Economic evaluation of intravenous alteplase for stroke with the time of onset between 4.5 and 9 hours

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ABSTRACT

Background A clinical trial proved the clinical effectiveness of perfusion imaging-guided intravenous thrombolysis with alteplase for patients with acute ischemic stroke (AIS) with the time of onset between 4.5 and 9 hours. This study aimed to assess the lifetime cost-effectiveness of alteplase versus placebo from the perspective of Chinese and United States (US) healthcare payers.

Methods A decision-analytic model was built to estimate lifetime costs and quality-adjusted life-years (QALYs) associated with alteplase or placebo. Model inputs were extracted from published sources. Incremental costs, incremental QALYs, and incremental cost-effectiveness ratio (ICER) were calculated to evaluate the base-case scenario. One-way and probabilistic sensitivity analyses were performed to evaluate uncertainty in the results.

Results In China, alteplase yielded an additional lifetime QALY of 0.126 with an additional cost of Chinese Yuan (¥) ¥9552 compared with placebo, and the ICER was ¥83 950 (US$12 157)/QALY. In the US, alteplase had a higher QALY (difference: 0.193) with a lower cost (difference: US$−2024) compared with placebo. In probabilistic sensitivity analyses, alteplase had a 42.54% to 78.3% probability of being cost-effective compared with placebo in China when the willingness-to-pay (WTP) threshold ranged from ¥72 447/QALY to ¥217 341/QALY. In the US, alteplase had a 93.47% to 93.57% probability of being cost-effective under the WTP threshold of US$100 000/QALY to US$150 000/QALY. These findings remained robust under one-way sensitivity analysis.

Conclusion For patients with AIS with a time of onset between 4.5 and 9 hours, perfusion imaging-guided intravenous alteplase was likely to be cost-effective in China and was cost-effective in the US when compared with placebo.

INTRODUCTION

Intravenous (IV) thrombolysis with alteplase, which has been approved by the United States (US) Food and Drug Administration (FDA) for two decades, is effective in reducing disability caused by acute ischemic stroke (AIS).1 However, current guidelines for AIS limit the time of initiating IV alteplase within 4.5 hours after the onset of stroke.2 Perfusion-diffusion magnetic resonance imaging (MRI) and computed tomography (CT) perfusion have been used to identify patients with potential viable brain tissue beyond 4.5 hours after stroke onset and these patients might benefit from reperfusion by means of thrombolysis.3 Recently, a multicenter randomized trial (the EXTEND trial, NCT00887328 and NCT01580839) found that for patients with AIS with the time of onset between 4.5 and 9 hours, IV alteplase guided by perfusion imaging was associated with better functional outcomes than the placebo. However, there were more cases of symptomatic intracranial hemorrhage (ICH) in the alteplase group than in the placebo group.4 In this study, we aim to evaluate the lifetime cost-effectiveness of IV alteplase guided by perfusion imaging for patients with AIS with the time of onset between 4.5 and 9 hours from the perspective of healthcare payers in China and the US.

METHODS

Model overview

This was a modeling study without the involvement of real human subjects and ethical approval from our institutional review board was waived. The study was conducted according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines (online supplemental table 1). A decision-analytic model was developed with TreeAge Pro 2020 (Williamstown, MA, USA) to evaluate the cost-effectiveness of IV alteplase versus placebo. The target population was analogous to that of the EXTEND trial. Patients were 71 years on average (range 60–80 years). They were assumed to have AIS with the time of stroke onset between 4.5 and 9 hours and have hypoperfused but salvageable regions of brain detected on automated perfusion imaging.

The structure of the model is shown in figure 1. In the first 3 months, patients entered the model to receive either IV alteplase or placebo and then moved to one of the seven possible health states based on the degree of disability as assessed by the modified Rankin Scale (mRS) score. After the first 3 months, a Markov state-transition model was used to simulate disease progression until all patients reached 99 years old. The cycle length of the Markov model was 3 months. After each cycle, patients would either stay in the same state, have a recurrent stroke, or die from other causes. The absorbing state was death (mRS 6) from stroke...
Ischemic stroke or other causes. The occurrence of ICH was considered in the model with additional costs and disutility.

**Transition probabilities**

Clinical parameters were derived from the EXTEND trial, institutional database, or published literature [Table 1]. The transition probabilities to mRS scores during the first 3 months were extracted directly from the EXTEND trial.4 The annual rate of stroke recurrent was 0.118 among the Chinese population5 and 0.05 among the US population.6 The death rate after recurrent stroke was 0.210 and 0.190 in China and the US, respectively.7 Like other similar studies,8–11 we assumed a constant recurrent rate in our study. Patients who survived after the recurrent stroke were assumed to be reallocated equally among health states of equal and greater disability.10 11 The background age-specific death rate was derived from the most recent published census of China12 and the US Life Tables.13 Disabled patients tend to have increased mortality and the death rate was adjusted according to the hazard ratios for each mRS health state.14 Annual transition probabilities were converted to 3-month probabilities according to the standard formula if necessary.15

**Costs**

This study was conducted from the perspective of healthcare payers and only direct costs were considered. In China, the additional cost of IV alteplase, cost of acute stroke treatment and ICH treatment, and posthospitalization cost were derived from another cost-effectiveness study which was based on the database of Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) and the China National Stroke Registry (CNSR).5 We assumed that all patients used MRI for perfusion imaging and the images were processed by the RAPID automated software (iSchemaView) according to the EXTEND trial. The cost of MRI was obtained from previous literature16 and the cost of image processing was derived from our institutional database. The cost of recurrent stroke was assumed to be the same across two different treatment arms since the type and severity of the recurrent stroke are unlikely to be predicted. We derived the cost of recurrent stroke from our institutional database as the mean expected cost to treat an average stroke without thrombolysis or thrombectomy.

In the US, the cost of MRI was obtained from the Centers for Medicare & Medicaid Services (CPT code 70557).17 Cost of acute stroke treatment, cost of ICH treatment, and posthospitalization cost were extracted from a previous study.8 These costs were validated and used by other similar cost-effectiveness studies.8–10 The additional cost of IV alteplase and the cost of recurrent stroke were reported previously.8 The average cost of imaging processing with RAPID software was US$12,000.19 We used a range of ±25% of the base-case value for the costs to account for the uncertainty. All costs were inflated to 2020 prices using the medical care component of the consumer price index if necessary.20 21

**Utility**

Health-related quality of life value (utility score) ranged from 0 to 1 and was assigned to all health states. A utility score of 1 means perfect health and 0 means death. Corresponding utility scores were multiplied by the life years spent in a particular health state and summed over the lifetime of the patient to obtain quality-adjusted life-years (QALYs). Currently, the Chinese population-specific utility score for different mRS scores was available in the previous literature. The same utility scores were used in China and the US, which were obtained from a previous validation study.14 Some other studies also used the same values.8 10 Patients with ICH were associated with a disutility of 0.38.22 A discount rate of 3% per year was applied for both costs and utilities.23

**Measuring cost-effectiveness**

No statistical tests were conducted and no level of statistical significance was relevant to our analysis. The base-case analysis
### Table 1  Base-case values and plausible ranges of input parameters

| Model input                                                                 | Base-case value | Range      | Distribution | Source |
|------------------------------------------------------------------------------|-----------------|------------|--------------|--------|
| Outcomes at first 3 months for patients with alteplase                       |                 |            |              |        |
| mRS 0                                                                         | 0.124           | 0–1        |              | 4      |
| mRS 1                                                                         | 0.230           |            |              |        |
| mRS 2                                                                         | 0.141           |            |              |        |
| mRS 3                                                                         | 0.133           |            |              |        |
| mRS 4                                                                         | 0.133           |            |              |        |
| mRS 5                                                                         | 0.124           |            |              |        |
| mRS 6                                                                         | 0.115           |            |              |        |
| Outcomes at first 3 months for patients with placebo                         |                 |            |              |        |
| mRS 0                                                                         | 0.107           | 0–1        | Dirichlet    | 4      |
| mRS 1                                                                         | 0.188           |            |              |        |
| mRS 2                                                                         | 0.134           |            |              |        |
| mRS 3                                                                         | 0.143           |            |              |        |
| mRS 4                                                                         | 0.214           |            |              |        |
| mRS 5                                                                         | 0.125           |            |              |        |
| mRS 6                                                                         | 0.089           |            |              |        |
| Probability of ICH with alteplase                                             | 0.062           | 0.030–0.122| Beta, SD 0.023| 4      |
| Probability of ICH with placebo                                              | 0.009           | 0.002–0.049| Beta, SD 0.012| 4      |
| Annual probability of recurrent stroke in China                              | 0.118           | 0.112–0.124| Beta, SD 0.003| 5      |
| Death after recurrent stroke in China                                         | 0.210           | 0.189–0.232| Beta, SD 0.011| 5      |
| Annual probability of recurrent stroke in the US                              | 0.050           | 0.040–0.060| Beta, SD 0.005| 6      |
| Death after recurrent stroke in the US                                        | 0.190           | 0.100–0.300| Beta, SD 0.05 | 7      |
| Death hazard ratios                                                           |                 |            |              |        |
| mRS 0                                                                         | 1               | 1–1.2      | Lognormal, SD 0.050 | 14 |
| mRS 1                                                                         | 1               | 1–1.2      | Lognormal, SD 0.050 | 14 |
| mRS 2                                                                         | 1.11            | 0.89–1.3   | Lognormal, SD 0.103 | 5 |
| mRS 3                                                                         | 1.27            | 1.02–1.52  | Lognormal, SD 0.125 | 5 |
| mRS 4                                                                         | 1.71            | 1.37–2.05  | Lognormal, SD 0.170 | 5 |
| mRS 5                                                                         | 2.37            | 1.90–2.84  | Lognormal, SD 0.235 | 5 |
| Cost in China (¥)                                                             |                 |            |              |        |
| MRI                                                                          | 600             | ±25%       | Gamma, SD 75 | 16 |
| Imaging processing with RAPID software                                        | 1000            | ±25%       | Gamma, SD 125 | Institutional database |
| Additional cost of rtPA treatment                                              | 13 886          | 10 751–16 194| Gamma, SD 1361 | 5 |
| Acute stroke (mRS 0–1)                                                        | 12 214          | 7055–15 379| Gamma, SD 2081 | 5 |
| Acute stroke (mRS 2–5)                                                        | 16 149          | 8875–21 177| Gamma, SD 3076 | 5 |
| Acute stroke (death)                                                          | 13 840          | 6503–18 293| Gamma, SD 2948 | 5 |
| ICH                                                                           | 2949            | 641–6155   | Gamma, SD 1379 | 5 |
| Annual posthospitalization (mRS 0–1)                                          | 8684            | 2600–11 077| Gamma, SD 2119 | 5 |
| Annual posthospitalization (mRS 2–5)                                          | 13 213          | 3323–16 616| Gamma, SD 3323 | 5 |
| Recurrent stroke                                                              | 18 000          | ±25%       | Gamma, SD 2250 | Institutional database |
| Cost in the US (US$)                                                          |                 |            |              |        |
| MRI                                                                          | 816             | ±25%       | Gamma, SD 102 | 17 |
| Imaging processing with RAPID software                                        | 12 000          | ±25%       | Gamma, SD 1500 | 19 |
| Additional cost of alteplase treatment                                         | 8619            | 4309–12 928| Gamma, SD 2155 | 8 |

Continued
Ischemic stroke was performed with the mean value of all input parameters. We measured the incremental cost-effectiveness ratio (ICER) which was calculated as the incremental cost per additional QALYs gained. There is no standard willingness-to-pay (WTP) threshold in China and we used the 1–3 × gross domestic product (GDP) per capita according to the suggestion of the World Health Organization (WHO). This WTP threshold corresponded to ¥72 447 (US$10 500)/QALY to ¥217 341 (US$31 499)/QALY in the year 2020. In the US, the WTP threshold was recommended to be US$100 000/QALY to US$150 000/QALY.

Sensitivity analysis
One-way sensitivity analyses were performed to identify key parameters related to the robustness of the results by varying one parameter while keeping others fixed. The ranges of different parameters are provided in table 1. Probabilistic sensitivity analysis was also performed with all parameters varying simultaneously. In this process, we assigned a distribution to each parameter. In all, costs were assigned with a gamma distribution, and transition probabilities and utilities were assigned with a beta or Dirichlet distribution. A total of 10 000 iterations were carried out to evaluate the impact of uncertainty. A cost-effectiveness acceptability curve based on the results of 10 000 iterations was generated to evaluate the likelihood that IV alteplase would be considered cost-effective at different WTP thresholds.

### Table 1

| Model input                    | Base-case value | Range        | Distribution | Source |
|-------------------------------|-----------------|--------------|--------------|--------|
| Acute stroke (mRS 0–3)        | 9268            | 4633–13 901  | Gamma, SD 2317 | 18     |
| Acute stroke (mRS 4–5)        | 14 115          | 7057–21 171  | Gamma, SD 3529 | 18     |
| Acute stroke (death)          | 16 457          | 8228–24 685  | Gamma, SD 4114 | 18     |
| ICH                           | 3399            | 2719–4079    | Gamma, SD 340  | 18     |
| Annual posthospitalization (mRS 0–3) | 8157 | 4078–12 235 | Gamma, SD 2039 | 18     |
| Annual posthospitalization (mRS 4–5) | 22 139 | 11 070–33 209 | Gamma, SD 5535 | 18     |
| Recurrent stroke              | 25 143          | 12 572–37 715| Gamma, SD 6286 | 18     |

| Utility                       |                 |              |              |        |
|-------------------------------|-----------------|--------------|--------------|--------|
| mRS 0                         | 0.80            | 0.64–1       | Beta, SD 0.090 | 14     |
| mRS 1                         | 0.80            | 0.64–1       | Beta, SD 0.090 | 14     |
| mRS 2                         | 0.65            | 0.52–0.78    | Beta, SD 0.065 | 14     |
| mRS 3                         | 0.50            | 0.4–0.6      | Beta, SD 0.050 | 14     |
| mRS 4                         | 0.35            | 0.28–0.42    | Beta, SD 0.035 | 14     |
| mRS 5                         | 0.20            | 0.16–0.24    | Beta, SD 0.020 | 14     |
| Death                         | 0.00            | NA           | NA           | NA     |
| Disutility of ICH             | 0.38            | 0.30–0.46    | Normal, SD 0.040 | 22     |
| Discount rate                 | 0.03            | 0–0.08       | Beta, SD 0.020 | 23     |

ICER, intracranial hemorrhage; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NA, not available; rt-PA, recombinant tissue-type plasminogen activator; SD, standard deviation; US, United States.

### Table 2

| Parameter           | China          | United States | Difference |
|---------------------|----------------|---------------|------------|
|                     | Alteplase      | Placebo       | Difference |
| Costs               | ¥122 223       | ¥111 623      | ¥9552      |
| QALY                | 3.474          | 3.348         | 0.126      |
| ICER                | ¥83 950        | Negative      |            |

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; US, United States.

### RESULTS

#### Base-case analysis

The results of base-case analysis are summarized in table 2. In China, alteplase was associated with an additional cost of ¥10 600 with an additional QALY of 0.126 over a lifetime when compared with placebo, and the ICER was ¥83 950 (US$12 167)/QALY. In the US, alteplase had a higher QALY (difference: 0.193) and a lower cost (difference: ¥−2024) over a lifetime when compared with placebo.

#### Sensitivity analysis

The results of one-way sensitivity analysis were presented in the tornado diagram. In China, the ICER was particularly sensitive to utility score of mRS 1, discount rate, average age of patients, posthospitalization cost for mRS 2–5, additional cost of alteplase, utility score of mRS 4, probability of ICH with IV alteplase, and posthospitalization cost for mRS 0–1 (figure 2). In the US, the ICER was more sensitive to posthospitalization cost for mRS 4–5, additional cost of alteplase, average age of patients, posthospitalization cost for mRS 0–3, and discount rate (figure 3). All the ICERs were below their corresponding WTP thresholds in China and the US.

According to the probabilistic sensitivity analysis, alteplase had a 42.54% to 78.3% probability of being cost-effective when compared with placebo.
Y72 447/QALY to Y217 341/QALY in China (figure 4, online supplemental figures 1, 2). In the US, alteplase had a 93.47% to 93.57% probability of being cost-effective under the WTP threshold of US$100 000/QALY to US$150 000/QALY (figure 5, online supplemental figure 3, 4).

**DISCUSSION**

For patients with AIS with the time of stroke onset between 4.5 and 9 hours, perfusion imaging-guided IV alteplase increased QALYs by 0.126 and 0.193 over a lifetime in China and the US, which were near 1.5 and 2.3 months of perfect health at excellent value. In China, IV alteplase had an additional cost of Y10 600 when compared with placebo over a lifetime, yielding an ICER of Y83 950/QALY and it was cost-effective under the current Chinese WTP threshold. In the US, IV alteplase had a lower cost and was cost-saving. We performed the one-way sensitivity analysis to test the robustness of our conclusion and the results show that the corresponding ICERs were all under the WTP threshold with the variation of parameters one by one. In the probabilistic sensitivity analysis, when the current Chinese WTP threshold increased from Y72 447/QALY to Y217 341/QALY , the probability of IV alteplase being cost-effective when compared with placebo would increase from 42.54% to 78.3%, showing that IV alteplase was likely to be cost-effective in China. In the US, when the WTP threshold was US$100 000/QALY to US$150 000/QALY, the probability of IV alteplase being cost-effective when compared with placebo was between 93.47% to 93.57%, indicating that IV alteplase was cost-effective in the US.

Numerous studies have investigated the cost-effectiveness of IV alteplase for the treatment of AIS, while the time windows in these studies were limited to 0–3, 3–4.5, or 0–6 hours. 27 28 Similar to our conclusions, nearly all studies demonstrated that IV alteplase was cost-effective or even cost-saving when compared with the traditional treatment. We also noticed a very recent cost-effectiveness study that investigated the cost-effectiveness of MRI-guided thrombolysis with alteplase for patients with stroke with an unknown time of onset. 29 This study was conducted from the perspective of German healthcare. The data for clinical effectiveness was extracted from the WAKE-UP trial, a multicenter randomized trial that explored MRI-guided IV alteplase based on a mismatch between diffusion-weighted imaging and fluid-attenuated inversion recovery images. 30 This study proved that MRI-guided IV alteplase was cost-effective for AIS with an unknown time of onset in Germany. The target population in the EXTEND trial differed from that of the WAKE-UP trial, in that the WAKE-UP trial used MRI to identify patients with AIS with an unknown time of onset that was likely to be within 4.5 hours. While in the EXTEND trial, the time of stroke onset was between 4.5 and 9 hours, and in some cases patients who were compared with placebo would increase from 42.54% to 78.3%, showing that IV alteplase was likely to be cost-effective in China.

Figure 2  Tornado diagram depicting results of one-way sensitivity analyses in China. The diagram shows how the higher and lower values of a single parameter affect the incremental cost-effectiveness ratio. ICH, intracranial hemorrhage; mRS, modified Rankin scale; QALY, quality-adjusted life-year.

Figure 3  Tornado diagram depicting results of one-way sensitivity analyses in the United States. ICH, intracranial hemorrhage; mRS, modified Rankin Scale; QALY, quality-adjusted life-year.

Figure 4  Cost-effectiveness acceptability curve of intravenous alteplase versus placebo in the treatment of patients with stroke with a time of onset between 4.5 to 9 hours in China. QALY, quality-adjusted life-year.

Figure 5  Cost-effectiveness acceptability curve of intravenous alteplase versus placebo in the treatment of patients with stroke with a time of onset between 4.5 to 9 hours in the United States. QALY, quality-adjusted life-year.
within approximately 12 hours from the onset of AIS might have been included.3

Both IV alteplase and endovascular thrombectomy have become part of the standard treatment for patients with AIS. However, it is a clinical dilemma as to which imaging. However, it is often a clinical dilemma to decide the appropriate imaging for the patient when to select IV alteplase or mechanical thrombectomy. Based on the EXTEND trial, more advanced imaging modalities such as MRI or CT perfusion were needed. According to the Guidelines for the Early Management of Patients With Acute Ischemic Stroke, when selecting patients with the time of stroke onset between 6 and 24 hours,2 obtaining CT perfusion or diffusion-weighted MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy. Therefore, diffusion-weighted MRI with MRI perfusion might be the appropriate imaging modality for AIS with an extended time window for IV alteplase or mechanical thrombectomy. However, more studies are needed to verify this suggestion.

This study has several limitations that should be noted. First, in the absence of relevant data, we assumed the probability of a recurrent stroke is the same across different levels of disability after the first stroke, while we might expect that more disabled patients would have a higher recurrent probability. However, sensitivity analysis proved that our model was not sensitive to this assumption. Second, we are not able to derive the data on input parameters from one single source. The inconsistency among different sources might lead to some bias. However, the sensitivity analysis has accounted for these uncertainties and we have limited the data source to a single geographic region based on different study perspectives. Third, the data for clinical effectiveness in the initial 3 months was extracted from the WAKE-UP trial that was conducted internationally. Most of the participants were from Australia, New Zealand, or Finland, while only a small portion of them was from Asia. It is unclear whether similar treatment effects would occur if the participants were limited to a Chinese or US population.

CONCLUSION

In summary, for patients with AIS with the time of stroke onset between 4.5 and 9 hours, perfusion imaging-guided IV alteplase was likely to be cost-effective in China and was cost-effective in the US when compared with placebo.

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