Stroke

CLINICAL AND POPULATION SCIENCES

Direct Oral Anticoagulants Versus Warfarin in the Treatment of Cerebral Venous Thrombosis (ACTION-CVT): A Multicenter International Study

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BACKGROUND: A small randomized controlled trial suggested that dabigatran may be as effective as warfarin in the treatment of cerebral venous thrombosis (CVT). We aimed to compare direct oral anticoagulants (DOACs) to warfarin in a real-world CVT cohort.

METHODS: This multicenter international retrospective study (United States, Europe, New Zealand) included consecutive patients with CVT treated with oral anticoagulation from January 2015 to December 2020. We abstracted demographics and CVT risk factors, hypercoagulable labs, baseline imaging data, and clinical and radiological outcomes from medical records. We used adjusted inverse probability of treatment weighted Cox-regression models to compare recurrent cerebral or systemic venous thrombosis, death, and major hemorrhage in patients treated with warfarin versus DOACs. We performed adjusted inverse probability of treatment weighted logistic regression to compare recanalization rates on follow-up imaging across the 2 treatments groups.

RESULTS: Among 1025 CVT patients across 27 centers, 845 patients met our inclusion criteria. Mean age was 44.8 years, 64.7% were women; 33.0% received DOAC only, 51.8% received warfarin only, and 15.1% received both treatments at different times. During a median follow-up of 345 (interquartile range, 140–720) days, there were 5.68 recurrent venous thrombosis, 3.77 major hemorrhages, and 1.84 deaths per 100 patient-years. Among 525 patients who met recanalization analysis inclusion criteria, 36.6% had complete, 48.2% had partial, and 15.2% had no recanalization. When compared with warfarin, DOAC treatment was associated with similar risk of recurrent venous thrombosis (aHR, 0.94 [95% CI, 0.51–1.73]; *P*=0.84), death (aHR, 0.78 [95% CI, 0.22–2.76]; *P*=0.70), and rate of partial/complete recanalization (aOR, 0.92 [95% CI, 0.48–1.73]; *P*=0.79), but a lower risk of major hemorrhage (aHR, 0.35 [95% CI, 0.15–0.82]; *P*=0.02).

CONCLUSIONS: In patients with CVT, treatment with DOACs was associated with similar clinical and radiographic outcomes and favorable safety profile when compared with warfarin treatment. Our findings need confirmation by large prospective or randomized studies.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anticoagulants ■ contraindications ■ dabigatran ■ hemorrhage ■ venous thrombosis

Nonstandard Abbreviations and Acronyms

ACTION-CVT	Anticoagulation in the Treatment of Cerebral Venous Thrombosis
CVT	cerebral venous thrombosis
DOAC	direct oral anticoagulants
HR	hazard ratio
IPTW	inverse probability of treatment weighted
OR	odds ratio
RESPECT-CVT	A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis
VTE	venous thromboembolism

Cerebral venous thrombosis (CVT) is an uncommon cause of stroke, usually affecting younger patients.[1] In the absence of contraindications, parenteral followed by oral anticoagulation is the recommended treatment.[2] Randomized trials[3–6] and guidelines[7–9] indicate that direct oral anticoagulants (DOACs) are a viable and preferred alternative to warfarin for the treatment of patients with venous thromboembolism (VTE). Although the favorable safety and efficacy of DOACs in VTE treatment is frequently extrapolated to patients with CVT, limited data exist to support this approach.

The RESPECT-CVT trial (A Clinical Trial Comparing Efficacy and Safety of Dabigatran Etexilate With Warfarin in Patients With Cerebral Venous and Dural Sinus Thrombosis), which randomized 120 patients with CVT to dabigatran versus warfarin, showed no significant differences in efficacy and safety outcomes between the 2 treatment groups.[10] However, this study was underpowered to show differences in safety or efficacy between the 2 groups due to the low rates of VTE recurrence and hemorrhagic complications.[10] Therefore, it remains uncertain whether DOACs are as safe and effective as warfarin in patients with CVT. A better understanding of this issue is important since the pathomechanism(s) underlying CVT and VTE and their subsequent risks may differ.[11,12]

Large randomized controlled trials are challenging to conduct given the low incidence of CVT. Observational, real-world data may help answer whether treatment with DOACs versus warfarin is associated with similar efficacy and safety outcomes. In this study, we sought to compare the safety and efficacy of DOACs to warfarin in patients with CVT by collecting observational real-world data from large stroke centers worldwide.

METHODS

Institutional Review Board approval was obtained from each participating center to perform the study. Informed Consent was waived by Institutional Board Review. De-identified data are available upon reasonable request to the corresponding author.

Patient Population

The ACTION-CVT (Anticoagulation in the Treatment of Cerebral Venous Thrombosis) study is a multicenter, international (United States, Italy, Switzerland, New Zealand; Figure S1) retrospective observational study that included consecutive adult patients with CVT confirmed on imaging admitted to each of the participating centers over a period of 6 years (January 1, 2015–December 31, 2020). Patients with CVT at each institution were initially identified using ICD-9 (325.0, 437.6, and 671.5) and ICD-10 codes (I67.6) with acceptable sensitivity and specificity.[13,14] This was followed by review of medical records and imaging studies to confirm the diagnosis of CVT.

We excluded patients who were not treated with oral anticoagulation as well as patients in whom a specific anticoagulation strategy (DOAC or warfarin) would typically be used or preferred such as in the setting of antiphospholipid antibody syndrome associated CVT (warfarin is the drug of choice),[15] active cancer (DOACs may be preferred over warfarin),[16] and pregnancy (oral anticoagulation particularly with warfarin is contraindicated).[17] For the recanalization analysis, we excluded patients who underwent endovascular treatment and those who were on both treatments (DOACs and warfarin) prior to completion of follow-up imaging.

Study Variables

The following variables were collected through medical record review:

1. Demographic factors: Age, sex, race (White, Black, or other), and ethnicity (Hispanic versus non-Hispanic).
2. CVT risk factors: Body mass index closest to the time of diagnosis, history of prior VTE, head trauma, lumbar puncture, mastoiditis/sinusitis within 3 months of CVT diagnosis, smoking history, oral contraceptive use, delivery within 12 weeks of CVT diagnosis, and family history of venous thrombosis.
3. Clinical variables: Days from first symptoms to diagnosis, duration of oral anticoagulation, days from initiation of anticoagulation to follow-up imaging, and clinical symptoms at presentation (headache, focal deficit, seizure, coma, etc.).
4. Imaging variables: Brain imaging findings (venous infarct, cerebral edema, or brain hemorrhage) and CVT location (deep venous sinus involvement versus no deep venous sinus involvement).
5. Laboratory variables closest to time of diagnosis: Platelet count, one or more antiphospholipid antibodies present at the time of diagnosis but not meeting criteria for antiphospholipid antibody syndrome at the time of evaluation, factor V Leiden mutation, and prothrombin gene mutation.
6. In-hospital treatments: Parenteral anticoagulation (low molecular weight heparin or intravenous heparin), endovascular treatment, and neurosurgical treatment (extraventricular drain or craniotomy).

Oral Anticoagulant Type

The primary predictor in this study was oral anticoagulant type (DOAC versus warfarin). Medical records were reviewed for compliance with anticoagulant therapy and international normalized ratio checks for patients prescribed warfarin. The times of oral anticoagulation initiation and cessation were recorded. In patients who remained on anticoagulation at the time of data abstraction, the last day of anticoagulation was considered as the last day of follow-up.

Outcomes

Study outcomes were abstracted by individual sites through review of all available medical records including outside hospital records at the time of data abstraction. The outcomes were (1) primary outcome: Recurrent venous thrombosis (VTE or CVT) during follow-up. Recurrent CVT included de novo CVT as well as extension of previous CVT occurring while on oral anticoagulation therapy. The inclusion of CVT extension is in line with the recurrent VTE definition in clinical trials[4,5] and is an important outcome to capture in CVT patients as CVT progression can lead to worsening venous infarction, cerebral edema, hemorrhage, or increased intracranial pressure. (2) Imaging outcomes: Recanalization status on last venous imaging study abstracted from radiology reports (no recanalization, partial recanalization, or complete recanalization). Complete recanalization was defined as full recanalization of the thrombosed vein or sinus without any residual thrombus. Partial recanalization was defined as improved opacification or flow in the affected cerebral sinus or vein, but with residual thrombus present on follow-up imaging. No recanalization was defined as no change or worsening in opacification or flow in the affected cerebral sinus or vein from baseline imaging. (3) Safety outcomes:

Major hemorrhage defined as new or worsening intracranial hemorrhage or major extracranial hemorrhage defined as systemic hemorrhage with at least 2 g/dL drop in hemoglobin level or requiring blood transfusion occurring while on oral anticoagulation therapy. Symptomatic intracranial hemorrhage was defined as any new or worsening intracranial hemorrhage on a follow-up brain imaging study causing new or worsening neurological signs or symptoms. (4) Any death during follow-up. All clinical outcomes were included if they occurred while on oral anticoagulation. Radiographic outcomes were included if the follow-up imaging study was done after initiation of oral anticoagulation.

Analytical Plan

Data verification was conducted by Drs Yaghi and Shu to ensure data integrity and consistency. Several queries were sent to participating sites regarding predictors, outcomes, and other variables. Missing data was not imputed. We used t test, χ^2 test, Fisher exact test, or Wilcoxon rank-sum test (Mann-Whitney 2-sample statistic) as appropriate to compare co-variates between those with versus those without 90-day follow-up.

For univariate analyses, patients were divided into 2 groups based on the oral anticoagulant used: strictly warfarin versus strictly DOAC use. Analysis of clinical outcomes used the full data set, and end points occurring on oral anticoagulation counted against the drug in use at the time. Radiographic outcomes were only considered in patients using strictly one anticoagulant (DOAC or warfarin) prior to the follow-up venous imaging study. Between-group comparisons were done by t test, χ^2 test, Fisher exact test or Wilcoxon rank-sum test (Mann-Whitney 2-sample statistic) as appropriate.

Unweighted and inverse probability of treatment weighted (IPTW) unadjusted and adjusted Cox-regression analyses with cluster frailty were used to test associations between oral anticoagulant type (DOAC versus warfarin) and clinical efficacy and safety outcomes. Patients who switched oral anticoagulant types were considered as crossovers from one arm to the other and analyzed using an as-treated approach. For each arm, the start of follow-up was considered as the time the oral anticoagulant was initiated and subjects were censored if they died, were lost to follow-up, or discontinued the oral anticoagulant prior to the outcome of interest. For the radiological outcome, we used unadjusted and adjusted binary logistic regression analyses to test associations between anticoagulant type and recanalization status. For the recurrent venous thrombosis outcome, we adjusted for variables associated with recurrent venous thrombosis in prior studies including age, sex, history of VTE,[18,19] as well as the presence of one or more positive antiphospholipid antibodies that may portend an increased risk based on pathophysiological considerations. For the major hemorrhage and death outcome, we adjusted for predictors of intracranial and extracranial hemorrhage, age, sex, intracranial hemorrhage at baseline[20,21] as well as deep CVT location, which is a predictor of poor functional outcome and mortality in CVT. The recanalization status outcome was adjusted for age, sex, intracranial hemorrhage at baseline, duration of anticoagulation therapy prior to follow-up imaging, and deep CVT location. These variables have either been shown to be directly or indirectly

associated with recanalization status in prior studies,[22] or are surrogate markers of thrombus burden and thus theoretically would be associated with lower likelihood of recanalization. Additional analyses were performed adding variables that differed between the 2 treatment groups (strictly DOACs versus strictly warfarin) to the models. Fully adjusted models included the prespecified variables above as well as variables that significantly differed between the 2 groups on univariate analysis, and these were used for IPTW weighting and propensity score matching.

Sensitivity analyses included propensity score matching (with and without replacement, caliper 0.05) to test the associations between anticoagulant type and study outcomes given differences between treatment groups at baseline. For the major hemorrhage outcome, a sensitivity analysis was performed excluding asymptomatic intracranial hemorrhages from the major hemorrhage outcome. Furthermore, as the recurrent CVT outcome included both CVT extension and de novo CVT, we attempted to investigate the effect of DOACs versus warfarin on each of the 2. Since our study could not differentiate between these 2 outcomes and since in the clinical setting, extension of a previous CVT is likely to occur in the early timeframe after diagnosis, we used time of recurrent CVT as a surrogate marker to identify CVT extension cases. We used Cox regression analyses to compare the effect on DOAC versus warfarin on recurrent CVT occurring at 0 to 90 days and >90 days from diagnosis, which represents the typical time frame for recanalization assessment. We also performed the same analyses using the 2-week time cutoff[23] as well as the 4-week time cutoff. Additional sensitivity analyses were done for the IPTW models, excluding biologically plausible co-variates that lack supportive data to include described above. For major hemorrhage and recanalization, we excluded the co-variates baseline hemorrhage and deep venous involvement from the models; for recurrent VTE, we excluded the co-variate positive antiphospholipid antibodies from the models. We also ran separate

IPTW models excluding patients with COVID-19 and those without 90-day follow-up.

For Cox regression models, proportionality was assessed using Schoenfeld residuals and parametric survival model was used when proportionality was not met. One year Kaplan-Meier survival curves of recurrent venous thrombosis, major hemorrhage, and death were plotted using unadjusted models with start of follow-up at the time of oral anticoagulation initiation and censoring at either an event of interest, death, loss of follow-up, or discontinuation/switch of oral anticoagulant therapy. Data were analyzed using Stata (version 15.1), and a $P<0.05$ was considered statistically significant.

RESULTS

Among 1025 patients with CVT from 27 sites in the United States, Europe, and New Zealand (Figure S1), 845 patients met the inclusion criteria (Figure 1 depicts the study flow chart). The mean age of included subjects was 44.8 years, 64.7% (547) were women, and 84.3% (712) had at least 90-day follow-up; 33.0% (279) received DOAC only, 51.8% (438) received warfarin only, and 15.1% (128) received both treatments at different times. Among patients who used DOACs, 13.5% (55) used dabigatran, 18.2% (74) used rivaroxaban, and 66.6% (271) used apixaban, 1.7% (7) used other or multiple DOACs. The median (interquartile range) time from diagnosis to first follow-up imaging study was 102 (49–180) days.

During a median follow-up of 345 (interquartile range, 140–720) days, there were 5.68 recurrent venous thromboses (17 VTE, 27 recurrent CVT, 2 had both VTE, and recurrent CVT), 3.77 major hemorrhages (23 intracranial hemorrhage [19 symptomatic and 4 asymptomatic] and 9 extracranial hemorrhages), and 1.84 deaths per
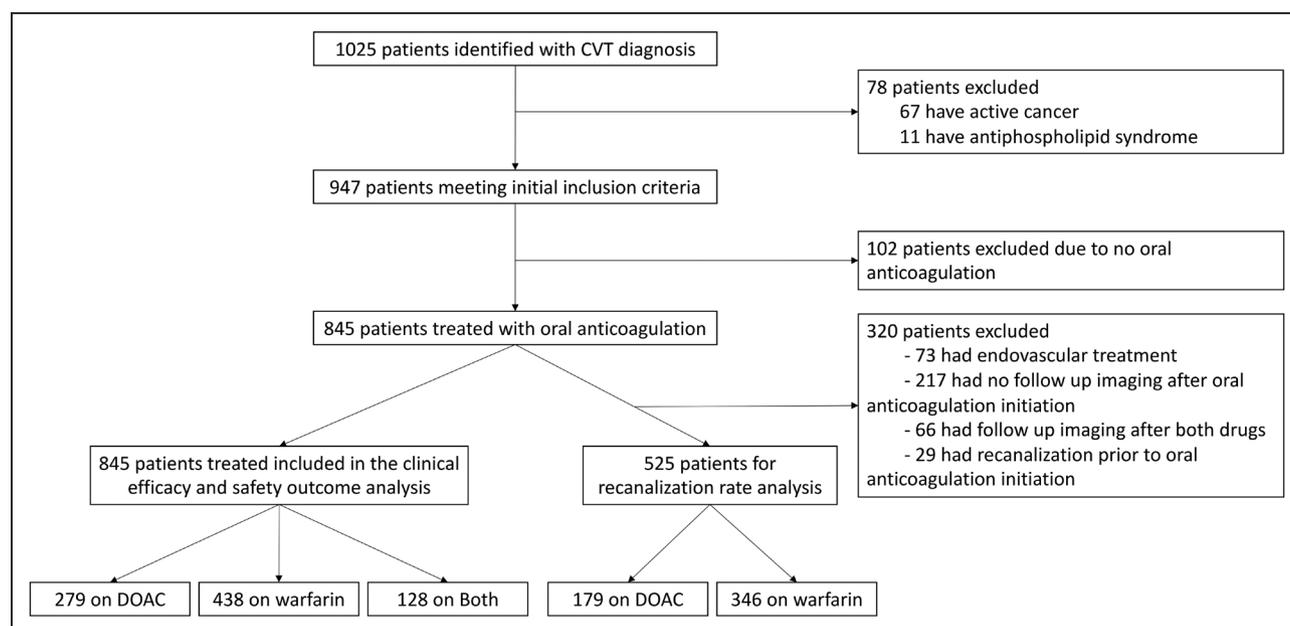
Figure 1. Study flow chart (note that some patients may have more than one reason for exclusion).
CVT indicates cerebral venous thrombosis; and DOAC, direct oral anticoagulants.

100 patient-years. Among 525 patients who met inclusion criteria for the recanalization outcome analysis, 192 (36.6%) had complete, 253 (48.2%) had partial, and 80 (15.2%) had no recanalization.

At least 90 day follow-up was available on 84.3% (712/845) of patients. compared with patients with <90 days of follow-up, patients with at least 90 days of follow-up data (n=712) were diagnosed later (4 days [interquartile range, 1–10] versus 3 days [interquartile range, 1–7]; P=0.033), had a higher BMI (29.6±7.7 versus 27.9±6.7; P=0.017), lower rates of tobacco use (11.7% versus 21.1%; P=0.004), and higher rate of endovascular treatment (9.7% versus 3.0%; P=0.011). Other characteristics were not significantly different between the 2 groups and are summarized in Table S1.

Univariate Analyses

In univariate analyses, when compared to patients treated strictly with warfarin, those treated strictly with DOACs were more likely to have a history of VTE (15.4% versus 6.6%, P<0.001), less likely to have one or more positive antiphospholipid antibodies (6.8% versus 12.1%, P=0.034), and less likely to have previously received low molecular weight heparin (33.3% versus 77.9%, P<0.001). Other characteristics including duration of anticoagulation and follow-up were not significantly different between the 2 groups (Table 1).

Association Between Oral Anticoagulation Type and Recurrent Venous Thrombosis

Figure 2 shows the 1-year Kaplan Meier survival analysis for recurrent venous thrombosis. Recurrent venous thrombosis during follow-up occurred in 5.26 per 100 patient-years on DOAC versus 5.87 per 100 patient years on warfarin (N=845, P=0.61). In unadjusted Cox-regression analyses, DOAC treatment was associated with a similar rate of recurrent VTE as warfarin treatment (hazard ratio [HR], 0.86 [95% CI, 0.47–1.56]; P=0.61). This finding remained unchanged after IPTW without adjustment (HR, 0.94 [95% CI, 0.50–1.74]; P=0.84), adjustment for prespecified variables (aHR, 0.94 [95% CI, 0.50–1.77]; P=0.86; model 1; Table 2) or variables that differed between the 2 groups (aHR, 0.94 [95% CI, 0.51–1.73]; P=0.84; model 2; Table 2).

Association Between Oral Anticoagulation Type and Major Hemorrhage

Figure 2 shows the 1-year Kaplan Meier survival analysis for major hemorrhage. Major hemorrhage occurred in 2.44 per 100 patient-years on DOAC versus 4.70 per 100 patient years on warfarin (N=845, P=0.06).

Intracranial hemorrhage occurred in 1.52 per 100 patient-years on DOAC versus 3.51 per 100 patient years on warfarin (N=845, P=0.05) and extracranial hemorrhage occurred in 0.91 per 100 patient-years on DOAC versus 1.15 per 100 patient years on warfarin (N=845, P=0.64). In unadjusted nonweighted Cox-regression analyses, DOAC treatment was associated with a marginally lower risk of major hemorrhage as compared with warfarin treatment (HR, 0.47 [95% CI, 0.21–1.04]; P=0.06). This finding became significant using IPTW without adjustment (HR, 0.34 [95% CI, 0.14–0.80]; P=0.01), adjustment for prespecified variables (aHR, 0.34 [95% CI, 0.15–0.80]; P=0.01; model 1; Table 2), and variables that differed between the 2 groups (aHR, 0.35 [95% CI, 0.15–0.82]; P=0.02; model 2; Table 2).

In sensitivity analysis excluding asymptomatic intracranial hemorrhage from the major hemorrhage outcomes and in the fully adjusted model (model 2), DOAC treatment was associated with a lower risk of major hemorrhage when compared with warfarin (N=720; aHR, 0.40 [95% CI, 0.16–0.995]; P=0.049).

Association Between Oral Anticoagulation Type and Death

Figure 2 shows the 1-year Kaplan Meier survival analysis for death. Death during follow-up occurred in 1.81 per 100 patient-years on DOAC versus 1.90 per 100 patient years on warfarin (N=845, P=0.97). In unadjusted nonweighted Cox regression analyses, DOAC treatment was associated with similar risk of death as warfarin treatment (HR, 1.02 [95% CI, 0.36–2.84]; P=0.97). This finding remained unchanged after IPTW, without adjustment (HR, 0.66 [95% CI, 0.22–2.02]; P=0.47), and after adjusting for prespecified variables (aHR, 0.75 [95% CI, 0.21–2.70]; P=0.66; model 1; Table 2) and variables that differed between the 2 groups (aHR, 0.78 [95% CI, 0.22–2.76]; P=0.70; model 2; Table 2).

Association Between Oral Anticoagulation Type and Venous Recanalization

Partial or complete recanalization occurred in 154 (86.0%) patients on DOAC versus 291 (84.1%) patients on warfarin (P=0.56). In unadjusted nonweighted binary-regression analyses DOAC treatment was associated with a similar rate of complete/partial recanalization as warfarin treatment (odds ratio [OR], 1.16 [95% CI, 0.70–1.94]; P=0.56). This finding remained unchanged after IPTW when unadjusted (OR, 0.88 [95% CI, 0.49–1.60]; P=0.69), adjusted for prespecified variables (aOR, 0.93 [95% CI, 0.47–1.83]; P=0.83; model 1; Table 2) and variables that differed between the 2 groups (aOR, 0.92 [95% CI, 0.48–1.73]; P=0.79; model 2; Table 2).

Table 1. Differences in Baseline Characteristics and Follow-Up Duration Across Patients Treated With DOAC Versus Warfarin

	Missing (n)	DOAC only (n=279)	Warfarin only (n=438)	P value
Age (mean±SD)	0	46.1±17.4	44.3±16.1	0.146
Sex (% women)	0	188/279(67.4%)	276/438(63.0%)	0.233
Race				
White	7	189/274(69.0%)	326/436(74.8%)	0.092
Black	7	47/274(17.2%)	54/436(12.4%)	0.077
Asian	7	15/274(5.5%)	16/436(3.7%)	0.252
Ethnicity (% Hispanic)	7	25/274(9.1%)	42/436(9.6%)	0.821
Body mass index (mean±SD)	41	29.4±7.9	29.2±7.5	0.742
History of VTE	0	43/279(15.4%)	29/438(6.6%)	<0.001
Family history of VTE	3	31/276(11.2%)	43/438(9.8%)	0.546
Recent head trauma	1	19/279(6.8%)	35/437(8.0%)	0.553
Recent mastoiditis or sinusitis	0	29/279(10.4%)	37/438(8.4%)	0.379
Recent lumbar puncture	0	11/279(3.9%)	18/438(4.1%)	0.912
Being within 12 weeks postpartum	6	9/278(3.2%)	17/433(3.9%)	0.633
Oral contraceptive use	15	65/278(23.4%)	117/424(27.6%)	0.213
Active smoking	3	28/277(10.1%)	64/437(14.6%)	0.078
Days from symptoms to diagnosis (median IQR)	54	4 (1−10)	4 (1−9)	0.391
Clinical presentation				
Headache	2	225/279(80.6%)	333/436(76.4%)	0.179
Focal deficit	1	111/279(39.8%)	169/437(38.7%)	0.766
Seizure	1	63/279(22.6%)	109/437(24.9%)	0.471
Coma*	1	5/279(1.8%)	8/437(1.8%)	1.000
Platelet count (mean SD)	15	269.8±93.9	269.8±102.8	0.994
One or more positive antiphospholipid antibody	111	16/235(6.8%)	45/371(12.1%)	0.034
Factor V and prothrombin mutation	189	24/201(11.9%)	31/327(9.5%)	0.369
Imaging findings				
Venous infarct	4	69/279(24.7%)	128/434(29.5%)	0.165
Cerebral edema	4	79/279(28.3%)	129/434(29.7%)	0.686
Intracranial hemorrhage	5	105/278(37.8%)	158/434(36.4%)	0.713
Heparin infusion	0	214/279(76.7%)	333/438(76.0%)	0.836
Low molecular weight heparin	0	93/279(33.3%)	341/438(77.9%)	<0.001
Endovascular treatment	0	25/279(9.0%)	28/438(6.4%)	0.200
Neurosurgical treatment	0	14/279(5.0%)	19/438(4.3%)	0.672
Duration of oral anticoagulation (median IQR)	0	194 (107−371)	202.5 (120−402)	0.459
Duration of treatment to imaging†	182	170 (88.5−257.5)	178 (90−309)	0.269
Duration of follow-up (median IQR)	0	308 (134−666)	307(130−718)	0.469
% and n with at least 90 days follow-up	0	238/279(85.3%)	357/438(81.5%)	0.187

DOAC indicates direct oral anticoagulants; IQR, interquartile range; and VTE, venous thromboembolism.
*Fisher exact test was performed instead.
†Imaging used for the recanalization analysis

Propensity Score Matching

Propensity score matching with replacement included 721 patients for primary outcome analysis, 720 patients for safety outcome and for death analyses, and 448 patients for recanalization outcome. In these analyses, DOAC treatment was associated with a similar risk of recurrent venous thrombosis (aHR, 0.95 [95% CI, 0.48−1.87]; P=0.88), death (aHR, 0.97 [95% CI, 0.31−2.99]; P=0.95), partial/complete recanalization (aOR, 0.59 [95% CI, 0.26−1.32]; P=0.20), and nonsignificantly lower risk of major hemorrhage (aHR, 0.42 [95% CI, 0.16−1.06]; P=0.07) as compared with warfarin treatment (Table 2). Using propensity score matching without replacement, the findings were similar for all outcomes: recurrent venous thrombosis (N=534; aHR, 0.72 [95% CI, 0.32−1.58]; P=0.41), major hemorrhage (N=532; aHR, 0.34 [95% CI, 0.12−0.95]; P=0.04),
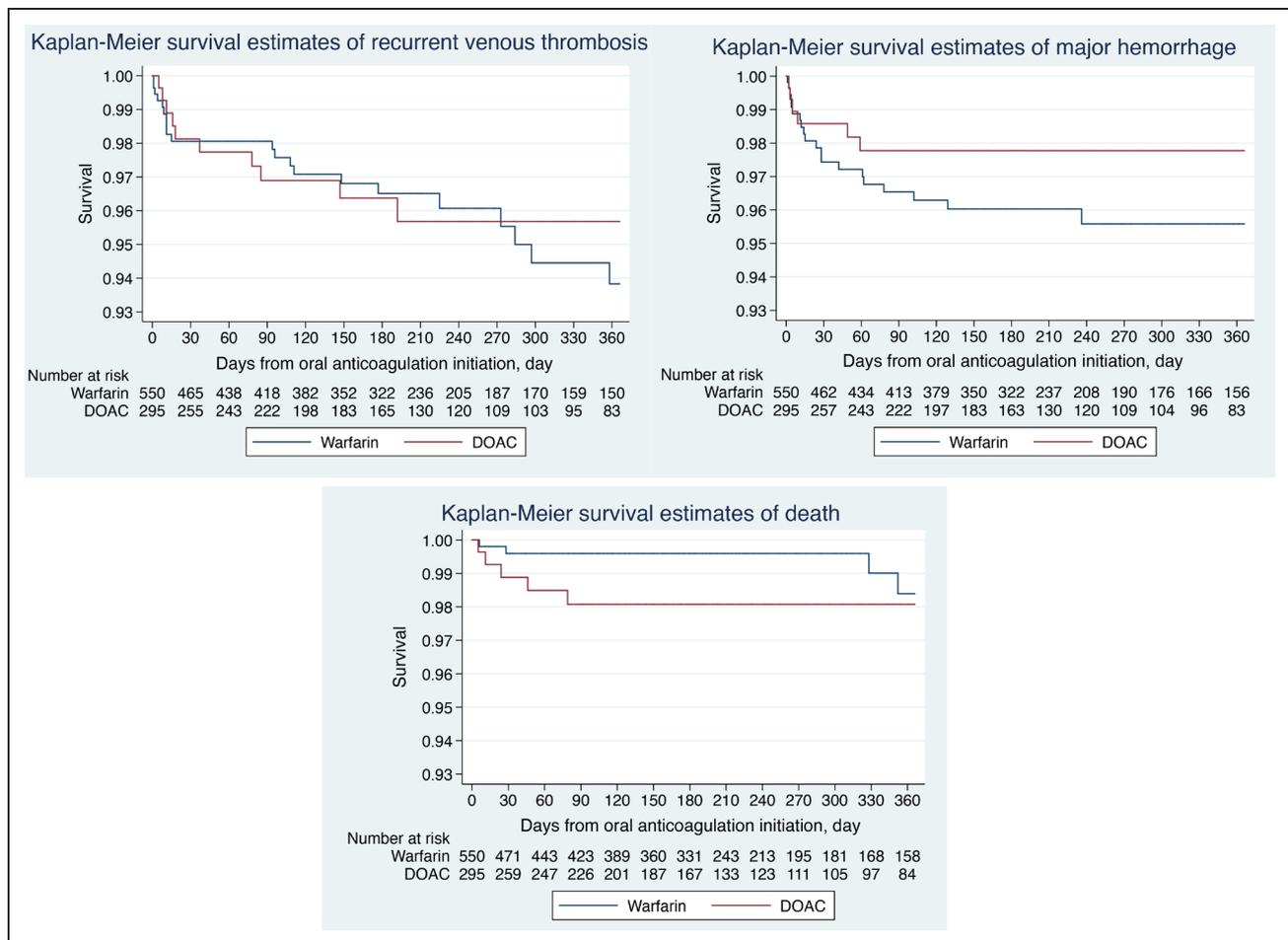
Figure 2. One-y Kaplan Meier survival analysis during follow-up.
Recurrent venous thrombosis (**left**), major hemorrhage (**right**), and death (**bottom**). Patients were included at the time of initiation of oral anticoagulation and were censored at the time of the event of interest, death, lost to follow-up, or discontinuation/switch anticoagulant therapy. DOAC indicates direct oral anticoagulants.

death (N=532; aHR, 0.83 [95% CI, 0.18–3.78]; P=0.81), and recanalization outcome (N=182; aHR, 1.47 [95% CI, 0.57–3.78]; P=0.43).

Sensitivity Analyses

Since deep venous involvement and baseline hemorrhage are not well-established predictors of recanalization and major hemorrhage, we performed sensitivity analyses excluding them from models 1 and 2. In these analyses, DOAC treatment was associated with similar partial or complete recanalization rates: model 1 (N=449; aOR, 0.87 [95% CI, 0.46–1.64]; P=0.66) and model 2 (N=449; aOR, 0.87 [95% CI, 0.47–1.59]; P=0.64), but lower risk of major hemorrhage during follow-up: model 1 (N=721; aHR, 0.34 [95% CI, 0.15–0.81]; P=0.01) and model 2 (N=721; aHR, 0.35 [95% CI, 0.15–0.81]; P=0.02).

In addition, since the presence of one or more positive antiphospholipid antibodies is not a known predictor of venous thrombosis recurrence and was not routinely performed on patients in our study, we performed sensitivity

analyses excluding this variable from models 1 and 2 of recurrent venous thrombosis outcome. In these analyses, DOAC treatment was associated with similar recurrent venous thrombosis rate: model 1 (N=845; aHR, 0.86 [95% CI, 0.49–1.49]; P=0.59) and model 2 (N=845; aHR, 0.85 [95% CI, 0.49–1.45]; P=0.55). Moreover, since the time of CVT recurrence may be a proxy for the CVT recurrence mechanism (extension versus de novo), we compared the 2 treatments with respect to recurrent CVT occurring within 90 days from oral anticoagulation initiation versus those occurring beyond 90 days from oral anticoagulation initiation. In these analyses using the fully adjusted IPTW model (model 2), DOAC was associated with a similar rate of CVT recurrence in the first 90 days (N=721; aHR, 1.13 [95% CI, 0.44–2.87]; P=0.80) versus beyond 90 days (N=721; aHR, 0.94 [95% CI, 0.33–2.72]; P=0.91). Using 2-week and 4-week cutoffs yielded similar findings.

Furthermore, we performed sensitivity analyses excluding patients who were event free of the outcome of interest but were lost to follow-up prior to 90 days. In these analyses and fully adjusted models (model 2),

Table 2.   Associations Between DOAC Versus Warfarin and Recurrent Venous Thrombosis, Major Hemorrhage, and Recanalization

	Unadjusted	Weighted unadjusted	Weighted model 1	Weighted model 2	Propensity matched*
Recurrent venous thrombosis	N=845	N=721	N=721	N=721	N=721
	HR, 0.86 (95% CI, 0.47–1.56); P=0.61	HR, 0.94 (95% CI, 0.50–1.74); P=0.84	HR, 0.94 (95% CI, 0.50–1.77); P=0.86	HR, 0.94 (95% CI, 0.51–1.73); P=0.84	HR, 0.95 (95% CI, 0.48–1.87); P=0.88
Major hemorrhage	N=845	N=720	N=720	N=720	N=720
	HR, 0.47 (95% CI, 0.21–1.04); P=0.06	HR, 0.34 (95% CI, 0.14–0.80); P=0.01	HR, 0.34 (95% CI, 0.15–0.80); P=0.01	HR, 0.35 (95% CI, 0.15–0.82); P=0.02	HR, 0.42 (95% CI, 0.16–1.06); P=0.07
Death	N=845	N=720	N=720	N=720	N=720
	HR, 1.02 (95% CI, −2.84); P=0.97	HR, 0.66 (95% CI, 0.22–2.02); P=0.47†	HR, 0.75 (95% CI, 0.21–2.70); P=0.66	HR, 0.78 (95% CI, 0.22–2.76); P=0.70	HR, 0.97 (95% CI, 0.31 −2.99); P=0.95
Partial/complete recanalization	N=525	N=448	N=448	N=448	N=448
	OR, 1.16 (95% CI, 0.70–1.94); P=0.56	OR, 0.88 (95% CI, 0.49–1.60); P=0.69	OR, 0.93 (95% CI, 0.47–1.83); P=0.83	OR, 0.92 (95% CI, 0.48–1.73); P=0.79	OR, 0.59 (95% CI, 0.26–1.32); P=0.20

Recurrent venous thrombosis: model 1 is adjusted for age, sex, history of prior VTE, one or more positive antiphospholipid antibody; model 2: adjusted for age, sex, history of prior VTE, one or more positive antiphospholipid antibody, and low molecular weight heparin use. Major hemorrhage and death: model 1 is adjusted for age, sex, intracranial hemorrhage at baseline, and deep CVT location; model 2 is adjusted for adjusted for age, sex, intracranial hemorrhage at baseline, deep CVT location, history of prior VTE, one or more positive antiphospholipid antibody, and low molecular weight heparin use. Partial complete recanalization: model 1 is adjusted for age, sex, intracranial hemorrhage at baseline, duration of anticoagulation therapy prior to repeat imaging, and deep CVT location; model 2 is adjusted for age, sex, intracranial hemorrhage at baseline, duration of anticoagulation therapy prior to repeat imaging, deep CVT location, history of prior VTE, one or more positive antiphospholipid antibody, and low molecular weight heparin us. Propensity matched models were adjusted for variables included in model 2 for each outcome

*Propensity matching with replacement, caliper 0.05.

†Parametric survival analysis was used as proportionality was not met per Schoenfeld residuals.

DOAC treatment was associated with a similar risk of recurrent venous thrombosis (N=623; aHR, 0.91 [95% CI, 0.50–1.67]; P=0.76), death (N=620; aHR, 0.69 [95% CI, 0.23–2.04]; P=0.50), and partial/complete recanalization (N=419; aOR, 0.91 [95% CI, 0.46–1.79]; P=0.79) but a lower risk of major hemorrhage (N=622; aHR, 0.33 [95% CI, 0.14–0.78]; P=0.01).

Finally, since part of the study was conducted during the COVID-19 pandemic, our study included patients with CVT in the setting of COVID-19 (n=6 patients). When such patients were excluded in sensitivity analyses, the findings remained unchanged.

DISCUSSION

This large, multicenter, international, retrospective, observational study found that, in a real-world cohort of patients diagnosed with CVT, DOAC treatment was associated with a similar risk of VTE recurrence, death, and CVT recanalization rates but a lower risk of major hemorrhage, as compared with warfarin treatment. These findings are consistent with other studies showing similar efficacy but improved safety with DOACs compared with warfarin.[24–26] Our findings are concordant with the RESPECT-CVT trial as well as systematic reviews and meta-analyses of small observational studies that suggested comparable outcomes with DOACs versus warfarin in patients with CVT.[10,27–29] Importantly, in contrast to previous studies,[10,27–29] we observed a reduced risk of major hemorrhage with DOACs compared with warfarin.

The goals of anticoagulation in patients with CVT are to reduce the risk of recurrent venous thrombosis, CVT extension, death, and achieve cerebral venous recanalization. Consistent with prior studies of VTE[3–6] or

CVT,[10,27–29] we observed a comparable risk of recurrent venous thrombosis and death in patients treated with warfarin versus DOACs. A further important goal in the management of patients with CVT is to promote recanalization, as it has been shown that lack of recanalization is associated with long-term morbidity including chronic headaches.[30] Arguably, recanalization aids in renormalizing elevated intracranial pressure and thus attenuates the risk of vision loss and chronic papilledema, as well as the development of a dural arterio-venous fistula due to persistent elevation in venous pressure. Similar to others,[10,27–29,31] we found similar recanalization rates in patients treated with DOAC versus warfarin treatment. It is also important to note that the recurrent CVT outcome in our study included progression of thrombosis while on oral anticoagulation. This is a clinically important outcome because thrombosis progression may lead to neurological deterioration, increased intracranial pressure, venous infarction, and promote intracerebral hemorrhage. This rate was captured in dabigatran treated patients in the RESPECT-CVT trial and was 1.7%,[10] which may possibly explain the difference between our recurrent CVT rate and that in prior observational studies.

The favorable safety profile of DOACs over warfarin in our study is consistent with data from non-CVT patient populations. For example, in patients with atrial fibrillation, apixaban has comparable risk of extracranial hemorrhage but lower risk of overall major and intracranial hemorrhage when compared with warfarin.[25] Rivaroxaban and dabigatran had similar rates of major and clinically relevant bleeding when compared with warfarin but lower risk of intracranial hemorrhage.[24,26] Furthermore, in patients with VTE, apixaban has been shown to have similar efficacy in recurrence VTE risk reduction but reduced

risk of hemorrhagic complications when compared with warfarin.[4] Additionally, a posthoc analysis of the RE-COVER and RE-COVER II trials (Efficacy and Safety of Dabigatran compared With Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism) showed similar risk of recurrent VTE or VTE-related mortality but reduced major hemorrhage in patients treated with dabigatran when compared with warfarin.[32] Interestingly, the improved safety of dabigatran over warfarin was only seen in younger patients, which more closely resembles the age group studied in our population.[32] An important challenge to consider about intracranial hemorrhage in the setting of CVT is that new or worsening hemorrhage may have been linked to progression of thrombosis and thus may be more linked to treatment efficacy as opposed to safety.

Our study supports current evidence that DOACs represent a reasonable alternative to warfarin in patients with CVT. Although DOACs do not require blood level monitoring, they generally are more expensive than warfarin. Thus, further studies are needed to test whether the improved safety profile of DOACs is cost-effective. Several studies suggest that DOACs offer a cost-effective alternative for patients with atrial fibrillation and those with VTE,[33,34] however, cost analyses are lacking for patients with CVT. Nevertheless, it is expected that once patent protection for DOACs expires more affordable generic drugs will become available.

Our study has several limitations inherent to its retrospective, observational design, and noncentral and non-blinded determination and adjudication of clinical and imaging outcomes. While we compared baseline characteristics between the 2 groups and included propensity score adjustment and matching, we cannot exclude the possibility of residual treatment-by-indication bias. Second, 15.7% of patients were lost to follow-up within 90-days. However, the baseline characteristics were overall similar between the patients with versus without at least 90-day follow-up, assuaging concerns about major attrition bias. Third, the low event rate of recurrent VTE in our study, which is consistent with other studies,[10,19,35] may have left us underpowered to show a difference between the 2 groups and precluded us from conducting detailed subgroup analyses. For example, CVT is a heterogenous disease for which it remains uncertain whether one treatment strategy may be better than the other in certain sub-populations. Fourth, recurrent CVT in our study included both de novo CVT as well as CVT extension. This may at least partially explain the higher recurrent CVT rates in our studies compared with others. While both are important outcomes to capture, we are unable to distinguish between the two with certainty in our study and thus it remains unknown if one treatment is superior to the other with respect to each of these outcomes. Fifth, we did not have data on international normalized ratio levels in warfarin treated

patients and thus some recurrence of venous thrombosis and major hemorrhage events may have been in the setting of subtherapeutic or supratherapeutic anticoagulation. This, however, reflects a true real-world experience in patients treated with warfarin. Sixth, the rate of asymptomatic hemorrhage in our study was likely low due to ascertainment bias since asymptomatic patients do not typically undergo follow-up brain imaging. Finally, the timing of follow-up imaging was heterogeneous among patients, limiting our recanalization status analysis.

CONCLUSIONS

Our findings provide real-world data supporting the use of DOACs as a reasonable alternative to warfarin treatment in patients with CVT. Given the study limitations, our findings should be interpreted with caution and require confirmation by large prospective observational studies such as the DOAC-CVT study (Direct Oral Anticoagulants in the Treatment of Cerebral Venous Thrombosis; https://clinicaltrials.gov; NCT04660747) and the ongoing randomized SECRET trial (Study of Rivaroxaban for Cerebral Venous Thrombosis; https://clinicaltrials.gov; NCT03178864).

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Disclosures

Supplemental Material

STROBE Checklist
Figure S1
Table S1

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