Circulation

ORIGINAL RESEARCH ARTICLE

Shorter Door-to-Needle Times Are Associated With Better Outcomes After Intravenous Thrombolytic Therapy and Endovascular Thrombectomy for Acute Ischemic Stroke

Shumei Man, MD, PhD; Nicole Solomon, PhD; Brian Mac Grory, MB, BCh, BAO, MRCP; Brooke Alhanti, PhD; Ken Uchino, MD; Jeffrey L. Saver, MD; Eric E. Smith, MD, MPH; Ying Xian, MD, PhD; Deepak L. Bhatt, MD, MPH; Lee H. Schwamm, MD; Muhammad Shazam Hussain, MD; Gregg C. Fonarow, MD

BACKGROUND: Existing data and clinical trials could not determine whether faster intravenous thrombolytic therapy (IVT) translates into better long-term functional outcomes after acute ischemic stroke among those treated with endovascular thrombectomy (EVT). Patient-level national data can provide the required large population to study the associations between earlier IVT, versus later, with longitudinal functional outcomes and mortality in patients receiving IVT+EVT combined treatment.

METHODS: This cohort study included older US patients (age ≥65 years) who received IVT within 4.5 hours or EVT within 7 hours after acute ischemic stroke using the linked 2015 to 2018 Get With The Guidelines–Stroke and Medicare database (38 913 treated with IVT only and 3946 with IVT+EVT). Primary outcome was home time, a patient-prioritized functional outcome. Secondary outcomes included all-cause mortality in 1 year. Multivariate logistic regression and Cox proportional hazards models were used to evaluate the associations between door-to-needle (DTN) times and outcomes.

RESULTS: Among patients treated with IVT+EVT, after adjusting for patient and hospital factors, including onset-to-EVT times, each 15-minute increase in DTN times for IVT was associated with significantly higher odds of zero home time in a year (never discharged to home) (adjusted odds ratio, 1.12 [95% CI, 1.06–1.19]), less home time among those discharged to home (adjusted odds ratio, 0.93 per 1% of 365 days [95% CI, 0.89–0.98]), and higher all-cause mortality (adjusted hazard ratio, 1.07 [95% CI, 1.02–1.11]). These associations were also statistically significant among patients treated with IVT but at a modest degree (adjusted odds ratio, 1.04 for zero home time, 0.96 per 1% home time for those discharged to home, and adjusted hazard ratio 1.03 for mortality). In the secondary analysis where the IVT+EVT group was compared with 3704 patients treated with EVT only, shorter DTN times (≤60, 45, and 30 minutes) achieved incrementally more home time in a year, and more modified Rankin Scale 0 to 2 at discharge (22.3%, 23.4%, and 25.0%, respectively) versus EVT only (16.4%, P<0.001 for each). The benefit dissipated with DTN>60 minutes.

CONCLUSIONS: Among older patients with stroke treated with either IVT only or IVT+EVT, shorter DTN times are associated with better long-term functional outcomes and lower mortality. These findings support further efforts to accelerate thrombolytic administration in all eligible patients, including EVT candidates.

Key Words: ischemic stroke ■ patient outcome assessment ■ thrombectomy ■ thrombolytic therapy

Correspondence to: Shumei Man, MD, PhD, Department of Neurology, Cerebrovascular Center, Neurological Institute, Cleveland Clinic, 9500 Euclid Ave, Desk S80, Cleveland, OH 44195. Email mans@ccf.org

This manuscript was sent to Vincent S Thijs, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at: https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.123.064053

For Sources of Funding and Disclosures, see page xxx

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In this large cohort study of patients (aged ≥65 years) treated with intravenous thrombolytic therapy (IVT) within 4.5 hours and endovascular thrombectomy (EVT) within 7 hours of acute ischemic stroke onset, shorter door-to-needle times for IVT were associated with more days at home and lower mortality during 1-year follow-up.
- Among patients treated with IVT+EVT combined therapy, each 15-minute increase in door-to-needle times was associated with fewer days at home and higher all-cause mortality in a year.
- Guideline recommended door-to-needle times (≤30, 45, and 60 minutes) for IVT were associated with better outcomes after IVT+EVT combined therapy.

What Are the Clinical Implications?

- Intravenous thrombolytic therapy should be administered as early as possible and should not be delayed even among patients who may undergo EVT treatment.
- These findings support further efforts to accelerate thrombolytic administration in all eligible patients, including potential EVT candidates.

Nonstandard Abbreviations and Acronyms

AHA/ASA	American Heart Association/ American Stroke Association
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
IVT	intravenous thrombolytic therapy
EVT	endovascular thrombectomy
DTN	door-to-needle
GWTG	Get With The Guidelines
IVT-to-EVT	from initiation of IVT bolus to arterial puncture of EVT
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
onset-to-EVT	from last known well to arterial puncture of EVT

Intravenous thrombolytic therapy (IVT) and endovascular thrombectomy (EVT) improve the outcomes of acute ischemic stroke, but the benefits are time-dependent.[1–8] Therefore, door-to-needle (DTN) time has become a target of local and national quality initiatives because DTN time is under the complete control of the hospital care team.[9] Studies have demonstrated that shorter DTN times are associated with better outcomes at discharge and lower 1-year mortality and readmission.[3,4] However, it remains unclear whether shorter DTN times for IVT are associated with better long-term functional outcomes among patients also undergoing EVT treatment. In addition, for patients with large vessel occlusion, the benefits of IVT preceding EVT have been questioned, leading to delaying or skipping thrombolytic therapy for faster EVT access in some practices. Six previous randomized clinical trials exploring the effect of IVT preceding EVT showed mixed results.[10–15] The trials were not powered sufficiently to study the time-dependent effect of IVT. In fact, the workflow of the trials may have delayed thrombolytic administration as a result of patient consent and randomization.[12]

In the present study, we used data from the large nationwide real-practice data Get With The Guidelines (GWTG)-Stroke to examine whether shorter DTN times were associated with better outcomes in 2 separate cohorts: patients treated with IVT only and patients treated with IVT+EVT combined therapy.[16,17] GWTG-Stroke provides access to a patient population an order of magnitude larger than any existing reperfusion therapy clinical trials.[4,8,16–18] It allows outcome analyses using reperfusion timeliness as a continuous variable, and patient stratification on the basis of the timeliness of both IVT and EVT, as well. By linking GWTG-Stroke data with Medicare data, we can calculate home time, defined as the total number of days alive and out of a health care facility.[19,20] Home time has been validated as a functional outcome and correlated with the 90-day modified Rankin Scale (mRS) among patients treated with IVT.[19,20] It was identified in patient surveys as an outcome that was the most relevant and meaningful to stroke survivors.[19,20] We hypothesized that longer DTN times would be associated with increased risk of poor outcomes in patients treated with EVT, knowing that EVT is a highly effective procedure for recanalization and that IVT usually fails to recanalize the occluded artery before EVT.

METHODS

Given that GWTG data were collected for clinical care and quality improvement, rather than primarily for research, data-sharing agreements require an application process for other researchers to access the data. Researchers interested in using GWTG data for research purposes, including for validation, can submit proposals at https://www.heart.org/en/professional/quality-improvement/quality-research-and-publications/national-level-program-data-research-opportunities. Additional information regarding the statistical analysis plan and analytic codes may also be available from Duke Clinical Research Institute on request.

Data Source and Study Population

This cohort study included US Medicare beneficiaries (aged ≥65 years) treated for acute ischemic stroke with IVT within 4.5 hours or EVT within 7 hours from last known well at

GWTG-Stroke participating hospitals from January 1, 2015, to December 31, 2018, with a 1-year follow-up through December 31, 2019. Patients aged <65 years at the time of the stroke admission were not included because the postdischarge data were not available in this population. A Study Flow Chart is provided in Figure S1. Patients with DTN time >4.5 hours or missing, onset-to-arrival time >24 hours or missing, discharge destination missing, or left against medical advice were excluded. In-hospital strokes were excluded because these patients often have thrombolytic contraindications and different disease profiles from patients presenting directly to the emergency department.[21–23]

Patient-level clinical data, including reperfusion treatment timeliness, were obtained from GWTG-Stroke. GWTG-Stroke is an ongoing data collection that was launched by the American Heart Association/American Stroke Association (AHA/ASA) to support continuous quality improvement.[16,17] Patient-level clinical data are collected by trained hospital personnel on consecutive patients with acute ischemic stroke and transient ischemic attack.[16,17] A previous audit demonstrated >90% accuracy of GWTG-Stroke for most variables and excellent ($\kappa \geq 0.75$) reliability for time-related performance measures.[17] Each participating hospital received either human research approval to enroll cases without individual patient consent under the common rule, or a waiver of authorization and exemption from subsequent review by their institutional review board. The Duke Clinical Research Institute serves as the data analysis center. The Institutional Review Board at Duke University Health approved this study.

Medicare is a national health insurance program in the United States and covers 98% of adults aged ≥65 years. To obtain longitudinal outcomes, GWTG-Stroke records were linked to Medicare claims files by matching on a series of indirect identifiers, including admission date, discharge date, hospital identification, and patient's date of birth and sex, as previously described and validated.[24]

Outcomes

Prespecified primary outcomes were home time at 90 days and 1 year from the date of hospital admission. Home time was zero days for patients who died during hospitalization.

Prespecified secondary outcomes included all-cause mortality and all-cause readmission in 1 year follow-up, and mRS at discharge and 90 days among those treated with EVT, as well. For patients who were treated with IVT only, mRS values were not routinely collected in GWTG-Stroke during the study period. Time of death or readmission was counted starting from the date of hospital discharge.

Data Analysis

Primary analyses examined the associations of DTN times with outcomes in the IVT-only group and IVT+EVT group separately. Secondary analyses compared the outcomes in the IVT+EVT group with different DTN times with the EVT-only treatment group. DTN time was analyzed as a continuous variable, per 15-minute increments, and as AHA/ASA Target:Stroke initiative predefined targets (within 30, 45, and 60 minutes) versus longer than those targets.[3,9,25,26] For transferred patients, arrival time at the first hospital was defined as "door" time. Because a large proportion of patients had zero days of home time, as shown on the histogram in Figure S2, the associations between DTN time and home time were analyzed using a 2-stage logistic regression model[27]: (1) a logistic regression analysis of the binary outcome home time=0 (never discharged to home as a result of death or long-term facility stay) versus home time>0 (those ever discharged to home), and (2) a logistic regression model with generalized estimating equation for patients with home time>0 (those ever discharged to home) where the outcome was the proportion of follow-up days at home. The odds ratio of each 1% home time increase was computed. A logit link was used to reflect the upper (90-day or 1-year) and lower (0 days) bounds on home time. Robust, empirical variance estimates were used in the generalized estimating equation model to account for potential clustering within sites and for data that may not follow an independent binomial distribution. Both models were adjusted for the covariates listed below. Restricted cubic splines with 4 knots were applied as appropriate to continuous variables. The associations of DTN times with mortality and readmission were analyzed using Cox proportional hazards models with robust sandwich covariance estimates to account for within-hospital clustering. The proportional hazards assumption was assessed with Schoenfeld residuals. For readmission, a cause-specific hazard model was used to account for the competing risk of mortality.[28]

The adjusted models controlled for potential confounders including (1) patient characteristics, including age, sex, race and ethnicity, insurance, comorbidities (atrial fibrillation/flutter, previous stroke and transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes, peripheral artery disease, hypertension, dyslipidemia, renal insufficiency, and smoking), antiplatelet or anticoagulant therapy, admission systolic blood pressure, heart rate, glucose, and stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS); and (2) hospital characteristics, including geographic region, urban/rural, total bed number, annual ischemic stroke volume, teaching status, and stroke center certification. For EVT treatment, the models also adjusted for onset-to-EVT times (time from last known well to arterial puncture).

Missing Data

Rates of missingness of key patient and hospital characteristics were low (Table S1). Patients missing socioeconomic variables or from sites with missing hospital characteristics were excluded from adjusted analyses. Covariates with ≥25% missingness were not used in the models. For remaining covariates with missing data, values were imputed using multiple imputation with 20 datasets. The missing rate of NIHSS was very low: 278 patients (0.7%) in IVT-only cohort and 19 patients (0.5%) in the IVT+EVT cohort. Evidence of modest bias in NIHSS documentation was observed in older GWTG-Stroke data (before 2012), but this bias has lessened because the documentation of NIHSS has improved in recent years.[29] Therefore, NIHSS was not imputed in the current analysis. The missing rates of mRS were high, especially at 90 days (Table S2). Therefore, the analyses of mRS were limited to those with documented mRS.

All statistical analyses were performed using SAS Version 9.4 software (SAS Institute). All tests were 2-sided, with $P<0.05$ considered statistically significant.

RESULTS

Among the 503 876 patients with matching records, 43 989 received IVT only, 4603 received IVT+EVT, and

9125 received EVT-only treatment (Figure S1). After excluding patients with incomplete records, in-hospital stroke, IVT initiated after 4.5 hours, EVT initiated after 7 hours of last known well, left against medical advice, and discharge status missing, the final analysis included 38913 patients treated with IVT only, 3946 with IVT+EVT, and 3704 with EVT only.

Shorter DTN Times Were Associated With More Home Time and Lower Mortality and Readmission in Patients Treated With IVT Only

Patient and hospital characteristics for the IVT-only cohort are provided in Table S3. The outcomes by every 15-minute increment of DTN times are provided in Table 1. Using DTN ≤30 minutes as the reference, the increase of DTN times to 31 to 45, 46 to 60, 61 to 75, 76 to 90, and >90 minutes was associated with incremented odds of zero home time in a year (never discharged to home as a result of death or long-term facility stay) (adjusted odds ratio [aOR], 0.95, 1.04, 1.15, 1.13, and 1.33, respectively) and with decrement of home time among those ever discharged to home (home time >0; aOR per 1% of 365 days, 0.98, 0.92, 0.90, 0.87, and 0.85, respectively). These associations held true in 90-day home time. The adjusted spline plots in Figure 1A and 1B delineate the relationship between home time and DTN times as a continuous variable, which showed a turning point at a DTN time of 90 minutes. Each 15-minute additional DTN time, up to 90 minutes, was associated with higher odds of zero home time in 1 year (aOR, 1.04 [95% CI, 1.01–1.07]), less home time among those discharged to home (aOR per 1% of 365 days, 0.96 [95% CI, 0.94–0.98]), higher all-cause mortality (adjusted hazard ratio [aHR], 1.03 [95% CI, 1.01–1.04]), and higher readmission (aHR, 1.02 [95% CI, 1.01-1.03]; Table 1). This directionality dissipated after a DTN time of 90 minutes.

The outcomes by AHA/ASA recommended DTN targets of 30, 45, and 60 minutes are shown in Table 2. DTN >45 minutes, compared with DTN ≤45 minutes, was associated with higher odds of zero home time in a year (aOR, 1.16 [95% CI, 1.08–1.26]), less home time (aOR, 0.90 per 1% [95% CI, 0.86–0.94]), higher all-cause mortality (aHR, 1.11 [95% CI, 1.06–1.16]), and higher readmission (aHR, 1.05 [95% CI, 1.02–1.09]). These associations were also evident with DTN >60 versus ≤60 minutes, and in the sensitivity analysis excluding DTN >90 minutes, as well (Table S4).

Shorter DTN Times Were Associated With More Home Time and Lower Mortality in IVT+EVT Combined Therapy

The outcomes by every 15-minute increment of DTN times in patients treated with IVT+EVT combined therapy are shown in Table 3. The adjusted spline plots are provided in Figure 1C and 1D. With the use of DTN ≤30 minutes as the reference group, the increase of DTN time to 31 to 45, 46 to 60, and >60 minutes was associated with incremented odds of zero home time in a year (aOR 1.20, 1.29, and 1.62, respectively), decrement in home time among those discharged to home (median 284, 237, and 200 days, respectively, versus 302 days in DTN ≤30 minutes; aOR per 1% of 365 days, 1.03, 0.88, and 0.72, respectively), and increment in mortality (aOR 0.99, 1.12, and 1.32, respectively). When DTN times were modeled as a continuous variable, each 15-minute increment of DTN time was associated with higher odds of zero home time in a year (aOR, 1.12 [95% CI, 1.06–1.19]), less home time among those discharged to home (aOR, 0.93 per 1% of 365 days [95% CI, 0.89–0.98]), and higher all-cause mortality (aHR 1.07 [95% CI 1.02–1.11]).

DTN times within 30, 45, and 60 minutes in IVT+EVT combined treatment, compared with longer than those targets, were associated with longer home time in 90 days and 1 year, and lower all-cause mortality in 1 year (Table 4). DTN >45 minutes, compared with DTN ≤45 minutes, had higher odds of zero home time in 1 year (aOR, 1.26 [95% CI, 1.05–1.51]), less home time among those discharged home (aOR, 0.80 per 1% [95% CI, 0.69–0.91]), and higher mortality (aHR, 1.20 [95% CI, 1.03–1.38]). Readmission risk did not differ. These associations held true in the sensitivity analysis excluding transferred patients (Table S5).

IVT-to-EVT Times and Door-to-EVT Times Were Also Associated With Outcomes in IVT+EVT Combined Treatment

The associations of IVT-to-EVT times with outcomes are shown in Table 5, and the sensitivity analyses excluding transferred patients are provided in Table S6. The unadjusted analyses did not show significant associations between IVT-to-EVT times with outcomes within each prespecified DTN time category. However, after adjusting for patient and hospital characteristics, and onset-to-arrival and DTN times, as well, the associations became statistically significant for some outcomes. Each 30-minute increase of IVT-to-EVT times was associated with less home time in 1 year among those who were discharged to home, but mortality did not differ. Similar directionality was observed when onset-to-needle times were within 3 hours (Table S7).

We further analyzed the associations of door-to-EVT times with outcomes in the IVT+EVT group (Table S8). Every 30-minute increase of door-to-EVT times was associated with higher odds of zero home time in a year (aOR, 1.07 [95% CI, 1.01–1.13]), less home time among those discharged to home (aOR, 0.94 per 1% of 365 days [95% CI, 0.90–0.98]), and higher all-cause mortality (aHR, 1.05 [95% CI, 1.00–1.09]), but not all-cause readmission (aOR, 1.02 [95% CI, 0.98–1.05]). These associations held true in the sensitivity analysis excluding transferred patients (Table S9).

Table 1. Home Time in IVT-Only Cohort With Every 15-Minute Increment of Door-to-Needle Times

Home time	Door-to-needle time							
	≤30 min	31–45 min	46–60 min	61–75 min	76–90 min	>90 min	Per 15-min increment*	
	Ref						DTN≤90 min	DTN>90 min
90-day home time (HT)								
Median [IQR]	71 [14–85]	71 [12–85]	71 [11–85]	69 [10–85]	70 [10–85]	70 [8–85]		
HT=0, never discharged to home within 90 days after acute stroke								
Unadjusted OR (95% CI)		0.99 (0.90–1.10)	1.03 (0.93–1.14)	1.07 (0.96–1.20)	1.07 (0.94–1.22)	1.20 (1.07–1.34)	1.03 (1.01–1.05)	1.01 (0.96–1.06)
Adjusted OR (95% CI)		0.96 (0.87–1.07)	1.03 (0.93–1.15)	1.07 (0.95–1.20)	1.10 (0.96–1.26)	1.28 (1.13–1.45)	1.03 (1.01–1.06)	1.04 (0.99–1.10)
HT>0, per 1% (of 90 days) increase of HT among those ever discharged to home								
Unadjusted OR (95% CI)		0.97 (0.91–1.04)	0.97 (0.91–1.03)	0.91 (0.85–0.98)	0.95 (0.87–1.03)	0.96 (0.89–1.03)	0.98 (0.97–0.99)	1.05 (1.02–1.08)
Adjusted OR (95% CI)		0.98 (0.92–1.04)	0.95 (0.89–1.01)	0.90 (0.84–0.96)	0.91 (0.84–0.99)	0.86 (0.80–0.92)	0.97 (0.96–0.98)	1.01 (0.98–1.04)
1-year home time								
Median [IQR]	335 [119–359]	334 [82–359]	335 [113–359]	335 [84–359]	331 [65–358]	332 [60–358]		
HT=0, never discharged to home in a year after acute stroke								
Unadjusted OR (95% CI)		0.99 (0.88–1.12)	1.05 (0.94–1.18)	1.16 (1.02–1.31)	1.11 (0.96–1.29)	1.26 (1.11–1.44)	1.04 (1.01–1.06)	1.01 (0.96–1.07)
Adjusted OR (95% CI)		0.95 (0.84–1.08)	1.04 (0.92–1.18)	1.15 (1.00–1.32)	1.13 (0.96–1.33)	1.33 (1.15–1.53)	1.04 (1.01–1.07)	1.05 (0.99–1.12)
HT>0, per 1% (of 365 days) increase of HT among those ever discharged to home								
Unadjusted OR (95% CI)		0.97 (0.90–1.04)	0.92 (0.85–1.00)	0.90 (0.84–0.98)	0.89 (0.81–0.98)	0.93 (0.86–1.01)	0.97 (0.95–0.98)	1.09 (1.05–1.13)
Adjusted OR (95% CI)		0.98 (0.91–1.05)	0.92 (0.85–0.99)	0.90 (0.83–0.97)	0.87 (0.79–0.97)	0.85 (0.78–0.92)	0.96 (0.94–0.98)	1.04 (1.00–1.08)
1-year all-cause mortality								
Unadjusted HR (95% CI)		0.98 (0.91–1.07)	1.04 (0.95–1.13)	1.07 (0.98–1.17)	1.08 (0.97–1.19)	1.06 (0.96–1.16)	1.03 (1.01–1.05)	0.93 (0.90–0.97)
Adjusted HR (95% CI)		0.99 (0.92–1.08)	1.08 (1.00–1.17)	1.09 (1.00–1.19)	1.12 (1.01–1.25)	1.15 (1.05–1.27)	1.03 (1.01–1.04)	–†
1-year all-cause readmission‡								
Unadjusted HR (95% CI)		1.01 (0.96–1.07)	1.01 (0.96–1.07)	1.04 (0.98–1.11)	1.04 (0.96–1.12)	1.08 (1.01–1.15)	1.02 (1.00–1.03)	0.99 (0.96–1.02)
Adjusted HR (95% CI)		1.01 (0.96–1.07)	1.03 (0.98–1.10)	1.06 (0.99–1.13)	1.08 (1.00–1.17)	1.14 (1.06–1.22)	1.02 (1.01–1.03)	–†

HT=0 refers to patients who either died or were unable to be discharged to home from acute care hospital or post–acute care facility as a result of severe disability. HT>0 refers to those ever discharged to home. Median HT was calculated among patients with HT>0. The associations of DTN with HT were estimated using a 2-stage model, producing 2 ORs for each DTN comparison. The ORs for "HT=0" indicated the ORs for having zero HT in the longer DTN group compared with the shorter DTN group; values >1 indicated that longer DTN was associated with higher odds of zero home days, an unfavorable outcome. The ORs for "HT>0, 1% increase" indicated the ORs of a 1% (of 90 days or 365 days) increase in the proportion of HT in the longer DTN group compared with the shorter DTN group among those who were discharged home; values <1 indicated that longer DTN times were associated with lower odds of additional days spent at home, an unfavorable outcome. For example, every 15-minute increase of DTN times up to 90 minutes was associated with higher odds of zero HT and, among those discharged to home, lower odds of a higher proportion of time spent at home, indicating that outcomes were worse with longer DTN times.

Covariates for the adjusted models are as follows: (1) patient characteristics: age, sex, race and ethnicity, insurance, comorbidities (atrial fibrillation/flutter, previous stroke and transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes, peripheral artery disease, hypertension, dyslipidemia, renal insufficiency, and smoking), antiplatelet or anticoagulant, admission systolic blood pressure, heart rate, glucose, and stroke severity as measured by the National Institutes of Health Stroke Scale; and (2) hospital characteristics: geographic region, urban/rural, total bed number, annual ischemic stroke volume, teaching status, and stroke center certification. DTN indicates door-to-needle time; HR, hazard ratio; IQR, interquartile range; IVT, intravenous thrombolytic therapy; OR, odds ratio; and Ref, reference.

*DTN time was modeled as continuous variable.

†Data were not available because there were too few events to fit the adjusted model.

‡Cause-specific model was used for readmission to account for competing risk of death.

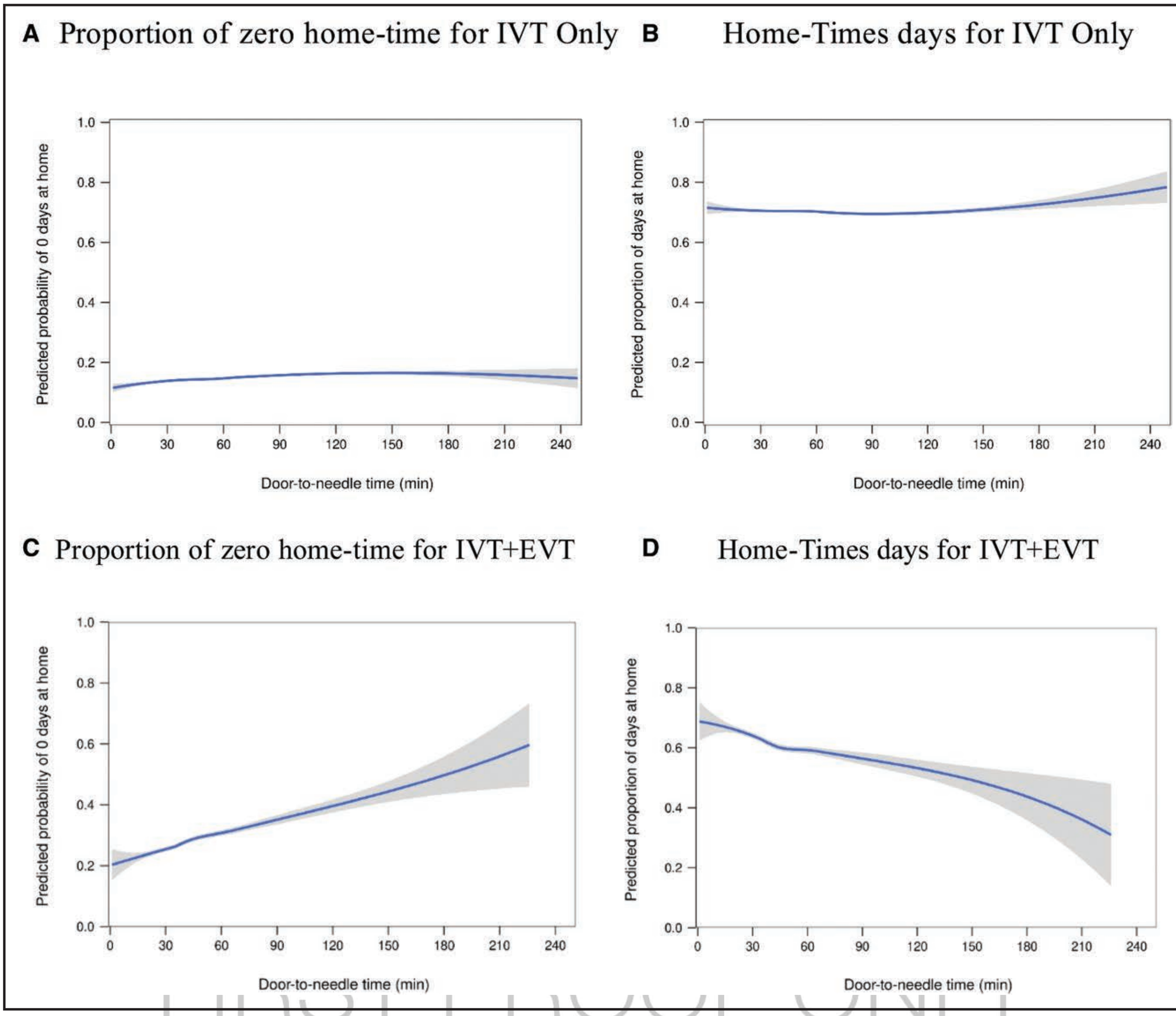

Figure 1. Adjusted spline plots of door-to-needle time vs 90-day home time.
A and **C** were drawn from the adjusted model of zero home time (patients who either died within 90 days of stroke admission or were unable to be discharged to home from acute hospital or post–acute care facility as a result of severe disability). **B** and **D** were drawn from the adjusted model predicting proportion of days at home for those with home time >0 (patients who were ever discharged to home within 90 days). The Y-axis represents proportion of 90 days. The gray zone represents 95% CI. In the IVT-only cohort, but not the IVT+EVT cohort, the association of home time and door-to-needle changed at a door-to-needle time of 90 minutes. Covariates for the adjusted models: (1) patient characteristics including age, sex, race and ethnicity, insurance, comorbidities (atrial fibrillation/flutter, previous stroke and transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes, peripheral artery disease, hypertension, dyslipidemia, renal insufficiency, and smoking), antiplatelet or anticoagulant, admission systolic blood pressure, heart rate, glucose, and stroke severity as measured by the National Institutes of Health Stroke Scale; and (2) hospital characteristics including geographic region, urban/rural, total bed number, annual ischemic stroke volume, teaching status, and stroke center certification. For EVT treatment (**B** and **D**), the models also adjusted for onset-to-EVT times. EVT indicates endovascular thrombectomy; and IVT, intravenous thrombolytic therapy.

Secondary Analysis: EVT+IVT With Shorter DTN Times Had Better Outcomes Than EVT Only

As a secondary analysis, we compared the outcomes among patients treated with IVT+EVT at different DTN times versus those treated with EVT only. As shown in Table S10, there were no significant differences between the 2 groups in terms of patient age, sex, race and ethnicity, most comorbidities, and stroke severity as measured by NIHSS. However, the IVT+EVT group had lower prevalence of atrial fibrillation, previous stroke, heart failure, and antiplatelet or anticoagulant before admission compared with the other groups. In addition, the IVT+EVT group had longer door-to-EVT time (median 102 versus 79, standardized difference 44.64), but shorter onset-to-EVT time (median 176 versus 245, standardized difference 39.19). The median annual EVT volume of the treating hospitals for the IVT+EVT group was lower than that for the EVT-only group (48 versus 56, standardized difference 25.41).

Table 2. Home Time in IVT-Only Cohort with Prespecified Door-to-Needle Time Targets

Home time	Door-to-needle time					
	≤30 min (Ref)	>30 min	≤45 min (Ref)	>45 min	≤60 min (Ref)	>60 min
90-day home time (HT)						
Median [IQR]	71 [14–85]	70 [10–85]	71 [13–85]	70 [10–85]	71 [12–85]	69 [9–85]
HT=0, never discharged to home within 90 days after acute stroke						
Unadjusted OR (95% CI)		1.05 (0.96–1.15)		1.08 (1.02–1.15)		1.10 (1.04–1.17)
Adjusted OR (95% CI)		1.04 (0.94–1.14)		1.12 (1.05–1.19)		1.13 (1.06–1.21)
HT>0, per 1% (of 90 days) increase of HT among those ever discharged to home						
Unadjusted OR (95% CI)		0.96 (0.90–1.01)		0.97 (0.93–1.00)		0.96 (0.92–0.99)
Adjusted OR (95% CI)		0.92 (0.87–0.98)		0.93 (0.89–0.96)		0.91 (0.88–0.95)
1-year home time						
Median [IQR]	335 [119–359]	334 [82–359]	335 [116–359]	333 [69–358]	335 [102–359]	331 [57–358]
HT=0, never discharged to home within a year after acute stroke						
Unadjusted OR (95% CI)		1.09 (0.98–1.20)		1.13 (1.06–1.21)		1.16 (1.08–1.24)
Adjusted OR (95% CI)		1.06 (0.95–1.19)		1.16 (1.08–1.26)		1.20 (1.11–1.29)
HT>0, per 1% (of 365 days) increase of HT among those ever discharged to home						
Unadjusted OR (95% CI)		0.93 (0.87–1.00)		0.94 (0.90–0.98)		0.95 (0.91–0.99)
Adjusted OR (95% CI)		0.91 (0.85–0.97)		0.90 (0.86–0.94)		0.91 (0.87–0.96)
1-year all-cause mortality						
Unadjusted HR (95% CI)		1.04 (0.96–1.12)		1.07 (1.02–1.12)		1.07 (1.02–1.12)
Adjusted HR (95% CI)		1.06 (0.99–1.14)		1.11 (1.06–1.16)		1.08 (1.03–1.14)
1-year all-cause readmission*						
Unadjusted HR (95% CI)		1.03 (0.98–1.08)		1.03 (1.00–1.06)		1.04 (1.01–1.08)
Adjusted HR (95% CI)		1.04 (0.99–1.10)		1.05 (1.02–1.09)		1.07 (1.03–1.11)

HT=0 refers to patients who either died or were unable to be discharged to home from acute hospital or post–acute care facility as a result of severe disability. HT> 0 refers to those ever discharged to home. Median home time was calculated among patients with HT>0. The associations of DTN with HT were estimated using a 2-stage model, producing 2 ORs for each DTN comparison. The ORs for "HT=0" indicated the ORs for having zero HT in the longer DTN group compared with the shorter DTN group; values >1 indicated that longer DTN was associated with higher odds of zero home days, an unfavorable outcome. The ORs for "HT>0, 1% increase" indicated the ORs of a 1% (of 90 days or 365 days) increase in the proportion of home time in the longer DTN group compared with the shorter DTN group among those who were discharged home; values <1 indicated that longer DTN times were associated with lower odds of additional days spent at home, an unfavorable outcome. For example, DTN >45 minutes was associated with higher odds of zero HT and, among those discharged to home, lower odds of a higher proportion of time spent at home, indicating that outcomes were worse with longer DTN times.

Covariates for the adjusted models: (1) patient characteristics: age, sex, race and ethnicity, insurance, comorbidities (atrial fibrillation/flutter, previous stroke and transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes, peripheral artery disease, hypertension, dyslipidemia, renal insufficiency, and smoking), antiplatelet or anticoagulant, admission systolic blood pressure, heart rate, glucose, and stroke severity as measured by the National Institutes of Health Stroke Scale; and (2) hospital characteristics: geographic region, urban/rural, total bed number, annual ischemic stroke volume, teaching status, and stroke center certification. DTN indicates door-to-needle time; HR, hazard ratio; IQR, interquartile range; IVT, intravenous thrombolytic therapy; OR, odds ratio; and Ref, reference.

*Cause-specific model was used for readmission to account for competing risk of death.

Adjusted outcome analyses were performed after patients were stratified by onset-to-EVT times and the results are provided in Table 6. Among patients treated with onset-to-EVT ≤180 minutes, combined therapy with DTN ≤30, 45, and 60 minutes had significantly more home time in a year (median 310, 304, and 286 days, respectively; aOR 1.48, 1.47, and 1.39 per 1% of 365 days) compared with the EVT-only group (median 225 days). DTN ≤45 or 60 minutes was associated with significantly lower 1-year mortality (aHR 0.76 and 0.81, respectively) compared with the EVT-only group. This association held true for onset-to-EVT 181- to 300-minute group and in the sensitivity analysis excluding transferred patients (Table S11). Adjusted analyses were not performed in some subgroups because of the small numbers of events.

The mRS at discharge is provided in Figure 2. The proportion of patients achieving good functional outcomes at discharge, defined as an mRS of 0 to 2, increased as DTN times shortened in the IVT+EVT group (22.3%, 23.4%, and 25.0%, for DTN ≤60, 45, and 30 minutes, respectively), compared with 16.4% in EVT-only group (P<0.001 for each). This outcome benefit in the IVT+EVT group dissipated at DTN >60 minutes (18.0%, P=0.404). This directionality was also observed at 90 days, but data missing rates were high (Figure S3).

Table 3. Outcomes in IVT+EVT Cohort with Every 15-Minute Increment of Door-to-Needle Times

Home time	Door-to-needle time				
	≤30 min (Ref)	31–45 min	46–60 min	>60 min	Per 15-min increment*
90-day home time (HT)					
Median [IQR]	56 [1–81]	48 [0–77]	33 [0–74]	18 [0–69]	
HT=0, never discharged to home within 90 days after acute stroke					
Unadjusted OR (95% CI)		1.11 (0.92–1.34)	1.32 (1.07–1.61)	1.55 (1.25–1.92)	1.12 (1.07–1.17)
Adjusted OR (95% CI)		1.08 (0.88–1.32)	1.19 (0.95–1.50)	1.43 (1.11–1.84)	1.10 (1.04–1.16)
HT>0, per 1% (of 90 days) increase of HT among those ever discharged to home					
Unadjusted OR (95% CI)		0.91 (0.79–1.04)	0.78 (0.67–0.91)	0.71 (0.60–0.83)	0.93 (0.90–0.96)
Adjusted OR (95% CI)		1.00 (0.87–1.14)	0.92 (0.79–1.08)	0.79 (0.67–0.94)	0.95 (0.92–0.99)
1-year home time					
Median [IQR]	302 [8–352]	284 [4–349]	237 [2–344]	200 [0–340]	
HT=0, never discharged to home within a year after acute stroke					
Unadjusted OR (95% CI)		1.23 (1.00–1.52)	1.43 (1.14–1.80)	1.74 (1.37–2.20)	1.13 (1.08–1.19)
Adjusted OR (95% CI)		1.20 (0.95–1.52)	1.29 (0.99–1.67)	1.62 (1.22–2.14)	1.12 (1.06–1.19)
HT>0, per 1% (of 365 days) increase of HT among those ever discharged to home					
Unadjusted OR (95% CI)		0.96 (0.82–1.13)	0.77 (0.64–0.92)	0.68 (0.56–0.83)	0.92 (0.88–0.95)
Adjusted OR (95% CI)		1.03 (0.87–1.22)	0.88 (0.72–1.07)	0.72 (0.58–0.90)	0.93 (0.89–0.98)
1-year all-cause mortality					
Unadjusted HR (95% CI)		1.01 (0.86–1.20)	1.24 (1.04–1.48)	1.34 (1.10–1.63)	1.08 (1.04–1.12)
Adjusted HR (95% CI)		0.99 (0.83–1.20)	1.12 (0.92–1.36)	1.32 (1.06–1.65)	1.07 (1.02–1.11)
1-year all-cause readmission†					
Unadjusted HR (95% CI)		1.09 (0.95–1.26)	1.16 (1.01–1.33)	1.03 (0.89–1.21)	1.02 (0.99–1.06)
Adjusted HR (95% CI)		1.09 (0.94–1.26)	1.05 (0.90–1.23)	1.00 (0.83–1.20)	1.01 (0.97–1.05)

HT=0 refers to patients who either died or were unable to be discharged to home from acute hospital or post–acute care facility as a result of severe disability. HT>0 refers to those ever discharged to home. Median HT was calculated among patients with HT>0. The associations of DTN with HT were estimated using a 2-stage model, producing 2 ORs for each DTN comparison. The ORs for "HT=0" indicated the ORs for having zero HT in the longer DTN group compared with the shorter DTN group; values >1 indicated that longer DTN was associated with higher odds of zero home days, an unfavorable outcome. The ORs for "HT>0, 1% increase" indicated the ORs of a 1% (of 90 days or 365 days) increase in the proportion of HT in the longer DTN group compared with the shorter DTN group among those who were discharged home; values <1 indicated that longer DTN times were associated with lower odds of additional days spent at home, an unfavorable outcome.

Covariates for the adjusted models: (1) patient characteristics: age, sex, race and ethnicity, insurance, comorbidities (atrial fibrillation/flutter, previous stroke and transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes, peripheral artery disease, hypertension, dyslipidemia, renal insufficiency, and smoking), antiplatelet or anticoagulant, onset-to-EVT times, admission systolic blood pressure, heart rate, glucose, and stroke severity as measured by the National Institutes of Health Stroke Scale; and (2) hospital characteristics: geographic region, urban/rural, total bed number, annual ischemic stroke volume, teaching status, and stroke center certification. DTN indicates door-to-needle time; EVT, endovascular thrombectomy; HR, hazard ratio; IQR, interquartile range; IVT, intravenous thrombolytic therapy; OR, odds ratio; and Ref, reference.

*DTN time was modeled as continuous variable.

†Cause-specific model was used for readmission to account for competing risk of death.

DISCUSSION

This large nationwide study of US older patients treated with IVT only and, importantly, IVT+EVT combined therapy demonstrated that shorter DTN times for IVT are associated with greater chance of being discharged to home, more time at home, and lower all-cause mortality within a year after acute ischemic stroke. The odds are modest in the IVT-only group and greater in the IVT+EVT group. The results in the IVT-only cohort confirmed that home time, a novel functional outcome measure, has the same associations with DTN times as traditional outcome measures such as all-cause mortality and readmission.[4] The results of the IVT+EVT combined treatment cohort is the first study to demonstrate that each 15-minute increase in DTN times, even followed by EVT, is associated with less home time and higher mortality in a year. The secondary analysis suggests that, for IVT+EVT combined treatment, when IVT is given with DTN ≤60 minutes and onset-to-EVT ≤300 minutes, is associated with more home time and lower mortality than EVT alone. Patients treated with combined therapy at shorter DTN times (up to 60 minutes) are more likely to achieve functional independence at discharge and 90 days.

This study provides important new information on the association of DTN times with outcomes in patients who also underwent EVT. Previous studies of DTN times have either excluded patients who had EVT or were based on small sample sizes or highly selected populations. A previous study from the HERMES collaboration found, like ours, that DTN delays are associated with worse outcomes in

Table 4. Outcomes in IVT+EVT Cohort with Prespecified Door-to-Needle Time Targets

Home time	Door-to-needle time					
	≤30 min (Ref)	>30 min	≤45 min (Ref)	>45 min	≤60 min (Ref)	>60 min
90-day home time (HT)						
Median [IQR]	56 [1–81]	35 [0–75]	51 [0–79]	24 [0–72]	46 [0–77]	18 [0–69]
HT=0, never discharged to home within 90 days after acute stroke						
Unadjusted OR (95% CI)		1.27 (1.08–1.49)		1.33 (1.16–1.54)		1.37 (1.15–1.64)
Adjusted OR (95% CI)		1.17 (0.97–1.41)		1.23 (1.04–1.44)		1.30 (1.07–1.60)
HT>0, per 1% (of 90 days) increase of HT among those ever discharged to home						
Unadjusted OR (95% CI)		0.82 (0.73–0.92)		0.79 (0.71–0.89)		0.79 (0.68–0.91)
Adjusted OR (95% CI)		0.94 (0.84–1.06)		0.87 (0.77–0.98)		0.82 (0.70–0.95)
1-year home time						
Median [IQR]	302 [8–352]	259 [2-345]	293 [5–351]	226 [0–342]	280 [4–349]	200 [0–340]
HT=0, never discharged to home within a year after acute stroke						
Unadjusted OR (95% CI)		1.40 (1.16–1.69)		1.38 (1.18–1.62)		1.44 (1.19–1.75)
Adjusted OR (95% CI)		1.29 (1.05–1.60)		1.26 (1.05–1.51)		1.37 (1.10–1.71)
HT>0, per 1% (of 365 days) increase of HT among those ever discharged to home						
Unadjusted OR (95% CI)		0.83 (0.72–0.96)		0.74 (0.66–0.84)		0.74 (0.63–0.88)
Adjusted OR (95% CI)		0.93 (0.79–1.08)		0.80 (0.69–0.91)		0.75 (0.62–0.89)
1-year all-cause mortality						
Unadjusted HR (95% CI)		1.15 (1.00–1.33)		1.27 (1.12–1.45)		1.25 (1.06–1.48)
Adjusted HR (95% CI)		1.08 (0.92–1.27)		1.20 (1.03–1.38)		1.27 (1.06–1.52)
1-year all-cause readmission*						
Unadjusted HR (95% CI)		1.10 (0.97–1.24)		1.05 (0.95–1.16)		0.96 (0.84–1.10)
Adjusted HR (95% CI)		1.06 (0.93–1.21)		0.98 (0.87–1.10)		0.95 (0.81–1.11)

HT=0 refers to patients who either died or were unable to be discharged to home from acute hospital or post–acute care facility as a result of severe disability. HT>0 refers to those ever discharged to home. Median HT was calculated among patients with HT>0.

The associations of DTN with home time were estimated using a 2-stage model, producing 2 ORs for each DTN comparison. The ORs for "HT=0" indicated the ORs for having zero HT in the longer DTN group compared with the shorter DTN group; values >1 indicated that longer DTN was associated with higher odds of zero home days, an unfavorable outcome. The ORs for "HT>0, 1% increase" indicated the ORs of a 1% (of 90 days or 365 days) increase in the proportion of HT in the longer DTN group compared with the shorter DTN group among those who were discharged home; values <1 indicated that longer DTN times were associated with lower odds of additional days spent at home, an unfavorable outcome. For example, DTN>45 minutes was associated with higher odds of zero HT and, among those discharged to home, lower odds of a higher proportion of time spent at home, indicating that outcomes were worse with longer treatment times. Covariates for the adjusted models: (1) patient characteristics: age, sex, race and ethnicity, insurance, comorbidities (atrial fibrillation/flutter, previous stroke and transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes, peripheral artery disease, hypertension, dyslipidemia, renal insufficiency, and smoking), antiplatelet or anticoagulant, onset-to-EVT times, admission systolic blood pressure, heart rate, glucose, and stroke severity as measured by the National Institutes of Health Stroke Scale; and (2) hospital characteristics: geographic region, urban/rural, total bed number, annual ischemic stroke volume, teaching status, and stroke center certification. DTN indicates door-to-needle time; EVT, endovascular thrombectomy; HR, hazard ratio; IQR, interquartile range; IVT, intravenous thrombolytic therapy; OR, odds ratio; and Ref, reference.

*Cause-specific model was used for readmission to account for competing risk of death.

patients treated with EVT.[31] However, that study was small (only 601 patients) and was performed in a highly selected trial population that was probably not representative of the patients treated in routine clinical practice. These novel findings have important implications for stroke systems of care and quality improvement. The findings demonstrate the importance of maintaining and strengthening focus on reducing DTN times in the era of highly effective EVT.

DTN time has been set as the target of the AHA/ASA Target:Stroke national quality initiative because it is directly under the control of hospital stroke teams and systems of care.[3,9,26] Our previous study showed that shorter DTN times, and achieving the Target:Stroke prespecified DTN time targets of ≤45 minutes and ≤60 minutes are associated with lower 1-year all-cause mortality and readmission after stroke.[4] These findings are extended in the present study with home time as a functional outcome measure that has been prioritized by stroke survivors.[19,20] These results support current guidelines to initiate IVT after noncontrast CT.[30] Advanced imaging, such as CT angiogram and MRI, including perfusion imaging, should not delay the thrombolytic therapy. The present study added novel data proving that, among patients treated with IVT+EVT combined therapy, accelerated DTN times are associated with clinically significant lower risk of zero home time (never discharged to home as a result of death or long-term care facility stay), more days at home, and lower mortality within a year. Every 15-minute delay in IVT administration, even

Table 5. Association of IVT-to-EVT Times with Outcomes in IVT+EVT Cohort

Door-to-needle	Home time, d, median [IQR]		Unadjusted OR/HR (95% CI)	Adjusted OR/HR (95% CI)	Unadjusted OR/HR (95% CI)	Adjusted OR/HR (95% CI)
	IVT-to-EVT ≤60 min	IVT-to-EVT >60 min	Ref: IVT-to-EVT ≤60 min		Per 30-min increment*	
Door-to-needle ≤30 min						
90-day HT=0			1.25 (0.94–1.66)	1.56 (1.12–2.19)	1.03 (0.92–1.14)	1.11 (0.98–1.26)
90-day HT>0, per 1% increase	61 [1–83]	44 [0–79]	0.87 (0.70–1.09)	0.77 (0.61–0.97)	0.97 (0.90–1.05)	0.91 (0.83–1.00)
1-year HT=0			1.09 (0.78–1.52)	1.38 (0.94–2.02)	1.04 (0.92–1.17)	1.15 (0.99–1.33)
1-year HT>0, per 1% increase	306 [9–354]	298 [7–352]	1.01 (0.77–1.34)	0.83 (0.62–1.10)	1.03 (0.93–1.14)	0.95 (0.85–1.06)
1-year mortality			0.89 (0.68–1.17)	–‡	0.98 (0.89–1.09)	–‡
1-year readmission†			1.05 (0.85–1.28)	–‡	1.01 (0.95–1.07)	–‡
Door-to-needle ≤45 min						
90-day HT=0			1.09 (0.91–1.32)	1.22 (1.00–1.51)	1.04 (0.98–1.11)	1.09 (1.01–1.17)
90-day HT>0, per 1% increase	57 [0–81]	41 [0–77]	0.82 (0.72–0.94)	0.76 (0.67–0.87)	0.94 (0.90–0.98)	0.91 (0.87–0.96)
1-year HT=0			1.00 (0.82–1.23)	1.12 (0.89–1.41)	1.00 (0.93–1.08)	1.04 (0.96–1.13)
1-year HT>0, per 1% increase	299 [5–351]	282 [5–350]	0.90 (0.77–1.05)	0.78 (0.66–0.93)	0.97 (0.92–1.03)	0.93 (0.88–0.99)
1-year mortality			1.04 (0.88–1.23)	1.20 (1.00–1.45)	1.00 (0.95–1.06)	1.06 (0.99–1.12)
1-year readmission†			1.11 (0.98–1.25)	1.20 (1.05–1.38)	1.01 (0.98–1.05)	1.02 (0.97–1.07)
Door-to-needle ≤60 min						
90-day HT=0			1.13 (0.97–1.32)	1.20 (1.01–1.43)	1.05 (0.99–1.10)	1.07 (1.01–1.13)
90-day HT>0, per 1% increase	54 [0–80]	34 [0–76]	0.80 (0.71–0.90)	0.75 (0.67–0.84)	0.93 (0.89–0.97)	0.91 (0.87–0.94)
1-year HT=0			1.06 (0.89–1.26)	1.14 (0.94–1.39)	1.02 (0.97–1.08)	1.05 (0.99–1.12)
1-year HT>0, per 1% increase	286 [4–350]	273 [4–348]	0.89 (0.78–1.02)	0.81 (0.70–0.94)	0.97 (0.93–1.01)	0.94 (0.90–0.99)
1-year mortality			1.07 (0.93–1.23)	1.16 (1.00–1.35)	1.01 (0.97–1.06)	1.05 (1.00–1.10)
1-year readmission†			1.06 (0.96–1.18)	1.13 (1.01–1.27)	1.01 (0.98–1.04)	1.01 (0.97–1.05)
Door-to-needle >60 min						
90-day HT=0			1.34 (0.97–1.84)	1.65 (1.12–2.44)	1.14 (1.03–1.27)	1.24 (1.09–1.40)
90-day HT>0, per 1% increase	24 [0–71]	10 [0–68]	0.92 (0.71–1.20)	0.77 (0.59–1.01)	0.98 (0.89–1.07)	0.92 (0.84–1.01)
1-year HT=0			1.15 (0.82–1.63)	0.72 (0.52–1.00)	1.07 (0.96–1.19)	1.17 (1.02–1.34)
1-year HT>0, per 1% increase	215 [0–341]	194 [0–337]	1.00 (0.74–1.36)	1.52 (0.99–2.34)	0.99 (0.89–1.10)	0.89 (0.79–0.99)
1-year mortality			0.98 (0.74–1.31)	–‡	0.99 (0.90–1.08)	–‡
1-year readmission†			1.06 (0.81–1.39)	–‡	1.00 (0.93–1.07)	–‡

Data are expressed as median [interquartile range], adjusted odds ratio (95% CI) for HT, or adjusted hazard ratio (95% CI) for mortality and readmission. HT=0 refers to patients who either died or were unable to be discharged home as a result of severe disability. HT>0 refers to those ever discharged home. Median HT was calculated among patients with HT>0. The associations of IVT-to-EVT times with HT were estimated using a 2-stage model, producing 2 adjusted ORs for each comparison. The ORs for "HT=0" indicated the ORs for having zero HT in the longer IVT-to-EVT group compared with the shorter IVT-to-EVT group; values >1 indicated that longer IVT-to-EVT was associated with higher odds of zero home days, an unfavorable outcome. The ORs for "HT>0, per 1% increase" indicated the ORs of a 1% (of 90 days or 365 days) increase in the proportion of time at home in the longer IVT-to-EVT group compared with the shorter IVT-to-EVT group among those who were discharged to home; values <1 indicated that longer IVT-to-EVT was associated with lower odds of additional days spent at home, an unfavorable outcome.

Covariates for the adjusted models: (1) patient characteristics: age, sex, race and ethnicity, insurance, comorbidities (atrial fibrillation/flutter, previous stroke and transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes, peripheral artery disease, hypertension, dyslipidemia, renal insufficiency, and smoking), antiplatelet or anticoagulant, onset-to-arrival times, door-to-needle times, admission systolic blood pressure, heart rate, glucose, and stroke severity as measured by the National Institutes of Health Stroke Scale; and (2) hospital characteristics: geographic region, urban/rural, total bed number, annual ischemic stroke volume, teaching status, and stroke center certification. IVT-to-EVT time was defined as the time from IVT bolus to arterial puncture for EVT. EVT indicates endovascular thrombectomy; HR, hazard ratio; HT, home time; IVT, intravenous thrombolytic therapy; and OR, odds ratio.

*IVT-to-EVT time was modeled as continuous variable.

†Cause-specific model was used for readmission to account for competing risk of death.

‡Data were not available because there were too few events to fit the adjusted model.

with concurrent modern EVT treatment, is associated with less home time and higher all-cause mortality in 1 year. These results also support the increased use of prehospital thrombolytic therapy in mobile stroke units, which provide fast thrombolytic treatment.[32,33] The greater effect of DTN times among the IVT+EVT combined treatment group might have been due to a synergistic effect of IVT and EVT. Systemic thrombolysis facilitates early recanalization of the thrombectomy procedure, and the recanalization of large vessels by EVT facilities IVT to lyse distal or hard-to-reach

Table 6. Secondary Analysis: Outcomes in EVT-Only Cohort versus EVT+IVT Cohort by Door-to-Needle Times

	EVT Only	EVT+IVT			
	Ref	DTN≤30 min	DTN≤45 min	DTN≤60 min	DTN>60 min
Onset to EVT ≤180 min					
90-day home time (HT)					
Median [IQR]	28 [0–74]	61 [2–83]	58 [1–81]	53 [0–80]	28 [0–75]
HT=0, never discharged to home after acute stroke, aOR (95% CI)		0.80 (0.60–1.05)	0.82 (0.66–1.03)	0.87 (0.71–1.07)	–*
HT>0, per 1% increase of home time among those ever discharged to home, aOR (95% CI)		1.33 (1.10–1.60)	1.32 (1.14–1.53)	1.29 (1.13–1.49)	–*
One-year home time					
Median [IQR]	225 [3–341]	310 [13–354]	304 [8–352]	286 [6–351]	250 [0–344]
HT=0, never discharged to home after acute stroke admission, aOR (95% CI)		0.74 (0.54–1.01)	0.84 (0.66–1.07)	0.86 (0.69–1.07)	–*
HT>0, per 1% increase of home time among those ever discharged to home, aOR (95% CI)		1.48 (1.20–1.82)	1.47 (1.24–1.74)	1.39 (1.18–1.62)	–*
1-year mortality, aHR (95% CI)		–*	0.76 (0.65–0.89)	0.81 (0.70–0.94)	–*
1-year readmission,† aHR (95% CI)		–*	0.85 (0.74–0.98)	0.90 (0.79–1.03)	–*
Onset to EVT 180–300 min					
90-day home time					
Median [IQR]	16 [0–71]	49 [0–79]	39 [0–76]	36 [0–75]	18 [0–69]
HT=0, never discharged to home after acute stroke, aOR (95% CI)		–*	0.84 (0.67–1.05)	0.82 (0.67–1.00)	–*
HT>0, per 1% increase of home time among those ever discharged to home, aOR (95% CI)		–*	1.29 (1.09, 1.52)	1.20 (1.03, 1.39)	–*
1-year home time					
Median [IQR]	186 [0–338]	283 [2–351]	274 [2–348]	272 [2–347]	209 [0–337]
HT=0, never discharged to home after acute stroke, aOR (95% CI)		–*	0.88 (0.68–1.14)	0.90 (0.72–1.13)	–*
HT>0, per 1% increase of home time among those ever discharged to home, aOR (95% CI)		–*	1.58 (1.31–1.91)	1.53 (1.30–1.81)	–*
1-year mortality, aHR (95% CI)		–*	–*	0.75 (0.64–0.88)	–*
1 -year readmission,† aHR (95% CI)		–*	–*	0.81 (0.70–0.94)	–*
Onset to EVT >300 min‡					
90-day home time					
Median [IQR]	14 [0–71]	30 [0–77]	18 [0–73]	18 [0–73]	1 [0–56]
1-year home time					
Median [IQR]	174 [0–338]	278 [10–346]	265 [2–344]	253 [1–345]	40 [0–327]

HT=0 refers to patients who either died or were unable to be discharged to home from acute care hospital or post–acute care facility as a result of severe disability. HT>0 refers to those ever discharged to home. Median HT was calculated among patients with HT>0. A 2-stage model was used for each HT comparison, producing 2 aORs. EVT-only group within each onset-to-EVT time category was used as the reference. The ORs for "HT=0" indicated the ORs for having zero HT in each DTN subgroup of the IVT+EVT group compared with EVT-only group; values <1 indicated that IVT+EVT had lower odds of zero home days, a favorable outcome. The ORs for "HT>0, 1% increase" indicated the ORs of a 1% (of 90 days or 365 days) increase in the proportion of HT in the IVT+EVT group compared with EVT-only group among those who were discharged to home; values >1 indicated that IVT+EVT had higher odds of additional days spent at home, a favorable outcome.

Covariates for the adjusted models: (1) patient characteristics: age, sex, race and ethnicity, insurance, comorbidities (atrial fibrillation/flutter, previous stroke and transient ischemic attack, history of coronary artery disease/myocardial infarction, heart failure, carotid stenosis, diabetes, peripheral artery disease, hypertension, dyslipidemia, renal insufficiency, and smoking), antiplatelet or anticoagulant, onset-to-EVT times, admission systolic blood pressure, heart rate, glucose, and stroke severity as measured by the National Institutes of Health Stroke Scale; and (2) hospital characteristics: geographic region, urban/rural, total bed number, annual ischemic stroke volume, teaching status, and stroke center certification. aHR indicates adjusted hazard ratio; aOR, adjusted odds ratio; DTN, door-to-needle; EVT, endovascular thrombectomy; IQR, interquartile range; IVT, intravenous thrombolytic therapy; and Ref, reference.

*Data were not available because there were too few events to fit the adjusted model.

†Cause-specific model was used for readmission to account for competing risk of death.

‡Adjusted model could not be constructed because there were too few events.

clots.[34] Pooled analyses of trials of EVT with and without alteplase, a thrombolytic agent, showed trends toward better functional outcomes in those who received both. However, it is also possible that patients with large vessel occlusion have greater disability and provide greater scope for demonstrating an effect of shorter DTN times.

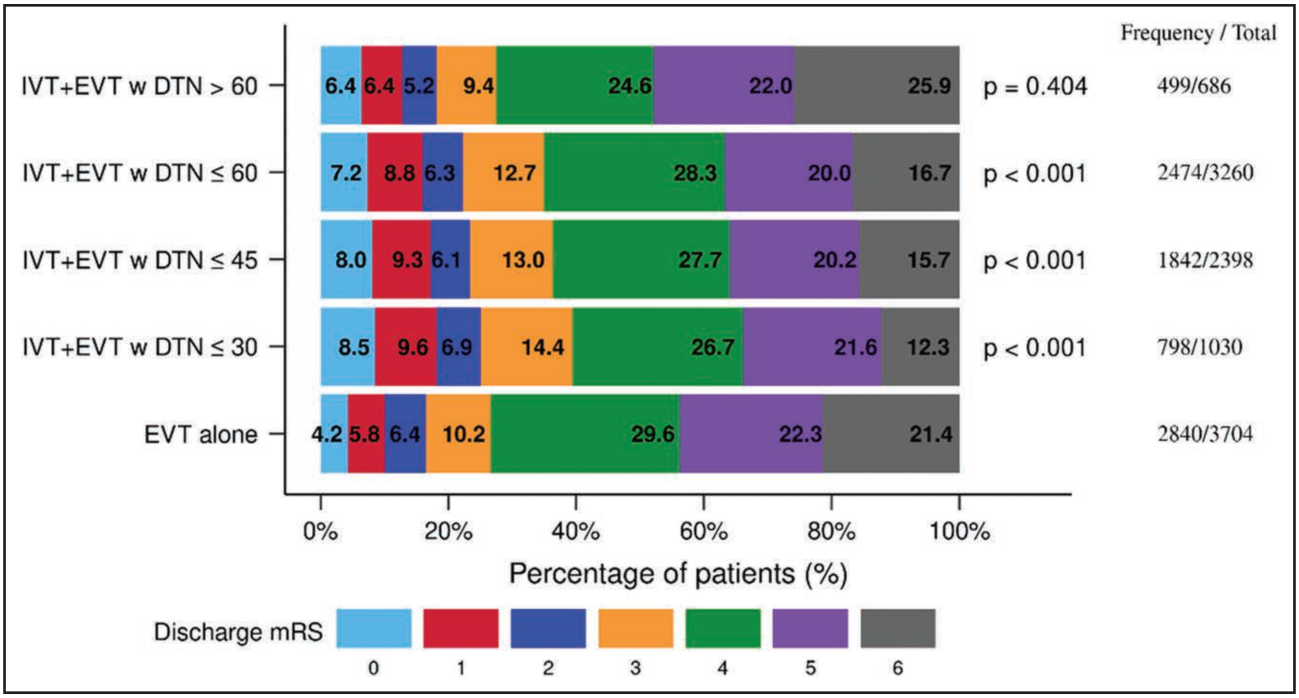

Figure 2. Secondary analysis: modified Rankin Scale at discharge among IVT+EVT vs EVT-only group.
P values were derived from the χ^2 of mRS 0 to 2 vs 3 to 6 for each DTN subgroup versus EVT-only group. DTN indicates door-to-needle time; EVT, endovascular thrombectomy; IVT, intravenous thrombolytic therapy; and mRS, modified Rankin Scale.

Our study provides novel information to support the current guidelines that both IVT and EVT should be provided for eligible patients and IVT should not be delayed because of planned EVT.[30,35] This is the first study to demonstrate the time effect of IVT before EVT by modeling DTN time as a continuous variable and taking advantage of the nationwide real-practice database with a patient population an order of magnitude larger than clinical trials. A subanalysis of the randomized clinical trials suggested that, among 203 patients that received combined therapy, the 90-day mortality was higher with DTN >1 hour versus 0 to 1 hour, but functional outcomes did not differ.[36] The positive associations of shorter DTN times with more home time and lower mortality among the patients receiving IVT+EVT treatment are indirect evidence that IVT before EVT has beneficial effect. Furthermore, the secondary analysis comparing combined therapy versus EVT alone provides a direct indication that, when EVT is started within 5 hours of stroke onset and IVT is given within 60 minutes of hospital arrival, combined therapy may offer more home time and lower mortality than EVT alone. These findings are strengthened by the analysis of mRS at discharge and 90 days follow-up in which more patients receiving combined treatment with shorter DTN times achieved good functional outcomes than patients receiving EVT only. The outcome benefits dissipate with DTN times >60 minutes. Although this finding needs to be confirmed in randomized clinical trials because of the potential selection bias in retrospective studies, it is in agreement with another study using GWTG-Stroke showing that patients treated with IVT+EVT were more likely to achieve home discharge, independent ambulation at discharge, and lower in-hospital mortality than EVT alone.[18] It should be noted that the data missing rates of 90-day mRS are high in the GWTG-Stroke database, although the missing rates are similar across subgroups. Therefore, the mRS analysis should be considered exploratory and as a support of the primary outcome analyses. Patients with missing mRS are likely alive because mortality data are well captured in Medicare files. This discrepancy might have contributed to the high mortality rate in our mRS analyses, in addition to the less strict patient selection in real-world EVT practice and older age in our cohort (age ≥65 years). However, the directionality of 90-day mRS is similar to discharge mRS, which has a low missing rate and has been shown to be highly predictive of 90-day outcomes.[37]

Our study was designed to complement the limitations of randomized clinical trials and provide important additional data to guide reperfusion therapy. Among the 6 noninferiority trials comparing EVT alone versus combined therapy, 2 trials demonstrated noninferiority and the other 4 did not.[10–15] The generalizability of the trials was limited by the wide noninferiority margin, modest sample size, excluding transferred patients, workflow limitations, and the high performing nature of the enrolling hospitals.[10–15,38] Furthermore, the trials could not account for the time-dependent benefit of either IVT or EVT treatment. The current study, an order of magnitude larger in size, offers substantially more power to study this complex treatment paradigm. We found statistically and clinically significant benefit in functional outcomes and mortality with faster IVT administration before EVT. In concert with previous studies,[5–8] our results demonstrate that faster EVT treatment is associated with more home time and lower mortality during the 1-year follow-up period. Our overall results indicate that IVT-to-EVT times may have a modest association with home time, after controlling for patient and hospital factors. Limited by the small number of patients getting EVT immediately after IVT (within 30 minutes), we were unable to study the effect of a very short IVT-to-EVT interval. Another consideration is that the use of advanced imaging, such as CT perfusion imaging , MRI, or MRI perfusion imaging, in patient selection for EVT may temper the associations of IVT-to-EVT times with outcomes. In other words, advanced imaging selection may select patients with slow infarct progression for EVT, which would reduce the strength of association with time and, therefore, such study results would be a conservative estimate. Patients with poor collateral blood flow on CT angiogram are more likely to have early infarct progression and become ineligible for EVT or have poor outcomes after EVT.[39] Advanced imaging selection is often used to determine EVT eligibility when patients present within 6 to 24 hours after stroke onset, in which better collaterals lead to slower stroke progression and better functional outcomes.[40] For patients who have EVT within 6.5 hours from stroke onset, the benefit of a shorter time to recanalization is independent of baseline collateral status.[6] The present study only included patients with EVT started within 7 hours of stroke onset in which perfusion imaging was not recommended. However, some patients might still have been selected on the basis of advance imaging. The results of advance imaging unfortunately are not available in the GWTG-Stroke database.

On the basis of these results, to improve outcomes in patients treated with IVT+EVT, it is necessary to reduce in-hospital delays in both IVT and EVT and to move quickly from the start of IVT infusion to arterial puncture and EVT.

Limitations

This study has several limitations. First, to obtain long-term outcomes, this study only included Medicare fee-for-service beneficiaries aged ≥65 who were treated at GWTG-Stroke participating hospitals, with complete data linked in these 2 databases. Previous work has demonstrated that patients in the linked GWTG-Stroke/Medicare database are representative of the national Medicare ischemic stroke population.[30] However, the results may not be generalizable to younger patients or other hospitals or countries. Second, although outcome analyses adjusted for patient-level and hospital-level factors, including stroke severity and onset-to-EVT time for EVT treatment, there might be residual measured and unmeasured confounding, including functional status before the index stroke, social determinants of health (such as housing, marriage status, availability of care providers at home, income, education level, and pollution), and institutional practice patterns that may influence DTN times or outcomes. Third, the secondary analysis comparing IVT+EVT versus EVT should be interpreted with caution and as hypothesis generating because of the imbalance in patient characteristics and potential selection bias. However, the signals may inform future clinical trial design in studying the effect of IVT before EVT to allow patient randomization on the basis of DTN times. Fourth, the study was limited to patients receiving intravenous thrombolytics within 4.5 hours and EVT within 7 hours of onset and may not be applicable to reperfusion therapy for stroke of unknown last known well or wake-up stroke when MRI or CT perfusion scans are needed to determine eligibility.[41–43] Fifth, during the study period, alteplase was used in most US hospitals as the intravenous thrombolytic agent, so the results may not be generalizable to other thrombolytic agents such as tenecteplase. Last, the study used several prespecified outcomes. The findings should be interpreted as exploratory given the absence of statistical correction for multiple comparisons.

Conclusions

Among patients aged ≥65 years with acute ischemic stroke, shorter DTN times for IVT are associated with more time at home and lower mortality in patients treated with IVT alone, and with IVT+EVT combined therapy, as well. These findings support further efforts to accelerate thrombolytic therapy in all eligible patients, including EVT candidates.

ARTICLE INFORMATION

Received January 18, 2023; accepted April 21, 2023.

Affiliations

Department of Neurology, Cerebrovascular Center, Neurological Institute, Cleveland Clinic, OH (S.M., K.U., M.S.H.). Duke Clinical Research Institute, Duke University, Durham, NC (N.S., B.A.). Department of Neurology, Duke University School of Medicine, Durham, NC (B.M.G.). Department of Neurology, University of California, Los Angeles (J.L.S.). Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Alberta, Canada (E.E.S.). Department of Neurology, University of Texas Southwestern Medical Center, Dallas (Y.X.). Mount Sinai Heart, Icahn School of Medicine at Mount Sinai Health System, New York, NY (D.L.B.). Department of Neurology, Massachusetts General Hospital, Boston (L.H.S.). Division of Cardiology, University of California, Los Angeles (G.C.F.).

Sources of Funding

The Get With The Guidelines–Stroke (GWTG-Stroke) is provided by the American Heart Association/American Stroke Association. GWTG-Stroke is sponsored, in part, by Novartis, Novo Nordisk, AstraZeneca, Bayer, Tylenol and Alexion, and AstraZeneca Rare Disease. The funders/sponsors had no role in the design and conduct of the study; analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures

Dr Mac Grory received funding from the National Institutes of Health (NIH; K23HL161426). Dr Uchino reported being on the data safety monitoring board for clinical trials sponsored by Genentech, Inc. and Evaheart, Inc. He is a consultant for Abbott Laboratories, Inc.Dr Saver reported receiving research support from the National Institute of Health and the American Heart Association; receiving contracted hourly payments from Medtronic, Stryker, Cerenovus, and Boehringer Ingelheim

(prevention only) and stock options from Rapid Medical for service on clinical trial steering committees advising on rigorous trial design and conduct; an employee of the University of California which holds a patent on an endovascular device for stroke. Dr Xian reported receiving research funding from the American Heart Association and Genentech and honoraria from Boeheim Ingelheim. Dr Bhatt disclosed the following relationships: Advisory Board: AngioWave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: AngioWave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Consultant: Broadview Ventures; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial (Portico Re-sheathable Transcatheter Aortic Valve System IDE), funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial [PEITHO Pulmonary Embolism Thrombolysis Study]), Cleveland Clinic (including for the ExCEED trial [CENTERA THV System in Intermediate Risk Patients Who Have Symptomatic, Severe, Calcific, Aortic Stenosis], funded by Edwards), Contego Medical (Chair, PERFORMANCE 2 [Protection Against Emboli During Carotid Artery Stenting Using the Neuroguard IEP System]), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial [Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation], funded by Daiichi Sankyo; for the ABILITY-DM trial [Randomized Comparison of Abluminus DES+ Sirolimus-Eluting Stents Versus Everolimus-Eluting Stents in Coronary Artery Disease Patients With Diabetes Mellitus Global], funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT trial [Myocardial Ischemia and Transfusion]); Honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial [Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting] steering committee funded by Boehringer Ingelheim; AEGIS-II [Study to Investigate CSL112 in Subjects With Acute Coronary Syndrome] executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial [A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease], funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS [Cardiovascular Outcomes for People Using Anticoagulation Strategies] operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent.) Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, *Braunwald's Heart Disease*); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Takeda. Dr Schwamm reported serving on the American Heart Association/Get With The Guidelines stroke systems of care advisory group and American Stroke Association Advisory Committee; stroke systems consultant to the Massachusetts Department of Public Health; scientific consultant regarding trial design and conduct to Genentech (late window thrombolysis, member of steering committee TIMELESS [Tenecteplase in Stroke Patients Between 4.5 and 24 Hours; NCT03785678]); member of a Data Safety Monitoring Board (DSMB) for Penumbra (MIND [MIND: Artemis in the Removal of Intracerebral Hemorrhage; NCT03342664]); Diffusion Pharma (PHAST-TSC [Efficacy and Safety of Trans Sodium Crocetinate (TSC) for Treatment of Suspected Stroke; NCT03763929]); National principal investigator (PI) or member of National Steering Committee for Medtronic (Stroke AF [Rate of Atrial Fibrillation Through 12 Months in Patients With Recent Ischemic Stroke of Presumed Known Origin; NCT02700945]); PI, StrokeNet Network National Institute of Neurological Disorders and Stroke (NINDS; New England Regional Coordinating Center U24NS107243); Co-I, The Impact of Telestroke on Patterns of Care and Long-Term Outcomes, NINDS (R01NS111952). Dr Hussain reported serving on the scientific advisory board and clinical events committee of Cerenovus, the principal investigator of Medtronic Core laboratory, data safety monitoring board for Stryker Neurovascular, and clinical events committee of Rapid Medical. Dr Fonarow reported receiving research support from the Patient Centered Outcome Research Institute and the National Institutes of Health, and employee of University of California which holds a patent on an endovascular device for stroke. Drs Man, Solomon, Alhanti, and Smith reported no relevant disclosure.

Supplemental Material

Figures S1–S3
Tables S1–S11

REFERENCES

1. 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
2. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, et al; Stroke Thrombolysis Trialists' Collaborative Group. 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
3. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Xian Y, Hernandez AF, Peterson ED, Schwamm LH. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA.* 2014;311:1632–1640. doi: 10.1001/jama.2014.3203
4. 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
5. Mulder MJHL, Jansen IGH, Goldhoorn RJB, Venema E, Chalos V, Compagne KCJ, Roozenbeek B, Lingsma HF, Schonewille WJ, Van Den Wijngaard IR, et al. Time to endovascular treatment and outcome in acute ischemic stroke: MR CLEAN Registry results. *Circulation.* 2018;138:232–240. doi: 10.1161/CIRCULATIONAHA.117.032600
6. Uniken Venema SM, Wolff L, Van Den Berg SA, Reinink H, Luijten SPR, Lingsma HF, Marquering HA, Boers AMM, Bot J, Hammer S, et al; MR CLEAN Registry Investigators. Time since stroke onset, quantitative collateral score, and functional outcome after endovascular treatment for acute ischemic stroke. *Neurology.* 2022;99:e1609–e1618. doi: 10.1212/WNL.0000000000200968
7. Goyal M, Jadhav AP, Bonafe A, Diener H, Mendes Pereira V, Levy E, Baxter B, Jovin T, Jahan R, Menon BK, et al; SWIFT PRIME investigators. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke: results from the SWIFT PRIME randomized controlled trial. *Radiology.* 2016;279:888–897. doi: 10.1148/radiol.2016160204
8. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA.* 2016;316:1279–1288. doi: 10.1001/jama.2016.13647
9. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Hernandez AF, Peterson ED, Sacco RL, Schwamm LH. Improving door-to-needle times in acute ischemic stroke: the design and rationale for the American Heart Association/American Stroke Association's target: stroke initiative. *Stroke.* 2011;42:2983–2989. doi: 10.1161/STROKEAHA.111.621342
10. Yang P, Zhang YY, Zhang L, Zhang YY, Treurniet KM, Chen W, Peng Y, Han H, Wang J, Wang S, et al; DIRECT-MT Investigators. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med.* 2020;382:1981–1993. doi: 10.1056/NEJMoa2001123
11. Zi W, Qiu Z, Li F, Sang H, Wu D, Luo W, Liu S, Yuan J, Song J, Shi Z, et al; DEVT Trial Investigators. Effect of endovascular treatment alone vs

intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA*. 2021;325:234–243. doi: 10.1001/jama.2020.23523
12. Suzuki K, Matsumaru Y, Takeuchi M, Morimoto M, Kanazawa R, Takayama Y, Kamiya Y, Shigeta K, Okubo S, Hayakawa M, et al; SKIP Study Investigators. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA*. 2021;325:244–253. doi: 10.1001/jama.2020.23522
13. LeCouffe NE, Kappelhof M, Treurniet KM, Rinkel LA, Bruggeman AE, Berkhemer OA, Wolff L, van Voorst H, Tolhuisen ML, Dippel DWJ, et al; MR CLEAN–NO IV Investigators. A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med*. 2021;385:1833–1844. doi: 10.1056/NEJMoa2107727
14. Mitchell PJ, Yan B, Churilov L, Dowling RJ, Bush SJ, Bivard A, Huo XC, Wang G, Zhang SY, Ton MD, et al; DIRECT-SAFE Investigators. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet*. 2022;400:116–125. doi: 10.1016/S0140-6736(22)00564-5
15. Fischer U, Kaesmacher J, Strbian D, Eker O, Cognard C, Plattner PS, Bütikofer L, Mordasini P, Deppeler S, Pereira VM, et al; SWIFT DIRECT Collaborators. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet*. 2022;400:104–115. doi: 10.1016/S0140-6736(22)00537-2
16. Fonarow GC, Reeves MJ, Smith EE, Saver JL, Zhao X, Olson DW, Hernandez AF, Peterson ED, Schwamm LH; GWTG-Stroke Steering Committee and Investigators. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. *Circ Cardiovasc Qual Outcomes*. 2010;3:291–302. doi: 10.1161/CIRCOUTCOMES.109.921858
17. Xian Y, Fonarow GC, Reeves MJ, Webb LE, Blevins J, Demyanenko VS, Zhao X, Olson DM, Hernandez AF, Peterson ED, et al. Data quality in the American Heart Association Get With The Guidelines-Stroke (GWTG-Stroke): results from a national data validation audit. *Am Heart J*. 2012;163:392–8, 398.e1. doi: 10.1016/j.ahj.2011.12.012
18. Smith EE, Zerna C, Solomon N, Matsouaka R, Mac Grory B, Saver JL, Hill MD, Fonarow GC, Schwamm LH, Messé SR, et al. Outcomes after endovascular thrombectomy with or without alteplase in routine clinical practice. *JAMA Neurol*. 2022;79:768–776. doi: 10.1001/jamaneurol.2022.1413
19. Fonarow GC, Liang L, Thomas L, Xian Y, Saver JL, Smith EE, Schwamm LH, Peterson ED, Hernandez AF, Duncan PW, et al. Assessment of home-time after acute ischemic stroke in Medicare beneficiaries. *Stroke*. 2016;47:836–842. doi: 10.1161/STROKEAHA.115.011599
20. Mishra NK, Shuaib A, Lyden P, Diener HC, Grotta J, Davis S, Davalos A, Ashwood T, Wasiewski W, Lees KR; Stroke Acute Ischemic NXY Treatment I Trialists. Home time is extended in patients with ischemic stroke who receive thrombolytic therapy: a validation study of home time as an outcome measure. *Stroke*. 2011;42:1046–1050. doi: 10.1161/STROKEAHA.110.601302
21. Akbik F, Xu H, Xian Y, Shah S, Smith EE, Bhatt DL, Matsouaka RA, Fonarow GC, Schwamm LH. Trends in reperfusion therapy for in-hospital ischemic stroke in the endovascular therapy era. *JAMA Neurol*. 2020;77:1486–1495. doi: 10.1001/jamaneurol.2020.3362
22. Cumbler E, Wald H, Bhatt DL, Cox M, Xian Y, Reeves M, Smith EE, Schwamm L, Fonarow GC. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With The Guidelines-Stroke. *Stroke*. 2014;45:231–238. doi: 10.1161/STROKEAHA.113.003617
23. Del Brutto VJ, Ardelt A, Loggini A, Bulwa Z, El-Ammar F, Martinez RC, Brorson J, Goldenberg F. Clinical characteristics and emergent therapeutic interventions in patients evaluated through the in-hospital stroke alert protocol. *J Stroke Cerebrovasc Dis*. 2019;28:1362–1370. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.001
24. Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to Medicare claims data using indirect identifiers. *Am Heart J*. 2009;157:995–1000. doi: 10.1016/j.ahj.2009.04.002
25. Man S, Xian Y, Holmes DJN, Matsouaka RA, Saver JL, Smith EE, Bhatt DL, Schwamm LH, Fonarow GC. Target: stroke was associated with faster intravenous thrombolysis and improved one-year outcomes for acute ischemic stroke in Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2020;13:e007150. doi: 10.1161/CIRCOUTCOMES.120.007150
26. Xian Y, Xu H, Lytle B, Blevins J, Peterson ED, Hernandez AF, Smith EE, Saver JL, Messé SR, Paulsen M, et al. Use of strategies to improve door-to-needle times with tissue-type plasminogen activator in acute ischemic stroke in clinical practice: findings from target: stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003227. doi: 10.1161/CIRCOUTCOMES.116.003227
27. Smith VA, Neelon B, Maciejewski ML, Preisser JS. Two parts are better than one: modeling marginal means of semicontinuous data. *Heal Serv Outcomes Res Methodol*. 2017;17:198–218. doi: 10.1007/s10742-017-0169-9
28. Poythress JC, Lee MY, Young J. Planning and analyzing clinical trials with competing risks: recommendations for choosing appropriate statistical methodology. *Pharm Stat*. 2020;19:4–21. doi: 10.1002/pst.1966
29. Reeves MJ, Smith EE, Fonarow GC, Zhao X, Thompson M, Peterson ED, Schwamm LH, Olson D. Variation and trends in the documentation of National Institutes of Health Stroke Scale in GWTG-Stroke hospitals. *Circ Cardiovasc Qual Outcomes*. 2015;8:S90–S98. doi: 10.1161/CIRCOUTCOMES.115.001775
30. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418. doi: 10.1161/STR.0000000000000211
31. Goyal M, Almekhlafi M, DIppel DW, Campbell BCV, Muir K, Demchuk AM, Bracard S, Davalos A, Guillemin F, Jovin TG, et al. Rapid alteplase administration improves functional outcomes in patients with stroke due to large vessel occlusions: meta-analysis of the noninterventional arm from the HERMES collaboration. *Stroke*. 2019;50:645–651.
32. Grotta JC, Yamal JM, Parker SA, Rajan SS, Gonzales NR, Jones WJ, Alexandrov AW, Navi BB, Nour M, Spokoyny I, et al. Prospective, multicenter, controlled trial of mobile stroke units. *N Engl J Med*. 2021;385:971–981. doi: 10.1056/NEJMoa2103879
33. Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C, Rozanski M, Kunz A, Koch P, Kellner PA, Gierhake D, et al; STEMO Consortium. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: a randomized clinical trial. *JAMA*. 2014;311:1622–1631. doi: 10.1001/jama.2014.2850
34. Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, Fusco MR. Mechanical thrombectomy outcomes with and without intravenous thrombolysis in stroke patients: a meta-analysis. *Stroke*. 2017;48:2450–2456. doi: 10.1161/STROKEAHA.117.017320
35. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, Schellinger PD, Toni D, de Vries J, White P, et al. European Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic Stroke Endorsed by Stroke Alliance for Europe (SAFE). *Eur Stroke J*. 2019;4:6–12. doi: 10.1177/2396987319832140
36. Meinel TR, Kaesmacher J, Buetikofer L, Strbian D, Eker OF, Cognard C, Mordasini P, Deppeler S, Pereira VM, Albucher JF, et al. Time to treatment with bridging intravenous alteplase before endovascular treatment: subanalysis of the randomized controlled SWIFT-DIRECT trial. *J Neurointerv Surg*. 2022;neurintsurg-2022-019207. doi: 10.1136/jnis-2022-019207
37. Elhabr AK, Katz JM, Wang J, Bastani M, Martinez G, Gribko M, Hughes DR, Sanelli P. Predicting 90-day modified Rankin Scale score with discharge information in acute ischaemic stroke patients following treatment. *BMJ Neurol Open*. 2021;3:e000177. doi: 10.1136/bmjno-2021-000177
38. Campbell BCV, Kappelhof M, Fischer U. Role of intravenous thrombolytics prior to endovascular thrombectomy. *Stroke*. 2022;53:2085–2092. doi: 10.1161/STROKEAHA.122.036929
39. Boulouis G, Lauer A, Siddiqui AK, Charidimou A, Regenhardt RW, Viswanathan A, Rost N, Leslie-Mazwi TM, Schwamm LH. Clinical imaging factors associated with infarct progression in patients with ischemic stroke during transfer for mechanical thrombectomy. *JAMA Neurol*. 2017;74:1361–1367. doi: 10.1001/jamaneurol.2017.2149
40. Liebeskind DS, Saber H, Xiang B, Jadhav AP, Jovin TG, Haussen DC, Budzik RF, Bonafe A, Bhuva P, Yavagal DR, et al; DAWN Investigators. Collateral circulation in thrombectomy for stroke after 6 to 24 hours in the DAWN trial. *Stroke*. 2022;53:742–748. doi: 10.1161/STROKEAHA.121.034471
41. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792
42. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718. doi: 10.1056/NEJMoa1713973
43. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho T-H, Fazekas F, Fiehler J, et al; WAKE-UP Investigators. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379:611–622. doi: 10.1056/NEJMoa1804355