Safety and efficacy of direct versus conventional transfer to angiography suite in patients with severe acute stroke treated with thrombectomy (DIRECT ANGIO) in France: a multicentre, open-label, blinded-endpoint, randomised controlled trial

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Summary

Background Direct transfer to angiography suite (DTAS) for patients with suspected stroke primarily admitted to an endovascular-capable centre could accelerate in-hospital workflow and improve outcome. We aimed to assess the safety and efficacy of DTAS for patients with acute severe neurological deficit highly suggestive of ischaemic stroke due to a large vessel occlusion (ASND-LVO).

Methods We did an open-label, multicentre, randomised controlled trial in ten comprehensive stroke centres in France. We enrolled adult patients (age ≤85 years) with ASND-LVO (unilateral motor deficit with a score ≥5 plus a cortical symptom with a score ≥1 based on the National Institues of Health Stroke Scale) admitted within 5 h of symptom onset. Patients were randomly assigned (1:1) with a web-based system to DTAS or conventional pathway (ie, imaging followed by transfer to the angiography suite for endovascular treatment if eligible). The primary outcome was functional independence defined as a modified Rankin Scale score 0 to 2 at 90 days in the intention-to-treat population—ie, all randomly assigned patients in their originally assigned treatment groups, irrespective of diagnosis, imaging findings, or treatments received. Symptomatic intracranial haemorrhage and all-cause mortality at 90 days were the main safety outcomes. This study was registered on ClinicalTrials.gov (NCT03969511).

Findings Between July 9, 2020, and April 18, 2023, 115 patients were randomly assigned to the DTAS group (n=57) or the conventional group (n=58). An interim analysis was done on Sept 27, 2023. The trial steering committee permanently stopped the trial on Dec 1, 2023, for safety reasons after unmasking and analysis of the data. In the intention-to-treat analysis, the risk of symptomatic intracranial haemorrhage was increased in the DTAS group compared with the conventional group (five [15%] of 34 *vs* zero [0%] of 42; adjusted odds ratio [OR] 11·0 [95% CI 1·28–1406]). All-cause mortality did not differ significantly between groups (ten [18%] of 56 *vs* six [11%] of 53; adjusted OR 1·65 [95% CI 0·52–5·55]). Functional independence was reached in 20 [36%] of 56 participants in the DTAS group *vs* 22 [42%] of 53 in the conventional group (adjusted OR 0·73 [95% CI 0·32–1·69]).

Interpretation DTAS for patients with ASND-LVO was associated with an increased risk of symptomatic intracranial haemorrhage without evidence of a beneficial effect on functional outcome at 90 days. However, because the trial was stopped early for safety reasons, the small sample size limits the precision of the effect estimates on the primary outcome and all secondary and safety outcomes. Therefore, further clinical trials are required to firmly conclude on the safety and efficacy of DTAS for patients with suspected acute ischaemic stroke due to a large vessel occlusion.

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Introduction

Endovascular treatment is the standard of care given within 24 h of onset for selected acute ischaemic stroke caused by anterior circulation large vessel occlusion, regardless of the ischaemic core size or the presence of a perfusion mismatch, especially in the early time window (<6 h of onset).[1–4] Still, within the early 0–6 h window, the clinical benefit of endovascular treatment is largely dependent on time, which is the main modifiable factor. As shown by the meta-analysis of individual patient data in the HERMES trial,[5] the degree of benefit from endovascular treatment declined with

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2015, to May 1, 2025, in any language, using search terms in the title and abstract which included: "ischemic stroke" OR "acute ischemic stroke", and "thrombectomy" OR "mechanical thrombectomy" OR "endovascular therapy" OR intra-arterial therapy", with "direct" OR "bypass" AND "angiosuite" OR "angio-suite" OR "angiography" OR "neuroangiosuite" or "neuroangiography". We identified one single-centre randomised controlled trial (ANGIOCAT, NCT04001738) evaluating the efficacy and safety of DTAS compared with conventional management. However, ANGIOCAT mainly enrolled patients transferred from a primary stroke centre (74·3%), where baseline cerebral imaging had already been done. Several observational studies have reported improved time metrics, especially time from admission to arterial puncture and to reperfusion, as well as improved functional outcomes at 90 days in patients with DTAS. We also did a search on ClinicalTrial.gov of ongoing trials and identified one multicentre randomised controlled trial (WE-TRUST, NCT04701684) comparing these two strategies.

Added value of this study

To our knowledge, DIRECT ANGIO is the first trial to compare DTAS and conventional management in patients with suspected acute ischaemic stroke without previous cerebral imaging. The DIRECT ANGIO trial shows that DTAS pathway did not improve functional outcomes at 90 days and 1 year compared with a conventional management, despite improved in-hospital time metrics (reducing median admission to puncture time by 38 min and onset to reperfusion time by 37 min). In addition, DTAS was associated with a higher rate of intracranial haemorrhages as well as symptomatic intracranial haemorrhages.

Implications of all the available evidence

By contrast to previous observational studies, our trial suggested that DTAS for patients with acute severe neurological deficit highly suggestive of ischaemic stroke due to a large vessel occlusion does not improve functional independence rate at 90 days. Furthermore, DTAS was associated with a higher risk of symptomatic intracranial haemorrhage. Overall, our findings raise safety concerns for patients primarily admitted in an endovascular-capable centre and bypassing baseline imaging, to improve time-metrics. However, due to the early termination of the trial for safety reasons limiting the precisions of the outcomes, further randomised studies are warranted to compare these two management strategies.

longer times from symptom onset to arterial puncture, and each 1 h delay to reperfusion with endovascular treatment from symptom onset was associated with a 5·2% absolute risk difference reduction of functional independence at 90 days. In routine clinical practice, where patients can present with less favourable clinical and imaging profile, this association might seem even more pronounced, with each 30 min delay in reperfusion associated with a 21% reduction in the odds of favourable outcome.[6] Among the several factors to explain these results in a highly selected population, the mandatory completion of baseline cerebral imaging (or its repetition for patients transferred from a primary stroke centre to an endovascular-capable centre) required for the decision to perform endovascular treatment, is often a major contributing factor to treatment delays. In this context, the development of novel strategies and workflows to reduce time to treatment and reperfusion have been developed. In cardiology, direct transfer to the angiography suite (DTAS) has become the gold standard for patients with electrically confirmed ST-segment-elevation myocardial infarction, reducing door-to-balloon time and improving clinical outcome after percutaneous coronary intervention.[7] Applied to the neurovascular field, several observational cohort studies and one pilot, single centre, randomised trial have assessed the feasibility and efficacy of DTAS compared with a conventional pathway.[8–11] The DTAS approach in these studies included a cone-beam CT (CBCT) in the angiography suite to rule-out haemorrhagic stroke and vascular imaging (either invasive or non-invasive) to confirm large vessel occlusion in patients with acute severe neurological deficit highly suggestive of ischaemic stroke due to a large vessel occlusion (ASND-LVO). However, these studies mainly enrolled patients with endovascular treatment indication transferred from a primary stroke centre (74·3%) where baseline cerebral imaging had already been done. Therefore, the DTAS approach was rather defined by bypassing the repeated cerebral imaging at the endovascular-capable centre.[8] Consequently, randomised data evaluating a primary DTAS approach (ie, direct transfer to the angiography suite of patients with ASND-LVO without previous imaging) are currently scarce. Here, we aimed to assess the safety and efficacy of DTAS versus a conventional pathway in patients with ASND-LVO eligible for endovascular treatment in the early time window.

Methods

Study design and participants

The DIRECT ANGIO trial was a pragmatic, investigator-initiated, multicentre, open-label, randomised controlled trial with masked outcome assessment (PROBE design). The trial protocol (appendix pp 5–60) was approved by the Comité de Protection des Personnes Ile-De-France 1 on

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See **Online** for appendix

Sept 27, 2019, and by the institutional review board at each participating site.[12] The trial was conducted in accordance with the revised Helsinki guidelines. It was designed and conducted by an executive committee, which included the principal investigator, three scientific coordinators, and one biostatistician who met regularly to oversee the trial, analyse data, and write the manuscript. An independent data and safety monitoring board, including one vascular neurologist, one neuro-interventionist, and one methodologist was responsible for safety and ethics oversight. Additionally, an independent clinical-events committee adjudicated all safety outcomes, procedure-related complications, and serious adverse events. All neuroimaging data were centrally assessed by a core laboratory masked to trial groups. Data management was performed by the Centre d'Investigation Clinique-Innovation Technologique at CHRU Nancy. The trial was funded by the French Ministry of Health (PHRC I 2018), with no commercial involvement in the design, planning, analysis, or reporting of the results. Eligibility assessments were conducted by the treating physician. In compliance with national legislation, a deferred-consent procedure was used, with patients or their legal representatives providing formal written informed consent as soon as possible after treatment.

The trial was conducted at ten endovascular-capable centres in France (appendix p 68), providing access to endovascular treatment for 24 h a day, 7 days a week. All trial centres were certified high-volume (>150 endovascular treatments per year) stroke centres in France. We included adult patients aged 18–85 years with an ASND-LVO at presentation and confirmed by the neurologist at hospital admission directly admitted to an endovascular-capable centre within 5 h from symptom onset. Symptom onset was defined as the witnessed onset of neurological symptoms; patients with unwitnessed onset or last well known timing were not eligible. Only patients arriving without any previous neuroimaging were eligible for randomisation, thereby excluding secondary transfers with imaging done at primary stroke centres. ASND-LVO was defined as: (1) a unilateral motor deficit with a score of 5 or more on the motor items of the National Institues of Health Stroke Scale (NIHSS) score (an 11-item neurological score, ranging from 0 [no symptoms] to 42 [most severe deficits]), including facial palsy (item 4), arm palsy (item 5) or leg palsy (item 6); and (2) a cortical symptom with a score of 1 or more on language or extinction items of the NIHSS score. Patients with pre-stroke disability (ie, a modified Rankin Scale [mRS] score of more than 2; scores on the mRS range from 0–6, with higher scores indicating greater disability, and 6 indicating death), any terminal illness with an expected survival less than 90 days, pregnancy or breastfeeding, or known severe allergy to contrast agents were excluded. Detailed inclusion and exclusion criteria have been published before[12] and are provided in the appendix (p 37).

On April 21, 2023, the data and safety monitoring board recommended an early interim analysis due to safety concerns during reviewing of the second safety analysis of the trial. A temporary suspension of enrolment was done. Following this interim analysis, on Sept 27, 2023, the data and safety monitoring board advised the trial steering committee to stop enrolment in the trial because of a safety concern in the DTAS group. The trial steering committee followed the advice with an immediate and permanent discontinuation of the trial. On Dec 1, 2023, the sponsor formally enacted this decision. No patients were enrolled after the advice of the data safety and monitoring board was obtained. The follow-up of patients already enrolled in the trial, but not yet at their 90-day follow-up, was finished before closure of the database. This study was registered on ClinicalTrials.gov (NCT03969511).

Randomisation and masking

Patients were randomly assigned (1:1) at hospital admission, using a secure web-based randomisation system, to either the DTAS group or the conventional group. Randomisation was stratified according to the centre and the time from symptom onset to hospital admission (<2·5 h *vs* ≥2·5 h) and used a minimisation algorithm with an 85% allocation factor. Patients, local investigators, and treating physicians were aware of trial groups. Patients randomly assigned in the DTAS group were directly transferred to the angiography suite where a CBCT was done to rule out intracranial haemorrhage. Details of the CBCT systems used across centres and the number of inclusions per centre are described in the appendix (p 68). Representative CBCT acquisition images are shown in appendix (p 77). If no primary intracranial haemorrhage was identified, a catheter cerebral angiogram was done, starting with the suspected supra-aortic target vessel, to identify a large vessel occlusion (intracranial internal carotid artery, M1 or proximal M2 segments of the middle cerebral artery, basilar artery, or P1 segment of the posterior cerebral artery). Tandem lesions were defined as the association of an extracranial carotid occlusion with an intracranial large vessel occlusion. In case of large vessel occlusion, endovascular treatment was immediately done without the need for any multimodal imaging modality (ie, perfusion was not mandatory) and intravenous thrombolysis using alteplase was also administered if eligibility was confirmed and left at the discretion of the local neurologist. Endovascular treatment was done under local anaesthesia, conscious sedation, or general anaesthesia following discussion between the interventional neuroradiologist and the anaesthesiologist in charge. If a distal or medium vessel occlusion was identified, intravenous thrombolysis was administered alone if eligible. Patients without primary intracranial haemorrhage on the baseline CBCT and without identified arterial occlusions on angiogram were treated with intravenous thrombolysis (if eligible) and immediately transferred to the radiology department for additional neuroimaging protocols (CT or MRI according to local practice). Patients presenting with a primary intracranial haemorrhage on the admission CBCT were transferred to the radiology department for additional dedicated imaging (CT or MRI according to local practice) and managed according to the current guidelines.[13]

Patients in the conventional group were managed in each centre as per standard of care (admission at the emergency or radiology department). The neurologist or the emergency physician did the first neurological examination and blood was sampled. A stroke imaging protocol was then carried out (CT or MRI). In case of large vessel occlusion with endovascular treatment indication, the patient was treated with intravenous thrombolysis (if eligible) and transferred as soon as possible to the angiography suite for endovascular treatment. All acute phase treatments (ie, antithrombotic drugs and endovascular technical intervention strategies) and post-stroke complication management (ie, neurological or respiratory) followed the current guidelines.[13] The intervention was considered complete upon achieving successful reperfusion (defined as a modified treatment in cerebral ischemia [mTICI] grade of 2b, 2c, or 3; mTICI grades ranges from 0 to 3, with higher grades indicating increased reperfusion and grades ≥2b indicating reperfusion of >50% of the treated territory) or upon femoral artery closure in case of unsuccessful endovascular treatment (mTICI <2b).

Outcomes

The primary outcome was the proportion of patients with functional independence, defined as an mRS score between 0 and 2 at 90 (±15) days. This outcome was centralised and assessed by a certified research nurse using a structured interview conducted by telephone, masked to trial groups.[14] Secondary efficacy outcomes included early neurological improvement defined as a reduction of at least 8 points in NIHSS score or NIHSS score of 0 or 1 at 24 (±6) h after endovascular treatment, NIHSS score at 5–7 days (or discharge if earlier), NIHSS and mRS scores at 90 (±15) days, the quality of reperfusion according to the mTICI score and the mRS score at 12 (±1) months. Secondary safety outcomes included the proportions of patients eligible to receive intravenous thrombolysis alone, of stroke mimics, of primary intracranial haemorrhages, the rate of symptomatic intracranial haemorrhage according to the European Cooperative Acute Stroke Study (ECASS) III classification,[15] the rate of patients requiring additional stroke imaging, and the proportion of decompressive hemicraniectomy and all-cause mortality at 90 (±15) days and 12 (±1) months. Secondary feasibility outcomes included the proportion and site of large vessel occlusion, and in-hospital time metrics (hospital admission to imaging, needle, puncture and reperfusion, imaging to puncture and reperfusion, and puncture to reperfusion). Because of premature termination of the trial, the pre-specified cost-utility assessment could not be performed. Secondary clinical efficacy and safety outcomes were assessed by certified neurologists or research nurses, masked to trial groups. Imaging endpoints were all centrally assessed by a core laboratory, also masked to trial groups.

Statistical analysis

Based on previous studies,[11,16,17] we estimated a 90-day functional independence rate (mRS 0–2) of 30% in the control group. We hypothesised that a DTAS strategy would result in an absolute increase of 20% (mRS 0–2 rate of 50%), reflecting the expected benefit of a 1-h reduction in time to reperfusion. To detect this difference with 80% power and a two-sided α of 0·05, 93 patients per group were required. Assuming a 10% attrition rate (including patients lost to follow-up or without large vessel occlusion), the total planned sample size was 208 patients (104 per group). This 10% inflation explicitly accounted for the expected proportion of randomly assigned patients without an angiographically confirmed large vessel occlusion (including primary intracranial haemorrhage and stroke mimics). However, because the trial was terminated early for safety reasons and did not reach its planned enrolment, this adjustment was never fully applied and thus does not affect the interpretation of the results.

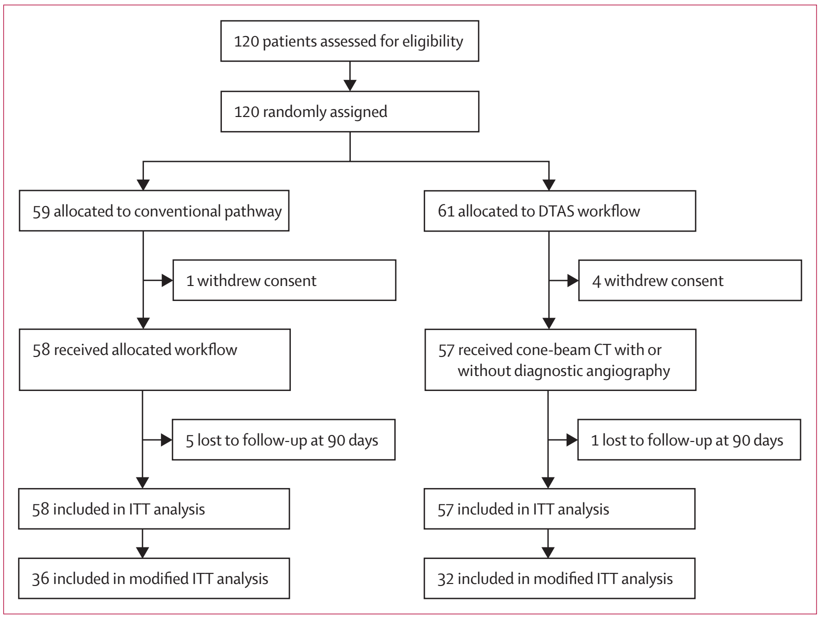

Figure 1: **Trial profile**
No formal screening log was maintained. As a result, the number of patients screened but not enrolled cannot be determined. Modified ITT population is defined as all patients with a large vessel occlusion. DTAS=direct transfer to angiography suite. ITT=intention-to-treat.

Continuous variables were summarised as medians with IQR. Categorical variables were summarised as counts and percentages. The number of missing observations for each variable was reported; all analyses were done on complete cases, without imputation. All primary analyses were done according to the intention-to-treat (ITT) principle, including all randomly assigned patients in their originally assigned treatment groups, irrespective of diagnosis, imaging findings, or treatments received. Prespecified secondary analyses were done in the modified ITT population, defined as all patients who had large vessel occlusion and analysed according to their assigned randomisation group. Binary outcomes (eg, functional independence at 90 days [mRS 0–2 *vs* 3–6], in-hospital mortality, 90-day mortality, 12-month mortality, early neurological improvement, and symptomatic intracranial haemorrhage according to the ECASS III and SITS MOST definition) were analysed using logistic regression models with treatment group as the main predictor. These endpoints were analysed in the subgroup of patients with ischaemic stroke only. For outcomes with sparse events, standard logistic models showed signs of non-convergence or separation; therefore, corresponding estimates are reported from Firth's penalised models. A second set of logistic regression analyses was stratified by study centre. Results are reported as odds ratios (ORs) with 95% CIs derived from profile likelihood; Wald intervals were substituted when profiling failed. Ordinal outcomes (NIHSS at 5–7 days and 90 days, and mRS distribution at 90 days and 12 months), were analysed using proportional odds ordinal logistic regression with treatment group as the main covariate. As prespecified in the statistical analysis plan, secondary analyses included models stratified by recruiting centre. Given the small number of events in several centres and the absence of meaningful clustering on descriptive assessment, centre was not modelled as a random effect.

The proportional odds assumption was assessed using the Brant test for mRS outcomes. For NIHSS outcomes, the Brant test was not computable due to structural singularities arising from sparse categories and quasi-separation across centre strata. In this case, we examined treatment-effect odds ratios across multiple clinically relevant cut-points of each ordinal scale. Forest plots of these cut-point analyses, with and without centre adjustment, showed stable odds ratios across thresholds, supporting the proportional odds assumption. Given the small number of symptomatic intracranial haemorrhage, an exploratory penalised logistic regression analysis (Firth correction) was additionally done for this outcome. The model included treatment allocation and intravenous thrombolysis administration as covariates. A single interim analysis was planned at mid-enrolment. For the primary endpoint, efficacy was assessed against a Haybittle-Peto threshold ($p<0\cdot001$), to preserve the final pre-planned two-sided 5% type I error. Given the premature discontinuation of the trial following data safety monitoring board recommendation, all statistical analyses were considered exploratory and descriptive. No adjustment for multiplicity was performed;[18] therefore, all p values are reported descriptively and should be interpreted with caution, without inferential intent. All analyses were done with R software (version 4.4.2), using the gtsummary, logistf, MASS, and ordinal packages, among others.

	DTAS group (n=57)	Conventional group (n=58)
Age, years	67 (62–75)	65 (59–73)
Sex		
Female	24/57 (42%)	26/58 (45%)
Male	33/57 (58%)	32/58 (55%)
Medical history		
Hypertension	36/57 (63%)	34/58 (59%)
Diabetes	14/57 (25%)	12/58 (21%)
Atrial fibrillation	6/57 (11%)	8/58 (14%)
Stroke	7/57 (12%)	7/58 (12%)
Myocardial infarction	4/57 (7%)	3/58 (5%)
Current smoker	10/57 (18%)	10/58 (17%)
Pre-stroke modified Rankin Scale score 0–2*	56/57 (98%)	58/58 (100%)
NIHSS score†	19 (14–22)	18 (15–20)
MRI at admission	..	53/58 (91%)
Final diagnosis, adjudicated		
Acute ischaemic stroke	35/57 (61%)	44/58 (76%)
Primary intracranial haemorrhage	19/57 (33%)	12/58 (21%)
Stroke mimics	3/57 (5%)	2/58 (3%)
Treatments		
Intravenous thrombolysis	17/57 (30%)	31/58 (53%)
Endovascular treatment	32/57 (56%)	32/58 (55%)
Intravenous thrombolysis plus endovascular treatment	17/57 (30%)	23/58 (40%)
Anaesthesia modality		
Local anaesthesia	6/57 (11%)	6/58 (10%)
Local anaesthesia to conscious sedation	2/57 (4%)	1/58 (2%)
Conscious sedation	19/57 (33%)	20/58 (34%)
Conscious sedation to general anaesthesia	1/57 (2%)	0/58 (0%)
General anaesthesia	7/57 (12%)	6/58 (10%)
Workflow, min		
From stroke onset to hospital admission	89 (71–121)	84 (54–120)
From hospital admission to arterial puncture	51 (35–80)	80 (64–100)
From hospital admission to reperfusion	87 (61–137)	125 (98–159)
From stroke onset to reperfusion	187 (148–245)	220 (171–262)

Data are median (IQR) or n/N (%). DTAS=direct to angiography suite. NIHSS=National Institutes of Health Stroke Scale. *Scores on the modified Rankin scale range from 0 (no functional limitations) to 6 (death), with higher scores indicating more severe functional disability; a score of 2 or less indicates functional independence. †NIHSS scores range from 0 (no deficits) to 42 (worst deficits in all items); two patients had a pure sensory stroke that was considered to be clinically disabling.

Table 1: **Baseline demographic and clinical characteristics of the intention-to-treat population**

Role of the funding source

The funders of the study had no role in study design, planning, data analysis, data interpretation, or writing of the report.

Results

From July 9, 2020, to April 18, 2023, 120 patients from ten centres with local endovascular capacities in France were assessed for eligibility and randomly assigned to the conventional group (n=59) or DTAS group (n=61). After the exclusion of five patients who withdrew consent, 115 patients were included in the ITT analysis (58 in the conventional group and 57 in the DTAS group; figure 1). Of these 115 patients, six (5%) were lost to follow-up.

The baseline characteristics were well balanced between the two groups (tables 1, 2). The median age was 67 years (IQR 62–75) in the DTAS group and 65 years (IQR 59–73) in the conventional group; 24 (42%) of 57 patients in the DTAS group and 26 (45%) of 58 patients in the conventional group were women. The median baseline NIHSS score was 19 (IQR 14–22) in the DTAS group and 18 (IQR 15–20) in the conventional group. Following adjudication, among the 57 patients allocated to the DTAS group, 19 (33%) were diagnosed with primary intracranial haemorrhage. The remaining 38 (67%) patients without intracranial haemorrhage on CBCT underwent diagnostic cerebral angiography, and in 32 of these 38 patients, endovascular treatment was done. Among the remaining six patients without large vessel occlusion on angiography, three had acute ischaemic stroke with distal occlusion, and three had stroke mimics (two had seizures and one had migraine). Among the 58 patients randomly assigned to the conventional group, 44 (76%) were ultimately diagnosed with acute ischaemic stroke, 12 (21%) with primary intracranial haemorrhage, and two (3%) with stroke mimics. Of the 44 patients with ischaemic stroke, 36 (82%) had a large vessel occlusion or medium vessel occlusion and 32 (73%) were treated with endovascular treatment. The distribution of occlusion sites in both groups for the pre-specified modified ITT population (ie, patients with large vessel occlusion; 32 patients in DTAS group and 36 in conventional group) are described in table 2. Overall, 17 (30%) of 57 patients in the DTAS group and 31 (53%) of 58 patients in the conventional group underwent intravenous thrombolysis, 17 (53%) of 32 patients and 23 (72%) of 32 patients being also treated with endovascular treatment, respectively (table 2). The exact distribution of patients according to the final diagnosis, presence of large vessel occlusion, use of intravenous thrombolysis or endovascular treatment, and occurrence of symptomatic intracranial haemorrhage is provided in the appendix (p 78).

The median time from hospital admission to arterial puncture was 51 min (IQR 35–80) in the DTAS group and 80 min (IQR 64–100) in the conventional group (table 1). In the ITT population, time from hospital admission to reperfusion was 87 min (IQR 61–137) in the DTAS group versus 125 min (IQR 98–159) in the conventional group (table 1). The median time from hospital admission to needle was 53 min (IQR 38–64) in the DTAS group and 60 min (IQR 45–80) in the

	DTAS group (n=32)	Conventional group (n=36)
Age, years	71 (55–77)	63 (52–73)
Sex		
Female	15/32 (47%)	18/36 (50%)
Male	17/32 (53%)	18/36 (50%)
Medical history		
Hypertension	20/32 (63%)	19/36 (53%)
Diabetes	6/32 (19%)	7/36 (19%)
Atrial fibrillation	4/32 (13%)	5/36 (14%)
Stroke	2/32 (6%)	6/36 (17%)
Myocardial infarction	0/32 (0%)	2/36 (6%)
Current smoker	6/32 (19%)	8/36 (22%)
Pre-stroke modified Rankin Scale 0–2*	32/32 (100%)	36/36 (100%)
NIHSS score†	20 (16–22)	17 (15–20)
Final diagnosis, adjudicated		
Acute ischaemic stroke	32/32 (100%)	36/36 (100%)
Imaging characteristics, centralised		
MRI at admission	NA	35/36 (97%)
ASPECTS‡	NA§	8 (6–9)
Occlusion location		
ICA	8/32 (25%)	9/36 (25%)
M1	14/32 (44%)	12/36 (33%)
M2	2/32 (6%)	7/36 (19%)
Tandem lesion	7/32 (22%)	8/36 (22%)
Basilar artery	1/32 (3%)	0/36 (0%)
Treatments		
Intravenous thrombolysis	17/32 (53%)	25/36 (69%)
Endovascular treatment	32/32 (100%)	32/36 (89%)
Intravenous thrombolysis plus endovascular treatment	17/32 (53%)	25/36 (69%)
No treatment	0 (0%)	2/36 (6%)
Anaesthesia modality¶		
Local anaesthesia	4/32 (13%)	5/32 (16%)
Local anaesthesia to conscious sedation	2/32 (6%)	1/32 (3%)
Conscious sedation	18/32 (56%)	20/32 (63%)
Conscious sedation with conversion to general anaesthesia	1/32 (3%)	0 (0%)
General anaesthesia	7/32 (22%)	6/32 (19%)
Workflow, min		
From stroke onset to admission	90 (76–122)	81 (59–107)
From hospital admission to arterial puncture	42 (33–77)	80 (64–100)
From hospital admission to reperfusion	87 (61–137)	125 (98–159)
From stroke onset to reperfusion	187 (148–245)	220 (171–262)

Data are median (IQR) or n/N (%). DTAS=direct to angiography suite. NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score. ICA=internal carotid artery. M1=first segment of the middle cerebral artery. M2=second segment of the middle cerebral artery. NA=non accessible. *Scores on the modified Rankin scale range from 0 (no functional limitations) to 6 (death), with higher scores indicating more severe functional disability; a score of 2 or less indicates functional independence. †NIHSS scores range from 0 (no deficits) to 42 (worst deficits in all items). ‡ASPECTS is a measure of the extent of early ischaemic changes on non-contrast CT; scores range from 0 to 10, with higher scores indicating fewer early ischaemic changes. §Specific ASPECTS could not be calculated in the DTAS group given the low quality of imaging. ¶Only patients treated with endovascular treatment received a sedation.

Table 2: **Baseline demographic and clinical characteristics of the modified intention-to-treat population**

	DTAS group	Conventional group	Odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
Intention-to-treat population				
Primary outcome				
Modified Rankin Scale score 0–2 at 90 days	20/56 (36%)	22/53 (42%)	0·78 (0·36 to 1·70)	0·73 (0·32 to 1·69)
Secondary outcomes				
Modified Rankin Scale score at 90 days	4 (2–4), n=56	3 (2–4), n=53	0·66 (0·4 to 1·29)	0·61 (0·29 to 1·24)
Modified Rankin Scale score at 12 months	3 (2–5), n=56	3 (1–4), n=55	0·57 (0·29 to 1·11)	0·50 (0·25 to 1·02)
Early neurological improvement†	23/54 (43%)	31/57 (54%)	0·62 (0·29 to 1·31)	0·60 (0·26 to 1·36)
NIHSS at day 5–7	7 (2–17), n=51	4 (1–12), n=54	1·46 (0·75 to 2·87)	1·62 (0·80 to 3·29)
NIHSS at 90 days	3 (0–10), n=46	2 (0–8), n=50	1·35 (0·67 to 2·75)	1·59 (0·77 to 3·27)
Modified intention-to-treat population‡				
Primary outcome				
Modified Rankin Scale score 0–2 at 90 days	13/32 (41%)	17/34 (50%)	0·68 (0·25 to 1·81)	0·61 (0·02 to 1·75)
Secondary outcomes				
Modified Rankin Scale score at 90 days	3 (2–4), n=31	2 (2–3), n=31	0·62 (0·26 to 1·48)	0·48 (0·18 to 1·24)
Modified Rankin Scale score at 12 months	3 (2–4), n=31	2 (2–3), n=35	0·61 (0·26 to 1·45)	0·43 (0·16 to 1·13)
Final reperfusion mTICI 2b-3	27/32 (87%)	31/32 (97%)	0·20 (0·01 to 1·48)	0·13 (0·006 to 1·05)
First pass effect mTICI 2b-3	15/32 (47%)	21/32 (66%)	0·46 (0·16 to 1·25)	0·29 (0·89 to 0·88)
Early neurological improvement	18/32 (56%)	24/36 (67%)	0·64 (0·24 to 1·72)	0·58 (0·18 to 1·76)
NIHSS at day 5–7	5 (2–10), n=30	3 (1–9), n=35	1·46 (0·62 to 3·44)	1·86 (0·74 to 4·68)
NIHSS at 90 days	2 (1–8), n=29	1 (0–5), n=34	2·14 (0·87 to 5·23)	2·65 (1·02 to 6·88)

DTAS=direct transfer to angiography suite. NIHSS=Nationale Institutes of Health Stroke Scale. mTICI=modified thrombolysis in cerebral infarction. *Treatment effects were adjusted for centre. †Early neurological improvement was defined as reduction of 8 or more points in NIHSS score or NIHSS score of 0 or 1 at 24 (±6) h after endovascular treatment. ‡The modified intention-to-treat population concerned patients with large vessel occlusion.

Table 3: **Primary and secondary efficacy outcomes in the intention-to-treat and modified intention-to-treat populations**

conventional group (figure 1). For patients with large vessel occlusion (modified ITT population), the median time from hospital admission to arterial puncture was 42 min (IQR 33–77) in the DTAS group and 80 min (IQR 64–100) in the conventional group (table 2). The median time from hospital admission to needle was 53 min (IQR 38–64) in the DTAS group and 54 min (IQR 44–68) in the conventional group.

In the efficacy analysis, functional independence (mRS score 0–2 at 90 days) was not significantly different in the DTAS group and the conventional group (20 [36%] of 56 patients *vs* 22 [42%] of 53 patients; adjusted OR 0·73 [95% CI 0·32–1·69]; table 3). Analysis in the modified ITT population yielded similar findings for the primary endpoint with an adjusted OR of 0·61 (95% CI 0·02–1·75; table 3).

Regarding secondary efficacy endpoints, the proportion of early neurological improvement at 24 h occurred in 23 (43%) of 54 patients in the DTAS group and 31 (54%) of 57 patients in the conventional group (adjusted OR 0·60 [95% CI 0·26–1·36]). At 90 days, the median score on the mRS was 4 (2–4) in the DTAS group and 3 (2–4) in the conventional group. The adjusted OR for a shift in the score on the mRS at 90 days comparing the DTAS group with the conventional group was 0·61 (95% CI 0·29–1·24; figure 2A), and 0·48 (95% CI 0·18–1·24) in the modified ITT population (figure 2B). At 12 months, the median score on the mRS was 3 (2–5) in the DTAS group and 3 (1–4) in the conventional group; the adjusted OR for a shift in the score on the mRS at 12 months comparing the DTAS group with the conventional group was 0·50 (95% CI 0·25–1·02). In the modified ITT population analysis, patients in the DTAS group had worse outcomes (mRS score) at 12 months compared with the conventional group (adjusted OR 0·43 [95% CI 0·16–1·13], respectively). A descriptive comparison of 90-day functional outcomes among patients with primary intracranial haemorrhage in the two treatment groups is provided in the appendix (p 79).

Regarding safety outcomes, compared with patients in the conventional group, ischaemic stroke patients in the DTAS group had higher rates of symptomatic intracranial haemorrhage (five [15%] of 34 patients *vs* zero [0%] of 42 patients; adjusted OR 11·0 [95% CI 1·28–1406]) as well as any intracranial haemorrhage (21 [62%] of 34 patients *vs* 13 [31%] of 42 patients; adjusted OR 4·38 [95% CI 1·57–13·2]; table 4). In the modified ITT population, the rate of any intracranial haemorrhage was higher in the DTAS group compared with the conventional group (21 [66%] of 32 patients *vs* 11 [31%] of 36 patients; adjusted OR 5·53 [95% CI 1·80–18·9]; table 4). Symptomatic intracranial haemorrhage according to the ECASS 3 classification occurred also significantly more frequently in the DTAS group (5 [16%] of 32 *vs* 0 [0%] of 36), corresponding to an adjusted odds ratio of 12·5 (95% CI 1·54–1513). Specifically, three of five patients in the DTAS group who suffered from symptomatic

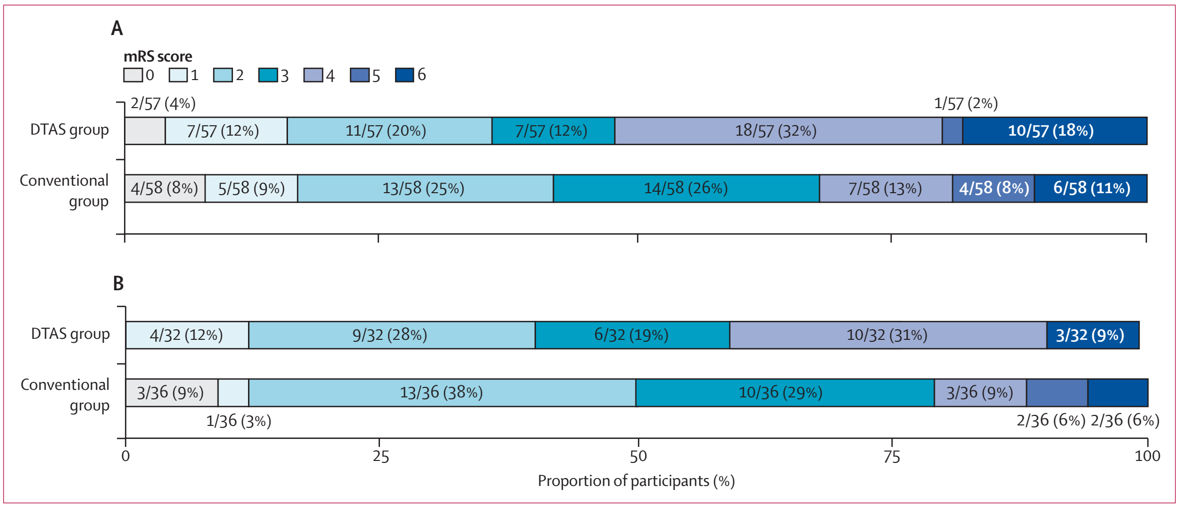

Figure 2: **Distribution of mRS scores at 90 days**
(A) mRS scores of all included patients with available 90-day follow-up data of the ITT population, which included all the patients who provided consent. Patients were included in the analysis according to their assigned trial group. (B) mRS scores of all included patients with available 90-day follow-up data of the modified ITT population, which included all the patients with a large vessel occlusion who provided consent. Patients were included in the analysis according to their assigned trial group. Scores range from 0 to 6, with 0 indicating no symptoms or disability after stroke, 1 indicating no clinically relevant disability, 2 indicating slight disability, 3 indicating moderate disability, 4 indicating moderate-to-severe disability, 5 indicating severe disability (complete dependence on daily care), and 6 indicating death. ITT=intention to treat. mRS=modified Rankin Scale. DTAS=direct transfer to angiography suite.

intracranial haemorrhage according to the ECASS III definition were treated with intravenous thrombolysis before endovascular treatment (appendix pp 71–75). Safety analysis after adjustment with previous use of intravenous thrombolysis were unchanged.

A description of any intracranial haemorrhage and symptomatic intracranial haemorrhage cases in both groups is provided in the appendix (pp 69–71). Overall, all-cause mortality in the ITT population was numerically higher in the DTAS group (10 [18%] of 56 patients) compared with the conventional group (six [11%] of 53 patients) at 90 days and at 12 months (13 [23%] of 57 patients *vs* nine [16%] of 58 patients, respectively; table 4). Post-hoc descriptive efficacy and safety analyses according to the use of intravenous thrombolysis in the ITT and modified ITT populations are provided in the appendix (appendix p 72). After adjustment for intravenous thrombolysis administration, allocation to the DTAS group remained significantly associated with an increased risk of symptomatic intracranial haemorrhage with an adjusted OR of about 15 (95% CI 1·57–2021; p=0·015). In contrast, intravenous thrombolysis administration was not independently associated with symptomatic intracranial haemorrhage, with wide confidence intervals reflecting limited statistical power.

Discussion

The DIRECT ANGIO trial provides the first randomised evidence evaluating a DTAS workflow in patients with ASND-LVO without any previous neuroimaging. In contrast to previous observational studies and the ANGIOCAT randomised pilot trial,[8–11,17] DTAS did not improve functional outcomes at 90 days or 12 months, despite substantially shorter in-hospital workflow times. More importantly, DTAS was associated with a higher rate of intracranial haemorrhage, including symptomatic intracranial haemorrhage, leading to early trial termination.

A central question raised by our findings is the potential contribution of intravenous thrombolysis to the excess haemorrhagic risk observed in the DTAS group. Although intravenous thrombolysis was numerically less frequently administered in DTAS group than in the conventional group, this imbalance does not, in itself, clarify its role. In France, where MRI-based selection remains common practice, neurologists might be more hesitant to administer intravenous thrombolysis solely on the basis of CBCT, particularly as image quality varies across platforms. This pragmatic behaviour might partly explain the lower intravenous thrombolysis rate in the DTAS group, independently of protocol intention. Yet, despite this lower overall exposure to intravenous thrombolysis, a harmful interaction between ultra-acute intravenous thrombolysis and immediate endovascular treatment cannot be excluded. Indeed, among the five patients with symptomatic intracranial haemorrhage in the DTAS group, three of them were treated with intravenous thrombolysis before endovascular treatment. In a DTAS workflow, intravenous thrombolysis and endovascular treatment might be initiated almost simultaneously, or even intravenous thrombolysis administered after endovascular treatment, a situation distinct from conventional pathway where intravenous thrombolysis typically precedes endovascular treatment by several minutes. Whether such near-simultaneous reperfusion therapies modify microvascular stability, distal

	DTAS group	Conventional group	Odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
Intention-to-treat population				
Any intracranial haemorrhage†	21/34 (62%)	13/42 (31%)	3·60 (1·42 to 9·60)	4·38 (1·57 to 13·2)
HI-1	3/21 (14%)	3/13 (23%)	..	..
HI-2	10/21 (48%)	5/13 (38%)	..	..
PH-1	3/21 (14%)	0/13 (0%)	..	..
PH-2	2/21 (9%)	2/13 (15%)	..	..
SAH	3/21 (14%)	2/13 (15%)	..	..
Remote haemorrhage	0/21 (0%)	1/13 (8%)	..	..
Symptomatic intracranial haemorrhage (ECASS III)‡	5/34 (15%)	0/42 (0%)	13·2 (1·43 to 1747)	11·0 (1·28 to 1406)
Symptomatic intracranial haemorrhage (SITS MOST)§	2/34 (6%)	0/42 (0%)	5·27 (0·42 to 733)	3·88 (0·33 to 473)
Hemicraniectomy	3/57 (5%)	1/58 (2%)	3·17 (0·39 to 65·1)	6·34 (0·66 to 153)
All-cause mortality at 90 days	10/56 (18%)	6/53 (11%)	1·70 (0·58 to 5·36)	1·65 (0·52 to 5·55)
All-cause mortality at 12 months	13/57 (23%)	9/58 (16%)	1·61 (0·63 to 4·25)	1·84 (0·68 to 5·17)
Modified intention-to-treat population¶				
Any intracranial haemorrhage	21/32 (66%)	11/36 (31%)	4·34 (1·61 to 12·4)	5·53 (1·80 to 18·9)
HI-1	3/21 (14%)	2/11 (18%)	..	..
HI-2	10/21 (48%)	4/11 (36%)	..	..
PH-1	3/21 (14%)	0/11 (0%)	..	..
PH-2	2/21 (9%)	2/11 (18%)	..	..
SAH	3/21 (14%)	2/11 (18%)	..	..
Remote haemorrhage	0/21 (0%)	1/11 (9%)	..	..
Symptomatic intracranial haemorrhage (ECASS III)	5/32 (16%)	0/36 (0%)	14·6 (1·55 to 1947)	12·5 (1·54 to 1513)
Symptomatic intracranial haemorrhage (SITS MOST)	2/32 (6%)	0/36 (0%)	5·98 (0·46 to 838)	4·84 (0·46 to 571)
Hemicraniectomy	1/32 (3%)	1/36 (3%)	1·13 (0·04 to 29·4)	1·81 (0·06 to 54·8)
All-cause mortality at 90 days	3/32 (9%)	2/34 (6%)	1·66 (0·26 to 13·2)	2·16 (0·31 to 18·6)
All-cause mortality at 12 months	4/32 (13%)	4/36 (11%)	1·14 (0·25 to 5·24)	1·56 (0·32 to 7·66)

DTAS=direct transfer to angiography suite. HI-1=haemorrhagic infarction type 1. HI-2=haemorrhagic infarction type 2. PH-1=parenchymal haematoma type 1. PH-2=parenchymal haematoma type 2. SAH=subarachnoid haemorrhage. *Treatment effects were adjusted for centre. †Any intracranial haemorrhage is reported for acute ischaemic stroke patients only. ‡Symptomatic intracranial haemorrhage reported for acute ischaemic stroke only and was defined according to the ECASS III definition. §Symptomatic intracranial haemorrhage reported for acute ischaemic stroke patients only and was defined according to the SITS-MOST definition. ¶The modified intention-to-treat population concerned patients with large vessel occlusion.

Table 4: **Safety outcomes in the intention-to-treat and modified intention-to-treat populations**

embolisation patterns, or the susceptibility to reperfusion injury remains uncertain, but could theoretically amplify haemorrhagic risk. Conversely, the reduced use of intravenous thrombolysis in DTAS might also have contributed to poorer outcomes.[19] Beyond its modest effect on early recanalisation,[20] intravenous thrombolysis has been associated with improved microcirculatory perfusion, mitigation of the no-reflow phenomenon, and overall clinical benefit.[21,22] Taken together, these observations highlight the complexity of integrating intravenous thrombolysis into a CBCT-based DTAS strategy. Further trials, such as the WE-TRUST trial (NCT04701684), will be essential to delineate the optimal role of intravenous thrombolysis in the DTAS paradigm.

A second key dimension concerns the diagnostic performance of CBCT in the DTAS workflow.[23] Across centres, substantial heterogeneity in CBCTs, acquisition protocols, and reconstruction algorithms resulted in variable image quality, limiting the reliable assessment of early ischaemic changes and precluding Alberta Stroke Program Early CT Score (ASPECTS) determination. This contrasts with the conventional pathway, in which CT or MRI provided more robust quantification of ischaemic burden and identification of ancillary markers such as cerebral microbleeds. Because microbleeds are not detectable on CBCT, and although they do not constitute a formal contraindication to intravenous thrombolysis, an imbalance in the distribution of patients with microbleeds between groups could theoretically have influenced haemorrhagic risk.[24] The same applies to patients with more advanced ischaemic injury: while intravenous thrombolysis was numerically less frequent in the DTAS group, the reduced radiological granularity of CBCT could still have exposed patients with substantial ischaemic core to intravenous thrombolysis (ie, patients who, under conventional imaging, might not have been considered appropriate candidates). These possibilities remain speculative but show the challenges of nuanced treatment selection when relying solely on CBCT. Imaging limitations might also have contributed to procedural differences, as we observed numerically lower rates of successful reperfusion and first-pass effect in the DTAS group. Although the sample size limits interpretation, it is conceivable that standard CT, CT angiography, or MRI offered operators clearer information on clot location, length, or morphology, helping device selection and procedural planning. In contrast, limited clot visualisation on CBCT might have reduced anticipatory planning and contributed to more demanding endovascular treatment attempts. Ongoing studies such as SPINNERS trial (NCT05458908) will be instrumental in clarifying the comparative performance of CBCT and conventional CT, thereby informing the safe and effective deployment of DTAS strategies across diverse clinical settings.

Finally, DIRECT ANGIO shows that even with stringent clinical criteria, a substantial fraction of patients managed under the DTAS paradigm had no treatable large vessel occlusion and ultimately did not undergo endovascular treatment. The imbalance in primary intracranial haemorrhage between groups likely reflects random variation inherent to the small sample size, but the broader observation remains: DTAS workflows inevitably generate a sizeable number of non-endovascular treatment activations. Although this is inherent to any triage model based solely on clinical severity, it carries concrete operational implications such as mobilisation of interventional and anaesthesiologist teams, and potential delays for other emergent procedures. This issue was far less pronounced in the ANGIOCAT trial, as many patients had already undergone imaging at the referring primary stroke centre.[8] Similar patterns exist in cardiology, in which up to 10–15% of catheterisation laboratory activations for suspected acute myocardial infarction reveal no culprit coronary lesion requiring intervention.[25] Such so-called negative activations are accepted as the operational cost of systems built to prioritise ultra-rapid treatment for true occlusions. Likewise, DTAS strategies must balance accelerated access to endovascular treatment against the resource implications of treating a heterogeneous population in whom only a subset will ultimately benefit.

Our trial has limitations. First, our results apply only to patients presenting directly to a centre capable of endovascular treatment. Second, the early termination limits the precision of the effect estimates on the primary outcome. However, an effect as assumed in the sample size estimation had to occur in the second half of the trial to compensate for the adverse effects in the first half. The data safety and monitoring board and trial steering committee considered this very unlikely. Moreover, because the trial was stopped early for safety rather than futility, the small sample size limits the precision of all secondary and safety outcomes, and early termination under such circumstances might tend to overestimate effect sizes. Third, several between-group imbalances might have influenced outcomes such as the DTAS group included more patients with primary intracranial haemorrhage. Fourth, the 10% attrition rate used in the sample-size calculation (to account for patients without large vessel occlusion or lost to follow-up) was likely conservative. At the time of protocol development, published estimates of intracranial haemorrhage and stroke mimics ranged widely (5–20%) depending on the clinical scale used.[26] Had the trial continued to full recruitment, this estimate would likely have been revised upward; however, because the study was terminated early for safety reasons, this assumption had no effect on the results. Fifth, the heterogeneity of imaging systems across centres, leading to variability in CBCT acquisition protocols and image quality, might have influenced diagnostic accuracy and treatment decisions. Sixth, no formal screening log was maintained. As a result, the number of patients screened but not enrolled cannot be determined, and potential selection patterns (ie, daytime *vs* nighttime admissions) could not be assessed. This absence of screening data limits our ability to evaluate selection bias or representativeness of the study population. Seventh, baseline infarct size and ASPECTS could not be determined in the DTAS arm. In this multicentre context, CBCT heterogeneity across vendors and acquisition protocols did not allow consistent gray–white differentiation, making ASPECTS ratings unreliable. Furthermore, final infarct volumes were not collected, as baseline infarct size could not be reliably determined in the DTAS group and meaningful volumetric comparisons would not have been interpretable, notably given the prematurely reduced sample size. Eighth, recruitment was slower than anticipated due to the COVID-19 pandemic, operational constraints inherent to the DTAS workflow (availability of angiography suite and combined neurology and interventional team), and competing research priorities in participating centres.

In conclusion, for patients with ASND-LVO admitted early in a comprehensive stroke centre, DTAS appears to be associated with an increased risk of symptomatic and asymptomatic intracranial haemorrhage while not benefitting functional outcome despite effectively reducing treatment workflow.

Contributors

BG, GH, and SR designed the trial. GH did the statistical analysis with input from BG and BM. BM and BG wrote the first draft of the report. All authors contributed to the collection of data and to the writing of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. BG, ACh, and GH have accessed and verified the data.

Declaration of interests

CA received consulting fees and payment for presentation from Medtronic. GM received consulting fees from Balt, Stryker Neurovascular, Sim and Cure, and Microvention; payment for paid lectures from Medtronic, Penumbra, Bracco, Wallaby Penox, and Johnson and Johnson; and participates in the steering committee of the Maestro study. All other authors declare no competing interests.

Data sharing

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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