Improved Outcomes in Stroke Thrombolysis with Pre-specified Imaging Criteria

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ABSTRACT: *Background:* A 1995 National Institute of Neurological Disorders (NINDS) study found benefit for intravenous tissue plasminogen activator (tPA) in acute ischemic stroke (AIS). The symptomatic intracranial hemorrhage (SICH) rate in the NINDS study was 6.4%, which may be deterring some physicians from using this medication. *Methods:* Starting December 1, 1998, patients with AIS in London, Ontario were treated according to NINDS criteria with one major exception; those with approximately greater than one-third involvement of the idealized middle cerebral artery (MCA) territory on neuroimaging were excluded from treatment. The method used to estimate involvement of one-third MCA territory involvement bears the acronym ICE and had a median kappa value of 0.80 among five physicians. Outcomes were compared to the NINDS study. *Results:* Between December 1, 1998 and February 1, 2000, 30 patients were treated. Compared to the NINDS study, more London patients were treated after 90 minutes (p<0.00001) and tended to be older. No SICH was observed. Compared to the treated arm of the NINDS trial, fewer London patients were dead or severely disabled at three months (p=0.04). Compared to the placebo arm of the trial, more patients made a partial recovery at 24 hours (p=0.02), more had normal outcomes (p=0.03) and fewer were dead or severely disabled at three months (p=0.004). *Conclusions:* The results of the NINDS study were closely replicated and, in some instances, improved upon in this small series of Canadian patients, despite older age and later treatment. These findings suggest that imaging exclusion criteria may optimize the benefits of tPA.

RÉSUMÉ: Amélioration des résultats de la trombolyse chez les patients porteurs d'un accident vasculaire cérébral et rencontrant des critères spécifiques à l'imagerie. *Introduction:* Une étude du NINDS effectuée en 1995 a démontré les bénéfices de l'administration intraveineuse de l'activateur du plasminogène tissulaire (tPA) en phase aiguë de l'accident vasculaire cérébral ischémique (AVCI). Le taux d'hémorragie intracrânienne symptomatique (HICS) dans l'étude NINDS était de 6.4%, ce qui peut décourager certains médecins d'utiliser ce médicament. *Méthodes:* Depuis le premier décembre 1998, les patients porteurs d'un AVCI à London, Ontario ont été traités selon les critères de l'étude NINDS avec une exception importante: ceux qui avaient une lésion impliquant plus d'un tiers du territoire de l'artère cérébrale moyenne reproduit par la neuro-imagerie ont été exclus du traitement. La méthode utilisée pour estimer le territoire impliqué porte l'acronyme ICE et avait une valeur kappa médiane de 0.80 parmi cinq médecins. Les résultats ont été comparés à ceux de l'étude NINDS. *Résultats:* 30 patients ont été traités entre le premier décembre 1998 et le premier février 2000. Plus de patients de London ont été traités après 90 minutes (p<0.00001) et ils étaient en général plus âgés que ceux qui ont participé à l'étude NINDS. Aucun cas de HICS n'a été observé. Moins de patients sont décédés ou avaient une invalidité sévère à trois mois (p=0.04) par rapport aux patients du bras avec traitement dans l'étude NINDS. Plus de patients ont eu une récupération partielle à 24 heures (p=0.02), plus de patients ont eu une récupération complète (p=0.03) et il y a eu moins de décès ou d'invalidité sévère à trois mois (p=0.004) par rapport aux patients à qui on avait administré le placebo dans l'étude. *Conclusions:* Les résultats de l'étude NINDS ont été reproduits et même améliorés dans certains cas, dans cette série de patients Canadiens, malgré l'âge plus avancé des patients et un traitement plus tardif. Ces observations suggèrent que des critères d'exclusion neuroradiologiques peuvent optimiser les bénéfices du traitement par le tPA.

In 1995, a two-part National Institute of Neurological Disorders (NINDS) study demonstrated the three-month efficacy of intravenous tissue plasminogen activator (tPA) when administered to patients within three hours of acute ischemic stroke onset.[1] Despite the positive trial result and subsequent reports of tPA in clinical practice suggesting similar results, there has been reluctance to use this medication because of the risk of symptomatic intracranial hemorrhage (SICH) demonstrated in multiple clinical trials and in real-world experiences.[1-7] The

literature suggests that deviation from the strict protocol guidelines outlined in the NINDS study results in higher rates of hemorrhage.[2,4,7] The concern over hemorrhage delayed approval of this medication in Canada until February 2000.

The only role of CT scanning in the NINDS study was to exclude hemorrhage as a cause of stroke symptoms. Early ischemic changes were noted but were not incorporated into decision-making. *Post hoc* analysis of a large European study[2] suggested that patients who had ischemic changes that involved more than one-third of the middle cerebral artery (MCA) territory on initial CT scan were more likely to suffer SICH.[2,8] Excluding such patients might lower the rate of SICH without sacrificing effectiveness.

A protocol was devised in London, Ontario which pre-specified the exclusion of patients with greater than approximately one-third involvement of the MCA territory on imaging who were otherwise eligible for tPA according to the NINDS guidelines. Outcomes and complications of the first 30 treated patients were then prospectively collected and analyzed.

METHODS

The patients in this cohort are part of a larger Canadian study (Canadian Activase in Stroke Effectiveness Study).[9] The use of follow-up data for research purposes, while protecting the identity of patients, was approved by the local internal review board.

Treatment protocol

Starting December 1998, patients presenting within three hours of ischemic stroke onset in London, Ontario were treated according to the guidelines of the NINDS study with one major exception: those with greater than one-third involvement of the MCA territory on imaging were excluded from treatment. For patients with acute symptoms, a central stroke pager was activated to notify a member of the stroke team. The treating physician was one of six stroke fellows and one attending level physician who were experienced in CT interpretation for acute ischemic stroke. Whenever possible, films were reviewed with one of four neuroradiologists on call or another stroke physician. Treatment was initiated at one of the three London adult emergency departments (London Health Sciences Centre – University Campus, St. Joseph's Hospital, and London Health Sciences Centre – South Street Campus). Because many surrounding community hospitals do not have CT scanners, patients presenting to a community hospital were transferred to London Health Sciences Centre – University Campus for further assessment, imaging and possible treatment. tPA was delivered primarily in the emergency room and, on occasion, in the CT scanner room. Following treatment, patients were transferred to a neurological observation unit for 24 hours post-tPA treatment.

Imaging methods

Neuroimaging consisted of a CT scan or MRI. An MRI was done when CT was not immediately available. Treatment decision was based on CT in 26 patients and on MRI in four patients. CT was performed on a GE HiSpeed Advantage slip ring third generation scanner. Scanning parameters were: space between slices 7 mm, DFOV 23.0 cm, matrix size 512 x 512. Average door-to-CT time was 51 minutes. MRI was performed

on a GE 1.5T Signa Horizon scanner with echoplanar capability and ultra-high speed gradients. Scanning parameters were: space between slices 5 mm, FOV 30 x 19, matrix size 128 x 128. Sequences obtained were scout images, axial diffusion-weighted images (B values of 0 and 1000), and axial gradient echo images (for the detection of parenchymal blood). Patients with evidence of bleeding on gradient-echo sequences were excluded from treatment. Average door-to-MRI time was 71 minutes. Factors presumed related to the increased door-to-imaging time for MRI included: 1) screening for metallic objects on the patient's body which are incompatible with MRI scanning, 2) transfer of the patient to an MRI-compatible stretcher, 3) adjustment of cardiovascular monitoring devices for the MRI, and 4) removal of MRI-incompatible objects from persons assisting in the transfer of the patient in the MRI suite. No screening for ferro-magnetic objects was required in patients undergoing CT. Patients who had CT were eligible for treatment in the scanning room.

CT scan interpretation

Because no specific criteria to estimate greater than one-third involvement of the MCA territory on the initial CT scan has been published, we devised a method which bears the acronym "ICE". Briefly, the ICE method is a three-step process (Figure 1). In step 1, a mentally formed geometric figure approximating a trapezoid is superimposed on the CT scan image to idealize (I) the MCA territory. In step 2, areas of presumed early infarction are identified and another mentally formed geographic figure which closes (C) around these areas is formed. In step 3, the area in step 2 is mentally superimposed on the area in step 1 (I) and an estimate (E) of the proportion of these two geometric areas is made. If the estimate is greater than one-third, then the patient is deemed ineligible for treatment. The same method applied to diffusion-weighted imaging. Interobserver reliability of this method was tested among five fellows who were blinded to any clinical information. With 20 test scans, the median kappa was 0.80.

A neuroradiologist (AJF) on the CT advisory panel for the ATLANTIS rt-PA study[10] reviewed all but two missing films of the 30 treated patients, approximately nine months after the last patient received treatment. Two of the reviewed CT studies were thought to show more than one-third MCA territory involvement (ie. treatment not recommended). Follow-up imaging of these patients, however, did not confirm the presence of infarction with more than one-third MCA territory involvement suggesting that either 1) more than one-third MCA territory involvement was not present on initial imaging, or, more remotely, 2) petechial hemorrhage had occurred on follow-up scans with pseudonormalization of these scans.[11] Films of patients excluded from treatment were also reviewed and were all corroborated as showing more than one-third MCA territory involvement.

Evaluation and follow-up

For all patients, a modified Rankin score was assigned for premorbid status, at discharge, and at three months. An NIH Stroke Scale score (NIHSSS) was measured at baseline, 24 hours, and three months. A follow-up imaging study was obtained on all patients within 24-72 hours. Intracranial hemorrhage was defined as an ovoid area of hyperdensity on CT scan or hypointensity on gradient-echo (blood sensitive) MRI
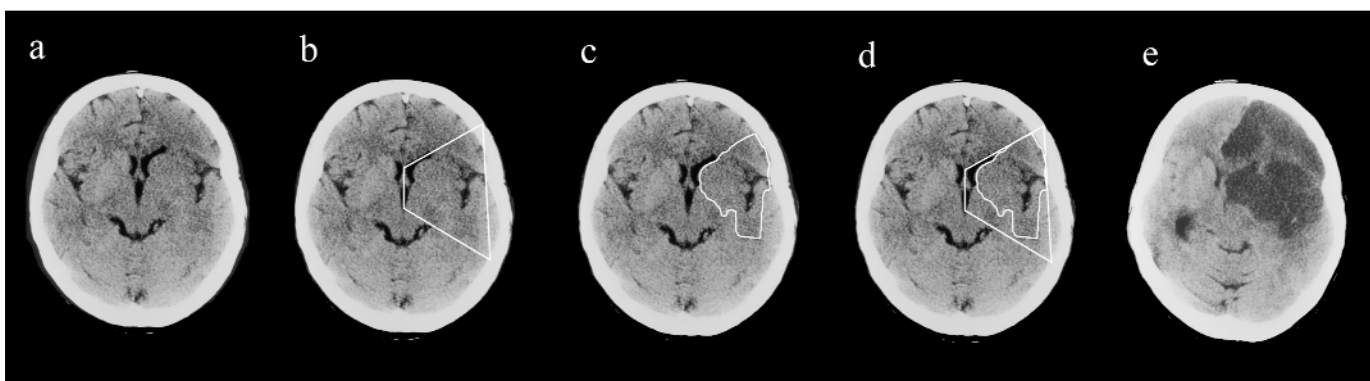
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Figure 1: *"ICE" method of estimation of greater than one-third middle cerebral artery infarction on initial CT scan: a. Baseline scan, b. Idealized MCA territory (trapezoid) onto baseline scan, c. Closure around area of abnormality, d. Estimate of ratio of C/I (figure c/figure d), e. 24-hour scan*

sequences. Symptomatic intracranial hemorrhage was defined as an intracranial hemorrhage accompanied by a 1-point decrease in level of consciousness or a 4-point or greater increase in the total NIHSSS, in accordance with the Prolyse in Acute Cerebral Thromboembolism (PROACT) definition.[12]

Other data collected included medical history, time of symptom onset, city of symptom onset, transfer times from peripheral hospitals, door-to-imaging time, imaging-to-treatment time, and door-to-treatment time. The driving distance from the city of onset to London was calculated using an Internet-based program.[13]

Statistical analysis

Comparisons were made between local patients and patients in the NINDS study.[1] When comparing baseline patient characteristics, comparisons were only made for age and time to treatment, factors that are known to be associated with increased risk for hemorrhage. A chi square test for associations was used. For cell values less than five, a two-tailed Fisher's exact test was used. Calculations were performed with Epi Info, version 6.04b.[14] Student's t-test was used to compare differences between means.

Confidence intervals (95%) were computed for hemorrhage rates. For 0 values, the "rule of threes" (3/n) was used to calculate the theoretical maximum risk (with 95% certainty).[15]

RESULTS

Between December 1, 1998 and February 1, 2000, 30 patients were treated in London, Ontario with intravenous tPA for acute ischemic stroke. Based on our prespecified imaging criteria, one patient who would have otherwise qualified for tPA was excluded. Her initial scan (Figure 1) showed apparent involvement of the majority of the MCA territory as well as anterior cerebral artery territory. Follow-up imaging corroborated these findings and the patient died of cerebral herniation. Baseline characteristics in comparison to the published information on part II of the NINDS rt-PA study are presented in Table 1. Patients in the London group were, on average, older (13% of patients were greater than age 80) and treated significantly later (97% beyond 90 minutes). Three patients had an initial NIHSSS greater than 20, two had a

violation of the traditional NINDS protocol (both with treatment greater than 180 minutes), two received tPA in the setting of recent catheterization, and one received tPA in the setting of a concomitant myocardial infarction.

Eighty-three percent of patients had symptom onset between 6:00 and 18:00 (Figure 2). Twenty-seven percent of patients treated in London were transferred from hospitals outside the city (Figure 3). The average time between arrival at the community hospital to arrival at the London hospital was 78 minutes (range 46-110 minutes). The average driving distance was 48 kilometers (range 29-98 kilometers). The average door-to-treatment time was 92 minutes for all patients (range 26-174 minutes).

Outcomes at 24 hours and three months in patients treated in London compared to patients in part II of the NINDS study are presented in Table 2. Follow-up imaging showed a new infarction in 80% of patients. There was no statistically significant difference between the London group and the treated arm of the NINDS tPA study in 24-hour 4-point improvements or
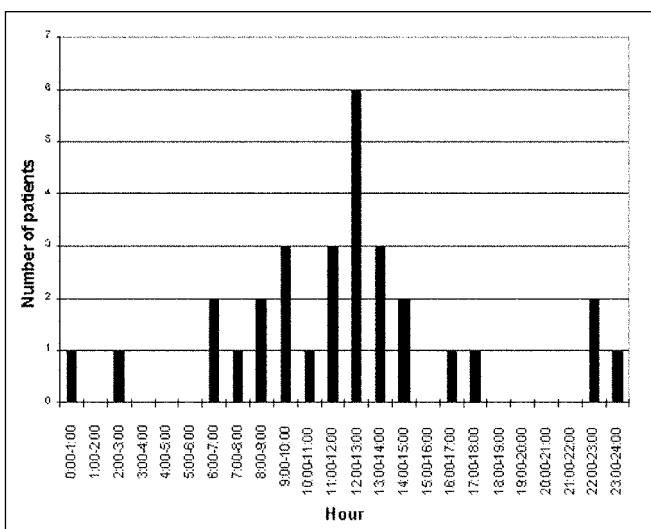

Figure 2: *Time of symptom onset*

Table 1: Baseline characteristics

	London (N=30)	NINDS treated (p-value) (N=168)	NINDS placebo (p-value) (N=165)
Mean age, (y+/-SD)	70+/-10	69+/-12	66+/-13 (<0.1)
Female (%)	63	43	42
White (%)	100	69	66
Baseline NIHSS (median)	14	14	15
Treated at 0-90 minutes (%)	3	51 (0.000001)	47 (0.000007)
Treated at 91-180 minutes (%)	90	49	53
Treated at 181-195 minutes	7	0	0
Hypertension (%)	60	67	67
Smoking (%)	27	27	35
Prior stroke (%)	30	12	9
Diabetes (%)	20	20	20
Coronary disease (%)	30	22	20
Atrial fibrillation (%)	17	20	16
Anti-platelet use (%)	37	40	26
Suspected lacunar syndrome (%)	17	14	9

Table 2: Outcomes

	London % (N=30)	NINDS treated % (p-value)* (N=168)	NINDS placebo % (p-value)* (N=165)
24 hours			
≥4 point improvement or normal	63	48 (0.11)	39 (0.02)
Three months			
NIHSSS			
0-1	37	31 (0.46)	20 (0.03)
2-8	43	30	32
>8	7	22	27
Death	13	17	21
death or severe disability	20	39 (0.04)	48 (0.004)
modified Rankin			
0-1	37	39 (0.79)	26 (0.23)
2-3	37	21	25
4-5	13	23	27
Death	13	17	21
death or severe disability	27	40 (0.15)	48 (0.03)

NIHSSS= National Institute of Health Stroke Scale score.

Severe disability is defined as an NIHSSS > 8 or modified Rankin score equal to 4 or 5.

*All statistical comparisons are made in reference to the London group.

Table 3: Complication rates

	London % (N=30)	NINDS treated % (N=312)	NINDS placebo % (N=312)
Symptomatic ICH	0	6.4	0.6
Fatal ICH	0	2.9	0.3
Asymptomatic ICH	3.3	4.5	2.9
Petechial hemorrhage	23.3	NA	NA
Major systemic hemorrhage	3.3	1.6	0

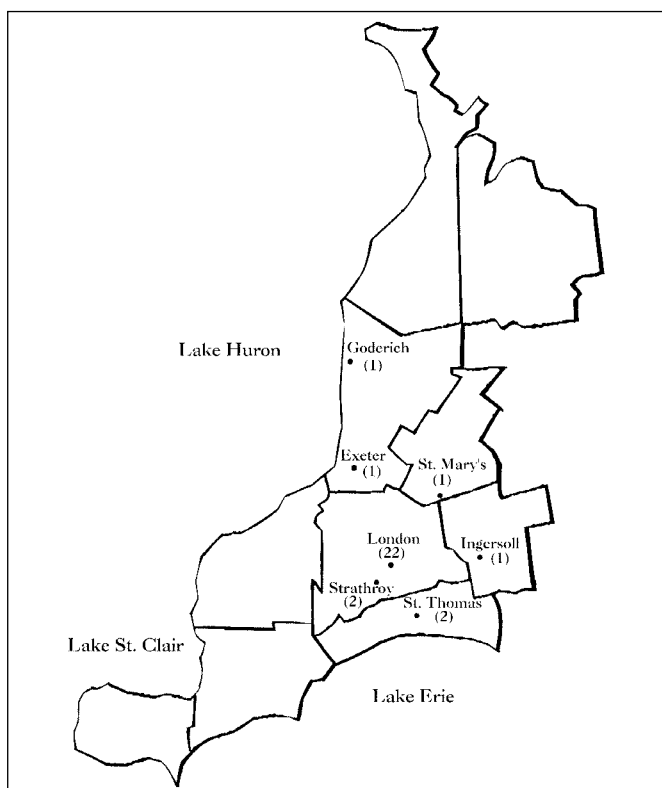ICH = intracranial hemorrhage: NA = not available: p>0.05 for all comparisons to London group

Figure 3: Map of the surrounding London area with numbers of patients from each city

three-month normal outcomes. A statistically significant reduction in death or severe disability was observed. In comparison to the placebo arm, statistically significant improvements in the 24 hour NIHSSS, and reduction in death or severe disability were observed.

Complication rates in comparison to patients in parts I and II of the NINDS tPA study are presented in Table 3. One patient treated locally developed a vitreous hemorrhage which resolved spontaneously. Because the number of patients treated in London is small at this time, a statistically significant reduction in symptomatic intracranial hemorrhage in comparison to the treatment arm could not be achieved (p=0.24 with two-tailed Fisher's Exact Test). Given that no SICH were observed in the London group, the maximum possible rate (with 95% certainty) is 10%, using the rule of threes. There was no statistically significant difference in overall intracranial hemorrhage rate (symptomatic and asymptomatic) between the London group and the NINDS placebo arm.

DISCUSSION

The outcomes of patients in this series are similar to, and in some respects better than, patients in the NINDS study. These data provide further support to growing evidence from other centers around the world that tPA can be given outside of the NINDS trial with similar rates of normal or near-normal function in those treated.[3-6,16-18]

Despite the beneficial effects of tPA in acute ischemic stroke, there has been a marginal increase in the use of this medication for this purpose. Most likely, the biggest fear is the risk of symptomatic and fatal intracranial hemorrhage.[19] Therefore, the decision to treat, or, in this case, not to treat, lies mainly in the fear of side effects despite overall benefit.

In the NINDS study, the risk of symptomatic intracranial hemorrhage with tPA was 6.4%.[1] *Post hoc* analysis suggested that several factors including advanced age and NIHSSS greater than 20 were associated with this increased risk. In The European Cooperative Acute Stroke Study-I, an additional risk factor was identified for the first time, namely greater than one-third involvement of the MCA territory on CT, as identified by experts.[2,8] Subsequent nonrandomized studies have supported this observation. Despite their retrospective nature, so suggestive were these findings that they were implemented as part of the exlusion criteria in a six-hour intra-arterial thrombolytic trial,[12] a 3-5-hour intravenous tPA trial,[10] and a 0-6-hour intravenous tPA trial.[20] The rates of SICH in these trials were 7.0%, 10.2%, and 8.8% respectively. These rates of hemorrhage are less than comparable trials with similar time windows and without prespecified CT exclusion criteria ie. 21.2% in 0-6 hours[21] and 12.6% in 0-4 hours.[22] Further, some animal studies have suggested that tPA may actually enlarge infarct volume after permanent brain injury has already occurred,[23,24] though others have failed to reproduce these findings.[25,26] The precise definition and method for one-third estimation has not been published. Nevertheless, the gestalt observation is important because it suggests a potential area of nonintervention. A recent study has shown only fair inter-rater reliability for the estimation.[27] In that study, participants did not employ a systematic method of estimation.

Though these data are based on a small number of patients, it appears that the prespecified use of CT exclusion criteria by treating physicians may reduce the rate of symptomatic intracranial hemorrhage and increase the rate of good outcomes at 24 hours despite recruitment of older patients at later treatment times. In addition, there was no increase in the risk of symptomatic intracranial hemorrhage in patients with relative contraindications (NIHSSS > 20 or age >80), or in patients with direct violations of the traditional protocol. We suppose that the lower rates of symptomatic intracranial hemorrhage are explained by the smaller volume of initial tissue infarction present for subsequent hemorrhage. Previous studies have suggested that those who have symptomatic hemorrhage are those who likely would have had poor outcomes despite thrombolytic therapy. Further, the finding of a trend towards an increased rate of good outcomes at 24 hours suggests that the patient population selected were those most likely to benefit (ie. those who had not already gone on to tissue infarction).

The implementation of a measure to reduce the occurrence of a suspected precipitant to an undesirable outcome has occurred in other settings. The New Zealand Cot Death study group suggested, through a case control study, that infants who slept in a prone position had an increased risk of sudden infant death syndrome.[28] In February 1991, a national campaign was launched to have babies sleep in the supine position. Concomitant with a major decline in the percentage of babies sleeping in the prone position, the rate of sudden infant death

syndrome in New Zealand dropped sharply from 4.2/1000 live births before the intervention to 2.5/1000 afterwards.[29] Despite the lack of a randomized study comparing prone sleeping to supine sleeping, many accept the above observations as powerful evidence for the need of such an intervention.

With respect to positive outcomes, similar three-month cure rates were observed compared to the treated arm of the NINDS study. Some might argue, therefore, that benefits gained at 24 hours have somehow been lost in subsequent follow-up. However, there are significantly less severely disabled or deceased patients at three months; these findings are potentially important given that 13% of the patients in this series were over the age of 80.

Thirty percent of treated patients were transferred from outside hospitals without CT scanner availability. We feel that emergency bypass protocols may further increase the percentage of patients eligible for this treatment by reducing the critical amount of time spent in transit to non-CT hospitals. The observation that 83% of treated patients had symptom onset between the 12 hours from 06:00 to 18:00 suggests that hospitals which can only operate CT scans during certain hours, a situation which is not uncommon in the Canadian setting, may still be able to treat the vast majority of patients. In addition, the observation that 80% of patients had a new infarction on follow-up imaging suggests that the vast majority of patients who are treated can correctly be identified as suffering from ischemic strokes, as opposed to other diagnoses, despite the paucity of time for diagnosis.

At this time, it would be difficult to suggest that these results might be generalizable to other groups of physicians because the treating physicians in this series were specifically trained in acute stroke treatment and CT interpretation. Nevertheless, these findings suggest that a well designed "stroke team" has the capacity to safely and effectively administer acute stroke treatment.

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