CT-guided thrombolytic treatment of patients with wake-up strokes☆

Carmel Armon[a,*,1], Jochay Wainstein[a,1], Aviv Gour[a,2], Ronen Levite[a], Avigail Bartal[a], Angela Kriboushay[a], Gilad Kenan[a], Fikri Khiri[a], Evelina Shevtzov[a], Rina Aroesty[a], Sarah Bhonkar[a], Sigal Tal[b], Eduard Ilgiyaev[c], Alex Blatt[d], Zoya Haitov[e], Samuel Bar-Hayim[f,3], Itzhak Kimiagar[a,c]

[a] Departments of Neurology, Sackler Faculty of Medicine and Shamir (Assaf Harofeh) Medical Center, Tel Aviv University, Tel Aviv, Israel
[b] Departments of Radiology, Sackler Faculty of Medicine and Shamir (Assaf Harofeh) Medical Center, Tel Aviv University, Tel Aviv, Israel
[c] Departments of Intensive Care, Sackler Faculty of Medicine and Shamir (Assaf Harofeh) Medical Center, Tel Aviv University, Tel Aviv, Israel
[d] Departments of Cardiac Intensive Care, Sackler Faculty of Medicine and Shamir (Assaf Harofeh) Medical Center, Tel Aviv University, Tel Aviv, Israel
[e] Departments of Anesthesiology, Sackler Faculty of Medicine and Shamir (Assaf Harofeh) Medical Center, Tel Aviv University, Tel Aviv, Israel
[f] Departments of Emergency Medicine, Sackler Faculty of Medicine and Shamir (Assaf Harofeh) Medical Center, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

Background: Observational studies of thrombolysis outcomes in wake-up acute ischemic stroke patients selected based on non-contrast brain CT criteria suggested that treated patients did as well as or better than those not treated, after adjustment for baseline characteristics. We began offering thrombolytic treatment (IVTPA) to patients presenting with wake-up strokes and normal non-contrast brain CTs, who could be treated within 4.5 h of being found.

Design/methods: A retrospective chart review was performed in patients presenting with AIS between November 2014 and December 2017 who received IVTPA. A planned subgroup analysis compared patients with wake-up strokes and normal non-contrast brain CTs to patients with witnessed stroke treated within 4.5 h of being found, or of witnessed onset, respectively.

Results: Three hundred and six patients were treated, 279 with witnessed-onset and 27 with wake-up strokes. The latter were not candidates for endovascular intervention. Efficacy and safety were similar in both groups. Discharges home, respectively, were 143(53%) and 13(48%); facility discharges were 112(40.1%) and 11(40.7%) and in-hospital mortality was 19 (6.8%) and 3 (11%). Treatment-related symptomatic bleeds were: 5(1.8%) and 1 (3.7%), respectively.

Conclusions: The findings affirm, in a new clinical series reflecting routine practice, that it is safe to treat with IVTPA patients with wake-up strokes and a normal brain CT scan, who are not candidates for endovascular intervention. We hypothesize, that when the non-contrast brain CT scan is normal, it may be safe to extend beyond 4.5 h the IVTPA treatment eligibility window in similar patients with witnessed-onset stroke.

1. Introduction

Intravenous TPA is safe and effective for appropriately selected patients with acute ischemic stroke (AIS) treated within 4.5 h from onset [1,2]. A pooled analysis of the ATLANTIS, ECASS, and NINDS rt-PA stroke trials showed that efficacy declined with each additional 90-minute window from onset. There was an increase in the hazard ratio for mortality in the 270–360 min window [3]. The balance between benefit and harm weighing against use of thrombolytic therapy in this window was highlighted by further analysis of these data, that showed

that 5.2% of patients treated between 270 and 360 min from stroke onset benefited and 7.3% were harmed [4]. An individual patient data meta-analysis of 8 randomized, double-blinded, placebo-controlled trials (including those analyzed previously [3]) showed that the 90-day outcome of the treated and untreated groups did not differ when treatment was given between 271 and 360 min [5]. The third international stroke trial (IST-3) assessed the value of extending the boundaries for TPA use by including patients even if over 80 years old and between 270 and 360 min from onset [6]. While it did not meet its primary outcome – an increase in the number of people alive and independent at 6 months, secondary analysis showed a significant shift within levels of disability in favor of treatment. An increase in early mortality (within 7 days) in the treatment group was offset by an increase in later mortality in the untreated group. At 18 months [7] – there was no difference in mortality between the groups and no difference in the proportion of patients living at home. However, 3.6% more treated patients were independent (NNT = 28), there was a favorable shift in the distribution of disability grades, and treated patients reported higher overall health. In subgroup analyses of efficacy at 6 months [6], point estimates of odds of benefit were discordant without attaining statistical significance. They favored treatment in the 270–360 min group, but weighed against treatment in the 180–270 min group: the 95% confidence intervals for both estimates spanned unity. These analyses were not provided in the 18 month follow up report [7]. Two meta-analyses [8,9] did not provide further resolution regarding the 270–360 min window, as the trials included were heterogenous for the > 180 min treatment window. The authors' conclusions [9] were that some patients "…may still derive benefit if treated up to six hours." Another meta-analysis of individual patient data from 9 RCTs [10] concluded that delay of > 4.5 h resulted in good outcome for 401 (32.6%) of 1229 versus 357 (30.6%) of 1166 (OR 1.15; 95% CI 0.95–1.40). This result translates to a point estimate of NNT = 50, without attaining statistical significance for treatment benefit in this window. It remained difficult to decide, based on these additional trials and meta-analyses, how best to deal with patients presenting in the 270–360 min window. It appeared, based on the early analyses [3,4], that there was potential for benefit that might be offset by the risk for harm. The challenge was to find criteria to select safely patients who might benefit from IV TPA treatment in this time window, while minimizing the risk for harm.

There are lessons to be learned from the mechanical thombectomy trials. After examining first treatment within 8-hours from onset and failing to show efficacy, a safe 6-hour treatment window was confirmed, based in part on refined selection criteria and in part on technological advances [11]. Very shortly thereafter, two clinical trials (DEFUSE3, DAWN) showed that the treatment window could be extended up to 24 h, based on a mismatch between presumed tissue at risk or clinical deficit and estimated irreversible stroke volume, based on MRI or CTP criteria [12,13]. While the results of these studies were not available until recently, the rationale underlying their design pervaded contemporary thinking at the time the patients reported here presented and were being considered for treatment.

Expansion of the temporal eligibility window for IVTPA use had been addressed indirectly in patients who arrive with an unknown time of stroke onset. The most common scenario was patients who woke up with a stroke. Many reports described the use of thrombolysis in subgroups of such patients, selected based on imaging criteria [14–19]. Most of these reports showed favorable outcomes, but represented Class IIa or IIb levels of evidence, applying the AHA/ASA classification schema [20]. For example, in one consecutive case series, the outcomes of 68 treated patients were (a) better than those of untreated patients, after adjusting for baseline patient characteristics [18], and (b) comparable to those treated within 4.5 h of known onset [19]. The chief limitation of most reports was lack of random allocation to treatment, with parallel untreated controls.

Two recent reports (2018) have provided data regarding use of

intravenous thrombolysis treatment of carefully-selected patients with wake-up strokes who have MRI findings suggesting early ischemia, but not completed infarction. The first was a case series (MR WITNESS) [21], evaluating safety relative to historical data. It was not designed or powered to demonstrate efficacy. The second was a clinical trial that randomized patients to thrombolysis or placebo (WAKE-UP) [22] and showed treatment benefit (NNT = 11), but also a possible indication of harm [23] that fell short of statistical significance due to small numbers; the study was stopped before target enrollment was attained, as funding ended.

However, most medical centers, including those providing endovascular treatments, use CT to evaluate patients presenting with AIS [3,24], as does ours [25], and the 2018 results [21,22], using MRI selection criteria, were not available to us when we had to make treatment decisions between 2014 and 2017.

Shamir (Assaf Harofeh) Medical Center (SMC) is a teaching hospital affiliated with the Tel Aviv University Sackler School of Medicine. In early 2013 we expanded our treatment of AIS patients, based on the AHA/ASA 2013 Guidelines [24]. We were impressed by the explicit statement, that "…a physician with expertise in acute stroke care may modify the list…" of indications and contraindications for TPA use (Table 10 Footnote) [24]. An endovascular unit was established at SMC in November 2014. We analyzed our patient outcomes for November 2014 through December 2017. The primary intent was internal quality control: to compare our outcomes to those of the immediately preceding 21 months [25]. We found continued efficacy and safety of reperfusion treatments at our center under changing treatment paradigms. In addition, weighing all the information available in 2014, we began to offer thrombolytic treatment on a case-by-case basis to patients with wake-up strokes and normal non-contrast brain CTs who could be treated within 4.5 h of being found, and were not candidates for endovascular intervention due to absence of a target – large vessel occlusion. We emphasize that these were only patients who woke up and found to have a stroke, not any patient presenting with a stroke of unknown time of onset. We reasoned that this approach might offer wake-up stroke patients the benefits of reperfusion therapy shown for patients treated beyond 270 min from known stroke onset [4] while striving to diminish the 7.3% risk of harm [4] experienced by those patients. We compare outcomes in these patients to outcomes in patients with witnessed onset who received thrombolysis within 4.5 h of onset.

2. Methods

A retrospective chart review was conducted of the medical records of all patients who received IV TPA for acute ischemic stroke (AIS) at SMC between November 2014 and December 2017 (38 months). The primary intent of our review was to assess the impact of introduction of on-site endovascular treatment capabilities in November 2014 and ongoing efforts to expand delivery of reperfusion therapy to our patients. Our primary comparison analyzed outcomes during this period compared to those of the preceding 21 months (February 2013 to October 2014) [25] that followed the publication and resultant implementation at our center of the 2013 AHA/ASA Guidelines [24]. To permit a valid comparison of system performance between the two periods – patients who received IV TPA and endovascular treatment were first analyzed and reported together with patients who received TPA alone. A subgroup analysis of patients treated in the latter period compared patients with wake-up strokes and normal non-contrast brain CT scans who were treated within 4.5 h of being found to patients with witnessed stroke treated within 4.5 h of onset.

Excluded from this report are patients who received endovascular treatment alone. There were no wake-up stroke patients in this group. Similarly excluded are patients who were transferred to SMC from other hospitals for consideration of endovascular treatment.

We excluded from the efficacy reporting "stroke mimics" [26,27] in

Table 1

Patient characteristics: Patients with witnessed onset vs. wake-up strokes.

	Total	Witnessed onset	Witnessed[b] onset, TPA only	Wakeup[b] stroke
Number of patients treated	306	279	254	27
Patients per year	97	88	80	9
Number (%) Men	179 (58.5%)	161 (57.5%)	152 (59.8%)	18 (66.6%)
Age (years) Mean ± SD	71.3 ± 13.3	71.2 ± 13.4	71.1 ± 13.5	72.0 + 13.3
Age range (years)	24–101	24–101	34–101	47–99
Admission NIHSS, Mean ± SD	8.2 ± 5.4	8.4 ± 5.5	7.7 ± 5.1	6.8 ± 3.4
NIHSS range	1–32	1–32	1–32	2–17
Patients with NIHSS ≥ 6	179(58.5%)	163 (58.4%)	138 (54%)	16 (59.3%)
Time, onset to ER (min)	87 ± 46	87 ± 47	88 ± 46	87 ± 43[a]
Range	0–213	0–213	0–213	30–178
Time, ER to treatment (min)	82 ± 35	81 ± 34	83 ± 34	87 ± 36
Range	26–201	26–201	26–201	49–177
Time, onset to treatment (min)	169 ± 54	168 ± 54	172 ± 52	174 ± 54[a]
Range	59–330	59–330	60–330	90–270

[a] Wake-up time to ER or to treatment.

[b] Differences between witnessed and wake-up strokes, TPA only treatment: p = NS.

whom other diagnoses became evident shortly after TPA administration and list their diagnoses and safety outcomes separately. We did not reclassify as stroke mimics patients in whom the suspicion of an alternative diagnosis arose when they presented at a later date with similar symptoms, or while reviewing their records to prepare this report.

Patient numbers, demographic features, stroke severity, work flow parameters, outcomes, and safety were reviewed.

For patients with wake-up strokes and normal CTs – we registered "time found" as "time of onset." We recognize that "time found" underestimates time of onset. The percentage of patients treated with IV TPA relative to total ischemic stroke discharges is calculated based on audited data reported to the Israel Ministry of Health [28]. As before [25], we continued to compare, in secondary subgroup analyses, outcomes in patients with more severe strokes, defined by admission NIHSS scores ≥ 6 (who would have been included in early thrombolysis series, including our own pre-2013 cohorts) and patients with milder strokes (NIHSS < 6).

Primary efficacy outcomes were: discharged home, discharged to inpatient rehabilitation or to a nursing home, and death. Safety outcomes were death and symptomatic parenchymal bleeds (PH2) [29], classified as defined [29]. The reported safety outcomes were assessed routinely as standards of practice at our institution. All patients were scanned approximately 24 h after treatment, or sooner if there was clinical deterioration. The occurrence of symptomatic bleeds was reflected in the medical records and they were reported contemporaneously to the MOH. In addition, in preparing this report, all instances where a bleed was suggested on the 24-h CT scan were reviewed, and its classification confirmed by the lead author (CA).

Differences between means and between proportions were assessed for significance using appropriate z-tests. Differences in the distributions of outcomes were assessed using the chi-squared test. Confidence intervals (CI) around the frequencies of rare adverse events were calculated assuming a binomial distribution. The study was approved by the SMC Institutional Review Board (IRB).

Data availability: De-identified primary patient data may be made available to qualified researchers subject to submission, via the corresponding author or his designee, of a scientifically sound protocol for use of this data to the SMC IRB; approval of said protocol by the SMC IRB; and subject to conditions set by the SMC IRB. In most cases, a requirement for consideration by the SMC IRB will be that there be a co-principal investigator from the SMC Department of Neurology.

3. Results

3.1. Primary analysis

Three hundred and six patients with AIS were treated between November 2014 and December 2017. They represented 17.1% of all patients discharged with a diagnosis of ischemic stroke during those 38 months. Twenty-five (8.1%) of these patients received, in addition, endovascular treatment. The percentage of AIS patients treated rose from 10.6% during February 2013–October 2014 to 17.1% during November 2014–December 2017 (p < .001). The average time between arrival at the ER and treatment decreased by 9 min, from 90 ± 33.5 (mean ± standard deviation) to 81 ± 34 min (P < .01). Median (IQR) severity of patients with NIHSS ≥ 6 was similar, nominally up from 9 (7,13) to 10 (7,15). There were no other differences in patient characteristics, work-flow and outcomes.

In-hospital mortality of treated patients was similar during the two periods. The number of symptomatic intra-parenchymal bleeds was low: 4 (4%) in the earlier 21- month period [25] and 6 (2%; 95% CI: 0.7–4.2%) in the current 38-month period. With one exception – all symptomatic bleeds occurred in patients with NIHSS ≥ 6. The exception was a patient with witnessed stoke onset who sustained a brain stem bleed following TPA administration, that led to complications resulting in death.

Four patients (not included in the 306 total) received IV TPA, in whom the diagnosis was determined soon after TPA administration to be other than AIS ("stroke mimics"). The correct diagnoses were found to be: superior sagittal sinus thrombosis (fatal outcome), intraspinal (epidural) hematoma producing face-sparing hemiplegia (underwent emergent spinal decompression surgery and extensive rehabilitation, recovery plateaued at mRS = 2), Bell's palsy and Todd's paralysis (no sequelae). On retrospective review of the records we suspect a small number of additional patients (1–2% of the total) may have been stroke mimics. The chief alternative diagnoses suspected are Functional Neurological Disorder and Todd's paralysis. They are included in the 306 total, as we did not have a systematic way to identify and reclassify these patients retrospectively.

3.2. Wake-up stroke patient analysis

Characteristics of patients with wake-up strokes and normal CT scans and of patients with witnessed stroke onset are summarized in Table 1. There were 279 patients with witnessed-onset strokes and 27 patients with wake-up strokes. Initial comparison of all patients with witnessed-onset strokes to the patients with wake-up strokes and normal CT scans shows that the patients with witnessed-onset strokes

Table 2

Patient outcomes: patients with witnessed onset vs. wake-up strokes.

	Total	Witnessed onset	Witnessed onset[a] TPA only	Wakeup[a] stroke TPA only (all)
Number of patients treated with IV TPA	306	279	254	27
Number TPA + EV	25 (8.1%)	25	0	0
DISPOSITION – ALL				
Discharged Home	161 (52.6%)	148 (53.1%)	142 (56%)	13 (48.1%)
Discharged to Rehab/NH	123 (40.2%)	112 (40.1%)	95 (37.4%)	11 (40.7%)
Deceased	22 (7.2%)	19(6.8%)	17 (6.7%)	3 (11.0%)
INTRACRANIAL BLEEDS				
Total (PH1 &PH2)	15 (4.9%)	14 (5%)	10 (3.3%)	1 (3.7%)
Symptomatic	6 (2%)	5 (1.8%)	4 (1.3%)	1 (3.7%)
% of NIHSS ≥ 6	5/179 = 2.8%	4	3	1
% of NIHSS < 6	1/127 = 0.8%	1	1	0
Disposition by admission NIHSS				
NIHSS ≥ 6 (N)	179 (58.5%)	163 (58.4%)	138 (54%)	16 (59.3%)
Discharged Home	70 (39.1%)	63 (38.6%)	57 (41.3%)	7 (43.7%)
Discharged to Rehab/NH	90 (50.2%)	83 (50.9%)	66 (47.8%)	7 (43.7%)
Deceased	19 (10.6%)	17 (10.4%)	15 (10.8%)	2 (12.5%)
NIHSS < 6 (N)	127	116	116	11
Discharged Home	91 (71.6%)	85 (73.2%)	85 (73.2%)	6 (54.5%)
Discharged to Rehab/NH	33 (26.0%)	29 (25.0%)	29 (25.0%)	4 (36.3%)
Deceased	3 (2.3%)	2 (1.7%)	2 (1.7%)	1 (9.0%)

[a] All differences are not statistically significant.

Table 3

Risk factor comparison: SMC-TPA vs. GWTG-TPA vs. SITS-MOST TPA vs. Israeli stroke population sample (NASIS).

	SMC-TPA (N = 306)	GWTG-TPA (N = 58,353)	SITS-MOST TPA (N = 6483)	NASIS-general (N = 6279)
Age (Mean ± SD)	70.8	70.4	68	69.8
Number (%) males	58.1%[a]	49.8%	60.2	53.9%
Diabetes Mellitus	141 (46.0%)[a]	25.3%	16.0%	39.3%
Hypertension	244 (79.7%)[a]	74.5%	58.7%	76.1%
Hypercholesterolemia	199 (65.0%)[a]	39.8%	34.8%	59.1%
Atrial Fibrillation – Total	96 (31.3%)	No data		
Known, preadmission	52 (17.0%)		23.9%	17.5%
Diagnosed this admiss.	37(12.0%)			
Diagnosed p disch.	7 (2.3%)			
Current smoking	101 (33.0%)[a]	19.0%	43.2%	20.3%
On antiplatelet therapy	140 (45.7%)			
On Heparin or LMWH	2 (0.65%)			
On Coumadin (sub-ther.)	11 (3.6%)			
On NOAC (lapse)	2 (0.65%)			

[a] $P < .05$ for comparison between SMC-TPA and GWTG-TPA proportions.

had higher NIHSS scores (Mean ± Standard Deviation: 8.4 ± 5.5, Range 1–32 compared to 6.8 ± 3.4, Range 2–17, ($P < .05$). However, none of the treated wake-up stroke patients were eligible for, or received, endovascular treatment: the requirement of a normal CT scan apparently excluded from consideration patients with wake-up stroke and large vessel occlusion. A more valid comparison is to witnessed-onset patients who were treated with TPA alone: their NIHSS scores (7.7 ± 5.1, range 1–32) were no different from those of the wake-up stroke patients. The percentage of patients with NIHSS ≥ 6 was also similar in both groups (circa 60%). There was no difference in cerebrovascular risk factors between treated patients with witnessed onset strokes and those with wake-up strokes.

Patient outcomes were the same in both groups (Table 2). Similar percentages of patients were discharged home (53%) or to rehabilitation (40%), and approximately 7% died. The similarities are evident also when looking separately at patients with NIHSS ≥ 6 and < 6.

Review of safety outcomes led to re-examination of the pre-treatment CT scan of the one patient in the wake-up stroke group who sustained a fatal intra-parenchymal bleed. Stringent inspection of that scan revealed that it showed subtle evidence of an intraparenchymal bleed: 2–3 tiny spots, indistinguishable from calcifications, at the level of resolution of the equipment, in a brain with severe atrophy. This had not been appreciated at the time. We include this patient in the reported wake-up stroke group to reflect completely the risks inherent in relying

on a normal CT scan to select patients for IVTPA treatment, in all patients. The two other patients in the wake-up stroke group who died – died of their stroke (severe stroke with complications).

4. Discussion

We met our primary quality and safety assurance goals, verifying that increasing the numbers of patients treated at SMC with IV TPA, the addition of on-site endovascular treatment, and treating select patients with wake-up strokes was accomplished safely and effectively. Our use of hospital disposition as an efficacy outcome variable, considering discharge home as the favorable outcome, is the same as the approach of the GWTG program in the United States [30]. As reported previously [25], our percent of home discharges is similar. The comparison is limited because of (a) somewhat lower admission median NIHSS scores in our population, even when only patients with NIHSS ≥ 6 are considered; and (b) greater prevalence of stroke risk factors in our TPA population, including risk factors that impact outcome, than in the GWTG population [30], the SITS-MOST population [31] and the overall Israeli stroke population [32] (Table 3).

Our overall in-hospital mortality has remained stable. The frequency of symptomatic hemorrhages was low, and comparable to the frequency reported by SITS-MOST [31] in patients treated within three hours.

We gave special attention to stroke mimics [26,27] identified in real time and sought to learn from the experience. Where an alternative neurologic diagnosis was found in real time, the patients were excluded from the efficacy assessments. They are reported explicitly and separately in our safety analysis, to benefit others, as two patients experienced adverse outcomes, one fatal. We did not have a systematic approach to identifying stroke mimics that might be re-diagnosed properly as "Functional Neurological Disorder mimicking stroke" and suspect that 1–2% of our patients may have fallen into this category. The literature [26,27,33–37] suggests that IVTPA treatment is safe in these patients. We have begun to consider this possibility when we see patients recur with similar symptoms. We did not reclassify patients based on the results of suspicions arising in retrospect. We suspect similar patients may have been included in other studies that did not report explicit methods to identify and exclude them.

Our comparison of patients with wake-up strokes and normal CT scans to patients with witnessed stroke onset, provided they could be treated within 4.5 h of being found, showed that the outcomes were comparable in both groups. The study design might permit classifying the evidence as Class III, using the American Academy of Neurology classification scheme [38].

We consider potential limitations of our report. We introduced the treatment of select patients with wake-up strokes in a gradual manner. This is consistent with our leadership philosophy regarding the best way to effect change. As such, there was no institutional protocol and no obligation to offer treatment. An alternative approach would not have been feasible, as it would have generated insurmountable push-back and delays, likely undermining the entire effort. We did not keep track of patients with wake-up stroke who were excluded from treatment based on CT findings, or who may have been eligible for consideration of treatment but were not considered. The issue of possible selection bias cannot be addressed by the data we collected. However, the similarity of the patients with wake-up strokes to the comparison group, in terms of age, severity and comorbidities, suggests that there was no large-scale bias that excluded sicker wake-up stroke patients.

An additional point that emerged during the study was that there were varying interpretations of "normal CT scan". The original intent was "absolutely normal," considering as abnormal findings: atrophy, white matter disease, old stroke, tumor, and early signs of the current stroke. However, the most common interpretation was "absence of early CT changes of ischemia in the clinically relevant area," as would be assessed to calculate an ASPECTS [39] score. This meant that all patients had an ASPECTS score of 10, but some had non-acute abnormalities. The wake-up stroke patients who received IVTPA did not have a dense MCA sign. Finally, our numbers are small. If our findings are taken in isolation, small numbers may translate into reduced confidence in the results. However, our observations should be considered in the context of the previous wake-up stroke treatment reports [8–14] that gave us confidence to treat these patients. Our results provide confirmatory data. Our occurrence of bleeds was lower, likely because we required a normal head CT scan. We do not imply that our approach to patients with wake-up stroke can be applied to patients with stroke of unknown time of onset who are not wake-up stroke patients and did not apply it to such patients.

The strengths of our findings are that they reflect a "real world" experience in a university teaching hospital, with rotating resident and attending physicians spanning several specialties collaborating in the care of patients with AIS. Our criterion for assessing the eligibility of wake-up stroke patients relied on the initial non-contrast brain CT. The test is readily available, inexpensive, and part of the usual work flow in over 90% of hospitals who treat AIS. No special resources were allocated. Our approach may serve as a model for the many teams who are motivated to seek safely additional patients who may benefit from IV TPA using readily available information. Patients who showed an extensive stroke estimated as > 6 h old on a non-contrast brain CT did not require further emergent imaging. Patients with mild or indeterminate

changes were eligible for consideration for endovascular treatment and were studied further with CTA and CTP. The outcomes we used to assess efficacy and safety are objective, and not dependent on the observer. They cannot be influenced by absence of masking to patient stroke onset status (witnessed or wake-up). It is telling, that the average process times (onset/found to ER, ER to treatment, onset/found to treatment) were virtually identical for both groups. We note as a strength, that we identified and report rare errors that resulted in harm, and address suspected mis-diagnoses that did not result in harm, setting the stage for further refinement of our assessment of patients for eligibility for IV TPA treatment.

The IST3 study [6,7] and subsequent meta-analyses [8–10] showed a tendency towards benefit with treatment during the 270–360 min window. Early (within 7 days) increased mortality was offset by later decreased mortality in the treated arm, but primary endpoints were not met [6,7], and within the largest meta-analysis [10] the NNT were large for non-significant point estimates pointing in the direction of benefit. This reflects the difficulty of recovering from the effect on overall outcomes of harm incurred early, even if in only a small percentage of patients. Recognizing this, subsequent studies that attempt to expand the treatment window safely have tried to select patients who are less likely to incur early harm.

Our findings suggest that the increased early risks associated with an extended time window from stroke onset, as demonstrated prior to and within the IST3 study and the subsequent meta-analyses, may be mitigated by the added safety conferred by absence of any ischemic changes on the initial CT scan. Nevertheless, our numbers are small, and expanded use may result in a higher rate of symptomatic bleeds.

Use of CT criteria in our patient selection process, while similar to the practice in most stroke centers, may introduce some uncertainty in the diagnosis when the non-contrast CT is normal and the CTA shows open vessels with no evidence of CTP abnormalities. A related limitation is that application of non-contrast brain CT selection criteria requires excellent imaging visualization skills. We have found application of the ASPECTS scale to be more challenging in patients with severe cerebral atrophy. However, this is no different than in patients presenting within 4.5 h of known onset, and the risk of misdiagnosis, on these grounds, are the same.

Recent studies have reported on the use of MRI criteria to select candidates with wake-up strokes for thrombolytic treatment [21,22]. This modality, the attendant staffing, and the entire infrastructure put in place to perform these studies are not available widely. Unless CT scans are being obtained in parallel, it may not be clear whether this greater effort translates into greater safety or efficacy than reliance on CT criteria alone, and generalizability will be challenging. Two studies have shown the value of MRI – DWI or of CTP-based selection criteria to extend the window for mechanical thrombectomy [12,13]. Thus, the concept of using criteria based on tissue physiology to select patients with AIS for reperfusion treatment, rather than time elapsed, is well-established. Individual medical centers may consider patient selection criteria optimal for them, considering available resources, balancing simplicity, inclusiveness and safety to permit a maximal number of current patients to benefit. The criterion we used, a normal brain CT, is more stringent than that used when administering TPA within the 270 min window, or within the IST3 study, which permits the presence of some CT changes. While minimizing the risk of bleeding, it may exclude some wake-up stroke patients who may benefit from IV TPA. It is challenging to consider relaxing this criterion in a risk-averse practice setting, and our data do not provide guidance. Clinical trials may identify circumstances where it is reasonable to ask patients to take risks up front, in the hope of future benefit. Our practice focused on minimizing the risks up front, in the hope that future benefit will mirror that incurred by other patients who had not experienced early harm. A final question, deriving from our and previous observations [8–16] in patients with wake-up stroke, is whether it may be safe to extend the treatment window beyond 4.5 h in patients with witnessed stroke onset,

provided that their non-contrast brain CT scan is normal (ASPECT score = 10). This would be equivalent to selecting, from within a population similar to that tested in IST3, a subgroup that is least likely to experience early harm. This is similar to the approach taken in ECASS [40] to establish the efficacy of IV TPA in the 180–270 min window, where patients thought more likely to experience harm were excluded. For the time being, we consider our findings as indications that it may be safe to offer IVTPA treatment to wake-up stroke patients with normal brain CTs, but insufficient to suggest that it should be mandatory to offer treatment to such patients. Our findings suggest further, that it may be safe to offer IVTPA treatment to patients in the 270–360 min window from witnessed onset if their CT scans are normal and they are not candidates for thrombectomy. The only way to prove efficacy unequivocally would be a randomized, double-blinded, placebo-controlled study. However, such a trial may not be practical due to the large sample size needed, and possibly to lack of equipoise, in some minds. Incremental local initiatives to expand the IVTPA treatment window for patients with AIS, maintaining patient safety by relying on a normal non-contrast brain CT scan, may be more feasible. We view this as our next challenge, in striving to expand delivery of reperfusion treatments to patients with acute ischemic strokes.

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Conflict of interest statement

All authors have no financial and other conflicts of interest that might bias the work reported herewith.

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