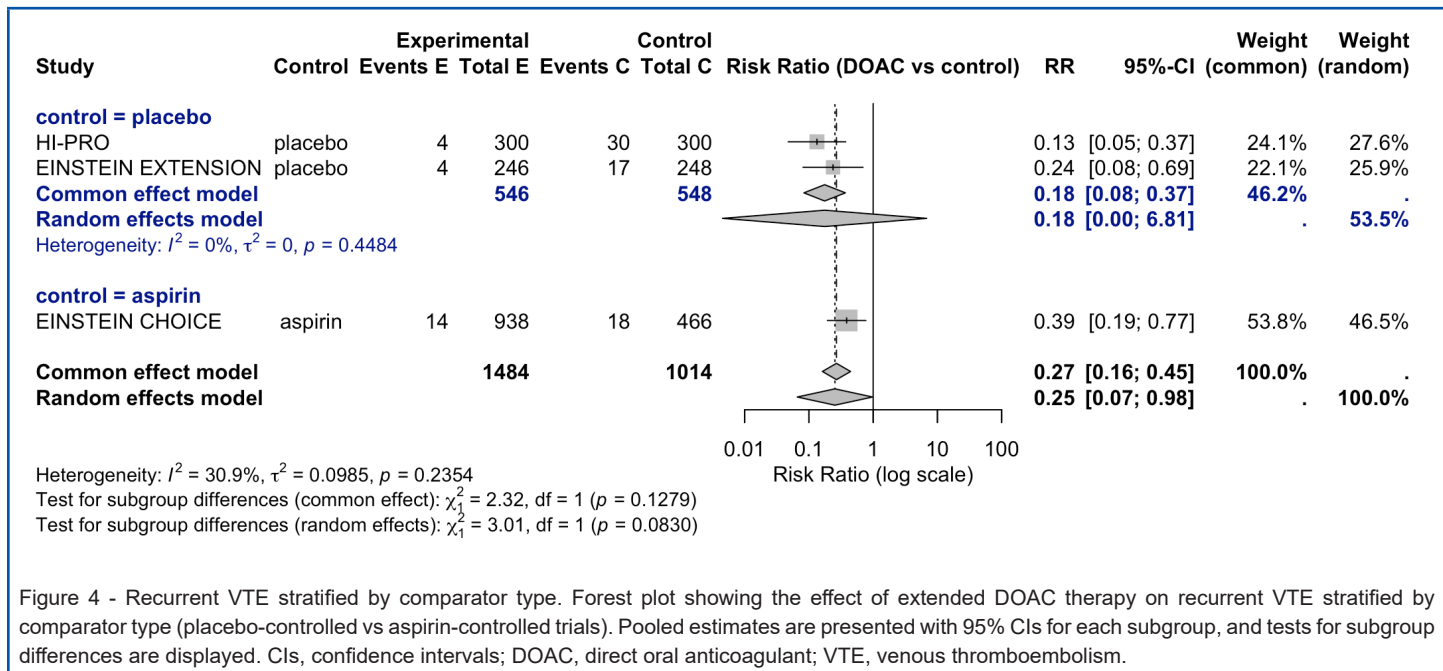
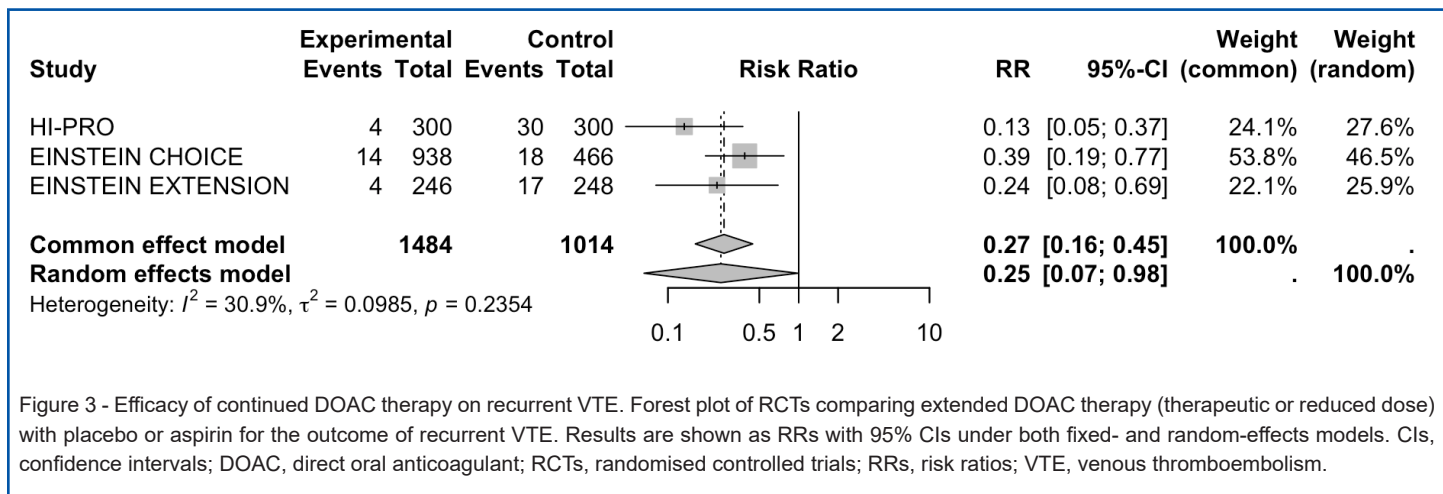
Major bleeding events were infrequent across all studies. Pooled analysis did not demonstrate a statistically significant difference in bleeding risk between extended DOAC therapy and control groups (random-effects RR 2.38, 95% CI 0.87–6.53; fixed-effects RR 2.40, 95% CI 0.39–14.86). There was no heterogeneity across studies

Table 1 - Summary of the studies included in this SRMA evaluating continued and reduced dose DOAC therapy in provoked VTE with persistent non-malignant risk factors.

Study (year), design	EINSTEIN CHOICE (2017), RCT	EINSTEIN Extension (2018), RCT	HI-PRO (2025), RCT
Sample size (subgroup included)	3365 (1404)	1196 (494)	600
DOAC dose	Rivaroxaban 20 mg and 10 mg OD	Rivaroxaban 20 mg	Apixaban 2.5 mg BD
Comparator	Aspirin 100 mg	Placebo	Placebo
Mean age (years)	58.5	58.3	59.5
% Male	55.4	57.9	43
Index event (DVT/PE/Both, %)	50.7/35.3/15.3	62/38	48/23.3/28.7
Duration of initial anticoagulation (months)	6–12 (<9 months in 75.8%)	6–12 (<9 months in 67.4%)	≥ 3 (Median 6.6)
Persistent risk factors* (Commonest)%	BMI > 30 kg/m ² : 68.6 Thrombophilia: 13.1 Creatinine clearance <50 mL/min: 10.8		BMI > 30 kg/m ² : 48.2 Chronic inflammatory or autoimmune disease: 52.2 ASCVD: 29.3 CKD: 10.7%
Follow up (months)	12	12	12
Primary efficacy outcome	Symptomatic recurrent VTE	Symptomatic recurrent VTE	Symptomatic recurrent VTE
Major bleeding definition	ISTH guidelines	ISTH guidelines	ISTH guidelines

ASCVD, atherosclerotic cardiovascular disease; BD, twice daily; BMI, body mass index; CKD, chronic kidney disease; DOAC, Direct oral anticoagulant; DVT, deep vein thrombosis; HF, heart failure; ISTH, International Society on Thrombosis and Haemostasis; OD, once daily; PE, pulmonary embolism; RCT, randomised controlled trial; SRMA, systematic review and meta-analysis; VTE, venous thromboembolism.

*Data extracted from Blood Adv. 2018 Apr 10;2(7):788–796.



($P = 0\%$) (Figure 6). Subgroup analyses by comparator type showed no significant interaction between treatment effect and control strategy (Figure 7). Absolute major bleeding rates across all trials were $<1\%$, yielding limited precision but supporting a favourable safety profile.

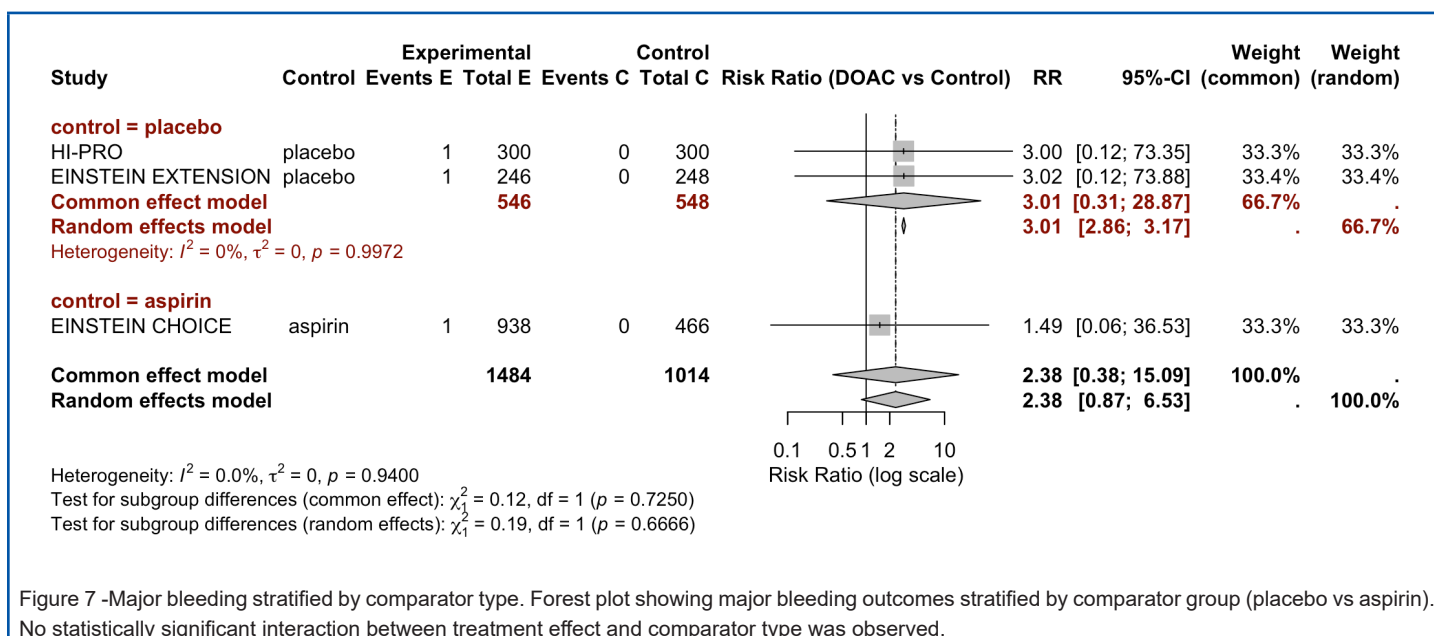
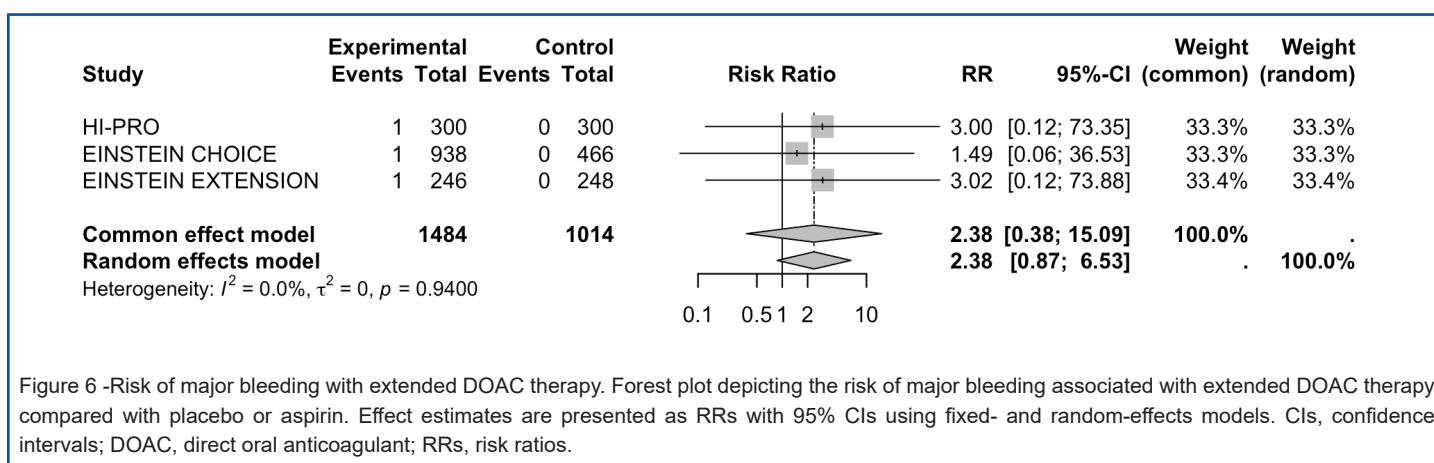
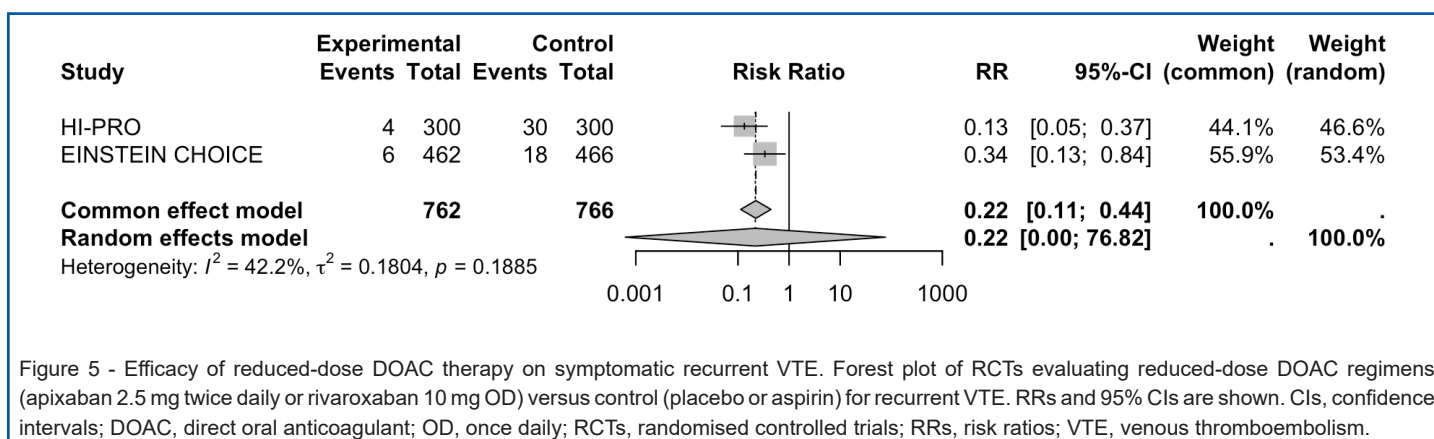
Discussion

This meta-analysis of randomised evidence suggests that continuing anticoagulation with DOACs beyond the initial treatment period is associated with a lower risk of recurrent VTE in patients with provoked events and persistent non-malignant risk factors. The observed benefit was consistent across both standard and reduced-dose regimens and was evident irrespective of whether the comparator was placebo or aspirin.

Our findings extend the evidence from large randomised trials EINSTEIN CHOICE and AMPLIFY-EXT, which demonstrated

that both standard- and reduced-dose DOACs are superior to aspirin or placebo in preventing recurrent VTE after completion of initial therapy^[8,11]. However, these trials, as well as several recent meta-analyses, include a heterogeneous mix of unprovoked and provoked cases, and patients with underlying malignancy^[12–18]. The present analysis specifically targets the subgroup – patients with comorbidities such as obesity, chronic cardiopulmonary disease or autoimmune disorders – who fall between the traditional “provoked” and “unprovoked” categories in terms of recurrence risk. Our results underscore that such individuals remain at appreciable risk and would benefit from continued anticoagulation beyond the standard treatment duration.

The interpretation of the pooled findings requires consideration of differences in how persistent risk factors were defined across studies. In the HI-PRO trial, these conditions were prospectively identified at enrolment, whereas in the EINSTEIN program, they were classified retrospectively through a centralised adjudication process using predefined criteria. Although both approaches aim to



capture a similar clinical construct, they are not identical, and some degree of heterogeneity is, therefore, unavoidable. Nevertheless, the consistency in treatment effect across studies suggests that the overall conclusion is robust despite these methodological differences.

From a safety standpoint, major bleeding events were uncommon, and no statistically significant increase was detected with extended

therapy. Although the low event rate limits precision, the consistency of findings across trials provides some reassurance regarding the safety of prolonged treatment, particularly with reduced-dose regimens.

The results of this analysis should also be considered in the context of the broader literature on extended anticoagulation. Trials

evaluating dabigatran and edoxaban have similarly demonstrated that continued anticoagulant therapy reduces recurrence in patients with VTE^[19,20]. However, these studies enrolled more heterogeneous populations and did not specifically report outcomes in patients with provoked VTE and persistent non-malignant risk factors. As such, their findings complement but do not directly inform the questions addressed in the present analysis.

Importantly, although observational data from Coleman et al. have suggested a similar protective association between extended anticoagulation and reduced recurrence risk in this population, that study was deliberately excluded from our primary analysis because of its non-randomised design and risk of confounding^[21]. While such real-world evidence supports the external validity of our findings, we elected to restrict inference to randomised data alone in order to minimise heterogeneity and confounding.

An additional consideration is the potential for occult malignancy in patients presenting with VTE^[22]. Although individuals with known active cancer were excluded from the trials included in this analysis, a proportion of patients may receive a cancer diagnosis during follow-up. This has important implications, as malignancy substantially alters both recurrence risk and the choice of anticoagulant therapy.

These findings have practical implications for clinical decision-making. Current guideline recommendations emphasise an individualised approach to determining the duration of anticoagulation, particularly in patients whose clinical profile does not clearly align with traditional provoked or unprovoked categories^[4,5,23]. In this setting, patients with persistent non-malignant risk factors represent a group in whom the risk of recurrence may remain clinically relevant even after completion of standard therapy. The results of this analysis suggest that extended treatment with DOACs, including reduced-dose regimens, may lower recurrence risk in such patients without a clear signal for increased major bleeding, although the low number of events warrants cautious interpretation. In practice, tools such as the VTE-PREDICT score may help support decision-making by providing individualised estimates of both recurrence and bleeding risk, thereby facilitating a more tailored approach to treatment duration^[24].

This study has several limitations. First, the number of eligible randomised trials was limited, and some data were derived from subgroup analyses rather than trials specifically designed for this population. Second, definitions of persistent non-malignant risk factors varied across studies, introducing clinical heterogeneity. Third, the low frequency of major bleeding events resulted in wide CIs, limiting the precision of safety estimates. Fourth, the analysis relied on aggregate data, which precluded adjustment for individual patient characteristics such as the type and burden of comorbid conditions. Finally, the small number of included studies prevented formal assessment of publication bias and limited exploration of heterogeneity.

Conclusion

In patients with provoked VTE and persistent non-malignant risk factors, extended anticoagulation with DOACs appears to reduce the

risk of recurrence without a clear increase in major bleeding. These findings support a more nuanced, risk-based approach to treatment duration beyond the traditional provoked versus unprovoked framework.

Registration

PROSPERO Registration ID: CRD420251180371

Abbreviation

ASCVD, atherosclerotic cardiovascular disease; ASH, American Society of Hematology; BD, twice daily; BMI, body mass index; CENTRAL, Cochrane Central Register of Controlled Trials; CI, confidence interval; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ESC, EUROPEAN Society of Cardiology; HF, heart failure; ISTH, International Society on Thrombosis and Haemostasis; OD, once daily; PE, pulmonary embolism; PICOTT, Population, Intervention, Comparator, Outcomes, Study Type; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trials; RoB2, Cochrane Risk of Bias 2.0 tool; RR, risk ratio; SRMA, systematic review and meta-analysis; VTE, venous thromboembolism.

Funding statement

No funding was acquired for this work.

Conflicts of Interest

The authors have each completed the International Committee of Medical Journal Editors Form for uniform Disclosure of Potential Conflicts of Interest. No authors have any potential conflict of interest to disclose.

Ethics Approval

The study was approved by an institutional medical research ethics committee and conducted in accordance with the Declaration of Helsinki.

Author contributions

MRM and AR contributed to the conception and design of this systematic review and meta-analysis. SRM, AK, HPL and MM were involved in data acquisition, MRM and MWM performed the analysis of the data. MRM wrote the initial manuscript. Prof AR critically revised the manuscript and is the guarantor of the study.

REFERENCES

- White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I4–I8. doi:10.1161/01.CIR.0000078468.11849.66. PubMed PMID: 12814979.
- Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. *Nat Rev Cardiol*. 2023;20(4):248–262. doi:10.1038/s41569-022-00787-6.
- Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost*. 2016;14(7):1480–1483. doi:10.1111/jth.13336.
- Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693–4738. doi:10.1182/bloodadvances.2020001830.
- Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41(4):543–603. doi:10.1093/eurheartj/ehz405.
- Khan F, Rahman A, Carrier M, Kearon C, Weitz JI, Schulman S, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: Systematic review and meta-analysis. *BMJ*. 2019;366:14363. doi:10.1136/bmj.l4363. PubMed PMID: 31340984; PubMed Central PMCID: PMC6651066.
- Piazza G, Bikkdeli B, Pandey AK, Krishnathasan D, Khairani CD, Bejjani A, et al. Apixaban for extended treatment of provoked venous thromboembolism. *N Engl J Med*. 2025;393(12):1166–1176. doi:10.1056/NEJMoa2509426. PubMed PMID: 40888734.
- Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211–1222. doi:10.1056/NEJMoa1700518. PubMed PMID: 28316279.
- Prins MH, Lensing AWA, Prandoni P, Wells PS, Verhamme P, Beyer-Westendorf J, et al. Risk of recurrent venous thromboembolism according to baseline risk factor profiles. *Blood Adv*. 2018;2(7):788–796. doi:10.1182/bloodadvances.2018017160. PubMed PMID: 29632234; PubMed Central PMCID: PMC5894264.
- EINSTEIN Investigators; Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499–2510. doi:10.1056/NEJMoa1007903.
- Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699–708. doi:10.1056/NEJMoa1207541. PubMed PMID: 23216615.
- Ibrahim A, Shalabi L, Zreigh S, Tawfik AM, Hamed BM, Elsayy M, et al. 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. *Thromb Res*. 2025;254:109476. doi:10.1016/j.thromres.2025.109476. PubMed PMID: 40957133.
- Bakht D, Arham M, Rashid Z, Amir M, Nasir Z, Naqvi MZ, et al. Reduced versus full-dose direct oral anticoagulants for venous thromboembolism in cancer patients: A systematic review and meta-analysis. *EJHaem*. 2025;6(5):e70155. doi:10.1002/jha2.70155. PubMed PMID: 41000253; PubMed Central PMCID: PMC12459301.
- de Lucena LA, Duarte AG, Hespanhol LC, Muniz J, Félix N, Medeiros K, et al. Reduced vs full-dose direct oral anticoagulants for extended treatment of cancer-associated venous thromboembolism: A systematic review and meta-analysis of randomized trials. *J Thromb Haemost*. 2025;S1538-7836(25)00645-2. doi:10.1016/j.jtha.2025.09.026. PubMed PMID: 41109354.
- Akhtar M, Nabi R, Saadia S, Ashraf DA, Hassan SM, Akhtar M, et al. Reduced-dose versus full-dose direct oral anticoagulants in the extended treatment of venous thromboembolism: A systematic review and meta-analysis. *Cardiovasc Drugs Ther*. 2025. doi:10.1007/s10557-025-07759-1. PubMed PMID: 40844745.
- Bilal AR, Umar SA, Arfin SMW, Bilal AR, Sajid M, Gaba H, et al. Efficacy and safety of reduced-dose versus full-dose DOACs in extended treatment of VTE: A systematic review and meta-analysis. *J Thromb Thrombolysis*. 2026;59(1):55–63. doi:10.1007/s11239-025-03172-5. PubMed PMID: 40879867.
- Marik PE, Cavallazzi R. Extended anticoagulant and aspirin treatment for the secondary prevention of thromboembolic disease: A systematic review and meta-analysis. *PloS One*. 2015;10(11):e0143252. doi:10.1371/journal.pone.0143252. PubMed PMID: 26587983; PubMed Central PMCID: PMC4654552.
- Vasanthamohan L, Boonyawat K, Chai-Adisaksopha C, Crowther M. Reduced-dose direct oral anticoagulants in the extended treatment of venous thromboembolism: A systematic review and meta-analysis. *J Thromb Haemost*. 2018;16(7):1288–1295. doi:10.1111/jth.14156. PubMed PMID: 29772108.
- The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406–1415. doi:10.1056/NEJMoa1306638.
- Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368(8):709–718. doi:10.1056/NEJMoa1113697.
- Coleman CI, Turpie AGG, Bunz TJ, Beyer-Westendorf J, Baker WL. Impact of prolonged anticoagulation with rivaroxaban on provoked venous thromboembolism recurrence: IMPROVE-VTE. *Am J Med*. 2019;132(4):498–504. doi:10.1016/j.amjmed.2018.11.040. PubMed PMID: 30582894.
- Beckers MMJ, Schutgens REG, Prins MH, Biesma DH. Prevalence and characteristics of occult cancer in patients with venous thromboembolism. *Blood*. 2005;106(11):1623. doi:10.1182/blood.V106.11.1623.1623.
- Writing Committee Members; Creager MA, Barnes GD, Giri J, Mukherjee D, Jones WS, et al. 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(12):e977–e1051. doi:10.1161/CIR.0000000000001415.
- de Winter MA, Buller HR, Carrier M, Cohen AT, Hansen JB, Kaasjager KAH, et al. Recurrent venous thromboembolism and bleeding with extended anticoagulation: The VTE-PREDICT risk score. *Eur Heart J*. 2023;44(14):1231–1244. doi:10.1093/eurheartj/ehac776.