Tenecteplase–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion

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Background and Purpose—Minor stroke and transient ischemic attack with an intracranial occlusion are associated with neurological deterioration and disability. Tenecteplase (TNK–tissue-type plasminogen activator) compared with alteplase is easier to administer, has a longer half-life, higher fibrin specificity, possibly a lower rate of intracranial hemorrhage, and may be an ideal thrombolytic agent in this population.

Methods—TNK–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion (TEMPO-1) was a multicenter, prospective, uncontrolled, TNK–tissue-type plasminogen activator dose-escalation, safety, and feasibility trial. Patients with a National Institutes of Health Stroke Scale ≤5 within 12 hours of symptom onset, intracranial arterial occlusion on computed tomographic angiography and absence of well-evolved infarction were eligible. Fifty patients were enrolled; 25 patients at a dose of 0.1 mg/kg, and 25 patients at 0.25 mg/kg. Primary outcome was the rate of drug-related serious adverse events. Secondary outcomes included recanalization and 90-day neurological outcome (modified Rankin Scale, 0–1).

Results—Median baseline National Institutes of Health Stroke Scale was 2.5 (interquartile range, 1), and median age was 71 (interquartile range, 22) years. There were no drug-related serious adverse events in tier 1. In tier 2, there was 1 symptomatic intracranial hemorrhage (4%; 95% confidence interval, 0.01–20.0). Stroke progression occurred in 6% of cases. Overall, 66% had excellent functional outcome (modified Rankin Scale, 0–1) at 90 days. Recanalization rates were high; 0.1 mg/kg (39% complete and 17% partial), 0.25 mg/kg (52% complete and 9% partial). Complete recanalization was significantly related to excellent functional outcome (modified Rankin Scale, 0–1) at 90 days (relative risk, 1.65; 95% confidence interval, 1.09–2.5; P=0.026).

Conclusions—Administration of TNK–tissue-type plasminogen activator in minor stroke with intracranial occlusion is both feasible and safe. A larger randomized controlled trial is needed to prove that this treatment is efficacious.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01654445.

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Key Words: ischemic attack, transient ■ stroke ■ therapeutic thrombolysis ■ tomography, x-ray computed

Among the ≈700,000 ischemic strokes per year in North America, most (≤70%)1,2 are minor and initially non-disabling presenting with transient or persistent minor stroke symptoms (transient ischemic attack or minor stroke). However, this seemingly mild presentation is misleading because the prognosis is not benign. Multiple studies have reported that among patients considered too mild for thrombolysis, up to one third are dead or disabled in short-term (90 days) follow-up.1–6

Thrombolytic treatment of minor ischemic stroke is controversial with much variation in practice. Most physicians

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do not treat patients with minor deficits presenting within the standard thrombolytic window. The widespread perception that the prognosis is good and the nonzero risk of harm with alteplase treatment frequently leads to a decision to treat with antiplatelet agents only. It is not clear whether all or any patients with minor stroke should be treated with thrombolysis. However, the subset of patients with minor stroke and documented intracranial vessel occlusion are at particularly high risk of early neurological deterioration and disability.5-9 Aggressive treatment of this patient population to prevent disability may be warranted.

Tenecteplase (TNK–tissue-type plasminogen activator [tPA]), a genetically engineered mutant tPA, has a longer half-life, is more fibrin specific, produces less systemic depletion of circulating fibrinogen, and is more resistant to plasminogen activator inhibitor10 than alteplase.11 These pharmacodynamic differences may result in more rapid reperfusion and lower intracranial hemorrhage rates and may be particularly important in a minor stroke population where the risk benefit balance means that any risk must be minimized.12

The thrombolysis for minor ischemic stroke with proven acute symptomatic occlusion using TNK-tPA (TEMPO-1) was designed to assess in a 2-cohort dose-escalation study whether the treatment of minor stroke with intracranial occlusion with TNK-tPA was safe and feasible.13

Methods

Participants
TEMPO-1 was a prospective, multicenter, 2-cohort, dose-escalation study to assess the safety and feasibility of the use of 2 doses of TNK-tPA for the treatment of minor stroke with intracranial occlusion. Adult subjects with minor stroke or transient ischemic attack (National Institutes of Health Stroke Scale [NIHSS], ≤5) within a 12-hour window and proven intracranial occlusion on computed tomographic angiography (CTA) were treated with TNK-tPA (Table 1). The institutional review boards of all participating centers approved the protocol. All patients or their surrogates provided written informed consent. The trial was administered from the TEMPO-1 coordinating center in Calgary, Canada. The study was conducted under a Health Canada CTA license and the study is registered at http://www.ClinicalTrials.gov (NCT01654445). The funders had no role in the design and management of the study.

Study Procedures
All patients were treated with intravenous TNK-tPA using their estimated weight to calculate a weight-adjusted dose. There were 2 dose tiers at 0.1 and 0.25 mg/kg. Advancement to the second dose-tier was dependent on safe completion of the first dose tier and the approval of the data safety and monitoring board. Treatment was administered as a single intravenous bolus over 1 to 2 minutes as per the standard instructions for use immediately after consent was obtained. A patient was considered enrolled once study drug had been given. At the beginning of the study, drug had to be given within 60 minutes of the first slice of the CTA; however, this was subsequently extended to 90 minutes.

Baseline imaging included a CT brain and a CTA from arch to vertex including the circle of Willis. Patients underwent a repeat CT angiogram of the intracranial circulation between 4 and 8 hours after treatment to determine whether there was complete or partial recanalization of the occluded artery. This repeat CTA was not completed if there was an allergic reaction to the first CTA or the estimated glomerular filtration rate was <40 mL/min per 1.73 m². All patients underwent standard of care medical management on an acute stroke unit and underwent follow-up brain imaging at 24 hours with CT or

### Table 1. Inclusion and Exclusion Criteria

<table>
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<th>Inclusion criteria</th>
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<tr>
<td>Acute ischemic stroke in an adult patient (aged, ≥18 y).</td>
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<tr>
<td>Onset (last-seen-well) time to treatment time &lt;12 h.</td>
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<td>Minor stroke defined as a baseline NIHSS &lt;6 at the time of randomization.</td>
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<td>Any acute intracranial occlusion (MCA, ACA, PCA, and vertebral arteries and basilar arteries) defined by noninvasive acute imaging (CT angiography) that is neurologically relevant to the presenting symptoms and signs.</td>
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<tr>
<td>Prestroke independent functional status in activities of daily living with prestroke estimated modified Barthel Index of ≥90 and premorbid mRS 0–1.</td>
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<tr>
<td>Informed consent from the patient or surrogate.</td>
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<td>Patients can be treated within 90 min of the CT/CTA being completed.</td>
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<td>Hyperdensity on CT brain consistent with intracranial hemorrhage. Any clinical suspicion of any intracranial hemorrhage even in the absence of visible blood on baseline brain imaging.</td>
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<td>Large acute stroke &gt;1/3 MCA territory or ASPECTS&lt;5 visible on baseline CT scan.</td>
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<td>Core of established infarction. No area of gray matter hypodensity at a similar density to white matter or in the judgment of the enrolling neurologist is consistent with a subacute ischemic stroke aged &gt;12 h.</td>
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<td>Clinical history, past imaging, and clinical judgment suggest that the intracranial occlusion is chronic.</td>
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<td>Patient is a candidate for and should receive standard of care IV IAP.</td>
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<td>Stroke occurring as an inpatient. An inpatient is a patient who has been officially admitted to the hospital to a ward bed. A patient in the ED who has not been formally admitted is still considered to be an outpatient.</td>
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<td>Patient has a severe or fatal or disabling illness that will prevent improvement or follow-up or such that the treatment would not likely benefit the patient.</td>
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<td>Patient cannot complete follow-up because of comorbid nonfatal illness or is visiting the host city and cannot return for follow-up.</td>
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<td>Pregnancy.</td>
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<td>Patient is actively taking dual antiplatelet medication (ASA and clopidogrel) in the last 48 h.</td>
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<tr>
<td>International normalized ratio &gt;1.4. For patients who are known not to be taking anticoagulant therapy, it is not necessary to wait for coagulation laboratory results (eg, PT, PTT) before treatment.</td>
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<tr>
<td>Standard thrombolysis exclusions (Taken from Canadian guidelines19). These are considered guidelines and therefore as relative contraindications.</td>
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<tr>
<td>Enrollment in TEMPO-1 and treatment with TNK-tPA may still be considered if there is reasonable clinical justification.</td>
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### Historical

- History of intracranial hemorrhage.
- Stroke or serious head or spinal trauma in the preceding 3 mo.
- Recent major surgery in the preceding 3 mo.
- Arterial puncture at a noncompressible site in the previous 7 d.
- Any other condition that could increase the risk of hemorrhage after TNK-tPA administration.

### Clinical

- Symptoms suggestive of subarachnoid hemorrhage.
- Stroke symptoms caused by another nonischemic acute neurological condition such as seizure with Post-ictal Todd paralysis or focal neurological signs because of severe hypo- or hyperglycemia.
- Hypertension refractory to antihypertensive medication such that target blood pressure <185/110 cannot be achieved before treatment.
- Laboratory
  - Elevated activated partial-thromboplastin time (any elevation above the upper limit of normal).
  - Platelet count below 100,000 per cubic millimeter.
- Active use of any standard or novel anticoagulant therapy will full anticoagulant dosing (DVT prophylaxis dosing shall not prohibit enrollment). Active use means that the patient has taken ≥1 dose of drug within 5 half-lives of the drug.
MR. All imaging was transferred to Calgary for central review by an independent neuroradiologist blinded clinical outcome.

The primary outcomes were safety and feasibility. Safety was assessed by the rate of expected serious adverse events associated with study drug. Expected study drug-related serious adverse events included (1) symptomatic intracranial hemorrhage (ICH) with associated neurological worsening (NIHSS increase of ≥2 points different than baseline), (2) symptomatic extracranial hemorrhage defined as requiring inotropic support or other means to maintain cardiac output, requiring blood transfusion of ≥2 U of packed red blood cells, or associated with a fall in hemoglobin ≥5 g/dL, (3) severe orolingual angioedema defined as airway obstruction requiring intubation, or (4) thrombolysis-associated hypotension defined as a drop in blood pressure that requires inotropic support. The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), European-Australasian Acute Stroke Study (ECASS), and National Institute of Neurological Disorders and Stroke definitions of symptomatic ICH were also assessed. Feasibility was assessed by the rate of recruitment.

Secondary outcomes included complete or partial recanalization, neurological and functional outcomes at 90 days, and recurrent events (stroke progression and recurrent stroke). For any recurrent event a patient who worsened as a result of a deterioration related to the presenting event would be rated as progression, and those with a second embolus would be rated as a recurrent stroke.17 Patients were followed up for 90 days with in-person follow-up at 24 hours, 48 hours, 5 days (or at discharge if earlier than 5 days), 30 days, and 90 days from enrollment. All study personal were trained in the application of the NIHSS and modified Rankin Scale (mRS) scores. NIHSS was completed at all follow-up time points and mRS/Barthel scores at 30 and 90 days. Excellent functional outcome was defined as mRS 0 to 1 at 90 days and good functional outcome as mRS 0 to 2 at 90 days. A blinded trained investigator assessed all outcomes.

### Statistical Analysis

The sample size was a convenience sample designed to provide at least modest precision around the point estimates. The dose-escalation safety design follows the design of Storrer14 and is based on cancer trials. Data are reported as simple proportions with associated exact 95% confidence intervals. Recanalization was assessed centrally by comparing the baseline scan with the follow-up scan and designated as complete, partial, or no recanalization.

### Results

Patients were screened at 8 sites in Canada between July 2012 and July 2014, and 50 patients were enrolled in the study (25 in tier 1 and 25 in tier 2) from 4 sites (please see the online-only Data Supplement). The rate of recruitment was 0.3 subjects per site per month with high variability between sites according to the use of CTA as a routine examination for patients with minor stroke. Baseline characteristics are shown in Table 2. Patients were treated early with a median time to treatment of 3.5 hours. A percentage of 62 (31/50) patients were treated within a 4.5-hour window.19 Sites of intracranial occlusions were middle cerebral artery (MCA)-M1 (9), MCA-M2 (23), MCA-M3 (10), posterior cerebral artery (2), and vertebral artery/posterior inferior cerebellar artery (3). There were 2 (4%) subjects who did not have evidence of an acute intracranial occlusion and 1 (2%) subject who was judged to have a chronic vertebral artery occlusion after central imaging review.

### Outcomes

The primary and secondary outcomes stratified by dose tier are shown in Table 3. There were no drug-related serious adverse events in tier 1. In tier 2, there was 1 symptomatic ICH (4%; 95% confidence interval, 0.01–20.0). There were no symptomatic ICH by the SITS-MOST definition.14 The single patient with a symptomatic parenchymal ICH had a small temporal lobe hemorrhage (20 mL), which was transient, and she had an independent outcome at 90 days (mRS=2). In this case, the occluded M2-MCA branch was effectively recanalized with TNK-tPA. There were no other drug-related serious adverse events in either dose tier. Repeat CTA (or other follow-up vascular imaging) at 4 to 8 hours was completed on 96% (48/50) of patients (in 1 subject, a follow-up MRA was completed instead of CTA showing a persistent occlusion and in 1 subject deterioration before follow-up CTA lead to a subsequent cerebral angiography with rescue endovascular therapy, which showed that the symptomatic vessel remained occluded). Patients without baseline occlusion were excluded from the recanalization analysis leaving 46 patients for recanalization analysis. There was a high rate of complete or partial recanalization in both dose tiers.
tiers with higher complete recanalization seen in the 0.25 mg/kg tier. Overall, 66% had excellent functional outcome (mRS=0–1) and 90% had an independent outcome (mRS=0–2) at 90 days. Breakdown of outcome by dose tier is shown in Figure 1. Complete recanalization was strongly associated with excellent functional outcome (mRS=0–1) at 90 days (relative risk, 1.65; 95% confidence interval, 1.09–2.5; P=0.026). Figure 2 shows 90-day functional outcomes by recanalization. Three (6%) patients had stroke progression and 2 (4%) had early recurrent stroke, too few outcomes to assess the relationship between recanalization and progression or recurrence. However, no patient who had complete recanalization underwent symptom progression. One patient (2%) with symptom progression was taken for endovascular rescue therapy.

Figure 1. The breakdown by dose tier of functional outcomes at 90 days as measured by the modified Rankin Scale (mRS).

**Discussion**

We have successfully demonstrated the safety and feasibility of thrombolysis using TNK-tPA for the acute treatment of minor ischemic stroke or transient ischemic attack with proven intracranial occlusion. Recanalization is strongly associated with an improved clinical outcome and rates of recanalization are high with moderate dose TNK-tPA (0.25 mg/kg). There was a single occurrence of ICH that did not affect functional independence at 90 days.

Previous work has shown that minor stroke can be associated with a high level of disability and that this risk is especially high among patients with intracranial occlusion.20,21 Overall, there is a high rate of functional impairment (mRS=3–6) approaching 10% in both dose tiers, and a 34% rate of any functional impairment (mRS=2–6). This is slightly lower than the 46% rate of any functional impairment that was seen in the NIHSS 0 to 5 tPA-treated subgroup in the third international stroke trial (IST-3).22 TEMPO-1 confirms that the prognosis of minor stroke and transient ischemic attack with proven occlusion is not benign.

High recanalization rates with thrombolysis are achievable in this population. Minor strokes frequently have distal occlusions that may respond more readily to thrombolytic therapy than more proximal occlusions because of a lower thrombus burden. Furthermore, there is a clear relationship between recanalization and excellent outcome.23 This has not been previously demonstrated in a minor stroke population.
and supports the hypothesis that thrombolytic treatment could result in better outcomes. Recent work examining the combined tPA trials suggests that there might be a therapeutic benefit to thrombolysis for patients with minor stroke defined simply by NIHSS≤5.26 Complete recanalization rates of 39% (0.1 mg/kg tier) and 52% (0.25 mg/kg) are lower than that were reported in a recent study using TNK-tPA in moderate/severe strokes (35% and 80%).12 However, the recanalization outcome in the previous study was measured at 24 hours after drug administration when compared with 4 to 8 hours, a much earlier time point in TEMPO-1.12 Assessment of recanalization rates at earlier time points is more likely to reflect a time period where recanalization could affect clinical outcome. We also observed a low rate of progression in patients with minor stroke and occlusion in TEMPO-1 when compared with our previous work in the (6% in TEMPO-1 versus 19% in CATCH).9 This could reflect a therapeutic effect of vessel recanalization arresting stroke progression. There is a low (but nonzero) risk of ICH associated with thrombolysis in this patient population. The background risk of symptomatic ICH defined by coronary thrombolysis (using any thrombolytic agent) trials is ≈0.5%.25 A recent study of thrombolysis in stroke mimics also found a low (1%), but nonzero risk of ICH.26 The recent individual patient thrombolysis meta-analysis found a 0.9% risk of fatal ICH in the NIHSS 0 to 4 subgroup.24 Nevertheless, because patients with minor stroke have either been excluded a priori or under-represented in most of the stroke thrombolysis trials, the balance between excellent outcome and the risk of ICH is not clear. The acceptable risk of ICH must be significantly less than in major stroke to justify the risk of death and disability as a complication of treatment. The use of 0.25 mg/kg TNK-tPA (50% of the approved coronary thrombolysis dose) as the dose choice reflects previous studies in major ischemic stroke.12,27,28 The longer half-life and favorable pharmacological properties of TNK-tPA may permit lower doses to have prolonged therapeutic effect with preserved safety.

During the course of this study, we showed that a single center that routinely uses CTA in clinical practice (Foothills Medical Center, Calgary) was able to randomize >20 patients/y. Other sites were not routinely using CTA in minor stroke and this resulted in a low average recruitment rate. A phase 3 trial in this population is feasible if sites routinely use CTA to screen all patients with ischemic stroke. This will be facilitated in Canada by the updated Canadian Secondary Prevention guidelines, which now recommend the use of CTA in the screening of these patients.29 With the recent publication of a positive trial30 for endovascular treatment of acute stroke, it is likely that more and more centers will routinely use CTA in the screening of all patients with stroke. Acute endovascular therapy was not a barrier to enrollment in TEMPO-1 because it was not routinely offered to patients with minor stroke. Within TEMPO-1 itself only 1 patient (2%) was taken for rescue endovascular therapy. Limitations of this study include the fact that this was a proof-of-concept safety study with a relatively small sample size.

We have shown, in a multicenter Canadian study, that it is safe and feasible to treat patients with minor stroke and intracranial occlusion with thrombolysis using TNK-tPA. Furthermore, even in this minor stroke population, recanalization is strongly associated with improved clinical outcome. A larger randomized controlled trial is needed to prove that this treatment is efficacious.

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Disclosures
Dr Dowlatshahi has provided an expert opinion on the topic of thrombolysis in a medical-legal case. The other authors report no conflicts.

References


SUPPLEMENTAL MATERIAL

Sites (PI designates site principal investigator).
Foothills Medical Centre, Calgary (n=43): SB Coutts (PI), MD Hill (PI), PA Barber, EE Smith, S Subramaniam, AM Demchuk, Menon BK, G Klein, D Pearson, A Trivedi, D Singh, E Klourfeld, P Choi, R Reddy, S Blayney, T Musuka, V Dubuc, A Alseraya, J Desai, J Mandzia, S Mishra, S Adata.
Ottawa (n = 4): D Dowlatshahi (PI), N Steffenhagen (PI), G Stotts, M Hogan, Shamy M, A Deshpande, D Blacquire, M Alhazzaa.
Quebec City (n=1): MC Camden, A Mackey, S Verreault.
Vancouver (n=2): T Field (PI), N Asdaghi (PI), C Murphy, P Teal, S Yip, S Mann.
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