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

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Lancet 2022; 400: 116–25

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Summary

Background The benefit of combined treatment with intravenous thrombolysis before endovascular thrombectomy in patients with acute ischaemic stroke caused by large vessel occlusion remains unclear. We hypothesised that the clinical outcomes of patients with stroke with large vessel occlusion treated with direct endovascular thrombectomy within 4·5 h would be non-inferior compared with the outcomes of those treated with standard bridging therapy (intravenous thrombolysis before endovascular thrombectomy).

Methods DIRECT-SAFE was an international, multicentre, prospective, randomised, open-label, blinded-endpoint trial. Adult patients with stroke and large vessel occlusion in the intracranial internal carotid artery, middle cerebral artery (M1 or M2), or basilar artery, confirmed by non-contrast CT and vascular imaging, and who presented within 4·5 h of stroke onset were recruited from 25 acute-care hospitals in Australia, New Zealand, China, and Vietnam. Eligible patients were randomly assigned (1:1) via a web-based, computer-generated randomisation procedure stratified by site of baseline arterial occlusion and by geographic region to direct endovascular thrombectomy or bridging therapy. Patients assigned to bridging therapy received intravenous thrombolytic (alteplase or tenecteplase) as per standard care at each site; endovascular thrombectomy was also per standard of care, using the Trevo device (Stryker Neurovascular, Fremont, CA, USA) as first-line intervention. Personnel assessing outcomes were masked to group allocation; patients and treating physicians were not. The primary efficacy endpoint was functional independence defined as modified Rankin Scale score 0–2 or return to baseline at 90 days, with a non-inferiority margin of –0·1, analysed by intention to treat (including all randomly assigned and consenting patients) and per protocol. The intention-to-treat population was included in the safety analyses. The trial is registered with ClinicalTrials.gov, NCT03494920, and is closed to new participants.

Findings Between June 2, 2018, and July 8, 2021, 295 patients were randomly assigned to direct endovascular thrombectomy (n=148) or bridging therapy (n=147). Functional independence occurred in 80 (55%) of 146 patients in the direct thrombectomy group and 89 (61%) of 147 patients in the bridging therapy group (intention-to-treat risk difference –0·051, two-sided 95% CI –0·160 to 0·059; per-protocol risk difference –0·062, two-sided 95% CI –0·173 to 0·049). Safety outcomes were similar between groups, with symptomatic intracerebral haemorrhage occurring in two (1%) of 146 patients in the direct group and one (1%) of 147 patients in the bridging group (adjusted odds ratio 1·70, 95% CI 0·22–13·04) and death in 22 (15%) of 146 patients in the direct group and 24 (16%) of 147 patients in the bridging group (adjusted odds ratio 0·92, 95% CI 0·46–1·84).

Interpretation We did not show non-inferiority of direct endovascular thrombectomy compared with bridging therapy. The additional information from our study should inform guidelines to recommend bridging therapy as standard treatment.

Funding Australian National Health and Medical Research Council and Stryker USA.

Introduction

The results of five randomised controlled studies comparing intravenous thrombolysis alone with combined bridging intravenous thrombolysis followed by endovascular thrombectomy showed a clear superiority of combined bridging therapy.[1–5] A subsequent pooled analysis (HERMES)[6] confirmed the beneficial effects of endovascular thrombectomy that extended across a spectrum of subgroups, with over 80% of these patients having bridging therapy with alteplase.[6] The use of

Research in context

Evidence before this study

Five individual trials published in 2015 and subsequent individual patient-level meta-analysis established that, in patients with large vessel occlusion and ischaemic stroke, bridging mechanical thrombectomy together with intravenous thrombolytic reduces disability compared with intravenous thrombolytic alone. Intravenous thrombolytic administration has potential advantages, including earlier onset of treatment and potential increased reperfusion, but might be associated with increased haemorrhagic complications, and might cause distal migration of thrombus to inaccessible vessels. Evidence for non-inferior outcomes in patients with stroke and large vessel occlusion eligible for intravenous thrombolytic and mechanical thrombectomy treated with mechanical thrombectomy alone is inconclusive. Two studies showed non-inferiority of mechanical thrombectomy compared with bridging therapy in patients from Asian regions; however, three studies in other populations did not. Varying approaches to selection of non-inferiority margins, thrombolytic dose, and time to treatment made overall interpretation difficult. Study-level meta-analysis following these studies acknowledged uncertainty and the need for further trials.

Added value of this study

Our study included patients treated with anterior and posterior circulation large vessel occlusion, from both Asian (China and Vietnam) and non-Asian (Australia and New Zealand) populations, treated with standardised dosing of thrombolytic agents. We showed low rates of haemorrhagic complications, high rates of reperfusion, and clinical outcomes that were similar across both treatment groups. We did not show non-inferiority of direct mechanical thrombectomy, with 55% of the direct thrombectomy group and 61% of the bridging therapy group achieving the primary outcome of functional independence modified Rankin Score 0–2 (intention-to-treat risk difference –0·051, two-sided 95% CI –0·160 to 0·059). In a prespecified subgroup analysis, in patients from the Asian regions bridging therapy was associated with better outcomes when compared with the direct thrombectomy group. In summary, the additional evidence from this study supports the conclusion that there is no evidence of benefit to remove thrombolytic therapy before thrombectomy, particularly in people from the Asian regions.

Implications of all the available evidence

The additional information from our study provides supporting evidence in favour of bridging therapy. Although bridging therapy should be the default, direct mechanical thrombectomy could be considered for selected patients with potential increased risk from thrombolytic therapy, including later time windows and larger infarct volumes, and who present directly to hospitals capable of rapid delivery of endovascular thrombectomy.

intravenous thrombolysis with alteplase is based on level one evidence of improved functional outcome when given within 4·5 h of stroke onset.[7] The published guidelines from the American Stroke Association and the European Stroke Organization recommend alteplase before endovascular thrombectomy as standard of care for patients with stroke onset within 4·5 h caused by large artery occlusion.[8,9]

However, it is relatively infrequent for recanalisation to occur with intravenous thrombolysis before commencement of the endovascular procedure (only 7·6% in the HERMES trials).[6] Although an effect of intravenous thrombolytic in facilitating thrombectomy is possible, thrombolytic therapy might cause clot fragmentation and subsequent distal migration that is out of reach of mechanical thrombectomy. The extent of reperfusion has been strongly correlated with clinical outcome, but whether the potential removal of distal emboli with thrombolytic outweighs the effect of fragmentation and possible reduction in endovascular success remains uncertain.[10] Additionally, bridging intravenous thrombolysis might increase the risk of symptomatic intracerebral haemorrhage (SICH).

Despite the completion of five randomised controlled studies comparing direct thrombectomy with thrombectomy and bridging alteplase, there have been conflicting results. Two trials in Asia showed non-inferiority, a third trial did not, and all trials had differing non-inferiority margins. Conversely, two trials in Europe showed neither superiority nor non-inferiority. Hence there is no consensus to guide clinical practice.[11–14] The fact that these studies exclusively enrolled Asian or European populations is worth considering; Asian and European patients respond differently to several cerebrovascular interventions, such as antiplatelet therapy, based on pharmacogenomic differences.[15] A formal study-level meta-analysis showed non-inferiority for some but not the more stringent non-inferiority margins, and hence identified the need for further trials.[16] We hypothesised that clinical outcomes of patients with ischaemic stroke with intracranial internal carotid artery, middle cerebral artery, or basilar artery occlusion treated with direct endovascular thrombectomy within 4·5 h would be non-inferior to standard bridging intravenous thrombolytic followed by endovascular thrombectomy. Further, we aimed to explore several prespecified hypotheses, including a potential differential response to these interventions among patients from Asian (China and Vietnam) versus non-Asian (Australia and New Zealand) regions.

Methods

Study design and participants

DIRECT-SAFE was an international, multicentre, prospective, randomised, open-label, blinded-endpoint

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trial. The treatment group was assigned to receive direct endovascular thrombectomy and the standard care group to receive intravenous thrombolytic plus endovascular thrombectomy (bridging therapy). The first patient was enrolled on June 2, 2018, with the final patient enrolled on June 10, 2021. The trial population included patients older than 18 years, with small to moderate early ischaemic changes on non-contrast CT and occlusion of the intracranial internal carotid artery, middle cerebral artery (M1 or M2), or basilar artery confirmed by vascular imaging (CT angiography or magnetic resonance angiography). Patients had to be eligible for intravenous thrombolytic and seen within 4·5 h of stroke onset. Endovascular thrombectomy had to commence within 90 min of randomisation. The trial was done at 25 acute-care hospitals in Australia (n=10 sites), New Zealand (n=1), China (n=11), and Vietnam (n=3). Ethics approval was obtained from the Melbourne Health Human Research Ethics Committee on April 18, 2017, HREC/16/MH/431. Informed consent was obtained from patients when possible, otherwise deferred consent was used. The study protocol has been previously published and is available online.[17]

Randomisation and masking

Patients were randomly assigned (1:1), within 90 min of hospital arrival, via a web-based, computer-generated randomisation, to either trial arm (treatment or control) and were stratified for site of baseline arterial occlusion (internal carotid artery, middle cerebral artery, and basilar artery) and geographical region (Australia and New Zealand *vs* China and Vietnam). Personnel assessing outcomes were masked to group allocation; patients and treating physicians were not. The allocation of the patient was disclosed to the interventionist after randomisation. Imaging data were evaluated by members of the central imaging core laboratory.

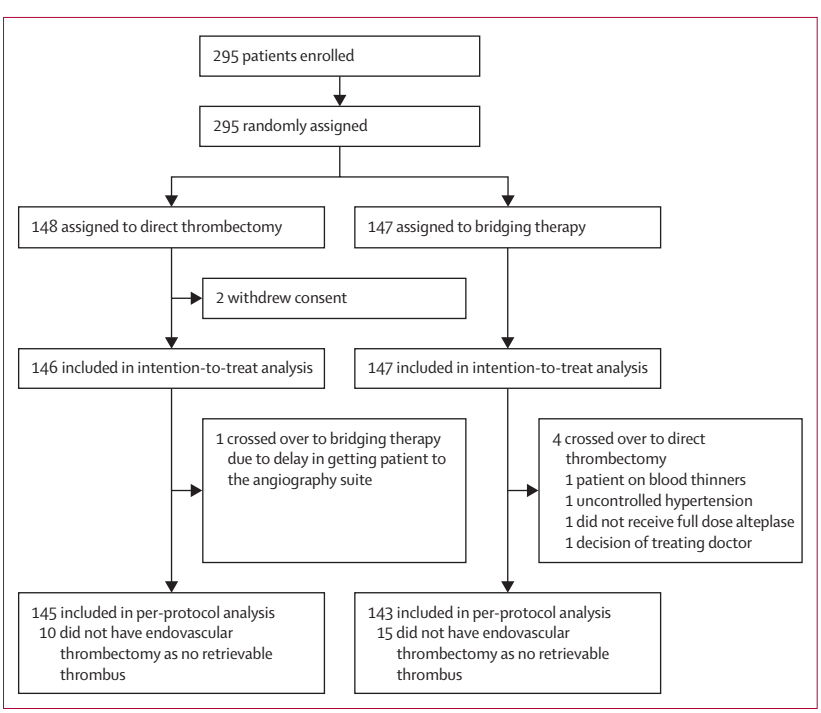

Figure 1: **Trial profile**

Procedures

Patients in the intravenous thrombolytic (alteplase or tenecteplase) group received intravenous thrombolytic as per standard care at each site. Vital signs were recorded during and after the period of infusion as per standard care. The thrombolytic agent used, time of thrombolytic commencement, and the dose administered were recorded.

All patients were then transferred to the interventional neuroradiology suite with an emphasis on minimising delays to arterial puncture. If drastic clinical recovery occurred in the interim, the patient still underwent diagnostic angiography to determine whether there was a persisting endovascular thrombectomy target. The use of conscious sedation or general anaesthesia for the procedure was at the investigator's discretion. Close attention was paid to maintaining stable blood pressure and minimising delays in starting the procedure. During the procedure, catheters could be flushed with heparinised saline at a concentration of 1000 units heparin per L in 0·9% sodium chloride. Endovascular thrombectomy used the Trevo device (Stryker Neurovascular, Fremont, CA, USA); standard of care) as the first-line intervention. The decision for proximal balloon guide and aspiration, distal intermediate catheter aspiration, or subsequent use of additional catheters or devices was at the discretion of the investigator. Stenting of the extracranial internal carotid artery or stenting in the case of intracranial atherosclerotic disease was permitted when absolutely necessary to obtain access to distal occlusion or to prevent acute reocclusion. The use of antiplatelet therapy for angioplasty or stent placement was at the discretion of the interventionist; otherwise no heparin, antiplatelets, or anticoagulants were given until at least 24 h after the procedure. Presence of intracranial atherosclerotic disease was recorded. Close neurological observation was done primarily during the first 48 h after treatment administration according to local clinical practice.

Imaging was done with CT and CT angiography, or MRI and magnetic resonance angiography acutely as part of standard care with imaging follow-up at 18–36 h. Major vessel occlusion (internal carotid artery, middle cerebral artery, and basilar) was required for study eligibility, and where possible, CT perfusion or magnetic resonance perfusion were done at baseline and at 18–36 h. All imaging was evaluated by a core imaging assessment laboratory masked to all clinical outcomes. The initial and final angiograms were centrally graded by

the imaging core laboratory for angiographic reperfusion using the modified treatment in cerebral infarction (mTICI) classification and any embolisation into new territories was documented. Diagnosis of intracranial atherosclerotic disease was based on the following criteria: more than 70% stenosis at the end of the procedure or the performance of intracranial angioplasty or stent placement. Haemorrhagic transformation was graded with the European Cooperative Acute Stroke Study classification by a central panel masked to treatment allocation. SICH was defined as large parenchymal haematoma occupying more than 30% of the infarct with substantial mass effect or subarachnoid haemorrhage, combined with a 4 or more point deterioration in National Institutes of Health Stroke Scale (NIHSS) score within 36 h of treatment.

Neurological impairment and functional scores were measured by a neurologist or health-care professional trained in their administration. The assessors were masked to the treatment group. The NIHSS is a validated neurological impairment score, which was done at baseline, at 24 h after treatment (or if initially under general anaesthetic, as soon as assessable), and on day 3. At day 90 (±7 days), the modified Rankin Score (mRS) was assessed via telephone and adjudicated by a central, masked panel to assess functional outcome.[18]

Outcomes

The primary outcome was functional independence, defined as having scores of 0–2 on the mRS (range 0 [no symptoms] to 6 [death]) or return to baseline score at 90 days. Secondary outcomes were excellent clinical outcome, defined by an mRS of 0–1 or return to baseline at 3 months; ordinal shift on mRS at 3 months; proportion of patients with death due to any cause at 3 months; proportion of patients with SICH up to 36 h after intervention; proportion of patients with good angiographic reperfusion (mTICI 2b–3) at completion; and proportion of patients with early neurological improvement, defined as more than 8 points reduction in NIHSS or reaching NIHSS 0–1 at 3 days.

Statistical analysis

A total sample size of 780 patients (390 patients in each group) was estimated to yield 80% power to show non-inferiority in the proportions of patients reaching the primary outcome in the direct thrombectomy group compared with standard bridging therapy, assuming this proportion to be 0·46 and a non-inferiority margin of –0·1 at a two-sided statistical significance threshold of p=0·05. An adaptive increase in sample size was to be done if the result of interim analysis with data from the first 600 patients was promising as per the methodology of Mehta and Pocock[19] with a maximum sample size of 900.

The primary non-inferiority analysis was based on both an intention-to-treat and per-protocol basis; the intention-to-treat analysis included all randomised and consenting patients. The intention-to-treat population was included in the safety analyses. The protocol specified a non-inferiority margin of –0·1 (meaning a <10% absolute difference) for the primary outcome of having an mRS of 0–2 or no change from baseline. Non-inferiority would be established if the lower bound of the two-sided 95% CI around the difference in proportions of patients who achieved the primary outcome was greater than the predefined non-inferiority margin. The two-sided 95% CI around the difference of proportions was estimated by

	Direct thrombectomy (N=146)	Bridging therapy (N=147)
Age, years	70 (61–78)	69 (60–79)
Sex		
Male	78/146 (53%)	88/147 (60%)
Female	68/146 (47%)	59/147 (40%)
Region		
Australia and New Zealand	79/146 (54%)	78/147 (53%)
China and Vietnam	67/146 (46%)	69/147 (47%)
NIHSS score*	15 (11–20)	15 (10–20)
Vascular risk factors		
Previous transient ischaemic attack or stroke	26/146 (18%)	18/147 (12%)
Previously diagnosed atrial fibrillation	46/146 (32%)	34/147 (23%)
History of hypertension	86/146 (59%)	89/147 (61%)
mRS score before stroke	0 (0)	0 (0)
ASPECTS score	10 (9–10)	10 (9–10)
Thrombolytic agent		
Tenecteplase	..	25/145 (17%)
Alteplase	..	120/145 (83%)
Duration, min		
From stroke onset to randomisation	136·0 (110·0–186·0), n=146	151·0 (108·0–204·0), n=147
From randomisation to start of thrombolytic	..	8·0 (4·0–15·5), n=144
From randomisation to groin puncture	29·0 (19·0–47·0), n=145	42·0 (29·0–59·0), n=147
From randomisation to revascularisation	86·5 (59·0–129·0), n=136	89·5 (64·0–121·0), n=132
From groin puncture to revascularisation	55·5 (26·0–88·5), n=136	44·5 (27·0–70·0), n=132
From hospital admission to thrombolysis	..	64·0 (47·0–87·0), n=144
From hospital admission to groin puncture	87·0 (65·0–113·0), n=145	101·0 (75·0–127·0), n=147
From hospital admission to revascularisation	144·0 (107·0–186·0), n=136	140·5 (111·5–199·5), n=132
Location of intracranial artery occlusion		
Intracranial internal carotid artery	33/145 (23%)	31/145 (21%)
M1 segment of middle cerebral artery	80/145 (55%)	83/145 (57%)
M2 segment of middle cerebral artery	21/145 (14%)	23/145 (16%)
Basilar artery	11/145 (8%)	8/145 (6%)
Tandem extracranial	27/145 (19%)	20/145 (14%)
Intracranial atherosclerotic disease	6/146 (4%)	8/146 (5%)

Data are n/N (%) or median (IQR). NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. ASPECTS=Alberta Stroke Program Early CT Score. M1=first segment of the middle cerebral artery. M2=second segment of the middle cerebral artery. *Standardised neurological examination ranges from normal (0) to death (42).

Table 1: **Baseline demographic and clinical characteristics of recruited patients**

See Online for appendix

	Direct thrombectomy	Bridging therapy
Procedural characteristics		
Intracranial stent	6/136 (4%)	5/131 (4%)
Extracranial stent	13/136 (10%)	8/131 (6%)
Proportion of patients with reperfusion on angiographic examination, assessed on digital subtraction angiography	1/146 (1%)	9/146 (6%)
GP2b inhibitor	9/136 (7%)	4/131 (3%)
Other antiplatelets	6/136 (4%)	0/131
Procedural complications		
Vessel dissection	0/146	1/146 (1%)
Contrast extravasation	4/146 (3%)	1/146 (1%)
Proportion of patients with distal embolisation	2/146 (1%)	3/146 (2%)

Data are n/N (%).

Table 2: **Procedural characteristics and complications**

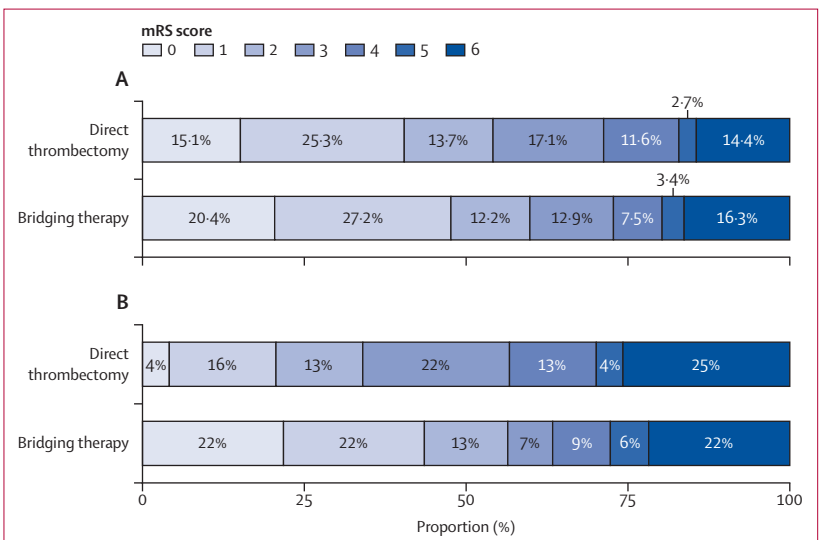

Figure 2: **Primary outcome overall and in prespecified Asian region subgroup**
(A) Primary outcome by overall distribution by direct thrombectomy and bridging therapy (risk difference −0·051; 95% CI −0·16 to 0·059; p=0·19). (B) Primary outcome distribution by direct thrombectomy and bridging groups in the Asian region prespecified subgroup (adjusted odds ratio 0·42; 95% CI 0·21 to 0·86; p=0·017). Horizontal stacked bar graphs show the primary outcome (mRS) distribution by direct thrombectomy and bridging therapy groups. Bars are labelled with proportions. mRS=modified Rankin Scale.

generating stratum-specific risk differences with corresponding 95% CIs for each of the four strata (age <60 years *vs* 60 years or older by baseline NIHSS 0–15 or 16 and above) with subsequent pooling across strata using the Mantel-Haenszel method.

The proportions of mRS 0–2 or no change from baseline and death due to any cause were compared between the direct thrombectomy group and the standard bridging therapy group, adjusted for geographical region, age, and baseline NIHSS score using a logistic regression model. The proportions of participants with good angiographic reperfusion (mTICI 2b–3) and SICH were compared between the two groups, adjusted for site of arterial occlusion and geographical region with logistic regression. The prespecified subgroup analysis included comparison of patients from the Asian regions with those from the non-Asian regions. The ordinal shift analysis of the mRS secondary outcome was done with ordinal logistic regression, since the proportional odds assumption was not violated. The statistical analysis plan was formulated and finalised before the study database lock (appendix pp 1–21).[17]

An independent data safety monitoring board including neurologists and a statistician met regularly to monitor progress of the trial. Two safety variables (death or symptomatic haemorrhage within 36 h of intervention) were monitored in safety interim analyses undertaken by the data safety monitoring board when 100 and 200 patients had completed the 3-month assessment. As there were no concerns about the safety of participants, the data safety monitoring board recommended to the trial steering committee to continue the trial on both occasions.

A random effect meta-analysis of DIRECT-MT, DEVT, SKIP, and MR CLEAN-NO IV[11–14] with the Der Simonian and Laird model estimated the pooled adjusted odds ratio (OR) to be 0·94 (95% CI 0·81–1·09). The lower boundary of the two-sided 95% CI (one-sided 97·5% CI) did not cross the OR 0·8 margin, thus showing that non-inferiority of direct thrombectomy was achieved based on the results of these trials.[11–14]

As a result, our independent data safety monitoring board recommended early termination of the trial (on July 8, 2021, with a final sample size of 295). There were no safety concerns for our trial. The trial is registered with ClinicalTrials.gov, NCT03494920.

Role of the funding source

DIRECT-SAFE was an investigator-led clinical trial. The sponsor of the trial was the Florey Institute. The trial was supported by a grant from the Australian National Health and Medical Research Council programme, and Stryker USA. The trial was managed by Neuroscience Trials Australia. Database management and central data monitoring and verification was performed by Neuroscience Trials Australia and independent statistical analysis done by the Methods and Implementation Support for Clinical and Health Research Hub at the University of Melbourne, VIC, Australia. The regulatory sponsor and funding agents did not participate in the study design.

Results

Between June 2, 2018, and July 8, 2021, 295 patients were randomly assigned to direct thrombectomy (n=148) or bridging therapy (n=147). After two patients withdrew consent, 146 patients remained in the direct thrombectomy group and 147 patients in the bridging therapy group for intention-to-treat analysis, with no

	Direct thrombectomy	Bridging therapy	Effect size (95% CI)	p value
Primary efficacy outcome (ITT)				
Functional independence: mRS 0–2 or return to baseline	80/146 (55%)	89/147 (61%)	Risk difference –0·051 (–0·160 to 0·059); adjusted OR 0·75 (0·45 to 1·24)	p=0·19 for non-inferiority; p=0·26 for superiority of bridging therapy
Primary efficacy outcome (PP)				
Functional independence: mRS 0–2 or return to baseline	79/145 (54%)	88/143 (62%)	Risk difference –0·062 (–0·173 to 0·049); adjusted OR 0·69 (0·41 to 1·15)	p=0·25 for non-inferiority; p=0·16 for superiority of bridging therapy
Secondary outcomes (ITT)				
mRS 0–1 or return to baseline	62/146 (42%)	71/147 (48%)	Adjusted OR 0·76 (0·46 to 1·24)	p=0·27
Score on mRS at 90 days				
0	22/146 (15%)	30/147 (20%)	..	..
1	37/146 (25%)	40/147 (27%)	..	..
2	20/146 (14%)	18/147 (12%)	..	..
3	25/146 (17%)	19/147 (13%)	..	..
4	17/146 (12%)	11/147 (7%)	..	..
5	4/146 (3%)	5/147 (3%)	..	..
6	21/146 (14%)	24/147 (16%)	..	..
Score on ordinal analysis	2 (1–4)	2 (1–4)	Common adjusted OR 0·85 (0·56 to 1·27)	p=0·42
Thrombectomy mTICI score 2b–3	127/143 (89%)	130/146 (89%)	Adjusted OR 0·84 (0·39 to 1·82)	p=0·66
NIHSS score within 72 h	4 (1–11), n=141	4 (1–11), n=142	..	..
Early neurological improvement*	84/141 (60%)	95/142 (67%)	Adjusted OR 0·73 (0·45 to 1·18)	p=0·20
Safety outcomes				
Death	22/146 (15%)	24/147 (16%)	Adjusted OR 0·92 (0·46 to 1·84)	p=0·82
Symptomatic intracerebral haemorrhage	2/146 (1%)	1/147 (1%)	Adjusted OR 1·70 (0·22 to 13·04)	p=0·61; Fisher's exact test p=0·62
Any intracerebral haemorrhage	31/146 (21%)	32/147 (22%)	Adjusted OR 0·97 (0·56 to –1·70)	p=0·92

Data are n/N (%) or median (IQR). ITT=intention to treat. mRS=modified Rankin Scale. PP=per protocol. OR=odds ratio. NIHSS=National Institutes of Health Stroke Scale. mTICI=modified Treatment in Cerebral Ischaemia. *NIHSS reduction of 8 points or more, or reaching 0–1 at 3 days, adjusted for baseline NIHSS and age.

Table 3: **Study outcomes**

patients lost to follow-up. In the per-protocol analysis after patient crossover, 145 remained in the direct thrombectomy group and 143 in the bridging therapy group (figure 1). In the direct thrombectomy group, ten patients did not have endovascular thrombectomy as there was no retrievable thrombus, whereas in the bridging therapy group, no retrievable thrombus was found in 15 patients who hence had no thrombectomy (figure 1).

Baseline characteristics were similar in the two groups (table 1). Overall, the median age of the patients was 68 years (IQR 61–78), and 166 (57%) of 293 were men. The median NIHSS score was 15 in both groups, and the median time from hospital admission to thrombolysis in the bridging therapy group was 64 min (IQR 47–87). The median time from randomisation to arterial puncture was 29 min (19–47) in the direct thrombectomy group and 42 min (29–59) in the bridging therapy group. Median times from arterial puncture to reperfusion were below 60 min in both groups (55·5 min [26·0–88·5] in the direct thrombectomy group and 44·5 min [27·0–70·0] in the bridging group; table 1). Table 2 shows procedural characteristics and complications.

Favourable outcome (mRS 0–2 or return to baseline) occurred in 80 (55%) of 146 patients in the direct thrombectomy group and 89 (61%) of 147 patients in the bridging therapy group (intention-to-treat risk difference –0·051, two-sided 95% CI –0·160 to 0·059), with the lower end of the confidence interval below the predefined non-inferiority margin of –0·1. The per-protocol analysis showed a favourable outcome in 79 (54%) of 145 patients in the direct thrombectomy group and 88 (62%) of 143 patients in the bridging therapy group (risk difference –0·062, two-sided 95% CI –0·173 to 0·049; figure 2). Hence, non-inferiority was not shown.

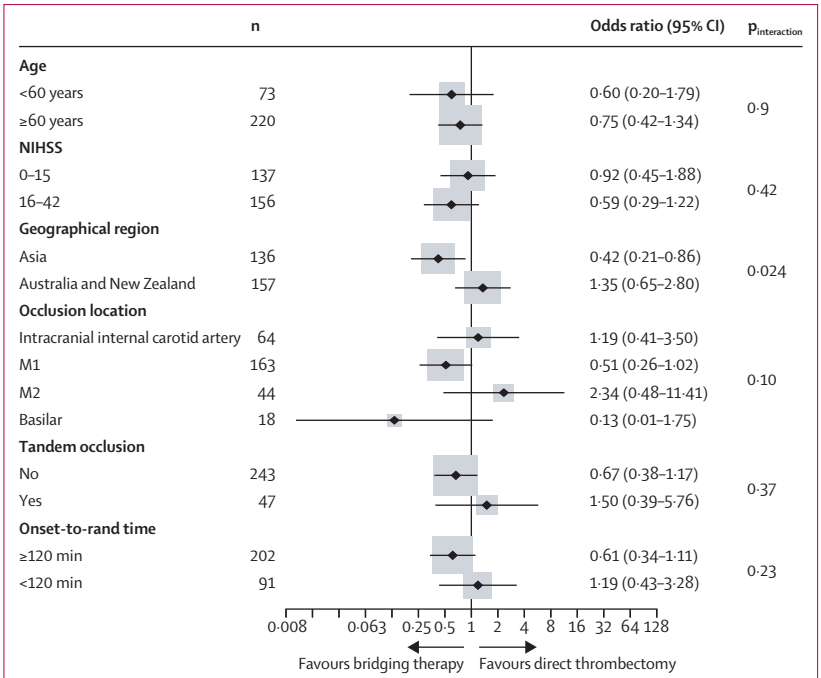

Figure 3: **Forest plot of prespecified subgroup analysis**
Forest plot of primary outcome in predefined subgroups in the intention-to-treat sample. Odds ratios of less than 1 favour bridging therapy over direct endovascular thrombectomy. Comparisons are unadjusted for multiplicity. Odds ratios are adjusted for age, baseline NIHSS score, and geographical region (for subgroups not based on these characteristics). NIHSS=National Institutes of Health Stroke Scale. M1=first segment of the middle cerebral artery. M2=second segment of the middle cerebral artery.

We found no significant differences in secondary outcomes, with successful reperfusion rates (mTICI 2b–3) similar in both groups, occurring in 127 (89%) of 143 patients in the direct thrombectomy group and in 130 (89%) of 146 patients in the bridging therapy group (adjusted OR 0·84, 95% CI 0·39–1·82). The secondary outcome of mRS 0–1 occurred in 62 (42%) of 146 patients in the direct thrombectomy group and 71 (48%) of 147 of patients in the bridging therapy group (adjusted OR 0·76, 95% CI 0·64–1·24). No significant between-group differences in proportions of patients with SICH or death were observed (table 3).

In a prespecified subgroup analysis (figure 3), in Asian regions, the primary outcome occurred in 39 (57%) of 69 patients in the bridging therapy group and 23 (34%) of 67 patients in the direct thrombectomy group (adjusted OR 0·42, 95% CI 0·21–0·86, p=0·017). This effect was significantly different to that observed in patients in non-Asian regions (1·35, 0·65–2·8, interaction p=0·024). Baseline characteristics in patients in Asian regions were well matched, with a median age of 68 years (IQR 61–76) in the direct thrombectomy group and 67 years (IQR 59–77) in the bridging therapy group. The median NIHSS was 14 (IQR 13–20) in the direct thrombectomy group and 15 (12–20) in the bridging therapy group. Time from randomisation to revascularisation was 105 min (71–154) in the direct thrombectomy group and 105·0 min (71·5–166·5) in the bridging therapy group. Time from hospital admission to revascularisation was 173 min (130–235) in the direct thrombectomy group and 196 min (133–250) in the bridging therapy group (appendix pp 24–26). Good reperfusion (mTICI 2b–3) occurred in 52 (79%) of 66 patients in the direct thrombectomy group and 56 (81%) of 69 in the bridging therapy group (adjusted OR 0·81, 95% CI 0·33 to 2·01, p=0·65). SICH occurred in two (3%) of 67 patients in the direct thrombectomy group and zero of 69 bridging patients but did not differ between groups (appendix pp 27–28). Time from hospital admission to thrombolytic was 80 min (IQR 56–108) in the sites in the Asian region and 64 min (47–87) in the non-Asian region.

Discussion

DIRECT-SAFE did not show non-inferiority of direct thrombectomy compared with standard therapy with bridging thrombolytic and endovascular thrombectomy, because the lower boundary of the 95% CI crossed the prespecified –0·1 non-inferiority margin, with the primary outcome of functional independence occurring in 80 (55%) of 146 patients in the direct thrombectomy group and 89 (61%) of 147 patients in the bridging therapy group. DIRECT-SAFE is now one of six randomised studies to test the hypothesis that direct thrombectomy is non-inferior to bridging thrombolytic with thrombectomy.[11–14] In contrast to these other studies, we enrolled patients from different global regions: a key strength of our trial is that around 50% of enrolled patients were from Asia. In the prespecified region-based subgroup analysis, we showed better outcomes in Asian patients with bridging therapy, with 23 (34%) of 67 patients in the direct thrombectomy group reaching functional independence compared with 39 (57%) of 69 patients in the bridging group (adjusted OR 0·42, 95% CI 0·21–0·86; p=0·017). Good reperfusion was similar in both groups and does not explain the difference in outcomes. Furthermore, no difference was observed in SICH, any intracerebral haemorrhage, or death between the two groups in this Asian subgroup. Previous trials have led to varied conclusions. As mentioned earlier, three of these were done exclusively in Asian populations, and two were from Europe. In the DIRECT-MT trial done in China, the investigators recruited 656 patients with acute ischaemic stroke with large vessel occlusion.[14] Direct thrombectomy was judged non-inferior to bridging therapy as the lower bound of the 95% CI did not cross the prespecified margin of 0·80 (adjusted common OR 1·07, 95% CI 0·81–1·40). The DEVT trial investigators recruited 234 patients with stroke also from China.[11] This trial was stopped early at an interim analysis with 54% of patients in the direct thrombectomy group and 47% of patients in the combined therapy group reaching the primary outcome of mRS 0–2 at 3 months. The absolute difference was 7·7% (one-sided

97·5% CI –5·1% to infinity), satisfying the non-inferiority margin of –10%. The SKIP trial investigators recruited 204 patients in Japan.[12] Non-inferiority was not shown, as the lower boundary of the 95% CI crossed the prespecified non-inferiority margin of 0·74 (mRS 0–2 59% in the direct thrombectomy group *vs* 57% in the bridging therapy group, OR 1·09, one-sided 97·5% CI 0·63 to infinity). The MR CLEAN NO IV trial investigators recruited 547 patients with stroke from three European countries. Direct thrombectomy was neither superior nor non-inferior (adjusted common OR 0·84, 95% CI 0·62–1·15; p=0·28).[20] The SWIFT DIRECT trial[21] recruited 408 patients in Europe and did not meet its non-inferiority margin of 12% (mRS 0–2 57% direct thrombectomy *vs* 65% bridging, adjusted risk difference –7·3%, 95% CI –16·6 to 2·1). Study-level meta-analysis confirmed inconclusive evidence for guideline modification and recommended further trials,[16] underlining the importance of the presentation and interpretation of the results of our study. When combining our data with previously published or presented trials (appendix pp 23), non-inferiority of direct thrombectomy is not shown, and recent expedited guidelines based on preliminary study-level meta-analysis of the six published and presented trials[22] conclude that patients eligible for intravenous thrombolytic should continue to receive bridging therapy. Our finding of a differential benefit between the Asian and non-Asian populations was somewhat surprising, with significant benefits of bridging therapy among Asian patients. Although there are clear clinical benefits of alteplase in the treatment of acute ischaemic stroke, there are also risks that should be considered, which might be different in Asian populations. In the ENCHANTED trial, which tested a lower dose of alteplase, approximately two-thirds of the patients were Asian, although there was no differential in risks or benefits between these and non-Asian centres.[23] Conversely, in clinical series of endovascular-treated patients, an increased incidence of SICH in patients who received intravenous alteplase was noted, particularly in those enrolled from the Asian region,[23] and in those with large ischaemic cores.[24] In addition, the Get With The Guidelines Stroke Program showed that Asian patients were more likely than non-Asian patients to develop SICH after intravenous thrombolytic.[25] Other investigators have also questioned the need for combined treatment with alteplase, given the increased cost.[26]

An additional matter worth considering is that patients with intracranial atherosclerosis (which is common in Asia and under-represented in the randomised trials, including this study) might require endovascular stenting combined with thrombectomy. These patients require more intensive antiplatelet therapy, which might further increase the risk of SICH in the setting of intravenous thrombolytic.

Patients in the bridging therapy group and the direct endovascular thrombectomy group in the Asian region had similar metrics, such as time from randomisation to reperfusion (105 min), similar reperfusion success (mTICI 2b–3; 79% and 81%), and similar rates of SICH. Baseline characteristics between the two groups were also similar; therefore, it is possible that the different outcomes in the Asian subgroup could be explained by variable pharmacological responses to thrombolytic. Alternatively, given multiple prespecified subgroup analyses, we cannot exclude the possibility that the findings might be due to chance. Further exploration of differential benefits between racial groups might be warranted in future studies of reperfusion therapies for stroke. Notably, 25 (17%) of 145 patients in the bridging therapy group received tenecteplase—all in the non-Asian sites. We considered this would add relevance to the increasing adoption of tenecteplase in certain geographical regions, and to the generalisability of the findings.

Limitations of our trial include its early termination; however, this also occurred in subsequent pivotal thrombectomy trials following publication of MR CLEAN.[1–5] A further limitation was the median time from hospital arrival to intravenous thrombolytic of 64 min (IQR 47–87), although these times were similar to those seen in the DEVT (61 min) and DIRECT-MT (59 min) trials, but longer than MR CLEAN NO IV (31 min [IQR 24–44]) and other thrombectomy trials.[1–5,27] In part, this might reflect the requirement to obtain consent for trial participation following completion of baseline imaging. In addition, we did not collect information regarding specific ethnicity in Asian and non-Asian regions; however, only 10% of Australians are of Asian background (2016 Australian census), and are therefore unlikely to affect the overall result.

DIRECT-SAFE provides valuable additional information concerning the clinical conundrum of direct thrombectomy versus a bridging approach to endovascular thrombectomy in an ethnically diverse population of patients with a broad range of large vessel occlusion sites. Patient-level meta-analysis of all six randomised controlled studies might identify subgroups of patients more likely to benefit.

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Contributors

PJM and BY were responsible for preparing the original draft. PJM, BY, LC, GAD, ZRM, and SMD conceptualised the study. LC provided overall input in research methodology. XCH was responsible for data curation, project administration, critical writing, and review and editing. GW, SYZ, MDT, DJC, TJK, HM, RVC, HB, AKC, BS, RS,

KR, FM, YL, DPD, HR, MWP, TYW, and H-TN were responsible for supervision, critical writing, review and editing. BCVC was responsible for critical writing, review and editing, data curation, and formal analysis. GAD, ZRM, and SMD were responsible for conceptualisation, funding acquisition, resources, formal analysis, critical writing, and review and editing. AB was responsible for the software, resources, project administration, and data curation. RJD and SJB were responsible for formal analysis, data curation, resources, visualisation, critical writing, and review and editing. LC was responsible for conceptualisation, resources, formal analysis, methodology, project administration, supervision, critical writing, and review and editing. PJM and BY were responsible for conceptualisation, funding, resources, formal analysis, methodology, project administration, supervision, writing of the original draft, critical writing, and review and editing. All coauthors provided critical input and revisions to the manuscript text. PJM, BY, and LC had full access to all the data in the study, and all authors had final responsibility for the decision to submit for publication.

Declaration of interests

AKC received webinar honoraria from Medtronic and educational honoraria from Stryker. BY received conference honoraria and institutional research grants from Medtronic and Stryker. BS was an unpaid member on the New South Wales Medical Board. GAD received grants from the Australian Medical Research Future Fund by the Australian National Health and Medical Research Council. GAD was on the advisory boards of Allergan and Argenica; received honoraria from Amgen; was on the data safety monitoring board of the STOP-MSU and EXTEND group of trials; was on the steering committee of DIRECT-SAFE; was shareholder in Argenica Therapeutics; and was on the board or committee of the Australian Stroke Alliance, Menzies Research Institute, Argenica Therapeutics, and the Colonial Foundation. MWP received payment to attend meetings by Boehringer Ingelheim. PJM received conference honoraria and institutional research grants from Medtronic and Stryker. SMD received grants from the Australian Medical Research Future Fund by the Australian National Health and Medical Research Council; received payment for participating on advisory boards of Boehringer Ingelheim, Medtronic, and CSL Behring; received speaker's honoraria from Amgen; was a member of the data safety monitoring board of the SELECT-2 trial; was on the steering committee of the DIRECT-SAFE trial and EXTEND group of trials; and was an unpaid cochair of the Australian Stroke Alliance and unpaid trustee of the RMH Neuroscience Foundation. TJK received honoraria from Boehringer Ingelheim. All other authors declare no competing interests.

Data sharing

Data from the DIRECT-SAFE study are not publicly available but our plan is to make the data publicly available in the future. When data are published, they will be fully de-identified. A data dictionary will be made available, and the study protocol, statistical analysis plan, and model informed consent documents will be made available. Criteria for gaining access and location of the data will be determined at a future date.

Acknowledgments

DIRECT-SAFE was an investigator-led clinical trial. The sponsor of the trial was the Florey Institute. The trial was supported by a grant from the Australian National Health and Medical Research Council programme, and Stryker USA. The trial was managed by Neuroscience Trials Australia. Database management and central data monitoring were done by Neuroscience Trials Australia and independent statistical analysis by the Methods and Implementation Support for Clinical and Health Research Hub, the University of Melbourne, Parkville, VIC, Australia.

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