

ORIGINAL RESEARCH

NCCT and CTA-based imaging protocol for endovascular treatment selection in late presenting or wake-up strokes

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ABSTRACT

Introduction Recently, the benefit of selecting patients for endovascular treatment (EVT) beyond the 6-hour time window using a tissue-based approach was demonstrated in two randomized trials. The optimal imaging protocol for selecting patients is under debate, and it is still unknown if a simpler and faster protocol may adequately select patients with wake-up stroke (WUS) and late-presenting stroke (LPS) for EVT.

Objective To compare outcomes of patients submitted to EVT presenting within 6 hours of symptom onset or 6–24 hours after last seen well, selected using non-contrast computed tomography (NCCT) and CT angiography (CTA).

Methods An observational study was performed, which included consecutive patients with anterior circulation ischemic stroke with large vessel occlusion treated with EVT. Patients presenting within 6 hours were treated if their NIH Stroke Scale (NIHSS) score was ≥ 6 and Alberta Stroke Program Early CT score (ASPECTS) was ≥ 6 , while patients presenting with WUS or 6–24 hours after last seen well (WUS/LPS) were treated if their NIHSS score was ≥ 12 and ASPECTS was ≥ 7 .

Results 249 patients were included, 63 of whom were in the WUS/LPS group. Baseline characteristics were similar between groups, except for longer symptom-recanalization time, lower admission NIHSS (16 vs 17, $P=0.038$), more frequent tandem occlusions (25.4% vs 11.8%, $P=0.010$), and large artery atherosclerosis etiology (22.2% vs 11.8%, $P=0.043$) in the WUS/LPS group. No differences in symptomatic intracranial hemorrhage, peri-procedural complications or mortality were found between groups. Three-month functional independence was similar in both groups (65.1% in WUS/LPS vs 57.0% in ≤ 6 hours, $P=0.259$) and no differences were found after adjustment for confounders.

Conclusions This real-world observational study suggests that EVT may be safe and effective in patients with WUS and LPS selected using clinical-core mismatch (high NIHSS/high ASPECTS in NCCT).

INTRODUCTION

Wake-up stroke (WUS) represents approximately 20% of strokes¹ and, together with late-presenting stroke (LPS, 6–24 hours from symptom onset/last seen well), they comprise an important group which, until recently, was not considered eligible

for reperfusion treatments based on a single factor: time.^{2–4} However, ischemic stroke is a dynamic condition in which the rate and extent of brain infarction depend on multiple factors—namely, collateral blood flow.^{2–6} DAWN⁷ and DEFUSE 3⁸ trials, using perfusion-based imaging protocols, recently showed the benefit of endovascular treatment (EVT) in selected patients presenting >6 hours after last seen well with a relatively small infarct volume and a significant volume of ischemic penumbra. We are therefore witnessing a shift to a new stroke treatment era, based on a tissue-window approach, in which baseline imaging characteristics can be used to select patients for reperfusion therapies. However, the optimal imaging protocol to select these patients is still a matter of debate.^{9–13} Non-contrast computed tomography (NCCT) has proved to be a valuable diagnostic tool in acute stroke, with good sensitivity¹⁴ and specificity¹⁵ in the definition of infarct core due to anterior circulation large vessel occlusion.

The aim of this study was to analyze our experience with EVT in patients with ischemic stroke presenting with WUS/LPS using an imaging protocol based on NCCT and CT angiography (CTA) and to evaluate the safety and efficacy of EVT.

METHODS

Study characteristics and patient selection

A prospective single-center observational registry study of consecutive patients with acute ischemic stroke submitted to EVT for anterior circulation large vessel occlusion between January 2015 and July 2017 was undertaken. EVT was routinely performed in patients with time from symptom onset to groin puncture <6 hours if the following criteria were met: age ≥ 18 years, baseline modified Rankin Scale (mRS) score <2 , admission National Institutes of Health Stroke Scale (NIHSS) score ≥ 6 , Alberta Stroke Programme Early CT Score (ASPECTS) ≥ 6 on NCCT, CTA with a large vessel occlusion (intracranial internal carotid artery (ICA), M1 or proximal M2 segments of middle cerebral artery, including tandem occlusions). In patients with WUS/LPS, EVT was performed if the following criteria were met: age ≥ 18 years, baseline mRS score <2 , NIHSS score ≥ 12 , ASPECTS ≥ 7 , and CTA with a large vessel occlusion. The imaging

protocol was identical for both groups and included NCCT to assess infarct core and ASPECTS, and CTA to determine the occlusion site.

Patient treatment and management

Treatment decisions were discussed by a vascular neurologist and an interventional neuroradiologist who reviewed all images before performing the treatment. EVT was performed in most cases with the Trevo stent retriever device (Stryker, Kalamazoo, Michigan, USA) or alternatively with thromboaspiration devices (Penumbra, Alameda, California, USA) at the discretion of the interventional neuroradiologist. All patients were subsequently admitted to the stroke unit or, when required, to the intensive care unit.

Definitions and outcomes

WUS was defined as stroke symptom onset on awakening and time to treatment was defined using the time since last seen well. Demographic information, clinical characteristics, imaging results, and procedural details were collected from the registry. Successful recanalization was defined as a score of 2b or 3 on the modified Treatment In Cerebral Ischemia (mTICI) scale. Collateral status on baseline cerebral angiography was retrospectively evaluated using the same scale as in the SWIFT trial¹⁶ and classified as poor (grades 0–2) or favorable (grades 3–4) by one of the authors (MR), blinded to the timing of treatment and 3-month outcome.

Symptomatic intracranial hemorrhage (sICH) was defined according to ECASS II criteria.¹⁷ Information regarding peri-procedural complications, mortality, and 3-month functional outcome (mRS assessed in person by vascular neurologists) was collected from the clinical records. Favorable clinical outcome was defined as 3-month functional independence (mRS score ≤ 2).

Statistical analysis

Statistical analysis was performed using SPSS V. 23.0. Pearson's χ^2 test, Fisher's exact test, and the Mann-Whitney U test were used to compare groups, as appropriate. We calculated unadjusted ORs and 95% CIs for the time between symptom onset and recanalization, and timing of treatment (≤ 6 hours as reference vs WUS/LPS) using the 3-month functional outcome as the dependent variable. We additionally constructed multivariate binomial logistic regression models to sequentially adjust ORs for the effect of variables known to influence functional outcome. The significance threshold was set at an alpha value of 0.05.

Ethical standards

This study was approved by the Ethics Committee of Centro Hospital de Vila Nova de Gaia/Espinho, which waived the need for a formal separate consent for participation in this study. Individual patient consent for EVT was obtained from all patients or next-of-kin according to institutional recommendations.

RESULTS

Baseline population characteristics

During the study period, 252 patients with acute ischemic stroke underwent EVT due to anterior circulation large vessel occlusion, 90.1% with stent retrievers. Three patients were lost to follow-up. Sixty-three patients (25.3%) were treated outside the 6-hour window, 34 with WUS and 29 with LPS. Baseline characteristics, treatment details, and clinical outcomes of both groups

Table 1 Baseline characteristics, interventional procedure data, and outcomes according to timing of treatment

	Wake-up stroke and late-presenting stroke (n=63)	≤ 6 hours of LSW (n=186)	P value
Age, years (min–max)	73 (59–80)	75 (65–81)	0.315
Female	34 (54.0)	100 (53.8)	0.978
Vascular risk factors			
Arterial hypertension	44 (69.8)	126 (68.5)	0.84
Diabetes	20 (31.7)	37 (20.1)	0.058
Dyslipidemia	39 (61.9)	95 (51.6)	0.158
Current smoking	13 (20.6)	28 (15.2)	0.319
Ischemic heart disease	12 (19.4)	39 (21.2)	0.757
Glucose at admission, mg/dL (min–max)	130.5 (105.5–159)	120 (108–143.5)	0.193
Admission NIHSS	16 (12–18)	17 (13–20)	0.038
Admission ASPECTS	8 (7–9)	8 (7–9)	0.13
Occlusion site			
Intracranial ICA	15 (23.8)	54 (29.0)	0.423
MCA M1 segment	35 (55.6)	99 (53.3)	0.749
MCA M2 segment	13 (20.6)	33 (17.7)	0.609
Tandem occlusion	16 (25.4)	22 (11.8)	0.01
Stroke etiology			
Cardioembolism	30 (47.7)	108 (58.1)	0.149
Large artery atherosclerosis	14 (22.2)	22 (11.8)	0.043
Undetermined etiology	14 (22.2)	50 (26.9)	0.464
Other etiology	5 (7.9)	6 (3.2)	0.152
Intravenous thrombolysis	22 (34.9)	139 (74.7)	<0.001
LSW-groin puncture time, min (min–max)	513 (425–817)	238 (194.5–305)	<0.001
LSW-recanalization time, min (min–max)	577.5 (486–858)	290 (235–366)	<0.001
Favorable baseline collateral status*	70 (55.1)	26 (59.1)	0.647
Number of passages	2 (1–3)	1 (1–3)	0.373
Successful recanalization	60 (95.2)	166 (89.2)	0.156
NIHSS at 24 hours	7 (3–13)	6 (3–15)	0.898
Symptomatic ICH	2 (3.2)	8 (4.3)	1
Peri-procedural complications†	4 (6.3)	11 (5.9)	1
Favorable 3-month outcome	41 (65.1)	106 (57.0)	0.259
Mortality at 3 months	5 (7.9)	29 (15.6)	0.126

Variable are expressed as n (%) or median (IQR).

*Collateral status available for 171 patients.

†Peri-procedural complications include cases of arterial perforation or dissection, access site complications, and distal embolization to a new territory.

ASPECTS, Alberta Stroke Programme Early CT Score; ICA, internal carotid artery; ICH, intracranial hemorrhage; LSW, last seen well; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

(≤ 6 hours vs WUS/LPS) are summarized in [table 1](#). In addition to the significantly shorter time since last seen well to groin puncture in the group treated within 6 hours (median 238 vs 513 min, $P < 0.001$), the only baseline differences observed between groups were a lower admission NIHSS score (median 16 vs 17,

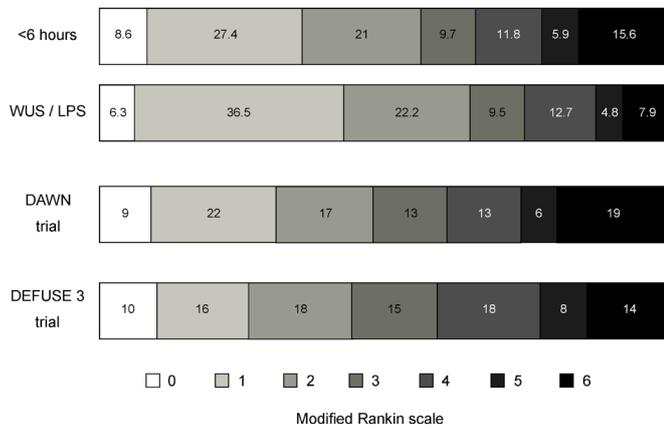


Figure 1 Three-month modified Rankin Scale distribution of patients with wake-up stroke (WUS) and late presenting stroke (LPS) and patients treated within 6 hours in the present study and in the intervention groups of the DAWN and DEFUSE 3 trials.

$P=0.038$) and a higher frequency of tandem occlusions (25.4% vs 11.8%, $P=0.010$) and large artery atherosclerosis etiology (22.2% vs 11.8%, $P=0.043$) in the WUS/LPS group. Collateral status assessment was not possible in 78 patients (31.3%) because of internal carotid artery occlusion precluding collateral visualization with ipsilateral carotid injection, absent venous phase images, inadequate field of view for complete collateral assessment, and poor quality images due to movement artifacts. The frequency of favorable collateral status was similar in patients treated within 6 hours ($n=70$, 55.1%) and in WUS/LPS patients ($n=26$, 59.1%) ($P=0.647$). However, it was numerically higher in LPS patients alone ($n=14$, 66.7%), although this difference was not statistically significant.

Revascularization treatments

Approximately one-third of patients in the WUS/LPS group was submitted to intravenous thrombolysis (IVT): 54.5% of these patients were treated with IVT in the primary stroke center within the 4.5-hour time window and the remaining patients were treated with IVT after the decision of the treating vascular neurologist. Successful recanalization was achieved with a similar frequency in both groups (89.2% vs 95.2%, $P=0.156$), with an identical number of passages of the stent retriever, comparable peri-procedural complications, and sICH frequency (4.3% vs 3.2%, $P=1.000$).

Mortality and functional outcome

There were no significant differences concerning 3-month mortality (15.6% vs 7.9%, $P=0.126$) or favorable 3-month outcome, which was achieved in 57.0% of the patients treated within 6 hours and in 65.1% of the patients with WUS/LPS ($P=0.259$). The distribution of the 3-month mRS score after stroke is shown for both groups in [figure 1](#), and is presented together with the distribution of the 3-month functional outcomes in the intervention groups of the DAWN and DEFUSE trials. Additionally, we did not find any statistically significant difference concerning outcomes when comparing WUS with LPS ([table 2](#)).

In the univariate analysis, the timing of treatment according to the defined groups (≤ 6 hours as reference vs WUS/LPS) was not predictive of 3-month functional outcome (OR 1.41, 95% CI 0.78 to 2.55, $P=0.260$). In the multivariable logistic regression model, adjustment for baseline clinical variables, treatment

Table 2 Baseline characteristics, interventional procedure data, and outcomes in patients treated 6–24 hours after last seen well

	Wake-up stroke (n=34)	Late presenting stroke (n=29)	P value
Age, years (min–max)	75.5 (64–83.5)	73 (54–80)	0.127
Female	20 (58.8)	14 (48.3)	0.402
Pre-stroke mRS <2	32 (94.1)	26 (89.7)	0.654
Vascular risk factors			
Arterial hypertension	26 (76.5)	18 (62.1)	0.214
Diabetes	9 (26.5)	11 (37.9)	0.33
Dyslipidemia	23 (67.6)	16 (55.2)	0.31
Current smoking	7 (20.6)	6 (20.7)	0.992
Ischemic heart disease	7 (20.6)	5 (17.2)	0.736
Glucose at admission, mg/dL	131 (104–154)	130.5 (109–207)	0.457
Admission NIHSS	16 (14–18)	15 (9–20)	0.516
Admission ASPECTS	8 (7–9)	8 (7–9)	0.822
Occlusion site			
Intracranial ICA	6 (17.6)	9 (31.0)	0.214
MCA M1 segment	21 (61.8)	14 (48.3)	0.283
MCA M2 segment	7 (20.6)	6 (20.7)	0.992
Tandem occlusion	9 (26.5)	7 (24.1)	0.832
Stroke etiology			
Cardioembolism	20 (58.8)	10 (34.5)	0.054
Large artery atherosclerosis	7 (20.6)	7 (24.1)	0.736
Undetermined etiology	7 (20.6)	7 (24.1)	0.736
Other etiology	0	5 (17.3)	0.017
Intravenous thrombolysis	5 (14.7)	17 (58.6)	<0.001
LSW-groin puncture time (min)	817.5 (676–1005)	462 (412–516)	<0.001
LSW-recanalization time (min)	997 (822–1275)	534 (470–585)	<0.001
Favorable collateral status*	12 (52.2)	14 (66.7)	0.329
Number of passages	2 (1–3)	1 (1–3)	0.474
Successful recanalization (mTICI $\geq 2b$)	33 (97.1)	27 (93.1)	0.59
NIHSS at 24 hours	8 (3–13)	7 (3–15)	0.825
mRS ≤ 2 at 3 months	21 (61.8)	20 (69.0)	0.55
Mortality at 3 months	4 (11.8)	1 (3.4)	0.363
Symptomatic ICH	1 (2.9)	1 (3.4)	1
Peri-procedural complications†	3 (8.8)	1 (3.4)	0.618

Continuous or ordinal variables are expressed as n (%) or median (IQR).

*Collateral status available for 44 patients.

†Peri-procedural complications include cases of arterial perforation or dissection, access site complications, and distal embolization to a new territory.

ASPECTS, Alberta Stroke Programme Early CT Score; ICA, internal carotid artery; ICH, intracranial hemorrhage; LPS, late-presenting strokes; LSW, last seen well; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified TICI; NIHSS, National Institutes of Health Stroke Scale; WUS, wake-up stroke.

with IVT, and collateral status did not change the results significantly ([table 3](#)). Age, admission NIHSS and ASPECTS scores were found to be independent predictors of 3-month outcome, and favorable collateral status was also associated with 3-month functional independence, although not significantly ([table 3](#)).

Table 3 Multivariable binomial logistic regression with favorable 3-month outcome as the dependent variable

	OR (95% CI)	P value
Age (per 1 year increment)	0.94 (0.91 to 0.97)	0.001
Female	0.83 (0.39 to 1.76)	0.624
Admission NIHSS (per 1 point increment)	0.90 (0.82 to 0.98)	0.017
ASPECTS (per 1 point increment)	1.56 (1.15 to 2.11)	0.004
Intravenous thrombolysis	1.76 (0.80 to 3.87)	0.162
Tandem occlusion	1.70 (0.39 to 7.36)	0.48
Favorable collateral status	1.86 (0.90 to 3.84)	0.097
WUS/LPS vs treatment <6 hours	1.75 (0.71 to 4.28)	0.222

ASPECTS, Alberta Stroke Programme Early CT Score; LPS, late presenting stroke; NIHSS, National Institutes of Health Stroke Scale; WUS, wake-up stroke.

To further explore the predictive role of time in the treatment of the whole population, we performed multivariable logistic regression analysis adjusted for baseline clinical variables for treatment with IVT and collateral status and found that time between symptom onset and recanalization was not a predictor of 3-month functional independence (adjusted OR per each 15 min increase of 1.00, 95% CI 0.98 to 1.03, $P=0.885$) (see online supplementary table 1).

DISCUSSION

Our study showed that, in a real-world setting, the selection of patients with WUS or LPS for EVT based solely on clinical characteristics, NCCT, and CTA resulted in similar rates of successful recanalization, sICH, favorable 3-month outcome, and 3-month mortality as in patients treated with EVT within 6 hours of last seen well.

Until recently, a strict time window was used as a mandatory criterion to appropriately select patients for EVT; however, the current perspective is that the treatment benefit depends on identifying patients with significant cerebral tissue at risk which can be saved with reperfusion, irrespective of time. Several ways to identify these patients have been adopted, mostly using advanced imaging modalities.^{18 19} The proof-of-concept provided by the DAWN trial⁷ and the DEFUSE 3 trial⁸ demonstrated the value of moving from a time-based paradigm towards a tissue-based paradigm in the treatment of patients with acute ischemic stroke. Selection of patients in the DAWN trial required the determination of the infarct core volume using MRI or perfusion CT⁷ while, in the DEFUSE 3 trial, determination of the volumes of the infarct core and of the penumbra was required and studied with MRI or perfusion CT.⁸ Our study is based on a 'low-tech' selection method for EVT of patients who present outside the recommended 6 hours since last seen well time window. The need to study the possibility of selecting patients using simpler imaging techniques was recognized by the authors of the DAWN trial,⁷ because this approach is more widely available and it may allow a significant reduction in the time to groin puncture²⁰ by bypassing more complex and time-consuming imaging methods²¹ without either increasing the occurrence of hemorrhagic complications or significantly decreasing the treatment benefit. There is evidence to suggest that ASPECTS in NCCT may be safely used to select ischemic stroke patients for EVT,^{22 23} and it has been shown to have a good sensitivity in the definition of infarct core, especially in LPS.²⁴ The analysis of early ischemic changes in NCCT has been associated with a moderate inter-rater reliability,²⁵ but it increases significantly with time since stroke onset.²⁶ Our strict clinical selection criteria for treatment in the

WUS/LPS group—namely, the presence of moderate and severe deficits (NIHSS ≥ 12) and small infarct cores (ASPECTS ≥ 7)—aimed at maximizing the likelihood of the existence of a significant volume of salvageable tissue and, at the same time, reducing the risk of sICH after recanalization.²⁷ This probably also contributed to the favorable 3-month functional outcome results when compared with the intervention groups of both the DAWN and DEFUSE 3 trials; however, we do not exclude the possibility that alternative NIHSS and ASPECTS cut-off points for the definition of clinical-core mismatch, namely with lower ASPECTS, may still allow benefit with EVT. In fact, the definition of a clinical-core mismatch using NIHSS and NCCT may vary with the location of the large vessel occlusion, and this strategy has been shown not to be inferior to CT perfusion to identify patients who potentially benefit with EVT.²⁸

Recently, Motyer *et al*²⁹ reported a retrospective case series of 25 patients with acute ischemic stroke submitted to EVT beyond 12 hours of last seen well, selected by NCCT-ASPECTS and multiphase CTA to assess collateral status, and showed good functional outcome in 52% of patients and acceptable safety. For patients with LPS, poor collateralization—a marker of fast infarct growth³⁰—is indicative of a high likelihood that the ischemic lesion is already completely established, and it has been clearly associated with poor outcomes even with successful recanalization.³¹ In our study, the proportion of patients with favorable collateral status in the group treated within 6 hours was similar to the WUS/LPS group. However, it was numerically higher in patients with LPS, which could suggest a link between relatively small recent ischemic changes and favorable collaterals in patients with large vessel occlusion presenting >6 hours after symptom onset. Our selection criteria did not include collateral assessment, and we did not find that collateral status was predictive of 3-month outcome, but the study population size (specifically of the LPS group) may have limited this analysis. Further studies are needed to clarify the benefit of collateral status assessment for selecting patients with LPS for EVT.

The main limitations of our observational study are the small sample size of the WUS/LPS group, absent information on patients who did not meet the selection criteria, outcome assessment by the treating physician, and absent information on collateral status in almost one-third of the patients.

CONCLUSION

Our results suggest that EVT is feasible and may be safe and beneficial in patients with ischemic stroke presenting beyond the 6-hour time window selected according to a tissue-window approach that only uses NCCT and CTA. More studies using fast and simple imaging selection protocols are needed to confirm their utility in the selection of patients for EVT who present >6 hours after symptom onset.

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