Computed Tomographic Perfusion Selection and Clinical Outcomes After Endovascular Therapy in Large Vessel Occlusion Stroke

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Background and Purpose—Different imaging paradigms have been used to select patients for endovascular therapy in stroke. We sought to determine whether computed tomographic perfusion (CTP) selection improves endovascular therapy outcomes compared with noncontrast computed tomography alone.

Methods—Review of a prospectively collected registry of anterior circulation stroke patients undergoing stent-retriever thrombectomy at a tertiary care center between September 2010 and March 2016. Patients undergoing CTP were compared with those with noncontrast computed tomography alone. The primary outcome was the shift in the 90-day modified Rankin scale (mRS).

Results—A total of 602 patients were included. CTP-selected patients (n=365, 61%) were younger (P=0.02) and had fewer comorbidities. CTP selection (n=365, 61%) was associated with a favorable 90-day mRS shift (adjusted odds ratio [aOR]=1.49; 95% confidence interval [CI], 1.06–2.09; P=0.02), higher rates of good outcomes (90-day mRS score 0–2: 52.9% versus 40.4%; P=0.005), modified Thrombolysis in Cerebral Infarction-3 reperfusion (54.8% versus 40.1%; P<0.001), smaller final infarct volumes (24.7 mL [9.8–63.1 mL] versus 34.6 mL [13.1–88 mL]; P=0.017), and lower mortality (16.6% versus 26.8%; P=0.005). When matched on age, National Institutes of Health Stroke Scale (NIHSS) score, and glucose (n=424), CTP remained associated with a favorable 90-day mRS shift (P=0.016), lower mortality (P=0.02), and higher rates of reperfusion (P<0.001). CTP better predicted functional outcomes in patients presenting after 6 hours (as assessed by comparison of logistic regression models: Akaike information criterion: 199.35 versus 287.49 and Bayesian information criterion: 196.71 versus 283.27) and those with an Alberta Stroke Program Early Computed Tomography Score ≤7 (Akaike information criterion: 216.69 versus 334.96 and Bayesian information criterion: 213.6 versus 329.94).

Conclusions—CTP selection is associated with a favorable mRS shift in patients undergoing stent-retriever thrombectomy. Future prospective studies are warranted. **(*Stroke*. 2017;48:1271-1277. DOI: 10.1161/STROKEAHA.116.015636.)**

Key Words: brain ischemia ■ perfusion imaging ■ reperfusion ■ stroke ■ thrombectomy

Endovascular therapy (ET) has become the gold-standard management for anterior circulation large vessel occlusion stroke presenting early in the therapeutic window.[1–5] Imaging-based selection methods in clinical trials have included measurements of irreversibly infarcted core by noncontrast computed tomography (NCCT) ASPECTS (Alberta Stroke Program Early Computed Tomography Score), magnetic resonance imaging (MRI) diffusion-weighting imaging ASPECTS, and computed tomographic perfusion (CTP) parameters. The higher rates of good outcomes in SWIFT-PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) and EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial), which used CTP, as compared with REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours) and ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke), which mainly used NCCT ASPECTS, suggest that optimizing selection with CTP imaging may lead to superior results. Although post hoc analysis of SWIFT-PRIME data has shown CTP to be an accurate predictor of final infarction volumes among both reperfused and nonreperfused patients, examination of the value and predictive power of CTP parameters compared with NCCT has this far been inconsistent.[6,7] Some multicenter studies have found no significant differences in clinical outcomes or final infarction volumes between the 2 methods.[8,9] Others have found that CTP-based selection provides unique information about the brain parenchyma status and doubles the likelihood of favorable clinical outcome compared with NCCT-selected patients.[10–12]

We sought to determine whether CTP selection leads to improved outcomes after ET as compared with NCCT alone.

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Methods

Patients Selection and Measures of Outcomes

We reviewed our prospectively collected large vessel occlusion stroke database between September 1, 2010, and March 31, 2016, to identify patients presenting with an anterior circulation stroke who underwent intra-arterial therapy with stent-retriever devices. Patients with posterior circulation strokes were excluded. Patients were categorized into 2 concurrent groups: (1) NCCT and (2) CTP-based selection for ET.

Baselines characteristics and demographics and procedural parameters were collected. The primary outcome measure was the comparison of the overall degree of disability between the 2 groups as measured by the modified Rankin scale (mRS) score at 90 days. Secondary end points included the rate of successful reperfusion as defined by the modified Thrombolysis in Cerebral Infarction score,[13] the rate of good outcomes (defined as 90-day mRS score 0–2), and final infarct volumes (FIV). Safety end points included the rate of significant hemorrhagic transformation (eg, any parenchymal hematoma and parenchymal hematoma type 2 defined as a bleed occupying >30% of the infarcted area as per the European Cooperative Acute Stroke Study criteria).[14]

Secondary analyses were performed for exploratory purposes including the following:

1. Matched CTP-NCCT cohorts based on weighted age, baseline National Institutes of Health Stroke Scale (NIHSS) score, and glucose levels as previously described to control for potential imbalances.[15]
2. Time stratification: Patients were dichotomized into 2 groups, those presenting within 6 hours from last known normal and those who presented later than 6 hours. The ability of CTP to predict good outcomes compared with NCCT was assessed by developing separate logistic regression models for each population and comparing the Akaike information criterions and Bayesian information criterions.[16]
3. ASPECTS stratification: We evaluated the potential impact of differences in baseline ischemic core size on the performance of CTP. Patients were categorized into 2 groups—those who had a NCCT ASPECTS score ≤7 and those who had a score >7—to assess the usefulness of CTP in larger infarcts using the aforementioned method.[17]

This study was approved by the local institutional review board.

Image Protocol/CT Perfusion Analysis

All patients underwent an institutional imaging protocol, including NCCT alone or with added CTP (±computed tomographic angiography). The choice of the imaging modality was based on the preferences of the stroke and neuroendovascular teams on call. Imaging acquisition parameters were the same for all patients included in the study.[18] CTP encompassing 8 cm of brain coverage was evaluated with a fully automated software environment (RAPID version 4.5.0; iSchemaView, Menlo Park, CA). The infarcted tissue volume (ischemic core) was defined by a voxel relative cerebral blood flow of <30% of the normal tissues. The total hypoperfused volume was defined by >6-second delay in the time to maximum of the tissue residue function (Tmax) and a penumbral volume of at-risk tissue defined by the difference between total hypoperfused and ischemic core tissue estimates.

Imaging Outcome

Follow-up imaging included NCCT or MRI documenting FIV within 5 days of the treatment. Diffusion-weighted imaging was preferentially used if MRI was obtained within the first 72 hours of the stroke, and fluid-attenuated inversion recovery was used if MRI was performed between 3 and 5 days. For NCCT, window/level settings were adjusted to maximize contrast between the normal and infarcted brain. Edema producing sulcal effacement was not excluded. Hemorrhagic transformation was incorporated in the FIV whenever present. FIV were measured after export of raw DICOM data to the Fiji release of the ImageJ software platform using a standardized, semiautomated approach (https://imagej.nih.gov/ij/).[18]

Matching Methodology

A matching method based on weighted Euclidean distances was used to obtain a pair of subjects considered to be the nearest neighbors in a 3-dimensional space of age, baseline NIHSS score, and pretreatment glucose levels, as previously described.[15] The distance between each CTP–NCCT pair was computed using the %FIND_NEIGHBORS Macro in SAS University Edition (SAS Institute, Cary, NC). Each CTP patient was matched with nearest NCCT patient (having the smallest Euclidian distance).

After matching, the distribution of Euclidian distances was studied to identify outliers, and a threshold was determined as follows: Thr eshold=Q75+1.5*(Q75−Q25), where Q25 and Q75 are respectively the 25th and 75th percentiles.[15] Pairs with distances greater than the threshold were considered extreme values at the tail of the distribution and eliminated from further consideration.

Statistical Analysis

The Shapiro–Wilk test was used to assess the normality of the variables. Continuous variables were reported as mean±SD if normally distributed or median (interquartile range) if nonparametric. Categorical variables were reported as proportions. Between groups, comparisons for continuous/ordinal variables were made with Student *t* test, Mann–Whitney *U* test, ANOVA, paired *t* test, or Wilcoxon rank-sum test, as appropriate. Categorical variables were compared by χ^2 test, Fisher exact test, or McNemar test for discordant pairs, as appropriate. The overall distribution of 90-day mRS was compared between groups (shift in disability levels) using the van Elteren test or Wilcoxon signed-rank test to account for the matching. Ordinal regression was computed for odds ratios to assess the association between CTP selection and mRS. Multivariate logistic regression analyses for predictors of good outcomes and full reperfusion were performed for variables at the 0.1 level of significance on univariate analysis. Significance was set at $P<0.05$, and all P values were 2 sided.

Statistical analysis was performed using IBM SPSS Statistics 23 (IBM-Armonk, NY) except for the McNemar test that was computed using the FREQ procedure in SAS University Edition (SAS Institute).

Results

During the study period, 885 out of 971 patients had anterior circulation strokes. Of those, 602 underwent ET with stent-retriever devices and thus were included in the primary analysis.

Primary Analysis: Overall Cohort

Baseline characteristics, procedural, efficacy, and safety data are summarized in Table 1. When compared with CTP-selected patients (n=237), NCCT-selected patients (n=365) were older (67.8±14.6 versus 63.9±5.23; $P=0.02$) and had higher rates of hypertension (78.5% versus 71.2%; $P=0.046$), dyslipidemia (42.2% versus 33.8%; $P=0.039$), and atrial fibrillation (48.9% versus 33.3%; $P<0.001$).

CTP selection was associated with a favorable shift in the overall distribution of 90-day mRS ($P<0.001$; Figure). The proportion of patients with good outcomes (mRS score 0–2) at 90 days was 52.9% versus 40.4% in the NCCT-selected patients ($P=0.005$). FIV were smaller (24.7 [9.8–63.1] versus 34.6 [13.1–88]; $P=0.02$), and mortality rates were lower (16.6% versus 26.8%; $P=0.005$) in CTP-selected patients. CTP patients also had higher rates of full reperfusion=modified Thrombolysis in Cerebral Infarction-3 score (54.8% versus 40.1%; $P<0.001$). The rates of any parenchymal hematoma were comparable. Multivariate logistic regression showed that CTP was independently associated with full reperfusion (odds ratio [OR], 1.79;

Table 1. Unmatched Cohort: Baseline Characteristics, Procedural Parameters, and Outcome Measures

	CTP Selection (n=365)	NCCT Selection (n=237)	*P* Value
Age, y	63.92±15.23	67.83±14.55	0.02
Sex (male)	184 (50.4)	132 (55.7)	0.211
Hypertension	259 (71.2)	186 (78.5)	0.046
Dyslipidemia	123 (33.8)	100 (42.2)	0.039
Atrial fibrillation	121 (33.3)	113 (48.9)	<0.001
Diabetes mellitus	80 (22)	60 (25.3)	0.375
Smoking	65 (17.9)	43 (18.2)	0.914
bNIHSS	18 (13–22)	19 (15–22)	0.085
ASPECTS	8 (7–9)	8 (6–9)	0.119
SBP, mm Hg	150.02±33.44	146.42±31.13	0.449
Glucose	130 (101.25–138.75)	125 (102–125)	0.08
IV tPA	145 (40.1)	111 (46.8)	0.109
Transfers	218 (65.3)	153 (64.8)	0.929
Night presentation (7:00 PM to 7:00 AM)	135 (37)	75 (31.6)	0.19
In-house CTA	244 (67)	76 (32.2)	<0.001
Procedure parameters			
LKN-puncture, mins	364.5 (243.5–587)	284 (208–425)	<0.01
CT puncture, mins	56 (37–92)	45 (30–79)	0.01
Procedure length, mins	67 (43–101)	72 (51–110)	0.549
mTICI 2b–3	351 (96.2)	212 (89.5)	0.002
mTICI 3	200 (54.8)	95 (40.1)	<0.001
Parenchymal hemorrhage			
PH-2	17 (4.7)	12 (5.1)	0.847
Any PH	33 (9)	24 (10.1)	0.671
Final infarct volume, mL	24.66 (9.84–63.14)	34.6 (13.11–88.03)	0.017
90-d mRS score 0–2	175 (52.9)	86 (40.4)	0.005
90-d mortality	55 (16.6)	57 (26.8)	0.005

Values are represented as n (%), mean±SD, or median (interquartile range) as appropriate. ASPECTS indicates Alberta Stroke Program Early CT score; bNIHSS, baseline National Institute of Health Stroke Scale; CTA, computed tomographic angiography; CTP, computed tomographic perfusion; LKN, last known normal; mRS, modified Rankin scale; mTICI, modified Thrombolysis in Cerebral Infarction; NCCT, noncontrast computed tomography; PH, parenchymal hematoma; PH-2, parenchymal hematoma type 2; SBP, systolic blood pressure; and tPA, tissue-type plasminogen activator.

95% confidence interval [CI], 1.27–2.53; *P*=0.001) and good outcomes (OR, 1.72; 95% CI, 1.10–2.67; *P*=0.017; Table 2) after adjustment for imbalances. Multivariate ordinal regression showed that CTP was an independent predictor of a favorable shift in the overall mRS distribution, after adjustment for the same confounding factors as enumerated in Table 2 (adjusted odds ratio [aOR]=1.49; 95% CI, 1.06–2.09; *P*=0.02). Further adjustment for in-house computed tomographic angiography as a potential confounder yielded similar results for CTP selection benefit (aOR=1.70; 95% CI, 1.16–7.29; *P*=0.006).

Secondary Analysis

Matched Cohort

The CTP-selected and NCCT-selected patients were matched in age, baseline NIHSS score, and glucose levels. Of the 237 pairs generated by the matching algorithm, 25 had a Euclidean distance higher than the defined threshold; 212 underwent analysis. Baseline characteristics were well balanced between the 2 groups except for higher rates of atrial fibrillation in NCCT-selected patients (48.6% versus 36.3%; *P*<0.01) and longer times from last known normal to puncture in CTP-selected patients (362 [240.5–556.8] versus 269 [205.5–424.3]; *P*=0.001; Table 3). CTP selection was associated with a favorable shift in the overall distribution of 90-day mRS (*P*=0.01). The proportion of patients with good outcomes (mRS score 0–2) at 90 days was 53.5% versus 44% in the NCCT-selected patients (*P*=0.06). The 90-day mortality was significantly lower in the CTP group (15.7% versus 23.6%; *P*=0.02). Multivariate ordinal regression showed that CTP was an independent predictor

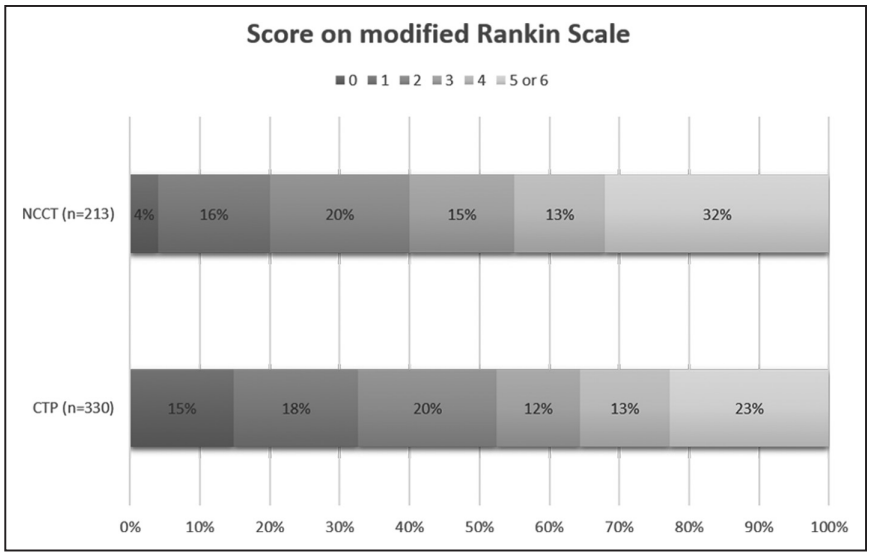

Figure. Functional outcome at 90 d according to the score on the modified Rankin scale. Shift analysis by Van Elteren test (P<0.001). CTP indicates computed tomographic perfusion; and NCCT, noncontrast computed tomography.

of a favorable shift in the overall mRS distribution, after adjustment for atrial fibrillation (OR, 1.5; 95% CI, 1.0–2.1; P=0.03).

Time Stratification

There was an advantage to using CTP to predict functional outcome in patients presenting later than 6 hours from last known normal as compared with those presenting within 6 hours, as assessed by Akaike information criterion and Bayesian information criterion (199.35 versus 287.49 and 196.71 versus 283.27, respectively).

Table 2. Unmatched Cohort: Predictors of Full Reperfusion and Good Outcomes

	OR	95% CI		*P* Value
Full reperfusion (mTICI-3)				
IV tPA	1.63	1.16	2.29	0.005
CTP	1.79	1.27	2.53	0.001
Procedure length	0.990	0.986	0.994	<0.001
Good outcomes (mRS score 0–2)				
Age	0.96	0.95	0.98	<0.001
Hypertension	1.10	0.66	1.85	0.709
Atrial fibrillation	1.13	0.70	1.83	0.606
Smoking	1.26	0.72	2.19	0.414
Glucose	0.99	0.986	0.997	0.002
SBP	0.99	0.98	1.00	0.179
bNIHSS	0.92	0.88	0.96	<0.001
ASPECTS	1.24	1.08	1.43	0.002
IV tPA	1.46	0.95	2.26	0.085
CTP	1.72	1.10	2.67	0.017
Procedure length	0.992	0.987	0.996	0.001

ASPECTS indicates Alberta Stroke Program Early CT score; bNIHSS, baseline National Institute of Health Stroke Scale; CTP, computed tomographic perfusion; mRS, modified Rankin scale; mTICI, modified Thrombolysis in Cerebral Infarction; SBP, systolic blood pressure; and tPA, tissue-type plasminogen activator.

ASPECTS Stratification

CTP-based selection resulted in a significant favorable shift in the degree of 90-day disability in patients with an ASPECTS ≤7, as compared with NCCT alone (n=233; OR, 1.91; 95% CI, 1.1–3.4; P=0.025 for adjusted multivariate ordinal regression). For those with an ASPECTS >7, there was a nonsignificant trend toward with a favorable shift in functional outcomes (OR, 1.54; 95% CI, 0.91–2.30; P=0.11).

The ability of favoring CTP selection to predict functional outcomes was better in patients with ASPECTS ≤7 as compared with those who had an ASPECTS >7, as assessed by Akaike information criterion and Bayesian information criterion (216.69 versus 334.96 and 213.6 versus 329.94, respectively).

Discussion

This study suggests the superiority of CTP selection compared with NCCT-based methods in selecting candidates for ET. We demonstrate a shift in the overall distribution of 90-day mRS favoring CTP-based selection, with higher rates of successful reperfusion and good outcomes (mRS score 0–2). There was no difference in rates of parenchymal hematomas, whereas mortality rates were lower. These results remained stable after adjustments in multivariate analysis and matching case–control analysis.

Data on the use of CTP selection have produced mixed results to date. In a cohort study of 556 patients comparing NCCT-, CTP-, and MRI-based selection, CTP, used in 190 patients (34%), was associated with similar rates of good outcomes as NCCT or MRI.[9] Similarly, Zhu et al[11] demonstrated in a study of 165 patients with anterior circulation strokes that CTP could not predict functional outcomes unless reperfusion status was taken into account, which renders this imaging method noncontributory in isolation. It is also noteworthy that the same authors, using the same study population, revealed that CTP-defined penumbra was a valuable piece of information that could not be replaced or predicted by clinical, NCCT, or computed tomographic angiography data and thus an important determining factor of outcomes.[19] Likewise, in the recently

Table 3. Matched Cohort: Baseline Characteristics, Procedural Parameters, and Outcome Measures

	CTP Selection (n=212)	NCCT Selection (n=212)	*P* Value
Age, y	65.05±15.01	66.89±14.11	0.35*
bNIHSS	18.5 (14–22)	18 (15–22)	0.91*
Glucose	119 (103–137.5)	121 (101.5–141.25)	0.81*
Sex (male)	106 (50)	119 (56.1)	0.17
Hypertension	158 (74.5)	163 (76.9)	0.56
Dyslipidemia	83 (39.2)	87 (41)	0.70
Atrial fibrillation	77 (36.3)	103 (48.6)	<0.01
Diabetes mellitus	45 (21.2)	48 (22.6)	0.7
Smoking	33 (15.6)	40 (19)	0.34
ASPECTS	8 (7–9)	8 (6.75–9)	0.249
SBP, mm Hg	147.53±33.78	144.7±30.11	0.774
Procedure parameters			
LKN puncture, mins	362 (240.5–556.75)	269 (205.5–424.25)	0.001
Procedure length, mins	70 (45–102.5)	72 (53.75–111.25)	0.595
mTICI 2b–3	199 (93.9)	191 (90.1)	0.17
mTICI 3	108 (50.9)	84 (39.6)	0.019
Parenchymal hemorrhage			
PH-2	11 (5.2)	11 (5.2)	1
Any PH	21 (9.9)	19 (9)	0.745
Final infarct volume, mL	25.7 (9.18–59.85)	32.61 (12–81.75)	0.216
90-d mRS score 0–2	106 (53.5)	84 (44)	0.06
90-d mortality	31 (15.7)	45 (23.6)	0.02

ASPECTS indicates Alberta Stroke Program Early CT score; bNIHSS, baseline National Institute of Health Stroke Scale; CTP, computed tomographic perfusion; LKN, last known normal; mTICI, modified Thrombolysis in Cerebral Infarction; NCCT, noncontrast computed tomography; PH, parenchymal hematoma; PH-2, parenchymal hematoma type 2; and SBP, systolic blood pressure.

*NCCT and CTP patients were matched for these criteria.

published positive randomized clinical trials, those that relied mainly on CTP (EXTEND-IA and SWIFT PRIME)[1,2] yielded similar results as those that used other imaging protocols,[3–5] which only adds to the uncertainty regarding the usefulness of CTP in selecting candidates for ET.

An important issue under consideration is the time cost of CTP imaging, which can add ≤17 minutes in acquisition and postprocessing.[20] Indeed, some studies have shown a significant difference in the median time from hospital presentation to vascular access between NCCT-imaged and CTP-imaged patients (61 minutes versus 114 minutes).[9] However, CTP has been found to be safe and effective in identifying candidates for ET irrespective of time to presentation, with similar rates of complications and favorable outcomes between both in-and-out of window (6 hours) patients.[21,22] Variable results on clinical outcomes, together with potential time delays, radiation, and potential kidney damage, have, therefore, kept the use of CTP inconsistent.

The aforementioned studies had several limitations, including the relatively small number of patients included, the absence of a control arm (NCCT only), and the potential nonuniformity of treatment (old versus new technology) and imaging paradigms including the utilization of different CTP acquisition protocols and postprocessing software across the multiple contributing centers. Moreover, EXTEND-IA and SWIFT PRIME excluded patients with a baseline ischemic core >70 and >50 mL, with a median core of 12 mL (interventional arm) and 6 mL, respectively,[2,6] leaving a gap in the understanding of the usefulness of CTP in patients with larger infarcts and leaving open the question of its universal use as a selection tool.

Our study confirmed historical data showing that CTP-selected patients had better outcomes than those selected solely based on NCCT, regardless of time of presentation. Further analysis showed that this was still true for patients with an ASPECTS ≤7. Thus, we think that CTP may help identify a subset of patients with relatively large infarcts that would still benefit from ET.[23]

Our study has several limitations inherent to its retrospective design. We did not investigate the rationale behind preferring one imaging-selection modality over another, which was predominantly decided by the treating team. Other imaging methods that were not addressed in this study (for instance

computed tomographic angiography) could have acted as confounders and might have influenced the treatment decision. Only patients with a positive treatment decision were analyzed in this study, resulting in a possible selection bias. Because this was a retrospective analysis of an endovascular database, we did not systematically capture those cases where the decision of not intervening was made after imaging, making the overall preselection patient denominator unknown. As such, although our results support the notion that CTP selection leads to better outcomes, we cannot refute the possibility that this may have happened at the cost of overselection and with the exclusion of patients who even to a lesser degree could still have benefited from endovascular treatment. Although this might significantly limit the application of our data to standard clinical care, we think that the main pragmatic value of our work resides on the fact that CTP selection seems to be a good approach to maximize the treatment results and as such may be a helpful strategy to optimize the planning of future clinical trials by reducing their sample sizes. It is also important to highlight that our findings are specific to a particular postprocessing CTP software, and as such, our results may not be generalizable to other system currently used.[24] To eliminate the potential effect of thrombectomy devices, we only included patients that underwent ET with stent retrievers, which have proven to be superior to early generation devices.[25] There were, however, imbalances in baseline characteristics between the 2 groups, which, though minimal, may have influenced the results. Nevertheless, CTP was still associated with better clinical outcomes after adjustment for historically known confounders such as age, NIHSS score, glucose, and IV tPA (tissue-type plasminogen activator), as well as in the matched analysis. Finally, our study did not address the potential cost, risks, and time delays caused by CTP imaging, although time-to-puncture was not a predictor of clinical outcomes in our analysis.

Conclusions

In conclusion, to date, there is no consensus about the optimal imaging selection paradigm for stroke ET. Our results suggest that use of CTP is associated with a favorable shift in functional outcome in patients undergoing ET. Future prospective studies are warranted.

Disclosures

Dr Nogueira is a PI for Stryker Neurovacular (Trevo-2 Trial PI and DAWN Trial PI), is a member of Steering Committee in Covidien (SWIFT and SWIFT-PRIME Steering Committee, STAR Trial Core Laboratory), and is a member of Executive Committee in Penumbra (3-D Separator Trial Executive Committee). The other authors report no conflicts.

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