How temporal evolution of intracranial collaterals in acute stroke affects clinical outcomes

Leonard L.L. Yeo, MBBS
Prakash Paliwal, MBBS
Adrian F. Low, MBBS
Edgar L.W. Tay, MBBS
Anil Gopinathan, MBBS
Mahendran Nadarajah,
MBBS
Eric Ting, MBBS
Narayanaswamy
Venketasubramanian,
MBBS
Raymond C.S. Seet,
MBBS
Aftab Ahmad, MBBS
Bernard P.L. Chan,
MBBS
Hock L. Teoh, MBChB
Derek Soon, MBBS
Rahul Rathakrishnan, BM
Vijay K. Sharma, MBBS

Correspondence to
Dr. Yeo:
leonard_ll_yeo@nuhs.edu.sg

ABSTRACT

Objective: We compared intracranial collaterals on pretreatment and day 2 brain CT angiograms (CTA) to assess their evolution and relationship with functional outcomes in acute ischemic stroke (AIS) patients treated with IV tissue plasminogen activator (tPA).

Methods: Consecutive AIS patients who underwent pretreatment and day 2 CTA and received IV tPA during 2010–2013 were included. Collaterals were evaluated by 2 independent neuroradiologists using 3 predefined criteria: the Miteff system, the Maas system, and 20-point collateral scale by the Alberta Stroke Program Early CT Score methodology. We stratified our cohort by baseline pre-tPA state of their collaterals and by recanalization status of the primary vessel for analysis. Good outcomes at 3 months were defined by a modified Rankin Scale score of 0–1.

Results: This study included 209 patients. Delayed collateral recruitment by any grading system was not associated with good outcomes. All 3 scoring systems showed that collateral recruitment on the follow-up CTA from a baseline poor collateral state was significantly associated with poor outcome and increased bleeding risk. When the primary vessel remained persistently occluded, collateral recruitment was significantly associated with worse outcomes. Interestingly, collateral recruitment was significantly associated with increased mortality in 2 of the 3 grading systems.

Conclusions: Not all collateral recruitment is beneficial; delayed collateral recruitment may be different from early recruitment and can result in worse outcomes and higher mortality. Prethrombolysis collateral status and recanalization are determinants of how intracranial collateral evolution affects functional outcomes. *Neurology*® 2016;86:434–441

GLOSSARY

AF = atrial fibrillation; **AIS** = acute ischemic stroke; **ASPECTS** = Alberta Stroke Program Early CT Score; **CI** = confidence interval; **CTA** = CT angiography; **IRB** = institutional review board; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **ROC** = receiver operating characteristic; **SICH** = symptomatic intracranial hemorrhage; **tPA** = tissue plasminogen activator.

Ischemic stroke is the largest contributor to disability in most developed countries. In clinical practice, infarct growth does not always progress to involve the full extent of the vascular territory, even if the affected intracranial artery fails to recanalize. The presence and recruitment of various collateral channels are believed to be responsible for this phenomenon in acute ischemic stroke (AIS).¹ These collaterals may also play an important role in influencing the safety and efficacy of acute revascularization approaches.²

Although blood supply from the leptomeningeal collaterals may temporarily maintain the ischemic penumbra, the persistence and effectiveness of this alternative circulatory supply is erratic and unpredictable. Some collaterals may disappear over time (collateral failure); this is one of the mechanisms responsible for clinical deterioration following initial improvement.³ Conversely, dramatic resolution of initial neurologic deficits may be seen though the occluded intracranial artery did not recanalize, often attributable to the rapid improvement of cerebral perfusion via effective collateral pathways (collateral recruitment). Therefore, the temporal

Supplemental data
at Neurology.org

From the Division of Neurology, Department of Medicine (L.L.L.Y., P.P., R.C.S.S., A.A., B.P.L.C., H.L.T., D.S., R.R., V.K.S.), Cardiac Department (A.F.L., E.L.W.T.), and Department of Diagnostic Imaging (A.G., E.T.), National University Health System; Department of Neuroradiology (M.N.), National Neuroscience Institute; and Raffles Neuroscience Centre (N.V.), Raffles Medical Group, Singapore.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

behavior of intracranial collaterals may play an important role in determining the functional outcome in AIS patients.

CT angiography (CTA) of the brain is acutely performed in AIS patients before or immediately after administering IV tissue plasminogen activator (tPA) in many centers. CTA is repeated on day 2 for the assessment of arterial recanalization in some centers. We evaluated the temporal evolution of intracranial collaterals during the first 24 hours for the assessment of its effect on functional outcome and hemorrhagic complications in IV-tPA-treated AIS patients.

METHODS A total of 359 (9.97% of all AIS hospitalized) patients received IV tPA up to 4.5 hours at our tertiary center between January 2010 and December 2013. Patients who underwent CTA of the brain before IV tPA and on day 2 were included in this study if they had a middle cerebral artery stroke. Patients with renal impairment and allergy to radiocontrast were excluded. A total of 209 (58.2% of IV tPA-treated patients) patients were included on these criteria. Data for demographic characteristics and vascular risk factors were extracted from the prospective thrombolysis registry. Systemic blood pressure values were recorded at presentation and at 24 hours after thrombolysis. AIS subtypes were determined using the Trial of Org 10172 in Acute Stroke Treatment classification.⁴ NIH Stroke Scale (NIHSS) scores were recorded by credentialed neurologists before IV tPA bolus, at 2 and 24 hours after treatment initiation. Functional outcome was assessed by the modified Rankin Scale (mRS) at 3 months by in-person visits by certified assessors blinded to treatment and images. An mRS score of 0–1 was defined as a good functional outcome. Symptomatic intracranial hemorrhage (SICH) was defined as the presence of new blood on the follow-up CT scan that was associated with an increase in NIHSS by 4 points or more.⁵

A noncontrast CT scan of the brain and high-resolution CTA were performed in all patients before administering IV tPA and another CTA was performed on day 2. Scans were performed on a 64-slice multidetector helical scanner (Philips, Best, the Netherlands) and images were acquired with 70 mL bolus injection of contrast. Scan parameters were slice thickness 1 mm, no slice gap, field of view 200 mm, matrix 512 × 512, and 230–250 mAs. Coverage was from the base of the skull to the vertex and the source images were reformatted into 3-mm-thick axial, coronal, and sagittal projections. The repeat CTA was performed at 24 ± 6 hours after IV tPA bolus for all patients using the same protocol.

CTA images were independently reviewed by 2 experienced neuroradiologists using maximum intensity projections in the axial planes. They were blinded to the patients' clinical status, outcome, and results of other neuroimaging modalities. Recanalization was grouped according to the arterial occlusive lesion score with 0 or 1 being an occluded vessel and a score of 2 or 3 being a vessel that had recanalized.⁶ Day 2 CTA was compared with the pretreatment CTA for collateral score, recruitment, and failure according to 3 predefined criteria. These scoring systems were chosen to encompass various existing methods of CTA collaterals scoring. The Miteff system focuses on the sylvian fissure vessels, the Maas system compares the vessels from side to side, and the Alberta Stroke Program Early CT Score (ASPECTS)

system subdivides the leptomeningeal collaterals into several more objective measurable areas. These scoring systems have been described previously and more details can be found in figures e-1–e-3 on the *Neurology*® Web site at Neurology.org.^{7–10} For our study, a 1-point improvement in grading was considered collateral recruitment, while a 1-point worsening was considered collateral failure.

Statistical methods. We present the numerical variables as mean and SD or median and range. Categorical variables are presented as percentages. Numerical predictors were tested by using 2-sample *t* test or Mann-Whitney *U* test where applicable. Categorical variables were evaluated using χ^2 test or Fisher exact test where applicable. Variables that were found to have a significant association ($p < 0.05$) were entered into the multivariable model to perform logistic regression for determining the independent predictors of the prespecified good and poor functional outcome at 3 months. To improve the robustness of our statistical model, variables with $p < 0.10$ were also included into a multivariable logistic regression model with backward stepwise selection procedure. Associations are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). Receiver operating characteristic (ROC) curves were computed for the imaging parameters studied. In a subanalysis, we stratified the cohort by recanalization status and collateral status on the pretreatment CTA for 2 further separate analyses. Finally, interobserver and intraobserver variability for assessment of collateral status between the 2 observers was tested using kappa statistics. Statistical analyses were performed using the Statistical Package for Social Sciences version 20 (SPSS Inc., Chicago, IL).

Standard protocol approvals, registrations, and patient consents. Ethical approval for this project was obtained from the institutional review board (IRB). The clinical and radiologic data were obtained from an ongoing prospective database and a waiver of consent was approved by the same IRB.

RESULTS A total of 359 patients were treated with IV tPA; overall, 209 (58.2% of all IV tPA-treated patients) were included. For the 150 excluded patients, reasons for their exclusion and their demographics are found in table e-1.

For the included patients, the median age was 64 years (range 29–92) and 131 (62.7%) patients were men. The pre-tPA median NIHSS score was 19 points (range 4–33). Median onset to treatment time was 160 minutes (range 66–291); 4 patients were treated outside the 4.5 hours window (table e-2). Hypertension was the commonest risk factor, with 132 (63.2%) patients, followed by dyslipidemia in 108 (51.7%) patients. Overall, 98 (46.8%) patients achieved good functional outcome at 3 months and mortality was noted in 16 (7.6%) patients (table 1).

The degrees of agreement between the 2 independent neuroradiologists for interpreting the collaterals were as follows: for Mass system, $\kappa = 0.82$ (95% CI 0.75–0.84) for leptomeningeal and $\kappa = 0.87$ (95% CI 0.80–0.91) for Sylvian fissure vessels; for the Miteff system, $\kappa = 0.91$ (95% CI 0.86–0.93); for the ASPECTS-based grading system, $\kappa = 0.77$ (95% CI 0.70–0.81).

Table 1 Baseline characteristics of the study population

Variables	No. (n = 209)
Age, y, median (range)	64 (29–92)
Male, n (%)	131 (62.7)
Hypertension, n (%)	132 (63.2)
Diabetes mellitus, n (%)	61 (29.2)
Dyslipidemia, n (%)	108 (51.7)
Smoker, n (%)	54 (25.8)
Atrial fibrillation, n (%)	70 (33.5)
Pre-tPA systolic BP, mm Hg, median (range)	150 (100–236)
Pre-tPA NIHSS score, median (range)	19 (4–33)
24-hour NIHSS score, median (range)	11 (0–31)
Onset to treatment time, min, median (range)	160 (66–291)
TOAST criteria	
Large artery atherosclerosis	82 (39.2%)
Cardioembolism	92 (44%)
Small vessel occlusion	11 (5.3%)
Undetermined cause	22 (10.5%)
Stroke of other etiology	2 (1%)
Modified Rankin Scale 0–1 at 3 mo, n (%)	98 (46.8)
Mortality at 3 mo, n (%)	16 (7.6)
Any bleeding, n (%)	28 (13.4)
Symptomatic intracranial hemorrhage, n (%)	18 (8.6)

Abbreviations: NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

Functional outcome. On univariable analysis, younger age, male sex, absence of hypertension, nonsmoker, absence of atrial fibrillation (AF), lower pre-tPA NIHSS scores at onset and 24 hours, collateral recruitment by ASPECTS method, and recanalization of the occluded intracranial artery were found to be associated with functional outcomes (table e-3). However, multivariate logistic regression analyses revealed only recanalization of the initially occluded vessel (OR 7.87, 95% CI 2.710–22.849, $p < 0.001$) as independent predictor of good functional outcome at 3 months. Conversely, older age (OR 1.07 per year, 95% CI 1.034–1.106, $p < 0.001$) and higher NIHSS scores (OR 1.17 per point, 95% CI 1.082–1.263, $p < 0.001$) were associated with poorer outcomes (mRS 2–6) (tables 2 and e-4). ROC curves for ASPECTS collateral recruitment were not significant (appendix e-1). Interestingly, collateral failure (day 2 CTA with reduction of the collaterals seen as compared to the initial CTA) showed no association with functional outcome at 3 months.

SICH. SICH was observed in 18 (8.6%) patients. On univariate analysis, collateral recruitment according to ASPECTS and the Miteff scoring system were associated with SICH. Other variables with association included hypertension, a higher NIHSS score, and the presence of recanalization (table e-3). On multivariate analysis, only NIHSS score at presentation (OR 1.18 per point increase, 95% CI 1.035–1.374, $p = 0.025$) was found to be an independent predictor of SICH. Collateral recruitment by ASPECTS methodology was not associated with SICH (OR 1.14 per point, 95% CI 0.997–1.308, $p = 0.055$) (figure 1). Collateral failure on the day 2 CTA was not associated with SICH (table e-4).

Mortality. A total of 16 (7.6%) patients died within 3 months after AIS. Factors associated with mortality on univariable analyses were higher NIHSS score at 24 hours, older age, AF, and collateral recruitment on day 2 CTA by the ASPECTS grading system and the Miteff grading system (table e-3). On multivariate analysis, higher NIHSS score at 24 hours (OR 1.14 per point, 95% CI 1.057–1.235, $p = 0.001$) and collateral score by the Miteff system (OR 3.38 per 1 grade, 95% CI 1.010–11.283, $p = 0.048$) and ASPECTS methodology (OR 1.160 per point, 95% CI 1.026–1.312, $p = 0.017$) were independent predictors of mortality (table 2). ROC curves for ASPECTS collateral recruitment were significant (appendix e-1). Collateral failure on the day 2 CTA did not show any association with mortality.

Stratification by initial collateral status. In our previous study, we noted that good early pretreatment CTA collaterals via the Miteff system were associated with good outcome at 3 months.¹¹ We stratified our cohort by good and poor collaterals on the initial CTA scan by the Miteff system to test if the initial collateral status had bearing on the evolution of collaterals and its associated clinical effects. For the group with good initial collaterals, collateral recruitment and collateral failure were not associated with good functional outcomes, mortality, or bleeding risk using the Maas, Miteff, or ASPECTS system. Interestingly, for the group with poor initial collaterals, collateral recruitment by the Miteff, Mass, or ASPECTS system was associated with worse outcomes and a higher risk of any intracranial hemorrhage but not mortality or SICH (figure 2, A–C). This bleeding risk was still significant when controlled for onset to treatment time and the use of prior antiplatelet or anticoagulation before IV tPA (data not shown).

Stratification by recanalization status. To determine if recanalization status affected the clinical effect of collateral change, we stratified our cohort by the recanalization status of the primarily occluded intracranial

Table 2 Independent predictors of functional outcome, mortality, and symptomatic intracranial hemorrhage

Variable	Odds ratio (95% CI)	p Value
Poor outcomes (mRS 2–6)		
Age	1.07 per year (1.034–1.106)	<0.001
NIHSS	1.17 per point (1.082–1.265)	<0.001
Recanalization of occluded vessel	0.14 (0.043–0.356)	<0.001
Mortality		
Miteff grading system improvement	3.38 (1.010–11.283)	0.048
ASPECTS grading system improvement	1.16 per point (1.026–1.312)	0.017
NIHSS at 24 hours	1.14 per point (1.057–1.235)	0.001
Symptomatic intracranial hemorrhage		
NIHSS	1.18 per point (1.035–1.374)	0.025

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; CI = confidence interval; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

For poor outcomes (mRS 2–6), we adjusted for hypertension, smoking, atrial fibrillation (AF), prior antiplatelet use, ASPECTS collateral recruitment and worsening, recanalization, age, and NIHSS at onset and 24 hours. For mortality, we adjusted for smoking, AF, previous stroke, Miteff recruitment, ASPECTS recruitment, age, prestroke mRS 0–1, and NIHSS at 24 hours. For SICH, we adjusted for hypertension, Miteff recruitment, ASPECTS recruitment, recanalization, NIHSS at onset, and glucose level at onset.

artery. In the group with recanalization of the occluded artery, collateral recruitment by the Miteff system was associated with good functional outcome at 3 months and a higher risk of any intracranial

Figure 1 Receiver operating characteristic curve for symptomatic intracranial hemorrhage and collateral recruitment by the ASPECT grading system

Area under the curve = 0.725, 95% confidence interval 0.604–0.857, $p = 0.002$. ASPECTS = Alberta Stroke Program Early CT Score.

hemorrhage (but not SICH). This bleeding risk was still significant when controlled for onset to treatment time and the use of prior antiplatelet or anticoagulation before IV tPA (data not shown). In the group without recanalization but with collateral recruitment, there was an association with worse outcome and mortality with the Miteff classification, while the ASPECTS system showed an association with mortality (figure 3).

DISCUSSION Contrary to general opinion, our study shows that substantial delayed collateral recruitment seen in the day 2 CTA in IV tPA–treated AIS patients resulted in a higher risk of poor outcome and mortality. Perhaps a delayed attempt to increase the regional cerebral perfusion is futile or even harmful and all attempts should be made to restore the arterial patency in AIS as early as possible.

Leptomeningeal collaterals in AIS are dynamic, especially during the first few hours or days of AIS. In rat studies, 3 different types of collaterals have been identified: transient collaterals that could be seen immediately after the stroke and last less than 90 minutes; impermanent collaterals that disappear after 90–150 minutes; and persistent collaterals, which can be seen for longer periods.¹² There is a dearth of literature on the temporal evolution of leptomeningeal collaterals in AIS in humans. Perhaps this is due to the emergent nature of AIS, which is not conducive to serial imaging required for elucidating this phenomenon.

Immediately after occlusion of a large artery, the ensuing drop in distal perfusion pressure and relaxation of smooth muscles generates a pressure gradient between adjacent arterial fields, leading to recruitment of potential collaterals.^{13,14} Besides the rapid compensatory reflex, there is a slower response, which occurs over several days following the occlusion, mediated by metabolic causes, angiogenesis, and other less well-understood factors.^{15–17} If the ischemia develops slowly over an even longer period, the human brain is good at maintaining persistent collaterals. One example of this phenomenon is evident in patients being asymptomatic despite bilateral and severe carotid artery atherosclerosis.¹⁸ A previous study evaluated the relation of perfusion mismatch and pretreatment angiographic collaterals to tissue fate in the immediate postischemic time frame. Patients with good collateral flow demonstrated less hypoperfused tissue and less infarct growth within the penumbra zone than those with poor collaterals.¹⁹ This relationship between good early collaterals on pretreatment imaging and smaller infarct volume with better outcomes has been described in several studies.^{20–22} Despite this positive relationship, its role in therapeutic decision-making for AIS patients

Figure 2 Stratification by the Miteff system, the Maas system, and the ASPECTS collateral system

(A) Stratification by the Miteff system: Using Miteff grading, we stratified good and poor collateral circulation by the initial CT angiogram (CTA), and then analyzed collateral recruitment (improved by 1 grade) or collateral failure (worsened by 1 grade) on day 2 CTA to predict outcomes. (B) Stratification by the Maas system: Using Maas grading, we stratified good and poor collateral circulation by the initial CTA, and then analyzed collateral recruitment (improved by 1 grade) or collateral failure (worsened by 1 grade) on the day 2 CTA to predict outcomes. (C) Stratification by the Alberta Stroke Program Early CT Score (ASPECTS) collateral system: Using the ASPECTS collateral grading system, we stratified good and poor collateral circulation by the initial CTA, and then analyzed collateral recruitment (improved by 1 grade) or collateral failure (worsened by 1 grade) on the day 2 CTA to predict outcomes. mRS = modified Rankin Scale; OR = odds ratio; Sympt bleed = symptomatic intracranial bleed.

Figure 3 Stratification by recanalization

We stratified the cohort by the presence (A) or absence (B) of recanalization of the occlusion on day 2 CT angiogram (CTA), and then analyzed collateral recruitment (improved by 1 grade) or collateral failure (worsened by 1 grade) on the day 2 CTA by the Maas, Miteff, and Alberta Stroke Program Early CT Score systems to predict outcomes. ASPECTS = Alberta Stroke Program Early CT Score; mRS = modified Rankin Scale; OR = odds ratio; Sympt bleed = symptomatic intracranial bleed.

remains poorly established. We recognize that good initial collaterals are beneficial but how does the change in collaterals affect our clinical management?

While the aforementioned study looked at early collaterals, we evaluated the longitudinal change in the collateral status during the first 24 hours. Analogous to rat studies, the recruited collaterals evaluated in our study were persistent rather than impermanent or transient.¹² In animal studies, if this subacute response resulted in hyperperfusion at day 4, it was associated with a larger final infarct size as compared to animals with maximal hyperperfusion at day 1.²³ Our study shows that collateral recruitment on the day 2 scan per se is an independent predictor of higher mortality, but not functional outcomes. This is contrary to our 2 previous studies that analyzed leptomeningeal collaterals in isolation at the pre-tPA CTA and at the repeat CTA; both studies showed that good collaterals are associated with good outcomes.^{11,24} We do not wish to give the impression that collaterals are undesirable, but rather that the

timing when these collaterals are recruited may be important. Even with a persistent occlusion, there can be both a failure of the collateral circulation and a recruitment of collaterals via other pathways (figure e-4, A and B). Interestingly, when we stratified our data by recanalization status, the patients with recanalization of the primary vessel and collateral recruitment achieved better functional outcome, albeit with a risk of bleeding, while patients without recanalization and collateral recruitment tended to have a higher risk of worse outcome and mortality. Thus, delayed collateral recruitment appears to be useful only with recanalization and is detrimental without it.

The initial state of the collateral circulation on the pretreatment CTA also has a bearing on the clinical effect of the collateral recruitment on the day 2 CTA. When stratified by the status of the collateral circulation on the pretreatment CTA, collateral recruitment with good pretreatment collaterals was not associated with any of our measured outcomes.

However, collateral recruitment with poor pretreatment collaterals was associated with poor functional outcome at 3 months and a higher risk of intracranial hemorrhage.

Why does delayed collateral recruitment lead to worse outcomes? One plausible mechanism could be related to the maximal vasodilation in the ischemic area and how collateral recruitment in the adjacent regions may trigger a steal-like phenomenon with resultant expansion of the ischemic core.^{25,26} Another possible mechanism could be related to failed autoregulation in the affected vascular territory, leading to increased hyperperfusion damage with a higher chance of bleeding.²³ In early animal studies, this pattern of subacute postischemic circulatory increase was termed reactive hyperemia and was always followed by a delayed reduction in blood flow and subsequent infarction.^{27–30}

Interestingly, failure of intracranial collaterals was unable to predict patient outcome. We postulate that the transient collaterals during the early critical period were more important. By the time we performed the imaging for collaterals (at day 2), the transient collaterals would have already disappeared. This could explain our observation that collateral failure on the day 2 CTA was not associated with worse outcomes, mortality, or SICH.

Our study has several limitations. Although our study represents the largest attempt at evaluating the effect of temporal evolution of intracranial collaterals on outcomes in thrombolized AIS patients, its retrospective nature may be considered as a limitation. Second, our study population had relatively severe strokes (median NIHSS score 19 points), as well as a high preponderance of AF. These might have influenced the behavior of various collaterals and an increased SICH rate. Third, we evaluated the collateral status on pretreatment and day 2 CTAs. We do not have data on the earlier transient and impermanent collaterals and we only had data on the presence of but not the timing of recanalization. These factors might serve as important determinants of outcome as well as hemorrhagic complications in thrombolized AIS patients. We would have ideally performed another CTA shortly after thrombolysis, but this is clinically not feasible. We appreciate that CTA provides only a snapshot of the passage of the contrast through the intracranial vasculature and hence the extent of collaterals may vary with the timing of image acquisition. We included only patients with MCA territory strokes in this study and the results should not be generalized to other vascular territories. Finally, we did not have the benefit of perfusion scans, neither were we able to quantify the volume of infarct for this study. The next step would be to perform objective quantitative analysis of collaterals with time to determine if this

can aid clinically in the subselection of patients for endovascular treatment.

Our study shows that the behavior of intracranial collaterals during the first 24 hours plays an important role in determining the outcomes in AIS. Good leptomeningeal collaterals have been shown previously to be desirable but recruitment of delayed collateral can conversely result in worse outcomes. It is important to note that the collateral scoring on day 2 CTA should not be done in isolation and the recanalization status of the primary arterial occlusion as well as collateral status on the pretreatment CTA should be taken into consideration.

AUTHOR CONTRIBUTIONS

Leonard L.L. Yeo was responsible for conception of the study, literature search, data collection, analysis and interpretation, and writing the manuscript. Prakash Paliwal was responsible for literature search, study design, data collection, data interpretation, and editing the manuscript. Adrian F. Low was responsible for study design and editing the manuscript. Edgar L.W. Tay was responsible for study design and editing the manuscript. Anil Gopinathan was responsible for study design and editing the manuscript. Mahendran Nadarajah was responsible for study design and editing the manuscript. Eric Ting was responsible for the figures, data analysis, and editing the manuscript. Narayanaswamy Venkatasubramanian was responsible for study design and editing the manuscript. Raymond C.S. Seet was responsible for study design and editing the manuscript. Aftab Ahmad was responsible for study design and editing the manuscript. Bernard P.L. Chan was responsible for study design and editing the manuscript. Hock L. Teoh was responsible for study design and editing the manuscript. Rahul Rathakrishnan was responsible for data interpretation, study design, and editing the manuscript. Vijay K. Sharma was responsible for study design, data interpretation, and editing the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

L. Yeo was sponsored by the National Medical Research Council (NMRC), Singapore; grant no. CNIG12nov001. P. Paliwal, A. Low, E. Tay, A. Gopinathan, M. Nadarajah, E. Ting, N. Venkatasubramanian, R. Seet, A. Ahmad, B. Chan, H. Teoh, D. Soon, R. Rathakrishnan, and V. Sharma report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received March 13, 2015. Accepted in final form October 9, 2015.

REFERENCES

1. Liberskind D. Collateral circulation. *Stroke* 2003;34:2279–2284.
2. Jung S, Gilgen M, Slotboom J, et al. Factors that determine penumbral tissue loss in acute ischaemic stroke. *Brain* 2013;136:3554–3560.
3. Alexandrov AV, Felberg RA, Demchuk AM, et al. Deterioration following spontaneous improvement: sonographic findings in patients with acutely resolving symptoms of cerebral ischemia. *Stroke* 2000;31:915–919.
4. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35–41.
5. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II):

- Second European-Australasian Acute Stroke Study Investigators. *Lancet* 1998;352:1245–1251.
6. Khair P, Neff J, Broderick JP, et al. Revascularization end points in stroke intervention trials: recanalization versus reperfusion in IMS-I. *Stroke* 2005;36:2400–2403.
7. Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiography collateral status in acute ischemic stroke. *Brain* 2009;132:2231–2238.
8. Maas MB, Lev MH, Ay H, et al. Collateral vessels on CT angiography predict outcome in acute ischemic stroke. *Stroke* 2009;40:3001–3005.
9. Menon BK, Smith EE, Modi J, et al. Regional leptomeningeal score on CT angiography predicts clinical and imaging outcomes in patients with acute anterior circulation occlusions. *AJNR Am J Neuroradiol* 2011;32:1640–1645.
10. Choi JY, Kim EJ, Hong JM, et al. Conventional enhancement CT: a valuable tool for evaluating pial collateral flow in acute ischemic stroke. *Cerebrovasc Dis* 2011;31:346–352.
11. Yeo LLL, Paliwal P, Teoh HL, et al. Assessment of intracranial collaterals on CT angiography in anterior circulation acute ischemic stroke. *Am J Neuroradiol* 2015;36:289–294.
12. Wang Z, Luo W, Zhou F, Li P, Luo Q. Dynamic change of collateral flow varying with distribution of regional blood flow in acute ischemic rat cortex. *J Biomed Opt* 2012;17:125001.
13. Symon L, Ishikawa S, Meyer JS. Cerebral arterial pressure changes and development of leptomeningeal collateral circulation. *Neurology* 1963;13:237–250.
14. Meyer JS, Denny-Brown D. The cerebral collateral circulation: I: factors influencing collateral blood flow. *Neurology* 1957;7:447–458.
15. Busch HJ, Buschmann IR, Mies G, Bode C, Hossmann KA. Arteriogenesis in hypoperfused rat brain. *J Cereb Blood Flow Metab* 2003;23:621–628.
16. Coyle P, Panzenbeck MJ. Collateral development after carotid artery occlusion in Fischer 344 rats. *Stroke* 1990;21:316–321.
17. Lim M, Cheshier S, Steinberg GK. New vessel formation in the central nervous system during tumor growth, vascular malformations, and moyamoya. *Curr Neurovasc Res* 2006;3:237–245.
18. Henderson RD, Eliasziw M, Fox AJ, Rothwell PM, Barnett HJ. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis: North American Symptomatic Carotid Endarterectomy Trial (NASCET) group. *Stroke* 2000;31:128–132.
19. Bang OY, Saver JL, Buck BH, et al. Impact of collateral flow on tissue fate in acute ischemic stroke. *J Neurol Neurosurg Psychiatry* 2008;79:625–629.
20. Roberts HC, Dillon WP, Furlan AJ, et al. Computed tomographic findings in patients undergoing intra-arterial thrombolysis for acute ischemic stroke due to middle cerebral artery occlusion: results from the PROACT II trial. *Stroke* 2002;33:1557–1565.
21. Lee KH, Cho SJ, Byun HS, et al. Triphasic perfusion computed tomography in acute middle cerebral artery stroke: a correlation with angiographic findings. *Arch Neurol* 2000;57:990–999.
22. Christoforidis GA, Mohammad Y, Kehagias D, Avutu B, Slivka AP. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. *AJNR Am J Neuroradiol* 2005;26:1789–1797.
23. Wegener S, Artmann J, Luft AR, Butxon RB, Weller M, Wong EC. The time of maximum post-ischemic hyperperfusion indicates infarct growth following transient experimental ischemia. *PLoS One* 8:e65322.
24. Yeo LL, Paliwal P, Teoh HL, et al. The collateral circulation on day-2 CT angiography is a reliable predictor of functional outcomes in acute ischemic stroke. *Neurology* 2014;82:S15.003. Abstract.
25. Pranevicius O, Pranevicius M, Pranevicius H, Liebeskind DS. Transition to collateral flow after arterial occlusion predisposes to cerebral venous steal. *Stroke* 2012;43:575–579.
26. Kuwabara Y, Ichiya Y, Sasaki M, Yoshida T, Masuda K. Time dependency of the acetazolamide effect on cerebral hemodynamics in patients with chronic occlusive cerebral arteries. Early steal phenomenon demonstrated by [¹⁵O] H₂O positron emission tomography. *Stroke* 1995;26:1825–1829.
27. Tomita M, Gotoh F, Amano T, Tanahashi N, Tanaka K. “Low perfusion hyperemia” following middle cerebral artery occlusion in cats of different age groups. *Stroke* 1980;11:629–636.
28. Synder JV, Nemoto EM, Carroll RG, Safar P. Global ischemia in dogs: intracranial pressure, brain blood flow and metabolism. *Stroke* 1975;6:21–27.
29. Korfke WA, Nemoto EM, Hossman KA, Taylor F, Kessler PD, Stezoki SW. Brain blood flow and metabolic after global ischemia and post-insult thiopental therapy in monkeys. *Stroke* 1979;10:554–560.
30. Pulsinelli WA, Levy DE, Duffy TE. Regional cerebral blood flow and glucose metabolism following transient forebrain ischemia. *Ann Neurol* 1982;11:499–502.