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ASPECTS score to select patients for endovascular treatment: the IMS-III trial

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Abstract

Background and Purpose—The IMS-III trial randomized acute ischemic stroke patients to IV tPA plus endovascular therapy versus IV tPA therapy alone within 3 hours from symptom onset. A pre-defined secondary hypothesis was that subjects with significant early ischemic change on the baseline scan would not respond to endovascular therapy.

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All authors provided key roles in study design, execution data collection, analysis and interpretation of the study results.

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Methods—The primary outcome was 90-day mRS 0–2. The baseline and follow-up CT scan images were reviewed centrally, blinded to any clinical information. We assessed whether the baseline ASPECTS score predicted outcome, and interacted with study treatment. We analyzed subgroups defined by time from onset to IV tPA initiation and baseline occlusion status at a pre-specified alpha = 0.01.

Results—Baseline demographic and clinical characteristics of 656 randomized patients were similar between subjects with a baseline ASPECTS score 8–10 (58% of the study sample) vs 0–7. Subjects with ASPECTS 8–10 were almost twice as likely [RR 1.8 CI_{99} 1.4–2.4] to achieve a favorable outcome. There was insufficient evidence of a treatment-by-ASPECTS interaction. In those treated with onset to IV tPA under 120 minutes, in CTA-proven ICA or MCA occlusion, and in both, results were similar. The probability of achieving recanalization (AOL 2–3) of the primary arterial occlusive lesion [RR 1.3 CI_{99} 1.0–1.8] or achieving TICI 2b/3 reperfusion [RR 2.0 CI_{99} 1.2–3.2] was higher among subjects with higher ASPECTS scores.

Conclusions—ASPECTS is a strong predictor of outcome and a predictor of reperfusion. ASPECTS did not identify a sub-population of subjects that particularly benefitted from endovascular therapy immediately after routine IV tPA.

Keywords

stroke; CT scan; thrombolysis; endovascular treatment; imaging

Introduction

With technically high quality non-contrast brain computed tomography, changes of acute ischemia may be observed in a high proportion of patients with major stroke.[1, 2] Radiological hypoattenuation varies linearly with brain tissue water content and increases linearly with time after middle cerebral artery (MCA) occlusion, and is thus a measure of net water uptake of ischemic brain tissue (ionic edema).[3, 4] Early ischemic change, scored semi-quantitatively using the Alberta Stroke Program Early CT Score (ASPECTS) has been shown to be a strong prognostic factor, equivalent in magnitude of effect to the assessment of clinical stroke severity using the National Institutes of Health Stroke Scale (NIHSS) score.[5–8] In two studies, a dichotomized ASPECTS score (8–10 vs 0–7) has been shown to modify the effect of endovascular thrombolytic therapy.[9, 10] Only patients with favorable baseline scans (ASPECTS 8–10) benefitted from endovascular revascularization therapy. The prospective evaluation of baseline CT scans in ECASS showed the best treatment response in patients with less than 1/3 middle cerebral artery territory hypoattenuation (N=215) compared to patients with normal CT (N=336) and patients with brain tissue hypoattenuation exceeding 1/3 of the MCA territory (N=52).[2]

We assessed the prognostic value of the CT ASPECTS score in the IMS-III study and in particular, whether response to treatment was different according to the baseline ASPECTS score.

Methods

The IMS III Trial was an international, phase III, randomized, open-label with blinded outcome assessment, clinical trial designed to test the *approach* of IV t-PA, started within 3 hours of symptoms onset, followed by protocol-approved endovascular treatment as compared to standard IV t-PA [Clinicaltrials.gov-NCT00359424].[11, 12] The trial was halted because a futility boundary was crossed at an interim analysis.

At the beginning of the Trial, CT angiography (CTA) was infrequently used at participating hospitals to assess the presence of arterial occlusions in acute stroke patients. Thus, the baseline National Institutes of Health Stroke Scale score (NIHSS), a clinical measure of neurologic deficit with a range of 0 (no deficit) to 42 (maximum possible deficit), was used to identify those patients (with a score ≥10) and a >80% likelihood of a major arterial occlusion on subsequent angiography following IV t-PA. In Amendment 3 [April 2009], after 284 participants were randomized, identification of occlusion using CTA was allowed to determine trial eligibility for those participants with NIHSS of 8 or 9, as its routine use increased rapidly during the early course of the study.

CT scans were performed at baseline, at 24 ± 6 hours, and in the setting of neurologic decline. A CTA was performed at baseline at those study sites that routinely included CTA in their baseline imaging protocol. CTA was planned for all participants at 24 hours to assess vascular patency. CT scans were acquired using contiguous non-contrast axial 5mm slices. A minority of CT images were acquired using 10 mm axial slices. The power (kV and mAs) and scan obliquity were not pre-specified. All CT scans were acquired within 3 hours of stroke onset. ASPECTS was scored [see supplementary methodology description in the online supplementary materials] on all baseline and follow-up CT scans using a 3-person panel consensus method, including a neuroradiologist for all interpretations. The reviewers were blind to all clinical data. Hemorrhage was scored using the Pessin criteria and formalized in the ECASS trials (Hemorrhagic infarction, types 1 & 2, Parenchymal hematoma, types 1 & 2).[13–15]

Statistical Methods

The primary clinical outcome was a modified Rankin scale score of 0–2 at 90 days from randomization. Secondary clinical outcomes included the modified Rankin scale score of 0–1 and NIHSS score of 0–1 at 90 days from randomization. Recanalization, defined as the arterial occlusion lesion (AOL), and reperfusion by the TICI score were secondary surrogate outcome measures. A priori, we divided ASPECTS into two groups: favorable (ASPECTS 8–10) and unfavorable (ASPECTS 0–7). Additionally, we evaluated a third group (ASPECTS 0–4), which correlates well with the previously defined 1/3rd MCA rule,[6] and which defines an ASPECTS trichotomy: ASPECT 8–10 as favorable, ASPECTS 5–7 as moderately favorable and ASPECTS 0–4 as unfavorable. Data are reported using conventional descriptive statistics, by group. We used an intention-to-treat approach in reporting the outcome data by ASPECTS group. Subjects with missing baseline CT images (n= 7) were imputed to have a poor ASPECTS (0–7) score. The CTA subset consisted of those patients who had a routine CTA prior to enrolment, which defined their location of arterial occlusion pre-treatment. For exploratory analyses, we considered the cohort of patients with proven baseline occlusions and with treatment within 2 hours of stroke onset.

Results

Baseline characteristics are shown in Table 1. Baseline demographic and clinical characteristics were similar between subjects with a baseline ASPECTS score 8–10 (58% of the study sample) vs 0–7. There was a gradient of more severe NIHSS scores with more unfavorable ASPECTS and an association between more proximal occlusion location and poorer ASPECTS scores. Thus, clinical stroke severity, vessel occlusion location and ASPECTS score are correlated variables. There was an increased chance of reperfusion at 24 hours with higher ASPECTS scores. Patients with favorable ASPECTS scores were more likely to show reperfusion overall [Table 2], but this effect was overcome by endovascular therapy with high rates of recanalization at 24 hours even in the ASPECTS 0–4 group.

The treatment effect was not modified by the dichotomized ASPECTS score (p=0.871). Because the study did not show benefit of one treatment arm over the other and both groups had active treatment, effect modification, as a secondary analysis would a priori be difficult to demonstrate unless there was a clear qualitative interaction with counter-balanced effects in each group. However, the direction of effect for endovascular therapy, although imprecise due to small sample size, was toward fewer good outcomes among patients with very unfavorable baseline CT scans (ASPECTS 0–4), similar to the analysis undertaken for IMS-1.[10] Among patients with favourable scans, a directional trend to a greater treatment effect was observed among patients treated earlier and with proven arterial occlusions. [Supplementary Table I, Supplementary Figure I]

Irrespective of treatment modality, ASPECTS was a strong prognostic variable. A favorable scan conferred a two-fold or greater chance of an independent functional outcome [Table 3]. This result was unchanged after multivariable adjustment. Similar to the above, the direction of effect showed a larger effect size among patients treated earlier and with proven arterial occlusions.[Tables 3] Remarkably, some 20% of patients with highly unfavorable scans (ASPECTS 0–4) achieved an independent functional outcome.[Table 4]

Discussion

ASPECTS is a measure of imaging-defined ischemic injury to the brain that is a strong and consistent predictor of clinical outcome. While previous smaller studies of endovascular therapy, a retrospective analysis of the PROACT-2 study and a historically controlled analysis of IMS-1,[9, 10] and prior IV thrombolysis studies,[13] showed evidence of effect modification (a multiplicative interaction) between favorable ASPECTS (score 8–10) and good clinical outcome, this was not demonstrated in our study. Subjects with low ASPECTS scores benefitted far less in IMS-III and this observation, consistent with prior trials of thrombolysis,[9, 10] supports the concept of non-nutritive, futile or even harmful reperfusion. Reperfusing dead brain is simply unhelpful to acute neurological recovery. While reliable and pragmatic imaging biomarkers for patient selection continue to be sought, these data do not convincingly support the use of non-contrast CT ASPECTS in isolation to select patients for an IV plus endovascular approach to therapy.

There are multiple limitations in the assessment of potential ASPECTS-by-treatment interactions, in the search for an imaging defined biomarker that helps select patients for treatment. These are generalizable in varying degree to other imaging modalities (including CTP and multimodal MR) and other potential biomarkers.

First, measurement error is underappreciated. The reliability of ASPECTS interpretation is moderate within 90 minutes of stroke onset, good between 90–180 minutes and excellent beyond that.[1, 16] There are subtleties of interpretation which may result in situations where a patient with an apparently unfavorable scan does well. Patients with unfavorable ASPECTS scores at baseline may do well if the infarcts are located in tolerant regions of brain such as the right temporal lobe; there is a “real-estate” effect. Additionally, patients may do well despite a large infarction if the capacity for regeneration, adaptation and recovery is exceptional.

Second, reperfusion therapy has only worked part of the time. While reperfusion rates were relatively high at 24 hours in IMS-III, the reperfusion rates early after treatment (1–4 hours) were not defined for the IV tPA only group. The quality and proportional recanalization in the endovascular arm (measured using the TICI scoring system) was poor. Thus, the relationship between outcome and pre-treatment ASPECTS score continues to be confounded by variability in treatment response.

Third, the baseline scan is a snapshot in time that reflects a physiological state only for a short period of time; the scan has a shelf-life and consequently the shorter the time interval from CT scan to reperfusion, the stronger the potential predictive value of ASPECTS.[17] In future studies it will be critical to measure the 'picture-to-puncture' and 'picture-to-reperfusion' times.[18] In IMS-III, the average time to treatment was long, during which time infarction progressed. Therefore, time to reperfusion is a related confounding variable.

Finally, most studies, including this one, are underpowered to assess for interaction effects. All of these issues applied less to the PROACT-2 analysis,[9] which did show evidence of interaction. Key differences between PROACT-2 and IMS-III were the much later onset-to-treatment time and the large difference in reperfusion rates between the two treatment groups in PROACT-2 compared to IMS III.[12, 19]

There is strong biological evidence that a low ASPECTS score implies a poor outcome irrespective of treatment. Consistent with past reports, a favorable ASPECTS predicted good outcome. Interestingly, patients with favorable ASPECTS were also more likely to recanalize and reperfuse. The stroke itself may be impacting defensive vascular mechanisms that are designed to restore blood flow in the brain. Favorable ASPECTS is associated with good collateral blood flow allowing ischemic brain tissue to survive for longer time periods and enabling IV thrombolytics to attack the thrombus from both sides.[20–22] Moreover, higher ASPECTS may be associated with more distal arterial occlusions with smaller sized thrombi compared to the proximal occlusion of major cerebral arteries. Intriguingly, we did observe that about one fifth of patients with highly unfavorable scans (ASPECTS 0–4) achieved a good functional clinical outcome. We attribute this finding to a linear combination of lower age, faster treatment, lower baseline stroke severity, lower baseline serum glucose, higher number of no baseline occlusion cases and fewer symptomatic ICH occurrences as principal reasons for good outcome in this group.[Table 4]

One limitation of our data was the imaging itself. Qualitatively, we found significant variability in image quality related to age of the CT scanner, helical vs. sequential scan acquisition, scanning energy used (keV and mAs settings), scanner-type image reconstruction algorithms including iterative reconstruction. Older scanners, helical image acquisition, lower scanning energy and non-optimized image reconstruction algorithms were associated with much poorer image contrast between grey and white matter. Optimizing CT scanner parameters may substantially improve measurement issues at an individual site.

Overall, ASPECTS is a strong prognostic variable. Until we can treat all patients very fast with 80–90% TICI-3 flow, we will not be able to understand the degree to which baseline imaging – using ASPECTS - is a useful method to select patients for combined IV thrombolysis immediately followed by endovascular therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics - ITT population

	ASPECTS 8–10	ASPECTS 0–7	ASPECTS 0–4
Demographics	N=378	N=278	N=92
Age (median, iqr)	70 (17)	67 (19)	69 (15.5)
Sex (female) % (n)	49% (187)	46% (129)	49% (45)
Caucasian % (n)	86% (326)	82% (228)	82% (75)
Historical Variables			
Hypertension % (n)	76% (288)	73% (202)	87% (80)
Diabetes mellitus % (n)	24% (92)	20% (56)	21% (19)
Atrial fibrillation % (n)*	32% (122)	36% (101)	34% (31)
Hyperlipidemia % (n)	51% (193)	48% (134)	50% (46)
Currentsmoker % (n)	21% (78)	31% (85)	34% (31)
Congestive heart failure % (n)	14% (52)	10% (29)	11% (10)
Peripheral vascular disease % (n)	7% (28)	9% (24)	15% (14)
Clinical Variables			
NIHSS (median, iqr)	16 (7)	18 (7)	19 (5)
Onset-to-IV tPA time, min (median, iqr)	120 (50)	120 (47)	122 (55.5)
Onset-to-groin puncture time, min(median, iqr) [N=424]	206.5 (60)	211 (70)	214 (80)
Glucose [mM] (median, iqr)	6.7 (2.7)	6.6 (2.3)	6.7 (1.9)
Treatment Assignment			
IV +endovascular arm % (n)	65% (247)	67% (187)	62% (57)

* afib from medical history and baseline ECG.

ITT = intention-to-treat; NIHSS = National Institutes of Health Stroke Scale; IV = intravenous; tPA = tissue plasminogen activator; ASPECTS = Alberta Stroke Program Early CT Score

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Table 2

ASPECTS and vascular occlusion status
CTA population but as randomized (as ITT, and specifically not as treated/per protocol)

	ASPECTS 8–10		**ASPECTS 0–7**		**ASPECTS 0–4**	
Baseline CTA*	N= 154		N=128		N=40	
ICA T or L or other ICA occlusion, % (n)†	16% (24)		33% (42)		43% (17)	
M1 occlusion % (n)	53% (82)		52% (67)		43% (17)	
M2 occlusion, % (n)	21% (33)		14% (18)		13% (5)	
M3 occlusion, % (n/N)	2% (3)		1% (1)		3% (1)	
M4 or distal occlusion, % (n)	1% (2)		0% (0)		0% (0)	
PCA occlusion, % (n)	2% (3)		---		---	
BA/VA occlusion, % (n)	3% (5)		---		---	
Treatment	N=177		N=129		N=40	
IV + endovascular arm % (n)	67% (119)		71% (92)		63% (25)	
Onset-to-IV tPA time (median, iqr)	120 (54)		116 (44)		119 (52)	
Onset-to-groin puncture time (median, iqr) [N=210]**	208.5 (69)		202.5 (62)		210 (71)	
Angiographic outcome (endovascular group only)						
AOL recanalization =3 (%n/N)	71% (60/84)		54% (46/85)		59% (13/22)	
TICI 2b-3 flow (% n/N)	60% (47/78)		31% (26/85)		45% (10/22)	
CTA 24h vascular outcome						
Recanalization (% n/N)	83% (104/126)		71% (64/90)		50% (13/26)	
	IV-IA	IV	IV-IA	IV	IV-IA	IV
	87% (73/84)	74% (31/42)	88% (42/48)	56% (9/16)	73% (11/15)	18% (2/11)
ICH						
Symptomatic	6% (10/177)		9% (11/129)		5% (2/40)	
Asymptomatic	20% (36/177)		27% (37/129)		30% (12/40)	

* 23 cases in ASPECTS 8–10 were missing CTA adjudication of the baseline occlusion site and 1 case in the ASPECTS 0–7 group.

** includes one subject randomized to IV who underwent acute endovascular treatment

† does not include proximal ICA occlusions

ITT = intention-to-treat; CTA=computed tomographic angiography; ICA = internal carotid artery; M1 = M1 middle cerebral artery occlusion; M2 = M2 branch middle cerebral artery; M3 = M3 branch middle cerebral artery; PCA = posterior cerebral artery; BA = basilar artery; VA = vertebral artery; IV = intravenous; tPA = tissue plasminogen activator; AOL = arterial occlusive lesion; TICI = thrombolysis in cerebral ischemia score; ICH = intracranial hemorrhage; ASPECTS = Alberta Stroke Program Early CT Score

Table 3

Outcomes ASPECTS as a predictor irrespective of treatment assignment

	ASPECTS 8–10	ASPECTS 0–7	RR (CI_{99})	ASPECTS 0–4
ITT population	N=378	N=278		N=92
mRS 0–2 at 90d %, n	49% (187)	27% (76)	1.8 (1.4–2.4)	21% (19)
mRS 0–1 at 90d %,n	34% (130)	18% (50)	1.9 (1.3–2.8)	12% (11)
NIHSS 0–1 at 90d, % n	33% (123)	17% (47)	1.9 (1.3–2.8)	7% (6)
Onset-to-IV tPA time <= 120 min	N=202	N=143		N=45
mRS 0–2 at 90d %, n	50% (101)	29% (42)	1.7 (1.2–2.5)	29% (13)
mRS 0–1 at 90d %, n	34% (69)	22% (31)	1.6 (1.0–2.5)	20% (9)
NIHSS 0–1 at 90d, % n	35% (71)	21% (30)	1.7 (1.0–2.7)	11% (5)
Baseline ICA and/or M1-MCA occlusion on CTA	N=106	N=109		N=34
mRS 0–2 at 90d %, n	57% (60)	25% (27)	2.3 (1.4–3.7)	15% (5)
mRS 0–1 at 90d %, n	40% (42)	14% (15)	2.9 (1.4–5.7)	6% (2)
NIHSS 0–1 at 90d, % n	39% (41)	16% (17)	2.5 (1.3–4.8)	3% (1)
Onset-IV tPA time <= 120 min AND baseline ICA and /or M1-MCA occlusion on CTA	N=57	N=65		N=17
mRS 0–2 at 90d %, n	61% (35)	25% (16)	2.5 (1.3–4.6)	12% (2)
mRS 0–1 at 90d %, n	44% (25)	17% (11)	2.6 (1.2–5.8)	12% (2)
NIHSS 0–1 at 90d, % n	44% (25)	20% (13)	2.2 (1.0–4.6)	6% (1)
Baseline ICA and/or MCA (M1-M4) occlusion on CTA	N=144	N=128		N=40
mRS 0–2 at 90d %, n	54% (78)	29% (37)	1.9 (1.2–2.8)	20% (8)
mRS 0–1 at 90d %, n	39% (56)	16% (20)	2.5 (1.4–4.5)	5% (2)
NIHSS 0–1 at 90d, % n	36% (52)	16% (21)	2.2 (1.2–4.0)	3% (1)
Onset-IV tPA time <= 120 min AND baseline ICA and /or MCA (M1-M4) occlusion on CTA	N=76	N=74		N=21
mRS 0–2 at 90d %, n	61% (46)	31%(23)	1.9 (1.2–3.2)	24% (5)
mRS 0–1 at 90d %, n	46% (35)	19% (14)	2.4 (1.2–4.9)	10% (2)
NIHSS 0–1 at 90d, % n	43% (33)	20% (15)	2.1 (1.1–4.2)	5% (1)

ITT = intention-to-treat; CTA = computed tomographic angiography; ICA = internal carotid artery; M1 = M1 middle cerebral artery occlusion; M2 = M2 branch middle cerebral artery; M3 = M3 branch middle cerebral artery; PCA = posterior cerebral artery; BA = basilar artery; VA = vertebral artery; IV = intravenous; tPA = tissue plasminogen activator; AOL = arterial occlusive lesion; TICI = thrombolysis in cerebral ischemia score; ICH = intracranial hemorrhage; ASPECTS = Alberta Stroke Program Early CT Score; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin scale score

Table 4

ASPECTS 0–4 patients only

ASPECTS 0–4 Group Only		
	mRS 0–2	mRS 3–6
Demographics	N=19	N=73
Age (median, iqr)	63 (22)	70 (15)
Sex (female) % (n)	42% (8)	51% (37)
Caucasian % (n)	84% (16)	81% (59)
Historical Variables		
Hypertension % (n)	89% (17)	86% (63)
Diabetes mellitus % (n)	11% (2)	23% (17)
Atrial fibrillation % (n)	47% (9)	30% (22)
Hyperlipidemia % (n)	58% (11)	48% (35)
Current smoker % (n)	37% (7)	33% (24)
Congestive heart failure % (n)	11% (2)	11% (8)
Peripheral vascular disease % (n)	16% (3)	15% (11)
Clinical Variables		
NIHSS (median, iqr)	16 (8)	19 (4)
Onset-to-IV tPA time (median, iqr)	115 (32)	125 (56)
Onset-to-groin puncture time (median, iqr)	196 (80)	215 (70)
Glucose [mM] (median, iqr)	6.3 (1.1)	6.9 (1.9)
Affected hemisphere on baseline imaging		
Left hemisphere	26% (5)	27% (20)
Right hemisphere	58% (11)	70% (51)
Unknown / Multiple	5% (1)	0% (0)
No acute occlusion	11% (2)	3% (2)
Treatment Assignment		
IV + endovascular arm % (n)	58% (11)	63% (46)
Safety Events		
Symptomatic ICH	0% (0)	7% (5)

IV = intravenous; tPA= tissue plasminogen activator; AOL = arterial occlusive lesion; TICI = thrombolysis in cerebral ischemia score; ICH = intracranial hemorrhage; ASPECTS = Alberta Stroke Program Early CT Score; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin scale score