Generalization of the right acute stroke promotive strategies in reducing delays of intravenous thrombolysis for acute ischemic stroke
A meta-analysis
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Abstract
The generalization of successful efforts for reducing time delays in intravenous thrombolysis (IVT) could help facilitate its utility and benefits in acute ischemic stroke (AIS) patients.

We searched the PubMed and Embase databases for articles reporting interventions to reduce time delays in IVT, published between January 1995 and September 2017. The IVT rate was chosen as the primary outcome, while the compliance rates of onset-to-door time (prehospital delay) and door-to-needle time (in-hospital delay) within the targeted time frame were the secondary outcomes. Interventions designed to reduce prehospital, in-hospital, or total time delays were quantitatively described in meta-analyses. The efficacy of postintervention improvement was illustrated as odds ratios (ORs) and 95% confidence intervals (95% CIs).

In total, 86 papers (17 on prehospital, 56 on in-hospital, and 13 on total delay) encompassing 17,665 IVT cases were enrolled, including 28 American, 23 Asian, 30 European, and 5 Australian studies. The meta-analysis revealed statistically significant improvement in promoting IVT delivery after prehospital improvement interventions with an OR of 1.45 (95% CI, 1.23–1.71) for the new transportation protocol, 1.38 (95% CI, 1.11–1.73) for educational and training programs, and 1.83 (95% CI, 1.44–2.32) for comprehensive prehospital stroke code. The benefits of reducing in-hospital delay were much greater in developed western countries than in Asian countries, with ORs of 2.90 (95% CI, 2.51–3.34), 2.17 (95% CI, 1.95–2.41), and 1.89 (95% CI, 1.74–2.04) in American, European, and Asian countries, respectively. And telemedicine (OR, 2.26; 95% CI, 2.08–2.46) seemed to work better than pre-notification alone (OR, 1.94; 95% CI, 1.74–2.17) and in-hospital organizational improvement programs (OR, 2.10; 95% CI, 1.97–2.23). Mobile stroke treatment unit and use of a comprehensive stroke pathway in the pre- and in-hospital settings significantly increased IVT rates by reducing total time delay, with ORs of 2.01 (95% CI, 1.60–2.51) and 1.77 (95% CI, 1.55–2.03), respectively.

Optimization of the work flow with organizational improvement or novel technology could dramatically reduce pre- and in-hospital time delays of IVT in AIS. This study provided detailed information on the net and quantitative benefits of various programs for reducing time delays to facilitate the generalization of appropriate AIS management.

Abbreviations: 95% CI = 95% confidence interval, AIS = acute ischemic stroke, DNT = door to needle time, EMS = emergency medical service, IVT = intravenous thrombolysis, mRS = modified Rankin Scale, MSTU = mobile stroke treatment unit, NIHSS = National Institutes of Health Stroke Scale, NINDS = National Institute of Neurological Disorders and Stroke rt-PA stroke trial, ODT = onset to door time, ONT = onset to needle time, OR = odds ratio, SICH = symptomatic intracranial hemorrhage.

Keywords: acute ischemic stroke, in-hospital delay, intravenous thrombolysis, organizational improvement, prehospital delay, stroke pathway, tissue plasminogen activator

1. Introduction
Intravenous thrombolysis (IVT) has been a mainstream therapy for acute ischemic stroke (AIS) since the publication of National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke trial in 1995. The utility and benefits of IVT are largely limited by the narrow therapeutic time window in which the time...
delays in the stroke pathway due to health system factors are main obstacles to IVT in clinical practice.[2] Various interventions to reduce time delays in the stroke pathway were promoted to improve IVT administration and the clinical outcome of AIS patients. The TARGET: Stroke quality improvement initiative showed that an improved timeliness of IVT following AIS was associated with better functional and safety outcomes.[3] However, it is important to implement practical and efficient strategies to reduce time delays of IVT in each specific institute. Optimal interventions for time delays (classified as prehospital, in-hospital, and total time delays) remain unknown in the absence of quantitative evidence. Here, we aim to compare the efficacy of various interventions to reduce time delays through a quantitative meta-analysis and conduct a comprehensive literature review of this topic.

2. Materials and methods

2.1. Inclusion/exclusion criteria

As most studies on this topic were observational, the Meta-analysis Of Observational Studies in Epidemiology guidelines[4] were followed. Systematic literature searches were independently performed by 2 authors following the standard selection criteria. Inclusion criteria were as follows: studies focused on reducing time delays (prehospital, in-hospital, or total delay) of IVT in cases of AIS; cohort study, case-controlled study, registry study, or clinical randomized controlled trial published in English; and completed data on pre- (control) and postintervention (experimental) group. Exclusion criteria were as follows: case series or report, review, or commentary paper; study reporting incomplete data for mentioned subgroups or data unavailable even in supplemental materials; and study using data published more than once. At least 2 of the study authors agreed to include each of the identified articles in the analysis.

2.2. Literature search

We searched the PubMed and Embase databases for articles published between January 1, 1995, and September 30, 2017. The following free or MeSH search terms were used: stroke, ischemic, thrombolytic treatment, thrombolysis, tissue plasminogen activator, tPA, alteplase, prehospital, public awareness, emergency medical service (EMS), in-hospital, door to needle time, registry, initiative, organizational model, implementation, and stroke pathway were used. We also manually searched the reference lists and citations of included articles for further articles. The detailed search process is reported in Supplemental Figure 1, http://links.lww.com/MD/C300.

2.3. Data collection

Two authors (H.Q. and Z.J.) independently extracted data from all included papers using a standardized data collection form. A third consultation was made in cases of disagreement regarding inclusion eligibility. Report characteristics (first and corresponding authors, journal, and year of publication), study design (type, location, and period), intervention classification (pre- and/or in-hospital setting improvement), study sample and characteristics (numbers of subjects, age, sex, baseline National Institutes of Health Stroke Scale (NIHSS), IVT use rate, median onset to door time (ODT), median door to needle time (DNT), median onset to needle time (ONT), compliance rate of ODT (prehospital delay) and DNT (in-hospital delay) in pre- (control) and postintervention (experimental groups), functional outcomes [measured on the modified Rankin Scale (mRS)], and safety outcomes (mortality and symptomatic intracranial hemorrhage (SICH)] were recorded. When reported, detailed information about the interventions, other time indicators, and clinical endpoint indicators were also recorded. Data of variables extracted from included papers followed preset criteria or definitions. When multiple papers drew on the same datasets, data were extracted only once from the most comprehensive available report. If the improvement interventions lasted for more than 1 time unit, the data from the last time unit before the interventions and the first time unit after the interventions were selected.

Stroke onset time was defined as the time when stroke symptoms first occurred or the last time known to be normal, door time as when the patient arrived at the emergency department of the hospital or mobile stroke treatment unit (MSTU), and needle time as when the administration of thrombolytic agent started. Pre-hospital delay was defined as ODT, in-hospital delay as DNT, and total time delay equal to ODT plus DNT.[3] The utilization rate of IVT (percentage of patients treated with IVT in all AIS cases) was chosen as primary outcome, while the compliance rates of ODT and DNT (the percentage of IVT patients achieving a qualified timeliness, e.g., ODT < 180 minutes and DNT < 60 minutes) were recorded as secondary outcomes. Clinical endpoint indicators such as favorable functional outcome at 3 months (defined as mRS 0–2), mortality, and SICH (defined as intracranial hemorrhage after IVT resulting in measurable neurological deterioration, e.g., NIHSS increased to ≥11[3]) were also included in the secondary analysis. When the preferred definitions for secondary outcomes and clinical endpoint indicators were not available, the authors’ definitions were adopted.

2.4. Data analysis

Statistical calculations were performed and graphics created using RevMan 5.1 software (Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). When data were not calculable in the software, descriptive analysis was used. The Mantel–Haenszel method was implemented by the fixed- or random-effects analysis models based on included study heterogeneity. The primary analysis was to compare the utilization rates of IVT in the pre- (control) and postintervention (experimental) groups. The secondary analysis involved detecting the differences in ODT and DNT compliance rates and other clinical indicators between the 2 groups. The unification data results were calculated as odds ratios (ORs) with 95% confidence intervals (CIs) considering 2-tailed P values < .05 statistically significant.

3. Results

3.1. Study characteristics

A total of 86 papers (17 on prehospital delay, 56 on in-hospital delay, and 13 on total delay) encompassing 17,665 IVT cases were included in this analysis. All articles included were published between 2003 and 2017, and the study period ranged from 1996 and 2017. There were 28 studies from American countries, 23 from Asian countries, 5 from Australia, and 30 from European countries, of which 81.1% (77/86) were randomized controlled studies and 44.2% (38/86) were conducted within 5 years. Features of the included papers are listed in Table 1.[6–90] The moderate risk of bias and the standard errors for included studies are depicted in the Supplemental Figures 2 to 8, http://links.lww.com/MD/C300.
| Refs | First author | Area | Year | Study period | IVT cases, no. | Female, % | Median age, y | Median NIHSS | Median ODT, min | Median DNT, min | Median ONT, min | mRS ≤ 2, % | Mortality, % | SICH, % |
|------|--------------|------|------|--------------|---------------|----------|--------------|--------------|----------------|----------------|----------------|----------------|-------------|----------|--------|
| [10] | Müller-Nordhorn et al | European | 2001 | 2001-2007 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [11] | Chin et al | American | 2002 | 2002-2007 | 8/9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| [12] | Quan et al | American | 2003 | 2003-2007 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [13] | Chen et al | American | 2004 | 2004-2007 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [14] | Reine-Deitmer et al | European | 2005 | 2005-2007 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [15] | Addo et al | European | 2006 | 2006-2007 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [16] | Sun et al | Asian | 2007 | 2007-2008 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [17] | Belvisi et al | European | 2008 | 2008-2009 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [18] | Jox et al | European | 2009 | 2009-2010 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [19] | Poulimaki et al | European | 2010 | 2010-2011 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [20] | Henry-Morrow et al | American | 2011 | 2011-2012 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [21] | Heo et al | Asian | 2012 | 2012-2013 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [22] | Nishijima et al | Asian | 2013 | 2013-2014 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [23] | Camerlingo et al | European | 2014 | 2014-2015 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [24] | Arai et al | Asian | 2015 | 2015-2016 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [25] | Nolte et al | European | 2016 | 2016-2017 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [26] | Etgen et al | European | 2017 | 2017-2018 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [27] | Eising et al | European | 2018 | 2018-2019 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [28] | Tataranni et al | European | 2019 | 2019-2020 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [29] | Bhatt et al | American | 2020 | 2020-2021 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [30] | McKirray et al | American | 2021 | 2021-2022 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |
| [31] | Nii et al | Asian | 2022 | 2022-2023 | 30.5 | 60.9 | 48.0 | 67.72<sup>2</sup> | 50.6 | 47.4 | 11.4 | 50.0 | 22.7 | 0.0 |

Table 1
Features of included studies.
| Study | Po/Pre | Po/Pre | Po/Pre | Po/Pre | Po/Pre | Po/Pre | Po/Pre | Po/Pre |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|
| 12/13 | 12/13  | 12/13  | 12/13  | 12/13  | 12/13  | 12/13  | 12/13  | 12/13  |
| 14/15 | 14/15  | 14/15  | 14/15  | 14/15  | 14/15  | 14/15  | 14/15  | 14/15  |
| 16/17 | 16/17  | 16/17  | 16/17  | 16/17  | 16/17  | 16/17  | 16/17  | 16/17  |
| 18/19 | 18/19  | 18/19  | 18/19  | 18/19  | 18/19  | 18/19  | 18/19  | 18/19  |
| 20/21 | 20/21  | 20/21  | 20/21  | 20/21  | 20/21  | 20/21  | 20/21  | 20/21  |
| 22/23 | 22/23  | 22/23  | 22/23  | 22/23  | 22/23  | 22/23  | 22/23  | 22/23  |
| 24/25 | 24/25  | 24/25  | 24/25  | 24/25  | 24/25  | 24/25  | 24/25  | 24/25  |
| 26/27 | 26/27  | 26/27  | 26/27  | 26/27  | 26/27  | 26/27  | 26/27  | 26/27  |
| 28/29 | 28/29  | 28/29  | 28/29  | 28/29  | 28/29  | 28/29  | 28/29  | 28/29  |
| 30/31 | 30/31  | 30/31  | 30/31  | 30/31  | 30/31  | 30/31  | 30/31  | 30/31  |

Data were presented as median values of subgroup comparisons between post- and pre-intervention. Studies 6–22 (n = 17) focused on reducing prehospital delay, 23–78 (n = 56) on reducing in-hospital delay, and 79–91 (n = 13) focused on reducing total time delay. ODT = onsets to door time, IVT = intravenous thrombolytics, mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale, NR = not reported in original paper, DNT = door to needle time, Po = postoperative, Pre = preoperative, SICH = symptomatic intra cranial hemorrhage.

* Citation [n] included data of 2 groups (Hub and Stroke hospitals).

† A statistical significance (P < .05) for the comparison.
3.2. Patient characteristics
A total of 17,665 IVT cases were enrolled in this review; 7491 in the preintervention (control) group and 10,174 in the post-intervention (experimental) group. The difference of sex distribution of 5 studies, median age in 10 studies, and the median NIHSS in 10 studies were statistically significant between the 2 groups (Table 1). A statistically significant increase in favorable functional outcomes was observed in 10 studies, while a statistically significant decrease in mortality and the SICH rate was noted in 1 and 2 studies, respectively.

3.3. Interventions to reduce prehospital delay
In the analysis for reducing prehospital delay, 15 studies offered data of the use rate of IVT and 11 studies for the compliance rates of ODT (ODT < 180 minutes in 9 studies and < 120 minutes in other 2 studies). Using random-effect models, the meta-analysis revealed statistically significant improvement in IVT delivery after prehospital improving interventions, with the OR of 1.45 (95% CI, 1.23–1.71) for new transportation protocol, OR of 1.38 (95% CI, 1.11–1.73) for educational and training programs, and OR of 1.83 (95% CI, 1.44–2.32) for comprehensive prehospital stroke code, respectively. A significant increase in IVT rate was also observed in 2 subgroups: OR of 1.83 (95% CI, 1.44–2.32) for comprehensive in-hospital organizational improvement program and OR of 1.49 (95% CI, 1.25–1.78) in the comprehensive improvement in the prehospital stroke code protocol but not in the new transportation method (OR, 1.22; 95% CI, 0.99–1.50; Fig. 1).

3.4. Interventions for reducing in-hospital delay
A total of 50 of the included studies focused on reducing in-hospital delay: 17 in American countries (America and Canada), 16 in Asia, 14 in Europe, and 3 in Australia. Details of the improving protocols were implemented via a telemedicine (telestroke or telephone consultation) system in 7 studies, using a pre-notification system alone by EMS in 4 studies, simply adding stroke team staff (emergency room nurse, pharmacist, or neurologist) in 4 studies, application of point-of-care laboratory platform based stroke management in 1 study, initiation of a comprehensive in-hospital organizational improvement program (which may include pre-notification, telemedicine system, or other above mentioned methods) in 29 studies.

Regarding IVT delivery, the benefits after interventions were much larger in developed countries (western countries) than in Asian countries with an OR of 2.90 (95% CI, 2.51–3.34) in American countries, OR of 2.17 (95% CI, 1.95–2.41) in European countries and Australia, and an OR of 1.89 (95% CI, 1.74–2.04) in Asian countries (Fig. 2). Regarding detailed methods of promoting IVT delivery, telemedicine (OR, 2.26; 95% CI, 2.08–2.46) seemed to work better than pre-notification alone (OR, 1.94; 95% CI, 1.74–2.17) and organizational improvement programs (OR, 2.10; 95% CI, 1.97–2.23).

| Study or Subgroup | Events Total | Odds Ratio | Study or Subgroup | Events Total | Odds Ratio |
|-------------------|-------------|------------|-------------------|-------------|------------|
| **1.1 Promoting IVT delivery with new transportation methods** | | | | | |
| Hessefeldt R 2014 | 22 65 87 265 4.8% | 1.05 [0.59, 1.86] | Joux J 2013 | 71 170 30 108 4.6% | 1.86 [1.11, 3.14] |
| Reiner-Deitemyer V 2011 | 745 1050 5842 38.8% | 1.45 [1.21, 1.74] | Subtotal (95% CI) | 980 6215 48.3% | 1.45 [1.23, 1.71] |
| **Total events** | 273 | 1167 | | | |
| Heterogeneity: Chi² = 21.29, df = 5 (P = 0.0007); I² = 77% | | | Test for overall effect: Z = 2.88 (P = 0.004) |

| **1.2 Promoting IVT delivery with educational and training programs** | | | | | |
| Addo J 2012 | 45 274 55 326 9.0% | 0.97 [0.63, 1.49] | Henry-Morrow TK 2017 | 16 57 8 30 1.6% | 1.07 [0.40, 2.90] |
| Lattimore SU 2005 | 44 420 3 200 0.8% | 7.68 [2.36, 25.06] | Müller-Nordhorn J 2009 | 17 598 13 544 2.8% | 1.20 [0.58, 2.48] |
| Nishijima H 2016 | 36 600 41 544 8.7% | 0.78 [0.49, 1.24] | Sun XG 2013 | 66 708 32 718 6.2% | 2.20 [1.43, 3.41] |
| Subtotal (95% CI) | 2657 | 2362 29.2% | 1.38 [1.11, 1.73] | | |
| **Total events** | 224 | 152 | | | |
| Heterogeneity: Chi² = 21.29, df = 5 (P = 0.0007); I² = 77% | | | Test for overall effect: Z = 2.88 (P = 0.004) |

| **1.3 Promoting IVT delivery with comprehensive pre-hospital stroke code** | | | | | |
| Atsumi C 2015 | 66 301 51 189 10.5% | 0.78 [0.50, 1.16] | Belvis R 2005 | 7 37 8 181 0.5% | 5.05 [1.70, 14.95] |
| Camerlingo M 2014 | 23 401 8 376 1.7% | 2.80 [1.24, 6.34] | Chenkin J 2009 | 56 290 18 145 4.2% | 1.69 [0.95, 3.00] |
| Prabhakaran S 2013 | 69 787 23 719 4.7% | 2.91 [1.79, 4.72] | Quain DA 2008 | 30 140 5 107 1.0% | 5.56 [2.08, 14.88] |
| Subtotal (95% CI) | 1956 | 1717 22.5% | 1.83 [1.44, 2.32] | | |
| **Total events** | 251 | 113 | | | |
| Heterogeneity: Chi² = 29.59, df = 5 (P < 0.0001); I² = 83% | | | Test for overall effect: Z = 4.93 (P < 0.00001) |

Figure 1. Post- versus pre-intervention in primary outcomes of reducing prehospital delay.
(Fig. 3). In the analysis of secondary outcomes, the compliance rates of DNT were improved to a greater degree in western countries (OR, 6.21; 95% CI, 4.45–8.67) in European countries and Australia and OR, 5.61; 95% CI, 4.41–7.13 in American countries) than in Asian countries (OR, 3.10; 95% CI, 2.45–3.92) (Fig. 4), while the pre-notification program served as a better way of increasing the rate of DNT < 60 minutes (OR, 14.44; 95% CI, 9.97–20.90) than the telemedicine protocol (OR, 6.19; 95% CI, 3.34–11.48) and the organizational improvement program (OR, 4.13; 95% CI, 3.50–4.93) (Fig. 5).

### 3.5. Interventions for reducing total time delay

Interventions aiming at reducing total time delay of IVT included using MSTU, and implementation of comprehensive improving stroke pathway in both the pre-hospital and in-hospital settings.
For the 2 subgroups (Fig. 6), the rates of IVT were both significantly increased after the application of MSTU or the comprehensive improving stroke pathway, with the OR of 2.01 (95% CI: 1.60–2.51) and OR of 1.77 (95% CI: 1.55–2.03), respectively.

4. Discussion

Various factors contributing to pre- and/or in-hospital delays for IVT in AIS have been identified and solutions addressing these factors proposed as our results showed. An optimal and continuous gain in thrombolysis administration for AIS involved
multifaceted interventions, including reorganization of in-hospital and prehospital systems, the application of new technologies and facilities, and targeted training and educational programs. A detailed analysis demonstrated that streamlining workflow for reducing in-hospital delays serves as the most efficient way to deliver IVT, of which the telestroke program was likely to be most successful and beneficial improving models.

The efficacy and safety of IVT with rt-PA in AIS is highly time-dependent, and the narrow therapeutic time window and time delays contributed to the most common of barriers of generalization of this therapy. A previous systematic review by Evenson et al[1] observed that prehospital delay comprised the majority of time delays and the median prehospital delay was in the range of 3 to 6 hours. However, only a few studies showing a moderate effect on increasing the rate of IVT implemented detailed interventions to reduce time delays in the prehospital period, and the interventions included, for example, mass media and public awareness campaigns, professional education programs, and streamlined ambulance protocols.[16,20,92–94] Noted that the effect of comprehensive improving prehospital stroke code (OR, 1.83) was better than new transportation method (OR, 1.45) or educational program (OR, 1.38) alone (Fig. 7), which implied that the efforts made in this area called for multifaceted departments other than the hospital side alone and the role of EMS in stroke symptom recognition, patient transportation, and communication with hospital staff deserved the most attention for reducing prehospital delay. However, given the huge gap in the structures of EMS systems between countries or even districts within a single country, experience achieved in other places might not easily be copied. The cost-effectiveness of prehospital educational programs and EMS improvement remains to be demonstrated (which is mainly due to

| Study or Subgroup | Experimental | Control | Odds Ratio | Odds Ratio |
|-------------------|--------------|---------|------------|------------|
|                   | Study Events | Total Events | Total Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 5.1 Improvement of reducing in-hospital delay in Asian countries | | | | |
| Ahro Kim 2014 | 59 | 77 | 13 | 16 | 2.9% | 0.76 [0.19, 2.95] |
| Chen CH2014 | 154 | 216 | 13 | 91 | 3.1% | 14.90 [7.73, 28.75] |
| Cho HJ2014 | 20 | 63 | 5 | 39 | 2.4% | 3.16 [1.08, 9.30] |
| Choi HY2016 | 64 | 118 | 40 | 111 | 11.0% | 2.10 [1.24, 3.58] |
| Hsieh CY2014 | 8 | 74 | 2 | 18 | 1.7% | 0.97 [0.19, 5.01] |
| Hsieh MJ2016 | 65 | 144 | 7 | 25 | 3.6% | 2.12 [0.83, 5.38] |
| Liang Z2016 | 13 | 20 | 5 | 13 | 1.2% | 2.97 [0.70, 12.62] |
| Huang Q2016 | 88 | 146 | 20 | 202 | 3.9% | 13.81 [7.82, 24.37] |
| Sakamoto Y2016 | 14 | 21 | 0 | 19 | 0.1% | 75.40 [3.98, 1429.52] |
| Sohn SW2015 | 11 | 252 | 23 | 71 | 19.9% | 0.10 [0.04, 0.21] |
| Subtotal (95% CI) | 1131 | 605 | 50.0% | 3.10 [2.45, 3.92] |

Total events: 496, Heterogeneity: Chisq = 137.64, df = 9 (P < 0.00001); I² = 93%
Test for overall effect: Z = 9.46 (P < 0.00001)

| 5.2 Improvement of reducing in-hospital delay European countries and Australia | | | | |
| Heikkilä 2016 | 31 | 33 | 22 | 31 | 0.8% | 6.34 [1.25, 32.26] |
| Khor MX2015 | 93 | 105 | 37 | 75 | 2.9% | 7.96 [3.75, 16.89] |
| Nardetto L2016 | 2 | 25 | 8 | 106 | 1.6% | 1.07 [0.21, 5.39] |
| Nolte CH2007 | 64 | 77 | 5 | 34 | 0.7% | 28.55 [9.31, 87.59] |
| Salottolo KM2011 | 62 | 108 | 5 | 15 | 2.2% | 2.70 [0.98, 6.42] |
| Thortveit ET 2013 | 19 | 82 | 19 | 6.5% | 4.07 [2.23, 7.44] |
| van Dishoeck AM2014 | 47 | 58 | 0 | 12 | 0.1% | 103.26 [4.69, 1875.11] |
| Van Schaik SM2014 | 174 | 185 | 29 | 41 | 1.6% | 6.55 [2.64, 16.22] |
| Subtotal (95% CI) | 747 | 396 | 16.4% | 6.21 [4.45, 8.67] |

Total events: 559, Heterogeneity: Chisq = 19.68, df = 7 (P = 0.006); I² = 64%
Test for overall effect: Z = 10.73 (P < 0.00001)

| 5.3 Improvement of reducing in-hospital delay in American countries | | | | |
| Chakraborty S 2015 | 24 | 37 | 9 | 15 | 2.6% | 1.23 [0.36, 4.23] |
| Mohralla M 2006 | 7 | 40 | 3 | 62 | 1.1% | 4.17 [1.01, 17.22] |
| Al Kasab SA2017 | 366 | 450 | 8 | 39 | 1.6% | 16.88 [7.49, 38.05] |
| Bhattacharya A2012 | 24 | 47 | 9 | 60 | 2.2% | 5.91 [2.38, 14.70] |
| Burnett MM2014 | 66 | 108 | 15 | 94 | 3.6% | 8.28 [4.22, 16.24] |
| Busby L2016 | 45 | 52 | 2 | 41 | 0.2% | 125.36 [24.59, 639.12] |
| Ford AL2013 | 68 | 67 | 68 | 132 | 6.5% | 3.37 [1.83, 6.22] |
| Gossler RA2016 | 20 | 67 | 6 | 38 | 3.1% | 2.27 [0.82, 6.27] |
| Greenberg K2014 | 31 | 35 | 10 | 32 | 0.7% | 17.05 [4.73, 61.43] |
| Ibrahim F2016 | 76 | 102 | 43 | 102 | 6.4% | 4.01 [2.21, 7.28] |
| Moran JL2014 | 99 | 122 | 27 | 44 | 4.3% | 2.77 [1.27, 5.78] |
| Shah S 2015 | 24 | 39 | 3 | 23 | 0.8% | 10.67 [4.22, 26.24] |
| Subtotal (95% CI) | 1186 | 682 | 33.6% | 5.61 [4.41, 7.13] |

Total events: 850, Heterogeneity: Chisq = 42.50, df = 11 (P < 0.00001); I² = 74%
Test for overall effect: Z = 14.04 (P < 0.00001)

Figure 4. Post- versus pre-intervention in secondary outcome of reducing in-hospital delay in different areas.
a larger number of emergency department visits for stroke mimic\textsuperscript{[92]} or alternative diagnoses other than stroke\textsuperscript{[82]}, and the positive effects could be decreased soon after the interventions.\textsuperscript{[78,92]}

Interventions to reduce in-hospital delays seemed to have made much greater progress than the former mentioned above and worked much better in developed areas (western countries) than in Asian countries (Fig. 3). One of the reasons for this could have been the initiative of national projects like the Safe Implementation of Thrombolysis in Stroke Monitoring Study\textsuperscript{[83,101]} the stroke registry in Australia,\textsuperscript{[76]} and Target: Stroke in America\textsuperscript{[13]} enable monitoring of therapeutic actions in IVT and teach many hospital staff how to improve their health care systems by reducing time delays. As the time consumed by noncritical tasks was saved (lean principle), the median DTN could be made short to <20 minutes in 1 advanced European hospital.\textsuperscript{[42]} Due to the detailed methods of promoting IVT delivery, telemedicine seemed to work better than pre-notification alone and organizational improvement programs (Fig. 4). That is, the population benefits of IVT were limited in rural areas and underdeveloped countries resulting from the restricted availability of stroke expertise and excellent medical resource, while the application of telemedicine could not only spread the excellent experience but also promote IVT use.\textsuperscript{[73,84,97]} Previous studies have also demonstrated IVT delivery in spoke hospitals through telestroke networks is as effective and safe as that in hub institutions\textsuperscript{[98]} and serves as a cost-saving protocol for remote practitioners.\textsuperscript{[99]} Therefore, telestroke is a promising modern strategy to overcome the practical limitations and extend existing progress of reducing in-hospital delays.

Comprehensively improving stroke pathways that aim to integrate and improve prehospital and in-hospital settings could cover almost all aspects of acute stroke care. A significant increase in IVT administration was noted in our analysis (Fig. 6) and accompanied by a sustained increase in the likelihood of favorable outcomes.\textsuperscript{[85]} Improvements in EMS including the

| Study or Subgroup | Treatment | Events | Total Events | Total Weight | Odds Ratio | 95% CI | P Value |
|-------------------|-----------|--------|--------------|--------------|------------|--------|---------|
| 6.1 Improvement of reducing in-hospital delay with telemedicine | Experimental | 8 | 74 | 2 | 18 | 1.8% | 0.97 [0.19, 5.01] |
| | Control | 2 | 25 | 8 | 106 | 1.8% | 1.07 [0.21, 5.35] |
| | Subtotal (95% CI) | 10 | 99 | 10 | 122 | 1.8% | 16.68 [7.49, 38.05] |
| 6.2 Improvement of reducing in-hospital delay with pre-notification | qiang huang 2016 | 88 | 146 | 20 | 202 | 4.2% | 13.81 [7.82, 24.37] |
| | Sakamoto Y2016 | 14 | 21 | 0 | 19 | 0.1% | 75.40 [3.98, 1429.52] |
| | Khor MX2015 | 93 | 105 | 37 | 75 | 3.1% | 7.96 [3.75, 16.89] |
| | van Dishoek AM2014 | 47 | 52 | 0 | 12 | 0.1% | 103.26 [5.69, 1875.11] |
| | Van Schaik SM2014 | 174 | 185 | 29 | 41 | 1.8% | 6.55 [2.64, 16.22] |
| | Busby L2016 | 45 | 52 | 2 | 41 | 0.2% | 125.36 [24.59, 639.12] |
| | Subtotal (95% CI) | 8 | 65 | 0 | 12 | 0.1% | 14.44 [9.97, 20.90] |
| 6.3 Improvement of reducing in-hospital delay with re-organizational program | Ahro Kim 2014 | 59 | 77 | 13 | 16 | 3.1% | 0.78 [0.19, 2.95] |
| | Chen CH2014 | 154 | 216 | 13 | 91 | 3.3% | 14.90 [7.73, 28.75] |
| | Cho HJ2014 | 20 | 63 | 5 | 39 | 2.6% | 3.16 [1.08, 9.30] |
| | Choi HY2016 | 64 | 118 | 40 | 111 | 11.8% | 2.10 [1.24, 3.58] |
| | Liang ZZ2016 | 13 | 20 | 5 | 13 | 1.3% | 2.97 [0.70, 12.82] |
| | qiang huang 2016 | 88 | 146 | 20 | 202 | 4.2% | 13.81 [7.82, 24.37] |
| | Song SW2015 | 11 | 5 | 23 | 71 | 21.5% | 0.10 [0.04, 0.21] |
| | Heikkila I2016 | 31 | 33 | 22 | 31 | 0.9% | 6.34 [1.25, 32.26] |
| | Nolte CH2007 | 6 | 77 | 5 | 34 | 0.7% | 28.55 [9.31, 87.59] |
| | Thortveit ET 2013 | 86 | 156 | 19 | 82 | 7.0% | 4.07 [2.23, 7.44] |
| | van Dishoek AM2014 | 47 | 58 | 0 | 12 | 0.1% | 103.26 [5.69, 1875.11] |
| | Van Schaik SM2014 | 174 | 185 | 29 | 41 | 1.8% | 6.55 [2.64, 16.22] |
| | Chakraborty S 2015 | 24 | 37 | 9 | 15 | 2.8% | 1.23 [0.36, 4.23] |
| | Mehdiratta M 2006 | 7 | 40 | 3 | 62 | 1.2% | 4.17 [1.01, 17.22] |
| | Burnett MM2014 | 68 | 108 | 15 | 94 | 3.9% | 8.28 [4.22, 16.24] |
| | Busby L2016 | 45 | 52 | 2 | 41 | 0.2% | 125.36 [24.59, 639.12] |
| | Ford AL2013 | 68 | 87 | 68 | 132 | 7.4% | 3.37 [1.83, 6.22] |
| | Ibrahim F2016 | 76 | 102 | 43 | 102 | 6.9% | 4.01 [2.17, 7.26] |
| | Moran JL2016 | 99 | 122 | 27 | 44 | 4.7% | 2.71 [1.27, 5.78] |
| | Subtotal (95% CI) | 1949 | 2333 | 85.3% | 4.15 [3.50, 4.93] |

| Experimental | Control | Odds Ratio | 95% CI | P Value |
|--------------|---------|------------|--------|---------|
| Events | Total Events | Total Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 6.1 Improvement of reducing in-hospital delay with telemedicine | 8 | 74 | 2 | 18 | 1.8% | 0.97 [0.19, 5.01] |
| 6.2 Improvement of reducing in-hospital delay with pre-notification | 88 | 146 | 20 | 202 | 4.2% | 13.81 [7.82, 24.37] |
| 6.3 Improvement of reducing in-hospital delay with re-organizational program | 59 | 77 | 13 | 16 | 3.1% | 0.78 [0.19, 2.95] |

Test for overall effect: Z = 14.15 (P < 0.00001)
centralization of stroke care (as in MSTU \cite{81,87}) and infrastructure advancement (such as pre-notification or consultation using telemedicine technology platforms \cite{43,87}) contributed the most to reducing total delays and tackling the problem of IVT under-treatment (Fig. 6). In a word, smooth coordination and timely communication between departments or disciplines (such as EMS staff, health authorities, and stroke physicians) are the intersections at which stroke can be managed most effectively.

Study limitations include the following. Use of the IVT rate as a performance measure to compare between centers and ethnic

| Study or Subgroup | Experimental Events | Control Events | Odds Ratio | Odds Ratio |
|-------------------|---------------------|----------------|------------|------------|
| 7.1 Reducing total time delay using new comprehensive stroke pathway | | | | |
| Edilberto Amorin 2013 | 113 1669 | 27 919 | 7.6% | 2.40 [1.56, 3.68] |
| Ahmed Ibrat 2015 | 16 100 | 13 56 | 3.3% | 1.63 [0.98, 2.63] |
| Kim DH2 2016 | 105 215 | 11 59 | 2.1% | 1.99 [0.84, 4.68] |
| O’Brien W2012 | 22 115 | 5 67 | 1.2% | 2.03 [0.65, 2.16] |
| Willett J 2014 | 213 1266 | 160 1238 | 31.7% | 2.59 [1.79, 3.75] |
| Gladstone DJ 2009 | 30 128 | 7 74 | 1.6% | 2.53 [1.02, 6.64] |
| Vidalis S 2016 | 51 1084 | 4 573 | 1.2% | 2.73 [1.21, 5.69] |
| Lahr MM 2012 | 62 283 | 113 801 | 10.9% | 1.71 [1.21, 2.41] |
| Berglund A 2012 | 60 243 | 113 801 | 9.3% | 2.00 [1.40, 2.84] |
| Wojner-Alexandrov AW 2005 | 533 | 21 198 | 6.3% | 1.15 [0.68, 1.94] |
| Subtotal (95% CI) | 5636 | 4786 | 75.2% | 1.77 [1.55, 2.03] |
| Total events | 737 | 474 | | |
| Heterogeneity: Chi² = 31.54, df = 9 (P = 0.0002); I² = 71% | | | | |
| Test for overall effect: Z = 8.24 (P < 0.00001) | | | | |

7.2 Reducing total time delay with mobile stroke treatment unit program

| Study or Subgroup | Experimental Events | Control Events | Odds Ratio | Odds Ratio |
|-------------------|---------------------|----------------|------------|------------|
| Walter S 2012 | 12 29 | 8 25 | 1.2% | 1.50 [0.49, 4.59] |
| Martin Ebinger 2014 | 200 614 | 200 1041 | 23.6% | 2.03 [1.62, 2.55] |
| Subtotal (95% CI) | 643 | 1066 | 24.8% | 2.01 [1.60, 2.51] |
| Total events | 212 | 208 | | |
| Heterogeneity: Chi² = 0.27, df = 1 (P = 0.00001); I² = 0% | | | | |
| Test for overall effect: Z = 6.09 (P < 0.00001) | | | | |

Figure 6. Post- versus pre-intervention in primary outcome of reducing total time delay.

| Study or Subgroup | Experimental Events | Control Events | Odds Ratio | Odds Ratio |
|-------------------|---------------------|----------------|------------|------------|
| 2.1 Reducing pre-hospital delay with new transportation methods | | | | |
| Reiner-Deltaymer V 2011 | 524 | 2668 3794 | 22.0% | 1.22 [0.99, 1.50] |
| Subtotal (95% CI) | 524 | 3794 | 22.0% | 1.22 [0.99, 1.50] |
| Total events | 389 | 2668 | | |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 1.85 (P = 0.06) | | | | |

2.2 Reducing pre-hospital delay with education and training programs

| Study or Subgroup | Experimental Events | Control Events | Odds Ratio | Odds Ratio |
|-------------------|---------------------|----------------|------------|------------|
| Addo J 2012 | 125 | 276 | 134 | 329 | 8.8% | 1.20 [0.87, 1.66] |
| Müller-Nordhorn J 2009 | 189 | 556 | 176 | 630 | 14.4% | 1.33 [1.04, 1.70] |
| Nishijima H 2016 | 334 | 600 | 253 | 544 | 15.5% | 1.44 [1.14, 1.82] |
| Chen S 2013 | 86 | 107 | 63 | 113 | 1.6% | 3.25 [1.78, 5.95] |
| Sun XG 2013 | 340 | 708 | 154 | 718 | 10.5% | 3.38 [2.68, 4.26] |
| Subtotal (95% CI) | 2247 | 2334 | 59.8% | 1.83 [1.62, 2.06] |
| Total events | 1074 | 780 | | |
| Heterogeneity: Chi² = 47.43, df = 4 (P < 0.00001); I² = 92% | | | | |
| Test for overall effect: Z = 9.71 (P < 0.00001) | | | | |

2.3 Reducing pre-hospital delay using new comprehensive stroke code

| Study or Subgroup | Experimental Events | Control Events | Odds Ratio | Odds Ratio |
|-------------------|---------------------|----------------|------------|------------|
| Camerlingo M 2014 | 91 | 401 | 60 | 376 | 6.3% | 1.55 [1.08, 2.22] |
| Chenkin J 2009 | 178 | 290 | 69 | 145 | 4.7% | 1.75 [1.17, 2.62] |
| Prabhakaran S 2013 | 194 | 767 | 134 | 719 | 14.2% | 1.33 [1.04, 1.71] |
| Quan DA 2008 | 68 | 122 | 26 | 64 | 2.0% | 1.84 [1.00, 3.40] |
| Subtotal (95% CI) | 1600 | 1304 | 27.2% | 1.49 [1.25, 1.78] |
| Total events | 521 | 289 | | |
| Heterogeneity: Chi² = 1.68, df = 3 (P = 0.60); I² = 0% | | | | |
| Test for overall effect: Z = 4.47 (P < 0.00001) | | | | |

Figure 7. Post- versus pre-intervention in secondary outcomes of reducing prehospital delay.
groups can be confounding because it is subject to selection and referral bias. For example, in developed countries (e.g., the United States), advanced medical resources could be available and more patients with AIS would be administrated rt-PA; thus, the progress from organizational and technological reforms could be more difficult to achieve than those in developing countries or underserved regions. However, IVT with rt-PA has long been a worldwide mainstream treatment of AIS since the publication of the NINDS results 22 years prior, which has made the process more normalized and generalized even without large gaps among countries.

5. Conclusion
Optimization in the work flow with organizational improvement or novel technology (e.g., MSTU) could dramatically reduce pre-and in-hospital time delays of IVT in AIS. Our study provided detail information on the net and quantitative benefits of various programs for promoting the delivery and reducing time delays of IVT, which could help the generalization of appropriate AIS management programs.

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