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Generalization of the right acute stroke promotive strategies in reducing delays of intravenous thrombolysis for acute ischemic stroke

A meta-analysis

Qiang Huang, MD[a], Jing-ze Zhang, MD[a], Wen-deng Xu, MD[a], Jian Wu, MD, PhD[a,b,*]

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.[1] The utility and benefits of IVT are largely limited by the narrow therapeutic time window in which the time

Editor: Weimin Guo.

Funding/support: This study is funded by Tsinghua University Initiative Scientific Research Program (20161080076) and supported by Beijing Hospital Authority "DengFeng Project (DFL20152201)."

This study does not require ethical approval and patient consent because the study was a systematic review of previous studies and does not involve patients.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Department of Neurology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, [b] Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China.

[*] Correspondence: Jian Wu, Department of Neurology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, 168 Litang Road, Changping District, Beijing 102218, China (e-mail: wujianxuanwu@126.com).

Medicine (2018) 97:25(e11205)

Received: 17 February 2018 / Accepted: 28 May 2018

http://dx.doi.org/10.1097/MD.0000000000011205

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, thombolysis, 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.[5] 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 $\geq$1[1]) 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 numeration 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 8.1% (7/86) 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.

Table 1

Features of included studies.

Refs	First author	Area	Year	Study period	IVT cases, no. Po/Pre	Female, % Po/Pre	Median age, y Po/Pre	Median NIHSS Po/Pre	Median ODT, min Po/Pre	Median DNT, min Po/Pre	Median ONT, min Po/Pre	mRS ≤ 2, % Po/Pre	Mortality, % Po/Pre	SICH, % Po/Pre
[6]	Lattimore et al	American	2003	2000–2001	44/3	NR	NR	NR	NR	NR	NR	NR	NR	NR
[7]	Belvís et al	European	2005	2001–2002	7/8	NR	67/72†	10/4	65/69	88/118	NR	NR	NR	NR
[8]	Quain et al	American	2008	2005–2007	30/5	48.0/49.0	71/68	NR	64/98	92/89	NR	NR	NR	NR
[9]	Chenkin et al	American	2009	2005–2006	56/18	NR	NR	NR	NR	NR	NR	NR	NR	NR
[10]	Müller-Nordhorn et al	European	2009	2004–2005	17/13	49.0/51.0	NR	NR	378/414	NR	NR	NR	3.1/2.7	NR
[11]	Reiner-Deitemyer et al	Australian	2011	2003–2009	180/1050	45.3/49.5	72/75	8/7	90/85	45/48	NR	NR	NR	NR
[12]	Addo et al	European	2012	2002–2012	45/55	NR	NR	NR	276/329	NR	NR	NR	NR	NR
[13]	Chen et al	Asian	2013	2008–2010	86/63	NR	NR	NR	79/180†	NR	NR	NR	NR	NR
[14]	Joux et al	European	2013	2007–2009	71/30	37.9/44.2	67/69	9/8	NR	NR	215/234	NR	NR	NR
[15]	Prabhakaran et al	American	2013	2010–2011	69/23	53.9/55.6	66/67	NR	NR	90/103	146/172†	NR	4.3/4.2	2.9/0
[16]	Sun et al	Asian	2013	2007–2011	66/32	50.4/51.5	54/55	NR	498/630†	NR	NR	NR	1.8/1.6	NR
[17]	Camerlingo et al	European	2014	2008–2011	23/8	49.1/51.1	75/75	NR	NR	NR	NR	25.0/16.0†	9.0/11.0	NR
[18]	Hesselfeldt et al	European	2014	2010–2011	22/87	41.0/48.0	72/72	10/8	35/53	46/45	156/165	59.0/54.0	0/9.4	NR
[19]	Atsumi et al	Asian	2015	2009–2013	66/51	38.1/48.9	71/70	NR	34/38†	78/75	117/132	34.8/23.5	NR	NR
[20]	Nishijima et al	Asian	2016	2010–2014	36/41	40.3/41.9	73/71†	7/7	NR	NR	NR	NR	NR	NR
[21]	Puolakka et al	European	2016	2010–2011	45/32	47.8/59.4	69/68	NR	68/69	NR	NR	NR	NR	NR
[22]	Henry-Morrow et al	American	2017	2014–2017	21/10	57.3/54.2	75/75	NR	NR	NR	NR	NR	NR	NR
[23]	Morgenstern et al	American	2003	1998–2000	44/3	NR	NR	NR	NR	NR	NR	NR	NR	NR
[24]	Mehdiratta et al	American	2006	1996–2002	47 /87	NR	NR	NR	NR	78/86	NR	NR	NR	NR
[25]	Demaerschalk et al	American	2008	1998–2008	320/4	NR	NR	NR	NR	NR	NR	NR	NR	NR
[26]	Abdullah et al	American	2008	2004–2005	18/16	52.0/57.0	75/71	9/6	66/90	NR	NR	NR	NR	NR
[27]	Kim et al	Asian	2009	2006–2007	47/44	29.8/36.7	63/63	12/13	109/70†	35/49†	144/119†	55.3/61.4	NR	10.0/4.9
[28]	Pedragosa et al	European	2009	2006–2007	19/9	NR	75/68	18/19	NR	NR	162/210	NR	NR	0/0
[29]	Heo et al	Asian	2010	2008–2009	312/199	NR	NR	14/13	62/67	57/72†	124/134†	59.2/55.6	14.6/15.2	NR
[30]	Bae et al	Asian	2010	2008–2009	18/33	22.3/48.5	64/68	NR	124/87†	30/42†	151/129†	NR	NR	NR
[31]	Dharmasaroja et al	Asian	2010	2007–2009	110/14	52.0/38.0	62/63	14/10	120/81†	49/56	170/137†	41.8/48.4	NR	1.7/3.0
[32]	Hoegerl et al	American	2011	2006–2008	12/4	45.6/43.0	72/73	NR	NR	49/86	NR	NR	NR	NR
[33]	Sung et al	Asian	2011	2009–2010	21/40	42.9/30.0	71/66	18/16	54/39	58/69†	121/113	28.6/35.0	NR	9.5/12.5
[34]	Etgen et al	European	2011	2005–2006	95/24	52.6/29.2	73/69†	13/13	66/64	39/62†	NR	NR	4.2/20.8†	2.1/4.2
[35]	Walter et al	European	2011	2009–2010	32/16	49.0/46.5	73/75	NR	NR	40/84†	NR	NR	NR	NR
[36]	Dirks et al	European	2011	2005–2008	393/308	50.0/49.0	72/72	8/8	91/90	70/73	NR	52.0/58.0†	17.0/17.0	5.6/4.6
[37]	Salottolo et al	European	2011	2006–2008	108/15	59.3/60.0	66/80	NR	48/50	55/78†	NR	NR	NR	NR
[38]	Rudd et al	European	2011	2007–2010	93/32	NR	75/76	14/14	NR	73/65	NR	48.0/55.0	19.6/18.1	0/3.0
[39]	Bhatt et al	American	2012	2009–2011	47/60	53.0/48.0	69/66	11/12	NR	68/93	NR	NR	NR	2.0/8.0
[40]	Ford et al	American	2012	2009–2012	87/132	56.0/52.0	61/70†	7/9†	67/62	39/60†	111/131†	43.0/49.0	NR	3.4/3.0
[41]	Ratanakorn et al	Asian	2012	2005–2006	16/0	NR	NR	NR	NR	NR	NR	NR	NR	NR
[42]	Meretoja et al	European	2012	1998–2011	372/149	NR	69/71	7/10	73/76	20/34†	118/120	38.0/41.0	6.013.0	NR
[43]	McKinney et al	American	2013	2009–2010	31/17	52.0/48.0	70/62	11/7†	NR	67/62	NR	NR	NR	NR
[44]	Scott et al	American	2013	2005–2010	235/89	NR	NR	NR	NR	NR	NR	NR	NR	NR
[45]	Meretoja et al	Australian	2013	2003–2012	48/85	NR	73/77†	11/12	73/77	46/61†	115/140	NR	NR	2.1/3.8
[46]	Nolte et al	European	2013	2007	34/77	62.0/53.0	74/72	13/9	59/55	35/54†	NR	NR	NR	NR
[47]	Thortveit et al	European	2013	2007–2011	82/156	NR	NR	NR	84/87	28/36†	NR	NR	NR	4.9/1.3
[48]	Burnett et al	American	2014	2008–2014	108/94	53.7/51.1	74/73	10/10	NR	56/82†	NR	NR	13.0/6.0	4.0/4.0
[49]	Greenberg et al	American	2014	2012–2014	35/32	63.0/68.0	NR	8/10	NR	35/83†	NR	71.4/37.5†	0/0	0/0
[50]	Kim et al	Asian	2014	2007–2011	202/44	41.1/36.4	71/64†	13/17†	NR	45/65†	NR	NR	NR	NR
[51]	Cho et al	Asian	2014	2004–2006	63/39	44.9/28.2	69/68	16/13	56/44	45/64†	NR	NR	NR	NR

(*continued*)

Table 1

(continued).

Refs	First author	Area	Year	Study period	IVT cases, no. Po/Pre	Female, % Po/Pre	Median age, y Po/Pre	Median NIHSS Po/Pre	Median ODT, min Po/Pre	Median DNT, min Po/Pre	Median ONT, min Po/Pre	mRS ≤ 2, % Po/Pre	Mortality, % Po/Pre	SICH, % Po/Pre
[52]	Chen et al	Asian	2014	2006–2010	216/91	43.5/35.2	68/69	12/15†	58/45†	51/88†	125/145†	50.5/44.0	3.2/6.6	4.6/7.7
[51]	Hsieh et al	Asian	2014	2009–2012	14/18	43.0/33.0	68/64	9/13	NR	57/93†	136/154	43.0/33.0	NR	21.0/17.0
[53]	Van Schaik et al	European	2014	2007–2012	58/12	46.3/42.2	70/75	NR	NR	25/60†	NR	NR	NR	7.3/4.9
[54]	van Dishoeck et al	European	2014	2006–2012	185/41	50.0/50.0	63/60	NR	NR	35/75†	NR	NR	NR	NR
[55]	Martínez-Sánchez et al	European	2014	2008–2010	18/12	50.2/49.0	72/70	7/7	74/88	66/144†	155/205†	83.3/75.0†	16.7/10.0	0/0
[56]	Chakraborty et al	American	2015	2009–2013	37/24	NR	NR	NR	NR	54/49	NR	NR	NR	NR
[57]	Shah et al	American	2015	2012–2013	23/39	47.8/57.5	71/74	7/7	75/68	55/93†	166/140	NR	NR	NR
[58]	Sohn et al	Asian	2015	2007–2013	252/71	42.5/32.4	67/64†	10/12	87/98	31/48†	123/142†	57.9/42.3†	11.5/12.7	2.8/7.2†
[59]	Bladin et al	Australian	2015	2011–2012	16/10	31.0/30.0	69/73	NR	NR	85/101	173/218	80.0/33.0†	6.0/10.0	6.0/0
[60]	Mazighi et al	European	2015	2006–2010	21/4	80.0/71.0	68/68	13/7†	70/73	NR	NR	28.0/59.1†	24.0/4.6	4.0/0
[61]	Khor et al	European	2015	2012–2014	100/75	51.0/43.0	75/72	12/11	90/81	35/61†	NR	NR	NR	NR
[62]	Ibrahim et al	American	2016	2008–2015	102/102	17.6/19.6	53/52	11/12	105/80†	47/83†	NR	73.3/47.1†	3.9/7.8	5.9/5.9
[63]	Moran et al	American	2016	2009–2011	122/44	51.0/46.0	73/68	13/14	NR	45/53†	110/118	54.0/41.0	12.0/18.0	NR
[64]	Busby et al	American	2016	2014–2015	52/41	52.0/32.0	70/64†	12/13	NR	25/62†	NR	NR	NR	NR
[65]	Gosser et al	American	2016	2008–2012	67/38	NR	NR	NR	NR	70/90†	NR	NR	NR	NR
[66]	Huang et al	Asian	2016	2011–2015	202/146	26.7/25.2	61/61	4/9†	106/110	53/116†	173/229†	NR	4.1/4.5	7.5/3.5
[67]	Liang et al	Asian	2016	2014–2015	20/13	20.0/15.4	64/62	8/9	NR	47/90†	170/163	75.0/30.8†	0/7.69	0/0
[68]	Sakamoto et al	Asian	2016	2014–2015	21/19	38.0/37.0	67/72	11/12	83/57	54/83†	138/162	67.0/53.0	NR	0/5.3
[69]	Choi et al	Asian	2016	2007–2012	118/111	NR	NR	13/15†	NR	40/46†	NR	NR	NR	NR
[70]	Hsieh et al	Asian	2016	2012–2014	144/25	35.5/48.3†	69/71	16/13	23/22	63/68	NR	NR	NR	NR
[71]	Heikkilä et al	European	2016	2012–2013	33/31	NR	NR	NR	NR	28/54†	101/139†	NR	NR	NR
[72]	Nardetto et al	European	2016	2011–2013	25 /106	NR	72/72	9/11	57/55	73/95	151/166	NR	NR	NR
[73]	Hubert et al	European	2016	2011–2013	1779/912	48.0/42.0†	76/69†	9/7†	65/88†	18/39†	115/117	NR	NR	NR
[74]	Al Kasab et al	American	2017	2008–2016	175/167	51.4/48.5	66/65	9/9	NR	46/62†	NR	NR	NR	NR
[74]	Al Kasab et al	American	2017	2008–2016	795/528	45.3/51.9	66/66	6/8	NR	65/90†	NR	NR	NR	NR
[75]	Jeon et al	Asian	2017	2014–2016	47/198	40.4/36.9	68/69	9/10	91/107	21/46†	103/129†	NR	NR	4.3/13.1†
[76]	Zhou et al	Asian	2017	2015–2016	231/88	43.0/41.7	69/72	7/7	NR	56/100†	NR	96.8/96.5	NR	NR
[77]	Candelaresi et al	European	2017	2013–2015	26/72	NR	70/74	11/12	66/60	56/92†	132/155†	76.9/53.4	8.0 /6.0	11.5 /5.6
[78]	Wojner-Alexandrov et al	American	2005	1999–2001	64/21	NR	NR	NR	42/46†	NR	NR	NR	NR	NR
[79]	Gladstone et al	American	2009	2005	30/7	NR	NR	NR	63/46	83/128†	141/195†	NR	NR	NR
[80]	O'Brien et al	Australian	2012	2007–2008	22/5	NR	NR	NR	76/59	56/102†	235/298†	NR	NR	NR
[81]	Walter et al	European	2012	2008–2011	53/47	42.0/32.0	72/71	5/6	NR	NR	NR	37.7/44.7	11.0/4.0	NR
[82]	Lahr et al	European	2012	2010	62/113	44.0/51.0	70/73	NR	84/72	35/47†	124/120	66.0/52.0	NR	2.0/3.0
[83]	Berglund et al	European	2012	2008	60/24	NS	NR	NR	NR	NR	58/57	NR	NR	NR
[84]	Amorim et al	American	2013	2005–2008	113/27	44.2/48.1	73/74	12/8	52/62	74/74	124/130	26.5/33.3	10.9/7.4	0.9/3.7
[85]	Willeit et al	Australian	2014	2010–2013	213/160	45.0/45.2	72/74	4/4	NR	44/49†	NR	65.5/56.3†	13.0/13.0	1.9/3.8
[86]	Ebinger et al	European	2014	2011–2013	200/220	54.0/50.6	77/75	11/9	NR	NR	103/119†	43.5/47.7	7.0/6.4	3.5/6.4
[87]	Itrat et al	American	2015	2014–2015	16/13	54.0/57.1	62/64	6/7	NR	32/58†	NR	NR	NR	NR
[88]	Kendall et al	European	2015	2012–2013	215/215	NR	NR	13/13	58/57	66/76†	154/165	NR	NR	NR
[89]	Kim et al	Asian	2016	2012–2015	28/187	39.3/36.9	68/68	11/10	60/62	20/29†	NR	NR	NR	NR
[90]	Vidale et al	European	2016	2014	51/4	63.3/54.6	74/73	9/7	216/234	142/171†	342/407†	NR	NR	NR

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.
DNT=door to needle time, IVT=intravenous thrombolysis, mRS=modified Rankin Scale, NIHSS=National Institute of Health Stroke Scale, NR=not reported in original paper, ODT=onset to door time, ONT=onset to needle time, Po=postoperative, Pre=preoperative, SICH=symptomatic intracranial hemorrhage.

* Citation [74] included data of 2 groups (Hub and Spoke 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. 62–2.06) in the educational campaign and training protocol 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)

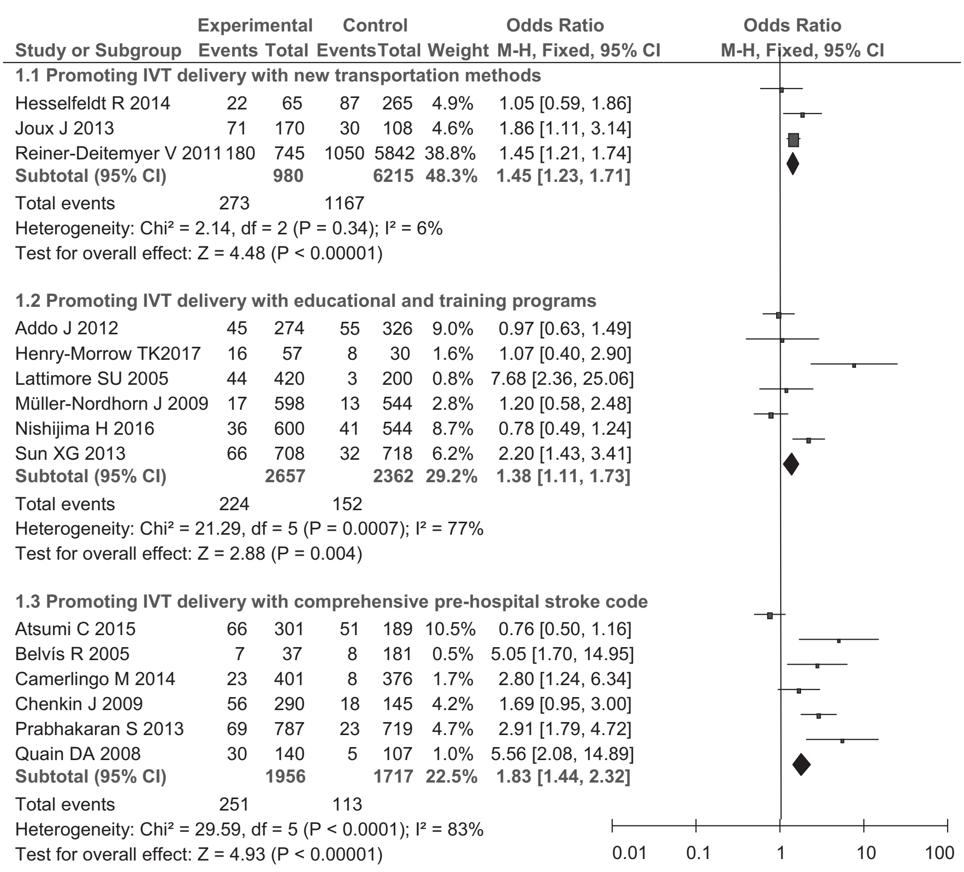

Figure 1. Post- versus pre-intervention in primary outcomes of reducing prehospital delay.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1 Improvement of promoting IVT delivery in Asian countries						
Kim SK2009	47	328	44	678	1.5%	2.41 [1.56, 3.72]
Ahro Kim 2014	77	130	16	48	0.6%	2.91 [1.45, 5.82]
Bae HJ2010	18	55	33	47	1.4%	0.21 [0.09, 0.48]
Chen CH2014	216	2512	91	3500	4.1%	3.52 [2.74, 4.53]
Cho HJ2014	63	799	39	888	2.0%	1.86 [1.23, 2.81]
Choi HY2016	118	2078	111	2172	6.1%	1.12 [0.86, 1.46]
Dharmasaroja PA2010	110	146	14	170	0.2%	34.05 [17.53, 66.13]
Heo JH2010	312	5404	199	5798	10.8%	1.72 [1.44, 2.07]
Hsieh CY2014	14	280	18	900	0.5%	2.58 [1.27, 5.25]
Hsieh MJ2016	118	2078	111	2172	6.1%	1.12 [0.86, 1.46]
Jeon SB2017	110	146	14	170	0.2%	34.05 [17.53, 66.13]
Liang Z2016	312	5404	199	5798	10.8%	1.72 [1.44, 2.07]
Huang Q 2016	14	280	18	900	0.5%	2.58 [1.27, 5.25]
Ratanakorn D2012	144	433	25	105	1.6%	1.59 [0.98, 2.61]
Sakamoto Y2016	20	31	13	35	0.3%	3.08 [1.13, 8.41]
Sohn SW2015	146	1374	202	2156	8.4%	1.15 [0.92, 1.44]
Sung SF2011	16	293	0	130	0.0%	15.52 [0.92, 260.66]
Zhou Y2017	21	151	19	250	0.7%	1.96 [1.02, 3.79]
Subtotal (95% CI)		**21922**		**25917**	**55.6%**	**1.89 [1.74, 2.04]**
Total events	1876		1166			
Heterogeneity: Chi² = 254.26, df = 17 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 16.02 (P < 0.00001)						
3.2 Improvement of promoting IVT delivery in European countries and Australia						
Meretoja A2012	372	1200	149	1100	6.4%	2.87 [2.32, 3.54]
Walter S2011	32	120	16	91	0.8%	1.70 [0.87, 3.35]
Bladin CF2015	16	57	10	52	0.4%	1.64 [0.67, 4.03]
Dirks M2011	393	880	308	777	10.8%	1.23 [1.01, 1.49]
Etgen T2011	95	743	24	500	1.5%	2.91 [1.83, 4.62]
Martínez-Sánchez P2014	18	225	12	259	0.6%	1.79 [0.84, 3.80]
Mazighi M2015	21	25	4	22	0.0%	23.63 [5.16, 108.26]
Meretoja A 2013	47	324	82	468	3.4%	0.80 [0.54, 1.18]
Nolte CH2007	51	77	14	34	0.4%	2.80 [1.22, 6.43]
Pedragosa A2009	19	198	9	201	0.5%	2.26 [1.00, 5.14]
Rudd M2011	93	968	32	969	1.7%	3.11 [2.06, 4.70]
van Dishoeck AM2014	58	261	12	262	0.6%	5.95 [3.11, 11.39]
Van Schaik SM2014	185	951	41	828	2.1%	4.64 [3.26, 6.60]
Subtotal (95% CI)		**6029**		**5563**	**29.2%**	**2.17 [1.95, 2.41]**
Total events	1400		713			
Heterogeneity: Chi² = 106.76, df = 12 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 14.42 (P < 0.00001)						
3.3 Improvement of promoting IVT delivery in American countries						
Chakraborty S 2015	37	110	15	43	0.9%	0.95 [0.45, 1.99]
Abdullah AR2008	18	44	16	74	0.4%	2.51 [1.11, 5.68]
Bhatt A2012	47	484	60	789	2.4%	1.31 [0.88, 1.95]
Busby L2016	52	397	41	414	2.1%	1.37 [0.89, 2.12]
DemaerschalkBM 2008	320	1800	4	1454	0.2%	78.38 [29.16, 210.67]
Hoegerl C2011	12	101	4	132	0.2%	4.31 [1.35, 13.81]
McKinney JS 2013	31	114	17	115	0.7%	2.15 [1.11, 4.17]
Moran JL2016	122	388	44	151	2.6%	1.12 [0.74, 1.68]
Morgenstern LB2003	23	266	2	233	0.1%	10.93 [2.55, 46.89]
Scott PA2013	235	8419	89	7119	5.6%	2.27 [1.77, 2.90]
Subtotal (95% CI)		**12123**		**10524**	**15.2%**	**2.90 [2.51, 3.34]**
Total events	897		292			
Heterogeneity: Chi² = 107.08, df = 9 (P < 0.00001); I² = 92%						
Test for overall effect: Z = 14.73 (P < 0.00001)						

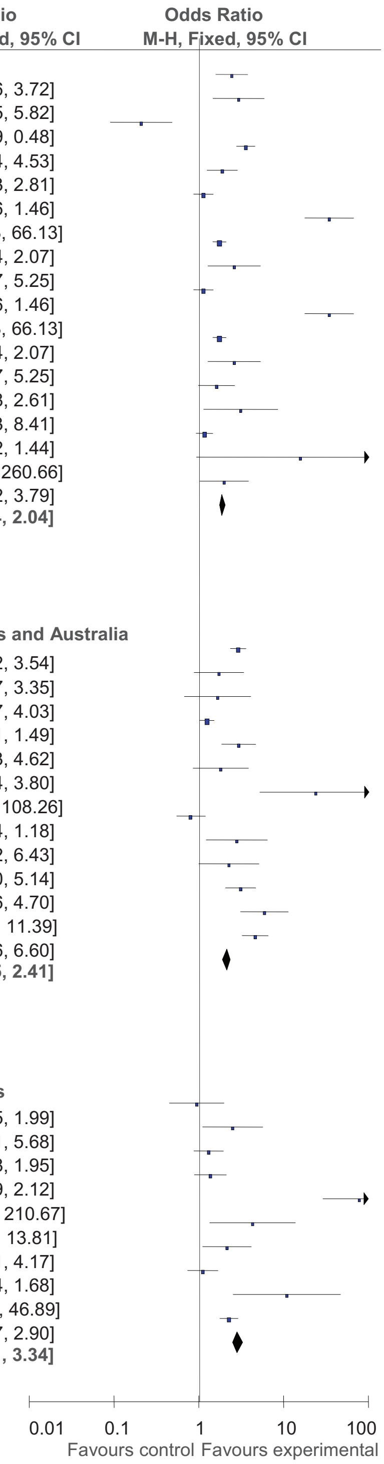

Figure 2. Post- versus pre-intervention in primary outcome of reducing in-hospital delay in different areas.

(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, 4.15; 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.

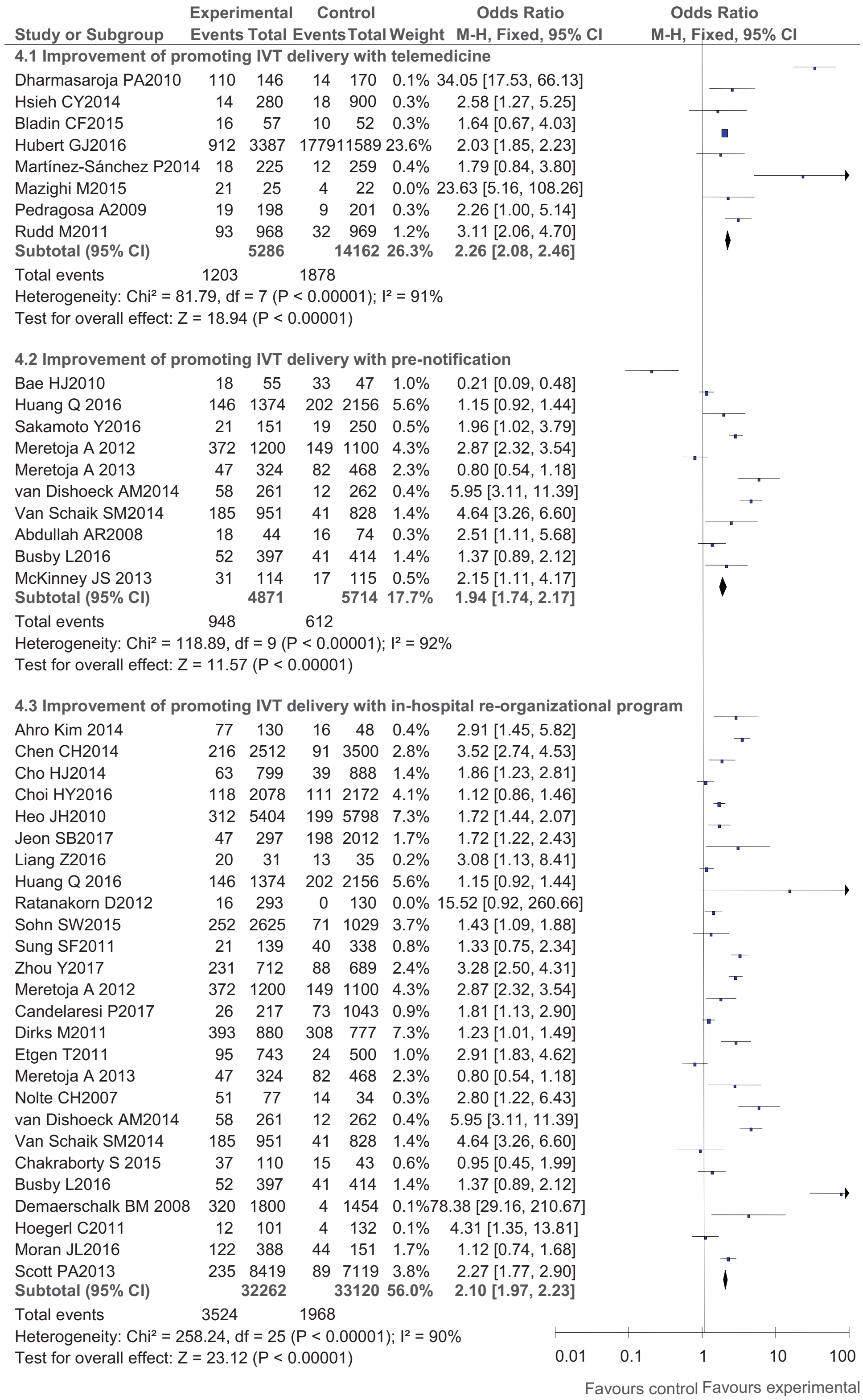

Figure 3. Post- versus pre-intervention in primary outcome of various methods for reducing in-hospital delay.

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 detected and solutions addressing these factors proposed as our results showed. An optimal and continuous gain in thrombolysis administration for AIS involved

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio 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	3.8%	2.12 [0.83, 5.38]
Liang Z2016	13	20	5	13	1.2%	2.97 [0.70, 12.62]
Huang Q 2016	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		128			
Heterogeneity: Chi² = 137.84, 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 I2016	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, 5.35]
Nolte CH2007	64	77	5	34	0.7%	28.55 [9.31, 87.59]
Salottolo KM2011	62	108	5	15	2.2%	2.70 [0.86, 8.42]
Thortveit ET 2013	86	156	19	82	6.5%	4.07 [2.23, 7.44]
van Dishoeck AM2014	47	58	0	12	0.1%	103.26 [5.69, 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		125			
Heterogeneity: Chi² = 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]
Mehdiratta M 2006	7	40	3	62	1.1%	4.17 [1.01, 17.22]
Al Kasab S2017	366	450	8	39	1.6%	16.88 [7.49, 38.05]
Bhatt 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	87	68	132	6.9%	3.37 [1.83, 6.22]
Gosser 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, 7.26]
Moran JL2016	99	122	27	44	4.3%	2.71 [1.27, 5.78]
Shah S 2015	24	39	3	23	0.8%	10.67 [2.70, 42.16]
Subtotal (95% CI)		**1186**		**682**	**33.6%**	**5.61 [4.41, 7.13]**
Total events	850		203			
Heterogeneity: Chi² = 42.50, df = 11 (P < 0.0001); I² = 74%						
Test for overall effect: Z = 14.04 (P < 0.00001)						

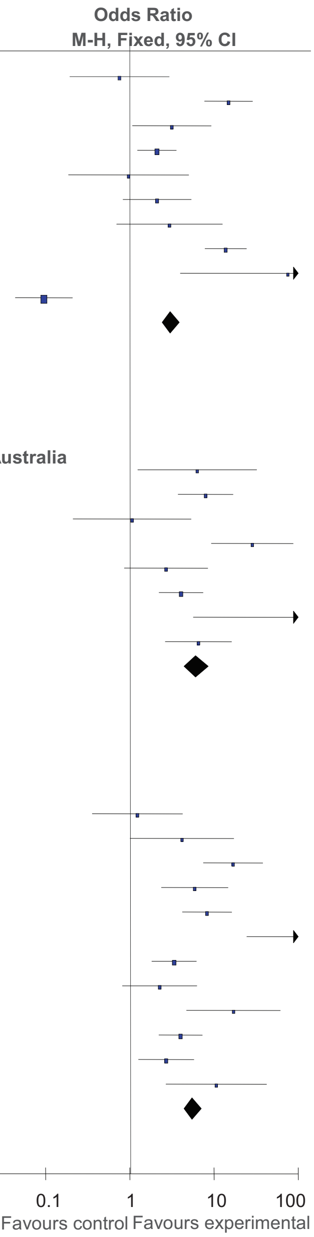

Figure 4. Post- versus pre-intervention in secondary outcome of reducing in-hospital delay in different areas.

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 streamline 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.[91] A previous systematic review by Evenson et al[5] 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 Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.1 Improvement of reducing in-hospital delay with telemedicine						
Hsieh CY2014	8	74	2	18	1.8%	0.97 [0.19, 5.01]
Nardetto L2016	2	25	8	106	1.8%	1.07 [0.21, 5.35]
Al Kasab S2017	366	450	8	39	1.7%	16.88 [7.49, 38.05]
Subtotal (95% CI)		**549**		**163**	**5.3%**	**6.19 [3.34, 11.48]**
Total events	376		18			
Heterogeneity: Chi² = 15.31, df = 2 (P = 0.0005); I² = 87%						
Test for overall effect: Z = 5.79 (P < 0.00001)						
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 Dishoeck 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]
Busby L2016	45	52	2	41	0.2%	125.36 [24.59, 639.12]
Subtotal (95% CI)		**567**		**390**	**9.4%**	**14.44 [9.97, 20.90]**
Total events	461		88			
Heterogeneity: Chi² = 15.09, df = 5 (P = 0.010); I² = 67%						
Test for overall effect: Z = 14.15 (P < 0.00001)						
6.3 Improvement of reducing in-hospital delay with re-organizational program						
Ahro Kim 2014	59	77	13	16	3.1%	0.76 [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 Z2016	13	20	5	13	1.3%	2.97 [0.70, 12.62]
qiang huang 2016	88	146	20	202	4.2%	13.81 [7.82, 24.37]
Sohn SW2015	11	252	23	71	21.5%	0.10 [0.04, 0.21]
Heikkilä I2016	31	33	22	31	0.9%	6.34 [1.25, 32.26]
Nolte CH2007	64	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 Dishoeck 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	66	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 [2.21, 7.26]
Moran JL2016	99	122	27	44	4.7%	2.71 [1.27, 5.78]
Subtotal (95% CI)		**1949**		**1233**	**85.3%**	**4.15 [3.50, 4.93]**
Total events	1196		361			
Heterogeneity: Chi² = 177.44, df = 18 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 16.23 (P < 0.00001)						

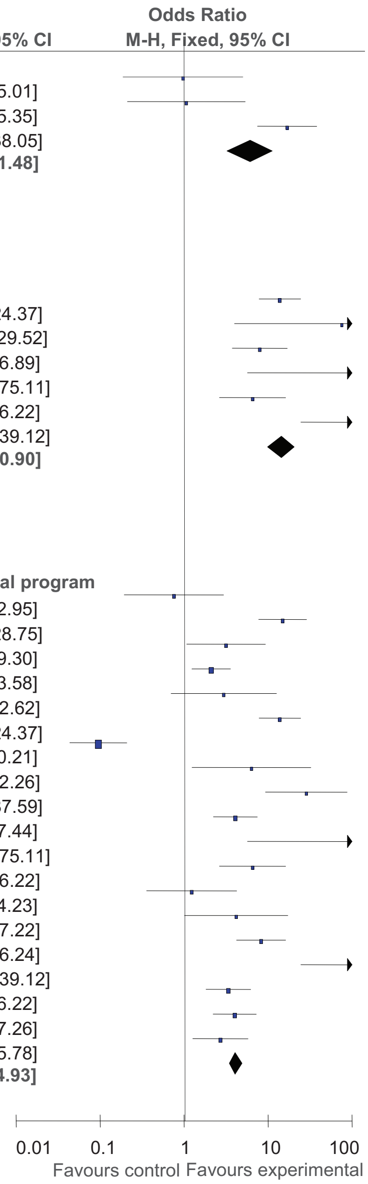

Figure 5. Post- versus pre-intervention in secondary outcome of various methods to reduce in-hospital delay.

a larger number of emergency department visits for stroke mimics[92] or alternative diagnoses other than stroke[82]), and the positive effects could be decreased soon after the interventions.[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),[95] the stroke registry in Australia,[96] and Target: Stroke in America [3] 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.[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.[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[98] and serves as a cost-saving protocol for remote practitioners.[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.[85] Improvements in EMS including the

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
7.1 Reducing total time delay using new comprehensive stroke pathway						
Edilberto Amorim 2013	113	1669	27	919	7.6%	2.40 [1.56, 3.68]
Ahmed Itrat 2015	16	100	13	56	3.3%	0.63 [0.28, 1.43]
Kim DH2 2016	106	215	11	59	2.1%	4.24 [2.09, 8.61]
O'Brien W2012	22	115	5	67	1.2%	2.93 [1.05, 8.16]
Willeit J 2014	213	1266	160	1238	31.7%	1.36 [1.09, 1.70]
Gladstone DJ 2009	30	128	7	74	1.6%	2.93 [1.22, 7.06]
Vidale S 2016	51	1084	4	573	1.2%	7.02 [2.53, 19.53]
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-AlexandrovAW 2005	64	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						
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 = 0.60); I² = 0%						
Test for overall effect: Z = 6.09 (P < 0.00001)						

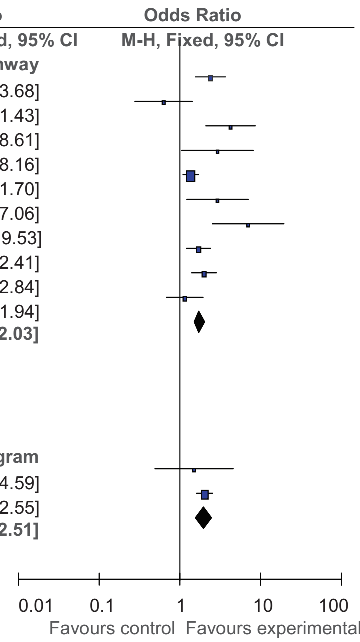

Figure 6. Post- versus pre-intervention in primary outcome of reducing total time delay.

centralization of stroke care (as in MSTU [81,87]) and infrastructure advancement (such as pre-notification or consultation using telemedicine technology platforms [43,87]) contributed the most to reducing total delays and tackling the problem of IVT undertreatment (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	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1 Reducing pre-hospital delay with new transportation methods						
Reiner-Deitemyer V 2011	389	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						
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**	**50.8%**	**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						
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	184	787	134	719	14.2%	1.33 [1.04, 1.71]
Quain 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 = 1.88, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 4.47 (P < 0.00001)						

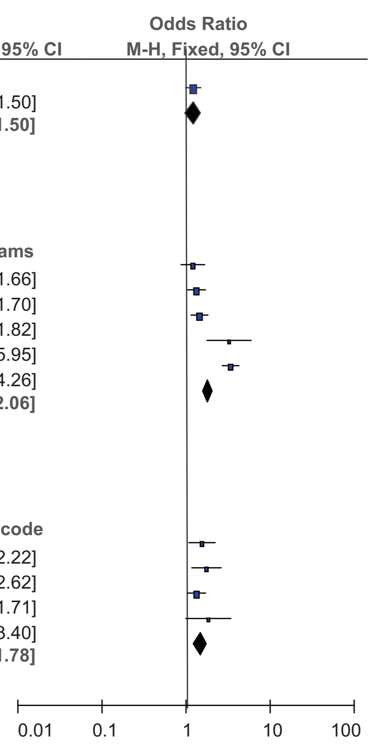

Figure 7. Post- versus pre-intervention in secondary outcomes of reducing prehospital delay.

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.

Author contributions

Conceptualization: Qiang Huang, Jian Wu.
Data curation: Qiang Huang, Jing-ze Zhang, Wen-deng Xu.
Formal analysis: Qiang Huang, Jian Wu.
Funding acquisition: Jian Wu.
Investigation: Qiang Huang, Wen-deng Xu, Jian Wu.
Methodology: Qiang Huang.
Project administration: Qiang Huang.
Resources: Qiang Huang.
Software: Qiang Huang.
Supervision: Jian Wu.
Validation: Qiang Huang.
Visualization: Qiang Huang.
Writing – original draft: Qiang Huang.
Writing – review & editing: Jing-ze Zhang, Wen-deng Xu, Jian Wu.

References

[1] National Institute of Neurological Disorders and Strole rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581–1587.
[2] Paul CL, Ryan A, Rose S, et al. How can we improve stroke thrombolysis rates? A review of health system factors and approaches associated with thrombolysis administration rates in acute stroke care. Implement Sci 2016;11:51.
[3] Fonarow GC, Zhao X, Smith EE, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. JAMA 2014;311:1632–40.
[4] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008–12.
[5] Evenson KR, Rosamond WD, Morris DL. Prehospital and in-hospital delays in acute stroke care. Neuroepidemiology 2001;20:65–76.
[6] Lattimore SU, Chalela J, Davis L, et al. Impact of establishing a primary stroke center at a community hospital on the use of thrombolytic therapy: the NINDS Suburban Hospital Stroke Center experience. Stroke 2003;34:e55–7.
[7] Belvis R, Cocho D, Marti-Fabregas J, et al. Benefits of a prehospital stroke code system. Feasibility and efficacy in the first year of clinical practice in Barcelona, Spain. Cerebrovasc Dis 2005;19:96–101.
[8] Quain DA, Parsons MW, Loudfoot AR, et al. Improving access to acute stroke therapies: a controlled trial of organised pre-hospital and emergency care. Med J Aust 2008;189:429–33.
[9] Chenkin J, Gladstone DJ, Verbeek PR, et al. Predictive value of the Ontario prehospital stroke screening tool for the identification of patients with acute stroke. Prehosp Emerg Care 2009;13:153–9.
[10] Muller-Nordhorn J, Wegscheider K, Nolte CH, et al. Population-based intervention to reduce prehospital delays in patients with cerebrovascular events. Arch Intern Med 2009;169:1484–90.
[11] Reiner-Deitemyer V, Teuschl Y, Matz K, et al. Helicopter transport of stroke patients and its influence on thrombolysis rates: data from the Austrian Stroke Unit Registry. Stroke 2011;42:1295–300.
[12] Addo J, Ayis S, Leon J, et al. Delay in presentation after an acute stroke in a multiethnic population in South London: the South London stroke register. J Am Heart Assoc 2012;1:e1685.
[13] Chen S, Sun H, Zhao X, et al. Effects of comprehensive education protocol in decreasing pre-hospital stroke delay among Chinese urban community population. Neurol Res 2013;35:522–8.
[14] Joux J, Olindo S, Girard-Claudon A, et al. Prehospital transfer medicalization increases thrombolysis rate in acute ischemic stroke. A French stroke unit experience. Clin Neurol Neurosurg 2013;115:1583–5.
[15] Prabhakaran S, O'Neill K, Stein-Spencer L, et al. Prehospital triage to primary stroke centers and rate of stroke thrombolysis. JAMA Neurol 2013;70:1126–32.
[16] Sun XG, Zhang N, Wang T, et al. Public and professional education on urgent therapy for acute ischemic stroke: a community-based intervention in Changsha. Neurol Sci 2013;34:2131–5.
[17] Camerlingo M, D'Asero S, Perego L, et al. How to improve access to appropriate therapy and outcome of the acute ischemic stroke: a 24-month survey of a specific pre-hospital planning in Northern Italy. Neurol Sci 2014;35:1359–63.
[18] Hesselfeldt R, Gyllenborg J, Steinmetz J, et al. Is air transport of stroke patients faster than ground transport? A prospective controlled observational study. Emerg Med J 2014;31:268–72.
[19] Atsumi C, Hasegawa Y, Tsumura K, et al. Quality assurance monitoring of a citywide transportation protocol improves clinical indicators of intravenous tissue plasminogen activator therapy: a community-based, longitudinal study. J Stroke Cerebrovasc Dis 2015;24:183–8.
[20] Nishijima H, Kon T, Ueno T, et al. Effect of educational television commercial on pre-hospital delay in patients with ischemic stroke. Neurol Sci 2016;37:105–9.
[21] Puolakka T, Vayrynen T, Erkkila EP, et al. Fire engine support and on-scene time in prehospital stroke care: a prospective observational study. Prehosp Disaster Med 2016;31:278–81.
[22] Henry-Morrow TK, Nelson BD, Conahan E, et al. An educational intervention allows for greater prehospital recognition of acute stroke. Am J Emerg Med 2017;35:1959–61.
[23] Morgenstern LB, Bartholomew LK, Grotta JC, et al. Sustained benefit of a community and professional intervention to increase acute stroke therapy. Arch Intern Med 2003;163:2198–202.
[24] Mehdiratta M, Woolfenden AR, Chapman KM, et al. Reduction in IV t-PA door to needle times using an Acute Stroke Triage Pathway. Can J Neurol Sci 2006;33:214–6.
[25] Demaerschalk BM, Bobrow BJ, Paulsen M. Development of a metropolitan matrix of primary stroke centers: the Phoenix experience. Stroke 2008;39:1246–53.
[26] Abdullah AR, Smith EE, Biddinger PD, et al. Advance hospital notification by EMS in acute stroke is associated with shorter door-to-computed tomography time and increased likelihood of administration of tissue-plasminogen activator. Prehosp Emerg Care 2008;12:426–31.
[27] Kim SK, Lee SY, Bae HJ, et al. Pre-hospital notification reduced the door-to-needle time for iv t-PA in acute ischaemic stroke. Eur J Neurol 2009;16:1331–5.
[28] Pedragosa A, Alvarez-Sabin J, Molina CA, et al. Impact of a telemedicine system on acute stroke care in a community hospital. J Telemed Telecare 2009;15:260–3.
[29] Heo JH, Kim YD, Nam HS, et al. A computerized in-hospital alert system for thrombolysis in acute stroke. Stroke 2010;41:1978–83.
[30] Bae HJ, Kim DH, Yoo NT, et al. Prehospital notification from the emergency medical service reduces the transfer and intra-hospital processing times for acute stroke patients. J Clin Neurol 2010;6:138–42.
[31] Dharmasaroja PA, Muengtaweepongsa S, Kommarkg U. Implementation of Telemedicine and Stroke Network in thrombolytic administration: comparison between walk-in and referred patients. Neurocrit Care 2010;13:62–6.

[32] Hoegerl C, Goldstein FJ, Sartorius J. Implementation of a stroke alert protocol in the emergency department: a pilot study. J Am Osteopath Assoc 2011;111:21–7.
[33] Sung SF, Huang YC, Ong CT, et al. A parallel thrombolysis protocol with nurse practitioners as coordinators minimized door-to-needle time for acute ischemic stroke. Stroke Res Treat 2011;2011:198518.
[34] Etgen T, Freudenberger T, Schwahn M, et al. Multimodal strategy in the successful implementation of a stroke unit in a community hospital. Acta Neurol Scand 2011;123:390–5.
[35] Walter S, Kostopoulos P, Haass A, et al. Point-of-care laboratory halves door-to-therapy-decision time in acute stroke. Ann Neurol 2011;69: 581–6.
[36] Dirks M, Niessen LW, van Wijngaarden JD, et al. Promoting thrombolysis in acute ischemic stroke. Stroke 2011;42:1325–30.
[37] Salottolo KM, Fanale CV, Leonard KA, et al. Multimodal imaging does not delay intravenous thrombolytic therapy in acute stroke. AJNR Am J Neuroradiol 2011;32:864–8.
[38] Rudd M, Rodgers H, Curless R, et al. Remote specialist assessment for intravenous thrombolysis of acute ischaemic stroke by telephone. Emerg Med J 2012;29:704–8.
[39] Bhatt A, Shatila A. Neurohospitalists improve door-to-needle times for patients with ischemic stroke receiving intravenous tPA. Neurohospitalist 2012;2:119–22.
[40] Ford AL, Williams JA, Spencer M, et al. Reducing door-to-needle times using Toyota's lean manufacturing principles and value stream analysis. Stroke 2012;43:3395–8.
[41] Ratanakorn D, Keandoungchun J, Sittichanbuncha Y, et al. Stroke fast track reduces time delay to neuroimaging and increases use of thrombolysis in an academic medical center in Thailand. J Neuroimaging 2012;22:53–7.
[42] Meretoja A, Strbian D, Mustanoja S, et al. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. Neurology 2012;79: 306–13.
[43] McKinney JS, Mylavarapu K, Lane J, et al. Hospital prenotification of stroke patients by emergency medical services improves stroke time targets. J Stroke Cerebrovasc Dis 2013;22:113–8.
[44] Scott PA, Meurer WJ, Frederiksen SM, et al. A multilevel intervention to increase community hospital use of alteplase for acute stroke (INSTINCT): a cluster-randomised controlled trial. Lancet Neurol 2013;12:139–48.
[45] Meretoja A, Weir L, Ugalde M, et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. Neurology 2013;81:1071–6.
[46] Nolte CH, Malzahn U, Kuhnle Y, et al. Improvement of door-to-imaging time in acute stroke patients by implementation of an all-points alarm. J Stroke Cerebrovasc Dis 2013;22:149–53.
[47] Thortveit ET, Boe MG, Ljostad U, et al. Organizational changes aiming to reduce iv tPA door-to-needle time. Acta Neurol Scand 2014;130: 248–52.
[48] Burnett MM, Zimmermann L, Coralic Z, et al. Simple text-messaging intervention is associated with improved door-to-needle times for acute ischemic stroke. Stroke 2014;45:3714–6.
[49] Greenberg K, Maxwell CR, Moore KD, et al. Improved door-to-needle times and neurologic outcomes when IV tissue plasminogen activator is administered by emergency physicians with advanced neuroscience training. Am J Emerg Med 2015;33:234–7.
[50] Kim A, Lee JS, Kim JE, et al. Trends in yield of a code stroke program for enhancing thrombolysis. J Clin Neurosci 2015;22:73–8.
[51] Hsieh CY, Chen WF, Chen CH, et al. Efforts to reduce the door-to-needle time of thrombolysis in acute ischemic stroke: video-assisted therapeutic risk communication. J Formos Med Assoc 2014;113:929–33.
[52] Chen CH, Tang SC, Tsai LK, et al. Stroke code improves intravenous thrombolysis administration in acute ischemic stroke. PLoS One 2014;9: e104862.
[53] Van Schaik SM, Van der Veen B, Van den Berg-Vos RM, et al. Achieving a door-to-needle time of 25 minutes in thrombolysis for acute ischemic stroke: a quality improvement project. J Stroke Cerebrovasc Dis 2014;23:2900–6.
[54] van Dishoeck AM, Dippel DW, Dirks M, et al. Measuring quality improvement in acute ischemic stroke care: interrupted time series analysis of door-to-needle time. Cerebrovasc Dis Extra 2014;4:149–55.
[55] Martinez-Sanchez P, Miralles A, Sanz DBR, et al. The effect of telestroke systems among neighboring hospitals: more and better? The Madrid Telestroke Project. J Neurol 2014;261:1768–73.
[56] Chakraborty S, Ross J, Hogan MJ, et al. Beating the clock: time delays to thrombolytic therapy with advanced imaging and impact of optimized workflow. J Stroke Cerebrovasc Dis 2015;24:1270–5.
[57] Shah S, Luby M, Poole K, et al. Screening with MRI for accurate and rapid stroke treatment: SMART. Neurology 2015;84:2438–44.
[58] Sohn SW, Park HS, Cha JK, et al. A systemized stroke code significantly reduced time intervals for using intravenous tissue plasminogen activator under magnetic resonance imaging screening. J Stroke Cerebrovasc Dis 2015;24:465–72.
[59] Bladin CF, Molocijz N, Ermel S, et al. Victorian Stroke Telemedicine Project: implementation of a new model of translational stroke care for Australia. Intern Med J 2015;45:951–6.
[60] Mazighi M, Meseguer E, Labreuche J, et al. TRUST-tPA trial: telemedicine for remote collaboration with urgentists for stroke-tPA treatment. J Telemed Telecare 2017;23:174–80.
[61] Khor MX, Bown A, Barrett A, et al. Pre-hospital notification is associated with improved stroke thrombolysis timing. J R Coll Physicians Edinb 2015;45:190–5.
[62] Ibrahim F, Akhtar N, Salam A, et al. Stroke thrombolysis protocol shortens "door-to-needle time" and improves outcomes-experience at a tertiary care center in Qatar. J Stroke Cerebrovasc Dis 2016;25:2043–6.
[63] Moran JL, Nakagawa K, Asai SM, et al. 24/7 neurocritical care nurse practitioner coverage reduced door-to-needle time in stroke patients treated with tissue plasminogen activator. J Stroke Cerebrovasc Dis 2016;25:1148–52.
[64] Busby L, Owada K, Dhungana S, et al. CODE FAST: a quality improvement initiative to reduce door-to-needle times. J Neurointerv Surg 2016;8:661–4.
[65] Gosser RA, Arndt RF, Schaafsma K, et al. Pharmacist impact on ischemic stroke care in the emergency department. J Emerg Med 2016;50:187–93.
[66] Huang Q, Song HQ, Ji XM, et al. Generalization of the right acute stroke prevention strategies in reducing in-hospital delays. PLoS One 2016;11: e154972.
[67] Liang Z, Ren L, Wang T, et al. Effective management of patients with acute ischemic stroke based on lean production on thrombolytic flow optimization. Australas Phys Eng Sci Med 2016;39:987–96.
[68] Sakamoto Y, Tanabe M, Masuda K, et al. Feasibility of using magnetic resonance imaging as a screening tool for acute stroke thrombolysis. J Neurol Sci 2016;368:168–72.
[69] Choi HY, Kim EH, Yoo J, et al. Decision-making support using a standardized script and visual decision aid to reduce door-to-needle time in stroke. J Stroke 2016;18:239–41.
[70] Hsieh MJ, Tang SC, Chiang WC, et al. Effect of prehospital notification on acute stroke care: a multicenter study. Scand J Trauma Resusc Emerg Med 2016;24:57.
[71] Heikkila I, Kuusisto H, Stolberg A, et al. Stroke thrombolysis given by emergency physicians cuts in-hospital delays significantly immediately after implementing a new treatment protocol. Scand J Trauma Resusc Emerg Med 2016;24:46.
[72] Nardetto L, Dario C, Tonello S, et al. A one-to-one telestroke network: the first Italian study of a web-based telemedicine system for thrombolysis delivery and patient monitoring. Neurol Sci 2016;37: 725–30.
[73] Hubert GJ, Meretoja A, Audebert HJ, et al. Stroke thrombolysis in a centralized and a decentralized system (Helsinki and Telemedical Project for Integrative Stroke Care Network). Stroke 2016;47:2999–3004.
[74] Al KS, Harvey JB, Debenham E, et al. Door to needle time over telestroke: a comprehensive stroke center experience. Telemed J E Health 2018; 24:111–5.
[75] Jeon SB, Ryoo SM, Lee DH, et al. Multidisciplinary approach to decrease in-hospital delay for stroke thrombolysis. J Stroke 2017;19:196–204.
[76] Zhou Y, Xu Z, Liao J, et al. New standardized nursing cooperation workflow to reduce stroke thrombolysis delays in patients with acute ischemic stroke. Neuropsychiatr Dis Treat 2017;13:1215–20.
[77] Candelaresi P, Lattuada P, Uggetti C, et al. A high-urgency stroke code reduces in-hospital delays in acute ischemic stroke: a single-centre experience. Neurol Sci 2017;38:1671–6.
[78] Wojner-Alexandrov AW, Alexandrov AV, Rodriguez D, et al. Houston paramedic and emergency stroke treatment and outcomes study (HoPSTO). Stroke 2005;36:1512–8.
[79] Gladstone DJ, Rodan LH, Sahlas DJ, et al. A citywide prehospital protocol increases access to stroke thrombolysis in Toronto. Stroke 2009;40:3841–4.
[80] O'Brien W, Crimmins D, Donaldson W, et al. FASTER (Face, Arm, Speech, Time, Emergency Response): experience of Central Coast Stroke Services implementation of a pre-hospital notification system for expedient management of acute stroke. J Clin Neurosci 2012;19:241–5.
[81] Walter S, Kostopoulos P, Haass A, 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.

[82] Lahr MM, Vroomen PC, Luijckx GJ, et al. Prehospital factors determining regional variation in thrombolytic therapy in acute ischemic stroke. Int J Stroke 2014;9(suppl A100):31–5.
[83] Berglund A, Svensson L, Sjostrand C, et al. Higher prehospital priority level of stroke improves thrombolysis frequency and time to stroke unit: the Hyper Acute STroke Alarm (HASTA) study. Stroke 2012;43:2666–70.
[84] Amorim E, Shih MM, Koehler SA, et al. Impact of telemedicine implementation in thrombolytic use for acute ischemic stroke: the University of Pittsburgh Medical Center telestroke network experience. J Stroke Cerebrovasc Dis 2013;22:527–31.
[85] Willeit J, Geley T, Schoch J, et al. Thrombolysis and clinical outcome in patients with stroke after implementation of the Tyrol Stroke Pathway: a retrospective observational study. Lancet Neurol 2015;14:48–56.
[86] Ebinger M, Winter B, Wendt M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: a randomized clinical trial. JAMA 2014;311:1622–31.
[87] Itrat A, Taqui A, Cerejo R, et al. Telemedicine in prehospital stroke evaluation and thrombolysis: taking stroke treatment to the doorstep. JAMA Neurol 2016;73:162–8.
[88] Kendall J, Dutta D, Brown E. Reducing delay to stroke thrombolysis: lessons learnt from the Stroke 90 Project. Emerg Med J 2015;32:100–4.
[89] Kim DH, Nah HW, Park HS, et al. Impact of prehospital intervention on delay time to thrombolytic therapy in a stroke center with a systemized stroke code program. J Stroke Cerebrovasc Dis 2016;25:1665–70.
[90] Vidale S, Arnaboldi M, Bezzi G, et al. Reducing time delays in the management of ischemic stroke patients in Northern Italy. Int J Cardiol 2016;215:431–4.
[91] Fassbender K, Balucani C, Walter S, et al. Streamlining of prehospital stroke management: the golden hour. Lancet Neurol 2013;12:585–96.
[92] Hodgson C, Lindsay P, Rubini F. Can mass media influence emergency department visits for stroke? Stroke 2007;38:2115–22.
[93] Soulleihet V, Nicoli F, Trouve J, et al. Optimized acute stroke pathway using medical advanced regulation for stroke and repeated public awareness campaigns. Am J Emerg Med 2014;32:225–32.
[94] Nishijima H, Ueno T, Kon T, et al. Effects of educational television commercial on pre-hospital delay in patients with ischemic stroke wore off after the end of the campaign. J Neurol Sci 2017;381:117–8.
[95] Basic KV, Zavoreo I, Vargek-Solter V, et al. Quantitative and qualitative evaluation tool in planning stroke treatment strategies: the "Safe implementation of treatments in stroke Monitoring Study (SITS MOST)" registry. Acta Neurol Belg 2014;114:95–106.
[96] Ferrari J, Seyfang L, Lang W. Can online benchmarking increase rates of thrombolysis? Data from the Austrian stroke unit registry. J Neurol 2013;260:2271–8.
[97] Chalouhi N, Dressler JA, Kunkel ES, et al. Intravenous tissue plasminogen activator administration in community hospitals facilitated by telestroke service. Neurosurgery 2013;73:667–71.
[98] Kepplinger J, Barlinn K, Deckert S, et al. Safety and efficacy of thrombolysis in telestroke: a systematic review and meta-analysis. Neurology 2016;87:1344–51.
[99] Switzer JA, Demaerschalk BM, Xie J, et al. Cost-effectiveness of hub-and-spoke telestroke networks for the management of acute ischemic stroke from the hospitals' perspectives. Circ Cardiovasc Qual Outcomes 2013;6:18–26.