Patients with transient ischemic attacks (TIA) and minor stroke are at high risk for recurrent cerebral ischemia. New treatment approaches are needed to reduce this early stroke recurrence. Few studies, however, have examined the recurrence risk in minor stroke or TIA patients when no definitive cause can be identified (cryptogenic stroke). This group is currently treated with antplatelet therapies despite a lack of clear pathophysiologic understanding of what causes recurrence in this group. In the only study that explored clinical and radiological event rates in cryptogenic stroke, a relatively low clinical event rate (2%) but a much higher silent radiological event rate (21%; 4/19) was seen. If this high radiological event rate is true, then it may allow for secondary stroke prevention treatment trials in this population to occur with smaller sample size.

We therefore sought to determine the recurrent clinical and radiological event rates in cryptogenic TIA and minor stroke population.

Subjects and Methods

Patients with high-risk TIA (transient focal neurological symptoms including motor or speech symptomatology lasting ≥5 minutes) or minor stroke (National Institutes of Health Stroke Scale score ≤3) were prospectively enrolled and imaged within 24 hours of symptom onset as part of 2 prospective imaging cohorts (VISION and CATCH). Details for each study have been previously described. Only patients with minor stroke or TIA as defined were included from the VISION study. Most patients underwent magnetic resonance imaging (MRI) of the brain, including diffusion-weighted imaging within 24 hours of symptom onset. All imaging was interpreted blind to clinical information other than symptom side. Stroke mechanism was categorized as per TOAST criteria after parenchymal, vascular imaging and cardiac investigations. Standard etiologic work-up for ischemic stroke in our institution would routinely include blood work, intracranial and extracranial vascular imaging, electrocardiogram, transthoracic echocardiogram, and 24-hour cardiac (Holter) monitoring. Most investigations were completed in hospital before discharge. Any amount of definite atrial fibrillation was considered a cardioembolic source. The treating physician labeled patients as cryptogenic at the time of the 90-day follow-up if all the investigations did not find another cause. Patients were followed for 90 days to document any clinical recurrent stroke and underwent repeat MRI either at day 30 (VISION) or at day 90 (CATCH). Only patients with a distinct recurrent stroke (not symptom progression) were included for the outcome of clinical recurrent stroke. Follow-up diffusion-weighted imaging and
fluid-attenuated inversion recovery sequences were directly compared with the baseline MRI to assess for new ischemic lesions as compared with the baseline MRI. A new lesion had to be separate from the initial lesion, and infarct growth was not considered a new lesion.

Results
Out of 693 patients enrolled, 333 (48%) had cryptogenic stroke mechanism. Clinical recurrent stroke was seen in 1.2% (4/333) within 90 days. Numbers of days from onset to recurrent stroke were 42, 44, 66, and 70, respectively. Of these cryptogenic patients, 62% (207/333) underwent follow-up imaging. There were no differences between patients who had follow-up imaging completed vs those who did not. Of the patients who underwent follow-up MRI, there were 101 (49%) males and median age was 66 years (interquartile range, 53–78). Baseline diffusion-weighted imaging lesion was seen in 47% (97/207) and an intracranial occlusion was seen in 11% (23/207). In the VISION study, 6.6% (5/76) of patients had new lesions on follow-up MRI at day 30, with 60% (3/5) of patients having lesions in a remote vascular territory. In the CATCH study, 14.5% (19/131) of patients had new lesions on follow-up MRI at day 90, with 9/19 (47%) having infarcts in remote vascular territory. There was no increased risk of new lesions on follow-up MRI if there was a diffusion-weighted imaging lesion at baseline (relative risk, 1.6; 95% confidence interval, 0.7–3.4; P=0.28, Fisher exact).

Discussion
We have found that a large proportion of patients with minor stroke or TIA have no identifiable cause (cryptogenic) despite comprehensive investigations. Cryptogenic TIA/minor stroke patients show evidence of a high rate of silent radiological accumulation of disease on follow-up imaging despite no identifiable cause found. The cumulative clinical stroke recurrence rate in cryptogenic TIA and minor stroke patients underestimates disease activity as compared with follow-up MRI surveillance. Furthermore, high rates of recurrent infarcts in remote arterial distribution point to an unidentified proximal source such as the heart or aortic arch in these cryptogenic patients. If this population is actively embolizing, then the best choice of antithrombotic treatment in this population is unclear. There is intriguing data suggesting a potential role for anticoagulant therapy rather than antiplatelet agents in cryptogenic stroke. The cryptogenic TIA/minor stroke population is an ideal target group for the new oral anticoagulants because of its lack of use is a potential limitation. The proportion of patients with cryptogenic etiology is high in this study, but it is similar to that seen in a recent large cohort study of TIA and minor stroke. This study highlights that follow-up brain imaging may be a useful surrogate marker for disease activity and may allow reduced sample sizes in randomized controlled trials of stroke prevention in this cryptogenic minor stroke and TIA population.

Sources of Funding
The CATCH study was supported by a grant-in-aid from the Canadian Institute of Health Research (CIHR) and a Pfizer Cardiovascular research award. The VISION study was supported by grant funding from CIHR and Heart and Stroke Foundation (HSF) of Alberta, NWT, and Nunavut.

Disclosures
Dr Coutts received salary support from the Alberta-Innovates-Health solutions and the Heart and Stroke Foundation of Canada’s Distinguished Clinician Scientist award, and is supported in partnership with the Canadian Institute of Health Research (CIHR), Institute of Circulatory and Respiratory Health, and AstraZeneca Canada Inc. Dr Demchuk receives salary support from Alberta Innovates-Health Solutions. Dr Coutts and Dr Demchuk have been advisory board members for Bristol Myer Squibb. Dr Demchuk has been an advisory board member for Boehringer Ingelheim and Bayer. All other authors report no conflicts of interest.

References
High Rate of Magnetic Resonance Imaging Stroke Recurrence in Cryptogenic Transient Ischemic Attack and Minor Stroke Patients
Simerpreet Bal, Shiel K. Patel, Mohammed Almekhlafi, Jayesh Modi, Andrew M. Demchuk and Shelagh B. Coutts

Stroke. published online October 2, 2012;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2012/10/02/STROKEAHA.112.671172

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/