Journal of the American Heart Association

ORIGINAL RESEARCH

Ultrashort Door-to-Needle Time for Intravenous Thrombolysis Is Safer and Improves Outcome in the Czech Republic: Nationwide Study 2004 to 2019

Robert Mikulík, PhD; Michal Bar, PhD; Silvie Bělašková, PhD; David Černík, PhD; Jan Fiksa, MD; Roman Herzig, PhD; René Jura, MD; Lubomír Jurák, PhD; Lukáš Klečka, MD; Jiří Neumann, MD; Svatopluk Ostrý, PhD; Daniel Šaňák, PhD; Petr Ševčík, PhD; Ondřej Škoda, PhD; Martin Šrámek, MD; Aleš Tomek, PhD; Daniel Václavík, PhD; on behalf of the Czech Stroke Unit Network*

BACKGROUND: The benefit of intravenous thrombolysis is time dependent. It remains unclear, however, whether dramatic shortening of door-to-needle time (DNT) among different types of hospitals nationwide does not compromise safety and still improves outcome.

METHODS AND RESULTS: Multifaceted intervention to shorten DNT was introduced at a national level, and prospectively collected data from a registry between 2004 and 2019 were analyzed. Generalized estimating equation was used to identify the association between DNT and outcomes independently from prespecified baseline variables. The primary outcome was modified Rankin score 0 to 1 at 3 months, and secondary outcomes were parenchymal hemorrhage/intracerebral hemorrhage (ICH), any ICH, and death. Of 31 316 patients treated with intravenous thrombolysis alone, 18 861 (60%) had available data: age 70±13 years, National Institutes of Health Stroke Scale at baseline (median, 8; interquartile range, 5–14), and 45% men. DNT groups 0 to 20 minutes, 21 to 40 minutes, 41 to 60 minutes, and >60 minutes had 3536 (19%), 5333 (28%), 4856 (26%), and 5136 (27%) patients. National median DNT dropped from 74 minutes in 2004 to 22 minutes in 2019. Shorter DNT had proportional benefit: it increased the odds of achieving modified Rankin score 0 to 1 and decreased the odds of parenchymal hemorrhage/ICH, any ICH, and mortality. Patients with DNT ≤20 minutes, 21 to 40 minutes, and 41 to 60 minutes as compared with DNT >60 minutes had adjusted odds ratios for modified Rankin score 0 to 1 of the following: 1.30 (95% CI, 1.12–1.51), 1.33 (95% CI, 1.15–1.54), and 1.15 (95% CI, 1.02–1.29), and for parenchymal hemorrhage/ICH: 0.57 (95% CI, 0.45–0.71), 0.76 (95% CI, 0.61–0.94), 0.83 (95% CI, 0.70–0.99), respectively.

CONCLUSIONS: Ultrashort initiation of thrombolysis is feasible, improves outcome, and makes treatments safer because of fewer intracerebral hemorrhages. Stroke management should be optimized to initiate thrombolysis as soon as possible optimally within 20 minutes from arrival to a hospital.

Key Words: acute ischemic stroke ■ door-to-needle time ■ intravenous thrombolysis ■ stroke logistics

Downloaded from http://ahajournals.org by on May 18, 2022

In clinical trials, patients benefitted more from intravenous thrombolysis if treatment was initiated sooner after symptom onset.[1] One of the estimations was that 1-minute shorter door-to-needle time (DNT) results in additional 1 to 2 days of disability-adjusted life-years.[2] The underlying biological reason is that during

Correspondence to: Robert Mikulík, PhD, Department of Neurology, St. Anne's University Hospital and Medical Faculty of Masaryk University, Pekařská 53, 65691 Brno, Czech Republic. Email: mikulik@hotmail.com

*A complete list of the Czech Stroke Unit Network members can be found in the Supplemental Material.

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023524

For Sources of Funding and Disclosures, see page 9.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Acute stroke care in the Czech Republic has improved in the past 16 years.
- In 2019, the door-to-needle time for intravenous thrombolysis within 20 minutes was accessible for almost 50% of patients with ischemic stroke.

What Are the Clinical Implications?

- Ultrashort initiation of thrombolysis is safer and is associated with a better outcome for patients with stroke.

Nonstandard Abbreviations and Acronyms

AHA	American Heart Association
DNT	door-to-needle time
ICH	intracerebral hemorrhage
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PH	parenchymal hemorrhage
RES-Q	Registry of Stroke Care Quality
SITS	Safe Implementation of Treatments in Stroke

each minute of acute stroke, ≈1.9 million neurons, 14 billion synapses, and 12 km of myelinated fibers die.[3]

In 2012, we demonstrated that in clinical practice in Eastern Europe shorter DNT was associated with better outcome.[4] This analysis was conducted based on data from patients treated with thrombolysis between 2003 and 2010. In this period, however, only 38% of patients who underwent thrombolysis had a DNT ≤60 minutes.[4] Later in 2012 to 2013, some highly experienced stroke centers, originally from Helsinki, documented that DNT could be shortened to 20 to 25 minutes.[5,6]

Several interventions (eg, development and accreditation of stroke centers, improvement of prehospital and hospital care, education, simulations in stroke care, and interhospital benchmarking) were subsequently used to implement the Helsinki model nationwide, aiming to bring the national median DNT to 20 minutes.[7] However, it remains unproven, based on previous data both from randomized clinical trials and clinical practice, whether dramatic shortening of DNT among all hospitals does not compromise safety and retains a positive influence on patients' outcome. To answer this question, we analyze the national sample including data after dramatic shortening of DNT has become frequent in clinical practice.

METHODS

This is a cohort study of prospectively collected patient cases treated in all stroke centers in the Czech Republic with intravenous thrombolysis alone between 2004 and 2019 to analyze the relationship between logistics for intravenous thrombolysis and patient outcome. The data set and statistical files supporting the conclusions of this article are available by reasonable request from the corresponding author.

The data for the present study were obtained from the SITS (Safe Implementation of Treatments in Stroke) registry and RES-Q (Registry of Stroke Care Quality).[8] SITS was used in the Czech Republic as a primary stroke registry between 2004 and 2018. Since 2016, RES-Q started to be used first for quality monitoring (www.qualityregistry.eu) and since 2019 also replaced SITS for collection of patients treated with thrombolysis and/or mechanical thrombectomy. Collection of all information on patients treated with thrombolysis and thrombectomy became standard practice in 2004 and was further reinforced by certification of stroke centers in 2011 by the Ministry of Health, which demanded collection of stroke cases in a registry as part of service assessment.[9] Because there are no competing registries, all cases have always been collected in a single registry. A detailed description of the development of national stroke services in the Czech Republic, interventions to shorten DNT and time trends of DNT, and yearly thrombolytic rates were published.[7]

Covariates

To minimize the risk of residual confounding, all baseline variables contained in the registry that were previously shown to be associated with modified Rankin Scale (mRS) or intracerebral hemorrhage (ICH)[10,11] and had ≤20% of missing cases were used for adjustments. These variables included age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline systolic blood pressure, mRS before stroke, history of arterial hypertension, diabetes, atrial fibrillation, congestive heart failure, smoking (current smoker), use of aspirin, clopidogrel, the onset-to-door time, and dose of alteplase (per body weight, the dose was 0.9 mg/kg throughout the whole study). Three sensitivity analyses were performed. For the first, the onset-to-door time was not used because of relationships between longer onset-to-door time and shorter DNT, as previously published.[3,12] For the second, only age and NIHSS were used for adjustment as these 2 variables are usually considered the most important

Downloaded from http://ahajournals.org by on May 18, 2022

and stable predictors of the outcome. The third sensitivity analysis limited the data set to patients treated only between 2015 and 2019 (to eliminate the influence of improvement of stroke care in general on our outcomes measures) and to include cases treated not only with intravenous thrombolysis but also with mechanical thrombectomy.

Outcome Measures

The primary outcome was a favorable clinical outcome as defined by an mRS score of 0 or 1 assessed during a hospital visit at 3 months. Secondary outcome measures included parenchymal hemorrhage (PH; PH/ICH, defined as a clot on imaging), any ICH (any ICH, defined as petechial hemorrhage or a clot on imaging) on follow-up computed tomography scan,[13] or death within 3 months as ascertained by investigators. We opted to use the radiological definition of hemorrhagic transformation because this information is collected, as primary information in the registry while ascertaining which ICH was or was not clinically symptomatic is not primary information and would have required taking into account additional information, eg, NIHSS at 2 and 24 hours. Such information is less reliable and more frequently missing as compared with baseline NIHSS.

Statistical Analysis

Continuous and categorical variables are reported as mean±SD, medians with percentiles, or frequencies with percentages. Only hospitals with >100 cases were included and data were checked for duplicities. Patients without information on DNT or mRS at 3 months were excluded from all analyses. All fields were examined for missing data or outliers, and outlying data were excluded if erroneous. There was no imputation of missing data for primary analysis, but, as part of sensitivity analysis, we performed multiple imputations of missing baseline variables. Markov chain Monte Carlo in PROC MI (SAS Institute Inc) has been used to create 10 complete data sets for analysis of each outcome. Proportions of missing data are reported.

Generalized mixed models were used for graphical presentation of the trend of favorable outcome, PH, any ICH, and mortality on DNT as a continuous variable with odds ratios (ORs) and 95% CIs using the normal approximation method. Hospital was used as a random effect variable. Estimated ORs were adjusted for all baseline variables.

To account for the clustering of patients within hospitals, generalized estimating equations were used to assess the association between the DNT ≤20 minutes, 40 minutes, 60 minutes, and ≥60 minutes, and clinical outcomes (mRS 0 or 1, PH/ICH, any ICH, death). The reason for stratification of DNT by 20 minutes is based on clinical consideration and is supported by evidence that achieving DNT ≤20 minutes is feasible in clinical practice.[5–7] The hospital was used as a cluster variable. Adjusted ORs (aORs) were obtained, along with 95% CIs, and a $P<0.05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc).

In both registries, data were collected as part of routine clinical practice to assess the utilization and quality of stroke services. Also, in both registries, data were collected in anonymized format. Therefore, patients were not required to provide informed consent. Multicenter St. Anne's ethical committee approved the analysis of these data.

Role of the Funding Source

The funding source had no role in the design of this study, during analysis, interpretation of the data, or decision to submit results.

RESULTS

Of 31 316 patients treated with intravenous thrombolysis alone between 2004 and 2019, 11 763 patients had missing either DNT or mRS data at 3 months, leaving 19 553 (62%) cases from 68 hospitals. Next, 692 (3.5%) patients were excluded because they were from 24 hospitals that treated <100 patients in the study period. The final number of cases was 18 861 (60% of all cases with intravenous thrombolysis) who were treated in 44 hospitals, representing 98% of all 45 certified stroke centers in the country. Baseline variables for excluded cases are shown in Table 1 and are the same or nearly the same (except for shorter onset-to-treatment time) as the included cases. For the included cases, the mean age of patients was 70±13 years, median NIHSS score at baseline was 8 (interquartile range, 5–14), and 45% were men; for the excluded cases, the mean age of patients was 70±13 years, median NIHSS score at baseline was 8 (interquartile range, 5–13), and 45% were men.

The median DNT dropped from 74 minutes in 2004 (n=124) to 60 minutes in 2012 (n=982), 40 minutes in 2016 (n=2131), and 22 minutes in 2019 (n=2498). DNT 0 to 20, 21 to 40, 41 to 60, and >60 minutes included 3536 (19%), 5333 (28%), 4856 (26%), and 5136 (27%) of patients, respectively. Overall, DNT ≤30 and ≤75 minutes were achieved by 6354 (34%) and 8718 (46%) of patients, respectively. In 2019 only, DNT ≤20, ≤30, ≤45, and ≤60 minutes were achieved by 47%, 71%, 88%, and 94% of patients, respectively.

Median onset-to-door time in patients with DNT 0 to 20, 21 to 40, 41 to 60, and >60 minutes was 85 minutes, 85 minutes, 80 minutes, 68 minutes, respectively ($P<0.0001$). Median onset-to-treatment time was 133 minutes (interquartile range, 100–175 minutes). More detailed demographic data are shown in Table 1.

Downloaded from http://ahajournals.org by on May 18, 2022

Table 1. Demographic Data of All Patients and According to Strata of DNT

	All, N=18 861 (100%)	Missing, n (%)	DNT ≤20 min, n=3536 (19%)	DNT 21–40 min, n=5333 (28%)	DNT 41–60 min, n=4856 (26%)	DNT >60 min, n=5136 (27%)	Excluded cases, n=12 455*
Age, mean (SD), y	70±13	20 (0.1)	71±13	71±13	70±13	69±13	70±13
Men, n (%)	8567 (45)	0 (0)	1695 (48)	2445 (46)	2177 (45)	2250 (44)	5594 (45)
NIHSS score at baseline, median (25th–75th percentile)	8 (5–14)	2416 (13)	7 (4–12)	7 (5–13)	8 (5–15)	9 (6–15)	8 (5–13)
Blood pressure systolic, mean±SD	159±25	663 (4)	157±24	158±25	159±25	160±26	159±26
mRS 0 or 1 before stroke, n (%)	15 243 (86)	1171 (6)	2865 (85)	4301 (85)	3970 (87)	4107 (87)	6562 (83)
Arterial hypertension, n (%)	13 818 (73)	243 (1)	2578 (74)	3884 (74)	3549 (74)	3807 (75)	6586 (75)
Diabetes, n (%)	5197 (28)	112 (1)	964 (28)	1503 (28)	1323 (27)	1407 (28)	2555 (29)
Atrial fibrillation, n (%)	3144 (17)	247 (1)	500 (14)	782 (15)	874 (18)	988 (19)	1587 (18)
Congestive HF, n (%)	1735 (9)	252 (1)	324 (9)	436 (8)	471 (10)	504 (10)	818 (9)
Current smoker, n (%)	3319 (18)	246 (1)	593 (17)	929 (18)	852 (18)	945 (19)	1603 (18)
Aspirin, n (%)	6009 (32)	111 (1)	1127 (32)	1742 (33)	1522 (32)	1618 (32)	2900 (33)
Clopidogrel, n (%)	1063 (6)	497 (3)	281 (8)	340 (7)	241 (5)	201 (4)	597 (7)
Dose of alteplase, mean±SD	71±14	650 (3)	71±14	70±14	71±13	71±14	70±14
ODT, mean±SD	91±61	621 (3)	101±71	99±66	91±55	77±49	90±67
ODT, median (25–75 percentile)	79 (54–120)	621 (3)	85 (57–135)	85 (55–131)	80 (55–120)	68 (45–99)	75 (46–116)
OTT, median (25–75 percentile)	133 (100–175)	621 (3)	100 (71–150)	115 (87–165)	132 (105–170)	157 (130–185)	120 (90–165)

DNT indicates door-to-needle time; HF, heart failure; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ODT, onset-to-door time; and OTT, onset-to-treatment time.
*The number of missing cases within excluded cases is not shown. Percentages in the column are calculated as positive values (shown) divided by nonmissing cases (not shown).

Downloaded from http://ahajournals.org by on May 18, 2022

At 3 months, mRS 0 to 1 was achieved in 9431 (50%) of patients (0% missing data), PH/ICH in 944 (6%; 12% missing data), any ICH in 1705 (10%; 12% missing data), and death in 2442 (15%; 12% missing data) patients. In patients with a DNT of 0 to 20 minutes, the proportion of PH in 2004 to 2009 versus 2010 to 2014 versus 2015 to 2019 was 10% (95% CI, 4–23) versus 7% (95% CI, 3–13) versus 4% (95% CI, 3–5), respectively.

Trends in the percentages of all outcome measures (mRS 0 or 1 PH/ICH, any ICH, and death) from 2004 to 2019 are shown in Figure 1. In patients with DNT ≤20, 21 to 40, 41 to 60, and >60 minutes, the percentage of patients achieving mRS 0 to 1 at 3 months was 55%, 54%, 49%, and 44%, respectively.

Outcome measures stratified by DNT are shown in Figure 2A through 2D. Shorter DNT proportionally increased the odds of achieving mRS 0 to 1 and decreased the odds of PH/ICH, any ICH, and mortality, as documented in Figure 2A through 2D. The relationship between DNT stratified by 20 minutes and mRS 0 to 1, PH/ICH, any ICH, and death is shown in Table 2. After adjusting for all baseline differences, patients with DNT ≤20, 21 to 40, and 41 to 60 minutes as compared with patients with DNT >60 minutes had the following ORs for mRS 0 to 1: 1.30 (95% CI, 1.12–1.51), 1.33 (95% CI, 1.15–1.54), 1.15 (95% CI, 1.02–1.29); for PH/ICH: 0.57 (95% CI, 0.45–0.71), 0.76 (95% CI, 0.61–0.94), 0.83 (95% CI, 0.70–0.99); for any ICH: 0.61 (95% CI, 0.49–0.76), 0.73 (95% CI, 0.63–0.86), 0.83 (95% CI, 0.71–0.98); and for death: 1.05 (95% CI, 0.74–1.48), 0.85 (95% CI, 0.72–1.02), 0.75 (95% CI, 0.64–0.87), respectively. Results were similar in sensitivity analysis using different adjustments (Table 2).

Limiting data sets to patients (n=23 147) treated only between 2015 and 2019 with intravenous thrombolysis alone (Figure 2E through 2H) but also with mechanical thrombectomy (Figure 2I through 2L), 9495 (41%) patients had missing either DNT or mRS information at 3 months, leaving 13 652 (62%) cases, of which 13 461 (99%) were from hospitals treating ≥100 patients. A total of 11 463 patients had intravenous thrombolysis alone and 1998 together with mechanical thrombectomy. Figure 2 demonstrating that shorter door-to-needle time for initiation of intravenous thrombolysis with or without mechanical thrombectomy is associated with a proportional increase of the odds of mRS 0 or 1 and decreased the odds of PH/ICH, any ICH, and mortality.

DISCUSSION

We studied the association between the speed of in-hospital logistics before initiation of intravenous

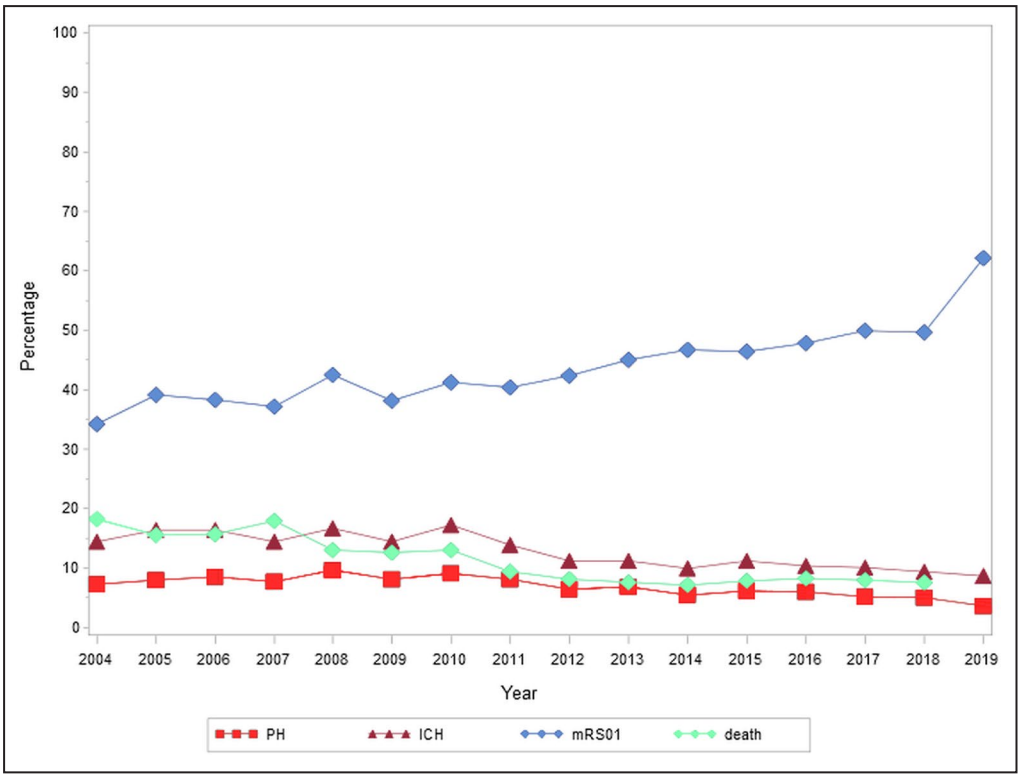

Figure 1. The frequency of primary and secondary outcomes associated with changed door-to-needle time during the period 2004 to 2019.
The data for death in 2019 are not yet available. ICH indicates intracerebral hemorrhage; mRS, modified Rankin Scale; and PH, parenchymal hemorrhage.

Downloaded from http://ahajournals.org by on May 18, 2022

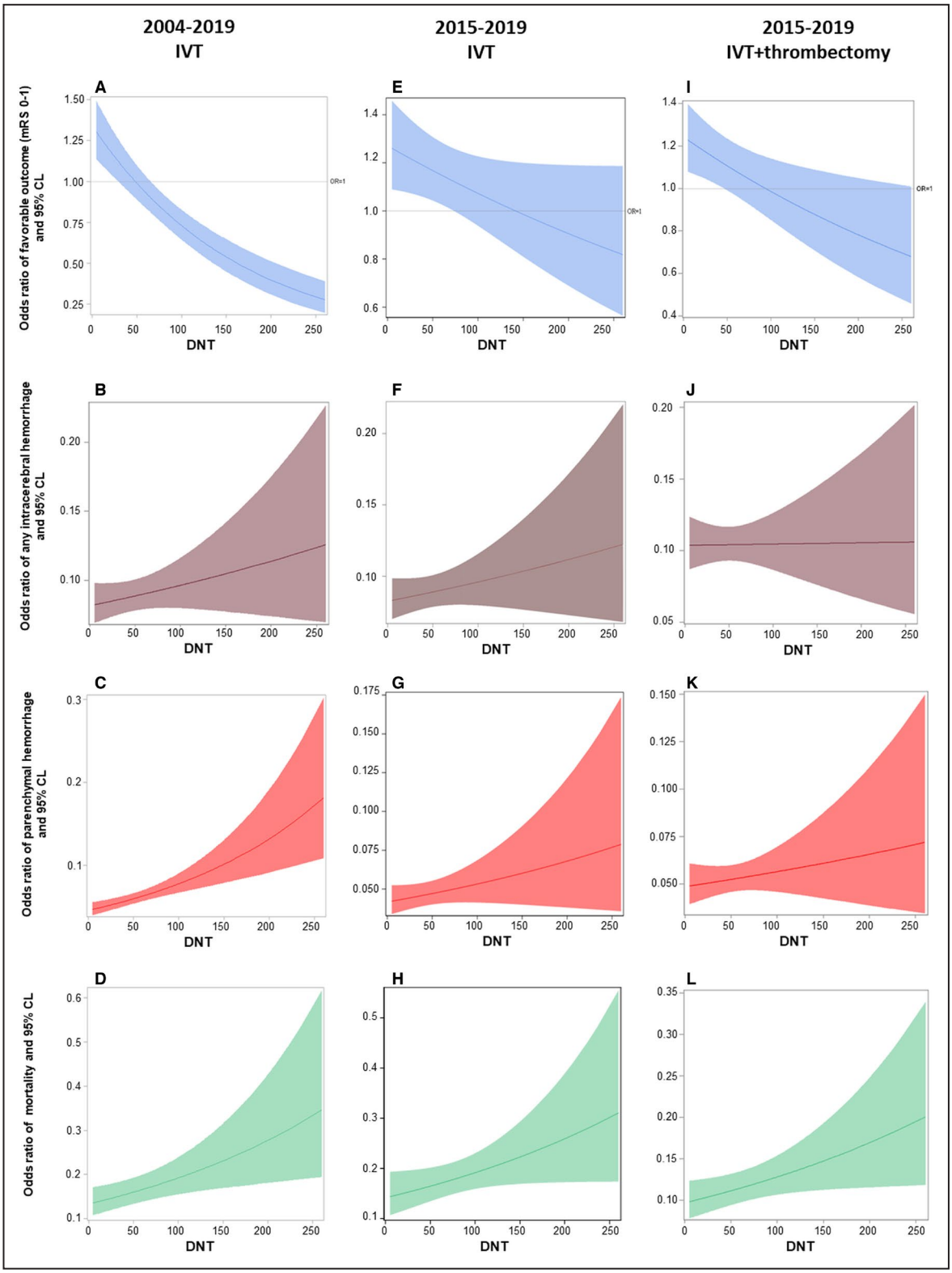

Figure 2. Logistic regression model showing the exponentiated parameter estimate with 95% confidence limits (CLs) for the main outcomes as a function of door-to-needle time (DNT).
A through **D**, All patients treated with intravenous thrombolysis (IVT) alone between 2004 and 2019 were included. (**A**) An odds ratio of 1 corresponds with a DNT of 51 minutes. Decreasing DNT increases the odds for a favorable outcome. **B** through **D**, With decreasing DNT, there is a decrease in brain parenchymal hemorrhage, any intracerebral hemorrhage, and mortality. **E** through **L**, Sensitivity analyses showing patients treated not only with IVT (**E** through **H**) alone but also with mechanical thrombectomy (**I** through **L**) between 2015 and 2019 were included.

Downloaded from http://ahajournals.org by on May 18, 2022

Table 2. Association Between DNT and Outcome Measures

	DNT ≤20 min vs DNT 21–40 min	DNT ≤20 min vs DNT 41–60 min	DNT ≤20 min vs DNT >60 min	DNT 21–40 min vs DNT 41–60 min	DNT 21–40 min vs DNT >60 min	DNT 41–60 min vs DNT >60 min	Excluded cases, %
mRS 0 or 1							
Unadjusted analysis, n=18 861	1.07 (0.98–1.17)	1.30 (1.16–1.45)*	1.59 (1.40–1.80)*	1.21 (1.11–1.33)*	1.48 (1.33–1.66)*	1.22 (1.12–1.33)*	0
Adjusted for age and NIHSS	1.01 (0.92–1.11)	1.13 (0.99–1.28)	1.33 (1.17–1.51)*	1.12 (1.01–1.24)*	1.32 (1.17–1.49)*	1.18 (1.06–1.32)*	13
Adjusted for all without ODT	0.98 (0.89–1.09)	1.14 (1.01–1.28)*	1.29 (1.11–1.49)*	1.16 (1.02–1.31)*	1.31 (1.14–1.50)*	1.13 (1.00–1.27)*	23
Adjusted for all†	0.98 (0.88–1.09)	1.14 (1.01–1.28)*	1.30 (1.12–1.51)*	1.16 (1.02–1.32)*	1.33 (1.15–1.54)*	1.15 (1.02–1.29)*	25
PH-ICH							
Unadjusted analysis, n=18 861	0.80 (0.64–1.00)	0.68 (0.52–0.89)*	0.56 (0.43–0.73)*	0.86 (0.73–1.01)	0.70 (0.58–0.85)*	0.82 (0.68–0.98)*	12
Adjusted for age and NIHSS	0.86 (0.68–1.11)	0.78 (0.58–1.05)	0.62 (0.47–0.82)*	0.90 (0.73–1.11)	0.72 (0.58–0.88)*	0.79 (0.66–0.95)*	22
Adjusted for all without ODT	0.78 (0.61–0.99)*	0.73 (0.56–0.94)*	0.61 (0.48–0.76)*	0.94 (0.76–1.15)	0.78 (0.63–0.96)*	0.83 (0.70–0.99)*	31
Adjusted for all	0.75 (0.58–0.96)*	0.68 (0.52–0.89)*	0.57 (0.45–0.71)*	0.91 (0.74–1.13)	0.76 (0.61–0.94)*	0.83 (0.70–0.99)*	33
Any ICH							
Unadjusted analysis, n=18 861	0.86 (0.72–1.02)	0.70 (0.59–0.82)*	0.58 (0.48–0.72)*	0.82 (0.72–0.93)*	0.68 (0.59–0.79)*	0.84 (0.72–0.97)*	12
Adjusted for age and NIHSS	0.91 (0.75–1.10)	0.78 (0.66–0.93)*	0.65 (0.52–0.80)*	0.86 (0.73–1.01)	0.71 (0.60–0.83)*	0.83 (0.71–0.95)*	22
Adjusted for all without ODT	0.84 (0.70–1.01)	0.75 (0.63–0.90)*	0.64 (0.51–0.79)*	0.90 (0.76–1.06)	0.76 (0.65–0.89)*	0.84 (0.72–0.99)*	31
Adjusted for all	0.83 (0.68–1.00)	0.73 (0.61–0.87)*	0.61 (0.49–0.76)*	0.88 (0.74–1.04)	0.73 (0.63–0.86)*	0.83 (0.71–0.98)*	33
Death							
Unadjusted analysis, n=18 861	1.06 (0.88–1.28)	1.02 (0.80–1.23)	0.82 (0.64–1.05)	0.97 (0.83–1.13)	0.77 (0.66–0.91)*	0.80 (0.70–0.92)*	12
Adjusted for age and NIHSS	1.21 (0.96–1.52)	1.28 (0.98–1.67)	0.96 (0.72–1.28)	1.06 (0.88–1.27)	0.80 (0.68–0.93)*	0.75 (0.65–0.87)*	25
Adjusted for all without ODT	1.23 (0.93–1.62)	1.43 (1.04–1.95)*	1.09 (0.76–1.55)	1.16 (0.99–1.37)	0.88 (0.74–1.05)	0.76 (0.66–0.88)*	35
Adjusted for all	1.22 (0.94–1.60)	1.40 (1.03–1.90)*	1.05 (0.74–1.48)	1.14 (0.97–1.34)	0.85 (0.72–1.02)	0.75 (0.64–0.87)*	37

Values are presented as odds ratios (95% CIs). All baseline variables include age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline systolic blood pressure, modified Rankin Scale (mRS) before stroke, history of arterial hypertension, diabetes, atrial fibrillation, congestive heart failure, smoking (current smoker), use of aspirin, clopidogrel, and dose of alteplase. DNT indicates door-to-needle time; ICH, intracerebral hemorrhage; ODT, onset-to-door time; and PH, parenchymal hemorrhage.

*Statistically significant results.

†Primary analysis included all baseline variables.

Downloaded from http://ahajournals.org by on May 18, 2022

thrombolysis and outcome. Nearly all hospitals nationally that admit patients with acute strokes and treat them with intravenous thrombolysis contributed to this analysis. The volume of thrombolytic treatments was high because, since 2016, >20% of all patients with ischemic strokes in the population received treatment (4200 of 21 943 cases).[14] Therefore, our results are relevant not only to all hospitals nationally but also to the majority of candidates for intravenous thrombolysis in the population. In a study period spanning >16 years, on average, 19% of cases were treated with "ultrashort" intravenous thrombolysis, ie, within 20 minutes after arrival to the hospital. However, in 2019, almost half (47%) of all patients received ultrashort thrombolysis. Such a high number of ultrashort deliveries of alteplase confirm the feasibility (details of implementation we previously reported[7]) and allowed us to analyze at the population level if, how, and why ultrashort delivery benefits the patients.

Patients who received intravenous thrombolysis with shorter DNT proportionally increased the odds of achieving mRS 0 to 1. Intravenous thrombolysis provided within 20 minutes or 20 to 40 minutes after patient arrival to the hospital had 30% higher odds of the better 3-month outcome in comparison to patients treated after 60 minutes after arrival to the hospital, irrespective of baseline differences. In absolute numbers, this represents 10% more patients being cured after a stroke if treated within an ultrashort period after arrival to the hospital as compared with treated later. The magnitude of the efficacy of such ultrashort treatment is far from negligible and similar to the thrombolytic treatment itself, ie, compared with placebo.

Our study provides some explanation of the mechanisms on why ultrashort delivery improves outcome. Patients who received intravenous thrombolysis, eg, within 20 minutes in comparison to patients treated after 60 minutes of arrival, had fewer complications after treatment (PH: 4% versus 7%; any ICH: 8% versus 13%). Therefore, not only does faster treatment not compromise safety, it actually improves it (overall proportion of PH was similar as reported in randomized clinical trials).[1] Patients with shorter DNT also had proportionally slightly decreased mortality, although, after (and because of) categorizing DNT, we observed opposite trends.

Our results are principally in agreement with previous data, although none of them achieved such short DNTs. First, in randomized clinical trials compared with placebo, alteplase had been shown to work better if provided with less delay.[1,15] Second, 2 large studies from the United States documented that shorter as compared with longer onset-to-treatment time[16] or DNT[17] improves both short- and long-term outcome using different outcome measures such as in-hospital and all-cause mortality, independent ambulation at discharge, increased discharge to home, or all-cause readmission. All of these studies, including ours, documented fewer hemorrhagic complications after intravenous thrombolysis, such as ICH. Our study provides additional evidence compared with previous studies because our patients were treated with much shorter DNT. In the previously mentioned and most recent study from the United States,[17] only 6% of patients were treated with DNT ≤30 minutes, while in our data set, overall, it was 34%. Another independent and large data set from the United States shows that in 2017 there were 41% of patients treated with DNT ≤45 minutes, while in our data set it was 79% in the same year (not shown in the Results section), again documenting different clinical practice between both countries.[18] Taking all of the evidence together, faster initiation of treatment means more benefit, including fewer complications after intravenous thrombolysis.

In 2019, the Czech national median DNT was 22 minutes. In addition, as many as 88% of patients received intravenous thrombolysis within 45 minutes after arrival to the hospital and 94% within 60 minutes. The Dutch national audit reported a similar median national DNT of 25 minutes, supporting the generalizability of the ultrashort and modern logistics for thrombolysis.[19] Both Czech and Dutch results substantially exceed even secondary and more demanding goals by the recent 2018 recommendation of the American Heart Association (AHA) stating that ≥50% of patients should achieve DNT ≤45 minutes.[20] The primary logistical goal by AHA guidelines, however, still remains at a median DNT of 60 minutes (ie, DNT ≤60 minutes in which 50% of patients are treated). Accumulating evidence suggests that a target of 60 minutes DNT for intravenous thrombolysis is obsolete.

The limitation of our study is that the data are based on a registry, which inherently contains missing and not validated data. The most missing variables were baseline NIHSS score and mRS at 3 months. First, however, 25% of the missing baseline NIHSS data were similar to other large registries in which baseline NIHSS data were missing in 24% to 29% of cases.[21,22] Second, excluded cases had basically the same demographic characteristics, including age and NIHSS score, and thus exclusion of cases seems unlikely to lead to bias. We also excluded 24 hospitals that treated <100 patients in the study period to avoid the extreme unequal center enrollments that may lead to loss of power and sensitivity to detect the treatment difference. However, these 24 hospitals treated only 3.5% of patients, and their exclusion could not have influenced the association between DNT and outcome. Another possible limitation is that we cannot rule out residual confounding. To limit such risk, we included a large number of baseline variables for adjustment and we conducted a sensitivity analysis (with a different set of baseline

Downloaded from http://ahajournals.org by on May 18, 2022

variables used for adjustment) to document that our results are robust. The only variable that we know that would influence the outcome and could not be used, because of missing values, was the baseline glucose level. Other confounders might exist such as results of multimodal imaging (eg, core volume) or hospital-level characteristics, but these were not available or captured in the registry.

The strengths of our study include the large unselected population covering 98% of Czech hospitals certified for acute stroke care into which all strokes are directed by law since 2012. For the same reason, our results may not be generalizable for stroke services not associated with thrombolysis. Another strength is that our study is generalizable for those thrombolytic treatments that are used as bridging to mechanical thrombectomy because sensitivity analysis documented that including mechanical thrombectomies shows a similar influence of DNT on outcomes.

CONCLUSIONS

In this population-based study, a large number of strokes were treated with intravenous thrombolysis with DNT ≤20 minutes, thus confirming the feasibility of ultrashort initiation of treatment and among different types of stroke units. Shorter DNT was associated with better outcome also as a result of fewer cases of PH and ICH.

ARTICLE INFORMATION

Received October 12, 2021; accepted January 28, 2022.

Affiliations

International Clinical Research Center and Department of Neurology (R.M., S.B.); Faculty of Medicine at Masaryk University (R.M., R.J.); Department of Neurology (M.B.); Comprehensive Stroke Center - Department of Neurology, Masaryk Hospital Ustí nad Labem - KZ a.s., Ustí nad Labem, Czech Republic (D.Č.); Department of Neurology, First Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic (J.F.); Comprehensive Stroke Center, University Hospital Hradec Králové, Charles University Faculty of Medicine in Hradec Králové, Czech Republic (R.H.); Department of Neurology, University Hospital Brno, Brno, Czech Republic (R.J.); Neurocenter, Regional Hospital Liberec, Liberec, Czech Republic (L.J.); Department of Neurology, Town Hospital Ostrava, Ostrava, Czech Republic (L.K.); Department of Neurology, Chomutov Hospital, KZ a.s., Chomutov, Czech Republic (J.N.); Comprehensive Stroke Center, Hospital České Budějovice, a.s., České Budějovice, Czech Republic (S.O.); Department of Neurosurgery and Neurooncology, First Faculty of Medicine, Charles University in Prague, Czech Republic (S.O.); Military University Hospital Prague, Prague, Czech Republic (S.O.); Comprehensive Stroke Center in Department of Neurology, Palacký Medical School and University Hospital, Olomouc, Czech Republic (D.Š.); Department of Neurology, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic (P.Š.); Department of Neurology, University Hospital Pilsen, Pilsen, Czech Republic (P.Š.); Department of Neurology, Hospital Jihlava, Jihlava, Czech Republic (O.Š.); Department of Neurology, 3rd Medical School of Charles University and Vinohrady University Hospital, Prague, Czech Republic (O.Š.); Department of Neurology, Central Military University Hospital Prague and Motol University Hospital, Prague, Czech Republic (M.Š.); Department of Neurology, 2nd Medical School of Charles University and Motol University Hospital, Prague, Czech Republic (A.T.); and Department of Neurology and AGEL Research and Training Institute, Ostrava Vítkovice Hospital, Ostrava, Czech Republic (D.V.).

Sources of Funding

Mikulík was supported by project number CA18118, IRENE COST Action funded by COST Association; by IRIS-TEPUS project number LTC20051, the INTER-EXCELLENCE INTER-COST Program of the Ministry of Education, Youth and Sports of the Czech Republic; by project number LQ1605, National Program of Sustainability II; and by STROCZECH within CZECRIN Large Research Infrastructure number LM2018128 funded by the state budget of the Czech Republic. Herzig was supported by the project number DRO – UHHK 00179906 from the Ministry of Health of the Czech Republic and by the grant project PROGRES Q40 from Charles University, Czech Republic.

Disclosures

Mikulík, Bar, Neumann, and Šaňák received honoraria payments and travel support from Boehringer Ingelheim. Herzig received honoraria payments from Bayer, Boehringer Ingelheim, and Gedeon Richter; and travel support from Biogen, Merck, and Teva Pharmaceuticals. Tomek reports personal fees from Boehringer Ingelheim, Pfizer, Amgen, MSD, Astra Zeneca, Medtronic, outside the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Appendix S1

REFERENCES

1. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5
2. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, Davis SM, Donnan GA, Churilov L. Stroke thrombolysis: save a minute, save a day. *Stroke*. 2014;45:1053–1058. doi: 10.1161/STROKEAHA.113.002910
3. Saver JL. Time is brain–quantified. *Stroke*. 2006;37:263–266. doi: 10.1161/01.STR.0000196957.55928.ab
4. Mikulík R, Kadlecová P, Czlonkowska A, Kobayashi A, Brozman M, Švigelj V, Csiba L, Fekete K, Kõrv J, Demarin V, et al. Factors influencing in-hospital delay in treatment with intravenous thrombolysis. *Stroke*. 2012;43:1578–1583. doi: 10.1161/STROKEAHA.111.644120
5. Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology*. 2012;79:306–313. doi: 10.1212/WNL.0b013e31825d6011
6. Meretoja A, Weir L, Ugalde M, Yassi N, Yan B, Hand P, Truesdale M, Davis SM, Campbell BC. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. *Neurology*. 2013;81:1071–1076. doi: 10.1212/WNL.0b013e3182a4a4d2
7. Mikulik R, Bar M, Cernik D, Herzig R, Jura R, Jurak L, Neumann J, Sanak D, Ostry S, Sevcik P, et al. Stroke 2020: implementation goals for intravenous thrombolysis. *Eur Stroke J*. 2021;6:151–159. doi: 10.1177/23969873211007684
8. Registry of Stroke Care Quality, RES-Q. FNUSA-ICRC; 2016. Available at: https://qualityregistry.eu. Accessed April 9, 2020.
9. Bryndová L, Bar M, Herzig R, Mikulík R, Neumann J, Šaňák D, Škoda O, Školoudík D, Václavík D, Tomek A. Concentrating stroke care provision in the Czech Republic: the establishment of Stroke Centres in 2011 has led to improved outcomes. *Health Policy*. 2021;125:520–525. doi: 10.1016/j.healthpol.2021.01.011
10. Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, Erilä T, Ford GA, Grond M, Hacke W, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). *Stroke*. 2008;39:3316–3322. doi: 10.1161/STROKEAHA.107.510768
11. Tong X, George MG, Yang Q, Gillespie C. Predictors of in-hospital death and symptomatic intracranial hemorrhage in patients with acute ischemic stroke treated with thrombolytic therapy: Paul Coverdell Acute Stroke Registry 2008–2012. *Int J Stroke*. 2014;9:728–734. doi: 10.1111/ijs.12155

Downloaded from http://ahajournals.org by on May 18, 2022

12. Strbian D, Michel P, Ringleb P, Numminen H, Breuer L, Bodenant M, Seiffge DJ, Jung S, Obach V, Weder B, et al. Relationship between onset-to-door time and door-to-thrombolysis time: a pooled analysis of 10 dedicated stroke centers. *Stroke*. 2013;44:2808–2813. doi: 10.1161/STROKEAHA.113.000995
13. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, Treurniet KM, Majoie CB, Marquering HA, Mazya MV, et al. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46:2981–2986. doi: 10.1161/STROKEAHA.115.010049
14. Sedova P, Brown RD, Zvolsky M, Kadlecova P, Bryndziar T, Kubelka T, Weiss V, Volný O, Bednarik J, Mikulik R. Incidence of hospitalized stroke in the Czech Republic: the National Registry of Hospitalized Patient. *J Stroke Cerebrovasc Dis*. 2017;26:979–986. doi: 10.1016/j.jstrokecerebrovasdis.2016.11.006
15. Tsivgoulis G, Saqqur M, Sharma VK, Brunser A, Eggers J, Mikulik R, Katsanos AH, Sergentanis TN, Vadikolias K, Perren F, et al. Timing of recanalization and functional recovery in acute ischemic stroke. *J Stroke*. 2020;22:130–140. doi: 10.5853/jos.2019.01648
16. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA*. 2013;309:2480–2488. doi: 10.1001/jama.2013.6959
17. Man S, Xian Y, Holmes DN, Matsouaka RA, Saver JL, Smith EE, Bhatt DL, Schwamm LH, Fonarow GC. Association between thrombolytic door-to-needle time and 1-year mortality and readmission in patients with acute ischemic stroke. *JAMA*. 2020;323:2170–2184. doi: 10.1001/jama.2020.5697
18. Tong X, Wiltz JL, George MG, Odom EC, Coleman King SM, Chang T, Yin X; Paul Coverdell National Acute Stroke Program Team, Merritt RK. A decade of improvement in door-to-needle time among acute ischemic stroke patients, 2008 to 2017. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004981. doi: 10.1161/CIRCOUTCOMES.118.004981
19. Kuhrij LS, Marang-van de Mheen PJ, van den Berg-Vos RM, de Leeuw FE, Nederkoorn PJ; Dutch Acute Stroke Audit Consortium. Determinants of extended door-to-needle time in acute ischemic stroke and its influence on in-hospital mortality: results of a nationwide Dutch clinical audit. *BMC Neurol*. 2019;19:265. doi: 10.1186/s12883-019-1512-2
20. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. doi: 10.1161/STR.0000000000000211
21. Messé SR, Khatri P, Reeves MJ, Smith EE, Saver JL, Bhatt DL, Grau-Sepulveda MV, Cox M, Peterson ED, Fonarow GC, et al. Why are acute ischemic stroke patients not receiving IV tPA? Results from a National Registry. *Neurology*. 2016;87:1565–1574. doi: 10.1212/WNL.0000000000003198
22. Ido MS, Frankel MR, Okosun IS, Rothenberg RB. Quality of care and its impact on one-year mortality: the Georgia Coverdell Acute Stroke Registry. *Am J Med Qual*. 2018;33:86–92. doi: 10.1177/1062860617696578

Downloaded from http://ahajournals.org by on May 18, 2022

SUPPLEMENTAL MATERIAL

Downloaded from http://ahajournals.org by on May 18, 2022

Appendix S1. Representatives of the Czech Stroke Unit network (alphabetically) of Comprehensive and Primary Stroke Centers of the Czech Republic participating in the study:

Comprehensive Stroke Centers	**Representatives**
Department of Neurology, Na Homolce Hospital, Prague	Martin Kovář
Department of Neurology, Faculty Hospital Královské Vinohrady, Prague	Petr Mikulenka
Primary Stroke Centers	**Representatives**
Department of Neurology, Hospital Blansko, Blansko	Jana Jankových
Department of Neurology, Hospital Břeclav, Břeclav	Zdena Bajková
Department of Neurology, Hospital Česká Lípa, Česká Lípa	Natalia Boitsová
Department of Neurology, Karlovy Vary Regional Hospital, a.s., Karlovy Vary	Igor Karpowicz
Department of Neurology, Mining Hospital Karviná, Karviná	Hana Palouškova
Department of Neurology, Regional Hospital Kladno, Kladno	Richard Brzezny
Department of Neurology, Regional Hospital Kolín, Hospital of Central Bohemian Region, Kolín	Radka Jebavá
Department of Neurology, Hospital Krnov, Krnov	Vladimír Šigut
Department of Neurology, Hospital Litoměřice, o.z. - KZ a.s., Litoměřice	Michaela Böhmová
Department of Neurology, Klaudian Hospital, Mladá Boleslav	Martin Koutný

Downloaded from http://ahajournals.org by on May 18, 2022

Department of Neurology, Regional Hospital Náchod, Náchod	Petr Štěpán
Department of Neurology, Hospital Pardubice, Pardubice	Petr Geier
Department of Neurology, Hospital Písek, Písek	Robert Rezek
Department of Neurology, Regional Hospital Příbram, a.s., Příbram	Helena Hlaváčová
Department of Neurology, Hospital Sokolov, Sokolov	Aleš Novák
Department of Neurology, Hospital Teplice - KZ a.s., Teplice	Marta Vachová
Department of Neurology, Hospital Třinec, Třinec	Lenka Žáková
Department of Neurology, Uherské Hradiště Hospital, Uherské Hradiště	Emanuela Habrovanská
Department of Neurology, Tomas Bata Regional Hospital, Zlín	Jan Bartoník
Department of Neurology, Hospital Znojmo, Znojmo	Viktorie Kopecká

Downloaded from http://ahajournals.org by on May 18, 2022