Original research

Novel selection paradigms for endovascular stroke treatment in the extended time window

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Received 30 September 2020
Accepted 31 May 2021

To cite: Bouslama M, Haussen DC, Rodrigues G, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2020-325284

ABSTRACT

Background and purpose The optimal selection methodology for stroke thrombectomy beyond 6 hours remains to be established.

Methods Review of a prospectively collected database of thrombectomy patients with anterior circulation strokes, adequate CT perfusion (CTP) maps, National Institute of Health Stroke Scale (NIHSS)≥10 and presenting beyond 6 hours from January 2014 to October 2018. Patients were categorised according to five selection paradigms: DAWN clinical-core mismatch (DAWN-CCM): between age-adjusted NIHSS and CTP core, DEFUSE 3 perfusion imaging mismatch (DEFUSE-3-PIM): between CTP-derived perfusion defect (Tmax >6 s lesion) and ischaemic core volumes and three non-contrast CT Alberta Stroke Program Early CT Score (ASPECTS)-based criteria: age-adjusted clinical-ASPECTS mismatch (aCAM): between age-adjusted NIHSS and ASPECTS, eloquence-adjusted clinical ASPECTS mismatch (eCAM): ASPECTS 6–10 and non-involvement of the right M6 and left M4 areas and standard clinical ASPECTS mismatch (sCAM): ASPECTS 6–10.

Results 310 patients underwent analysis. DEFUSE-3-PIM had the highest proportion of qualifying patients followed by sCAM, eCAM, aCAM and DAWN-CCM (93.5%, 92.6%, 90.6%, 90% and 84.5%, respectively). Patients meeting aCAM, eCAM, sCAM and DAWN-CCM criteria had higher rates of 90-day good outcome compared with their non-qualifying counterparts(43.2% vs 12%,p=0.002; 42.4% vs 17.4%, p=0.02; 42.4% vs 11.2%, p=0.009; and 43.7% vs 20.5%, p=0.007, respectively). There was no difference between patients meeting DEFUSE-3-PIM criteria versus not(40.8% vs 31.3%,p=0.45). In multivariate analysis, all selection modalities except for DEFUSE-3-PIM were independently associated with 90-day good outcome.

Conclusions ASPECTS-based selection paradigms for late presenting and wake-up strokes ET have comparable proportions of qualifying patients and similar 90-day functional outcomes as DAWN-CCM and DEFUSE-3-PIM. They also might lead to better outcome discrimination. These could represent a potential alternative for centres where access to advanced imaging is limited.

INTRODUCTION

The benefit of thrombectomy in large vessel acute ischaemic stroke (LVOS) in late presenting and wake-up strokes is now well established. The landmark DAWN (clinical mismatch in the triage of wake up and late presenting strokes undergoing neuro-intervention with Trevo)[1] and DEFUSE 3 (endovascular therapy following imaging evaluation for ischemic stroke 3)[2] trials have proven the superiority of endovascular therapy (ET) to medical management in patient presenting between 6 and 24 hours from last known well. However, they used different selection methodologies leaving the question on optimal selection paradigms wide open.[3] Moreover, both relied on advanced imaging to determine eligibility for ET, which may limit access to treatment in centres where those imaging modalities are not readily available.

We sought to evaluate different simple non-contrast CT (NCCT)-based paradigms and assess their selection rates and ability to discriminate outcomes as compared with the DAWN and DEFUSE 3 criteria.

METHODS

Patients selection and measures of outcomes

We retrospectively reviewed our prospectively collected database at a tertiary care academic centre for all mechanical thrombectomies performed between January 2014 and October 2018. Our institutional protocol for endovascular stroke treatment in the extended window does not include any prespecified imaging criteria other than definite loss of gray-white matter differentiation involving large areas of eloquent cortex. Specifically, we do not employ any specific Alberta Stroke Program Early CT Score (ASPECTS) or CT perfusion (CTP) parameter cut-offs in isolation to exclude patients. In the current analysis, we included all consecutive acute anterior circulation LVOS patients presenting beyond the 6-hour window with who had adequate CTP imaging maps. In addition, we limited the baseline stroke severity to National Institute of Health Stroke Scale (NIHSS)≥10, as patients with a lower NIHSS have not yet been definitely shown to benefit from treatment.[2 4] Patients were then retrospectively categorised according to following clinical-imaging criteria:

1. DAWN clinical core mismatch (DAWN-CCM) positive was defined by one of the following:
   - NIHSS≥10 and core infarct <31 cc (and age <80 years old).
   - NIHSS≥20 and core infarct <51 cc (and age <80 years old).
   - NIHSS≥10 and core infarct <21 cc (and age ≥80 years old).
2. DEFUSE 3 perfusion imaging mismatch (DEFUSE-3-PIM) positive patients met all the following criteria:

- CTP-derived infarction core lesion <70 cc.
- CTP mismatch (Tmax >6 s lesion – infarction core lesion) ≥15 cc and ratio >1.8.

3. Age-adjusted clinical ASPECTS mismatch (aCAM) positive was defined as ASPECTS 6–10 on non-contrast CT and one of the following:
   - NIHSS ≥10 and 0–1 cortical-ASPECTS (M1-6 areas) involvement (any age).
   - NIHSS ≥10 and 0–2 cortical-ASPECTS (M1-6 areas) involvement (and age <80 years old).
   - NIHSS ≥20 and 0–3 cortical-ASPECTS (M1-6 areas) involvement (and age <80 years old).
4. Eloquence-adjusted clinical ASPECTS mismatch (eCAM) positive was defined as ASPECTS 6–10 on non-contrast CT and non-involvement of the right M6 and left M4 areas regardless of age and NIHSS strata.[5]
5. Standard clinical ASPECTS mismatch (sCAM) positive was defined as ASPECTS 6–10 on non-contrast CT regardless of age and NIHSS strata.

The primary outcome measures included the proportion of qualifying patients per the different selection paradigms and the ability of the latter to discriminate 90-day good outcome (modified Rankin scale, mRS 0–2). Secondary outcomes included rates of successful reperfusion (mTICI 2b-3). Safety parameters comprised 90-day mortality and rates of any parenchymal haematoma (any PH).

Imaging protocol

All patients included in the study underwent the same institutional imaging protocol, including NCCT and CTP. Imaging acquisition parameters were the same for all patients included in the study. Large vessel occlusion was documented on CT angiography or conventional angiography for all patients.

CT perfusion

CTP encompassing 8 cm of brain coverage was evaluated with by a fully automated software (RAPID V.4.5.0, iSchemaView, Menlo Park, California). The ischaemic core was defined by a voxel relative cerebral blood flow of <30% of the contralateral normal tissue. The total hypoperfused volume was defined by a >6 s delay in the time to maximum of the tissue residue function (Tmax), and the volume of at-risk tissue defined by the difference between total hypoperfused and ischaemic core tissue estimates. The RAPID software is used as part of our centre's clinical stroke protocol.

e-Stroke Suite ASPECTS

The ASPECTS score was retrospectively calculated on baseline NCCT by the e-ASPECTS tool (e-Stroke Suite V.8.0; Brainomix, Oxford, UK, www.brainomix.com). e-ASPECTS is the NCCT module of the e-Stroke Suite and preferentially processes thin slice non-contrast CT images (<2 mm slice thickness), resampling and standardising the Digital Imaging and Communications in Medicine data. A machine learning classifier, which has been trained on historical stroke and negative control data, segments the image and creates a voxel-wise probability map of the early ischaemic change in the MCA territory. This map is then used to calculate the equivalent ASPECT score. The e-Stroke Suite software was provided for free under a limited research license.

Statistical analysis

Normality was assessed with Shapiro-Wilk test and continuous variables were reported as mean±SD or median (IQR), as appropriate. Categorical variables were reported as proportions. Between groups, comparisons for continuous variables were made with Student's t-test or Mann-Whitney U, as appropriate. Categorical variables were compared by χ^2 test, Fisher's exact test, or McNemar test for discordant pairs, as appropriate.

The ability of the individual selection tool to predict 90-day good outcome was assessed by constructing separate binomial logistic regression models with each selection paradigm as predictor variable and controlling for variables for variables at the 0.1 level of significance on univariate analysis. Significance was set at $p<0.05$ and all p values were two sided. Statistical analysis was performed using IBM SPSS Statistics 24 (IBM).

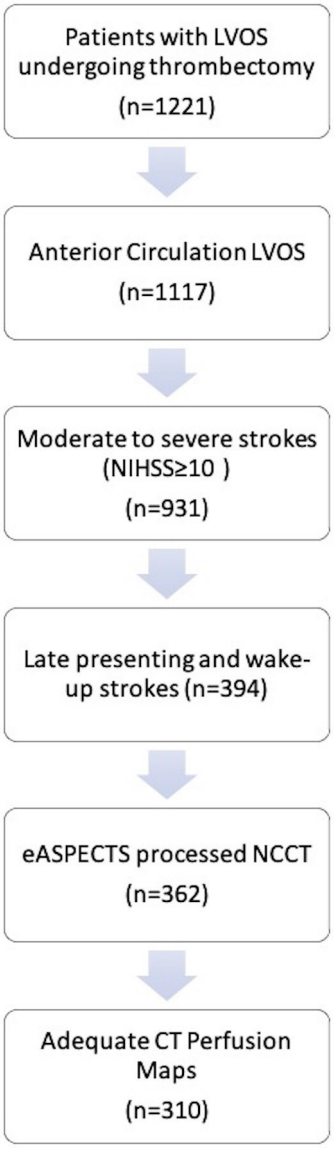


Figure 1 Study sample. ASPECTS, Alberta Stroke Program Early CT Score; LVOS, large vessel acute ischaemic stroke; NCCT, non-contrast CT.

RESULTS

Primary analysis

A total of 310 patients fit inclusion criteria (figure 1). Baseline characteristics are summarised in table 1. The median (IQR) age was 67 (55–76), 20% were 80 years old or older and 46.8% of the patients were male. The median (IQR) baseline NIHSS and e-ASPECTS were 17 (14–21) and 8 (7–9), respectively. The

Table 1 Overall baseline characteristics and outcome measures of the study population

Characteristic	N (%) or median (IQR)
Age (years)	67 (55–76)
Gender, male	145 (46.8)
Hypertension	246 (79.4)
Dyslipidaemia	116 (37.4)
Atrial fibrillation	94 (30.3)
Diabetes	82 (26.5)
Smoking	63 (20.3)
Glucose	122 (103–151)
Baseline SBP	150 (130–175)
Baseline NIHSS	17 (14–21)
e-ASPECTS	8 (7-9)
CTP core (CBF <30%)	6.6 (0–23.75)
IV t-PA	47 (15.2)
Occlusion site	
ACA	2 (0.6%)
Extracranial ICA	12 (3.9%)
Intracranial ICA	51 (16.5%)
MCA-M1	154 (49.7%)
MCA-M2	45 (14.5%)
MCA-M3	7 (2.3%)
Tandem occlusion*	39 (12.6%)
Time from LWN to arterial puncture (min)	645(478–900)
mTICI (2b-3)	300 (96.8)
Any PH	31 (10)
90-day mRS 0–2†	102 (40.2)
90-day mortality†	63 (24.8)

*Intracranial occlusion site: ICA-T: 15/39 (38.5%), MCA-M1: 19/39 (48.7%) and MCA-M2: 5/39 (12.8%).
†n=254.
ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CTP, CT perfusion; ICA, internal carotid artery; LKN, Last Known Normal; NIHSS, baseline National Institute of Health Stroke Scale; PH, parenchymal haematoma; SBP, systolic blood pressure.

median (IQR) time from last seen normal to arterial puncture was 645 (478–900) min with 15 patients (4.8%) presenting beyond 24 hours.

DEFUSE-3-PIM (290/310, 93.5%) had the highest numbers of qualifying patients followed sCAM (287/310, 92.6%), eCAM (281/310, 90.6%); aCAM (279/310, 90%) and DAWN-CCM (262/310, 84.5%). Agreement/disagreement between the different selection modalities is summarised in table 2 and figure 2. DAWN-CCM and sCAM had statistically different selected patients when compared with the other paradigms two by two.

Ninety-day outcome data were available in 254/310 patients (81.9%). The rate of 90-day good outcomes for the entire cohort was 40.2% and overall mortality was 24.8%. The aCAM, eCAM, sCAM and DAWN-CCM paradigms were all associated with 90-day good outcomes (when comparing patients who met the selection criteria vs those that did not (absolute difference, Δ): 43.2% vs 12% (Δ+31.2%), p=0.002; 42.4% vs 17.4% (Δ+25%), p=0.02; 42.4% vs 11.2% (Δ+31.2%), p=0.009; and 43.7% vs 20.5% (Δ+23.2%), p=0.007, respectively). However, there was no difference between those that did qualify for DEFUSE-3-PIM criteria versus not: 40.8% versus 31.3% (Δ+9.5%), p=0.45.

In addition, aCAM was associated with lower rates of any PH and 90-day mortality (8.6% vs 22.6%; Δ −14%, p=0.02% and 22.7% vs 44%; Δ −21.3%, p=0.02, respectively).

Table 2 Disagreement between the different selection paradigms

Disagreement	N	P value*
DEFUSE-3-PIM(+)/DAWN-CCM(–)	40	<0.001
DEFUSE-3-PIM(–)/DAWN-CCM(+)	12	
DEFUSE-3-PIM(+)/mCAM(–)	28	0.14
DEFUSE-3-PIM(–)/mCAM(+)	17	
DEFUSE-3-PIM(+)/eCAM(–)	26	0.22
DEFUSE-3-PIM(–)/eCAM(+)	17	
DEFUSE-3-PIM(+)/sCAM(–)	20	0.74
DEFUSE-3-PIM(–)/sCAM(+)	17	
DAWN-CCM(+)/mCAM(–)	20	0.03
DAWN-CCM(–)/mCAM(+)	37	
DAWN-CCM(+)/eCAM(–)	19	0.02
DAWN-CCM(–)/eCAM(+)	38	
DAWN-CCM(+)/sCAM(–)	15	0.001
DAWN-CCM(–)/sCAM(+)	40	
mCAM(+)/eCAM(–)	4	0.75
mCAM(–)/eCAM(+)	6	
mCAM(+)/sCAM(–)	0	0.008
mCAM(–)/sCAM(+)	8	
eCAM(+)/sCAM(–)	0	0.03
eCAM(–)sCAM(+)	6	

(+) denotes selection by the specified methodology, while (–) denotes exclusion for ET by that methodology.
*McNemar test for discordant pairs.
aCAM, age-adjusted clinical ASPECTS mismatch; DAWN-CCM, DAWN clinical core mismatch; DEFUSE-3-PIM, DEFUSE 3 perfusion imaging mismatch; eCAM, eloquence-adjusted clinical ASPECTS mismatch.

There was a non-significant trend towards lower rates of any PH in the other ASPECTS-based selection criteria (eCAM: 8.9% vs 20.7%; Δ −12%, p=0.05; and sCAM: 9.1% vs 21.7%; Δ −12.6%, p=0.07) while there was no difference between DEFUSE-3-PIM, DAWN-CCM and eCAM positive versus negative patients in terms of mortality (figure 3).

In multivariate analysis, adjusting for age, NIHSS, glucose and atrial fibrillation, all selection modalities except for DEFUSE-3-PIM were independent predictors of 90-day good outcomes: aCAM(+) (aOR 6.93, 95% CI [1. 58–30.51], p=0.01), DAWN-CCM(+) (aOR 3.34, 95% CI [1.39 to 8.03], p=0.007), eCAM(+) (aOR 4.15, 95% CI [1.16 to 14.84], p=0.029), sCAM(+) (aOR 11.63, 95% CI [1.55 to 86.97], p=0.017) and DEFUSE-3-PIM(+) (aOR 2.25, 95% CI [0.69 to 7.38], p=0.181).

Additionally, after adjusting for intravenous thrombolysis, only aCAM was associated with any PH (aOR 0.36, 95% CI 0.16 to 0.86). None of the studied selection paradigms were associated with 90-day mortality after adjusting for potential confounders.

Sensitivity analysis

For sensitivity analysis, only patients with an intracranial ICA, MCA M1 or M2 occlusion and complete 90-day outcomes were included (n=205). DEFUSE-3-PIM and sCAM had the highest numbers of included patients (192/205, 93.7%) followed by eCAM (187/310, 91.2%); aCAM (186/310, 90.7%) and DAWN-CCM (176/205, 85.9%).

In terms of outcomes only DAWN-CCM and aCAM paradigms were associated with 90-day good outcomes when comparing patients who met the selection criteria vs those who did not (absolute difference, Δ) (42% vs 20.7% (Δ+21.3%), p=0.029% and 41.4% vs 15.8% (Δ+25.6%), p=0.029, respectively). There was a trend of favourable outcome in patients

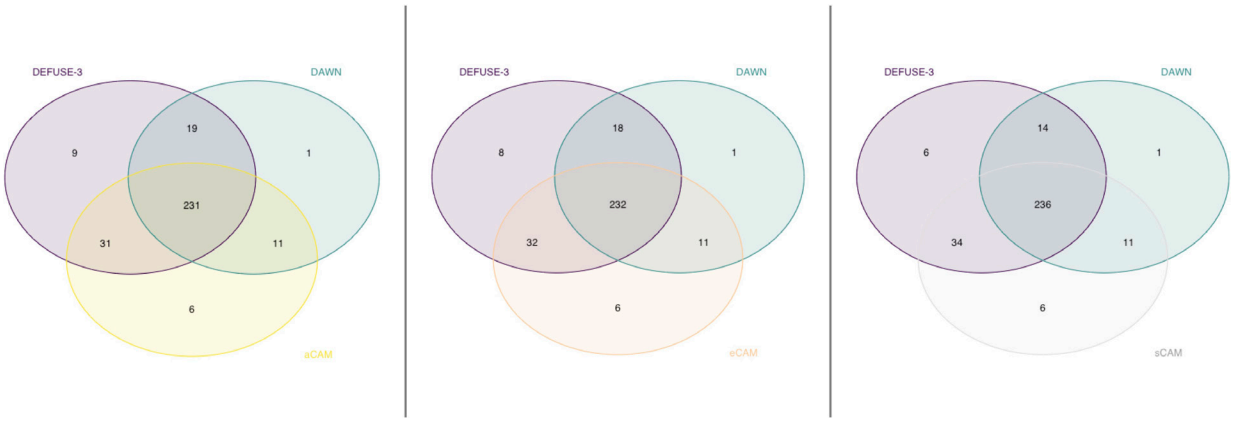


Figure 2 Venn diagrams for the different selection modalities. ASPECTS, Alberta StrokeProgram Early CT score; aCAM indicates age-adjusted clinical-ASPECTS mismatch; eCAM, eloquence-adjusted clinical-ASPECTS mismatch; sCAM, standard clinical-ASPECTS mismatch.

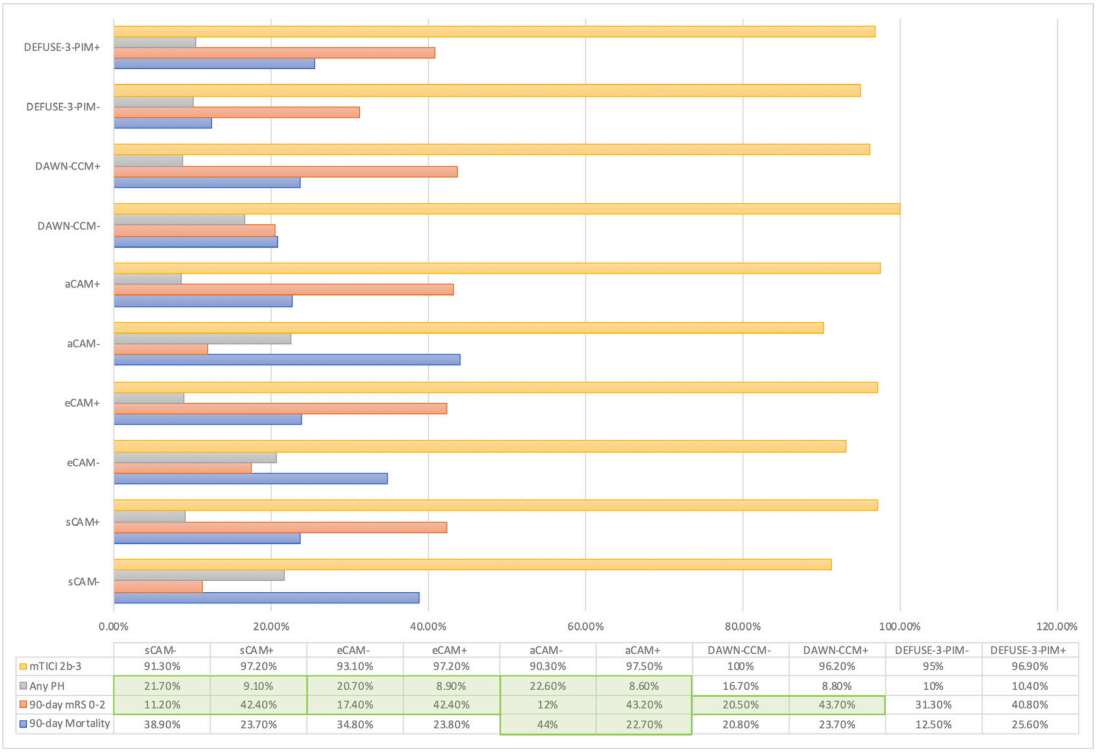
fulfilling sCAM criteria (40.6% vs 15.4% (Δ+25.2%), p=0.071) while there was no difference between those that did qualify for DEFUSE-3-PIM and eCAM selection criteria versus not (39.1% vs 38.5% (Δ+0.6%), p=0.97% and 40.6% vs 22.2% (Δ+18.4%), p=0.126, respectively).

In multivariate analysis, adjusting for age, NIHSS, glucose and HTN, all selection modalities except for DEFUSE-3-PIM and eCAM were independent predictors of 90-day good outcomes: aCAM(+) (aOR 5.23, 95% CI 1.38 to 24.09, p=0.034), DAWN-CCM(+) (aOR 2.91, 95% CI 1.07 to 7.92, p=0.037), eCAM(+) (aOR 2.94, 95% CI 0.78 to 11.05, p=0.11), sCAM(+) (aOR 8.59, 95% CI 1.08 to 68.27, p=0.047) and DEFUSE-3-PIM(+) (aOR 2.28, 95% CI 0.36 to 4.6, p=0.702). Notably, 12 (92.3%) out of the 13 DEFUSE-3-PIM(−) patients fulfilled criteria by at least one selection modality that was independently associated with good outcomes (eg, aCAM, DAWN-CCM or sCAM). On the other hand, only five patients did not meet any of the aCAM, DAWN-CCM or sCAM criteria, of which 4 DEFUSE-3-PIM (+) with only one having a good outcome at 90 days.

None of the selection modalities were associated with any PH or 90-day mortality in multivariate analysis.

DISCUSSION

Our study shows that, when comparing patients that met the different paradigm criteria versus those that did not, selection in late presenting or wake-up strokes based on itemised ASPECTS resulted in similar rates of good procedural, functional and safety outcomes as compared with the DAWN and DEFUSE 3 criteria. Moreover, all ASPECTS paradigms had a high proportion of qualifying patients and performed better in terms of outcome



	sCAM-	sCAM+	eCAM-	eCAM+	aCAM-	aCAM+	DAWN-CCM-	DAWN-CCM+	DEFUSE-3-PIM-	DEFUSE-3-PIM+
mTICI 2b-3	91.30%	97.20%	93.10%	97.20%	90.30%	97.50%	100%	96.20%	95%	96.90%
Any PH	21.70%	9.10%	20.70%	8.90%	22.60%	8.60%	16.70%	8.80%	10%	10.40%
90-day mRS 0-2	11.20%	42.40%	17.40%	42.40%	12%	43.20%	20.50%	43.70%	31.30%	40.80%
90-day Mortality	38.90%	23.70%	34.80%	23.80%	44%	22.70%	20.80%	23.70%	12.50%	25.60%

Figure 3 Outcome measures per selection paradigm. Significant results are highlighted in green. mRS indicates modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; PH, parenchymal haematoma.

discrimination when compared with DEFUSE 3. In fact, patients without a perfusion imaging mismatch had similar clinical outcomes as those who met the DEFUSE 3 criteria. This held true in multivariate analysis adjusting for potential confounders where DEFUSE-3-PIM did not show to be independently associated with good outcome at 90-days suggesting that PIM might be a poor discriminator of treatment response. On the other hand, the DAWN-CCM and the ASPECTS based paradigms were independently associated with 90-day good outcome.

The AHA/ASA guidelines extending the thrombectomy treatment window state that either the DAWN or DEFUSE 3 trial criteria could be used to determine eligibility for ET in that patient population.[3] It is important to recognise that both required the use of MRI or CTP to assess infarct core volume (DAWN and DEFUSE 3) and hypoperfusion/imaging mismatch (DEFUSE 3). These 'high tech' approaches are not typically available in clinical settings where resources are more limited. Therefore, in the absence of simpler selection paradigms, ET may not be offered to many patients that could still benefit from treatment. Additionally, there is still debate with regards to whether the use of advanced imaging is associated with improved clinical outcomes post thrombectomy. A meta-analysis of 10 clinical trials by Tsivgoulis *et al* showed that the use of advanced neuroimaging was associated with higher treatment effects as compared with conventional imaging,[6] whereas a more recent analysis of the Trevo registry failed to reveal any benefit of an imaging selection modality over another in the early and extended treatment windows.[7] Moreover, given the potential higher radiation, contrast-induced kidney injury and longer times to treatment,[8] identifying and validating selection modalities relying on simpler imaging tools become paramount.

There is growing evidence that using NCCT and ASPECTS might be safe and effective in selecting late presenting stroke patients for ET.[9–11] Recently, Santos *et al* in a cohort of 249 patients found that patients with wake-up or late presenting strokes selected with a clinical-ASPECTS mismatch paradigm had similar outcomes as those that presented within 6 hours from last known well.[9] Similarly, Nagel *et al* did not find any differences in clinical outcomes between patients with and without a perfusion imaging mismatch. Moreover, in multivariate analysis, the performance of MRI or CTP parameters did not influence outcome and ASPECTS was the only imaging parameter associated with good outcome.[10] Our results are also in agreement with a recent study demonstrating that the prevalence of DAWN-CCM among patients within the same ASPECTS categories (9–10 vs 6–8 vs 0–5) does not decline over time, further reinforcing an ASPECTS-based paradigm for patient selection in the extended window.[12]

ASPECTS is a simple and widely used tool in clinical practice for patient selection. Several studies have shown it to be a reliable predictor of outcomes.[13–15] However, despite its speed and ubiquity, ASPECTS has major shortcomings including poor ability to predict baseline infarction volumes[16] and low inter-rater agreement.[17] While these are valid concerns and could be problematic when caring for patients presenting early in the treatment window, ASPECTS has been shown to be reliable in identifying infarct core in late presenting strokes.[18] Similarly, the inter-rater agreement improves as time elapses.[19]A major flaw in relation to the ASPECTS concept derives from the fact that ASPECTS is not a linear scale since, as compared with the cortical regions, the deep areas of the brain are lower in both volume and eloquence (the posterior limb of the internal capsule representing an important exception).[20–22] Our two newly proposed ASPECTS based selection paradigms have therefore adjusted for this critical issue and should be further explored in future larger prospective studies.

In our study, for consistency, we relied on an automated ASPECTS assessment (e-ASPECTS, e-Stroke Suite V.8.0; Brainomix, Oxford, UK, www.brainomix.com). The software has been proven to be non-inferior to expert reader's performance[23] and e-ASPECTS were found to be correlated with stroke severity and clinical outcomes.[23] Given that automated software may surpass the human eye in neuroimaging assessment,[24] the use of an automated ASPECTS software allowed us to focus on the merit of each selection paradigm and limit the confounding effect of 'human' versus 'machine' measurement. Our approach, using the itemised score, incorporated stroke topology which we believe refines selection criteria. As discussed above, the anatomic regions covered by ASPECTS have been reported to be unequally weighted[25] and topological information has been shown to affect clinical outcome over and above the effect of infarct size.[5] Another interesting finding is the potential superiority of aCAM to the eCAM ASPECTS selection tool as demonstrated by the larger absolute difference in good outcomes between those meeting the criteria and their negative counterparts. Age and core volume have been repeatedly identified as strong predictors of outcomes and we have shown in previous studies not only that age-adjusted selection paradigms were superior to non-adjusted approaches in outcome discrimination[26] but also that final infarct volume cut-offs to predict outcomes decreased with age.[27 28] In the current analysis, we failed to demonstrate any definite advantage of these adjusted paradigms over the simpler sCAM in predicting 90-day good outcome. Moreover, our data hint that the adoption of an aCAM might lead to refined haemorrhagic transformation (any PH) and mortality discrimination.

Our study has several limitations mostly inherent to its retrospective design and its relatively limited sample size. Additionally, the absence of a control group comprising untreated patients limits out ability to measure treatment effects in comparison to each selection-positive group. However, we believe this absence underestimates the discernment between favourable and unfavourable outcomes, as all patients in this study did receive ET, increasing the likelihood of favourable outcomes and biasing analysis towards the null. Another limitation associated with our study is that the increase in familywise error rate across the reported statistical analysis was not corrected. We consider our research hypothesis generating as only prospective randomised controlled trials will be able to properly address this important clinical dilemma. Despite these limitations, our analysis suggests that using ASPECTS-based selection methods for late presenting and wake-up strokes might result in similar proportions of treated patients, with comparable rates of good outcomes to the DAWN and DEFUSE 3 criteria, and refined outcome discrimination. Fortunately, the hypothesis that simpler imaging paradigms can be used in the selection for endovascular treatment in the late window is currently being tested in two randomised studies (MR CLEAN LATE, https://www.mrclean-late.nl; RESILIENT-Extend, ClinicalTrials.gov Identifier: NCT04256096).

CONCLUSIONS

Non-contrast CT ASPECTS-based selection paradigms for late presenting and wake-up strokes ET have comparable proportions of qualifying patients and similar 90-day functional outcomes as DAWN-CCM and DEFUSE-3-PIM. They also might lead to better outcome discrimination as compared with DEFUSE-3 criteria. These could represent a potential alternative for centres

where access to advanced imaging is limited. Future prospective studies are warranted.

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Contributors Study design: MB, RGN. Drafting the original manuscript: MB. Data collection, analysis and interpretation; revising the work critically for important intellectual content; final approval; agreement to be accountable for all aspects of the work: all authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests RGN: Stryker Neurovascular (Trevo-2 Trial PI - modest, DAWN Trial PI – no payment, Trevo Registry Steering Committee – no payment, Physician Advisory Board/ Consultant - significant), Covidien/Medtronic (SWIFT and SWIFT-PRIME Steering Committee - modest, STAR Trial Core Lab - significant), and Penumbra (3-D Separator Trial Executive Committee – no payment), Neuravi/ Cerenovus (ARISE-II Trial Steering Committee – no payment, Physician Advisory Board - modest), Phenox (Physician Advisory Board/ Consultant – modest), Genentech (Physician Advisory Board/ Consultant – modest).

Patient consent for publication Not required.

Ethics approval Local institutional review board (IRB)/Emory University IRB.

Provenance and peer review Not commissioned; externally peer reviewed.

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

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