Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

The “STEP” means (1) **S**trategies, namely intervention characteristics: a group of best practice strategies developed from the “Target: Stroke Initiative” according to the outer and inner settings of hospitals in China. It aimed to construct the Green Channel for reperfusion therapy and to optimize the workflow of rescuing patients in stroke centers, including hospital prenotification, rapid triage, a single call activation of the stroke team, a designated staff supporting the whole process of reperfusion therapy, a patient-specific chart with time records, a principle of prioritizing CT scans for patients with acute ischemic stroke, a stroke team that goes directly to the CT room, the rapid acquisition and interpretation of brain imaging, prioritizing laboratory testing for stroke patients, rtPA regularly stored in the thrombolysis room of the emergency department and providing IVT/EVT as soon as possible. All related staff, including the administrators, physicians, nurses, and someone supportive from different departments, were all trained at the beginning of the first month when entering into the intervention phase. Some other written documents from the China Stroke Association (CSA) or National Center for Healthcare Quality Management in Neurological Diseases were provided to receive administrative support from hospital management because the multidisciplinary organization and coordination mainly relied on the head of the administration (e.g., the president or vice-president) in public hospitals in the health settings of China; (2) **T**oolkit: an integrated toolkit for acute ischemic stroke treatment was designed according to the AHA/ASA and CSA guidelines. It is presented as a handbook and includes triage protocol, clinical pathways, recommended time intervals for different departments, brain CT/MRI interpretation

protocols, indications and contraindications of IVT/EVT, stroke-specific order sets, rt-PA application process, calculated dosage by different weights, peri-IVT/EVT management, frequently used stroke scales, updated guidelines for acute stroke management and relevant contact information (i.e., telephone number) of all staff working in the whole process of reperfusion therapy. Considering the characteristics of each individual, informed consent forms with full consideration of medical humanities for IVT/EVT were implemented to get trust from patients or their proxies; (3) **E**xploration: a new intervention strategy was explored by providing expert guidance to hospitals entering into the intervention stage to reduce the unequal distribution of high-quality health resources. In this exploration, a group of experienced experts from Beijing Tiantan Hospital, Capital Medical University, was invited to join a regular teleconference to provide professional or technical guidance or training that was specific to the hospital in need 1:1 when each cohort crossed from the control step to the interventional step. This was a much more localized strategy in accordance with the medical system in China. (4) **P**aradigm: the paradigm of the feedback system served to make a Plan-Do-Study-Act (PDSA) circle, including on-site monitoring. All information of included patients, especially those related to reperfusion therapy, was collected and uploaded through a web-based case report form which additionally contained a Patient Management Tool (GaiDe, Inc, Beijing, China) for feedback. After crossing from the control to the intervention stage, all feedback data of the current adherent rate of reperfusion therapy would be sent to each site weekly, and the participating hospital could check it online through an authorized username and password. Meanwhile, all these data reports would be sent to the principal investigator and the

administrator of reperfusion therapy in each hospital via WeChat App and email. An improvement meeting was required weekly or biweekly within sites. Onsite audits or teleconference communication were conducted by month to find the existing problems during the intervention, and the steering committee would make a way to solve them. The online and offline data checks of all patients were performed within two weeks after inclusion. The interventions were administered to administrators, physicians, and nurses in the participating hospitals but not to the individual patients.

eTable 1. Baseline Characteristics Of the IMPROVE Stroke Care In China Patients And Hospitals Between Included and Excluded Patients.

Characteristics	Included (N=12132 [76.4%])	Excluded (N=3756 [23.6%])	Difference (95% CI)
Patient characteristics			
Demographic			
Age, mean (SD), y	66.1±12.1	66.1±11.9	-0.1 (-0.5 to 0.4)
Male	7759 (64.0)	2433 (64.8)	-0.8 (-2.6 to 0.9)
BMI, mean (SD), kg/m2	23.8±3.8	24.0±4.7	-0.2 (-0.4 to -0.0)
NIHSS at admission	5.0 (2.0 – 10.0)	4.0 (2.0 – 7.0)	-1.0 (-1.0 to -1.0)
Current smoking	3238 (26.7)	1038 (27.6)	-0.9 (-2.6 to 0.7)
Drinking	2993 (24.7)	939 (25.0)	-0.3 (-1.9 to 1.3)
Medical history			
Stroke or TIA	3445 (28.4)	1193 (31.8)	-3.4 (-5.1 to -1.7)
Hypertension	7457 (61.5)	2328 (62.0)	-0.5 (-2.3 to 1.3)
Diabetes	2401 (19.8)	831 (22.1)	-2.3 (-3.8 to -0.8)
Dyslipidemia	725 (6.0)	199 (5.3)	0.7 (-0.2 to 1.5)
Myocardial infarction	242 (2.0)	70 (1.9)	0.1 (-0.4 to 0.6)
Atrial fibrillation	1107 (9.1)	275 (7.3)	1.8 (0.8 to 2.8)
Peripheral vascular disease	165 (1.4)	28 (0.7)	0.6 (0.3 to 1.0)
Medication history			
Antiplatelet agent	2250 (18.5)	635 (16.9)	1.6 (0.3 to 3.0)
Anticoagulant drugs	552 (4.5)	130 (3.5)	1.1 (0.4 to 1.8)
Antihypertensive drugs	5377 (44.3)	1667 (44.4)	-0.1 (-1.9 to 1.8)
Antidiabetics	1904 (15.7)	676 (18.0)	-2.3 (-3.7 to -0.9)
Statins	1961 (16.2)	528 (14.1)	2.1 (0.8 to 3.4)
Onset to door time in minutes,min	95.0 (55.0 – 145.0)	255.0 (227.0 – 298.0)	161.0 (159.0 to 164.0)
Hospital characteristics			
Hospital level			
Tertiary	8060 (66.4)	2591 (69.0)	-2.5 (-4.2 to -0.8)
Secondary	4072 (33.6)	1165 (31.0)	2.5 (0.8 to 4.2)
Hospital location			
Eastern	5574 (45.9)	1420 (37.8)	8.1 (6.4 to 9.9)
Central	3664 (30.2)	1532 (40.8)	-10.6 (-12.3 to -8.8)
Western	2894 (23.9)	804 (21.4)	2.5 (0.9 to 3.9)

Abbreviation: SD, standard deviation; BMI: body mass index; NIHSS, the National Institutes of Health Stroke Scale. TIA, transient ischemic attack.

eTable 2. Baseline Characteristics of the IMPROVE Stroke Care in China Patients and Hospitals among Patients With and Without Values of mRS at 90 Days.

Characteristics	With (N=10398 [85.7%])	Without (N=1734 [14.3%])	Difference (95% CI)
Patient characteristics			
Demographic			
Age, mean (SD), y	65.7±12.0	68.4±12.3	-2.7 (-3.3 to -2.1)
Male	6654 (64.0)	1105 (63.7)	0.3 (-2.2 to 2.7)
BMI, mean (SD), kg/m2	23.8±3.8	23.6±3.9	0.2 (0.0 to 0.4)
NIHSS at admission	4.0 (2.0 – 9.0)	6.0 (3.0 – 14.0)	2.0 (1.0 to 2.0)
Current smoking	2825 (27.2)	413 (23.8)	3.4 (1.2 to 5.5)
Drinking	2590 (24.9)	403 (23.2)	1.7 (-0.5 to 3.8)
Medical history			
Stroke or TIA	3013 (29.0)	432 (24.9)	4.1 (1.8 to 6.3)
Hypertension	6446 (62.0)	1011 (58.3)	3.7 (1.2 to 6.2)
Diabetes	2081 (20.0)	320 (18.5)	1.6 (-0.4 to 3.5)
Dyslipidemia	625 (6.0)	100 (5.8)	0.2 (-0.9 to 1.4)
Myocardial infarction	195 (1.9)	47 (2.7)	-0.8 (-1.6 to -0.0)
Atrial fibrillation	871 (8.4)	236 (13.6)	-5.2 (-6.9 to -3.5)
Peripheral vascular disease	143 (1.4)	22 (1.3)	0.1 (-0.5 to 0.7)
Medication history			
Antiplatelet agent	1947 (18.7)	303 (17.5)	1.3 (-0.7 to 3.2)
Anticoagulant drugs	482 (4.6)	70 (4.0)	0.6 (-0.4 to 1.6)
Antihypertensive drugs	4653 (44.7)	724 (41.8)	3.0 (0.5 to 5.5)
Antidiabetics	1668 (16.0)	236 (13.6)	2.4 (0.7 to 4.2)
Statins	1698 (16.3)	263 (15.2)	1.2 (-0.7 to 3.0)
Onset to door time in minutes,min	95.0 (55.0 – 145.0)	91.5 (54.0 – 142.0)	-1.0 (-4.0 to 2.0)
Hospital characteristics			
Hospital level			
Tertiary	6914 (66.5)	1146 (66.1)	0.4 (-2.0 to 2.8)
Secondary	3484 (33.5)	588 (33.9)	-0.4 (-2.8 to 2.0)
Hospital location			
Eastern	4798 (46.1)	776 (44.8)	1.4 (-1.1 to 3.9)
Central	3272 (31.5)	392 (22.6)	8.9 (6.7 to 11.0)
Western	2328 (22.4)	566 (32.6)	-10.2 (-12.6 to -7.9)

Abbreviation: SD, standard deviation; BMI: body mass index; NIHSS, the National Institutes of Health Stroke Scale. TIA, transient ischemic attack.

eTable 3. Results Of Disability At 90 Days From Multiple Imputations.

	Primary Analysis[a]		Covariates-Adjusted Analysis[b]	
Outcomes	RD (95% CI)	OR (95% CI)	RD (95% CI)	OR (95% CI)
Disability at 90d	-1.4 (-5.3 to 2.5)	0.93 (0.73-1.13)	-0.8 (-4.6 to 3.1)	0.97 (0.76–1.17)

Abbreviations: RD, risk difference; and OR, odds ratio.

[a] Results were yielded from generalized estimating equation logistic regression models with adjustment for the hospital clustering effect and temporal period.

[b] Results were yielded from generalized estimating equation logistic regression models with adjustment for the hospital clustering effect, temporal period, and imbalanced baseline covariates (medical history of stroke or transient ischemic attack, medication history of antiplatelet agent and statin, and hospital area).

eTable 4. Subgroup Analysis For the Effect Of Intervention On Reperfusion Treatment For Other Secondary Outcomes.

Outcomes	Subgroup	No.of Patients	Event in Intervention No.(%)	Event in Control No.(%)	Covariate-adjusted Anaysis[a]		P for interaction
					Adjusted RD(95% CI)	Adjusted OR(95% CI)	
DNT within 60 min	Overall	5442	2018 (71.3)	1701 (65.1)	7.1 (-5.3 to 19.4)	1.39 (0.77–2.54)	
	Age,y						0.41
	<65	2332	852 (72.1)	747 (65.0)	6.3 (-6.2 to 18.7)	1.35 (0.74–2.44)	
	≥65	3110	1166 (70.8)	954 (65.3)	7.9 (-5.0 to 20.9)	1.44 (0.76–2.73)	
	Sex						0.21
	Female	1946	719 (71.7)	600 (63.6)	9.9 (-3.1 to 22.8)	1.56 (0.81–3.00)	
	Male	3496	1299 (71.1)	1101 (66.0)	5.5 (-7.2 to 18.1)	1.31 (0.72–2.38)	
	Hospital level						0.31
	Secondary	1978	798 (75.1)	589 (64.3)	11.7 (-2.7 to 26.0)	1.77 (0.73–4.27)	
	Tertiary	3464	1220 (69.0)	1112 (65.6)	4.8 (-11.8 to 21.4)	1.22 (0.57–2.58)	
DPT within 90 min	Overall	506	62 (23.0)	86 (36.4)	7.1 (-5.3 to 19.4)	0.27 (0.14–0.52)	
	Age,y						0.96
	<65	209	28 (26.7)	41 (39.4)	-17.3 (-38.0 to 3.5)	0.42 (0.16–1.06)	
	≥65	297	34 (20.6)	45 (34.1)	-29.4 (-46.4 to -12.3)	0.16 (0.06–0.46)	
	Sex						0.42
	Female	185	17 (18.5)	31 (33.3)	-26.2 (-53.6 to 1.1)	0.21 (0.06–0.71)	
	Male	321	45 (25.3)	55 (38.5)	-22.9 (-38.1 to -7.8)	0.28 (0.12–0.66)	
	Hospital level						0.68
	Secondary	88	2 (3.9)	3 (8.1)	4.1 (-1.2 to 9.3)	NA	
	Tertiary	418	60 (27.4)	83 (41.7)	-25.7 (-39.3 to -12.2)	0.28 (0.15–0.55)	
In-hospital death	Overall	12 132	146 (2.6)	165 (2.6)	-0.3 (-1.2 to 0.6)	0.93 (0.61–1.41)	
	Age,y						0.08
	<65	5186	20 (0.8)	35 (1.2)	-0.8 (-1.5 to -0.1)	0.39 (0.18–0.83)	
	≥65	6946	126 (3.8)	130 (3.6)	0.1 (-1.2 to 1.5)	1.08 (0.70–1.67)	
	Sex						0.90

	Female	4373	63 (3.1)	73 (3.1)	0.4 (-1.0 to 1.7)	1.02 (0.60–1.75)	
	Male	7759	83 (2.3)	92 (2.2)	-0.6 (-1.5 to 0.3)	0.89 (0.54–1.45)	
	Hospital level						0.72
	Secondary	4072	46 (2.5)	53 (2.4)	-0.1 (-1.3 to 1.2)	1.22 (0.67–2.23)	
	Tertiary	8060	100 (2.6)	112 (2.6)	-0.5 (-1.6 to 0.6)	0.84 (0.48–1.47)	
Disability at 90d	Overall	10 398	1215 (25.9)	1439 (25.2)	-0.9 (-5.1 to 3.2)	0.96 (0.77–1.20)	
	Age,y						0.04
	<65	4576	299 (14.8)	415 (16.2)	-2.8 (-5.7 to 0.2)	0.81 (0.63–1.02)	
	≥65	5822	916 (34.4)	1024 (32.4)	0.2 (-4.6 to 5.0)	1.02 (0.82–1.26)	
	Sex						0.71
	Female	3744	532 (31.5)	623 (30.3)	0.8 (-4.2 to 5.7)	1.04 (0.82–1.32)	
	Male	6654	683 (22.8)	816 (22.3)	-1.8 (-5.9 to 2.4)	0.92 (0.72–1.17)	
	Hospital level						0.10
	Secondary	3484	448 (28.7)	490 (25.5)	3.0 (-4.1 to 10.1)	1.18 (0.82–1.70)	
	Tertiary	6914	767 (24.5)	949 (25.1)	-2.9 (-8.2 to 2.3)	0.87 (0.66–1.16)	

Abbreviations: DNT: door-to-needle time; DPT: door-to-punctuation time.

[a] Results were yielded from generalized estimating equation logistic regression models with adjustment for the hospital clustering effect, temporal period, and imbalanced baseline covariates (medical history of stroke or transient ischemic attack, medication history of antiplatelet agent and statin, and hospital area).

eTable 5. Baseline Characteristics of the IMPROVE Stroke Care in China Patients and Hospitals by Reperfusion.

Characteristics	No IV/EV (N=6256 [51.6%])	IV/EV (N=5876 [48.4%])	Differece (95% CI)
Patient characteristics			
Demographic			
Age, mean (SD), y	66.1±12.2	66.1±11.9	0.0 (-0.4 to 0.5)
Male	3985 (63.7)	3774 (64.2)	-0.5 (-2.2 to 1.2)
BMI, mean (SD), kg/m2	24.1±4.0	23.4±3.6	0.7 (0.5 to 0.8)
NIHSS at admission	3.0 (2.0–6.0)	6.0 (3.0–12.0)	-3.0 (-3.0 to -2.0)
Current smoking	1561 (25.0)	1677 (28.5)	-3.6 (-5.2 to -2.0)
Drinking	1561 (25.0)	1432 (24.4)	0.6 (-1.0 to 2.1)
Medical history			
Stroke or TIA	2207 (35.3)	1238 (21.1)	14.2 (12.6 to 15.8)
Hypertension	3908 (62.5)	3549 (60.4)	2.1 (0.3 to 3.8)
Diabetes	1381 (22.1)	1020 (17.4)	4.7 (3.3 to 6.1)
Dyslipidemia	408 (6.5)	317 (5.4)	1.1 (0.3 to 2.0)
Myocardial infarction	126 (2.0)	116 (2.0)	0.0 (-0.5 to 0.5)
Atrial fibrillation	441 (7.0)	666 (11.3)	-4.3 (-5.3 to -3.3)
Peripheral vascular disease	124 (2.0)	41 (0.7)	1.3 (0.9 to 1.7)
Medication history			
Antiplatelet agent	1492 (23.8)	758 (12.9)	10.9 (9.6 to 12.3)
Anticoagulant drugs	399 (6.4)	153 (2.6)	3.8 (3.0 to 4.5)
Antihypertensive drugs	2865 (45.8)	2512 (42.8)	3.0 (1.3 to 4.8)
Antidiabetics	1110 (17.7)	794 (13.5)	4.2 (2.9 to 5.5)
Statins	1348 (21.5)	613 (10.4)	11.1 (9.8 to 12.4)
Onset to door time,min			
Hospital characteristics			
Hospital level			
Tertiary	4210 (67.3)	3850 (65.5)	1.8 (0.1 to 3.5)
Secondary	2046 (32.7)	2026 (34.5)	-1.8 (-3.5 to -0.1)
Hospital location			
Eastern	2910 (46.5)	2664 (45.3)	1.2 (-0.6 to 3.0)
Central	1981 (31.7)	1683 (28.6)	3.0 (1.4 to 4.7)
Western	1365 (21.8)	1529 (26.0)	-4.2 (-5.7 to -2.7)

Abbreviation: SD, standard deviation; BMI: body mass index; NIHSS, the National Institutes of Health Stroke Scale. TIA, transient ischemic attack.

eTable 6. Results of Disability at 90 Days From Raw Data.

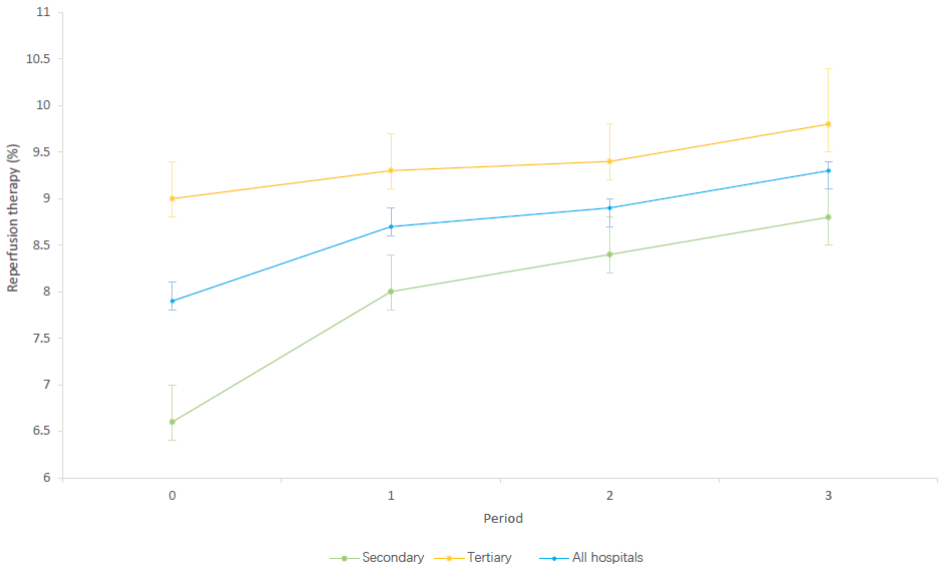
Outcomes	Reperfusion		Raw Analysis		Primary Analysis[a]		Covariates-Adjusted Analysis[b]	
	Yes	No	RD (95% CI)	OR (95% CI)	RD (95% CI)	OR (95% CI)	RD (95% CI)	OR (95% CI)
Disability at 90d	1381/4980 (27.7)	1273/5418 (23.5)	4.2 (1.6 to 6.8)	1.25 (1.09–1.44)	4.1 (1.6 to 6.6)	1.24 (1.08-1.42)	-4.0 (-6.1 to -1.9)	0.80 (0.70–0.91)

[a] Results were yielded from generalized estimating equation logistic regression models with adjustment for the hospital clustering effect and temporal period.

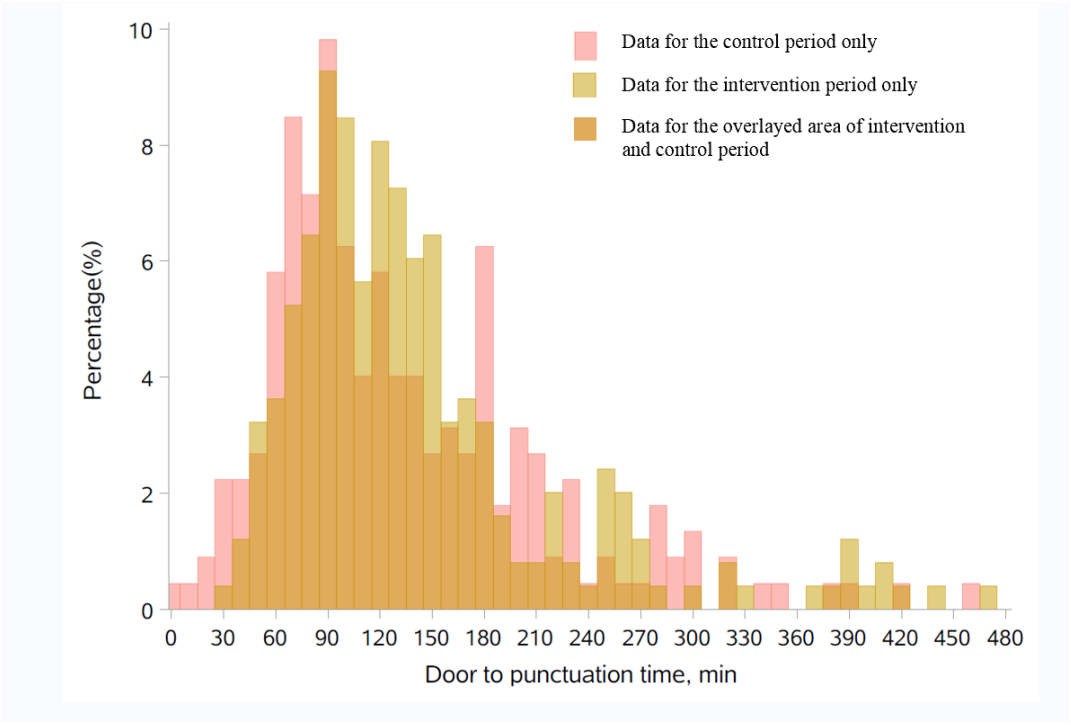
[b] Results were yielded from generalized estimating equation logistic regression models with adjustment for the hospital clustering effect, temporal period, and imbalanced baseline covariates (medical history of stroke or transient ischemic attack, medication history of antiplatelet agent and statin, and hospital area).

Potential causes for the low rate of reperfusion therapy in China	Designed STEP interventions component
* The unorganized stroke care in stroke centers	➢ **S**trategies: a group of best practice strategies developed from the "Target: Stroke Initiative"; an official written documents provided to receive administrative support from the head of public hospitals
* The eroded patient-physician trust that encountered during structural and social transformations	➢ **T**oolkit: an integrated toolkit presented as a handbook and designed according to the American Heart Association/American Stroke Association and Chinese Stroke Association guidelines, including an informed consent form with full consideration of medical humanities for intravenous thrombolysis/endovascular thrombectomy .
* Unequal distribution of high-quality health resources	➢ **E**xploration: an explorative intervention strategy of providing point-to-point experienced expert guidance to the hospitals entered into the intervention stage
* The unorganized stroke care in stroke centers	➢ **P**aradigm: the continuously improved paradigm of the feedback system served to make a Plan-Do-Study-Act circle

eFigure 1. The Design Of "STEP" Intervention.
STEP indicates Strategies, Toolkit, Exploration, and Paradigm.



eFigue 2. Reperfusion Therapy In The Chinese Center Association Alliance Hospitals Not Participating in the IMPROVE Stroke Care In China Trial



eFigue 3. Distribution of Door-to-Puncture Time in the IMPROVE Stroke Care in China Trial.