Years of Disability-Adjusted Life Gained as a Result of Thrombolytic Therapy for Acute Ischemic Stroke

Keun-Sik Hong, MD, PhD; Jeffrey L. Saver, MD

Background and Purpose—Disability-adjusted life year (DALY) metric reflects years of healthy life lost because of living with disability and years of life lost because of premature mortality. Widely used in epidemiological analyses, DALY has not been applied to acute stroke trials.

Methods—From previous studies, we derived, for each modified Rankin Scale level, disability weights, disability-linked mortality hazard ratios, and age-specific life expectancies. We then analyzed patient level data from the 2 publicly available National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator trials. For each subject, we abstracted age, treatment assignment, and 3-month modified Rankin Scale outcome and calculated the DALYs lost resulting from the qualifying stroke.

Results—The disability-linked hazard ratios for premature annual mortality for a modified Rankin Scale score of 0 to 5 were 1.53, 1.52, 2.17, 3.18, 4.55, and 6.55, respectively. In the NINDS recombinant tissue plasminogen activator trials, DALYs (mean±SE) lost as a result of the qualifying stroke were substantially less with recombinant tissue plasminogen activator than with placebo (4.64±0.17 versus 5.91±0.21; P<0.0001), a finding that remained robust after adjustment for baseline prognostic factors. When DALYs gained were apportioned to the 29% of patients experiencing any benefit from lytic therapy, each patient gained an average of 4.4 DALYs. DALY analysis showed greater power than dichotomized modified Rankin Scale analysis in discriminating treatment effects overall and in patients ≥70 years of age.

Conclusion—For patients who benefit from treatment, <3-hour thrombolytic therapy adds the equivalent of 4.4 years of healthy life, free of disability. The DALY metric provides a continuous scale that increases statistical power, is intuitively understandable, and is applicable to a wide range of conditions and treatments. (Stroke. 2010;41:471-477.)

Key Words: DALY ■ NINDS rt-PA trial ■ thrombolysis ■ acute stroke trial ■ outcome

For diseases that cripple as well as kill, mortality measures alone offer an incomplete guide to treatment decisions by patients, clinicians, and policy-makers. Functional outcome measures are a critical additional index of therapeutic effect. However, a potentially bewildering variety of functional scales are used in clinical trials to assess outcomes for different diseases and performance domains. Consequently, interpretation of scale results is challenging for patients and policy-makers, and comparison of treatment benefits across disease states is difficult. Clinical trials and comparative effectiveness studies urgently need an outcome metric that incorporates both death and disability that is intuitively accessible to lay decision-makers and that can be used as a uniform benchmark to all therapies for all conditions.

One promising approach is to apply to clinical trial results the disability-adjusted life year (DALY) metric. The World Health Organization originally developed the DALY to measure the relative and total global burden of all diseases with a common metric. One DALY is 1 year of healthy life, free of disability. The DALY metric integrates both mortality (years of life lost [YLL] because of premature death) and functional outcome (years of healthy life lost because of living with disability [YLD]). The DALY was first developed as a tool to assess the global epidemiological burden of hundreds of diseases. Subsequently, it has been used to analyze treatment intervention effects at coarse, large-scale population levels. However, DALY analysis has not been previously applied to index more fine-grained effects observed in individual clinical trials.

This investigation was performed to apply the DALY metric to quantifying the benefit of <3-hour IV thrombolytic therapy for ischemic stroke.

Methods

Patient level data from the 2 publicly available National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) trials were analyzed. For each enrolled subject, we abstracted age, treatment assignment, and final global disability outcome at 3 months, as measured by the modified Rankin Scale (mRS). From these data, we calculated for each patient the DALYs lost because of the stroke that were not averted by the
trial treatment. Each patient’s DALYs lost is given by the formula: \( \text{DALY} = \text{YLL} + \text{YLD} \).

### Years of Life Lost

The YLL for each patient is the difference between the patient’s age-specific life expectancy without stroke and the patient’s age-specific life expectancy given his or her observed poststroke final disability outcome. The full technical formula for YLL also includes discount rate and age-weighting factors. The discount rate reflects the standard health policy modeling assumption that patients value a year of healthy life gained in the future less than a year of healthy life gained in the immediate present, setting the discount rate to 3% annually. The age-weighting factor reflects the standard health policy assumption that patients assign different values to different years of life, higher in young adult ages than in infancy or old ages. The complete equation for YLL is:

\[
\text{YLL} = \text{DKC}_{\text{er}A} \left( e^{rL} - e^{rA} \right) \left[ 1 - \left( 1 - e^{-rA} \right) \right] - \left[ 1 - \left( 1 - e^{-rL} \right) \right] - 1,
\]

where \( K \) indicates age-weighting modulation factor (\( K = 1 \) or 0); \( \beta \), parameter from age-weighting function (\( \beta = 0.04 \) or 0); \( r \), discount rate (\( r = 0.03 \) or 0); \( C \), constant (\( C = 0.1658 \)); \( A \), age of death; \( L \), life expectancy of general population at age \( A \).

Each patient’s age-specific life expectancy without stroke was taken from the 2004 US life table appropriate for that patient’s gender and race.\(^6\) Life tables were available for white and black race categories. For Asian and other race categories for which race-specific tables were not available, the life expectancies for whites were used.

To determine each patient’s age-specific life expectancy given their observed poststroke final disability outcome, we conducted a systematic literature review that identified 2 studies providing life expectancy data indexed to mRS stroke outcomes: the UK Lothian Cohort Study and the Swedish Riks-Stroke Cohort Study.\(^7,8\) Both found that long-term life expectancy decreases monotonically as mRS level increases. We calculated the mortality rate hazard ratios (HRs) of each mRS level compared with the lowest mRS level in each study and then further adjusted these by calculating the HR between the lowest mRS level and the general population mortality rate in the Swedish and UK populations at ages 68 through 70.

In the main analysis of this study, we used the mean of the HRs derived from the Swedish and UK studies.

### YLL Because of Disability

As with YLL, the full technical formula for YLD also includes discount rate (\( r \)) and age-weighting (\( K \), \( \beta \)) factors. The complete equation for YLD is:

\[
\text{YLD} = \text{DKC}_{\text{er}A} \left( e^{rL} - e^{rA} \right) \left[ 1 - \left( 1 - e^{-rA} \right) \right] - \left[ 1 - \left( 1 - e^{-rL} \right) \right] - 1.
\]

Figure 1. DALY curves of white female stroke patients with various mRS levels.
Table 2. Comparison of DALYs Between t-PA and Placebo Groups

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>Unadjusted DALY, Mean±SE</th>
<th>Adjusted DALY*, Mean±SE</th>
<th>Adjusted DALY, Mean±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t-PA</td>
<td>Placebo</td>
<td>t-PA</td>
</tr>
<tr>
<td>DALY[3, 1]</td>
<td>4.64±0.17</td>
<td>5.91±0.21</td>
<td>1.28 (0.74–1.81)</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td>8.13±0.21</td>
<td>9.59±0.23</td>
<td>1.46 (0.85–2.06)</td>
</tr>
<tr>
<td>DALY[0, 1]</td>
<td>6.74±0.25</td>
<td>8.57±0.32</td>
<td>1.83 (1.04–2.63)</td>
</tr>
<tr>
<td>DALY[0, 0]</td>
<td>12.04±0.30</td>
<td>14.21±0.35</td>
<td>2.16 (1.26–3.07)</td>
</tr>
</tbody>
</table>

UK population only

| DALY[3, 1]       | 4.49±0.18                | 5.83±0.22               | 1.34 (0.79–1.89)         | 5.70±0.28               | 6.63±0.28               | <0.0001                 | 0.93 (0.48–1.39)         |
| DALY[3, 0]       | 7.89±0.22                | 9.44±0.24               | 1.56 (0.92–2.19)         | 9.25±0.34               | 10.44±0.34              | <0.0001                 | 1.19 (0.64–1.75)         |
| DALY[0, 1]       | 6.51±0.25                | 8.44±0.33               | 1.93 (1.12–2.73)         | 8.12±0.36               | 9.31±0.36               | <0.0001                 | 1.19 (0.61–1.77)         |
| DALY[0, 0]       | 11.69±0.30               | 14.01±0.36              | 2.32 (1.39–3.24)         | 13.46±0.41              | 14.92±0.42              | <0.0001                 | 1.47 (0.79–2.14)         |

Swedish population only

| DALY[3, 1]       | 4.76±0.17                | 6.00±0.21               | 1.23 (0.71–1.76)         | 5.91±0.26               | 6.74±0.26               | <0.0001                 | 0.82 (0.40–1.24)         |
| DALY[3, 0]       | 8.33±0.20                | 9.72±0.22               | 1.39 (0.81–1.97)         | 9.58±0.31               | 10.60±0.31              | <0.0001                 | 1.03 (0.52–1.53)         |
| DALY[0, 1]       | 6.93±0.24                | 8.69±0.32               | 1.77 (1.08–2.55)         | 8.44±0.32               | 9.45±0.33               | <0.0001                 | 1.01 (0.49–1.54)         |
| DALY[0, 0]       | 12.30±0.29               | 14.38±0.35              | 2.08 (1.19–2.97)         | 13.91±0.36              | 15.12±0.36              | <0.0001                 | 1.21 (0.62–1.80)         |

DALY[3, 1] indicates age-weighting and future discount rate applied; DALY[3, 0], only future discount rate applied; DALY[0, 1], only age weighting applied; DALY [0, 0], neither age weighting nor future discount rate applied.

*Adjusted for age, NIHSS, age×NIHSS, onset to treatment, history of diabetes mellitus, preexisting disability, center, and trial part.
P value; Mann–Whitney test for univariate analysis and ANCOVA for multivariate analysis.

DALYs=8.21; and if a 68-year-old white woman has a stroke resulting in mild disability and vocational impairment at 3 months (mRS=2), YLL=2.73, YLD=1.48, and total DALYs=4.21.

Sensitivity Analyses

Criticisms have been made on ethical grounds of the standard DALY formulas for reducing the relative value of future years (discounting) and for reducing the relative value of years experienced in infancy and in old age (age weighting).10 To explore the effect of removing these assumptions, we calculated 3 additional sets of DALYs in which future discounting was not used, age weighting was not used, and neither future discounting nor age weighting were used. We also performed 2 sensitivity analyses for different possible life expectancy estimates using the data from the UK Lothian stroke cohort alone and the Swedish Riks-Stroke cohort alone, rather than the average of the 2. To examine the effect of the DALY approach in subgroup analysis, we also analyzed NINDS study outcomes separately for patients <70 years of age and ≥70 using both simple dichotomization of the mRS at 0 to 1 versus 2 to 6 and 0 to 2 versus 3 to 6 and the DALY method.

Statistical Analysis

The Mann–Whitney test was used to compare the DALYs lost between the rt-PA and placebo groups for univariate analyses. An ANCOVA test was used to adjust for age, baseline National Institutes of Health (NIH) Stroke Scale, interaction between age and NIH Stroke Scale, onset to treatment, history of diabetes, preexisting disability, centers, and trial part 1 or part 2. For the ANCOVA test, natural logarithmic transformation was applied because of unequal variances of DALYs between the 2 groups.

Because the benefit of fibrinolytic therapy is not experienced uniformly by all patients, but rather some are helped, some harmed, and some not affected, we performed an additional distribution analysis. In this analysis, the DALYs gained as a result of therapy, instead of being divided equally among all treated patients, were divided among 29% of patients, the proportion previously shown to result in mild disability and vocational impairment at 3 months.
mRS levels. At the extremes, mRS scores of 0 and 1 yield nearly the same modest loss of DALYs, whereas mRS scores of 5 and 6 yield nearly the same substantial loss. Levels 2 and 3 of the mRS yield about one-third the loss of DALYs as mRS scores of 5 and 6, whereas an mRS score of 4 yields about two-thirds the loss of DALYs as mRS scores of 5 and 6. These relative relationships are stable across the sensitivity analyses in which future discounting and age weighting are not used. In the NINDS trials, a mild treatment group imbalance in age was noted, with mean age in the placebo arm lower than the rt-PA arm (rt-PA, 68.0±11.3 versus placebo; 65.9±11.9; P<0.029), but the groups were not substantially imbalanced in different age categories (supplemental Figure I, available online at http://stroke.ahajournals.org). These findings were incorporated into analyses adjusting for covariates including age and analyses of individual age strata.

DALYs Saved by <3-Hour IV rt-PA Treatment
In the treatment effect analysis, patients receiving placebo experienced an average loss of 5.91 (±0.21 SE) DALYs as a result of their stroke, whereas patients treated with rt-PA experienced an average loss of 4.64 (±0.17) DALYs. Accordingly, rt-PA treatment was associated with an average gain of 1.28 DALYs (95% CI, 0.74 to 1.81; P<0.0001; Table 2). Rt-PA treatment shifted the distribution of DALYs lost, with a substantial increase in the proportion of patients losing <4 DALYs because of their stroke (Figure 2). As shown in Table 2, the treatment effect magnitude was stable when the analysis was adjusted for group differences at baseline in outcome prognostic factors and when the mRS-specific life expectancies observed in the UK and the Swedish cohorts were used alone rather than averaged. Adjustment for baseline prognostic factors reduced the rt-PA-associated DALYs averted to a modest degree. However, when future discounting and age weighting were removed, the treatment effect was magnified (Table 2; Figure 2).

The distribution analysis took into account findings from a previous joint outcome table analysis indicating that the benefit of rt-PA is not uniform across all treated patients; rather, for every 100 patients treated, ∼32 have a better final outcome and 3 a worse final outcome, resulting in net benefit in 29 per 100 patients. Assigning the DALY benefit to these patients indicated that each patient who benefits from rt-PA therapy gains an average of 4.41 (±1.28/0.29) DALYs as a result.

DALYs Saved in Age Subgroups
The results of analyses in the age subgroups of <70 years and ≥70 are shown in Tables 3 and 4. Using simple dichotomized analysis of the mRS (Table 3), rt-PA beneficial effects reached conventional levels of significance for patients <70 years of age but failed to do so for older patients in 3 of 4 adjusted and unadjusted analyses at mRS dichotomizations at 0 to 1 and 0 to 2. In contrast, the DALY analysis showed benefit for older patients in an adjusted analysis and a strong trend in unadjusted analysis (Table 4), findings that were robust across discount rate and age-weighting sensitivity analyses. The DALY analysis also provided insight into the different degree of benefit conferred by therapy in these age groups, with an average gain of 1.61 DALYs per patient among younger subjects and an average gain of 0.34 DALYs among older subjects.
Daly analysis of the two NINDS rt-PA trials provides additional evidence that <3-hour fibrinolytic therapy for acute ischemic stroke confers substantial benefit for patients. On average, patients receiving active, lytic therapy experienced an average of >1 year and 3 months of additional healthy life. Taking into account the likely clustering of benefits, fibrinolytic therapy is projected to confer an average of 4 years and 5 months of healthy life on the nearly one-third of patients who benefit from therapy. The validity of these findings is supported by consistent results in unadjusted analyses and analyses adjusted for baseline prognostic factors. The treatment effect is modestly increased if standard health policy modeling assumptions of future discounting and age weighting are not used.

In addition, this study provides a proof of concept demonstration that the DALY metric can be applied to enhance the interpretation of findings of randomized clinical trials. The DALY metric offers several advantages for delineating treatment effects. For example, difficulty expressing treatment effects. For example, difficulty expressing treatment effects. For example, difficulty expressing treatment effects. For example, difficulty expressing treatment effects. For example, difficulty expressing treatment effects.

**Discussion**

DALY analysis of the 2 NINDS rt-PA trials provides additional evidence that <3-hour fibrinolytic therapy for acute ischemic stroke confers substantial benefit for patients. On average, patients receiving active, lytic therapy experienced an average of >1 year and 3 months of additional healthy life. Taking into account the likely clustering of benefits, fibrinolytic therapy is projected to confer an average of 4 years and 5 months of healthy life on the nearly one-third of patients who benefit from therapy. The validity of these findings is supported by consistent results in unadjusted analyses and analyses adjusted for baseline prognostic factors. The treatment effect is modestly increased if standard health policy modeling assumptions of future discounting and age weighting are not used.

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In addition to severity of disability, duration of disability and life years lost because of premature death linked to disability are critically important aspects of stroke outcomes that matter greatly to patients, families, and society. However, standard stroke trial outcome measures are one-time, snapshot metrics that fail to take these long-term sequelae of stroke into account. A particular strength of health-adjusted life year metrics, such as the DALY or quality-adjusted life year (QALY), is that they are explicitly designed to reflect both premature mortality resulting from disease as well as the reduced human flourishing possible during a patient’s remaining years of life because of disease.

The impact of poststroke disability level on subsequent mortality is profound. The studies identified in our systematic review showed that moderate poststroke disability doubles, and severe poststroke disability multiplies nearly 7-fold the subsequent annual mortality rate among stroke survivors. Stroke can occur at any age. Younger stroke survivors will live with the sequelae of their stroke longer than the elderly, and therefore will have more years of their lives curtailed by disability. The DALY metric captures the greater burden to society, family, and the patient when a stroke occurs earlier in life. Among patients with an identical mRS score, younger patients will have larger DALY scores than older patients.

In addition to allowing translation of trial results into benefits and risk values useful for individual treatment decision-making, the DALY permits straightforward projection of treatment effects observed in a given clinical trial onto large populations. For example, based on the findings in this study, and given an annual incidence of ischemic stroke of 690,000 in the United States, it can be projected that increasing the <3-hour IV rt-PA treatment rate from 2% to 5% would provide the US population with 26,400 more years of healthy life each year. DALY analysis of clinical trials can aid health system planners and policy-makers.

No previous analysis of the NINDS rt-PA trials has been performed using the DALY metric. Our findings complement and extend a previous study that analyzed the NINDS rt-PA trials using a related health-adjusted life year metric: QALY. Our analysis found a 2-fold greater benefit of rt-PA treatment than the previous study. Rt-PA treatment was associated with a gain of 1280 DALYs per 1000 patients treated; in the previous study, rt-PA treatment generated an additional 564 QALYs per 1000 patients treated.

This discrepancy largely reflects differences in poststroke life expectancy estimates used in the 2 studies. In the absence of any available Rankin-specific data at the time, the previous study projected that long-term mortality rates beyond the first poststroke year are the same across all 5 levels of mRS poststroke disability. Subsequently reported studies have now shown this assumption to be incorrect: long-term mortality rates increase substantially with increasing mRS levels. A more minor source of variation between the 2 studies is modest differences in valuation of health states. QALYs are derived from patient valuations of outcome states, whereas DALYs are derived from health provider valuations of outcome states. Each approach has advantages. QALY utility values for health states directly reflect the inner experience of disease and the values of patients, but patient ratings of multiple disease states may not be fully reliable because the raters are only directly familiar with one specific disease and disability level. DALY disability weights for health states reflect the direct but external experience of health providers, but the raters are familiar with diverse diseases and disease state intensities. Whereas DALY disability weight values are available for all 6 mRS levels achievable by stroke survivors, mRS-specific quality utility values are not. The previous study took utility value data on 3 non-mRS poststroke states, projected them onto the mRS, and interpolated 3 additional utility values using healthcare professional judgment. Nonetheless, despite the different derivations, the DALY disability weights assigned by health providers that we used and the QALY utility values derived by mixed patient and provider methods used in the previous study were generally comparable.

This study has limitations. We applied disability-specific mortality rates derived from studies of the British and Swedish populations to clinical trial findings performed in a US population. Ideally, the mortality rates would have been generated from a US stroke cohort study, but these data were not available. Data were also not available to indicate whether patient age modifies the effect of disability in increasing the mortality HR. Consequently, for each mRS disability level, we applied the same mortality HR across all patient ages.

Because the DALY values of the 2 treatment groups showed non-normal distributions, we applied nonparametric tests for univariate analyses. However, for multivariate analysis, there is no widely accepted statistical analysis of nonparametric test that can be used instead of ANCOVA. We applied natural logarithmic transformation, which increased the number of distributions meeting normality criteria, attenuating but not eliminating this difficulty.

The NINDS rt-PA trials had a higher proportion of patients treated in the early, <90-minute time epoch than typically occurs in clinical practice. Treatment is more effective in this early time frame. Our findings apply to populations matching the NINDS rt-PA trial time to treatment distribution and mildly overestimate the benefit to be expected in a typical practice setting.

In conclusion, DALY analysis confirms that <3-hour thrombolytic therapy is a treatment of substantial benefit for individual patients and for society. For the nearly one-third of patients who benefit from treatment, thrombolytic therapy adds the equivalent of 4.4 years of healthy life, free of disability. The DALY metric is a continuous outcome scale that can increase statistical power in analyzing clinical trial results, is intuitively understandable, and is applicable to a wide range of conditions and treatments.

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References

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