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Recanalization after cerebral venous thrombosis. A randomized controlled trial of the safety and efficacy of dabigatran etexilate versus dose-adjusted warfarin in patients with cerebral venous and dural sinus thrombosis

José M Ferro[1,2,3], Martin Bendszus[4], Olav Jansen[5], Jonathan M Coutinho[6], Francesco Dentali[7], Adam Kobayashi[8], Diana Aguiar de Sousa[1,2,3], Lia L Neto[3,9], Corinna Miede[10], Jorge Caria[11], Holger Huisman[12], Hans-Christoph Diener[13] and on behalf of the RE-SPECT CVT Study Group

Abstract

Background: The effect of different anticoagulants on recanalization after cerebral venous thrombosis has not been studied in a randomized controlled trial.

Methods: RE-SPECT CVT (ClinicalTrials.gov number: NCT02913326) was a Phase III, prospective, randomized, parallel-group, open-label, multicenter, exploratory trial with blinded endpoint adjudication. Acute cerebral venous thrombosis patients were allocated to dabigatran 150 mg twice daily, or dose-adjusted warfarin, for 24 weeks, after 5–15 days' treatment with unfractionated or low-molecular-weight heparin. A standardized magnetic resonance protocol including arterial spin labeling, three-dimensional time-of-flight venography, and three-dimensional contrast-enhanced magnetic resonance angiography was obtained at the end of the treatment period. Cerebral venous recanalization at six months was assessed by two blinded adjudicators, using the difference in a score of occluded sinuses and veins (predefined secondary efficacy endpoint) and in the modified Qureshi scale (additional endpoint), between baseline and the end of the treatment.

Results: Of 120 cerebral venous thrombosis patients randomized, venous recanalization could be evaluated in 108 (55 allocated to dabigatran and 53 to warfarin, 1 patient had a missing occlusion score at baseline). No patient worsened in the score of occluded cerebral veins and sinuses, while 33 (60%) on dabigatran and 35 (67%) on warfarin improved. The mean score change from baseline in the occlusion score was similar in the two treatment groups (dabigatran −0.8, SD 0.78; warfarin −1.0, SD 0.92). In the modified Qureshi score, full recanalization was adjudicated in 24 (44%) and 19 (36%), and partial recanalization in 23 (42%) and 26 (49%) patients in the dabigatran and warfarin arms, respectively. No statistically significant treatment difference in the modified Qureshi score could be detected ($p = 0.44$).

Conclusion: The majority of patients with cerebral venous thrombosis, anticoagulated with either dabigatran or warfarin for six months, showed partial or complete recanalization of occluded sinuses and veins at the end of the treatment.

[1]Department of Neurosciences and Mental Health, Serviço de Neurologia, Hospital Santa Maria, Lisbon, Portugal
[2]Instituto de Medicina Molecular, Universidade de Lisboa, Lisboa, Portugal
[3]Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
[4]Neurologische Klinik, Abteilung für Neuroradiologie, Universitätsklinikum Heidelberg, Heidelberg, Germany
[5]Department of Radiology and Neuroradiology, University of Kiel, Kiel, Germany
[6]Department of Neurology, Amsterdam University Medical Centers, Amsterdam, the Netherlands
[7]Department of Medicine and Surgery, Insubria University, Varese, Italy
[8]Faculty of Health Sciences and Physical Education, Kazimierz Pulaski University of Technology and Humanities, Radom, Poland
[9]Serviço de Neuroradiologia, Hospital Santa Maria/Centro Hospitalar Lisboa Norte, Lisboa, Portugal
[10]HMS Analytical Software GmbH, Weimar (Lahn), Germany
[11]Boehringer Ingelheim International, Ingelheim am Rhein, Germany
[12]Boehringer Ingelheim B.V., Alkmaar, the Netherlands
[13]Faculty of Medicine, University Duisburg-Essen, Essen, Germany

Corresponding author:
José M Ferro, Faculdade de Medicina, Hospital Santa Maria, Neurology, Universidade de Lisboa, 6th Floor, Avenida Professor Egas Moniz s/n 1649-035 Lisbon, Portugal.
Email jmferro@medicina.ulisboa.pt

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Introduction

After cerebral venous thrombosis (CVT), recanalization of thrombosed dural sinuses and cerebral veins has been reported in 80–89% of CVT patients.[1] Recanalization is associated with better outcomes[1] and in some studies with a lower risk of CVT recurrence.[1,2] No randomized trials have evaluated the effects of anticoagulation, or of different types of anticoagulants, on recanalization after CVT.

We report the effect of dabigatran and of dose-adjusted warfarin on recanalization after CVT in a randomized, controlled trial (RE-SPECT CVT).[3,4]

Methods

RE-SPECT CVT (ClinicalTrials.gov number: NCT02913326) was a Phase III, prospective, randomized, parallel-group, open-label, multicenter, exploratory trial with blinded endpoint adjudication.[3,4] Enrolled patients had acute CVT confirmed by magnetic resonance (MR) imaging plus MR venography, computed tomography (CT) plus computed tomographic venography, or intra-arterial venography. Patients were allocated to dabigatran 150 mg twice daily or dose-adjusted warfarin, for 24 weeks, after 5–15 days' treatment with unfractionated or low-molecular weight heparin. A standardized MR protocol including three-dimensional (3D) T1, diffusion-weighted imaging, 2D fluid attenuated inversion recovery, susceptibility-weighted imaging, T2*, venous 3D time-of-flight angiography, 3D contrast-enhanced MR angiography, and T2-weighted turbo spin echo was applied at the end of treatment (see Supplementary Methods in the Supplementary Materials).

As a secondary efficacy outcome, we assessed cerebral venous recanalization, measured by the change from baseline to repeat neuroimaging at the end of the trial by two blinded independent adjudicators (senior neuroradiologists with expertise in CVT) using the cerebral venous occlusion score (CVOS) (thrombus load).[5] Full occlusion was scored 1 point, and no or partial occlusion 0 points, applied to each dural sinus and to the deep and superficial cerebral and to cerebellar veins. Additionally, as a further efficacy endpoint, the modified Qureshi scale[6] (see Supplementary Methods in Supplementary Materials) was calculated after 24 weeks. The standard procedure for adjudication of recanalization was as follows: for the first 10 cases adjudication was performed by the two neuroradiologists. If there was concordance on the occlusion total score in at least 9 out of 10 cases, adjudication would continue with one reviewer; otherwise, adjudication would proceed with two reviewers for the next 10 cases, until there was concordance in 9 or 10 out of 10 cases.

Statistical analysis

The frequencies of recanalization on the CVOS were analyzed descriptively both using shift tables and by means of descriptive statistics. For the modified Qureshi scale, shift tables were also provided. The comparison of the modified Qureshi scale between treatment arms (dabigatran and warfarin) was done by an exploratory analysis using the van Elteren test, adjusting for the presence of intracranial hemorrhage at baseline. Grades II A and II B were combined to Grade II for this analysis. Patients with missing or not analyzable MR imaging scans at the end of treatment were excluded from this analysis.

Based on previous medical knowledge, we considered treatment arm, occlusion score at baseline, age, sex, body mass index, thrombophilia, days on treatment, and days on heparin as potential predictors of recanalization. For the Qureshi score, we used a stepwise, multivariable, ordinal, logistic regression analysis including these potential predictors as explanatory variables and applying a backward selection with 0.2 as the significance level of the Wald chi-square for an effect to stay in the model in a backward elimination step. For the CVOS at the end of treatment, a stepwise factorial analysis of covariance (ANCOVA) was performed, including all the above-mentioned potential predictors as explanatory variables and applying the same backward selection algorithm, but keeping "occlusion score at baseline" as a covariate in any case.

We explored the influence of recanalization on outcome, defined by the modified Rankin Scale (mRS) at the end of the trial, using different categorizations for the mRS scores. The association of recanalization with outcome was analyzed with a Cochran-Armitage trend

test (mRS score categorized as 0, 1, and >1 versus modified Qureshi scale grade dichotomized as grade 0 and grade I, II, III combined) and multivariable logistic regression analysis (mRS score dichotomized as 0–1 versus >1; modified Qureshi scale grades dichotomized as 0 versus I, II, and III; CVOS scores). Furthermore, the mRS score (categorized as 0, 1, 2, and >2) was analyzed by the dichotomized modified Qureshi scale using a shift table.

The study was approved by each site's institutional review board/Ethics Committee and by National Ethics Committees for Clinical Research whenever required.

Results

Twelve patients out of 120 randomized patients with CVT could not participate in the recanalization analysis: eight patients did not undergo repeat follow-up imaging, one had no baseline imaging for review, one had baseline, and two had follow-up imaging of insufficient quality. Therefore, 108 patients were included in the analysis; 55 were allocated to dabigatran and 53 to warfarin (Figure 1). The characteristics of these patients are described in Table 1. For one patient, the CVOS from baseline to the end of the treatment was missing due to a missing baseline occlusion score; the modified Qureshi scale could be assessed for this patient though.

There was concordance between the two adjudicators on the total occlusion score and on the Qureshi grading in at least 9 of 10 cases after 30 cases. For the remaining cases, adjudication proceeded with only one adjudicator. The mean CVOS change from baseline was similar in the two treatment groups (dabigatran −0.8, SD 0.78; warfarin −1.0, SD 0.92). The frequencies of recanalization on the CVOS and Qureshi scale were similar for dabigatran and warfarin (Table 2). No statistically significant treatment difference in the

Figure 1. Patient disposition.

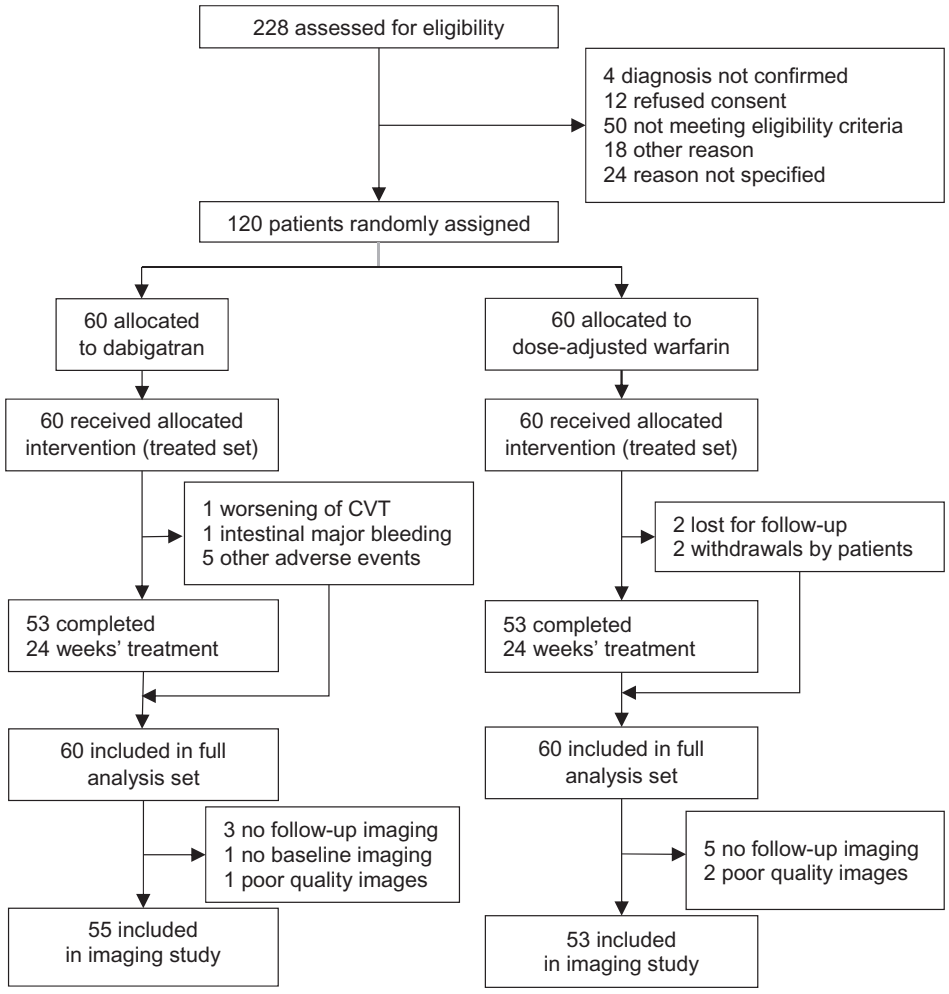

Table 1. Baseline characteristics (108 patients)

	Dabigatran ($n = 55$)	Warfarin ($n = 53$)
Sex (%)		
Male	24 (43.6)	21 (39.6)
Female	31 (56.4)	32 (60.4)
Age (years) (%)		
<30	7 (12.7)	7 (13.2)
30–49	32 (58.2)	30 (56.6)
≥50	16 (29.1)	16 (30.2)
Diagnosis of CVT (%)		
MR with MR venography	46 (83.6)	41 (77.4)
CT with CT venography	13 (23.6)	19 (35.8)
MR with catheter angiography	2 (3.6)	3 (5.7)
CT with catheter angiography	4 (7.3)	3 (5.7)
Parenchymal lesion on diagnostic neuroimaging (%)		
Any lesion	23 (41.8)	21 (39.6)
Nonhemorrhagic lesion	10 (18.2)	10 (18.9)
Hemorrhagic lesion	17 (30.9)	18 (34.0)
Sinuses involved (%)		
Superior sagittal sinus	23 (41.8)	19 (35.8)
Left lateral sinus	24 (43.6)	30 (56.6)
Right lateral sinus	30 (54.5)	24 (45.3)
Straight sinus	8 (14.5)	9 (17.0)
Deep venous system	7 (12.7)	5 (9.4)
Cortical veins	11 (20.0)	14 (26.4)
Cerebellar veins	0	1 (1.9)
Jugular vein	20 (36.4)	18 (34.0)
Cavernous sinus	1 (1.8)	2 (3.8)
Other vein or sinus	5 (9.1)	5 (9.4)
Symptoms/signs (%)		
Coma (Glasgow Coma Scale <9)	0	0
Decreased alertness (Glasgow Coma Scale 9–14)	2 (3.6)	3 (5.7)

(continued)

Table 1. Continued

	Dabigatran ($n = 55$)	Warfarin ($n = 53$)
Mono-/Hemiparesis	10 (18.2)	8 (15.1)
Seizure	12 (21.8)	14 (26.4)
Headache	51 (92.7)	48 (90.6)
Mental status disorder	3 (5.5)	4 (7.5)
Aphasia	5 (9.1)	6 (11.3)
Visual loss	7 (12.7)	3 (5.7)
Papilledema	9 (16.4)	4 (7.5)
Diplopia, oculomotor palsy	5 (9.1)	4 (7.5)
Risk factors/associated conditions (%)		
Oral contraceptive use	18 (32.7)	18 (34.0)
Body mass index $\geq$25 to $<$30 kg/m^2	14 (25.5)	22 (41.5)
Body mass index $\geq$30 kg/m^2	12 (21.8)	14 (26.4)
Previous venous thromboembolism	3 (5.5)	6 (11.3)
Previous cerebral venous thrombosis	0	2 (3.8)
Genetic thrombophilia	4 (7.3)	3 (5.7)
Infection (ear, nose, throat)	4 (7.3)	2 (3.8)
Surgery	3 (5.5)	2 (3.8)
Puerperium	1 (1.8)	1 (1.9)
Severe dehydration	1 (1.8)	1 (1.9)
Drugs with prothrombotic effect	2 (3.6)	0
Malignancy (>6 months)	0	1 (1.9)
Inflammatory bowel disease	0	1 (1.9)
Other inflammatory systemic disorder	0	1 (1.9)
Mechanical precipitants	1 (1.8)	0
National Institutes of Health Stroke Scale (%)		
0	41 (74.5)	43 (81.1)
1–4	13 (23.6)	9 (17.0)
5–15	1 (1.8)	1 (1.9)
16–42	0	0

CT: computed tomography; CVT: cerebral venous thrombosis; MR: magnetic resonance.

modified Qureshi score could be detected (van Elteren test: $p = 0.44$). On the Qureshi scale, only 14–15% of the patients did not show any recanalization.

The final model of the stepwise factorial ANCOVA suggests that female sex and days on oral anticoagulant treatment predicted recanalization on the CVOS, while the final model of the multivariable ordinal logistic regression included treatment arm (dabigatran), female sex, CVOS at baseline, and days on oral anticoagulant as predictors for recanalization on the Qureshi scale (Table 3).

Table 2. Recanalization at the end of the treatment (24 weeks)

	Dabigatran	Warfarin
Cerebral venous occlusion score	55 patients	52 patients*
Improved	33 (60.0%)	35 (67.3%)
No change	22 (40.0%)	17 (32.7%)
Modified Qureshi score	55 patients	53 patients
Full recanalization	24 (43.6%)	19 (35.8%)
Partial recanalization	23 (41.8%)	26 (49.1%)
No recanalization	8 (14.5%)	8 (15.1%)

*In one patient, baseline images were of insufficient quality to assess cerebral venous occlusion score.

At the end of the treatment, 82 (75.9%), 19 (17.6%), and 7 (6.5%) patients were classified respectively 0, 1, and 2 on the mRS. No patient scored more than 2. There was no statistically significant difference (Cochran-Armitage trend test = 0.36) on functional outcome between patients with no recanalization and any degree of recanalization on the Qureshi scale in the total population of 108 patients (Supplementary Table). On logistic regression, recanalization was not a statistically significant predictor of functional outcome, either on the Qureshi scale or on the CVOS (Table 4).

Discussion

We observed that the majority of patients with acute CVT anticoagulated with either dabigatran or warfarin for six months showed partial or complete recanalization of occluded sinuses and veins at the end of the treatment. Recanalization rates (85–86% Qureshi scale) were within the range reported in a recent meta-analysis (85%; 95% confidence interval 80–89%).[1] The recanalization results are in line with the primary outcome result of the trial, which showed that the number of patients with recurrent venous thrombotic events or major bleedings was very low and similar in the two treatment arms. Multivariable regression analyses suggest that for both scales, longer time on treatment was a predictor of recanalization.

This prespecified secondary analysis of the RESPECT CVT study benefits from the trial strengths.

Table 3. Predictors of recanalization.

	CVOS at the end of the treatment		
	Estimate	95% CI	*p* Value
Female versus male	−0.208	−0.355 to −0.600	0.006
Days on treatment	−0.002	−0.005 to 0.001	0.170
Factorial ANCOVA controlling for CVOS at baseline. Number of observations used in final model obtained with backward selection, $p<0.2$: 107.			
	Qureshi scale (0, I, II, III) at the end of the treatment		
	Odds ratio	95% CI	*p* Value
Dabigatran versus warfarin	0.62	0.30–1.26	0.188
Female versus male	0.46	0.22–0.95	0.040
Occlusion score at baseline	0.68	0.42–1.11	0.122
Days on treatment (each 28 days)	0.61	0.40–0.93	0.021

Multivariable ordinal logistic regression analysis; number of observations used in the final model obtained with backward selection, $p < 0.2$: 107. Odds ratios are for a lower response. ANCOVA: analysis of covariance; CI: confidence interval; CVOS: cerebral venous occlusion score.

Table 4. Multivariable logistic regression analysis for the influence of recanalization on functional outcome (dichotomized modified Rankin Scale)

	mRS 0–1 versus >1		
	OR	95% CI	*p* Value
Qureshi scale 0 versus I, II, and III			
Recanalization versus no recanalization	2.50	0.44–14.17	0.30
Treatment			
Dabigatran versus warfarin	0.76	0.16–3.59	0.73
Cerebral venous occlusion score			
Occlusion score at baseline	0.66	0.25–1.74	0.40
Occlusion score at the end of treatment	0.51	0.09–2.86	0.44
Treatment			
Dabigatran versus warfarin	0.74	0.15–3.53	0.70

CI: confidence interval; mRS: modified Rankin Scale; OR: odds ratio.

RESPECT CVT is the largest randomized clinical trial in CVT up to now and the first to assess the efficacy and safety of oral anticoagulants on cerebral venous recanalization. To document recanalization, an end-of-treatment, standardized MR/MR angiography with contrast was performed and two expert adjudicators evaluated recanalization blindly.

Nevertheless, our study has several limitations. RESPECT CVT was an exploratory trial not powered to detect statistically significant differences between the two treatment arms. Thus, the results presented here are from exploratory analyses. The severity of CVT in the patients included in the study was mild to moderate, as we had to exclude patients who could not swallow, because dabigatran capsules cannot be smashed. So, we cannot exclude that differences between the two treatment arms could have been detected in a larger sample or in patients not included in a clinical trial. Baseline (CT + CT venography or MR + MR venography) and end-of-treatment evaluations (MR + MR venography) used different imaging modalities and protocols in some patients. Still, the blinded adjudicators compared the baseline with the end-of-treatment images to establish the degree of recanalization. The patients included in the trial received unfractionated or low-molecular-weight heparin for 5–15 days until they were stable and before being allocated to dabigatran or warfarin. A recent prospective cohort study found that as early as eight days after diagnosis, 68% of the CVT patients already showed partial, and 6% full, recanalization of the occluded sinuses or veins.[7] As we did not obtain cerebral venous imaging at the end of heparin treatment, but only at end of the trial, we cannot exclude that the main effect on venous recanalization was due to heparin treatment and not to the action of oral anticoagulants.

We found no influence of recanalization on functional outcome (mRS). This result diverges from the results of a recent meta-analysis,[1] which showed a better outcome in patients with any degree of cerebral venous recanalization. However, our study was not powered to detect a difference in outcome based on recanalization status. Furthermore, there were no subjects classified in the mRS as >2 at the end of the treatment. Nevertheless, our results suggest that the meta-analysis deserves to be updated.

Days on oral anticoagulant treatment predicted recanalization. The clinical relevance of this finding needs confirmation by trials comparing different duration of anticoagulant treatment after acute CVT.[8]

In conclusion, there were no differences in cerebral venous recanalization as measured by two different recanalization scales after 24 weeks of treatment with either dabigatran or warfarin, preceded by 5–15 days of parenteral heparin.

Data-sharing statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the International Committee of Medical Journal Editors criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can also be requested via the link https://trials.boehringer-ingelheim.com/

All requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of one year, which may be extended upon request.

Researchers should use the https://trials.boehringer-ingelheim.com/ link to request access to study data.

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ORCID iDs

José M Ferro https://orcid.org/0000-0002-2343-9097
Diana Aguiar de Sousa https://orcid.org/0000-0002-6702-7924
Holger Huisman https://orcid.org/0000-0001-8344-6267
Hans-Christoph Diener https://orcid.org/0000-0002-6556-8612

Supplemental material

Supplemental material for this article is available online.

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