Pre-existing Statin Use is Associated with Greater Reperfusion in Hyper-Acute Ischemic Stroke

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Abstract

Background and Purpose—Statin pretreatment has been associated with improved outcomes in patients with ischemic stroke. Although several mechanisms have been examined in animal models, few have been examined in patients. We hypothesized that patients using statins before stroke onset may have greater reperfusion than patients not using statins.

Methods—Acute ischemic stroke patients underwent two MR scans: within 4.5 (tp1) and at 6 hours (tp2) after stroke onset. Regions of reperfusion were defined by prolonged MTT at tp1 which normalized at tp2. Four MTT thresholds were assessed to ensure that results were not spuriously based on an arbitrary threshold. Baseline characteristics, relative reperfusion, and change in NIH Stroke Scale between tp1 and 1-month follow-up (ΔNIHSS) were compared between patients who were taking statins at stroke onset and those who were not.

Results—Thirty-one stroke patients were prospectively enrolled; 12 were taking statins, while 19 were not. Baseline characteristics did not differ between the two groups except the statin group had greater coronary artery disease (p=0.03). Patients using statins showed significantly greater reperfusion compared to untreated patients across all MTT thresholds. For MTT=4 seconds, median relative reperfusion was 50% (IQR 30%,56%) in the pre-existing statin group vs. 13% (IQR=5%,36%) in the untreated group, p=0.014. The statin group had greater ΔNIHSS (8.8±4.0 points) compared to the untreated group (4.4±5.7 points), p=0.028.

Conclusion—Statin use prior to ischemic stroke onset was associated with greater early reperfusion and NIHSS improvement. Further studies in larger populations are required to confirm our preliminary findings.

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Introduction

3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) are widely prescribed for the prevention of vascular events. The Stroke Prevention with Aggressive Reduction of Cholesterol Level (SPARCL) trial demonstrated that atorvastatin reduced risk of recurrent stroke by 16% compared to placebo[1]. In addition to having fewer events, patients taking atorvastatin showed a trend towards improved neurological outcomes at 90 days after their stroke outcome event[2]. Several additional studies have found that patients taking statins at the time of stroke onset had improved outcomes and lower mortality than those who were not taking statins[3–6]. Moreover, withdrawal of statins in patients admitted for ischemic stroke has been associated with worse neurological outcomes, greater early neurological deterioration, and larger infarct sizes[7].

While the neuroprotective mechanisms of statins in ischemia have not been fully elucidated, several potential roles in both animals and humans have been studied. In rodent models, statins have been shown to promote fibrinolysis, inhibit prothrombotic pathways, and limit infarct size[8–11]. In models of ischemia-reperfusion, statins have protected multiple organ systems against reperfusion injury[12, 13] and have augmented cerebral blood flow (CBF) secondary to upregulation of endothelial nitric oxide synthase (eNOS)[14], although such a CBF effect was not reproduced in humans with atherosclerotic carotid occlusion[15]. In other clinical studies, statin use was associated with greater recanalization in a cohort of ischemic stroke patients undergoing acute intervention[16], and in aneurysmal subarachnoid hemorrhage, patients treated with statins were less likely to develop vasospasm[17]. In several studies, the neuroprotective effects have been independent of cholesterol lowering[10, 11]. Given the potential vascular effects of statins in the setting of ischemia, we hypothesized that improved neurological outcomes observed with statin pretreatment may be related to greater reperfusion during the hyper-acute phase of ischemic stroke. Thus, we measured early reperfusion (within 6 hours of stroke onset) in acute ischemic stroke patients, comparing patients with pre-existing statin use to untreated patients.

Methods

Patients and Inclusion Criteria

This was a retrospective analysis of data from a prospectively collected observational study of serial MRI's performed in acute ischemic stroke patients at a large urban tertiary care referral center, admitting over 800 ischemic strokes per year. Data from the first 31 patients in this study (with planned enrollment of 75 patients) were used for a retrospective analysis of the effect of statins on reperfusion. After Institutional Review Board approval, the study enrolled consecutive patients within 4.5 hours of stroke onset based on the following pre-specified inclusion criteria: clinically-suspected acute cortical ischemic stroke; age $\geq$ 18 years; NIHSS $\geq$ 5; and patient or patient's next of kin capable of informed consent. Exclusion criteria included bilateral strokes or any acute endovascular or surgical intervention. Both tPA-treated and untreated patients were included. For patients receiving tPA, the study imposed no delay in time-to-tPA-treatment and no deviation from standard practices. The NIHSS was collected prospectively by a stroke neurologist on admission, at both imaging time points, and at one month follow-up. Clinical data including demographic data, past medical history, and home medications were obtained by the research coordinator prospectively during enrollment.

Magnetic Resonance Imaging Protocol

Patients were scanned with MRI within 4.5 hours (tp1) and at 6 hours (tp2) after stroke onset, on a 3T Siemens whole body Trio system with a circular polarized head coil. For patients receiving tPA, the tp1 scan was performed as soon as possible after tPA bolus. The protocol included diffusion-weighted images, FLAIR images [TR/TE=10000/115 ms; inversion time = 2500 ms; matrix=512×416; 20 slices, slice thickness (TH)=5mm], and dynamic susceptibility contrast (DSC) perfusion images with Gadolinium contrast injected at 5 ml/s with a power injector (a T2*-weighted gradient echo EPI sequence; TR/TE=1500/43 ms; 14 slices, TH=5mm, zero interslice gap; matrix=128×128). Magnetic resonance angiography (MRA) was not performed.

Data analysis

Mean transit time [MTT=cerebral blood volume (CBV)/CBF[18]] was chosen to define the perfusion deficit because MTT is uniform across gray and white matter (unlike CBF or CBV), allowing for use of a single threshold across both tissue types[19, 20]. Voxels within the middle cerebral artery (MCA) territory of the contralateral hemisphere were manually chosen to obtain an arterial input function. Six parameter rigid image registration was performed to align all images across both scans for each patient using FSL 3.2 (FMRIB, Oxford, UK)[21]. Accuracy of image registration was evaluated manually.

MTT prolongation for each voxel within the ischemic hemisphere was calculated as: [MTT of ischemic voxel] – [median MTT of contralateral hemisphere]. A voxel was defined as "prolonged" if MTT was ≥ a pre-defined threshold. Because the perfusion deficit volume varies depending on the MTT threshold chosen[22, 23], four MTT prolongation thresholds (3, 4, 5, and 6 seconds) were tested to determine if results were consistent across a range of putative thresholds. Prolonged MTT volumes provided measures of perfusion deficit volumes at tp1 and tp2. The absolute volume of reperfusion was calculated as: [prolonged MTT volume at tp1] – [prolonged MTT volume at tp2]. Subsequently, the relative volume of reperfusion was calculated as: [prolonged MTT at tp1 – prolonged MTT at tp2] / [prolonged MTT at tp1] (Figure 1). The individuals performing the reperfusion calculations were blinded to the treatment status of the patient. Isolated regions of abnormal perfusion < 1 ml were removed from the analysis to minimize inclusion of misregistered regions or noise-induced variations.

Statistical Analysis

Pre-existing statin use and untreated groups were compared using the Wilcoxon Rank Sum test for continuous variables except when data was Gaussian (confirmed by the Kolmogorov-Smirnov and D'Agostino-Pearson omnibus tests), where the t-test was used. Fisher's Exact test compared categorical baseline characteristics between the two groups. Alpha ≤ 0.05 was required for statistical significance. Statistical analyses were performed using STATA 10.1.

Statins and Relative Reperfusion

Relative reperfusion for each MTT threshold (3, 4, 5, and 6 seconds) was compared between the untreated and statin groups. In addition to the total group, the tPA-treated subgroup was analyzed to ensure that statin effects were not confounded by the higher proportion of statin patients receiving tPA. A linear regression model was developed as a prediction model for relative reperfusion based on the MTT=4 second threshold (as this is a commonly used threshold of ischemia in acute stroke literature). Predictors were selected with a forward stepwise procedure in which a p-value ≤ .20 was required for entry and p-value ≤ .05 was required to be retained in the model. At each step, regression diagnostics evaluated

distributional assumptions of the residuals and functional form of the covariates. Ten potential covariates were considered: pre-existing statin use, tPA treatment, volume of tp1 perfusion deficit (MTT=4sec), age, gender, admission NIHSS, admission mean arterial pressure (MAP), admission glucose, LDL, and time between tp1 and tp2 scans. Diffusion weighted imaging (DWI) volume at tp1 was considered for inclusion in the model, however, DWI volume demonstrated strong covariance (r=0.74, p<0.0001) with volume of tp1 perfusion deficit, leading to multi-collinearity. Therefore, we chose to include only volume of tp1 perfusion deficit in the model to control for baseline volume of initial ischemia. Model goodness-of-fit was assessed by Akaike's information criterion. Potential interactions between statin use and tPA treatment or MAP were assessed.

Statins and Neurological Improvement

Neurological improvement, as assessed by ΔNIHSS (NIHSS on admission - NIHSS at 1 month), was compared in the untreated and pre-existing statin use groups. This comparison was performed in all patients and in the tPA-treated subgroup. In the same way as described for relative reperfusion, a forward stepwise procedure for a linear regression model was created to identify which, of 10, baseline clinical variables predicted neurological improvement as measured by ΔNIHSS. Potential interactions between statin use and tPA treatment or age were assessed.

Results

Of 31 acute ischemic stroke patients enrolled, 12 were taking statins at stroke onset, while 19 were not. Patient demographics and baseline characteristics were not significantly different between the two groups except that the statin group had significantly more patients with a history of coronary artery disease (CAD) (p=0.03) (Table 1). Patients were imaged with MRI at 3.0±0.8 hours (tp1) and 6.4±0.4 hours (tp2) after onset. The co-registered images were well-aligned with the template images, yielding inaccuracies < three voxels in any direction. In order to assess whether the location of perfusion deficit territories were balanced between the untreated and pre-existing statin use groups, perfusion deficit territories based on tp1 MTT maps were assigned to one of four groups: 1) internal carotid artery (ICA), (2) complete MCA, (3) partial MCA, and (4) small MCA (Figure 2). There were no significant differences between the two groups.

To assess how representative our study population (N=31) was relative to our hospital stroke population (N=2057) over the 2.5 year enrollment time period, we compared characteristics of both groups. While age, gender, and race were similar, the mean NIHSS score was higher in the study cohort for non-tPA-treated patients. In addition, for tPA-treated patients, the mean door-to-needle time in the study cohort was shorter compared to the hospital tPA-treated patients (51 vs. 60 min, p=0.04). There was no difference is rate of symptomatic intracerebral hemorrhage (Online Supplementary Data).

Statin Use is Associated with Increased Relative Reperfusion

We compared relative reperfusion in the untreated group and statin group for each of four MTT thresholds to determine if findings were consistent across all MTT thresholds. Relative reperfusion was greater in the statin group compared with the non-statin group for all MTT thresholds (Figure 3a). Median reperfusion across the four MTT thresholds for the statin group was 48% (IQR 28%, 64%) and for the untreated group was 13% (IQR 4%, 35%).

Because tPA treatment was more common in the statin group, we performed the same analysis as above in the subset of 23 patients treated with tPA to determine if the statin effect persisted in this subgroup. We continued to observe greater relative reperfusion in the

statin group in three of the four MTT thresholds, with a strong trend for MTT=3 seconds (Figure 3b). For tPA-treated patients, median reperfusion across the four MTT thresholds for the statin group was 48% (IQR 26%, 56%) and for the untreated group, was 15% (IQR 2%, 30%).

A forward selection stepwise procedure determined which clinical variables best predicted early reperfusion after stroke. In addition to statin use, nine baseline variables which were hypothesized to possibly affect reperfusion were included (Table 1, top nine variables). Clinical variables which remained in the final model included: (1) statin use, β (SE) [regression coefficient (standard error)]=17.9(7.3), p=0.021; (2) volume tp1 perfusion deficit, β(SE) =−0.156(0.06), p=0.024; and (3) admission MAP, β(SE)=−0.318(0.15), p=0.040. The final model explained 41.1% of the variance in relative reperfusion (Table 2). Therefore, at stroke onset, statin use, smaller perfusion deficit, and lower blood pressure best predicted relative reperfusion.

Statin Use Predicts NIHSS Improvement

After assessing variables associated with reperfusion, we evaluated how pre-existing statin use may predict neurological improvement, defined by the absolute change in NIHSS from admission to one month follow-up (ΔNIHSS). ΔNIHSS was greater in the statin group, 8.8 ±4.0 (mean +/− SD) points, compared to the untreated group, 4.4±5.7 points, p=0.028 (Figure 4a). When, the tPA-treated subgroup (n=23) were evaluated in a separate analysis, ΔNIHSS continued to be greater in patients taking statins at stroke onset, 8.9±4.2 points, compared to those who were not 4.4±4.9 points, p=0.048 (Figure 4b).

A forward selection stepwise procedure was utilized to develop a prediction model of ΔNIHSS. Clinical variables which remained in the final model included: (1) pre-existing statin use, β(SE)=4.82(1.7), p=0.010 and (2) age, β(SE)= −0.163(0.06), p=0.015. In this model, statin use and younger age were associated with NIHSS improvement, together explaining 31.9% of the variance in ΔNIHSS (Table 2).

Discussion

Statins and Early Reperfusion

In this retrospective study of prospectively collected MRI data, patients using statins prior to stroke onset had 2-3-fold greater early reperfusion than patients not taking statins. This difference persisted across all MTT thresholds examined, indicating that regardless of how the perfusion deficit was defined (conservatively or liberally), statin use was associated with greater reperfusion. Given the increased frequency of tPA treatment in the statin group, we analyzed this group separately and found that statin use continued to be associated with greater relative reperfusion.

Based on vasculoprotective effects of statins, we hypothesized that early reperfusion may be responsible, in part, for the improved clinical outcomes seen in statin pretreated populations in large clinical trials. Regardless of statin type, animal studies have found decreased infarct size with statin pretreatment[10, 24]; however, pathways underlying this neuroprotection continue to be investigated. Potential mechanisms leading to early reperfusion fall into three broad categories: (1) improved blood flow / vasomotor reactivity, (2) anti-thrombotic effects, and (3) anti-inflammatory effects. Before cholesterol-lowering properties take effect, statins exert pleiotropic effects on the vascular wall, including the upregulation of endothelial nitric oxide synthase (eNOS), increasing nitric oxide production with resultant increased CBF[13, 14, 25]. Consistent with this mechanism, statins decreased perfusion deficits following rodent middle cerebral artery occlusion (MCAO)[26] and improved cerebral vasomotor reactivity in stroke patients undergoing SPECT imaging[27]. The anti-thrombotic

effects of statins act via increasing endogenous tPA levels[9] as well as by inhibiting plasminogen activator-1[8]. Moreover, increased nitric oxide leads to decreased platelet activation and aggregation[10]. Finally, the anti-inflammatory effect of statins was demonstrated in large clinical trials showing prevention of vascular events in patients with concurrent lowering of C-reactive protein[28, 29]. By inhibition of leukocyte and cytokine activation, statins mitigate ischemia-reperfusion injury and accordingly may prevent 'no-reflow', a phenomenon in which tissue reperfusion is not restored despite vessel recanalization[30, 31].

In a linear regression model, we identified three baseline variables which explained 41% of the variance in relative reperfusion: statin use, perfusion deficit volume at tp1, and baseline MAP. Our data suggests that larger perfusion deficits have relatively less reperfusion, a finding supported by a recent report in a smaller cohort of tPA-treated patients[32]. A smaller initial perfusion deficit may signify less clot burden, facilitating recanalization either spontaneously or in the presence of thrombolytics. Clinical studies demonstrated that larger perfusion lesions, baseline stroke severity, and large-vessel occlusion predicted infarct growth, stroke evolution, and early neurological deterioration[33, 34].

Our model revealed that higher blood pressure (BP) was significantly associated with less reperfusion. While several observational studies have associated elevated BP early after stroke onset with increased disability, several of these studies, including the International Stroke Trial, found a U-shaped curve in which low BP was also associated with poor outcomes[35]. Moreover, this negative relationship of BP and reperfusion opposes a common approach of stroke physicians to avoid BP lowering, especially in chronically hypertensive patients. In our sample, three (of seven) patients did not receive tPA due to elevated BP, suggesting the possibility of less reperfusion due to no tPA treatment; however, tPA was not a significant predictor of reperfusion in our sample; thus, the relationship between BP and reperfusion warrants further study.

We chose to use reperfusion determined by MTT as an outcome measure rather than recanalization (using MRA) because reperfusion is a more sensitive and quantitative measure than recanalization which relies on crude measures of stenosis. Studies have shown that recanalization may occur without tissue reperfusion due to proximal clot breakdown with distal embolization, and reperfusion may occur in the absence of recanalization likely due to collateral flow[36–38]. Moreover, a recent study comparing computed topography (CT) perfusion to CT angiography suggested that reperfusion more accurately predicted infarct volumes than recanalization[39].

Statins and Neurological Improvement

Pre-existing statin use predicted greater neurological improvement as measured by ΔNIHSS in the entire sample as well as in tPA-treated patients. In a multivariable model, besides statin use, lower age also predicted improved neurological status, a finding that was not surprising since age is one of the strongest predictors of disability after stroke[40, 41].

Our finding that statin pretreatment was associated with greater neurological improvement in NIHSS may be consistent with findings from several large clinical studies which found improved clinical outcomes in statin pretreated patients[2–6]. Besides vasculoprotective effects, statins have been reported to stimulate production of anti-apoptotic protein, Bcl-2, in neurons and human neuroblastoma cells[42, 43] and prevent glutamate-induced excitotoxicity in cortical neurons[44]. Statins administered within one day of stroke were found to improve synaptogenesis, neurogenesis, and angiogenesis in a rodent MCAO model[45].

Our study has several limitations. Limited sample size may result in type II errors due to insufficient power. Although the study was prospective, there was no randomization of treatment, which may lead to selection bias. The treatment groups were unblinded; however, the investigators performing the reperfusion analysis were blinded to the clinical data. We obtained information on statin use from patients and family without independent confirmation. Patients using statins received more tPA than the untreated patients (though not statistically significant), so we performed the analysis in the tPA-treated subgroup to eliminate tPA as an independent variable, and found similar results. Ideally, the study would be repeated with a larger sample of non-tPA treated patients. We identified greater CAD in the statin group, as might be expected since CAD is a major indication for statin use. This imbalance may have introduced bias favoring reperfusion due to better medical care prior to stroke onset or limiting reperfusion due to greater medical comorbidities in CAD patients. Our study cohort included strokes of greater severity compared to the hospital stroke patients admitted to our institution; therefore, our results cannot be directly applied to patients with low stroke severity. Furthermore, our study did not include MRA which would have given information about site of occlusion and degree of recanalization. However, by evaluating the location of the tp1 perfusion deficit territories, we did not find any significant imbalance between the two groups (Figure 2), suggesting that bias due to unequal distribution of occlusion sites is less likely.

Conclusions

Pre-existing statin use was associated with greater reperfusion and neurological improvement, raising the hypothesis that statin pretreatment may improve clinical outcomes after stroke by enhancing early reperfusion. Due to the small patient sample with non-randomized treatment, further studies are required to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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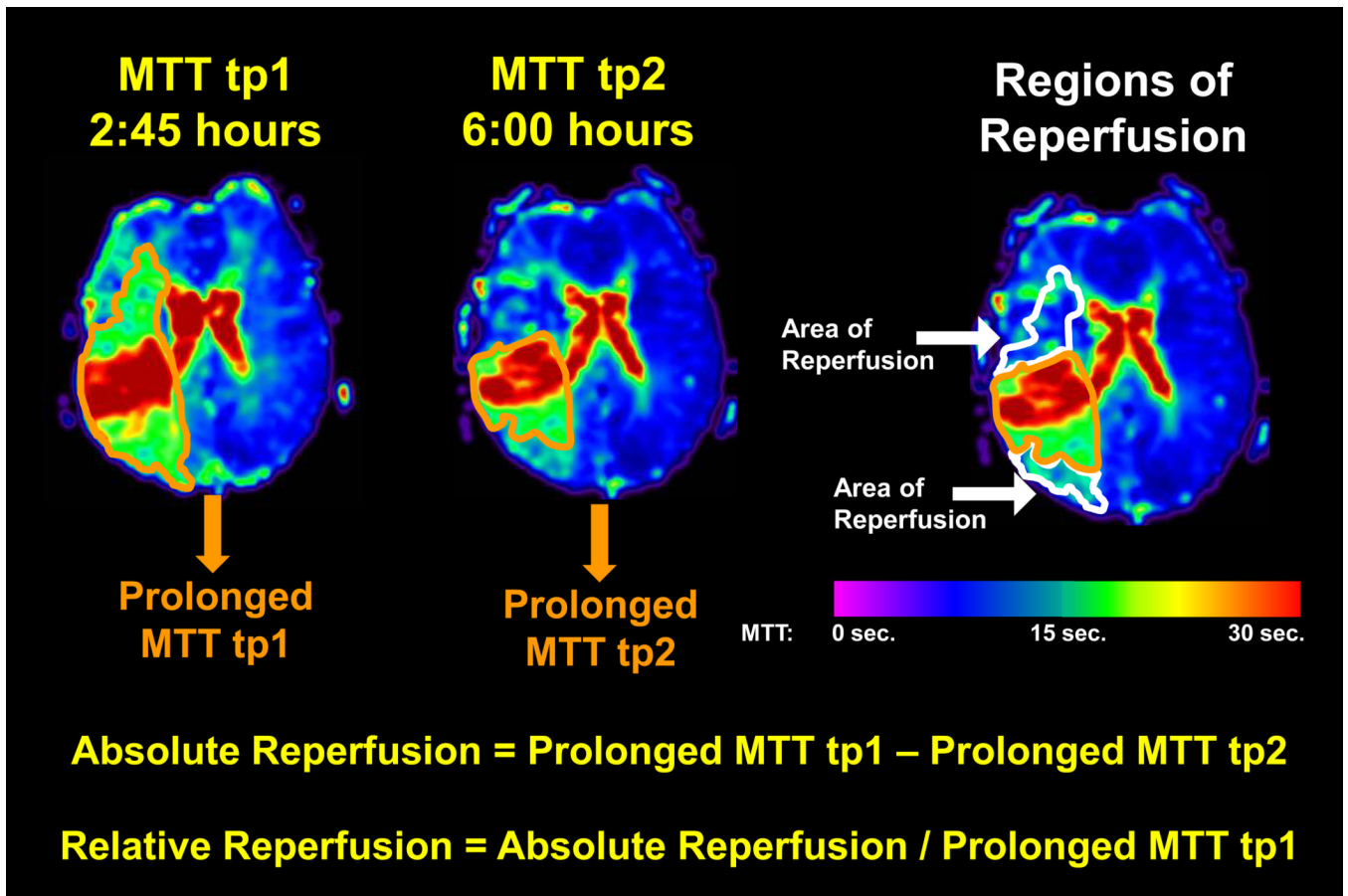
Figure 1. Calculation of Relative Reperfusion

MTT maps were prepared for each time-point. For each MTT threshold, all voxels with values > the chosen MTT threshold were defined as "prolonged". Prolonged MTT volumes provided a measure of the perfusion deficit volume at tp1 and tp2. Absolute and relative reperfusion volumes were calculated as shown. Warm colors represent maximal hypoperfusion with longer MTT and cool colors represent no hypoperfusion with short MTT, as shown on the color bar. The orange outline delineates a perfusion deficit defined by an MTT threshold > 4 seconds longer than the median MTT of the contralateral hemisphere. At tp2, the perfusion deficit shrinks; thus, the white outline delineates regions of reperfusion using this threshold (> 4 seconds).
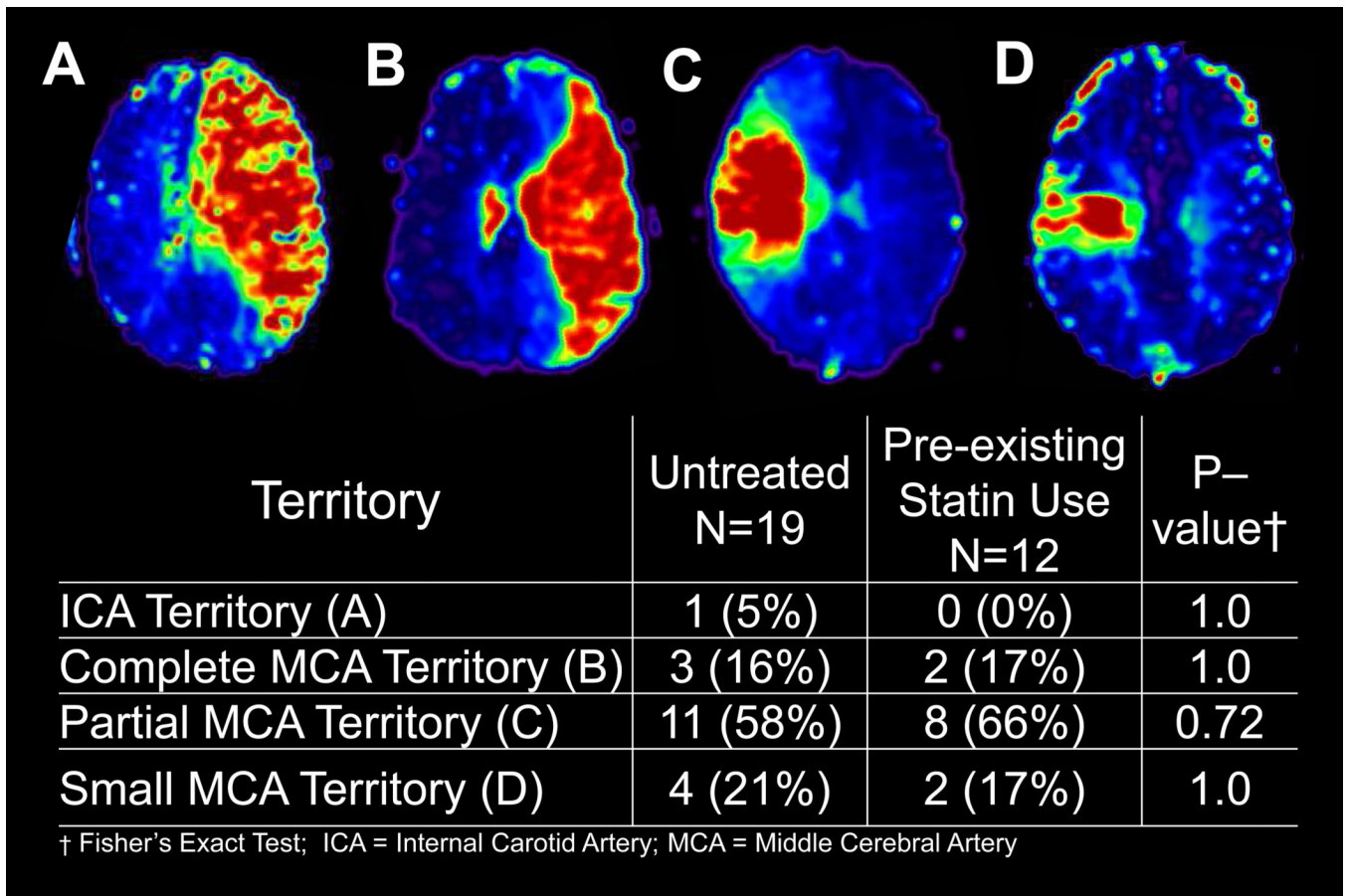
Territory	Untreated N=19	Pre-existing Statin Use N=12	P–value†
ICA Territory (A)	1 (5%)	0 (0%)	1.0
Complete MCA Territory (B)	3 (16%)	2 (17%)	1.0
Partial MCA Territory (C)	11 (58%)	8 (66%)	0.72
Small MCA Territory (D)	4 (21%)	2 (17%)	1.0

† Fisher's Exact Test; ICA = Internal Carotid Artery; MCA = Middle Cerebral Artery

Figure 2. Distribution of Perfusion Deficits at tp1 (based on MTT)
In order to assess whether the location of perfusion deficit territories were balanced between the untreated and pre-existing statin use groups, tp1 perfusion deficit territories were assigned to one of four groups: 1) internal carotid artery (ICA), (2) complete middle cerebral artery (MCA), (3) partial MCA, and (4) small MCA (Figure 2). There were no significant differences between the two groups. Example of MTT maps for each of the four groups are shown in the upper panel, labeled A, B, C, and D for ICA, complete MCA, partial MCA, and small MCA, respectively.
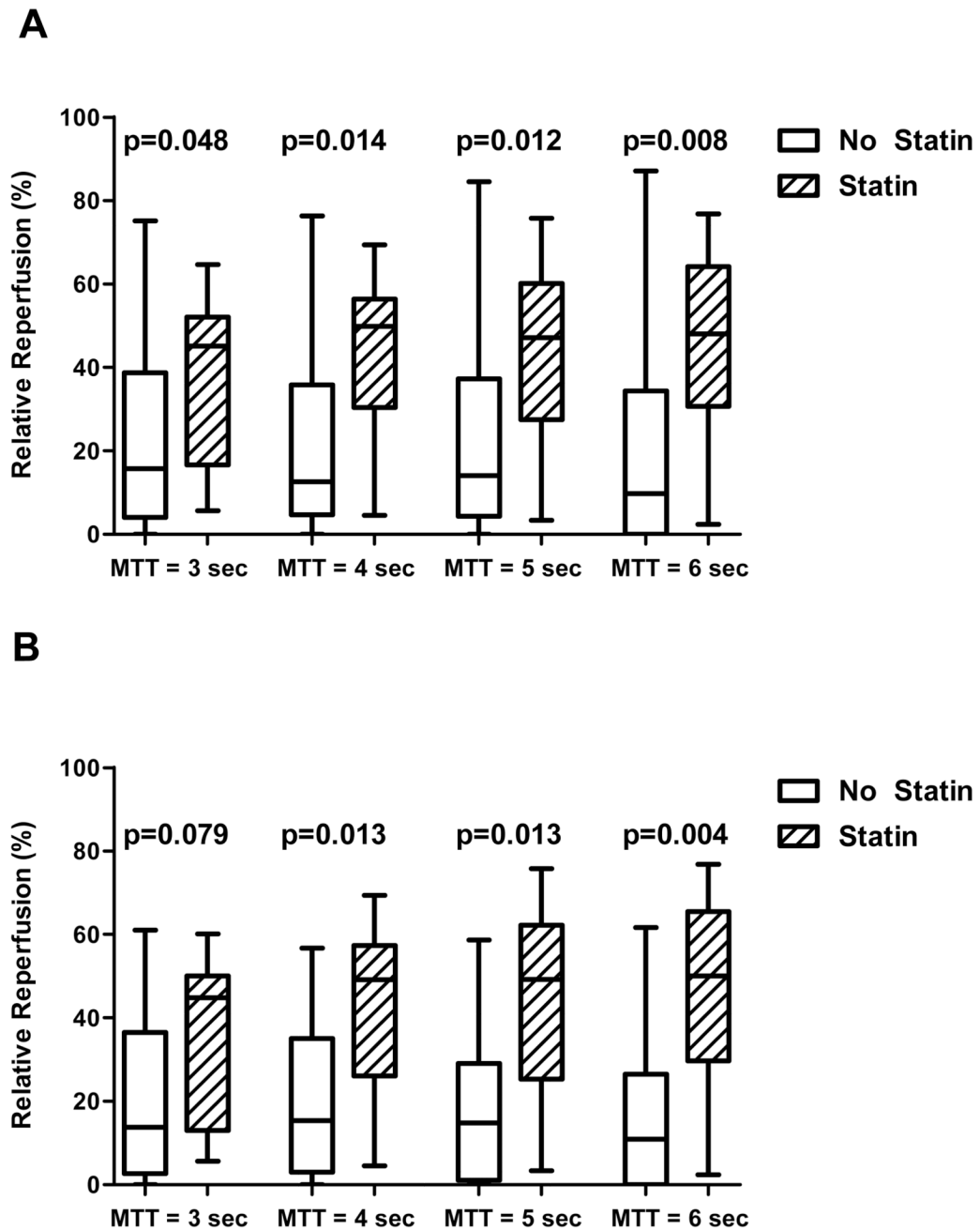
A

B

Figure 3. Statin use and relative reperfusion
(A) Entire sample, n=31: Boxplots (median, IQR) for relative reperfusion at each MTT threshold are shown for all 31patients. For each MTT threshold, there was significantly greater reperfusion in the statin group compared to the untreated group. **(B) tPA-treated patients only, n=23:** Boxplots for relative reperfusion at each MTT threshold are shown for tPA-treated patients only. For each MTT threshold except MTT=3 seconds, there was significantly greater reperfusion in the statin group compared to the untreated group.
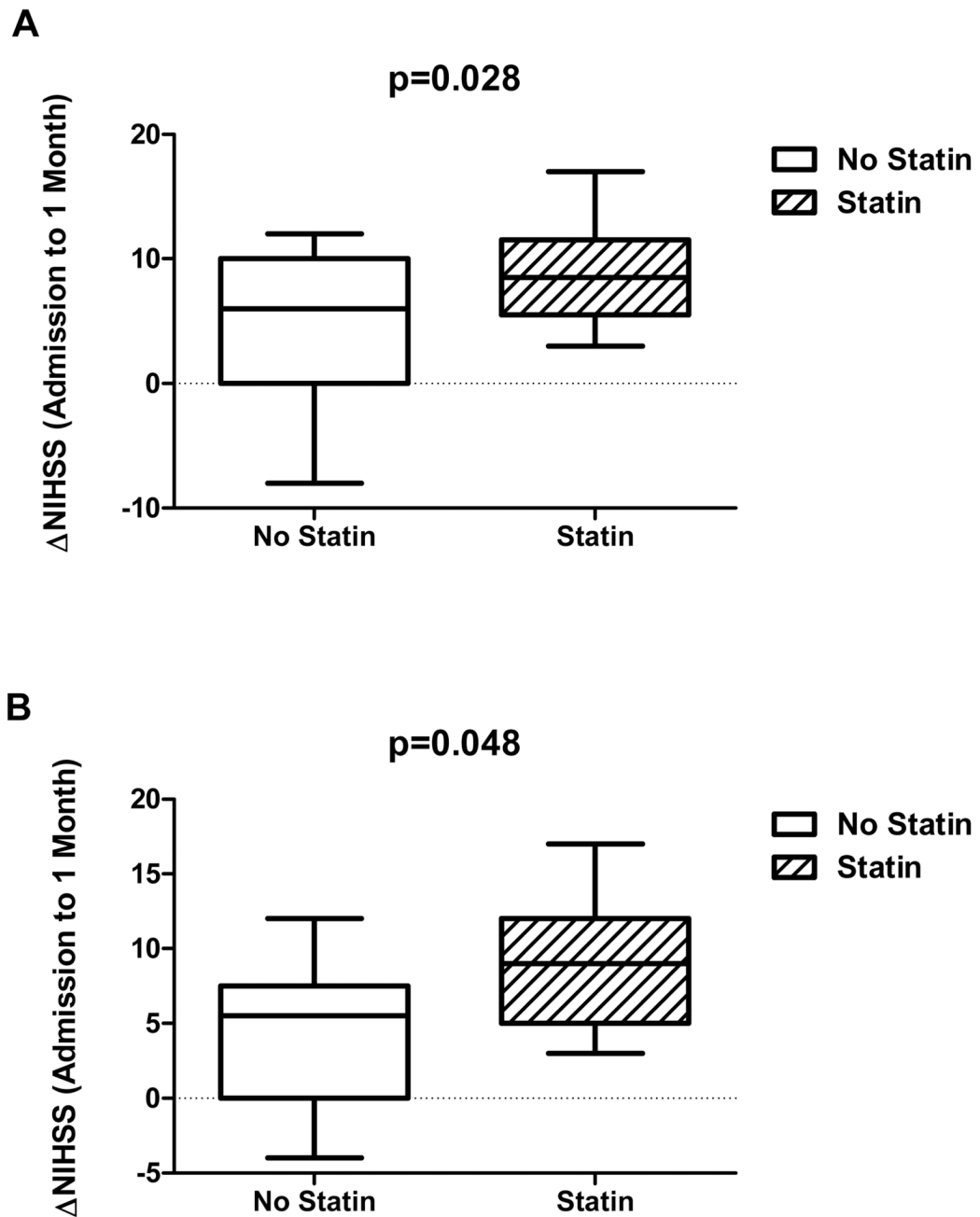
A

p=0.028

B

p=0.048

Figure 4. Statin use and neurological improvement
(A) Entire sample, n=31: Boxplots (median, IQR) for improvement in NIHSS from admission to 1 month follow-up (ΔNIHSS) are shown for all 31 patients. There was greater NIHSS improvement in the statin group compared to the untreated group. **(B) tPA-treated patients only, n=23:** Boxplots for ΔNIHSS are shown for tPA-treated patients only. There was significantly greater improvement in NIHSS in the statin group.

Table 1

Baseline characteristics of the untreated and pre-existing statin use groups

	Untreated N=19	Pre-existing Statin Use N=12	P–value[†]
Female, n (%)[*]	11 (58%)	3 (25%)	0.14
Age (years), median (IQR)[‡]	60 (54, 72)	62 (59, 66)	0.72
Admission NIHSS, median (IQR)	16 (10, 18)	18 (13, 20)	0.60
tPA treatment, n (%)[*]	12 (63%)	11 (92%)	0.11
Volume tp1 perfusion deficit (ml), median (IQR)	62 (23,116)	50 (17,88)	0.73
Time between tp1 and tp2 (min), median (IQR)	215 (187, 239)	195 (159, 223)	0.19
Admission MAP (mmHg), median (IQR)	110 (94, 145)	112 (108, 116)	0.86
Admission Glucose (mg/dl), median (IQR)	128 (101, 146)	145 (121, 165)	0.26
LDL (mg/dl), median (IQR)	100 (73, 119)	72 (59, 103)	0.16
African-American, n (%)[*]	6 (32%)	4 (33%)	1.0
Time from tPA-bolus to tp1 (min), median (IQR)	44 (23, 54)	50 (41, 60)	0.32
Absolute Volume Reperfusion (ml), median (IQR)	6 (3, 13)	12 (7,31)	0.06
Volume DWI lesion tp1 (ml), median (IQR)	32 (7, 55)	15 (8, 30)	0.51
Onset-to-needle time (min), median (IQR)	110 (99, 121)	110 (101, 133)	0.65
History of Hypertension, n (%)[*]	15 (79%)	10 (83%)	1.0
History of Diabetes, n (%)[*]	7 (37%)	6 (50%)	0.71
History of Congestive Heart Failure, n (%)[*]	5 (26%)	1 (8%)	0.36
Current Tobacco Use, n (%)[*]	7 (37%)	5 (42%)	1.0
History of Coronary Artery Disease, n (%)[*]	2 (10%)	6 (50%)	0.03
History of Stroke or TIA, n (%)[*]	2 (10%)	4 (33%)	0.17

[†] Wilcoxon Rank Sum Test unless indicated by (*).

[*] Fisher's Exact Test was used for assessing difference in frequencies between two groups.

[‡] Due to small sample size, results are expressed as median and inter-quartile range (IQR).

NIHSS = NIH Stroke Scale; MAP = Mean Arterial Pressure; LDL=Low Density Lipoprotein; DWI = Diffusion Weighted Imaging; TIA = Transient Ischemic Attack

Table 2

Multivariable model of clinical variables predicting relative reperfusion and ΔNIHSS

Predictors of Relative Reperfusion*		
Clinical Variable	**β (SE)**[†]	**P-value**[‡]
Pre-existing Statin Use	17.9 (7.3)	0.021
Volume Prolonged MTT at tp1	−0.156 (0.06)	0.024
Mean Arterial Pressure	−0.318 (0.15)	0.040

Predictors of ΔNIHSS from Admission to One Month[§]		
Clinical Variable	**β (SE)**[†]	**P-value**[‡]
Pre-existing Statin Use	4.82 (1.7)	0.010
Age	−0.163 (0.06)	0.015

[†] β(SE)=regression coefficient(standard error)

[‡] $P < 0.05$ was considered statistically significant.

[*] Model including pre-existing statin use, volume of prolonged MTT at tp1, and admission mean arterial pressure explained 41.1% of the variance in relative reperfusion.

[§] Model including the pre-existing statin use and age explained 31.9% of the variance in ΔNIHSS.