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The Growth Rate of Early DWI Lesions is Highly Variable and Associated with Penumbra Salvage and Clinical Outcomes Following Endovascular Reperfusion

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Abstract

Importance—The degree of variability in the rate of early DWI expansion in acute stroke has not been well characterized.

Objective—We hypothesized that patients with slowly expanding DWI lesions would have more penumbral salvage and better clinical outcomes following endovascular reperfusion than patients with rapidly expanding DWI lesions.

Methods—In the first part of this substudy of DEFUSE 2, growth curves were constructed for patients with >90% reperfusion and <10% reperfusion. Next, the initial growth rate was determined in all patients with a clearly established time of symptom onset, assuming a lesion volume of 0ml just prior to symptom onset. Patients who achieved reperfusion (>50% reduction in PWI after endovascular therapy), were categorized into tertiles according to their initial DWI growth rates. For each tertile, penumbral salvage (comparison of final volume to the volume of PWI (Tmax > 6 sec)/ DWI mismatch prior to endovascular therapy), favorable clinical response (NIHSS improvement of ≥ 8 points or 0-1 at 30 days), and good functional outcome (90 day modified Rankin score of ≤ 2) were calculated. A multivariate model assessed whether infarct growth rates were an independent predictor of clinical outcomes.

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Disclosures

G. Albers has equity interest in iSchemaView and has worked as a consultant for Covidien and Stryker. R Bammer has equity interest in iSchemaView. G. Zaharchuk receives modest research funding support from GE Healthcare. All other authors report no conflicts of interest.

Results—65 patients were eligible for this study; the median initial growth rate was 3.1 ml/hr (IQR 0.7-10.7). Target mismatch patients (n=42) had initial growth rates that were significantly slower than the growth rates in Malignant profile (n=9) patients ($p < 0.001$). In patients who achieved reperfusion (n=38), slower early DWI growth rates were associated with better clinical outcomes ($p < 0.05$) and a trend toward more penumbral salvage (n=31, $p = 0.103$). A multivariate model demonstrated that initial DWI growth rate was an independent predictor of achieving a 90 day modified Rankin score of ≤ 2 .

Conclusions—The growth rate of early DWI lesions in acute stroke patients is highly variable; Malignant profile patients have higher growth rates than patients with Target mismatch. A slower rate of early DWI growth is associated with a greater degree of penumbral salvage and improved clinical outcomes following endovascular reperfusion.

Introduction

Several previous studies have suggested that initial DWI lesion volume is an independent predictor of clinical outcomes.^{1, 2, 3, 4} However, the baseline DWI volumes have not been obtained at uniform time points in these studies and many patients are categorized based on the time the patient was last seen well, rather than the time of symptom onset. Some studies have suggested that DWI lesions can remain stable for several hours⁵; however, the clinical implication of the growth rate of early DWI lesions has received little attention. For example, a DWI volume of 25 ml might have a different prognosis if it is obtained 1 hour after symptom onset (indicating rapid DWI growth) compared to that same DWI volume obtained 8 hours after symptoms onset.

If early DWI growth rates vary substantially between patients, they could have important therapeutic implications. For example, if a patient has developed a very large DWI lesion within 2 hours of symptom onset they may be less likely to respond favorably to reperfusion therapy. In contrast, later arriving patients with large vessel occlusion that have small DWI lesions appear to respond favorably to reperfusion.⁶ Furthermore, since the time between initiating a reperfusion therapy and when reperfusion actually occurs may be substantial, patients with rapidly growing DWI lesions may have more DWI expansion, and therefore potentially less penumbral salvage, compared to those with slower growing lesions.

Recent studies have shown that patients with different MRI profiles have a differential clinical response following early reperfusion.^{3, 7} In particular, patients with the Target mismatch profile have shown favorable clinical responses in association with reperfusion while patients with the Malignant profile had unfavorable responses.⁸

We hypothesized that the duration of growth would be much shorter for patients with $>90\%$ reperfusion, rendering divergent growth curves in patients with and without successful reperfusion. We hypothesized that growth rates would be highly variable between patients and that patients with the Malignant profile would have significantly larger growth rates than patients with the Target mismatch profile. We also hypothesized that patients with slowly expanding DWI lesions would have more penumbral salvage and better clinical outcomes following endovascular reperfusion than patients with rapidly expanding DWI

lesions. In addition we investigated whether DWI growth rates are an independent predictor of clinical outcomes.

Methods

This is a substudy of DEFUSE 2.³ DEFUSE 2 was a multicenter cohort study of consecutive patients scheduled to undergo endovascular therapy within 12 hours of stroke onset. MRI scans with diffusion and perfusion imaging were obtained immediately prior to the endovascular procedure as well as post-procedure and at 5 days. We included all DEFUSE 2 patients in the MRI profile cohort who had technically adequate baseline DWI and PWI imaging, early follow-up imaging after attempted endovascular reperfusion, and 5 day FLAIR imaging available. The initial portion of this study focused on attempting to characterize a representative growth curve for patients with either successful reperfusion or failed reperfusion; therefore, patients with either <10% or >90% reperfusion were included in Part 1. Later portions of this study focused on the initial growth rate; in order to most accurately quantify the time between stroke onset and the initial MRI scan, only patients with witnessed onset of symptoms were included in Part 2-4 of the study. Patients with wake-up strokes or unclear onset of presenting signs were excluded from these portions.

The DEFUSE 2 MRI protocols have been previously reported.³ DWI and PWI maps and lesion volumes were initially generated using a fully automated software program (RAPID).⁹ A systematic procedure was utilized to obtain DWI volumes for this sub-study using the medical imaging software mipav (<http://mipav.cit.nih.gov/>). A semi-automatic application of the program was utilized to verify and correct the RAPID-generated volume estimations for each DWI lesion. The process involved using a standard window and leveling function, followed by a manual determination of a mask for each lesion. The program “Paint” function allowed for most lesions to be outlined by the program in 1-2 mouse clicks on the area of the lesion. Following independent assessment of each DWI volume, comparisons of agreement were made between two DEFUSE 2 core lab members (HMW and MI). Volumes that differed by > 5cc and > 10% were re-analyzed and a consensus agreement was reached.

Part 1 Lesion Growth Curve Fitting

For this portion of the analysis, patients from the DEFUSE 2 dataset were included if they had >90% reperfusion or <10% reperfusion, representing successful and failed endovascular reperfusion. The goal of this portion of the study was to compare representative growth curves in these two subsets of patients. We hypothesized that the ischemic lesions would grow monotonically from zero at onset to reach an asymptote and that the asymptote volume would be lower, and reached earlier, in patients with > 90% reperfusion compared with <10% reperfusion. We also hypothesized that the growth curves for patients with <10% reperfusion would exhibit linear, or nearly linear, DWI growth during at least the first 8 hours after symptom onset. Furthermore, if this assumption of “early linear growth” could be established for patients with <10% reperfusion, then we would assume that lesion growth during the initial hours prior to reperfusion could be estimated using a linear growth rate for all patients. In patients with <10% reperfusion, we used the baseline DWI lesion, early-

follow up DWI lesion, and 5 day FLAIR lesion volumes, as well as a volume of zero at time of symptom onset, to model lesion growth curves. For patients with >90% reperfusion, we used lesion volumes of the DWI at baseline and FLAIR at day 5, as well as a starting volume of zero, to model lesion growth curves. The early follow-up DWI outlined lesion volume was not used in patients with successful reperfusion, due to the issue of transient reversal following endovascular reperfusion.¹⁰ We used a Simfit program v6.9.3 (W.G. Bardsley, University of Manchester, U.K.), which fits $y=f(t)$ by weighted least squares as given by the following generalized parametrization for monotonic growth model: $f(t)=B(1)\{1-\exp[-k(1)t]\} + \dots + B(n)\{1-\exp[-k(n)t]\}$. Using values produced by the program's formulas for the fitting curves, we estimated the lesion volumes at each hour for the first 24 hours from onset, and then every 12 hours up to 5 days from onset for each patient. From there, we estimated mean values and 95% CI of the lesion volumes at each timepoint for both reperfusion groups (>90 and <10%) and plotted lesion growth curves based on those values.

Part 2 Initial DWI Growth Rates

Part 1 results demonstrated that the early growth curves for patients with <10% reperfusion exhibited nearly linear DWI growth during the first 8 hours after symptom onset. Therefore, for the subsequent parts of the study, the initial DWI growth rates for all patients were determined using the baseline DWI volume divided by the time between symptom onset and the MRI (this approach assumes a DWI volume of 0 just prior to symptom onset). Initial growth rates (median, range and IQR) were determined and compared for patients with Target Mismatch patients and Malignant profile patients. The Target Mismatch Profile is thought to represent a favorable profile, with a perfusion lesion that is more than 1.8 times larger than the diffusion (with an absolute difference greater than or equal to 15 ml), a diffusion lesion that is less than 70 ml, and a $T_{max}>10\text{sec}$ less than 100 ml. The Malignant Profile is defined by a baseline DWI greater than 70 ml and/or a $T_{max}>10\text{sec}$ that is more than 100 ml.

Part 3 Clinical Outcomes and Penumbra Salvage following Reperfusion

The baseline perfusion images were compared with the post-procedure images to determine whether early reperfusion was achieved. Reperfusion was defined as a >50% reduction in PWI ($T_{max}>6\text{sec}$) lesion volume between the baseline and early follow-up MRI. If the early follow-up study was of insufficient quality, not obtained, or obtained >18 hours from end of the endovascular procedure, then reperfusion was based on angiographic criteria (perfusion reestablished to >50% of the territory supplied by the occluded vessel at completion of the angiographic procedure).

The volume of the ischemic lesion on day 5 was determined by manual outlining of the lesion on FLAIR. This volume was subsequently adjusted to exclude intracerebral hemorrhage and cytotoxic edema using a validated technique to determine the final infarct volume.¹¹

Patients who achieved successful reperfusion were categorized into tertiles according to their initial DWI growth rates. For each tertile, penumbral salvage was calculated using a

comparison of final lesion volume to the baseline volume of PWI ($T_{max} > 6$ sec), divided by (PWI-DWI) mismatch prior to endovascular therapy. Additionally, rates of favorable clinical response (FCR) at 30 days and good functional outcome (GFO) at 90 days were calculated. Favorable clinical response was defined as greater than 8 points improvement in NIHSS or a score of 0-1 at 30 days; good functional outcome was defined as mRS of 0-2 at 90 days.

Part 4 Multivariable Analysis

A multivariable model was generated to determine if initial DWI growth rate was an independent prediction of clinical outcomes (both FCR at 30 days and GFO at 90 days were assessed). Based on the results of the primary DEFUSE 2 multivariable analysis, we controlled for both age and DWI volume at baseline and kept in the model only significant at $\alpha < 0.05$ variables. Other variables included in the analysis were baseline $T_{max} > 6$ sec and baseline $T_{max} > 10$ sec. Initial growth rate was analyzed as a continuous variable.

Results

Part 1

Ten patients with $<10\%$ reperfusion and 31 patients with $>90\%$ reperfusion were eligible for this analysis and had SimFit-generated growth curves created; the baseline characteristics of these patients are presented in Table 1. After generation of individual curves, a representative curve was created for each of the two subgroups in the manner described above. Examination of the growth curves in patients with $>90\%$ reperfusion and $<10\%$ reperfusion show the two curves initially travel together in an approximately linear fashion, and then begin to diverge at less than 10 hours post-onset.

The baseline PWI for both sets of patients was roughly 80 ml. However, the non-reperusers reached an asymptote of about 100ml, whereas the reperusers reached an asymptote of just over 40 ml. Of note, while the reperusers diverge from the initially linear growth and quickly level out at their asymptote, the non-reperusers continue to grow rapidly for nearly 24 hours post-onset and demonstrate near-linear growth during the first 8 hours. Comparing the two curves via the Kolmogorov-Smirnov test shows a significant difference between the two distributions ($p < 0.001$).

Part 2

65 patients were eligible for this portion of the study and their baseline characteristics are presented in (Table 2). Initial growth rates are shown in Figure 2 (plot of all). Overall, these patients had a median initial growth rate of 3.1 ml/hr (IQR 0.7-10.7). The initial growth rate ranged from 0 to 117 ml/hr. Target mismatch patients ($n=42$) had a median initial growth rate of 2.9 ml/hr (IQR 0.7-6.2) with a range of 0 to 42 ml/hr. This was significantly less ($p < 0.001$) than the initial growth rates in Malignant profile ($n=9$) patients, who had a median growth rate of 43.9 ml/hr (IQR 25.6-50.9). Malignant profile patients had a range of initial growth rates from 12.5 to 117 ml/hr. Of the 9 patients identified by the DEFUSE investigators as having the Malignant profile, the five with the largest initial DWI lesions (all >100 ml) also had the fastest initial growth rates (ranging from 44 ml/hr to as high as 117

ml/hr). These five patients also had very large Tmax(>10sec) lesion volumes (all >100ml). (see Table 2a).

An evaluation of initial growth rates stratified by vessel occlusion shows 19 patients with ICA occlusion had a median initial growth rate of 6.2 ml/hr (ICR, 2.8-12.7) and range 0-117, 33 patients with MCA-M1 occlusion had a median initial growth rate of 2.9 ml/hr (ICR, 1.3-7.6) and range 0- 50.9, and 10 patients with MCA (distal) occlusion had a median initial growth rate of 0.4 ml/hr (IQR, 0-6.5) and range 0-51.1. These were evaluated for a difference between groups ($p=0.085$, Kruskal-Wallis test) and for trend ($p=0.022$, Jonckheere-Terpstra Test). One patient did not have angiographic images obtained due to the groin bleeding; two patients did not have lesions.

Part 3

Thirty-eight patients achieved successful reperfusion and were eligible for this analysis (Table 3); the median initial growth rate in these patients was 3.3 ml/hr (IQR 1.7-12.0). The initial growth rate in these patients ranged from 0 to 117 ml/hr. The 12 patients in tertile 1 (the slowest growth tertile) had a median growth rate of 0.7 (range 0.0 to 2.0 ml/hr), the 13 patients in tertile 2 had a median rate of 3.2 (range 2.0 to 6.2 ml/hr), and the 13 patients in tertile 3 had a median rate of 18.3 (range 7.5 to 117 ml/hr). In patients with the slowest initial growth rate (tertile 1), 83% achieved a favorable clinical response at 30 days and 75% achieved good functional outcome at 90 days. Fiftyfour percent of patients in the middle growth tertile achieved a favorable clinical response at 30 days and 39% achieved good functional outcome at 90 days. Of the patients in the fastest growth tertile, 31% achieved a favorable clinical response at 30 days and 15% achieved good functional outcome at 90 days (see figure 3) (FCR30: $p=0.042$ Fisher's Exact & $p=0.010$ Cochran-Armitage trend test; GFO90: $p=0.013$ & $p=0.004$ respectively),

Patients in the tertile 1 ($n=10$) had a median penumbral salvage of 88% (IQR 27-99), patients in the tertile 2 ($n=11$) had a median penumbral salvage of 80% (IQR 45-94), and patients in tertile 3 ($n=10$) had a median penumbral salvage of 31% (IQR -14-68); $p=0.103$, Jonckheere-Terpstra Test for ordered alternatives.

Part 4

We found that age at enrollment was a significant independent predictor of attaining Rankin of 3-6 at 90 days (Poor Functional Outcome); OR 1.12, CI (1.03-1.23) for each year of age. The initial DWI growth rate was also a significant independent predictor of attaining Poor Functional Outcome; OR 1.51 (1.06-2.14) for each ml/hr increase in growth rate. Interpretation of the odds ratio suggests that there is a 50% increase in the odds of achieving poor functional outcome for each 1 ml/hr increase in growth rate. For Favorable Clinical Response, initial growth rate was not found to be a significant independent predictor of not achieving a favorable clinical response. Age at enrollment was an independent predictor; OR 1.05 (1.00-1.10), as was the baseline DWI volume; OR 1.05 (1.00- 1.09).

Discussion

The analysis of mean lesion growth in patients who achieved >90% vs. <10% reperfusion demonstrates substantially different ischemic lesion evolution. Infarct growth ceased more rapidly and final lesion volumes were considerably lower in patients with >90% reperfusion. For patients with <10% reperfusion, the ischemic lesions typically grew rapidly (including many hours of near linear growth) for the first 24 hours; they subsequently continued to grow, but at a much lower rate over the next 24-48 hours. These data are compatible with a serial MRI study in untreated patients that demonstrated a relatively consistent pattern of growth for 3 days with maximum lesion volumes attained at a mean of 74 hours after symptom onset.¹² While the growth in the <10% reperfusion group typically did not follow linear trajectory for an extended period of time, it is evident that the natural history of stroke evolution in these patients without reperfusion is for continued growth for many hours beyond the hyper-acute period. Additionally, examining the two representative curves shows an initially rapid, nearly equivalent, and approximately linear growth in both subsets of patients, which lasted for several hours after stroke onset. From the DEFUSE 2 main study, the median time from symptom onset to baseline DWI was 4.6 hours in Target Mismatch patients (IQR 3-6.7 hours) and 3.6 hours in non-Target Mismatch patients (IQR 2.5-4.9 hours).³ Thus we suspect that the majority of patients were following this initially linear trajectory at the time of the baseline DWI.

The growth rate of early DWI lesions in acute stroke patients is highly variable ranging from 0 ml/hr to as high as 117 ml/hr. Patients with the Malignant profile have very high growth rates which is likely related to the fact that this profile is defined in part by large initial DWI volumes. These patients also had very large volumes of Tmax > 10 sec perfusion lesions which have been shown to correlate with poor collaterals on conventional angiography¹⁴ and are likely to account for the accelerated DWI growth. However, even among patients with the Target Mismatch profile, growth rates were highly variable. Growth rates also varied considerably for patients who had occlusions of the same vessel. This variability is likely mediated by the adequacy of collateral blood flow as well as genetic factors and the metabolic milieu of individual stroke patients.

The clinical outcomes following reperfusion were significantly better in patients with lower growth rates. A similar trend was present even when the analysis was restricted to patients with the Target mismatch profile. We hypothesized that patients with higher growth rates would have less penumbral salvage because substantial additional growth might occur between the time of the baseline MRI and when reperfusion was obtained. We demonstrated that patients in the highest growth tertile had about half as much penumbral salvage compared with patients in the 2 lower growth tertiles.

The sample size of this study is small and therefore conclusions about the relationships between infarct growth and functional outcomes require confirmation in larger studies. In addition, the clinical characteristics of the patients with high, medium and low growth rates differed considerably (Table 3). These differences may have contributed to the difference in clinical outcomes observed. The multivariate analysis was performed to account for these imbalances but may not adequately control for these differences due to the limited sample

size. To estimate early growth rate, we assumed an infarct volume of 0 mL just prior to symptom onset; we cannot be certain that the DWI lesion growth did not begin sometime before symptom onset, nor can we determine at what time after symptom onset the DWI lesions first become apparent. Additionally, early infarct growth was modeled as a linear function, an assumption that was based on the shape of the DWI growth curves generated in Part 1 of this study. We had limited data points to utilize during the early hours of stroke evolution; therefore our finding of near-linear early growth should be confirmed by studies which obtain repeated DWI images in the first hours after symptoms onset in a large group of patients at pre-specified time points. Therefore, we are cautious about drawing conclusions regarding the prognostic value of the early growth rate. Additionally, given that this was a selected patient population we are unable to generalize the results to a broader population. Further studies to confirm that rate of early infarct growth has prognostic significance, independent of DWI volume, are warranted.

In conclusion, the growth rate of early DWI lesions in the DEFUSE 2 patients was highly variable. A slower rate of DWI growth was associated with a greater degree of penumbral salvage and improved clinical outcomes following reperfusion. These findings suggest that an assessment of acute infarct growth rates could help identify patients who are most likely benefit from reperfusion therapies.

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Figure 1.
Predicted growth curves for patients with <10% reperfusion vs. >90% reperfusion.
Kolmogorov-Smirnov test shows a significant difference between the two distributions ($p < 0.001$).

Figure 2.

Initial DWI growth rate for the 65 patients with known time of stroke onset. Graphed based on the assumption of infarct volume of 0 ml just prior to symptom onset and linear growth (based on initial findings in Part I of this study). Overall, median initial growth rate was 3.1 ml/hr, with a range from 0 ml/hr to 117 ml/hr.

Figure 3.

Initial DWI growth rates and clinical and radiographic outcomes. Thirty-eight patients with successful reperfusion divided into three statistical tertiles to evaluate for association of initial growth rate and patient outcomes. Tertile 1 represents the slowest initial growth rate tertile (median initial growth rate 0.7 ml/hr). Tertile 2 is the middle growth tertile (median initial growth rate 3.2 ml/hr). Tertile 3 is the fastest growth tertile (median initial growth rate 18.3 ml/hr). Cochran-Armitage trend test shows $p = 0.010$ for Favorable Clinical Response. Cochran-Armitage trend test shows $p = 0.004$ for Good Functional Outcome. Mann-Whitney U Test comparing 1st and 2nd tertiles to 3rd tertile shows $p = 0.057$ for percent penumbral salvage.

Table 1

	>90% Reperfusion	< 10% Reperfusion
CHARACTERISTICS	(n=31)	(n=10)
Age - mean (SD)	66 (15)	59 (16)
Male sex - no. (%)	13 (42)	8 (80)
Caucasian - no. (%)	26 (84)	8 (80)
TMM by Investigator - no. (%)	24 (77)	13 (81)
Baseline NIHSS - med (IQR)	16 (11-20)	13.5 (11-16)
COMORBIDITIES - no. (%)		
Previous MI	0 (0)	0 (0)
Hypertension - no. (%)	18 (58)	1 (10)
Atrial Fibrillation	12 (38)	3 (30)
Diabetes	6 (19)	2 (20)
Hyperlipidemia	11 (35)	8 (80)
VOLUMES (ml) - med (IQR)		
Baseline DWI	13 (5-35)	15 (6-56)
Baseline PWI tmax6	79 (54-115)	75 (50-106)
Follow-up DWI	14 (5-42)	40 (14-121)
Follow-up PWI tmax6	0 (0-4)	84 (50-155)
5 day FLAIR	24 (13-67) *	52 (37-148) **
TREATMENTS - no. (%)		
IA tPA	14 (45)	5 (31)
Merci	18 (58)	5 (31)
Penumbra	11 (35)	9 (56)
Other	13 (42)	4 (25)

*
n=29**
n=9

Table 2

CHARACTERISTICS	
Age - mean (SD)	66 (16.6)
Male sex - no. (%)	34 (52.3%)
White ethnicity - no. (%)	53 (81.5%)
COMORBIDITIES	
Previous MI - no. (%)	9 (13.8%)
Hypertension - no. (%)	47 (72.3%)
Atrial Fibrillation - no. (%)	21 (32.3%)
Diabetes - no. (%)	14 (21.5%)
Hyperlipidemia - no. (%)	34 (52.3%)
VOLUMES - median (IQR), ml	
Baseline DWI	11.6 (3.9-33.3)
Baseline PWI tmax6	88.5 (44.9-119.4) ***
Baseline PWI tmax10	31.1 (14.0-51.1) ***
Follow-up DWI	20.6 (8.4-75.2)
Follow-up PWI tmax6	30.1 (4.1-75.3) **
Follow-up PWI tmax10	9.1 (0.0-30.6) **
5 Day FLAIR (corrected)	44.3 (13.0-78.6) ^{††}
REPERFUSION	
IV tPA pretreatment - no. (%)	44 (67.7%)
TMM by Investigator - no. (%)	42 (71.2%) **
Number with Reperfusion - no. (%)	38 (61.3%) *
Percent Reperfusion - median (IQR)	59.6 (15.4-93.7) [†]
TIME - median (IQR), hours	
Onset to MRI	3.7 (2.7-4.7)
MRI to Cathlab	0.6 (0.5-0.8)
Angiography to Early Follow-up MRI	2.7 (1.2-5.4)
Onset to FLAIR	115.4 (86.1-129.6)
OUTCOMES	
Favorable Clinical Response (30d) - no. (%)	37 (56.9%)
Good Functional Outcome (90d) - no. (%)	24 (36.9%) [†]

*
n=62**
n=59***
n=58[†]
n=52

^{††}
^{††}n=46

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Table 2a

Malignant Profile Patient	Baseline DWI Volume (ml)	Initial Growth Rate	Tmax(>10sec) (ml)
* 1	60.8	12.7	64.2
2	76.8	12.5	No Baseline PWI
3	81.1	25.6	103.8
4	89.7	35.2	89.6
5	106.2	43.9	124.9
6	114.5	50.9	112.7
7	143.2	51.1	101.5
8	189.5	49.4	108.4
9	393.3	116.8	172

* Malignant status per initial clinician designation. This patient had DWI lesion >70ml based on B100 map, but < 70ml based on RAPID ADC threshold (<600).

Table 4

CHARACTERISTICS	Tertile 1 (n=12)	Tertile 2 (n=13)	Tertile 3 (n=13)
Age - mean (SD)	65 (21)	62 (18)	63 (14)
Male sex - no. (%)	3 (25)	7 (54)	7 (54)
Caucasian - no. (%)	10 (83)	12 (92)	11 (85)
TMM by investigator *	10 (100) *	12 (100) ***	6 (50) ***
COMORBIDITIES - no. (%)			
Previous MI	1 (8)	3 (23)	1 (8)
Hypertension - no. (%)	6 (50)	9 (69)	11 (85)
Atrial Fibrillation	6 (50)	3 (23)	4 (31)
Diabetes	0 (0)	3 (23)	3 (23)
Hyperlipidemia	4 (33)	7 (54)	5 (39)
VOLUMES (ml) - med (IQR)			
Baseline DWI ††	4 (0-7)	12 (10-13)	61 (39-90)
Baseline PWI tmax6 ††	66 (54-88) *	87 (70-108) ***	133 (105-165) ***
Follow-up DWI ††	5 (4-12)	18 (11-33)	75 (57-107)
Follow-up PWI tmax6 ††	5 (2-8)	15 (0-29) ***	43 (4-52)
5 day FLAIR ††	16 (4-42) *	35 (14-54) **	110 (83-135) *
REPERFUSION - no. (%)			
IA tPA	6 (50)	6 (46)	3 (23)
Merci	8 (67)	7 (54)	6 (46)
Penumbra	4 (33)	3 (23)	6 (46)
Other	4 (33)	4 (31)	6 (46)
CLASSIFICATION - no. (%)			
TIMES (hr) - med (IQR)			
Onset to Baseline MRI †	4.7 (3.9-6.3)	3.6 (2.4-4.5)	3.0 (2.8-3.7)
Baseline MRI to Cath Lab	0.7 (0.5-0.8)	0.6 (0.5-0.7)	0.6 (0.5-0.7)
Angiography to Early Follow Up MRI	2.3 (1.1-4.2)	3.9 (2.5-5.7)	2.9 (2.0-9.5)
Baseline MRI to Early Follow Up MRI	3.1 (1.5-4.9)	4.4 (3.3-6.1)	3.5 (2.7-10.9)
Onset to FLAIR	105 (75-128)	121 (96-135) ***	116 (95-123) ***

*
n=10**
n=11***
n=12†
p<0.05 between tertiles††
p<0.05 for trend