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Recanalization and Clinical Outcome of Occlusion Sites at Baseline CT Angiography in the Interventional Management of Stroke III Trial[1]

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For the IMS III Investigators

Purpose: To use baseline computed tomographic (CT) angiography to analyze imaging and clinical end points in an Interventional Management of Stroke III cohort to identify patients who would benefit from endovascular stroke therapy.

Materials and Methods: The primary clinical end point was 90-day dichotomized modified Rankin Scale (mRS) score. Secondary end points were 90-day mRS score distribution and 24-hour recanalization. Prespecified subgroup was baseline proximal occlusions (internal carotid, M1, or basilar arteries). Exploratory analyses were subsets with any occlusion and specific sites of occlusion (two-sided $\alpha = .01$).

Results: Of 656 subjects, 306 (47%) underwent baseline CT angiography or magnetic resonance angiography. Of 306, 282 (92%) had arterial occlusions. At baseline CT angiography, proximal occlusions ($n = 220$) demonstrated no difference in primary outcome (41.3% [62 of 150] endovascular vs 38% [27 of 70] intravenous [IV] tissue-plasminogen activator [tPA]; relative risk, 1.07 [99% confidence interval: 0.67, 1.70]; $P = .70$); however, 24-hour recanalization rate was higher for endovascular treatment ($n = 167$; 84.3% [97 of 115] endovascular vs 56% [29 of 52] IV tPA; $P < .001$). Exploratory subgroup analysis for any occlusion at baseline CT angiography did not demonstrate significant differences between endovascular and IV tPA arms for primary outcome (44.7% [85 of 190] vs 38% [35 of 92], $P = .29$), although ordinal shift analysis of full mRS distribution demonstrated a trend toward more favorable outcome ($P = .011$). Carotid T- or L-type occlusion (terminal internal carotid artery [ICA] with M1 middle cerebral artery and/or A1 anterior cerebral artery involvement) or tandem (extracranial or intracranial) ICA and M1 occlusion subgroup also showed a trend favoring endovascular treatment over IV tPA alone for primary outcome (26% [12 of 46] vs 4% [one of 23], $P = .047$).

Conclusion: Significant differences were identified between treatment arms for 24-hour recanalization in proximal occlusions; carotid T- or L-type and tandem ICA and M1 occlusions showed greater recanalization and a trend toward better outcome with endovascular treatment. Vascular imaging should be mandated in future endovascular trials to identify such occlusions.

Online supplemental material is available for this article.

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In the Interventional Management of Stroke (IMS) III trial, the approach of combining intravenous (IV) tissue-plasminogen activator (tPA) with endovascular therapies was tested in an attempt to improve revascularization and clinical outcomes compared with IV tPA alone in the setting of moderate to severe acute ischemic stroke. The overall results were neutral, with no significant improvement in clinical outcome with the endovascular approach added to IV tPA compared with IV tPA alone (1). Vascular imaging was not mandated for trial enrollment but was performed at a number of centers routinely as part of standard clinical care. Subjects with lower baseline National Institutes of Health Stroke Scale (NIHSS) scores (scores 8–9) were also eligible for the trial if a proximal occlusion was identified at baseline vascular imaging after protocol amendment 3 was implemented in January 2009. At centers where baseline computed tomographic (CT) angiography was performed routinely, the absence of a visible intracranial occlusion served as an exclusion from eligibility after amendment 5 was enacted in June 2011.

The subgroup of IMS III subjects for whom baseline CT angiography or magnetic resonance (MR) angiography was performed may provide valuable insight into which subgroups of patients with moderate or severe acute ischemic stroke may benefit from endovascular therapy versus IV tPA alone. The trial mandated follow-up (24-hour) CT angiography or MR angiography to evaluate recanalization rates for all subjects in both treatment arms. We present analyses to evaluate this baseline (pre–IV tPA) CT angiography and MR angiography information within the IMS III trial as a predictor of both the imaging end point of 24-hour recanalization and 90-day modified Rankin Scale (mRS) score for the two treatment groups.

Advances in Knowledge

- In the prespecified analysis of subjects with proximal occlusion observed at baseline CT angiography, combined intravenous (IV) tissue-plasminogen activator (tPA) and endovascular treatment has higher 24-hour recanalization rates (84.3%) compared with standard IV tPA (56%) as identified with CT angiography and MR angiography ($P < .0001$).
- Terminal and tandem occlusions of the internal carotid artery (ICA) and M1 segment showed greater recanalization (83.3% vs 27.8%, $P = .0001$) and a trend toward better outcomes (26% vs 4%, $P = .047$) with endovascular treatment as compared with IV tPA alone in post hoc analysis.
- Future endovascular and/or thrombolytic trial design should include baseline vascular imaging and focus on enrollment of patients with evidence of intracranial occlusion, particularly involving the ICA, given the wide differences in clinical effects and recanalization according to occlusion sites seen in the Interventional Management of Stroke III study.

Materials and Methods

The study was funded by the National Institutes of Health and the National Institute of Neurologic Diseases and Stroke (grant numbers UC U01NS052220, MUSC U01NS054630, and U01NS077304). Genentech supplied the drug used for intraarterial tPA in the endovascular group. EKOS, Concentric, and Cordis Neurovascular supplied the study catheters during the period when amendments 1–3 were in effect. In Europe, IMS III investigator meeting support was provided in part by Boehringer Ingelheim.

Implications for Patient Care

- Recanalization rates at 24 hours are higher for endovascular treatment compared with standard IV tPA.
- Subjects with a large thrombus burden identified at CT angiography, involving the extracranial or intracranial ICA and M1 middle cerebral artery, are unlikely to achieve good outcomes with standard IV tPA.

Patients and Procedures

Patient eligibility criteria and IMS III trial methods have been detailed previously (1,2). Subjects were recruited from August 25, 2005, to April 17, 2012. The identification of a proximal arterial occlusive lesion was centrally adjudicated by the CT Imaging Analysis Centre at the University of Calgary (the central core laboratory). Each CT angiography or MR angiography study was interpreted by a consensus panel of two readers (stroke neurologists A.M.D. and M.D.H. and neuroradiologist M.G., each with at least 10 years of stroke imaging experience) at each session. Guidance for 24-hour CT angiography imaging parameters was provided (see Appendix E1 [online]), but specific CT angiography or

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Abbreviations:
ICA = internal carotid artery
IMS = Interventional Management of Stroke
IV = intravenous
mRS = modified Rankin Scale
NIHSS = National Institutes of Health Stroke Scale
SICH = symptomatic intracerebral hemorrhage
tPA = tissue-plasminogen activator

Author contributions:
Guarantors of integrity of entire study, A.M.D., T.A.T., J.P.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, A.M.D., M.D.H., M.R., O.O.Z., D.F., K.C., P.K., T.A.T., J.P.B.; clinical studies, A.M.D., M.G., J.C., M.D.H., T.G.J., D.F., R.v.K., K.C., P.K., D.S.L., T.A.T., Y.Y.P., J.P.B.; experimental studies, T.A.T.; statistical analysis, S.D.Y., L.D.F., Y.Y.P.; and manuscript editing, A.M.D., M.G., S.D.Y., M.D.H., T.G.J., M.R., B.Y., O.O.Z., D.F., R.v.K., K.C., P.K., D.S.L., T.A.T., Y.Y.P., J.P.B.

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Conflicts of interest are listed at the end of this article.

MR angiography protocols were not mandated. Each segment of the extracranial and intracranial arterial vasculature was assessed for the presence of contrast material within the lumen and was graded for any stenosis or occlusion. The grading of segments for stenosis and occlusion and occlusion site locations are described in Appendix E1 (online). Recanalization according to specific site of occlusion by comparing the baseline and follow-up CT angiography and MR angiography findings is defined in Appendix E1 (online).

The primary clinical end point was a functionally independent outcome as manifested by mRS score of 0–2 at 90 days. One of the secondary clinical end points was 90-day mRS score distribution. Recanalization was measured in those who demonstrated intracranial occlusion at baseline CT angiography and/or MR angiography. Successful recanalization was defined as grade 3–5 flow in previously occluded (grade 1–2) segments of symptomatic intracranial arteries at 24-hour CT angiography and/or MR angiography. Subjects without 24-hour CT angiography and/or MR angiography data were excluded from further recanalization analysis. The primary safety outcomes were mortality within 90 days and symptomatic intracerebral hemorrhage (SICH), defined as an intracranial hemorrhage temporally related to a decline in neurologic status, as well as new or worsening neurologic symptoms in the judgment of the clinical investigator that may warrant medical intervention within 30 hours of IV tPA initiation.

Statistical Analysis

The analysis of mRS scores 0–2 among subjects with internal carotid artery (ICA), M1, or basilar arterial occlusions was prespecified (1). Subjects with 90-day outcome missing or collected outside the prespecified window were assigned an mRS score higher than 2. Other subgroup analyses, according to presence or absence of any occlusion or various specific occlusion locations, were considered exploratory. Within each subgroup, treatment arms were compared with respect to both effectiveness (clinical and recanalization) and safety end points. The χ^2 test, or Fisher exact test in the case of small cell counts, was used to compare the treatment arms with respect to binary end points. The effect of treatment on recanalization was further described via risk difference and corresponding 95% confidence intervals, derived according to the Newcombe score. The distribution of ordinal mRS scores was analyzed by using the generalized Wilcoxon test; subjects with mRS score missing or obtained outside of the prespecified window were excluded from this analysis, and mRS scores 5 and 6 were combined into one category.

For the specific sites of occlusion, baseline differences between treatment arms were tested (and considered significant if P was less than .01) for the following variables: age; sex; baseline NIHSS score; baseline Alberta Stroke Program Early CT Score, or ASPECTS; atrial fibrillation (according to electrocardiography findings or medical history); time from onset to IV tPA treatment time; and baseline glucose level. Given the exploratory nature of the various analyses described that were not prespecified for the different occlusion sites, as well as the number of analyses anticipated, significance required a P value less than .01 to minimize false-positive results that arose from multiple hypothesis testing.

Results

Of the 656 subjects enrolled in the IMS III trial, 306 (47%) underwent baseline vascular imaging, including 292 CT angiography examinations and 14 MR angiography examinations. Heretofore, subjects who underwent either baseline CT angiography or MR angiography are referred to as subjects who underwent baseline CT angiography. In 78% (45 of 58) of enrollment centers in the trial, at least one subject underwent baseline CT angiography. Of the 282 subjects with any occlusion at baseline CT angiography, 66 had no 24-hour CT angiography or MR angiography data, of whom nine died within 31 hours. The remaining 216 subjects had both baseline and 24-hour vascular imaging data that were used for analysis of 24-hour recanalization.

Baseline CT Angiography versus No Baseline CT Angiography

The baseline demographics of subjects with baseline CT angiography data versus those without are shown in Table 1. Significantly ($P < .01$) less hyperlipidemia and shorter times from IV tPA bolus to groin puncture time and from groin puncture to start of endovascular therapy were observed in the CT angiography group. This could be explained by the high rate of direct to comprehensive stroke center enrollment in the baseline CT angiography population (95%) compared with only 77% in those where baseline CT angiography was not performed.

Among direct to comprehensive stroke center subjects, no differences were seen in the time from IV tPA bolus to groin puncture ($P = .08$); however, time from groin puncture to start of intraarterial therapy was still shorter in the CT angiography group ($P = .002$). Subjects who underwent CT angiography were more likely to have a favorable clinical outcome (mRS score of 0–2) versus those who did not (45.4% [139 of 306] vs 35.4% [124 of 350], $P = .009$). Related to safety, the mean baseline creatinine level was similar in both the baseline CT angiography and no CT angiography subgroups (92.4 μmol/L ± 29.9 and 94.4 μmol/L ± 34.3, respectively) and was not different on day 5 (or at discharge) (77.1 μmol/L ± 29.2 and 79.4 μmol/L ± 47.8, respectively). In the IV tPA treatment arm, no differences in favorable clinical outcome were observed in the study sample that underwent baseline CT angiography versus those that did not (39% [37 of 95] versus 38.6% [49 of 127], $P = .956$).

Baseline CT angiography demonstrated an occlusion in 282 of 306 subjects (92.2%). The occlusion sites were distributed as follows: two isolated extracranial ICA occlusions, four intracranial ICA occlusions only, 58 ICA

T- or L-type occlusions, 11 tandem ICA and M1 occlusions, 60 proximal M1 occlusions without ICA involvement, 79 distal M1 occlusions without ICA involvement, 54 M2 occlusions with or without ICA involvement; five M3 and M4 occlusions, five basilar artery (with or without vertebral artery) occlusions, and four posterior cerebral artery occlusions.

Baseline CT Angiography Subgroups

The only prespecified baseline CT angiography analysis was a comparison of treatment arms in the subset of subjects with proximal occlusions (ICA, M1, or basilar arteries; $n = 220$) with regard to 90-day mRS score of 0–2 and 24-hour recanalization. No difference in the primary outcome was seen (41.3% [62 of 150] endovascular vs 38% [27 of 70] IV tPA; relative risk, 1.07 [99% confidence interval: 0.67, 1.70]). Figure 1 illustrates the 90-day mRS distribution of the two treatments for this prespecified subgroup (generalized Wilcoxon test, $P = .11$); eight subjects were excluded from this analysis because outcome data were missing or were obtained outside the 90-day assessment window. The rate of recanalization at 24 hours was better with endovascular therapy (84.3% [97 of 115] endovascular versus 56% [29 of 52] IV tPA, $P < .001$).

Subsequent analyses were all performed post hoc. The baseline CT angiography population was divided into subjects with no baseline occlusion and those with a baseline occlusion for subsequent analyses. Among subjects with no occlusion, a 90-day mRS score of 0–2 occurred in 81% (17 of 21) in the endovascular arm versus 67% (two of three) in the IV tPA arm ($P = .52$). Only one of 89 subjects (1%) with baseline NIHSS score of at least 20 had no visible occlusion, and 23 of 217 subjects (10.6%) with baseline NIHSS score of 8–19 had no visible occlusion. Within the endovascular arm, there were three of 20 subjects without visible occlusion at CT angiography that had evidence of intracranial occlusion at conventional angiography (M2 middle cerebral artery in two subjects and M3 middle cerebral artery in one subject). Median 24-hour

Table 1

Baseline Characteristics: Baseline CT Angiography versus No Baseline CT Angiography Performed

Parameter	Baseline CT Angiography ($n = 306$)	No Baseline CT Angiography ($n = 350$)
Median age (y)*	70 (23–83)	68 (23–89)
No. of men	163 (53.3)	177 (50.6)
No. of black, African American, and African Canadian subjects	25 (8.2)	45 (12.8)
No. of Hispanic or Latino subjects	11 (3.6)	12 (3.4)
Median baseline NIHSS score*	17 (7–40)	17 (9–40)
No. of subjects with ASPECTS score of 8–10	177 (57.8)	201 (57.4)
Presumptive stroke location		
Left hemisphere	151 (49.3)	179 (51.1)
Right hemisphere	147 (48.0)	159 (45.4)
Brain stem and/or cerebellum	7 (2.3)	7 (2.0)
Unknown location and/or multiple locations	1 (0.3)	5 (1.4)
No. of subjects with atrial fibrillation	111 (36.3)	112 (32.0)
No. of subjects with history of hypertension	227 (74.2)	263 (75.1)
No. of subjects with history of diabetes	58 (19.0)	90 (25.7)
Mean baseline glucose level (mmol/L)†	7.3 ± 2.8	7.6 ± 3.1
No. of subjects with history of congestive heart failure	28 (9.2)	53 (15.1)
No. of subjects with history of coronary artery disease	71 (23.2)	103 (29.4)
No. of subjects with history of hyperlipidemia‡	135 (44.1)	192 (54.8)
Mean time from onset to IV tPA initiation (min)†	123 ± 33.4	121.1 ± 34.0
Mean time from IV tPA to groin puncture (min)†‡	80.7 ± 26.3	90.1 ± 35.5
Mean time from groin puncture to intraarterial therapy administration (min)†‡	40.5 ± 21.6	49.9 ± 24.2

Note.—Unless specified otherwise, numbers in parentheses are percentages. ASPECTS = Alberta Stroke Program Early CT Score.

* Numbers in parentheses are ranges.

† Data are mean ± standard deviation.

‡ Differences were considered significant at the $P < .01$ level.

Figure 1

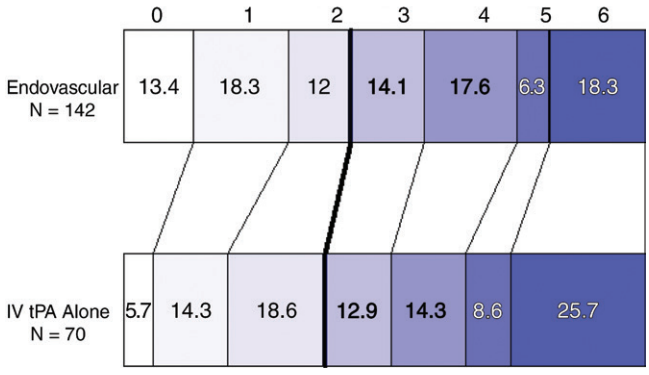

Figure 1: Diagram shows prespecified baseline CT angiography distribution of proximal occlusions (ICA, M1, basilar artery). The mRS distribution was not significantly different (generalized Wilcoxon test, $P = .1068$).

infarct volume was 0.3 mL (interquartile range, 0–5.0 mL) in this group, and 10 of 23 subjects with follow-up CT data had no visible infarct.

The baseline CT angiography occlusion subgroup includes all sites of occlusion detected. Baseline demographics were all similar in the two treatment arms (Table 2). The baseline CT angiography occlusion subgroup did not demonstrate significant differences between the endovascular and IV tPA (alone) arms for the primary effectiveness outcome (44.7% [85 of 190] vs 38% [35 of 92], $P = .29$) and safety end points (SICH, 7.9% [15 of 190] vs 6% [six of 92], $P = .68$; 90-day mortality, 14.7% [28 of 190] vs 26% [24 of 92], $P = .021$). The full mRS distribution is shown in Figure 2, with a direction of treatment effect favoring endovascular therapy ($P = .011$). This excludes eleven subjects without mRS information (missing or obtained outside the assessment window).

Individual sites of occlusion were subdivided in an exploratory fashion to identify any potentially unique differences in clinical outcomes between treatment arms. The 24-hour recanalization rates according to specific site of occlusion are reported in Table 3.

The carotid T- and L-type occlusions were combined with tandem ICA and M1 occlusions, as these occlusions represent the largest thrombus volumes. No significant baseline imbalances between treatment arms were present. In this subgroup, the direction of treatment effect was in favor of endovascular treatment compared with IV tPA alone for the primary effectiveness end point (26% [12 of 46] vs 4% [one of 23], $P = .047$). The safety end points (SICH, 11% [five of 46] vs 13% [three of 23], $P > .99$; 90-day mortality, 37% [17 of 46] vs 48% [11 of 23], $P = .39$) were not significantly different. The full mRS distribution is shown in Figure 3a, with a direction of treatment effect favoring endovascular therapy ($P = .02$).

The proximal M1 involvement (but no ICA occlusion) subgroup showed no treatment effect between the endovascular ($n = 41$) and IV tPA (alone) ($n = 19$) arms for both primary effectiveness (46% [19 of 41] vs 42% [eight of 19], $P = .76$) and safety end points (SICH, 7% [three of 41] vs 5% [one of 19], $P > .99$; 90-day mortality, 17% [seven of 41] vs 16% [three of 19], $P > .99$). Analysis of the full mRS distribution (Fig 3b) was not significant ($P = .93$).

The distal M1 involvement (but no ICA occlusion) subgroup showed no treatment effect between endovascular

Table 2

Baseline Characteristics: Population with Baseline Occlusions in the Two Treatment Arms

Parameter	Endovascular Therapy ($n = 190$)	IV tPA Only ($n = 92$)
Median age (y)*	70 (23–83)	70 (38–83)
No. of men	94 (49.5)	55 (60)
No. of black, African American, and African Canadian subjects	19 (10.0)	6 (6)
No. of Hispanic or Latino subjects	7 (3.7)	3 (3)
Median baseline NIHSS score*	17 (7–40)	17 (8–30)
No. of subjects with ASPECTS score of 8–10	99 (52.1)	55 (60)
Presumptive stroke location		
Left hemisphere	96 (50.5)	42 (46)
Right hemisphere	90 (47.4)	48 (52)
Brain stem and/or cerebellum	4 (2.1)	1 (1)
Unknown location and/or multiple locations	0 (0)	1 (1)
No. of subjects with atrial fibrillation	76 (40.0)	33 (36)
No. of subjects with history of hypertension	141 (74.2)	72 (78)
No. of subjects with history of diabetes	35 (18.4)	18 (20)
Mean baseline glucose level (mmol/L)†	7.2 ± 2.7	7.5 ± 3.0
No. of subjects with history of congestive heart failure	17 (8.9)	9 (10)
No. of subjects with history of coronary artery disease	41 (21.6)	26 (28)
No. of subjects with history of hyperlipidemia	80 (42.1)	46 (50)
Mean time from onset to IV tPA initiation (min)†	124.0 ± 32.7	118.3 ± 33.5

Note.—Unless specified otherwise, numbers in parentheses are percentages. ASPECTS = Alberta Stroke Program Early CT Score.

* Numbers in parentheses are ranges.

† Data are mean ± standard deviation.

Figure 2

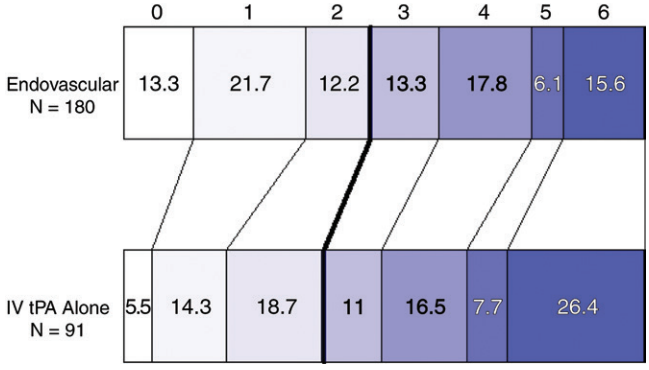

Figure 2: Diagram shows post hoc baseline CT angiography distribution of any visible occlusions. The mRS distribution was not significantly different (generalized Wilcoxon test, $P = .011$).

Table 3

24-Hour Recanalization Rates in Each Treatment Arm according to CT Angiography–based Site of Occlusion

Baseline Primary Occlusion Vessel Category	Percentage of Occlusions Recanalized in Subjects with 24-Hour CT Angiography Data		
	Endovascular Therapy	IV tPA Only	Treatment Difference
All occlusions*	86.3 (79.6, 91.4)	64.7 (52.2, 75.9)	21.6 (9.4, 34.3)
Proximal ICA, M1, basilar artery occlusion	84.3 (76.4, 90.5)	55.8 (41.3, 69.5)	28.6 (13.8, 43.1)
ICA T- or L-type occlusion or tandem ICA and M1 occlusion	83.3 (65.3, 94.4)	27.8 (9.7, 53.5)	55.6 (26.9, 73.5)
Proximal M1 occlusion, no ICA involvement	90.3 (74.3, 98.0)	80.0 (44.4, 97.5)	10.3 (−10.6, 42.0)
Distal M1 occlusion, no ICA involvement	85.1 (71.7, 93.8)	85.7 (63.7, 97.0)	−0.6 (−16.4, 21.1)
M2 occlusion with or without ICA involvement	88.5 (69.9, 97.6)	78.6 (49.2, 95.3)	9.9 (−12.4, 37.1)
M3 and M4 occlusion with or without ICA involvement	100.0 (NA)	100.0 (NA)	NA
Basilar artery, vertebral artery with basilar artery, posterior cerebral artery occlusion	83.3 (35.9, 99.6)	33.3 (0.8, 90.6)	50.0 (−10.7, 80.4)

Note.—Numbers in parentheses are 95% confidence intervals. NA = not applicable.

* Two subjects with isolated extracranial ICA occlusions were excluded.

Figure 3

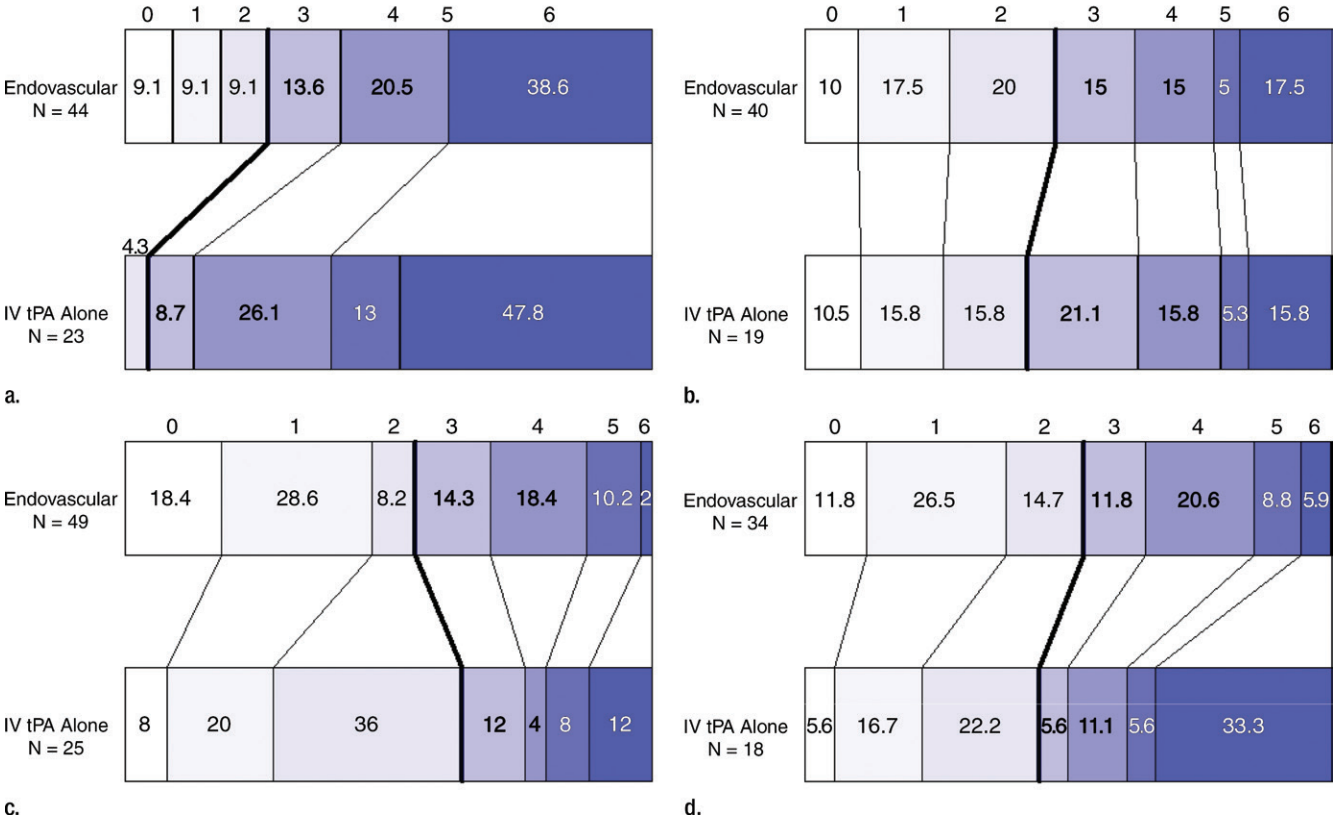

Figure 3: Diagrams show distribution of findings at baseline CT angiography. **(a)** Carotid T- or L-type occlusions or tandem ICA and M1 occlusions. The mRS distribution was not significantly different (generalized Wilcoxon test, $P = .02$). **(b)** Proximal M1 occlusions without ICA involvement. The mRS distribution was not significantly different (generalized Wilcoxon test, $P = .93$). **(c)** Distal M1 occlusions without ICA involvement. The mRS distribution was not significantly different (generalized Wilcoxon test, $P = .48$). **(d)** M2 occlusion with or without ICA involvement. The mRS distribution was not significantly different (generalized Wilcoxon test, $P = .14$).

and IV tPA (alone) arms for both the primary effectiveness (50% [27 of 54] vs 64% [16 of 25], $P = .25$) and the safety end points (SICH, 7% [four of 54] vs 0% [zero of 25], $P = .30$; 90-day mortality, 2% [one of 54] vs 12% [three of 25], $P = .09$). Analysis of the full mRS distribution (Fig 3c) was also not significant ($P = .47$).

The M2 segment with or without ICA occlusion subgroup showed no treatment effect between the endovascular and IV tPA (alone) arms for both the primary effectiveness (50% [18 of 36] vs 44% [eight of 18], $P = .70$) and SICH end point (6% [two of 36] vs 11% [two of 18], $P = .59$). A trend in favor of endovascular treatment was seen for 90-day mortality (6% [two of 36] vs 33% [six of 18], $P = .012$). The analysis of the full mRS distribution (Fig 3d) was not significant ($P = .14$).

There were too few subjects in the subgroup with M3 and M4 involvement or anterior cerebral artery involvement with or without ICA occlusion ($n = 5$) and the subgroup with posterior circulation (basilar artery alone, vertebral artery and basilar artery, posterior cerebral artery) occlusion ($n = 9$) to make useful comparisons.

Discussion

This baseline CT angiography subgroup of the IMS III trial represents a large cohort of randomized subjects with prerandomization vascular imaging information. Few randomized acute stroke trials have served to capture baseline vascular imaging with standardized follow-up imaging, and none have involved comparison of IV tPA and IV tPA followed by endovascular therapy. This current analysis demonstrated no differences in the primary outcome measure for the prespecified subgroup of subjects with the proximal occlusion subgroup of ICA, M1, and basilar arteries as identified with baseline vascular imaging. However, in a post hoc analysis of the entire baseline CT angiography subgroup with an intracranial occlusion, a trend toward better outcomes with endovascular treatment versus IV tPA alone was observed. This effect was largely driven by the subpopulation of occlusions that involved the ICA (carotid T- and L-type or tandem ICA and M1 occlusions). In the subgroup of the trial with both baseline and 24-hour CT angiography information available, recanalization at 24 hours was significantly more frequent in the endovascular arm than the IV tPA arm. This difference was also most evident in subjects with ICA occlusions where a low rate of 24-hour recanalization was seen with IV tPA alone. The large differential recanalization and clinical treatment effects with endovascular treatment in tandem ICA and M1 occlusions or terminal ICA occlusions is the most important finding and implies that in future clinical trials, investigators should pay particular attention to this subgroup and perhaps even stratify enrollment on the basis of the presence of a carotid T- or L-type or tandem ICA and M1 occlusion (3).

Another important finding of this analysis was the safety (4) of baseline vascular imaging in reperfusion treatment trials of IV tPA versus combined therapy. No differences in clinical outcome were seen in the trial subgroup that received IV tPA alone and underwent CT angiography versus those that did not, suggesting no evidence for impaired thrombolytic effect of radiographic contrast material on tPA activity as postulated in the cardiac literature (5,6). Contrast material–induced nephropathy was not prominent, and no differences in creatinine levels were seen on day 5 or in discharge rates between those that underwent baseline CT angiography and those that did not.

A wide variability in the rate of recanalization and clinical outcome with IV tPA administration according to the specific site of occlusion has been reported previously in nonrandomized cohort studies (7–13). The IV tPA 1–2-hour recanalization rates for intracranial ICA occlusion have been reported as being very low (4%–8%) (7,10) with correspondingly low rates of 90-day good outcome (0%–29%) (3,12–15). Rates of recanalization for intracranial ICA occlusions exceed 50% after endovascular treatment (16). Good clinical outcome with endovascular treatment in ICA occlusions ranges from 10% to 56%. Cervical ICA occlusions are associated with better outcomes than terminal ICA occlusions (15). Isolated M1 occlusions fare much better with systemic thrombolysis alone, with 1–2-hour recanalization rates of 26%–32% (7,10) and good outcome in the 24%–67% range, depending on exact origin of occlusion within the M1 segment (13). Endovascular treatment has been associated with high rates of good clinical outcome in M1 occlusions (17,18). The differential effects of endovascular treatment according to the presence and site of occlusion are consistent with prior trials, such as the Echoplanar Imaging Thrombolytic Evaluation Trial, or EPITHET, where the ICA occlusion population had very poor outcomes despite undergoing IV tPA treatment (3). This analysis provides compelling data, from a randomized trial, that a treatment effect in favor of endovascular treatment over standard IV tPA may exist for ICA occlusions. The planned third International Stroke Trial, or IST-3, analysis of prerandomization vascular imaging data to compare IV tPA with placebo will provide an interesting set of data to compare with those in the IMS III (19).

On the basis of prior literature, the two unexpected results of the study were the high rates of good outcome with IV tPA alone in M1 occlusions and the lack of relationship between higher 24-hour recanalization and better rates of good outcome. Twenty-four–hour recanalization rates of M1 occlusions were similar and were high in the two treatment arms. Distal M1 occlusions did particularly well with IV tPA treatment alone, perhaps owing to smaller clot length. Very early treatment and larger sample sizes are likely to be required in future trials when comparing newer endovascular technologies (ie, stentrievers or aspiration) to IV tPA alone in M1 occlusions. The proximal occlusion subgroup had a 25% higher rate of 24-hour recanalization with endovascular therapy, but this translated into only a 3% higher rate of favorable clinical outcome. Patient selection (20,21), use of general anesthesia (22),

endovascular treatment delays (23), extent of reperfusion despite recanalization (24), and endovascular treatment-related adverse events are possible explanations that require further study. The 24-hour recanalization end point may also be too late and have less effect on clinical outcome than an early (1–2-hour posttreatment) recanalization or reperfusion end point.

This analysis of baseline CT angiography and recanalization has limitations. Only 47% of all enrolled subjects in the IMS III trial underwent baseline vascular imaging. Baseline CT angiography was performed in at least one subject at 78% of all enrollment sites in the trial. Although this subgroup may not fully represent the entire IMS III population, baseline characteristics were similar to those of the population who did not undergo baseline CT angiography, with the exception of shorter time to endovascular treatment. This reflects a bias that centers where baseline CT angiography is performed follow a direct to comprehensive stroke center model in which patients are transported directly to a hospital where they may undergo endovascular treatment. Pertaining to the 24-hour recanalization end point, some subjects did not undergo repeat CT angiography, potentially creating a bias toward those with higher recanalization rates and better outcomes among those well enough to undergo repeat imaging. Another limitation is the use of a nonstandardized assessment of CT angiography recanalization; no CT angiography–based recanalization scales have been published to date. We focused specifically on the proximal intracranial arterial occlusive lesion and not downstream lesions, which may have led to the overestimation of the degree of recanalization overall. We also cannot comment on tissue-based reperfusion because single-phase CT angiography is limited to a snapshot in time in the arterial or early venous phase of imaging. This is best accomplished with conventional angiography, time-resolved and/or multiphase CT angiography, or CT perfusion imaging.

We conclude from this analysis that no clear differences in outcome were identified in the population with proximal occlusion in the IMS III trial. A post hoc analysis of carotid T- or L-type occlusions and tandem ICA and M1 occlusions showed greater recanalization and a trend toward better outcomes with endovascular treatment compared with IV tPA alone. A pooled analysis of recently completed and current endovascular trials is needed to confirm this encouraging finding in favor of endovascular treatment. Future comparisons of endovascular and thrombolytic treatment with thrombolytic treatment alone should include baseline vascular imaging in trial design, given the safety of CT angiography and wide differences in clinical effects and recanalization according to occlusion site seen in the IMS III trial. In such trials, investigators could then stratify enrollment on the basis of the presence of a carotid T- or L-type occlusion or a tandem ICA and M1 occlusion.

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References

1. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368(10):893–903.
2. Khatri P, Hill MD, Palesch YY, et al. Methodology of the Interventional Management of Stroke III trial. Int J Stroke 2008;3(2):130–137.

3. De Silva DA, Brekenfeld C, Ebinger M, et al. The benefits of intravenous thrombolysis relate to the site of baseline arterial occlusion in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). Stroke 2010; 41(2):295–299.

4. Dzialowski I, Puetz V, Buchan AM, Demchuk AM, Hill MD; Calgary Stroke Program. Does the application of x-ray contrast agents impair the clinical effect of intravenous recombinant tissue-type plasminogen activator in acute ischemic stroke patients? Stroke 2012;43(6):1567–1571.

5. Dehmer GJ, Gresalfi N, Daly D, Oberhardt B, Tate DA. Impairment of fibrinolysis by streptokinase, urokinase and recombinant tissue-type plasminogen activator in the presence of radiographic contrast agents. J Am Coll Cardiol 1995;25(5):1069–1075.

6. Pislaru S, Pislaru C, Szilard M, Arnout J, Van de Werf F. In vivo effects of contrast media on coronary thrombolysis. J Am Coll Cardiol 1998;32(4):1102–1108.

7. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 1992;32(1):78–86.

8. Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007; 38(3):948–954.

9. Zangerle A, Kiechl S, Spiegel M, et al. Recanalization after thrombolysis in stroke patients: predictors and prognostic implications. Neurology 2007;68(1):39–44.

10. Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke 2010;41(10): 2254–2258.

11. Hirano T, Sasaki M, Mori E, et al. Residual vessel length on magnetic resonance angiography identifies poor responders to alteplase in acute middle cerebral artery occlusion patients: exploratory analysis of the Japan Alteplase Clinical Trial II. Stroke 2010;41(12): 2828–2833.

12. Linfante I, Llinas RH, Selim M, et al. Clinical and vascular outcome in internal carotid artery versus middle cerebral artery occlusions after intravenous tissue plasminogen activator. Stroke 2002;33(8):2066–2071.

13. Saarinen JT, Sillanpää N, Rusanen H, et al. The mid-M1 segment of the middle cerebral artery is a cutoff clot location for good outcome in intravenous thrombolysis. Eur J Neurol 2012;19(8):1121–1127.

14. Paciaroni M, Balucani C, Agnelli G, et al. Systemic thrombolysis in patients with acute ischemic stroke and Internal Carotid ARtery Occlusion: the ICARO study. Stroke 2012; 43(1):125–130.

15. Mokin M, Kass-Hout T, Kass-Hout O, et al. Intravenous thrombolysis and endovascular therapy for acute ischemic stroke with internal carotid artery occlusion: a systematic review of clinical outcomes. Stroke 2012;43(9):2362–2368.

16. Flint AC, Duckwiler GR, Budzik RF, Liebeskind DS, Smith WS; MERCI and Multi MERCI Writing Committee. Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials. Stroke 2007; 38(4):1274–1280.

17. Toyota S, Sugiura S, Iwaisako K. Simultaneous combined intravenous recombinant tissue plasminogen activator and endovascular therapy for hyperacute middle cerebral artery M1 occlusion. Interv Neuroradiol 2011; 17(1):115–122.

18. Cohen JE, Rabinstein AA, Ramirez-de-Noriega F, et al. Excellent rates of recanalization and good functional outcome after stent-based thrombectomy for acute middle cerebral artery occlusion. Is it time for a paradigm shift? J Clin Neurosci 2013;20(9):1219–1223.

19. Wardlaw JM, von Kummer R, Carpenter T, et al. Protocol for the perfusion and angiography imaging sub-study of the Third International Stroke Trial (IST-3) of alteplase treatment within six-hours of acute ischemic stroke. Int J Stroke 2013 Jan 22. [Epub ahead of print]

20. Morais LT, Leslie-Mazwi TM, Lev MH, Albers GW, Yoo AJ. Imaging-based selection for intra-arterial stroke therapies. J Neurointerv Surg 2013;5(Suppl 1):i13–i20.

21. Demchuk AM, Menon B, Goyal M. Imaging-based selection in acute ischemic stroke trials - a quest for imaging sweet spots. Ann N Y Acad Sci 2012;1268:63–71.

22. Abou-Chebl A, Lin R, Hussain MS, et al. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke: preliminary results from a retrospective, multicenter study. Stroke 2010;41(6):1175–1179.

23. Mazighi M, Chaudhry SA, Ribo M, et al. Impact of onset-to-reperfusion time on stroke mortality: a collaborative pooled analysis. Circulation 2013;127(19):1980–1985.

24. Jayaraman MV, Grossberg JA, Meisel KM, Shaikhouni A, Silver B. The clinical and radiographic importance of distinguishing partial from near-complete reperfusion following intra-arterial stroke therapy. AJNR Am J Neuroradiol 2013;34(1):135–139.