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ORIGINAL RESEARCH

Comparative Effectiveness of Endovascular Treatment for Acute Ischemic Stroke: A Population-Based Analysis

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BACKGROUND: A heterogeneous patient population receives endovascular treatment (EVT) for acute ischemic stroke caused by proximal large-vessel occlusion every day. We aimed to conduct a population-based study of EVT in the province of Alberta, Canada, to understand the effectiveness in a complete population and how the magnitude of effect differs from the artificial world of clinical trials.

METHODS AND RESULTS: Within a 3-year period (April 2015 to March 2018), 576 patients fit the inclusion criteria of our study and constituted the EVT group of our analysis. The medical treatment group of the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT [Computed Tomography] to Recanalization Times) trial had 150 patients. Thus, our total sample size was 726. We captured outcomes in clinical routine using administrative data and a linked database method. Primary outcome of our study was home-time. Home-time refers to the number of days that the patient was back at premorbid living situation without increase in level of care within 90 days of index stroke event. Median age of patients was 70 years (interquartile range, 59–81 years), and 47.8% were women. Median National Institutes of Health Stroke Scale score was 17 (interquartile range, 13–20). EVT was associated with an increased 90-day home-time by an average of 8.5 days compared with medical treatment alone using Cragg hurdle regression (P=0.009). Age and higher National Institutes of Health Stroke Scale score were associated with decreased 90-day home-time (both P<0.001). Multivariable logistic regression showed no association between EVT and mortality at 90 days (odds ratio, 0.76; 95% CI, 0.47–1.24).

CONCLUSIONS: EVT for acute ischemic stroke caused by proximal large-vessel occlusion was effective in our province-wide population-based study and results in an increase of 90-day home-time by ~8.5 days.

Key Words: acute stroke ■ comparative effectiveness ■ ischemic stroke ■ thrombectomy ■ treatment outcome

Endovascular treatment (EVT) of acute ischemic stroke in the anterior circulation caused by large-vessel occlusion has been established as the new standard of care. In randomized trials, eligibility varied slightly by age, baseline stroke severity, treatment time from stroke onset, concurrent alteplase treatment, and extracranial carotid artery occlusion or stenosis, but the results of each of the trials clearly favor EVT. A meta-analysis of all trials showed that EVT led to reduced disability compared with control patients who received standard medical treatment alone (odds ratio [OR], 2.49; 95% CI, 1.76–3.53).[1]

Multiple practice guidelines recommending the use of EVT were published shortly after conclusion of these positive trials. Clinical practice guidelines, in an attempt to promote optimal care for all patients, do

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CLINICAL PERSPECTIVE

What Is New?

- Estimation of the effect of endovascular treatment for acute ischemic stroke in a complete population.
- Using home-time as a novel and patient-centered outcome meaningful to the patients, their caregivers/family, and the health system.

What Are the Clinical Implications?

- Adult patients undergoing endovascular treatment for acute ischemic stroke on average spent >1 week longer at home within the first 90 days compared with patients receiving medical treatment alone.
- Real-world evidence confirmed the external validity of the clinical trials, but with attenuated effect size when compared with the more selected ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT [Computed Tomography] to Recanalization Times) trial treatment group.
- Home-time as a meaningful patient-centered outcome has the advantage of having complete ascertainment because it can be established through linkage with an administrative health database.

Nonstandard Abbreviations and Acronyms

EVT	Endovascular treatment
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT [Computed Tomography] to Recanalization Times
QuICR	Quality Improvement and Clinical Research
DAWN	Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention
DEFUSE-3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3
NIHSS	National Institutes of Stroke Scale
GAIN	Glycine Antagonist (gavestinel) in Neuroprotection
mRS	Modified Rankin Scale
ASPECTS	Alberta Stroke Program Early CT [Computed Tomography] Score
HERMES	Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials
MR CLEAN	Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands
SWIFT-PRIME	Solitaire™ With the Intention For Thrombectomy as PRIMary Endovascular Treatment
EXTEND-IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial
REVASCAT	RandomizEd Trial of reVascularizAtion With Solitaire FR® Device Versus Best mediCal Therapy in the Treatment of Acute Stroke Due to anTerior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset
IV tPA	Intravenous tissue Plasminogen Activator

not consider the heterogeneity of the patient population or the complexity of medical decisions and are tightly aligned with the evidence provided by clinical trials.[2] As a result, healthcare providers are often left to consider therapeutic interventions in patients who may not have met the eligibility criteria for trial participation (namely, older adults with significant comorbidity). In such instances, population-based comparative effectiveness research can be useful after efficacy is well established in clinical trials and in this case help ensure that the largest appropriate group of patients gains access to this life-saving and disability-sparing treatment.[3]

Our objective was to conduct a population-based study of EVT in the province of Alberta, Canada, and provide greater understanding of how the benefits and risks of EVT might vary across the population. This knowledge will inform the clinical decision-making process on EVT. Our primary outcome was home-time, which is a novel and patient-centered outcome that reflects health circumstances that are easy to understand and meaningful to patients and their caregivers. We hypothesized that there would be at least a 15% difference in effect size between all patients across the province who presented with an acute ischemic stroke caused by a large-vessel occlusion in the anterior circulation and who were treated with EVT compared with the medical treatment arm of the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT

[Computed Tomography] to Recanalization Times) trial.

METHODS

The data that support the findings of this study are not publicly available at this time.

Provincial EVT Data

Data are from the QuICR (Quality Improvement and Clinical Research) Registry. The registry was designed for quality improvement purposes and captures and tracks all treated acute stroke patients in the province of Alberta, Canada. Alberta has an estimated population of 4 million, and its area is ≈660,000 km^2. There are 2 comprehensive stroke centers (in Calgary and Edmonton) and 15 primary stroke centers. The registry data are collected in routine clinical care and considered part of the medical record. The current study was approved by the local ethics committee, and informed consent by individual participants was waived. We extracted data over 3 years from April 2015 to March 2018 to cover a time period between publication of the positive endovascular trials up until the publication of the 2 clinical trials evaluating imaging selection and EVT in late presenting patients (DAWN [Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention] and DEFUSE-3 [Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3]), which might have changed practice patterns.

We included all patients aged ≥18 years who underwent EVT for an acute ischemic stroke caused by a proximal large-vessel occlusion of the anterior circulation (internal carotid artery, middle cerebral artery M1 and M2 segments, or anterior cerebral artery). We excluded patients with posterior circulation stroke and patients not residing in the province of Alberta because the primary outcome could not be obtained for them. Data of interest were age, sex, stroke severity according to National Institutes of Health Stroke Scale (NIHSS) score, date and time of stroke onset or time last seen well, intravenous alteplase treatment (yes/no), and interval time metrics for treatment. Onset-to-treatment time was defined as time from onset to first hyperacute treatment (either intravenous alteplase or EVT).

Linkage With Administrative Health Data and Outcomes

We captured outcomes in clinical routine using administrative data. Administrative health data are not generated for research purposes but instead are collected for payment, monitoring, planning, priority setting, and evaluation of health systems.[4] These data can come from different interactions with the healthcare system (through hospitalizations, ambulatory care, and emergency department visits) and are usually captured over a prolonged period.

The primary outcome of our study was home-time. Home-time refers to the number of days that the patient was back at his/her respective premorbid living situation without an increase in level of care within 90 days of the index stroke event. The premorbid living situation was determined from administrative health data and was assigned as any form of continuing care facility if that is where the patient had resided in the 2-week period before the index stroke admission or was otherwise inferred to be the private home. By definition, patients who died in hospital after the index stroke admission have a home-time of 0 days. Initially developed from data of the GAIN (Glycine antagonist [gavestinel] in neuroprotection) International trial, home-time was found to be a useful and robust outcome marker for stroke in 2008.[5] Recent work has shown that home-time is obtainable in a complete population through administrative health data collection, which makes it less vulnerable to attrition bias compared with prospective studies.[6] Home-time after stroke was found to be a valid proxy marker for functional recovery, according to an analysis of Medicare beneficiaries in the United States as well as a large linked data analysis of the Scottish Stroke Care Audit with routine healthcare data.[7,8] Discharge to home from hospital within the Canadian health system depends solely on the patient's functional status; it is not governed by administrative rules for length of stay. If the patient is in need of rehabilitation or indefinitely not able to care for himself/herself, discharge will occur to an alternate care facility (eg, rehabilitation facility or long-term care facility) instead of home. Stay in such facilities is well coded through administrative data.

Secondary outcomes included dichotomized home-time at 90 days (>80 equivalent to modified Rankin Scale [mRS] 0–1 and >50 equivalent to mRS 0–2, according to prior correlation[6]) and mortality at 90 days, which was determined from linkage with the provincial vital statistics registry.

ESCAPE Trial: Historical Control Data (Medical Treatment)

The historical control group within this study was the medical treatment arm from the ESCAPE trial.[9] The trial involved sites across the world, but most patients (64.7%) were from Canada, making it an ideal control group. Patients with disabling stroke were

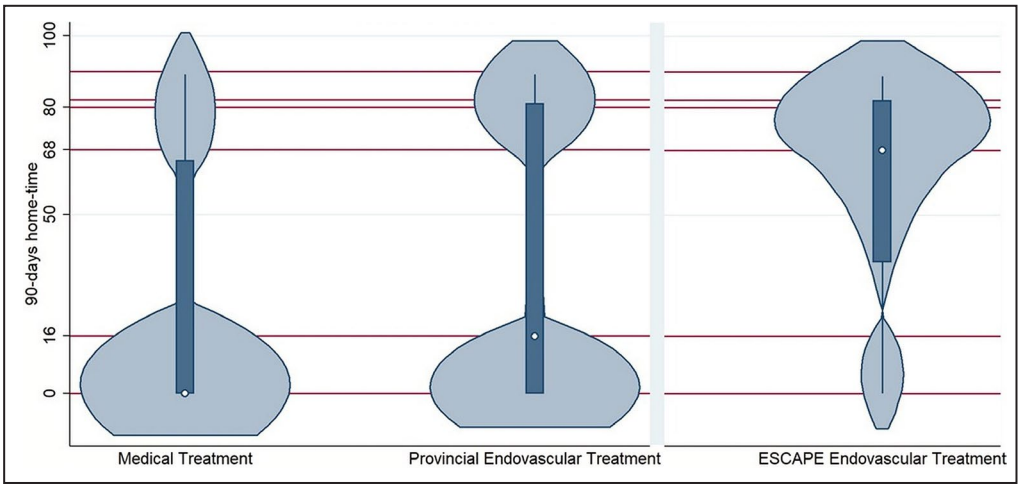

Figure 1. Violin plots of 90-day home-time return to baseline by treatment.
Violin plots illustrate the probability density distributions of home-time for medical treatment and endovascular treatment. Medians are marked by the white dot, and the interquartile range is marked by a vertical black bar. Nonoutlier values are marked by the thinner vertical black line. Median home-time (quartiles 1–3): medical treatment 0 (0–65) days and endovascular treatment 16 (0–81) days. ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT (Computed Tomography) to Recanalization Times.

enrolled within 12 hours of onset, and only included if imaging revealed all of the following: small infarct core, defined as Alberta Stroke Program Early CT Scale score ≥6; an occlusion of the anterior circulation involving a proximal artery; and moderate to good collateral circulation. Home-time and mortality at 90 days were collected as part of the trial. Onset-to-treatment time was defined as time from onset to first hyperacute treatment (in this case intravenous alteplase). We have also analyzed the ESCAPE trial EVT group as a reference to provide context for the study results.

Minimal Detectable Difference

Using our available sample size over 3 years with a power of 80%, we estimated that we will be able in patients who received EVT to detect a 15.5% decrease in the risk of not returning home (home-time 0) within 90 days compared with patients who received medical treatment alone.

Missing Data

Within the provincial EVT group, we had 43 (7.5%) missing NIHSS scores, and 6 (1.0%) patients had missing onset-to-treatment times. We imputed the NIHSS scores with the group mean and the onset-to-treatment times with the group median from the remaining available data. Within the ESCAPE trial data, we had 1 missing onset-to-treatment time and 3 with missing 90-day outcomes in the medical treatment group. We imputed the onset-to-treatment time with the group median from the remaining available data and mortality at 90 days with the worst possible outcome (death) but conducted a sensitivity analysis with the best possible outcome (alive). Thirty-two patients who did not receive intravenous alteplase did not have an onset-to-treatment time recorded. Those times were imputed with the formula of randomization time plus 30 minutes, similar to the approach used in the HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials) collaboration analyses.[10] In the ESCAPE trial EVT group, we had 1 missing onset-to-treatment time and 3 missing 90-day home-times, which we again imputed with the median from the remaining available data.

Statistical Analysis

Standard descriptive statistics were used to measure central tendency and variability of baseline characteristics. Visualization of home-time was shown using violin plots (Figure 1).

Home-time as our primary outcome was truncated at 0 and had excess 0 counts. The minimum amount of days that can be spent at home during the first 90 days is 0, and the maximum is 90 days (if patients were theoretically to be discharged on the same day of the procedure). Because many patients did not return to their home/prior residence within 90 days of the index stroke, our data had excess 0 counts. We explored the use of a negative binomial regression model by graphic assessment (hanging rootogram) as well as other analysis (Akaike's information criterion) for model fit. We used a Cragg hurdle regression

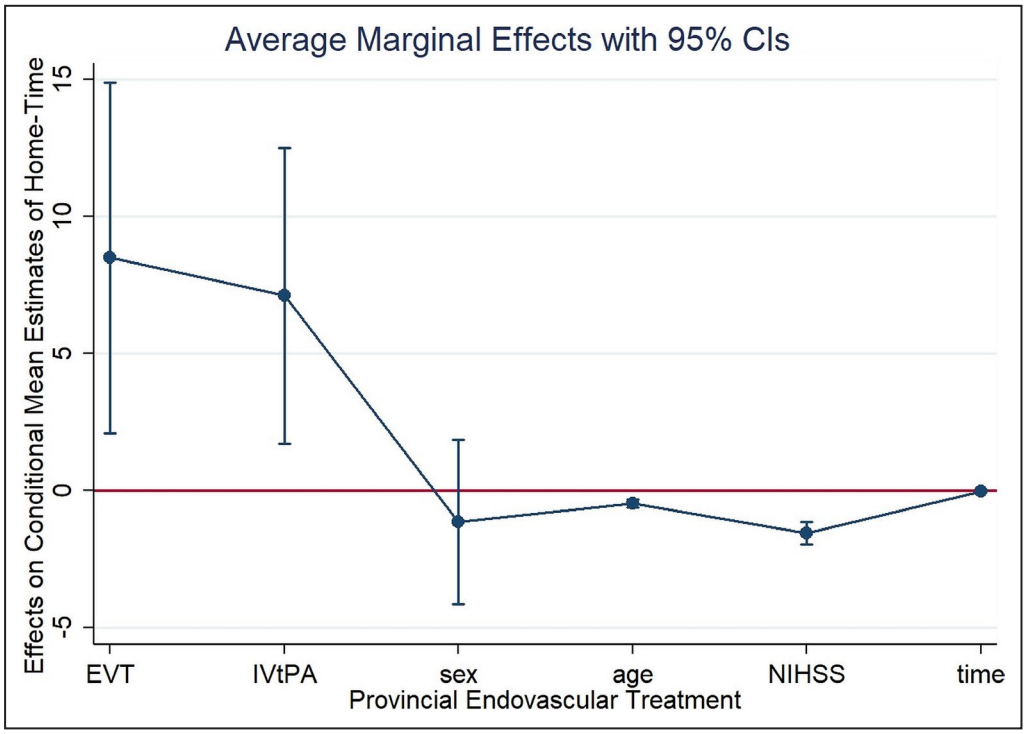

Figure 2. Margins plot showing the effect of baseline variables on the conditional mean estimates of 90-day home-time in the provincial endovascular treatment (EVT) group.
IVtPA indicates intravenous tissue Plasminogen Activator (alteplase); NIHSS, National Institute of Health Stroke Scale; and time, onset-to-treatment-time.

model because it provided the best fit for the data.[11] As a first part of the Cragg hurdle regression model, a Bernoulli probability directs the binary outcome of 0 (failure, hurdle is not crossed, or patient does not return to home within 90 days after stroke) or 1 (success defined as any positive count, hurdle is crossed, or patient does return home within 90 days after stroke). For the second part of the model, once the hurdle is crossed, a truncated-at-0 count model is used. Intravenous alteplase treatment, EVT, age, and baseline NIHSS score were selected as a priori hurdle variables on the basis of their clinical significance for poststroke outcomes and discharge disposition. In addition, the clinically important baseline variables age, sex, onset-to-treatment time, NIHSS score, and intravenous alteplase status were included as covariates in the truncated-at-0 count model. We did not include imaging variables because these were not routinely available. Margins plots were used to visualize the effects of the individual variables on the conditional mean estimates of 90-day home-time (Figure 2).

For our secondary outcomes, which were both binary, we used logistic regression analysis to model dichotomized home-time (>80 equivalent to mRS 0–1 and >50 equivalent to mRS 0–2, according to prior correlation[6]) and mortality at 90 days. The same clinically relevant baseline variables as stated above were included in those models.

$P<0.05$ (2 sided) was considered to indicate statistical significance. All statistical analyses were performed using STATA (Stata 16; Stata Corp, College Station, TX).

RESULTS

Within the 3-year period (April 2015 to March 2018), 611 patients were treated with EVT in the province of Alberta. We excluded 26 patients who had a permanent residence outside of province and thus their outcome could not be determined through administrative health data linkage and 9 additional patients who were treated for an isolated occlusion in the posterior circulation. The remaining 576 patients constituted the EVT group of our analysis. The medical treatment group of the ESCAPE trial had a sample size of 150 patients.

The median age of all patients was 70 years (interquartile range, 59–81 years), and 47.8% were women. The median NIHSS score at baseline was 17 (interquartile range, 13–20). Intravenous alteplase was given to 56.6% (326/576) patients in the EVT group and 78.7% (118/150) patients in the control group. Further baseline characteristics are shown in

Table 1. Baseline Characteristics

Variable	ESCAPE Control Group	ESCAPE EVT Group	QuICR Registry EVT Group
Age, median (25%–75%), y	70.1 (60.2–81.4)	71.3 (60.3–81.4)	70.2 (58.2–80.7)
Women, %	52.7	47.9	46.5
Race, %			
Asian	6.0	6.1	8.9
Black	4.0	4.8	0.2
White	87.3	87.3	46.7
First Nations	N/A	N/A	1.2
Hispanic	N/A	N/A	1.2
Undetermined	2.7	1.8	41.8
NIHSS score, median (25%–75%)	17 (12–20)	16 (13–20)	17 (12–21)
Intravenous alteplase given, %	78.7	72.7	56.6
Onset-to-treatment time, median (25%–75%), min	145.5 (92–229)	126 (90–210)	140 (90–250)
Onset-to-treatment time, %			
<4.5 h	84.67	81.21	76.91
4.5–6 h	5.33	4.85	6.94
>6 h	10.00	13.94	16.15
Death at day 90, %	19.1	11.5	19.6
Time to death, median (25%–75%), d	7 (2–17)	5 (2–35)	7 (3–14)
Discharge disposition, %			
Home	15.3	23.6	27.5
Home with support	12.0	12.1	5.5
Rehabilitation	49.3	47.9	25.7
Long-term care	10.7	7.9	3.9
Death	12.7	7.3	16.9
Transfer to other hospital	N/A	N/A	20.5
Home time, %			
≥80 d (equivalent mRS 0–1)	28.0	29.1	35.6
≥50 d (equivalent mRS 0–2)	31.3	64.8	38

ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT (Computed Tomography) to Recanalization Times; EVT, endovascular treatment; mRS, modified Rankin Scale; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; and QuICR, Quality Improvement and Clinical Research.

Table 1. The median 90-day home-time was 16 (interquartile range, 0–81) days in the EVT group compared with 0 (interquartile range, 0–65) days in the medical treatment group. The difference in distribution of home-time between both groups is illustrated in Figure 1.

EVT was associated with an increased 90-day home-time by an average 8.5 days compared with medical treatment alone in adjusted analysis (P=0.009). A similar association was found with intravenous alteplase (P=0.010), with an average 7.1 days increase in home-time. The nonmodifiable predictors age and higher NIHSS score were associated with decreased 90-day home-time (both P<0.001). Every 5-year increase in age was associated with 2.3 days less time at home within the first 90 days after stroke. Every 5-point increase in the baseline NIHSS score signifying increased stroke severity was associated with 7.8 days less time at home within the first 90 days after stroke. The modifiable predictor onset-to-treatment time was also associated with a mean decrease of 90-day home-time after stroke (P=0.001). A 50-minute delay in onset-to-treatment time was associated with a mean decrease of 90-day home-time by 1 day (meaning a 30-minute delay led to ≈0.5 days less home-time). Patient sex was not associated with 90-day home-time. Detailed results of the model and comparative results of the ESCAPE trial EVT group are displayed in Table 2 and Figures 2 and 3. There was no evidence of collinearity among the independent variables (the variance inflation factors for all variables were <5).

Provincial EVT was associated with home-time >80 days (equivalent to mRS 0–1) with an OR of 1.62 (95% CI, 1.06–2.47) and home-time >50 days (equivalent to mRS 0–2) with an OR of 1.78 (95% CI, 1.16–2.75) in a logistic regression analysis adjusted for age, sex, NIHSS, intravenous alteplase treatment, and onset-to-treatment time. In comparison, EVT within

Table 2. Results From Cragg Hurdle Regression Analysis of Home-Time at 90 Days

Variable	QuICR Registry EVT Group	ESCAPE EVT Group
EVT given	8.5 (2.1 to 14.9)	25.7 (20.1 to 31.2)
Intravenous alteplase given	7.1 (1.7 to 12.5)	3.4 (–5.7 to 12.6)
Sex (being woman)	–1.1 (–4.2 to 1.9)	5.9 (1.8 to 10.0)
Age (per year older)	–0.5 (–0.6 to –0.3)	–0.5 (–0.7 to –0.3)
NIHSS score (per point higher)	–1.6 (–2.0 to –1.2)	–1.5 (–2.1 to –0.9)
Onset-to-treatment time (per minute longer)	–0.02 (–0.03 to –0.01)	0.003 (–0.02 to 0.02)

Data are given as conditional mean estimate (95% CI) days. EVT indicates endovascular treatment; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT (Computed Tomography) to Recanalization Times; NIHSS, National Institutes of Health Stroke Scale; and QuICR, Quality Improvement and Clinical Research.

the ESCAPE trial was also associated with home-time >80 days with an OR of 4.55 (95% CI, 2.74–7.56) and home-time >50 days (equivalent to mRS 0–2) with an OR of 1.70 (95% CI, 0.99–2.93).

There was no association between EVT and mortality at 90 days (OR, 0.76; 95% CI, 0.47–1.24) in adjusted analysis. However, older age and higher NIHSS were independent predictors of mortality at 90 days (both $P<0.001$). These results remained true in sensitivity analysis (Table S1). We further explored this associated by stratification according to treatment modality and found differences in mortality rates as well as onset-to-treatment times across subgroups. Details are provided in Tables 3.

DISCUSSION

Our study shows that adult patients undergoing EVT for acute ischemic stroke caused by a proximal vessel occlusion spent on average >1 week longer at home within the first 90 days compared with patients receiving medical treatment alone. Home-time is a novel, health-economic, and patient-centered outcome that reflects health circumstances that are both easy to understand and meaningful to the patients, their caregivers/family, and the health system.

Other efforts of comparative effectiveness research on EVT for acute ischemic stroke have been made or are currently underway. Endovascular therapy has been shown to significantly reduce healthcare use up to 1 year after stroke.[12] The ongoing prospective TREVO Retriever Registry represents real-world data

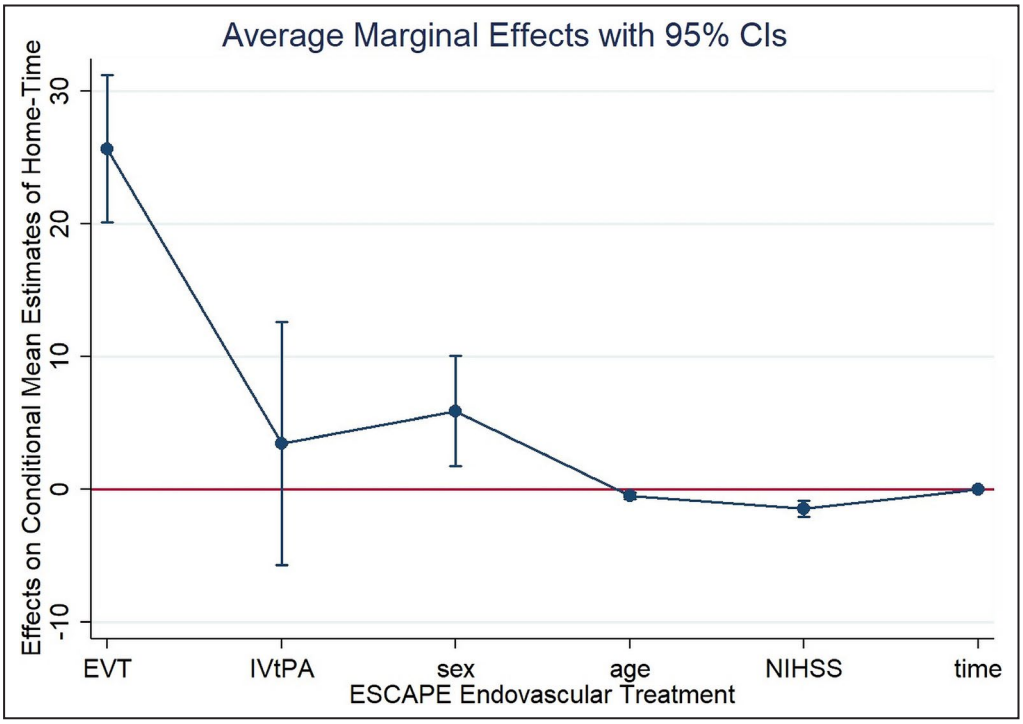

Figure 3. Margins plot showing the effect of baseline variables on the conditional mean estimates of 90-day home-time in the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT [Computed Tomography] to Recanalization Times) trial endovascular treatment (EVT) group.
IVtPA indicates intravenous tissue Plasminogen Activator (alteplase); NIHSS, National Institute of Health Stroke Scale; and time, onset-to-treatment-time.

Table 3. Stratum-specific results according to treatment modality

Variable	Neither EVT nor Intravenous Alteplase (n=32)	Only Intravenous Alteplase (n=118)	Only EVT (n=283)	EVT and Intravenous Alteplase (n=293)
Mortality at 90 d, %	15.63	22.03	24.03	15.36
Median age, y	70.6	70.1	71.3	69.5
Median NIHSS score	16.5	17	17	17
Median onset-to-treatment time, min	317	125	198	105
Female sex, %	56.3	51.7	48.4	44.7
Home time, %				
≥80 d (equivalent mRS 0–1)	25.0	28.8	29.3	40.8
≥50 d (equivalent mRS 0–2)	31.3	31.4	32.2	43.7

EVT indicates endovascular treatment; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

with stent retriever and to date demonstrated similar reperfusion rates and outcomes in the community compared with the rigorous centrally adjudicated randomized controlled trials.[13] Concurrently, the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) concluded that EVT in routine clinical practice was at least as effective and safe as in the setting of a randomized controlled trial when using mRS as the outcome.[14] The real-world evidence of the current study confirms the external validity of the clinical trials, but with attenuated effect size when compared with the ESCAPE trial treatment group.[9] However, our data in combination with other comparative effectiveness research are relevant to effectively translate the results of the randomized controlled trials to the greatest number of stroke patients possible and strengthen the evidence for EVT compared with medical treatment alone in patients with acute ischemic stroke caused by large-vessel occlusion.

The effect size of intravenous alteplase in our study was similarly large and resulted in 7.1 days more home-time within 90 days. Of note, the provincial EVT group included several distal anterior circulation occlusions (M2 and Anterior Cerebral Artery [ACA]), which with their smaller thrombus burden would be more susceptible to a thrombolytic effect. Intravenous alteplase in both the EVT groups as well as the medical treatment group was given per physician's discretion. Patients who presented early and with less comorbidities would have been given intravenous alteplase. These patients have a higher likelihood of good outcome compared with their non-intravenous alteplase-eligible counterparts, which translates to longer home-time within 90 days.

Age and baseline stroke severity emerged once again as nonmodifiable predictors of worse outcome or, in terms of our study, less home-time within 90 days.[15] The same association was true with prolonged onset-to-treatment time, which is in keeping with multiple studies, including an analysis of data from the Get With The Guidelines-Stroke Program, showing that earlier intravenous alteplase treatment was associated with reduced symptomatic intracranial hemorrhage rates and higher rates of discharge home after acute ischemic stroke.[16] Further analysis from the HERMES collaborators showed that the paradigm "time is brain" also holds true with EVT.[10] As such, the process metric of onset-to-treatment time (and its counterpart door-to-needle time) can and should be used as the focus for stroke system performance improvement, which will result in improved patient outcomes, including more home-time.[17,18]

The MR CLEAN, SWIFT-PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment), EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial), and REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset) trials found no difference in mortality between their EVT groups and medical treatment groups.[19–22] In contrast, the ESCAPE trial documented reduced mortality in the EVT group at 90 days (10.4% versus 19.0%; rate ratio, 0.5; 95% CI, 0.3–1.0), a result that we believe is likely because of the fast treatment times observed in this trial.[9] In our current study, EVT was not associated with mortality. Stratification by intravenous alteplase status showed that the subgroup who had received only EVT but no intravenous alteplase had the highest mortality rate and a median onset-to-treatment time that was >60 minutes longer than the subgroup who received intravenous alteplase only and >90 minutes longer than the subgroup who received both EVT and intravenous alteplase. An average patient with acute ischemic stroke caused by large-vessel occlusion loses 1.9 million neurons each minute in which the stroke is untreated, and delayed presentation is a strong

predictor of poor outcome and mortality.[23] With the delay in onset-to-treatment time comes the observed higher mortality in the EVT only group, which might be an important reason why we were not able to replicate the survival benefit of EVT overall in this study.

Overall, EVT in routine care has a slightly reduced effect size.

A key strength of our study is that it represents the complete case capture of an entire population in the province of Alberta and therefore reflects real-world practice at a population level. Thus, data should be generalizable to other provinces and territories across Canada and elsewhere if EVT is provided in similarly high-volume experienced centers and the patient population has similar racial diversity. Home-time as a patient-centered outcome marker has the advantage of having complete ascertainment because it can be established through linkage with an administrative health database.

Even though Canadians have universal access to publicly funded health care and thus hospitalization and in-patient rehabilitation, numeric home-time may not account for the amount of social and financial support that each patient has that might influence his/her ability to actually return home. Thus, the average home-time herein incorporates the average socioeconomic status of the province of Alberta. We do not have comorbidity data to complete further adjusted outcome estimates, and we have limited data on the occurrence of symptomatic intracranial hemorrhages or procedural complications. In this respect, home-time provides a meaningful global outcome assessment, but it does obscure some details on the adverse effect of major treatment complications.

CONCLUSIONS

EVT for acute ischemic stroke caused by large-vessel occlusion is effective according to our province-wide population-based study and results in an increase of 90-day home-time by an average of 8.5 days.

ARTICLE INFORMATION

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Disclosures

Dr Hill was the principal investigator of the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT [Computed Tomography] to Recanalization Times) trial. The remaining authors have no disclosures to report.

Supplementary Materials

Table S1

REFERENCES

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731.
2. Woolf SH. Do clinical practice guidelines define good medical care? The need for good science and the disclosure of uncertainty when defining "best practices." *Chest*. 1998;113:166s–171s.
3. Kukull WA, Ganguli M. Generalizability: the trees, the forest, and the low-hanging fruit. *Neurology*. 2012;78:1886–1891.
4. Yu AY, Holodinsky JK, Zerna C, Svenson LW, Jette N, Quan H, Hill MD. Use and utility of administrative health data for stroke research and surveillance. *Stroke*. 2016;47:1946–1952.
5. Quinn TJ, Dawson J, Lees JS, Chang TP, Walters MR, Lees KR. Time spent at home poststroke: "home-time" a meaningful and robust outcome measure for stroke trials. *Stroke*. 2008;39:231–233.
6. Yu AYX, Rogers E, Wang M, Sajobi TT, Coutts SB, Menon BK, Hill MD, Smith EE. Population-based study of home-time by stroke type and correlation with modified Rankin score. *Neurology*. 2017;89:1970–1976.
7. Fonarow GC, Liang L, Thomas L, Xian Y, Saver JL, Smith EE, Schwamm LH, Peterson ED, Hernandez AF, Duncan PW, O'Brien EC, Bushnell C, Prvu Bettger J. Assessment of home-time after acute ischemic stroke in Medicare beneficiaries. *Stroke*. 2016;47:836–842.
8. McDermid I, Barber M, Dennis M, Langhorne P, Macleod MJ, McAlpine CH, Quinn TJ. Home-time is a feasible and valid stroke outcome measure in national datasets. *Stroke*. 2019;50:1282–1285.
9. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030.
10. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288.
11. Cragg JG. Some statistical models for limited dependent variables with application to the demand for durable goods. *Econometrica*. 1971;39:829–844.
12. Kamal N, Rogers E, Stang J, Mann B, Butcher KS, Rempel J, Jeerakathil T, Shuaib A, Goyal M, Menon BK, Demchuk AM, Hill MD. One-year healthcare utilization for patients that received endovascular treatment compared with control. *Stroke*. 2019;50:1883–1886.

13. Binning MJ, Bartolini B, Baxter B, Budzik R, English J, Gupta R, Hedayat H, Krajina A, Liebeskind D, Nogueira RG, et al. Trevo 2000: results of a large real-world registry for stent retriever for acute ischemic stroke. *J Am Heart Assoc*. 2018;7:7:e010867. DOI: 10.1161/JAHA.118.010867.
14. Jansen IGH, Mulder M, Goldhoorn RB. Endovascular treatment for acute ischaemic stroke in routine clinical practice: prospective, observational cohort study (MR CLEAN Registry). *BMJ*. 2018;360:k949.
15. Rost NS, Bottle A, Lee JM, Randall M, Middleton S, Shaw L, Thijs V, Rinkel GJ, Hemmen TM. Stroke severity is a crucial predictor of outcome: an international prospective validation study. *J Am Heart Assoc*. 20165:e002433. DOI: 10.1161/JAHA.115.002433.
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.
17. Kamal N, Holodinsky JK, Stephenson C, Kashayp D, Demchuk AM, Hill MD, Vilneff RL, Bugbee E, Zerna C, Newcommon N, et al. Improving door-to-needle times for acute ischemic stroke: effect of rapid patient registration, moving directly to computed tomography, and giving alteplase at the computed tomography scanner. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003242.
18. Kamal N, Shand E, Swanson R, Hill MD, Jeerakathil T, Imoukhuede O, Heinrichs I, Bakker J, Stoyberg C, Fowler L, Duckett S, Holsworth S, Mann B, Valaire S, Bestard J. Reducing door-to-needle times for ischaemic stroke to a median of 30 minutes at a community hospital. *Can J Neurol Sci*. 2019;46:51–56.
19. Berkhemer OA, van Zwam WH, Dippel DW. Stent-retriever thrombectomy for stroke. *N Engl J Med*. 2015;373:1076.
20. Saver JL, Goyal M, Diener HC. Stent-retriever thrombectomy for stroke. *N Engl J Med*. 2015;373:1077.
21. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018.
22. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Roman L, Serena J, Abilleira S, Ribo M, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306.
23. Saver JL. Time is brain—quantified. *Stroke*. 2006;37:263–266.

Table S1. Results from logistic regression analysis of of mortality at 90 days (three missing values imputed with worst outcome (upper results) and best outcome (lower results).

	Odds Ratio	95% confidence interval lower limit	95% confidence interval lower limit
Endovascular treatment given	0.76	0.47	1.24
Age	1.04	1.03	1.06
NIHSS	1.07	1.04	1.11
Endovascular treatment given	0.88	0.54	1.44
Age	1.05	1.03	1.06
NIHSS	1.07	1.03	1.11