Early Rivaroxaban Use After Cardioembolic Stroke May Not Result in Hemorrhagic Transformation
A Prospective Magnetic Resonance Imaging Study

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Background and Purpose—Early anticoagulation after cardioembolic stroke remains controversial because of the potential for hemorrhagic transformation (HT). We tested the safety and feasibility of initiating rivaroxaban ≤14 days after cardioembolic stroke/transient ischemic attack.

Methods—A prospective, open-label study of patients with atrial fibrillation treated with rivaroxaban ≤14 days of transient ischemic attack or ischemic stroke (National Institute of Health Stroke Scale <9). All patients underwent magnetic resonance imaging <24 hours of rivaroxaban initiation and day 7. The primary end point was symptomatic HT at day 7.

Results—Sixty patients (mean±SD age 71±19 years, 82% stroke/18% transient ischemic attack) were enrolled. Median (interquartile range) time from onset to rivaroxaban was 3 (5) days. At treatment initiation, median National Institute of Health Stroke Scale was 2 (4), and median diffusion-weighted imaging volume was 7.9 (13.7) mL. At baseline, HT was present in 25 (42%) patients (hemorrhagic infarct [HI]1=19, HI2=6). On follow-up magnetic resonance imaging, no patients developed symptomatic HT. New asymptomatic HI1 developed in 3 patients, and asymptomatic progression from HI1 to HI2 occurred in 5 patients; otherwise, HT remained unchanged at day 7.

Conclusions—These data support the safety of rivaroxaban initiation ≤14 days of mild–moderate cardioembolic stroke/transient ischemic attack. Magnetic resonance imaging evidence of petechial HT, which is common, does not appear to increase the risk of symptomatic HT. (Stroke. 2016;47:1917-1919. DOI: 10.1161/STROKEAHA.116.013491.)

Key Words: atrial fibrillation ■ cerebrovascular disease ■ magnetic resonance imaging ■ stroke ■ transient ischemic attack

Patients with atrial fibrillation who have suffered a transient ischemic attack (TIA) or ischemic stroke are at high risk for recurrence and require long-term anticoagulation. The optimal timing of anticoagulation after an ischemic stroke is controversial. Although anticoagulation in acute stroke patients is associated with reduced early stroke recurrence rates, these benefits are offset by a comparable increase in the rate of symptomatic hemorrhagic transformation (HT).1

Rivaroxaban is a non–vitamin K antagonist oral anticoagulant (NOAC)2 used to prevent ischemic stroke in atrial fibrillation patients. All safety data related to rivaroxaban come from trials that excluded patients ≤14 days after stroke and 3 days after TIA.3 The primary aim of this prospective study was to assess the rate of magnetic resonance imaging (MRI)–detected HT associated with initiating rivaroxaban therapy ≤14 days after cardioembolic stroke/TIA.

Methods
This was an investigator-initiated prospective, open-label, single-arm study (NCT 02279940). Patients with documented nonvalvular atrial fibrillation and acute TIA or moderate ischemic stroke (National Institute of Health Stroke Scale [NIHSS] ≤9) were enrolled. Patients were approached for study participation after the treating physician’s decision to treat with rivaroxaban ≤14 days after stroke/TIA. Patients with estimated glomerular filtration rate <30 mL/min or contraindications to MRI were excluded. The research protocol was approved by our local Human Research Ethics Board.

The dose of rivaroxaban was determined based on renal function (estimated glomerular filtration rate 30–50 mL/min:15 mg daily, estimated glomerular filtration rate >50 mL/min:20 mg daily). Study participants were followed for 90 days after rivaroxaban initiation. NIHSS score was assessed at baseline, day 7, and day 90. All patients had an MRI at baseline (≤24 hours from study recruitment) and 7±2 days after enrollment. Day-7 MRI assessors had access to baseline scans. The volume of ischemic diffusion-weighted imaging (DWI) lesions were measured planimetrically (Analyze 12.0, Biomedical Imaging Resource, Rochester). HT was graded...
on susceptibility-weighted sequences using European Cooperative Acute Stroke Study criteria for hemorrhagic infarction (HI1 and HI2) and parenchymal hemorrhage (PH1 and PH2).

The primary end point was symptomatic HT at day 7 (defined as PH2 associated with ≥4-point increase in NIHSS score). Secondary outcomes included PH at day 7 and recurrent stroke within 90 days. Serious adverse events within the study period were reported to the local Human Research Ethics Boards and Health Canada. A convenience sample of 50 patients with 2 evaluable MRI scans was planned. Based on observed symptomatic HT rates (2.4%–2.9%) in acute stroke patients treated with heparin, an a priori stopping rule governed study continuation; enrollment would be halted if ≥2 symptomatic HT events occurred.

Results

Sixty patients were enrolled, with a median time from symptom onset to rivaroxaban initiation of 3 (1.5–6) days (Table). Sixty-four percent of patients received rivaroxaban 20 mg daily and the remainder 15 mg daily. Patients with TIA (n=11) had a shorter interval between onset and rivaroxaban initiation (1 [1–3] days) than patients with ischemic stroke (n=49; 4 [2–6] days; P=0.27). At the time of treatment initiation, the median NIHSS was 2 (0–4) and median DWI lesion volume was 7.9 (1.5–14.7) mL (range 0–174.6 mL). Time to rivaroxaban initiation was correlated with DWI volume (r=0.58; P<0.001).

On baseline susceptibility-weighted sequences, HT was present in 25 (42%) patients (HI1, n=19; H12, n=6; PH 1/2, n=0; Figure in the online-only Data Supplement). Patients with HT had larger median infarct volumes (15.3 [11.6–37.5] mL) than those patients without HT (2.2 [0.3–5.4] mL; P<0.001). Median time to rivaroxaban initiation was longer in patients with baseline HT (6 [3–7] days) than those without (2 [1–4] days; P<0.001).

Clinical and Imaging Follow-Up

Ten patients were lost to follow-up during the study period (transfer to facilities without MRI before day 7, n=2; consent withdrawal after baseline MRI, n=8). Enrollment was extended to obtain 50 evaluable patients with follow-up MRI. Median DWI lesion volume was similar in patients who underwent day 7 MRI (7.9 [1.2–15.3] mL) and those who did not (6.8 [1.1–12.4] mL; P=0.99). Two patients lost to follow-up had baseline HI1.

The post-treatment MRI occurred at a median 7 (6–10) days after rivaroxaban initiation. All patients were compliant with rivaroxaban therapy at day 7. On follow-up MRI, no patients developed symptomatic HT or PH. HT remained unchanged in the majority of patients. New asymptomatic HI1 developed in 3 patients and asymptomatic progression (from HI1 to HI2) occurred in 5 patients (Table I in the online-only Data Supplement). Follow-up DWI revealed 2 new asymptomatic ischemic lesions (0.20 and 0.45 mL) in 2 patients.

At day 90, the median NIHSS was 0 (0–1) and median mRS score was 1 (0–2). Recurrent ischemic events were limited to one TIA (day 5, MRI negative) and one ischemic stroke (small cerebellar infarcts on day 28 computed tomography scan in a 95-year-old patient who never left hospital after the initial stroke and later died after withdrawal of care). One other

<table>
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<tr>
<th>Table. Baseline Patient Characteristics</th>
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<tr>
<td><strong>All Patients (n=60)</strong></td>
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<tr>
<td><strong>Age, y (mean±SD)</strong></td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
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<tr>
<td><strong>CHA2DS2-VASc score, median (IQR)</strong></td>
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<tr>
<td><strong>HAS-BLED score</strong></td>
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<tr>
<td><strong>Index event</strong></td>
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<tr>
<td><strong>Ischemic stroke</strong></td>
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<tr>
<td><strong>DWI volume</strong></td>
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<tr>
<td><strong>DWI location</strong></td>
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<tr>
<td><strong>Subcortical</strong></td>
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<tr>
<td><strong>No lesion</strong></td>
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<tr>
<td><strong>CMB, n (%)</strong></td>
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<tr>
<td><strong>No. of CMB/patient, median (IQR)</strong></td>
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<tr>
<td><strong>NIHSS at rivaroxaban initiation</strong></td>
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<tr>
<td><strong>Time to rivaroxaban initiation (days)</strong></td>
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CHA2DS2-VASc indicates congestive heart failure, hypertension, age, diabetes mellitus, stroke (doubled), vascular disease, age, and sex category (female); CMB, cerebral microbleeds; DWI, diffusion-weighted imaging; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; HT, hemorrhagic transformation; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; and TIA, transient ischemic attack.

*P value between patients with and without HT (independent t-test [parametric] and Kruskal–Wallis [nonparametric] data, Chi-square for dichotomous variables).
patient died from aspiration pneumonia. No systemic bleeding complications or other serious adverse events occurred.

Discussion
This small prospective MRI study provides data supportive of the safety and feasibility of rivaroxaban initiation ≤14 days after cardioembolic stroke/TIA. Our findings suggest that MRI evidence of petechial HT at the time of anticoagulation initiation with rivaroxaban does not seem to increase the risk of symptomatic HT. The lack of association between HT precipitation or aggravation seen with rivaroxaban may be similar in patients treated with other NOACs, but these studies have not been completed.

There are limited safety data related to early anticoagulation with NOACs after stroke. In one study of 89 atrial fibrillation patients, rivaroxaban was started a median 5 days after stroke and 3 days after TIA. No symptomatic HT was observed during the 15-month follow-up period, but information regarding stroke severity or ischemic lesion burden was lacking. Another Japanese registry reported that early NOAC use after cardioembolic TIA/stroke was more common in patients with smaller infarcts, assessed semiquantitatively. There were no cases of intracerebral hemorrhage before discharge, although standardized imaging assessments were not completed.

Using MRI, we found that spontaneous HT before anticoagulation is common and more frequent than previously reported. This likely reflects the fact that we assessed HT with susceptibility-weighted sequences, instead of computed tomography, which is less sensitive for petechial bleeding. The overall stability of petechial HT on day 7 MRI is supportive, although not definitively, of the safety of early NOAC use after cardioembolic stroke.

Enrolling patients after the treating physician’s decision to start rivaroxaban ≤14 days after TIA/stroke reflects current practice patterns. Patients with a wide range of infarct volumes were enrolled in our study. Although infarct volume has not been shown to be a predictor of HT after anticoagulation, most clinicians delay anticoagulation in patients with large lesions. This treatment bias is seen in our study, where patients with larger infarct volumes were started on rivaroxaban later than those with smaller lesions. This practice pattern was not associated with an increased rate of HT in the patients with large infarct volumes.

Limitations
This small, nonrandomized study does not provide definitive evidence for the safety of early anticoagulation after cardioembolic stroke/TIA. Inclusion of TIA patients with normal MRI may have overestimated the safety of early NOAC use after cardioembolic infarction. Patients lost to follow-up also impair our ability to conclusively determine the safety of early NOAC initiation, although even in these patients there was no symptomatic HT while in hospital—the time where this is most likely to occur. Finally, patients with severe stroke were excluded from our study. Only 5 patients had infarct volumes >50 mL, and therefore, caution with respect to early NOAC use in these patients is warranted. Future trials may provide data in this group of patients (clinicaltrials.gov NCT02283294).

Conclusions
Early anticoagulation with rivaroxaban ≤14 days after cardioembolic stroke was not associated with symptomatic HT in this small nonrandomized study. Evidence of petechial HT on MRI at the time of rivaroxaban initiation does not seem to increase the risk of symptomatic HT.

Sources of Funding
This was an investigator-initiated study funded by Bayer, Inc. The sponsor had no role in the design or conduct of the study nor in the reporting of the results.

Disclosures
Dr Gioia has received ad board honoraria from Bayer Inc. Drs Butcher, Shuaib, and Buck have received speakers honoraria from Bayer, Boehringer Ingehein, and Pfizer/BMS.

References
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Supplemental Figure I. Examples of Hemorrhagic Transformation (HT) of patients enrolled in the study. Stability of asymptomatic hemorrhagic infarct (HI)1 (A) and HI2 (B) on day 7 MRI despite rivaroxaban initiation. C: Example of asymptomatic HT progression from HI1 to HI2. Microbleeds (MB) are indicated by white dotted arrows. Please note that not all MB have been indicated in the figure.
Supplemental Table I. Details of Hemorrhagic Transformation in Study Patients

<table>
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<tr>
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<th>Baseline MRI (N=60)</th>
<th>Day 7 MRI (n=50)*</th>
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<tbody>
<tr>
<td>Any Hemorrhagic Transformation (HT) (n,%)</td>
<td>25 (42%)</td>
<td>26 (52%)</td>
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<tr>
<td>HI 1</td>
<td>19</td>
<td>-</td>
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<tr>
<td>- HI 1 Stability</td>
<td>-</td>
<td>12</td>
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<tr>
<td>- Progression (HI1 to HI2)</td>
<td>-</td>
<td>5</td>
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<tr>
<td>HI 2</td>
<td>6</td>
<td>-</td>
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<tr>
<td>- HI 2 stability</td>
<td>-</td>
<td>6</td>
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<tr>
<td>PH 1/2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>New HT while on rivaroxaban</td>
<td>-</td>
<td>3 **</td>
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</table>

*2 patients lost to follow-up had HI 1 on baseline MRI
**all new HT on day 7 was asymptomatic HI 1