Novel Factor Xa Inhibitor for the Treatment of Cerebral Venous and Sinus Thrombosis
First Experience in 7 Patients

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Background and Purpose—Thrombosis of cerebral veins and sinus (cerebral venous thrombosis) is a rare stroke pathogenesis. Pharmaceutical treatment is restricted to heparin and oral anticoagulation with vitamin K antagonists (VKAs).

Methods—Between January 2012 and December 2013, we recorded data from our patients with cerebral venous thrombosis. The modified Rankin scale was used to assess clinical severity; excellent outcome was defined as modified Rankin scale 0 to 1. Recanalization was assessed on follow-up MR angiography. Patients were then divided into 2 treatment groups: phenprocoumon (VKA) and a novel factor Xa inhibitor. Clinical and radiological baseline data, outcome, recanalization status, and complications were retrospectively compared.

Results—Sixteen patients were included, and 7 were treated with rivaroxaban. Overall outcome was excellent in 93.8%, and all patients showed at least partial recanalization. No statistical significant differences were found between the groups, except the use of heparin before start of oral anticoagulation \((P=0.03)\). One patient in the VKA and 2 patients in the factor Xa inhibitor group had minor bleeding \((P=0.55)\) within the median (range) follow-up of 8 months (5–26).

Conclusions—Factor Xa inhibitor showed a similar clinical benefit as VKA in the treatment of cerebral venous thrombosis. Further systematic prospective evaluation is warranted. (Stroke. 2014;45:2469-2471.)

Key Words: cerebral veins ■ rivaroxaban ■ thrombosis
partial or complete according to Stolz et al\(^3\) by 2 investigators blinded to treatment on consensus basis (C.H. and S.N.). Excellent outcome was defined as modified Rankin scale 0 to 1. Patients were divided into 2 groups according to the regime of OAC. We then compared the treatment groups regarding clinical and radiological baseline data, outcome, recanalization status, and complications. All analyses were done retrospectively with the Fisher, \(\chi^2\), or the Mann–Whitney test.

### Table. Description of the Entire Cohort and the Comparison of the 2 Treatment Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients</th>
<th>VKA</th>
<th>FXal</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex female</td>
<td>13 (81.25%)</td>
<td>6</td>
<td>7</td>
<td>0.21</td>
</tr>
<tr>
<td>Age (median, min–max)*</td>
<td>36, 17–75</td>
<td>43, 17–69</td>
<td>31, 18–75</td>
<td>0.61</td>
</tr>
<tr>
<td>Oral contraception</td>
<td>5/13 (38.5%)</td>
<td>3/6</td>
<td>2/7</td>
<td>0.59</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (25%)</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy/puerperium</td>
<td>2 (12.5%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Steroids</td>
<td>2 (12.5%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>4 (25%)</td>
<td>2</td>
<td>2</td>
<td>0.55</td>
</tr>
<tr>
<td>Previous thrombembolic event</td>
<td>4 (25%)</td>
<td>3</td>
<td>1</td>
<td>0.58</td>
</tr>
<tr>
<td>Clinical syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11 (68.75%)</td>
<td>5</td>
<td>6</td>
<td>0.31</td>
</tr>
<tr>
<td>Seizures</td>
<td>6 (37.5%)</td>
<td>4</td>
<td>2</td>
<td>0.63</td>
</tr>
<tr>
<td>Paresis</td>
<td>3 (18.75%)</td>
<td>3</td>
<td>0</td>
<td>0.21</td>
</tr>
<tr>
<td>Aphasia</td>
<td>4 (25%)</td>
<td>3</td>
<td>1</td>
<td>0.58</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>4 (25%)</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Affected vessel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse sinus</td>
<td>14 (87.5%)</td>
<td>8</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Superior sagittal sinus</td>
<td>6 (37.5%)</td>
<td>5</td>
<td>1</td>
<td>0.15</td>
</tr>
<tr>
<td>Deep veins, including inferior sagittal sinus and straight sinus</td>
<td>2 (12.5%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cortical veins</td>
<td>4 (25%)</td>
<td>1</td>
<td>3</td>
<td>0.26</td>
</tr>
<tr>
<td>Jugular vein</td>
<td>8 (50%)</td>
<td>6</td>
<td>2</td>
<td>0.36</td>
</tr>
<tr>
<td>Brain lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>5 (31.25%)</td>
<td>4</td>
<td>1</td>
<td>0.31</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4 (25%)</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Venous infarction</td>
<td>3 (18.75%)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>mRS on admission (median, min–max)*</td>
<td>1, 0–4</td>
<td>1, 0–4</td>
<td>1, 0–3</td>
<td>0.61</td>
</tr>
<tr>
<td>mRS at discharge (median, min–max)*</td>
<td>1, 0–2</td>
<td>0, 0–2</td>
<td>1, 0–1</td>
<td>0.76</td>
</tr>
<tr>
<td>Duration of hospital stay (median, min–max)*</td>
<td>5, 3–11</td>
<td>5, 3–11</td>
<td>6, 3–8</td>
<td>0.92</td>
</tr>
<tr>
<td>Heparin regime†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>4 (25%)</td>
<td>4</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>LMWH</td>
<td>9 (56.25%)</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Both (switch)</td>
<td>3 (18.75%)</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Start of OAC (days: median, min–max)*</td>
<td>5, 1–21</td>
<td>5, 1–21</td>
<td>6, 3–9</td>
<td>1</td>
</tr>
<tr>
<td>Duration of OAC (months: median, min–max)*‡</td>
<td>9, 6–26</td>
<td>9, 7–26</td>
<td>8, 6–12</td>
<td>0.23</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to follow-up (months: median, min–max)*</td>
<td>8, 5–26</td>
<td>10, 6–26</td>
<td>7, 5–12</td>
<td>0.14</td>
</tr>
<tr>
<td>Excellent (mRS 0–1)</td>
<td>15 (93.75%)</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>mRS 2</td>
<td>1 (5.9%)</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Recanalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to last MRI (months: median, min–max)*</td>
<td>7, 6–26</td>
<td>6, 6–26</td>
<td>7, 6–12</td>
<td>0.54</td>
</tr>
<tr>
<td>Overall complete recanalization</td>
<td>8 (50%)</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Overall partial recanalization</td>
<td>8 (50%)</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Minor bleeding complication</td>
<td>3 (18.75%)</td>
<td>1</td>
<td>2</td>
<td>0.55</td>
</tr>
</tbody>
</table>

LMWH indicates low molecular weight heparin; mRS, modified Rankin scale; OAC, oral anticoagulation; and UFH, unfractioned heparin.

Statistical analysis was performed with the Mann—Whitney test (*), the Fisher, or the \(\chi^2\) (†).

‡One patient in each group aquired a lifelong indication for OAC, and 2 patients in each group are still on OAC.
A thrombus 9 months later (with CVT). Recanalization rates and clinical outcome were previously published and prospectively collected cohort of patients lesions of our patients are comparable to the largest previ-
ously published and prospectively collected cohort of patients.

Demographic data, risk factors, affected vessels, and brain
volumes of the jugular vein (A) and the overall complete recanalization with a small residual
thrombus 9 months later (B). T2-weighted imaging shows hemor-
rhage in the temporal lobe (A) and the gliotic scar on follow-up (B).

Results
Of 30 patients with CVT, 14 had to be excluded because of
the above mentioned criteria. Seven of the remaining 16
were treated with rivaroxaban, another 9 with phenprocou-
mon. Detailed characteristics of all patients are summarized
in the Table. Within the whole cohort, long-term outcome
was excellent in 93.75%, and 50% achieved complete overall
recanalization (Figure); the rest showed at least overall partial
recanalisation on the last follow-up MR angiography. No rele-
vant complications or recurrent thrombotic events occurred.
None of the variables were significantly different between the
2 groups, except the use of heparin (P=0.03). All patients of
the FXaI group were treated with low molecular weight hepa-
arin until the beginning of OAC, and no patient in the VKA
group switched from unfractioned heparin to low molecular
weight heparin or vice versa. The starting dose of rivaroxaban
varied between 2×15 mg (21 days then 20 mg, 4 of 7) and 20
mg (3 of 7) daily. Two patients of the FXaI group had recur-
rent nose bleeding, which led to reduction of the rivaroxaban
dose by the treating general practitioner to 10 and 15 mg QD
after 3 and 4 months of therapy, respectively. One patient of
the VKA group had intensified menstruation.

Discussion
Demographic data, risk factors, affected vessels, and brain
lesions of our patients are comparable to the largest previ-
ously published and prospectively collected cohort of patients
with CVT. Recanalization rates and clinical outcome were
excellent in both groups. No relevant and statistical signifi-
cant difference between the VKA and FXaI group were found,
except for the concept of heparin use before OAC. This differ-
ence is explained by the more common use of low molecular
weight heparin in our institution since the publication of the
study of Misra et al. Although symptoms were not signifi-
cantly different, imbalances in clinical severity on admission
between both groups cannot be excluded.

The median start of OAC was 5 days after bridging with
heparin. Although rivaroxaban may be started first line for
the treatment of deep vein thrombosis, we still use an ini-
tial phase with heparin until stable conditions after CVT are
achieved. In 3 patients with additional hemorrhage, infar-
cion or brain edema treatment was initiated with 20 mg QD
(instead of 2×15 mg for 21 days, which is recommended for
the acute treatment of deep vein thrombosis), owing to the
potential risk of further brain hemorrhage. Follow-up MRI,
especially in these patients, showed no further complications
(Figure).

One patient of the VKA group and 2 patients of the FXaI
group had minor bleeding complications that led to dose
reduction in the case of both FXaI patients. However, no
patient had intracranial or other major bleeding complication,
and no recurrent thrombotic events were observed during the
median follow-up of 8 months.

Our study has a retrospective, uncontrolled design and a
small sample size. Nonetheless, in these first reported cases of
CVT, rivaroxaban showed a similar clinical benefit as phen-
procoumon. Especially for young patients with CVT, rivar-
oxaban might be a desirable treatment alternative to vitamin K
antagonists because of its known application and metabolism
benefits. Our experience warrants further systematic prospec-
tive evaluation of rivaroxaban and other new oral anticoagu-
lants for the treatment of CVT.

Disclosures
Dr Ringleb received travel expenses and speaker honoraria (<1000
Euros) from Bayer Healthcare. The other authors report no conflicts.

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