

# Limited evidence on persistence with anticoagulants, and its effect on the risk of recurrence of venous thromboembolism: a systematic review of observational studies

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**Purpose:** The risk of venous thromboembolism (VTE) recurrence is high following an initial VTE event, and it persists over time. This recurrence risk decreases rapidly after starting with anticoagulation treatment and reduces by ~80%–90% with prolonged anticoagulation. Nonpersistence with anticoagulants could lead to increased risk of VTE recurrence. This systematic review aimed to estimate persistence at 3, 6, and 12 months with anticoagulants in patients with VTE, and to evaluate the risk of VTE recurrence in nonpersistent patients.

**Methods:** PubMed and Embase® were searched up to May 3, 2014 and the search results updated to May 31, 2015. Studies involving patients with VTE aged  $\geq 18$  years, treatment with anticoagulants intended for at least 3 months or more, and reporting data for persistence were included. Proportions were transformed using Freeman–Tukey double arcsine transformation and pooled using the DerSimonian–Laird random-effects approach.

**Results:** In total, 12 observational studies (7/12 conference abstracts) were included in the review. All 12 studies either reported or provided data for persistence. The total number of patients meta-analyzed to estimate persistence at 3, 6, and 12 months was 71,969 patients, 58,940 patients, and 68,235 patients, respectively. The estimated persistence for 3, 6, and 12 months of therapy was 83% (95% confidence interval [CI], 78–87;  $I^2=99.3\%$ ), 62% (95% CI, 58–66;  $I^2=98.1\%$ ), and 31% (95% CI, 22–40;  $I^2=99.8\%$ ), respectively. Only two studies reported the risk of VTE recurrence based on nonpersistence – one at 3 months and the other at 12 months.

**Conclusion:** Limited evidence showed that persistence was suboptimal with an estimated 17% patients being nonpersistent with anticoagulants in the crucial first 3 months. Persistence declined over 6 and 12 months. Observational data on persistence with anticoagulation treatment, especially direct oral anticoagulants, in patients with VTE and its effect on risk of VTE recurrence were scarce and further research is required.

**Keywords:** meta-analysis, deep vein thrombosis, recurrence, vitamin K antagonists, direct oral anticoagulants

## Introduction

Venous thromboembolism (VTE) is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE associated with known acquired risk factors is referred to as “provoked;” if there is no known clinical risk factor present, it is referred to as “unprovoked.”<sup>1</sup> It is estimated that there are 300,000–600,000 incident VTE cases annually in the USA.<sup>2</sup> Across six major European countries, the estimated incidence per 100,000 person-years was 148 for DVT and 95 for PE.<sup>3</sup> Subsequent VTE

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events after an index VTE are referred to as “recurrent VTE”. The risk of recurrent VTE decreases rapidly after starting with anticoagulation treatment.<sup>4</sup> Risk of recurrent VTE is 50% higher if anticoagulation is interrupted within 4–6 weeks compared with 3 months or later.<sup>5</sup> Prolonged anticoagulation treatment beyond 3 months reduces the risk of recurrent VTE by ~80%–90% when treated with vitamin K antagonist (VKA)<sup>6,7</sup> or direct oral anticoagulants (DOACs).<sup>8</sup> The risk of VTE recurrence is high in the first 6–12 months and does not return to baseline;<sup>9</sup> therefore, persistence with the prescribed regimen of anticoagulation treatment is crucial. Persistence reflects “the duration of time from initiation to discontinuation of therapy” in an individual patient,<sup>10</sup> being defined as the proportion of patients who continue the treatment for a specified period of time without exceeding a prespecified gap. Premature discontinuation of treatment indicates nonpersistence. Evaluating the persistence in routine clinical practice is important because deviation from a prescribed regimen may lead to subtherapeutic responses and increased risk of VTE recurrence. This report summarizes the evidence on persistence with anticoagulation treatment and its effect on the risk of VTE recurrence.

## Objectives

The objective of this systematic review was to estimate persistence at 3, 6, and 12 months after initiation of anticoagulant treatment in patients with VTE, and to evaluate the risk of VTE recurrence in nonpersistent patients.

## Methods

### Search strategy and study screening

A comprehensive search strategy was formulated using keywords such as “deep vein thrombosis”, “pulmonary embolism”, “venous thromboembolism”, “thrombosis”, “patient compliance”, “medication adherence”, “persistence”, “discontinuation”, “non-compliance”, “non-persistence”, “non-adherence”, “health behaviour”, “concordance”, “drug regimen”, “withdrawal”, “patient drop-outs”, “warfarin”, “coumarin”, “heparin”, “low molecular weight heparin”, “acenocoumarol”, “phenprocoumon”, “fondaparinux”, “dalteparin”, “enoxaparin”, “nadroparin”, “dabigatran”, “rivaroxaban”, “anticoagulants”, “vitamin K antagonists”, “VKA”, “observational study”, “retrospective study”, “prospective study”, “cohort study”, “longitudinal studies”, “case control study”, “meta-analysis”, “systematic review” (full strategy available with the authors). A broad search strategy was used to ensure that outcomes of interest were captured even if reported as secondary outcomes. PubMed and Embase® were searched up to May 3, 2014,

along with Google Scholar. Additional search was carried out up to May 31, 2015 and the results were used to update this review. The identified references were screened by the first author (PV) using EndNote® X7 (Thomson Reuters, USA).

### Inclusion and exclusion criteria

Observational studies (full-text/conference abstracts) were included if they fulfilled the following criteria:

- Patients  $\geq 18$  years of age
- Patients diagnosed with VTE which includes DVT and PE with or without DVT
- Treatment with anticoagulants intended for at least 3 months or more
- Data reported for persistence.

Studies of pregnant patients, prophylaxis, and other therapy/indications were excluded. Guidelines, case reports, case series, reviews, clinical trials, randomized controlled trials, and editorials were also excluded. Review articles and systematic reviews were screened for references before exclusion.

### Data analysis

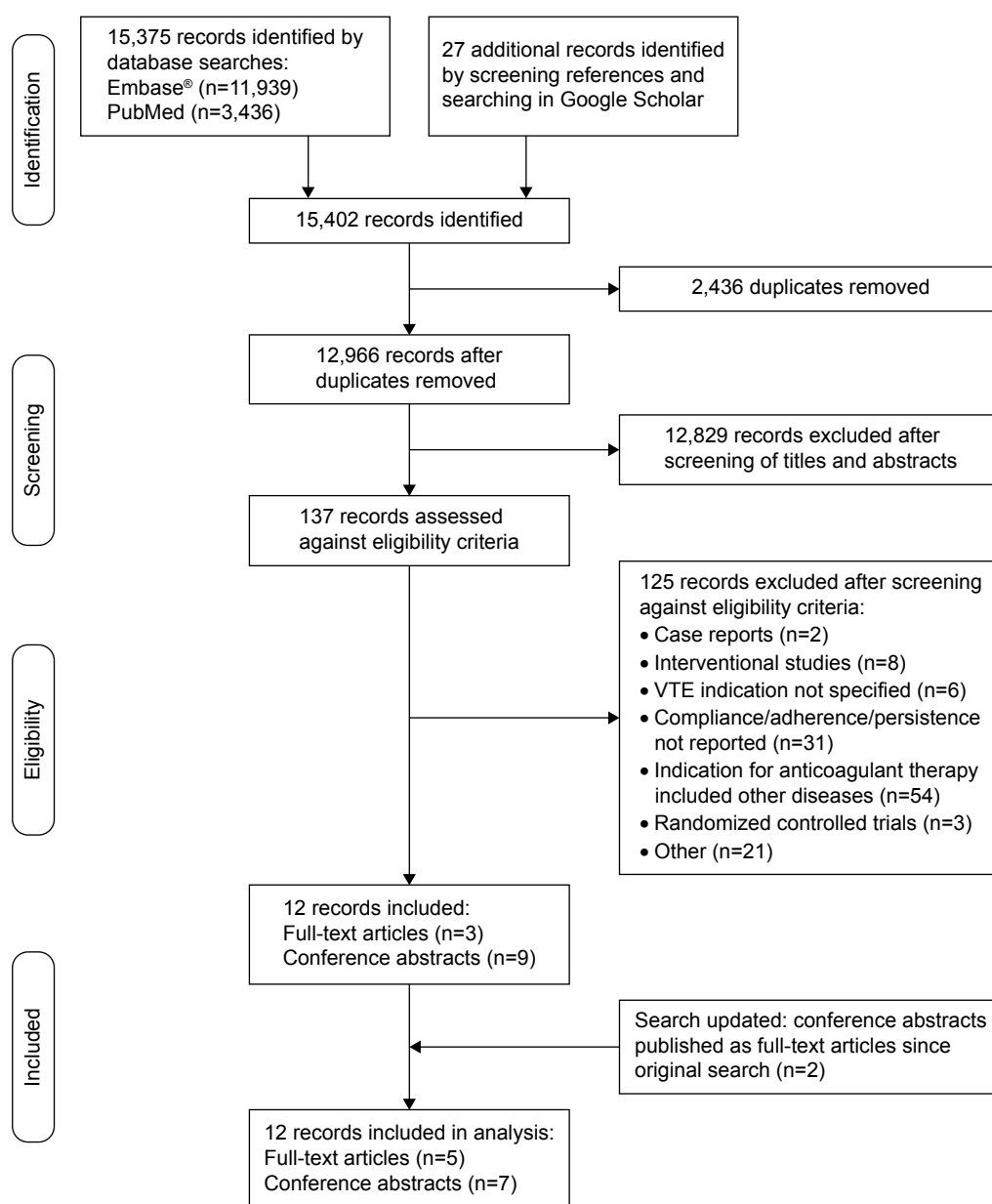
The methodological quality of the studies was assessed using a tool developed by the Cochrane Bias Method Group.<sup>11</sup> Time points of 3, 6, and 12 months were used for persistence, as they reflect different recurrence risk periods. The 3-month time point reflects the period of active treatment to suppress acute events of thrombosis with the highest risk of recurrence, whereas the 6- and 12-month time points reflect recurrence risk periods with prolonged anticoagulation, which is based on the type of index VTE and individual risk factors.<sup>1,12</sup> The proportion of patients persistent with treatment, if not reported, was calculated using data published in the studies. Freeman–Tukey double arcsine transformation was used to stabilize the variances of the raw proportions before pooling them.<sup>13</sup> The DerSimonian–Laird random-effects approach was used to calculate the between-study variance and pooled persistence.<sup>14</sup> This approach gave an overall weighted estimate of persistence. Analyses were conducted in R version 3.2.0 using the R packages “meta” and “metafor”.<sup>15,16</sup> The  $I^2$  index was used as a measure of the variability in effect estimates due to between-study heterogeneity. Sensitivity analysis was performed to determine the effect of sample size on the final pooled estimate. Possible sources of heterogeneity were explored by univariate meta-regression using treatment type (VKA vs DOAC), where  $P$ -values of  $<0.05$  were considered significant. Meta-regression was performed using transformed proportions and transformed within-study standard errors.

## Results

### Study characteristics

The screening process and the final number of studies included are shown in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Figure 1). After the search update (May 31, 2015), two conference abstracts<sup>17,18</sup> were published as full-text articles and no new references were found relevant to be included in the review. In total, 12 observational studies were included, of which five were full-text articles<sup>19–23</sup> and seven were conference abstracts.<sup>24–30</sup> Five studies were from the USA,<sup>19–23</sup> five from Germany,<sup>25,27–30</sup> and one each from Canada<sup>24</sup> and

the UK.<sup>26</sup> All 12 studies either reported or provided data for persistence. Of the 12 studies, five reported on DOAC (rivaroxaban),<sup>25,27–30</sup> six reported on VKAs,<sup>19–21,23,24,26</sup> and one reported on multiple anticoagulants (93% were warfarin users).<sup>22</sup> The total number of patients meta-analyzed to estimate persistence was 71,969 at 3 months, 58,940 at 6 months, and 68,235 at 12 months. Eleven studies reported patients with VTE with average age ranging 52–67 years; one study involving nursing home residents reported median age of 80 years.<sup>20</sup> Six studies included patients with recurrent VTE (24%–57% of the study populations)<sup>21,25,27–30</sup> and the remaining six included index VTE patients. Five studies



**Figure 1** PRISMA flow diagram.

**Abbreviations:** PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; VTE, venous thromboembolism.

included patients with cancer (11%–21% of the study population),<sup>19–23</sup> two included noncancer patients,<sup>24,26</sup> and the cancer status could not be determined for the remaining five studies. Out of the 12 studies, four studies categorized VTE into provoked and unprovoked; two studies had 63% and 62% unprovoked VTE patients, respectively,<sup>22,26</sup> one

study had 37.3% unprovoked VTE patients,<sup>24</sup> one study was totally based on unprovoked VTE patients (n=37,664),<sup>23</sup> and the remaining eight studies did not categorize VTE. The characteristics of the studies are illustrated in Table 1. The summary of risk of bias for each of the 12 studies (available on request from the authors).

**Table 1** Characteristics of studies included in the review

Source and year	Study design	Country	Database	Number of participants	Age, years, mean (SD)	Female, %	Measure
Beyer-Westendorf et al <sup>27</sup> (2013) <sup>a</sup>	Prospective registry	Germany	NOAC registry	233	63.5	54.9	Discontinuation
Beyer-Westendorf et al <sup>28</sup> (2013) <sup>a</sup>	Prospective registry	Germany	NOAC registry	168	62.5	NA	Discontinuation
Cohen et al <sup>26</sup> (2013) <sup>a</sup>	Retrospective cohort	UK	CPRD	8,504 (7,676 in analysis)	63.5	53.6	Persistence
—	—	—	—	Subgroup (3,130)	—	—	Persistence
—	—	—	—	Subgroup (4,546)	—	—	Persistence
Gelbricht et al <sup>30</sup> (2012) <sup>a</sup>	Prospective registry	Germany	NOAC registry	105	62.5 (±18.2)	55.2	Discontinuation
Koehler et al <sup>29</sup> (2012) <sup>a</sup>	Prospective registry	Germany	NOAC registry	126	64.4 (±15.1)	42.1	Discontinuation
Köhler et al <sup>25</sup> (2013) <sup>a</sup>	Prospective registry	Germany	NOAC registry	72	67.3	55.6	Discontinuation
Tagalakakis et al <sup>24</sup> (2013) <sup>a</sup>	Retrospective cohort	Canada (Quebec)	Administrative health care databases	40,776 (20,806 in analysis)	>60 (78% of the cohort)	58.3	Persistence
—	—	—	—	Subgroup (13,041)	—	—	Persistence
—	—	—	—	Subgroup (7,765)	—	—	Persistence
Chen et al <sup>19</sup> (2013) <sup>c</sup>	Retrospective cohort	USA	MarketScan database	8,040	61.2 (±14.8)	40.6	Persistence
Deitelzweig et al <sup>21</sup> (2010) <sup>c</sup>	Retrospective cohort	USA	Integrated Healthcare Information Services	8,380	52	51.1	Persistence
Reardon et al <sup>20</sup> (2012) <sup>c</sup>	Retrospective cohort	USA	AnalytiCare LTC database	489	80 (median)	70	Persistence
Kaatz et al <sup>22</sup> (2014) <sup>c</sup>	Retrospective cohort	USA	HealthCore Integrated Research Database	2,002	57 (±15)	47.7	Persistence
—	—	—	—	Subgroup (758)	—	—	—
—	—	—	—	Subgroup (1,244)	—	—	—
Xie et al <sup>23</sup> (2015) <sup>c</sup>	Retrospective cohort	USA	MarketScan database	37,664	60.2	41.3	Persistence

**Notes:** <sup>a</sup>Conference abstract; <sup>b</sup>risk of recurrence for patients with discontinuation of warfarin within 3 months compared with discontinuation after ≥3 months; <sup>c</sup>full-text article; <sup>d</sup>risk of recurrence after completing 1 year of therapy for patients nonpersistent compared with persistent during 1 year of anticoagulant therapy; <sup>e</sup>93% warfarin users and 7% users of enoxaparin, heparin, tinzaparin, dalteparin, or fondaparinux.

**Abbreviations:** CI, confidence interval; CPRD, clinical practice research datalink; DOAC, direct oral anticoagulant; HR, hazard ratio; NA, not available; NOAC, novel oral anticoagulants; PE, pulmonary embolism; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism; INR, international normalized ratio.

## Threshold and time points

In six studies, persistence was determined using a pre-specified gap which varied from 37 to 90 days based on prescription refills, and exceeding this gap meant discontinuation (nonpersistence).<sup>19–23,26</sup> Five studies reported premature discontinuation of the treatment

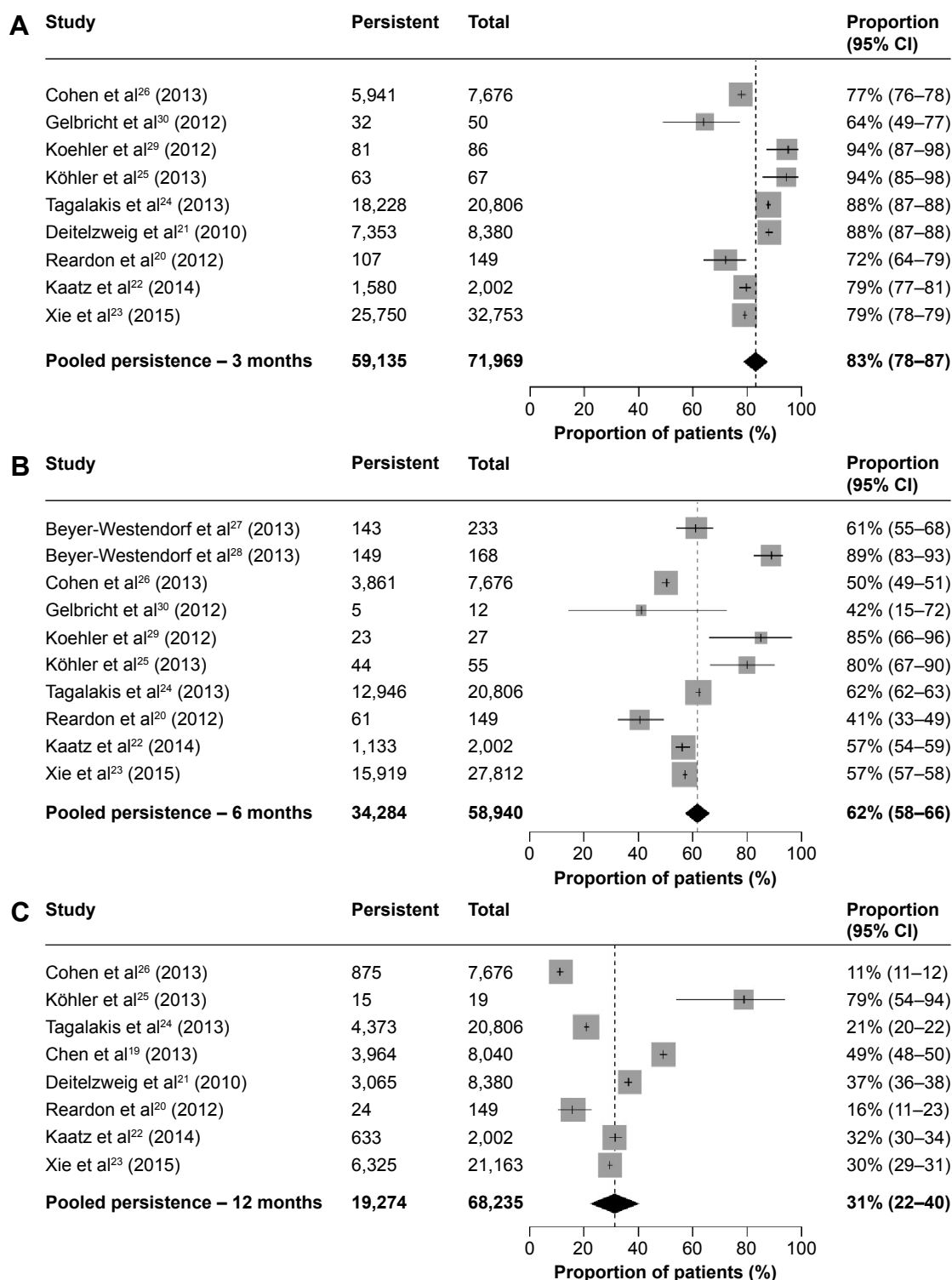
(nonpersistence)<sup>25,27–30</sup> and one study did not report the gap (conference abstract).<sup>24</sup> Most studies reported persistence at multiple time points within the same study: six studies reported all three time points (3, 6, and 12 months),<sup>20,22–26</sup> two studies reported two time points (3 and 6 months),<sup>29,30</sup> one study reported two time points (3 and 12 months),<sup>21</sup>

Technique	Criterion for nonpersistence	Condition	Treatment	Persistence, % (n/N)			Risk of VTE recurrence
				3 months	6 months	12 months	
Phone visits	NA	Acute VTE	DOAC (rivaroxaban)	NA	61.5	NA	NA
Phone visits	NA	Chronic VTE	DOAC (rivaroxaban)	NA	88.5	NA	NA
Prescription fills	Gap of 56 days	VTE (complete cohort)	VKA (unspecified)	77.4	50.3	11.4	NA
Prescription fills	Gap of 56 days	Provoked VTE (noncancer)	VKA (unspecified)	76.8	49.0	10.3	NA
Prescription fills	Gap of 56 days	Unprovoked VTE	VKA (unspecified)	77.8	51.1	11.9	NA
Phone visits	NA	Acute VTE	DOAC (rivaroxaban)	64 (32/50)	41.7 (5/12)	NA	NA
Phone visits	NA	Extended VTE treatment	DOAC (rivaroxaban)	94.2 (81/86)	85.2 (23/27)	NA	NA
Phone visits	NA	Acute PE	DOAC (rivaroxaban)	94 (63/67)	80 (44/55)	78.9 (15/19)	NA
Prescription fills	NA	VTE (complete cohort)	VKA (unspecified)	87.6	62.2	21.0	NA
Prescription fills	NA	Provoked VTE (noncancer)	VKA (unspecified)	86.9	59.5	19.9	NA
Prescription fills	NA	Unprovoked VTE	VKA (unspecified)	88.8	66.8	22.9	NA
Prescription fills	Gap of 90 days	VTE	VKA (warfarin)	NA	NA	49.3	HR <sup>d</sup> : 1.48; 95% CI: 1.09–2.01
Prescription fills	Gap between expected and observed refill date	VTE	VKA (warfarin)	87.7	NA	36.6	HR <sup>b</sup> : 1.45; 95% CI: 1.18–1.77
Prescription fills	Gap of 37 days	VTE	VKA (warfarin)	72	41	16	NA
Prescription fills	Gap of 60 days and INR test every 42 days	VTE (complete cohort)	Multiple <sup>e</sup>	78.9	56.6	31.6	NA
–	–	Provoked VTE (incl cancer related)	–	NA	NA	NA	NA
–	–	Unprovoked VTE	–	NA	NA	NA	NA
Prescription fills	Gap of 45 days after end date of previous prescription	Unprovoked VTE	VKA (warfarin)	78.6 (25,750/32,753)	57.2 (15,919/27,812)	29.9 (6,325/21,163)	NA

two studies reported one time point (6 months),<sup>27,28</sup> and one study reported one time point (12 months).<sup>19</sup> Therefore, nine studies had 3-month persistence data,<sup>20–26,29,30</sup> ten had 6-month persistence data,<sup>20,22–30</sup> and eight had 12-month persistence data.<sup>19–26</sup>

## Persistence

The estimated persistence with anticoagulation treatment at 3 months was 83% (95% confidence interval [CI], 78–87;  $I^2=99.3\%$ ) (Figure 2A), at 6 months was 62% (95% CI, 58–66;  $I^2=98.1\%$ ) (Figure 2B), and at 12 months was 31%



**Figure 2** Pooled proportion of patients persistent with anticoagulation treatment.

**Notes:** (A) 3 months. (B) 6 months. (C) 12 months.

**Abbreviation:** CI, confidence interval.

(95% CI, 22–40;  $I^2=99.8\%$ ) (Figure 2C). Univariate meta-regression for 3 months persistence revealed that treatment type (VKA vs DOAC) did not significantly contribute to heterogeneity ( $P=0.4074$ ); however, it was significant for 6 months ( $P=0.0068$ ) and 12 months ( $P=0.0065$ ).

Two studies reported persistence to anticoagulation treatment for 3, 6, and 12 months stratified by provoked noncancer VTE and unprovoked VTE. For provoked noncancer VTE, persistence at 3 months was 76.8% and 86.9%, at 6 months was 49% and 59.5%, and at 12 months was 10.3% and 19.9% for each study, respectively. For unprovoked VTE, persistence at 3 months was 77.8% and 88.8%, at 6 months was 51.1% and 66.8%, and at 12 months was 11.9% and 22.9% for each study, respectively.<sup>24,26</sup> One study that was based only on unprovoked VTE patients reported that 78.6%, 57.2%, and 29.9% were persistent at 3, 6, and 12 months, respectively.<sup>23</sup>

## Sensitivity analysis

Four studies (3-month persistence),<sup>20,25,29,30</sup> six studies (6-month persistence),<sup>20,25,27–30</sup> and two studies (12-month persistence)<sup>20,25</sup> with small sample size were excluded to evaluate the effect of sample size on pooled estimates. After exclusion, the estimates of 3-, 6-, and 12-month persistence remained almost the same (3 months, 82% [95% CI, 77–87;  $I^2=99.6\%$ ]; 6 months, 57% [95% CI, 52–61;  $I^2=99.1\%$ ]; 12 months, 29% [95% CI, 20–39;  $I^2=99.9\%$ ]).

## Risk of recurrence

Only two studies reported the risk of recurrence based on discontinuation (nonpersistence) – one at 3 months and the other at 12 months;<sup>19,21</sup> therefore, these data could not be pooled for analysis. Deitelzweig et al<sup>21</sup> reported that patients who discontinued VKA (warfarin) treatment within 3 months had a 45% increased risk of VTE recurrence compared with patients who discontinued at or after 3 months (hazard ratio, 1.45; 95% CI, 1.18–1.77). Chen et al<sup>19</sup> reported the risk of VTE recurrence after 12 months of treatment with VKA (warfarin) and found that patients who were nonpersistent with or discontinued VKA treatment within 12 months had a 48% increased risk of VTE recurrence compared with patients who were persistent with VKA for 12 months (hazard ratio, 1.48; 95% CI, 1.09–2.01).

## Discussion

The findings of this systematic review suggest that, in routine clinical practice, the estimated persistence with anticoagulation treatment for the first 3 months after a VTE event was 83% and it declined to 31% at 12 months.

Clinical guidelines suggest that patients with VTE should be treated with anticoagulants for at least 3 months as the risk of recurrence is high during this early period.<sup>1,12</sup> In this review, an estimated 17% of patients were nonpersistent with anticoagulation treatment at 3 months, placing them at high risk of recurrence. After 3 months, the treatment duration is extended based on the type of VTE (provoked and unprovoked), individual patient factors, and weighing benefits–risks (eg, bleeding risk).<sup>1,12</sup> Guidelines also suggest that the risk of recurrence reduces after 3 months of anticoagulant therapy but persists over time, especially for unprovoked and cancer-related VTE.<sup>1</sup> The present review estimated that 38% and 69% were nonpersistent at 6 and 12 months, respectively. The results of this study suggest that persistence with anticoagulant therapy in routine clinical practice was suboptimal, indicating patients might be at risk of recurrent VTE. Of the studies included in this review, only two explored the risk of VTE recurrence based on persistence. Although the number of studies included was limited, data suggest that the risk of VTE recurrence is high in nonpersistent patients. Another finding of this review was that studies investigating persistence or discontinuation rates in VTE patients were available only for VKA and rivaroxaban (preliminary data as conference abstracts) and were lacking for heparins and other DOACs such as dabigatran and apixaban. To the best of our knowledge, there are no previous reviews that have summarized and pooled data from observational studies on persistence in VTE patients at different time points and the risk of VTE recurrence in nonpersistent patients.

There are some limitations to this review and its findings. First, subgroup analysis based on type of VTE (provoked vs unprovoked), type of treatment (DOAC vs VKA), and other variables was not feasible because of limited data. Unprovoked VTE has a higher risk of recurrence than provoked VTE and future studies should investigate these subgroups separately.<sup>31</sup> Second, the threshold for persistence was reported as a prespecified gap in six studies.<sup>19–23,26</sup> The prespecified gap used varied across the studies, which may be due to differences in pattern of prescriptions and pack size across countries. Third, complexity of the treatment regimen should be taken into consideration when estimating real-world persistence. In most of the studies included in this review, patients were taking VKA, which is a well-established therapy for VTE; however, it requires routine anticoagulation monitoring and is associated with food and drug interactions which might affect long-term persistence.<sup>32</sup> Seven out of the 12 studies were based on administrative or claims database that rely on pharmacy refill records which might not reflect actual consumption.<sup>19–24,26</sup> Five studies

included in this review were preliminary data of ongoing studies on rivaroxaban with small sample sizes and presented as conference abstracts.<sup>25,27–30</sup> Also, 6/12 included studies did not examine all the three time points (3, 6, and 12 months) for persistence within the same study.<sup>19,21,27–30</sup> Heterogeneity was high for the pooled estimates and remained high in the sensitivity analysis, suggesting that a subgroup analysis is needed. The limited number of studies and missing information precluded a complete meta-regression and subgroup meta-analysis. Covariates such as mean age, proportion of women, and threshold for persistence could not be included in the meta-regression because of limited or missing information. Consequently, heterogeneity could not be explored, and therefore, all results must be interpreted with caution.

## Conclusion

This systematic review revealed that data on real-world persistence were limited, but the available data showed that persistence was suboptimal with an estimated 17% patients being nonpersistent with anticoagulants in the crucial first 3 months and at high risk of recurrence. Being persistent beyond 3 months of anticoagulation treatment is important; however, persistence declined with increased duration of treatment. Data on the risk of VTE recurrence in nonpersistent patients were limited, but two studies showed an increased risk of VTE recurrence. Recurrent VTE is associated with substantial health care resource utilization, increased morbidity and mortality, and impacts patient's quality of life. As a result, it is important to educate patients about the importance of remaining on the anticoagulation treatment to prevent recurrent VTE. Therefore, further research is required to evaluate the risk of VTE recurrence in nonpersistent patients, reasons for poor persistence, and steps to improve it, thus creating a robust body of evidence to inform decision making and management of individual patients.

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## Author contributions

All authors made a substantial contribution to the concept and design of the review and interpretation of results. P Vora was responsible for the search strategy, extraction of data, statistical analysis, interpretation of results, and drafting of the manuscript. G Persson Brobert was the main supervisor for this project. K Suzart and M Soriano-Gabarró

co-supervised the project. All authors were involved in critical revision of the manuscript. All authors gave final approval of the submitted version of the manuscript.

## Disclosure

All authors are employees of Bayer Pharma AG. The authors report no other conflicts of interest in this work.

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