Annals of Internal Medicine

REVIEW

Long-Term Risk for Major Bleeding During Extended Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism

A Systematic Review and Meta-analysis

Faizan Khan, MSc; Tobias Tritschler, MD; Miriam Kimpton, MD; Philip S. Wells, MD; Clive Kearon, MD, PhD†; Jeffrey I. Weitz, MD; Harry R. Büller, MD, PhD; Gary E. Raskob, PhD; Walter Ageno, MD; Francis Couturaud, MD, PhD; Paolo Prandoni, MD, PhD; Gualtiero Palareti, MD; Cristina Legnani, PhD; Paul A. Kyrle, MD; Sabine Eichinger, MD; Lisbeth Eischer, MD; Cecilia Becattini, MD, PhD; Giancarlo Agnelli, MD, PhD; Maria Cristina Vedovati, MD; Geert-Jan Geersing, MD, PhD; Toshihiko Takada, MD, PhD; Benilde Cosmi, MD, PhD; Drahomir Aujesky, MD; Letizia Marconi, MD, PhD; Antonio Palla, MD; Sergio Siragusa, MD; Charlotte A. Bradbury, MD, PhD; Sameer Parpia, PhD; Ranjeeta Mallick, PhD; Anthonie W.A. Lensing, MD, PhD; Martin Gebel, PhD; Michael A. Grosso, MD; Kednapa Thavorn, PhD; Brian Hutton, PhD; Gregoire Le Gal, MD, PhD; Dean A. Fergusson, PhD; and Marc A. Rodger, MD; and the MAJESTIC Collaborators*

Background: The long-term risk for major bleeding in patients receiving extended (beyond the initial 3 to 6 months) anticoagulant therapy for a first unprovoked venous thromboembolism (VTE) is uncertain.

Purpose: To determine the incidence of major bleeding during extended anticoagulation of up to 5 years among patients with a first unprovoked VTE, overall, and in clinically important subgroups.

Data Sources: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to 23 July 2021.

Study Selection: Randomized controlled trials (RCTs) and prospective cohort studies reporting major bleeding among patients with a first unprovoked VTE who were to receive oral anticoagulation for a minimum of 6 additional months after completing at least 3 months of initial anticoagulant treatment.

Data Extraction: Two reviewers independently abstracted data and assessed study quality. Unpublished data required for analyses were obtained from authors of included studies.

Data Synthesis: Among the 14 RCTs and 13 cohort studies included in the analysis, 9982 patients received a vitamin K antagonist (VKA) and 7220 received a direct oral anticoagulant (DOAC). The incidence of major bleeding per 100 person-years was 1.74 events (95% CI, 1.34 to 2.20 events) with VKAs and 1.12 events (CI, 0.72 to 1.62 events) with DOACs. The 5-year cumulative incidence of major bleeding with VKAs was 6.3% (CI, 3.6% to 10.0%). Among patients receiving either a VKA or a DOAC, the incidence of major bleeding was statistically significantly higher among those who were older than 65 years or had creatinine clearance less than 50 mL/min, a history of bleeding, concomitant use of antiplatelet therapy, or a hemoglobin level less than 100 g/L. The case-fatality rate of major bleeding was 8.3% (CI, 5.1% to 12.2%) with VKAs and 9.7% (CI, 3.2% to 19.2%) with DOACs.

Limitation: Data were insufficient to estimate incidence of major bleeding beyond 1 year of extended anticoagulation with DOACs.

Conclusion: In patients with a first unprovoked VTE, the long-term risks and consequences of anticoagulant-related major bleeding are considerable. This information will help inform patient prognosis and guide decision making about treatment duration for unprovoked VTE.

Primary Funding Source: Canadian Institutes of Health Research. (PROSPERO: CRD42019128597)

Ann Intern Med. doi:10.7326/M21-1094 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 14 September 2021.
* All members of the MAJESTIC Collaborators are listed in the byline and meet *Annals* criteria for authorship.
† Deceased.

Venous thromboembolism (VTE) is a major contributor to the global burden of disease: The annual incidence of acute VTE is 1 to 2 cases per 1000 persons (1, 2). Most VTE episodes are classified as unprovoked or associated with minor transient risk factors (that is, weakly provoked; see **Supplement Table 1** [available at Annals.org] for examples) (1, 3). Venous thromboembolism should be treated with anticoagulant therapy for at least 3 to 6 months (4–6); during this period, the risk for a potentially fatal recurrent VTE if treatment is discontinued clearly exceeds the risk for a potentially fatal major bleeding event associated with anticoagulation (7, 8). Deciding whether to continue anticoagulant therapy beyond the initial 3 to 6 months (termed *extended anticoagulation*) requires estimating the net balance between

See also:

Summary for Patients

Web-Only
Supplement

absolute treatment benefits and harms through careful consideration of the long-term risks and case-fatality rates of both recurrent VTE if anticoagulation is discontinued and major bleeding if anticoagulation is continued. This framework for decision making about treatment duration is most relevant to patients with a first unprovoked or weakly provoked VTE, for whom indefinite anticoagulation is often suggested (3, 9), but the net clinical benefit of extended anticoagulation is uncertain.

In a recent meta-analysis, we determined that the overall risk for recurrent VTE after discontinuation of anticoagulant therapy for a first unprovoked or weakly provoked VTE is 10% at 1 year and 36% at 10 years, with 4% of recurrent VTE events resulting in death (10). Although the clinical benefits of extended anticoagulation are clear—more than 80% reduction in risk for recurrent VTE as long as treatment is continued (11, 12)—estimates for counterbalancing absolute *long-term* risk for major bleeding during extended anticoagulation for a first unprovoked or weakly provoked VTE are not well established. This evidence gap makes it difficult to estimate the net balance between benefits and harms of extended anticoagulation, thereby hampering decision making about long-term management of this common patient population.

A previous systematic review and meta-analysis of randomized controlled trials (RCTs) and prospective cohort studies reported a major bleeding incidence of 2.74 events (95% CI, 2.71 to 2.77 events) per 100 person-years during extended anticoagulation with vitamin K antagonists (VKAs) in patients with VTE (8). This estimate was based on 9 studies that included 2422 patients who received extended anticoagulation with VKAs beyond the initial 3 months of treatment (8). However, the duration of extended anticoagulation in most of the 9 studies was limited to 3 additional months (that is, total treatment duration of 6 months), leaving an important knowledge gap about *long-term* bleeding risk (8). Also, that meta-analysis (8) did not focus on patients with unprovoked VTE, did not provide bleeding risk estimates in clinically important subgroups or assess risk for major bleeding over time, and included only studies published up to May 2001. Since then, several prospective studies, some with an extended treatment duration of up to 5 years, and studies of direct oral anticoagulants (DOACs) have been published. Therefore, updated information about the potential harms of extended anticoagulant therapy is needed.

We formed the MAJESTIC (MAJor blEeding riSk during exTended antICoagulation) collaboration to undertake a systematic review and meta-analysis, with the objective of determining the risk for major bleeding during extended anticoagulation of up to 5 years among patients with a first unprovoked VTE and in clinically important subgroups.

METHODS

This systematic review and meta-analysis was done in accordance with our study protocol, which was registered in PROSPERO (CRD42019128597) and has been published (13). Our study is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (14).

Search Strategy and Study Selection

In collaboration with an academic information specialist, we searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from the date of inception to 23 July 2021 (search strategy for Embase is presented in **Supplement Table 2**, available at Annals.org). No language restrictions were applied, and content experts were consulted to identify other potentially eligible studies. Two reviewers (F.K. and T.T. or M.K.) independently screened titles, abstracts, and full-text articles. Disagreements were resolved by discussion or by consultation with a third reviewer (M.A.R. or G.L.G.).

Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: 1) were an RCT or a prospective cohort study; 2) included patients with a first symptomatic VTE that had been objectively confirmed and was categorized as either unprovoked or provoked by minor transient risk factors according to the definition from the International Society on Thrombosis and Haemostasis (ISTH) (**Supplement Table 1**); 3) had a treatment group that received an approved oral anticoagulant regimen (that is, apixaban, dabigatran, edoxaban, rivaroxaban, or VKA [international normalized ratio, 2.0 to 3.0]) for a minimum of 6 additional months beyond completion of at least 3 months of initial anticoagulation; and 4) reported major bleeding during extended anticoagulation. The publication with the longest follow-up was included when several articles reported on duplicate patient populations.

Outcomes

The primary outcome was a first major bleeding event, as defined by the ISTH criteria or by the individual studies. The ISTH criteria define major bleeding as overt bleeding that is associated with a decrease in hemoglobin concentration of at least 20 g/L, requires transfusion of at least 2 units of red blood cells or whole blood, occurs in a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or is fatal or contributes to death. Secondary outcomes were intracranial bleeding and fatal bleeding.

Data Extraction

Two reviewers (F.K. and T.T.) independently extracted the following data from each eligible study, with clarifications requested from the study's authors when necessary: study design, duration of initial anticoagulant treatment, maximum duration of follow-up and regimen during extended anticoagulation, definition of unprovoked VTE, and definition of major bleeding.

We contacted the principal investigators of each potentially relevant study to request aggregate data on number of bleeding events (major, intracranial, and fatal) and number of person-years (to ensure appropriate censoring of deaths, patients lost to follow-up, and patients withdrawn from the study) during extended anticoagulation, stratified by type of anticoagulant (VKA or DOAC, when applicable), among patients with a first unprovoked

VTE (and within-study subgroups outlined in Subgroup and Sensitivity Analyses). Our requests to principal investigators also ensured that these aggregate data excluded major bleeding events that did not occur while patients were receiving extended anticoagulation and excluded patients who did not satisfy our eligibility criteria (for example, those who had cancer, had a history of VTE, or had not completed at least 3 months of initial anticoagulant treatment).

Risk-of-Bias Assessment

Because our objective was to determine the incidence of major bleeding during follow-up of patients receiving extended anticoagulation, we assessed each study, including each group of an RCT, as an independent observational cohort. As such, we used a modified version of the Newcastle-Ottawa Scale (15) based on 3 selection and 3 outcome criteria, including whether a representative sample of eligible patients was included, the outcome of interest was not present at the start of patient follow-up, the outcome of interest was independently and blindly adjudicated, and follow-up was sufficiently long and complete. Criteria assessing comparability were considered irrelevant in the context of this systematic review and meta-analysis. Two reviewers (F.K. and T.T.) independently assessed risk of bias among the included studies for the primary outcome of major bleeding, and clarifications were requested from the study authors when necessary. Following quality assessment standards of previous meta-analyses (10, 16), we considered studies that scored at least 4 points on the modified Newcastle-Ottawa Scale to have low risk of bias.

Data Synthesis and Analysis

Primary Analysis

Using the numbers of events and person-years of follow-up acquired from the principal investigators of included studies, we calculated the incidence rate (expressed as events per 100 person-years) of a first major bleeding event in each study cohort. Unless heterogeneity was high, a random-effects model with the DerSimonian–Laird method was used to obtain pooled estimates of the incidence across all studies, and individual study cohorts were weighted according to their inverse variance (17). We also calculated the incidence rate ratio (IRR) to statistically compare major bleeding rates between subgroups. A treatment group continuity correction was used if 1 or both subgroups of a study cohort had 0 events.

To assess bleeding risk over time, we categorized the incidence of major bleeding into the following 3 intervals of follow-up during extended anticoagulation: year 1, year 2, and years 3 to 5. Using our calculated incidence (based on exact person-time at risk during each of the studied intervals, obtained from authors of included studies), we estimated the 2- and 5-year cumulative incidence of major bleeding as follows: We first estimated the cumulative proportion of patients who did not have major bleeding as the product of the proportion of patients who did not have major bleeding during each of the studied intervals; we then estimated the cumulative proportion of patients who had major bleeding as the complement of the cumulative proportion of patients who did not have major bleeding (10). For example, the 5-year cumulative incidence of major bleeding was estimated as follows: If the incidence of major bleeding per 100 person-years was 2.0 events in the first year, 1.5 events in the second year, and 1.0 events in years 3 to 5, then the proportion of patients who did not have major bleeding in years 1 to 5 was estimated as $(98.0\%_{year\ 1}) \times (98.5\%_{year\ 2}) \times ([99.0\%]^{3}_{years\ 3\text{-}5}) = 93.7\%$. The proportion of patients who had major bleeding in years 1 to 5 was then estimated as $100\% - 93.7\% = 6.3\%$.

To estimate the lower and upper limits of the 95% CI for the cumulative incidence, we used the lower and upper limits of the incidence rates in the calculation described in the previous paragraph.

Finally, we calculated the case-fatality rate of major bleeding as the total (that is, during the entire follow-up period) number of fatal bleeding events divided by the total number of major bleeding events.

Heterogeneity between studies was assessed using the I^2 statistic; values of 75% or higher were interpreted as evidence of substantial heterogeneity (18). All meta-analyses were done using StatsDirect, version 3.3.5 (StatsDirect) (19).

Subgroup and Sensitivity Analyses

To establish the long-term risk for major bleeding in clinically important subgroups, we did prespecified, within-study subgroup analyses based on the following patient characteristics: sex, age (>65 vs. ≤65 years), site of initial VTE (isolated proximal deep venous thrombosis [DVT] vs. isolated pulmonary embolism [PE] vs. concomitant DVT and PE), creatinine clearance (<50 vs. ≥50 mL/min), history of bleeding, concomitant use of antiplatelet therapy, and hemoglobin concentration (<100 vs. ≥100 g/L). We also did subgroup analyses according to study design (RCT vs. prospective cohort). Last, we did sensitivity analyses restricted to studies in which the duration of initial anticoagulant treatment was exclusively 3 months and those restricted to studies that used the ISTH definition of major bleeding.

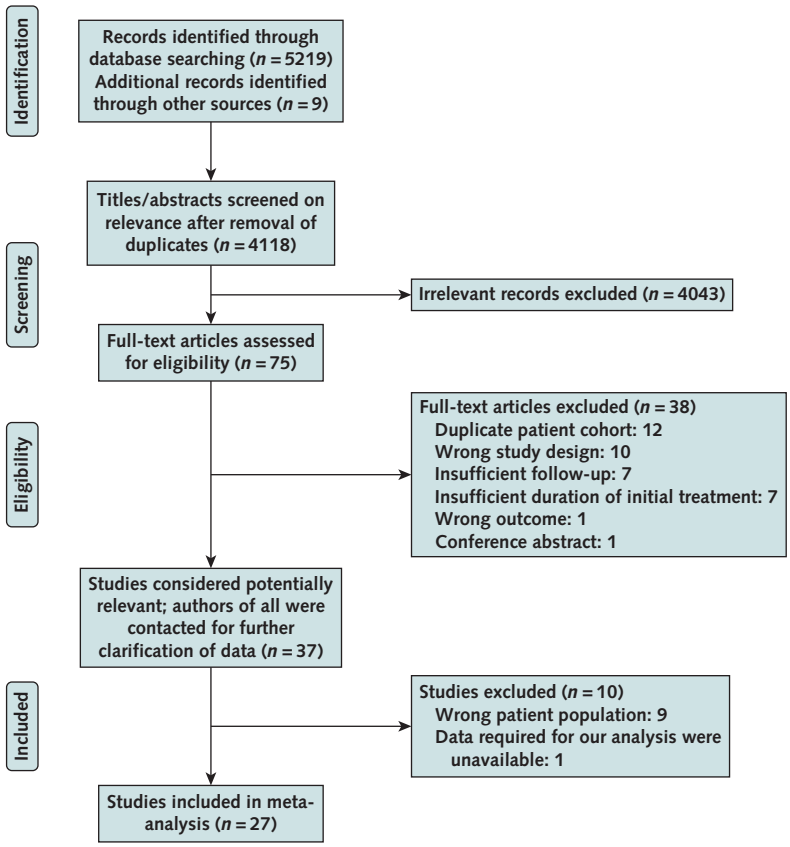
Role of the Funding Source

The funding sources had no role in the study design, analysis, interpretation of data, writing of the manuscript, or decision to submit the manuscript for publication.

RESULTS

The systematic literature search identified 5219 records. After full-text review, 28 studies (supplemented with 9 additional studies identified from other sources) were considered potentially relevant for inclusion in the meta-analysis (**Figure 1**). After contacting the principal investigators of all 37 potentially relevant studies for further clarification of data, we deemed 9 studies (20–28) ineligible because they had the wrong patient population (**Supplement Table 3**, available at Annals.org). Among the remaining 28 studies deemed eligible for inclusion, data required for our analysis were obtained from 27 studies (11, 29–53); 1 study (54) was excluded because information required for our analysis was unavailable (**Figure 1** and **Supplement Table 3**).

Figure 1. Evidence search and selection.



Characteristics of Included Studies and Patients

Among the 27 studies (11, 29–53) included in the analysis, 14 were RCTs and 13 were prospective cohort studies (**Supplement Table 4**, available at Annals.org). A total of 17 202 patients with a first unprovoked or weakly provoked VTE who had completed at least 3 months of initial anticoagulant treatment were included in the analysis (**Supplement Table 5**, available at Annals.org). Seventeen studies used the ISTH definition of major bleeding (**Supplement Table 4**). The overall risk of bias among the included studies was considered to be low (**Supplement Table 4**); the component Newcastle-Ottawa Scale scores for all studies are presented in **Supplement Table 6** (available at Annals.org).

Incidence of Major Bleeding

The incidence of major bleeding per 100 person-years was 1.74 events (CI, 1.34 to 2.20 events) among 9982 patients receiving extended anticoagulation with a VKA and 1.12 events (CI, 0.72 to 1.62 events) among 7220 patients receiving a DOAC (IRR, 1.66 [CI, 1.18 to 2.39]) (**Table 1**; **Supplement Tables 7** and **8**, available at Annals.org). The incidence rate of major bleeding with VKAs overlapped in each of the studied intervals of follow-up. The 5-year cumulative incidence of major bleeding with VKAs was 6.3% (CI, 3.6% to 10.0%) (**Table 1**). Data were insufficient to estimate incidence of major bleeding beyond 1 year of extended anticoagulation with DOACs.

Subgroup Analyses

In patients receiving a VKA, the incidence of major bleeding was statistically significantly higher among women than men (IRR, 1.55 [CI, 1.17 to 2.06]) (**Figure 2**), whereas in those receiving a DOAC, we found no statistically significant difference according to sex (IRR, 1.00 [CI, 0.51 to 1.95]). The 5-year cumulative incidence of major bleeding with VKAs was 8.5% (CI, 4.0% to 15.0%) in women and 6.5% (CI, 4.2% to 9.2%) in men (**Appendix Table 1**, available at Annals.org).

The incidence of major bleeding was statistically significantly higher among those older than 65 years than those aged 65 years or younger (IRR, 1.84 [CI, 1.32 to 2.57] with VKAs and 2.92 [CI, 1.50 to 5.70] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 8.3% (CI, 4.0% to 14.3%) among patients older than 65 years and 4.4% (CI, 2.5% to 6.7%) in those aged 65 years or younger (**Appendix Table 2**, available at Annals.org).

We found no statistically significant difference in the incidence of major bleeding between patients with initial isolated proximal DVT and those with isolated PE (IRR, 0.77 [CI, 0.54 to 1.09] for VKAs and 1.65 [CI, 0.49 to 8.66]

Table 1. Incidence of Major Bleeding*

Interval of Follow-up During Extended Anticoagulation	Study Cohorts, *n*	Events, *n*			Person-Years, *n*	Incidence Rate per 100 Person-Years (95% CI)		
		Major Bleeding	Intracranial Bleeding	Fatal Bleeding		Major Bleeding	Intracranial Bleeding	Fatal Bleeding
Overall								
VKA	24	207	37	15	12 251	1.74 (1.34–2.20)	0.39 (0.25–0.57)	0.16 (0.10–0.24)
DOAC	11	40	9	2	3934	1.12 (0.72–1.62)	0.29 (0.14–0.50)	0.10 (0.03–0.23)
Year 1								
VKA	24	128	26	9	6989	2.00 (1.56–2.50)	0.53 (0.35–0.74)	0.18 (0.10–0.30)
DOAC	11	40	9	2	3768	1.20 (0.74–1.77)	0.31 (0.15–0.53)	0.11 (0.03–0.24)
Year 2†								
VKA	18	48	7	2	2707	1.65 (0.99–2.48)	0.42 (0.20–0.72)	0.21 (0.07–0.41)
Years 3–5†								
VKA	5	31	4	4	2555	0.95 (0.35–1.83)	0.22 (0.08–0.44)	0.20 (0.07–0.42)

	Cumulative Incidence (95% CI), %		
	Major Bleeding	Intracranial Bleeding	Fatal Bleeding
After 2 y†			
VKA	3.6 (2.5–4.9)	0.9 (0.5–1.5)	0.4 (0.2–0.7)
After 5 y†			
VKA	6.3 (3.6–10.0)	1.6 (0.8–2.7)	1.0 (0.4–1.9)

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.
* I^2 range, 31%–54% for major bleeding and 0%–1% for intracranial and fatal bleeding.
† For DOACs in these follow-up intervals, data were insufficient to estimate incidence.

for DOACs); between patients with initial isolated proximal DVT and those with concomitant PE and DVT (IRR, 0.98 [CI, 0.67 to 1.42] with VKAs and 0.80 [CI, 0.34 to 2.10] with DOACs); or between patients with isolated PE and those with concomitant PE and DVT (IRR, 1.27 [CI, 0.88 to 1.85] with VKAs and 0.49 [CI, 0.83 to 2.02] with DOACs) (**Appendix Table 3**, available at Annals.org). The 5-year cumulative incidence of major bleeding with VKAs was 6.8% (CI, 2.5% to 14.0%) for patients with isolated proximal DVT, 7.6% (CI, 3.3% to 13.3%) for patients with isolated PE, and 7.9% (CI, 4.1% to 12.7%) for patients with concomitant PE and DVT (**Appendix Table 3**).

The incidence of major bleeding was statistically significantly higher among those with creatinine clearance less than 50 mL/min than those with creatinine clearance of 50 mL/min or higher (IRR, 2.83 [CI, 1.90 to 4.22] with VKAs and 3.71 [CI, 1.51 to 9.13] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 21.9% (CI, 7.8% to 40.2%) among patients with creatinine clearance less than 50 mL/min and 6.0% (CI, 4.0% to 8.5%) in those with creatinine clearance of 50 mL/min or higher (**Appendix Table 4**, available at Annals.org).

The incidence of major bleeding was statistically significantly higher among those with a history of bleeding than those without (IRR, 3.47 [CI, 1.86 to 6.50] with VKAs and 18.81 [CI, 9.54 to 37.07] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 20.9% (CI, 3.9% to 46.4%) among patients with a history of bleeding and 12.7% (CI, 2.5% to 33.4%) in those without (**Appendix Table 5**, available at Annals.org).

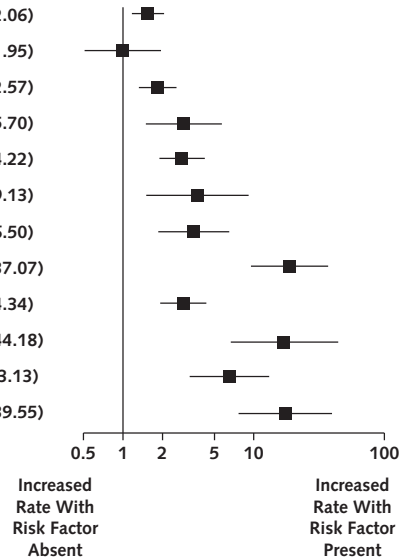
The incidence of major bleeding was statistically significantly higher among those with concomitant use of antiplatelet therapy than those without (IRR, 2.89 [CI, 1.93 to 4.34] with VKAs and 17.18 [CI, 6.68 to 44.18] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 15.6% (CI, 5.8% to 29.6%) among patients with concomitant use of antiplatelet therapy and 6.6% (CI, 3.9% to 9.9%) in those without (**Appendix Table 6**, available at Annals.org).

The incidence of major bleeding was statistically significantly higher among those with hemoglobin levels less than 100 g/L than those with hemoglobin levels of 100 g/L or higher (IRR, 6.51 [CI, 3.23 to 13.13] with VKAs and 17.41 [CI, 7.67 to 39.55] with DOACs) (**Figure 2**). The 5-year cumulative incidence of major bleeding with VKAs was 15.6% (3.8% to 57.2%) among patients with hemoglobin levels less than 100 g/L and 7.2% (4.5% to 10.6%) in those with hemoglobin levels of 100 g/L or higher (**Appendix Table 7**, available at Annals.org).

We found no statistically significant difference in the incidence of major bleeding between study cohorts derived from RCTs and those derived from prospective cohort studies (IRR, 1.10 [CI, 0.80 to 1.51] with VKAs and 0.59 [CI, 0.30 to 1.15] with DOACs) (**Appendix Table 8**, available at Annals.org). No RCTs had follow-up beyond 2 years of extended anticoagulation with VKAs (**Appendix Table 8**). The 5-year cumulative incidence of major bleeding with VKAs among cohorts derived from prospective cohort studies was 6.4% (CI, 3.2% to 10.6%) (**Appendix Table 8**).

Figure 2. Incidence of major bleeding, according to presence and absence of risk factors for major bleeding.

Risk Factor	Study Cohorts, *n*	Major Bleeding Events/Person-Years, *n*/*N*		Incidence Rate per 100 Person-Years (95% CI)		IRR (95% CI)
		Risk Factor Present	Risk Factor Absent	Risk Factor Present	Risk Factor Absent	
Female sex						
VKA	23	94/4476	109/7685	2.02 (1.38–2.78)	1.55 (1.20–1.94)	1.55 (1.17–2.06)
DOAC	11	15/1483	26/2450	1.22 (0.67–1.93)	1.16 (0.70–1.72)	1.00 (0.51–1.95)
Age >65 y						
VKA	22	105/4964	74/6664	1.98 (1.41–2.64)	1.22 (0.87–1.63)	1.84 (1.32–2.57)
DOAC	11	25/1332	15/2606	2.01 (1.26–2.94)	0.66 (0.38–1.02)	2.92 (1.50–5.70)
Creatinine clearance <50 mL/min						
VKA	12	28/816	119/7853	2.89 (1.53–4.67)	1.58 (1.12–2.12)	2.83 (1.90–4.22)
DOAC	7	2/227	27/2642	1.41 (0.30–3.32)	1.13 (0.57–1.87)	3.71 (1.51–9.13)
History of bleeding						
VKA	10	8/230	119/6546	4.08 (1.97–6.91)	1.75 (1.23–2.35)	3.47 (1.86–6.50)
DOAC	10	9/102	27/3497	9.19 (4.13–16.0)	0.85 (0.55–1.21)	18.81 (9.54–37.07)
Concomitant antiplatelet therapy						
VKA	15	31/806	145/8689	3.98 (2.52–5.76)	1.61 (1.19–2.08)	2.89 (1.93–4.34)
DOAC	10	3/144	33/3385	3.45 (1.16–6.90)	1.05 (0.56–1.70)	17.18 (6.68–44.18)
Hemoglobin level <100 g/L						
VKA	12	7/333	139/8578	2.73 (1.13–4.98)	1.45 (0.92–2.10)	6.51 (3.23–13.13)
DOAC	9	2/80	29/3235	4.03 (0.96–9.07)	1.00 (0.59–1.52)	17.41 (7.67–39.55)



I2 = 0% for all IRRs. DOAC = direct oral anticoagulant; IRR = incidence rate ratio; VKA = vitamin K antagonist.

Case-Fatality Rate of Major Bleeding

The pooled case-fatality rate of major bleeding was 8.3% (CI, 5.1% to 12.2%) among patients receiving a VKA and 9.7% (CI, 3.2% to 19.2%) among those receiving a DOAC (Table 2; Supplement Table 9, available at Annals.org).

Sensitivity Analyses

Estimates of major bleeding rates in the primary analyses did not differ from those in analyses restricted to studies in which the duration of initial anticoagulant treatment was exclusively 3 months or to studies that used the ISTH definition of major bleeding (Supplement Tables 6 and 7).

Discussion

In this systematic review and meta-analysis of 27 studies and 17 202 patients with a first unprovoked or weakly provoked VTE receiving extended anticoagulant therapy, we found that the incidence of major bleeding per 100 person-years was 1.7 events with VKAs and 1.1 events with DOACs. The 5-year cumulative incidence of major bleeding with VKAs was 6%. In patients receiving either a VKA or a DOAC, the incidence of major bleeding was statistically significantly higher among those who were older than 65 years or had creatinine clearance less than 50 mL/min, history of bleeding, concomitant use of antiplatelet therapy, or a hemoglobin level less than 100 g/L.

We also provide contemporary estimates for the clinical effect of anticoagulant-related major bleeding, defined as risk for intracranial and fatal bleeding, as well as the case-fatality rate of major bleeding. Of note, in our meta-analysis of patients with VTE, the case-fatality rate of major bleeding seemed to be similar with DOACs (9.7% [CI, 3.2% to 19.2%]) and VKAs (8.3% [CI, 5.1% to 12.2%])—a finding different from that reported in a previous meta-analysis of phase 3 RCTs comparing DOACs (7.6% [CI, 6.5% to 8.7%]) with VKAs (11.0% [CI, 9.2% to 13.1%]) in patients with atrial fibrillation (55).

Given the need for precise estimates of the absolute long-term risk and case-fatality rate of major bleeding during extended anticoagulant therapy to guide decisions about treatment duration in unprovoked VTE, our findings are likely to affect clinical practice. For patients with a first unprovoked proximal DVT or PE who have completed at least 3 to 6 months of initial treatment, the 2016 guidelines from the American College of Chest Physicians and 2020 guidelines from the American Society of Hematology suggest continuing anticoagulation indefinitely over discontinuing it, except for those considered to have high risk for major bleeding (5, 6). Because the case-fatality rate of major bleeding is 2- to 3-fold higher than that of recurrent VTE (10), it has been proposed that patients with a major bleeding risk of 3% or higher per year be classified as having high risk and thus not be considered for indefinite anticoagulation, regardless of their risk for recurrent VTE (5, 56, 57). However, no standardized approach currently exists to

Table 2. Case-Fatality Rate of Major Bleeding*

Type of Anticoagulant	Study Cohorts, *n*	Fatal Bleeding Events, *n*	Major Bleeding Events, *n*	Case-Fatality Rate (95% CI), %
Any	33	17	247	8.4 (5.4–12.1)
Vitamin K antagonists	22	15	207	8.3 (5.1–12.2)
Direct oral anticoagulants	11	2	40	9.7 (3.2–19.2)

* I^2 = 0% for all case-fatality rates.

identify such a subgroup of patients with unprovoked VTE. Expert consensus opinion and previous individual studies aimed at identifying patients with VTE at high risk for anticoagulant-related major bleeding have proposed that female sex, advanced age (such as >65 years), renal insufficiency, history of bleeding, concomitant use of antiplatelet therapy, and anemia are common independent risk factors for bleeding (56–59). The American College of Chest Physicians guidelines suggest that the prevalence of these risk factors could be used to categorize the risk for bleeding as low (no risk factors) or high (≥2 risk factors) (5). Our meta-analysis supports the existence of a clinically meaningful difference in long-term risk for anticoagulant-related major bleeding among patients with a first unprovoked VTE stratified according to presence or absence of the following risk factors: age older than 65 years, creatinine clearance less than 50 mL/min, history of bleeding, concomitant use of antiplatelet therapy, and hemoglobin level less than 100 g/L.

Taken together, our results provide clinicians, patients, and policymakers with a management framework in which to consider the long-term risks for and consequences of major bleeding if anticoagulation is continued beyond the initial 3 to 6 months. When weighed against the long-term risks for and consequences of recurrent VTE if anticoagulation is discontinued, our results could be used to balance the benefits and harms of extended anticoagulation for unprovoked VTE. For example, a patient with a first unprovoked VTE who has completed at least 3 months of initial anticoagulant treatment and either is receiving concomitant antiplatelet therapy or has a history of bleeding (factors associated with a point estimate for major bleeding risk ≥3% per year in our analysis) may not be a candidate for extended anticoagulation with a VKA: If anticoagulation is discontinued, the risk for death from recurrent VTE at 5 years would be about 1.0% (25% risk for recurrent VTE at 5 years multiplied by 4% case-fatality rate of recurrent VTE) (10); if anticoagulation is continued, the risk for death from major bleeding at 5 years would be greater than 1.2% (>15% risk for major bleeding at 5 years multiplied by 8% case-fatality rate of major bleeding, as determined in our analysis). Over a 10-year horizon, the risk for death from recurrent VTE if anticoagulation is discontinued would be about 1.4% (36% risk for recurrent VTE at 10 years multiplied by 4% case-fatality rate of recurrent VTE) (10) and the risk for death from major bleeding if anticoagulation is continued would be greater than 2.4% (>30% risk at 10 years multiplied by 8% case-fatality rate of major bleeding).

Last, we found that the incidence of major bleeding during extended anticoagulation is lower with DOACs than VKAs—a finding consistent with that established for the initial treatment of VTE (60). However, in our analysis, only 1 study cohort exclusively received extended anticoagulation with DOACs beyond 13 months. As such, our systematic review emphasizes the need for future prospective studies focused on establishing the long-term (beyond 1 year of extended anticoagulation) risk for major bleeding with DOACs.

Our study has several notable strengths. First, our systematic review involved a comprehensive search and included unpublished data from studies with an overall low risk of bias. Second, many of the included studies had a heterogeneous patient population that included persons with VTE provoked by major transient or persistent risk factors, as well as those with a history of VTE. However, with help from principal investigators of included studies, we extracted and combined data on more than 17 000 patients who had a first episode of unprovoked or weakly provoked VTE and were prospectively followed for major bleeding during extended anticoagulant therapy with a VKA or DOAC. Moreover, we standardized durations of follow-up across study cohorts and used exact person-time at risk during each of the studied intervals to assess the risk for major bleeding over time, and we compared bleeding risks in several patient subgroups that are clinically important.

Limitations of this study include limited data (from insufficient number of studies) to compare bleeding risk between reduced- and therapeutic-dose DOACs and limited data beyond 1 year of extended anticoagulation with DOACs. Most DOAC cohorts included in our analysis received extended anticoagulation with rivaroxaban; thus, our estimates for the incidence of major bleeding with DOACs may not always be generalizable to all DOACs. Also, we found moderate statistical heterogeneity for the primary outcome of major bleeding; however, this heterogeneity was largely explained through the various prespecified subgroup and sensitivity analyses. Moreover, we used the DerSimonian–Laird random-effects model, which may have underestimated the true between-study variance, potentially producing overly narrow 95% CIs for our meta-analyses involving fewer than 10 study cohorts and moderate statistical heterogeneity (61). Finally, owing to constraints in time; resource use; and access to raw, individual-level data, particularly from the included industry-sponsored studies, we did not do an individual-patient data meta-analysis, which would have allowed us to compute direct estimates of the cumulative incidence over time and adjust estimates by various risk factors (and potential interactions between risk factors).

In conclusion, this systematic review and meta-analysis determined the risk for major bleeding during extended anticoagulation of up to 5 years among patients with a first unprovoked VTE and in clinically important subgroups. Findings from this study will help inform physician–patient discussions about long-term risks and consequences of anticoagulant-related major bleeding and help balance the net benefits and

harms of extended anticoagulation to guide treatment duration for unprovoked VTE.

From University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada (F.K., K.T., B.H.); Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (T.T., D.A.); Ottawa Hospital Research Institute, University of Ottawa, and The Ottawa Hospital, Ottawa, Ontario, Canada (M.K., P.S.W., G.L.); McMaster University and Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada (C.K., J.I.W.); Amsterdam University Medical Center, Amsterdam Cardiovascular Sciences, Amsterdam, the Netherlands (H.R.B.); University of Oklahoma Health Sciences Center, Hudson College of Public Health, Oklahoma City, Oklahoma (G.E.R.); University of Insubria, Varese, Italy (W.A.); Brest University Hospital, Brest, France (F.C.); Arianna Foundation on Anticoagulation, Bologna, Italy (P.P., G.P., C.L.); Medical University of Vienna, Vienna, Austria (P.A.K., S.E., L.E.); University of Perugia, Perugia, Italy (C.B., G.A., M.C.V.); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (G.G., T.T.); Sant'Orsola-Malpighi University Hospital, Bologna, Italy (B.C.); University of Pisa, Pisa, Italy (L.M., A.P.); University of Palermo, Palermo, Italy (S.S.); University of Bristol, Bristol, United Kingdom (C.A.B.); McMaster University, Hamilton, Ontario, Canada (S.P.); Ottawa Hospital Research Institute, Ottawa, Ontario, Canada (R.M.); Bayer, Wuppertal, Germany (A.W.L., M.G.); Daiichi Sankyo, Basking Ridge, New Jersey (M.A.G.); University of Ottawa, Ottawa Hospital Research Institute, and The Ottawa Hospital, Ottawa, Ontario, Canada (D.A.F.); and Ottawa Hospital Research Institute, Ottawa, Ontario, and McGill University, Montreal, Quebec, Canada (M.A.R.).

Financial Support: Mr. Khan and Drs. Tritschler, Kimpton, Wells, Kearon, Weitz, Parpia, Thavorn, Le Gal, Fergusson, and Rodger are members of the CanVECTOR Network; the Network receives grant funding from the Canadian Institutes of Health Research (CDT-142654). Mr. Khan holds the Frederick Banting and Charles Best doctoral research scholarship from the Canadian Institutes of Health Research. Dr. Weitz holds the Canada Research Chair (Tier I) in Thrombosis and the Heart and Stroke Foundation of Canada J.F. Mustard Chair in Cardiovascular Research. Dr. Tritschler held an Early Postdoc.Mobility Award from the Swiss National Science Foundation (SNSF P2ZHP3_177999) and a Fellowship Award from the CanVECTOR Network. Dr. Le Gal holds the Chair on Diagnosis of Venous Thromboembolism at the Department of Medicine, University of Ottawa, and a Clinician-Scientist Award from the Heart and Stroke Foundation of Canada. Dr. Rodger is the McGill University Harry Webster Thorp Professor of Medicine.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-1094.

Reproducible Research Statement: *Study protocol*: Registered at PROSPERO (CRD42019128597). *Statistical code*: Not available. *Data set*: See Supplement Tables (available at Annals.org) for data from individual studies.

Corresponding Author: Faizan Khan, MSc, Center for Practice Changing Research, The Ottawa Hospital - General Campus, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada; e-mail, fakhan@ohri.ca.

Current author addresses and author contributions are available at Annals.org.

References

1. **Heit JA.** Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12:464-74. [PMID: 26076949] doi:10.1038/nrcardio.2015.83

2. **ISTH Steering Committee for World Thrombosis Day.** Thrombosis: a major contributor to global disease burden. Thromb Res. 2014;134:931-8. [PMID: 25312343] doi:10.1016/j.thromres.2014.08.014

3. **Khan F, Tritschler T, Kahn SR, et al.** Venous thromboembolism. Lancet. 2021;398:64-77. [PMID: 33984268] doi:10.1016/S0140-6736(20)32658-1

4. **Tritschler T, Kraaijpoel N, Le Gal G, et al.** Venous thromboembolism: advances in diagnosis and treatment. JAMA. 2018;320:1583-1594. [PMID: 30326130] doi:10.1001/jama.2018.14346

5. **Kearon C, Akl EA, Ornelas J, et al.** Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149:315-352. [PMID: 26867832] doi:10.1016/j.chest.2015.11.026

6. **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;4:4693-4738. [PMID: 33007077] doi:10.1182/bloodadvances.2020001830

7. **Boutitie F, Pinede L, Schulman S, et al.** Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. BMJ. 2011;342:d3036. [PMID: 21610040] doi:10.1136/bmj.d3036

8. **Linkins LA, Choi PT, Douketis JD.** Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism. A meta-analysis. Ann Intern Med. 2003;139:893-900. [PMID: 14644891]

9. **Konstantinides SV, Meyer G, Becattini C, et al; ESC Scientific Document Group.** 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543-603. [PMID: 31504429] doi:10.1093/eurheartj/ehz405

10. **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. [PMID: 31340984] doi:10.1136/bmj.l4363

11. **Couturaud F, Sanchez O, Pernod G, et al; PADIS-PE Investigators.** Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized clinical trial. JAMA. 2015;314:31-40. [PMID: 26151264] doi:10.1001/jama.2015.7046

12. **Wang KL, van Es N, Cameron C, et al.** Extended treatment of venous thromboembolism: a systematic review and network meta-analysis. Heart. 2019;105:545-552. [PMID: 30327391] doi:10.1136/heartjnl-2018-313617

13. **Khan F, Kimpton M, Tritschler T, et al.** Risk of major bleeding during extended oral anticoagulation in patients with first unprovoked venous thromboembolism: a systematic review and meta-analysis protocol. Syst Rev. 2019;8:245. [PMID: 31661033] doi:10.1186/s13643-019-1175-5

14. **Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group.** Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264-9, W64. [PMID: 19622511]

15. **Wells GA, Shea B, O'Connell D, et al.** The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.asp on 28 December 2020.
16. **Douketis J, Tosetto A, Marcucci M, et al.** Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. BMJ. 2011;342:d813. [PMID: 21349898] doi:10.1136/bmj.d813
17. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88. [PMID: 3802833]
18. **Higgins JP, Thompson SG, Deeks JJ, et al.** Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. [PMID: 12958120]
19. StatsDirect. StatsDirect statistical software. Accessed atwww.statsdirect.com on 20 July 2021.
20. **Palareti G, Leali N, Coccheri S, et al; Italian Study on Complications of Oral Anticoagulant Therapy.** Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Lancet. 1996;348:423-8. [PMID: 8709780]
21. **Kearon C, Ginsberg JS, Kovacs MJ, et al; Extended Low-Intensity Anticoagulation for Thrombo-Embolism Investigators.** Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003;349:631-9. [PMID: 12917299]
22. **Ridker PM, Goldhaber SZ, Danielson E, et al; PREVENT Investigators.** Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003;348:1425-34. [PMID: 12601075]
23. **Kurtoglu M, Koksoy C, Hasan E, et al; TROMBOTEK Study Group.** Long-term efficacy and safety of once-daily enoxaparin plus warfarin for the outpatient ambulatory treatment of lower-limb deep vein thrombosis in the TROMBOTEK trial. J Vasc Surg. 2010;52:1262-70. [PMID: 20732787] doi:10.1016/j.jvs.2010.06.070
24. **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. [PMID: 23216615] doi:10.1056/NEJMoa1207541
25. **Schulman S, Kearon C, Kakkar AK, et al; RE-MEDY Trial Investigators.** Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368:709-18. [PMID: 23425163] doi:10.1056/NEJMoa1113697
26. **Poli D, Antonucci E, Testa S, et al; FCSA Italian Federation of Anticoagulation Clinics.** The predictive ability of bleeding risk stratification models in very old patients on vitamin K antagonist treatment for venous thromboembolism: results of the prospective collaborative EPICA study. J Thromb Haemost. 2013;11:1053-8. [PMID: 23578305] doi:10.1111/jth.12239
27. **Zenati N, Gaboreau Y, Provencher CB, et al.** Anaemia as an independent key risk factor for major haemorrhage in patients treated with vitamin K antagonists: results of the SCORE prospective cohort. Thromb Res. 2017;151:83-88. [PMID: 28109541] doi:10.1016/j.thromres.2016.10.027
28. **Rief P, Raggam RB, Hafner F, et al.** Calculation of HAS-BLED score is useful for early identification of venous thromboembolism patients at high risk for major bleeding events: a prospective outpatients cohort study. Semin Thromb Hemost. 2018;44:348-352. [PMID: 29165742] doi:10.1055/s-0037-1607433
29. **Agnelli G, Prandoni P, Santamaria MG, et al; Warfarin Optimal Duration Italian Trial Investigators.** Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. N Engl J Med. 2001;345:165-9. [PMID: 11463010]
30. **Agnelli G, Prandoni P, Becattini C, et al; Warfarin Optimal Duration Italian Trial Investigators.** Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med. 2003;139:19-25. [PMID: 12834314]
31. **Palareti G, Cosmi B, Legnani C, et al; PROLONG Investigators.** D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med. 2006;355:1780-9. [PMID: 17065639]
32. **Prandoni P, Prins MH, Lensing AW, et al; AESOPUS Investigators.** Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis. A randomized trial. Ann Intern Med. 2009;150:577-85. [PMID: 19414836]
33. **Eischer L, Gartner V, Schulman S, et al; AUREC-FVIII investigators.** 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol. 2009;88:485-90. [PMID: 18931845] doi:10.1007/s00277-008-0626-1
34. **Palla A, Ribas C, Rossi G, et al.** The clinical course of pulmonary embolism patients anticoagulated for 1 year: results of a prospective, observational, cohort study. J Thromb Haemost. 2010;8:68-74. [PMID: 19817998] doi:10.1111/j.1538-7836.2009.03647.x
35. **Cosmi B, Legnani C, Tosetto A, et al; PROLONG Investigators (on behalf of Italian Federation of Anticoagulation Clinics).** Usefulness of repeated D-dimer testing after stopping anticoagulation for a first episode of unprovoked venous thromboembolism: the PROLONG II prospective study. Blood. 2010;115:481-8. [PMID: 19965693] doi:10.1182/blood-2009-08-237354
36. **Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators.** Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499-510. [PMID: 21128814] doi:10.1056/NEJMoa1007903
37. **Siragusa S, Malato A, Saccullo G, et al.** Residual vein thrombosis for assessing duration of anticoagulation after unprovoked deep vein thrombosis of the lower limbs: the extended DACUS study. Am J Hematol. 2011;86:914-7. [PMID: 21953853] doi:10.1002/ajh.22156
38. **Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators.** Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287-97. [PMID: 22449293] doi:10.1056/NEJMoa1113572
39. **Palareti G, Cosmi B, Legnani C, et al; DULCIS (D-dimer and ULtrasonography in Combination Italian Study) Investigators.** D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. Blood. 2014;124:196-203. [PMID: 24879813] doi:10.1182/blood-2014-01-548065
40. **Kearon C, Spencer FA, O'Keeffe D, et al; D-dimer Optimal Duration Study Investigators.** D-dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy. A cohort study. Ann Intern Med. 2015;162:27-34. [PMID: 25560712] doi:10.7326/M14-1275
41. **Marconi L, Carrozzi L, Aquilini F, et al.** Five-year follow-up of pulmonary embolism under anticoaugulation: the PISA-PEET (Pulmonary Embolism Extension Therapy) Study. Medicine (Baltimore). 2016;95:e4364. [PMID: 27559946] doi:10.1097/MD.0000000000004364
42. **Hofmann E, Faller N, Limacher A, et al.** Educational level, anticoagulation quality, and clinical outcomes in elderly patients with acute venous thromboembolism: a prospective cohort study. PLoS One. 2016;11:e0162108. [PMID: 27606617] doi:10.1371/journal.pone.0162108
43. **Ageno W, Mantovani LG, Haas S, et al.** Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol. 2016;3:e12-21. [PMID: 26765643] doi:10.1016/S2352-3026(15)00257-4
44. **Raskob G, Ageno W, Cohen AT, et al.** Extended duration of anticoagulation with edoxaban in patients with venous thromboembolism: a post-hoc analysis of the Hokusai-VTE study. Lancet Haematol. 2016;3:e228-36. [PMID: 27132697] doi:10.1016/S2352-3026(16)00023-5
45. **Prandoni P, Vedovetto V, Ciammaichella M, et al; Morgagni Investigators.** Residual vein thrombosis and serial D-dimer for the long-term management of patients with deep venous thrombosis. Thromb

Res. 2017;154:35-41. [PMID: 28407492] doi:10.1016/j.thromres.2017.04.002

46. **Rodger MA, Le Gal G, Anderson DR, et al; REVERSE II Study Investigators.** Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. BMJ. 2017;356:j1065. [PMID: 28314711] doi:10.1136/bmj.j1065

47. **Weitz JI, Lensing AWA, Prins MH, et al; EINSTEIN CHOICE Investigators.** Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med. 2017;376:1211-1222. [PMID: 28316279] doi:10.1056/NEJMoa1700518

48. **Kreutz R, Mantovani LG, Haas S, et al.** XALIA-LEA: an observational study of venous thromboembolism treatment with rivaroxaban and standard anticoagulation in the Asia-Pacific, Eastern Europe, the Middle East, Africa and Latin America. Thromb Res. 2019;176:125-132. [PMID: 30825694] doi:10.1016/j.thromres.2019.02.010

49. **Couturaud F, Pernod G, Presles E, et al; "PADIS-DVT" investigators.** Six months versus two years of oral anticoagulation after a first episode of unprovoked deep-vein thrombosis. The PADIS-DVT randomized clinical trial. Haematologica. 2019;104:1493-1501. [PMID: 30606789] doi:10.3324/haematol.2018.210971

50. **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;188:962-975. [PMID: 31713863] doi:10.1111/bjh.16275

51. **Geersing GJ, Hendriksen JMT, Zuithoff NPA, et al.** Effect of tailoring anticoagulant treatment duration by applying a recurrence risk prediction model in patients with venous thromboembolism compared to usual care: a randomized controlled trial. PLoS Med. 2020;17:e1003142. [PMID: 32589630] doi:10.1371/journal.pmed.1003142

52. **Vedovati MC, Mancuso A, Pierpaoli L, et al.** Prediction of major bleeding in patients receiving DOACs for venous thromboembolism: a prospective cohort study. Int J Cardiol. 2020;301:167-172. [PMID: 31761402] doi:10.1016/j.ijcard.2019.11.105

53. **Wells PS, Kovacs MJ, Anderson D, et al.** Prediction of bleeding risk in patients on extended oral anticoagulation for venous thromboembolism [Abstract]. Blood. 2016;128:139. Abstract no. 332. doi:10.1182/blood.V128.22.139.139

54. **Kearon C, Gent M, Hirsh J, et al.** A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med. 1999;340:901-7. [PMID: 10089183]

55. **Chai-Adisaksopha C, Hillis C, Isayama T, et al.** Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost. 2015;13:2012-20. [PMID: 26356595] doi:10.1111/jth.13139

56. **Kimpton M, Rodger MA.** Web exclusive. Annals for Hospitalists inpatient notes - can I withdraw anticoagulants in this patient with prior venous thromboembolism. Ann Intern Med. 2020;172:HO2-HO3. [PMID: 32539500] doi:10.7326/M20-1253

57. **Kearon C, Kahn SR.** Long-term treatment of venous thromboembolism. Blood. 2020;135:317-325. [PMID: 31917402] doi:10.1182/blood.2019002364

58. **Klok FA, Huisman MV.** How I assess and manage the risk of bleeding in patients treated for venous thromboembolism. Blood. 2020;135:724-734. [PMID: 31951652] doi:10.1182/blood.2019001605

59. **Klok FA, Kooiman J, Huisman MV, et al.** Predicting anticoagulant-related bleeding in patients with venous thromboembolism: a clinically oriented review. Eur Respir J. 2015;45:201-10. [PMID: 25102964] doi:10.1183/09031936.00040714

60. **van Es N, Coppens M, Schulman S, et al.** Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124:1968-75. [PMID: 24963045] doi:10.1182/blood-2014-04-571232

61. **Veroniki AA, Jackson D, Viechtbauer W, et al.** Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods. 2016;7:55-79. [PMID: 26332144] doi:10.1002/jrsm.1164

Current Author Addresses: Mr. Khan and Drs. Kimpton, Wells, Mallick, Thavorn, Hutton, Le Gal, and Fergusson: The Ottawa Hospital, General Campus, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada.
Drs. Tritschler and Aujesky: Inselspital, Bern University Hospital, Freiburgstrasse, 3010 Bern, Switzerland.
Drs. Kearon and Weitz: David Braley Research Institute C5-121, 237 Barton Street East, Hamilton, ON L8L 2X2, Canada.
Dr. Büller: Amsterdam University Medical Centre, De Boelelaan 1117, 1118, 1081 HV Amsterdam, the Netherlands.
Dr. Raskob: Hudson College of Public Health, University of Oklahoma Health Sciences Center, 801 NE 13th Street, Oklahoma City, OK 73104.
Dr. Ageno: University of Insubria, Via Ravasi, 2, 21100 Varese, Italy.
Dr. Couturaud: Brest University Hospital, 2 Avenue Foch, 29200 Brest, France.
Drs. Prandoni, Palareti, and Legnani: Arianna Foundation on Anticoagulation, Via Paolo Fabbri, 1/3, 40138 Bologna, Italy.
Drs. Kyrle, Eichinger, and Eischer: Medical University of Vienna, Spitalgasse 23, 1090 Wien, Austria.
Drs. Becattini, Agnelli, and Vedovati: University of Perugia, 1, 06123 Perugia, Italy.
Drs. Geersing and Takada: University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
Dr. Cosmi: Sant'Orsola-Malpighi University Hospital, Via Giuseppe Massarenti, 9, 40138 Bologna, Italy.
Drs. Marconi and Palla: University of Pisa, Lungarno Antonio Pacinotti, 43, 56126 Pisa, Italy.
Dr. Siragusa: University of Palermo, Piazza Marina, 61, 90133 Palermo, Italy.
Dr. Bradbury: School of Cellular and Molecular Medicine, University of Bristol, Bristol University Walk, Bristol BS8 1TD, United Kingdom.
Dr. Parpia: McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada.
Drs. Lensing and Gebel: Bayer, Friedrich-Ebert-Straße 217/333, 42117 Wuppertal, Germany.
Dr. Grosso: Daiichi Sankyo, 211 Mt Airy Road, Basking Ridge, NJ 07920.
Dr. Rodger: McGill University, 1001 Decarie Boulevard, D05-2212, Montreal, QC H4A 3J1, Canada.

Author Contributions: Conception and design: F. Khan, T. Tritschler, M. Kimpton, B. Hutton, G. Le Gal, D.A. Fergusson, M. A. Rodger.
Analysis and interpretation of the data: F. Khan, T. Tritschler, M. Kimpton, P.S. Wells, C. Kearon, J.I. Weitz, H.R. Büller, G.E. Raskob, W. Ageno, F. Couturaud, P. Prandoni, G. Palareti, C. Legnani, P.A. Kyrle, S. Eichinger, L. Eischer, C. Becattini, G. Agnelli, M.C. Vedovati, G.J. Geersing, T. Takada, B. Cosmi, D. Aujesky, L. Marconi, A. Palla, S. Siragusa, C.A. Bradbury, S. Parpia, R. Mallick, A.W.A. Lensing, M. Gebel, M.A. Grosso, K. Thavorn, B. Hutton, G. Le Gal, D.A. Fergusson, M.A. Rodger.
Drafting of the article: F. Khan, T. Tritschler, D.A. Fergusson, M. A. Rodger.
Critical revision of the article for important intellectual content: F. Khan, T. Tritschler, M. Kimpton, P.S. Wells, C. Kearon, J.I. Weitz, H.R. Büller, G.E. Raskob, W. Ageno, F. Couturaud, P. Prandoni, G. Palareti, C. Legnani, P.A. Kyrle, S. Eichinger, L. Eischer, C. Becattini, G. Agnelli, M.C. Vedovati, G.J. Geersing, T. Takada, B. Cosmi, D. Aujesky, L. Marconi, A. Palla, S. Siragusa, C.A. Bradbury, S. Parpia, R. Mallick, A.W.A. Lensing, M. Gebel, M.A. Grosso, K. Thavorn, B. Hutton, G. Le Gal, D.A. Fergusson, M.A. Rodger.
Final approval of the article: F. Khan, T. Tritschler, M. Kimpton, P.S. Wells, C. Kearon, J.I. Weitz, H.R. Büller, G.E. Raskob, W. Ageno, F. Couturaud, P. Prandoni, G. Palareti, C. Legnani, P.A. Kyrle, S. Eichinger, L. Eischer, C. Becattini, G. Agnelli, M.C. Vedovati, G.J. Geersing, T. Takada, B. Cosmi, D. Aujesky, L. Marconi, A. Palla, S. Siragusa, C.A. Bradbury, S. Parpia, R. Mallick, A.W.A. Lensing, M. Gebel, M.A. Grosso, K. Thavorn, B. Hutton, G. Le Gal, D.A. Fergusson, M.A. Rodger.
Provision of study materials or patients: P.S. Wells, C. Kearon, J. I. Weitz, H.R. Büller, G.E. Raskob, W. Ageno, F. Couturaud, P. Prandoni, G. Palareti, C. Legnani, P.A. Kyrle, S. Eichinger, L. Eischer, C. Becattini, G. Agnelli, M.C. Vedovati, G.J. Geersing, T. Takada, B. Cosmi, D. Aujesky, L. Marconi, A. Palla, S. Siragusa, C.A. Bradbury, S. Parpia, R. Mallick, A.W.A. Lensing, M. Gebel, M.A. Grosso, M.A. Rodger.
Statistical expertise: S. Parpia, R. Mallick, M. Gebel, K, Thavorn, B. Hutton, D.A. Fergusson.
Obtaining of funding: F. Khan, M.A. Rodger.
Administrative, technical, or logistic support: F. Khan, G. Le Gal, D.A. Fergusson, M.A. Rodger.
Collection and assembly of data: F. Khan.

Appendix Table 1. Risk for Major Bleeding: According to Sex

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events/Person-Years, *n/N*		Incidence Rate per 100 Person-Years (95% CI)	
	Women	Men	Women	Men
Year 1				
VKA	58/2565	66/4337	2.38 (1.76–3.08); I^2 = 11%	1.78 (1.30–2.33); I^2 = 23%
DOAC	15/1422	26/2345	1.29 (0.70–2.06); I^2 = 20%	1.22 (0.70–1.87); I^2 = 37%
Year 2				
VKA	21/1017	27/1690	2.06 (1.11–3.29); I^2 = 19%	1.78 (1.21–2.47); I^2 = 0%
DOAC*	–	–	–	–
Years 3–5				
VKA	15/892	16/1663	1.44 (0.38–3.19); I^2 = 53%	1.02 (0.60–1.57); I^2 = 0%
DOAC*	–	–	–	–

	Cumulative Incidence (95% CI), %	
	Women	Men
After 2 y		
VKA	4.4 (2.9–6.3)	3.5 (2.5–4.7)
DOAC*	–	–
After 5 y		
VKA	8.5 (4.0–15.0)	6.5 (4.2–9.2)
DOAC*	–	–

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.
* Data were insufficient to estimate incidence.

Appendix Table 2. Risk for Major Bleeding: According to Age

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events/Person-Years, *n/N*		Incidence Rate per 100 Person-Years (95% CI)	
	Age >65 y	Age ≤65 y	Age >65 y	Age ≤65 y
Year 1				
VKA	58/2776	53/3825	2.16 (1.49–2.95); I^2 = 31%	1.50 (1.14–1.91); I^2 = 0%
DOAC	25/1277	15/2494	2.09 (1.27–3.11); I^2 = 25%	0.72 (0.39–1.16); I^2 = 17%
Year 2				
VKA	26/1103	13/1433	2.17 (1.20–3.40); I^2 = 21%	1.04 (0.58–1.63); I^2 = 0%
DOAC*	–	–	–	–
Years 3–5				
VKA	21/1080	8/1406	1.43 (0.45–2.96); I^2 = 56%	0.63 (0.28–1.11); I^2 = 0%
DOAC*	–	–	–	–

	Cumulative Incidence (95% CI), %	
	Age >65 y	Age ≤65 y
After 2 y		
VKA	4.3 (2.7–6.2)	2.5 (1.7–3.5)
DOAC*	–	–
After 5 y		
VKA	8.3 (4.0–14.3)	4.4 (2.5–6.7)
DOAC*	–	–

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.
* Data were insufficient to estimate incidence.

Appendix Table 3. Risk for Major Bleeding: According to Site of Initial Venous Thromboembolism

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events/Person-Years, *n/N*			Incidence Rate per 100 Person-Years (95% CI)		
	Isolated Proximal DVT	Isolated PE	Concomitant PE and DVT	Isolated Proximal DVT	Isolated PE	Concomitant PE and DVT
Overall						
VKA	68/4556	69/3547	54/3535	1.49 (1.16–1.89)	1.95 (1.51–2.46)	1.53 (1.15–1.99)
DOAC	20/2040	3/504	8/652	0.98 (0.60–1.51)	0.60 (0.12–1.74)	1.23 (0.53–2.42)
Year 1						
VKA	47/3054	41/1846	25/1639	1.68 (1.25–2.16); I^2 = 0%	2.27 (1.20–3.66); I^2 = 58%	1.73 (1.16–2.41); I^2 = 0%
DOAC	20/1997	3/456	8/578	1.17 (0.45–2.24); I^2 = 66%	0.97 (0.28–2.08); I^2 = 0%	1.45 (0.30–3.11); I^2 = 54%
Year 2						
VKA	12/907	19/847	16/865	1.61 (0.89–2.52); I^2 = 0%	2.14 (1.03–3.62); I^2 = 29%	2.24 (0.76–4.47); I^2 = 30%
DOAC*	–	–	–	–	–	–
Years 3–5						
VKA	9/595	9/854	13/1031	1.22 (0.13–3.39); I^2 = 55%	1.13 (0.38–2.28); I^2 = 30%	1.38 (0.76–2.18); I^2 = 0%
DOAC*	–	–	–	–	–	–

	Cumulative Incidence (95% CI), %		
	Isolated Proximal DVT	Isolated PE	Concomitant PE and DVT
After 2 y			
VKA	3.3 (2.1–4.6)	4.4 (2.2–7.1)	3.9 (1.9–6.8)
DOAC*	–	–	–
After 5 y			
VKA	6.8 (2.5–14.0)	7.6 (3.3–13.3)	7.9 (4.1–12.7)
DOAC*	–	–	–

DOAC = direct oral anticoagulant; DVT = deep venous thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonist.
* Data were insufficient to estimate incidence.

Appendix Table 4. Risk for Major Bleeding: According to Creatinine Clearance

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events /Person-Years, *n/N*		Incidence Rate per 100 Person-Years (95% CI)	
	Creatinine Clearance <50 mL/min	Creatinine Clearance 50 mL/min	Creatinine Clearance <50 mL/min	Creatinine Clearance 50 mL/min
Year 1				
VKA	10/437	70/4030	2.74 (1.42–4.46); I^2 = 0%	1.80 (1.36–2.31); I^2 = 14%
DOAC	2/224	32/3216	1.54 (0.36–3.54); I^2 = 0%	1.13 (0.63–1.77); I^2 = 54%
Year 2				
VKA	9/187	27/1761	5.33 (2.60–8.96); I^2 = 0%	1.04 (0.58–1.63); I^2 = 0%
DOAC*	–	–	–	–
Years 3–5				
VKA	9/192	22/2059	5.33 (1.35–11.75); I^2 = 55%	1.12 (0.71–1.62); I^2 = 0%
DOAC*	–	–	–	–

	Cumulative Incidence (95% CI), %	
	Creatinine Clearance <50 mL/min	Creatinine Clearance ≥50 mL/min
After 2 y		
VKA	7.9 (4.0–13.0)	2.8 (1.9–3.9)
DOAC*	–	–
After 5 y		
VKA	21.9 (7.8–40.2)	6.0 (4.0–8.5)
DOAC*	–	–

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.
* Data were insufficient to estimate incidence.

Appendix Table 5. Risk for Major Bleeding: According to History of Bleeding

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events/Person-Years, *n/N*		Incidence Rate per 100 Person-Years (95% CI)	
	History of Bleeding	No History of Bleeding	History of Bleeding	No History of Bleeding
Year 1				
VKA	4/138	74/4090	3.97 (1.40–7.77); I^2 = 0%	1.84 (1.35–2.41); I^2 = 27%
DOAC	9/96	27/3336	9.75 (4.31–17.09); I^2 = 0%	0.91 (0.56–1.36); I^2 = 28%
Year 2				
VKA	9/187	27/1761	6.79 (1.85–14.50); I^2 = 0%	1.87 (1.02–2.97); I^2 = 32%
DOAC*	–	–	–	–
Years 3–5				
VKA	1/40	26/1724	4.04 (0.25–12.09); I^2 = 0%	3.23 (0.05–11.08); I^2 = 70%
DOAC*	–	–	–	–

	Cumulative Incidence (95% CI), %	
	History of Bleeding	No History of Bleeding
After 2 y		
VKA	10.5 (3.2–21.1)	3.7 (2.4–5.3)
DOAC*	–	–
After 5 y		
VKA	20.9 (3.9–46.4)	12.7 (2.5–33.4)
DOAC*	–	–

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.
* Data were insufficient to estimate incidence.

Appendix Table 6. Risk for Major Bleeding: According to Concomitant Use of Antiplatelet Therapy

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events/Person-Years, *n/N*		Incidence Rate per 100 Person-Years (95% CI)	
	Concomitant Antiplatelet Therapy	No Concomitant Antiplatelet Therapy	Concomitant Antiplatelet Therapy	No Concomitant Antiplatelet Therapy
Year 1				
VKA	14/3820	79/4536	4.31 (2.52–6.55); I^2 = 0%	1.78 (1.34–2.28); I^2 = 20%
DOAC	3/137	33/3225	3.53 (1.13–7.19); I^2 = 0%	1.37 (0.58–1.88); I^2 = 64%
Year 2				
VKA	14/232	29/1981	5.58 (2.46–9.87); I^2 = 26%	1.34 (0.57–2.44); I^2 = 53%
DOAC*	–	–	–	–
Years 3–5				
VKA	4/198	27/2204	2.24 (0.32–5.81); I^2 = 36%	1.21 (0.69–1.87); I^2 = 15%
DOAC*	–	–	–	–

	Cumulative Incidence (95% CI), %	
	Concomitant Antiplatelet Therapy	No Concomitant Antiplatelet Therapy
After 2 y		
VKA	9.6 (4.9–15.8)	3.1 (1.9–4.7)
DOAC*	–	–
After 5 y		
VKA	15.6 (5.8–29.6)	6.6 (3.9–9.9)
DOAC*	–	–

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.
* Data were insufficient to estimate incidence.

Appendix Table 7. Risk for Major Bleeding: According to Hemoglobin Concentration

Interval of Follow-up During Extended Anticoagulation	Major Bleeding Events/Person-Years, *n/N*		Incidence Rate per 100 Person-Years (95% CI)	
	Hemoglobin Level <100 g/L	Hemoglobin Level 100 g/L	Hemoglobin Level <100 g/L	Hemoglobin Level 100 g/L
Year 1				
VKA	6/171	74/4420	4.64 (2.04–8.22); I^2 = 0%	1.63 (1.08–2.28); I^2 = 50%
DOAC	2/80	29/3202	3.91 (0.85–9.05); I^2 = 0%	1.01 (0.60–1.53); I^2 = 39%
Year 2				
VKA	0/79	36/1989	0.0 (0.0–4.67); I^2 = 26%	1.46 (0.53–2.83); I^2 = 68%
DOAC*	–	–	–	–
Years 3–5				
VKA	1/85	30/2168	3.98 (0.59–21.23); I^2 = 61%	1.44 (0.98–1.99); I^2 = 0%
DOAC*	–	–	–	–

	Cumulative Incidence (95% CI), %	
	Hemoglobin Level <100 g/L	Hemoglobin Level ≥100 g/L
After 2 y		
VKA	4.6 (2.0–12.5)	3.1 (1.6–5.0)
DOAC*	–	–
After 5 y		
VKA	15.6 (3.8–57.2)	7.2 (4.5–10.6)
DOAC*	–	–

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.
* Data were insufficient to estimate incidence.

Appendix Table 8. Incidence of Major Bleeding According to Study Design

Interval of Follow-up During Extended Anticoagulation	Study Cohorts, *n*		Major Bleeding Events/Person-Years, *n/N*		Incidence Rate per 100 Person-Years (95% CI)	
	RCT	Cohort	RCT	Cohort	RCT	Cohort
Overall						
VKA	12	12	55/3025	152/9225	1.95 (1.31–2.71); I^2 = 39%	1.61 (1.09–2.30); I^2 = 69%
DOAC	6	5	19/2382	21/1553	0.89 (0.55–1.30); I^2 = 0%	1.34 (0.50–2.58); I^2 = 69%
Year 1						
VKA	12	12	49/2519	79/4470	2.16 (1.47–2.97); I^2 = 26%	1.90 (1.31–2.60); I^2 = 46%
DOAC	6	5	19/2382	21/1386	0.89 (0.55–1.30); I^2 = 0%	1.56 (0.53–3.11); I^2 = 73%
Year 2						
VKA	7	9	6/506	42/2200	1.35 (0.51–2.59); I^2 = 5%	1.79 (0.90–2.97); I^2 = 55%
DOAC*	–	–	–	–	–	–
Years 3–5						
VKA*	0	5	–	31/2555	–	0.95 (0.35–1.83); I^2 = 55%
DOAC*	–	–	–	–	–	–

	Cumulative Incidence (95% CI), %	
	RCT	Cohort
After 2 y		
VKA	3.5 (2.0–5.5)	3.7 (2.2–5.5)
DOAC*	–	–
After 5 y		
VKA*	–	6.4 (3.2–10.6)
DOAC*	–	–

DOAC = direct oral anticoagulant; RCT = randomized controlled trial; VKA = vitamin K antagonist.
* Where indicated by dashes, data were insufficient to estimate incidence.