Dabigatran Therapy in Acute Ischemic Stroke Patients Without Atrial Fibrillation

Mahesh Kate, DM; Laura Gioia, MD; Brian Buck, MD; Leka Sivakumar, MSc; Thomas Jeerakathil, MD; Ashfaq Shuaib, MD; Kenneth Butcher, MD, PhD

Background and Purpose—Acute ischemic stroke patients are at risk of early recurrence. We tested the feasibility and safety of initiating dabigatran in patients, within 24 hours of minor stroke in patients without atrial fibrillation.

Methods—Minor stroke patients (National Institutes of Health Stroke Scale score ≤3) without atrial fibrillation and evidence of acute infarction on magnetic resonance imaging were treated with dabigatran. Treatment began within 24 hours of onset and was continued for 30 days. The primary end point was symptomatic hemorrhagic transformation.

Results—A total of 53 patients with median (interquartile range) age of 68 (57–77) years and National Institutes of Health Stroke Scale score of 1 (0–2) were enrolled. Baseline diffusion-weighted imaging volume was 0.8 (0.3–2.4) mL. No patients experienced symptomatic hemorrhagic transformation. Three patients had evidence of asymptomatic petechial hemorrhagic transformation on day 7, which remained stable at day 30, while continuing dabigatran.

Conclusions—Dabigatran treatment within 24 hours of minor stroke is feasible. A larger randomized trial is required to confirm the safety and efficacy of this treatment approach.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 01769703. (Stroke. 2015;46:2685-2687. DOI: 10.1161/STROKEAHA.115.010383.)

Key Words: anticoagulants ■ brain infarction ■ dabigatran ■ stroke

Transient ischemic attack (TIA) patients, particularly those with magnetic resonance imaging (MRI) evidence of parenchymal injury on diffusion-weighted imaging (DWI), are at risk of early recurrent stroke.1 Acute combination antiplatelet therapy has been shown to reduce recurrent stroke event rates,2 albeit with modest benefits and increased hemorrhagic complications.3 This approach will insufficiently protect patients who are subsequently found to be in atrial fibrillation (AF). Although, anticoagulation in acute stroke patients may be associated with reduced early stroke recurrence rates, these benefits are offset by a comparable increase in the rate of symptomatic hemorrhagic transformation (HT).4

Dabigatran is a direct oral anticoagulant shown to be associated with a reduction in ischemic stroke rates and a much lower risk of intracranial hemorrhagic complications compared with warfarin in patients with AF.5 All safety data related to dabigatran comes from trials that excluded patients within 14 days of minor stroke and 6 months of severe stroke. This is precisely the period when stroke patients are at highest risk of recurrent events and likely to derive benefit from anticoagulation. We designed a single-arm treatment trial aimed at assessing the feasibility and safety of 30 days of acute dabigatran treatment initiated within 24 hours of ischemic stroke in patients without AF.

Methods

Patients
This was an investigator-initiated open-label single-arm treatment trial (clinicaltrials.gov: NCT 01769703). Patients with confirmed cerebral infarction, on MRI, were treated with dabigatran for 30 days (Figure I in the online-only Data Supplement). Our institutional ethics committee approved the study. Adult patients diagnosed with TIA/stroke (NIHSS score ≤3) were screened. Patients were included only if they had MRI evidence of ischemic injury and if dabigatran could be initiated within 24 hours of symptom onset or time last known well. Patients with estimated glomerular filtration rate <30 mL/min were excluded. Thrombolysis or endovascular intervention for the index event was exclusion criteria. Patients with a clear indication for anticoagulation, including AF, were ineligible.

Procedures

Dabigatran Therapy
The dose of dabigatran was determined by age and renal function. Patients >80 years old or with estimated glomerular filtration rate 30
to 50 mL/min, or both, received 110 mg BID. All other patients were treated with 150 mg BID.

Imaging Procedures and Image Analysis
All patients had an MRI at baseline, 7, and 30 days. MRI sequences included DWI, fluid-attenuated inverse recovery, and a susceptibility weighted imaging (to assess HT) sequence.6 DWI sequences were assessed for the presence, number, and total volume of regions with diffusion restriction (ANALYZE 11.0, Biomedical Imaging Resource, Rochester, Figure 1).7

Statistical Analysis and Stopping Rule
A convenience sample size of 50 patients was planned. The primary end point was symptomatic HT, defined as a parenchymal hematoma associated with clinical worsening (≥4 point increase in NIHSS score), within 30 days of enrollment. Based on HT rates in 2 heparin in acute stroke studies (2% to 6%), the acceptable number of symptomatic HT was 4%4,8 (stopping rule: >2 patients with symptomatic HT).

Results
A total of 53 patients were enrolled with a median (interquartile range) age of 68 (57–77) years (Figure I in the online-only Data Supplement; Table). In 23 (43%) patients, the symptoms were transient (2 [0.4–6] hours). The median baseline DWI lesion was 0.8 (range, 0.1–43.2) mL (Figure 1). The majority of patients (42/53) received the 150 mg BID dabigatran dose. Forty-nine of 50 patients reported compliance with the medication at day 7 and day 30.

Primary End Point
Three patients had evidence of asymptomatic HT (hemorrhagic infarction type I) on the day 7 MRI scan (Figure 2). In 2 of these patients, the petechial HT was evident at baseline and was unchanged at day 7. Dabigatran was continued in all 3 patients. Repeat MRI at day 30 did not demonstrate any additional/worsening hemorrhagic events.

Adverse Events
One patient died within 30 days of symptom onset. This patient was found deceased in his home on day 24. He was not brought to hospital and an autopsy was not conducted. No patients developed systemic bleeding complications. Three patients reported dyspepsia on day 7.

Recurrent Ischemic Events and Clinical Outcomes
None of the patients experienced symptomatic recurrent cerebrovascular events. Clinically asymptomatic DWI lesions were evident in 7 patients on the day 7 MRI scan (mean volume, 0.3±0.1 mL) and another 2 on the day 30 scan (0.5±0.5 mL; Figure II in the online-only Data Supplement). At day 90, the median modified Rankin Scale score was 1 (0–2) and Barthel Index score was 100 (95–100). The most common cause of stroke was cardioembolism, the majority of whom had paroxysmal AF identified with a 24-hour Holter monitor (n=1) or 30-day external loop recorder (n=14) after enrollment (Figure III in the online-only Data Supplement).

Discussion
This is the first report of dabigatran use in acute stroke patients with confirmed infarcts but no evidence of AF. It is also the first study of dabigatran use in ischemic stroke patients within 24 hours of symptom onset. These preliminary data support the feasibility and safety of a randomized study of dabigatran in acute stroke patients without a clear indication for anticoagulation.

Implications for Practice
Two approaches to prevent early recurrent stroke prevention are currently being tested. Short-term dual (NCT00991029) or novel single (NCT01994720) antiplatelet trials are underway. This approach may expose patients with occult paroxysmal AF, which was the case in 1 of 3 of our patients, to a higher risk of recurrence. Two other trials (NCT02239120

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<th>Table. Patient Characteristics</th>
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<td>Variables</td>
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<td>Age</td>
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<tr>
<td>NIHSS score</td>
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<td>ABCD2 score</td>
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<tr>
<td>DWI volume, mL</td>
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<td>eGFR, mL/min</td>
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<td>Location of acute DWI lesion(s)*</td>
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<tr>
<td>Cortical</td>
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<td>Subcortical</td>
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<td>Anterior circulation</td>
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ABCD2 indicates age, blood pressure, clinical symptoms, duration of symptoms and diabetes mellitus; DWI, diffusion-weighted imaging; eGFR, estimated glomerular filtration rate (Cockcroft–Gault formula); IQR, interquartile range; MRI, magnetic resonance imaging; and NIHSS, National Institutes of Health Stroke Scale.

*Several patients had discrete cortical and subcortical lesions or lesions in both the anterior and posterior circulation.
and NCT02313909) of long-term anticoagulation therapy with a direct oral anticoagulant in patients presenting with an Embolic Stroke of Undetermined Source are also underway. Although this approach will benefit individuals with occult paroxysmal AF, it may unnecessarily expose other patients to the risks of long-term anticoagulation. An alternative may be short-term acute anticoagulation in all patients presenting with an acute ischemic cerebrovascular syndrome, during which stroke cause can be investigated.

Limitations
This small, nonrandomized study does not provide definitive evidence of safety. The single patient who died suddenly represents a probable vascular death. The possibility that this was related to HT or cardiac ischemia cannot be ruled out.

Conclusions
Acute dabigatran therapy following ischemic stroke is feasible. Based on these pilot data, a more definitive randomized controlled trial aimed at assessing the safety of this approach is underway (NCT02295826).

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Disclosures
Drs Shuaib and Butcher received speaker’s honoraria related to direct oral anticoagulant use in atrial fibrillation patients. The other authors report no conflicts.

References
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Short Title: Novel Anticoagulants in Non-cardioembolic Stroke.

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**Supplementary Figures And Figure Legends**

**Figure I:** Trial Profile. MRI, Magnetic Resonance Imaging; DWI, Diffusion-Weighted Imaging; mRS, modified Rankin Scale; BI, Barthel Index

121 patients screened with MRI

- 68 patients excluded
  - 30 Could not be randomized within 24 h of known onset
  - 11 No DWI lesion on screening MRI
  - 4 Contraindication to dabigatran (i.e. renal impairment)
  - 2 Follow-up MRI not possible
  - 7 Consent refused
  - 14 Enrolled in competing trial (POINT)

53 patients enrolled

50 patients prescribed Dabigatran x 30 days

- 1 Lost to follow-up
  - 2 withdrew consent prior to first MRI scan
    - 1 Difficulty swallowing capsules
    - 1 Reconsidered risk/benefit

48 patients scanned with MRI on Day 7

- 2 patients not scanned
  - 1 MRI scanner failed at time of scan
  - 1 patient refused scan

49 patients scanned with MRI on Day 30

- 1 patient died on day 24

46 patients assessed in clinic on Day 90 (mRS, BI)

- 3 patients lost to clinic follow-up
  - All 3 patients contacted by phone and confirmed to be alive and independent.
Figure II: Example of recurrent infarction in a 65-year-old man seen on follow-up diffusion-weighted imaging (DWI) on day 7. The new lesion was asymptomatic and no longer evident on repeat DWI (not shown) or FLAIR (Fluid-Attenuated Inverse Recovery) images at day 30.
**Figure III:** Stroke etiological classification at day 90 for all treated patients. The cause of stroke was determined using the Test of Org 10172 in Acute Stroke Treatment (TOAST) criteria. The most common stroke mechanism was cardioembolism. ‘Other’ represents two patients with vertebral artery dissection and brainstem infarcts.