Continued versus discontinued oral anticoagulant treatment for unprovoked venous thromboembolism: target trial emulation

Kueiyu Joshua Lin,[1,2] Dae Hyun Kim,[3,4] Daniel E Singer,[2] Yichi Zhang,[1] Alexander Cervone,[1] Anna R Kehoe,[1] Katsiaryna Bykov[1]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02120, USA

[2]Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, MA, USA

[3]Frailty Research Center, Marcus Institute for Aging Research, Hebrew SeniorLife, and Harvard Medical School, Boston, MA, USA

[4]Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, MA, USA

Correspondence to: K J Lin
jklin@bwh.harvard.edu;
(ORCID 0000-0003-4564-3715)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2025;391:e084380
http://dx.doi.org/10.1136/bmj-2025-084380

Accepted: 09 September 2025

ABSTRACT

OBJECTIVE

To compare the effect on health outcomes of continuing or discontinuing oral anticoagulants (OACs) among patients with unprovoked venous thromboembolism (VTE) after initial treatment for at least 90 days.

DESIGN

Target trial emulation.

SETTING

Optum Clinformatics Data Mart (Optum CDM) from 1 January 2009 to 28 Februray 2025, and Medicare fee-for-service claims from 1 January 2009 to 31 December 2022, United States.

PARTICIPANTS

Adults with VTE aged ≥18 years (Optum CDM) or ≥65 years (Medicare) initiating OACs (warfarin or direct OACs) within 30 days after a first hospital admission with VTE without reversible provoking factors and who continued treatment for ≥90 days. Propensity score one-to-one matching was performed between patients who continued and those who discontinued treatment (ie, absence of a refilled prescription within 30 days).

MAIN OUTCOME MEASURES

The primary outcomes were hospital admission for recurrent VTE (effectiveness) and major bleeding (safety). Secondary outcomes were net clinical benefit (a composite of recurrent VTE and bleeding) and mortality. Cox proportional hazards models estimated hazard ratios and generalized linear models estimated rate differences per 1000 person years. Analyses were stratified by length of initial OAC treatment (90-179, 180-359, 360-719, 720-1079, or ≥1080 days).

RESULTS

The study cohort included 30 554 propensity score matched pairs who had continued or discontinued an OAC (mean age 73.9 years, 57.0% women). After initial anticoagulation of ≥90 days, compared with those who discontinued treatment, those who continued treatment had markedly lower rates of recurrent VTE (adjusted hazard ratio 0.19, 95% confidence interval (CI) 0.13 to 0.29; adjusted rate difference per 1000 person years −25.50, 95% CI −39.38 to −11.63), higher rates of major bleeding (1.75, 1.52 to 2.02; 4.78, 1.95 to 7.61), lower mortality rates (0.74, 0.69 to 0.79; −14.31, −22.02 to −6.59), and greater net clinical benefit (0.39, 0.36 to 0.42; −21.01, −32.31 to −9.71). The greater net clinical benefit was consistent across OAC types and length of initial OAC treatment.

CONCLUSION

Based on two US nationally representative routine care databases, continuing versus discontinuing OAC after initial anticoagulation of ≥90 days was associated with lower risk of recurrent VTE, higher risk of major bleeding, and a net clinical benefit. This observation persisted among those using OACs for at least three years after VTE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Extended oral anticoagulant (OAC) treatment can reduce the risk of recurrent venous thromboembolism compared with discontinuation of treatment, but the long term risk of bleeding complications is unclear

Randomized controlled trials comparing continuation with discontinuation of OAC after initial anticoagulation of 3-6 months underrepresented the highly frail and complex patients seen in routine care

WHAT THIS STUDY ADDS

In two US national routine care populations, continuing versus discontinuing OAC after initial anticoagulation of at least 90 days was associated with a lower risk of recurrent VTE, higher risk of major bleeding, and a favorable net clinical benefit, regardless of treatment duration

This positive net clinical benefit persisted among those using anticoagulation for at least three years after venous thromboembolism

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, represents a major disease burden globally.[1] In the US, about 1.2 million cases will have a diagnosis of VTE annually,[2] with a one year mortality rate of about 20%.[3] Oral anticoagulants (OACs) are effective in reducing VTE recurrence, but they also increase bleeding risk. Clinical guidelines recommend anticoagulation for at least 3-6 months for patients with deep vein thrombosis provoked by transient VTE risk factors such as major trauma, surgery, and pregnancy, and extended treatment beyond three months if the VTE is unprovoked or if the risk factors are not reversible (eg, metastatic cancer).[4 5]

Several randomized controlled trials have compared the safety and efficacy of extended OAC treatment (ie, anticoagulation beyond 3-6 months) with discontinuation of OAC treatment and reported that extended anticoagulation substantially reduced the risk of recurrent VTE.[6 7] However, these trials were underpowered to detect a difference in major bleeding and unable to provide full data for estimating the risk-to-benefit profile for extended OAC treatment in VTE.[6 7] It is also unclear if the observed efficacy and safety patterns in the highly selected trial populations can be translated to routine care enriched with frail and complex patients at higher risk of bleeding. In addition, the limited follow-up of the published randomized controlled trials did not provide data to

inform decisions beyond the first 1-2 years of extended anticoagulation.

Observational data to assess the effect of continuing OACs for unprovoked VTE are also limited. Two small studies without any adjustment for confounding did not find an association between discontinuation of OACs and reduction in major bleeding.[8 9] Also, all the published studies were too small to assess effects by individual OAC or length of initial treatment. Therefore, while the clinical guidelines recommend extending anticoagulation for longer than 3-6 months for unprovoked deep vein thrombosis, no direct evidence informs optimal treatment duration of anticoagulation. In this study, we compared the outcomes of recurrent VTE, major bleeding, and mortality among adults with VTE without reversible provoking factors who continued versus discontinued OAC treatment, stratified by length of initial anticoagulation period from 90 days to almost three years.

Methods

Data sources

We used data from two large US health insurance databases: Optum's deidentified Clinformatics Data Mart Database (Optum CDM) and Medicare fee-for-service Parts A (inpatient), B (outpatient), and D (pharmacy claims). Optum CDM includes a commercially insured US population. Medicare is a federal health insurance programme providing healthcare coverage for US individuals aged ≥65 years or those with disabilities. The databases contain deidentified, longitudinal, individual level data on healthcare use, inpatient and outpatient diagnoses, diagnostic tests and procedures, and pharmacy dispensing of drugs.

Study population and OAC use

Using a target trial emulation framework,[10 11] we emulated a hypothetical clinical trial to compare the risk of recurrent VTE and major bleeding among adults who continued versus discontinued OACs (ie, warfarin, apixaban, rivaroxaban, dabigatran, or edoxaban) after at least 90 days of initial treatment. The treatment needed to have been initiated within 30 days after a first recorded hospital admission with VTE (without any previous VTE) from 1 January 2009 to 28 February 2025 in the Optum CDM population and from 1 January 2009 to 31 December 2022 in the Medicare population without use of any OAC in the preceding year. The study cohort was additionally required to meet the following criteria: age ≥18 years in the Optum CDM population and ≥65 years in the Medicare population, and with at least 365 days of continuous medical and pharmacy insurance enrollment before cohort entry and with information on age or sex, or both (to ensure the patient had adequate information to determine eligibility criteria). Among this study cohort, we identified people who had discontinued OACs as those with an absence of a refill within 30 days any time after the initial 90 days of treatment. To account for potential leftover pills from previous prescriptions, the discontinuation date was set at 30 days after the end of the last prescription. For each individual who had discontinued treatment, we selected an individual who had continued treatment among those who met the eligibility criteria and were still receiving treatment, matched on days since the index hospital admission with VTE and whether the index VTE was a pulmonary embolism or deep vein thrombosis. The cohort entry (index) date was the date of discontinuation for those individuals who discontinued treatment, and the matched continued-discontinued pairs were assigned the same index date (ie, matched on cohort entry date). The baseline assessment period comprised the 365 days before (and including) the index date. We excluded those with multiple OACs on the index date; a reversible provoking factor (ie, pregnancy, pelvic or orthopedic surgery, joint replacement, a lower limb fracture,[12 13] use of oral contraceptives or hormone therapy, or prolonged hospital stay of >7 days) in the 90 days before the index VTE; recurrent VTE since OAC initiation; history of bleeding requiring hospital admission during the initial OAC treatment period and in the baseline assessment period; hospice care; atrial fibrillation, hypercoagulable state (anticardiolipin syndrome, antiphospholipid syndrome, primary thrombophilia, activated protein C resistance or factor V Leiden, prothrombin gene mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, and homocystinuria), or cancer (except for non-melanoma skin cancers) in the baseline assessment period; or missing information on age or sex (see supplementary appendix study protocol for definitions of these conditions and how the hypothetical trial was emulated in our data).

Outcomes and follow-up

The primary outcomes were hospital admission for recurrent VTE (effectiveness) and major bleeding (safety). The VTE[14 15] and major bleeding (including intracranial, gastrointestinal, and other major bleeding)[16 17] events were ascertained based on validated algorithms (see supplementary appendix study protocol for definition and performance). Secondary outcomes included all cause mortality and net clinical benefit defined by a composite of recurrent VTE and major bleeding. Follow-up began on the index date until the earliest of occurrence of study outcome, disenrollment from insurance, calendar end of the data, or change of index drug use status—that is, starting an OAC among those who had discontinued treatment, or discontinuing the OAC among those who had continued treatment, corresponding to an as-treated analysis).

Baseline covariates

We assessed a total of 89 characteristics using information in the baseline assessment period, including personal information, comorbidities, medication use, measures of healthcare utilization, and calendar year. The 89 covariates were selected based on clinical knowledge (consensus from KJL, DHK, DES,

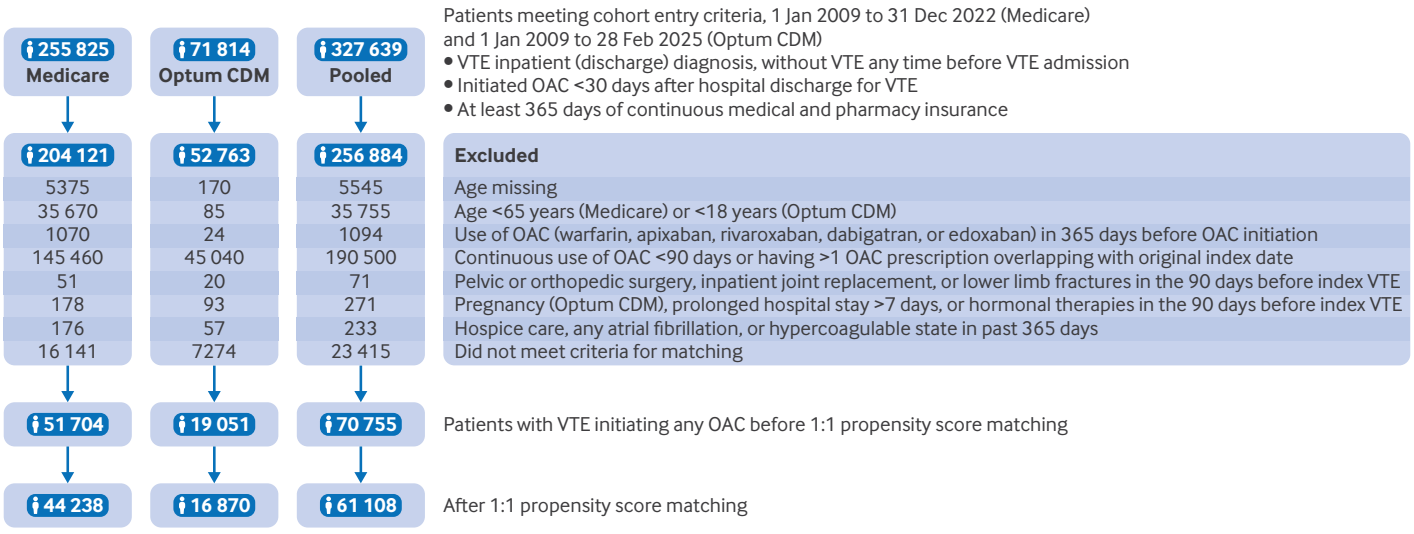

Fig 1 | Patient flow chart. Optum CDM=Optum's deidentified Clinformatics Data Mart Database; OAC=oral anticoagulation; VTE=venous thromboembolism

and KB, doctors and pharmacists on our team) and based on previous literature related to comparative safety and effectiveness of oral anticoagulants in patients with VTE.[15 18] We also calculated the following risk scores: VTE-BLEED[18] for bleeding risk, a combined comorbidity score for overall burden of comorbidity,[19] a predicted score for time within treatment range of international normalized ratio that was validated against laboratory test results,[20] and a validated claims based frailty index.[21-23] The study protocol in the supplementary appendix defines the study variables.

Statistical analysis

The absolute standardized mean difference was used to compare clinical characteristics between those who continued versus discontinued OAC treatment, and the covariate balance was considered adequate if the absolute standardized mean difference was <0.1.[24] We used 1:1 propensity score matching to adjust for confounding. The propensity score was estimated using a logistic regression that modeled the probability of OAC treatment being continued (versus discontinued) as a function of the 89 covariates. We conducted the propensity score estimation and matching within each database. In the matched cohort, we estimated hazard ratios and the corresponding 95% confidence intervals (CIs) using Cox proportional hazards models. The proportionality assumption was checked using Kaplan-Meier curves, which was satisfied in our analyses. We estimated rate differences using generalized linear models. Random effects meta-analysis was used to pool the database specific estimates.[25] We conducted subgroup analyses by length of the initial anticoagulation treatment (90-179, 180-359, 360-719, 720-1079, ≥1080 days); OAC type (warfarin, apixaban, or rivaroxaban as we did not have a sufficient sample size for dabigatran (<1%) and edoxaban users (<0.03% of all people who initiated an OAC)[26] to assess subgroup effects); personal characteristics (age and sex); pulmonary embolism or deep vein thrombosis as the initial VTE event; and presence of chronic kidney disease. We used the χ^2 statistic from the Cochran's Q test to test for heterogeneity of treatment effect across the subgroups.[27]

Sensitivity analysis

We conducted several sensitivity analyses. First, we extended the refill gap to define OAC discontinuation from 30 to 60 days. Second, we conducted the intention-to-treat analysis in which we followed patients according to use of the index drug regardless of change of drug use for a maximum of 365 days. Third, to reduce residual unmeasured confounding, we used the high dimensional propensity score,[28] which automatically identifies and adjusts for potential proxy confounders.[28-32] Fourth, we used the Fine and Gray model to account for the competing risk due to death.[33 34] Lastly, we used the E value to assess the amount of unmeasured confounding that could potentially explain away our findings.[35] Analyses were conducted in the Aetion Evidence Generation Platform, version release-5.31.1.[36-38] Statistical computations were conducted using R version 4.3.1.

Patient and public involvement

Our study was based on an analysis of secondary data. No patients or members of the public were involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Patient characteristics

After applying the cohort eligibility criteria, we identified 70 755 individuals (51 704 in the Medicare population and 19 051 in the Optum CDM population). Figure 1 summarizes the process for cohort formation. Among these patients, after 1:1 propensity score matching, our analysis included 30 554 patients who

Table 1 | Selected characteristics of patients who continued versus discontinued anticoagulation after at least 90 days of initial treatment, pooled across Medicare and Optum CDM populations. Values are number (percentage) unless stated otherwise

	Before propensity score matching			After propensity score matching		
Characteristics	Continued OAC (n=35 378)	Discontinued OAC (n=35 377)	Absolute SMD	Continued OAC (n=30 554)	Discontinued OAC (n=30 554)	Absolute SMD
Demographics						
Mean (SD) age (years)	74.1 (9.37)	73.8 (9.81)	0.03	73.9 (9.47)	73.9 (9.69)	0.00
Women	20 447 (57.8)	20 189 (57.1)	0.01	17 424 (57.0)	17 402 (57.0)	0.00
Medicaid dual eligibility	1992 (5.6)	1490 (4.2)	0.07	1325 (4.3)	1310 (4.3)	0.00
Low income subsidy	5636 (15.9)	4567 (12.9)	0.09	4045 (13.2)	4072 (13.3)	0.00
Race						
Black	3578 (10.1)	3467 (9.8)	0.01	3004 (9.8)	3014 (9.9)	0.00
White	27 500 (77.7)	27 470 (77.6)	0.00	23 718 (77.6)	23 729 (77.7)	0.00
Other	4300 (12.2)	4440 (12.6)	0.01	3832 (12.5)	3811 (12.5)	0.00
Region						
North	5581 (15.8)	5179 (14.6)	0.03	4617 (15.1)	4571 (15.0)	0.00
Midwest	9972 (28.2)	9752 (27.6)	0.01	8526 (27.9)	8552 (28.0)	0.00
South	13 362 (37.8)	13 729 (38.8)	0.02	11 668 (38.2)	11 695 (38.3)	0.00
West	6463 (18.3)	6717 (19.0)	0.02	5743 (18.8)	5736 (18.8)	0.00
Index VTE event						
Pulmonary embolism	23 846 (67.4)	23 509 (66.5)	0.02	20 522 (67.2)	20 541 (67.2)	0.00
Deep vein thrombosis	11 532 (32.6)	11 868 (33.5)	0.02	10 032 (32.8)	10 013 (32.8)	0.00
Lifestyle factors						
Alcohol abuse or dependence	611 (1.7)	768 (2.2)	0.03	570 (1.9)	576 (1.9)	0.00
Obesity	10 689 (30.2)	10 478 (29.6)	0.01	9126 (29.9)	9149 (29.9)	0.00
Smoking	11 845 (33.5)	12 249 (34.6)	0.02	10 414 (34.1)	10 389 (34.0)	0.00
Risk scores						
Mean (SD) combined comorbidity score	2.83 (2.48)	2.83 (2.55)	0.00	2.78 (2.44)	2.77 (2.50)	0.00
VTE-BLEED score (365 days)	2.36 (1.22)	2.40 (1.27)	0.03	2.36 (1.24)	2.36 (1.25)	0.00
Frailty score: empirical version (365 days)	0.20 (0.00)	0.20 (0.07)	0.00	0.19 (0.07)	0.19 (0.07)	0.00
Chronic risk factors for VTE						
Ischemic stroke or ICH*	54 (0.2)	44 (0.1)	0.01	43 (0.1)	41 (0.1)	0.00
Cardiovascular diseases						
Acute myocardial infarction	1603 (4.5)	1521 (4.3)	0.01	1300 (4.3)	1326 (4.3)	0.00
Congestive heart failure	7349 (20.8)	7189 (20.3)	0.01	6135 (20.1)	6130 (20.1)	0.00
Coronary revascularization	220 (0.6)	340 (1.0)	0.04	214 (0.7)	218 (0.7)	0.00
Diabetes	11 208 (31.7)	10 928 (30.9)	0.02	9433 (30.9)	9447 (30.9)	0.00
Hypertension	28 211 (79.7)	27 960 (79.0)	0.02	24 153 (79.1)	24 117 (78.9)	0.00
Ischemic heart disease	10 712 (30.3)	11 194 (31.6)	0.03	9334 (30.5)	9321 (30.5)	0.00
Ischemic stroke	925 (2.6)	933 (2.6)	0.00	776 (2.5)	749 (2.5)	0.01
PVD or PVD surgery	4331 (12.2)	4376 (12.4)	0.00	3683 (12.1)	3641 (11.9)	0.00
Comorbidities						
Acute renal failure	4587 (13.0)	4854 (13.7)	0.02	3990 (13.1)	3952 (12.9)	0.00
Chronic kidney disease	3406 (9.6)	3564 (10.1)	0.01	2937 (9.6)	2976 (9.7)	0.00
Anemia	9476 (26.8)	9887 (27.9)	0.03	8199 (26.8)	8096 (26.5)	0.01
COPD	6983 (19.7)	7268 (20.5)	0.02	6031 (19.7)	6004 (19.7)	0.00
Falls	2358 (6.7)	2683 (7.6)	0.04	2093 (6.9)	2066 (6.8)	0.00
Fractures	2692 (7.6)	3443 (9.7)	0.08	2484 (8.1)	2520 (8.2)	0.00
Liver disease	3058 (8.6)	3297 (9.3)	0.02	2709 (8.9)	2714 (8.9)	0.00
Peptic ulcer	791 (2.2)	946 (2.7)	0.03	721 (2.4)	730 (2.4)	0.00
Health services						
Receiving home healthcare	14 696 (41.5)	15 634 (44.2)	0.05	6672 (21.8)	6681 (21.9)	0.00
Mean (SD) No of ED visits	1.12 (1.91)	1.24 (2.09)	0.06	1.15 (1.97)	1.15 (1.82)	0.00
Mean (SD) No of ED visits†	0.07 (0.32)	0.07 (0.35)	0.01	0.06 (0.33)	0.06 (0.32)	0.00
Mean (SD) No of inpatient days during BAP	4.60 (4.74)	5.15 (6.56)	0.10	4.67 (4.76)	4.62 (4.96)	0.01
Mean (SD) No of inpatient days‡	0.09 (0.90)	0.25 (1.87)	0.11	0.10 (0.96)	0.10 (0.92)	0.00
Mean (SD) No of office visits	12.96 (9.13)	13.85 (9.38)	0.10	13.35 (9.24)	13.36 (8.97)	0.00
Mean (SD) No of SNF days	2.89 (20.09)	2.94 (16.73)	0.00	3.78 (20.61)	3.69 (18.20)	0.00
Mean (SD) No of SNF days‡	0.15 (2.04)	0.54 (3.67)	0.13	0.15 (2.02)	0.14 (1.82)	0.01
Mean (SD) total healthcare copay at baseline ($)†	4027.91 (3590.18)	4305.12 (4151.60)	0.07	4037.90 (3583.40)	4021.11 (3384.18)	0.00
Mean (SD) total healthcare cost at baseline ($)†	36 995.86 (40 686.17)	38 539.64 (44 965.17)	0.04	37 005.58 (40 374.73)	36 707.51 (42 744.05)	0.01

$1.00 (£0.74; €0.85).
BAP=baseline assessment period; Optum CDM=Optum's deidentified Clinformatics Data Mart Database; COPD=chronic obstructive pulmonary disease; ED=emergency department; ICH=intracerebral hemorrhage; OAC=oral anticoagulant; PVD=peripheral vascular disease; SD=standard deviation; SMD=standardized mean difference; SNF=skilled nursing facility; VTE=venous thromboembolism.
BAP was 365 days before cohort entry date.
*90 day before the first hospital admission with VTE.
†Assessed in BAP.
‡30 days before cohort entry date.

doi: 10.1136/bmj-2025-084380 | *BMJ* 2025;391:e084380 | the bmj

Table 2 | Clinical outcomes in patients continuing versus discontinuing anticoagulation after at least 90 days of initial treatment, after propensity score matching, pooled across Medicare and Optum CDM populations

	Continued OAC		Discontinued OAC			
	No of patients	No of events (incidence rate/1000 person years)	No of patients	No of events (incidence rate/1000 person years)	Adjusted hazard ratio (95% CI)	Adjusted rate difference/1000 person years (95% CI)
Recurrent VTE						
Any OAC	30 554	285 (7.34)	30 554	1880 (32.89)	0.19 (0.13 to 0.29)	−25.50 (−39.38 to −11.63)
Apixaban	9528	60 (5.57)	9528	434 (35.97)	0.15 (0.10 to 0.21)	−30.12 (−37.07 to −23.17)
Rivaroxaban	6733	61 (6.51)	6733	483 (30.85)	0.18 (0.12 to 0.28)	−23.92 (−33.25 to −14.59)
Warfarin	11 152	144 (10.82)	11 152	824 (29.7)	0.24 (0.19 to 0.32)	−18.92 (−30.33 to −7.50)
P value*					0.09	0.22
Major bleeding						
Any OAC	30 554	473 (10.15)	30554	337 (5.41)	1.75 (1.52 to 2.02)	4.78 (1.95 to 7.61)
Apixaban	9528	90 (7.67)	9528	84 (6.52)	1.15 (0.85 to 1.55)	1.21 (−1.03 to 3.44)
Rivaroxaban	6733	106 (8.98)	6733	100 (5.57)	1.67 (1.25 to 2.22)	3.56 (−0.96 to 8.08)
Warfarin	11 152	226 (15.86)	11 152	179 (5.97)	2.22 (1.80 to 2.75)	9.83 (7.41 to 12.24)
P value*					0.002	<0.001
Net clinical benefit†						
Any OAC	30 554	733 (17.12)	30 554	2185 (38.03)	0.39 (0.36 to 0.42)	−21.01 (−32.31 to −9.71)
Apixaban	9528	147 (13.53)	9528	508 (41.82)	0.29 (0.24 to 0.35)	−28.82 (−34.95 to −22.69)
Rivaroxaban	6733	162 (16.02)	6733	571 (36.07)	0.39 (0.33 to 0.47)	−21.07 (−25.97 to −16.18)
Warfarin	11 152	359 (26.76)	11 152	974 (35.23)	0.52 (0.46 to 0.58)	−9.70 (−20.07 to 0.68)
P value*					<0.001	0.006
All cause mortality						
Any OAC	30 554	1466 (31.99)	30 554	2768 (46.17)	0.74 (0.69 to 0.79)	−14.31 (−22.02 to −6.59)
Apixaban	9528	433 (35)	9528	688 (52.82)	0.65 (0.45 to 0.93)	−17.67 (−23.17 to −12.17)
Rivaroxaban	6733	281 (25.46)	6733	745 (41.78)	0.69 (0.60 to 0.80)	−16.93 (−24.96 to −8.89)
Warfarin	11 152	510 (32.24)	11 152	1607 (51.32)	0.68 (0.61 to 0.76)	−19.36 (−37.30 to −1.42)

Optum CDM=Optum's deidentified Clinformatics Data Mart Database; CI=confidence interval; OAC=oral anticoagulant; VTE=venous thromboembolism.
*P for heterogeneity by OAC type.
†Composite of recurrent VTE and major bleeding.

continued OACs matched with 30 554 patients who discontinued OACs. Table 1 presents selected personal and clinical characteristics of the study cohort (see supplemental tables S1 and S2 for all characteristics). Before propensity score matching, the characteristics of patients who continued and discontinued OACs were similar (mean age 74.1 *v* 73.8; female 57.8% (n=20 447) *v* 57.1% (n=20 189), though some baseline healthcare utilization (eg, hospital admission, nursing home stays, and office visits) was lower in those who continued than discontinued treatment (eg, mean hospital stay 4.60 *v* 5.15 days). After propensity score matching, all covariates were well balanced (table 1).

Clinical outcomes after 90 days of initial OACs

The median follow-up time was 241 days (interquartile range (IQR) 517 days) in the continued OAC group and 174 (IQR 865) days in the discontinued OAC

	No of events/incidence rate				
Length of initial treatment (days)	Continued OAC	Discontinued OAC	Adjusted rate difference (95% CI)	Adjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Recurrent VTE					
90-179	102/9.38	702/31.96	-22.75 (-36.26 to -9.24)	0.22 (0.16 to 0.32)	
180-359	141/7.84	1003/36.7	-28.87 (-39.80 to -17.94)	0.17 (0.13 to 0.23)	
360-719	70/5.75	310/33.38	-27.77 (-39.23 to -16.31)	0.15 (0.11 to 0.20)	
720-1079	28/6.21	63/33.17	-25.85 (-48.55 to -3.15)	0.18 (0.07 to 0.49)	
≥1080	14/4.78	29/31.47	-27.36 (-39.02 to -15.71)	0.13 (0.04 to 0.41)	
Major bleeding					
90-179	174/13.8	119/5.09	8.81 (4.26 to 13.35)	2.38 (1.88 to 3.02)	
180-359	216/9.87	159/5.52	4.44 (-0.16 to 9.04)	1.92 (1.56 to 2.37)	
360-719	144/9.7	54/5.4	4.52 (1.00 to 8.05)	1.85 (1.34 to 2.57)	
720-1079	50/13.31	<11/6.22	7.09 (1.42 to 12.76)	2.04 (0.96 to 4.36)	
≥1080	28/10.01	<11/8.13	1.88 (-5.60 to 9.37)	1.00 (0.40 to 2.48)	

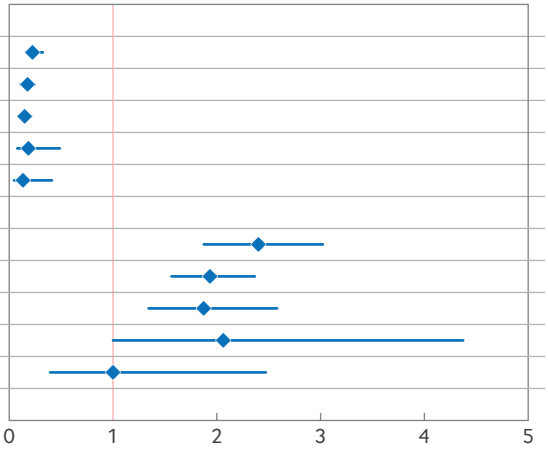

Fig 2 | Subgroup analysis comparing patients who continued versus discontinued OAC by number of days after initial treatment. OAC=oral anticoagulant; VTE=venous thromboembolism

Length of initial treatment (days)	No of events/incidence rate: Continued OAC	No of events/incidence rate: Discontinued OAC	Adjusted rate difference (95% CI)	Adjusted hazard ratio (95% CI)
90-179	272/23.04	813/36.89	-14.31 (-23.32 to -5.29)	0.50 (0.43 to 0.57)
180-359	346/17.39	1146/42.08	-25.11 (-30.83 to -19.40)	0.37 (0.32 to 0.41)
360-719	207/15.05	358/38.46	-23.99 (-31.35 to -16.62)	0.38 (0.32 to 0.45)
720-1079	77/15.63	70/35.72	-21.21 (-39.33 to -3.09)	0.36 (0.26 to 0.50)
≥1080	42/12.06	35/37.37	-25.35 (-38.39 to -12.31)	0.27 (0.17 to 0.43)

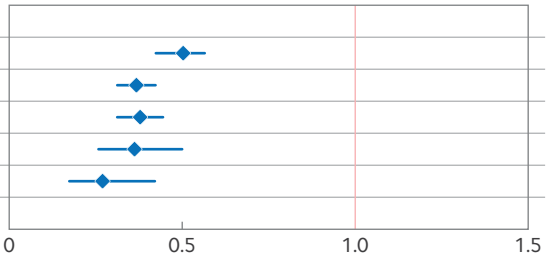

Fig 3 | Net clinical benefit comparing patients who continued versus discontinued OAC by number of days after initial treatment. The net clinical benefit was a composite of recurrent VTE and major bleeding. OAC=oral anticoagulant; VTE=venous thromboembolism

group, with 21 155 (69.2%) and 16 173 (52.9%) participants censored, respectively, owing to change of status for initial drug use (see supplemental table S3). In the reference group of participants who continued treatment, 25% used an OAC for ≤189 days, 50% for ≤331 days, and 75% for ≤706 days. The median duration of treatment (from initiation until discontinuation) was 357 (IQR 599) days in the continued OAC group and 105 (IQR 118) days in the discontinued OAC group. After at least 90 days of initial anticoagulation, compared with the discontinued OAC group, the continued OAC group had markedly lower rates of recurrent VTE (adjusted hazard ratio 0.19, 95% CI 0.13 to 0.29; adjusted rate difference −25.50 per 1000 person years, 95% CI −39.38 to −11.63), higher rates of major bleeding (1.75, 1.52 to 2.02; 4.78, 1.95 to 7.61), and greater net clinical benefit (ie, lower rate of the composite outcome) (0.39, 0.36 to 0.42; −21.01, −32.31 to −9.71). Among the recurrent VTE events, 74% were pulmonary embolism and the remainer were deep vein thrombosis. Mortality rates were also lower among the continued OAC group (adjusted hazard ratio 0.74, 0.69 to 0.79; adjusted risk difference −14.31, −22.02 to −6.59). Similar results were observed between the two groups for apixaban, rivaroxaban, and warfarin and recurrent VTE, whereas absolute increased bleeding risk attributed to OAC continuation (versus discontinuation) was smaller in users of direct OACs than in users of warfarin (table 2).

Clinical outcomes after predefined days of initial OAC treatment

We observed a consistent magnitude of reduced rates of recurrent VTE when comparing the continued OAC group with the discontinued OAC group after initial anticoagulation of 90-179 days (adjusted hazard ratio 0.22, 95% CI 0.16 to 0.32), 180-359 days (0.17, 0.13 to 0.23), 360-719 days (0.15, 0.11 to 0.20), 720-1079 days (0.18, 0.07 to 0.49), and ≥1080 days (0.13, 0.04 to 0.41). The association between increased rates of major bleeding among the continued OAC group was also fairly consistent, diminishing only among those with the longest period of OAC use after VTE: the adjusted hazard ratio after initial OAC treatment was 2.38 (1.88 to 3.02) for 90-179 days, 1.92 (1.56 to 2.37) for 180-359 days, 1.85 (1.34 to 2.57) for 360-719 days, 2.04 (0.96 to 4.36) for 720-1079 days, and 1.00 (0.40 to 2.48) for ≥1080 days, although the estimates for ≥720 days were based on small event numbers. The net clinical benefit was consistent on the absolute scale across different lengths of initial anticoagulation. The adjusted rate differences per 1000 person years were −14.31 for 90-179 days' follow-up, −25.11 for 180-359 days, −23.99 for 360-719 days, −21.21 for 720-1079 days, and −25.35 for ≥1080 days (fig 2, fig 3).

Subgroup and sensitivity analysis by comorbidities

We did not observe significant heterogeneity of treatment effect by subgroups of age, sex, chronic kidney disease, pulmonary embolism versus deep vein thrombosis as the index event, or VTE-BLEED score (fig 4, fig 5). Database specific results were consistent across the Optum CDM and Medicare databases (see supplemental figure S1). Results from sensitivity analyses using a longer refill gap (60 days) to define discontinuation, high dimensional propensity score, and Fine and Gray model were similar to the primary results. The 365 day intention-to-treat analysis yielded more attenuated effect estimates compared with the primary analysis, but the general trends remained consistent (see supplemental table S4). This E value analysis showed that to account for our recurrent VTE findings we would need a strong unmeasured confounder that is differentially distributed among those who continued OAC treatment versus those who discontinued by a ratio >9.5 to 1 and simultaneously associated with a 9.5-fold increased risk of recurrent VTE.

Discussion

Based on two US national claims databases, patients with unprovoked VTE who continued OAC treatment after initial anticoagulation for at least 90 days experienced substantially lower rates of VTE recurrence compared with patients who discontinued OAC treatment. These benefits were observed across a range of lengths of initial OAC use, including standard use for 90-179 days and 180-359 days, but also among

	No of events/incidence rate				
	Continued OAC	Discontinued OAC	Adjusted rate difference (95% CI)	Adjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Recurrent VTE					
Age (years)					
≥75	140/7.32	964/37.69	-30.66 (-38.67 to -22.66)	0.16 (0.13 to 0.19)	
<75	134/7.02	850/29.54	-22.29 (-36.17 to -8.42)	0.21 (0.12 to 0.37)	
Heterogeneity P value			0.31	0.35	
Sex					
Female	163/7.34	1059/31.26	-24.21 (-38.36 to -10.06)	0.18 (0.13 to 0.24)	
Male	115/7.49	787/34.58	-26.88 (-40.13 to -13.63)	0.19 (0.10 to 0.38)	
Heterogeneity P value			0.79	0.83	
Chronic kidney disease					
Yes	19/5.03	169/36.68	-31.65 (-37.62 to -25.67)	0.12 (0.07 to 0.19)	
No	192/7.37	1335/39.90	-32.52 (-34.90 to -30.14)	0.16 (0.14 to 0.18)	
Heterogeneity P value			0.47	0.10	
Index pulmonary embolism					
Yes	191/7.14	1302/35.41	-28.45 (-42.55 to -14.35)	0.17 (0.12 to 0.22)	
No	102/8.64	540/27.31	-18.11 (-30.52 to -5.69)	0.28 (0.15 to 0.53)	
Heterogeneity P value			0.28	0.15	
VTE-BLEED score					
<2	131/6.38	936/31.44	-24.71 (-40.09 to -9.34)	0.18 (0.10 to 0.35)	
≥2	154/8.48	901/33.98	-25.70 (-36.73 to -14.66)	0.20 (0.16 to 0.24)	
Heterogeneity P value			0.92	0.85	
Major bleeding					
Age (years)					
≥75	320/14.55	229/8.17	6.93 (4.75 to 9.11)	1.69 (1.42 to 2.03)	
<75	137/6.46	100/3.35	3.12 (1.64 to 4.59)	1.82 (1.40 to 2.36)	
Heterogeneity P value			0.005	0.66	
Sex					
Female	320/12.26	202/5.82	6.58 (2.88 to 10.28)	1.96 (1.63 to 2.36)	
Male	159/8.31	121/4.67	3.61 (1.93 to 5.29)	1.69 (1.34 to 2.14)	
Heterogeneity P value			0.15	0.30	
Chronic kidney disease					
Yes	92/20.33	59/9.36	9.90 (4.96 to 14.85)	1.85 (1.33 to 2.59)	
No	379/9.05	259/4.64	4.42 (1.10 to 7.75)	1.85 (1.58 to 2.17)	
Heterogeneity P value			0.07	0.96	
Index pulmonary embolism					
Yes	312/9.85	190/4.81	5.09 (1.99 to 8.20)	1.96 (1.63 to 2.36)	
No	154/11.29	132/5.84	5.36 (3.06 to 7.67)	1.64 (1.29 to 2.09)	
Heterogeneity P value			0.89	0.23	
VTE-BLEED score					
<2	180/6.71	115/3.55	3.14 (-1.97 to 8.24)	1.79 (1.04 to 3.06)	
≥2	300/15.46	193/6.81	8.45 (6.29 to 10.61)	2.00 (1.57 to 2.54)	
Heterogeneity P value			0.92	0.85	

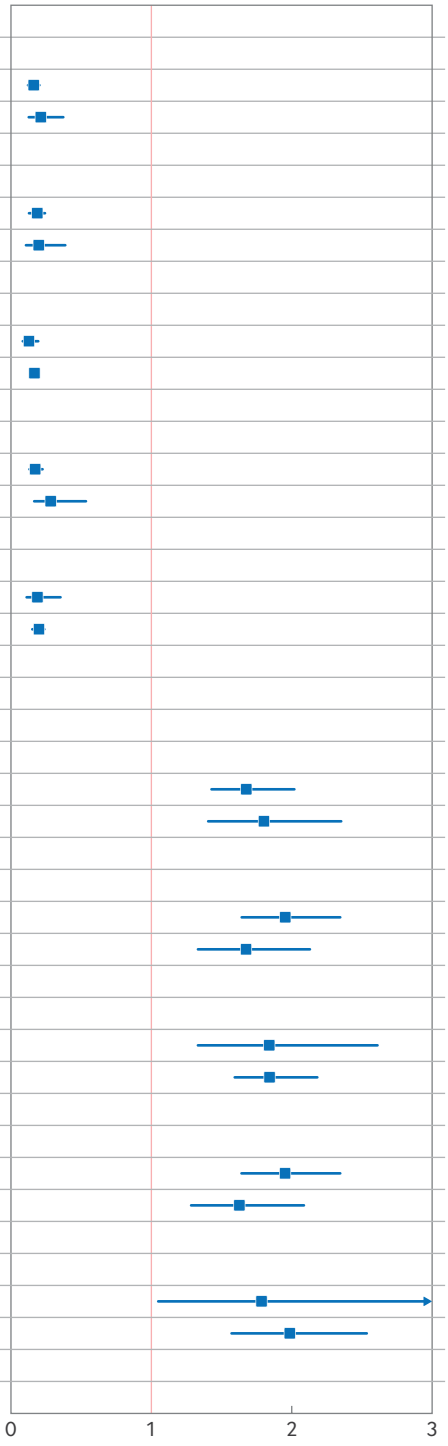

Fig 4 | Subgroup analysis comparing patients who continued versus discontinued OAC after at least 90 days of initial treatment, by patient characteristics. OAC=oral anticoagulant; VTE=venous thromboembolism

patients with initial OAC treatment for at least 1080 days after VTE. Patients receiving extended anticoagulation experienced higher rates of major bleeding, although this effect was not seen in those with the longest period of initial OAC use, perhaps reflecting a survivor effect. The net clinical benefit, as measured by the composite outcome of recurrent VTE and major bleeding, favored continued OAC use after initial anticoagulation for up to three years. We observed consistent patterns for apixaban, rivaroxaban, and warfarin users. The

	No of events/incidence rate				
	Continued OAC	Discontinued OAC	Adjusted rate difference (95% CI)	Adjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Age (years)					
≥75	443/20.97	1172/45.21	-25.35 (-30.76 to -19.94)	0.42 (0.38 to 0.47)	
<75	266/13.74	942/32.77	-19.26 (-31.92 to -6.61)	0.35 (0.28 to 0.44)	
Heterogeneity P value			0.39	0.17	
Sex					
Female	471/19.12	1242/36.66	-17.80 (-28.94 to -6.67)	0.43 (0.39 to 0.48)	
Male	265/15.78	898/39.13	-23.69 (-35.41 to -11.97)	0.35 (0.30 to 0.40)	
Heterogeneity P value			0.48	0.02	
Chronic kidney disease					
Yes	112/24.81	252/42.56	-19.01 (-28.66 to -9.36)	0.49 (0.39 to 0.61)	
No	619/16.66	1891/37.28	-20.74 (-32.83 to -8.65)	0.38 (0.35 to 0.42)	
Heterogeneity P value			0.83	0.05	
Index pulmonary embolism					
Yes	484/16.42	1473/40.06	-23.78 (-35.03 to -12.53)	0.36 (0.32 to 0.40)	
No	251/21.11	664/32.81	-12.72 (-25.82 to 0.39)	0.52 (0.38 to 0.71)	
Heterogeneity P value			0.21	0.02	
VTE-BLEED score					
<2	301/13.2	1042/34.93	-21.83 (-32.30 to -11.35)	0.33 (0.29 to 0.38)	
≥2	441/23.33	1076/40.39	-17.69 (-28.52 to -6.87)	0.48 (0.43 to 0.53)	
Heterogeneity P value			0.92	0.85	

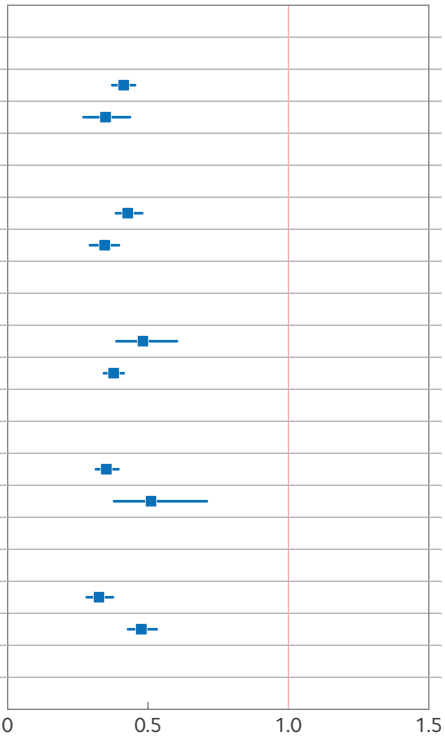

Fig 5 | Net clinical benefit comparing patients who continued versus discontinued OAC after at least 90 days of initial treatment, by patient characteristics. The net clinical benefit was a composite of recurrent VTE and major bleeding. OAC=oral anticoagulant; VTE=venous thromboembolism

observed effect sizes were somewhat attenuated in the intention-to-treat analysis as would be expected, as patients discontinued OAC over time.

Comparison with other studies

Although clinical guidelines recommend extending anticoagulation beyond the initial 3-6 months for patients with unprovoked VTE,[4 5] previous randomized controlled trials were not adequately powered to provide long term bleeding outcomes for extended anticoagulation.[39] Our study, based on two nationally representative cohorts in routine care, provides evidence of the long term effect of continuing OAC treatment on recurrent VTE and major bleeding, stratified by specific OAC type and the length of initial anticoagulation. Our findings for preventing VTE recurrence were consistent with previous randomized controlled trials. A meta-analysis including 17 randomized controlled trials comparing the efficacy and safety of continuing versus discontinuing anticoagulation among patients with unprovoked VTE reported that warfarin (odds ratio 0.25, 95% CI 0.13 to 0.49), rivaroxaban (0.18, 0.03 to 0.90), and apixaban (0.18, 0.04 to 0.85) were associated with a lower risk of recurrent VTE compared with placebo.[39] However, these randomized controlled trials either failed to estimate the effect of major bleeding due to insufficient event numbers, or yielded imprecise estimates for major bleeding. For example, the pooled odds ratio of major bleeding risk comparing continuation of apixaban with discontinuation was 10.65 (95% CI 1.06 to 107.13) in the meta-analysis.[39] In the EINSTEIN trial, extended treatment with rivaroxaban 20 mg for an additional six or 12 months after initial VTE treatment was compared with placebo in the extended treatment period; only four major bleeding events occurred in the rivaroxaban group and none in the placebo group.[7] A more recent randomized controlled trial comparing extended treatment for two years versus discontinuation after the initial 90 day anticoagulation period reported a non-significant increase in major bleeding (adjusted hazard ratio 2.99, 95% CI 0.81 to 11.05), based on only three events in the group that discontinued treatment.[40]

Although large observational studies have compared OACs used for extended treatment of VTE,[15 41] real world evidence comparing extended anticoagulation versus discontinued anticoagulation for unprovoked VTE is limited. One study based on a Japanese registry without any adjustment for confounding found that continuing versus discontinuing anticoagulation at 180 days was not associated with an increased risk of bleeding.[8] An Italian study without adjustment for confounding reported a risk ratio of 0.14 (95% CI 0.06 to 0.27) for recurrent VTE, comparing continuation versus discontinuation of anticoagulation at any time after initiation. This study was not powered

to investigate bleeding outcomes.[9] A Danish study comparing extended treatment (>365 days) versus OAC of intermediate duration (91-365 days) after an unprovoked VTE found that OAC was associated with a reduction in recurrent VTE and increased risk of major bleeding.[42] None of the previous studies had sufficient power to investigate subgroup effects by OAC type or treatment duration. To address these knowledge gaps, we used two US national cohorts to investigate long term VTE and bleeding events and found a favorable net clinical benefit associated with extended OAC treatment for VTE even beyond three years of initial treatment, provided the patients tolerated the initial period of anticoagulation well.

Previous meta-analyses reported that the case fatality rate was 2-3 times higher in patients with major bleeding than those with recurrent VTE[43-45] after initial anticoagulation. Yet, individualized estimation of mortality needs to consider the type of VTE (ie, the mortality rate for pulmonary embolism is about twice as high as that for deep vein thrombosis[43 46]) and the type of OAC (eg, the case fatality rate of bleeding is higher among warfarin users compared with direct OAC users[45 47]). In our study, 74% of the recurrent VTE events were pulmonary embolism. Our results also showed that the absolute increase in bleeding risk associated with continued OAC treatment (versus discontinued treatment) was smaller among direct OAC users than among warfarin users (eg, rate difference per 1000 person years was 1.21 in apixaban users and 9.83 in warfarin users). Although our findings showed a favorable overall net clinical benefit for extended anticoagulation treatment, particularly for direct OACs, each decision of long term anticoagulation required an individualized shared decision making process.

Strengths and limitations of this study

The current study has several strengths. The large size of the cohort enabled detailed subgroup analyses by OAC type, length of anticoagulation, personal characteristics, and comorbidities. The national cohorts that we used, including older adults from the Medicare database and younger adults from commercial datasets, also enhanced the generalizability of our findings. Next, we applied a target trial emulation analytical framework with rigorous analytical strategies that have been shown to replicate the findings of randomized controlled trials successfully.[10 11 48 49] We acknowledge several limitations. Our administrative claims data lacked information on over-the-counter drug use (eg, aspirin), socioeconomic status, functional status, cognitive function, body mass index, or laboratory test results, including hemoglobin values that can help define major bleeding outcomes and international normalized ratio values that can quantify the anticoagulation effects during warfarin treatment. Also, we did not have information on the reasons for discontinuing OAC. Because people could discontinue an OAC for reasons associated with a poor prognosis (eg, non-adherence, medical futility), lack of such adjustment could lead to residual confounding in favor of extended anticoagulation. For some confounders that were not measured directly in our database, we used validated proxy scores, including predicted time within treatment range[15 18] and claims based frailty index.[21-23] To further minimize unmeasured confounding, we applied a validated algorithm as a proxy to adjust for confounding, high dimensional propensity score,[28] and found similar results. Moreover, we assessed the amount of unmeasured confounding that could potentially account for our findings by E value and found it unlikely.[35] Also, because we did not have direct information on quality of life, it was not possible to assess the effect of OAC use on quality of life, which could be considered in future studies. We relied on dispensing data for use of OACs, which can be discordant with actual consumption in the setting of medication non-adherence. Our discontinuation definition of absence of a refill within 30 days is subject to misclassification. Reassuringly, our sensitivity analysis using a larger refill gap of 60 days to define discontinuation yielded similar results. Our outcome definition of recurrent VTE was based on a validated algorithm requiring an inpatient diagnosis of VTE in the primary position that yielded a high positive predictive value.[14] Diagnosis codes in the outpatient setting or a non-primary position are more likely to be a history of VTE as opposed to incident VTE. However, requiring an inpatient diagnosis omitted milder VTE events treated in the outpatient setting. Lastly, although we used one public and one private national health insurance dataset that reflect routine delivery of care, our study cohorts include only patients with medical insurance coverage and may not fully represent the US population in terms of demographics and socioeconomic status. Therefore, our findings may not be generalizable to uninsured populations or people with other types of insurance, such as public insurance for adults with a low income and younger than 65 years.

Conclusions

Based on two national US cohorts of patients with VTE but without reversible provoking factors receiving anticoagulation for at least 90 days, we found that continuing OACs was associated with lower rates of VTE recurrence compared with discontinuing OACs, regardless of treatment duration. Extended OAC use was also associated with higher rates of bleeding, but the composite outcome of recurrent VTE and major bleeding (ie, net clinical benefit) still favored continuation over discontinuation of OACs even after initial OAC use as long as 1080 days. We found consistent results across specific OAC types. Supplementing those randomized controlled trials that lacked the power to investigate long term bleeding events, our findings showed a favorable net clinical benefit for extended anticoagulation for preventing recurrent VTE after initial anticoagulation of up to three years. These results reflect the average effect of continuing OACs and should help inform decisions on continuation of treatment, which should be

individualized for each patient with an unprovoked VTE.

Contributors: All authors contributed to the conception, design, and methodology of the manuscript. KJL obtained the funding and drafted the manuscript. YZ, AC, and AK contributed to the statistical analysis and implemented the study. KJL, DHK, DES, and KB supervised the research. All authors contributed to the interpretation of the data and critical revision of the manuscript, and approved the final and revised versions of the manuscript. KJL is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This research was supported by a grant from the US National Institute on Aging (R01AG081412). DES was partially supported by the Eliot B and Edith C Shoolman Fund of the Massachusetts General Hospital. KB was supported by grants from US National Institute on Aging (K01AG068365) and Patient-Centered Outcomes Research Institute (PCORI) Project Program Award (NOACs-1511-33068). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: supported by a grant from the US National Institute on Aging for the submitted work; DES was partially supported by the Eliot B and Edith . Shoolman Fund of the Massachusetts General Hospital; KB was supported by grants K01AG068365 from US National Institute on Aging and Patient-Centered Outcomes Research Institute (PCORI) Project Program Award (NOACs-1511-33068); no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the Mass General Brigham institutional review board (protocol # 2021P003597).

Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at jklin@bwh.harvard.edu.

Transparency: The lead author (KJL) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: Results of the study will be shared with policy makers, professional societies, and the public through press release and social media.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet* 2016;388:3060-73. doi:10.1016/S0140-6736(16)30514-1
2 Virani SS, Alonso A, Aparicio HJ, et al, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation* 2021;143:e254-743. doi:10.1161/CIR.0000000000000950
3 Søgaard KK, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation* 2014;130:829-36. doi:10.1161/CIRCULATIONAHA.114.009107
4 Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(Suppl):e419S-96S. doi:10.1378/chest.11-2301
5 Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv* 2020;4:4693-738. doi:10.1182/bloodadvances.2020001830
6 Agnelli G, Buller HR, Cohen A, et al, AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;368:699-708. doi:10.1056/NEJMoa1207541
7 Bauersachs R, Berkowitz SD, Brenner B, et al, EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-510. doi:10.1056/NEJMoa1007903
8 Kaneda K, Yamashita Y, Morimoto T, et al, COMMAND VTE Registry-2 Investigators. Anticoagulation strategies and long-term recurrence in patients with venous thromboembolism in the era of direct oral anticoagulants. *Eur J Intern Med* 2023;118:59-72. doi:10.1016/j.ejim.2023.08.007
9 Bortoluzzi C, Bernardi E, Camporese G, et al. Safety and Efficacy of Rivaroxaban for Extended-Phase Anticoagulation of Patients with Unprovoked or Recurrent Venous Thromboembolism: Real-Life Data from the MAC Project. *Life (Basel)* 2022;12:1657. doi:10.3390/life12101657
10 Wang SV, Schneeweiss S, Franklin JM, et al, RCT-DUPLICATE Initiative. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA* 2023;329:1376-85. doi:10.1001/jama.2023.4221
11 Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. *JAMA* 2022;328:2446-7. doi:10.1001/jama.2022.21383
12 Amin A, Neuman WR, Lingohr-Smith M, Menges B, Lin J. Influence of the duration of hospital length of stay on frequency of prophylaxis and risk for venous thromboembolism among patients hospitalized for acute medical illnesses in the USA. *Drugs Context* 2019;8:212568. doi:10.7573/dic.212568
13 Xie L, Liu X, Phatak H, et al. Warfarin Discontinuation in Patients With Unprovoked Venous Thromboembolism: A Large US Insurance Database Analysis. *Am J Ther* 2016;23:e1744-53. doi:10.1097/MJT.0000000000000167
14 Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;21(Suppl 1):154-62. doi:10.1002/pds.2341
15 Pawar A, Gagne JJ, Gopalakrishnan C, et al. Association of Type of Oral Anticoagulant Dispensed With Adverse Clinical Outcomes in Patients Extending Anticoagulation Therapy Beyond 90 Days After Hospitalization for Venous Thromboembolism. *JAMA* 2022;327:1051-60. doi:10.1001/jama.2022.1920
16 Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf* 2011;20:560-6. doi:10.1002/pds.2109
17 Graham DJ, Reichman ME, Wernecke M, et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. *JAMA Intern Med* 2016;176:1662-71. doi:10.1001/jamainternmed.2016.5954
18 Klok FA, Hösel V, Clemens A, et al. Prediction of bleeding events in patients with venous thromboembolism on stable anticoagulation treatment. *Eur Respir J* 2016;48:1369-76. doi:10.1183/13993003.00280-2016
19 Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol* 2011;64:749-59. doi:10.1016/j.jclinepi.2010.10.004
20 Lin KJ, Singer DE, Glynn RJ, et al. Prediction Score for Anticoagulation Control Quality Among Older Adults. *J Am Heart Assoc* 2017;6:e006814. doi:10.1161/JAHA.117.006814
21 Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci* 2018;73:980-7. doi:10.1093/gerona/glx229
22 Kim DH, Patorno E, Pawar A, Lee H, Schneeweiss S, Glynn RJ. Measuring Frailty in Administrative Claims Data: Comparative Performance of Four Claims-Based Frailty Measures in the U.S. Medicare Data. *J Gerontol A Biol Sci Med Sci* 2020;75:1120-5. doi:10.1093/gerona/glz224
23 Gautam N, Bessette L, Pawar A, Levin R, Kim DH. Updating International Classification of Diseases 9th Revision to 10th Revision of a Claims-Based Frailty Index. *J Gerontol A Biol Sci Med Sci* 2021;76:1316-7. doi:10.1093/gerona/glaa150
24 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083-107. doi:10.1002/sim.3697
25 Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1:97-111. doi:10.1002/jrsm.12
26 Iyer GS, Tesfaye H, Khan NF, Zakoul H, Bykov K. Trends in the Use of Oral Anticoagulants for Adults With Venous Thromboembolism in the US, 2010-2020. *JAMA Netw Open* 2023;6:e234059. doi:10.1001/jamanetworkopen.2023.4059
27 Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;2:121-45. doi:10.1177/096228029300200202

28 Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009;20:512-22. doi:10.1097/EDE.0b013e3181a663cc
29 Rassen JA, Choudhry NK, Avorn J, Schneeweiss S. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 2009;120:2322-9. doi:10.1161/CIRCULATIONAHA.109.873497
30 Garbe E, Kloss S, Suling M, Pigeot I, Schneeweiss S. High-dimensional versus conventional propensity scores in a comparative effectiveness study of coxibs and reduced upper gastrointestinal complications. *Eur J Clin Pharmacol* 2013;69:549-57. doi:10.1007/s00228-012-1334-2
31 Le HV, Poole C, Brookhart MA, et al. Effects of aggregation of drug and diagnostic codes on the performance of the high-dimensional propensity score algorithm: an empirical example. *BMC Med Res Methodol* 2013;13:142. doi:10.1186/1471-2288-13-142
32 Hallas J, Pottegård A. Performance of the High-dimensional Propensity Score in a Nordic Healthcare Model. *Basic Clin Pharmacol Toxicol* 2017;120:312-7. doi:10.1111/bcpt.12716
33 Gray B. cmprsk: Subdistribution Analysis of Competing Risks. R package version 2.2-11. https://CRAN.R-project.org/package=cmprsk2022
34 Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999;94:496-509doi:10.1080/01621459.1999.10474144.
35 VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;167:268-74. doi:10.7326/M16-2607
36 Wang SV, Verpillat P, Rassen JA, Patrick A, Garry EM, Bartels DB. Transparency and Reproducibility of Observational Cohort Studies Using Large Healthcare Databases. *Clin Pharmacol Ther* 2016;99:325-32. doi:10.1002/cpt.329
37 Fralick M, Kesselheim AS, Avorn J, Schneeweiss S. Use of Health Care Databases to Support Supplemental Indications of Approved Medications. *JAMA Intern Med* 2018;178:55-63. doi:10.1001/jamainternmed.2017.3919
38 Kim SC, Solomon DH, Rogers JR, et al. Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis: A Multi-Database Cohort Study. *Arthritis Rheumatol* 2017;69:1154-64. doi:10.1002/art.40084
39 Li D, Liu Y, Song Y, Wen A. Antithrombotic therapy for secondary prevention of unprovoked venous thromboembolism: a systematic review and network meta-analysis of randomized controlled trials. *Ann Med* 2022;54:253-61. doi:10.1080/07853890.2022.2026002
40 Bradbury C, Fletcher K, Sun Y, et al. A randomised controlled trial of extended anticoagulation treatment versus standard treatment for the prevention of recurrent venous thromboembolism (VTE) and post-thrombotic syndrome in patients being treated for a first episode of unprovoked VTE (the ExACT study). *Br J Haematol* 2020;188:962-75. doi:10.1111/bjh.16275
41 Fang MC, Reynolds K, Fan D, et al. Clinical Outcomes of Direct Oral Anticoagulants vs Warfarin for Extended Treatment of Venous Thromboembolism. *JAMA Netw Open* 2023;6:e2328033. doi:10.1001/jamanetworkopen.2023.28033
42 Johnsen SP, Rasmussen TB, Falstie-Jensen AM, et al. Effectiveness and safety of oral anticoagulation treatment beyond 1 year after venous thromboembolism in patients at intermediate recurrence risk. *Basic Clin Pharmacol Toxicol* 2021;129:210-20. doi:10.1111/bcpt.13625
43 Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Intern Med* 2010;152:578-89. doi:10.7326/0003-4819-152-9-201005040-00008
44 Khan F, Rahman A, Carrier M, et al, MARVELOUS Collaborators. 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:l4363. doi:10.1136/bmj.l4363
45 Khan F, Tritschler T, Kimpton M, et al, MAJESTIC Collaborators. Long-Term Risk for Major Bleeding During Extended Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism : A Systematic Review and Meta-analysis. *Ann Intern Med* 2021;174:1420-9. doi:10.7326/M21-1094
46 Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007;5:692-9. doi:10.1111/j.1538-7836.2007.02450.x
47 Wu C, Alotaibi GS, Alsaleh K, Sean McMurtry M. Case fatality of bleeding and recurrent venous thromboembolism during, initial therapy with direct oral anticoagulants: a systematic review. *Thromb Res* 2014;134:627-32. doi:10.1016/j.thromres.2014.07.001
48 Franklin JM, Schneeweiss S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials?*Clin Pharmacol Ther* 2017;102:924-33. doi:10.1002/cpt.857
49 Stürmer T, Wang T, Golightly YM, Keil A, Lund JL, Jonsson Funk M. Methodological considerations when analysing and interpreting real-world data. *Rheumatology (Oxford)* 2020;59:14-25. doi:10.1093/rheumatology/kez320

Supplementary information: Supplementary figures S1 and S2, tables S1-S4, study protocol, and study variables