Endovascular therapy for ischemic stroke
Save a minute—save a week

ABSTRACT
Objective: To quantify the patient lifetime benefits gained from reduced delays in endovascular therapy for acute ischemic stroke.

Methods: We used observational prospective data of consecutive stroke patients treated with IV thrombolysis in Helsinki (1998–2014; n = 2,474) to describe distributions of age, sex, stroke severity, onset-to-treatment times, and 3-month modified Rankin Scale (mRS) in routine clinical practice. We used treatment effects by time of endovascular therapy in large vessel occlusion over and above thrombolysis as reported by the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) study to model the shift in 3-month mRS distributions with reducing treatment delays. From the 3-month outcomes we derived patient-expected lifetimes and cumulative long-term disability with incremental treatment delay reductions.

Results: Each minute saved in onset-to-treatment time granted on average 4.2 days of extra healthy life, with a 95% prediction interval 2.3–5.4. Women gained slightly more than men due to their longer life expectancies. Patients younger than 55 years with severe strokes of NIH Stroke Scale score above 10 gained more than a week per each minute saved. In the whole cohort, every 20 minutes decrease in treatment delays led to a gain of average equivalent of 3 months of disability-free life.

Conclusions: Small reductions in endovascular delays lead to marked health benefits over patients’ lifetimes. Services need to be optimized to reduce delays to endovascular therapy.

GLOSSARY
DALY = disability-adjusted life-years; ICA = internal carotid artery; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio; tPA = tissue plasminogen activator.

With multiple positive trials published in rapid succession, endovascular therapy for acute ischemic stroke is the new gold standard for large artery occlusion.1 The treatment effect of endovascular therapy, expressed as odds of achieving a better 3-month functional outcome compared to IV thrombolysis alone, is equally good irrespective of patients’ age and stroke severity.1 Just as with thrombolysis with IV tissue plasminogen activator (tPA),2 endovascular therapy is highly time-critical.3,4

Streamlining of acute stroke management to hasten IV thrombolysis has been an implementation success globally.5–8 Quantification of the potential patient benefits from rapidly administered endovascular therapy could also promote practice change with the new model of acute stroke care. The aim of the present study is to quantify the patient lifetime benefits gained from reduced delays in endovascular treatment.

METHODS Overview of the model. To estimate the effect of endovascular treatment time on patient lifetime outcomes, we constructed a model based on an observational cohort of consecutive tPA patients, published pooled analysis of tPA randomized controlled trials, the benefit of endovascular therapy over tPA alone by time, general population survival data, and previously reported disability...
weights for various modified Rankin Scale (mRS) categories. The observational cohort was used to derive demographic and outcome distributions in real-life tPA use in the setting of large vessel occlusion; the pooled tPA analysis and endovascular treatment effect were used to derive how the treatment effect of tPA and endovascular therapy varies by treatment delays; the population survival data were used to model long-term survival of patients at various mRS categories compared to the general population; and the disability weights were used to value the loss of healthy life in each mRS category. The present model is built upon a previous report on the importance of speed in tPA alone, titled “Save a Minute. Save a Day.”

**Standard protocol approvals, registrations, and patient consents.** Our observational cohort consisted of the Helsinki Stroke Thrombolysis Registry. This institutionally approved routine observational quality registry does not require patient consent, making it possible to include all consecutive patients.

**Observational cohort.** For the present analysis, we excluded patients treated with tPA beyond 4½ hours of stroke onset, those with missing data on onset-to-tPA time or mRS outcome, and those with basilar artery occlusions who in Helsinki were always treated with concomitant full-dose heparin infusion.

The patients of the observational cohort who only received tPA, without endovascular therapy, were used to construct binary logistic regression models estimating baseline probabilities of achieving individual mRS categories in the setting of tPA alone for any given combinations of age, baseline NIH Stroke Scale (NIHSS) score, and onset-to-tPA time, as described previously. These probability distributions were not used to estimate the effect of faster treatment, only to describe the cohort characteristics. The effect of faster treatment was estimated based on published trial data.

Within the tPA cohort, we modeled the effect of endovascular therapy on the subgroup of patients with either a proven internal carotid artery (ICA)/M1/M2 occlusion on CT angiography or, in the absence of CT angiography, a dense middle cerebral artery sign on CT. The effect of faster treatment was only analyzed in this endovascular eligible cohort, using published trial data.

**Treatment effect over time.** To estimate how the treatment effect of tPA alone changes with onset-to-treatment time, we used the pooled analysis of tPA randomized controlled trials by Lees and coworkers. This analysis provides graphically odds ratios (OR) by onset-to-treatment time for favorable outcome (mRS 0–1) and mortality (mRS 6) of tPA compared to placebo.

We used these to model how changing the onset-to-treatment time affects the probability of mRS 0–1 and mRS 6 after tPA alone, as described previously. We only included tPA treatment up to 270 minutes, since that is the evidence-based upper time limit, also adopted in current guidelines.

To estimate the treatment effect of endovascular therapy by time, we used similar data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) study, as the other endovascular trials have not reported the detailed relationship of endovascular therapy over tPA alone by time. For modeling of the endovascular effect, we assumed all patients to receive endovascular therapy 90 minutes after tPA. This tPA to groin time, although less than observed in the MR CLEAN trial, is similar to most endovascular trials and allows for treatment of all patients within 6 hours of onset as adopted in current guidelines.

**Disability-adjusted life-years (DALY) lost.** From the observational data we had 3-month mRS probabilities for each patient at the observed onset-to-tPA time, and from the tPA pooled analysis and MR CLEAN data we could derive how those probabilities shifted if treatment delays would have changed. To translate this 3-month outcome data into a meaningful long-term metric, we used DALY lost, calculated with the weights and assumptions as described in table 1, without discounting or age-weighting as per WHO standard methodology. DALYs lost over a person’s lifetime is the sum of 2 components: (1) years lost

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**Table 1: Model inputs**

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<th>Model variables</th>
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Abbreviations: MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio; tPA = tissue plasminogen activator.
due to premature death and (2) health lost due to disability during lifetime, i.e., years of life multiplied by disability weight. Long-term excess mortality by mRS category over and above that of the general population was based on population-based consecutive data from Sweden and Scotland.\textsuperscript{13} Disability weights by mRS category were derived from published sources.\textsuperscript{14}

We calculated DALYs lost for each individual patient over the whole lifetime in the observational cohort at the observed treatment delays and then modeled what these would have been if both tPA and endovascular therapy had been given a minute earlier.

Robustness analysis and validation. To evaluate model robustness with regard to uncertainties in the inputs, we first performed one-way analyses by varying each model input to the upper and lower 95% confidence interval, followed by probabilistic robustness analysis, and report the 95% prediction interval of these simulations. The methodology of the modeling has been extensively validated.\textsuperscript{15} A summary of the validation of the present model is provided in appendix e-1 at Neurology.org.

Implementation. Baseline characteristics are reported as numbers with percentage or both mean with SD and median with interquartile range. Distributions are compared with the Mann-Whitney U test, \chi² test, or Student t test, as appropriate, with 2-sided statistical significance set at \( p = 0.05 \). The mRS category-specific life expectancies and DALYs lost for each combination of age and sex were calculated on linked Excel 2010 worksheets (Microsoft, Redmond, WA). All other analyses were performed on STATA IC version 13 (StataCorp, College Station, TX).

RESULTS Between July 8, 1995, and September 30, 2014, a total of 2,799 patients were treated with tPA in Helsinki. Of these, 192 (6.9%) were treated beyond 4.5 hours from onset, 88 (3.6%) had basilar artery occlusions, and 45 had missing data on either 3-month mRS (\( n = 43, 1.6\% \)) or time from onset to tPA (\( n = 2, 0.1\% \)) and were excluded, leaving a study cohort of 2,474 patients.

A total of 729 (29.5%) patients of the study cohort either received (\( n = 146, 5.9\% \)) or would have been eligible for endovascular therapy had the therapy been available at the time (table 2). Eligibility was either due to an ICA/M1/M2 occlusion on CT angiography (\( n = 249, 10.1\% \)) or a dense middle cerebral artery sign on noncontrast CT in the absence of angiography (\( n = 334, 13.5\% \)). The range for age was 14–100 years, the range for NIHSS was 0–30, and the range for onset to tPA was 35–270 minutes. This endovascular suitable cohort included 116 (16%) patients older than 80 years of age. The positive predictive value of a dense middle cerebral artery sign on CT for a retrievable clot on subsequent CTA was 99.2%.

We used the observed 3-month outcomes of the patients who did not receive endovascular therapy (\( n = 2,328 \)) to estimate an outcome after IV tPA alone with any given combination of age, sex, NIHSS, and onset to IV tPA time. We then applied these expected outcomes after tPA alone to the endovascular cohort patients (\( n = 729 \)) at their observed age, sex, NIHSS, and onset to IV tPA time. Finally, we used the adjusted common OR from the MR CLEAN trial at 90 minutes from the observed tPA time of each patient to estimate the added value of endovascular therapy over and above tPA alone on that patient outcome as a shift in the mRS score.

For every minute of earlier treatment, the cohort over their lifetime gained on average an equivalent of 4.2 healthy days of healthy life. The result was robust in univariate analyses (table 3) with a 95% probabilistic uncertainty interval of 2.3–5.4 days. The gained benefit from faster treatment varied by patient characteristics (figure and table e-1), so that younger patients and women with longer overall life expectancies gained more over their lifetime. When limited to only patients with modified treatment in cerebral infarction (mTICI) 2b-3 radiologic outcomes, the average added value of 1 minute saved was 4.3 days of extra healthy life (95% prediction interval 2.0–5.4).

DISCUSSION We demonstrated that every minute counts when one intervenes with endovascular therapy, even more so than for tPA alone. On average, patients gain many days of healthy life for every minute saved in delivering the therapy while the more severe strokes can gain a week or more with each minute saved. Patients with long life expectancies stand to gain and lose more: a young patient with a severe stroke can lose 2 years of healthy life with every hour
the endovascular therapy is delayed. It must be noted that the outcomes we have demonstrated here are what an average patient gains, i.e., population benefits—an individual may gain more or less depending on their individual collateral circulation, success of reperfusion, and complications.

Compared to IV tPA alone, where we previously reported that every minute saved in delays provides 1.8 days of healthy life, speed is even more essential in endovascular therapy. Importantly, all patients gain from faster treatment. As endovascular services are being set up around the world, time needs to be taken into account as a critical component of service design. As imaging requirements in endovascular patient selection are more complex, special attention should be given to streamlining the acute imaging protocols. Our findings should promote the rational allocation of endovascular services and ambulance transfer patterns. Hence, it is of utmost importance to streamline both tPA delivery and endovascular treatment thereafter. The methods to achieve this have been described and validated in detail.5,7,8,16

Several previous analyses on the effect of time on endovascular benefit have been published. The earlier observational analyses by Mazighi et al.,17 Khatri et al.,18 and Sheth et al.19 had no comparator arm and hence could not allow for analysis of causal relationships between time to treatment and outcome. The recent meta-analysis from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials (HERMES) collaboration suggested a number needed to treat of 40 for functional independence at 3 months for every 15 minutes reduction in reperfusion time, and suggested there was treatment benefit in starting the endovascular procedure for up to 7 hours and 18 minutes from symptom onset.20

Our study has limitations. First, we used an observational cohort from Finland with special interest and experience in stroke thrombolysis. Other centers may have different distributions of age, severity, and treatment delays, although our patient characteristics were similar to those in the MR CLEAN trial (median age 69 years in Helsinki vs 66 years in MR CLEAN; NIHSS 13 vs 17; onset to tPA 106 vs 86 minutes). The proportion of patients older than 80 years was the same (16%) in our cohort and the MR CLEAN trial. While the trial was independently positive in this age group, the relatively small number of patients limits the precision of our model. The robustness analyses demonstrated that the observational cohort was of sufficient size overall to estimate the effect of patient characteristics on outcome with a high level of precision (table 3). Second, our assumptions on how the treatment effect of tPA and endovascular intervention varies by time were derived from randomized controlled trials.2–4 The effectiveness of tPA or endovascular therapy may be different in routine clinical practice. To counteract this, we started our model with the observed 3-month outcomes of

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</tbody>
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Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; tPA = tissue plasminogen activator.

a Upper and lower 95% CI by time from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands trial.4

b Upper and lower 95% CI from the pooled analysis of Lees et al.2

c Upper and lower 95% CI from the logistic regression model in the observational cohort.

d Probabilistic 95% prediction interval.

Figure Healthy days gained per minute of faster treatment

Relationship between disability-adjusted days gained per minute of faster treatment by sex ([A] male, [B] female), age, and stroke severity (NIH Stroke Scale [NIHSS]).
real-life patients and only used the trial data to demonstrate the effect of changing treatment delays. Third, we modeled our cohort based on the assumption that everyone received endovascular therapy 90 minutes after tPA. In real life, the interval between tPA and endovascular therapy should be shorter. When the model was run with the assumption that all patients received endovascular therapy 45 minutes after tPA, the results remained unchanged (table 3).

We have demonstrated that on average acute ischemic stroke patients with large vessel occlusions and eligible for endovascular therapy stand to gain 4.2 days of healthy life for every minute of reduction in treatment delays while young patients with severe strokes gain more than a week per minute per every period.

**AUTHOR CONTRIBUTIONS**

Dr. Meretoja, M. Keshtkaran, and Dr. Churilov conceived the study and analyzed the data. Dr. Meretoja drafted the manuscript. Dr. Meretoja, M. Keshtkaran, and Dr. Churilov performed the statistical analyses. Dr. Meretoja and Dr. Churilov supervised and coordinated the study. Dr. Meretoja and Dr. Tatlisumak acquired the data. All authors interpreted the data, edited the manuscript for intellectual content, and approved the final submission.

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**DISCLOSURE**

A. Meretoja has received speakers’ bursaries and consulted for Siemens, Boehringer Ingelheim, Stryker, Nestle, and Phagenesis. M. Keshtkaran reports no disclosures relevant to the manuscript. T. Tatlisumak serves has served on advisory boards for Boehringer Ingelheim, Bayer, Pfizer, Lumosa Pharm, and Medfield Diagnostics; consulted for Boehringer Ingelheim, H. Lundbeck A/S, BrainsGate, Bayer, and Pfizer; has has had research contracts with Boehringer Ingelheim, BrainsGate, Bayer, Portola Pharmaceuticals, and Pfizer; holds a patent for mast cell stabilization in thrombolytic therapy for stroke; and has been reimbursed for travel and accommodation expenses from an-for-profit organizations. G. Donnan has consulted for and received support for meeting costs from Boehringer Ingelheim. L. Churilov reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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**REFERENCES**


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