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Guideline

Update of the Korean Clinical Practice Guidelines for Endovascular Recanalization Therapy in Patients with Acute Ischemic Stroke

Keun-Sik Hong,[a] Sang-Bae Ko,[b] Kyung-Ho Yu,[c] Cheolkyu Jung,[d] Sukh Que Park,[e] Byung Moon Kim,[f] Chul-Hoon Chang,[g] Hee-Joon Bae,[h] Ji Hoe Heo,[i] Chang Wan Oh,[j] Byung-Chul Lee,[c] Bum-Tae Kim,[k] Bum-soo Kim,[l] Chin-Sang Chung,[m] Byung-Woo Yoon,[b] Joung-Ho Rha[n]

[a]Department of Neurology, Inje University Ilsan Paik Hospital, Goyang, Korea
[b]Department of Neurology, Seoul National University College of Medicine, Seoul, Korea
[c]Department of Neurology, Hallym University College of Medicine, Anyang, Korea
[d]Department of Radiology, Seoul National University Bundang Hospital, Seongnam, Korea
[e]Department of Neurosurgery, Soonchunhyang University Seoul Hospital, Soonchunhyang University, Seoul, Korea
[f]Department of Radiology, Yonsei University College of Medicine, Seoul, Korea
[g]Department of Neurosurgery, Yeungnam University School of Medicine, Daegu, Korea
[h]Department of Neurology, Seoul National University Bundang Hospital, Seongnam, Korea
[i]Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
[j]Department of Neurosurgery, Seoul National University Bundang Hospital, Seongnam, Korea
[k]Department of Neurosurgery, Soonchunhyang University, Bucheon Hospital, Bucheon, Korea
[l]Department of Radiology, Seoul St.Mary's Hospital, The Catholic University of Korea, Seoul, Korea
[m]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[n]Department of Neurology, Inha University College of Medicine, Incheon, Korea

Patients with severe stroke due to acute large cerebral artery occlusion are likely to be severely disabled or dead without timely reperfusion. Previously, intravenous tissue plasminogen activator (IV-TPA) within 4.5 hours after stroke onset was the only proven therapy, but IV-TPA alone does not sufficiently improve the outcome of patients with acute large artery occlusion. With the introduction of the advanced endovascular therapy, which enables more fast and more successful recanalization, recent randomized trials consecutively and consistently demonstrated the benefit of endovascular recanalization therapy (ERT) when added to IV-TPA. Accordingly, to update the recommendations, we assembled members of the writing committee appointed by the Korean Stroke Society, the Korean Society of Interventional Neuroradiology, and the Society of Korean Endovascular Neurosurgeons. Reviewing the evidences that have been accumulated, the writing members revised recommendations, for which formal consensus was achieved by convening a panel composed of 34 experts from the participating academic societies. The current guideline provides the evidence-based recommendations for ERT in patients with acute large cerebral artery occlusion regarding patient selection, treatment modalities, neuroimaging evaluation, and system organization.

Keywords Guidelines; Acute ischemic stroke; Large cerebral artery occlusion; Thrombolysis; Reperfusion; Endovascular recanalization therapy

Correspondence: Joung-Ho Rha
Department of Neurology, Inha University Hospital, Inha University College of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, Korea
Tel: +82-32-890-3668
Fax: +82-32-890-3864
E-mail: jhrha@inha.ac.kr

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Introduction

Previously, intravenous tissue plasminogen activator (IV-TPA) within 4.5 hours after stroke onset was the only therapy with proven efficacy from randomized clinical trials (RCTs) for acute ischemic stroke.[1-3] However, patients with severe stroke due to acute large cerebral artery occlusion are less responsive to IV-TPA alone and are likely to be severely disabled or dead. For these patients, endovascular recanalization therapy (ERT) has been expected to achieve better recanalization and better outcome. A single RCT and a meta-analysis showed that ERT compared to no thrombolytic therapy increased recanalization rate and improved clinical outcomes.[4,5] Despite an increased risk of symptomatic intracranial hemorrhage (SICH) with ERT, it was not translated to an increased mortality.[5] In contrast, when compared to IV-TPA, 3 RCTs published in 2013 failed to show the benefit of ERT.[6-8] These trials had major limitations of 1) the failure to confirm large artery occlusions in all patients before randomization and 2) the use of old endovascular technologies with insufficient and delayed recanalization. With the introduction of stent-retriever thrombectomy devices, multiple RCTs were simultaneously or consecutively initiated between December 2010 and February 2013, and their final results were published between December 2014 and April 2015.[9-13] All the trials consistently and convincingly demonstrated the benefit of ERT added to IV-TPA in patients with severe stroke due to acute large cerebral artery occlusion. The successes of the 5 RCTs are likely attributed to 1) right devices with better and faster recanalization, 2) right patient selection with appropriate vascular imaging, and 3) right system enabling to provide an expedited and organized care for ERT. Accordingly, the guideline writing committee decided to revise the Korean Clinical Practice Guidelines for Stroke to inform physicians of the new evidences from RCTs and to help incorporate the ERT into clinical practice by implementing of stroke care system.

Previous guidelines

The 2012 Korean Clinical Practice Guidelines for intra-arterial (IA) thrombolysis in patients with acute ischemic stroke provided the following recommendations.[3]

1. Intra-arterial thrombolysis can be considered for patients who have occlusions in the middle cerebral artery or the internal carotid artery of ≤ 6 hours, or those who are contraindicated for intravenous thrombolysis (for example, recent surgery) (Level of Evidence Ia, Grade of Recommendation A). – Revisions made in the LOE and GOR.

2. The institution conducting IA thrombolysis should accommodate a rapid access to cerebral angiography and experienced interventionalists. Each institution is encouraged to define criteria of interventionalists who can perform IA thrombolysis (good practice points [GPP]). – Revisions made in the LOE and GOR.

3. IA thrombolysis can be considered for patients who have occlusions in the posterior circulation such as the basilar artery, depending on the criteria of each institution (LOE III, GOR B). – Revisions made in the LOE and GOR.

4. In patients indicated for IV-TPA, IV-TPA should be administered first. For patients who have not responded to IV-TPA, additional IA thrombolysis can be considered (LOE III, GOR B). – New recommendation.

5. Mechanical thrombectomy can be considered for patients presenting < 8 hours with major ischemic strokes caused by large artery occlusions. Stent retrievers are preferred to other devices, but the selection of treatment method should be made by responsible interventionalists, taking into account of the patient's conditions (LOE Ib, GOR A). – New recommendation.

Methodology

Organization of the writing committee

The Clinical Practice Guideline Committee of the Korean Stroke Society assembled the writing members appointed by the Korean Stroke Society, the Korean Society of Interventional Neuroradiology, and the Society of Korean Endovascular Neurosurgeons.

Evidence search and data analysis

To review and summarize the effect of ERT in acute ischemic stroke, we conducted a systematic review. We searched Pubmed and EMBASE (January 1998 to May 2015) with the terms of ischemic stroke and intra-arterial and thrombolysis or thrombectomy with restriction to humans and clinical trials. Additional relevant articles were identified from manual searches of bibliographies of all trials and were solicited from the writing members. Two investigators (Ko SB and Hong KS) reviewed and selected eligible studies. The selection criteria for the systematic review were 1) RCT, 2) ERT in the active arm, 3) the control arm receiving standard therapy including IV-TPA, but not treated with ERT, and 4) modified Rankin Scale (mRS) score reported at 90 days or at the end of the trial. From the literature review, we identified 15 relevant RCTs that tested ERT and reported mRS outcome in 2,899 patients: 1,575 in the ERT group and 1,324 in the control group. Of the 15 RCTs, 6 trials did not use IV-TPA in control arms (IV uro-

kinase in one trial[14]),[4,14-18] and 9 trials provided IV-TPA to 29.6%[8] to 100%[6,11,12] of patients randomized to control arms.[6-13,19] In 5 RCTs, patients randomized to ERT were mainly treated with stent-retriever thrombectomy (77.1% to 95.1%).[9-13] We assessed and summarized the quality of each RCT using the Cochrane risk of-bias algorithm (www.cochrane.org/training/cochrane-handbook)[20] and reported it in another article.[21] Data from eligible trials were independently abstracted by the two investigators (Ko SB and Hong KS), and discrepancies were resolved by consensus or discussion with other investigators (Yu KH and Rha JH). We estimated pooled effects of ERT for various clinical outcomes, and the detailed results were published elsewhere.[21]

In addition, we searched updated guidelines or consensus statement for the organization of care system for ERT from credited academic societies, and identified 3 reports published since 2013.[22-24] At the inception, we reviewed articles published until May 2015. However, during the guideline writing after our literature search, an updated guideline of the American Stroke Association was released on 29 June 2015, which we additionally reviewed.[25] All recommendations and statements provided in the selected guidelines and statements were reviewed and reflected, if necessary, in the current guidelines.

LOE and GORs

We determined the LOE and the GOR for each recommendation largely based on the suggestion of the US Agency for Healthcare Policy and Research (currently the Agency for Healthcare Research and Quality) in 1993 (Table 1).[26]

Evidence summary

The characteristics and results of the 15 RCTs and their meta-analyses are summarized in Table 2.

Patient selection and ERT modality

Time window

The time window in the 15 RCTs ranged from 3[19] to 24 hours[17], and 8 RCTs randomized patients with 6 hours from onset.[4,9,11,12,14-16,18] Of the recent 5 stent-retriever RCTs, the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA), and Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trials enrolled patients within 6 hours from stroke onset.[9,11,12] The Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) and Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trials enrolled patients up to 8 hours and 12 hours, but 90.3% of patients in REVASCAT and 84.5% of those in ESCAPE were enrolled within 6 hours.[10,13]

In the 5 stent-retriever RCTs, on average, the groin puncture from onset was achieved within 4.5 hours (ranged in 185 minutes[10] and 269 minutes[13]), and the first reperfusion was initiated within 6 hours (ranged in 241 minutes[10] and 355 minutes[13]) from stroke onset. In particular, the ESCAPE and SWIFT PRIME trials emphasized the speed of workflow, which shortened the time from initial imaging to groin puncture of 51 minutes and 57 minutes and from initial imaging to first reperfusion of 84 minutes and 81 minutes respectively.[10,12]

Infarct core, perfusion, and collaterals evaluation

Noncontrast CT is the most readily and widely available imaging modality to exclude hemorrhagic stroke and to identify patients with early extensive ischemic injury who would

Table 1. Level of evidence (LOE) and grade of recommendation (GOR)

LOE	
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities
GOR	
A (LOE Ia, Ib)	Required - at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B (LOE IIa, IIb, III)	Required - availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (LOE IV)	Required - evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. This grade indicates absence clinical of directly applicable studies of good quality
Good practice points (GPP)	Recommended best practice based on the clinical experience of the guideline development group

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Table 2. Characteristics and results of 15 randomized clinical trials (RCTs) and 2 meta-analyses testing endovascular recanalization therapy (ERT) in acute ischemic stroke

Trial	Prolyse in Acute Cerebral Thromboembolism (PROACT)	PROACT II	Keris et al.	Ducrocq et al.	Macleod et al.	MELT
Publication year	1998	1999	2001	2005	2005	2007
Participants (n)	40	180	45	27	16	114
Age (year)	67.6	64.0	61.8	58.7	63.9	67.1
Female (%)	52.5	41.1	40.0	25.9	37.5	35.1
Baseline National Institute of Health Stroke Scale (NIHSS) (active/control)	17/19	17/17	25/26	Not analyzed (NA)	23/18	14/14
Time window (hour)	6.0	6.0	6.0	6.0	24.0	6.0
Large artery occlusion confirmation (%)	100	100	100	NA	100	100
Internal carotid artery/M1 occlusion (%)	2.5/52.5	NA/61.7	6.7/20.0 (active arm only)	7.4/40.7 (active arm only)	Basilar artery or vertebral artery occlusion	0/71.0
Onset to randomization/groin puncture/first reperfusion (minute)	NA/276/330	290/NA/318	NA/NA/229	NA/NA/324	NA/NA/710	197/NA/227
Active arm	Intra-arterial prourokinase	Intra-arterial prourokinase	TPA (Intra-arterial [IA]+Intravenous (IV)	IA urokinase	IA urokinase	IA urokinase
Control arm	Placebo	Placebo	None	IV urokinase	None	None
IV tissue plasminogen activator (IV-TPA) (active/control), (%)	0/0	0/0	100/0	0/0	0/0	0/0
ERT performed in active arm (%)	100.0	89.3	100.0	100.0	100.0	98.2
Stent-Retriever in active arm (%)	0.0	0.0	0.0	0.0	0.0	0.0
modified Thrombolysis in Cerebral Infarction 2b-3 in active arm (%)	NA	NA	NA	31	NA	53.0
Outcome assessment (day)	90	90	30	90	180	90
Modified Rankin Scale (mRS) 0-2: active vs. control (%) Odds ratio (OR) (95% confidence interval [CI]) or *P* value	NA NA	39.7 vs. 25.4 *P*=0.04	NA NA	46.2 vs. 28.6 *P*=0.6	50.0 vs. 12.5 7.14 (0.70, 50.0), *P*=0.28	49.1 vs. 38.6 1.54 (0.73, 3.23), *P*=0.345
mRS 0-1: active vs. control (%) OR (95% CI) or *P* value	30.8 vs. 21.4 2p=0.72	26.4 vs. 16.9 *P*=0.16	NA NA	NA NA	37.5 vs. 0.0 NA	42.1 vs. 22.8 2.46 (1.09, 5.54), *P*=0.045
Shift analysis, OR (95% CI) or *P* value	NA	NA	NA	NA	NA	NA
Mortality: active vs. control (%) OR (95% CI) or *P* value	26.9 vs. 42.9 2p=0.48	24.8 vs. 27.1 *P*=0.80	16.7 vs. 48.5 NA	23.1 vs. 28.6 *P*=0.9	50.0 vs. 50.0 NA	5.3 vs. 3.5 *P*=1.00
mRS 5-6: active vs. control (%) OR (95% CI) or *P* value	NA NA	33.9 vs. 33.9 NA	NA NA	NA NA	50.0 vs. 62.5 NA	21.1 vs. 22.8 NA
Symptomatic intracranial hemorrhage (SICH): active vs. control (%) OR (95% CI) or *P* value	15.4 vs. 7.1 2p=0.64	10.2 vs. 1.9 *P*=0.06	0.0 vs. 3.0 NA	15.4 vs. 0.0 *P*=0.4	0.0 vs. 0.0 NA	8.8 vs. 1.8 *P*=0.206

Trial	SYNTHESIS pilot	Synthesis: A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS EXPANSION)	MR RESCUE	Interventional Management of Stroke (IMS) III	Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN)	Endovascular Treatment for Small Core (ESCAPE)
Publication year	2010	2013	2013	2013	2015	2015
Participants (n)	54	362	118	656	500	315
Age (year)	62.4	66.5	65.5	68.7	65.7	71.5
Female (%)	22.2	42.3	51.7	48.2	41.6	52.4

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Table 2. Continued

Trial	SYNTHESIS pilot	Synthesis: A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS EXPANSION)	MR RESCUE	Interventional Management of Stroke (IMS) III	Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN)	Endovascular Treatment for Small Core (ESCAPE)
Baseline NIHSS (active/control)	17/16	13/13	17.4/17.7	17/16	17/18	16/17
Time window (hour)	3.0	4.5	8.0	5.0	6.0	12.0
Large artery occlusion confirmation (%)	NA	NA	100.0	43.0	100.0	100.0
Internal carotid artery/M1 occlusion (%)	NA/NA	NA/NA	16.9/66.1	22.1/41.1 (active arm only)	27.6/63.8	26.7/68.6
Onset to randomization/groin puncture/first reperfusion (minute)	125/NA/195	146/NA/225	330/381/NA	146/208/244	200/260/NA	170/185/241
Active arm	ERT only	ERT only	ERT with standard care	ERT with IV-TPA	ERT with standard care	ERT with standard care
Control arm	IV-TPA	IV-TPA	Standard care	IV-TPA	Standard care	Standard care
IV-TPA (active/control) (%)	0/96.6	0/98.3	43.8/29.6	100/100	87.1/90.6	72.7/78.7
ERT performed in active arm (%)	76.0	91.2	95.3	77.0	83.7	91.5
Stent-Retriever in active arm (%)	4.0	12.7	0.0	0.9	81.5	78.8
modified Thrombolysis in Cerebral Infarction 2b-3 in active arm (%)	NA	NA	25.0	41.0	58.7	72.4
Outcome assessment (day)	90	90	90	90	90	90
mRS 0-2: active vs. control (%) OR (95% CI) or *P* value	56.0 vs. 31.0 NA	42.0 vs. 46.4 NA	18.8 vs. 20.4 NA	42.7 vs. 40.2 Absolute difference, 1.5% (-6.1 to 9.1)	32.6 vs. 19.1 2.16 (1.39, 3.38)	53.0 vs. 29.3 1.7 (1.3, 2.2), *P*<0.001
mRS 0-1: active vs. control (%) OR (95% CI) or *P* value	48.0 vs. 27.6 3.2 (0.9, 11.4), *P*=0.067	30.4 vs. 34.8 0.71 (0.44, 1.14), *P*=0.16	14.1 vs. 13.0 NA	29.4 vs. 27.1 NA	11.6 vs. 6.0 2.07 (1.07, 4.02)	35.4 vs. 17.7 NA
Shift analysis, OR (95% CI) or *P* value	NA	NA	*P*=0.99	*P*=0.25	1.67 (1.21, 2.30)	3.1 (2.0, 4.7), *P*<0.001
Mortality: active vs. control (%) OR (95% CI) or *P* value	24.0 vs. 17.2 No difference, *P* value not provided	14.4 vs. 9.9 *P*=0.22	18.8 vs. 24.1 No difference, *P* value not provided	20.0 vs. 22.4 *P*=0.52	21.0 vs. 22.1 No difference, *P* value not provided	10.4 vs. 19.0 0.5 (0.3, 0.8), *P*=0.04
mRS 5-6: active vs. control (%) OR (95% CI) or *P* value	24.0 vs. 17.2 NA	19.9 vs. 17.1 NA	42.2 vs. 35.2 NA	24.8 vs. 29.4 NA	27.0 vs. 34.1 NA	17.1 vs. 31.3 NA
SICH: active vs. control (%) OR (95% CI) or *P* value	8.0 vs. 13.8 0.5 (0.1, 3.3), *P*=0.675	5.5 vs. 5.5 *P*=0.99	4.7 vs. 3.7 No difference, *P* value not provided	6.2 vs. 5.9 *P*=0.83	7.7 vs. 6.4 No difference, *P* value not provided	3.6 vs. 2.7 1.2 (0.3 to 4.6), *P*=non-significant

Trial	Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA)	Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME)	Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT)	Meta-analysis Lee et al.	Meta-analysis Hong et al.
Publication year	2015	2015	2015	2010	2015
Participants (n)	70	196	206	395 (5 RCTs)	2,899 (15 RCTs)

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Table 2. Continued

Trial	Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA)	Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME)	Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT)	Meta-analysis Lee et al.	Meta-analysis Hong et al.
Age (year)	69.4	65.6	66.5	NA	NA
Female (%)	51.0	49.0	47.1	NA	NA
Baseline NIHSS (active/control)	17/13	17/17	17/17	NA	NA
Time window (hour)	6.0	6.0	8.0	NA	NA
Large artery occlusion confirmation (%)	100.0	100.0	100.0	NA	NA
Internal carotid artery/M1 occlusion (%)	31.4/54.3	16.3/68.4	26.2/63.6	NA	NA
Onset to randomization/groin puncture/ first reperfusion (minute)	169/210/NA	185/224/252	225/269/355	NA	NA
Active arm	ERT with IV-TPA	ERT with IV-TPA	ERT with standard care	ERT	ERT
Control arm	IV-TPA	IV-TPA	Standard care	No thrombolysis	IV-TPA or no IV-TPA
IV-TPA (active/control) (%)	100/100	100/100	68.0/77.0	NA	NA
ERT performed in active arm (%)	85.7	88.8	95.1	NA	NA
Stent-Retriever in active arm (%)	77.1	88.8	95.1	NA	NA
modified Thrombolysis in Cerebral Infarction 2b-3 in active arm (%)	86.2	88.0	65.7	NA	NA
Outcome assessment (day)	90	90	90	90, 180, or 365	30, 60, or 90
mRS 0-2: active vs. control (%) OR (95% CI) or *P* value	71.4 vs. 40.0 4.2 (1.4, 12), *P*=0.01	60.2 vs. 35.5 1.70 (1.23, 2.33), *P*< 0.001	43.7 vs. 28.2 2.1 (1.1, 4.0)	42.9 vs. 28.1 2.05 (1.33, 3.14), *P*=0.001	43.3 vs. 31.9 1.79 (1.34, 2.40), *P*<0.0001
mRS 0-1: active vs. control (%) OR (95% CI) or *P* value	51.4 vs. 28.6 2.4 (0.87, 6.6), *P*=0.09	42.9 vs. 19.4 NA	24.3 vs. 12.6 NA	31.1 vs. 18.1 2.14 (1.31, 3.51), *P*=0.003	28.4 vs. 19.4 1.81 (1.34, 2.44), *P*=0.0001
Shift analysis, OR (95% CI) or *P* value	2.0 (1.2, 3.8), *P*=0.006	2.63 (1.57, 4.40), *P*<0.001	1.7 (1.05, 2.8)	NA	NA
Mortality: active vs. control (%) OR (95% CI) or *P* value	8.6 vs. 20.0 0.45 (0.1, 2.1), *P*=0.31	9.2 vs. 12.4 0.74 (0.33, 1.68), *P*=0.50	18.4 vs. 15.5 1.2 (0.6, 2.2), *P*=0.6	20.5 vs. 24.0 0.83 (0.48, 1.39), *P*=0.46	17.6 vs. 19.4 0.87 (0.71, 1.05), *P*=0.1508
mRS 5-6: active vs. control (%) OR (95% CI) or *P* value	8.6 vs. 31.4 NA	12.2 vs. 24.7 NA	30.1 vs. 35.9 NA	NA NA	24.3 vs. 29.2 0.77 (0.61, 0.97), *P*=0.0246
SICH: active vs. control (%) OR (95% CI) or *P* value	0.0 vs. 5.7 Absolute difference: -6% (-13, 2), *P*=0.49	0.0 vs. 3.1 *P*=0.12	1.9 vs. 1.9 1.0 (0.1, 7.0), *P*=1.00	8.9 vs. 2.3 2.87 (1.21, 6.83), *P*=0.02	5.8 vs. 4.6 1.19 (0.83, 1.69), *P*=0.3453

be less responsive to and at high risk of SICH with ERT. Alberta Stroke Program Early CT Score of 6-10 was defined as a small infarct core and one of the inclusion criteria in the ESCAPE, SWIFT PRIME (perfusion imaging at the inception and then modified to Alberta Stroke Program Early CT Score during the trial), and REVASCAT trials.[10,12,13] MR CLEAN did not use Alberta Stroke Program Early CT Score for the patient selection, but only 5.6% of the enrolled patients had very low Alberta Stroke Program Early CT Score of 0-4.[9] In contrast, EXTEND-IA used CT perfusion to select patients with a small ischemic core (area of cerebral blood flow less than 30% of normal tissue: < 70 mL on CT perfusion).[11] The SWIFT PRIME trial also evaluated baseline perfusion imaging in 81% of the enrolled patients and selected patients with ischemic core less than 50 mL.[12]

Patients with good collaterals are likely to have more salvageable tissue and to achieve good outcome with reperfusion. In addition, good collateral status was associated with a lower risk of SICH. The ESCAPE trial, using a collateral assessment with multiphase CT angiography (CTA), selected patients with moderate-to-good collaterals defined as > 50% filling of the middle cerebral artery territory.[10]

Target vessel occlusion

Now, CTA (MR angiography in some centers) is widely and immediately available in the emergent setting in most stroke centers. Patients with severe stroke are likely to have large cerebral artery occlusion. However, among patients with the National Institute of Health Stroke Scale (NIHSS) score of 9 or more presenting within 3 hours, 19.3% had no major arterial occlusion.[27] Of the 656 patients enrolled in the Interventional Management of Stroke (IMS) III trial, 306 (47%) underwent baseline CTA or MR angiography and a target vessel occlusion by vascular imaging was confirmed only in 282 (43%) before randomization. As a result, of the 434 patients assigned to ERT, 80 (18.4%) patients were judged by site investigators to have no thrombus deemed treatable by ERT.[6] In an exploratory analysis of 220 patients with proximal artery occlusion confirmed by baseline CTA, ERT was associated with a higher recanalization rate at 24 hours and a favorable shift on the mRS score at 90 days.[28] In contrast, all the 5 stent-retriever RCTs used CTA or MR angiography to select patients who had a target vessel occlusion in the intracranial carotid and/or middle cerebral artery. Of the patients enrolled in the 5 stent-retriever RCTs, 16.6%-31.4% had internal carotid artery occlusion, and 54.3%-68.6% had M1 occlusion. Therefore, vascular imaging is strongly recommended in patients with severe stroke to assess large cerebral artery occlusions.

ERT modality

Prolyse in Acute Cerebral Thromboembolism (PROACT) II was the first phase 3 trial that assessed the effect of IA recombinant prourokinase.[4] PROACT II did not allow mechanical disruption. After then, the strategy to enhance recanalization has evolved from mechanical disruption with microguidewire through Merci embolectomy device and Penumbra aspiration to stent-retriever thrombectomy. In two phase 2 trials comparing stent-retriever thrombectomy device (Solitaire Flow Restoration Device in one and Trevo Retriever in another trial) with Merci device, the stent-retrievers had better recanalization rates, which were translated into improved clinical outcomes.[29,30] In the Synthesis: A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS Expansion) trial that failed to show the superiority of ERT over IV-TPA, 66% of 165 patients receiving ERT were treated with IA TPA infusion plus mechanical disruption with a micro-guidewire and only 13.9% with Solitaire or Trevo device.[7] The IMS III trial also used old endovascular technologies in most cases: IA infusion of TPA in 47.9%, Merci device in 28.4%, and Penumbra in 16.2%. Only 1.5% were treated with Solitaire stent-retriever. Of patients treated with ERT in IMS III, only 41% achieved good recanalization defined as modified Thrombolysis in Cerebral Infarction 2b-3.[6] In contrast, in the 5 stent-retriever trials, 58.7%[9] and 88.0%[12] of patients assigned to ERT achieved recanalization of modified Thrombolysis in Cerebral Infarction 2b-3.

Efficacy and safety of ERT

RCTs comparing ERT versus standard therapy since 1998

Overall, 15 RCTs involving 2,899 patients (1,575 in the ERT group and 1,324 in the control group) compared mRS outcome between the ERT and control groups (for control arms, no IV-TPA in 6 trials[4,14-18] and IV-TPA between 29.6% to 100% in 9 trials[6-13,19]). In our updated meta-analysis,[21] ERT was associated with increased mRS 0-2 outcome (pooled odds ratio [95% confidence interval], 1.79 [1.34, 2.40]; $P < 0.0001$; number needed-to-treat [NNT] = 9), mRS 0-1 outcome (1.81 [1.34, 2.44]; $P = 0.0001$; NNT = 11), good neurological outcome (3.11 [2.14, 4.53]; $P < 0.0001$; NNT = 6), good activity of daily living (2.24 [1.78, 2.82]; $P < 0.0001$; NNT = 5), and partial or complete recanalization (4.50 [1.97, 10.27]; $P = 0.0003$; NNT = 3). The ERT and control groups did not differ in the rates of SICH (1.19 [0.83, 1.69]; $P = 0.8695$) and 90-day mortality (0.87 [0.71, 1.05]; $P = 0.1508$; NNT = 55). However, ERT significantly reduced the extreme disability or death outcome (mRS 5-6) (0.77 [0.61, 0.97]; $P = 0.0246$; NNT = 21).

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RCTs comparing stent-retriever thrombectomy versus standard IV-TPA

The 5 stent-retriever RCTs enrolled 1,278 patients: 633 in the ERT group and 645 in the control group. The median NIHSS score at baseline ranged from 13 to 18 in the control groups and from 16 to 17 in the ERT groups. IV-TPA was administered in 77.0%[13] to 100%[11,12] in the control groups and 68.0%[13] to 100%[11,12] in the ERT groups. The percentage of patients achieving good outcome defined by mRS 0-2 at 90 days ranged between 32.6%[9] and 71.4%[11] in the ERT groups and between 19.1%[9] and 40%[11] in the control groups. Across the trials, the absolute increase of mRS 0-2 outcome with ERT compared to standard therapy ranged between 13.5%[9] and 31.4%[11], which was statistically highly significant. Therefore, the magnitude of benefit was substantial with an NNT for mRS 0-2 outcome between 3 and 7. ERT was significantly associated with a favorable shift on the mRS scores: the odds of improvement of 1 point on the mRS score, 1.67[9] to 3.1[10].

SICH occurred in 0%[11,12] to 7.7%[9] in the ERT groups and 1.9%[13] to 6.4%[9] in the control groups, and the absolute increase in the SICH rate ranged between -5.7%[11] and 1.3%[9]. In all trials, ERT did not significantly increase the risk of SICH. In the ESCAPE trial, 90-day mortality was significantly lower in the ERT group than in the control group,[10] whereas, in the other 4 trials, 90-day mortality was non-significantly lower in the ERT groups than in the control groups.[9,11-13]

When pooling data of the 5 stent-retriever RCTs,[21] ERT was associated with increased mRS 0-2 outcome (pooled odds ratio [95% confidence interval]; 2.39 [1.88, 3.04]; $P<0.0001$; NNT = 5), mRS 0-1 outcome (2.49 [1.85, 3.36]; $P<0.0001$; NNT = 7), good neurological outcome (3.62 [2.26, 5.78]; $P<0.0001$; NNT = 4), good activity of daily living (2.53 [1.83, 3.52]; $P<0.0001$; NNT = 5), and partial or complete recanalization (5.68 [3.09, 10.45]; $P<0.0001$; NNT = 3). The SICH rate was comparable between the ERT and control groups (1.08 [0.61, 1.88]; $P=0.7983$). Mortality reduction with ERT was not significant (0.78 [0.54, 1.12]; $P=0.1770$; NNT = 29), but the extreme disability or death outcome (mRS 5-6) was significantly reduced with ERT (0.57 [0.41, 0.78]; $P=0.0006$; NNT = 9).

ERT in patients with posterior circulation stroke

Patients with severe stroke due to large artery occlusion in the posterior circulation usually have severe disability and mortality without timely recanalization. However, the benefit of ERT in these patients has not been confirmed by large RCTs. In a small RCT including only 16 patients, good outcome was achieved in 50% of patients treated with ERT and 12.5% in the control group ($P=0.28$).[17] In another 3 RCTs, 3.0%-19.3% of patients had posterior circulation strokes, but the result of subgroup analysis for posterior circulation was not reported or showed no benefit of ERT.[6,7,19] The 5 stent-retriever RTCs exclusively enrolled patients with large artery occlusion in the anterior circulation. In a recent meta-analysis of 45 observational studies (41 ERT and 4 IV-TPA studies) involving 2,056 patients with acute basilar artery occlusion, ERT was associated with reduced death or dependency (0.67 [0.61, 0.72]) and reduced mortality (0.48 [0.42, 0.55]).[31]

Other Issues

IV-TPA before ERT

IV-TPA within 4.5 hours of stroke onset is a proven therapy despite its limited efficacy in patients with acute large cerebral artery occlusion. In the 5-stent retriever RCTs, IV-TPA was given to most patients randomized to the ERT (68.0%[13] to 100%[11,12]) and control (77.0%[13] to 100%[11,12]) arms. Since the SICH rates did not differ between the ERT and control groups, IV-TPA might account for the SICH in most patients. However, IV-TPA before ERT could result in complete recanalization of proximal large cerebral artery occlusion in some patients, facilitate recanalization of proximal artery occlusion with ERT, and improve reperfusion in the distal branch. In the SYNTHESIS Expansion trial that failed to show the superior efficacy of ERT over IV-TPA alone, patients assigned to ERT were not treated with IV-TPA.[7] Therefore, there is no evidence to avoid IV-TPA in patients eligible for ERT. For patients treated with IV-TPA, REVASCAT selected patients with persistent arterial occlusion after 30 minutes of IV-TPA infusion,[13] and MR CLEAN did not specifically report whether the investigators waited for clinical response to IV-TPA.[9] In contrast, to start ERT as soon as possible, the ESCAPE, EXTEND-IA, and SWIFT PRIME trials proceeded ERT during IV-TPA administration without waiting for clinical response to IV-TPA.[10-12]

Because both ERT and IV-TPA would increase the risk of SICH, some physicians might consider a low dose of IV-TPA for patients indicated for ERT. The IMS III trial employed a reduced IV-TPA dose of 0.6 mg/kg for patients in the ERT group at the inception. However, it was changed to the standard dose of 0.9 mg/kg after the protocol amendment during the trial.[6] All the 5 stent-retriever trials used the standard dose of IV-TPA for both the ERT and control groups.[9-13] Accordingly, the current evidence suggest that the standard IV-TPA dose of 0.9 mg/kg would be reasonable in patients eligible for ERT.

Conscious sedation versus general anesthesia

Severe stroke patients indicated for ERT are usually poorly

cooperated and sometimes seriously agitated, which might increase the risk of endovascular procedure complication. Therefore, several centers prefer general anesthesia over conscious sedation. However, general anesthesia likely delays treatment initiation, potentially results in hypotension that would worsen perfusion in penumbra, and precludes neurological monitoring.

In a recent meta-analysis of 9 studies, general anesthesia was associated with increased risks of death (pooled odds ratio [95% confidence interval], 2.59 [1.87, 3.58]) and respiratory complication (2.09 [1.36, 3.23]), and was associated with decreased odds of good functional outcome (0.43 [0.35, 0.53]). Since patients on general anesthesia had more severe stroke, the results might be confounded by stroke severity.[32] However, in retrospective observational studies that adjusted covariates including NIHSS score, patients receiving general anesthesia had worse outcome.[33-35] In the 5 stent-retriever trials, 6.7%[13] to 37.8%[9] of patients in the ERT groups received general anesthesia. Currently, of the 5 stent-retriever RCTs, data on the effect of general anesthesia are available from MR CLEAN where 37.8% of patients in the ERT group received general anesthesia. In this post hoc analysis, patients on general anesthesia had no benefit of ERT, and general anesthesia was associated with treatment delay.[36]

System organization and quality improvement of ERT

ERT for acute ischemic stroke is the most complex and resource-intensive therapy that would not be available in all centers. Therefore, it would be reasonable to develop regional comprehensive stroke centers, which are closely connected to hospitals that are capable of IV-TPA treatment but incapable of ERT. It is generally recommended that centers providing ERT should implement an organized system of critical pathway and a multidisciplinary team that is responsible for initial evaluation, decision making, and ERT procedure.

Time is brain with ERT as well as with IV-TPA. A preplanned analysis of data from the IMS III trial showed that faster reperfusion was significantly associated with good outcome: 90-day good outcome of mRS 0-2 was achieved in 51.8% of patients with reperfusion within 5 hours, 45.4% in those within 5 to 6 hours, and only 26.5% in those after 6 hours. Every 30-minute delay in reperfusion was associated with a 12% decreased likelihood of achieving good outcome of mRS 0-2.[37] In another study analyzing data of patients treated with Solitaire Flow Restoration stent-retriever, for every 15-minute acceleration of reperfusion, 31 per 1,000 treated patients had a favorable shift on the mRS score.[38] Therefore, recent guidelines or consensus statements emphasize the expeditious assessment, decision, and initiation of ERT. The multisociety consensus quality improvement guidelines recommend door-to-neuroimaging evaluation within 25 minutes and door-to-neuroimaging interpretation within 45 minutes in ≥80%, door-to-groin puncture within 120 minutes in ≥75%, and groin-puncture-to-first attempt to recanalization within 45 minutes in ≥50% of ERT-treated patients.[23] Therefore, each center is encouraged to monitor and improve the time metrics.

Since the RCTs testing ERT were generally conducted in experienced centers and selectively enrolled patients based on specific inclusion and exclusion criteria, the efficacy and safety findings from the RCTs might not be generalized to real world practice. Therefore, to further ensure the efficacy and safety of ERT in the setting of routine clinical practice, the data of clinical outcomes and complication need to be complied at individual center level or more preferably at multicenter registry level.

Consensus achievement

The writing members made a first draft including proposal of recommendations. To achieve consensus for the proposed recommendations using a modified Delphi method, we convened a panel of 42 experts: 20 from the Korean Stroke Society, 11 from the Korean Society of Interventional Neuroradiology, and 11 from the Society of Korean Endovascular Neurosurgeons. Using a 9-point scale modified from RAND Corporation method, we asked experts to individually provide their ratings on individual recommendations: a score of 9 as strong agreement and a score of 1 as strong disagreement.[39] We defined scores 7-9 as agreement, 4-6 as uncertainty, and 1-3 as disagreement. We considered that consensus on recommendation was reached if 75% or more experts agreed. For recommendations with an agreement rate of less than 75% experts, additional Delphi rounds were conducted.

Among 42 experts convened, 34 (81%) provided their ratings, and the list of participants is provided in Supplemental Table 1. In the first Delphi round, consensus was achieved in 18 recommendations, and the scores and agreement rates were generally high (Supplemental Table 2). In two recommendations, the agreement rate was 68% and 71%, respectively. Therefore, we revised the recommendations reflecting the opinion of respondents. In the second Delphi round, we achieved consensus with the agreement rate of 100% and 96%. The final draft of the current guidelines was reviewed and approved by the participating academic societies.

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Table 3. Summary of recommendations

Recommendations	References
Endovascular Recanalization Therapy (ERT)	
1. In patients with major ischemic stroke due to an acute large artery occlusion in the anterior circulation (internal carotid artery, M1, and possibly large M2 branch) within 6 hours, ERT is recommended to improve clinical outcomes (level of evidence [LOE] Ia, grade of recommendation [GOR] A).	9-13,21
2. In patients eligible for intravenous tissue plasminogen activator (IV-TPA), administration of IV-TPA is recommended before the initiation of ERT (LOE Ia, GOR A). Since IV-TPA should not significantly delay ERT, it is recommended to simultaneously proceed ERT during IV-TPA treatment without waiting for clinical response to IV-TPA.	9-13,21
3. In patients who are contraindicated for IV-TPA, ERT is recommended as a first-line therapy in patients with major ischemic stroke due to an acute large artery occlusion in the anterior circulation within 6 hours (LOE IIa, GOR B).	9-13
4. In patients with major ischemic stroke due to acute large artery occlusion in the poster circulation (basilar artery, P1, and vertebral artery) within 6 hours, ERT can be considered (LOE III, GOR B).	31
5. For patients with acute large artery occlusion in the anterior or posterior circulation presenting after 6 hours, ERT can be considered for patients having favorable multimodal imaging profiles regarding expected benefit and safety. Each center is encouraged to define own selection criteria (LOE IV, GOR C).	10,13
6. If indicated, ERT should be initiated as fast as possible (LOE IIa, GOR B).	37,38
7. Stent-retriever thrombectomy is recommended as a first-line ERT (LOE Ia, GOR A).	9-13,21,29,30
8. If recanalization is not achieved with stent-retriever thrombectomy, the addition of other ERT modalities can be considered after taking into account the expected efficacy and safety (LOE IV, GOR C).	9,10,21
9. Other mechanical thrombectomy or thrombus aspiration devices may be considered as a first-line modality at the discretion of responsible interventionists after taking into account technical aspects (LOE IV, GOR C).	9,10,21
10. During ERT, conscious sedation is generally preferred to general anesthesia. However, the decision should be made after consideration of patient's condition and center's experience (LOE III, GOR B).	33-36
Neuroimaging evaluation	
1. Noncontrast CT or MRI should be conducted to exclude hemorrhagic stroke or other non-stroke etiologies (good practice points [GPP]).	4,14-18,6-13,19
2. Non-invasive vascular imaging (CT angiography or MR angiography) is recommended to confirm acute large artery occlusion for patients with major ischemic stroke (GPP).	9-13
3. For patients who are not able to perform non-invasive vascular imaging, stroke severity or clot sign on noncontrast CT can guide decision for ERT (GPP).	24
4. For selecting patients, neuroimaging evaluation for extensive early ischemic injury can guide decision for ERT (GPP).	9-13,28,29
5. Advanced multimodal imaging to assess collaterals, extent of ischemic core, or perfusion-diffusion mismatch can be considered to identify patients who are likely to benefit from ERT (GPP). However, the multimodal imaging should not significantly delay ERT.	9-13
System organization	
1. For centers capable of providing ERT, the organization and implementation of critical pathway and formal protocol are recommended to accelerate the delivery of ERT (GPP).	10,12,22-24
2. For centers that are not adequately staffed for ERT, it is encouraged to have a referral plan to a center capable of ERT for patients eligible for ERT. If indicated, initiating IV-TPA before referral is encouraged (GPP).	13,22-24,32
3. Each center is encouraged to define own criteria for the multidisciplinary ERT team that is responsible for initial evaluation, decision making, and ERT procedure (GPP).	22-24
4. To assess and improve the quality of ERT, each center is encouraged to monitor key time metrics of door-to-neuroimaging and door-to-groin puncture (GPP).	22-24
5. It is encouraged to assess functional outcome, recanalization rate, and complication rate after ERT (GPP).	22-24

Recommendations

Recommendations for ERT, neuroimaging evaluation, and system organization are summarized in Table 3.

Estimation of ERT candidates in Korea

In Korea, about 75,000 ischemic strokes occur annually.[40] In a large prospective stroke registry enrolling 27,851 patients with acute ischemic strokes between April 2008 and November 2013, 4.6% were treated with ERT.[41] However, the centers participated in the registry are likely to have a higher rate of ERT than an average rate in Korea. Data from a large hospital-based registry of the USA showed that about 2.0% of patients with ischemic stroke received ERT in 2012.[42] Accordingly, a reasonable projected rate of ERT in Korea would range from 2.0% to 3.0%, indicating that currently 1,500-2,250 patients per year might receive ERT. However, according to a registry study in Korea, about 20% of patients had a severe stroke of baseline NIHSS score of ≥ 10,[41] which were likely to be caused by large cerebral artery occlusion. Therefore, the number of patients who are indicated for ERT, if they arrive earlier, would be much greater. Patients with large cerebral artery occlusion are usually severely disabled and dead without timely

reperfusion, and thereby we need to set up an organized stroke care system for ERT at regional or national level.

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Supplemental Table 1. Members of expert panel participating in the Delphi consensus

Participants	Affiliation
Chin-Sang Chung	Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
Bum-Tae Kim	Department of Neurosurgery, Soonchunhyang University, Bucheon Hospital, Bucheon, Korea
Bum-soo Kim	Department of Radiology, Seoul St.Mary's Hospital, The Catholic University of Korea, Seoul, Korea
Jaseong Koo	Department of Neurology, Cerebrovascular Center, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea
Sun U. Kwon	Department of Neurology, University of Ulsan College of Medicine, Seoul, Korea
Gyeong-Moon Kim	Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
Oh Young Bang	Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
Joung-Ho Rha	Department of Neurology, Inha University College of Medicine, Incheon, Korea
Dong-Eog Kim	Department of Neurology, Stroke Center and Korean Brain MRI Data Center, Dongguk University Ilsan Hospital, Goyang, Korea
Hee-Joon Bae	Department of Neurology and Cerebrovascular Center, Seoul National University Bundang Hospital, Seongnam, Korea
Byung-Woo Yoon	Department of Neurology, Seoul National University College of Medicine, Seoul, Korea
Kyung-Ho Yu	Department of Neurology, Hallym University College of Medicine, Anyang, Korea
Kyung-Yul Lee	Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
Byung-Chul Lee	Department of Neurology, Hallym University College of Medicine, Anyang, Korea
Jun Lee	Department of Neurology and Stroke Center, Yeungnam University Medical Center, Daegu, Korea
Ji Hoe Heo	Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
Keun-Sik Hong	Department of Neurology, Stroke Center, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea
Woo-Keun Seo	Department of Neurology, College of Medicine, Korea University Guro Hospital, Korea University, Seoul, Korea
Jin Soo Lee	Department of Neurology, Ajou University School of Medicine, Suwon, Korea
Hong Gee Roh	Department of Radiolog, Konkuk University Medical Center, Seoul, Korea
Byungjun Kim	Department of Radiology, Korea University Anam Hospital, Seoul, Korea
Hyuk Won Chang	Department of Radiology, Dong San Medical center, Keimyung University School of Medicine, Daegu, Korea
Jun Soo Byun	Department of Radiology, Chung-Ang University College of Medicine, Seoul, Korea
Yoodong Won	Department of Radiology, Uijeongbu St. Mary's Hospital, Uijeongbu, Korea
Hae Woong Jeong	Department of Diagnostic Radiology, Busan Paik Hospital, Inje University, Busan, Korea
Kyungsool Jang	Department of Neurosurgery, Incheon St. Mary's Hospital, Catholic University of Korea, Incheon, Korea
Jae Il Lee	Department of Neurosurgery, Pusan National University, School of Medicine, Busan, Korea
Gyojun Hwang	Department of Neurosurgery, Seoul National University Bundang Hospital, Seongnam, Korea
Young-Je Son	Department of Neurosurgery, Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea
Dong-Hun Kang	Department of Radiology and Neurosurgery, School of Medicine, Kyungpook National University, Daegu, Korea
Seung Hoon You	Department of Neurosurgery, Gangneung Asan Hospital, Ulsan College of Medicine, Gangneung, Korea
Soon Chan Kwon	Department of Neurosurgery, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea
Tae-Sun Kim	Department of Neurosurgery, Chonnam National University Hospital & Medical School, Gwangju, Korea
Chang Wan Oh	Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea

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Supplemental Table 2. Results of Delphi consensus

Recommendations	Delphi round achieving consensus	Agreement (score 7-9), (%)	Uncertainty (score 4-6), (%)	Disagreement (score 1-3), (%)
Endovascular Recanalization Therapy				
1. In patients with major ischemic stroke due to an acute large artery occlusion in the anterior circulation (internal carotid artery, M1, and possibly large M2 branch) within 6 hours, endovascular recanalization therapy (ERT) is recommended to improve clinical outcomes (LOE Ia, GOR A).	First round	91.2	5.9	2.9
2. In patients eligible for intravenous tissue plasminogen activator (IV-TPA), administration of IV-TPA is recommended before the initiation of ERT (LOE Ia, GOR A). Since IV-TPA should not significantly delay ERT, it is recommended to simultaneously proceed ERT during IV-TPA treatment without waiting for clinical response to IV-TPA.	First round	94.1	2.9	2.9
3. In patients who are contraindicated for IV-TPA, ERT is recommended as a first-line therapy in patients with major ischemic stroke due to an acute large artery occlusion in the anterior circulation within 6 hours (LOE IIa, GOR B).V	First round	97.1	2.9	0
4. In patients with major ischemic stroke due to acute large artery occlusion in the poster circulation (basilar artery, P1, and vertebral artery) within 6 hours, ERT can be considered (LOE III, GOR B).	First round	91.2	8.8	0
5. For patients with acute large artery occlusion in the anterior or posterior circulation presenting after 6 hours, ERT can be considered for patients having favorable multimodal imaging profiles regarding expected benefit and safety. Each center is encouraged to define own selection criteria (LOE IV, GOR C).	First round	88.2	8.8	2.9
6. If indicated, ERT should be initiated as fast as possible (LOE IIa, GOR B).	First round	91.2	5.9	2.9
7. Stent-retriever thrombectomy is recommended as a first-line ERT (LOE Ia, GOR A).	First round	76.5	20.6	2.9
8. If recanalization is not achieved with stent-retriever thrombectomy, the addition of other ERT modalities can be considered after taking into account the expected efficacy and safety (LOE IV, GOR C).	First round	91.2	8.8	0
9. Other mechanical thrombectomy or thrombus aspiration devices may be considered as a first-line modality at the discretion of responsible interventionists after taking into account technical aspects (LOE IV, GOR C).	First round	85.3	11.8	2.9
10. During ERT, conscious sedation is generally preferred to general anesthesia. However, the decision should be made after consideration of patient's condition and center's experience (LOE III, GOR B).	First round	91.2	8.8	0
Neuroimaging evaluation				
1. Noncontrast CT or MRI should be conducted to exclude hemorrhagic stroke or other non-stroke etiologies (GPP).	First round	91.2	5.9	2.9
2. Non-invasive vascular imaging (CT angiography or MR angiography) is recommended to confirm acute large artery occlusion for patients with major ischemic stroke (GPP).	First round	91.2	5.9	2.9
3. For patients who are not able to perform non-invasive vascular imaging, stroke severity or clot sign on noncontrast CT can guide decision for ERT (GPP).	First round	91.2	5.9	2.9
4. For selecting patients, neuroimaging evaluation for extensive early ischemic injury can guide decision for ERT (GPP).	Second round	100	0	0
5. Advanced multimodal imaging to assess collaterals, extent of ischemic core, or perfusion-diffusion mismatch can be considered to identify patients who are likely to benefit from ERT (GPP). However, the multimodal imaging should not significantly delay ERT.	First round	82.4	11.8	5.9
System organization				
1. For centers capable of providing ERT, the organization and implementation of critical pathway and formal protocol is recommended to accelerate the delivery of ERT (GPP).	First round	91.2	8.8	0
2. For centers which are not adequately staffed for ERT, it is encouraged to have a referral plan to a center capable of ERT for patients eligible for ERT. If indicated, initiating IV-TPA before referral is encouraged (GPP).	First round	88.2	11.8	0
3. Each center is encouraged to define own criteria for the multidisciplinary ERT team that is responsible for initial evaluation, decision making, and ERT procedure (GPP).	Second round	96	4	0
4. To assess and improve the quality of ERT, each center is encouraged to monitor key time metrics of door-to-neuroimaging and door-to-groin puncture (GPP).	First round	91.2	8.8	0
5. It is encouraged to assess functional outcome, recanalization rate, and complication rate after ERT (GPP).	First round	91.2	8.8	0