JoS JOURNAL OF STROKE

Journal of Stroke 2025;27(1):118-121
https://doi.org/10.5853/jos.2024.02005

Letter to the Editor

Thrombectomy With Bridging Thrombolytic May Benefit Asian Patients More Than Non-Asian Patients: Insights From DIRECT-SAFE Sub-Analysis

James L. Barker,[1] Oshi Swarup,[1] Yohanna Kusuma,[1,2,3] Leonid Churilov,[1] Geoffrey Donnan,[1] Stephen M. Davis,[1] Peter J. Mitchell,[4] Bernard Yan[1]

[1]Department of Neurology, Melbourne Brain Centre, The Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia
[2]School of Medicine, Deakin University, Waurn Ponds, Australia
[3]Department of Neurology National Brain Centre, Jakarta, Indonesia
[4]Department of Radiology, The Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia

Dear Sir:

Current guideline-based management of acute ischemic stroke supports the use of bridging therapy (BT) with intravenous thrombolytics (IVT) prior to endovascular thrombectomy (EVT) in eligible patients. However, the evidence for BT is variable, with trials demonstrating non-inferiority for direct EVT[1,2] as well as others not reaching non-inferiority margins[3-6] over BT. The recent DIRECT-SAFE (A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval versus Standard Bridging Therapy) trial, which failed to show non-inferiority for direct EVT over BT, demonstrated a statistically significant benefit for BT on overall outcome, even more so than the non-Asian cohorts.[3] This finding created an opportunity to analyze these two regions as individual groups of hospital centers to highlight potential reasons for the difference in outcome.

The aim of this study was to compare the differences in time metrics and risk factors between the BT and direct EVT groups of the DIRECT-SAFE trial. Due to the descriptive nature of this study, no causal hypothesis was formulated for this analysis.

This is a *post hoc* analysis of all patients in the DIRECT-SAFE trial cohort, a multicenter, prospective, randomized, open-label, blinded endpoint trial with 1:1 randomization for patients presenting with ischemic stroke within 4.5 hours in Australia and New Zealand (non-Asian region); and China, Vietnam (Asian region). Among the 295 patients, 136 were from China and Vietnam, and 157 were from Australia and New Zealand.[3] The primary study (DIRECT-SAFE) had already obtained ethics approval, which encompassed further analysis of the original data.

Patient demographics, baseline comorbidities, National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores, and workflow time metrics during the treatment course were recorded. The presence of a tandem occlusion, as defined by the presence of simultaneous high-grade stenosis or occlusion of the extracranial internal carotid artery and embolic occlusion of the intracranial carotid artery or its branches,[7] was also recorded. These were separated into the non-Asian (Australia and New Zealand) and Asian region (China and Vietnam). It is notable that ethnicity data were not collected in the primary trial. The primary outcome was the ordinal mRS and mRS 0–2 or return to baseline assessed at 90 days after randomization. The secondary outcomes were rates of symptomatic intracranial hemorrhage (sICH), and mortality; angiographic outcomes of Thrombolysis in Cerebral Infarction (TICI) 2b-3; and clinical outcome of NIHSS at day 3.

Categorical data were analyzed using Fisher's exact test, and continuous variables were analyzed using the Wilcoxon rank-sum test. To assess associations, within-region effects of the two treatment arms were estimated using adjusted logistic regression, controlling for age and NIHSS (as per the primary manuscript). Respective effect sizes are reported as odds ratio (OR) with 95% confidence intervals (CI), and statistical significance is indicated by *P* value less than 0.05. Treatment interaction by region was investigated by a multiplicative interaction term in

respective regression models.

Baseline demographic data are summarized in Table 1. Both groups were equally matched in age, sex, baseline NIHSS, and comorbidities. The initial Alberta Stroke Program Early CT Score (ASPECTS) imaging was similar between regions with median ASPECTS of 10.[8,9] There was a higher proportion of baseline mRS 2 and 3 patients in the non-Asian region (5.1% and 3.8%, respectively) compared to the Asian region (2.2% and 0%, respectively). Tandem lesions and a large artery atherosclerosis etiology were more prevalent in the Asian region than in the non-Asian region (22.4% vs. 10.9%, *P*=0.010; and 47.1% vs. 19.1%, *P*<0.001). Stroke of undetermined etiology was seen more frequently in the non-Asian region (27.4% vs. 2.9%). Intracranial atherosclerotic disease as stroke etiology comprised a small proportion of patients and was similar between regions (6.6% in the Asian region vs. 3.2% in the non-Asian region, *P*=0.272).

Table 1. Comparison of baseline demographic data between non-Asian region (Australia and New Zealand) and Asian region (China and Vietnam), including comorbidities, baseline mRS, stroke etiology, and baseline ASPECTS

Demographics	Non-Asian region (n=157)	Asian region (n=136)	*P*
Patients randomized to direct arm	79 (50.3)	67 (49.3)	
Age (yr)	71 (61–79)	68 (60–76)	0.074
Male sex	81 (51.6)	85 (62.5)	0.076
Premorbid mRS score	0 (0–0)	0 (0–0)	0.006
mRS 0	132 (84.1)	128 (94.1)	
mRS 1	11 (7.0)	5 (3.7)	
mRS 2	8 (5.1)	3 (2.2)	
mRS 3	6 (3.8)	0 (0)	
ASPECTS	10 (9–10)	10 (9–10)	0.687
NIHSS	15 (8–20)	15 (12–20)	0.373
Previous stroke/TIA	20 (12.7)	24 (17.7)	0.255
Atrial fibrillation	40 (25.5)	40 (29.4)	0.511
Hypertension	100 (63.7)	75 (55.2)	0.153
Intracranial atherosclerotic disease	5 (3.2)	9 (6.6)	0.272
Tandem lesion*	17 (10.9)	30 (22.4)	0.010
Stroke etiology			<0.001
Large artery atherosclerosis	30 (19.1)	64 (47.1)	
Cardioembolism	63 (40.1)	64 (47.1)	
Small vessel occlusion	4 (2.6)	0 (0)	
Stroke of other determined etiology	5 (3.2)	2 (1.5)	
Stroke of undetermined etiology – two or more causes identified	3 (1.9)	0 (0)	
Stroke of undetermined etiology – negative evaluation	9 (5.7)	2 (1.5)	
Stroke of undetermined etiology – incomplete evaluation	43 (27.4)	4 (2.9)	

Values are presented as median (interquartile range) or n (%).
mRS, modified Rankin Scale; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.
*Tandem lesions are defined as extracranial high-grade stenosis or occlusion with distal embolic occlusion of the distal internal carotid artery or its branches.

Time metrics are summarized in Table 2. Statistically significant differences were observed for time metrics in non-Asian and Asian regions, respectively, for stroke onset to randomization (127 min vs. 171 min, *P*<0.001), stroke onset to revascularization (203 min vs. 285 min, *P*<0.001), hospital arrival to IVT (52.5 min vs. 81.5 min, *P*<0.001), arterial puncture (84 min vs. 105 min, *P*<0.001), and revascularization (124 min vs. 180 min, *P*<0.001). Similar findings were observed for randomization to revascularization (83 min vs. 105 min, *P*<0.001) and arterial puncture to revascularization (36 min vs. 66 min, *P*<0.001). There was no statistically significant difference in time from randomization to IVT (7 min vs. 9.5 min, *P*=0.307).

The interaction of direct EVT on angiographic, clinical, and safety outcomes between the non-Asian and Asian regions is summarized in Table 3. Angiographic outcomes of TICI 2b–3 were similar between regions, with ORs of 1.26 (95% CI, 0.2–8.14) and 0.81 (95% CI, 0.33–2.01), respectively ($P_{interaction}$=0.552). For clinical outcomes, a good clinical outcome (mRS 0–2 at 90 days) was more frequent in the direct EVT arm compared to BT in the non-Asian region, with an OR of 1.35 (95% CI, 0.65–2.80), compared to the Asian region, with an OR of 0.42 (95% CI, 0.21–0.86) ($P_{interaction}$=0.024). Similar findings were observed for excellent outcomes (mRS 0–1), with ORs of 1.26 (95% CI, 0.66–2.43) and 0.40 (95% CI, 0.19–0.85), respectively ($P_{interaction}$=0.023), and for ordinal mRS (OR 1.31 [95% CI, 0.75–2.31] vs. OR 0.54 [95% CI, 0.30–1.00], $P_{interaction}$=0.028). Early neurological improvement, defined as an NIHSS reduction of 8 points or return to 0–1 at day 3, was similar between regions, with ORs of 1.04 (95% CI, 0.47–2.43) in the non-Asian region and 0.50 (95% CI, 0.25–1.01) in the Asian region ($P_{interaction}$=0.173). Safety outcomes, including sICH and mortality, were not dependent on the treatment arm in either region. The interaction of treatment on sICH was not able to be determined due to the low sample size.

This descriptive sub-analysis of the DIRECT-SAFE cohort highlights the differences in time metrics, and time to revascularization as a potential factors for the failure to meet non-inferior outcomes in direct EVT trials. With the similar time to IVT between regions, this analysis supports a role for IVT in patients who may have potential delays to EVT. However, IVT should be administered as early as possible to improve outcomes, preferably within 2 hours and 20 minutes.[8] Further confounders to this are the higher frequency of tandem occlusions and strokes due to large artery atherosclerotic disease indicating a higher

Table 2. Comparison of time metrics for total participants in non-Asian region (Australia and New Zealand) and Asian region (China and Vietnam)

Time metrics	Non-Asian region (n=157)	Asian region (n=136)	*P*
Stroke to randomization less than 120 min	72 (45.9)	19 (14.0)	<0.001
Stroke to randomization (min)	127 (102–163)	171 (132–208.5)	<0.001
Stroke to revascularization (min)	203 (170–258)	285 (230–347)	<0.001
Arrival to intravenous thrombolytic (min)	52.5 (41–73.5)	81.5 (55.5–108)	<0.001
Arrival to arterial puncture (min)	84 (64–110)	105 (82–135)	<0.001
Arrival to revascularization (min)	124 (94–157)	180 (134–240)	<0.001
Randomization to intravenous thrombolytic (min)	7 (4–13)	9.5 (4–19)	0.307
Randomization to revascularization (min)	83 (54–103)	105 (72–154)	<0.001
Arterial puncture to revascularization (min)	36 (24–56)	66 (41–107)	<0.001

Values are presented as n (%) or median (interquartile range). Continuous variables were analyzed using Wilcoxon rank-sum test.

Table 3. Comparison of outcome data between non-Asian region (Australia and New Zealand) and Asian region (China and Vietnam)

Item	Non-Asian region			Asian region			$P_{interaction}$
	BT (n=78)	Direct EVT (n=79)	OR (95% CI)	BT (n=69)	Direct EVT (n=67)	OR (95% CI)	
Angiographic outcomes							
TICI 2b-3	74 (96.1)	75 (97.4)	1.26 (0.20–8.14)	56 (81.2)	52 (78.8)	0.81 (0.33–2.01)	0.552
Clinical outcomes							
mRS at 90 days	1 (1–3)	1 (1–3)	1.31 (0.75–2.31)	2 (1–5)	3 (2–6)	0.54 (0.30–1.00)	0.028
Outcome: mRS 0–2 or back to baseline at 90 days	50 (64.1)	57 (72.2)	1.35 (0.65–2.80)	39 (56.5)	23 (34.3)	0.42 (0.21–0.86)	0.024
Outcome: mRS 0–1 at 90 days	41 (52.6)	47 (59.5)	1.26 (0.66–2.43)	30 (43.5)	15 (22.4)	0.40 (0.19–0.85)	0.023
NIHSS reduction by 8 or reaching 0–1 at 3 days	60 (79.0)	60 (79.0)	1.04 (0.47–2.32)	35 (53.0)	24 (36.9)	0.50 (0.25–1.01)	0.173
Safety outcomes							
sICH	3 (3.9)	0 (0)	0.14 (0.01–2.67)	4 (5.8)	4 (5.8)	1.03 (0.25–4.31)	Unable to estimate
Mortality	9 (11.5)	4 (5.1)	0.50 (0.14–1.81)	15 (21.7)	18 (26.9)	1.23 (0.53–2.87)	0.250

Adjusted for age and NIHSS. Values are presented as median (interquartile range) or n (%). Within-region effects are displayed as OR, and interactions between the non-Asian region and Asian region are indicated when estimable, with a *P* value less than 0.05.
BT, bridging therapy; EVT, endovascular thrombectomy; OR, odds ratio; CI, confidence interval; TICI, Thrombolysis in Cerebral Infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage.

degree of procedural complexity in this cohort. However, given the *post hoc* nature of this analysis, we are unable to draw a causal relationship or further delineate the reasons for the procedural or workflow delays.

There were multiple limitations to this analysis, the major one being its retrospective *post hoc* nature. Since the randomization for DIRECT-SAFE was performed for the treatment effect rather than for the Asian versus non-Asian region, we cannot rely on the randomized nature of the original study for this causal analysis. Therefore, appropriately performing such analysis would have required a different design, with a number of important causal assumptions to be validated, and a much larger sample size. Simple adjustments for presumed confounders in such situations may lead to erroneous conclusions.[9] The low number of patients in each arm and region also reduces the ability to draw conclusions on safety outcomes, particularly with findings such as the observed frequency of hemorrhagic transformation. Another important limitation was that ethnicity data were not collected for each region and were therefore not available for analysis. This is relevant as the frequency of intracranial atherosclerotic disease in the Asian region cohort was 6.6%, which is much lower than the expected values of 33%–50% in this region.[10]

In conclusion, there was an observed difference in the benefits of BT compared to direct EVT between the Asian and non-Asian populations in the DIRECT-SAFE cohort. Delays to EVT and higher incidence of tandem occlusions and large artery atherosclerotic disease in the Asian cohort may have contributed to a greater response to BT. Overall, these findings highlight the need to consider IVT in eligible patients where there may be potential delays to EVT.

https://doi.org/10.5853/jos.2024.02005

Funding statement

None

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: BY, JB. Study design: BY, JB. Methodology: BY, JB, LC. Investigation: BY, JB, LC. Statistical analysis: LC. Writing—original draft: JB. Writing—review & editing: all authors. Approval of final manuscript: all authors.

Acknowledgments

We thank all the study participants and study sites involved in the original DIRECT-SAFE study.

References

1. Yang P, Zhang Y, Zhang L, Zhang Y, Treurniet KM, Chen W, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981-1993.
2. Zi W, Qiu Z, Li F, Sang H, Wu D, Luo W, et al. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;325:234-243.
3. Mitchell PJ, Yan B, Churilov L, Dowling RJ, Bush SJ, Bivard A, et al. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet* 2022;400:116-125.
4. Suzuki K, Matsumaru Y, Takeuchi M, Morimoto M, Kanazawa R, Takayama Y, et al. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021;325:244-253.
5. Hund HM, Boodt N, Hansen D, Haffmans WA, Lycklama À Nijeholt GJ, Hofmeijer J, et al. Association between thrombus composition and stroke etiology in the MR CLEAN registry biobank. *Neuroradiology* 2023;65:933-943.
6. Fischer U, Kaesmacher J, Strbian D, Eker O, Cognard C, Plattner PS, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022;400:104-115.
7. Di Donna A, Muto G, Giordano F, Muto M, Guarnieri G, Servillo G, et al. Diagnosis and management of tandem occlusion in acute ischemic stroke. *Eur J Radiol Open* 2023;11:100513.
8. Kaesmacher J, Cavalcante F, Kappelhof M, Treurniet KM, Rinkel L, Liu J, et al. Time to treatment with intravenous thrombolysis before thrombectomy and functional outcomes in acute ischemic stroke: a meta-analysis. *JAMA* 2024;331:764-777.
9. Conroy S, Murray EJ. Let the question determine the methods: descriptive epidemiology done right. *Br J Cancer* 2020;123:1351-1352.
10. Chen LH, Spagnolo-Allende A, Yang D, Qiao Y, Gutierrez J. Epidemiology, pathophysiology, and imaging of atherosclerotic intracranial disease. *Stroke* 2024;55:311-323.

Correspondence: Bernard Yan
Department of Neurology, Melbourne Brain Centre, Royal Melbourne Hospital, 300 Grattan St. Parkville, Victoria, Australia
Tel: +61-(03)-9342-7000
E-mail: bernard.yan@mh.org.au
https://orcid.org/0000-0001-8802-9606

Received: May 27, 2024
Revised: August 8, 2024
Accepted: October 8, 2024