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

- Cerebral venous thrombosis (CVT) is an uncommon cause of stroke, usually affecting younger patients.
- In the absence of contraindications, parenteral followed by oral anticoagulation is the recommended treatment.
- 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.

AIM of the study

- 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 (I)

- The ACTION-CVT (Anticoagulation in the Treatment of Cerebral Venous Thrombosis) study is a multicenter, international (United States, Italy, Switzerland, New Zealand), retrospective, observational study that included consecutive adult patients with CVT treated with oral anticoagulation (warfarin or DOACs) over a period of 6 years.
- Demographics and CVT risk factors, hypercoagulable labs, baseline imaging data, and clinical and radiological outcomes were recorded.
- The outcomes of the study were:

✓ 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.

Methods (II)

- ✓Imaging outcomes: Recanalization status on last venous imaging study abstracted from radiology reports (no recanalization, partial recanalization, or complete recanalization).
- ✓Safety outcomes: Major hemorrhage defined as new or worsening intracranial hemorrhage or major extracranial hemorrhage defined as systemic hemorrhage.
- ✓Any death during follow-up.

Results (I)

- 845 patients met the 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 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.

Results (II)

- When compared with warfarin, DOAC treatment was associated with similar risk of recurrent venous thrombosis (P=0.84), death (P=0.70), and rate of partial/complete recanalization (P=0.79), but a lower risk of major hemorrhage (P=0.02).

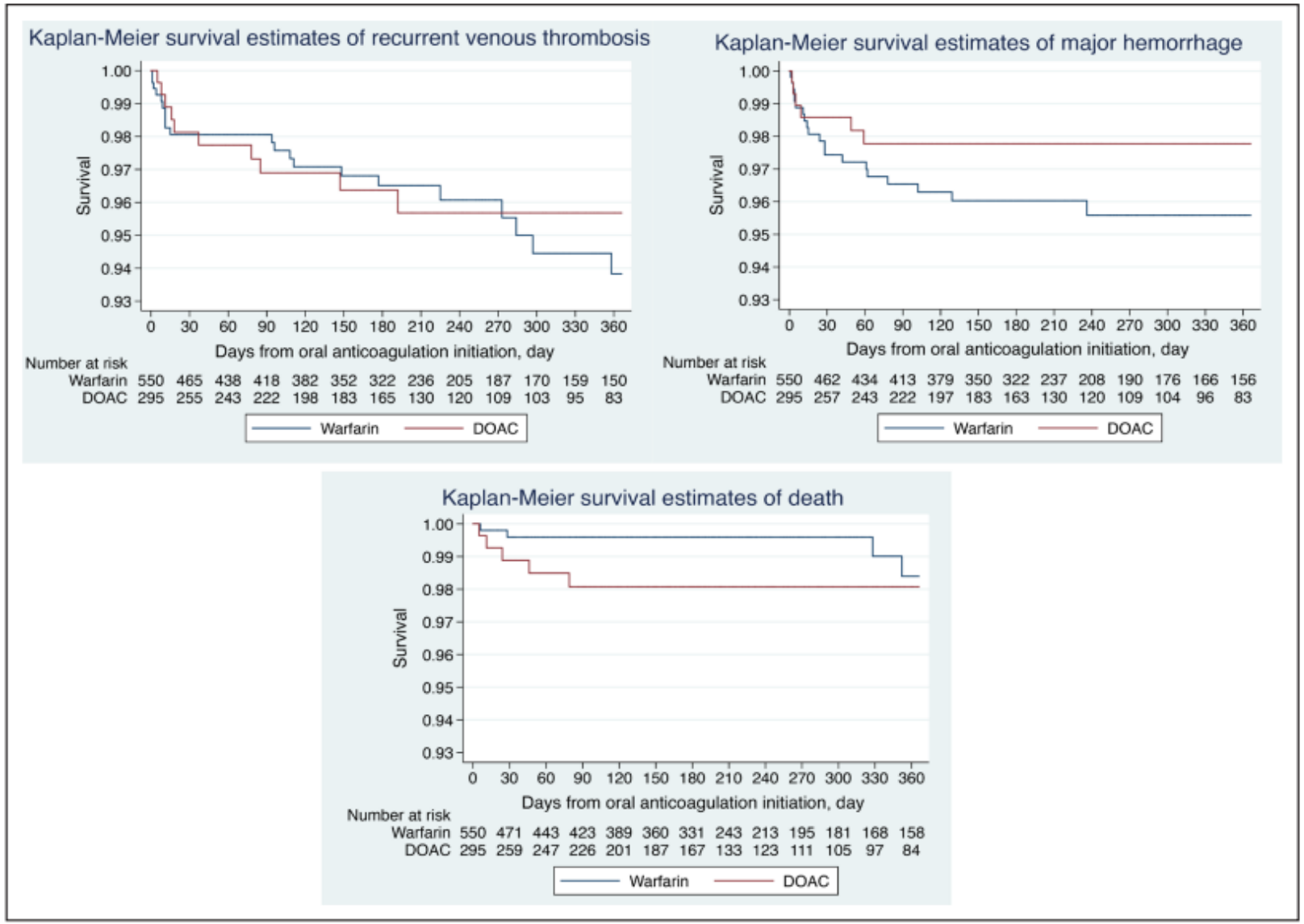

Figure 2. One-y Kaplan Meier survival analysis during follow-up.
Recurrent venous thrombosis (**left**), major hemorrhage (**right**), and death (**bottom**). Patients were included at the time of initiation of oral anticoagulation and were censored at the time of the event of interest, death, lost to follow-up, or discontinuation/switch anticoagulant therapy. DOAC indicates direct oral anticoagulants.

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, 0.36 –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.

Conclusions

- 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.
- Our study supports current evidence that DOACs represent a reasonable alternative to warfarin in patients with CVT.
- These findings 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.