Stroke

American Heart Association

American Stroke Association

Stroke Thrombolysis: Save a Minute, Save a Day

Atte Meretoja, Mahsa Keshtkaran, Jeffrey L. Saver, Turgut Tatlisumak, Mark W. Parsons,
Markku Kaste, Stephen M. Davis, Geoffrey A. Donnan and Leonid Churilov

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/45/4/1053

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/03/13/STROKEAHA.113.002910.DC1.html

Stroke Thrombolysis
Save a Minute, Save a Day

Atte Meretoja, MD; Mahsa Keshtkaran, MSc; Jeffrey L. Saver, MD; Turgut Tatlisumak, MD;
Mark W. Parsons, MD; Markku Kaste, MD; Stephen M. Davis, MD; Geoffrey A. Donnan, MD;
Leonid Churilov, PhD

Background and Purpose—Stroke thrombolysis is highly time-critical, but data on long-term effects of small reductions in treatment delays have not been available. Our objective was to quantify patient lifetime benefits gained from faster treatment.

Methods—Observational prospective data of consecutive stroke patients treated with intravenous thrombolysis in Australian and Finnish centers (1998–2011; n=2258) provided distributions of age, sex, stroke severity, onset-to-treatment times, and 3-month modified Rankin Scale in daily clinical practice. Treatment effects derived from a pooled analysis of thrombolysis trials were used to model the shift in 3-month modified Rankin Scale distributions with reducing treatment delays, from which we derived the expected lifetime and level of long-term disability with faster treatment.

Results—Each minute of onset-to-treatment time saved granted on average 1.8 days of extra healthy life (95% prediction interval, 0.9–2.7). Benefit was observed in all groups: each minute provided 0.6 day in old severe (age, 80 years; National Institutes of Health Stroke Scale [NIHSS] score, 20) patients, 0.9 day in old mild (age, 80 years; NIHSS score, 4) patients, 2.7 days in young mild (age, 50 years; NIHSS score, 4) patients, and 3.5 days in young severe (age, 50 years; NIHSS score, 20) patients. Women gained slightly more than men over their longer lifetimes. In the whole cohort, each 15 minute decrease in treatment delay provided an average equivalent of 1 month of additional disability-free life.

Conclusions—Realistically achievable small reductions in stroke thrombolysis delays would result in significant and robust average health benefits over patients' lifetimes. The awareness of concrete importance of speed could promote practice change.   (***Stroke***. 2014;45:1053-1058.)

Key Words: stroke ■ thrombolytic therapy

Intravenous thrombolysis (tissue-type plasminogen activator, tPA) is the only medical therapy shown to improve patient outcomes in acute ischemic stroke.[1] The treatment is more effective when given early after symptom onset.[2] The odds ratio (OR) of tPA compared with placebo for disability-free outcome is 2.6 when treatment is initiated <1.5 hours of symptom onset and 1.3 when started later, at 3 to 4.5 hours. The number needed to treat to achieve a disability-free, 3-month outcome correspondingly increases from 5 to 14.[2]

However, measures such as OR and number needed to treat communicate poorly the overall patient health benefits of being treated slightly faster. Physiological modeling exercises examining brief time increments suggest an average of 2 million neurons gained every minute with earlier reperfusion of a major ischemic stroke.[3] Clinically, outcomes depend heavily on the age of the patient, severity of stroke, and treatment delays.

Although numerous interventions to reduce delays in ischemic stroke thrombolysis have been described[4] with median door-to-needle times down to 20 minutes at the best practice centers,[5] median in-hospital delays in American, Australian, and European centers are at 70 to 80 minutes.[6–8] Therefore, the potential for accelerating treatment by up to an hour exists in an average patient. Quantifying the long-term health benefits of faster treatment could help promote practice change.

The aim of the present study was to estimate the effect of speed in stroke thrombolysis over a patient's lifetime.

Methods

Overview of the Model
To estimate the effect of tPA treatment delays 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, general population survival data, and previously reported disability weights for various modified Rankin Scale (mRS) categories (Figure 1). The observational cohort was used to derive demographic and outcome distributions in real-life tPA use; the pooled analysis was used to derive how the treatment effect of tPA varies by treatment delays; the population survival data were used to model long-term survival of patients at various mRS categories compared with the general population; and the disability weights were used to value the loss of healthy life in each mRS category.

Observational Cohort

Our observational cohort consisted of 2 databases: the Helsinki Stroke Thrombolysis Registry[5] and the Safe Implementation of Treatments in Stroke (SITS)-Australia.[7] Between March 1998 and December 2011, there were 1998 patients treated with tPA in the Helsinki University Central Hospital. After excluding patients treated >4.5 hours (n=150, of which 118 basilar artery occlusions treated at median 12 hours from symptom onset) and those with missing data on onset-to-treatment time, stroke severity (National Institutes of Health Stroke Scale, NIHSS) or mRS outcome (n=65), and basilar artery occlusions pretreated with heparin infusion (n=56), we included 1727 patients from Helsinki. Additionally, there were 704 patients registered in the SITS-Australia database between December 2002 and December 2008 from 14 hospitals. Of these, we excluded 173 with missing data and included 531 patients. The observational registries have been approved by institutional authorities. Because these are routine observational quality registries, no patient consent for registration was required. This made it possible to register all consecutive patients.

The observational cohort was used to construct binary logistic regression models estimating baseline probabilities of individual mRS categories for any given combinations of age, baseline NIHSS, and onset-to-treatment time (Methods in the online-only Data Supplement).

Treatment Effect Over Time

To estimate how treatment effect of tPA changes with onset-to-treatment time, we used the pooled analysis of tPA randomized controlled trials by Lees et al.[2] This analysis provides ORs by onset-to-treatment time for favorable outcome (mRS, 0–1) and mortality (mRS, 6) of tPA compared with placebo. We used these to model how a change in onset-to-treatment time affects the probability of mRS 0 to 1 and mRS 6 (Figure 1; see also Methods in the online-only Data Supplement).

We assumed no tPA treatment after 270 minutes, because that is the evidence-based upper time limit,[2] also adopted in current guidelines.[1] For simulating extended delays, we assumed mRS 0 and mRS 6 probabilities that correspond to OR=1, that is, that of placebo, when treatment could not be initiated <270 minutes from stroke onset.

Disability-Adjusted Life-Years Lost

From observational data, we had 3-month mRS probabilities for each patient at the observed onset-to-treatment time, and from pooled analysis, 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 disability-adjusted life-years (DALYs) lost. DALY is a measure consisting of 2 components: years of life lost due to premature death (YLL), and years of life lost due to disability (YLD).

YLL is calculated as the difference between life expectancy of a person in the general population at a given age and sex, that is, life expectancy of a person without a stroke, and age- and sex-matched life expectancy of a stroke patient in a certain mRS category. The
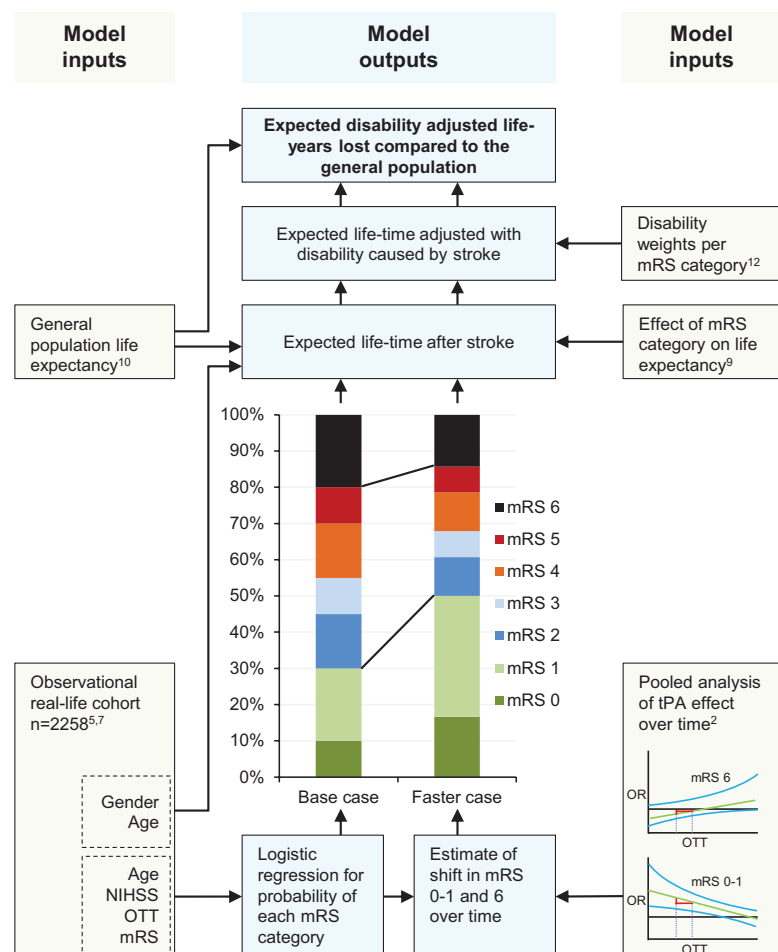

Figure 1. Overview of the model. DALY indicates disability-adjusted life-years; mRS, modified Rankin Scale at 3 months; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; and tPA, tissue-type plasminogen activator.

long-term annual risk of death after stroke was taken from published literature (1.53, 1.52, 2.17, 3.18, 4.55, and 6.55 times that of the general population for mRS categories 0–5, respectively).[9] We used Australian Bureau of Statistics data for age- and sex-specific life expectancies of the general population.[10] The average life expectancy for Australians and Finns differs little and is presently, at birth, 79.2 versus 76.8 years in men and 83.8 versus 83.3 years in women.[11]

YLD is calculated by multiplying the life expectancy of a stroke patient by a disability weight and, therefore, demonstrates how much the value of life has diminished in years lived after stroke. The disability weights were taken from published literature (0.000, 0.053, 0.228, 0.353, 0.691, and 0.998 for mRS categories 0–5, respectively).[12]

We calculated DALYs lost for each patient in the observational cohort at observed treatment delays. We then modeled DALYs lost for each patient if tPA had been given earlier or later.

Traditionally, DALYs have been reported with discounting and age-weighting the value of future years.[9,13,14] Age-weighting principally denotes that years lost beyond the age of 63 progressively are of less value than those lost during productive years. In 2012, the World Health Organization (WHO) made a major policy change and stopped using age-weighting and discounting for DALY calculations.[15] We report our data according to this new policy, but additionally provide sensitivity analyses with discounting to present values at 3% per annum, both with or without age-weighting, according to standard methodology.[13]

Robustness Analysis

To evaluate model robustness with regard to uncertainties in inputs, we first performed 1-way analyses by varying each model input to their upper and lower 95% confidence interval, followed by probabilistic robustness analysis (Methods in the online-only Data Supplement), and report the 95% prediction interval of these simulations.

Implementation

mRS category–specific life expectancies and DALYs lost for each combination of age and sex were calculated on linked Excel 2010 worksheets (Microsoft Corp, Redmont, WA). All other analyses were performed on STATA IC version 12 (StataCorp, College Station, TX).

Results

The observational tPA cohort consisted of 2258 patients (Table 1). In the whole cohort, each minute saved provided a mean 1.8 days of DALY (SD, 0.8; median, 1.7; interquartile range, 1.1–2.3; range, 0.1–4.6 days). The effect of faster treatment varied with age and NIHSS. Each minute saved provided on average 0.6 day in old patients with severe stroke, 0.9 day in old and mild, 2.7 days in young and mild, and 3.5 days in young and severe patients (Figure 2). Greatest gains from faster treatment were reaped by youngest patients with longest life expectancies after their stroke, and women gained a little more over their longer lifetime (Figure 3; Table I in the online-only Data Supplement for 95% prediction intervals). The benefit was greatest in patients with moderately severe stroke deficits at presentation (NIHSS, 10–19).

Robustness Analyses

Our results were generally robust. Discounting and age-weighting varied the tPA effect differently for young and old patients as shown in Figure 2. In the whole cohort, each minute saved produced on average 1.3 days of DALYs after discounting and 0.9 day of DALYs after discounting and age-weighting. In 1-way robustness analyses, varying the model inputs one at a time only slightly changed the results (Table 2). Incorporating input uncertainties simultaneously in probabilistic robustness analyses provided a 95% prediction interval of 0.9 to 2.7 days per minute saved around our point estimate of 1.8 days per minute.

Discussion

This study demonstrates that a few minutes saved in delivering intravenous tPA translates to significant benefits equivalent to days, weeks, and even months of disability-free life over

Table 1. Characteristics of the Observational Cohort

Characteristics and Outcomes	Total (n=2258)	Helsinki (n=1727)	SITS-Australia (n=531)	P Value
Age, y	70 (60–78)	70 (60–77)	73 (62–80)	<0.001
	68±13	67±13	70±13	<0.001
Male sex	1247 (55%)	939 (54%)	308 (58%)	0.161
Hypertension	1361 (60%)	1018 (59%)	343 (65%)	0.020
Diabetes mellitus	329 (15%)	242 (14%)	87 (16%)	0.176
Atrial fibrillation	660 (29%)	473 (27%)	187 (35%)	<0.001
NIHSS at baseline	9 (6–15)	8 (5–14)	13 (8–19)	<0.001
	11±6	10±6	14±7	<0.001
Onset-to-treatment time, min	125 (92–162)	117 (86–160)	145 (123–167)	<0.001
	129±46	125±49	143±32	<0.001
Door-to-needle time, min	36 (20–67)	26 (17–48)	74 (56–97)	<0.001
	47±36	37±31	79±32	<0.001
sICH	127 (5.8%)	97 (5.7%)	30 (6.4%)	0.532
3-Month mRS score 0 to 1	850 (37.6%)	664 (38.4%)	183 (34.5%)	0.097
3-Month mRS score 0 to 2	1290 (57.1%)	1031 (59.7%)	259 (48.8%)	<0.001
3-Month case fatality	252 (11.2%)	155 (9.0%)	97 (18.3%)	<0.001

Data are n (%), median (interquartile range), or mean±SD. Distributions of Helsinki and SITS-Australia data compared with Mann–Whitney U test χ^2 test, or Student t test as appropriate, with 2-sided statistical significance set at $P=0.05$. mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracerebral hemorrhage (second European-Australasian Acute Stroke Study definition); and SITS, Safe Implementation of Treatments in Stroke.
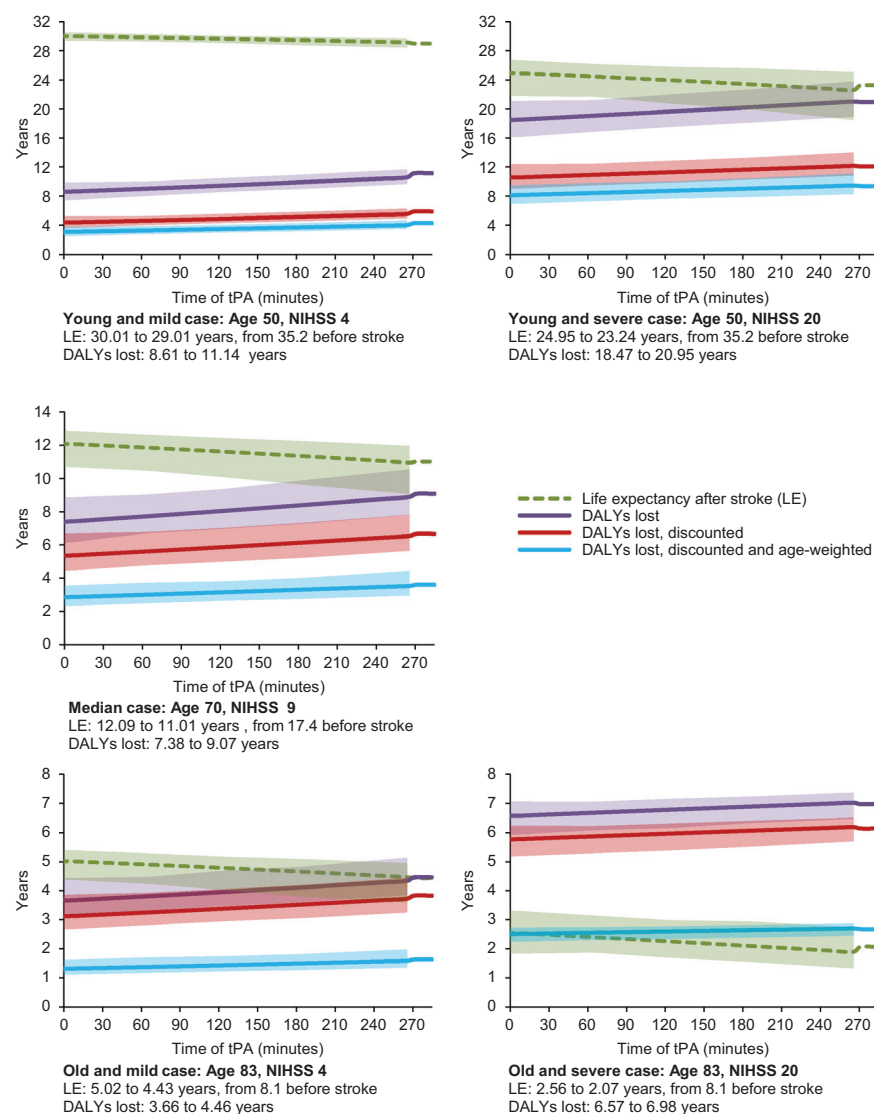
Young and mild case: Age 50, NIHSS 4
LE: 30.01 to 29.01 years, from 35.2 before stroke
DALYs lost: 8.61 to 11.14 years

Young and severe case: Age 50, NIHSS 20
LE: 24.95 to 23.24 years, from 35.2 before stroke
DALYs lost: 18.47 to 20.95 years

- – – Life expectancy after stroke (LE)
— DALYs lost
— DALYs lost, discounted
— DALYs lost, discounted and age-weighted

Median case: Age 70, NIHSS 9
LE: 12.09 to 11.01 years , from 17.4 before stroke
DALYs lost: 7.38 to 9.07 years

Figure 2. Effect of treatment delay with 95% prediction interval on life expectancy (LE) and disability-adjusted life-years (DALYs) in 5 individual female cases with median, top, and bottom decile age/National Institutes of Health Stroke Scale (NIHSS). No thrombolysis assumed after 270 min from onset. tPA indicates tissue-type plasminogen activator.

Old and mild case: Age 83, NIHSS 4
LE: 5.02 to 4.43 years, from 8.1 before stroke
DALYs lost: 3.66 to 4.46 years

Old and severe case: Age 83, NIHSS 20
LE: 2.56 to 2.07 years, from 8.1 before stroke
DALYs lost: 6.57 to 6.98 years

the patient's lifetime. Although patients of all age and disease severity seem to benefit, younger patients and women gain more from faster treatment over their longer lifetime. Except for oldest patients with most severe strokes, patients gain an equivalent of at least a day of healthy life for each minute saved; hence Save a Minute, Save a Day summarizes our findings.

Observational cohorts suggest that faster treatment is associated with better in-hospital and 3-month outcomes, and that tPA efficacy in real life and in randomized controlled trials is similar.[16–19] Compared with a pooled analysis of these trials,[2] our patients were slightly older (median age, 70 versus 68 years), with milder strokes (median NIHSS, 9 versus 11), lower
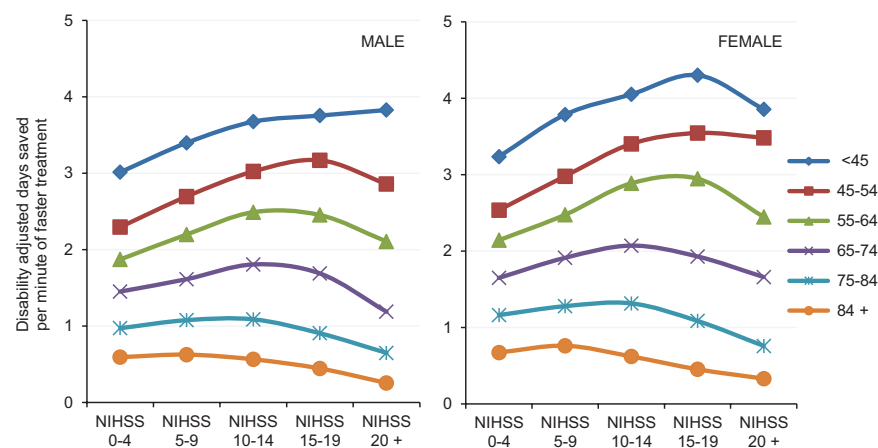

Figure 3. Relationship between disability-adjusted days gained per minute of faster treatment, age, and stroke severity. Baseline stroke severity measured with the National Institutes of Health Stroke Scale (NIHSS) where higher scores indicate more severe stroke.

Table 2.   Robustness of Model When Inputs Changed One at a Time

	Disability-Adjusted Days Saved Per Minute of Faster Treatment	
	Lower Value	Upper Value
Odds of mRS 0–1*	0.84	2.75
Odds of mRS 6*	1.41	2.08
Effect of age on outcome†	1.65	1.90
Effect of NIHSS on outcome†	1.75	1.81

The point estimate is 1.78 d per min in all cases. mRS indicates modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Upper and lower 95% confidence intervals (CIs) from the pooled analysis of Lees et al.[2]

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

mortality (11.2% versus 13.9%), and less common mRS 0 to 1 at 3 months (37.6% versus 41.6%). Our mean onset-to-treatment times (129 minutes) were similar to the National Institute of Neurological Disorders and Stroke (NINDS) trial (120 minutes) and published clinical practice series ranging from 108 to 157 minutes.[4] The cohort was collected from institutions with variable patient characteristics and treatment delays, improving generalizability. It is likely that our results can be generalized to other populations with similar demographics and treatment practices, in keeping with comparisons of tPA versus no tPA (Table II in the online-only Data Supplement). Our results can also be translated to populations with different onset-to-treatment times, because the marginal effect of speed on DALY gained is stable in the tPA time window (Figure 2) and to patients of different age and stroke severity (Figure 3).

Several interventions are known to reduce thrombolysis delays, although optimal reductions in delays are not achievable by any single intervention but rather result from continuous analysis and stepwise improvement of the system as a whole.[4,5,20–24] Although typical routine practice in a stroke center has substantial room for improvement,[6] many centers around the world are already down to <30 minutes from arrival to treatment.[5,21] It is important to realize, based on the present analysis, that finetuning even the best of services is beneficial.

Prehospital thrombolysis using portable CT machines and point-of-care laboratories in ambulances has been recently demonstrated feasible.[25,26] There is potential for significant reductions in treatment delays where such advanced service is available, but this requires heavy investment in personnel, education, and equipment. Our data provide inputs for evaluations of cost-effectiveness of such services.

One finding in our analysis relates to the previously reported effect of increased mortality[2] close to the end of treatment time window at around 4 to 4.5 hours from symptom onset, compared with not treating at all (Figure 2). It would seem that when the absolute risk of death is high and the absolute chance of becoming disability-free is small, as is the case with most severe strokes, treating around the 4.5-hour time mark may reduce the long-term overall outcome of patients, that is, the relatively small mortality increase is large in absolute terms and outweighs the small absolute increase in the chance of becoming disability-free. However, the Effect of the European Cooperative

Acute Stroke Study (ECASS) III trial subgroup analyses did not demonstrate loss of treatment effect at 4 to 4.5 hours or in the most severe cases when analyzed at 3 months[27]; so our results regarding theoretical loss of efficacy over a patient's lifetime in this specific situation should be interpreted with caution.

Study Limitations

First, we used observational data from select centers in Australia and 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 not strikingly different from published series or randomized controlled trials. The robustness analysis demonstrated that the observational cohort was of sufficient size to estimate the effect of patient characteristics on outcome with very high precision (Table 2). Second, there is uncertainty about disability and excess death at various mRS categories.[9,12] We used disability weights for various mRS categories derived using the original expert-based WHO methodology. The recent WHO methodology provides weights as valued by the general public for mild (0.021), moderate (0.076–0.312), and severe (0.539–0.567) stroke, but these cannot be directly translated to mRS categories.[28] The expert-based granular mRS disability weights we used generally mapped well to the lay-person based disability weights. Excess postacute risk of death after stroke was from patients of 1990 to 2006.[9] Survival after stroke might have improved mainly in the first 3 months and likely otherwise reflect general population trends. Third, our assumption on how the treatment effect of tPA is increased over time was derived from pooled analysis of tPA randomized controlled trials.[2] The effectiveness of tPA may be different in routine clinical practice. To counteract this, we started our model with observed 3-month outcomes of real-life patients and only used the relative efficacy data of randomized controlled trials to demonstrate the effect of changing treatment delays. Fourth, it is known that around half of the patients who are given tPA do not recanalize. Therefore, in practice, half of the patients do not benefit from faster tPA treatment and the other half benefit twice as much as we describe here; however, there is no precise method of identifying the patients that will or will not recanalize, so haste should be made in all patients. Finally, our model did not take into account the fact that reductions in delays potentially allow for tPA treatment of more patients who would otherwise have been too late for thrombolysis. We did not have detailed data on consecutive non-tPA–treated patients from our hospitals, but other series suggest that only 3% of suitable ischemic stroke patients arrive in the 4- to 5.5-hour time window, and the effect of adding these patients into our model would have been small.[29,30]

Conclusions

We demonstrated that minutes saved in stroke thrombolysis translate to days, weeks, and months of disability-free life over a patient's lifetime. Therefore, all attempts should be made to reduce treatment delays. A gap of around 60 minutes exists between the best and the average centers. The methods to close this gap have been clearly described.[5,6,21,31] These are simple organization changes that cost little or nothing. Every 15 minutes of expediting tPA can provide on average an equivalent of 1 month of healthy life for each treated patient.

References

1. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947.
2. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375:1695–1703.
3. Saver JL. Time is brain–quantified. *Stroke*. 2006;37:263–266.
4. Meretoja A, Kaste M. Pre- and in-hospital intersection of stroke care. *Ann N Y Acad Sci*. 2012;1268:145–151.
5. Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ, Kaste M. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology*. 2012;79:306–313.
6. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation*. 2011;123:750–758.
7. Simpson MA, Dewey HM, Churilov L, Ahmed N, Bladin CF, Schultz D, et al. Thrombolysis for acute stroke in Australia: outcomes from the Safe Implementation of Thrombolysis in Stroke registry (2002-2008). *Med J Aust*. 2010;193:439–443.
8. Mikulík R, Kadlecová P, Czlonkowska A, Kobayashi A, Brozman M, Svigelj V, et al; Safe Implementation of Treatments in Stroke-East Registry (SITS-EAST) Investigators. Factors influencing in-hospital delay in treatment with intravenous thrombolysis. *Stroke*. 2012;43:1578–1583.
9. Hong KS, Saver JL. Years of disability-adjusted life gained as a result of thrombolytic therapy for acute ischemic stroke. *Stroke*. 2010;41:471–477.
10. Australian Bureau of Statistics. http://www.abs.gov.au/ausstats. Accessed March 15, 2013.
11. Wang H, Dwyer-Lindgren L, Lofgren KT, Rajaratnam JK, Marcus JR, Levin-Rector A, et al. Age-specific and sex-specific mortality in 187 countries, 1970-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2071–2094.
12. Hong KS, Saver JL. Quantifying the value of stroke disability outcomes: WHO global burden of disease project disability weights for each level of the modified Rankin Scale. *Stroke*. 2009;40:3828–3833.
13. Fox-Rushby JA, Hanson K. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy Plan*. 2001;16:326–331.
14. WHO. http://www.who.int/healthinfo/bod/en/index.html. Accessed March 15, 2013.
15. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2197–2223.
16. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al; SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369:275–282.
17. Meretoja A, Putaala J, Tatlisumak T, Atula S, Artto V, Curtze S, et al. Off-label thrombolysis is not associated with poor outcome in patients with stroke. *Stroke*. 2010;41:1450–1458.
18. Strbian D, Soinne L, Sairanen T, Häppölä O, Lindsberg PJ, Tatlisumak T, et al; Helsinki Stroke Thrombolysis Registry Group. Ultraearly thrombolysis in acute ischemic stroke is associated with better outcome and lower mortality. *Stroke*. 2010;41:712–716.
19. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA*. 2013;309:2480–2488.
20. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Hernandez AF, Peterson ED, et al. 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.
21. Köhrmann M, Schellinger PD, Breuer L, Dohrn M, Kuramatsu JB, Blinzler C, et al. Avoiding in hospital delays and eliminating the three-hour effect in thrombolysis for stroke. *Int J Stroke*. 2011;6:493–497.
22. Ford AL, Williams JA, Spencer M, McCammon C, Khoury N, Sampson TR, et al. Reducing door-to-needle times using Toyota's lean manufacturing principles and value stream analysis. *Stroke*. 2012;43:3395–3398.
23. Tilley BC, Lyden PD, Brott TG, Lu M, Levine SR, Welch KM. Total quality improvement method for reduction of delays between emergency department admission and treatment of acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *Arch Neurol*. 1997;54:1466–1474.
24. Curtze S, Meretoja A, Mustanoja S, Putaala J, Lindberg T, Leppä M, et al. Does time of day or physician experience affect outcome of acute ischemic stroke patients treated with thrombolysis? A study from Finland. *Int J Stroke*. 2012;7:511–516.
25. Walter S, Kostopoulos P, Haass A, Keller I, Lesmeister M, Schlechtriemen T, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *Lancet Neurol*. 2012;11:397–404.
26. Weber JE, Ebinger M, Rozanski M, Waldschmidt C, Wendt M, Winter B, et al; STEMO-Consortium. Prehospital thrombolysis in acute stroke: results of the PHANTOM-S pilot study. *Neurology*. 2013;80:163–168.
27. Bluhmki E, Chamorro A, Dávalos A, Machnig T, Sauce C, Wahlgren N, et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurol*. 2009;8:1095–1102.
28. Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2129–2143.
29. Bembenek J, Kobayashi A, Sandercock P, Czlonkowska A. How many patients might receive thrombolytic therapy in the light of the ECASS-3 and IST-3 data? *Int J Stroke*. 2010;5:430–431.
30. de Los Rios la Rosa F, Khoury J, Kissela BM, Flaherty ML, Alwell K, Moomaw CJ, et al. Eligibility for intravenous recombinant tissue-type plasminogen activator within a population: the Effect of the European Cooperative Acute Stroke Study (ECASS) III trial. *Stroke*. 2012;43:1591–1595.
31. Meretoja A, Weir L, Ugalde M, Yassi N, Yan B, Hand P, et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. *Neurology*. 2013;81:1071–1076.

ONLINE SUPPLEMENT
Meretoja et al. Stroke Thrombolysis. Save a Minute – Save a Day.

Atte Meretoja[1,2,3]   MD
Mahsa Keshtkaran[1]   MSc
Jeffrey L Saver[4]   MD
Turgut Tatlisumak[3]   MD
Mark W Parsons[5]   MD
Markku Kaste[3]   MD
Stephen M Davis[2]   MD
Geoffrey A Donnan[1]   MD
Leonid Churilov[1]   PhD

[1]The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia.
[2]Departments of Neurology and Medicine, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia.
[3]Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland
[4]UCLA Stroke Center, Los Angeles, USA
[5]John Hunter Hospital and the Hunter Medical Research Institute, University of Newcastle, Newcastle, Australia

Contents:

Supplementary Statistical Methods.

Supplementary Table I. Point estimates and 95% prediction intervals for disability adjusted days gained per minute saved in tPA delivery, per age, sex, and stroke severity.

Supplementary Table II. Studies comparing long-term utility of tPA to no tPA in acute ischemic stroke.

Supplementary Figure I. Histogram of onset-to-treatment time distributions

Supplementary Statistical Methods.

Step1: Generating patient-specific probabilities of achieving specific modified Rankin Scale (mRS) categories at the cohort observed onset-to treatment time (OTT) t_0.

Using a randomly selected 80% sample of the combined observational cohort, we constructed seven separate binary logistic regression models with individual mRS category as the dependent variable and age, baseline National Institutes of Health Stroke Scale (NIHSS), and OTT as independent variables and used those to generate patient-specific predicted probabilities for each mRS. Following a simple normalization scaling procedure to ensure that the sum of probabilities of individual mRS categories for every patient is equal to one, the resulting probabilities were validated on the remaining 20% of the data through simulation. Twenty independent simulation runs were undertaken where each patient in the 20% sample was assigned a mRS according to the patient-specific mRS probability distribution generated earlier and the resulting distribution was compared with the distribution actually observed in the 20% subgroup. Despite a large sample resulting from this simulation, no significant differences in mRS profiles were observed using the chi-square test ($P=0.51$), thus validating the derived probability profiles. The resulting distributions were subsequently used to generate patient-specific probabilities of achieving a given mRS category at the observed OTTs t_0.

Step2: Changing probabilities of achieving mRS 0-1 and mRS 6 over time

To model how changing the onset-to-treatment time affects the probability of mRS0–1 and mRS6 for a specific patient, the graphs expressing the OR of achieving mRS0-1 and mRS6 as a function of OTT between 60 and 360 minutes presented by Lees et al. (Lancet 2010;375(9727): 695–1703) were utilized. As no analytical expressions for the relationships depicted in these graphs were presented by Lees et al (2010), we derived relevant analytic expressions for mRS0-1 and mRS6 curves using the best fit (as judged by R^2) criterion. For both curves the corresponding values were 0.999. The role of these equations is to express the ORs for mRS0-1 and mRS6 as a function of OTT for any value of OTT between 0 and 270 minutes.

The *OR(t)* reported by Lees et al (2010) presents the ratio of odds of achieving mRS0-1 (or, respectively, mRS6), by the patients treated with tPA at a time point *t* and the odds of achieving the same outcome by the patients not treated by tPA.

Assuming that:

    a) for any given patient not treated with tPA, the odds of achieving a specific mRS outcome remain constant over the specified time period;

    b) the probability of achieving mRS0-1 for a non-treated patient is equal to that of a probability for a treated patient at t_{mRS0-1}^{*}=350min (based on Lees et al. 2010);

    c) the probability of achieving mRS6 for a non-treated patient is equal to that of a probability for a treated patient at t_{mRS6}^{*}=165min (based on Lees et al. 2010);

to estimate the probabilities of mRS0-1 and mRS6 at any given time *t*, we used the formula:

$$p(t)=1/\{1+(OR(t_0)/OR(t))*[(1-p(t_0))/p(t_0)]\}$$

where *p(t₀)* represents the probability of mRS0-1 (or, respectively, mRS6) at OTT=*t₀* time, and *OR(t)* represents the fitted value of ORs for mRS0-1 (mRS6) at a given time.

Step3: Estimating probabilities of achieving a specific mRS at any time

As the results reported by Lees et al (2010) only concerned mRS0-1 and mRS6, there was no direct way to use these results to analytically estimate the probabilities for all mRS categories at any given time *t*. In order to achieve this, having previously estimated patient-specific probabilities of achieving mRS0-1 and mRS6 at any given time *t*, we estimated the probabilities of achieving individual mRS categories (both for treated and non-treated patients) so that the ratios of probabilities for achieving individual mRS categories remain identical to those obtained in Step 1 from the logistic regression models based on the observed cohort data. In other words, given patient-specific probabilities of achieving mRS0-1 and mRS6 at any time point *t*, the relative ratios of probabilities of achieving mRS0 and mRS1, as well as the relative ratios of achieving mRS categories 2-5, are assumed to be identical to those at the observed time *t₀* and to remain constant for any time *t* between 0 and 270 min.

Step4: Disability-adjusted life years (DALY) lost

DALY lost is calculated from the formula *DALY=YLL + YLD*, where *YLL* is the years of life lost due to premature death and *YLD* is the years of healthy life lost due to disability. Specific details are presented in the main article.

Step5: Robustness analysis

Two approaches were applied to verify the robustness of the model: one-way analysis and probabilistic analysis. In the one-way analysis, we varied different inputs of the model to their upper and lower 95% CI and evaluated the model robustness with regard to those uncertainties in the inputs. In regard to the uncertainties of the cohort data, we performed a series of one-way analyses by substituting the upper and lower 95%CI value for the coefficients for the age and NIHSS, with one change at a time, generated by the binary logistic regression models. In regard to uncertainties of the pooled analysis by Lees et al (2010), we modified the equations of *OR(t)* for mRS 0-1 and mRS6 in the mRS probability distribution formula to sequentially reflect the upper and lower 95% confidence limits for these two mRS categories as reported by Lees et al (2010). The results are reported in Table in the main article.

Probabilistic robustness analyses were performed by sampling according to an underlying Normal distribution from the feasible space of the mRS0-1 and mRS6 *OR(t)* curves bounded by the 95% confidence limits reported by Lees et al (2010) and reflecting various potential time effects based on the pooled analysis, through set of 1000 independent runs. The resulting probability profiles for all mRS categories were then used to estimate DALYs gained or lost if either the whole cohort or an individual patient would have been treated faster or slower.

Supplementary Table I. Point estimates and 95% prediction intervals for disability adjusted days gained per minute saved in tPA delivery, per sex, age, and stroke severity.

Sex, Age	NIHSS 0-4	NIHSS 5-9	NIHSS 10-14	NIHSS 15-19	NIHSS 20 +
Male					
<45	3.01 (1.02-5.01)	3.40 (1.56-5.24)	3.67 (1.62-5.73)	3.75 (1.91-5.60)	3.83 (2.18-5.48)
45-54	2.30 (0.80-3.79)	2.70 (1.08-4.31)	3.02 (1.26-4.79)	3.17 (1.26-5.08)	2.86 (1.31-4.41)
55-64	1.87 (0.73-3.01)	2.20 (0.97-3.43)	2.49 (1.08-3.90)	2.45 (1.23-3.68)	2.11 (1.06-3.15)
65-74	1.45 (0.72-2.18)	1.61 (0.71-2.52)	1.81 (0.82-2.80)	1.69 (0.81-2.57)	1.19 (0.68-1.69)
75-84	0.97 (0.51-1.44)	1.08 (0.48-1.68)	1.09 (0.56-1.62)	0.91 (0.44-1.37)	0.65 (0.29-1.01)
85 +	0.59 (0.37-0.81)	0.63 (0.29-0.97)	0.57 (0.27-0.86)	0.45 (0.25-0.64)	0.26 (0.14-0.37)
Female					
<45	3.24 (1.80-4.67)	3.79 (1.90-5.67)	4.05 (1.74-6.36)	4.30 (2.57-6.04)	3.86 (2.16-5.55)
45-54	2.54 (1.03-4.05)	2.98 (1.25-4.71)	3.40 (1.33-5.47)	3.55 (1.80-5.29)	3.48 (0.47-6.50)
55-64	2.14 (0.98-3.31)	2.48 (1.17-3.79)	2.89 (1.49-4.29)	2.95 (1.44-4.45)	2.45 (1.05-3.84)
65-74	1.65 (0.78-2.52)	1.91 (0.91-2.91)	2.07 (0.97-3.18)	1.93 (0.96-2.90)	1.66 (0.74-2.58)
75-84	1.16 (0.58-1.75)	1.28 (0.62-1.94)	1.32 (0.70-1.94)	1.09 (0.54-1.64)	0.76 (0.37-1.15)
85 +	0.67 (0.37-0.98)	0.76 (0.46-1.06)	0.62 (0.35-0.89)	0.45 (0.27-0.63)	0.33 (0.15-0.51)

Supplementary Table II. Studies comparing long-term utility of tPA vs. no tPA in acute ischemic stroke.

Study	Population	Time horizon	Discount rate of future utilities	QALYs or DALYs gained per tPA treated patient
Fagan et al. 1998[1]	USA	30 years	0%	0.75
Sinclair et al. 2001[2]	Canada	30 years	3%	3.46
Sandercock et al. 2004[3]	UK	Lifetime	6%	0.04
Mar et al. 2005[4]	Spain	Lifetime	3%	0.53 to 0.66
Ehlers et al. 2007[5]	Denmark	30 years	5%	0.43
Johnston 2010[6]	USA	30 years	0%	0.75
Tung et al. 2011[7]	USA	Lifetime	3%	0.28
NICE TA264[8]	UK	Lifetime	3.5%	0.33
Present paper	Finland and Australia	Lifetime	0%	0.71*
			3%	0.52*

*Median onset-to-treatment of 125 minutes compared to not treating at all.

References

1. Fagan SC, Morgenstern LB, Petitta A, Ward RE, Tilley BC, Marler JR, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology*. 1998;50:883-890.
2. Sinclair SE, Frighetto L, Loewen PS, Sunderji R, Teal P, Fagan SC, et al. Cost-Utility analysis of tissue plasminogen activator therapy for acute ischaemic stroke: a Canadian healthcare perspective. *Pharmacoeconomics*. 2001;19:927-936.
3. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, et al. Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs. *Stroke*. 2004;35:1490-1497.
4. Mar J, Begiristain JM, Arrazola A. Cost-effectiveness analysis of thrombolytic treatment for stroke. *Cerebrovasc Dis*. 2005;20:193-200.
5. Ehlers L, Andersen G, Clausen LB, Bech M, Kjolby M. Cost-effectiveness of intravenous thrombolysis with alteplase within a 3-hour window after acute ischemic stroke. *Stroke*. 2007;38:85-89.
6. Johnston SC. The economic case for new stroke thrombolytics. *Stroke*. 2010;41:S59-62.
7. Tung CE, Win SS, Lansberg MG. Cost-effectiveness of tissue-type plasminogen activator in the 3- to 4.5-hour time window for acute ischemic stroke. *Stroke*. 2011;42:2257-2262.
8. National Institute for Health and Clinical Excellence (NICE). TA264 Alteplase for treating acute ischaemic stroke (review of technology appraisal guidance 122). [published online September 26, 2012] http://guidance.nice.org.uk/TA264/Guidance/pdf/English. Accessed January 23, 2014

Supplementary Figure I. Histogram of onset-to-treatment time distributions.